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IMPLEMENTING OCCUPATIONAL-BASED HELICOBACTER PYLORI SCREENING FOR GASTRIC CANCER PREVENTION

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This thesis is based on the scientific research produced in support of the HPOS study – Helicobacter pylori screening on Hospital Workers, and presents the first results of the implemented intervention. This project has been conducted in collaboration with Prof Dino Vaira, Dr Giulia Fiorini and Dr Matteo Pavoni, with the resources, coordination and support of Prof Paolo Boffetta. It raised from an idea first developed in November 2019, and shared with Dr Andrea Farioli, who was the first to encourage this project.
This PhD thesis id dedicated to Andrea.

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Contents

Implementing occupational-based Helicobacter pylori screening for gastric cancer prevention

1. Abstract

Future medicine is grounded in prevention, consistently supported by epidemiological evidence demonstrating its effectiveness in reducing disease burden, improving population health outcomes, and enhancing the sustainability of health services.

In recent years, increasing attention has been devoted to workplace health promotion, including cancer prevention, within the framework of the Total Worker Health approach. This perspective extends beyond the control of occupational hazards to encompass the overall health and wellbeing of the working population, recognizing the workplace as a strategic setting for disease prevention and health equity. This is especially relevant in the context of the current shortage of health providers and the progressive ageing of the workforce, which together generate growing healthcare needs while limited medical resources.

In Italy, a legislation enacted on 31 October 2025 promotes access to cancer screening during working hours, favoring the spread of cancer prevention awareness and the participation in cancer screening programs. The decree also strengthens the role of the occupational physician, expanding it beyond traditional occupational health surveillance to include the active promotion of cancer screening participation and the integration of extended cancer prevention within corporate welfare.

Helicobacter pylori (Hp) infection is a paradigmatic target in preventive medicine. For decades, Hp remained a largely unrecognized pathogen, until its causal role in peptic ulcer disease was established, leading to the Nobel Prize in 2005 to Warren and Marshall. Hp has been identified as the cause of a large spectrum of gastric and extra-gastric conditions, encompassing both benign and malignant diseases. Notably, Hp is the leading cause of infection-related cancer worldwide. Despite the extensive scientific evidence showing that Hp eradication reduces the risk of gastric cancer, population-based screening and treatment strategies remain poorly implemented, except for some countries in Asia such as Japan, South Korea, and China, where infection prevalence and gastric cancer incidence are particularly high.

This doctoral thesis investigates Hp infection as a modifiable determinant of health, focusing on its carcinogenic role and on the potential of Hp control to reduce the burden of gastric cancer. The overarching aim is to explore the feasibility and effectiveness of workplace-based Hp screening, where occupational health surveillance is a unique, structured, and underutilized opportunity for large-scale gastric cancer prevention. The thesis is structured as a collection of studies conducted and published (or in publication) during the PhD program. These include investigations into the epidemiology of Hp–related gastric cancer, global estimates of the burden of gastric cancer attributable to Hp, and analyses of cancer attributable to infectious agents in Italy. Furthermore, this research explores the implementation of workplace-based Hp screening according to a Total Worker Health approach, as through the ongoing Horizon Europe project Cancer Prevention at Work, which extends the scope of this thesis to an international context and to other oncogenic infections. The specific goal of this project is the implementation of a screening of Hp infection for gastric cancer prevention in a population of hospital workers, in specific the employees of Sant'Orsola University Hospital in Bologna. The results of this study, conducted between 2023 and 2025, provides real-world evidence on the feasibility and acceptability of workplace-based Hp screening for gastric cancer prevention, and contributes to the knowledge of Hp epidemiology in hospital workers.

2. Introduction

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2.1 Trends in gastric cancer mortality 1990–2019 in 36 countries worldwide, with predictions to 2025, and incidence, overall and by subtype

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Abstract

Background: Gastric cancer (GC) incidence is declining heterogeneously worldwide. We aimed to calculate updated mortality trends for GC.

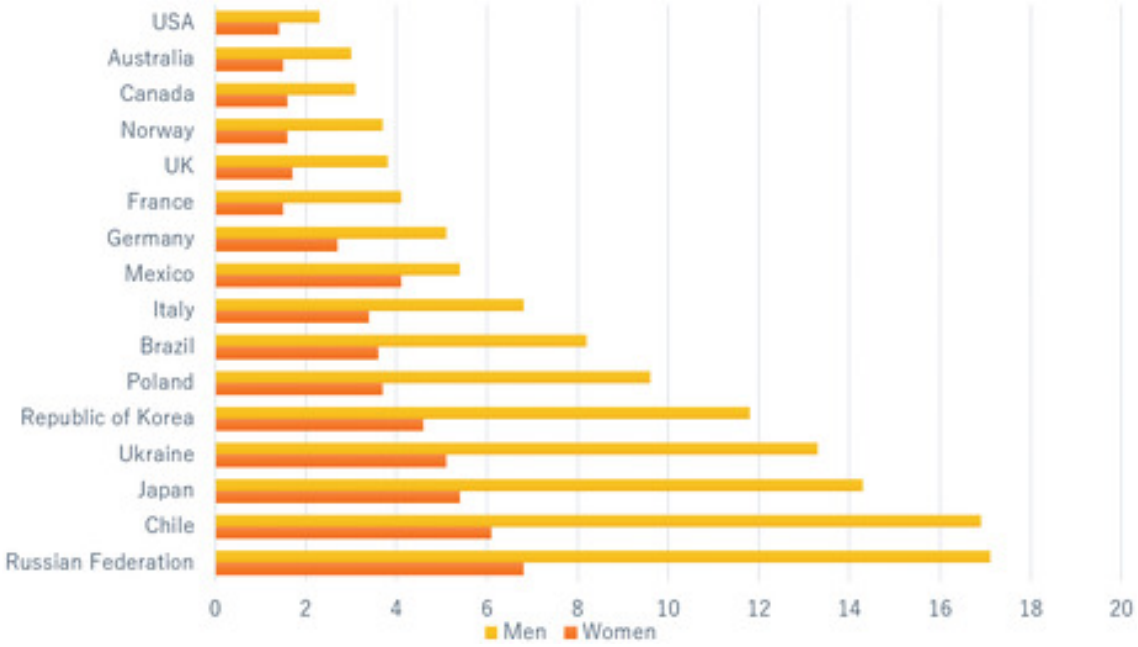
Methods: We investigated time trends for selected countries using the World Health Organization database. We computed age-standardized mortality rates (ASMR) per 100,000 persons over the 1990–2019 period. We reported rates for the 2010–2014 and 2015–19 calendar periods, and the corresponding percent changes. We used joinpoint regression analysis to identify changes in the slope of mortality trends, and predict the number of deaths and rates for 2025. We also reported 2008–2012 incidence rates of cardia and noncardia GC.

Results: Mortality trends from GC have been favorable since 1990 for all countries analyzed and the European Union (EU 27), in both sexes and all ages. GC mortality is predicted to decline in all countries for both sexes, except for French and US women aged 35–64 years, and Canadian men aged 35–64. The highest proportions of cardia GC were observed in Northern and Central Europe while the lowest ones in Southern and Eastern Europe. Elsewhere, the highest proportions were registered in countries with low incidence and mortality rates, whereas high-mortality countries showed lower proportions of cardia GC.

Conclusion: Observed and predicted GC mortality trends declined in most countries in both sexes, with few exceptions, likely due to the control of GC risk factors, in particular *Hp* infection.

Keywords: cardia, gastric cancer, incidence, mortality, trends

Age-standardized mortality rates from gastric cancer per 100,000, 2015-2019, in men and women in selected countries



INTRODUCTION

Gastric cancer (GC) was the leading cancer worldwide until 1975, [1] it still accounts for over one million new cases (https://gco.iarc.fr), being the fourth cause of cancer mortality in 2020. [2] GC prognosis is poor, the disease is often diagnosed at an advanced stage where aggressive surgery is needed. [3] Consequently, prevention to control the burden of GC is crucial. Infection with *Helicobacter pylori* (*Hp*) is the major cause of GC and is widespread globally, with differences by country, socioeconomic status (SES), and birth cohort. [4] Infection prevalence has been declining progressively over the years, largely thanks to water sanitation. [5] Tobacco smoking, alcohol consumption, unbalanced diet, and other factors associated with low SES are major concomitant factors, while occupational and genetic factors play an additional role. [6] The burden of GC is larger among individuals with low SES and in low- and middle-income countries. [7] Asian countries experience a heavier burden of GC compared to other regions, with Mongolia, Japan and the Republic of Korea being the countries with the highest GC incidence in 2020. [8] Cardia and noncardia GC subtypes (this latter including fundus, corpus, large and lesser curvatures and antrum) representing 15% and 75% of cases, respectively, can be identified based on the proximal or distal origin of the neoplastic lesions. [9] Given that the

anatomical locations are associated with different risk factors, with cardia GC sharing risk factors with esophageal adenocarcinoma such as obesity and gastroesophageal reflux while noncardia GC is strongly associated with *Hp* infection, GC shows different patterns across subgroups of the population and geographical areas. Conversely, the histological distinction of GC into intestinal and diffuse type does not translate into heterogeneity in GC epidemiology. [3] Upper-endoscopy is the gold standard for GC diagnosis, which is based on biopsy analysis. [10]

We aimed at estimating and interpreting the mortality trends of GC worldwide between 1990 and 2019, with emphasis on the last 10 years, focusing on sex and age differences. We also showed the proportion of cardia to noncardia incidence subtypes. Moreover, we reported the projected mortality rates and deaths for the 2025 calendar year.

MATERIALS AND METHODS

Mortality

Using the WHO mortality database, [11] we analyzed official numbers of certified deaths from GC coded as C16 according to the 10th Revision of the International Classification of Disease, [12] in selected countries worldwide. The European Union as a whole was defined as the 27 member states, EU (27), as of January 2020. We restricted our analyses to countries with high-mortality coverage (i.e., over 90%), high data quality, and more than 5 million inhabitants identifying 36 countries worldwide plus the EU. [13] We extracted estimates of resident populations from the same WHO database [11] for European and Australasian countries and from the Pan American Health Organization (PAHO) database for American countries. [14] When population data were missing, we retrieved them from EUROSTAT [15] or the United Nations (UN) Population Division [16] databases. Thus, we derived figures for the calendar periods from 1990 up to the most recent available year.

For each country, calendar year, and sex, we calculated 5 years' age-specific rates and the age-standardized mortality rates (ASMRs) per 100,000 person-years, using the world standard population, [17] at all ages and for the 35–64 year age group. We then fitted

joinpoint regression models [18] from 1990 until the most recent available year, for the most populous (≥10 million) countries and the EU (27), to identify significant changes in the linear slope (on a log scale) of ASMRs. For each identified linear segment, we estimated annual percent change (APC) and, for the entire study period, the average annual percent change (AAPC). [19,20]

For countries with ≥20 million inhabitants (i.e., 15 countries plus the EU as a whole), we also predicted the number of deaths for the year 2025, by fitting a Poisson joinpoint regression model, with a maximum of 5 possible joinpoints [19] to the number of deaths in each 5-year age group and running a linear regression over the most recent trend segment identified, the joinpoint model was restricted to identifying models with the final segment having at least 5 data points. Using the matrices of predicted age-specific death counts and predicted populations, we computed predicted ASMRs and their 95% prediction intervals (PIs). The predicted populations were extracted using the PAHO database for North American and Latin American countries, the EUROSTAT database for European countries, and the UN database for Asian and Oceanian countries.

Incidence

We obtained incidence data for GC for the 2008–2012 calendar period from the Cancer Incidence in Five Continents database, volume XI. [21] For countries with more than one cancer registry, we aggregated data to ensure the largest geographic coverage, and we restricted analyses to the longest common calendar period between registries. We presented, separately by sex, the number of cardia (C16.0) and noncardia (C16.1–6) incident cases of GC in various countries worldwide, in order to show the proportion of cardia cases.

We only considered publicly available data, so no clearance by Ethical Committee was necessary. For statistical analyses, we used R version 4.1.3 (R Development Core Team, 2017), SAS version 9.4 (SAS Institute Inc.), and Joinpoint Regression Program version 4.9.1.

RESULTS

Table 1 shows the annual average number of deaths and ASMRs from GC per 100,000 person-years of all ages and both sexes in selected countries worldwide and the EU (27), for the periods 2010–14 and 2015–19, together with the corresponding percent changes. The ASMRs ordered from the highest to the lowest one during the most recent period displayed by bar plots for men and women are also shown in Figure 1. Except for Greek males, the change in rates was favorable in all countries and both sexes. During 2015–2019, the highest male rates were reported in the Russian Federation, Chile, and Belarus with rates higher than 15/100,000, followed by Japan, Ukraine, Romania, South Korea, and Portugal with rates higher than 10/100,000. The lowest rates were observed in the United States, Sweden, Australia, and Canada with rates around 2–3/100,000 males. Similarly for females, the Russian Federation, Chile, Belarus, Japan, Portugal, and Ukraine showed the highest ASMRs during the 2015–2019 calendar period (rates varied from 5.1 to 6.8/100,000). The lowest ASMRs were registered in the United States, Australia, Canada, Belgium, Norway, Sweden, and Finland; with rates around 1.5–1.7/100,000 females. Corresponding figures for truncated rates in the 35–64 years age group are reported in Table S1 and Figure S1. The change in rates from 2010–2014 to 2015–2019 was favorable in all countries considered and both sexes, except for Denmark (+3.3%), Greece (+5.9%), Norway (+10.0%), Switzerland (+1.4%), and Mexico (+0.4%) in males and the United States (+1.0%) in females, where the rates were higher in the most recent period. Table S2 and Figure S2 report ASMRs among order adults aged 65 or more. Among the elderly, the change in rates from 2010–2014 to 2015–2019 was favorable in all countries considered and both sexes. The ranking was similar to the all ages one with some differences, that is, Chile and Japan were the first-ranking countries for the elderly and the second and fourth one at all ages. This indicates steeper declines in young and middle age in those countries as compared to Russia and other eastern European countries.

Figure 2 shows the trends in ASMRs from GC at all ages (full dots) and 35–64 years (empty dots) along with the corresponding joinpoint models (lines) for 23 selected countries worldwide and the EU-27, over the study period among males.

The corresponding figures for females are shown in Figure 3. Results from the joinpoint analyses are reported in Tables S2 and S3, respectively, for males and females. For the largest countries and the EU (27), the predicted ASMRs at all ages and 35–64 years for the calendar year 2025 with the corresponding 95% PIs are also shown. Detailed results for the 2025 predicted deaths and ASMRs are reported in Table 2. Male ASMRs resulted in a decrease since 1990 in all countries considered and the EU (27) and for both all ages and truncated 35–64 years. The Republic of Korea showed the highest decrease over the considered period, with an AAPC of −5.2 for all ages. Czech Republic, Netherlands, Sweden, and the United Kingdom reported moderate decreases (AAPCs greater than −4% per year) too, while Greece, Argentina, Cuba, and Mexico reported less consistent but still significant decrements (<2% per year). The EU (27) reported a significant decrease over time, with an AAPC -3.3. Results for males aged 35–64 years were similar to those for all ages.

The Republic of Korea reported the steepest fall in trend over time in females too (AAPC -5.2 for all ages). Belgium, the Czech Republic, and the United Kingdom showed favorable trends over time as well (AAPC around −4). Greece, Argentina, Brazil, Cuba, and Mexico had the smallest AAPCs—lower than 2—but still significant. The EU (27) showed a decrease over time with an AAPC of −3.3. Corresponding figures for females aged 35–64 were consistent with the decrease observed at all ages, albeit smaller.

Predicted rates for the year 2025 are downwards for all countries and the EU (27), for both sexes, and for all ages and adults aged 35–64, except for females aged 35–64 in France (% difference in rates versus 2015–19: +20.3) and in the United States (+7.3%), and for males aged 35–64 in Canada (+2.7%); however, these populations had comparatively low rates. Likewise, the predicted number of deaths in 2025 was favorable for all countries, sexes and ages except for Argentina, Brazil, Mexico, and the United States, for which the predicted deaths are higher than the ones observed in 2015–2019, due to population aging and growth. The most favorable predicted rates for 2025 are those in the Republic of Korea (% difference in rates versus 2015–19: −53.3 and −54.0, respectively, for men and women), followed by those calculated in Japan (−32.3% and −37.3%, respectively, for men and women). In the EU (27), the ASMR is predicted to

decline in men and women, with, respectively, a −23.9% and −28.3% decrease from 2015–19 to 2025 for all ages and −26.6% and −22.7% for adults aged 35–64 years.

Figure 4 gives the proportion of cardia and noncardia GC in men and women, respectively, for selected countries from Europe and other countries worldwide. For men, among European countries, the proportion of cardia ranged between 10.3% in Belarus and 62.0% in Denmark, being higher in Northern and Central Europe and lower in Southern and Eastern Europe (Table S5). Among other countries worldwide, the highest male proportion of cardia cancers (around 40%) was observed in countries with low incidence and mortality rates such as Canada, the United States, and Australia, while those with high rates, such as Argentina and the Republic of Korea had the lowest proportion (around 6%) of cardia subtype. Among women, a similar geographic pattern was observed (Table S6). In Europe, the lowest female proportion of cardia cases was observed in Belarus (6.9%), followed by Italy (7.4%), Spain (8.2%), and Austria (9.4%), while the highest proportion was observed in Denmark (35.1%). Worldwide, Argentina and the Republic of Korea showed the lowest proportions of cardia cases (respectively, 3.5 and 4.8%) while Canada, the United States, and Australia registered the highest ones (over 20%) among women.

DISCUSSION

Our results show a declining GC mortality trend, observed since the 1990 s has continued in the 2010 s in all countries. The decline in mortality was more pronounced in countries with higher rates, such as Japan and Korea, compared to countries with lower rates, such as the United States and Canada, consistently with previous results. [22] , [23] A strong reduction in GC death rates was also observed in the Russian Federation, Poland, and Italy. During the most recent calendar years, we observed the lowest rates of GC mortality around or below 2/100,000 (for men in United States, and for women, in several northern Europe countries, Australia and North America). A further marked decline is predicted in Japan and South Korea for both sexes up to 2025, while the United States and Canada are expected to experience less favorable trends, including a possible increase in young age

groups. Our predictions for 2025 estimate mortality rates in women in low-risk countries, such as the United Kingdom and the United States, in the order of 1/100,000/year or lower, the conventional threshold for the definition of a rare cancer. This raises interesting questions on whether further reduction could be achieved and what the base incidence of noncardia GC in the absence of *Hp* infection could be. The first symptoms of GC such as dyspepsia and early satiety largely overlap with benign conditions such as gastritis and reflux, while more severe symptoms like pain, weight loss, and hematemesis/anemia appear late. [9] Indeed, GC is mainly diagnosed at stages III and IV, when survival is poor. [3] According to Arnold and coauthors, about half of the GC cases diagnosed in Canada, Ireland, Denmark, and the United Kingdom in 2012–2014 belong to stage IV disease. [23] The authors also described a geographical variation in GC survival for patients with diagnosis of localized disease (e.g., 94.3% in New Zealand and 75.5% in Australia at 1 year and 86.5% in New Zealand and 59.9% in the United Kingdom at 3 years from diagnosis). Smaller differences emerged when comparing survival from distant disease, ranging from 26.6% to 20.7% at 1-year and from 8.0% to 3.8% at 3-year postdiagnosis. [23]

Endoscopy and multiple biopsy sampling are the gold standard for GC diagnosis. Also, endoscopic ultrasound helps in identifying wall infiltrations, while endoscopic mucosal resection and endoscopic mucosal dissection provide reliable staging information, allowing in addition the treatment of superficial early-stage lesions. The endoscopy is subject to the compliance of the patients and the availability of both a trained specialist and an endoscope and endoscopy room. Indeed, it is an invasive and expensive test, and is limitedly available in less affluent countries. [10] Despite surgical resection may be curative, most patients relapse. The most recent ESMO Clinical Practice Guidelines indicate that stage IB-III disease requires radical gastrectomy. [24] Nodal dissection accompanying radical gastrectomy is indicated to cover at least 15 lymph nodes according to the AJCC/UICC TNM, which again implies the availability of large upper-GI surgical units and highly specialized peri-operative care centers, which are more common in Asia than in other countries. [24] Preoperative and postoperative chemotherapy is recommended in all ≥IB resectable GC, possibly including fluoropyrimidine, a platinum agent and docetaxel. [24] When focusing on locally advanced unresectable or metastatic disease, the

prognosis is very poor, with less than 1 year survival. [24] However, combined chemotherapy has been demonstrated to be more effective than single-agent chemotherapy or supportive care only. Moreover, survival improvement has been reached by using chemotherapy combined with immunotherapy (nivolumab or trastuzumab). [24]

Part of the mortality decline is due to screening programs and early diagnosis in high-incidence countries like Japan and Korea. Nearly three-quarters of new GC cases occur in Asia, but large differences can be found when observing GC trend in Asian countries. A recent study highlighted how the different socioeconomic development, the historical background of cancer control programs explain the different trends in incidence by birth cohorts, where Japan underwent a decline in younger cohorts while China did not. [22] These authors attributed this difference primarily to the high-quality cancer control policies undertaken in Japan 22 years earlier than in China. Our results corroborate previous analyses focused on GC trends during 1980–2011, and identified a decrease in GC mortality which was more pronounced for noncardia cancer in non-Asian countries. [22] The authors interpreted these results as the progress in *Hp* infection control matched with a birth-cohort effect characterized by lower prevalence of infection in subsequent generations, causing a lower rates of noncardia GC cases. Also, they described a gradually smaller decline in GC mortality trends in US and predicted no further reduction for France after 2015. [22]

Our findings also agree with the projections to 2040 made in a recent study, which described the estimated incidence and mortality of GC worldwide to be particularly high in Asia and in men, with about two thirds of all cases occurring in the male sex. [23]

When considering subtypes, noncardia is responsible for more cases and, assuming comparable case fatality between the two types, [25] it likely causes more deaths than cardia GC. Noncardia GC is more frequent than cardia in most countries, with a ratio between 2:1 and 3:1. [26] Diet and obesity as well as gastroesophageal reflux disease are implicated in the increasing number of cardia cases in US and EU countries. [27, 28]

In addition, the ratio reflects past (given 20–30 years of latency for cancer development) prevalence of *Hp*. The high prevalence of infection is responsible for the high ratio in South America, East Asia, and Southern and Eastern Europe.

When looking at the numbers of cardia GC, possible anatomical location misclassification should be taken into account. Indeed, the increased number of cancers of the esophageal junction and of the cardia in cancer registries may be partially due to differences in tumor classification because of discrepancies in the anatomic subsite classification. This discrepancy was observed in a study based on Swedish Cancer Registry, where the authors also noticed a bidirectional misclassification between cancer of the lower esophagus and cancer of the gastric cardia. [29] Another study also based on Swedish Cancer Registry estimated that true cardia GC incidence could be up to 45% higher or 15% lower than that reported, possibly explaining the increasing number of cardia GC cases in the country. [30] A subsequent analysis on Cancer Registry of the Swiss Canton of Vaud over the period from 1976 and 1997 aimed at interpreting the reported increasing incidence in cardia GC, did not find an absolute increase in cardia GC cases, but rather a decrease of noncardia GC cases, which resulted in an increase in the proportion of cardia GC. [31] However, as noted by several authors, [32, 33] the classification of upper GI cancers remains problematic given the lack of a universally accepted and clearly reproducible anatomic landmark separating the gastric cardia from the lower esophagus, and even when the landmarks are defined, cancer often destroys the anatomy of the organ where it occurs, making landmarks become unrecognizable.

Based on our data, the reduction in GC mortality is similar in both sexes, with few exceptions (e.g., Denmark, Greece, and Norway, where declining rates were greater among women), although GC incidence and mortality remain higher in men. Previous studies explained this difference with the distribution of smoking habits and *Hp* infection, which are higher in men than in women: Countries where *Hp* infection shows larger gender gaps (e.g., USA and EU) have a stronger gender difference in mortality rates for GC as well. [34, 35]

It will be interesting to see if in countries where cardia GC and its risk factors are not so frequent (e.g., Asian countries) there will be a further decrease in GC overall, because of

the low incidence of cardia coupled with a continuous decrease in noncardia GC. Whether the incidence of cardia GC will increase, following the increasing prevalence of its risk factors such as obesity[48] remains an open question.

For some countries, including the United Kingdom, Brazil, Mexico, Canada, and the United States, the overall reduction in GC mortality was less pronounced among younger subjects, furthermore rising incidence rates in young adults have been reported recently.[26,34,35,36,37] Age-cohort effects would suggest a lower incidence of GC among the new generations, due to the birth-cohort effect of *Hp* infection [38] —well known to be less prevalent in the young [39] —as well as smoking habits, declining progressively in subsequent birth cohorts. [40] These results are consistent with the findings of Wang and collaborators, who calculated GC incidence rates in the United States between 1999 and 2013: New GC cases have been reported to overall diminish, except for patients diagnosed under 50 years of age. [41] Moreover, the incidence of advanced noncardia cases has been observed among under-50 years old Hispanics. [42] These elements could justify the smaller decrease in GC mortality in the young population. The lower reduction in the young could also be referred as the overall small incidence rate in this population. Also, this can be due to more aggressive forms of cancer affecting this subgroup in these areas. [42] Besides this, we could not consider neither the stage and grade at diagnosis to explain this difference more in detail.

Mortality trends are intrinsically limited by death certification validity. For this reason, we only included countries with WHO death certification data with over 90% death certification coverage, with good data quality, as declared by the WHO, [13] and with a resident population of over 5 million, and over 20 for prediction analysis, in order to minimize issues of excessive variability. Predicted statistics for cancer mortality should be interpreted with caution, the selected prediction method is based on age-specific joinpoint models, as such it is apt for short to medium term projections based on recent trends. Very recent changes in trends, occurring in the final 2–3 years of available data, and major changes in cohort effect trends could be difficult to detect with this prediction model. However, our previous European cancer mortality predictions, that have been running for over 10 years, have proved to be reliable and valid. [38] Further, a previous age-

period-cohort analysis displays monotonal descending cohort effects for the age groups and cohorts involved in these predictions, and comparing our previous prediction analysis on GC mortality published in 2014 with up to date registered data we found that the estimated projected ASMRs were accurate. [38] , [43] Broken line models, such as the joinpoint model used in this study, may also suffer from issues of overfitting. However, the NCI's joinpoint software is conservative in its model selection algorithms, and the frequentist permutation model selection method we use is the most conservative. [19] The previous age-period-cohort analysis found an asymptotic trend in GC mortality in subjects born since the 1940 s in some Nordic and Western countries, foretelling the lack of progress in French middle-aged women. [38] One issue is whether misclassification on death certificates has changed over time: If it has remained the same, it would not affect the results on trends. In any case, the surveillance of trends in younger adults is needed to monitor mortality changes by age and to plan potential preventive interventions towards this subgroup. [42]

The analysis of 35–64 years truncated age group was performed for data quality and certification issues. That this truncated age group has higher mortality than the overall is expected, due to the weighting of the world standard population that gives younger age groups greater weights.

A major strength of this analysis is the high number of countries included for which real data were available, making our results more reliable than those based on estimates. The data provided in this manuscript are based on large countries, those reducing statistical fluctuation. Moreover, we could present results for both GC anatomical sites, namely cardia and noncardia.

CONCLUSION

Our findings confirm the declining mortality of GC in all countries with valid data. Unfortunately no high-quality data were available for China and other Asian, South American, and African countries, which are major contributos to the burden of GC, thus

limiting the representativeness of these results at a global level. [22] The pattern of reduction is not homogeneous by geographical area and seems to follow the prevalence of *Hp* infection. The reduction in mortality rates is less pronounced in US and EU countries, where the prevalence of infection has already reached a stable point, while high-risk areas such as Eastern Europe and Asia have undergone an important decline in GC mortality, and will likely experience a further decrease in 2025. Indeed, aggressive programs of screening and eradication of *Hp* infection may lead to a dramatic decrease in GC mortality in a relatively short time, in high-risk populations. [44]

The distribution by anatomical site showed that the proportions of cardia and noncardia GC are getting close in many areas. Again, this may reflect the distribution of GC risk factors, with prevention of *Hp* infection and its eradication leading to a promising downscaling of noncardia GC in the EU and US, where cardia GC remains linked to lifestyle factors and obesity. The development of predictive models, the identification of high-risk subjects, and the early "test-and-treat" of *Hp* at the population level may represent important preventive tools.

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REFERENCES

1. Balakrishnan M, George R, Sharma A, Graham DY. Changing trends in stomach cancer throughout the world. Curr Gastroenterol Rep. 2017;19(8):36.

2. Global cancer observatory: cancer today. International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today (Last accessed May 2022).

3. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet. 2020;396(10251):635-648.

4. Plummer M, Franceschi S, Vignat J, Forman D, de Martel C. Global burden of gastric cancer attributable to helicobacter pylori. Int J Cancer. 2015;136(2):487-490.

5. Sjomina O, Pavlova J, Niv Y, Leja M. Epidemiology of helicobacter pylori infection. Helicobacter. 2018;23(Suppl 1):e12514.

6. Lyons K, Le LC, Pham YT, et al. Gastric cancer: epidemiology, biology, and prevention: a mini review. Eur J Cancer Prev. 2019;28(5):397-412.

7. Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA Cancer J Clin. 2004;54(2):78-93.

8. https://www.wcrf.org/cancer-trends/stomach-cancer-statistics/

9. Franck C, Zimmermann N, Goni E, et al. Different prevalence of alarm, dyspeptic and reflux symptoms in patients with cardia and non-cardia gastric cancer. J Gastrointestin Liver Dis. 2021;30(4):431-437.

10. Wilhelm TJ, Mothes H, Chiwewe D, Mwatibu B, Kähler G. Gastrointestinal endoscopy in a low budget context: delegating EGD to non-physician clinicians in Malawi can be feasible and safe. Endoscopy. 2012;44(2):174-176.

11. World Health Organization Statistical Information System . WHO mortality database. World Health Organization; 2020. Available at: https://www.who.int/data/data-collection-tools/who-mortality-database (Last accessed March 2022).

12. World Health Organization . International Statistical Classification of Disease and Related Health Problems: 10th Revision. World Health Organization; 1992.

13. World Health Organization . WHO methods and data sources for country-level causes of death 2000-2019. Global Health Estimates Technical Paper WHO/DDI/DNA/GHE/2020.2. World Health Organization; 2020:7-15.

14. Pan American Health Organization (PAHO) .Health Information Platform for the Americas. Available at: https://www.paho.org/data/index.php/en/106-cat-data-en/308-poblacion-nac-en.html?showall=101.

15. European Commission . EUROSTAT population database. Available at: https://ec.europa.eu/eurostat/web/main/data/database (Last accessed January 2022).

16. United Nations DoEaSA, Population Division 2017 . World Population Prospects: the 2017 Revision, DVD Edition. United Nations; 2017.

17. Doll R, Smith PG. Comparison between registries: age-standardized rates. Vol. IV. IARC Sci Publ No. 42. In: JAH W, Muir CS, Shanmugaratnam K, Powell J, Peacham D, Whelan S, eds. Cancer Incidence in Five Continents. IARC; 1982:671-675.

18. National Cancer Institute . Joinpoint Regression Program, version 4.9.1. Available at: https://surveillance.cancer.gov/joinpoint/.

19. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med. 2000;19(3):335-351.

20. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. Stat Med. 2009;28(29):3670-3682.

21. Bray FCM, Mery L, Piñeros M, et al. Cancer Incidence in Five Continents, Vol. XI (Electronic Version). International Agency for Research on Cancer; 2017. Available from: https://ci5.iarc.fr

22. Morgan E, Arnold M, Camargo MC, et al. The current and future incidence and mortality of gastric cancer in 185 countries, 2020-40: a population-based modelling study. EClinicalMedicine. 2022;47:101404.

23. Arnold M, Morgan E, Bardot A, et al. International variation in oesophageal and gastric cancer survival 2012-2014: differences by histological subtype and stage at diagnosis (an ICBP SURVMARK-2 population-based study). Gut. 2022;71(8):1532-1543.

24. Lordick F, Carneiro F, Cascinu S, et al. ESMO guidelines committee. Electronic address: clinicalguidelines@ESMO.Org. Gastric cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33:1005-1020.

25. Asplund J, Kauppila JH, Mattsson F, Lagergren J. Survival trends in gastric adenocarcinoma: a population-based study in Sweden. Ann Surg Oncol. 2018;25(9):2693-2702.

26. Colquhoun A, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut. 2015;64(12):1881-1888.

27. Camargo MC, Freedman ND, Hollenbeck AR, Abnet CC, Rabkin CS. Height, weight, and body mass index associations with gastric cancer subsites. Gastric Cancer. 2014;17(3):463-468.

28. Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: emerging biological mechanisms and perspectives. Metabolism. 2019;92:121-135.

29. Lindblad M, Ye W, Lindgren A, Lagergren J. Disparities in the classification of esophageal and cardia adenocarcinomas and their influence on reported incidence rates. Ann Surg. 2006;243(4):479-485.

30. Ekström AM, Signorello LB, Hansson LE, Bergström R, Lindgren A, Nyrén O. Evaluating gastric cancer misclassification: a potential explanation for the rise in cardia cancer incidence. J Natl Cancer Inst. 1999;91(9):786-790.

31. Levi F, Te V-C, Randimbison L, La Vecchia C. Re: evaluating gastric cancer misclassification: a potential explanation for the rise in cardia cancer incidence. JNCI: Journal of the National Cancer Institute. 1999;91(18):1585a-1586a.

32. Chandrasoma P, Wickramasinghe K, Ma Y, DeMeester T. Adenocarcinomas of the distal esophagus and "gastric cardia" are predominantly esophageal carcinomas. Am J Surg Pathol. 2007;31(4):569-575. doi: 10.1097/01.pas.0000213394.34451.d2

33. Taghavi N, Nasrollahzadeh D, Merat S, et al. Epidemiology of upper gastrointestinal cancers in Iran: a sub site analysis of 761 cases. World J Gastroenterol. 2007;13(40):5367-5370.

34. Arnold M, Park JY, Camargo MC, Lunet N, Forman D, Soerjomataram I. Is gastric cancer becoming a rare disease? A global assessment of predicted incidence trends to 2035. Gut. 2020;69(5):823-829. doi: 10.1136/gutjnl-2019-320234

35. Carioli G, Bertuccio P, Levi F, et al. Cohort analysis of epithelial cancer mortality male-to-female sex ratios in the European Union, USA, and Japan. Int J Environ Res Public Health. 2020;17(15):5311.

36. Heer EV, Harper AS, Sung H, Jemal A, Fidler-Benaoudia MM. Emerging cancer incidence trends in Canada: the growing burden of young adult cancers. Cancer. 2020;126(20):4553-4562.

37. Lage J, Uedo N, Dinis-Ribeiro M, Yao K. Surveillance of patients with gastric precancerous conditions. Best Pract Res Clin Gastroenterol. 2016;30(6):913-922.

38. Malvezzi M, Bonifazi M, Bertuccio P, et al. An age-period-cohort analysis of gastric cancer mortality from 1950 to 2007 in Europe. Ann Epidemiol. 2010;20(12):898-905.

39. Roosendaal R, Kuipers EJ, Buitenwerf J, et al. Helicobacter pylori and the birth cohort effect: evidence of a continuous decrease of infection rates in childhood. Am J Gastroenterol. 1997;92(9):1480-1482.

40. Vaneckova P, Wade S, Weber M, et al. Birth-cohort estimates of smoking initiation and prevalence in 20th century Australia: synthesis of data from 33 surveys and 385,810 participants. PLoS One. 2021;16(5):e0250824.

41. Wang Z, Graham DY, Khan A, et al. Incidence of gastric cancer in the USA during 1999 to 2013: a 50-state analysis. Int J Epidemiol. 2018;47(3):966-975.

42. Wang Z, El-Serag HB, Thrift AP. Increasing incidence of advanced non-cardia gastric cancers among younger Hispanics in the USA. Dig Dis Sci. 2021;66(5):1669-1672.

43. Ferro A, Peleteiro B, Malvezzi M, et al. Worldwide trends in gastric cancer mortality (1980-2011), with predictions to 2015, and incidence by subtype. Eur J Cancer. 2014;50(7):1330-1344.

44. Asaka M, Kato M, Sakamoto N. Roadmap to eliminate gastric cancer with helicobacter pylori eradication and consecutive surveillance in Japan. J Gastroenterol. 2014;49(1):1-8.

Table 1. Annual average deaths and age-standardized (world population) mortality rates from gastric cancers per 100,000 person-years in 2010-14 and 2015-19 for both sexes, along with the corresponding change in rates.

	Men					Women				
	Annual average deaths 2010-2014	**ASMR 2010-2014**	**Annual average deaths 2015-2019**	**ASMR 2015-2019**	**% change 2015-2019 vs 2010-2014**	**Annual average deaths 2010-2014**	**ASMR 2010-2014**	**Annual average deaths 2015-2019**	**ASMR 2015-2019**	**% change 2015-2019 vs 2010-2014**
Europe										
Austria	499	5.60	447	4.61	-17.7	384	2.96	334	2.55	-13.9
Belarus	1219	19.53	1064	15.75	-19.4	823	7.47	679	5.86	-21.6
Belgium	468	4.06	457	3.77	-7.1	297	1.75	269	1.57	-10.3
Czech Republic	664	6.91	594	5.52	-20.1	470	3.52	408	2.85	-19.0
Denmark	254	4.51	274	4.45	-1.3	144	2.14	140	1.91	-10.7
Finland	265	4.64	244	3.86	-16.8	197	2.57	179	2.25	-12.5
France	2959	4.58	2848	4.10	-10.5	1657	1.72	1531	1.54	-10.5
Germany	5675	5.91	5270	5.13	-13.2	4221	3.14	3698	2.68	-14.6
Greece	799	6.04	819	6.10	1.0	510	3.06	495	2.83	-7.5
Hungary	947	10.97	845	9.23	-15.9	709	5.07	618	4.24	-16.4
Israel	287	5.48	288	4.76	-13.1	200	3.08	196	2.69	-12.7
Italy	5728	7.65	5489	6.75	-11.8	4115	3.85	3882	3.40	-11.7
Kyrgyzstan	417	23.58	461	22.23	-5.7	194	8.01	216	7.78	-2.9
Netherlands	836	4.89	769	3.94	-19.4	539	2.53	452	1.93	-23.7
Norway	191	3.87	197	3.70	-4.4	140	2.16	113	1.63	-24.5
Poland	3436	11.21	3271	9.63	-14.1	1845	4.06	1812	3.70	-8.9
Portugal	1406	12.94	1370	11.76	-9.1	932	5.87	900	5.33	-9.2
Romania	2282	12.98	2177	11.84	-8.8	1182	4.74	1115	4.27	-9.9
Russian Federation	18,481	19.95	16,914	17.09	-14.3	13,886	8.19	12,168	6.76	-17.5
Serbia	653	9.11	603	8.07	-11.4	375	4.15	324	3.61	-13.0
Spain	3452	7.11	3285	6.19	-12.9	2208	3.23	2074	2.88	-10.8
Sweden	371	3.36	339	2.92	-13.1	267	2.05	222	1.67	-18.5
Switzerland	331	4.07	340	3.81	-6.4	202	1.94	205	1.78	-8.2
Ukraine	5360	17.16	4160	13.34	-22.3	3427	6.65	2620	5.12	-23.0
United Kingdom	3003	4.30	2842	3.84	-10.7	1770	1.96	1592	1.72	-12.2
EU (27)	33,010	7.24	31,533	6.44	-11.0	21,672	3.36	20,234	2.99	-11.0
America										
Argentina	1826	7.39	1901	7.08	-4.2	1056	3.10	1069	2.91	-6.1
Brazil	8825	9.32	9350	8.19	-12.1	4905	3.97	5257	3.59	-9.6
Chile	2178	19.85	2186	16.90	-14.9	1104	7.28	1085	6.08	-16.5
Cuba	518	5.46	547	5.19	-4.9	338	3.08	350	2.90	-5.8
Mexico	2912	5.57	3267	5.42	-2.7	2588	4.23	2834	4.10	-3.1
Canada	1153	3.45	1228	3.14	-9.0	753	1.81	738	1.59	-12.2
USA	6688	2.54	6760	2.34	-7.9	4551	1.38	4548	1.31	-5.1
Australasia										
Australia	729	3.53	712	3.03	-14.2	420	1.67	422	1.53	-8.4
Hong Kong SAR	397	5.70	419	5.35	-6.1	266	3.15	268	2.86	-9.2
Japan	32,279	17.70	29,813	14.33	-19.0	16,847	6.65	15,594	5.43	-18.3
Republic of Korea	6137	17.69	5206	11.81	-33.2	3301	6.63	2833	4.63	-30.2

ASMR, age-standardized mortality rates using the world standard population

Table 2. Number of predicted deaths and mortality rates from gastric cancer, for both sexes, for the year 2025 and comparison figures for 2015-2019, for selected (>20 million inhabitants) countries worldwide and the EU as a whole, with 95% prediction intervals.

	Men					Women				
	Observed mean number of deaths 2015-19	**Predicted number of deaths 2025 (95% PI)**	**Observed ASMR 2015-19**	**Predicted ASMR 2025 (95% PI)**	**% difference 2025 versus 2015-19**	**Observed mean number of deaths 2015-19**	**Predicted number of deaths 2025 (95% PI)**	**Observed ASMR 2015-19**	**Predicted ASMR 2025 (95% PI)**	**% difference 2025 versus 2015-19**
Europe										
France										
All ages	2848	2620 (2450-2800)	4.1	3.32 (3.03-3.6)	-19.1	1531	1180 (1000-1370)	1.54	1.36 (1.23-1.49)	-11.8
35-64 years	787	630 (520-750)	5.58	4.55 (3.77-5.33)	-18.5	310	370 (330-410)	2.13	2.56 (2.27-2.86)	20.3
Germany										
All ages	5270	4440 (4040-4840)	5.13	3.75 (3.45-4.06)	-26.8	3698	2980 (2670-3300)	2.68	2.15 (1.96-2.34)	-19.8
35-64 years	1328	1210 (1110-1310)	6.49	5.42 (4.85-5.99)	-16.5	704	690 (600-770)	3.54	3.48 (3.01-3.95)	-1.8
Italy										
All ages	5489	5090 (4830-5340)	6.75	5.17 (4.81-5.54)	-23.3	3882	3310 (3100-3520)	3.4	2.49 (2.24-2.73)	-26.8
35-64 years	997	640 (520-750)	7.11	4.25 (3.48-5.02)	-40.2	602	520 (420-620)	4.1	3.25 (2.6-3.9)	-20.7
Poland										
All ages	3271	2540 (2310-2770)	9.63	6.16 (5.49-6.83)	-36.1	1812	1590 (1440-1750)	3.7	2.84 (2.48-3.21)	-23.2
35-64 years	1063	450 (300-590)	12.04	5.51 (3.72-7.3)	-54.2	470	320 (240-400)	5.12	3.77 (2.87-4.67)	-26.3
Russian Federation										
All ages	16,914	15,040 (13000-17070)	17.09	13.29 (11.7-14.88)	-22.2	12,168	7610 (5970-9250)	6.76	3.84 (3.19-4.48)	-43.2
35-64 years	7178	4440 (4040-4850)	23.17	14.63 (13.25-16.01)	-36.9	3465	1600 (1340-1850)	9.16	4.32 (3.61-5.02)	-52.9
Spain										
All ages	3285	2920 (2710-3140)	6.19	4.58 (4.23-4.94)	-25.9	2074	1750 (1580-1930)	2.88	2.39 (2.13-2.64)	-17.2
35-64 years	780	710 (630-790)	7.45	5.94 (5.24-6.63)	-20.3	414	410 (360-460)	3.85	3.5 (3.04-3.95)	-9.2

	Men					Women				
	Observed mean number of deaths 2015-19	**Predicted number of deaths 2025 (95% PI)**	**Observed ASMR 2015-19**	**Predicted ASMR 2025 (95% PI)**	**% difference 2025 versus 2015-19**	**Observed mean number of deaths 2015-19**	**Predicted number of deaths 2025 (95% PI)**	**Observed ASMR 2015-19**	**Predicted ASMR 2025 (95% PI)**	**% difference 2025 versus 2015-19**
UK										
All ages	2842	2310 (2120-2510)	3.84	2.76 (2.49-3.04)	-28	1592	790 (640-930)	1.72	0.86 (0.68-1.03)	-50.2
35-64 years	543	560 (460-650)	4.02	3.81 (3.2-4.42)	-5.2	284	270 (230-320)	2.08	1.84 (1.52-2.16)	-11.6
EU (27)										
All ages	31,533	28,440 (27740-29140)	6.44	4.9 (4.76-5.05)	-23.9	20,234	15,840 (15060-16610)	2.99	2.14 (2.04-2.25)	-28.3
35-64 years	8239	6390 (6100-6670)	8.1	5.95 (5.68-6.21)	-26.6	4061	3220 (2950-3480)	3.91	3.02 (2.77-3.27)	-22.7
America										
Argentina										
All ages	1901	1960 (1860-2060)	7.08	5.78 (5.48-6.08)	-18.4	1069	1170 (1080-1260)	2.91	2.66 (2.45-2.87)	-8.5
35-64 years	657	610 (550-670)	9.43	7.75 (7.03-8.46)	-17.8	324	340 (310-380)	4.29	4.07 (3.62-4.52)	-5.2
Brazil										
All ages	9350	9990 (9720-10250)	8.19	6.09 (5.92-6.26)	-25.6	5257	5860 (5620-6100)	3.59	2.95 (2.83-3.08)	-17.7
35-64 years	3665	3890 (3760-4030)	10.35	9.18 (8.86-9.51)	-11.3	1971	2220 (2110-2330)	4.99	4.79 (4.56-5.02)	-4.1
Mexico										
All ages	3267	3790 (3620-3960)	5.42	4.38 (4.19-4.58)	-19.1	2834	3280 (3160-3410)	4.1	3.32 (3.19-3.45)	-19.0
35-64 years	1299	1660 (1540-1770)	7.16	7.15 (6.66-7.64)	-0.1	1168	1310 (1240-1370)	5.93	5.18 (4.91-5.45)	-12.7
Canada										
All ages	1228	1290 (1200-1370)	3.14	2.49 (2.3-2.69)	-20.6	738	720 (640-800)	1.59	1.31 (1.17-1.46)	-17.4
35-64 years	329	350 (300-390)	3.8	3.9 (3.41-4.39)	2.7	179	180 (150-210)	2.06	2.04 (1.68-2.4)	-0.9
USA										

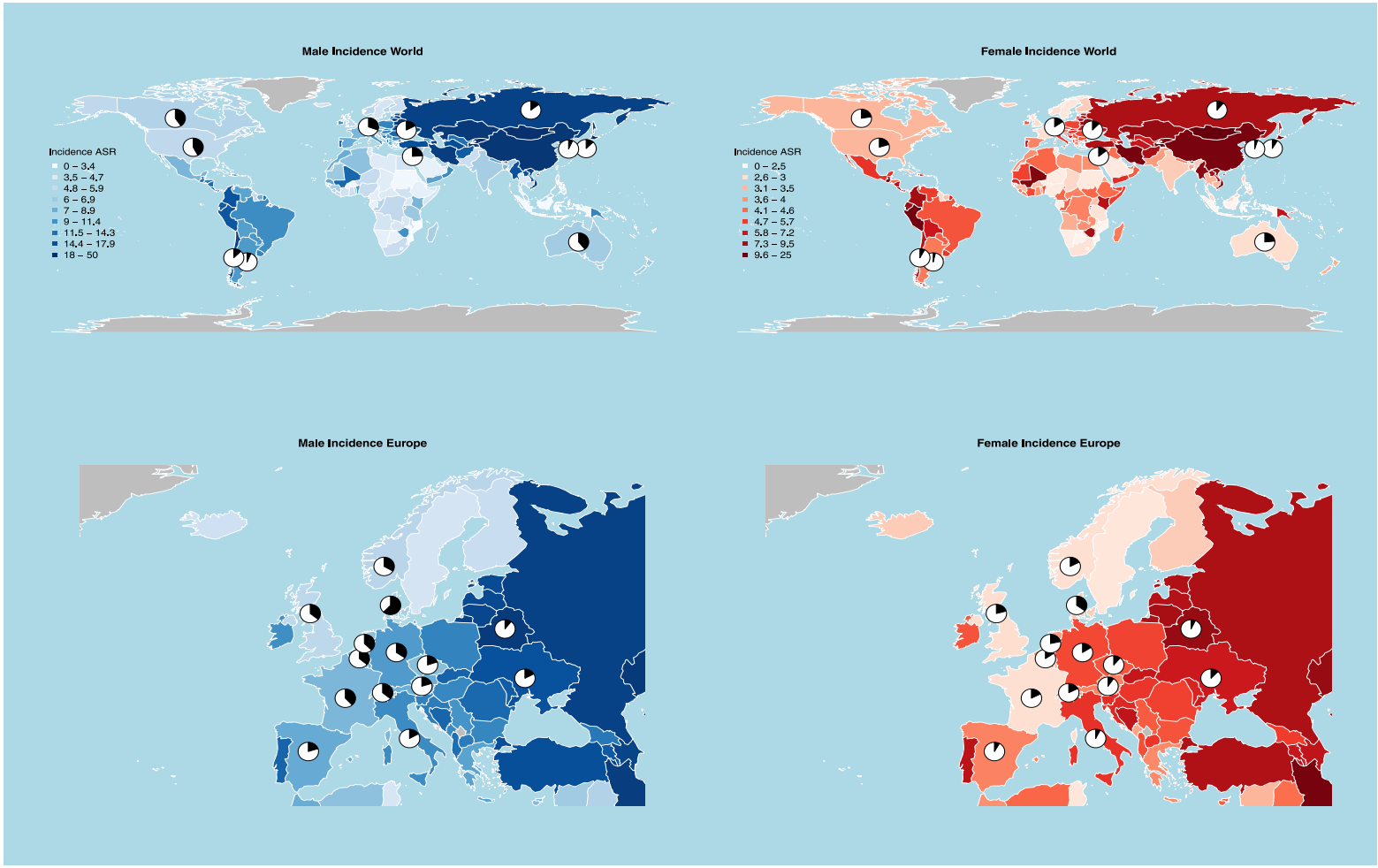
	Men					Women				
	Observed mean number of deaths 2015-19	**Predicted number of deaths 2025 (95% PI)**	**Observed ASMR 2015-19**	**Predicted ASMR 2025 (95% PI)**	**% difference 2025 versus 2015-19**	**Observed mean number of deaths 2015-19**	**Predicted number of deaths 2025 (95% PI)**	**Observed ASMR 2015-19**	**Predicted ASMR 2025 (95% PI)**	**% difference 2025 versus 2015-19**
All ages	6760	6640 (6340-6940)	2.34	1.79 (1.7-1.89)	-23.3	4548	4420 (4190-4650)	1.31	1.12 (1.06-1.18)	-14.3
35-64 years	2332	2160 (1980-2340)	3.33	2.97 (2.7-3.24)	-10.9	1384	1490 (1390-1590)	1.98	2.12 (1.97-2.28)	7.3
Australasia										
Australia										
All ages	712	670 (580-750)	3.03	2.25 (1.9-2.6)	-25.8	422	410 (370-460)	1.53	1.28 (1.09-1.47)	-16.3
35-64 years	185	180 (150-210)	3.78	3.34 (2.71-3.96)	-11.7	106	100 (80-130)	2.1	1.89 (1.42-2.37)	-9.8
Japan										
All ages	29,813	25,230 (24280-26170)	14.33	9.71 (8.99-10.43)	-32.3	15594	13,520 (12930-14100)	5.43	3.4 (3.02-3.79)	-37.3
35-64 years	3656	490 (0-1050)	12.9	2.24 (0.38-4.1)	-82.6	1735	230 (30-440)	6.34	1.13 (0.39-1.86)	-82.2
Republic of Korea										
All ages	5206	3660 (3390-3930)	11.81	5.52 (5.02-6.02)	-53.3	2833	1950 (1750-2160)	4.63	2.13 (1.78-2.49)	-54.0
35-64 years	1746	1000 (840-1150)	13.31	6.34 (5.16-7.52)	-52.4	781	550 (460-630)	6.29	3.83 (3.14-4.53)	-39.1

ASMR, age-standardized mortality rates using the world standard population.
PI, prediction interval.

Figure 1. Annual age-standardized (World standard population) mortality rates per 100,000 males from gastric cancer in major countries (>10 million inhabitants) worldwide and the EU (27), the resulting joinpoint regression models and predicted rates (only for countries with > 20 million inhabitants and the EU)for the year 2025 with 95% prediction intervals. Note: the Y axes in the figure (Deaths per 100,000) are not uniform.
/// All ages
/ 35-64 years

Figure 2. Annual age-standardized (World standard population) mortality rates per 100,000 females from gastric cancer in major countries (>10 million inhabitants) worldwide and the EU, the resulting joinpoint regression models and predicted rates (only for countries with > 20 million inhabitants and the EU) for the year 2025 with 95% prediction intervals. Note: the Y axes in the figure (Deaths per 100,000) are not uniform.
/// All ages
/ 35-64 years

Figure 3. Gastric cancer age-standardised (World standard population) incidence rate estimates for the year 2020 from Globocan in males and females, proportion of cardia (black) and non-cardia (white) incident cancers from Cancer Incidence in 5 Continents Vo. XI.



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2.2 Understanding the Epidemiology of Gastric Cancer: A Review and Case-Only Analysis from Italy

Short title: Epidemiology of gastric cancer

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Keywords: gastric cancer, non-cardia gastric cancer, epidemiology, Helicobacter pylori, cancer prevention, histopathology

Abstract

Background: Gastric cancer (GC) epidemiology evolved rapidly in the last century, shifting from being one of the main causes of cancer-related death to the sixth in developed countries.

Methods: We conducted a narrative review on GC epidemiology. Our review focused on trends of GC and its relationship with Helicobacter pylori infection; cardia- and non-cardia GC risk factors; early onset GC; second primary cancers in GC patients; and implementation of GC prevention strategies. Additionally, we provided results of a case-only analysis of recently diagnosed GC from a middle-risk population.

Results: Literature consistently describes the ongoing declining trend of GC rates and the overall increase in in absolute number of incident cases due to change in population. The evolving distribution of risk factors prevalence impacts the epidemiology of GC, with increase in early onset and in cardia GC. In particular, a negative correlation was observed between Helicobacter pylori prevalence and the proportion of cardia GC. of The analysis of 117 GC cases observed between 2016 and 2020 in Bologna, Italy, showed that smoking and epigastric pain were significantly associated with increased risk of early-onset GC after accounting for confounders.

Conclusions: Multifaceted strategies are needed to address challenges in GC control, early diagnosis and clinical management in a changing epidemiological landscape. Prevention remains the cornerstone to reduce GC burden.

Introduction

Gastric cancer (GC) is one of the most prevalent malignancies worldwide, although its incidence and mortality have significantly declined in many countries over the past decades (1). This trend is attributed to improved socioeconomic conditions, reduced prevalence of Helicobacter pylori (Hp) infection, and changes in dietary and lifestyle habits (2,3). Nevertheless, GC remains a major public health concern due to its aggressive nature and late-stage diagnosis in many cases (3). GC is a heterogeneous disease, often classified anatomically into cardia and non-cardia subtypes (1,3). These subtypes differ in their epidemiology, risk factors, and pathogenesis (1,3). Non-cardia GC, strongly associated with Hp infection, accounts for the majority of cases globally, while cardia GC is more common in regions with high prevalence of obesity and gastroesophageal reflux disease (GERD) (1-3). Notably, the relative prevalence of these subtypes is evolving, with an increasing proportion of cardia GC, especially in countries where obesity is on the rise, such as the United States and parts of Europe (3). The etiological landscape of GC highlights the interplay between genetic predisposition and environmental factors. For instance, individuals with a family history of GC or hereditary syndromes, such as hereditary diffuse gastric cancer (HDGC), are at an elevated risk (5). Furthermore, polymorphisms in genes involved in alcohol metabolism, such as aldehyde dehydrogenase-2 (ALDH2), exacerbate the risk in certain populations, particularly among East Asians (6). This review explores the epidemiological trends and risk factors associated with GC, with a particular focus on Hp infection and its global impact. Additionally, it presents an analysis of a series of cases of GC in a middle-risk population in Italy, aiming to elucidate their histopathological patterns as well as sociodemographic and clinical characteristics.

Modifiable risk factors of gastric cancer

GC is largely preventable, as it results from the interplay of multiple risk factors which are, for the most, modifiable (7,8).

While cardia and non-cardia subtypes share many of the risk factors implied in stomach carcinogenesis, the contribution of each specific carcinogen differ in its extent towards cancer sites (8,9). For instance, the main risk factors for cardia GC are overweight and obesity, which may cause acid reflux which damages the cells of the gastro-esophageal junction and therefore the cardia (10). Helicobacter pylori (Hp) is the most important cause of non-cardia GC, in particular its Cag-A positive strain (11). Other risk factors of cardia and non-cardia GC are illustrated in Table 1 (7,8,12-15).

Increasing evidence supports the causal role of Hp in cardia GC (11,16), next to non-cardia GC. This has been observed especially among Asians rather than non-Asians (11). Moreover, an interaction between several major risk factors of GC has been reported, implying that the co-occurrence of different risk factors can modify the overall effect and likelihood of developing stomach neoplasm. For example, Hp positive individuals who also consume alcohol, or who are used to highly salty diet, are at particularly high risk of GC (17); on the contrary, vitamin C reduces the risk of GC in infected subjects by contrasting Hp and atrophic gastritis (18,19).

Among the factors which are suspected to be associated with GC are Epstein-Barr Virus (14) and chronic use of proton pump inhibitors (20), whereas use of aspirin/COX-inhibitors (9) and fiber and yoghurt intake as potential protective factors (7). Moreover, opium use has been suggested to increase the risk of GC based on recent studies (15). Evidence on these risk and protective factors is still limited, and little is known on their subsite-specific effect.

Table 1. Non-genetic risk factors of gastric cancer, by subsite (adapted from 12,13)

Risk factor	**Cardia cancer**	**Non-cardia cancer**
Old age	+++	+++
Male sex	++	+++
Tobacco smoking	+	+
Family history of gastric cancer	++	++
Ionizing radiation	+	+
Helicobacter pylori infection (particularly CagA+ strains)	+	+++
Low SES		++
Dietary salt intake		++
Red and processed meat intake		+
Intake of smoked food		+
Alcohol drinking	++	+
Overweight/obesity	+++	+
Low physical activity	+	+
GERD	+++	
Garlic/allium vegetables intake	-	--
Citrus fruit	-	-
Yoghurt intake	?	?
Fiber intake	?	-
EBV	?	?
Aspirin and COX-inhibitors	?	?
Chronic PPI use	?	?
Opium use	?	?

++ Strong risk factor (relative risk <2). + Weak risk factor (1 < relative risk <2). ? Suspected risk factor. SES, socioeconomic status; GERD, gastroesophageal reflux disease; EBV, Epstein-Barr Virus; COX-inhibitors, cyclooxygenase inhibitors; PPI, proton pump inhibitors

Genetics in the risk of gastric cancer

Few genetics conditions are related to GC development [Table 2, (5, 21-29)]. These conditions represent a variety of inherited genetic mutations that predispose individuals to gastric cancer, and in some cases, other cancers as well. They include HDGC, gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) and familial intestinal gastric cancer (FIGC) (5). HDGC is connoted by the inactivation of CDH1. The mutation of this gene, encoding for E-cadherin, leads to loss of adhesion of epithelial cells of gastric mucosa, which in turn favor cancer progression and diffusion (21). Innate mutations of certain genes, not as part of hereditary syndromes, also confer a predisposition to GC. The association between polymorphisms of alcohol dehydrogenase (ADH) and GC is well known: carriers of acetaldehyde dehydrogenase-2 (ALDH2) inactivating mutations are exposed to higher doses of acetaldehyde, which produces oxidative damage and DNA adducts (6,30-32). Certain polymorphisms are especially frequent among Asians, explaining at least in part the high incidence of GC in these populations (6, 32, 33).

Table 2. Genetic conditions related to increased risk of gastric cancer (5, 21-29)

Condition	Alteration	Notes	Ref
Hereditary diffuse gastric cancer (HDGC)	CDH1, CTNNA1	Higher risk of diffuse GC and of lobular breast cancer. Incomplete and variable penetrance. Unpredictable onset requiring prophylactic gastrectomy in early adulthood; hysto-pathological peculiarities are *in situ* signet ring cell carcinoma, pagetoid spread of signet ring cells	Decourtye-Espiard L and Guilford P, 2023 (21) Gullo et al., 2020 (5)
Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)	*APC* promoter 1b	Autosomal dominant cancer predisposition syndrome with incomplete penetrance. Increased risk of GC in the context of proximal polyposis of the stomach. Undistinguishable from sporadic intestinal GC. Hysto-pathological findings include fundic gland polyps, hyperplastic polyps, intestinal and mixed GC. Age of GC onset 23-75, mainly proximal GC.	Gullo et al., 2020 (5)
Familial intestinal gastric cancer (FIGC)	NA	Autosomal dominant cancer syndrome, higher risk of intestinal GC. Mean age at GC diagnosis is 72 years.	Gullo et al., 2020 (5)
Familial	APC	Increased risk of GC; gastrointestinal	Carneiro,

Adenomatous Polyposis (FAP)		polyps, including in the stomach.	2022 (22)
MUTYH-Associated Polyposis (MAP)	MUTYH	Increased risk of intestinal GC. Autosomal recessive cancer predisposition due to MUTYH mutations. Associated with colorectal polyps and, among extra-colonic manifestations, gastric fundic gland polyps and skin tumors. Carriers should be offered upper gastrointestinal endoscopy starting from 20 to 25 years.	Sampson et al., 2009 (23)
Peutz-Jeghers Syndrome	LKB1	Genetic syndrome connoted by gastrointestinal polyps, associated with the risk of GC, cancer of the small intestine and colorectal cancer. Risk increases with age.	Latchford and Clark, 2022 (24)
Juvenile Polyposis Syndrome	SMAD4, BMPR1A	Autosomal dominant syndrome. Increased risk of gastrointestinal cancers, including GC, due juvenile polyps in the stomach and colon. GC predominantly associated with SMAD4 mutations.	Brosens et a., 2011 (25)
Lynch Syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	Increased risk of gastric cancer along with colorectal and endometrial cancers.	Carneiro, 2022 (22)
Li-Fraumeni Syndrome	TP53	Increased risk of various cancers, including gastric cancer, typically diagnosed at a young age.	Bougeard et al, 2015 (26)
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	BRCA1, BRCA2	Increased risk for various cancers, including GC	Friedenson, 2005 (27)
Cowden Syndrome	PTEN	Increased risk for various cancers, including GC	Carneiro, 2022 (22)
Alcohol dehydrogenase, aldehyde dehydrogenase 2 polymorphisms	ADH, ALDH2	Inactive ALDH2 OR=1.26, 95% CI=1.04-1.52 compared to active ALDH2. Moderate/heavy alcohol consumption increased GC risk in individuals with inactive ALDH2 (OR = 2.23, 95% CI: 1.63-3.05) more than those with active ALDH2 (OR = 1.40, 95% CI: 0.98-2.01)	Jelski and Smitkowski, 2008 (28) Asanuma et al., 2024 (29)

Autoimmune gastritis and risk of gastric cancer

A role of autoimmune atrophic gastritis (AAG) in gastric carcinogenesis has been debated (34). AAG is a chronic condition caused by autoantibodies directed against parietal cells of the oxyntic mucosa, namely the acid secretive component of the stomach. Chronic inflammation of corpus and fundus, which are the portion of the stomach interested by the autoimmune damage, progressively leads to mucosal atrophy together with decrease of acid secretion and intrinsic factor production (34).

AAG is more common in women and in subjects aged older than 60. Current guidelines depict AAG as a precancerous condition and ESGE/EHMSG/ESP suggest that patients with autoimmune gastritis should have high quality endoscopic follow-up every 3 years to detect gastric cancer and neuroendocrine tumors (35).

Consistent evidence describes AAG as a precancerous condition for neuroendocrine tumor. Levels of gastrin have been suggested to predict neuroendocrine tumor development in AAG patients. Neuroendocrine tumors of the stomach represent 80% of gastric carcinoids, which are the 1% of cancers of the stomach (36)., Consistent evidence describes AAG as a precancerous condition for neuroendocrine tumor. Level of gastrin have been suggested to predict neuroendocrine tumor development in AAG patients (36). Neuroendocrine tumors of the stomach represent 80% of gastric carcinoids, which are the 1% of cancers of the stomach, However, whether factors other than AAG are causative of a small increased risk of GC is unclear. In fact, the investigation of the association between AAG and GC is affected by several limitations, due to possible misdiagnosis of AAG, which is often confused with atrophy of different nature, and the challenging assessment of Hp infection history (37,38). A recent publication reported comparable mucosal damage of Hp and AAG, namely incomplete intestinal metaplasia associated with gastric cancer (39). A systematic review and meta-analysis published in 2023 reported a 0.14% incidence rate of GC per person-year based on 13 studies (40). Lenti et al. compared AAG patients with and without history of Hp infection. Of 1598 AAG patients, 15 (0.9%) developed GC and 153 (9.6%) developed neuroendocrine tumor (41). Solid evidence regarding the relationship between Hp naïve AAG and cancer comes from the study by Rugge et al., where Hp infection was excluded through multiple tests

(serology, histology and molecular biology) (38). No GC case was identified among 211 AAG patients during a follow-up time of 10 541 person years (38). Instead, 10/211 patients (4.7%) were diagnosed with neuroendocrine tumors (38). Overall, literature indicates that AAG increases the risk of neuroendocrine tumors of the stomach, while it remains unclear whether the excess risk of GC associated to AAG is attributable to underdiagnosed present or past Hp infection.

Declining trends of gastric cancer in relation to Helicobacter pylori changing prevalence

Epidemiology of GC illustrates the changes that diseases undergo in time because of lifestyle and environmental changes. In fact, until the '30s, GC was the first cause of cancer death in the USA, where in 2022 it was the 16th (42,43). Recent literature consistently suggests a declining pattern for GC mortality, with geographical heterogeneity (1,3,43). In particular, a more marked decline has been predicted in those countries with higher GC rates such as Japan and Korea, rather than in lower-rates regions such as North America (1,3,43). This is likely to be due to Hp control (e.g., introduction of Hp screening programs in Korea in the early 2010s), as well as to decrease of smoking prevalence (1). Despite the progressive decline in incidence rates, an increment of the absolute number of new GC caseshas been predicted in several countries, mainly due to population growth and ageing next to changes in prevalence of GC risk factors (44). For example, Arnold et al. reported a more than doubled number of incident cases in Canada, Cyprus, Korea, Slovakia and Thailand by 2035 (43). The authors calculated the contribution of population change (growth and ageing) and risk change on GC trends for selected countries. For example, population change was estimated to increase the number of GC in China by 99.9% and change in risk factors to reduce it by -47.2% (43).

Gender differences in GC incidence and mortality are in part due to the higher cigarette smoking prevalence in men than in women (43,45). In fact, a larger decline in GC incidence has been reported in many countries among men than women, likely because of the parallel larger decline in smoking habit in men (1).

Non-cardia GC is more frequent than cardia in most countries, with a ratio between 2:1 and 3:1 (46). However, this ratio differs by geographic area (3). This can be due to intrinsic characteristics of the populations as well as to environmental risk factors (3). Diet, obesity (47,48) and GERD (48) are implicated in the increasing number of cardia cases in US and EU countries. In addition, the non-cardia/cardia ratio reflects the changing prevalence of Hp worldwide. In order to quantify this phenomenon, we calculated the proportion of cardia over total GC cases occurred in 2010s based on EUROGAST data (49), considering Hp prevalence from the 1980s in men and women of two different age ranges (Table 3). We detected a negative correlation between Hp infection prevalence and the proportion of cardia GC in both sexes and age groups (7 countries), which was statistically significant for women of the older age group. A shift in the incidence of anatomical subsites of GC was already reported by Camargo et al. in an analysis based on two major disease registries in the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and the US Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) (50). Such estimates emphasize the importance of continuous monitoring of GC epidemiology and the investigation of parallel trends of different cancer subtypes and their risk factors in the populations.

Table 3. Combination of proportion of cardia cases and Helicobacter pylori prevalence in selected countries.

Country	**% Cardia**		**Prevalence of Helicobacter pylori infection (%)***			
			25-34 years old		55-64 years old	
	Men	Women	Men	Women	Men	Women
Belgium	36.2	15.2	20	17	60	47
Denmark	62.0	35.1	23	5	34	27
Germany	34.6	15.8	26	35	65	72
Italy	16.8	7.4	17	14	38	57
Japan	12.3	8.4	63	59	89	83
UK	35.9	20.8	17	9	49	41
US	42.3	20.2	13	16	36	32
Corr-coeff			*-0.52*	*-0.59*	*-0.60*	*-0.81*
P-corr			*0.24*	*0.16*	*0.15*	*0.03*

*Data derived from the EUROGAST study (40). Prevalence of Helicobacter pylori from around the 1980s provide the possibility to estimate the correspondent attributable fraction of gastric cancer cases in the 2010s, because of the latency needed for the infection to exert a carcinogenic effect.

Corr-coeff, correlation coefficient between sex- and age-specific prevalence of Helicobacter pylori and corresponding proportion of cardia gastric cancer.
P-corr, p value of the correlation coefficient.

Challenging conditions: early onset gastric cancer and second primary cancers in gastric cancer survivors

High-risk conditions require more personalized monitoring to control the risk of GC. Among those, there are early onset GC and second primary cancers occurring in GC survivors.

As recently reported by Li et al., despite the general declining trends of GC independently from the onset age, the incidence of GC occurring in young adults has increased in recent years (51). Bergquist and coauthors have conducted a comprehensive comparative analysis based on SEER database, including more than 75,000 early onset GC cases (52). In this analysis, the proportion of early onset cases has risen between 1990 and 2012 (52). Arnold et al. estimated that age-standardized rates of early onset GC were higher in 2035 than in 2010 for several countries such as USA, UK, Canada, Spain, the Netherlands, and was more pronounced increasing pattern among men than women (43). The increase in early onset GC is likely due to change in the prevalence of risk factors among young adults, despite its occurrence remains largely unclear and deserves further investigation (43).

Characteristics of early onset GC include high grade, frequent signet-ring cells which indicate low differentiation, diffuse histology, diagnosis at late stage with metastases at presentation. These features support the hypothesis of genetic and molecular patterns determining a higher risk of its development (53). Smoking and heavy alcohol drinking increase the risk of early onset GC (54). EBV infection has been associated with GC in young adults (52), in particular in the framework of Hp and EBV coinfection (55). Furthermore, a recent meta-analysis observed a significant association with family history of GC (56). Several studies reported higher CDH1 mutations rates in early onset than in traditional GC (57-59). Hereditary syndromes may predispose to early onset GC (5). Lifelong surveillance aimed at early detection of gastric lesions is required in these individuals (60). Management includes regular upper-endoscopy screening starting at young age and, in certain conditions, prophylactic gastrectomy (60). In case of hereditary GC syndromes, genetic testing and counseling play a pivotal role in helping the patients to understand the subsequent surveillance and treatment options (60).

Survivors of GC are at an increased risk of developing second primary cancers, including cancers of other gastrointestinal organs (61). A recent analysis based on the SEER database reported an overall incidence of second primary cancers of 4.3% out of more than 44,000 GC cases, with a standardized incidence ratio equal to 1.36 (95% confidence interval [CI] 1.32-1.40) compared to the general population. This risk could be attributable to several factors, including the treatments for GC (e.g., chemotherapy, radiation), as well as lifestyle habits such as smoking, alcohol consumption, unhealthy diet, as well as some of the abovementioned hereditary syndromes, like Lynch and FAP (61). Given their high-risk condition, long-term follow-up care is essential for the early detection of secondary malignancies in GC patients (61). Monitoring strategies include regular endoscopic screenings for esophageal and colorectal cancers, especially in patients treated with chemotherapy or radiation.

Gastric cancer prevention and prediction

GC prevention strategies focus on addressing modifiable risk factors while leveraging advancements in genetic and lifestyle research (62). Hp eradication remains a cornerstone of primary prevention, with robust evidence indicating a 50% reduction in GC risk and significant decreases in GC-related mortality following treatment (62). These benefits are particularly pronounced in regions with a high prevalence of Hp infection, where systematic screening and eradication programs have demonstrated substantial impact (62).

On a global scale, prevention strategies must account for regional variations in GC epidemiology. While Hp eradication programs should be prioritized in high-prevalence areas, dietary education and obesity reduction are essential in regions with rising cardia GC rates (48,63). GC screening programs have been implemented in Korea, China and Japan. Such screenings are based on upper endoscopy (64). High costs and invasiveness of endoscopy are among the limitations of these strategies (64, 65), and the control of GC through Hp test-and-treat represents a reasonable option (63-65). The major advantages of Hp screening for GC prevention rely on characteristic including being non-invasive

and inexpensive compared to endoscopy (64). Moreover, the detection and eradication of Hp infection would substantially help in reducing Hp prevalence by interrupting the route of transmission of the bacterium (13). To date, no community-based screening for Hp infection has been implemented yet, despite the evidence of its cost-effectiveness in GC prevention in high-risk populations (64, 65).

Among the most important risks of a population-based Hp test-and-treat program there is antimicrobial resistance, which might be further fueled by administration of antimicrobial treatment in the infected, who represent a large portion of the population worldwide (66). In addition, the possibility of increased risk of esophageal cancer after Hp eradication, due to unbalance of acid secretion and following GERD, have been pointed out (67). Few large-scale longitudinal population-based studies on Hp screening and treatment have been conducted to date, leaving a lack of real-world evidence on the possible adverse effects of mass Hp eradication. In this panorama, the identification of high-risk individuals is of utmost importance to direct and optimize the use of preventive strategies against GC. Among the Hp screening programs which have been studied, the one presented by Chiang and coauthors offers particularly important findings (68). A mass Hp eradication program based on urea breath test (UBT) was launched in Taiwan between 2004 and 2018. This unique study structured a dynamic screening program consisting of repeated UBT, with the aim to monitor Hp prevalence in the population, also accounting for possible treatment failure or reinfections (68). Moreover, the study included antibiotic susceptibility analyses, allowing to describe the trend of antimicrobial resistance in the screened population (68). The screening led to a dramatic decrease in Hp prevalence (from 64% in 2004 to 15% in 2008), with <1 reinfection per 100 person-years; premalignant lesions, GC incidence and mortality significantly declined (68). Finally, this study revealed no significant increase in antibiotic resistance nor esophageal or colorectal cancer during the full implementation of such screening program, providing significant evidence supporting test-and-treat in high-risk populations (68).

Emerging research highlights the critical role of predictive models in tailoring prevention strategies. Studies from Korea, Japan, and Vietnam have developed models integrating genetic markers, such as MUC1 polymorphisms, with lifestyle factors to estimate GC risk

more accurately. For instance, the prediction model developed by Eom et al. (69) in the Korean population incorporates health behaviors and clinical variables, offering a practical tool for identifying high-risk individuals. Similarly, Charvat et al. (70) created a model for the Japanese population that predicts the 10-year probability of GC occurrence, enabling targeted interventions. In Vietnam, Nguyen et al. (71) demonstrated the potential of combining genetic polymorphisms and health-risk behaviors to refine GC risk assessments. These models underscore the importance of integrating genetic susceptibility with modifiable risk factors to optimize prevention strategies (69-71).

To date, no prediction scheme has been validated at global level for the general population (9). Machine learning has been exploited to this scope, for example by using pre-neoplastic endoscopic and histologic findings to build personalized predictive model for GC (72). Moreover, artificial intelligence was shown to perform better than expert endoscopists in detecting gastric lesions, possibly representing a support to medical practice for early detection of GC (73,74). In addition, increasing evidence on gut dysbiosis (75) in patients affected by gastric diseases has led to the investigation of microbiota profiling (76), including salivary microbiota, as biomarker for GC risk. Next to Hp infection management and personalized medicine, lifestyle interventions remain pivotal in GC prevention (77-79). Jin et al. (80) emphasized that adherence to healthy behaviors—such as a diet rich in fiber and fruits, regular physical activity, and avoiding tobacco and alcohol—can reduce GC risk, even among genetically predisposed individuals. In parallel, chemoprevention like aspirin and other NSAIDs has shown promise in reducing GC incidence, though their routine use requires careful evaluation of potential risks, such as gastrointestinal bleeding (81). In summary, integrating predictive models with Hp screening, lifestyle interventions and chemoprevention offers a comprehensive framework for reducing the global burden of GC.

Gastric cancer in a middle-risk population in Italy: a case-only analysis

Methods

A retrospective study on GC was established at the University Hospital in Bologna, with the aim of investigating the epidemiology of GC in an Italian population in recent years. Bologna is a city of Emilia Romagna Region, in central-northern Italy, which has historically been among the areas in Italy with highest rates of GC (82). In particular, based on AIRTUM estimates, GC accounted for 1.6% of total mortality and 5.6% of cancer mortality in Emilia Romagna in 2018, with SMR of 17.5 over 100,000 (83). This might be related to prevalence of Hp infection, dietary habits, and potential exposure to environmental risk factors (82).

A total of 117 GC cases were identified from pathology records for the period 2016-2020, based on surgical specimens of patients operated in the hospital. Pathological data and sociodemographic data were provided in that dataset, while additional information was extracted from medical records referring to hospitalization linked to GC. A detailed case report form was built to collect information on (i) sociodemographic factors (sex, age, residential place, birthplace, marital status, occupation, education, siblings); (ii) lifestyle factors (smoking, alcohol, physical activity); (iii) diet (intake of red meat, white meat, fish, vegetables, fruit, sugary foods, coffee, tea, yoghurt, other dairies); (iv) comorbidities and family history of cancer; (v) use of medications; (vi) symptoms at the time of the endoscopy; (vii) results of laboratory tests, including Hp infection status. The study was approved by Emilia-Romagna Ethical Committee in June 2021 with the code 539/2021/Oss/AOUBo.

Cases were distinguished into intestinal or diffuse GC according to Lauren classification (84). Cases which did not fit the classification were considered among "other" type. Similarly, anatomical site was distinguished into cardia and non-cardia based on information reported in the dataset; when these definitions were not specified, we classified as non-cardia cases those identified in antrum, small curve, large curve, fundus, corpus, pylorus, according to the ICD-10 code.

We performed descriptive analyses (Table 4) by sex. The cahracteristics of our study population were compared with those of 151 GC cases diagnosed between 2002 and 2010 in "A.Gemelli" teaching hospital in Rome, based on a previous Italian study (85). Hp status was considered positive if infection was reported in the biopsy, or whether history of Hp diagnosis or treatment was described in the clinical records. In this way, we accounted for reverse causation, allowing to identify a more reliable picture of Hp prevalence in this population. We performed multivariable logistic regression models (Table 5) to calculate the odds ratios (ORs) and 95% confidence intervals (C95% CI) of the associations between early onset GC, defined as GC diagnosed at age <=50, and (i) main epidemiological characteristics of the study population (including sex, family history of GC, smoking status and Hp infection) and (ii) red flag symptoms (weight loss, nausea, dysphagia, dyspepsia, epigastric pain, GI bleeding). Regression models included sex and age as potential confounding variables.

Results

Among the 117 gastric cancer (GC) cases, 56.4% were men, with a mean age of 72.1 years. Overall, 8 cases (6.8%) were diagnosed at age ≤50 years, accounting for 10% of GC cases in men and 4% in women (p=0.27). Regarding Hp status, men were slightly more likely to test positive (34.9%) compared to women (29.4%), although the difference was not statistically significant (p=0.53). A relatively high prevalence of peptic ulcer was observed in both sexes (approximately 45%).

No significant differences emerged by histological subtype, tumor location, or grade. Clinical history was comparable between sexes: previous cancer was reported in 3.9% of women and 3.0% of men, while a family history of GC was present in 19.6% of women and 15.2% of men.

With respect to red flag symptoms, epigastric pain (35.0%) and weight loss (28.2%) were the most frequently reported, with weight loss slightly more common among women (p=0.06).

Data from these recently diagnosed GC cases in Bologna were compared with a historical cohort of 151 GC cases (47.0% women, 53.0% men) diagnosed in Rome between 2002

and 2010. In the Rome cohort, early-onset GC was observed in 8 women (11.3%) and 5 men (6.2%). Male patients were significantly more likely to be smokers ($p<0.001$). Hp infection was common in both sexes and did not differ significantly by sex; however, its overall prevalence was significantly higher than that observed in the Bologna cohort ($p<0.001$). Cardia GC was diagnosed in 18 cases (11.9%) in Rome, compared to only 4 cases (3.4%) in Bologna, a statistically significant difference ($p=0.02$).

A focused analysis of early-onset versus late-onset GC was conducted on 92 Bologna cases with complete data. Current smoking emerged as a significant risk factor for early-onset GC (OR=8.9, 95% CI: 1.36–59.1), while no associations were found with sex, family history of GC, or Hp infection. Finally, based on the full sample of 117 cases, early-onset GC was significantly associated with the presence of epigastric pain (OR=6.5, 95% CI: 1.14–37.2) compared to late-onset GC.

Table 4. Sociodemographic, lifestyle, anatomopathological characteristics, and clinical features in a series of gastric cancer cases from Bologna, Italy, 2016-2020. Data compared with gastric cancer cases from Rome, Italy, 2002-2010, based on information availability.

GC patients characteristics	GC diagnosed in Bologna, 2016-2020 (N=117)			GC diagnosed in Rome, 2002-2010 8N=151)		
	Women (N=51, 43.6%)	Men (N=66, 56.4%)	p-value of difference	Women (N=71, 47.0%)	Men (N=80, 53.0%)	p-value of difference
Year of diagnosis			0.62	NA	NA	
- 2016	7 (13.7)	4 (6.1)				
- 2017	6 (11.8)	12 (18.2)				
- 2018	17 (33.3)	26 (39.4)				
- 2019	11 (21.6)	11 (16.7)				
- 2020	10 (19.6)	13 (19.7)				
Marital status			0.37	NA		
- Unmarried	7 (13.7)	9 (13.6)			NA	
- Married	28 (54.9)	42 (63.6)				
- Divorced	4 (7.8)	1 (1.5)				
- Widow	8 (15.7)	7 (10.6)				
- Missing	4 (7.8)	7 (10.6)				
Mean age	73.4 (70.3-76.5)	72.1 (68.9-75.3)	0.56	66.3 (63.4-69.1)	67.3 (65.0-69.6)	0.58
Early onset (<=50)			0.27			0.27
- No	49 (96.9)	60 (90.0)		63 (88.7%)	75 (93.8%)	
- Yes	2 (3.9)	6 (10.0)		8 (11.3%)	5 (6.2%)	
Residence			0.84	NA	NA	
- Emilia-Romagna	27 (52.9)	33 (50.0)				
- North	7 (13.7)	10 (15.2)				
- Center-South	15 (29.4)	21 (31.8)				
- Foreign country*	2 (3.9)	2 (3.0)				
Occupation			0.20			0.05
- Blue collar	22 (33.3)	22 (43.1)		10 (14.1)	18 (22.5)	
- White collar	14 (21.2)	7 (13.7)		5 (7.0)	13 (16.3)	
- Missing	30 (45.5)	22 (43.1)		56 (78.9)	49 (61.2)	
Smoking			0.28			<0.001
- Never	22 (43.1)	20 (30.3)		54 (76.1)	21 (26.3%)	
- Former	10 (19.6)	27 (40.9)		5 (7.0)	38 (47.5%)	

- Current	6 (11.8)	7 (10.6)		12 (16.9)	21 (26.2%)	
- Missing	13 (25.5)	12 (18.2)		0	0	
Quality of sleep			0.56	NA	NA	
- Normal	26 (51.0)	32 (48.5)				
- Altered	8 (15.7)	7 (10.6)				
- Missing	17 (33.3)	27 (40.9)				
Mean BMI at diagnosis	24.6, 23.1-26.1 (n=10 missing)	24.8, 24.0-25.7 (n=3 missing)	0.82	25.6, 23.7-27.4 (n=38 missing)	24.7, 23.5-25.9 (n=44 missing)	0.41
Hp status**			0.53			0.62
- Negative	36 (70.6)	43 (65.1)		9 (12.7%)	9 (11.2%)	
- Positive	15 (29.4)	23 (34.9)		49 (69.0)	63 (78.8)	
- Missing	0	0		13 (18.3)	8 (10.0)	
Histological type			0.53			0.23
- Intestinal	15 (29.4)	16 (24.2)		28 (39.4)	29 (36.2)	
- Diffuse	3 (5.9)	7 (10.6)		25 (35.2)	21 (26.5%)	
- Mixed type	27 (52.9)	36 (54.6)		1(1.4)	6 (7.5%)	
- Missing	5 (9.8)	6 (8.1)		17 (23.9)	24 (30.0)	
Cancer site			0.37			0.88
- Non-cardia	42 (35.9)	44 (37.6)		43 (60.1)	45 (56.3%)	
- Cardia	1 (2.00)	3 (4.6)		8 (11.3)	10 (12.5%)	
- Undefined or missing	75 (62.1)	70 (57.8)		20 (28.6)	25 (31.2%)	
Grade			0.37			0.82
- G1	4 (7.8)	11 (16.7)		2 (2.8)	1 (1.2)	
- G2	8 (15.7)	12 (18.2)		12 (16.9)	13 (16.3)	
- G3	32 (62.8)	37 (56.1)		30 (42.3)	32 (40.0)	
- Missing	7 (13.7)	6 (9.1)		27 (38.0)	34 (42.5)	
Infiltration			0.21	NA	NA	
- No	0 (0.0)	2 (3.0)				
- Yes	40 (78.4)	51 (77.3)				
- Missing	11 (21.6)	13 (19.7)				
Ulcerated lesion			0.61			
- No	31 (68.8)	37 (56.1)		NA	NA	
- Yes	20 (39.2)	29 (43.9)				
Peptic ulcer			0.39	NA	NA	
- No	28 (54.9)	36 (54.5)				
- Yes	23 (45.1)	30 (45.5)				

Active gastritis - No - Yes	 42 (82.3) 9 (17.7)	 53 (80.3) 13 (19.7)	0.80	NA	NA	
Chronic gastritis - No - Yes	 26 (51.0) 25 (49.0)	 31 (47.0) 35 (53.0)	0.59	NA	NA	
Lymph-nodes - No - Yes - Missing	 23 (45.1) 28 (54.9)	 27(40.9) 39 (59.1)	0.94	 19 (26.8) 40 (56.3) 12 (16.9)	 20 (25.0) 46 (57.5) 14 (17.5)	0.82
Previous cancer - No - Yes	 49 (96.1) 2 (3.9)	 64 (97.0) 2 (3.0)	 0.79	NA	NA	
Family history of GC - No - Yes	 41 (80.4) 10 (19.6)	 56 (84.8) 10 (15.2)	 0.53	NA	NA	
Family history of any cancer - No - Yes	 33 (64.7) 18 (35.3)	 43 (69.7) 23 (30.3)	0.29	NA	NA	
Diabetes - No - Yes	 42 (82.3) 9 (17.7)	 52 (78.8) 14 (21.2)	0.63	 61 (85.9) 10 (14.1)	 66 (82.5) 14 (17.5)	0.56
Weight loss - No - Yes	 32 (62.8) 19 (37.2)	 52 (78.8) 14 (21.2)	0.06	NA	NA	
Nausea and/or vomit - No - Yes	 40 (78.4) 11 (21.6)	 51 (77.3) 15 (22.7)	0.88	NA	NA	
Dysphagia - No - Yes	 44 (86.3) 7 (13.7)	 57 (86.4) 9 (13.6)	0.99	NA	NA	
Dyspepsia - No - Yes	 39 (76.5) 12 (23.5)	 54 (81.8) 12 (18.2)	0.48	NA	NA	
Epigastric pain			0.41	NA	NA	

- No - Yes	31 (60.8) 20 (39.2)	45 (68.2) 21 (31.8)				
GI bleeding - No - Yes	 45 (88.2) 6 (11.8)	 54 (81.8) 12 (18.2)	0.34	NA	NA	
Mean Hb at diagnosis	10.8, 10.1-11.5 (n=2 missing)	11.7, 11.1-12.3 (n=2 missing)	0.33	NA	NA	
Mean survival length (months)				28.7 (22.9-34.5) (n=12 missing)	25.6 (20.9-30.4) (n=14 missing)	0.68

GC, gastric cancer; N, number; NA, not applicable; BMI, body mass index; Hp, Helicobacter pylori; GI, gastro-intestinal; Hb, Hemoglobin
*Including Albania, Poland and Romania
** In Bologna, Hp data refer to detection of the infection on the biopsy sample or information reported on clinical records; in Rome, Hp data refers only to the detection on biopsy sample

Table 5. Odds ratios and 95% confidence intervals of the association between selected characteristics of the study population and early onset gastric cancer.

Variable* (N=92)	**OR, 95% CI**
Sex	
- Men	1.0 (Ref)
- Women	2.30, 0.35-15.1
Smoking status	
- Never	1.0 (Ref)
- Former	0.44, 0.04-5.35
- Current	8.95, 1.36-59.0
Helicobacter pylori	
- No	1.0 (Ref)
- Yes	1.09, 0.19-6.43
Family history of gastric cancer	
- No	
- Yes	1.0 (Ref)
	2.12, 0.30-15.3
Red flag symptoms (N=117)**	**OR, 95% CI**
Nausea	1.31, 0.22-7.81
Weight loss	0.88, 0.14-5.32
Dysphagia	4.66, 0.77-28.2
Dyspepsia	1.96, 0.37-10.4
Epigastric pain	6.51, 1.14-37.2
Gastrointestinal bleeding	0.84, 0.07-9.47

*Multivariate logistic regression adjusted for sex, smoking status, Helicobacter pylori infection and family history of gastric cancer
**Multivariate logistic regression adjusted for sex, nausea, weight loss, dysphagia, dyspepsia, epigastric pain and gastrointestinal bleeding.

Discussion

We collected information on several aspects of GC in a middle-risk Italian population from Bologna University Hospital. The analyses evidenced (i) low prevalence of Hp infection; (ii) predominance of high grade, infiltrating lesions at diagnosis, with a high prevalence of peptic ulcer associated to the cancer or ulcerated cancer lesion; (iii) relatively high prevalence of family history of GC and of other cancers; (iv) low prevalence of red flag symptoms, with weight loss more often observed in women than in men. Cancer site and histological type were often recorded as undefined or mixed, evidencing limitation in the recording of such data.

The analysis conducted on 151 GC cases from Rome "A.Gemelli" Hospital revealed a significantly higher prevalence of Hp, which might partially reflect the declining trend of the infection. Also, a higher proportion of cardia GC cases was observed, which could be in part explained by accuracy in the classification of the biopsy samples and the lower proportion of undefined cases. We observed an association between early onset GC and smoking, while no difference was observed for sex, family history of GC nor Hp. Our analyses also support a strict relationship between smoking and early onset GC. Moreover, as epigastric pain was found to be more likely to occur in early onset than in other cases, this element might be further investigated to inform the clinician about the importance of this symptom, which can be attributed to both benign diseases (eg., gastritis, ulcer) and to malignancy of the stomach.

Conclusions

This paper provides a comprehensive overview of the evolving epidemiology and risk factors of GC, emphasizing the role of Hp in gastric carcinogenesis. The observed decline in Hp prevalence and its influence on the incidence of non-cardia GC underscores the need for ongoing surveillance of infection trends and the development of targeted prevention strategies. Findings from the case-only analysis in a middle-risk Italian population reveal a predominance of non-cardia GC, a relatively low prevalence of Hp infection, and notable challenges in achieving accurate pathological classification. These insights highlight the urgent need to improve diagnostic accuracy and data recording practices. The study also sheds light on early-onset GC and second primary cancers, both of which require specific attention due to their unique risk profiles and implications for patient management. Early-onset GC, in particular, is associated with distinct genetic and environmental factors, reinforcing the importance of continued investigation into its causes and preventive measures (52). Prevention remains the cornerstone of reducing GC morbidity and mortality (62). Primary prevention efforts including Hp test-and-treat strategies, dietary education, and lifestyle interventions are especially critical in high-risk populations. (62-65). The integration of advanced predictive models combining genetic susceptibility and modifiable risk factors offers new opportunities for personalized

approches (69-72). Meanwhile, secondary and tertiary prevention efforts, including endoscopic surveillance, chemoprevention, and management of precancerous lesions, must be further refined and implemented systematically (62,63,69).

Overall, the findings emphasize the need for a multifaceted strategy that combines population-level interventions with personalized care to address the evolving challenges of GC prevention, early diagnosis, and clinical management in a changing epidemiological landscape.

References

1- Lin Y, Zheng Y, Wang HL, Wu J. Global Patterns and Trends in Gastric Cancer Incidence Rates (1988-2012) and Predictions to 2030. Gastroenterology. 2021 Jul;161(1):116-127.e8.

2- Chen YC, Malfertheiner P, Yu HT, Kuo CL, Chang YY, Meng FT, et al. Global Prevalence of Helicobacter pylori Infection and Incidence of Gastric Cancer Between 1980 and 2022. Gastroenterology. 2024 Apr;166(4):605-619.

3- Collatuzzo G, Santucci C, Malvezzi M, La Vecchia C, Boffetta P, Negri E. Trends in gastric cancer mortality 1990-2019 in 36 countries worldwide, with predictions to 2025, and incidence, overall and by subtype. Cancer Med. 2023 Apr;12(8):9912-9925.

4- Lyons K, Le LC, Pham YT, Borron C, Park JY, Tran CTD, et al. Gastric cancer: epidemiology, biology, and prevention: a mini review. Eur J Cancer Prev. 2019 Sep;28(5):397-412.

5- Gullo I, Grillo F, Mastracci L, Vanoli A, Carneiro F, Saragoni L, et al. Precancerous lesions of the stomach, gastric cancer and hereditary gastric cancer syndromes. Pathologica. 2020 Sep;112(3):166-185.

6- Hidaka A, Sasazuki S, Matsuo K, Ito H, Sawada N, Shimazu T, et al. Genetic polymorphisms of ADH1B, ADH1C and ALDH2, alcohol consumption, and the risk of gastric cancer: the Japan Public Health Center-based prospective study. Carcinogenesis. 2015 Feb;36(2):223-31.

7- Pelucchi C, La Vecchia C, Bonzi R, Negri E, Corso G, Boccia S, et al. The global gastric cancer consortium: an update from the Stomach cancer Pooling (StoP) project. Eur J Cancer Prev. 2024 Sep 1;33(5):433-437. 8- World Cancer Research Fund. https://www.wcrf.org/a-spotlight-on-stomach-cancer-subtypes/ , Accessed on 3 November 2023

9- Thrift AP, El-Serag HB. Burden of Gastric Cancer. Clin Gastroenterol Hepatol. 2020 Mar;18(3):534-542.

10- Azizi N, Zangiabadian M, Seifi G, Davari A, Yekekhani E, Safavi-Naini SAA, et al. Gastric Cancer Risk in Association with Underweight, Overweight, and Obesity: A Systematic Review and Meta-Analysis. Cancers (Basel). 2023 May 16;15(10):2778.

11- Han Z, Liu J, Zhang W, Kong Q, Wan M, Lin M, et al. Cardia and non-cardia gastric cancer risk associated with Helicobacter pylori in East Asia and the West: A systematic review, meta-analysis, and estimation of population attributable fraction. Helicobacter. 2023 Apr;28(2):e12950.

12- Boffetta P., Boccia S., La Vecchia C. Springer; New York: 2014. A Quick Guide to Cancer Epidemiology.

13- Collatuzzo G, Fiorini G, Vaira B, Violante FS, Farioli A, Boffetta P. The role of the occupational physician in controlling gastric cancer attributable to Helicobacter pylori infection: A review. Prev Med Rep. 2021 Aug 18;24:101527.

14- Bae JM, Kim EH. Epstein-Barr Virus and Gastric Cancer Risk: A Meta-analysis With Meta-regression of Case-control Studies. J Prev Med Public Health. 2016 Mar;49(2):97-107.

15- Mohammadi M, Tadger P, Sadeghi A, Salehi N, Rajabnia M, Paraandavaji E, et al. Opium use and gastrointestinal cancers: a systematic review and meta-analysis study. Gastroenterol Hepatol Bed Bench. 2024;17(2):104-120.

16- Yang L, Kartsonaki C, Yao P, de Martel C, Plummer M, Chapman D, et al. The relative and attributable risks of cardia and non-cardia gastric cancer associated with Helicobacter pylori infection in China: a case-cohort study. Lancet Public Health. 2021 Dec;6(12):e888-e896.

17- Collatuzzo G, Pelucchi C, Negri E, López-Carrillo L, Tsugane S, Hidaka A, et al. Exploring the interactions between Helicobacter pylori (Hp) infection and other risk factors of gastric cancer: A pooled analysis in the Stomach cancer Pooling (StoP) Project. Int J Cancer. 2021 Sep 15;149(6):1228-1238.

18- Toh JWT, Wilson RB. Pathways of Gastric Carcinogenesis, Helicobacter pylori Virulence and Interactions with Antioxidant Systems, Vitamin C and Phytochemicals. Int J Mol Sci. 2020 Sep 3;21(17):6451.

19- Kim DS, Lee MS, Kim YS, Kim DH, Bae JM, Shin MH, Ahn YO. Effect modification by vitamin C on the relation between gastric cancer and Helicobacter pylori. Eur J Epidemiol. 2005;20(1):67-71.

20- Ng AK, Ng PY, Ip A, Cheung KS, Siu CW. Association between proton pump inhibitors after percutaneous coronary intervention and risk of gastric cancer. BMJ Open Gastroenterol. 2021 Aug;8(1):e000719.

21- Decourtye-Espiard L, Guilford P. Hereditary Diffuse Gastric Cancer. Gastroenterology. 2023 Apr;164(5):719-735.

22- Carneiro F. Familial and hereditary gastric cancer, an overview. Best Pract Res Clin Gastroenterol. 2022 Jun-Aug;58-59:101800.

23- Sampson JR, Jones N. MUTYH-associated polyposis. Best Pract Res Clin Gastroenterol. 2009;23(2):209-18.

24- Latchford AR, Clark SK. Gastrointestinal aspects of Peutz-Jeghers syndrome. Best Pract Res Clin Gastroenterol. 2022 Jun-Aug;58-59:101789.

25- Brosens LA, Langeveld D, van Hattem WA, Giardiello FM, Offerhaus GJ. Juvenile polyposis syndrome. World J Gastroenterol. 2011 Nov 28;17(44):4839-44.

26- Bougeard G, Renaux-Petel M, Flaman JM, Charbonnier C, Fermey P, Belotti M, et al. Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. J Clin Oncol. 2015 Jul 20;33(21):2345-52.

27- Friedenson B. BRCA1 and BRCA2 pathways and the risk of cancers other than breast or ovarian. MedGenMed. 2005 Jun 29;7(2):60.

28- Jelski W, Szmitkowski M. Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) in the cancer diseases. Clin Chim Acta. 2008 Sep;395(1-2):1-5.

29- Asanuma K, Chiba T, Tadano T, Kato K. Genetic Polymorphism in Alcohol Metabolism and Drinking Behavior are Associated with Gastric Cancer Risk in Men. Intern Med. 2024 May 9.

30- Zhang FF, Hou L, Terry MB, Lissowska J, Morabia A, Chen J, et al. Genetic polymorphisms in alcohol metabolism, alcohol intake and the risk of stomach cancer in Warsaw, Poland. Int J Cancer. 2007 Nov 1;121(9):2060-2064.

31- Na HK, Lee JY. Molecular Basis of Alcohol-Related Gastric and Colon Cancer. Int J Mol Sci. 2017 May 24;18(6):1116.

32- Sim W, Pan JT, Chua CWX, Fong KY, Wong SH, Lee B, et al. Association between alcohol flushing syndrome and cancer: A systematic review and meta-analysis. Ann Acad Med Singap. 2024 Jul 30;53(7):420-434.

33- Loh M, Koh KX, Yeo BH, Song CM, Chia KS, Zhu F, et al. Meta-analysis of genetic polymorphisms and gastric cancer risk: variability in associations according to race. Eur J Cancer. 2009 Sep;45(14):2562-8.

34- Castellana C, Eusebi LH, Dajti E, Iascone V, Vestito A, Fusaroli P, et al. Autoimmune Atrophic Gastritis: A Clinical Review. Cancers (Basel). 2024 Mar 28;16(7):1310.

35- Dinis-Ribeiro M, Libânio D, Uchima H, Spaander MCW, Bornschein J, Matysiak-Budnik T, et al. Management of epithelial precancerous conditions and early neoplasia of the stomach (MAPS III): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG) and European Society of Pathology (ESP) Guideline update 2025. Endoscopy. 2025 May;57(5):504-554.

36- Nehme F, Rowe K, Palko W, Tofteland N, Salyers W. Autoimmune metaplastic atrophic gastritis and association with neuroendocrine tumors of the stomach. Clin J Gastroenterol. 2020 Jun;13(3):299-307.

37- Miceli E, Lenti MV, Gentile A, Gambini G, Petrucci C, Pitotti L, et al. Long-Term Natural History of Autoimmune Gastritis: Results From a Prospective Monocentric Series. Am J Gastroenterol. 2024 May 1;119(5):837-845.

Rugge M, Bricca L, Guzzinati S, Sacchi D, Pizzi M, Savarino E, et al. Autoimmune gastritis: long-term natural history in naïve Helicobacter pylori-negative patients. Gut. 2023 Jan;72(1):30-38.

39- Hoft SG, Brennan M, Carrero JA, Jackson NM, Pretorius CA, Bigley TM,et al. Unveiling Cancer-Related Metaplastic Cells in Both Helicobacter pylori Infection and Autoimmune Gastritis. Gastroenterology. 2025 Jan;168(1):53-67.

40- Chen C, Yang Y, Li P, Hu H. Incidence of Gastric Neoplasms Arising from Autoimmune Metaplastic Atrophic Gastritis: A Systematic Review and Case Reports. J Clin Med. 2023 Jan 30;12(3):1062.

41- Lenti MV, Miceli E, Lahner E, Natalello G, Massironi S, Schiepatti A, et al. Distinguishing Features of Autoimmune Gastritis Depending on Previous Helicobacter pylori Infection or Positivity to Anti-Parietal Cell Antibodies: Results From the Autoimmune gastRitis Italian netwOrk Study grOup (ARIOSO). Am J Gastroenterol. 2024 Dec 1;119(12):2408-2417.

42- Paik DC, Saborio DV, Oropeza R, Freeman HP. The epidemiological enigma of gastric cancer rates in the US: was grandmother's sausage the cause? Int J Epidemiol. 2001 Feb;30(1):181-2.

43- Arnold M, Park JY, Camargo MC, Lunet N, Forman D, Soerjomataram I. Is gastric cancer becoming a rare disease? A global assessment of predicted incidence trends to 2035. Gut. 2020 May;69(5):823-829. doi: 10.1136/gutjnl-2019-320234. Epub 2020 Jan 30.

44 - Lin JL, Lin JX, Lin GT, Huang CM, Zheng CH, Xie JW, et al. Global incidence and mortality trends of gastric cancer and predicted mortality of gastric cancer by 2035. BMC Public Health. 2024 Jul 2;24(1):1763.

45- Carioli G, Bertuccio P, Levi F, Boffetta P, Negri E, La Vecchia C, et al. Cohort Analysis of Epithelial Cancer Mortality Male-to-Female Sex Ratios in the European Union, USA, and Japan. Int J Environ Res Public Health. 2020 Jul 23;17(15):5311.

46- Colquhoun A, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut. 2015 Dec;64(12):1881-8.

47- Camargo MC, Freedman ND, Hollenbeck AR, Abnet CC, Rabkin CS. Height, weight, and body mass index associations with gastric cancer subsites. Gastric Cancer. 2014;17(3):463-8.

48- Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: Emerging biological mechanisms and perspectives. Metabolism. 2019 Mar;92:121-135.

49- An international association between Helicobacter pylori infection and gastric cancer. The EUROGAST Study Group. Lancet. 1993 May 29;341(8857):1359-62.

Camargo MC, Anderson WF, King JB, Correa P, Thomas CC, Rosenberg PS, et al. Divergent trends for gastric cancer incidence by anatomical subsite in US adults. Gut. 2011 Dec;60(12):1644-9.

51- Li Y, Hahn AI, Laszkowska M, Jiang F, Zauber AG, Leung WK. Global burden of young-onset gastric cancer: a systematic trend analysis of the global burden of disease study 2019. Gastric Cancer. 2024 Jul;27(4):684-700.

52-Bergquist JR, Leiting JL, Habermann EB, Cleary SP, Kendrick ML, Smoot RL, et al. Early-onset gastric cancer is a distinct disease with worrisome trends and oncogenic features. Surgery. 2019 Oct;166(4):547-555.

53- Milne AN, Offerhaus GJ. Early-onset gastric cancer: Learning lessons from the young. World J Gastrointest Oncol. 2010 Feb 15;2(2):59-64.

54- Kang SJ, Shin CM, Han K, Jung JH, Jin EH, Lim JHet al. Impact of Smoking and Alcohol Consumption on Early-Onset Gastric Cancer Development in Young Koreans: A Population-Based Study. J Gastric Cancer. 2024 Apr;24(2):145-158.

55- Rihane FE, Erguibi D, Elyamine O, Abumsimir B, Ennaji MM, Chehab F. Helicobacter pylori co-infection with Epstein-Barr virus and the risk of developing gastric adenocarcinoma at an early age: Observational study infectious agents and cancer. Ann Med Surg (Lond). 2021 Jul 31;68:102651.

56- Li Y, Hahn AI, Laszkowska M, Jiang F, Zauber AG, Leung WK. Clinicopathological Characteristics and Risk Factors of Young-Onset Gastric Carcinoma: A Systematic Review and Meta-analysis. Clin Transl Gastroenterol. 2024 Jun 1;15(6):e1.

57- Cho SY, Park JW, Liu Y, Park YS, Kim JH, Yang H, et al. Sporadic Early-Onset Diffuse Gastric Cancers Have High Frequency of Somatic CDH1 Alterations, but Low Frequency of Somatic RHOA Mutations Compared With Late-Onset Cancers. Gastroenterology. 2017 Aug;153(2):536-549.e26.

58- Setia N, Wang CX, Lager A, Maron S, Shroff S, Arndt N, et al. Morphologic and molecular analysis of early-onset gastric cancer. Cancer. 2021 Jan 1;127(1):103-114

59- Zhou Q, Tao F, Qiu L, Chen H, Bao H, Wu X, et al. Somatic Alteration Characteristics of Early-Onset Gastric Cancer. J Oncol. 2022 Apr 22;2022:1498053.

60- Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015 Feb;110(2):223-62; quiz 263.

Morais S, Castro C, Antunes L, Peleteiro B, Bento MJ, Lunet N. Second primary cancers and survival in patients with gastric cancer: association with prediagnosis lifestyles. Eur J Cancer Prev. 2019 May;28(3):159-166.

62- Ford AC, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut. 2020 Dec;69(12):2113-2121.

63- Eusebi LH, Telese A, Marasco G, Bazzoli F, Zagari RM. Gastric cancer prevention strategies: A global perspective. J Gastroenterol Hepatol. 2020 Sep;35(9):1495-1502.

64- Januszewicz W, Turkot MH, Malfertheiner P, Regula J. A Global Perspective on Gastric Cancer Screening: Which Concepts Are Feasible, and When? Cancers (Basel). 2023 Jan 21;15(3):664.

65- Kowada A. A Population-Based Helicobacter pylori Eradication Strategy Is More Cost-Effective than Endoscopic Screening. Dig Dis Sci. 2023 May;68(5):1735-1746.

66- Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, et al. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut. 2013 Jan;62(1):34-42.

67- Doorakkers E, Lagergren J, Santoni G, Engstrand L, Brusselaers N. Helicobacter pylori eradication treatment and the risk of Barrett's esophagus and esophageal adenocarcinoma. Helicobacter. 2020 Jun;25(3):e12688.

68- Chiang TH, Chang WJ, Chen SL, Yen AM, Fann JC, Chiu SY, et al. Mass eradication of Helicobacter pylori to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands. Gut. 2021 Feb;70(2):243-250.

69- Eom BW, Joo J, Kim S, Shin A, Yang HR, Park J, et al. Prediction Model for Gastric Cancer Incidence in Korean Population. PLoS One. 2015 Jul 17;10(7):e0132613.

70- Charvat H, Shimazu T, Inoue M, Iwasaki M, Sawada N, Yamaji T, et al. Estimation of the performance of a risk prediction model for gastric cancer occurrence in Japan: Evidence from a small external population. Cancer Epidemiol. 2020 Aug;67:101766.

71- Nguyen NT, Dang NDT, Vu QV, Dang AK, Ta TV. A Model for Gastric Cancer Risk Prediction Based on MUC1Polymorphisms and Health-risk Behaviors in a Vietnamese Population. In Vivo. 2023 Sep-Oct;37(5):2347-2356.

72- Arai J, Aoki T, Sato M, Niikura R, Suzuki N, Ishibashi R, et al. Machine learning-based personalized prediction of gastric cancer incidence using the endoscopic and histologic findings at the initial endoscopy. Gastrointest Endosc. 2022 May;95(5):864-872.

73- Sharma P, Hassan C. Artificial Intelligence and Deep Learning for Upper Gastrointestinal Neoplasia. Gastroenterology. 2022 Apr;162(4):1056-1066.

Oura H, Matsumura T, Fujie M, Ishikawa T, Nagashima A, Shiratori W,. Development and evaluation of a double-check support system using artificial intelligence in endoscopic screening for gastric cancer. Gastric Cancer. 2022 Mar;25(2):392-400.

75- Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I, Costa JL, Carneiro F, Machado JC, et al. Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota. Gut. 2018 Feb;67(2):226-236.

76- Zhang X, Li C, Cao W, Zhang Z. Alterations of Gastric Microbiota in Gastric Cancer and Precancerous Stages. Front Cell Infect Microbiol. 2021 Mar 3;11:559148.

77- Huang K, Gao X, Wu L, Yan B, Wang Z, Zhang X, et al. Salivary Microbiota for Gastric Cancer Prediction: An Exploratory Study. Front Cell Infect Microbiol. 2021 Mar 10;11:640309.

78- Xia R, Jiang Z, Zhou Y, Pan L, Wang Y, Ma Y, et al. Oral microbiota and gastric cancer: recent highlights and knowledge gaps. J Oral Microbiol. 2024 Aug 16;16(1):2391640.

79- You HS, Park JY, Seo H, Kim BJ, Kim JG. Increasing correlation between oral and gastric microbiota during gastric carcinogenesis. Korean J Intern Med. 2024 Jul;39(4):590-602.

80- Jin G, Lv J, Yang M, Wang M, Zhu M, Wang T, et al. Genetic risk, incident gastric cancer, and healthy lifestyle: a meta-analysis of genome-wide association studies and prospective cohort study. Lancet Oncol. 2020 Oct;21(10):1378-1386.

81- Shah SC, Peek RM Jr. Chemoprevention Against Gastric Cancer. Gastrointest Endosc Clin N Am. 2021 Jul;31(3):519-542.

82- Mancini S, Ravaioli A, Giuliani O, Giorgetti S, Falcini F, Colamartini A, Bucchi L. Gastric cancer incidence in the Romagna Region of Italy: A spatial and temporal analysis. Dig Liver Dis. 2015 Dec;47(12):1076-81.

83- Atlante di mortalità, Regione Emilia Romagna. https://salute.regione.emilia-romagna.it/normativa-e-documentazione/rapporti/atlante-di-mortalita Accessed on 6.2.25

84- Lauren P. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.

85- De Feo E, Simone B, Persiani R, Cananzi F, Biondi A, Arzani D, et al. A case-control study on the effect of Apolipoprotein E genotypes on gastric cancer risk and progression. BMC Cancer. 2012 Oct 25;12:494. doi: 10.1186/1471-2407-12-494.

Collatuzzo G, Dajti E, Secco M, Bazzoli F, Boffetta P, Zagari RM. Burden of gastric cancer attributable to Helicobacter pylori in 27 countries from seven geographic regions in 2022. Gastric Cancer. 2025 Oct 20.

2.3 Burden of gastric cancer attributable to *Helicobacter pylori* in 27 countries from seven regions in 2022

Running title: Gastric cancer attributable to Helicobacter pylori in 2022

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ABSTRACT

Background and aim: *Helicobacter (H.) pylori* is the major risk factor of gastric cancer (GC). We aimed to estimate the attributable fraction (AF) of GC for *H. pylori* and the number of new GC cases and deaths for GC attributable to *H. pylori* in different geographic regions and countries in 2022.

Methods: The AF was estimated using region- and country-specific pooled prevalence of *H. pylori* in the period 2000-2010, that was obtained through a systematic review and meta-analysis, and a risk ratio of 5.9 for the association between *H. pylori* and GC. The number of new GC cases and deaths for GC attributable to *H. pylori* was calculated using the AF and the estimates of GC incidence and mortality reported by GLOBOCAN 2022.

Results: The burden of GC due to *H. pylori* was calculated for 26 countries from 7 geographic regions. The average AF was 69.7 %, ranging from 40.7% in Malaysia to 82.3% in South Africa. The AF was > 70% in all countries in the African, East Mediterranean, Latin American and Western Pacific regions, except for Malaysia, and in some countries in Europe, including Poland, Spain, Albania and Germany. The largest number of *H. pylori*-related GC cases and deaths for GC were estimated in China (GC:252.850, deaths 184.666) and Japan (GC:92.166, deaths: 31,809) followed by Korea (GC:21.855, deaths: 6.359), Brazil (GC: 17.327, deaths:13.646) and Iran (GC: 12.711, deaths: 1168). In Europe, the highest numbers were observed in Germany (GC: 9703, deaths: 6026), Spain (GC: 5308, deaths: 3752) and Poland (GC: 5305, deaths: 4098).

Conclusions: More than two-thirds of new GC cases in the countries in the analysis were due to *H. pylori* in 2022. Our estimates may contribute to better investigate cost-effectiveness of *H. pylori* screening strategies for GC prevention in different countries worldwide.

INTRODUCTION

Gastric cancer (GC) is an important cause of morbidity and mortality and, despite the decreasing incidence rate, the total number of cases and deaths due to GC are increasing worldwide. (1,2) *Helicobacter (H.) pylori* infection is the most important cause of GC leading to gastric adenocarcinoma through chronic gastritis, atrophic gastritis, intestinal metaplasia and dysplasia (3). The eradication of *H. pylori* is the most effective weapon for the primary prevention of GC primary (3,4). However, cost-effectiveness and antimicrobial resistance are the main concern for *H. pylori* "screen and treat" strategies in the general population (3).

The current burden of GC attributable to *H. pylori* in different countries is still unclear. The prevalence of *H. pylori* infection and the incidence of GC vary in different countries and geographic area (5,6). In addition, the prevalence of *H. pylori* is dynamic being progressively declining and subjected to the birth-cohort effect (7). Thus, estimates of proportion and number of new GC cases attributable to *H. pylori* may vary by geographic region and, in particular, by country.

Only few studies have performed a comprehensive analysis to estimate the burden of GC due to *H. pylori* from a global perspective. In addition, previous estimates of the attributable fraction (AF) of GC for *H. pylori* have some limitations related to the calculation of AF. For example, some studies calculated the AF retrospectively using the prevalence of *H. pylori* in GC cases rather than prospectively in the general population (8-11), while others studies assumed that the prevalence of *H. pylori* in GC cases can be used as an estimate of AF (2, 10-12, 14), whereas other studies calculated the AF in all age groups rather than adults only (13); furthermore, other reports used a risk ratio (RR) for the association between *H. pylori* and GC estimated including case-control studies (15-18), which may underestimate the strength of association because the infection might be cleared in GC cases.

Improving estimates of the burden of GC due to *H. pylori* in different countries is essential for health policy makers to evaluate cost-effectiveness of *H. pylori* screening and treatment programs for the primary prevention of GC.

The aim of this study was to estimate the AF of GC for *H. pylori* and the number of new GC cases and deaths for GC attributable to *H. pylori* in different countries worldwide in 2022.

METHODS

The AF of GC for *H. pylori* was calculated applying the formula originally described by Levin (20): $AF = \frac{p\,(RR-1)}{(1+p\,(RR-1))}$ where p is the prevalence of infection in the general population and RR is the relative risk of GC associated with *H. pylori* infection.

In order to estimate the AF prospectively**,** we performed a systematic review and meta-analysis to estimate the country-specific prevalence of *H. pylori* in the adult general population in the period 2000-2010, considering 12-to-22-year latency between infection and GC. The RR for the association between *H. pylori* and GC was assumed to be constant worldwide, and so we used a single RR estimate in the calculation of each AF. Considering that non-cardia GC represents the majority of the GC cases worldwide (80-90%), we used the RR of 5.9, that was calculated for non-cardia GC through a meta-analysis of cohort studies (21). We applied the same RR to calculate AF for incidence and mortality and for men and women, assuming no effect of infection on cancer survival and no infection–sex interaction (22).

The number of new GC cases and deaths for GC attributable to *H. pylori* was calculated by multiplying the AF by the number of new GC cases and deaths for GC estimated from GLOBOCAN 2022 (1). In particular, GLOBOCAN data were restricted to age 40+, therefore considering population at higher risk of GC (4). We calculated the AF of GC for *H. pylori* only for those countries for which was possible to estimate the prevalence of *H. pylori* in the general population in the period 2000-2010. The number of new GC cases and deaths for GC attributable to H. pylori was calculated for those countries for which incidence and mortality data on GC from GLOBOCAN 2022 were also available

Prevalence of *H. pylori* in the general population: systematic review and meta-analysis

The systematic review and meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline (17). We searched MEDLINE via Pubmed and Embase up to January 1st 2023 using the following keywords: "*Helicobacter pylori*", "*H. pylori*", "*HP*", "*Campylobacter pylori*" and "*prevalence*". We did not restrict for language or type of publication. The search strategy is reported in the Supplementary 1.

Two authors (ED and MS) did the initial selection based on titles and abstracts. Subsequently, they independently performed a detailed full text assessment of potentially relevant studies and any disagreement was solved by a third author (RMZ). Selected studies were included in the review if they reported the prevalence of *H. pylori* in the adult general population in the period 2000-2010, regardless of the year of publication. We excluded studies that did not meet the inclusion criteria, or if essential information was missing and could not be obtained by the authors.

Two authors (ED and MS) extracted independently the following items from each study: country, region, study period, inclusion and exclusion criteria, total number of participants, average age and gender, test for *H. pylori* diagnosis, number and percentage of *H. pylori*-positive subjects. Two authors (ED and MS) independently assessed the quality of the selected studies using the Newcastle-Ottawa Quality Assessment Scale (17) and any disagreement was solved through discussion and, if necessary, arbitration by a third author (RMZ). Supplementary Table 1 shows the quality assessment of included studies.

We calculated pooled country-specific prevalence of *H. pylori* infection in the general population with 95% confidence interval (CI) using a random effect model.

The heterogeneity among the studies was assessed using the I^2 and the Cochran Q-statistic.

All the analyses were performed using STATA 16 (Stata Corp., College Station, TX, USA) (19).

RESULTS

Prevalence of *H. pylori* infection in the general population in the period 2000-2010: systematic review and meta-analysis.

The systematic review of the literature identified 40 articles that reported the *H. pylori* prevalence in the general population in 27 countries from 7 geographic regions in the period 2000-2010 (23-62). Two articles provided data from two cohorts of population: one study provided data from Greece and Albania (43) and one other from two cohorts in China (61). Supplementary Figure 1 shows the flow-chart of the selection process.
The regions with the highest number of studies were Western Pacific (n=14) and Europe (n=12), followed by Latin America (n=6), Eastern Mediterranean (n=6), Africa (n=2), North America (n=1) and South-East Asia (n=1). Supplementary Table 2 shows the characteristics of the included studies.

The overall prevalence of *H. pylori* was 52% (95%CI: 45%-60%) (108.698 out of 209,035 subjects) ranging from 14.2% in Malaysia to 95% in South Africa; there was high heterogeneity among the studies (I^2 = 99.9%).

The countries with the highest *H. pylori* prevalence were South Africa (95%), Benin (86.2%), Chile (74.6%), Ecuador (72.2%) and Brazil (70.7%), while the countries with the lowest *H. pylori* prevalence were Greece (33.7%), Australia (29%) and Malaysia (14.2%) (Table 1).

Attributable fraction of gastric cancer for *H. pylori* infection

Using the estimates of *H. pylori* prevalence in the general population, we calculated the AF of GC for *H. pylori* in 27 countries from seven regions in 2022. The average AF was 69.7% (95%CI:67.8-71.0) ranging from 40.7% in Malaysia to 82.3% in South Africa. The AF of GC for *H. pylori* was high in all countries in the analysis in Africa (South Africa: 82.3%, Benin: 80.8%), East Mediterranean region (Tunisia: 75.5%, Iran: 75.2%), Latin America (Chile: 78.6%, Ecuador: 77.9%, Brazil: 77.7%, Guadalupe: 72.6%, Panama: 72.6% and Mexico: 65.1%) and Western Pacific region (Korea: 75.8%, Japan:

72.9%, China 71.8%, Taiwan 65.6%, Australia: 58.7%), except for Malaysia. In Europe, Poland (77.2%), Spain (74.9%), Albania (72.2%) and Germany (69.7%) showed the highest AF, while Norway (56%) and Denmark (49.5%) registered the lowest. Table 2 shows the estimates of AF of GC for *H. pylori* by WHO regions and countries.

Number of new gastric cancers and deaths for GC attributable to *H. pylori*

Using our estimates of AF and the estimates of GC incidence and mortality reported by GLOBOCAN (23), we calculated the number of new GC cases (Table 3) and deaths for GC (Table 4) attributable to *H. pylori* in 26 countries in 2022. Estimates for Taiwan were not provided because data from GLOBOCAN 2022 were lacking.

A total of 454.802 new cases of GC and 287.829 deaths for GC could be attributable to *H. pylori* infection across 26 countries in 2022.
The highest numbers of new GC cases and deaths for GC due to *H. pylori* were seen in China (GC: 252.850, deaths: 184.666) and Japan (GC: 92.166, deaths: 31.809) followed by Korea (GC: 21.855, deaths: 6.359). In Latin America, Brazil showed the highest number of new GC cases and deaths due to *H. pylori* (GC: 17.327, deaths:13.646), that instead were less than 6000 in the other countries, including Chile, Ecuador, Guadalupe, Mexico and Panama. In Europe, the number of new GC cases and GC deaths attributable to *H. pylori* was remarkably in Germany (GC: 9703, deaths: 6026), Spain (GC: 5308, deaths: 3752) and Poland (GC: 5305, deaths: 4098), while GC cases *H. pylori*-related were less than 1000 in Albania, Czech Republic, Denmark, Greece, Norway and Netherlands. In the East Mediterranean region, the number of new GC cases and deaths due to *H. pylori* was high in Iran (GC: 12.711, deaths: 10168) and low in Tunisia (GC: 384, deaths: 331). Finally, in Africa there was the lowest number of new GC cases (n. 1773) and GC deaths (n.1535) attributable to *H. pylori,* despite the high *H. pylori* prevalence and AF of GC for *H. pylori*. As expected, the number of new GC cases (Table 3) and deaths for GC (Table 4) attributable to *H. pylori* were about two times higher in men than women in all regions and countries.

DISCUSSION

This study provides estimates of the burden of GC attributable to *H. pylori* infection in 26 countries from seven geographic regions in 2022. Attributable fractions are based on country-specific pooled prevalence of *H. pylori* in the general population in the period 2000-2010 estimated through a systematic review and meta-analysis. Using estimates of AF and the estimates of GC incidence and mortality provided by GLOBOCAN (23), we calculated the number of new GC cases and deaths for GC attributable to *H. pylori* infection in the different countries.

Our data confirm the major role played by *H. pylori* in the burden of GC (6, 9), in particular in China, Japan, Korea and in some Latin America and European countries. We found that the average AF of GC for *H. pylori* was 69.7% in 2022. This estimate is only slightly lower than those previously reported in 2008 (77.3%) (9) and in 2012 (79.3%) (10). The AF ranged from 40.7% in Malaysia to 82.3% in South Africa. Obviously, the AF varied across different geographic regions and countries in line with the variation of *H. pylori* prevalence, which is in agreement with other pooled analyses (63, 64). We did not provide a global estimate of the prevalence of *H. pylori* infection and of the burden of GC attributable to it, as other authors have done (6, 9-11), because of the many assumptions needed to derive global estimates. Rather, we decided to focus on the countries with data of acceptable quality, thus giving priority to validity over generalizability. The relatively large number of countries in the analysis, including several major countries, on the other hand, provides clinical and public health relevance of our findings.

Notably, we found that in China, Japan and Korea the AF of GC for *H. pylori* was higher than 70%. Previous estimates of the AF in these countries were not consistent (12,14,15,63-65). In the study by Ji, the AF of GC for *H. pylori* was 58%, 30.9% and 35.2% in Japan, China and Korea, respectively (15). Similarly, Han et al. reported low estimates of AF in East Asia including China (45.6%), Japan (57.1%) and Korea (40.5%), even though the sub-group analysis of studies with a follow-up time >10 years showed an AF of non-cardia GC of 71.2% (64). Similarly, a large case-control study including about 500.000 adults reported in China an AF of 78.5% for non-cardia gastric cancer and

62.1% for cardia gastric cancer (65). In line with this study, we provide further evidence that more than two third of new GC cases in Japan, China and Korea are due to *H. pylori* infection. In particular, *H. pylori* may have caused about 255000 cases of GC and 182000 deaths for GC in China and 92000 cases of GC and 32000 deaths for GC in Japan. The number of GC cases due to *H. pylori* was different in different countries, also due to differences in the total number of incident GC cases occurring in the general population. The total number of incident GC is very high in China and Japan (70), and this would partially explain the largest number of GC cases and deaths due to *H. pylori* in these countries. This also result in the different number of GC cases due to *H. pylori* that occurred in different countries within Latin America and Europe. In fact, In Latin America *H. pylori* caused about 17.000 cases of GC and 14.000 deaths for GC in Brazil, but up to 3.000 in Ecuador and Chile. Similarly, in Europe *H. pylori* caused about 10.000 cases of GC and 6.000 deaths for GC in Germany, but less than 1.000 in other countries including Albania, Czeck Republic, Denmark and Norway. In Africa, *H. pylori* prevalence and AF of GC for *H. pylori* were more that 80%, but the number of GC cases and deaths attributable to *H. pylori* was very low due to the low incidence of GC in Africa. This supports the historical concept of the "African Enigma", based on the low GC rates despite the persistently high prevalence of *H.pylori* (71).

Current guidelines suggest focusing on GC prevention through population-based *H. pylori* screen-and-treat strategies (3). Notably, *H. pylori* screening and treatment programs present many challenges, including high costs, complex study protocols and design and possible may increase antimicrobial resistance in the general population (3). However, in Asia *H. pylori* screening and treatment programs seem to be cost-effective (3, 72, 73). Kowada et al reported that *H. pylori* screening performs better in terms of cost-effectiveness than endoscopy program in Japan, and that it is most effective in asymptomatic adults aged 50 or older (73). Notably, in order to further reduce the GC burden, Japan and Korea added *H. pylori* screening and eradication to the health insurance policy in the early 2010s (2). Indeed, our finding further support the suggestion that *H. pylori* screening and treatment programs in Asia, in particular in China and Japan, would be cost-effective for reducing the high burden of GC in the general population. Whether a *H. pylori* screen-and-treat strategy is cost-effective in non-Asian countries is still under

debate (3, 74,75). The 2022 Council of the European Union Recommendation on Cancer Screening recommended the implementation of screen and treat strategies in those countries with high GC incidence (> 20 cases per 100000) (76). We estimated the number of GC cases and deaths for GC preventable through *H. pylori* eradication in several European countries and we showed that the burden of GC *H. pylori*-related preventable by a screening strategy would be substantially higher in Germany, Spain and Poland than in other European countries. Indeed, our results may help health policy makers to better explore cost-efficacy of population-based *H. pylori* screening programs in some countries in Europe. In addition, the development of solid prediction models and risk stratification would allow to integrate *H. pylori* eradication programs to the already implemented cancer screening (3, 77-79).

Our study has several strengths. We estimated the burden of GC attributable to *H. pylori* using region and country-specific data and accurate statistical methods. In particular, we calculated the AF prospectively using the region- and country-specific prevalence of *H. pylori* infection in the general population estimated through a systematic-review and meta-analysis; data referred to general adult population, reflecting the actual exposure in the timeframe considered. Furthermore, we considered a 10-20 years latency between *H. pylori* infection and the development of GC. Such latency was not always considered (8-10, 14, 67, 68); given the secular decline of *H. pylori* prevalence in most countries (6,7), this would have resulted in an underestimation of the AF of GC for *H. pylori*.

This study has also some limitations. The first limitation is the paucity of data on *H. pylori* prevalence for certain geographical areas, such as Africa, East Mediterranean and South-East Asia, that may affect the accuracy of the estimates of AF and prevented us from providing estimates of attributable cases and deaths by region and globally. Moreover, we assumed that RR between *H. pylori* and GC was constant worldwide, assuming no differences in the strength of this association by geographical area. While this is a common statistical approach, it may not represent the reality as pathogen- and individual-related factors may play a role in the association between infection and GC; for example, interactions with smoking or dietary factors could modify the carcinogenetic effect of *H. pylori* (64); *H.pylori* strains also influence carcinogenicity, with CagA positive ones

being known for their stronger association with cancer (27,33,57). However, other studies adopted values of RR that were estimated by pooling case-control rather than cohort studies, likely leading to an underestimation of the strength of the association between *H. pylori* and GC due to the possibility that GC cases lose infection, and therefore to an underestimation of the AF (12, 14-16). Finally, we did not provide data by GC anatomical sub-site, i.e. for cardias and non-cardia GC. It is well that known that *H. pylori* have different strength of association with cardia and non-cardia GC (65). However, on a global scale most of GC are non-cardia that are strongly related with *H. pylori* infection.

In conclusion, *H. pylori* infection remains the most important cause of GC worldwide. However, the burden of GC due to *H. pylori* varies among different countries, even though they belong to the same geography region and have similar *H. pylori* prevalence. Therefore, country-specific data on the number of new GC cases and deaths for GC attributable to *H. pylori* are essential in the perspective of population-based *H. pylori* screening programs for the prevention of GC. Our findings represent an important contribution to further investigate the cost-effectiveness of such strategies in different countries worldwide. Given the changing trends in *H. pylori* prevalence and GC incidence, studies providing accurate and updated estimates of country-specific burden of GC attributable to *H. pylori* are needed in the future.

REFERENCES

1. https://gco.iarc.fr/en Accessed on 15 March 2024
2. Lin Y, Zheng Y, Wang HL, Wu J. Global Patterns and Trends in Gastric Cancer Incidence Rates (1988-2012) and Predictions to 2030. Gastroenterology 2021;161:116-127.
3. Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, et al. Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report. Gut. 2022; 71:1724-1762.
4. Yan L, Chen Y, Chen F, Tao T, Hu Z, Wang J, et al. Effect of Helicobacter pylori Eradication on Gastric Cancer Prevention: Updated Report From a Randomized Controlled Trial With 26.5 Years of Follow-up. Gastroenterology. 2022;163:154-162.
5. GBD 2017 Stomach Cancer Collaborators. The global, regional, and national burden of stomach cancer in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease study 2017. Lancet Gastroenterol Hepatol. 2020;5:42-54

6. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020 Feb;8(2):e180-e190.

7. den Hoed CM, Vila AJ, Holster IL, Perez-Perez GI, Blaser MJ, de Jongste JC, et al. Helicobacter pylori and the birth cohort effect: evidence for stabilized colonization rates in childhood. Helicobacter. 2011;16:405-9.

8. Yan L, Chen Y, Chen F, Tao T, Hu Z, Wang J, et al. Effect of Helicobacter pylori Eradication on Gastric Cancer Prevention: Updated Report From a Randomized Controlled Trial With 26.5 Years of Follow-up. Gastroenterology. 2022;163:154-162.

9. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 2016;4:e609-16.

10. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13:607-15.

11. Plummer M, Franceschi S, Vignat J, Forman D, de Martel C. Global burden of gastric cancer attributable to Helicobacter pylori. Int J Cancer. 2015;136:487-90.

12. Park Y, Ki M. Population Attributable Fraction of Helicobacter pylori Infection-Related Gastric Cancer in Korea: A Meta-Analysis. Cancer Res Treat. 2021;53:744-753.

13. Huang H, Hu XF, Zhao FH, Garland SM, Bhatla N, Qiao YL. Estimation of Cancer Burden Attributable to Infection in Asia. J Epidemiol. 2015;25:626-38.

14. Jiang, J., Chen, Y., Shi, J. *et al.* Population attributable burden of *Helicobacter pylori*-related gastric cancer, coronary heart disease, and ischemic stroke in China. *Eur J Clin Microbiol Infect Dis* 2017; 36:199–212.

15. Ji X, He G, Wang K, Zhang Y, Yin J, Wang K. Estimation of gastric cancer burden attributable to Helicobacter pylori infection in Asia. J Public Health. 2024;45:40-46.

16. Azevedo E Silva G, de Moura L, Curado MP, Gomes Fda S, Otero U, Rezende LF, et al. The Fraction of Cancer Attributable to Ways of Life, Infections, Occupation, and Environmental Agents in Brazil in 2020. PLoS One. 2016;11:e0148761.

17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n 71.

18. https://www.who.int/countries Accessed on 15 March 2024

19. StataCorp (2019) Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX.

20. Levin ML: The occurrence of lung cancer in man. *Acta Unio Int Contra Cancrum* 1953;9:531–541.

21. Helicobacter and Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001; 49: 347–53.

22. Di Maso M, Bravi F, Polesel J, Negri E, Decarli A, Serraino D et al. Attributable fraction for multiple risk factors: Methods, interpretations, and examples. Stat Methods Med Res. 2020;29:854-865.

23. Aguemon BD, Struelens MJ, Massougbodji A, Ouendo EM. Prevalence and risk-factors for Helicobacter pylori infection in urban and rural Beninese populations. Clin Microbiol Infect. 2005.

24. Dube C, Nkosi TC, Clarke AM, Mkwetshana N, Green E, Ndip RN. Helicobacter pylori antigenemia in an asymptomatic population of Eastern Cape Province, South Africa: public health implications. Rev Environ Health. 2009 Jul-Sep;24(3):249-55. doi: 10.1515/reveh.2009.24.3.249.

25. Santos IS, Minten GC, Valle NC, Tuerlinckx GC, Boccio J, Barrado DA, et al. Helicobacter pylori and anemia: a community-based cross-sectional study among adults in Southern Brazil. Cad Saude Publica. 2009;25:2653-60.

26. Ferreccio C, Rollán A, Harris PR, Serrano C, Gederlini A, Margozzini P, et al. Gastric cancer is related to early Helicobacter pylori infection in a high-prevalence country. Cancer Epidemiol Biomarkers Prev. 2007;16:662-7.

27. Sasaki T, Hirai I, Izurieta R, Kwa BH, Estevez E, Saldana A, et al. Analysis of Helicobacter pylori genotype in stool specimens of asymptomatic people. Laboratory Medicine. 2009;40:412–4.

28. Sasaki T, Hirai I, Yamamoto Y. [Analysis of Helicobacter pylori infection in a healthy Panamanian population]. Kansenshogaku Zasshi. 2009;83:127-32.

29. Weill FX, Margeridon S, Broutet N, Le Hello S, Neyret C, Mégraud F. Seroepidemiology of Helicobacter pylori infection in Guadeloupe. Trans R Soc Trop Med Hyg. 2002 Sep-Oct;96(5):517-9.

30. Cardenas VM, Mena KD, Ortiz M, Karri S, Variyam E, Behravesh CB, et al. Hyperendemic H. pylori and tapeworm infections in a U.S.-Mexico border population. Public Health Rep. 2010;125:441-7.

31. Alavi SM, Adel SMH, Rajabzadeh A. Seroprevalence study of Helicobacter pylori infection among visitors of cardiac patients in Razi hospital in Ahvaz, Iran. Jundishapur Journal of Microbiology. 2010;3:28–31.

32. Farshad S, Japoni A, Alborzi A, Zarenezhad M, Ranjbar R. Changing prevalence of Helicobacter pylori in South of Iran. Iranian Journal of Clinical Infectious Diseases. 2010;5(2):65–9.

33. Jafarzadeh A, Salari M. Seroprevalence of anti–Helicobacter pylori and anti–CagA antibodies in peptic ulcer and healthy subjects in the city of Rafsanjan. Journal of Research in Medical Sciences. 2006;11:285–91.

34. Jafarzadeh A, Rezayati MT, Nemati M. Specific serum immunoglobulin G to H pylori and CagA in healthy children and adults (south-east of Iran). World J Gastroenterol. 2007 Jun 14;13(22):3117-21.

35. Nouraie M, Latifi-Navid S, Rezvan H, Radmard AR, Maghsudlu M, Zaer-Rezaii H, et al.. Childhood hygienic practice and family education status determine the prevalence of Helicobacter pylori infection in Iran. Helicobacter. 2009;14:40-6.

36. Mansour KB, Keita A, Zribi M, Masmoudi A, Zarrouk S, Labbene M, et al.

Seroprevalence of Helicobacter pylori among Tunisian blood donors (outpatients), symptomatic patients and control subjects. Gastroenterol Clin Biol. 2010;34:75-82.

37. Katsanos KH, Tatsioni A, Tsakiris V, Christodoulou D, Tsianos EV. Helicobacter pylori is a major public health priority in western Balkans: An endoscopy referral center experience. European Journal of Internal Medicine. 2010;21:306–9.
38. Bures J, Kopacova M, Koupil I, Vorisek V, Rejchrt S, Beranek M, et al. Epidemiology of Helicobacter pylori infection in the Czech Republic. Helicobacter. 2006;11:56–65.
39. Kornerup LS, Jepsen P, Bartels LE, Dahlerup JF, Vilstrup H. Lower Incidence of Hepatobiliary Cancer in *Helicobacter pylori*-Infected Persons: A Cohort Study of 53.633 Persons. J Clin Exp Hepatol. 2022;12:793-799.
40. Holleczek B, Schöttker B, Brenner H. Helicobacter pylori infection, chronic atrophic gastritis and risk of stomach and esophagus cancer: Results from the prospective population-based ESTHER cohort study. Int J Cancer. 2020;146:2773-2783.
41. Loffeld RJLF, Van Der Putten ABMM. Changes in prevalence of Helicobacter pylori infection in two groups of patients undergoing endoscopy and living in the same region in The Netherlands. Scandinavian Journal of Gastroenterology. 2003;38:938–41.
42. van Blankenstein M, van Vuuren AJ, Looman CW, Ouwendijk M, Kuipers EJ. The prevalence of Helicobacter pylori infection in the Netherlands. Scandinavian Journal of Gastroenterology. 2013;48:794–800.
43. Asfeldt AM, Straume B, Steigen SE, Lochen ML, Florholmen J, Bernersen B, et al. Changes in the prevalence of dyspepsia and Helicobacter pylori infection after 17 years: The Sorreisa gastrointestinal disorder study. European Journal of Epidemiology. 2008;23:625–33.
44. Breckan RK, Paulssen EJ, Asfeldt AM, Mortensen L, Straume B, Florholmen J. The impact of body mass index and Helicobacter pylori infection on gastro–oesophageal reflux symptoms: A population–based study in Northern Norway. Scandinavian Journal of Gastroenterology. 2009;44:1060–6
45. Celinski K, Kurzeja–Miroslaw A, Slomka M, Cichoz–Lach H, Madro A, Kasztelan–Szczerbinska B. The effects of environmental factors on the prevalence of Helicobacter pylori infection in inhabitants of Lublin province. Annals of Agricultural and Environmental Medicine. 2006;13:185–91.
46. Baena Diez JM, Garcia Lareo M, Marti Fernandez J, Leon Marin I, Muniz Llama D, Teruel Gila J, et al. [Prevalence of Helicobacter pylori infection in primary care: sero–epidemiological study]. Atencion Primaria. 2002;29:553–7.
47. Sanchez Ceballos F, Taxonera Samso C, Garcia Alonso C, Alba Lopez C, Sainz de Los Terreros Soler L, Diaz–Rubio M. [Prevalence of Helicobacter pylori infection in the healthy population of Madrid (Spain)]. Revista Espanola de Enfermedades Digestivas. 2007;99(9):497–501.
48. Cardenas VM, Mulla ZD, Ortiz M, Graham DY. Iron deficiency and Helicobacter pylori infection in the United States. American Journal of Epidemiology. 2006;163(2):127–34.
49. Ang TL, Fock KM, Dhamodaran S, Teo EK, Tan J. Racial differences in Helicobacter pylori, serum pepsinogen and gastric cancer incidence in an urban Asian population. Journal of Gastroenterology and Hepatology. 2005;20(10):1603–9.
50. Moujaber T, MacIntyre CR, Backhouse J, Gidding H, Quinn H, Gilbert GL. The seroepidemiology of Helicobacter pylori infection in Australia. International Journal of

Infectious Diseases. 2008;12:500–4.

51. Windsor HM, Abioye–Kuteyi EA, Leber JM, Morrow SD, Bulsara MK, Marshall BJ. Prevalence of Helicobacter pylori in Indigenous Western Australians: Comparison between urban and remote rural populations. Medical Journal of Australia. 2005;182:210–3.
52. Chen J, Bu XL, Wang QY, Hu PJ, Chen MH. Decreasing seroprevalence of Helicobacter pylori infection during 1993–2003 in Guangzhou, southern China. Helicobacter. 2007;12:164–9.
53. Cheng H, Hu F, Zhang L, Yang G, Ma J, Hu J, et al. Prevalence of helicobacter pylori infection and identification of risk factors in rural and Urban Beijing, China. Helicobacter. 2009;14:128–33.
54. Shi R, Xu S, Zhang H, Ding Y, Sun G, Huang X, et al. Prevalence and risk factors for helicobacter pylori infection in chinese populations. Helicobacter. 2008;13:157–65.
55. Zhang DH, Zhou LY, Lin SR, Ding SG, Huang YH, Gu F, et al. Recent changes in the prevalence of Helicobacter pylori infection among children and adults in high– or low–incidence regions of gastric cancer in China. Chinese Medical Journal. 2009;122:1759–63.
56. Fujimoto Y, Furusyo N, Toyoda K, Takeoka H, Sawayama Y, Hayashi J. Intrafamilial transmission of Helicobacter pylori among the population of endemic areas in Japan. Helicobacter. 2007;12:170–6.
57. Hirai I, Sasaki T, Kimoto A, Fujimoto S, Moriyama T, Yamamoto Y. Assessment of East Asian–type cagA–positive Helicobacter pylori using stool specimens from asymptomatic healthy Japanese individuals. Journal of Medical Microbiology. 2009;58:1149–53.
58. Kim N, Lee SW, Cho SI, Park CG, Yang CH, Kim HS, et al. The prevalence of and risk factors for erosive oesophagitis and non–erosive reflux disease: A nationwide multicentre prospective study in Korea. Alimentary Pharmacology and Therapeutics. 2008;27:173–85.
59. Sung KC, Rhee EJ, Ryu SH, Beck SH. Prevalence of Helicobacter pylori infection and its association with cardiovascular risk factors in Korean adults. International Journal of Cardiology. 2005;102:411–7.
60. Yim JY, Kim N, Choi SH, Kim YS, Cho KR, Kim SS, et al. Seroprevalence of Helicobacter pylori in South Korea. Helicobacter. 2007;12:333–40.
61. Sasidharan S, Uyub AM. Prevalence of Helicobacter pylori infection among asymptomatic healthy blood donors in Northern Peninsular Malaysia. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2009;103:395–8.
62. Lin YL, Chiang JK, Lin SM, Tseng CE. Helicobacter pylori infection concomitant with metabolic syndrome further increase risk of colorectal adenomas. World Journal of Gastroenterology. 2010;16:3841–6.
63. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology. 2017;153:420-429.
64. Han Z, Liu J, Zhang W, Kong Q, Wan M, Lin M, et al. Cardia and non-cardia gastric cancer risk associated with Helicobacter pylori in East Asia and the West: A systematic review, meta-analysis, and estimation of population attributable fraction. Helicobacter. 2023;28:e12950.

65. Yang L, Kartsonaki C, Yao P, de Martel C, Plummer M, Chapman D, et al. The relative and attributable risks of cardia and non-cardia gastric cancer associated with Helicobacter pylori infection in China: a case-cohort study. Lancet Public Health. 2021;6:e888-e896.

66. Parkin, Donald Maxwell; Hämmerl, Lucia; Ferlay, Jacques; Kantelhardt, Eva Johanna . (2019). *Cancer in Africa 2018: the role of infections. International Journal of Cancer, ().*

67. Shield KD, Marant Micallef C, de Martel C, Heard I, Megraud F, Plummer M, et al. New cancer cases in France in 2015 attributable to infectious agents: a systematic review and meta-analysis. Eur J Epidemiol. 2018;33:263-274.

68. Collatuzzo G, La Vecchia C, Parazzini F, Alicandro G, Turati F, Di Maso M, et al. Cancers attributable to infectious agents in Italy. Eur J Cancer. 2023;183:

69. Lin Y, Zheng Y, Wang HL, Wu J. Global Patterns and Trends in Gastric Cancer Incidence Rates (1988-2012) and Predictions to 2030. Gastroenterology. 2021;161:116-127.

70. Camargo MC, Freedman ND, Hollenbeck AR, Abnet CC, Rabkin CS. Height, weight, and body mass index associations with gastric cancer subsites. *Gastric Cancer*. 2014; **17**: 463-468.

71. Taylor CS, McMahon MV, Ward ZJ, Alarid-Escudero F, Camargo MC, Laszkowska M, Roa J, Yeh JM. Birth cohort and age-specific trends in global *Helicobacter pylori* seroprevalence: a scoping review. Lancet Reg Health Am. 2024 Aug 29;41:100877.

72. Yan L, Chen Y, Chen F, Tao T, Hu Z, Wang J, et al. Effect of Helicobacter pylori Eradication on Gastric Cancer Prevention: Updated Report From a Randomized Controlled Trial With 26.5 Years of Follow-up. Gastroenterology. 2022;163:154-162.

73. Kowada A. A Population-Based Helicobacter pylori Eradication Strategy Is More Cost-Effective than Endoscopic Screening. Dig Dis Sci. 2023

74. Kim YI, Choi IJ. Current Evidence for a Paradigm Shift in Gastric Cancer Prevention From Endoscopic Screening to *Helicobacter pylori* Eradication in Korea. J Gastric Cancer. 2022;22:169-183.

75. Leja M. Where are we with gastric cancer screening in Europe in 2024? Gut. 2024;73:2074-2082.

76. European Commission Directorate-General for Health and Food Safety Council recommendation on strengthening prevention through early detection: a new EU approach on cancer screening replacing council recommendation 2003/878/ec. 2022

77. Collatuzzo G, Boffetta P. Cancers Attributable to Modifiable Risk Factors: A Road Map for Prevention. Annu Rev Public Health. 2023;44:279-300.

78. Gu J, Chen R, Wang SM, Li M, Fan Z, Li X, et al. Prediction Models for Gastric Cancer Risk in the General Population: A Systematic Review. Cancer Prev Res. 2022;15:309-318.

79. Huang RJ, Laszkowska M, In H, Hwang JH, Epplein M. Controlling Gastric Cancer in a World of Heterogeneous Risk. Gastroenterology. 2023;164:736-751.

Table 1. Pooled prevalence of *H. pylori* in the general population in 27 countries and 7 geographic regions in the period 2000-2010.

WHO Regions/Countries	Studies (n)	Pooled prevalence of *H. pylori* (%)	95% Confidence Intervals (%)
Overall	40	52	45-60
Africa	**2**	**92**	**90-94**
Benin	1	86.2	81-91
South Africa	1	95	91-97
North America	**1**	**27**	**26-28**
USA	1	27.1	26.1- 28.1
Latin America	**6**	**61**	**50-71**
Brazil	1	70.7	67.9- 73.6
Chile	1	74.6	72.9- 76.2
Ecuador	1	72.2	63.0- 81.5
Guadeloupe (France)	1	53.7	51.7- 58.8
Mexico	1	38.1	31.7- 44.6
Panama	1	54.1	42.7- 65.4
South-East Asia	**1**	**44**	**37-51**
Thailand	3	43.6	36.5- 50.8
Europe	**12**	**43**	**34-52**
Albania	1	53.5	43.7- 63.2
Czech Republic	1	41.7	39.8-43.6
Denmark	1	19.7	19-20
Germany	1	47	46-48
Greece	1	33.7	24.5-42.9
Norway	2	26	24-27
Poland	1	68.7	65-72.5
Spain	2	61	58-65

The Netherlands	2	38	37-39
East Mediterranean region	**6**	**62**	**54-71**
Iran	5	62	51-72
Tunisia	1	63.2	57.2- 69.2
Western Pacific region	**14**	**49**	**38-61**
Australia	2	29	27-30
China	5	52	44-59
Japan	2	55	53-56
Korea	3	64	55-72
Malaysia	1	14.2	13.2-15.1
Taiwan	1	39.2	38.3-40.2

Table 2. Attributable fraction of gastric cancer due to *Helicobacter pylori* infection in 27 countries and 7 geographic regions in 2022.

Regions and countries	**Attributable fraction**	**95% Confidence Interval**
Overall	**69.7**	**67.8-71.0**
African region	**81.8**	**81.5-82.1**
Benin	80.8	79.9-81.5
South Africa	82.3	81.7-82.6
North America	**57.0**	**56.0-57.8**
USA	57.0	56.0-57.8
Latin America	**74.9**	**71.0-77.7**
Brazil	77.7	76.9-78.2
Chile	78.6	78.2-78.8
Ecuador	77.9	75.2-79.7
Guadeloupe (France)	72.6	71.0-73.6
Mexico	65.1	61.8-68.3
Panama	72.6	67.8-76.1
South-East Asian Region	68.3	65.0-71.4
Thailand	68,3	64.5-71.8
European Region	**67.8**	**62.5-71.8**
Albania	72.2	68,.3-75.5
Czech Republic	67.3	66.2-68.3
Denmark	49.5	48.2-49.5
Germany	69.7	69.3-70.2
Greece	62.5	55.1-67.8
Norway	56.0	54.0-57.0
Poland	77.2	76.1-77.9
Spain	74.9	74.0-76.1
The Netherlands	65.1	64.4-76.1
Eastern Mediterranean Region	**75.2**	**72.6-77.9**
Iran	75.2	71.4-77.9

Tunisia	75.5	73.6-77.2
Western Pacific Region	70.6	65.1-74.9
Australia	58.7	57.0-59.5
China	71.8	68.3-74.3
Japan	72.9	72.2-73.3
Korea	75.8	72.9-77.9
Malaysia	40.7	38.9-42.4
Taiwan	65.6	65.0-66.2

RR used for AF calculations: 5.9 [based on (21)]

Table 3. Number of new gastric cancer cases attributable to *Helicobacter pylori* infection in 26 countries and 7 geographic regions in 2022.

WHO Region/Country	**Number of new cases of gastric cancer***			**Number of new cases of gastric cancer attributable to *Helicobacter pylori***		
	Total	Males	Females	Total	Males	Females
Africa						
Benin	378	254	124	305	205	100
South Africa	1784	1080	704	1468	889	579
North America						
USA	24668	14976	9692	14060	8536	5524
Latin America						
Brazil	22300	14402	7898	17327	11190	6135
Chile	4902	3327	1575	3853	2615	1238
Ecuador	2586	1513	1073	2015	1179	836
Guadeloupe (France)	124	70	54	90	51	39
Mexico	9001	4784	4217	5860	3114	2745
Panama	472	291	181	342	211	131
South-East Asia						
Thailand	3907	2147	1760	2669	1467	1202
Europe						
Albania	701	460	241	506	332	174
Czech Republic	1228	730	498	826	491	335
Denmark	725	473	252	359	234	125
Germany	13917	8263	5654	9703	5761	3942
Greece	1857	1168	689	1161	730	431
Norway	512	339	173	287	190	97
Poland	6874	4431	2443	5305	3420	1885
Spain	7084	4224	2860	5308	3165	2143
The Netherlands	1814	1088	726	1180	708	472
East Mediterranean Region						
Iran	16895	10671	6224	12711	8028	4683
Tunisia	508	312	196	384	236	148
Western Pacific Region						
Australia	2776	1718	1058	1629	1008	621
China	352084	243507	108577	252850	174875	77975
Japan	126366	83816	42550	92166	61132	31034
Korea	28823	19511	9312	21855	14794	7061
Malaysia	1431	969	462	582	394	188

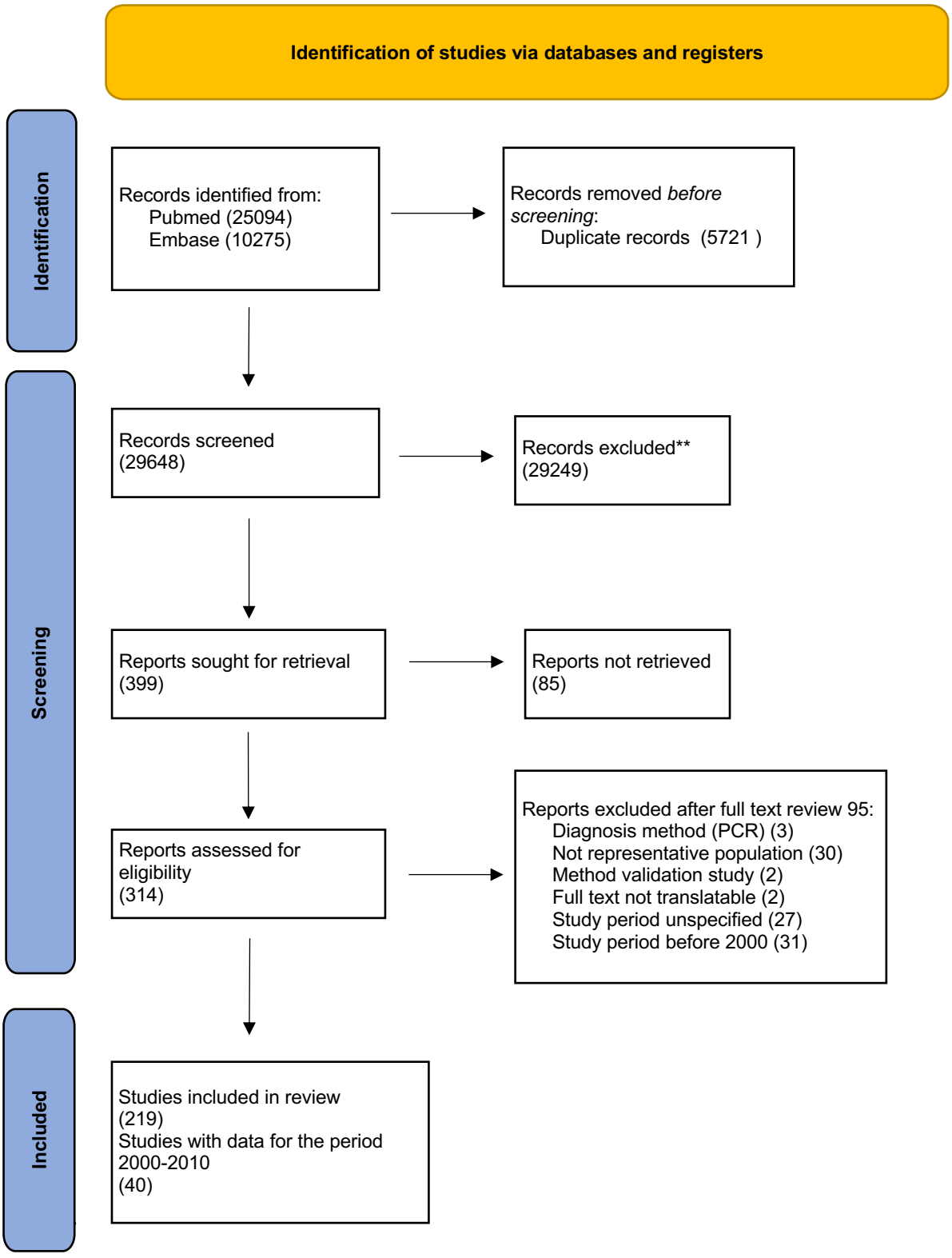
*Data derived by GLOBOCAN 2022 (1).

Table 4. Number of gastric cancer deaths attributable to *Helicobacter pylori* infection in 26 countries and 7 geographic regions in 2022.

WHO Region/Country	**Number of deaths for gastric cancer***			**Number of deaths for gastric cancer attributable to *Helicobacter pylori***		
	Total	Males	Females	Total	Males	Females
Africa						
Benin	324	217	107	261	175	86
South Africa	1548	859	689	1274	707	567
North America						
USA	10650	6451	4199	9747	6070	3677
Latin America						
Brazil	17569	11335	6234	13646	8804	4842
Chile	3876	2620	1256	3047	2060	987
Ecuador	2104	1223	881	1639	953	686
Guadeloupe (France)	96	59	37	70	43	27
Mexico	6819	3619	3200	4437	2355	2082
Panama	355	219	136	258	159	99
South-East Asia						
Thailand	2970	1638	1332	2029	1119	910
Europe						
Albania	555	366	189	401	264	137
Czech Republic	923	547	376	621	368	253
Denmark	465	306	159	231	152	79
Germany	8643	5178	3465	6026	3610	2416
Greece	1243	788	455	776	492	284
Norway	320	187	133	180	105	75
Poland	5311	3411	1900	4098	2632	1466
Spain	5008	3047	1961	3752	2283	1469
The Netherlands	1172	722	450	763	470	293
East Mediterranean Region						
Iran	13515	8848	4667	10168	6657	3511
Tunisia	439	269	170	331	203	128
Western Pacific Region						
Australia	1309	841	468	769	494	275
China	257141	179964	77177	184666	129241	55425
Japan	43611	27529	16082	31809	20079	11730
Korea	8386	4914	3472	6359	3726	2633
Malaysia	1158	821	337	471	334	137

*Data derived by GLOBOCAN 2022 (1).

Figure 1. Flow chart of the process of selection of the included studies.



Reference	Country	WHO Region	Study period	N subjects	Hp %	Hp N	95% CI	Diagnosis	Age range	Study design	Type of population
Aguemon, B. D. et al. (29)	Benin	Africa	2003-2004	247	86,23	213	70.0-80.9	serology	16-74	prospectic	healthy volunteers
Dube, C. et al. (30)	South Africa	Africa	2008	228	94,7	216	83.3-90.3	stool antigen	25->60	prospectic	healthy volunteers
Santos, I. S. et al. (31)	Brazil	Americas	2006-2007	1001	70,7	708	67.9-73.6	UBT	18-45	prospectic	healthy volunteers
Ferreccio, C. et al. (32)	Chile	Americas	2003	2615	74,6	1951	72.9-76.2	serology	>17	prospectic	healthy volunteers
Sasaki, T et al. (33)	Ecuador	Americas	2007	90	72,2	65	63.0-81.5	stool antigen	21-82	prospectic	healthy volunteers
Weill, F. X. et al. (35)	Guadeloupe	Americas	2000	854	53,7	459	51.7-58,8	serology	18-70	prospectic	healthy volunteers
Cardenas, V. M. et al. (36)	Mexico	Americas	2004	288	38,1	110	31,7-44,6	stool antigen	>0	prospectic	healthy volunteers
Sasaki T. et al. (34)	Panama	Americas	2007	74	54,1	40	42.7-65.4	stool antigen	21-82	prospectic	healthy volunteers
Alavi, S. M. et al. (37)	Iran	Eastern Mediterranean Region	2004-2005	96	57,3	55	47.4-67.2	serology	<30->60	prospectic	patients' visitors
Farshad, S. et al. (38)	Iran	Eastern Mediterranean Region	2005-2007	226	41,6	94	35.2-48.0	CLO	18-83	prospectic	Patients referring to the endoscopy room

Jafarzadeh, A. et al. (39)	Iran	Eastern Mediterranean Region	2004	138	73,2	101	65.8-80.6	serology	17-60	prospectic	healthy volunteers
Jafarzadeh, A. et al. (40)	Iran	Eastern Mediterranean Region	2005	200	67,5	135	61.0-74.0	serology	20-60	prospectic	healthy volunteers
Nouraie, M. et al. (41)	Iran	Eastern Mediterranean Region	2005	2326	69	1605	67.1-70.9	serology	18-65	prospectic	healthy volunteers
Mansour, K. B. et al. (42)	Tunisia	Eastern Mediterranean Region	2006-2007	250	63,2	158	57.2-69.2	serology	25-55	prospectic	healthy volunteers
Katsanos, K. H. et al. (43)	Albania	European Region	2005-2008	101	53,5	54	43.7-63.2	histology	<20→50	retrospective	patients referring to the endoscopy room
Bures, J et al. (44)	Czech Republic	European Region	2001	2509	41,7	1046	39.8 -43.6	UBT	5-100	prospectic	healthy volunteers
Kornerup L.S. et al. (45)	Denmark	European Region	2002 - 2012	53633	19,7	10552		UBT	>18	retrospective	patients undergoing UBT
Holleczek B. et al. (46)	Germany	European Region	2000-2002	9940	48	4708		serology	62,2 mediana	prospectic	volunteers
Katsanos, K. H. et al. (43)	Greece	European Region	2005-2008	101	33,7	34	24.5-42.9	histology	<20→50	retrospective	pazienti che accedono a endoscopia
Loffeld L. J. R. F. et al. (47)	Netherland	European Region	1993-2002	8190	39,04	3201		histology	tutte età	Retrospective	pazienti sottoposti a endoscopia

Van Blankestein M. et al. (48)	Netherland	European Region	2005	1551	31,7	491		serology	17-80	Retrospectiveo	donatori di sangue
Asfeldt, A. M. et al. (49)	Norway	European Region	2004	916	38	348	34.9-41.1	histology	18-85	prospectic	volontari sani (ma 30% dispepsia)
Breckan, R. K et al. (50)	Norway	European Region	2004-2005	1736	21,2	368	19.3-23.1	stool antigen	18-85	prospectic	healthy volunteers
Celinski, K et al. (51)	Poland	European Region	2000-2003	585	68,7	402	65.0-72. 5	serology	19-89	prospectic	healthy volunteers
Baena Diez, J. M. et al. (52)	Spain	European Region	1999-2001	208	63,9	133	46.4-58.4	serology	>20	prospectic	healthy volunteers
Sanchez Ceballos F. et al. (53)	Spain	European Region	2004-2006	481	60,3	290	55.9-64.7	UBT	apr-82	prospectic	healthy volunteers
Cardenas, V. M. et al. (54)	USA	North America	1999–2000	7462	27,1	2022	26.1-28.1	serology		retrospective	healthy volunteers
Ang, T. L et al. (55)	Thailand	South-East Asian Region	2007–2008	179	43,6	78	36.3-50.8	stool antigen	40-80	prospectic	healthy volunteers
Moujaber, T et al. (56)	Australia	Western Pacific Region	2002	1811	17,94	325	13.7-16.6	serology	>15	retrospective	healthy volunteers
Windsor, H. M. et al. (57)	Australia	Western Pacific Region	2003-2004	520	76	395	72.3-79.6	UBT	feb-90	prospectic	healthy volunteers
Chen, J et al. (58)	China	Western Pacific Region	2003	1006	56,16	565	44.5 -49.6	serology	20-92	prospectic	healthy volunteers

Cheng, H. et al. (59)	China	Western Pacific Region	2003	1232	46,8	577	44 .0-49.5	UBT	feb-79	prospectic	healthy volunteers
Shi, R. et al. (60)	China	Western Pacific Region	2004 –2005	1371	62,1	851	59.5-64.6	serology, UBT	5-100	prospectic	healthy volunteers
Zhang, D. H et al. (61)	China	Western Pacific Region	2006	503	41,4	208	37.1-45.7	stool antigen	40-79	prospectic	healthy volunteers
Zhang, D. H et al. (61)	China	Western Pacific Region	2006	526	51	268	46.7-55.2	histology	40 -79	prospectic	healthy volunteers
Fujimoto, Y et al. (62)	Japan	Western Pacific Region	2002	3819	55,4	2116	46.2-58.9	serology	17-84	prospectic	healthy volunteers
Hirai, I et al. (63)	Japan	Western Pacific Region	2007	186	40,3	75	33.3-47.4	stool antigen	40 -63	prospectic	healthy volunteers
Kim, N. et al. (64)	Korea	Western Pacific Region	2006	20154	60,4	12173	59.7-61.1	serology, CLO , histology	16 ->70	prospectic	healthy volunteers
Sung.K.C et al. (65)	Korea	Western Pacific Region	2001 –2002	58981	70,9	41818	70.5-71.3	serology	<30/>60	retrospctive	healthy volunteers
Yim, J. Y. et al. (66)	Korea	Western Pacific Region	2005	8020	59,6	4780	58.5-60. 7	serology	≥ 20	prospectic	healthy volunteers
Sasidharan, S. et al. (67)	Malaysia	Western Pacific Region	2000-2002	5370	14,2	763	13.2-15.1	serology		prospectic	healthy volunteers
Lin, Y. L. et al. (68)	Taiwan	Western Pacific Region	2004 –2006	9311	39,2	3650	38.3-40.2	CLO	>40	prospectic	healthy volunteers

Supplementary table 1.

N, number; Hp, Helicobacter pylori; CI, confidence interval; UBT, urea breath test; CLO, Campylobacter-like organism test

A Letter to the Editor was published (Collatuzzo G, Camargo MC, Malvezzi M, Dajti E, Secco M, Boffetta P, Zagari RM. Gastric cancer attributable to *Helicobacter pylori* in 2040. Gut. 2026 Jan 28:gutjnl-2025-337499.) based on the data presented in the following study.

2.4 Gastric cancer attributable to *Helicobacter pylori* in 2040

Running title: *Helicobacter pylori*-related gastric cancer in 2040

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ABSTRACT

Background: We aimed at estimating *H. pylori*-related GC burden for 2040.

Methods: The attributable fraction (AF) in all countries with available data was estimated using region- and country-specific prevalence of *H. pylori* infection in adults derived from public literature and a relative risk of 5.9 for *H. pylori*-GC association. The number of new GC cases and deaths for GC attributable to *H. pylori* was calculated using the AF and the projected GC incidence and mortality reported by GLOBOCAN for 2040. A secondary analysis was conducted on selected countries using an alternative approach which considers recent trends in mortality.

Results: The AF ranged from 66.0% in European region to 72-0% in African and East Mediterranean region. Western Pacific region had the highest number of *H.pylori*-related GC in 2040, with >550,000 cases and >350,000 deaths, followed by Europe, with >130,000 cases and about 100,000 deaths. Countries with the highest projected numbers of GC cases attributable to *H. pylori* were China (249,450 in men and 119,192 in women), Japan (57,827 in men and 29,506 in women), India (50,985 in men and 23,968 in women), Russia (20,561 in men and 15,579 in women), Iran (16,516 in men and 10,648 in women) and Brazil (15,484 in men and 8,448 in women). The secondary analysis was conducted on 20 countries and produced lower estimated deaths (e.g., -75.2% for men in Korea, -81.8% for women in Japan).

Conclusions: The future fraction of GC attributable to *H. pylori* infection remained remarkably high, although recent trend will likely result in an attenuation in the number of attributable cases and death. *H. pylori* screen and treat strategies remain a priority for GC primary prevention in the foreseeable future.

INTRODUCTION

Gastric cancer (GC) is undergoing a major epidemiological change, with declining trends in most countries worldwide (1-3). In 2022, GC was the cancer with the 5th highest estimated incidence (age standardized rates – ASR 9.2 per 100,000), with highest figure in Asia (11 per 100,000) (4).

The primary driver of GC declining trend is the progressive reduction in *Helicobacter (H.) pylori* infection prevalence (1,5,6). This reduction is mainly attributed to improvement of quality life, and hygienic conditions (6,7). Changes in *H. pylori* and GC epidemiology vary between high-income countries (HICs) and low-middle income countries (LMICs), despite consistent declining trends (6). Moreover, *H. pylori* rates underwent the major decline in different periods worldwide (6), with Japan, South Korea, and China being the first countries to implement GC prevention strategies (8-10). Nevertheless, absolute numbers of GC cases at a global scale are remarkable and expected to increase (1, 11-13) due to population growth and aging (11-13).

H. pylori screening and eradication have been demonstrated to be cost-effective in controlling GC (14). To better understand the potential benefit of population-based prevention strategies, predictions on GC incident cases and deaths and estimates of *H. pylori*-related fraction are needed (6,12). Predicted GC incidence and mortality have been estimated for selected countries, e.g., China and other East Asian countries (15,16), whereas other studies provided data at a broader geographic scale (1,12). The GLOBOCAN dataset also provides, through standardized methods, predictions of GC incidence and mortality up to 2040 (4).

The attributable fraction (AF) represents an epidemiological measure of the proportional reduction in disease burden which could have been avoided if the exposure to a risk factor were reduced to a target level, potentially zero for completely avoidable risk factors (17, 18). Numbers of attributable cases or deaths can be derived from the AF.

We aimed at estimating the predicted AF of GC for *H. pylori* infection worldwide, and to calculate the country-specific number of GC cases and deaths attributable to *H. pylori* infection in 2040.

METHODS

The AF of GC for *H. pylori* infection was calculated applying the formula originally described by Levin (18): AF = *p* (RR-1) / (1+ *p* (RR-1)) where p is the prevalence of infection in the general population and relative risk (RR) is the relative risk of GC associated with *H. pylori* infection.

The RR for the association between *H. pylori* infection and GC was assumed to be constant worldwide, and so we used a single RR estimate in the calculation of each AF. Considering that non-cardia GC represents most of the GC cases worldwide (80-90%), we used the RR of 5.9, that was calculated through a meta-analysis of cohort studies (19). We applied the same RR to calculate AF for incidence and mortality and for men and women, assuming no effect of infection on cancer survival and no infection–sex interaction (20).

Country-specific prevalence of *H.pylori* infection derived from a recently published systematic review and meta-analysis by Chen and coauthors (21). In particular, we retrieved data for adult population for period 2010-2022 or before (21). This allowed us to estimate the AF prospectively**,** and to consider >=18 yearslatency between infection and GC (22).

The number of new GC cases and deaths for GC attributable to *H. pylori* was calculated by multiplying the AF by the number of new GC cases and deaths from GC estimated to occur in 2040 according to the GLOBOCAN project (4). In particular, GLOBOCAN data were restricted to age 40+, therefore considering population at higher risk of GC (4).

We calculated AF and number of new GC cases and deaths from GC attributable to *H. pylori* for those countries for which *H.pylori* prevalence data were available as according to Chen et al. (21).

In a secondary analysis restricted to 20 countries with usable mortality data from the WHO Mortality Database (22), we first fitted a log Poisson joinpoint regression model

to the observed number of deaths in each 5-year age group, and we then estimated the age-specific number of deaths for 2040 by fitting a linear regression model to the mortality figures for each age group over the most recent trend segment identified by the joinpoint model (23). We then calculated age-specific and age-standardized death rates using the estimated age-specific number of deaths and the projected population from the UN database for the year 2040 (24).

To calculate the % difference between absolute numbers of attributable deaths obtained with this secondary analysis (J_N) and those obtained based on GLOBOCAN data (GLOBOCAN_N), we used the formula [(GLOBOCAN_N – J_N)/GLOBOCAN_N]*100.

RESULTS

We calculated the AF of GC for *H. pylori* for different WHO regions (Table 1) and countries (Table 2). Regional AF were overall homogeneous, ranging between 66.0% in Europe and 72.3% in Africa. The AF varied by country, from 31.0% in Finland and New Zealand to 81.3% in Jordan.

Using our estimates of AF and the projected number of GC cases and deaths estimated by GLOBOCAN (23), we calculated the country-specific number of new GC cases and deaths for GC attributable to *H. pylori* in 2040 in men and women (Table 2). Countries with the highest projected number of GC cases attributable to *H. pylori* included China (249,450 and 119,192 in men and women respectively), Japan (57,827 and 29,506 in men and women respectively), India (50,985 and 23,968 in men and women respectively), Russia (20,561 and 15,579 in men and women respectively) and Brazil (15,484 and 8,448 in men and women respectively). Countries of African region had the lowest estimated GC cases attributable to *H.pylori* in 2040, with Algeria, Ethiopia and Kenya reaching >1,000 attributable cases in both sexes. When considering East Mediterranean Region, the highest number of projected cases attributable to *H. pylori* was estimated in Iran (16,516 in men and 10,648 in women), followed by Pakistan (3,132 and 2,634 respectively). Among the countries of the region of the Americas, United States (9,333 and 5,867 cases in men and women respectively), Colombia (7,342 and 4,673) and Mexico (6,405 and 5,739) had the highest estimated attributable cases after

Brazil. As for Europe, after Russia, the highest numbers were calculated for Italy (5,862 and 4,128), Germany (5,371 and 3,732), Poland (4,376 and 2,271) and Spain (4,126 and 2,677)

After India, Bangladesh (6,898 and 3,440) and Myanmar (4,450 and 2,858) were the countries with the highest estimated number of GC case in 2040. The number of *H.pylori*-related GC largely varied across countries of Western Pacific region, where some of the highest (China, Japan) and lowest (Brunei, New Zealand) global numbers were estimated.

The secondary analysis based on the joinpoint regression modeling was feasible in 20 countries: Brazil, Canada, Chile, Colombia, Mexico, United States (US), Venezuela, France, Germany, Israel, Italy, Poland, Russia, Spain, United Kingdom, Australia, Japan, and South Korea (Table 3). Compared to the primary analysis, this approach yielded lower absolute numbers of GC deaths predicted for 2040, and therefore a lower GC burden attributable to *H. pylori*. Such differences were particularly strong for South Korea (-75.2% for men and -71.6% for women), United Kingdom (-64.2% for men and -66.0% for women), women in Japan (-81.8%), Germany (-64.5%) and France (-62.4%).

DISCUSSION

We estimated the burden of GC attributable to *H. pylori* infection in different WHO regions and countries worldwide for the year 2040. We adopted recent country-specific pooled prevalence of *H. pylori* in the general adult populations for updated meta-analyses (Chen). The country-specific AF of GC for *H. pylori* infection was estimated and used to calculate the number of new GC cases and deaths for GC which could be attributable to *H. pylori* based on total number of cases and deaths from GLOBOCAN (4). Moreover, we computed a comparative joinpoint regression analysis for 20 selected countries with available data and observed lower absolute numbers of GC deaths attributable to *H. pylori* expected in 2040.

To our knowledge, no comprehensive estimates, based on standardized methodological approach and homogeneous data sources, have been produced to date

as regard to *H. pylori*-related GC in the future. Therefore, our results are only partially comparable to available literature (1,12,16, 25, 26). For example, Arnold et al. provided prediction of GC incidence by 2035 for 34 countries, without considering country-specific *H. pylori* prevalence data (1). Based on GLOBOCAN data, Park and colleagues estimated 15.6 millions new GC cases would occur in the lifetime (up to age 84 years) of individuals born between 2008 and 2017; the authors considered global changes in the population structure, but assumed no change in *H.pylori* prevalence (25).

Our analysis confirms the relevance of *H. pylori* in worldwide morbidity and mortality, projecting the role of this infection in 2040 in many countries from different geographic areas. *H. pylori* is responsible for 30-80% of GC, therefore represents in all countries a major cause of cancer despite its variable prevalence. A previous study found that the average AF of GC for *H. pylori* was 69.7% in 2022 (27). This estimate is only slightly lower than those previously reported in 2008 (77.3%) (28) and in 2012 (79.3%) (29) and that provided by Park et al (76.0%) (25). According to our estimates, among countries with the largest AF of *H. pylori*-related GC there were several classified as High Sociodemographic Index (SDI) (Ecuador, Costa Rica, Colombia, Russia, Bahamas, Estonia, Peru, Mexico, Albania, Poland), next to South Korea which recorded the highest AF among the countries with Very High SDI. The relatively low AF of GC for *H. pylori* in Japan, Malaysia and Australia likely reflects the rapidly decreasing prevalence in these countries (26, 30-32).

Besides this, the highest burden of GC for *H. pylori* in terms of absolute number of new cases and deaths was still observed in China and Japan. The third most burdened country was India, followed by Russia and Brazil.

Comparable data for countries of the American continent were provided by Torres-Roman and colleagues (33). Declining GC mortality was observed consistently in different countries between 1997 and 2017, confirmed in the projections for 2030, with some peculiar age pattern in men and women (33). For example, age-standardized mortality rates in Brazil slightly diminished in men but resulted stable in women between 2017 and 2030 (33).

The secondary analysis, which incorporated recent trends in the estimate of future GC deaths, resulted in lower estimates in all 20 countries in which this analysis was feasible. A recent study restricted to China, which adopted a similar methodology, showed a reduction in absolute numbers of GC cases compared with previous decades (32). The predicted number of GC deaths we calculated for 2040 in Japan is close to that provided by the Japanese National Cancer Center for the period 2040-2045 (30,976 GC cases, including 19,600 in men and 11,376 in women) (34), corroborating the reliability of our secondary analysis.

The difference between the primary and the secondary analysis is explained by the fact that the former accounts only for demographic changes in the population, whereas the latter accounts also for recent trends (35). While the latter approach is methodologically superior, it requires reliable data on age-specific trends, which are available for a limited number of populations (35). The difference between the two estimates has been used in other works as a measure of lives saved by progress in cancer prevention, therapy and management (35)

The remarkable numbers of GC cases and deaths in 2040 we predicted may be explained by population aging and, in part, early detection of GC, as previously described (12). Particularly relevant are numbers estimated in the US and in certain European countries: our former study showed a prevalence of infection which is comparable or higher than in areas traditionally considered at high risk (e.g., Latin America or Eastern-Asia). The decrease in the burden of *H. pylori*-related GC in certain Asian countries including Japan, China and South Korea compared to estimates provided for previous years (27) might indicate the beneficial effect of *H. pylori* and GC screening implemented in these countries (26,28, 30, 32, 36, 37). This hypothesis is supported by the fact that the effect of *H. pylori* treatment on GC prevention becomes more evident with time (37).

These findings highlight the importance of primary prevention of GC through *H. pylori* screening and eradication, which are largely lacking to date. Our predictions are in contrast with a non-interventional approach based on the common assumption that, given the progressive decline of *H. pylori* prevalence (38), GC will become a rare disease (1). It would be interesting to predict the reduction of the burden of GC for *H.*

pylori which could be achieved through the implementation of test-and-treat strategy in countries where AF is estimated to remain high in the near future.

We observed a low burden of GC related to *H. pylori* in African countries; while this finding is overall consistent with the "African Enigma", our estimates mainly result from the relatively low prevalence of infection recorded in the included African countries, and might only in part reflect the current prevalence of infection in the continent (39). Recent data suggest that gastric atrophy and GC are not so rare in the African continent as previously described (40-43). In fact, a meta-analysis (44) reported that gastritis was the most frequent finding from upper-GI endoscopy across Africa (33.3%). Studies monitoring *H. pylori* prevalence in Africa are needed to further understand the epidemiology of infection-related diseases in this geographical area and predict with sufficient accuracy the expected morbidity and mortality linked to it.

Epidemiology of GC is changing (6, 12), with increasing cardia/non-cardia ratio especially in non-Asian countries and increasing burden among young individuals (<50 years old) (45-47). Therefore, the collection of GC incidence and mortality data in the young adults, and by anatomical subsite, would be important to further interpret our estimates and to plan tailored intervention for GC control.

The epidemiology of GC is progressively shifting also due to other risk factors which might compete with *H. pylori* infection. This reflects on the changing pathology of GC, with increasing proportion of histological types unrelated to the bacterium. As for SEER-22 data, for example, gastrointestinal stromal tumors (GIST) (48) and neuroendocrine tumors (NET) (49) are increasing. This increase was observed with similar pattern across population strata, suggesting this might be likely due to lifestyle or environmental risk factors rather than to improved diagnostic methodologies (48). Furthermore, recent trends in rates of cancer incidence in the USA indicate GC to have undergone a +4.8% average annual percent change, overcoming any other cancer type, among women between 2018 and 2022 (50).

Our study has several strengths. First, we provided novel, comprehensive data on the burden of GC attributable to *H. pylori* in 2040, covering the seven WHO regions and different countries worldwide. We used country-specific pooled *H.pylori* prevalence,

focused on population-based studies of adult population based on recent meta-analysis (21). Solid standardized methodology was adopted to calculate the AF. In addition, we offered alternative estimates based on original GC mortality predictions for 20 selected countries with available high-quality data.

Limitations should be also considered. First, our estimates depend on availability and quality of retrieved data. *H. pylori* prevalence was lacking in some countries, and for others it might not be representative. This impaired our ability to provide robust estimates for selected countries, as well as globally. Moreover, despite the information were derived from reliable updated source and restricted to studies on adult population in order to prevent underestimation, the fact that *H.pylori* prevalence might include data collected before 2010 and data collected on symptomatic populations might partially deviate the prevalence in general adult population for recent years. Furthermore, we assumed that RR between *H. pylori* and GC was constant in all countries (12); while this is a common statistical approach, it may not correspond to reality, as pathogen- (e.g., bacterial strains) and individual-related factors (e.g., dietary habits, genetics) may play a role in this association (12). On the other hand, this approach allowed us to avoid underestimation of the association and therefore of the AF which could have occurred in studies which adopted pooled RR values obtained from case-control studies rather than cohort studies (12, 14). Also, recent evidence suggests that the RR of non-cardia GC for *H. pylori* infection might be higher than 5.9 (51). For example, Morais et al. calculated a RR of 9.22, which however referred to the association with non-cardia GC in particular (51). Last, the number of *H. pylori*-related GC cases and deaths predicted in 2040 is subject to uncertainty and should be interpreted with caution. Our study shows that ~70% of GC cases and deaths would be avoided in 2040 if *H. pylori* infection were eradicated, demonstrating the impactful potential of *H. pylori* test-and-treat approach in cancer control.

Our findings contribute to answer three key questions of the Taipei Global Consensus: 1) "Is gastric cancer still a public health threat and underestimated in the world?" 2) "Does *H. pylori* infection, the major cause of gastric cancer, remain prevalent in the world?" and 3) "What is the proportion of gastric cancer attributable to *H. pylori* infection?"), representing valuable source of data for Global Guidelines for *H. pylori* screening and treatment (52).

Future studies might predict the impact of primary prevention strategies based on *H. pylori* screening and eradication on GC incidence and mortality in the next decades. To this aim, national registries on *H. pylori* infection prevalence and population-based cancer registries including GC anatomical subsite would add important information.

References

1- Arnold M, Park JY, Camargo MC, Lunet N, Forman D, Soerjomataram I. Is gastric cancer becoming a rare disease? A global assessment of predicted incidence trends to 2035. Gut. 2020 May;69(5):823-829. doi: 10.1136/gutjnl-2019-320234. Epub 2020 Jan 30.

2- Paik DC, Saborio DV, Oropeza R, Freeman HP. The epidemiological enigma of gastric cancer rates in the US: was grandmother's sausage the cause? Int J Epidemiol. 2001 Feb;30(1):181-2. doi: 10.1093/ije/30.1.181.

3- Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024 Jan-Feb;74(1):12-49. doi: 10.3322/caac.21820. Epub 2024 Jan 17.

4- https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf

5- Wong MCS, Huang J, Chan PSF, Choi P, Lao XQ, Chan SM, Teoh A, Liang P. Global Incidence and Mortality of Gastric Cancer, 1980-2018. JAMA Netw Open. 2021 Jul 1;4(7):e2118457.

6- Chen YC, Malfertheiner P, Yu HT, Kuo CL, Chang YY, Meng FT, et al. Global Prevalence of Helicobacter pylori Infection and Incidence of Gastric Cancer Between 1980 and 2022. Gastroenterology. 2024 Apr;166(4):605-619.

7- Collatuzzo G, Boffetta P. Cancers Attributable to Modifiable Risk Factors: A Road Map for Prevention. Annu Rev Public Health. 2023 Apr 3;44:279-300.

8- Hiroi S, Sugano K, Tanaka S, Kawakami K. Impact of health insurance coverage for Helicobacter pylori gastritis on the trends in eradication therapy in Japan: retrospective observational study and simulation study based on real-world data. BMJ Open. 2017 Jul 31;7(7):e015855.

9- Hu Y, Zhu Y, Lu NH. The management of Helicobacter pylori infection and prevention and control of gastric cancer in China. Front Cell Infect Microbiol. 2022 Dec 1;12:1049279.

10- Kim YI, Choi IJ. Current Evidence for a Paradigm Shift in Gastric Cancer Prevention From Endoscopic Screening to Helicobacter pylori Eradication in Korea. J Gastric Cancer. 2022 Jul;22(3):169-183.

11- Leja M. Where are we with gastric cancer screening in Europe in 2024? Gut. 2024 Nov 11;73(12):2074-2082.

12- Morgan E, Arnold M, Camargo MC, Gini A, Kunzmann AT, Matsuda T, et al. The current and future incidence and mortality of gastric cancer in 185 countries, 2020-40: A population-based modelling study. EClinicalMedicine. 2022 Apr 21;47:101404.

13- Lin JL, Lin JX, Lin GT, Huang CM, Zheng CH, Xie JW, Wang JB, Lu J, Chen QY, Li P. Global incidence and mortality trends of gastric cancer and predicted mortality of gastric cancer by 2035. BMC Public Health. 2024 Jul 2;24(1):1763.

14- Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, et al. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. Gut. 2022 Aug 8:gutjnl-2022-327745.

15- Yang H, Zhou S, Wang W, Zhao Y, Qiu Y, Jiang X, et al. The Trends of Gastric Cancer in China From 1990 to 2019 and Predictions to 2040: A Bayesian Age-Period-Cohort Prediction Study. Cancer Control. 2024 Jan-Dec;31:10732748241293982.

16- Zhang T, Zhang Y, Leng X. Trends in gastric cancer burden in the Western Pacific region from 1990 to 2021 and projections to 2040. Front Oncol. 2025 Mar 12;15:1506479.

17- Mansournia MA, Altman DG. Population attributable fraction. BMJ. 2018 Feb 22;360:k757.

18- LEVIN ML. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum. 1953;9(3):531-41. Helicobacter and Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001; 49: 347–53.

19- Di Maso M, Bravi F, Polesel J, Negri E, Decarli A, Serraino D et al. Attributable fraction for multiple risk factors: Methods, interpretations, and examples. Stat Methods Med Res. 2020;29:854-865.

20- Chen YC, Malfertheiner P, Yu HT, Kuo CL, Chang YY, Meng FT, et al. Global Prevalence of Helicobacter pylori Infection and Incidence of Gastric Cancer Between 1980 and 2022. Gastroenterology. 2024 Apr;166(4):605-619

21- WHO Mortality Database - https://www.who.int/data/data-collection-tools/who-mortality-database Accessed on November 2024.

22- Collatuzzo G, Santucci C, Malvezzi M, La Vecchia C, Boffetta P, Negri E. Trends in gastric cancer mortality 1990-2019 in 36 countries worldwide, with predictions to 2025, and incidence, overall and by subtype. Cancer Med. 2023 Apr;12(8):9912-9925.

23- https://data.un.org/ Accessed on November 2024

24- Park JY, Georges D, Alberts CJ, Bray F, Clifford G, Baussano I. Global lifetime estimates of expected and preventable gastric cancers across 185 countries. Nat Med. 2025 Jul 7.

25- Wang C, Nishiyama T, Kikuchi S, Inoue M, Sawada N, Tsugane S, Lin Y. Changing trends in the prevalence of H. pylori infection in Japan (1908-2003): a systematic review and meta-regression analysis of 170,752 individuals. Sci Rep. 2017 Nov 14;7(1):15491.

26- Collatuzzo G et al., submitted to Gastric Cancer

27- de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012 Jun;13(6):607-15.

28- Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 2016 Sep;4(9):e609-16. doi: 10.1016/S2214-109X(16)30143-7. Epub 2016 Jul 25.

29- Leow AH, Lim YY, Liew WC, Goh KL. Time trends in upper gastrointestinal diseases and Helicobacter pylori infection in a multiracial Asian population--a 20-year

experience over three time periods. Aliment Pharmacol Ther. 2016 Apr;43(7):831-7.

30- Congedi J, Williams C, Baldock KL. Epidemiology of Helicobacter pylori in Australia: a scoping review. PeerJ. 2022 May 31;10:e13430.

31- He F, Wang S, Zheng R, Gu J, Zeng H, Sun K, et al. Trends of gastric cancer burdens attributable to risk factors in China from 2000 to 2050. Lancet Reg Health West Pac. 2024 Jan 6;44:101003.

32- Torres-Roman JS, Alvarez CS, Guerra-Canchari P, Valcarcel B, Martinez-Herrera JF, Dávila-Hernández CA, et al. Sex and age differences in mortality trends of gastric cancer among Hispanic/Latino populations in the United States, Latin America, and the Caribbean. Lancet Reg Health Am. 2022 Oct 7;16:100376.

33- National Cancer Center Japan. https://ganjoho.jp/reg_stat/statistics/data/dl/en.html Accessed on July 2025

34- Santucci C, Malvezzi M, Levi F, Camargo MC, Boffetta P, La Vecchia C, Negri E. Cancer mortality predictions for 2023 in Latin America with focus on stomach cancer. Eur J Cancer Prev. 2023 Jul 1;32(4):310-321.

35- Wang Z, Han W, Xue F, Zhao Y, Wu P, Chen Y, Yang C, Gu W, Jiang J. Nationwide gastric cancer prevention in China, 2021-2035: a decision analysis on effect, affordability and cost-effectiveness optimisation. Gut. 2022 Dec;71(12):2391-2400.

36- Kim T, Seo SI, Lee KJ, Park CH, Kim TJ, Kim J, Shin WG. Decreasing Incidence of Gastric Cancer with Increasing Time after Helicobacter pylori Treatment: A Nationwide Population-Based Cohort Study. Antibiotics (Basel). 2022 Aug 3;11(8):1052.

37- *Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev 2014;23:700–13*

38- Taylor CS, McMahon MV, Ward ZJ, Alarid-Escudero F, Camargo MC, Laszkowska M, Roa J, Yeh JM. Birth cohort and age-specific trends in global Helicobacter pylori seroprevalence: a scoping review. Lancet Reg Health Am. 2024 Aug 29;41:100877.

39- Roro GM, Annose RT, Gilja OH. Changing trends in upper gastrointestinal endoscopic findings in Ethiopia: A comparison of eighteen thousand exams across two periods. World J Gastrointest Endosc. 2025 May 16;17(5):106690.

40- Nakaganda A, Spencer A, Mpamani C, Nassolo C, Nambooze S, Wabinga H, et al. Estimating regional and national cancer incidence in Uganda: a retrospective population-based study, 2013-2017. BMC Cancer. 2024 Jul 2;24(1):787.

41- Yibrehu B, Mohammed TO, Murthy S, Aderibigbe AS, Daramola OB, Arije O, et al. Gastric Cancer at a Nigerian Tertiary Referral Center: Experiences With Establishing an Institutional Cancer Registry. J Surg Oncol. 2025 Mar;131(4):630-636.

42- Mazhindu TA, Ndlovu N, Borok M, Nyangwara VA, Chikondowa P, Madeleine MH, et al. Trends in gastrointestinal cancer burden in Zimbabwe: 10-year retrospective study 2009-2018. Ecancermedicalscience. 2025 Feb 6;19:1839.

43- Abdu SM, Assefa EM, Abdu H. Indications and endoscopic findings of upper gastrointestinal diseases in Africa: A systematic review & meta-analysis. PLoS One. 2025 Mar 13;20(3):e0319854.

44- Inoue M. Epidemiology of Gastric Cancer-Changing Trends and Global Disparities. Cancers (Basel). 2024 Aug 24;16(17):2948.

45- Anderson WF, Rabkin CS, Turner N, Fraumeni JF Jr., Rosenberg PS, Camargo MC. The Changing Face of Noncardia Gastric Cancer Incidence Among US Non-Hispanic Whites. J Natl Cancer Inst 2018;110:608–15.

46- Camargo MC, Anderson WF, King JB, Correa P, Thomas CC, Rosenberg PS, et al. Divergent trends for gastric cancer incidence by anatomical subsite in US adults. Gut 2011;60:1644–9

47- Alvarez CS, Piazuelo MB, Fleitas-Kanonnikoff T, Ruhl J, Pérez-Fidalgo JA, Camargo MC. Incidence and Survival Outcomes of Gastrointestinal Stromal Tumors. *JAMA Netw Open*. 2024;7(8):e2428828.

48- Dasari A, Wallace K, Halperin DM, Maxwell J, Kunz P, Singh S, Chasen B, Yao JC. Epidemiology of Neuroendocrine Neoplasms in the US. JAMA Netw Open. 2025 Jun 2;8(6):e2515798.

49- https://seer.cancer.gov/statfacts/html/common.html Accessed July 2025

50- Morais S, Costa A, Albuquerque G, Araújo N, Tsugane S, Hidaka A, et al. "True" Helicobacter pylori infection and non-cardia gastric cancer: A pooled analysis within the Stomach Cancer Pooling (StoP) Project. Helicobacter. 2022 Jun;27(3):e12883.

51- Liou JM, Malfertheiner P, Lee YC, Sheu BS, Sugano K, Cheng HC, et al. Screening and eradication of Helicobacter pylori for gastric cancer prevention: the Taipei global consensus. Gut. 2020 Dec;69(12):2093-2112.

Table 1. Attributable Fraction and attributable Gastric Cancer cases and deaths for *Helicobacter pylori* in 2040 by World Health Organization region.

WHO region	Hp *	RR	AF%	GC cases in 2040			GC deaths in 2040			Attributable GC cases in 2040			Attributable GC deaths in 2040		
				Men	Women	Both sexes	Men	Women	Both sexes	Men	Women	Both sexes	Men	Women	Both sexes
African region	0,534	5,9	0,72	23766	20918	44684	20669	18678	39347	17195	15134	32329	14954	13513	28467
Eastern Mediterranean region	0,519	5,9	0,72	40138	27265	67402	33661	22548	56209	28810	19570	48379	24161	16184	40345
European region	0,395	5,9	0,66	122026	78412	200438	90266	57300	147566	80457	51700	132157	59516	37780	97297
Region of the Americas	0,426	5,9	0,687	93295	58465	151760	64657	41245	105902	63077	39528	102605	43715	27889	71601
South-East Asia region	0,48	5,9	0,70	99545	49195	148741	89299	43471	132770	69848	34519	104367	62658	30502	93161
Western Pacific region	0,434	5,9	0,68	556188	274618	830806	360368	178926	539294	378299	186785	565084	245109	121699	366808

*Based on Chen et al., 2024, Supplementary Table 6.

Table 2. Country-specific Attributable Fraction and attributable Gastric Cancer cases and deaths for *Helicobacter pylori* in 2040.

WHO region and country	HDI (2019)	Hp	AF	GC deaths in 2040		GC cases in 2040		Attributable GC deaths in 2040		Attributable GC cases in 2040	
				Men	Women	Men	Women	Men	Women	Men	Women
Africa											
Algeria	Medium	0,56	0,73325509	2425	1500	3002	1836	1778	1100	2201	1346
Burkina Faso	Low	0,47	0,69634398	230	406	245	428	160	283	171	298
Cameroon	Low	0,57	0,73635645	352	391	412	446	259	288	303	328
Ethiopia	Low	0,48	0,69947408	1640	1934	1775	2089	1147	1353	1242	1461
Ghana	Low	0,52	0,71853978	878	715	972	795	631	514	698	571
Kenya	Low	0,44	0,68363441	1441	1663	1686	1928	985	1137	1153	1318
Nigeria	Low	0,48	0,69947408	1230	1518	1407	1721	860	1062	984	1204
Rwanda	Low	0,71	0,77697986	428	567	476	634	333	441	370	493
South Africa	Low	0,56	0,73395057	1459	1289	1805	1230	1071	946	1325	903
Uganda	Low	0,71	0,77649136	433	424	515	502	336	329	400	390
Zimbabwe	Low	0,71	0,77649136	453	703	521	802	352	546	405	623
East Mediterranean Region											
Afghanistan	Low	0,72	0,7796289	1924	1266	2098	1420	1500	987	1636	1107
Bahrain	High	0,79	0,79552611	56	24	59	31	45	19	47	25
Egypt	Medium	0,49	0,7055446	1956	1923	2594	2546	1380	1357	1830	1796
Iran	High	0,56	0,73325509	18434	12384	22524	14521	13517	9081	16516	10648
Iraq	Medium	0,54	0,72646206	1167	941	1377	1098	848	684	1000	798
Jordan	Medium	0,89	0,81278317	500	199	574	232	406	162	467	189
Kuwait	High	0,41	0,66927936	202	97	225	102	135	65	151	68
Lebanon	Medium	0,42	0,67507148	151	93	160	101	102	63	108	68

Libya	Medium	0,8	0,79674797	194	208	209	230	155	166	167	183
Morocco	Medium	0,76	0,78875322	1927	1268	2141	1401	1520	1000	1689	1105
Pakistan	Low	0,45	0,68558403	4083	3412	4569	3843	2799	2339	3132	2635
Qatar	High	0,41	0,6671216	65	22	76	23	43	15	51	15
Saudi Arabia	High	0,38	0,65297057	1202	442	1452	547	785	289	948	357
Sudan	Low	0,57	0,73737427	481	448	570	507	355	330	420	374
Tunisia	Medium	0,63	0,75590705	438	300	499	336	331	227	377	254
United Arab Emirates	High	0,5	0,70848881	231	119	266	136	164	84	188	96
Yemen	Low	0,82	0,80110585	942	664	1041	753	755	532	834	603
Region of the Americas											
Bahamas	High	0,58	0,74071097	35	32	41	37	26	24	30	27
Bolivia	Medium	0,66	0,76381672	540	481	699	616	412	367	534	471
Brazil	High	0,4	0,65991022	18693	10235	23464	12802	12336	6754	15484	8448
Canada	Very high	0,38	0,64999475	2466	1482	3993	1993	1603	963	2595	1295
Chile	High	0,53	0,72123104	4833	2126	6049	2640	3486	1533	4363	1904
Colombia	High	0,83	0,80283523	7072	4528	9145	5821	5678	3635	7342	4673
Costa Rica	High	0,78	0,79177078	834	500	1357	632	660	396	1074	500
Dominican Republic	High	0,59	0,74234773	492	438	642	563	365	325	477	418
Ecuador	High	0,86	0,80766642	2253	1671	2764	2008	1820	1350	2232	1622
Guatemala	Medium	0,87	0,809	1053	1506	1211	1727	853	1220	981	1399
Haiti	Low	0,45	0,68703055	722	375	848	413	496	258	583	284
Honduras	Medium	0,83	0,8018782	812	321	830	373	651	257	666	299
Mexico	High	0,71	0,77550791	6286	5649	8259	7400	4875	4381	6405	5739

Nicaragua	Medium	0,83	0,80321546	477	354	554	413	383	284	445	332
Paraguay	Medium	0,68	0,76811057	311	192	405	249	239	147	311	191
Peru	High	0,63	0,75532175	4073	3356	5528	4486	3076	2535	4175	3388
United States	Very high	0,18	0,46305842	9263	5960	20156	12671	4289	2760	9333	5867
Venezuela	Medium	0,81	0,79934587	2065	1000	2675	1279	1651	799	2138	1022
Europe											
Albania	High	0,63	0,75532175	479	287	610	397	362	217	461	300
Armenia	High	0,39	0,65705271	294	284	385	365	193	187	253	240
Austria	Very high	0,47	0,69814055	538	422	941	588	376	295	657	411
Belgium	Very high	0,22	0,51648777	638	350	1200	626	330	181	620	323
Bulgaria	High	0,58	0,74071097	660	419	936	566	489	310	693	419
Croatia	High	0,13	0,39456318	478	295	664	435	189	116	262	172
Cyprus	High	0,35	0,62832187	123	66	166	80	77	41	104	50
Czech Republic	Very high	0,3	0,59352898	663	435	865	552	394	258	513	328
Denmark	Very high	0,19	0,47949198	391	202	584	305	187	97	280	146
Estonia	High	0,69	0,77225107	188	150	268	206	145	116	207	159
Finland	Very high	0,09	0,30838924	286	204	414	280	88	63	128	86
France	Very high	0,29	0,58357625	4178	2241	6118	3339	2438	1308	3570	1949
Georgia	High	0,56	0,73150038	317	264	422	342	232	193	309	250
Germany	Very high	0,26	0,55545677	6439	4165	9669	6719	3577	2313	5371	3732
Greece	High	0,45	0,68893866	924	551	1358	823	637	380	936	567
Hungary	High	0,32	0,61133352	952	615	1250	802	582	376	764	490
Iceland	Very high	0,23	0,52437574	10	12	24	20	5	6	13	10
Israel	Very high	0,46	0,69082365	461	335	698	501	318	231	482	346

Italy	High	0,29	0,58778185	7541	5197	9973	7023	4432	3055	5862	4128
Kazakhstan	High	0,62	0,7535489	1940	969	2612	1675	1462	730	1968	1262
Latvia	High	0,55	0,73079201	269	153	343	194	197	112	251	142
Lithuania	High	0,26	0,56213329	421	237	531	295	237	133	298	166
Netherlands	Very high	0,24	0,53731551	1018	612	1425	924	547	329	766	496
Norway	Very high	0,33	0,61716627	293	196	498	244	181	121	307	151
Poland	High	0,6	0,74682262	4597	1409	5860	3041	3433	1052	4376	2271
Portugal	High	0,5	0,70890461	1874	1339	2583	1819	1328	949	1831	1289
Romania	High	0,38	0,64939345	2478	1216	2949	1431	1609	790	1915	929
Russia	High	0,8	0,79695019	18381	14417	25800	19548	14649	11490	20561	15579
Serbia	High	0,39	0,65355967	599	355	774	454	391	232	506	297
Spain	Very high	0,48	0,70297324	4330	1665	5869	3808	3044	1170	4126	2677
Sweden	Very high	0,16	0,44	440	283	675	415	191	123	293	180
Switzerland	Very high	0,27	0,57042828	581	327	895	507	331	187	511	289
Tajikistan	Medium	0,63	0,75619865	1117	828	1298	983	845	626	982	743
United Kingdom	Very high	0,26	0,56307074	3682	2036	5122	2773	2073	1146	2884	1561
Uzbekistan	Medium	0,81	0,79934587	2418	1456	3160	1884	1933	1164	2526	1506
South East Asia											
Bangladesh	Medium	0,62	0,75325092	8267	4135	9157	4567	6227	3115	6898	3440
Bhutan	Medium	0,7	0,77451577	119	62	133	69	92	48	103	53
Myanmar	Low	0,58	0,74038112	5390	3386	6011	3860	3991	2507	4450	2858
India	Medium	0,6	0,74460478	62297	29122	68473	32189	46387	21684	50985	23968
Indonesia	Medium	0,14	0,41369606	4378	1022	4829	1290	1811	423	1998	534
Nepal	Low	0,45	0,68846382	1440	847	1546	957	991	583	1064	659

Thailand	High	0,35	0,62899755	2748	2269	3349	2758	1728	1427	2107	1735
Western Pacific											
Australia	Very high	0,25	0,54857349	1333	756	2538	1633	731	415	1392	896
Brunei	High	0,27	0,57133059	48	35	53	46	27	20	30	26
Cambodia	Low	0,31	0,60301707	569	409	640	449	343	247	386	271
China	High	0,42	0,67455332	292554	138013	369800	176698	197343	93097	249450	119192
Japan	Very high	0,35	0,63167588	32572	19202	91546	46711	20575	12129	57827	29506
Malaysia	High	0,2	0,49743693	1594	675	1819	916	793	336	905	456
Mongolia	Medium	0,79	0,79428948	1084	687	1216	710	861	546	966	564
New Zealand	Very high	0,09	0,31072512	281	184	418	318	87	57	130	99
Singapore	Very high	0,42	0,67087941	1075	600	1268	773	721	403	851	519
South Korea	Very high	0,55	0,72900463	5025	2107	6167	2588	3663	1536	4496	1887
Vietnam	Medium	0,37	0,64326484	13186	8138	15778	9481	8482	5235	10149	6099

Notes: Hp, *Helicobacter pylori*, N, Number; AF, Attributable Fraction; GC, Gastric Cancer; NA, Not Available.
*Based on GLOBOCAN year 2040, adults aged 40+ (4).

Table 3. Predicted deaths from gastric cancer and correspondent deaths attributable to *Helicobacter pylori* in 2040 based on alternative analyses for 20 countries within four geographical Regions, with percentage difference with estimates based on GLOBOCAN.

UN Region and country	HDI (2019)	Hp	AF	Projected GC deaths in 2040		Attributable GC deaths in 2040		% difference with GLOBOCAN
				Men	Women	Men	Women	
Region of the Americas								
Brazil	High	0,4	0,659910216	10000	6546	6599	4320	-46.5 and -36.0
Canada	Very high	0,38	0,64999475	1385	827	900	538	-43.8 and -44.2
Chile	High	0,53	0,721231044	2029	1009	1463	728	-58.0 and -52.6
Colombia	High	0,83	0,802835229	4095	2833	3288	2274	-42.1 and -37.5
Mexico	High	0,71	0,775507913	4380	3993	3397	3097	-30.1 and -20.3
United States	Very high	0,18	0,463058419	6049	3935	2801	1822	-34.7 and -34.0
Venezuela	Medium	0,81	0,799345868	1039	875	831	699	-49.7 and -12.5
Europe								
France	Very high	0,29	0,583576247	1942	843	1133	492	-53.5 and -62.4
Germany	Very high	0,26	0,555456768	3557	1479	1976	822	-44.7 and -64.5
Israel	Very high	0,46	0,690823646	285	228	197	158	-38.1 and -31.9
Italy	High	0,29	0,587781854	3829	2544	2251	1495	-49.2 and -51.0
Poland	High	0,6	0,746822624	3049	882	2277,	659	-33.7 and -37.4
Russia	High	0,8	0,796950192	16452	8400	13111	6694	-10.5 and -41.7
Spain	Very high	0,48	0, 702973238	1742	1725	1225	1213	-59.7 and -3.5
United Kingdom	Very high	0,26	0,563070739	1320	693	743	390	-64.2 and -66.0
Western Pacific								
Australia	Very high	0,25	0,548573492	811	368	445	202	-39.2 and -51.3
Japan	Very high	0,35	0,631675875	19264	10506	12169	6636	-40.9 and -81.8
South Korea	Very high	0,55	0,729004634	2888	2038	2105,365383	1486	-75,2 and -71,6

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BURDEN OF GASTRIC CANCER ATTRIBUTABLE TO *HELICOBACTER PYLORI* IN 26 COUNTRIES FROM DIFFERENT GEOGRAPHIC REGIONS IN 2022

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INTRODUCTION

H. pylori infection is the major risk factor of gastric cancer (GC)., and the major responsible of infectious-related cancer worldwide.
Previous estimated of the burden of GC attributable to *H. pylori* infection are impaired by several limitations:
some studies assumed that the prevalence of *H.pylori* in GC cases was an estimate of AF (→ overestimate);
other studies calculated the AF in all age groups rather than adults only (→ underestimate);
some used a relative risk (RR) for the association between *H.pylori* and GC estimated including case-control studies (→ underestimate);
or, no country-specific *H.pylori* prevalence data were used.

Large-scale population-based data on *H.pylori* prevalence are difficult to be collected, especially in less developed countries, because of the dynamic nature of the infection which is continuously changing, heterogeneous by country and subgroups, and because of factors related to detection methods and to bacteria strains which have different cancerogenicity.
This represents a great challenge when describing accurately *H.pylori* epidemiology and estimating the burden of disease related to this infection.

AIMS

We aimed to estimate the burden of GC due to *H. pylori* in different countries worldwide in 2022 through the calculation of the attributable fraction (AF) of GC and the number of new GC cases and deaths due to *H. pylori*, accounting for 10-year latency between country-specific *H. pylori* exposure and GC.

METHODS

A **systematic review and meta-analysis** of studies was conducted in order to assess country-specific *H.pylori* prevalence. To note, study selection was restricted to prevalence referred to **period 2000-2010**, in order to account for 10-22 years of latency time between the exposure and the outcome. A **relative risk (RR) of 5.9** between *H. pylori* and GC was used.
We calculated the AF of GC due to *H. pylori* adopting the formula **AF = *p* (RR-1) / (1+ *p* (RR-1),** where *p* is the prevalence of *H. pylori* and RR is the relative risk of GC associated with *H. pylori* infection.
The number of new GC cases and deaths attributable to *H. pylori* was calculated by multiplying the country-specific AF by the number of new GC cases and deaths for each country estimated from **GLOBOCAN 2022.**

CONCLUSIONS

Hp eradication would prevent **two-thirds of GC** worldwide.
Accurate estimates not available for all countries worldwide: limited comparability with previous literature
We provided **accurate estimates for selected countrie**s with solid, available data
We calculated country-specific *H.pylori* prevalence accounting for **latency time** (period 2000-2010 → restricted literature review!)
Highest impact of *H.pylori* on GC in **China and Japan** as compared with other countries; low-income countries have a huge burden of GC due to *H.pylori.*

Important residual *limitations*: no distinction cardia vs non-cardia; RR assumed to be the same in all countries (not considering for effect modification exerted by lifestyle factors), no *H.pylori* strains data.

Next steps:
Attributable Fraction of GC due to *H. pylori* in 2040**.**

70% of GC were attributable to *H.pylori* infection.
The largest burden of GC due to H.pylori was observed in China.
The second most burdened country resulted to be Japan. High mortality numbers were observed even in countries where *H.pylori* and GC screening strategies have been implemented.
Our results may be helpful for policy makers and cost-effectiveness analyses on GC prevention strategies focused on *H. pylori* "screen-and-treat".

RESULTS

WHO Regions/Countries	Studies (n)	Pooled prevalence of Hp (%)	WHO Regions/Countries	Studies (n)	Pooled prevalence of Hp (%)	WHO Regions/Countries	Studies (n)	Pooled prevalence of Hp (%)
Overall	40	52						
Africa	2	92	South-East Asia	1	44	East Mediterranean region	6	62
Benin	1	86.2	Thailand	3	43.6	Iran	5	62
South Africa	1	95	Europe	12	43	Tunisia	1	63.2
North America	1	27	Albania	1	53.5	Western Pacific region	14	49
USA	1	27.1	Czech Republic	1	41.7	Australia	2	29
Latin America	6	61	Denmark	1	19.7	China	5	52
Brazil	1	70.7	Germany	1	47	Japan	2	55
Chile	1	74.6	Greece	1	33.7	Korea	3	64
Ecuador	1	72.2	Norway	2	26	Malaysia	1	14.2
Guadeloupe (France)	1	53.7	Poland	1	68.7	Taiwan	1	39.2
Mexico	1	38.1	Spain	2	61	Korea	3	64
Panama	1	54.1	The Netherlands	2	38			

Regions and countries	Attributable fraction	Regions and countries	Attributable fraction	Regions and countries	Attributable fraction
Overall	69,7	South-East Asian Region		Eastern Mediterranean Region	
African region		Thailand	68,3	Iran	75,2
Benin	80,8	European Region		Tunisia	75,5
South Africa	82,3	Albania	72,2	Western Pacific Region	
North America		Czech Republic	67,3	Australia	58,7
USA	57,0	Denmark	49,5	China	71,8
Latin America		Germany	69,7	Japan	72,9
Brazil	77,7	Greece	62,5	Korea	75,8
Chile	78,6	Norway	56,0	Malaysia	40,7
Ecuador	77,9	Poland	77,2		
Guadeloupe (France)	72,6	Spain	74,9		
Mexico	65,1	The Netherlands	65,1		
Panama	72,6				

WHO Region/Country	Number of new cases of gastric cancer			Number of new cases of gastric cancer attributable to Hp		
	Total	Males	Females	Total	Males	Females
Africa						
Benin	378	254	124	305	205	100
South Africa	1784	1080	704	1468	889	579
North America						
USA	24668	14976	9692	14060	8536	5524
Latin America						
Brazil	22300	14402	7898	17327	11190	6135
Chile	4902	3327	1575	3853	2615	1238
Ecuador	2586	1513	1073	2015	1179	836
Guadeloupe (France)	124	70	54	90	51	39
Mexico	9013	4784	4277	5860	3114	2745
Panama	472	291	181	342	211	131
South-East Asia						
Thailand	3907	2147	1760	2669	1467	1202
Europe						
Albania	701	460	241	506	332	174
Czech Republic	1228	730	498	826	491	335
Denmark	725	473	252	359	234	125
Germany	13917	8263	5654	9703	5761	3942
Greece	1857	1168	689	1161	730	431
Norway	512	339	173	287	190	97
Poland	6874	4431	2443	5305	3420	1885
Spain	7084	4224	2860	5308	3165	2143
The Netherlands	1814	1088	726	1180	708	472
East Mediterranean Region						
Iran	16895	10671	6224	12711	8028	4683
Tunisia	508	312	196	384	236	148
Western Pacific Region						
Australia	2776	1718	1058	1629	1008	621
China	352084	243507	108577	252850	174875	77975
Japan	126366	83816	42550	92166	61132	31034
Korea	28823	19551	9332	21855	14794	7061
Malaysia	1431	969	462	582	394	188
Total	633777	424524	209993	454802	304855	149843

Overall AF: 69.7%

Range:
40.7% (Malaysia) – 82.2% (South Africa)

Clear pattern: high numbers in Eastern Asia

Absolute number of deaths from GC attributable to Hp is largely the highest in China, also compared to other highly populated nations (eg. USA, Brazil)

Japan has higher numbers compared to other countries with similar population density (eg. Mexico)

WHO Region/Country	Number of deaths from gastric cancer			Number of deaths from gastric cancer attributable to Hp		
	Total	Males	Females	Total	Males	Females
Africa						
Benin	324	217	107	261	175	86
South Africa	1548	859	689	1274	707	567
North America						
USA	10650	6451	4199	9747	6070	3677
Latin America						
Brazil	17569	11335	6234	13646	8804	4842
Chile	3876	2630	1256	3047	2060	987
Ecuador	2104	1223	881	1639	953	686
Guadeloupe (France)	101	57	44	79	45	34
Mexico	6859	3639	3220	4437	2355	2082
Panama	355	219	136	258	159	99
South-East Asia						
Thailand	2970	1638	1332	2029	1119	910
Europe						
Albania	555	366	189	401	264	137
Czech Republic	923	547	376	621	368	253
Denmark	465	306	159	231	152	79
Germany	8643	5778	3465	6026	3610	2416
Greece	1243	788	455	776	492	284
Norway	320	187	133	180	105	75
Poland	5311	3411	1900	4098	2632	1466
Spain	5008	3047	1961	3752	2283	1469
The Netherlands	1172	722	450	763	470	293
East Mediterranean Region						
Iran	13535	8848	4687	10168	6857	3311
Tunisia	439	269	170	331	203	128
Western Pacific Region						
Australia	1309	841	468	769	494	275
China	257141	179364	77777	184666	129241	55425
Japan	43611	27529	16082	31809	20079	11730
Korea	8386	4914	3472	6359	3726	2633
Malaysia	1158	821	337	471	334	137
Total	395330	265978	129352	287829	193555	95184

REFERENCES

GBD 2017 Stomach Cancer Collaborators. The global, regional, and national burden of stomach cancer in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease study 2017. Lancet Gastroenterol Hepatol. 2020 Jan;5(1):42-54.

de Martel C et al. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020 Feb;8(2):e180-e190. doi: 10.1016/S2214-109X(19)30488-7. Epub 2019 Dec 17. PMID: 31862245.

Plummer M et al. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 2016 Sep;4(9):e609-16. doi: 10.1016/S2214-109X(16)30143-7. Epub 2016 Jul 25. PMID: 27470177.

Collatuzzo G et al. Cancers attributable to infectious agents in Italy. Eur J Cancer. 2023 Apr;183:69-78. doi: 10.1016/j.ejca.2023.01.010. Epub 2023 Jan 25. PMID: 36801622.

Ji X, He G et al. Estimation of gastric cancer burden attributable to Helicobacter pylori infection in Asia. J Public Health. 2024;45:40-46.

Park Y & Ki M. Population Attributable Fraction of Helicobacter pylori Infection-Related Gastric Cancer in Korea: A Meta-Analysis. Cancer Res Treat. 2021;53:744-753.

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Collatuzzo G, La Vecchia C, Parazzini F, Alicandro G, Turati F, Di Maso M, Malvezzi M, Pelucchi C, Negri E, Boffetta P. Cancers attributable to infectious agents in Italy. Eur J Cancer. 2023 Apr;183:69-78.

2.5 Cancers attributable to infectious agents in Italy

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Abstract

Objectives: To provide an evidence-based, comprehensive assessment of the current burden of infection-related cancer in Italy.

Methods: We calculated the proportion of cancers attributable to infectious agents (Helicobacter pylori [Hp]; Hepatitis B and C Viruses [HBV, HCV]; Human Papillomavirus [HPV]; Human Herpes Virus-8 [HHV8]; Epstein-Barr Virus [EBV]; and Human Immunodeficiency Virus [HIV]) to estimate the burden of infection-related cancer incidence (2020) and mortality (2017). Data on prevalence of infections were derived from cross-sectional surveys of Italian population, and relative risks from meta-analyses and large-scale studies. Attributable fractions were calculated based on the counterfactual scenario of lack of infection.

Results: We estimated that 7.6% of total cancer deaths in 2017 were attributable to infections, with a higher proportion in men (8.1%) than in women (6.9%). Corresponding figures for incident cases were 6.5%, 6.9% and 6.1%. Hp was the first cause of infection-related cancer deaths (3.3% of the total), followed by HCV (1.8%), HIV (1.1%), HBV (0.9%), HPV, EBV and HHV8 (each ≤0.7%). Regarding incidence, 2.4% of the new cancer cases were due to Hp, 1.3% to HCV, 1.2% to HIV, 1.0% to HPV, 0.6% to HBV, and < 0.5% to EBV and HHV8.

Conclusions: Our estimate of 7.6% of cancer deaths and 6.9% of incident cases were attributable to infections in Italy are larger than those estimated in other developed countries. Hp is the major cause of infection-related cancer in Italy. Prevention, screening and treatment policies are needed to control these cancers, which are largely avoidable.

Keywords: infection; cancer; attributable fraction; estimates; Italy

Introduction

The discovery of infections as etiological factors of cancer dramatically changed cancer prevention and medical practice, because of the avoidable nature of infective causes.
Several viruses may cause cancer in humans, including: Hepatitis B virus (HBV), Hepatitis C virus (HCV) which cause liver cancer, with HCV also causing non-Hodgkin lymphoma (NHL) [1]; Human Papillomavirus (HPV), primarily linked to cervical cancer, but also related to other anogenital cancers and cancer of oropharynx [2]; Epstein-Barr Virus (EBV), causing nasopharyngeal cancers and Hodgkin lymphoma [3]; HHV8, causing Kaposi Sarcoma; and Human Immunodeficiency Virus (HIV), which is associated to Kaposi Sarcoma, anal cancer and non-Hodgkin lymphoma (HL) [4].
Among bacteria, Helicobacter pylori (Hp) is the only established oncogenic agent, being the main risk factor of gastric cancer and gastric mucosa-associated-lymphoid tissue lymphoma (MALT) [5]. Parasites of the Schistosoma, Opistorchis and Clonorchis genera are established causes of bladder cancer and liver cholangiocarcinoma [6]. Other infectious agents are suspected causes of cancer, including the bacterium, Mycobacterium tuberculosis (Mt) [7] and the parasite, Plasmodium falciparum (Pf) [8].

Martel et al., based on the GLOBOCAN 2018 database, estimated a total of 2.2 million infection-attributable cancers worldwide in 2018, with Hp being the leading cause of cancer, followed by HPV, HBV and HCV [9]. National estimates of attributable cancers due to infections have been calculated for several countries, including China [10], Vietnam [11], Korea [12], Japan [13], France [14], the UK [15], Brazil [16], the USA [17] and Denmark [18]. Such estimates, however, are not available for Italy. This study aims at estimating the burden of cancer attributable to infections in the Italian population, based on mortality data from 2017 and cancer incidence data from 2020. Such estimates are important to set priorities and design interventions to reduce infection-related cancers, as well as to establish the cost-effectiveness of population-based preventive interventions in Italy.

Methods

Our study is part of a systematic analysis of attributable causes of cancer in Italy, based on an evidence-based research with the purpose to estimate the numbers of cancer deaths in 2017 and cancer cases in 2020 in Italy which could be attributable to known carcinogens, including smoking, alcohol, occupational exposures, infections, and nutritional, reproductive and anthropometric factors.

The proportion of disease in the total population that can be attributable to a risk factor is defined as attributable fraction (AF) and commonly expressed as a percentage. We applied the classic formula originally described by Levin (1953) [19] to calculate the AF of cancer for specific infectious agents. It is a function of the relative risk (RR) of the disease (e.g., a specific cancer) associated with exposure to the risk factor (e.g., a particular infection) and the prevalence of the risk factor (P) in the population:

$$AF = \frac{P*(RR-1)}{[\ P*(RR-1)\ ]+1}$$

To estimate the AF we used no infections as counterfactual scenario. We considered all infectious agents classified in Group 1 (established human carcinogens) by the International Agency for Research on Cancer (IARC) [20].

The RR of the cancer incidence and mortality related to specific infectious agents and cancers were obtained from meta-analyses or large studies, as specified in Table 1. Data on prevalence of infection around the year 2000 (i.e., we allowed a 15-to-20-year latency between infection and cancer) were obtained from several sources, as shown in Table 1 [21-31].

The sex-specific number of cancer deaths and incident cancer cases were obtained from the 2020 Report of the Italian Association of Cancer Registries (AIRTUM) [32]. We developed algorithms to estimate the number of deaths and cases of cancers not included in the AIRTUM Report, such as cardia and non-cardia gastric cancer (details are shown in Supplementary Table 1), and the number of cancer deaths and cases used in the analysis are listed in Table 2.

For cancers related to multiple infectious agents, like liver and anal cancer, we calculated partial AF based on the assumptions of independence of infection prevalence and RR (i.e., no interaction according to a multiplicative model) [33].

The data source and approach used to define exposure, RR and prevalence are reported below.

Definition of exposure

We included the following cancers and their corresponding infectious agents in our study: liver cancer following infection with HBV and HCV; NHL following HCV; cervical, oral, pharyngeal, penis, anal, vaginal and vulvar cancers following HPV infection; nasopharyngeal (NPC) and HL following EBV infection; gastric cancer, separately for cardia and non-cardia subsites, and gastric MALT following infection with Hp; Kaposi sarcoma following the infection with HHV8 and HIV; anal cancer, and HL and NHL related to HIV infection.

Burkitt lymphoma was not included among the cancers associated to EBV because of the very low incidence of this disease in Italy. Chlonorchis sinensis, Opistorchis viverrine and Schistosoma haematobium were not considered among the infectious agents because of the sporadic occurrence of these infection in Italy. Similarly, Merkel cell polyomavirus, associated with the homonymous skin carcinoma [34], was not accounted because of the rarity of this cancer. Two infectious agents suspected to cause cancer in humans (Mt and Pf) were not included in the main analysis, but we provided separate estimates for them as well.

Data used for RR and prevalence

RR used in the calculation of AFs were derived from meta-analyses or large-scale cohort studies (Table 2). We applied the same RR to men and women (i.e., we assumed no infection-sex interaction), and to mortality and incidence data (i.e., we assumed no effect of infection on cancer survival).

Results

AF and attributable cancer cases and deaths in Italy are given in Tables 3 and 4. In 2017, 7.6% of all cancer deaths in Italy were attributable to infections (N=13,670), corresponding to 8,124 deaths among men (8.1%) and 5,546 (6.9%) among women. Gastric cancer (including non-cardia, cardia and MALT-lymphoma) following Hp infection represented 3.3% of total cancer deaths, with higher proportion in men (3.4%) than in women (3.0%). Liver cancer following either HBV or HCV infection represented 2.7% of cancer deaths, with 0.9% being attributable to HBV and 1.8% to HCV, and higher proportion in men than in women. HPV accounted for 0.6% of cancer deaths, with higher proportion in women compared than men (0.9% vs 0.3%). We estimated 1.1% of cancer deaths due to HIV, with similar proportions in men (1.2%) and women (1.0%).
The other infectious agents accounted for no more than 0.7% of cancer deaths each.

The number of cancer cases attributable to infections in Italy in 2020 was about 24,500.
Hp was responsible for 2.4% of cancer cases, including 8976 gastric cancers (8512 non-cardia and 464 cardia cases in particular), and 167 gastric MALT cases. HBV and HCV resulted to cause respectively 0.6% and 1.3% of cancer cases, equal to 2381 and 4519 liver cancer cases respectively, with HCV also causing 203 non-Hodgkin lymphoma cases. HPV accounted for the 1.0% of total cancer cases (n=3691), including 2365 cervical, 557 pharyngeal, 252 anal, 186 oral,174 vulvar, 81 vaginal, and 76 penal cancer cases.
We calculated that 1.2% of cancer cases were attributable to HIV; of those, 899 were Kaposi sarcoma cases, 2884 NHL cases, 376 anal cancer cases and 359 HL cases. Also, 0.3% of cancer cases were attributable to EBV, in particular 424 cases of nasopharyngeal cancer and 774 of HL. Finally, HHV8 accounted for all 927 cases of Kaposi sarcoma, corresponding to 0.2% total incident cancers.

The AF calculated for Italy were higher than for many developed countries (Table 5).

Discussion

As the first study to assess the overall infection-related cancer burden in Italy using standardized methods, our research found that a total of 24,584 cancer cases in 2020 and 13,670 cancer deaths (8124 in men and 5546 in women) in 2017 in Italy were attributable to infections, corresponding to 6.5% and 7.6% of all cancer cases and deaths respectively. In particular, 8.1% of cancers death in men and 6.9% of cancer deaths in women resulted to be attributable to infections. The main infective cause of cancer in Italy is Hp, with 3.3% attributable cancer deaths from cancer in 2017, followed by HCV (1.8%), HBV (0.9%) and HPV (0.6%). Infection-related cancers accounted for a larger proportion of cancer deaths than that of cancer cases due to the high fatality of most infection-related cancers, notably liver cancer.

Based on our estimates, a higher proportion of cancers were attributable to infections in Italy compared to other European countries, such as France [14], Denmark [18] and the UK [15], as well as the US [17]. In addition, the AF of cancer related to infection in the Italian population is similar to that of less developed countries such as Brazil [16] and Vietnam [11]. This is largely due to the high proportion of gastric cancer from Hp infection and liver cancer from HBV and HCV infection in those countries and in Italy, and to the high HPV prevalence in Brazil and Vietnam [16, 11].

Our estimates are based on infectious agents with sufficient evidence for a causal role in cancer occurrence. Other infectious agents suspected to cause cancer in humans include Mt [7] for lung cancer and Pf for Burkitt lymphoma [8]. In addition, established carcinogenic agents might cause cancers other than those included in our analysis, such as EBV for gastric cancer [35]. The number and types of cancer due to EBV are still to be defined [35], with increasing evidence reporting an association with gastric cancer [36]. Assuming these associations are causal, we estimated that a small number of cancers would be attributable to these additional agents. For example, the proportion of lung cancers attributable to infection with Mt, based on a reported prevalence of latent infection of 2.1% [37] and a RR of lung cancer equal to 1.76 [38], would be 0.16%, corresponding to 54 deaths and 65 cases.

The inclusion of these agents may be worth in studies conducted in high-risk populations for these infections (e.g., from middle- and low-income countries).

The proportion of cancer caused by infectious agents is a dynamic indicator, depending on temporal changes of the prevalence of relevant agents. Some of these changes are the result of preventive measures (e.g., HPV vaccination), while other occur without planned interventions (e.g., decrease in prevalence of Hp infection [39]). Moreover, it is difficult to estimate the proportion of cancers due to co-infections, which is particularly relevant for liver cancer, due to concomitant HBV and HCV. To this purpose, potential interactions between multiple infectious agents in determining the risk of a specific cancer need to be accounted for, but data on the patterns of interaction are limited [40-44]. Precise and updated estimates of the proportion of HBV-HCV coinfection prevalence in Italy are scarce [45, 46]; we therefore assumed independence of effect of the two infections, and estimated that 6.3% of liver cancers were attributable to HBV-HCV coinfection. Similarly, when considering anal cancer, we calculated that 10% of the cases were attributable to concomitant HIV-HPV infections [47].

Change in infections prevalence heavily impacts the number of cancers, implying a large potential of prevention. This particularly concerns infections for neoplasms for which therapies and/or vaccines are available. Hp can be easily detected with non-invasive diagnostic tests [48] and first line eradication therapies has more than 80% of effectiveness [49, 50]. HBV vaccination is mandatory in all Italian newborns since 1991 and all those born since 1980 were vaccinated at age 12 [51]. Current therapies are able to control liver disease from both HBV and HCV infection [52-54]. Moreover, both HBV and HCV are screened on a regular basis in some high-risk settings such as hospitals through health care workers' surveillance [55-57], and prisons [58-60]. The fact that prevalence of major infectious agents is progressively declining leads to the continuous change in the AF, which indeed deserves to be periodically updated to have the most representative estimates for a certain country in a certain timeframe.
Regarding HP, vaccination coverage rates remain suboptimal in Italy [61], with a decreasing trend in the last years for different birth cohorts and both sexes, which was

further impacted by the COVID-19 pandemic [62]. The proportion of cancers attributable to HPV in Italy reflects the lack of vaccination in women born before 1996, with a birth-cohort effect due to introduction of HPV vaccination. Further, we have to consider the higher risk of cervical cancer observed in Italy among recently immigrated women (representing about 9% of women living in Italy) which have different rates of HPV infection, cervical screening and vaccination coverage [63].

The cultural and lifestyle heterogeneity due to Italian geographical areas (i.e., Northern, Central and Southern, including major islands), next to the environmental differences between these areas, determine distinct patterns of risk factors, and different incidence and mortality rates of cancer [64]. Participation to the available cancer screenings in the different Italian areas, varying between 62% to 90% considering planned and private screening for cervical cancer [65]. At the same time, head-and-neck HPV-related cancers in Italy are increasing, consistently with other countries [66]. The higher rates in men likely reflect different lifestyle habits by sex, and consequent exposure to infection hazards including use of injective drugs and men who have sex with men, given the potential transmission of the infection via blood and sexual contact [67-69]. This applies also to HIV- and HHV8-related cancers, observed mainly in men.

Hp infection accounted for the largest AF of infection-related cancers in Italy. Our study allowed to translate common knowledge on Hp etiological link to gastric cancer with objective proportions and numbers, also drawing possible figures by cancer subsite. In particular, 21% of cardia cancer deaths were caused by Hp infection, corresponding to 300 deaths in 2017. These, summed up to the 5500 deaths from non-cardia gastric cancer, and 57 deaths from MALT of the stomach, make Hp responsible for up to 3.3% deaths from cancer in 2017 in Italy. Noticeably, the knowledge on the role of Hp in gastric cancer subtypes is evolving, as increasing evidence underlines its causal role in both cardia and non-cardia cancer with this latter showing a stronger association than th former, as commonly known. A large analysis which has been recently conducted within the China Kadoorie Biobank found a significant association of 3.06 between Hp and cardia gastric cancer [70], higher than that we adopted based on more comprehensive data [9]. If on the

one side the link between Hp and either anatomical subsite of gastric cancer has been reported of higher magnitude in Chinese population than in European one, previous studies may have missed to identify the relationship with cardia cancer because of issues related to the methods of detection, as discussed by the authors [70]. Therefore, our results could be a conservative estimate of the number of cardia cancers attributable to Hp infection.
To date, no standardized and organized screening program for Hp infection exists [71], despite the non-invasive diagnostic tests and the antibiotic therapies available for the infection. Most population-based study on Hp test-and-treat have been conducted in Asian countries, given the high incidence of gastric cancer and the diffusion of virulent Hp strains [72-75]. Recently released Italian guidelines for the management of Hp infection states with moderate level of evidence and high grade of recommendation that the test and treat of Hp should be performed in dyspeptic subjects younger than 50, and in subjects using non-steroidal anti-inflammatory drugs or aspirin with a history of peptic ulcer [76]. Our analysis calls for intervention to control Hp infection in Italy on a broader scale.

Infectious agents are heterogeneously distributed in the population. Many studies have described a higher prevalence of infection, including Hp [77], HBV [78], HCV [79] HPV [80] and HIV [81], in less affluent subgroups, including immigrants and less educated subjects. Indeed, infectious-related cancers are characterized by social disparities [82-86]. As more deprived subgroups of the population have suboptimal access to healthcare interventions, despite the public nature of health care system in Italy can limit this phenomenon, specific plans should be developed to enhance their involvement in ongoing prevention programs, such as HPV and HBV vaccination [87,88]; also, deprived subgroups could be targeted with new potential preventive interventions. A possibility is that high-risk subjects should be identified, during general health visits, or occupational surveillance [89-91], and recommended to undergo specific tests of screening for infection status and, when possible, to be targeted with available interventions. In fact, given the long latency a high proportion of cancer could be avoided by eradicating the infected, with benefit also for the young generations through the reduction of the infection reservoir. The benefit would also be projected within the household, where the transmission is more likely, with benefit for the new generations.

Moreover, vaccination for HBV [92] and HPV [93, 94] should be made available and strongly recommended in unvaccinated subjects of both sexes. The eradication and vaccination against the mentioned infections would help shaping the AF of related cancers in the future generations, reducing the reservoir of infection and interrupting route of transmissions [95].

Our study has a few limitations. First, some of the data we used were not derived from representative samples of the general Italian population. This especially regards less prevalent infectious agents. Also, we were unable to consider geographical differences within the country of infection-related cancer by geographical areas, given the heterogeneous availability of data from different regions. Moreover, mortality data for some specific cancers were not available and were then derived from incidence data, as described in the Annex. Further, we used RR derived from studies conducted in other countries, which did not comprehensively account for potential background factors and virulence of the infective agents, which vary across the countries. The use of a single source to estimate the prevalence of infections does not take into account its temporal trend, and the latency chosen between infection and cancer diagnosis or death is subject to uncertainty. Also, despite we accounted for coinfections, we assumed no interaction among the agents, possibly introducing some bias in both directions (overestimating cases if the interactions were more than multiplicative and underestimating cases if less than multiplicative). Finally, we did not account for the uncertainties around the AF point estimates. Such uncertainties depend on the statistical precision of the data on prevalence and the RR, as well as on the accuracy of these data to the national Italian population.

This study has also several strengths. First, we provided for the first time an estimate of the burden of cancer related to infections in Italy, using recent mortality and incidence data.
All the main known oncogenic infectious agents with a substantial prevalence in Italy were included, in association to all the cancers they are known to cause. The AF were calculated using standardized methodology, based on data from recent systematic reviews and meta-analyses and cancer registries. Also, we accounted for the latency period between infection and cancer occurrence, to draw an accurate picture of infection-related cancer in Italy.

In conclusion, our results provide a systematic assessment of infection-associated cancer risk in Italy. The AF of cancer due to infections appears high. These results indicate that most of the cancer burden related to infections in Italy is due to two agents for which vaccinations are available, namely HPV and HBV, and two other agents for which screening and treatment is possible, Hp and HCV. A better management and prevention of relevant infections may lead to a better control of the burden of infection-related cancers in Italy, for example through vaccination and screening campaigns in schools and at the workplace, as well as public health campaigns targeting high-risk populations [96].

A large portion of infection-related cancers are avoidable by preventive program, including screening for infection, vaccination (also in adults) and therapies as appropriate.

Updated estimates should be provided in the future for the Italian population, allowing to draw the trends of infectious-related cancer in time based on the variation of the prevalence of the infections.

References

1- Momin B, Richardson L. An analysis of content in comprehensive cancer control plans that address chronic hepatitis B and C virus infections as major risk factors for liver cancer. J Community Health. 2012 Aug;37(4):912-6.
2- Szymonowicz KA, Chen J. Biological and clinical aspects of HPV-related cancers. Cancer Biol Med. 2020 Nov 15;17(4):864-878
3- Farrell PJ. Epstein-Barr Virus and Cancer. Annu Rev Pathol. 2019 Jan 24;14:29-53.
4- Zheng J, Shi Y, Feng Z, Zheng Y, Li Z, Zhao Y et al.Oncogenic effects of exosomes in γ-herpesvirus-associated neoplasms. J Cell Physiol. 2019 Nov;234(11):19167-19179
5- Alipour M. Molecular Mechanism of Helicobacter pylori-Induced Gastric Cancer. J Gastrointest Cancer. 2021 Mar;52(1):23-30
6- Arora N, Kaur R, Anjum F, Tripathi S, Mishra A, Kumar R et al.Neglected Agent Eminent Disease: Linking Human Helminthic Infection, Inflammation, and Malignancy. Front Cell Infect Microbiol. 2019 Dec 6;9:402.
7- Hwang SY, Kim JY, Lee HS, Lee S, Kim D, Kim S et al.Pulmonary Tuberculosis and Risk of Lung Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 2022 Jan 30;11(3):765.
8- Ellis T, Eze E, Raimi-Abraham BT. Malaria and Cancer: a critical review on the established associations and new perspectives. Infect Agent Cancer. 2021 May 13;16(1):33.

9- de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020 Feb;8(2):e180-e190.
10- Xiang W, Shi JF, Li P, Wang JB, Xu LN, Wei WQ et al.Estimation of cancer cases and deaths attributable to infection in China. Cancer Causes Control. 2011 Aug;22(8):1153-61.
11- Nguyen TP, Luu HN, Nguyen MVT, Tran MT, Tuong TTV, Tran CTD et al.Attributable Causes of Cancer in Vietnam. JCO Glob Oncol. 2020 Feb;6:195-204.
12- Shin A, Park S, Shin HR, Park EH, Park SK, Oh JK et al. Population attributable fraction of infection-related cancers in Korea. Ann Oncol. 2011 Jun;22(6):1435-1442.
13- Inoue M, Hirabayashi M, Abe SK, Katanoda K, Sawada N, Lin Y et al.Burden of cancer attributable to modifiable factors in Japan in 2015. Glob Health Med. 2022 Feb 28;4(1):26-36.
14- Boffetta P, Tubiana M, Hill C, Boniol M, Aurengo A, Masse R et al.The causes of cancer in France. Ann Oncol. 2009 Mar;20(3):550-5.
15- Brown KF, Rumgay H, Dunlop C, Ryan M, Quartly F, Cox A et alThe fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. Br J Cancer. 2018 Apr;118(8):1130-1141.
16- Azevedo E Silva G, de Moura L, Curado MP, Gomes Fda S, Otero U, Rezende LF et al.The Fraction of Cancer Attributable to Ways of Life, Infections, Occupation, and Environmental Agents in Brazil in 2020. PLoS One. 2016 Feb 10;11(2):e0148761.
17- Brown HE, Dennis LK, Lauro P, Jain P, Pelley E, Oren E. Emerging Evidence for Infectious Causes of Cancer in the United States. Epidemiol Rev. 2019 Jan 31;41(1):82-96.
18- Tybjerg AJ, Friis S, Brown K, Nilbert MC, Morch L, Køster B. Updated fraction of cancer attributable to lifestyle and environmental factors in Denmark in 2018. Sci Rep. 2022 Jan 11;12(1):549.
19- Levin ML: The occurrence of lung cancer in man. *Acta Unio Int Contra Cancrum* 1953, 9:531–541.
20- https://www.cancer.org/healthy/cancer-causes/general-info/known-and-probable-human-carcinogens.html
21- Helicobacter and Cancer Collaborative Group. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut. 2001 Sep;49(3):347-53.
22- Palli D, Decarli A, Cipriani F, Sitas F, Forman D, Amadori D et al.Helicobacter pylori antibodies in areas of Italy at varying gastric cancer risk. Cancer Epidemiol Biomarkers Prev. 1993 Jan-Feb;2(1):37-40. PMID: 8420610.
23- Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ et al.Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018 Jan;68(1):31-54.
24- Sagnelli E, Sagnelli C, Pisaturo M, Macera M, Coppola N. Epidemiology of acute and chronic hepatitis B and delta over the last 5 decades in Italy. World J Gastroenterol. 2014 Jun 28;20(24):7635-43.
25- Buscarini E, Tanzi E, Zanetti AR, Savi E, Sbolli G, Civardi G et al. High prevalence of antibodies to hepatitis C virus among family members of patients with anti-HCV-positive chronic liver disease. Scand J Gastroenterol. 1993 Apr;28(4):343-6.

26- Ronco G, Giorgi-Rossi P, Carozzi F, Dalla Palma P, Del Mistro A, De Marco L et al. Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial. Lancet Oncol. 2006 Jul;7(7):547-55.
27- Ronco G, Segnan N, Giorgi-Rossi P, Zappa M, Casadei GP, Carozzi F, et al. New Technologies for Cervical Cancer Working Group. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. J Natl Cancer Inst. 2006 Jun 7;98(11):765-74.
28- Serraino D, Toma L, Andreoni M, Buttò S, Tchangmena O, Sarmati L et al. A seroprevalence study of human herpesvirus type 8 (HHV8) in eastern and Central Africa and in the Mediterranean area. Eur J Epidemiol. 2001;17(9):871-6.
29- Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 2016 Sep;4(9):e609-16.
30- Mentzer AJ, Brenner N, Allen N, Littlejohns TJ, Chong AY, Cortes A et al. Identification of host-pathogen-disease relationships using a scalable multiplex serology platform in UK Biobank. Nat Commun. 2022 Apr 5;13(1):1818.
31- Vescio MF, Gallo P, Farchi F, Avellis L, Spadea T, Giuliani M et al.Prevalence and attitudes to HIV testing among adults visiting public outpatient clinics in Rome: results of the MeDi (Measuring health Disparities in HIV prevention) survey. Part 1. Ann Ist Super Sanita. 2020 Jan-Mar;56(1):19-29.
32- https://www.registri-tumori.it/cms/pubblicazioni/i-numeri-del-cancro-italia-2020
33- Di Maso M, Bravi F, Polesel J, Negri E, Decarli A, Serraino D et al. Attributable fraction for multiple risk factors: Methods, interpretations, and examples. Stat Methods Med Res. 2020 Mar;29(3):854-865.
34- Wijaya WA, Liu Y, Qing Y, Li Z. Prevalence of Merkel Cell Polyomavirus in Normal and Lesional Skin: A Systematic Review and Meta-Analysis. Front Oncol. 2022 Mar 22;12:868781.
35- Ozoya OO, Sokol L, Dalia S. EBV-Related Malignancies, Outcomes and Novel Prevention Strategies. Infect Disord Drug Targets. 2016;16(1):4-21.
36- Saito M, Kono K. Landscape of EBV-positive gastric cancer. Gastric Cancer. 2021 Sep;24(5):983-989.
37- Coppeta L, Pietroiusti A, Neri A, Janni A, Baldi S, Papa F et al. Prevalence and Risk Factors for Latent Tuberculosis Infection among Healthcare Workers in a Low Incidence Country. Open Respir Med J. 2019 Apr 30;13:1-4
38- Cabrera-Sanchez J, Cuba V, Vega V, Van der Stuyft P, Otero L. Lung cancer occurrence after an episode of tuberculosis: a systematic review and meta-analysis. Eur Respir Rev. 2022 Jul 27;31(165):220025.
39- Burucoa C, Axon A. Epidemiology of Helicobacter pylori infection. Helicobacter. 2017 Sep;22 Suppl 1.
40- Abdelaal R, Yanny B, El Kabany M. HBV/HCV Coinfection in the Era of HCV-DAAs. Clin Liver Dis. 2019 Aug;23(3):463-472.

41- Cho J, Lee SS, Choi YS, Jeon Y, Chung JW, Baeg JY et al.Occult hepatitis B virus infection is not associated with disease progression of chronic hepatitis C virus infection. World J Gastroenterol. 2016 Nov 14;22(42):9427-9436.
42- Mak LY, Wong DK, Pollicino T, Raimondo G, Hollinger FB, Yuen MF. Occult hepatitis B infection and hepatocellular carcinoma: Epidemiology, virology, hepatocarcinogenesis and clinical significance. J Hepatol. 2020 Oct;73(4):952-964.
43- Dreyer G. Clinical implications of the interaction between HPV and HIV infections. Best Pract Res Clin Obstet Gynaecol. 2018 Feb;47:95-106.
44- Guidry JT, Scott RS. The interaction between human papillomavirus and other viruses. Virus Res. 2017 Mar 2;231:139-147.
45- Fabris P, Baldo V, Baldovin T, Bellotto E, Rassu M, Trivello R et al. Changing epidemiology of HCV and HBV infections in Northern Italy: a survey in the general population. J Clin Gastroenterol. 2008 May-Jun;42(5):527-32.
46- Stroffolini T, Sagnelli E, Sagnelli C, Smedile A, Furlan C, Morisco F et al.The burden of HBV infection in HCV patients in Italy and the risk of reactivation under DAA therapy. Dig Liver Dis. 2019 Mar;51(3):434-437.
47- Rovelli C, Poli A, Galli L, Cernuschi M, Tamburini AM, Racca S et al.Presence of multiple genotypes in subjects with HPV-16 infection is highly associated with anal squamous intraepithelial lesions in HIV-1 infected males. PLoS One. 2017 Oct 31;12(10):e0186367. This study is from S.Raffaele, and talks about coinfections. Should we instead cite the study based on which we calculated a 10% of coinfections in Italy?
48- Best LM, Takwoingi Y, Siddique S, Selladurai A, Gandhi A, Low B et al.Non-invasive diagnostic tests for Helicobacter pylori infection. Cochrane Database Syst Rev. 2018 Mar 15;3(3):CD012080.
49- Fiorini G, Zullo A, Saracino IM, Gatta L, Pavoni M, Vaira D. Pylera and sequential therapy for first-line Helicobacter pylori eradication: a culture-based study in real clinical practice. Eur J Gastroenterol Hepatol. 2018 Jun;30(6):621-625.
50- Zullo A, Fiorini G, Scaccianoce G, Portincasa P, De Francesco V, Vassallo R et al. Sequential therapy for first-line Helicobacter pylori eradication: 10- or 14-day regimen? J Gastrointestin Liver Dis. 2019 Mar;28(1):11-14.
51- Stroffolini T, Morisco F, Ferrigno L, Pontillo G, Iantosca G, Cossiga V et al.Effectiveness of Hepatitis B Vaccination Campaign in Italy: Towards the Control of HBV Infection for the First Time in a European Country. Viruses. 2022 Jan 26;14(2):245.
52- Juan J, Feld JJ. Hepatitis B virus and hepatitis C virus treatment and management in patients receiving immune-modifying agents. Curr Opin Rheumatol. 2014 Jul;26(4):395-403.
53- Lanini S, Ustianowski A, Pisapia R, Zumla A, Ippolito G. Viral Hepatitis: Etiology, Epidemiology, Transmission, Diagnostics, Treatment, and Prevention. Infect Dis Clin North Am. 2019 Dec;33(4):1045-1062.
54- Stella L, Santopaolo F, Gasbarrini A, Pompili M, Ponziani FR. Viral hepatitis and hepatocellular carcinoma: From molecular pathways to the role of clinical surveillance and antiviral treatment. World J Gastroenterol. 2022 Jun 7;28(21):2251-2281.
55- Bianchi FP, Vimercati L, Mansi F, De Nitto S, Stefanizzi P, Rizzo LA et al. Compliance with immunization and a biological risk assessment of health care workers as part of an

occupational health surveillance program: The experience of a university hospital in southern Italy. Am J Infect Control. 2020 Apr;48(4):368-374.

56- Barchitta M, Basile G, Lopalco PL, Agodi A. Vaccine-preventable diseases and vaccination among Italian healthcare workers: a review of current literature. Future Microbiol. 2019 Jun;14:15-19.

57- https://www.ccmnetwork.it/documenti_Ccm/prg_area1/Inf_Oss/Normativa_naz/Circolare52_1985.pdf

58- Fiore V, De Matteis G, Ranieri R, Saderi L, Pontali E, Muredda A et al. HCV testing and treatment initiation in an Italian prison setting: A step-by-step model to micro-eliminate hepatitis C. Int J Drug Policy. 2021 Apr;90:103055.

59- Fiore V, Rastrelli E, Madeddu G, Ranieri R, De Vito A, Giuliani R et al. HCV spread among female incarcerated population and treatment pathways to viral elimination in Italian prison settings: clinical perspectives and medico legal aspects. BMC Infect Dis. 2022 Jul 7;22(1):601.

60- Masarone M, Caruso R, Aglitti A, Izzo C, De Matteis G, Attianese MR et al. Hepatitis C virus infection in jail: Difficult-to-reach, not to-treat. Results of a point-of-care screening and treatment program. Dig Liver Dis. 2020 May;52(5):541-546.

61- https://www.europeancancer.org/resources/199:hpv-vaccine-tracker.html

62- https://www.quotidianosanita.it/allegati/allegato660418.pdf

63- Campari C, Fedato C, Iossa A, Petrelli A, Zorzi M, Anghinoni E et al. Cervical cancer screening in immigrant women in Italy: a survey on participation, cytology and histology results. Eur J Cancer Prev. 2016 Jul;25(4):321-8.

64- https://www.salute.gov.it/imgs/C_17_notizie_5681_0_file.pdf

65- https://www.epicentro.iss.it/passi/dati/ScreeningCervicale

66- Boscolo-Rizzo P, Zorzi M, Del Mistro A, Da Mosto MC, Tirelli G, Buzzoni C et al. The evolution of the epidemiological landscape of head and neck cancer in Italy: Is there evidence for an increase in the incidence of potentially HPV-related carcinomas? PLoS One. 2018 Feb 7;13(2):e0192621.

67- Bendinelli B, Palli D, Assedi M, Facchini L, Grioni S, Agnoli C et al. Alcohol, smoking and rectal cancer risk in a Mediterranean cohort of adults: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Italy cohort. Eur J Gastroenterol Hepatol. 2020 Apr;32(4):475-483.

68- Varì R, Scazzocchio B, D'Amore A, Giovannini C, Gessani S, Masella R. Gender-related differences in lifestyle may affect health status. Ann Ist Super Sanita. 2016 Apr-Jun;52(2):158-66.

69- Millarini V, Caini S, Allamani A, Ermini I, Querci A, Masala G et al. Prevalence and co-occurrence of unhealthy lifestyle habits and behaviours among secondary school students in Tuscany, central Italy. Public Health. 2019 Jan;166:89-98.

70- Yang L, Kartsonaki C, Yao P, de Martel C, Plummer M, Chapman D et al. The relative and attributable risks of cardia and non-cardia gastric cancer associated with Helicobacter pylori infection in China: a case-cohort study. Lancet Public Health. 2021 Dec;6(12):e888-e896.

71- Eusebi LH, Telese A, Marasco G, Bazzoli F, Zagari RM. Gastric cancer prevention strategies: A global perspective. J Gastroenterol Hepatol. 2020 Sep;35(9):1495-1502.

72- Ding SZ, Du YQ, Lu H, Wang WH, Cheng H, Chen SY et al. Chinese Consensus Report on Family-Based *Helicobacter pylori* Infection Control and Management (2021 Edition). Gut. 2022 Feb;71(2):238-253.
73- Ma J, Yu M, Shao QQ, Yu XC, Zhang C, Zhao JB et al. Both family-based Helicobacter pylori infection control and management strategy and screen-and-treat strategy are cost-effective for gastric cancer prevention. Helicobacter. 2022 Aug;27(4):e12911.
74- Gotoda T, Kusano C, Suzuki S, Horii T, Ichijima R, Ikehara H. Clinical impact of vonoprazan-based dual therapy with amoxicillin for H. pylori infection in a treatment-naïve cohort of junior high school students in Japan. J Gastroenterol. 2020 Oct;55(10):969-976.
75- Ford AC, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut. 2020 Dec;69(12):2113-2121.
76- Romano M, Gravina AG, Eusebi LH, Pellegrino R, Palladino G, Frazzoni L et al. Management of Helicobacter pylori infection: Guidelines of the Italian Society of Gastroenterology (SIGE) and the Italian Society of Digestive Endoscopy (SIED). Dig Liver Dis. 2022 Sep;54(9):1153-1161.
77- Varga MG, Butt J, Blot WJ, Le Marchand L, Haiman CA, Chen Y et al. Racial Differences in *Helicobacter pylori*CagA Sero-prevalence in a Consortium of Adult Cohorts in the United States. Cancer Epidemiol Biomarkers Prev. 2020 Oct;29(10):2084-2092.
78- Morisco F, Stroffolini T, Lombardo FL, Guarino M, Camera S, Cossiga V et al. Prevalence of and risk factors for HBV infection in a metropolitan Southern Italian area: Evidence for the effectiveness of universal Hepatitis B vaccination. Dig Liver Dis. 2017 Nov;49(11):1257-1261.
79- Pan CQ, Rabinovich C, Gayam V, Normatov M, Fidman B, Wang D. Late presenters among minority patients with chronic hepatitis C infection in the USA. Int J Public Health. 2020 Sep;65(7):1181-1191.
80- Olusola P, Banerjee HN, Philley JV, Dasgupta S. Human Papilloma Virus-Associated Cervical Cancer and Health Disparities. Cells. 2019 Jun 21;8(6):622.
81- Probst C, Simbayi LC, Parry CDH, Shuper PA, Rehm J. Alcohol Use, Socioeconomic Status and Risk of HIV Infections. AIDS Behav. 2017 Jul;21(7):1926-1937.
82- Collatuzzo G, Teglia F, Boffetta P. Role of Occupation in Shaping Cancer Disparities. Cancers (Basel). 2022 Aug 31;14(17):4259.
83- Pike LRG, Royce TJ, Mahal AR, Kim DW, Hwang WL, Mahal BA et al. Outcomes of HPV-Associated Squamous Cell Carcinoma of the Head and Neck: Impact of Race and Socioeconomic Status. J Natl Compr Canc Netw. 2020 Feb;18(2):177-184.
84- Olusola P, Banerjee HN, Philley JV, Dasgupta S. Human Papilloma Virus-Associated Cervical Cancer and Health Disparities. Cells. 2019 Jun 21;8(6):622.
85- Gupta S, Tao L, Murphy JD, Camargo MC, Oren E, Valasek MA et al. Race/Ethnicity-, Socioeconomic Status-, and Anatomic Subsite-Specific Risks for Gastric Cancer. Gastroenterology. 2019 Jan;156(1):59-62.e4.
86- Giorgi Rossi P, Baldacchini F, Ronco G. The Possible Effects on Socio-Economic Inequalities of Introducing HPV Testing as Primary Test in Cervical Cancer Screening Programs. Front Oncol. 2014 Feb 10;4:20.
87-Adjei Boakye E, Tobo BB, Rojek RP, Mohammed KA, Geneus CJ, Osazuwa-Peters N. Approaching a decade since HPV vaccine licensure: Racial and gender disparities in knowledge

and awareness of HPV and HPV vaccine. Hum Vaccin Immunother. 2017 Nov 2;13(11):2713-2722.
88- Scognamiglio P, Girardi E, Fusco M, Piselli P, Spena SR, Maione C et al. Lack of implementation of Hepatitis B Virus (HBV) vaccination policy in household contacts of HBV carriers in Italy. BMC Infect Dis. 2009 Jun 7;9:86.
89- Collatuzzo G, Fiorini G, Vaira B, Violante FS, Farioli A, Boffetta P. The role of the occupational physician in controlling gastric cancer attributable to *Helicobacter pylori*infection: A review. Prev Med Rep. 2021 Aug 18;24:101527.
90-Leone Roberti Maggiore U, Scala C, Toletone A, Debarbieri N, Perria M, et al. Susceptibility to vaccine-preventable diseases and vaccination adherence among healthcare workers in Italy: A cross-sectional survey at a regional acute-care university hospital and a systematic review. Hum Vaccin Immunother. 2017 Feb;13(2):470-476.
91- Napolitano F, Pelullo CP, Della Polla G, Angelillo IF. HPV Vaccination Attitudes and Behaviors among General Practitioners in Italy. Vaccines (Basel). 2021 Jan 19;9(1):63.
92- Lu PJ, Hung MC, Srivastav A, Grohskopf LA, Kobayashi M, Harris AM et al.Surveillance of Vaccination Coverage Among Adult Populations -United States, 2018. MMWR Surveill Summ. 2021 May 14;70(3):1-26.
93- Garbuglia AR, Lapa D, Sias C, Capobianchi MR, Del Porto P. The Use of Both Therapeutic and Prophylactic Vaccines in the Therapy of Papillomavirus Disease. Front Immunol. 2020 Feb 18;11:188.
94- Du J, Ährlund-Richter A, Näsman A, Dalianis T. Human papilloma virus (HPV) prevalence upon HPV vaccination in Swedish youth: a review based on our findings 2008-2018, and perspectives on cancer prevention. Arch Gynecol Obstet. 2021 Feb;303(2):329-335.
95- Douglas R. Lowy; John T. Schiller. Reducing HPV-Associated Cancer Globally. *Cancer Prev Res (Phila)* (2012) 5 (1): 18–23.
96- Choi SE, Choudhary A, Huang J, Sonis S, Giuliano AR, Villa A. Increasing HPV vaccination coverage to prevent oropharyngeal cancer: A cost-effectiveness analysis. Tumour Virus Res. 2022 Jun;13:200234.

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Data availability statement : The data that support the findings of this study are openly available from the authors upon reasonable request.

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Table 1- Relative risks (RR) and prevalence of exposure to infectious agents used in the calculation of attributable fractions

Agent	Prevalence %	Cancer	RR	Reference RR	Reference prevalence
Hp	0.45	Cardia gastric	1.6	de Martel 2020 [9]/ /HCCG 2001 [21]	
		Non-cardia gastric	5.9	Islami 2018* [23]	
HBV	0.01	Liver	23.4	Islami 2018* [23]	Palli 1993 [22]
					Sagnelli 2014 [24]
HCV	0.02	Liver	27.6	Islami 2018* [23]	Buscarini 1993 [25]
		NHL	1.78	Islami 2018* [23]	
HPV	0.06	Cervix	∞	Islami 2018* [23]	Ronco 2006 a,b **[26,27]
		Oral cancer	1.94	Islami 2018* [23]	
		Pharynx	8.6	Islami 2018* [23]	
		Anus	6.7	Islami 2018* [23]	
		Vagina	10.9	Islami 2018* [23]	
		Vulva	4.4	Islami 2018* [23]	
		Penis	5.3	Islami 2018* [23]	
HHV-8	0.19	Kaposi Sarcoma	∞	Islami 2018* [23]	Serraino 2001 [28]
EBV	0.95	HL	3.7	Plummer 2016 [29]	Mentzer 2019 [30]
		Nasopharyngeal	10.14	Plummer 2016 [29]	
HIV	0.02	NHL	15	Islami 2018* [23]	Vescio 2020 [31]
		HL	11	Islami 2018* [23]	
		Anus	32	Islami 2018* [23]	
		Cervix	5	Islami 2018* [23]	
		Kaposi sarcoma	1584	Islami 2018* [23]	

Notes: Helicobacter pylori [Hp]; Hepatitis B and C Viruses [HBV, HCV]; Human Papillomavirus [HPV]; Human Herpes Virus-8 [HHV8]; Epstein-Barr Virus [EBV]; and Human Immunodeficiency Virus [HIV]

HL= Hodgkin Lymphoma; NHL= Non-Hodgkin Lymphoma; MALT= mucosal-associated lymphoid tissue

HCCG= Helicobacter and Cancer Collaborative Group

*See references for specific agents in Supporting Table 3 of [23]

**Weighed average of two age groups; prevalence in women used for both sexes

Table 2-Number of deaths from selected cancers in 2017 and of cases of selected cancers in 2020 in Italy.

Site	ICD 10	Male		Female	
		Deaths	Cases	Deaths	Cases
Oral cavity	C00-C06	1056	2177	656	1314
Nasopharynx	C11	183	377	76	152
Pharynx	C09,C10,C12-C14	669	1379	199	398
Gastric cardia	C16	828	1269	583	915
Gastric non-cardia	C16	4690	7189	3306	5183
Anus	C21	180	398	255	588
Liver	C22	6156	8978	3107	4034
Kaposi Sarcoma	C46.1	495	669	191	258
Vulva	C51	-	-	214	1024
Vagina	C52	-	-	45	218
Cervix	C53	-	-	494	2365
Penis	C60	168	371	-	-
HL	C81	441	1222	357	929
NHL	C82-86	2479	7011	2041	6171
Gastric MALT	C88.4	45	126	37	111
All cancers	C00-97	100,123	194,754	79,962	181,857

Notes: HL= Hodgkin Lymphoma; NHL= Non-Hodgkin Lymphoma; MALT= mucosal-associated lymphoid tissue

Table 3-Total number of cancer deaths in 2017 and cancer cases in 2020 attributable to infectious agents in Italy, by sex and infectious agent.

Infectious agent	N deaths, males	N deaths, females	Total N deaths	N cases, males	N cases, females	Total N cases
HPV						
Oral cavity	56	35	91	116	70	186
Pharynx	209	62	271	432	125	557
Anus	46	65	111	102	150	252
Cerivx	-	494	494	-	2365	2365
Vulva	-	36	36	-	174	174
Vagina	-	17	17	-	81	81
Penis	17	-	17	76	-	76
Total	328	709	1037	726	2965	3691
% total cancer	0.3	0.9	0.6	0.4	1.6	1.0
HP						
Gastric cardia	176	124	300	270	194	464
Gastric non-cardia	3227	2274	5501	4946	3566	8512
Gastric MALT	31	26	57	89	78	167
Total	3434	2424	5858	5305	3838	9143
% total cancer	3.4	3.0	3.3	2.7	2.1	2.4
HBV						
Liver	1127	569	1696	1643	738	2381
% total cancer	1.1	0.7	0.9	0.8	0.4	0.6
HCV						
Liver	2138	1079	3217	3118	1401	4519
Non-Hodgkin lymphoma	38	31	69	108	95	203
Total	2176	1110	3286	3226	1496	4722
% total cancer	2.2	1.4	1.8	1.7	0.8	1.3
EBV						
Nasopharynx	146	61	259	302	122	424
Hodgkin lymphoma	159	129	288	440	334	774
Total	305	190	495	742	456	1198
% total cancer	0.3	0.2	0.3	0.4	0.3	0.3
HIV						
Anus	69	98	167	152	224	376
Kaposi Sarcoma	480	185		649	250	899
Hodgkin lymphoma	73	60	133	204	155	359
Non-Hodgkin lymphoma	572	471	1043	1534	1350	2884
Total	1194	814	2008	2539	1979	4518
% total cancer	1.2	1.0	1.1	1.3	1.0	1.2
HHV8						
Kaposi Sarcoma	495	191	686	669	258	927
% total cancer	0.5	0.2	0.4	0.3	0.1	0.2

Notes: Helicobacter pylori [Hp]; Hepatitis B and C Viruses [HBV, HCV]; Human Papillomavirus [HPV]; Human Herpes Virus-8 [HHV8]; Epstein-Barr Virus [EBV]; and Human Immunodeficiency Virus [HIV]

Table 4-Total number of cancer deaths in 2017 and cancer cases in 2020 attributable to infectious agents in Italy, by cancer sex and cancer site.

Cancer site	N deaths, males	N deaths, females	Total N deaths	N cases, males	N cases, females	Total N cases
Oral cavity	56	35	91	116	70	186
Nasopharynx	146	61	207	302	122	424
Pharynx	209	62	271	432	125	557
Gastric cardia	176	124	300	270	194	464
Gastric non-cardia	3227	2274	5501	4946	3566	8512
Gastric MALT	31	26	57	89	78	167
Anus	97	138	235	215	318	533
Liver	2873	1450	4323	4190	1883	6073
Kaposi Sarcoma	495	191	686	669	258	927
Vulva	-	36	36	-	174	174
Vagina	-	17	17	-	81	81
Cervix	-	494	494	-	2365	2365
Penis	34	-	34	72	-	72
HL	206	167	373	570	434	1004
NHL	572	471	1043	1618	1424	3024
All cancers N	8,124	5,546	13,670	13,493	11,091	24,584
All cancers AF	8.1 %	6.9%	7.6%	6.9%	6.1%	6.5%

Notes: HL= Hodgkin Lymphoma; NHL= Non-Hodgkin Lymphoma; MALT= mucosal-associated lymphoid tissue; N= number; AF=attributable fraction

Table 5. Population attributable fraction of cancer deaths related to infectious agents in selected countries, by sex.

Sex	Italy (present study)	China [10]	Vietnam [11]	United States [20]	United Kingdom [15]	Brazil [16]	France [14]	Denmark [18]
Men %	8.1	30.6	34.7	3.4	3.1	5.9	3.1	2.3
Women %	6.9	24.1	22.1	3.3	4.3	13.8	4.4	3.6

Appendix - Estimate of the number of cases of cancers for which no national data are available

Cancer	Results	Justification, reference
Oral cavity cancer	50.2% of oral and pharyngeal cancers	Based on distribution of incidence of subtypes of oral and pharyngeal cancer in 5 Italian cancer registries* [1]
Nasopharyngeal cancer	8.7% of oral and pharyngeal cancers	Based on distribution of incidence of subtypes of oral and pharyngeal cancer in 5 Italian cancer registries* [1]
Pharyngeal cancer	31.8% of oral and pharyngeal cancers	Based on distribution of incidence of subtypes of oral and pharyngeal cancer in 5 Italian cancer registries* [1]
Cardia gastric cancer	15% of gastric cancer	Based on distribution of incidence of subtypes of gastric cancer in 5 Italian cancer registries* [1]
Non-cardia gastric cancer	85% of gastric cancer	Based on distribution of incidence of subtypes of gastric cancer in 5 Italian cancer registries* [1]
Anal cancer	1.7% of colorectal cancer	Based on distribution of incidence of subtypes of colorectal cancer in 5 Italian cancer registries* [1]
Vulvar cancer	43.3% of cervical cancer	Based on ratio of incidence of cervical cancer to that of vulvar cancer in 5 Italian cancer registries* [1]
Vaginal cancer	9.2% of cervical cancer	Based on ratio of incidence of cervical cancer to that of vaginal cancer in 5 Italian cancer registries* [1]
Penal cancer	1.1% of prostate cancer	Based on ratio of incidence of prostate cancer to that of penal cancer in 5 Italian cancer registries* [1]
Hodgkin lymphoma	15.1% of lymphoma	Based on distribution of incidence of subtypes of lymphoma in 5 Italian cancer registries* [1]
Non-Hodgkin lymphoma	84.9% of lymphoma	Based on distribution of incidence of subtypes of lymphoma in 5 Italian cancer registries* [1]
Gastric MALT	1.8% of lymphoma	Based on distribution of incidence of subtypes of lymphoma in 5 Italian cancer registries* [1]

* Milan; Veneto Region; Modena; Naples; Eastern-Sicily

MALT, mucosal-associated lymphoid tissue

[1] Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer, 2020. Available from: https://gco.iarc.fr/

3. The HPOS study as pilot of the CPW project

Prev Med Rep. 2021 Aug 18;24:101527.

3.1 The role of the occupational physician in controlling gastric cancer attributable to *Helicobacter pylori* infection: A review

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Keywords: *Helicobacter pylori*, Gastric cancer, Prevention, Occupational medicine, Workplace

Abstract

This review aimed to describe the potential role of occupational physician in the implementation of a screening program for *Helicobacter pylori* (Hp) infection for gastric cancer prevention. We reviewed the epidemiological background of gastric cancer and its association with Hp, exploring the hypothesis of a "test-and-treat" protocol among working population. Clinical trials and model-based studies were collected to provided empirical evidence of the feasibility of eradication on large scale. In particular, previous studies conducted in occupational settings were discussed. Hp prevalence ranges between about 20 and 90%, with higher rates in Asia and Latin America and lower rates in Europe and North America. Large-scale trials on screening and treatment of infection have been conducted especially in East Asia, lacking elsewhere. Only few studies investigated Hp prevalence among workers. The benefit of eradication at occupational level has not yet been adequately studied. The design of a workplace-based Hp screening program appears to be innovative and could contribute to controlling gastric cancer. The benefit would involve not only high-risk subjects, but also their families, since the route of transmission is principally within the household. An occupational setting for a Hp screening would have positive consequences in terms of individual and public health.

- Helicobacter pylori eradication would contribute to stomach cancer prevention.
- The workplace is a privileged setting for Helicobacter pylori screen-and-treat program.
- The benefit of eradication at occupational level has not yet been adequately studied.

1. Introduction

Although the age-adjusted incidence rate of gastric cancer has decreased in most populations (Supplementary Fig. 1), the burden of the disease remains high (Bray et al., 2017). According to Global Burden of Disease (GBD) study, in 2017 more than 1.22 million new cases of gastric cancer were diagnosed worldwide, and close to 865.000 people died from the disease, making it the third most frequent cause of neoplastic death (The global, regional, and national burden of stomach cancer in 195 countries, 2017). In most populations gastric cancer is more frequent in men than in women: the incidence rate in the 2018 in the US was 15.7/100,000 and 7.0/100,000 respectively (Thrift and El-Serag, 2020). The incidence is higher in less-developed countries and in the least affluent groups of the population. Survival has only modestly improved in many countries over the last decades; 5-year survival ranges from 65 to 70% in countries in which imaging-based screening is implemented, such as Japan and South Korea, to 15–30% in US and Europe. The high fatality rates are explained by the fact that, despite a long latency, gastric cancer is usually diagnosed at late stage, when prognosis is poor.

Gastric cancer can be distinguished by subsite into cardia and non-cardia type (Boffetta et al., 2014), the latter mainly caused by infection with *Helicobacter pylori* (Hp) (Marshall and Warren, 1984). Other environmental and genetic risk factors have been identified: they are summarized in Table 1 (Boffetta et al., 2014).

Table 1. Non-genetic risk factors of gastric cancer, by subsite (adapted from Boffetta et al., 2014).

Risk factor	Cardia cancer	Non-cardia cancer
Old age	++	++
Male sex	++	++
Tobacco smoking	+	+
Family history of gastric cancer	++	++
Ionizing radiation	+	+
Helicobacter pylori infection		++
Low SES		++
Dietary salt intake		++
Intake of smoked food		+
Alcohol drinking	?	?
Overweight/obesity	++	
GERD	++	

++ Strong risk factor (relative risk <2). + Weak risk factor (1 < relative risk <2). ? Suspected risk factor.

Hp infection typically occurs during childhood and, if untreated, persists lifelong (Malaty et al., 2002). The route of transmission is not fully known but it involves fecal-oral and oral-oral contacts primarily from mother to child (Mamishi et al., 2016, Konno et al., 2008, Okuda et al., 2019, Brown, 2000). Low education, parents' low education, poor dental hygiene, crowded living places in childhood and several other indicators of low socioeconomic status are the main risk factors for Hp infection (Nouraie et al., 2009).

In addition to gastric cancer, chronic infection with Hp is causally associated with other gastrointestinal diseases, including gastritis, peptic ulcer, and gastric mucosa associated lymphoid tissue lymphoma (MALT) (Valenzuela et al., 2015). Moreover, Hp infection is also involved in extra-gastric diseases, including in particular idiopathic thrombocytopenic purpura, vitamin B12 deficiency and iron-deficient anemia (Gravina et al., 2018).

Despite most of the infections have an asymptomatic course, all chronically infected individuals develop chronic gastritis, which can become active in conjunction with concomitant factors, such as tobacco smoking, low-quality diet, and psychogenic stress (Gravina et al., 2018).

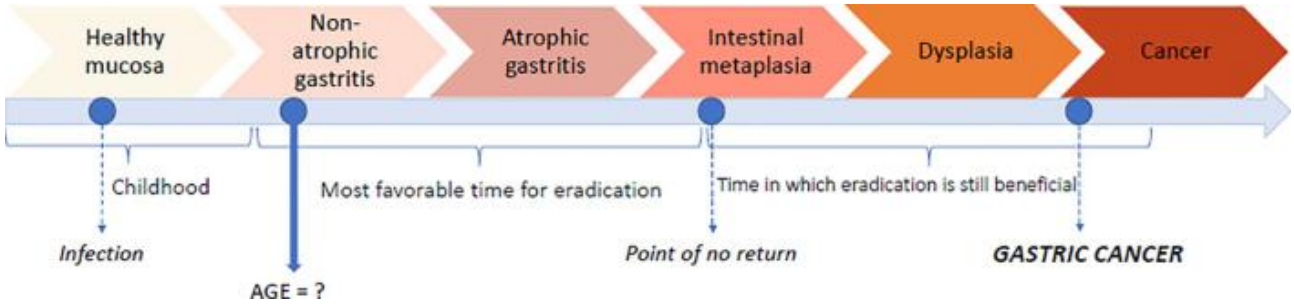
Because of its strong association with gastric cancer, Hp represents the most important infectious cause of cancer, with an estimated burden of 810.000 new cases per year (8.7 cases per 100,000 person-years) worldwide (de Martel et al., 2020). This represents approximately 89% of non-cardia gastric cancer, corresponding to 78% of all gastric cancer cases (IHPWG, 2014). Hp acts through a variety of virulence factors (Nejati et al., 2018) where Cag-A protein connotes the strain most strongly related to malignant transformation (Nejati et al., 2018, Hatakeyama, 2004, Park et al., 2018). Specifically, infection with CagA-positive compared to CagA-negative strains are associated to an almost 2-fold increased risk of non-cardia gastric cancer (Huang et al., 2003). Differences in the distribution of Hp strains contribute to the geographic heterogeneity of the association between Hp infection and gastric cancer risk (Brown, 2000).

The global prevalence of Hp infection is estimated to be higher than 50%, i.e., 4.4 billion individuals (Hooi et al., 2017), with inter- and intra-regional differences and a variability between different populations that has not still been systematically described. Public sanitation and progressive introduction of eradication strategies have contributed to limit Hp spreading, so that the infection has decreased over time in several countries (Leja et al., 2019). For example, the prevalence in Korea was 66.9% in 1998, 59.6% in 2005, 54.4% in 2011, and 43.9% in 2016–2017 (Leja et al., 2019). The evidence on the effectiveness of prevention of gastric cancer through Hp eradication is reviewed below.

2. Etiologic role of Helicobacter pylori infection in gastric carcinogenesis

Gastric carcinogenesis, described by Correa as a cascade (Fig. 1), is a long-latency process that affects susceptible individuals and passes through different pre-neoplastic lesions (Correa, 1988). It is sustained by inflammatory and immunological mechanisms which lead to progressive mucosal damage and neoplastic transformation (Valenzuela et al., 2015, Correa and Houghton, 2007, Liu et al., 2016).

Fig. 1. Steps in gastric carcinogenesis and opportunities for prevention [18].



Marshall and Warren first suggested a possible role for Hp in the etiology of gastric cancer (Marshall and Warren, 1984). Their hypothesis prompted laboratory, animal, and epidemiologic studies, which consistently demonstrated a causal association, leading to the classification of Hp as established human carcinogen in 1994 (International Agency for Research on Cancer, 1994).

Intervention studies have provided evidence that Hp eradication may reduce the risk of gastric cancer. A meta-analysis showed 35% reduction in gastric cancer risk in those who were treated for Hp (Fuccio et al., 2009). In addition, a randomized study of 544 patients with early gastric cancer showed a 65% reduction in the incidence of metachronous lesions in those who were treated for Hp (Fukase et al., 2008).

According to a large pooled analysis, the relative risk (RR) of non-cardia gastric cancer associated with Hp resulted to be 5.9, while no association was detected with cardia cancer (Helicobacter and Cancer Collaborative Group, 2001). The risk was lower (RR=2.4) among those subjects who developed cancer within 10 years from Hp detection. This is due to the fact that the progressive damage caused by the microorganism compromises its own colonization of gastric mucosa. Thus, there might be an underestimate of cases attributed to Hp infection, as the bacterium might no longer be detectable when cancer occurs. When considering histological types (intestinal and diffuse), the relation between Hp infection and gastric cancer is comparable (Holton et al., 2011).

3. Screening and treatment of H. pylori infection

As for other cancer prevention interventions, there is a paradox due to the fact that those countries with a higher prevalence of infection are the ones with less possibility to set up a screening program because of the lack of resources, while preventive actions can be implemented in more developed countries, where the prevalence of Hp and the incidence of gastric cancer are relatively low. However, even in low-prevalence countries, there is a large proportion of the population at risk of developing gastric cancer, e.g., from 18.9 % in Switzerland to 26.2% in Sweden (Hooi et al., 2017).

Current evidence demonstrates that eradication therapy is the most powerful tool to prevent gastric cancer development, with at least a one third reduction of risk (Leja et al., 2019). A large number of studies corroborate the beneficial impact of eradication in term of gastric cancer prevention, which were included in systematic reviews and meta-analyses, including one by Fuccio and colleagues in which the OR 0.65 (95% CI, 0.43 to 0.98) in favor of treatment (Fuccio et al., 2009).

The value of primary prevention through Hp treatment is clearly stated in the Kyoto consensus guidelines, which state that *"Hp infected individuals should be offered eradication therapy, unless there are competing considerations"* (Sugano et al., 2015). The justification of this statement stems from the fact that through eradication the pathogenesis of Hp-related diseases would be stopped (individual benefit), and the reservoir of infection would drastically decrease, with consequent economic and public health advantages.

Several noninvasive methods are available to detect Hp. Urea breath test (UBT) exploits the peculiar urease activity of Hp to assess the state of infection. It represents an ideal diagnostic test, because of its simple and quick execution and its great validity: studies report more than 95% of sensitivity and specificity before eradication and even higher values in assessing the success of the treatment (100% sensitivity, 98.6% specificity) (Gatta et al., 2006). Stool antigen test (SAT) seems to be better suited for screening protocols as it is cheaper than UBT, and it doesn't require the intervention of healthcare professionals. A prospective study conducted in Taiwan has proven the feasibility of the one-step Hp SAT in primary care setting and in the mass screening, with a sensitivity of 88%, a specificity of 100%, a positive predictive value of 100%, a negative predictive value of 89%, and an accuracy of 94% (Lee et al., 2014).

In most patients, Hp can be eradicated with the use of 7–14 days therapy combining a proton pump inhibitor and antibiotics (Malfertheiner et al., 2017). The eradication rate depends mainly on the sensitivity of the bacterial strain to antimicrobial drugs. The therapy for Hp has the important

characteristic to be a short and, in most of cases, one-time-in-life treatment. In fact, reinfection is relatively infrequent and inversely correlated with country development, with a recurrence rate estimated to be 2.82 +/- 1.16% per patient-year globally (Yan et al., 2013). Table 2 shows different first-line antibiotic regimens for Hp, according to different guidelines (Fallone et al., 2019). According to the most recent American College of Gastroenterology (ACG) guidelines, evidence-based first line therapies are clarithromycin triple therapy (PPI, clarithromycin and amocixillin or metronidazole for 14 days), bismuth quadruple therapy (PPI, bismuth, tetracycline and nitroimidazole for 10–14 days) and concomitant therapy (PPI, clarithromycin, amoxicillin and nitroimidazole for 10–14 days) (Chey et al., 2017). If the first line fails, the second line therapy must avoid antibiotics that were previously administered.

Table 2. First-Line Treatment Recommendations by the Toronto Consensus, Maastricht V/Florence Consensus and the American College of Gastroenterology (ACG) Guidelines (modified from Fallone et al., 2019).

Therapy	Toronto	Maastricht V/Florence	ACG
Bismuth quadruple therapy	R	R (only choice if high dual resistance*)	R
Concomitant therapy	R	R if high C-Res or if bismuth unavailable	R
PPI triple therapy	R in areas of <15% C-Res or proven eradication success >85%	R only in areas of low C-Res	R in areas of C-Res <15% and no previous macrolide exposure
Sequential and hybrid therapies	RAU	NR	S‡
Levofloxacin regimens	NR	–	S‡

R, recommended; NR, not recommended; RAU, recommended against use; S, suggested. C-Res, clarithromycin resistance. * Dual refers to resistance to both clarithromycin and metronidazole. ‡ Suggested means that the ACG finds it permissible for practice but not ideal.

Treatment outcomes have been recently studied by Nyssen and colleagues, who analyzed 21,533 subjects from the European Registry on Helicobacter pylori management (Hp-EuReg) who followed different first-line eradication schemes between 2013 and 2018 (Nyssen et al., 2021). The results suggest that effectiveness varies by region and over time. Compliance clearly improves the effectiveness of any therapeutic protocol, while clarithromycin resistance reduces it to below 50%. From this review, quadruple therapies appear to be the only regimens able to guarantee and optimal (90% or more) eradication rate.

Primary resistance represents the main limitation to eradication, especially when considering therapies including macrolides (e.g., clarithromycin). This was recognized by the World Health Organization, which in 2017 put Hp clarithromycin-resistant among the high priority pathogens for which new antibiotics are urgently needed (World Health Organization, 2017). Moreover, a suboptimal compliance of the patient affects eradication range, so that the complexity of antibiotic administration (e.g., frequency and number of pills) should be considered when choosing the treatment.

Antibiotic susceptibility varies among populations, following the different patterns of antibiotic prescription between and within countries, as well as among different subpopulations. For example, resistance is more often observed in women who have been prescribed antibiotic for gynecological infections (Savoldi et al., 2018). This explains why even in areas where a specific antibiotic resistance is low there are niches of people with high prevalence of resistant Hp strains. Several studies have shown how clarithromycin resistance has spread over the years, showing that where Hp prevalence is low, antibiotic resistance does not increase considerably, while countries with high prevalence of infection are dramatically affected by this problem.

A variety of studies demonstrated that a test-and-treat strategy would be favorable in high-risk countries from Asia (Yeh et al., 2009, Han et al., 2020). However, relatively few data are available from lower risk countries. In a Swedish population-based study (Doorakkers et al., 2018) Doorakkers et al. observed a decreased risk of gastric adenocarcinoma, both considering the cardia and non-cardia types, during the follow up of 95,176 individuals who received eradication therapy: the standardized incidence ratio of non-cardia gastric cancer decreased proportionally with the time after treatment, from 10.7 (95% CI 7.77–14.4) at 1–3 years, to 0.43 (95% CI 0.16–0.93) at 5–7.5 years.

The cost-effectiveness of Hp screening has been further investigated in several model-based studies (Yeh et al., 2009, Han et al., 2020, Doorakkers et al., 2018, Kowada, 2018, Fendrick et al., 1999, Xie et al., 2008, Roderick et al., 2003, Teng et al., 2017, Leivo et al., 2004). These studies have been reviewed and meta analyzed by Lansdorp-Vogelaar and Sharp, 2013, Areia et al., 2013. Assumptions varied about key aspects, including infection prevalence, age range of screened population, sensitivity and specificity of Hp test, and adherence and effectiveness of treatment, this heterogeneity making difficult to outline a comprehensive frame. In particular, the assumed prevalence of infection varied from 13% in a study from Finland to over 40% in studies from Singapore and Japan (Kowada, 2018, Xie et al., 2008, Leivo et al., 2004). In all these analyses the intervention was estimated to be cost-effective, with larger benefit in populations with higher prevalence of infection.

Beside model-based studies, only few clinical trials have provided empirical evidence of the cost-effectiveness of eradication in countries where the prevalence of infection is low (Table 3) (Ford et al., 2005, Harvey et al., 2010, Høgh et al., 2019). Two trials from UK results in a positive effect of the intervention despite relatively low prevalence of infection, while a study from Denmark did not suggest an improvement in quality-adjusted life-years in the treated group; in the latter study, however, only 54% of the enrolled subjects were included in the follow-up.

Table 3. Characteristics of trial of cost-effectiveness of Hp eradication in asymptomatic individuals.

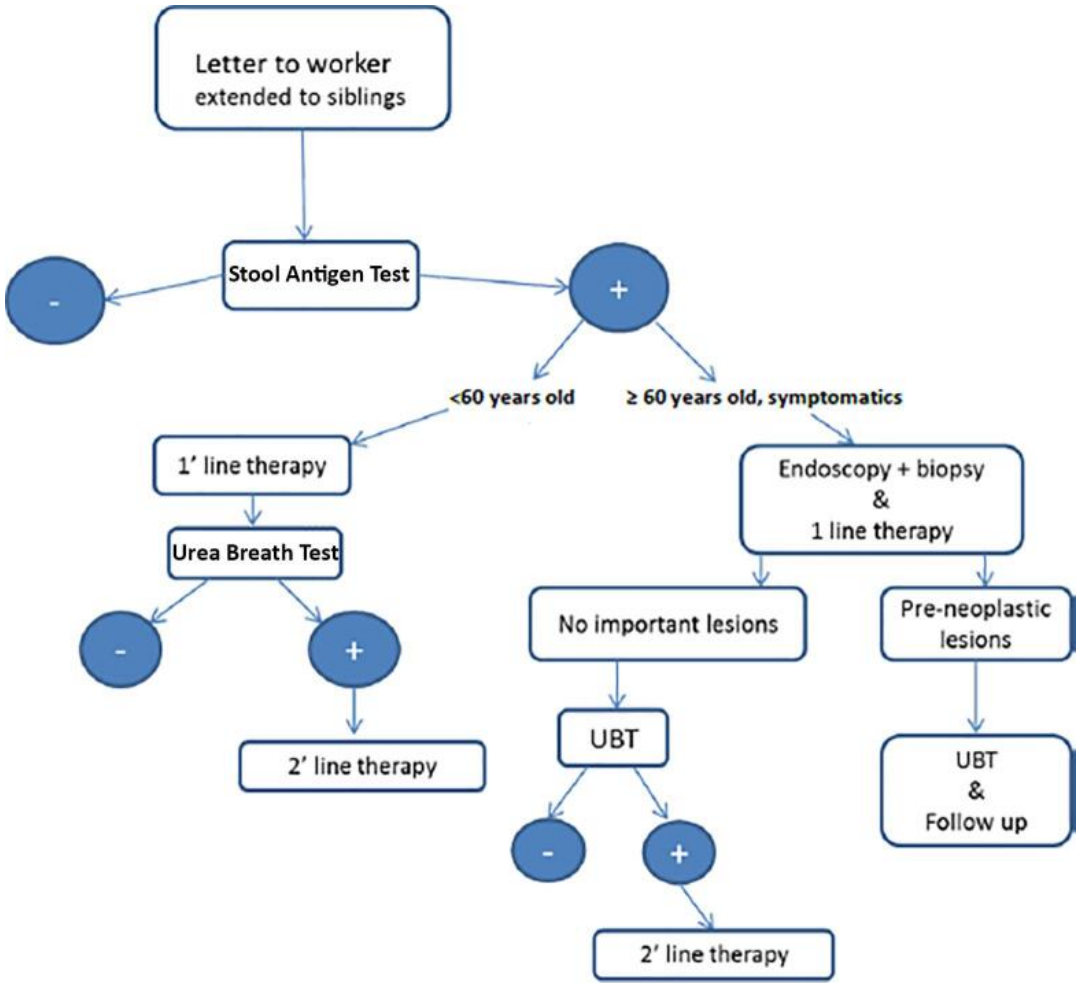
Reference	Country	Age	Method	Prevalence	FU duration	FU rate	Outcome	Result
Ford et al. (2005)	UK	40–49	UBT	27.6%	2 yr	90%	Cost	Positive
Harvey et al. (2010)	UK	20–59	UBT	15.5%	7 yr	97%	Treatment	Positive
Høgh et al. (2019)	Denmark	40–65	Ser + UBT	17.5%	13 yr	54%	QALY	Negative

UBT, urea breath test; Ser, serology; FU, follow-up; QALY, quality-adjusted life-years.

Overall, both model-based and data-based studies showed that under most circumstances eradication of Hp is cost-effective, even in populations with low infection prevalence. Specific subgroups of the population could be targeted for screening protocols, because of their higher risk of developing gastric cancer following Hp infection. Family history of gastric cancer appears to be an important risk factor independent of the bacterium. As a consequence, control of Hp infection can, at least in part, reduce the incidence of gastric cancer among individuals with family history: this population should therefore be screened and treated if Hp positive (El-Omar et al., 2000).

Based on these considerations, it is possible to devise a screen-and-treat protocol with multiple pathways (Fig. 2). In particular, as the development of gastric cancer implies a long latency, a screening program should take into consideration individual characteristics (Liu et al., 2016); in addition, all Hp positive subjects should be followed up after treatment to assess general health status, including symptoms occurrence, and adverse events attributable to antibiotics, and undergo second Hp testing to assess the successful eradication. Subjects ≥60 years of age and with symptoms, as well as those with a high-risk profile (e.g., family history of gastric cancer) should be recommended to undergo additional diagnostic procedures (Malfertheiner et al., 2017, Moayyedi et al., 2017), including gastroscopy, in order to exclude the presence of lesions needing for further monitoring, while younger individuals would benefit of changes in their lifestyle and, if cured, would no longer represent a reservoir of infection for children.

Fig. 2. Pathways in a workplace-based screen-and treat approach for Hp eradication.



Planning a standardized screening program, which would include a questionnaire on health status and possible risk factors of the individuals, would allow to collect complete and reliable data on the distribution of Hp infection and the identification of the population subgroups to which further efforts should be addressed. A screening protocol would also entail general health implications, since making people aware of the presence of a risk factor, especially when asymptomatic, would enable them to make better choices in the daily life, possibly encouraging healthier behaviors that can positively impact their overall wellness. A population-based screening program, however, is not devoid of potential limitations. They are listed on Table 4, together with potential benefits. In particular, treatment failure and consequent facilitation of antimicrobial resistance in general population are of main concern in implementing test-and-treat protocols. Moreover, therapy can be burdened by side effects as diarrhea, abdominal pain, nausea, taste alteration, vomiting, and constipation (Shi et al., 2019). In particular, the occurrence of these symptoms reported in a meta-analysis was 39.0% in the controls compared to 18.9% when probiotics are added to the eradication scheme (Shi et al., 2019). An occupational-based screening for Hp would face several challenges and limitations. In order to avoid misconceptions on the importance, benefits and possible risks, an effective communication

strategy would be required (Lier et al., 2019). The implementation of large-scale screening at workplaces would also require adequate testing setting, laboratory facilities and trained staff. These requirements would be particularly challenging in low- and medium-size enterprises. In addition, absenteeism might occur for workers who test positive for Hp, because of the need for additional diagnostic procedures and treatment. Finally, the treatment itself might have a short-term impact on work performance because of its side effects, thus reducing the perception of long-term benefits of the intervention (Tsai et al., 2019, Reif et al., 2020).

Table 4. Potential benefits and limitations of a *population-based*^ Hp screening program and additional specific benefits and limitations of a *workplace based*§ Hp screening program.

Benefit^	**Limitations**^	**Benefits**§	**Limitations**§
Improved quality of life Improved health status consciousness Opportunity for disease treatment and prevention, reducing Hp-related burden of disease Epidemiology description of Hp burden Identification of higher risk subgroups for infection Feasibility of Hp testing* Possibility of reducing Hp reservoir Reduction of antibiotic use for Hp eradication in future generations Public health saving for gastric disease complications and gastric cancer	Lack of compliance to therapy Possibility of treatment failure due to strain resistance and adverse effects Low participation in screening program† Need for long follow-up for gastric atrophy and cancer Endoscopy is needed for documenting mucosal damage Contraindication to therapy Antimicriobial resistance spreading pressure	Promotion of general wellbeing at the workplace Healthier workforce Improved work performance Strengthened loyalty of the employee Increased workers satisfaction and happiness Reduction of sick leave due to gastric-related disease Possibility to extend the screening and reach employees' family Reduction of workplace reservoir of Hp Optimal age group for primary prevention of gastric cancer Help general practitioner management of the individual Possible integration in more general health promotion programs already implemented	Need for communication strategy Need for testing setting and staff Possible absenteeism for additional procedures among Hp positive workers Possible impact of side effects of therapy on working performance

* Characteristics of Hp testing: non-invasive, safe, fast, economic, highly sensible and specific.

† Possible reasons for low participation: fear of positive result, fear of therapy, fear of endoscopy, lack of interest, lack of time, inhibition about stool manipulation.

4. Screening working populations for *Helicobacter pylori*

Occupation is a risk factor for Hp infection. A systematic review of 98 studies identified several high-risk occupational categories, including health professionals, especially among those working in gastrointestinal units, agricultural, forestry and fishery workers, as well as sewage workers, miners, and workers at institutions for the intellectually disabled (Kheyre et al., 2018).

The workplace directly influences the physical, mental, economic and social well-being of workers and in turn that of their families, communities and society (Schulte and Vainio, 2010, Eng et al., 2016, Goetzel and Pronk, 2010, Parkinson, 2018). In addition, the health of workers is affected by extra-occupational factors, including infectious agents (Rebmann et al., 2009). Occupational medical surveillance programs offer an ideal setting and infrastructure to support the promotion of health of the workers. The recent COVID-19 epidemic offers an example of the potential of workplace-based intervention for disease prevention (Shaw et al., 2020, Baker et al., 2020, Rafeemanesh et al., 2020, Public Health Ontario, 2020). The use of occupational setting has also been considered for primary prevention of cancer (Lang et al., 2020, Nahmias et al., 2016, Marshall, 2013, Mojica et al., 2016). For example, high rates of screening for colorectal cancer have been achieved among employees (Mojica et al., 2016, Ou et al., 2019, Walsh et al., 2014).

Occupational health visits, that are mandated in many countries, offer an opportunity to screen healthy individuals for Hp infection, and to apply treatment strategies based on recommended practice (Fallone et al., 2019). Different health professionals would be involved in different steps of the process (Supplementary Fig. 2): occupational physician could invite workers to undergo Hp testing, explaining the meaning of a screening program for gastric disease and cancer and referring positive subjects to their general practitioner; this latter could prescribe eradication therapy to positive patients in the absence of contraindications, check the eradication outcome by a second Hp test and refer high-risk cases (e.g., old age, family history of gastric cancer) to the specialist in gastroenterology; finally, the gastroenterologist could take in charge the patient considering endoscopy, antimicrobial susceptibility testing, targeted therapy and follow-up.

Only a small number of studies investigated the effectiveness of this approach. Zober et al. determined the prevalence of Hp infection by serology in 6,143 workers in a chemical factory in Germany, and assessed its association with upper GI tract symptoms, personal history of ulcer, and family history of gastric cancer (Zober et al., 1998). The prevalence of infection, measured with immunoglobulin G serology, was 38.2%. Positive serology was weakly but consistently associated with cigarette smoking and shift work. Further diagnostic evaluation and eradication therapy was recommended in

795 workers (12.9%), based on a combination of positive serology and either upper GI tract complaints or family gastric cancer history. The therapy was completed for 541 workers (68.1%). These authors used aggregate medical claims data to evaluate the illness experience of 5,160 of the workers included in the surveillance program during the 2 years after versus the 2 years before the intervention (Ott et al., 2004). Across all participants, a 2.1-fold reduction (95% confidence interval [CI] 1.4–3.1) in ulcer-related illness episodes and a 1.1-fold reduction (95% CI 0.9–1.4) in episodes due to other stomach and duodenal diseases were observed. Improvement in claims experience was most notable among 250 employees with ulcer findings at the screening examination.

Madisch et al. studied the outcome of Hp eradication in 267 factory workers from Germany who reported uninvestigated chronic dyspepsia (Madisch et al., 2002). They assessed Hp infection status at baseline using the 13C-UBT, and positive workers (N = 111, 41.6%) were offered eradication therapy. Dyspeptic symptoms, quality of life and health care utilization were assessed by questionnaires at baseline, as well as at 2 and 12 month follow-up. The infection was cured in 90.4% of treated subjects. Upper abdominal pain and dyspeptic symptoms at 12 months were reduced and quality of life increased in Hp responders compared to baseline and to untreated subjects. In addition, disease-related absence from work, visits to family physicians, and antacid consumption were decreased in Hp responders compared with reference.

The limited evidence available from the literature offers support to the conclusions that (i) workplace-based surveillance for Hp infection is feasible and effective in identifying individuals for targeted interventions, and (ii) such interventions are effective in reducing the burden of Hp-associated disease. While no studies have included gastric cancer as outcome, as such studies would require a large population and a long follow-up and could not include for ethical reasons an untreated high-risk group, the available results imply that workplace-based screening and intervention might lead to the prevention of gastric cancer.

5. Gastric cancer prevention at the workplace

Among the potential benefits gained through workplace-based screening and intervention are reduced sickness absence, reduced medical costs, improved productivity, reduced disease burden, as well as promotion of happiness and loyalty of workers (Reif et al., 2020). Because of disparities in access to surveillance across population groups, offering a screening on the workplace would represent an important contribution to health promotion, whose benefits extend beyond the working population (Kim et al., 2016). In this regard, workers constitute an ideal age group to target Hp screening, because the intervention might impact the transmission within families. In fact, household members of

subjects colonized by Hp represent a group at high-risk subgroup for Hp-related diseases and should receive priority for testing (El-Serag et al., 2018). Indeed, family has been presented as a target for test-and-treat strategy in a recent work by Ding, so reaching families through screening among employees seems to meet this demand (Ding, 2020).

A screening program should be addressed to and be offered as a way to promote general wellbeing of the individual. In order to reach as many people as possible, public events have been used for cancer screening promotion (Escoffery et al., 2014). With regard to gastric cancer in particular, a test-and-treat strategy has been implemented in school setting in Japan (Kaji et al., 2020). Similarly, the workplace has already been recognized as an important environment for health promotion (Wanjau and Zapata-Diomedi, 2019). In fact, workers represent an important segment of the general population. For this reason, a screen-and-treat strategy among workers would represent an approach that could be reproduced in other settings. This would offer the possibility to interrupt the circulation of the infection, providing a health benefit to the household and, in the long term, new generations. Even if only a fraction of those who test positive perform eradication therapy, the impact on the burden of Hp-related disease would be significant. As mentioned above, Table 4 illustrates potential advantages and limitations of a workplace-based Hp screening program. In particular, reduction of antibiotic use for Hp eradication in future generations is a potential benefit of this type of intervention, which may also lead to public health saving for gastric disease complications and gastric cancer.

In order to optimize the effectiveness of the intervention, detailed data are needed on the prevalence of infection in different occupational groups, taking into account the prevalence in the general population, and the possible interactions between occupational risk factors and Hp infection. Limited data are available on these issues, therefore additional studies on workplace determinants of Hp infection and on risk of gastric cancer would enable the comparison of risk between different groups of workers and the design of screening interventions.

In conclusion, an occupational screening for Hp would have a major public health impact. Its feasibility and cost-effectiveness should be assessed depending on the prevalence of infection, the distribution of Hp strains and other circumstances. Such a perspective would be highly innovative, since few trials have been conducted in occupational settings. Particular effort would be required to overcome common barriers towards screening including the motivation of occupational physicians and the population at large in the possibility to prevent gastric cancer by controlling its main etiological factor.

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References

1. Areia M., Carvalho R., Cadime A.T., Rocha Gonçalves F., Dinis-Ribeiro M. Screening for gastric cancer and surveillance of premalignant lesions: a systematic review of cost-effectiveness studies. Helicobacter. 2013;18(5):325–337.
2. Baker M.G., Peckham T.K., Seixas N.S. Estimating the burden of United States workers exposed to infection or disease: A key factor in containing risk of COVID-19 infection. PLoS ONE. 2020;15
3. Bray, F., Colombet, M., Mery, L., et al Cancer Incidence in Five Continents, Vol. XI. Lyon, France: International Agency for Research on Cancer 2017.
4. Boffetta P., Boccia S., La Vecchia C. Springer; New York: 2014. A Quick Guide to Cancer Epidemiology.
5. Brown L.M. Helicobacter pylori: epidemiology and routes of transmission. Epidemiol Rev. 2000;22(2):283–297.
6. Chey W.D., Leontiadis G.I., Howden C.W., et al. ACG clinical guideline: treatment of helicobacter pylori infection. Am. J. Gastroenterol. 2017;112:212–239.
7. Correa P. A human model of gastric carcinogenesis. Cancer Res. 1988;48:3554–3560.
8. Correa P., Houghton J. Carcinogenesis of Helicobacter pylori. Gastroenterology. 2007;133(2):659–672.
9. de Martel C., Georges D., Bray F., et al. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020;8:e180–e190.
10. Ding S.Z. Global whole family based-Helicobacter pylori eradication strategy to prevent its related diseases and gastric cancer. World J Gastroenterol. 2020;26:995–1004.
11. Doorakkers E., Lagergren J., Engstrand L., Brusselaers N. Helicobacter pylori eradication treatment and the risk of gastric adenocarcinoma in a Western population. Gut. 2018;67(12):2092–2096.
12. El-Omar E.M., Oien K., Murray L.S., et al. Increased prevalence of precancerous changes in relatives of gastric cancer patients: critical role of H. pylori. Gastroenterology. 2000;118:22–30.
13. El-Serag H.B., Kao J.Y., Kanwal F., et al. Houston consensus conference on testing for helicobacter pylori infection in the United States. Clin. Gastroenterol. Hepatol. 2018;16:992–1002.
14. Eng J.Y., Moy F.M., Bulgiba A. Impact of a workplace health promotion program on employees' blood pressure in a public university. PLoS ONE. 2016;11

15. Escoffery C., Rodgers K.C., Kegler M.C., et al. A systematic review of special events to promote breast, cervical and colorectal cancer screening in the United States. BMC Public Health. 2014;14(1).
16. Fallone C.A., Moss S.F., Malfertheiner P. Reconciliation of recent helicobacter pylori treatment guidelines in a time of increasing resistance to antibiotics. Gastroenterology. 2019;157(1):44–53.
17. Fendrick A.M., Chernew M.E., Hirth R.A., Bloom B.S., Bandekar R.R., Scheiman J.M. Clinical and economic effects of population-based Helicobacter pylori screening to prevent gastric cancer. Arch. Intern. Med. 1999;159(2):142.
18. Ford A.C., Forman D., Bailey A.G., Axon A.T.R., Moayyedi P. A community screening program for Helicobacter pylori saves money: 10-year follow-up of a randomized controlled trial. Gastroenterology. 2005;129(6):1910–1917.
19. Fuccio L., Zagari R.M., Eusebi L.H., et al. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? Ann. Intern. Med. 2009;151:121–128.
20. Fukase K., Kato M., Kikuchi S., et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet. 2008;372(9636):392–397.
21. Gatta L., Ricci C., Tampieri A., et al. Accuracy of breath tests using low doses of 13C-urea to diagnose Helicobacter pylori infection: a randomised controlled trial. Gut. 2006;55:457–462.
22. Goetzel R.Z., Pronk N.P. Worksite health promotion how much do we really know about what works? Am. J. Prev. Med. 2010;38(2 Suppl):S223–225.
23. Gravina A.G., Zagari R.M., Musis C.D., Romano L., Loguercio C., Romano M. Helicobacter pyloriand extragastric diseases: a review. World J. Gastroenterol. 2018;24(29):3204–3221.
24. Han Y., Yan T., Ma H., et al. Cost-effectiveness analysis of helicobacter pylori eradication therapy for prevention of gastric cancer: a Markov model. Dig. Dis. Sci. 2020;65(6):1679–1688.
25. Harvey, R.F., Lane, J.A., Nair, P., et al. Clinical trial: prolonged beneficial effect of Helicobacter pylori eradication on dyspepsia consultations – the Bristol Helicobacter Project. Aliment. Pharmacol. Ther. 2010;32:394-400.
26. Hatakeyama M. Oncogenic mechanisms of the Helicobacter pylori CagA protein. Nat. Rev. Cancer. 2004;4(9):688–694.
27. Helicobacter and Cancer Collaborative Group Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut. 2001;49:347–353.
28. Høgh M.B., Kronborg C., Hansen J.M., Schaffalitzky de Muckadell O.B. The cost effectiveness of Helicobacter pylori population screening-economic evaluation alongside a randomised controlled trial with 13-year follow-up. Aliment. Pharmacol. Ther. 2019;49(8):1013–1025.
29. Holton J., Figura N., Vaira B. Clinical Publishing Service; Oxford, UK: 2011. Helicobacter Pylori: Atlas of Investigation and Management.
30. Hooi J.K.Y., Lai W.Y., Ng W.K., et al. Global Prevalence of Helicobacter pylori infection: systematic review and meta-analysis. Gastroenterology. 2017;153(2):420–429.

31. Huang J.Q., Zheng G.F., Sumanac K., Irvine E.J., Hunt R.H. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. Gastroenterology. 2003;125(6):1636–1644.
32. IHPWG. Helicobacter Pylori Eradication as a Strategy for Preventing Gastric Cancer (IARC Working Group Reports, N. 8). Lyon, France: International Agency for Research on Cancer, 2014.
33. International Agency for Research on Cancer Schistosomes, liver flukes and Helicobacter pylori. IARC Monogr Eval Carcinog Risks Hum. 1994;61:1–241.
34. Kaji E., Yoden A., Otani M., et al. Helicobacter pylori test-and-treat strategy for second-year junior high school students aimed at the prevention of gastric cancer in Takatsuki City. Helicobacter. 2020;25
35. Kheyre H., Morais S., Ferro A., et al. The occupational risk of Helicobacter pylori infection: a systematic review. Int. Arch. Occup. Environ. Health. 2018;91(6):657–674.
36. Kim S.J., Han K.-T., Park E.-C. Impact of job status on accessibility of cancer screening. Cancer Res Treat. 2016;48(2):825–833.
37. Konno, M., Yokota, S., Suga, T., et al. Predominance of mother-to-child transmission of Helicobacter pylori infection detected by random amplified polymorphic DNA fingerprinting analysis in Japanese families. Pediatr. Infect. Dis. J., 2008;27:999–1003.
38. Kowada A. Cost-effectiveness of Helicobacter pylori screening followed by eradication treatment for employees in Japan. Epidemiol. Infect. 2018;146(14):1834–1840.
39. Lang J.E., Mummert A., Roemer E.C., Kent K.B., Koffman D.M., Goetzel R.Z. The CDC Worksite Health ScoreCard: an assessment tool to promote employee health and well-being. Am. J. Health Promot. 2020;34(3):319–321.
40. Lansdorp-Vogelaar I., Sharp L. Cost-effectiveness of screening and treating Helicobacter pylori for gastric cancer prevention. Best Pract. Res. Clin. Gastroenterol. 2013;27(6):933–947.
41. Lee Y.-C., Tseng P.-H., Liou J.-M., et al. Performance of a one-step fecal sample-based test for diagnosis of Helicobacter pylori infection in primary care and mass screening settings. J. Formos. Med. Assoc. 2014;113(12):899–907.
42. Leivo T., Salomaa A., Kosunen T.U., et al. Cost-benefit analysis of Helicobacter pylori screening. Health Policy. 2004;70(1):85–96.
43. Leja M., Grinberga-Derica I., Bilgilier C., et al. Review: Epidemiology of Helicobacter pylori infection. Helicobacter. 2019;24(Suppl 1)
44. Lier L.M., Breuer C., Dallmeyer S. Organizational-level determinants of participation in workplace health promotion programs: a cross-company study. BMC Public Health. 2019;19:268.
45. Liu K.S., Wong I.O., Leung W.K. Helicobacter pylori associated gastric intestinal metaplasia: treatment and surveillance. World J. Gastroenterol. 2016;22:1311–1320.
46. Madisch A., Hotz J., Grabowski G., et al. Efficacy of Helicobacter pylori eradication in uninvestigated chronic dyspeptic staff members of a large factory: a prospective, long-term, follow-up, workplace outcome study. Eur. J. Gastroenterol. Hepatol. 2002;14(1):61–69.

47. Malaty H.M., El-Kasabany A., Graham D.Y., et al. Age at acquisition of Helicobacter pylori infection: a follow-up study from infancy to adulthood. Lancet. 2002;359(9310):931–935.
48. Malfertheiner P., Megraud F., O'Morain C.A., et al. Management of Helicobacter pylori infection-the maastricht V/Florence consensus report. Gut. 2017;66(1):6–30.
49. Mamishi S., Eshaghi H., Mahmoudi S., et al. Intrafamilial transmission of Helicobacter pylori: genotyping of faecal samples. Br. J. Biomed. Sci. 2016;73(1):38–43.
50. Marshall H. Workplace cancer screening. Lancet Oncol. 2013;14(8):694.
51. Marshall B.J., Warren J.R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984;(i):1311–1315.
52. Moayyedi, P., Lacy, B.E., Andrews, C.N., et al. ACG and CAG Clinical guideline: management of dyspepsia. Am. J. Gastroenterol., 2017;112:988–1013. Erratum in: Am J Gastroenterol. 2017 Sep;112:1484.
53. Mojica C.M., Morales-Campos D.Y., Carmona C.M., Ouyang Y., Liang Y. Breast, cervical, and colorectal cancer education and navigation: results of a community health worker intervention. Health Promot. Pract. 2016;17(3):353–363.
54. Nahmias Z., Townsend J.S., Neri A., Stewart S.L. Worksite cancer prevention activities in the national comprehensive cancer control program. J. Community Health. 2016;41(4):838–844.
55. Nejati S., Karkhah A., Darvish H., Validi M., Ebrahimpour S., Nouri H.R. Influence of Helicobacter pylori virulence factors CagA and VacA on pathogenesis of gastrointestinal disorders. Microb. Pathog. 2018;117:43–48.
56. Nouraie, M., Latifi-Navid, S., Rezvan, H., et al. Childhood hygienic practice and family education status determine the prevalence of Helicobacter pylori infection in Iran. Helicobacter. 2009;14:40–46.
57. Nyssen O.P., Bordin D., Tepes B., et al. European Registry on Helicobacter pylori management (Hp-EuReg): patterns and trends in first-line empirical eradication prescription and outcomes of 5 years and 21 533 patients. Gut. 2021;70(1):40–54.
58. Okuda M., Lin Y., Kikuchi S. Helicobacter pylori Infection in Children and Adolescents. Adv. Exp. Med. Biol. 2019;1149:107–120.
59. Ott M.G., Zober A., Messerer P., Riemann J.F., Schilling D. Illness experience before and after an initiative to identify, treat, and prevent Helicobacter pylori-related diseases in the workplace. J. Occup. Environ. Med. 2004;46(3):227–233.
60. Ou JY, Warner EL, Nam GE, et al. Colorectal cancer knowledge and screening adherence among low-income Hispanic employees. Health Educ. Res., 2019;34:400–414.
61. Park J., Forman D., Waskito L., Yamaoka Y., Crabtree J. Epidemiology of helicobacter pylori and CagA-positive infections and global variations in gastric cancer. Toxins. 2018;10(4):163.
62. Parkinson M.D. The healthy health care workplace: a competitive advantage. Curr. Cardiol. Rep. 2018;20:98.

63. Public Health Ontario. Updated IPAC recommendations for use of personal protective equipment for care of individuals with suspect or confirmed COVID-19. 2020.
64. Rafeemanesh E., Ahmadi F., Memarzadeh M. A review of the strategies and studies on the prevention and control of the new coronavirus in workplaces. Arch. Bone Jt. Surg. 2020;8(Suppl1):242–246.
65. Rebmann T., Wilson R., LaPointe S., Russell B., Moroz D. Hospital infectious disease emergency preparedness: a 2007 survey of infection control professionals. Am. J. Infect. Control. 2009;37(1):1–8.
66. Reif, J., Chan, D., Jones, D., Payne, L., Molitor, D., 2020. Effects of a workplace wellness program on employee health, health beliefs, and medical use: a randomized clinical trial. JAMA Intern. Med., 180:952–60.
67. Roderick P., Davies R., Raftery J., et al. Cost-effectiveness of population screening for Helicobacter pylori in preventing gastric cancer and peptic ulcer disease, using simulation. J. Med. Screen. 2003;10(3):148–156.
68. Savoldi A., Carrara E., Graham D.Y., et al. Prevalence of antibiotic resistance in Helicobacter pylori: a systematic review and meta-analysis in world health organization regions. Gastroenterology. 2018;155:1372–1382.e1317.
69. Schulte P., Vainio H. Well-being at work–overview and perspective. Scand. J. Work Environ. Health. 2010;36(5):422–429.
70. Shaw W.S., Main C.J., Findley P.A., et al. Opening the workplace after COVID-19: what lessons can be learned from return-to-work research? J. Occup. Rehabil. 2020;30:299–302.
71. Shi X., Zhang J., Mo L., Shi J., et al. Efficacy and safety of probiotics in eradicating Helicobacter pylori: a network meta-analysis. Medicine. 2019;98
72. Sugano K., Tack J., Kuipers E.J., et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut. 2015;64(9):1353–1367.
73. Teng A.M., Kvizhinadze G., Nair N., McLeod M., Wilson N., Blakely T. A screening program to test and treat for Helicobacter pylori infection: cost-utility analysis by age, sex and ethnicity. BMC Infect Dis. 2017;17(1) doi: 10.1186/s12879-017-2259-2.
74. The global, regional, and national burden of stomach cancer in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease study 2017. Lancet, Gastroenterol. Hepatol., 2020;5:42-54.
75. Thrift A.P., El-Serag H.B. Burden of gastric cancer. Clin. Gastroenterol. Hepatol. 2020;18(3):534–542.
76. Tsai R., Alterman T., Grosch J.W., Luckhaupt S.E. Availability of and participation in workplace health promotion programs by sociodemographic, occupation, and work organization characteristics in US workers. Am. J. Health Promot. 2019;33(7):1028–1038.
77. Valenzuela M.A., Canales J., Corvalán A.H., et al. Helicobacter pylori-induced inflammation and epigenetic changes during gastric carcinogenesis. World J. Gastroenterol. 2015;21:12742–12756.

78. Walsh J.M.E., Potter M.B., Arora M., Gildegorin G., Terdiman J. A workplace colorectal cancer screening program in firefighters: lessons learned. Occup. Med. 2014;64(4):255–258.
79. Wanjau M.N., Zapata-Diomedi B., et al. Health promotion at the workplace setting: a protocol for a systematic review of effectiveness and sustainability of current practice in low-income and middle-income countries. BMJ Open. 2019;9
80. World Health Organization . WHO; Geneva: 2017. Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics.
81. Xie F., Luo N., Lee H.P. Cost effectiveness analysis of population-based serology screening and (13)C-Urea breath test for Helicobacter pylori to prevent gastric cancer: a markov model. World J. Gastroenterol. 2008;14:3021–3027.
82. Yan T.-L., Hu Q.-D., Zhang Q., Li Y.-M., Liang T.-B. National rates of Helicobacter pylori recurrence are significantly and inversely correlated with human development index. Aliment. Pharmacol. Ther. 2013;37(10):963–968.
83. Yeh J.M., Kuntz K.M., Ezzati M., Goldie S.J. Exploring the cost-effectiveness of Helicobacter pylori screening to prevent gastric cancer in China in anticipation of clinical trial results. Int. J. Cancer. 2009;124(1):157–166.
84. Zober A., Schilling D., Ott M.G., Schauwecker P., Riemann J.F., Messerer P. Helicobacter pylori infection: prevalence and clinical relevance in a large company. J. Occup. Environ. Med. 1998;40(7):586–594

3.2 Cancer Prevention at Work – CPW

The Cancer Prevention at Work (CPW) project is a Horizon Europe Mission Cancer action, researching the cost effectiveness and social acceptance of incorporating prevention of cancers associated with Helicobacter pylori, Hepatitis C virus and Human Papillomavirus into ongoing primary occupational health surveillance programmes.

Funding information

The Cancer Prevention at Work project is funded by the European Union through the European Commission's Horizon Europe Research and Innovation Programme. It is part of the Cancer Mission programme and is a contributor to the Mission Cancer 'Prevention and early detection' cluster.

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Duration: May 2023 - April 2027
Project coordinator: Prof. Paolo Boffetta, University of Bologna (UNIBO), IT

Understanding Helicobacter pylori

Helicobacter pylori (Hp) is a widespread pathogen, affecting approximately half of the world's population. Infections are typically acquired during childhood, especially in densely populated areas with inadequate sanitation. Due to its association with non-cardia gastric cancer and mucosal-associated lymphoid tissue lymphoma, Hp has been classified as a Group 1 carcinogen (like smoke for lung cancer). Early detection is crucial to prevent the infection from developing into cancer and other serious health complications.

The CPW Intervention focuses on the early detection of Hp through blood sample and stool antigen test, identifying subjects at higher risk of gastric cancer, with possibility of primary prevention through Hp eradication.

Pilot study on Helicobacter pylori (Hp)

Hp screening and eradication as primary prevention of stomach cancer within occupational health surveillance programs. Hp emerges as a pivotal player in the realm of cancer burden, its significance underscored by its classification as a Group 1 carcinogen by the International Agency for Research

on Cancer. This classification stems from Hp's link to non-cardia gastric cancer and its specific association with mucosal-associated lymphoid tissue (MALT) lymphoma of the stomach. The scope of Hp's influence extends further, as it's responsible for prevalent diseases like gastritis and peptic ulcers. Beyond the gastronomic realm, Hp-positive subjects are more likely to experience extra-gastric conditions such as syderopenic anaemia and thrombocytopenic purpura, amplifying the urgency for robust prevention measures.

Despite its profound impact, Hp remains a subject that has not received systematic investigation within any population. Both in general population and occupational health settings, Hp testing is conspicuously absent. This clinical study is the first of its kind to address this critical gap and extends beyond individual workers to encompass their households and leverages the periodic nature of occupational health visits to implement effective follow-up mechanisms, ensuring the efficacy of primary interventions.

Pilot study on Hepatitis C virus (HCV)

HCV screening and treatment as primary prevention of liver cancer within occupational health surveillance programs. Liver cancer risk is a serious concern, with Hepatitis B and C infections at its core. In the EU/EAA, 3.9 million people are grappling with chronic HCV infection. While vaccination isn't an option for Hepatitis C, effective treatment is. This makes screening and treatment essential strategies for cancer prevention. However, action plans to diagnose and raise awareness about HBV and HCV infections in the European Region face challenges. By 2017, only six EU nations achieved this target. The COVID-19 pandemic has magnified the importance of timely HCV management. Delayed treatment could lead to 45,000 additional HCC cases and 72,000 more liver-related deaths globally by 2030. Our clinical study aligns with the "Total Worker Health" concept and focuses on unexplored primary prevention programs for HCV-caused liver cancer. We are reaching out to workers from various sectors along with their households.

Pilot study on Human Papillomavirus (HPV)

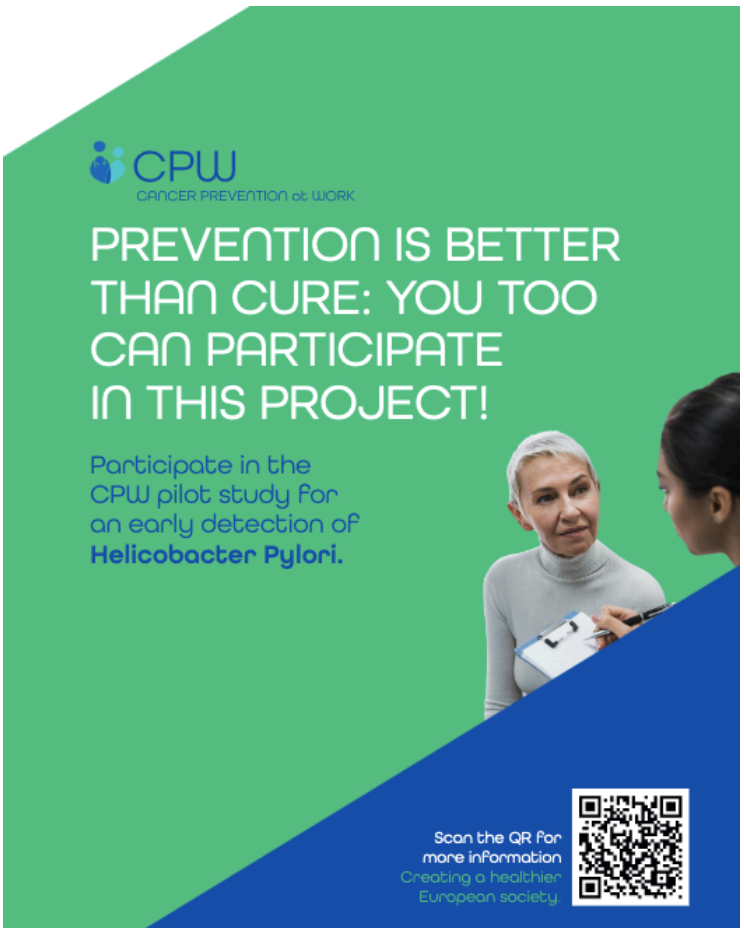
Vaccination as primary prevention of HPV infection and its complications, within occupational health surveillance programs. This study targets cervical and other HPV-caused cancers into ongoing occupational health surveillance systems, which offers a unique vantage point for addressing HPV-related cancer prevention directly. Widespread HPV vaccine use dramatically reduces the number of women who will develop cervical cancer, and upcoming vaccines hold even more promise against cervical precancer and cancer. This focus does not compromise secondary prevention via cervical

cancer screening—a proven public health strategy for at-risk women. By collaborating with medical experts, this initiative strives to lower cancer incidence linked to HPV infection by raising awareness and encouraging participation in preventive activities, notably HPV vaccination, in middle-income European countries.

Within this project, Worker Health Programs aim to empower occupational health service (OHS) workers to address vaccine hesitancy by enhancing their communication skills. In a personalized approach, the pilot phase tailors strategies within selected companies. This approach will be mainly innovative in countries where test and treatment of Hp and HCV, and HPV vaccination, have not yet been implemented.

Expected impact of CPW

The CPW Project could contribute to the control and prevention of stomach, liver, cervical, and oropharyngeal cancers by assessing the implementation of HP, HCV, and HPV infections prevention into occupational health surveillance programs targeting workers from different types of industries and occupations.



ABOUT THE HELICOBACTER PYLORI BACTERIUM

Helicobacter pylori (Hp) is a widespread pathogen, affecting approximately half of the world's population. Infections are typically acquired during childhood, especially in densely populated areas with inadequate sanitation.

Due to its association with non-cardia gastric cancer and mucosal-associated lymphoid tissue lymphoma, Hp has been classified as a Group 1 carcinogen (like smoke for lung cancer).

Early detection is crucial to prevent the infection from developing into cancer and other serious health complications.

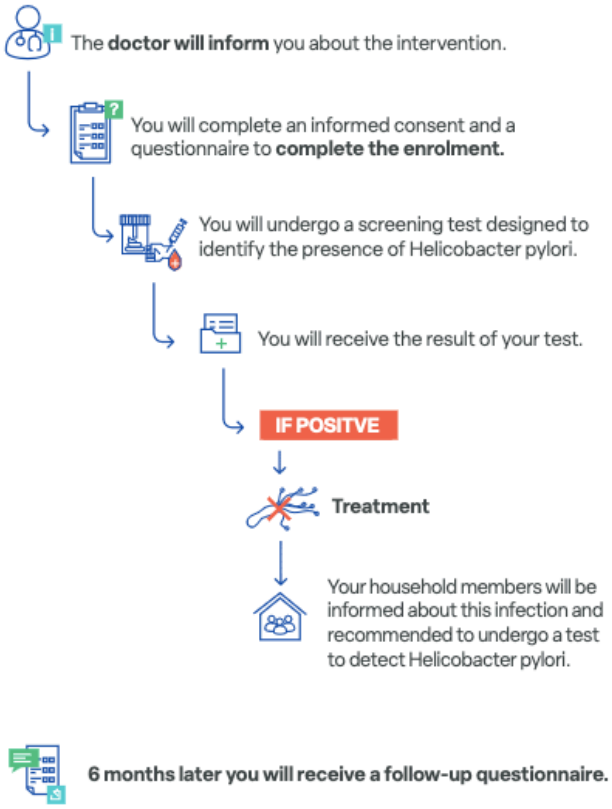
The CPW Intervention focuses on the early detection of Hp through blood sample and stool antigenic test, identifying subjects at higher risk of gastric cancer, with possibility of primary prevention through Hp eradication.

What is Cancer Prevention at Work (CPW)?

The Cancer Prevention at Work Project is dedicated to developing and implementing innovative surveillance protocols targeting infection-related cancers, including those associated with Hp, in occupational health surveillance visits through targeted pilot interventions across diverse worker groups.

Intervention Breakdown. Step by step

When you attend your health surveillance visit...



6 months later you will receive a follow-up questionnaire.

Collatuzzo G, Godono A, Fiorini G, Vencovsky D, Giordani S, Biagioli V, Pinto-Vidal FA, Seyyedsalehi MS, Kostrzewa M, Honrado A, Bruno D, Tardon A, Mates D, Schneider-Kamp A, Fabianova E, Boffetta P. Expanding Cancer Prevention: Strategies Integrated into Occupational Health Surveillance. Cancers (Basel). 2025 Oct 31;17(21):3535.

3.3 Expanding cancer prevention: strategies integrated into occupational health surveillance

Short title: Workplace-based expanded cancer prevention

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Keywords: cancer prevention, cancer screening, health promotion, health surveillance, workplace, total worker health

Abstract

Background: Participation in cancer prevention programs is suboptimal. Socioeconomic backgrounds play a role in cancer awareness and prevention programs.

Methods: We conducted a narrative state-of-the-art literature review, summarizing the evidence on the integration of cancer prevention extended to non-occupational risk factors at the workplace.

Results: Cancer prevention programs include screenings (colonoscopy, mammography, Pap-test), vaccinations (anti-HPV, anti-HBV), and interventions focused on lifestyle changes. Such strategies may face several barriers, related to individual or environmental factors. The workplace is potentially an ideal setting for implementing extended cancer prevention strategies because (i) occupational health surveillance (OHS) is mandatory for all workers in many countries, (ii) OHS targets adult population including subgroups which are difficult to reach in community-based initiatives; (iii) OHS is structured and includes health records and medical exams for worker's risk assessment; (iv) OHS offers a key opportunity for raising cancer awareness and prevention through interactions between occupational health professionals and workers. Such an innovative approach would, however, requires organized effort to build network of professionals and management of the high-cancer-risk workers. Financial support and proactive participation of physicians, employers, and workers would be needed for the successful implementation of this approach.

Conclusions: Occupational-based cancer prevention programs represent a novel and promising approach; the feasibility and cost-effectiveness of such programs require a large-scale investigation.

Introduction

The growing focus on prevention in the medical field has contributed to reducing morbidity and mortality from major diseases, including cancer [1]. An essential component of effective cancer prevention programs is the identification of modifiable risk factors [2]. While cancer etiology has traditionally been attributed to genetics and chance, most cancers are due to modifiable risk factors, including lifestyle, nutritional, infectious, occupational and environmental exposures [3,4,5], implying that many cancers are avoidable [4].

Despite the implementation of some preventive strategies, the proportion of avoided cancer is still unsatisfactory due to several challenges [4,6-10]. These include disparities in cancer prevention programs availability, suboptimal adherence to cancer screening and prevention measures, resistance to lifestyle changes, low health literacy, barriers to healthcare access, costs of prevention initiatives, and the slow integration of scientific evidence into medical practice [9].

Cancer prevention programs must address these challenges by offering accessible, cost-effective, noninvasive, and easy-to-use services, favoring population participation [10,11]. Tailoring programs based on risks enhances cost-effectiveness and allows more targeted efforts [12] in specific settings [13,14] and specific demographic groups [15-19].

The workplace is a promising setting for cancer prevention initiatives [20-23], which could be part of structured occupational health surveillance (OHS) [24]. OHS often focuses narrowly on occupational hazards [24]. Prevention or minimization of exposure to carcinogens at the workplace is a major required measure, as for current European legislation [25,26]. Besides this, many employers voluntarily expand their occupational health services to include broader preventive measures. The "Total Worker Health" (TWH) approach, developed by the National Institute for Occupational Safety and Health (NIOSH) [27], emphasizes protecting workers not only from occupational risks, but also from non-occupational risk factors of chronic diseases that impact their overall well-being. The integration of wide cancer prevention strategies at the occupational level aligns with the TWH approach. It implies (i) interventions targeting also non-occupational cancers, and therefore (ii) extended to all workers. Studies suggest that workplace-based interventions increase cancer screening engagement and empower workers to adopt healthier lifestyles, benefiting both individuals and their families [28]. However, additional research is needed to evaluate the feasibility and cost-effectiveness of workplace-based cancer prevention programs.

In this narrative state-of-the-art review, we explore the integration of wide cancer prevention strategies into workplace settings as a novel approach.

Methods

We aimed at providing an overview on the possible implementation of an innovative cancer prevention approach integrated into OHS. We searched for relevant evidence regarding cancer prevention strategies supporting the framework of workplace-based expanded interventions, through a narrative state-of-the-art literature review [29]. In particular, we addressed the following points: the role of occupational physician on population health; prevention of avoidable cancers; social determinants of health and disparities in cancer prevention; characteristics of workplace setting which can turn into barriers or facilitators; implementation of integrated occupational-based cancer prevention strategies extended to non-occupational risk factors.

The role of the occupational physician on population health

European healthcare landscape is currently facing doctors shortage, which became evident with COVID-19 pandemic [30]. A sizeable proportion of the European Union (EU) population does not regularly engage with their general practitioner (GP), whilst many countries require employers to ensure that workers are regularly seen by an occupational physician [31]. This implies limited opportunities for offering cancer screening and vaccination. For example, Eurostat data show that, in 2017, 24% of the EU population did not see their GP at all [32]. Recent decreases in GP consultation rates have been reported in England [33].

GP consultation rates vary between EU countries, with those characterized by the lowest primary care engagement and highest OHS frequency being best suited for extended cancer prevention. In 2019, the percentage of the population that did not see their GP for more than 12 months ranged from around 15% in France and Belgium to 49% in Romania [34]. On the other hand, in some countries, OHS is widely accessed by employees, including for non-work-related health issues [35]. Factors such as no cost for employees, the lack of need for referral from other physicians, and service availability likely contribute to the high participation of workers in OHS [35].

These features present a valuable opportunity to expand the scope of occupational medicine to include larger preventive healthcare measures, according to a TWH model. In specific, the occupational physician could play a significant role in primary prevention of both occupational- and non-occupational cancers, complementing GP activity and contributing to public health.

Avoidable cancers prevention

Cancer prevention encompasses three key levels: primary, secondary, and tertiary, all designed to reduce cancer-related mortality by implementing timely and effective strategies. **Table 1** [36-40] summarizes possible cancer-specific prevention strategies, which include lifestyle and behavioral interventions, health education, nutritional education and counselling, vaccinations, as well as medical examinations and/or imaging within cancer screening programs. The occupational physician might influence workers' choices of healthy behaviors, including quitting smoking, reducing alcohol consumption and engaging in regular physical activity. Also, the identification of high-risk workers (eg., sex, age, body mass index, lifestyle habits, family history of cancer) allows the occupational physician to refer individuals to specialists for consultancy, or suggesting instrumental exams such as endoscopy [27]. Furthermore, the occupational physician can substantially contribute to the increase in cancer screening and vaccination uptake, by raising awareness and spreading health literacy among working population.

Globally, three major cancer screening programs are widely implemented [1]: mammography (breast cancer prevention), colonoscopy (colorectal cancer prevention) and Pap-test (cervical cancer prevention). These screening initiatives form the cornerstone of secondary prevention, enabling early detection and, thereby, timely and effective treatment.

Vaccines targeting carcinogenic infections have emerged as transformative tools in primary cancer prevention. For example, the introduction of the vaccine against hepatitis B virus (HBV) in 1982 led to a 98% reduction in infections among US healthcare workers between 1983 and 2010 [41]. In Taiwan, the risk of hepatocellular carcinoma significantly decreased among individuals born after the 1984 introduction of the anti-HBV vaccine [42]. Similarly, the vaccine against human papillomavirus (HPV) has dramatically reduced cervical cancer incidence [43].

Scaling global anti-HPV vaccine coverage to 80–100% could prevent 6.7–7.7 million cervical cancer cases over the next 50 years [43]. Despite promising well-documented outcomes, vaccination rates remain suboptimal in some countries and among disadvantaged groups. Japan's hesitancy toward the anti-HPV vaccine [44], fueled by negative media coverage and cultural taboos, led to a dramatic drop in coverage to less than 1% in 2018 [44,45]. Proactive anti-HPV vaccine recommendations were reinstated in 2022, and initial vaccination rates among adolescent girls rose to 31% by 2023 [44]. This case underscores the critical role of public perception, communication strategies, and policy frameworks in shaping vaccine uptake and public health outcomes [44,45].

In addition, the proven causal relationship of HPV infection with cancers at other locations than the cervix, including oropharyngeal and anogenital locations, highlights the exceptional primary preventive importance of anti-HPV vaccination in both men and women [46].

To overcome persistent challenges with less-than optimal coverage, tailored vaccination strategies targeting high-risk populations and marginalized groups are essential.

Social determinants of health and cancer prevention disparities

Recent data show increasing absolute numbers of new cases and deaths [48], mainly due to population aging, despite the ongoing downtrend of cancer incidence in most countries worldwide.
Socioeconomic disparities in cancer prevention persist despite the progressive expansion of public health policies and services aimed at equity [9].
Social determinants of health include individual demographic and economic factors (e.g., sex, age, employment) [49,50] sociocultural context (family, support networks, education, local culture, religion) [49,51], and governmental policies (health insurance, access to screening) [49-53]. These determinants significantly impact adherence to implemented cancer prevention services (**Figure 1** [49-58]). For instance, participation in cervical cancer screening and HPV vaccination is notably lower in low- and middle-income countries. This is, in part, due to taboos and religious constraints [51,58-60], but also to economic factors such as vaccine pricing and costs for journeys to vaccination centers [48]. At the same time, vulnerable populations, including certain groups of immigrants and other individuals of low socioeconomic status, are disproportionately affected by cancer due to increased exposure to risk factors such as smoking, alcohol use, and poor diet [53].
Addressing cancer disparities requires culturally sensitive, evidence-based interventions [61,62] delivered through diverse channels [61-67], including libraries [63, 64], churches [65], public events, and informal community networks [66,67]. Such "informal" channels outside the hospital borders have the potential to improve health education and provide access to health services to a wide heterogeneous public comprised of individuals with varying ages and social backgrounds, raising awareness of cancer prevention and increasing participation in cancer screening programs [62].
In this framework, the occupational setting offers unique opportunities for cancer prevention [28,68]. The integration of extended cancer prevention into OHS could have a ripple effect on workers' households too, spreading health education and increasing the overall participation of the general population to cancer prevention initiatives [68, 69]. Moreover, occupational factors and employment

status [53,54] are among the main social determinants of health and related disparities, requiring an aware and proactive attitude of the employers and the healthcare providers in leveraging health inequities, recognizing health as a value for business and profitability [70].
Extended cancer prevention also has the potential to address some of the imbalances in primary care utilisation between men and women, as well as different age cohorts. Data from Eurostat (2019) [33] indicate that GP consultation rates at the EU level are generally higher among women than men. In 2019, the proportion of men that declared that they had not seen their GP in the preceding 12 months ranged from around 19% in Belgium to 55% in Romania, whilst the corresponding proportion of women ranged from 11% in France to 44% in Romania. This is further confirmed by Song et al [71], who examined 2019 data on GP consultations in the UK and concluded that, whilst overall 23% of the population did not consult their GP at all in the last 12 months, the frequency of GP consultations was higher among women and those aged ≥75. Baker provides consistent data for UK people in working age (<65 years old) in 2022 [72]. However, when it comes to consultations at OHS, both men and women appear to visit with similar frequency. Therefore, a proportion of the general population might visit more often the occupational physician than their GP.
Targeting workers with extended cancer prevention programs would allow to reach heterogeneous populations, including vulnerable subgroups who often remain uncovered by health services and reluctant subjects. This would make workplaces a cornerstone for broader health care initiatives [73].

The workplace as a setting for cancer prevention programs

Occupational medicine practice is highly heterogeneous by country, ad implemented to different extent. Workers exposed to occupational carcinogens are subjected in many countries to OHS scheduled with specific timing and including targeted exams [24].
Employers can also offer their employees additional health check-ups through the occupational health service [73], as well as interventions aimed at health promotion. However, interventions aimed at reducing cancer risk among workers, other than risk from exposure to known occupational carcinogens, are not required of employers in any country.

The cognition of general health and wellbeing as a critical aspect to protect and promote among workers has become increasingly spread [73]. This approach attributes to the occupational physician a central role in protecting the workers not only from occupational-related risks and injuries but also from developing chronic diseases, which can compromise their work ability [27]. Further, such view

strengthens the role of occupational health personnel as health educators and active promoters of healthy lifestyle [27]. Literature offers large evidence on occupational interventions which positively impacted healthy choices, based on the TWH approach [27, 69, 74,75]. This positions TWH as a potentially impactful approach for public health.

With regard to cancer prevention, some examples of occupational-based interventions have been proposed, including breast, gastric, colorectal and cervical cancer screening [28, 68, 69, 76]. A recent systematic review has summarized the overall effectiveness of workplace-based interventions, which were found to enhance the overall knowledge and uptake of cancer screening tests [28]. Some studies have also addressed the primary prevention of cancer among workers, mostly addressing skin cancer through the use of sun protection equipment [77]. Notably, interventions which provide information (e.g., campaigns for sensitization, educational programs on cancer prevention) and instruments (e.g., vaccinations, screening tests) to the workers carry a durable benefit: they empower workers with a deeper understanding of cancer risk factors and their possible preventive measures, generating a healthier population at lower risk of developing cancer [78]. Health promotion campaigns in the EU have played a positive role in raising health awareness among workers [79]. For instance, the Healthy Workplaces Campaigns have been running since 2000, providing important support and guidance to workers and employers to manage different areas of occupational health [79].

While further evidence is needed for the implementation of standardized OHS-based cancer prevention programs, some protocols have been proposed [68,69]. For example, previous works have identified Helicobacter pylori screening for gastric cancer prevention as an intervention amenable to the TWH approach [68,69].

Table 4 highlights the key characteristics of a screening program integrated with OHS. For each of them, the challenges, but also the opportunities that can be obtained as a result of this particular screening setting are listed. A key aspect of occupational medicine is regularity and structure of OHS [24, 80], scheduled based on the occupational risk-profile of each worker. OHS is mandatory and free for all workers [24, 80], guaranteeing equity and reaching different strata of the general population, including minorities and less affluent subgroups. Also, OHS includes follow-up visits and longitudinal monitoring of the worker [24, 80], which are both important in cancer prevention programs. Questionnaires for risk stratification and medical tests (e.g., blood and urine sample, hearing check) are often included in OHS [24, 80]. Cancer risk-stratification of the worker could easily be performed through specifically designed questionnaires, while tailored tests could be administered based on risk profiles acquired during regular OHS visits. The collection of information aimed at creating a “cloud” of personal health data is in line with a more personalized model of

medicine. However, this raises concern regarding confidentiality [81]: the workers might be hesitant to share some personal information out of the fear that they could be reported to the employer [82]. A multidisciplinary team (including healthcare providers, general practitioners, nutritionists, physiotherapists, psychologists, and other experts) would be needed for successful workplace-based cancer prevention programs, where the professionals cooperate in different phases (pre-test, management of the test results, follow-up) [83]. The positive impact of interaction between different professionals has been documented especially in the return-to-work of disabled or chronically ill subjects [84-86]. A systematic review on workplace interventions led by healthcare professionals on cardiovascular risk described higher success of interventions which were multicomponent, tailored on high-risk populations, offering motivational support and face-to-face counseling, and characterized by longitudinal follow-up [86]. The expansion of literature regarding occupational interventions towards cancer risk could clarify the role of these characteristics in the success of workplace-based cancer prevention programs. An occupational-based cancer prevention program would imply a high level of commitment, both from the employer and the medical side [83]. In the meantime, occupational health providers and the employers can jointly increase participation rates in cancer prevention programs by motivating the workers to engage in health practices [70, 87].
Residual disparities may also occur: unemployed individuals would not benefit from these interventions; if the implementation of such programs is restricted to individual companies, some workers might remain excluded by these benefits. To avoid this problem, policy makers could purpose to introduce cancer prevention as a mandatory component of OHS.

Integrating cancer prevention in occupational health surveillance

To date, evidence on the systematic integration of cancer prevention programs within the workplace is few and far between. As a consequence, discussing its possible implementation is mainly theoretical and based on few empirical examples. Evidence highlighted the importance of resource availability (in terms of funds, personnel, and integration with public services) and multidisciplinary, experts' support in allowing employers to run health promotion programs in their enterprises [28, 87].

A personalized and holistic approach targeting workers has been designed by the Onconauti Association, established within several centers in Italy [88]. It promotes education of all the workers around health and cancer prevention strategies, and clinical management of high-risk workers through several health professional interventions including nutritional and psychological counseling, physiotherapy, and body-mind practices sessions [89-91].

Workplace-based campaigns aiming to raise health awareness are carried out at large. Days dedicated to work safety courses and training are already part of common workplace calendars in several countries [92, 93], offering a model for cancer education interventions. However, these do not include extended cancer prevention education [92,93]. The organization of educational courses regarding overall cancer risks and prevention represents a promising avenue for raising awareness among workers [92-95].

The full and effective integration of extended cancer prevention into occupational medicine practice would require particular attention to addressing the needs of the workers at high oncological risk. In fact, a proper and adequate integrated system would cover risk profiling and clinical management of high-risk worker. To this end, access to specialized care and second-level diagnostics is a key element. Connectivity plays a crucial role [88,95]: ideally, private occupational medicine should be linked to a network of different professionals, including the general practitioners of the workers, through established channels. In a private healthcare system, this would require the engagement of stakeholders, with a primary role for private occupational health services in establishing agreements with specialized local organizations and health centers. In other words, occupational physicians should be enabled to provide the workers with clinical pathways tailored to specific risk profiles assessed through the OHS [88,96].

The close collaboration between local organizations and political offices, government agencies, social services, and advocacy and supporting groups in providing financial support and shaping cancer prevention policies is of utmost importance.

Although extended cancer prevention can entail costs for employers, it also has the potential to bring benefits. Overall, a healthy workforce offers advantages to employers, including increased worker productivity, as well as reduced absenteeism, insurance contribution, and sick-leave payments [97]. Indirectly, employers at large can also benefit from a reduced demand to fund the national healthcare system via taxes due to a reduced cancer burden. Extended healthcare provision at the workplace can result in improved corporate reputation. Wider research on Corporate Social Responsibility (CSR) [shows that, more generally, corporate reputation is one of the drivers of company performance and value [98, 99] and can have a positive impact on staff retention and satisfaction [100].

The main benefit for employers arises from reduced incidence of cancer among workers. Recent impact assessments within the field of occupational health and safety field [97] have employed the median cost to employers associated with a single case of a high-severity accident or disease, as

estimated in [101], as a proxy for the costs to an employer of a worker undergoing cancer treatment. When adjusted to 2024 prices using the Harmonised Index of Consumer Prices [102], this cost is estimated to be around €15,700 per worker diagnosed with cancer.

Worker absence can have significant implications for employers, as a temporary or permanent replacement for the affected worker has to be found and paid. In addition, a replacement may need to be found. These costs are often modelled using the concept of a 'friction period' that focuses on the disruption during the time period required for adjustment [103, 104]. This period can be significant; for instance, a recent survey of workers diagnosed with cancer reports an average absence of 15 weeks, equating to 75 working days for a full-time employee [105.

Despite the fact that some cost savings may occur after an employee has left the company or retired, employers are still expected to benefit financially from a reduction in cancer incidence among their workforce in the long-term. Research shows that the share of workers remaining with the same employer for 10 years or more is around 50% [106] .Whilst the majority of cancer cases (65%) are diagnosed in individuals aged 65 and older, estimates from the European Cancer Information System (ECIS, 2025) [107] based on data from cancer registries and administrative sources indicate that a substantial share of cancer incidence occurs in the working-age population (34% based on ECIS data for individuals aged 20–64).

Conclusions

In a landscape where population aging and scarce control of modifiable risk factors contribute to unfavorable cancer patterns, strategies aimed at raising awareness and increasing participation in cancer screening are urgent [9,65]. This is a critical public health issue, especially concerning less affluent strata of the population, which often experience a low participation in cancer screening despite a high cancer risk [65,102].

The workplace is an ideal setting where to integrate extended cancer prevention strategies, targeting adults from different socioeconomic backgrounds [65,102]. Occupational-based cancer prevention could enable at the same time to raise the workers' awareness of available preventive programs and offer direct access to cancer screening, according to a TWH approach [28]. In particular, such programs could be integrated into regular OHS and corporate welfare and leverage occupational medical records for the development of risk-assessment tools aimed at identifying high-risk individuals. In this innovative model, the occupational physician would not only be responsible for the aspects of workers' health directly related to the occupational risks, but would also educate, to

specific health practices, identify high-risk workers and monitor their cancer risk profile longitudinally, contributing to public health [74,75]. The design of extended cancer prevention programs to be integrated at the occupational level should account for the characteristics of the work environment and the working population, possible barriers such as costs and employers' resistance, and facilitators such as involvement of public health authorities and workers' unions [88]. Notably, this approach would benefit from multiple expertise and involvement of different institutions, where the tailored clinical management of high-risk workers is the turning point to optimize the results in terms of cancer prevention.

To date, few studies focused on the implementation of cancer prevention interventions at the occupational level, showing promising results [28,65,70,71,75]. The cost-effectiveness and feasibility of such innovative models need to be further investigated in order to provide scientific evidence for their possible implementation on a large scale.

Table 1. Examples of cancer prevention strategies by cancer types [36-40].

Cancer type	Main modifiable risk factors	Prevention strategy			OHS contribution
		Primary	*Secondary*	*Tertiary*	
Lung cancer	Smoking Second-hand smoke Occupational exposures	No smoking/stop smoking Avoid exposure to second-hand smoke Limit occupational exposures Use of PPE at the workplace	Low-dose CT	Rehabilitation programs Return to work programs Psychological support Nutritional counselling Promotion of physical activity and healthy lifestyle Smoking cessation Personalized support via telemedicine Sexual recovery	Occupational exposure limits PPE provision and check Quitting smoking counseling contact Risk profiling
Breast cancer	Obesity Low physical activity Alcohol No breastfeeding Reproductive factors	Promotion of healthy lifestyle and physical activity Health education at any age Promotion of breastfeeding	Mammography Breast ultrasound Mammotome Regular self-examination of the breast		Nutritional counseling Family history investigation Investigation and recommendation of screening and self-examination Physical activity indications Alcohol use investigation and education Recommendation of lifestyle changes Weight monitoring Risk profiling
Colorectal cancer	Obesity Low physical activity Diet Alcohol Smoking	Promotion of healthy lifestyle and physical activity Health education at any age Nutritional counseling Use of low-dose aspirin Microbiota analysis	Colonoscopy Rectosigmoidoscopy FOBT		Nutritional counseling Family history investigation Investigation and recommendation of screening Physical activity indications Recommendation of lifestyle changes

					Weight monitoring Risk profiling
Gastric cancer	Helicobacter pylori Smoking Diet Alcohol	Hp test and treat Nutritional counseling No smoking/stop smoking	EGDS with biopsy sampling Gastric panel (pepsinogen, gastrin and Hp IgG)		Hp test-and-treat recommendation Nutritional counseling Recommendation of lifestyle changes Weight monitoring Risk profiling
Cervical cancer	HPV Smoking	HPV vaccination Sex and health education No smoking/stop smoking Regular PAP and HPV test	PPA test HPV test		Investigation and recommendation of screening HPV vaccination Recommendation of lifestyle changes Sexual health education Risk profiling
Liver cancer	HCV HBV Alcohol Obesity Low physical activity	HBV vaccination HCV test Promotion of healthy lifestyle and physical activity Health education at any age Serology Nutritional counseling Support for alcohol use disorder	Abdominal ultrasound CT Biomarkers (AFP)		HBV vaccination HBV, HCV screening Alcohol use investigation and education Nutritional counseling Physical activity indications

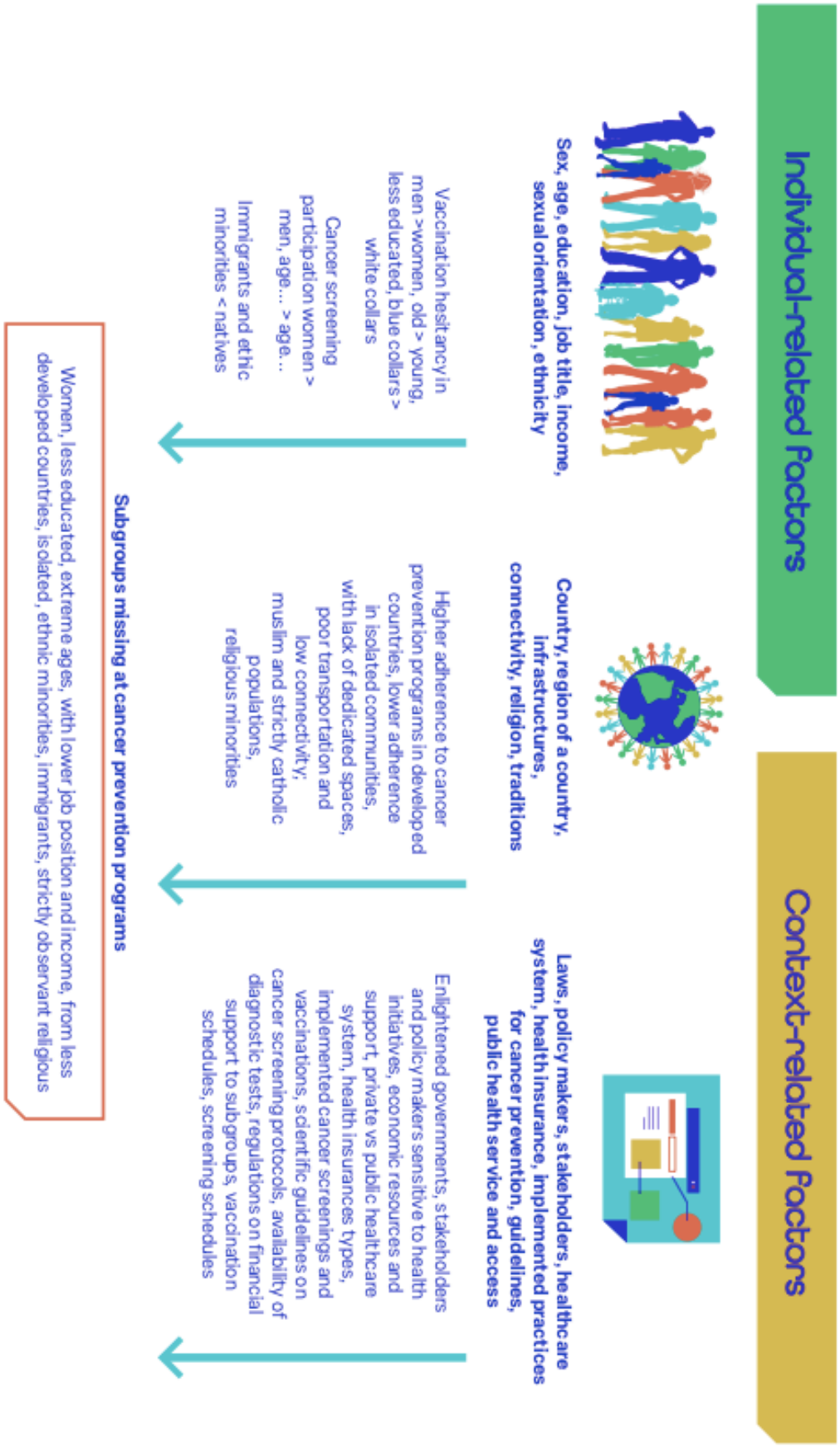
					Recommendation of lifestyle changes Weight monitoring Risk profiling
Prostate cancer	Obesity Low physical activity	Promotion of healthy lifestyle and physical activity PSA screening Clinical prostate examination	TRUS		PSA monitoring Physical activity indications Weight monitoring Recommendation of lifestyle changes

OHS, Occupational Health Surveillance; CT, computed tomography; FOBT, fecal occult blood test; EGDS, esophagogastroduodenoscopy; AFP, alpha-fetoprotein; PSA, prostate-specific antigen; TRUS, transrectal ultrasound

Table 2. Characteristics of occupational setting in the perspective of extended cancer prevention program.

Key characteristics	Challenges	Opportunities
General adult population; heterogeneous categories of population (including less advantaged subgroups)	Non-compliance, specific age limits, missing unemployed	Equity, addressing socioeconomic barriers, age- and sex-specific interventions
Structured setting of OHS	Logistics and organization of testing, test results communication, visits duration	Regular follow-up and longitudinal monitoring of the worker's health and adherence to cancer prevention
Available spaces for medical visits and tests	Availability and quality of instruments and infrastructures (eg., laboratory,)	Adequate environment for test/vaccination provision and storage
Planned administration of questionnaires and tests (drug test, alcohol test, blood sample, visual test, hearing check…)	Required sample collection and preservation, test elimination	Adding cancer screening tests and cancer biomarkers to already planned tests
Interaction of different professionals (occupational physician, occupational nurse, employer, occupational safety representatives)	Multiple expertise required, need for enlightened figures, high responsibilities of the involved figures, increased workload of the occupational health providers	Network made of multidisciplinary team
Hierarchic structure	Hesitancy and reluctance from employers and/or occupational physicians	Welfare policies of the company, enhanced wellbeing and support of workers and stakeholders, financial support
Medical records	Privacy issues, unfit for work	Personalized dataset, risk profiling, 4-P medicine, data cloud
Prevention of injuries, occupation-related diseases and workers health vulnerabilities	High effort requirement for extended occupational health approach	Total worker health (one health)
Focused on risk assessment and early diagnosis	Lack of treatment	Closer to clinics, vaccine administration, recommendation for further diagnostic tests, behavioral interventions (nutrition, physical activity, lifestyle care)
Overall healthy people	Management of high-risk subjects, missing subgroups of population unemployed for medical reasons	Cancer risk assessment, complementary role of occupational physician to general practitioner, support to public health practice on the general population

Figure 1. Social determinants of health [49-58] (original figure).



References

1. Lippman SM, Hawk ET. Cancer prevention: from 1727 to milestones of the past 100 years. Cancer Res. 2009 Jul 1;69(13):5269-84.
2. Bauer UE, Briss PA, Goodman RA, Bowman BA. Prevention of chronic disease in the 21st century: elimination of the leading preventable causes of premature death and disability in the USA. Lancet. 2014 Jul 5;384(9937):45-52.
3. Angelini M, Collatuzzo G, Teglia F, Sassano M, Siea AC, Boffetta P. The role of chance in cancer causation. Med Lav. 2022 Dec 7;113(6):e2022056.
4. Collatuzzo G, Boffetta P. Cancers Attributable to Modifiable Risk Factors: A Road Map for Prevention. Annu Rev Public Health. 2023 Apr 3;44:279-300.
5. GBD 2019 Cancer Risk Factors Collaborators. The global burden of cancer attributable to risk factors, 2010-19: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2022 Aug 20;400(10352):563-591.
6. Dillner J. Early detection and prevention. Mol Oncol. 2019 Mar;13(3):591-598.
7. Greenwald P, Dunn BK. Do we make optimal use of the potential of cancer prevention? Recent Results Cancer Res. 2009;181:3-17.
8. Chow LW, Yip AY, Ng EL. Prevention of oncological diseases: primary and secondary prevention. Int J Biol Markers. 2012 Dec 27;27(4):e337-43.
9. Bizuayehu HM, Ahmed KY, Kibret GD, Dadi AF, Belachew SA, Bagade T, et al. Global Disparities of Cancer and Its Projected Burden in 2050. JAMA Netw Open. 2024 Nov 4;7(11):e2443198.
10. Hallgren E, Yeary KHK, DelNero P, Johnson-Wells B, Purvis RS, Moore R, et al. Barriers, facilitators, and priority needs related to cancer prevention, control, and research in rural, persistent poverty areas. Cancer Causes Control. 2023 Dec;34(12):1145-1155.
11. Pinsky PF. Principles of Cancer Screening. Surg Clin North Am. 2015 Oct;95(5):953-66.
12. Lopez AM, Hudson L, Vanderford NL, Vanderpool R, Griggs J, Schonberg M. Epidemiology and Implementation of Cancer Prevention in Disparate Populations and Settings. Am Soc Clin Oncol Educ Book. 2019 Jan;39:50-60.
13. Kaji E, Yoden A, Otani M, Okuhira T, Aomatsu T, Tamai H, Ashida A. Helicobacter pylori test-and-treat strategy for second-year junior high school students aimed at the prevention of gastric cancer in Takatsuki City. Helicobacter. 2020 Aug;25(4):e12696.
14. Davies C, Stoney T, Hutton H, Parrella A, Kang M, Macartney K, et al. School-based HPV vaccination positively impacts parents' attitudes toward adolescent vaccination. Vaccine. 2021 Jul 5;39(30):4190-4198.
15. Schoenberg NE, Hatcher J, Dignan MB, et al. Faith Moves Mountains: an Appalachian cervical cancer prevention program. Am J Health Behav 2009;33:627–38;
16. Matthews AK, Steffen AD, Kuhns LM, Ruiz RA, Ross NA, Burke LA, Li CC, King AC. Evaluation of a Randomized Clinical Trial Comparing the Effectiveness of a Culturally Targeted and Nontargeted Smoking Cessation Intervention for Lesbian, Gay, Bisexual, and Transgender Smokers. Nicotine Tob Res. 2019 Oct 26;21(11):1506-1516.
17. Reiter PL, Katz ML, Bauermeister JA, Shoben AB, Paskett ED, McRee AL. Increasing Human Papillomavirus Vaccination Among Young Gay and Bisexual Men: A Randomized Pilot Trial of the Outsmart HPV Intervention. LGBT Health. 2018 Jul;5(5):325-329.
18. Birnbaum JA, Guttman D, Parulekar M, Omarufilo F, Emeasoba EU, Nguyen J, Tokunboh O, Coe J, Akiyama MJ, Sigal SH. Eliminating hepatitis B vaccination disparities for West African immigrants. Vaccine. 2023 Oct 6;41(42):6255-6260.

19. Cox JE, Bogart LM, Elliott MN, Starmer AJ, Meleedy-Rey P, Goggin K, et al. Improving HPV Vaccination Rates in a Racially and Ethnically Diverse Pediatric Population. Pediatrics. 2022 Oct 1;150(4):e2021054186.
20. Nahmias Z., Townsend J.S., Neri A., Stewart S.L. Worksite cancer prevention activities in the national comprehensive cancer control program. J. Community Health. 2016;41(4):838–844.
21. Marshall H. Workplace cancer screening. Lancet Oncol. 2013;14(8):694.
22. Mojica C.M., Morales-Campos D.Y., Carmona C.M., Ouyang Y., Liang Y. Breast, cervical, and colorectal cancer education and navigation: results of a community health worker intervention. Health Promot. Pract. 2016;17(3):353–363.
23. Walsh J.M.E., Potter M.B., Arora M., Gildegorin G., Terdiman J. A workplace colorectal cancer screening program in firefighters: lessons learned. Occup. Med. 2014;64(4):255–258.
24. World Health Organization. Regional Office for Europe. (2002). Good practice in occupational health services : a contribution to workplace health. Copenhagen : WHO Regional Office for Europe;
25. GBD 2016 Occupational Carcinogens Collaborators. Global and regional burden of cancer in 2016 arising from occupational exposure to selected carcinogens: a systematic analysis for the Global Burden of Disease Study 2016. Occup Environ Med. 2020 Mar;77(3):151-159.
26. https://eur-lex.europa.eu/legal-content/IT/TXT/?uri=CELEX%3A32004L0037 Accessed on 21/01/2025;
27. Schill AL, Chosewood LC. The NIOSH Total Worker Health™ program: an overview. J Occup Environ Med. 2013 Dec;55(12 Suppl):S8-11.
28. Mon HM, Robb KA, Demou E. Effectiveness of workplace cancer screening interventions: a systematic review. BMC Cancer. 2024 Aug 12;24(1):999.
29. Grant, M. J., & Booth, A. (2009). A typology of reviews: An analysis of 14 review types and associated methodologies. *Health Information & Libraries Journal*, 26(2), 91–108. https://doi.org/10.1111/j.1471-1842.2009.00848.x
30. https://www.eurofound.europa.eu/en/publications/2023/measures-tackle-labour-shortages-lessons-future-policy accessed on 1 May 2025
31. Steel JS, Godderis L, Luyten J. Short-term effectiveness of face-to-face periodic occupational health screening versus electronic screening with targeted follow-up: results from a quasi-randomized controlled trial in four Belgian hospitals. Scand J Work Environ Health. 2022 Apr 1;48(3):220-228.
32. Eurostat (undated): Self-reported time elapsed since last visit to a medical professional by sex, age and educational attainment level, Online data code: hlth_ehis_am1e https://doi.org/10.2908/HLTH_EHIS_AM1E;
33. Wyatt S, Mohammed MA, de Dumast L, et alLong-term trends in English general practice consultation rates from 1995 to 2021: a retrospective analysis of two electronic health records databases BMJ Open 2024;14:e088845.
34. Eurostat. (2019). How often do you see a doctor? https://ec.europa.eu/eurostat/web/products-eurostat-news/-/ddn-20190225-1
35. Räsänen K, Notkola V, Husman K. Work-related interventions during office visits to occupational health physicians. Prev Med. 1997 May-Jun;26(3):333-9.
36. Loomans-Kropp, H.A., Umar, A. Cancer prevention and screening: the next step in the era of precision medicine. *npj Precision Onc* **3**, 3 (2019).
37. Gu KJ, Li G. An Overview of Cancer Prevention: Chemoprevention and Immunoprevention. J Cancer Prev. 2020 Sep 30;25(3):127-135.
38. de Boer AG, Tamminga SJ, Boschman JS, Hoving JL. Non-medical interventions to enhance return to work for people with cancer. Cochrane Database Syst Rev. 2024 Mar 5;3(3):CD007569.
39. Galiano-Castillo N, Cantarero-Villanueva I, Fernández-Lao C, Ariza-García A, Díaz-Rodríguez L, Del-Moral-Ávila R, Arroyo-Morales M. Telehealth system: A randomized controlled trial evaluating

the impact of an internet-based exercise intervention on quality of life, pain, muscle strength, and fatigue in breast cancer survivors. Cancer. 2016 Oct 15;122(20):3166-3174.
40. Devine KA, Viola AS, Coups EJ, Wu YP. Digital Health Interventions for Adolescent and Young Adult Cancer Survivors. JCO Clin Cancer Inform. 2018 Dec;2:1-15.
41. Schillie S., Vellozzi C., Reingold A., Harris A.,Haber P., et al. 2018. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm. Rep.* 67:1–31;
42. Chang M-H, You S-L, Chen C-J, Liu C-J, Lai M-W, et al. 2016. Long-term effects of hepatitis B immunization of infants in preventing liver cancer. *Gastroenterology* 151:472–80.e1;
43. Simms KT, Steinberg J, Caruana M,. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study. Lancet Oncol. 2019;20:394-407
44. https://immunizationdata.who.int/global/wiise-detail-page/human-papillomavirus-(hpv)-vaccination-coverage?CODE=JPN&ANTIGEN=15HPV1_F&YEAR= Accessed on 10 February 2025
44. Miyagi E. Human papillomavirus (HPV) vaccination in Japan. J Obstet Gynaecol Res. 2024 Oct;50 Suppl 1:65-71.
45. Yagi A, Ueda Y, Oka E, Nakagawa S, Kimura T. Human Papillomavirus Vaccination by Birth Fiscal Year in Japan. JAMA Netw Open. 2024 Jul 1;7(7):e2422513.
46. IARC List of classifications by cancer sites with sufficient or limited evidence in humans, IARC Monographs Volumes 1 – 137. https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf 21/01/2025;
47.Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024 Jan- Feb;74(1):12-49. doi: 10.3322/caac.21820. Epub 2024 Jan 17.
48.Ragelienė T, Schneider-Kamp A, Askegaard ST. Barriers and facilitators of prevention of infections related to cancer: A systematic literature review. Heliyon. 2024 Oct;10(19):e37959;
49. Birnbaum JA, Guttman D, Parulekar M, Omarufilo F, Emeasoba EU, Nguyen J, Tokunboh O, Coe J, Akiyama MJ, Sigal SH. Eliminating hepatitis B vaccination disparities for West African immigrants. Vaccine. 2023 Oct 6;41(42):6255-6260.
50. Marmot M, Allen J, Bell R, Bloomer E, Goldblatt P. WHO European review of social determinants of health and the health divide. The Lancet. 2012 Sep 15;380(9846):1011–29;
51. Wong LP, Wong PF, Megat Hashim MMAA, Han L, Lin Y, Hu Z, Zhao Q, Zimet GD. Multidimensional social and cultural norms influencing HPV vaccine hesitancy in Asia. Hum Vaccin Immunother. 2020 Jul 2;16(7):1611-1622.
52. Sun J, Perraillon MC, Myerson R. The Impact of Medicare Health Insurance Coverage on Lung Cancer Screening. Med Care. 2022 Jan 1;60(1):29-36.
53. Kogevinas M, Pearce N, Susser M, Boffetta P. Social Inequalities and Cancer. IARC Science Publications No 138 Lyon: International Agency for Research on Cancer; 1997.
54. Collatuzzo G, Teglia F, Boffetta P. Role of Occupation in Shaping Cancer Disparities. Cancers (Basel). 2022 Aug 31;14(17):4259.
55. Stephens NM, Markus HR, Fryberg SA. Social class disparities in health and education: reducing inequality by applying a sociocultural self model of behavior. Psychol Rev. 2012 Oct;119(4):723-44.
56. Kim TV, Pham TND, Le DH, Dao DVB, Phan LTB, Le A, Trang A, Tang HK, Liu JJ, Dao DY. Significant gaps in hepatitis B vaccination in adults in Viet Nam: Important targets toward hepatitis B

elimination by 2030. Vaccine. 2023 Jan 23;41(4):976-988.

57. Kim TV, Pham TND, Do B, Dao DVB, Nguyen DX, Lee W, et al. Low HBV knowledge is associated with low HBV vaccination uptake in general adult population despite incentivization of HBV vaccination. BMC Infect Dis. 2024 May 3;24(1):470.

58. Downs LS Jr, Scarinci I, Einstein MH, Collins Y, Flowers L. Overcoming the barriers to HPV vaccination in high-risk populations in the US. Gynecol Oncol. 2010 Jun;117(3):486-90.
59. Aoki ES, Yin R, Li K, Bhatla N, Singhal S, Ocviyanti D, et al. National screening programs for cervical cancer in Asian countries. J Gynecol Oncol. 2020 May;31(3):e55.
60. Zhao S, Huang L, Basu P, Domingo EJ, Supakarapongkul W, Ling WY, et al. Cervical cancer burden, status of implementation and challenges of cervical cancer screening in Association of Southeast Asian Nations (ASEAN) countries. Cancer Lett. 2022 Jan 28;525:22-32.

61.Jou K, Sterling MR, Ramos R, Antoine F, Nanus DM, Phillips E. Eliciting the Social Determinants of Cancer Prevention and Control in the Catchment of an Urban Cancer Center. Ethn Dis. 2021 Jan 21;31(1):23-30.

62. Centers for Disease Control and Prevention. *The Road to Better Health: A Guide to Promoting Cancer Prevention in Your Community.* Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2012;
63. Choi YJ, Lee HY, An S, Yoon YJ, Oh J. Predictors of Cervical Cancer Screening Awareness and Literacy Among Korean-American Women. J Racial Ethn Health Disparities. 2020 Feb;7(1):1-9.

64. Rapkin BD, Weiss E, Lounsbury D, Michel T, Gordon A, Erb-Downward J, et al. Reducing Disparities in Cancer Screening and Prevention through Community-Based Participatory Research Partnerships with Local Libraries: A Comprehensive Dynamic Trial. Am J Community Psychol. 2017 Sep;60(1-2):145-159.

65. Schoenberg NE, Hatcher J, Dignan MB, Shelton B, Wright S, Dollarhide KF. Faith Moves Mountains: an Appalachian cervical cancer prevention program. Am J Health Behav. 2009 Nov-Dec;33(6):627-38.

66. https://preventcancer.org/news/prevent-cancer-annual-cancer-prevention-early-detection/ accessed on 04/12/2024;
67.https://www.fsitaliane.it/content/fsitaliane/en/media/press-releases/2024/9/30/frecciarosa-2024-cancer-prevention-train-is-back.html accessed on 04/12/2024;
68. Collatuzzo G, Fiorini G, Vaira B, Violante FS, Farioli A, Boffetta P. The role of the occupational physician in controlling gastric cancer attributable to *Helicobacter pylori* infection: A review. Prev Med Rep. 2021 Aug 18;24:101527.

69. Fernandez-Tardon G, Gan RK, Rodriguez-Suarez MM, Tardon A, Arcos-González P. Total worker health® based *Helicobacter pylori* public health prevention strategy. Curr Opin Epidemiol Public Health. 2024 May 28;3(2):33-39. 70.
70. Blacker A, Dion S, Grossmeier J, Hecht R, Markle E, Meyer L, Monley S, Sherman B, VanderHorst N, Wolfe E. Social Determinants of Health-an Employer Priority. Am J Health Promot. 2020 Feb;34(2):207-215.
71. Song F, Bachmann M, Howe A. Factors associated with the consultation of GPs among adults aged ≥16 years: an analysis of data from the Health Survey for England 2019. BJGP Open. 2023 Sep 19;7(3):BJGPO.2022.0177.

72. Baker, P. (2024), Missing persons? Men's use of primary care services. Trends Urology & Men Health, 15: 2-5.

73. Benavides FG, Serra C, Delclos GL. What can public health do for the welfare state? Occupational health could be an answer. J Epidemiol Community Health. 2019 Dec;73(12):1141-1144.

74. Thorndike AN, McCurley JL, Gelsomin ED, Anderson E, Chang Y, Porneala B, Johnson C, Rimm EB, Levy DE. Automated Behavioral Workplace Intervention to Prevent Weight Gain and Improve Diet: The ChooseWell 365 Randomized Clinical Trial. JAMA Netw Open. 2021 Jun 1;4(6):e2112528.

75. Wang C, Lu EY, Sun W, Chang JR, Tsang HWH. Effectiveness of interventions on sedentary behaviors in office workers: a systematic review and meta-analysis. Public Health. 2024 May;230:45-51.

76. Allen JD, Stoddard AM, Mays J, Sorensen G. Promoting breast and cervical cancer screening at the workplace: results from the Woman to Woman Study. Am J Public Health. 2001 Apr;91(4):584-90.

77. Symanzik C, John SM. Sun protection and occupation: Current developments and perspectives for prevention of occupational skin cancer. Front Public Health. 2022 Dec 23;10:1110158.

78. Huang HL, Chang M. Effects of Two Teaching Programs on Workplace Women's Cervical Cancer Screening Knowledge, Health Beliefs and Behavior. Nurs Res. 2000;8(1):111–123. In Chinese;

79.https://osha.europa.eu/en/campaigns-and-awards/healthy-workplaces-campaigns accessed on 21/01/2025;

80. International Labour Office, Geneva – Technical and Ethical Guidelines for Workers' Health Surveillance, available at https://www.ilo.org/publications/technical-and-ethical-guidelines-workers-health-surveillance;

81. Price WN 2nd, Cohen IG. Privacy in the age of medical big data. Nat Med. 2019 Jan;25(1):37-43.

82. Steel JS, Godderis L, Luyten J. Disclosure in Online vs. Face-to-Face Occupational Health Screenings: A Cross-Sectional Study in Belgian Hospital Employees. Int J Environ Res Public Health. 2021 Feb 4;18(4):1460.

83. Stratil J, Rieger MA, Voelter-Mahlknecht S. Optimizing cooperation between general practitioners, occupational health and rehabilitation physicians in Germany: a qualitative study. Int Arch Occup Environ Health. 2017 Nov;90(8):809-821.

84. Persechino B, Fontana L, Buresti G, Rondinone BM, Laurano P, Fortuna G, et al. Collaboration of occupational physicians with national health system and general practitioners in Italy. Ind Health. 2017 Apr 7;55(2):180-191.

85. Tenney L, Brown CE, Schilz M, Goering M, Dally M, Dye-Robinson A, et al. Engaging Oncology and Occupational Medicine to Inform Design of a Total Worker Health® Intervention to Address Employment, Financial, and Well-being Outcomes in Cancer Survivors. J Occup Environ Med. 2024 Nov 1;66(11):e537-e543.

86. Zusman EZ, Kapanen AI, Klaassen A, Reardon J. Workplace cardiovascular risk reduction by healthcare professionals-a systematic review. Occup Med (Lond). 2021 Oct 1;71(6-7):270-276.

87.Jiménez P, Bregenzer A, Kallus KW, Fruhwirth B, Wagner-Hartl V. Enhancing Resources at the Workplace with Health-Promoting Leadership. Int J Environ Res Public Health. 2017 Oct 20;14(10):1264.

88. ONCONAUTI https://onconauti.it/chi-siamo/;

89. Civilotti C, Lucchini D, Fogazzi G, Palmieri F, Benenati A, Buffoli A, et al. The role of integrated psychological support in breast cancer patients: a randomized monocentric prospective study evaluating the Fil-Rouge Integrated Psycho-Oncological Support (FRIPOS) program. Support Care Cancer. 2023 Apr 14;31(5):266. d

90. Inbaraj G, Sathyaprabha TN, Udupa K, Ram A, Patil S, Rajeswaran J, Nandakumar KK, et al. Impact of integrated yoga therapy on cognitive impairment and cardiac dysfunction in relation to quality of

life in breast cancer patients undergoing chemotherapy: Study protocol for a two-arm randomized controlled trial. Front Oncol. 2022 Sep 16;12:955184.
91. Hanvey GA, Kacel EL, Bacharz KC, et al. Proof-of-Concept of an Integrated Yoga and Psychological Intervention in Mitigating Distress Among Diverse Women With Gynecologic, Gastrointestinal, and Thoracic Cancers. Integrative Cancer Therapies. 2024;23.
92. Sinelnikov S, Bixler EA, Kolosh A. Effectiveness of safety training interventions for supervisors: A systematic review and narrative synthesis. Am J Ind Med. 2020 Oct;63(10):878-901.
93. Ryan M, Erck L, McGovern L, McCabe K, Myers K, Nobrega S, Li W, et al. "Working on Wellness:" protocol for a worksite health promotion capacity-building program for employers. BMC Public Health. 2019 Jan 25;19(1):111.
94. Rafie CL, Hauser L, Michos J, Pinsky J. Creating a Workplace Culture of Preventive Health: Process and Outcomes of the Colon Cancer-Free Zone at Virginia Cooperative Extension. J Cancer Educ. 2020 Dec;35(6):1135-1140.
95. Nobrega S, Morocho C, Robertson MM, Kurowski A, Rice S, Henning RA, Punnett L. A mixed-method approach to tailor the implementation of a participatory Total Worker Health® program. Int J Workplace Health Manag. 2021 Jul 21;14(4):409-425.
96. Bollati V, Ferrari L, Leso V, Iavicoli I. Personalised Medicine: implication and perspectives in the field of occupational health. Med Lav. 2020 Nov 25;111(6):425-444.
97. European Commission: COWI, Directorate-General for Employment, Social Affairs and Inclusion, EPRD, FoBIG, RPA, Garrett, S., Vencovsky, D.Collins, H., Study on collecting information on substances with the view to analyse health, socio-economic and environmental impacts in connection with possible amendments of Directive 98/24/EC (Chemical Agents) and Directive 2009/148/EC (Asbestos) – Methodological note and data collection synopsis, Publications Office, 2021, https://data.europa.eu/doi/10.2767/734383
98. Kim, J.Y., Keane, A. Corporate social responsibility and performance in the workplace: a meta-analysis. *Int J Educ Vocat Guidance* **24**, 781–807 (2024).
99. Velte, P. Meta-analyses on Corporate Social Responsibility (CSR): a literature review. *Manag Rev Q* **72**, 627–675 (2022).
100. Paruzel A, Klug HJP and Maier GW (2021) The Relationship Between Perceived Corporate Social Responsibility and Employee-Related Outcomes: A Meta-Analysis. Front. Psychol. 12:607108.
101. European Commission, Directorate-General for Employment, Social Affairs and Inclusion, 'Socio-economic costs of accidents at work and work-related ill health – final report', 2011, http://ec.europa.eu/social/BlobServlet?docId=7416&langId=en
102. Eurostat (2025): HICP - annual data (average index and rate of change), https://doi.org/10.2908/PRC_HICP_AIND
103. Leal J, Luengo-Fernandez R, Sullivan R, Witjes JA. Economic Burden of Bladder Cancer Across the European Union. Eur Urol. 2016 Mar;69(3):438-47.
104. Hanly, P., Ortega Ortega, M., Pearce, A. *et al.* Estimating Global Friction Periods for Economic Evaluation: A Case Study of Selected OECD Member Countries. *PharmacoEconomics* **41**, 1093–1101 (2023). https://doi.org/10.1007/s40273-023-01261-y;
105. Reframe Cancer (2024): The Employee Experience report: Living and working with cancer, available at https://www.reframe.co.uk/blog/the-1.6-billion-cancer-absence-cost-to-uk-businesses-in-2024;

106. Goulart, K., & Oesch, D. (2024). Job tenure in Western Europe, 1993–2021: Decline or stability? European Journal of Industrial Relations, 30(3), 329-346. https://doi.org/10.1177/09596801241268144;
107. ECIS (2025): ECIS - European Cancer Information System, Estimates of cancer incidence and mortality, 2022, for all countries.

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IMPLEMENTING CANCER PREVENTION STRATEGIES IN THE OCCUPATIONAL SETTING: THE CANCER PREVENTION AT WORK (CPW) STUDY PROTOCOL

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CPW CANCER PREVENTION at WORK

EACR25-0066

INTRODUCTION

Chronic infections account for 13% of human cancer (1). Helicobacter pylori (Hp), Hepatitis C Virus (HCV) and Human Papilloma Virus (HPV) are responsible together for 75% of this burden (2). The occupational health surveillance (OHS) would be a suitable framework for implementing health promotion activities to prevent infection-related cancers, given its structured program.

AIMS

(i) To conduct pilot protocols for occupational-based prevention of cancers caused by Hp, HCV and HPV;

(ii) To estimate the cost-effectiveness of these interventions;

(iii) To develop plans for the large-scale implementation of such interventions and engage stakeholders;

(iv) To identify barriers and facilitators of occupational-based preventive interventions targeting Hp, HCV and HPV;

(v) To provide data on prevalence of infection and of adherence to cancer prevention strategies in different types of workers.

METHODS

CPW is held in N centers across four European countries with a high prevalence of cancer-related infections: Italy, Spain, Romania and Slovakia. Population involved include healthcare, retail, finance, metal and manufacture workers. Three interventions - Hp test; HCV test; HPV vaccination - will be implemented during the OHS as a prospective pilot study involving at least 1000 workers in each center. The recruitment started in summer 2024 and will continue for 12-18 months. Workers who tested positive for Hp and HCV and their family members (FMs) will be addressed to the general practitioner and the specialist for management of the infection through confirmatory diagnostic tests and eventual treatment. HPV vaccination will be offered to eligible workers (men and women aged <45) and their FMs. A 6-month follow-up questionnaire will be administered to Hp and HCV positives and to participants who agreed to undergo HPV vaccination.

RESULTS

The project is expected to identify cost-effectiveness advantages from using OHS to implement interventions that are broader in scope than occupational disease prevention. If such advantages are identified, the project has a significant potential to influence future research efforts and practical initiatives within the OHS that prevent all (including non-occupational) cancers.

Results will include participation rates and determinants, adherence to the purposed protocols, epidemiology of Hp and HCV infections, attitude towards HPV vaccination, and behavioral determinants of health of different working populations in European countries.

The project will also describe the determinants of the cost-effectiveness of the interventions, providing evidence for decision makers.

Figure 1: CPW Project's Approach

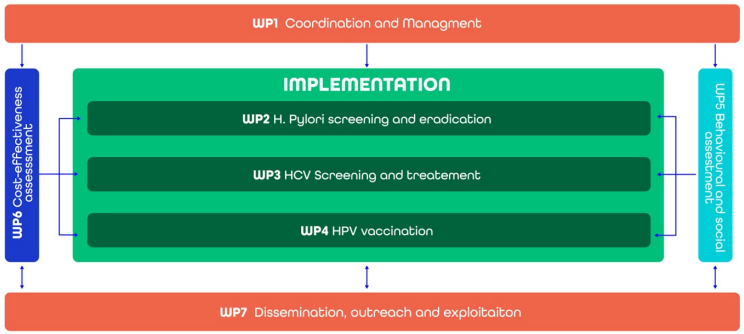

Figure 2: Prevention of three infection-related cancer via implementation of interventions within regular occupational health surveillance programs

Pilot study on Hepatitis C virus (HCV)

HCV screening and treatment as primary prevention of liver cancer within occupational health surveillance programs.

Pilot study on Human Papillomavirus (HPV)

Vaccination as primary prevention of HPV infection and its complications, within occupational health surveillance programs.

Pilot study on Helicobacter pylori (Hp)

Hp screening and eradication as primary prevention of stomach cancer within occupational health surveillance programs.

CONCLUSIONS

The workplace represents an innovative context for cancer prevention implementation and might offer an effective contribution to cancer control, reaching heterogeneous populations and rising awareness about cancer prevention.

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REFERENCES

(1) World Health Organization. Cancer. Geneva: World Health Organization; 2025 Feb 3.

(2) de Martel C et al. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health 2020

Expanding cancer prevention: strategies integrated into occupational health surveillance

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Key characteristics	Challenges	Opportunities
Structured setting of OHS	Logistics and organization of testing, test results communication, visits duration	Regular follow-up and longitudinal monitoring of the worker's health and adherence to cancer prevention
Available spaces for medical visits and tests	Instruments and infrastructures	Adequate environment for test/vaccination provision and storage
Planned administration of questionnaires and tests	Required sample collection and preservation, test elimination	Adding cancer screening tests and cancer biomarkers to already planned tests
Interaction of different professionals	Multiple expertise required, high responsibilities of the involved figures, increased workload	Network made of multidisciplinary team
Hierarchic structure	Hesitancy and reluctance from employers and/or occupational physicians	Welfare policies, enhanced wellbeing and support of workers and stakeholders, financial support
Medical records	Privacy issues, unfit for work	Personalized dataset, risk profiling, 4-P medicine, data cloud
Focused on prevention within workplace	High effort requirement for extended occupational health approach	Total worker health (one health)
Focused on risk assessment	Lack of treatment	Closer to clinics, behavioral interventions
Overall healthy employed people	Management of high-risk subjects, missing unemployed for medical reasons, lack of compliance, age limits	Equity, age- and sex-specific interventions, cancer risk assessment, complementary role of occupational physician to general practitioner, support to public health

- Eurostat data: in 2017, 24% of the EU population did not see their general practitioner.
- In countries where it is implemented, OHS is widely accessed by employees. Possible reasons: no cost for employees, lack of need for referral from other physicians, service availability.

→ opportunity to **expand the scope of occupational medicine** to include larger preventive healthcare measures, according to a **Total Worker Health** model.

→ The occupational physician could play a **primary prevention of both occupational- and non-occupational cancers, complementing GP activity and contributing to public health** significant role in.

Innovative model integrating multiple cancer prevention strategies (education, screening, vaccination, behavioral interventions) into Occupational Health Surveillance

→ rise cancer prevention awareness, total health promotion, overcome socioeconomic and infrastructural barriers, increase work effectiveness, decrease cancer burden

Cancer Prevention at Work
Horizon Europe, Mission Cancer
Grant N 101104716

4. Workplace-based Screening for Helicobacter pylori infection: the HPOS study

Title: A Real-world Workplace-based Screening for Helicobacter pylori Infection - the HPOS study

Running head: Helicobacter pylori screening at the workplace

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Authors contribution: Conceptualization: GC, PB, DV; methodology: PB, GC; investigation: GC, GF, MP, MVCP, ACS, MZ, LA, LM, TR, ND, DV, PB; data management: MDA, SM, GC; data analysis: GC; writing—original draft preparation: GC; writing—review and editing: GF, MP, DV, PB; supervision: PB; project administration: PB; funding acquisition: PB. All authors have read and agreed on the published version of the manuscript.

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Competing interests: The authors declare no competing interests.

Ethics statement: The study was approved by the ethical committee Area Vasta Emilia Romagna – AVEC, internal code 988/2021/Oss/AOUBo; all subjects provided written consent to participate to this study.

Data availability: The original de-identified data will be made available upon reasonable request.

Abstract

Objectives: *Helicobacter pylori* (Hp) eradication contributes to gastric cancer prevention, yet many subjects are unaware of their infection status. We implemented a workplace-based Helicobacter pylori (Hp) screening for gastric cancer prevention.

Design: This is a cross-sectional study conducted among a population of hospital workers (HW), enrolled during occupational health surveillance (OHS). Stool antigen test (SAT) was adopted for Hp diagnosis. Hp positive HW were referred to their general practitioner (GP) or a gastroenterologist and were followed-up at three months. Participation, prevalence of infection, participant's experience and treatment rates were investigated through descriptive and multivariable analyses.

Setting: The study was carried out between 2023 and 2025 at S.Orsola Univeristy Hospital in Bologna, Italy.

Participants: The study targeted hospital workers (HW) aged 40-65 employed at S.Orsola University Hospital.

Results: Of 593 eligible HW contacted at OHS, 399 were enrolled (67.3%); the largest proportion were women (72.9%) and nurses (37.1%). Additional 151 HW engaged as volunteers, giving 550 total participants. Dropout rate was 20.9% (N=115), leaving 435 HW with SAT result. Hp prevalence was 16.6%. None of the investigated factors predicted Hp infection ($p>0.05$). 62 Hp-positive HW (86.1%) were successfully followed-up: 93.5% contacted a physician, of those 85.5% received a treatment. Confirmatory test rate was suboptimal, while eradication rate was 97.3% (36/37 HW) when considering those with confirmatory test result. Across followed-up HW, average quality of experience was 8.9/10; 13 had a family member tested following this intervention.

Conclusions: The intervention integrated into OHS was well received and extended to family members of the participants, suggesting that a workplace-based Hp screening might contribute to gastric cancer prevention. Replications in other workplaces are warranted.

Key words: Helicobacter pylori; screening; gastric cancer prevention; stool antigen test; workplace; occupational health surveillance; total worker health

What is already known on this topic – Subjects infected with Helicobacter pylori (Hp) are often asymptomatic, however they are at increased risk of gastric cancer (GC). The screen-and-treat approach would significantly reduce GC risk.

What this study adds – We implemented the first Hp screening program integrated into occupational health surveillance in Italy for primary prevention of GC, leading to ~70% participation rate and recruitment of volunteers. The majority of Hp-positive workers referred to the general practitioner or gastroenterologist, were treated and eradicated.

How this study might affect research, practice or policy – This study carries important implications for implementing workplace-based Hp screening strategies, according to a Total Worker Health approach. Such intervention might contribute to GC prevention, with broader public health impact. Future studies should investigate the impact of workplace-based Hp screening on absenteeism, productivity and wellbeing.

Introduction

Occupational medicine (OM) is dedicated to prevention, diagnosis and management of work-related diseases and injuries (1). Its aims include assessing occupational risks and promoting a safe and healthy work environment (1).
According to the concept of Total Worker Health (TWH) (2), the potential of OM in contributing to public health extends beyond work-related diseases. Workplace-based cancer screening is part of a TWH approach. In fact, the workplace might represent an ideal setting for the implementation of cancer screenings given the structured, periodical character of occupational health surveillance (OHS), which is mandatory and free for all workers (3,4).

Helicobacter pylori (Hp) infection is the leading cause of infection-related cancer worldwide (6). In Italy, Hp was estimated to have caused 2.4% of total cancer cases and 3.3% of cancer deaths in 2020 (7). The non-invasiveness of Hp detection methods and the availability of antibiotic-based therapies make GC preventable through Hp test-and-treat strategies (8). Despite clear evidence supporting the effectiveness of these strategies for GC prevention, no standardized large-scale Hp screening has been implemented yet (9), also resulting in low awareness of Hp-related risks (10-13).
Recent literature highlights the need for GC prevention in Europe (14). A targeted approach might represent a facilitator for the successful implementation of a Hp screening. In particular, workplace-based Hp screening has been previously proposed (4,14).

The HPOS-(*Helicobacter pylori* screening among hospital workers [HW]) study was established to assess the feasibility and acceptability of a workplace-based Hp screening as part of the occupational health surveillance (OHS). It is the pilot study of the Cancer Prevention at Work (CPW), a multicenter international project currently ongoing in Europe, which includes the implementation of Hp screening across different workplace settings (15).
In this paper, we illustrate the design, results and impact of the HPOS study.

Methods

The HPOS study is a cross-sectional interventional study based in Bologna, Italy, targeting HW. The study was developed by a multidisciplinary team of occupational health providers and gastroenterologists from the University of Bologna and the IRCSS S.Orsola University Hospital. The study was approved by the local ethics committee and was conducted between March 2023 and

March 2025. The estimated target was 496 workers, based on an expected Hp prevalence of 25.0% and a 10.0% dropout rate.

The OM Unit in Italy operates in compliance with regulations (16) mandating that all employees undergo baseline medical examination to assess their fitness for work. In brief, the intervention consisted of Hp screening via stool antigen test (SAT) offered during routine OHS, supported by educational materials to raise awareness on Hp-related diseases, including GC. Hp-positive HW received a written report, including recommendation on Hp management, and were referred to their general practitioner (GP); they were followed-up at three months to investigate infection management, collect feedback, and to support family members interested in Hp screening.

The primary aims of this study were (i) to test the feasibility of a workplace-based Hp screening integrated into OHS, (ii) to describe the prevalence of Hp infection, and (iii) to evaluate the impact of the intervention in a population of Italian HW at 3-month from diagnosis.

Before the study commenced, informational sessions were organized for all OM providers to outline the study process. Additionally, training sessions were conducted for the research team to ensure protocol adherence throughout all phases. Enrolment progress was regularly reviewed, and issues were promptly addressed.

Study population

The target population consisted of HW employed at S. Orsola University Hospital, Bologna, Italy. Next to employment at that hospital, inclusion criteria were age 40-65 and provision of written consent form. Age range was established based on (i) birth-cohort effect of Hp prevalence, with increasing likelihood of infection with age (17); (ii) possible expanded effect on workers' adult family members (18); (iii) rationale for eradication treatment. Exclusion criteria were pregnancy/breastfeeding, gastrectomy, active cancer and severe disease condition, and rectal bleeding/diarrhea. Workers who were short-time users of proton pump inhibitors (PPI) or antibiotics were temporarily excluded, and considered for enrollment after four weeks from the end of the therapy (8); similarly, those using antiacid were considered for enrollment after 10 days from stopping the treatment (8). Workers willing to participate despite chronic therapy with PPI were not recommended to interrupt their therapy, and were referred to their GP. The remaining subjects under chronic PPI treatment were considered ineligible.

Workers who had ever been tested or treated for Hp infection were not excluded, given that our aim was to describe the prevalence of infection within this population.

Enrollment strategies

Figure 1 illustrates the enrolment strategies adopted within the HPOS intervention scheme. The study was supported by communication materials: posters presenting the study were placed at the entrance of the OM Unit, at the reception desk and in strategic areas such as the canteen and the main Hospital pavilion. Two types of enrolment could be distinguished: (i) workers recruited at the moment of the regular OHS, wither in the waiting room or during the visit (active enrollment); (ii) workers who referred spontaneously to the research team following either information posted though poster and online, or recommendation from colleagues (volunteer enrollment). The latter group was excluded from the analysis of participation rate, but was included in other analyses.

Documents provided to the HW are included in **Appendices A-E**. A trained researcher illustrated the study to potential participants, also providing informative materials (**Appendices A and B**) if the person was interested. Workers who agreed to participate signed an informed consent (**Appendix C**), were given a numerical code, and completed a questionnaire (details below). A stool sample kit was provided, together with specific information on its use, storage and return. In particular, HW were indicated to return to the OM Unit the stool sample within 48 hours of collection to guarantee that samples were analyzed within 24 hours of return.

Questionnaires, communication of test result and three-month follow-up

The baseline questionnaire (**Appendix D**) comprised 8 sections: sociodemographic; occupational; lifestyle; dietary; Hp infection knowledge and personal Hp history; gastric disease history; other clinical history; gastrointestinal symptoms. The follow-up questionnaire (**Appendix E**) investigated whether the HW had taken contact with a physician to manage Hp infection, treatment and further testing undergone, change in health status and feedback on the study experience. Participants filled out the paper questionnaire at the time of enrollment. They were given the option to fill the questionnaire at home and return it with the stool sample. Data of the compiled questionnaires were then de-identified and inserted in the dedicated database.

SAT returned by the HW were stored in a fridge at the OM Unit before transfer to the laboratory, which was located close to the OM Department. In particular, stool specimens were stored at 4 °C for no longer than 48 hours. The detection of Hp antigen was carried out using the Curian® HpSA®

assay (Meridian Bioscience Europe, Milan, Italy), a rapid, qualitative fluorescent immunoassay specifically designed for human stool samples, with an analytical turnaround time of approximately 20 minutes (19-21). At the beginning of each analytical session, one positive and one negative control were included to verify assay reliability. Test results were recorded in the dedicated database.

To increase compliance for returning the SAT and questionnaire (if not completed at enrolment), each participant was solicited by phone call up to 3 times. HW who agreed to participate in the study but did not return either the questionnaire or the SAT were considered dropout.
SAT results were communicated via e-mail, with the official report attached. In the event of a positive result, the report was preceded by a phone call during which the worker was informed of the diagnosis and advised to consult the GP for continuation of the therapeutic pathway. After three months, positive HW were recontacted by phone for the follow-up interview.

Statistical analysis
We distinguished three age groups, namely 40-45, 46-55, and 56-65. Job titles were coded as nurse, health assistant, physicians/researchers (including resident physicians and PhD students), technicians and other health professionals, and non-healthcare workers (including office workers, maintenance workers, cooks, and gardeners).
Gastroenterology and endoscopy departments were considered at high-risk for Hp infection (22). HW were considered symptomatic when they referred to at least one of the following disturbances: nausea, epigastric discomfort/pain, regurgitation or heartburn.
Descriptive analyses were performed by engagement status and by Hp status. Chi-square tests among categories were computed. Multivariate logistic regression models accounting for sex, age and job title were run to investigate the determinants of enrollment, expressed as odds ratio (OR) and 95% confidence interval (CI). We also analyzed prevalence and determinants of Hp infection through models adjusted by sex and age.
Descriptive analyses were conducted to explore the impact of Hp diagnosis and our intervention after three months.
Statistical analyses were conducted using Stata v16 (23).

Results

Of 593 eligible HW contacted at OHS, 399 were enrolled (67.3%) and 194 refused to participate (32.7%). An additional 151 HW engaged as volunteers, leading to 550 total participants. Overall, 494 HW filled the questionnaire and 435 were successfully tested for Hp through SAT, while 115 HW dropped from the study. **Figure 2** illustrates the flow diagram of the recruitment process.
Table 1 shows the characteristics of the study population. The majority of participants were women (291, 72.9%, p-het=0.02) and aged 46-55 (172, 43.1%, p-het=0.57), mean age 51 (50.2-51.7).

A higher proportion of women accepted to be enrolled compared than men (70.3% vs 60.3%, p=0.02). While most enrolled HW were employed as nurse (N=148, 37.1%) or health assistant (N=84, 21.0%), we observed the highest enrollment rate among technicians and other healthcare professionals (75.0%), followed by health assistants (72.4%). Refusals were 194/593 (32.7%), constituted in the largest part of women (63.4%), HW aged 46-55 (39.2%), and employed as nurse (40.2%). The proportion of refusals was higher in men (39.7%) than in women (29.7%). The refusal rate followed the order physician/researcher > non-healthcare professionals > nurse > health assistant > technicians and other healthcare professionals.
Among the 151 volunteers, 120 were women (79.5%). The largest proportion were aged 46-55 (41.7%) and worked as nurse (48.3%) or health assistant (21.2%). When considering dropouts, men were slightly more likely to drop than women (20.1% vs 18.5%), as well as younger HW subgroup was compared to the others (27.5% of those 40-45 compared to 17.1% among 46-55 and 20.5% among 56-65 year-old). The largest proportion of HW who dropped the study was represented by physicians/researchers (40.5%), followed by health assistants (25.9%).
Of the 115 dropouts, 10 were recorded among volunteers (8.7%) and 105 among actively recruited HW (91.3%).

Results of the multivariate analysis of determinants of enrollment are reported in Supplementary **table 1**: men were significantly less likely to engage the study compared than women (OR=0.68, 95% CI=0.47-0.99). No additional pattern was observed by age and job title.
The analysis on knowledge, history and determinants of Hp infection was conducted on 494 HW with available questionnaire data (**Supplementary table 2**). Among them, 32 (6.5%) reported to be unaware of Hp infection as health issue at the time of the study. When asked what is the level of knowledge of the Hp infection among the general population, the most frequent answer was “poorly known” (38.1%), and the second was “well known” (34.2%). Most HW reported to have learned

about Hp during the studies/at the workplace (72.5%), rather than within their family (8.3%), from the GP (6.7%) or from the media (7.0%). A total of 17.2% reported a first-degree family member who resulted Hp-positive, and 11.3% reported family history of GC.

Table 2 presents the relationship between Hp infection and sociodemographic, lifestyle and occupational characteristics. Of 435 screened individuals, 72 (16.6%) resulted Hp-positive, including 49 HW enrolled during OHS and 23 volunteers. No statistically significant sex or age differences was observed, despite a slightly higher prevalence of infection was observed in women than in men, and in the oldest group. Prevalence of Hp did not differ between HW enrolled as volunteers and those enrolled at OHS. Health assistants showed the highest Hp prevalence (24.4%) and physician/researchers the lowest (10.6%), although these differences were not statistically significant. Hp prevalence was inversely associated with educational level (OR=0.41, 95% CI=0.18-0.93 for the highest educational level vs the lowest). A borderline higher risk of Hp infection was observed for separated/widowed compared to married/in couple workers. Lifestyle habits were not associated to Hp prevalence in the study population, nor were upper-GI symptoms.

Table 3 summarizes the data collected at three-month follow-up. Of the 72 Hp-positive HW, 10 (13.9%) did not answer the phone calls or dropped from the study, leaving 62 HW who were followed-up (86.1%). Of the 62 followed-up HW, four did not contact any doctor (6.5%) and 58 did (93.5%); in particular, the majority contacted their GP (67.2%) and the remaining contacted a gastroenterologist (32.8%). Of those who contacted a physician, 13 HW underwent upper endoscopy (22.4%), 11 being diagnosed with atrophic gastritis, one with erosive gastritis, and one found negative at further Hp testing but with gastric polyposis.

A total of 53/62 (85.5%) Hp-positive HW were prescribed an eradication treatment, while five were not (8.6%) either because they resulted negative at a second Hp test (N=3) or were asymptomatic (N=2) and therefore not needed treatment according to the GP. Among the 53 HW who were prescribed a treatment, 47.2% underwent the 10 days sequential therapy and 37.7% the 10 days concomitant/quadruple therapy; the remaining received either 14 days triple therapy, modified triple therapy or hybrid therapy. Furthermore, 26/53HW (49.1%) were prescribed probiotics next to eradication treatment.

At the time of follow-up, 40/53 HW (75.7%) have repeated a confirmatory test after treatment. Of the 53 HW who underwent eradication treatment, 36 were successfully eradicated according to the confirmatory test (67.9%). In particular, 33 HW were eradicated with first-line treatment while three turned negative after second-line therapy. When restricting to the 37 HW who have received and

reported the result of a confirmatory test after treatment, eradication rate was 97.3%, with one individual having interrupted the treatment because of allergic reaction.
Data on adverse effects of the treatment were available for 50/53 treated HW. The most commonly reported conditions were nausea (45.3%) and altered feces color (34.0%), while 22.6% had diarrhea. Among the relevant conditions, one subject reported intense diarrhea and one allergic reaction leading to treatment interruption, and another manifested extrasystole and tachycardia during the treatment, yet none needed hospitalization. Most treated HW referred complete compliance with the therapy (87.8%). Half of HW judged the therapy moderately difficult, while 10.0% reported high difficulty.
Factors related to the GP indicated a generally positive attitude towards the proposed screening, with a focus on recommending treatment adherence. However, a lack of sufficient information regarding potential adverse effects was reported.
When asked about their screening experience, HW included in the follow-up rated it positively (mean score: 8.9/10) and considered it very useful (78.4%). The majority stated they would recommend Hp screening (40 out of 50; 80.0%). Finally, 28 HW expressed interest in involving their family members in the screening process; among them, 13 had one or more family members screened.

Discussion

We implemented the first real-world Hp screening program among HW in Italy, representing the first workplace-based initiative for GC prevention, achieving a nearly 70% participation rate. An additional group of HW was enrolled as volunteers, showing strong interest towards the program. Higher participation was observed among women and nurses, while men and physicians were less likely to be successfully engaged. Hp prevalence was 16.6%, lower than expected. The three-month follow-up evidenced that most positive HW referred to their GP, who were often favorable to the proposed screening. We recorded around 30% incomplete adherence to recommendations at follow-up, often due to procrastination of Hp management after diagnosis. Nevertheless, eradication rate was 97.3%. A subgroup of Hp-positive HW underwent upper endoscopy, with one HW diagnosed with erosive gastritis as the most severe finding. The Hp screening was well received, with about 80% of HW rating it highly useful and indicating they would recommend it.

To our knowledge, this is one of the few workplace-based Hp screenings implemented globally. Zober et al. assessed Hp prevalence via serology among 6,143 chemical workers in Germany as a health promotion initiative within the OHS in 1995-1996 (24). In particular, 4,488 were recruited during OHS and 1,655 on a voluntary basis. However, participation rate is unclear, as the authors did

not specify the total number of invited workers (24). Madisch et al. conducted a Hp screening using urea breath test among German factory workers who referred to OM center for dyspepsia (25). Of 526 workers who contacted the center, 110 were ineligible, 149 refused and 267 were enrolled, corresponding to 64.2% of participation rate (25).

Our study corroborates the hypothesis that the workplace might be a suitable setting for the implementation of a Hp screening (4,14,15). Many HW valued the chance to rece an additional health test during OHS, and multiple HW interviewed at follow-up referred they would recommend Hp screening during OHS as part of the standard practice. This favorable attitude reflects alignment with the concept of TWH (2-4). Hp screening gains value from its unique nature of one-time, lifelong preventive measure for GC if eradication is achieved, since the infection is mainly acquired in early childhood and reinfection is unlikely (8,14).
The success of this intervention can be attributed to different strengths. Informative materials (eg., poster, brochures, Hospital webpage) likely encouraged participation and word-of-mouth dissemination. The hospital setting facilitated adherence in all phases (3,14), and ensured the infrastructures for implementation (3,14). Proximity between the OM Unit and the laboratory promoted timely SAT transfer. Similarly, the multidisciplinary expertise of occupational physicians and gastroenterologists fostered trust and engagement.

The lower participation rate of men aligns with data showing less engagement in preventive programs compared to women (26,27,28). In particular, female sex was associated to higher participation in a previous Hp screening among 40-64 aged individuals from Latvia (28). This supports findings that men underestimate health risks and show reluctance toward medical contact (29,30). Lower participation among physicians and researchers likely reflects time constraints and busy schedules. Adherence to the HPOS protocol was challenged by time-sensitive SAT collection. We adopted SAT rather than serological tests for its (i) higher sensitivity and specificity than serology (19,20), (ii) established cost-effectiveness for screening strategies (8). Moreover, ethical considerations related to post-COVID-19 pandemic prevented the use of the urea breath test (31).

The observed Hp prevalence was lower than suggested in literature but consistent with the declining trend of Hp infection which has been widely described (32). Despite certain HW categories, such as endoscopy staff, might be at higher risk (22), no pattern was detected, likely due to the small subgroup size. An association with educational level was observed, as in previous studies (33,34).

A relatively high proportion of HW were unaware of Hp infection and related health risks. This confirms the persisting knowledge gap about this carcinogenic bacterium even among health professionals (9-12). The finding also reinforces the educational value of workplace health promotion, empowering workers and communities for Hp control and GC prevention (4,15).

Follow-up was incomplete for several HW, partly due to missed contact and management delays. Overall, most of the followed-up positive HW referred to a physician, which was a fundamental step for Hp eradication. The GP referral was often unsatisfactory, showing procrastination from both patients and physicians. The screening was extended to the adult family members of some of the infected HW, confirming the broader public health potential of workplace-based Hp screening. Treatment schemes largely reflected current guidelines (8). Probiotics were inconsistently prescribed, despite evidence of their beneficial effect (8, 35). Treatment was demanding, with some recurring symptoms (36), but only one case led to discontinued.
Few HW reported a noticeable clinical improvement. A prolonged longitudinal observation (eg. 12-24 months) would better capture changes in health status, and several years are needed to assess GC prevention impact (37). Hp screening may also reduce benign conditions such as gastritis, a common cause of sick leave and reduced productivity (38). Thus, workplace-based Hp screening could yield occupational benefits (38). This area remains largely unexplored (38), In fact, workplace-based Hp screening might convey occupational benefits, such as reduced absenteeism for sick leave due to Hp-related disease and impaired work performance (38). This aspect is, to date, largely unexplored (38), requiring longitudinal studies.

This study has some limitations. The low Hp prevalence we observed resulted in low statistical power, limiting the identification of pattern of risk of Hp infection in the study population. Analyses were further impaired by the incomplete follow-up data. While the 3-month time point offers a early post-treatment picture, a longer observation would reveal delayed health effects.

In conclusion, the HPOS study demonstrated the feasibility of integrating a workplace-based Hp screening within routine OHS in an Italian hospital, achieving high participation and strong acceptance. Although Hp prevalence was relatively low, most infected individuals consulted a physician following the diagnosis and underwent eradication therapy consistent with current guidelines. Several family members of Hp-positive HW were also tested through local health system. This study carries important implications for implementing workplace-based Hp screening strategies. Our approach could be reproduced in other occupational settings, as in ongoing CPW

project interventions (15). Expanding such screening across occupational groups could help understand determinants of participation and guide engagement strategies. Future studies should investigate the impact of workplace-based Hp screening on absenteeism, productivity and wellbeing.

References

1- Occupational Safety and Health Administration – OSHA. Available at: http://www.osha.gov/ Accessed on 2.11.2025
2- Leso, V., Carugno, M., Carrer, P. et al. The Total Worker Health® (TWH) approach: a systematic review of its application in different occupational settings. BMC Public Health **24**, 2037 (2024).
3- Collatuzzo, G; Godono, A; Fiorini G; Vencovsky, D; Giordani, S; Biagioli, V et al. Expanding Cancer Prevention: Strategies Integrated Into Occupational Helath Surveillance. Cancers 2025, 17, 3535.
4- Fernandez-Tardon G, Gan RK, Rodriguez-Suarez MM, Tardon A, Arcos-González P. Total worker health®based Helicobacter pylori public health prevention strategy. Curr Opin Epidemiol Public Health. 2024 May 28;3(2):33-39.
5- de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020 Feb;8(2):e180-e190.
6- Collatuzzo G, La Vecchia C, Parazzini F, Alicandro G, Turati F, Di Maso M, et al. Cancers attributable to infectious agents in Italy. Eur J Cancer. 2023 Apr;183:69-78. Doi: 10.1016/j.ejca.2023.01.010. Epub 2023 Jan 25.
7- Gatta L, Ricci C, Tampieri A, Vaira D. Non-invasive techniques for the diagnosis of Helicobacter pylori infection. Clin Microbiol Infect. 2003 Jun;9(6):489-96.
8- Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, et al. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. Gut. 2022 Aug 8:gutjnl-2022-327745.
9- Wu Y, Su T, Zhou X, Lu N, Li Z, Du Y. Awareness and attitudes regarding Helicobacter pylori infection in Chinese physicians and public population: A national cross-sectional survey. Helicobacter. 2020 Aug;25(4):e12705.
10- Liu N, Luo Q, Gou L, Shen X, Zhang D. Knowledge and Practices of Helicobacter pylori Infection Management Among Physicians in Gansu Province, China: A Cross-Sectional Study. Helicobacter. 2024 Sep-Oct;29(5):e13137.
11- Boltin D, Kimchi N, Dickman R, Gingold-Belfer R, Niv Y, Birkenfeld S. Attitudes and practice related to Helicobacter pylori infection among primary care physicians. Eur J Gastroenterol Hepatol. 2016 Sep;28(9):1035-40.
12- Bailey KS, Brown HE, Lekic V, Pradeep K, Merchant JL, Harris RB. Helicobacter pylori treatment knowledge, access and barriers: A cross-sectional study. Helicobacter. 2023 Apr;28(2):e12954.
13- Leja M. Where are we with gastric cancer screening in Europe in 2024? Gut. 2024 Nov 11;73(12):2074-2082.
14- Collatuzzo G, Fiorini G, Vaira B, Violante FS, Farioli A, Boffetta P. The role of the occupational physician in controlling gastric cancer attributable to Helicobacter pylori infection: A review. Prev Med Rep. 2021 Aug 18;24:101527.
15- Cancer Prevention at Work (CPW): Occupational health surveillance in the implementation of prevention of infection-related cancer. Available at: http://cordis.europa.eu/project/id/101104716/reporting, Accessed on 2.11.25.
16- Italian National Law 81/2008. https://www.lavoro.gov.it/en/single-digital-gateway/health-and-safety-work/mandatory-health-and-safety-measures-all-companies
17- Taylor CS, McMahon MV, Ward ZJ, Alarid-Escudero F, Camargo MC, Laszkowska M, et al. Birth cohort and age-specific trends in global *Helicobacter pylori* seroprevalence: a scoping review. Lancet Reg Health Am. 2024 Aug 29;41:100877. doi: 10.1016/j.lana.2024.100877.
18- Ding SZ. Global whole family based-*Helicobacter pylori* eradication strategy to prevent its related diseases and gastric cancer. World J Gastroenterol. 2020 Mar 14;26(10):995-1004. doi: 10.3748/wjg.v26.i10.995.

19- Opekun AR, Zierold C, Rode A, Blocki FA, Fiorini G, Saracino IM, et al. Clinical Performance of the Automated LIAISON® Meridian H. pylori SA Stool Antigen Test. Biomed Res Int. 2020 Mar 19;2020:7189519.
20- Ricci C, Holton J, Vaira D. Diagnosis of Helicobacter pylori: invasive and non-invasive tests. Best Pract Res Clin Gastroenterol. 2007;21(2):299-313.
21- Meridian Bioscience. https://www.meridianbioscience.com/diagnostics/disease-areas/gastrointestinal/h-pylori/curian-hpsa/?country=IT Accessed on 2.5.2025
22- Kheyre H, Morais S, Ferro A, Costa AR, Norton P, Lunet N, Peleteiro B. The occupational risk of Helicobacter pylori infection: a systematic review. Int Arch Occup Environ Health. 2018 Aug;91(6):657-674.
23- StataCorp (2019) Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX.
24- Zober A, Schilling D, Ott MG, Schauwecker P, Riemann JF, Messerer P. Helicobacter pylori infection: prevalence and clinical relevance in a large company. J Occup Environ Med. 1998 Jul;40(7):586-94.
25- Madisch A, Hotz J, Grabowski G, Guth A, Malfertheiner P, Plein K, et al. Efficacy of Helicobacter pylori eradication in uninvestigated chronic dyspeptic staff members of a large factory: a prospective, long-term, follow-up, workplace outcome study. Eur J Gastroenterol Hepatol. 2002 Jan;14(1):61-9.
26- Davis JL, Buchanan KL, Katz RV, Green BL. Gender differences in cancer screening beliefs, behaviors, and willingness to participate: implications for health promotion. Am J Mens Health. 2012 May;6(3):211-7.
27- Valery JR, Applewhite A, Manaois A, Dimuna J, Sher T, Heckman MG, et al. A Retrospective Analysis of Gender-Based Difference in Adherence to Initial Colon Cancer Screening Recommendations. J Prim Care Community Health. 2020 Jan-Dec;11:2150132720931321.
28- Leja M, Cine E, Poļaka I, Daugule I, Murillo R, Parshutin S, et al. Factors influencing participation in preventive interventions for gastric cancer: the results from the GISTAR study. Eur J Cancer Prev. 2022 Mar 1;31(2):128-136. doi: 10.1097/CEJ.0000000000000682.
29- Banks I. No man's land: men, illness, and the NHS. BMJ. 2001 Nov 3;323(7320):1058-60.
30- Thompson AE, Anisimowicz Y, Miedema B, Hogg W, Wodchis WP, Aubrey-Bassler K. The influence of gender and other patient characteristics on health care-seeking behaviour: a QUALICOPC study. BMC Fam Pract. 2016 Mar 31;17:38.
31- Mattar R. Breath tests for gastrointestinal diseases – will it be safe to conduct breath tests after the COVID-19 pandemic? Clinics (Sao Paulo). 2020 Jun 22;75:e2092.
32- Chen YC, Malfertheiner P, Yu HT, Kuo CL, Chang YY, Meng FT, et al. Global Prevalence of Helicobacter pylori Infection and Incidence of Gastric Cancer Between 1980 and 2022. Gastroenterology. 2024 Apr;166(4):605-619. doi: 10.1053/j.gastro.2023.12.022. Epub 2024 Jan 2. Erratum in: Gastroenterology. 2025 Apr;168(4):850.
33- Boffetta P. Infection with Helicobacter pylori and parasites, social class and cancer. IARC Sci Publ. 1997;(138):325-9.
34- Zhang F, Pu K, Wu Z, Zhang Z, Liu X, Chen Z, et al. Prevalence and associated risk factors of Helicobacter pylori infection in the Wuwei cohort of north-western China. Trop Med Int Health. 2021 Mar;26(3):290-300. doi: 10.1111/tmi.13517. Epub 2020 Dec 20.
35- Casas Deza D, Alcedo J, Lafuente M, López FJ, Perez-Aisa Á, Pavoni M, et al. Probiotics Prescribed With Helicobacter pylori Eradication Therapy in Europe: Usage Pattern, Effectiveness, and Safety. Results From the European Registry on Helicobacter pylori Management (Hp-EuReg). Am J Gastroenterol. 2025 Feb 4.
36- Nyssen OP, Perez-Aisa A, Tepes B, Castro-Fernandez M, Kupcinskas J, Jonaitis L, et al. Adverse Event Profile During the Treatment of Helicobacter pylori: A Real-World Experience of 22,000 Patients From the European Registry on H. pylori Management (Hp-EuReg). Am J Gastroenterol. 2021 Jun 1;116(6):1220-1229.
37- Yan L, Chen Y, Chen F, Tao T, Hu Z, Wang J, et al. Effect of Helicobacter pylori Eradication on Gastric Cancer Prevention: Updated Report From a Randomized Controlled Trial With 26.5 Years of Follow-up. Gastroenterology. 2022 Jul;163(1):154-162.e3.
38- Sander GB, Mazzoleni LE, Francesconi CF, Balbinotto G, Mazzoleni F, Wortmann AC, et al. Influence of organic and functional dyspepsia on work productivity: the HEROES-DIP study. Value Health. 2011 Jul-Aug;14(5 Suppl 1):S126-9.

Appendices

A- Informative materials: background of the HPOS study.

Helicobacter pylori screening among hospital workers – Prospective observational study conducted on a population of Hospital Workers

Dear Sir/Madam,

We illustrate you a new study entitled "Helicobacter pylori screening among hospital workers – Prospective observational study conducted on a population of Hospital Workers," promoted by University of Bologna.

The main objective of this study is to determine the prevalence of Helicobacter pylori (Hp) infection in hospital workers (HW), identifying individuals at higher risk of diseases related to the bacterium.

Additional objectives are to analyze the risk factors related to Hp infection in HW and to evaluate the feasibility of a screening protocol for Hp infection in a work environment, studying its impact on the prognosis and potential health benefits for the individual.

Helicobacter pylori infection is widespread globally, with prevalence rates reaching up to 50% in developing countries, especially in areas with poor hygiene conditions and inadequate medical treatment. Hp is a significant risk factor for chronic gastritis and gastric ulcers. Additionally, the International Agency for Research on Cancer (IARC) has classified Hp as a Group 1 carcinogen due to its association with gastric cancer.

Although most infected individuals remain asymptomatic, some may develop severe conditions such as gastric cancer. Given the potentially severe health outcomes and the possibility of effective antibiotic treatment, early detection and treatment of Hp infection are essential for prevention.

Study Design and Methods

The study will involve a sample of approximately 496 healthcare workers aged between 40 and 65 years, employed at the S. Orsola Hospital and referred to the Occupational Medicine Department for routine occupational health surveillance. The study will span two years as an observational prospective study.

The protocol involves testing for Hp infection through stool antigen test. Participants will receive a sample collection kit, and results will be communicated via email and/or phone. Participants who test positive will be informed of the therapeutic options available and referred to a medical specialist if needed.

Participation and Consent

Participation in the study is voluntary. Participants may withdraw their consent at any time without providing any justification, and this will not affect their future healthcare or employment.

Participants will be informed of their results, and in the case of a positive diagnosis, the research team will provide guidance on the next steps and therapeutic interventions.

Key Benefits of the Study

- **Non-invasive testing**: Diagnosis will be conducted using a non-invasive stool antigen test.
- **Targeted Population**: The study will focus on hospital workers aged 40-65 during their routine occupational health visits.
- **Risk Reduction**: Early detection and treatment can eliminate a risk factor for gastric cancer and ensure effective prevention.

For further information or questions regarding the study, participants may contact the research team during the entire duration of the study.

The participant's general practitioner will evaluate the eradication therapy. In case of necessity, the research team may also refer the participant to the study's medical specialists for further consultations or specialized gastroenterological evaluations regarding Hp infection. Additionally, participants who test positive will be encouraged to have family members screened, as they represent a high-risk population for Hp infection.

Workers who test positive will be contacted again three months after the infection is identified to assess their general health status and gather information on the therapeutic pathway undertaken.

Diagnosis of Hp infection allows to identify subjects at increased risk of gastric cancer, which develops over decades and results from the combination of several factors. Cancer, although rare, occurs in a minority of cases and is preceded by easily detectable precancerous lesions during an endoscopic examination. Invasive investigation might be requested based on the single case, such as warning symptoms (eg., unexplained weight loss or anemia); some laboratories recommend an esophagogastroduodenoscopy if the patient is over 45 years old.

A negative Hp test excludes a significant risk factor for gastric cancer over the individual's lifetime. The eradication of the infection and its follow-up reduce the risk of developing gastric cancer by healing chronic mucosal inflammation and, in most cases, reversing precancerous lesions.

The detection of Hp infection represents a starting point to improve the individual's health and well-being and allows the early identification of a major risk factor of stomach disease. The worker can make informed decisions regarding their health status through specialist consultations.

B- INFORMATION FOR STUDY PARTICIPANTS

Helicobacter pylori screening among hospital workers – Prospective observational study conducted on a population of Hospital Workers

For further information, please contact Dr. Giulia Collatuzzo (giulia.collatuzzo3@ unibo.it) or Dr. Giulia Fiorini (giulia.fiorini@aosp.bo.it)

Dear Colleague,

Your collaboration is very important; therefore, we kindly ask you to read this information sheet carefully. We and our collaborators are available for any clarifications. Helicobacter pylori (Hp) is a bacterium associated with stomach diseases such as gastritis and ulcers. The infection is also linked to gastric cancer, of which it is the main risk factor. The study will assess the prevalence of Hp infection in a hospital environment and identify related factors. The hypothesis is that healthcare workers are, on one hand, at higher risk Hp infection, and on the other hand, have multiple protective factors such as hygienic habits and greater health awareness.

- **USE OF THE STOOL COLLECTION KIT**

Upon providing informed consent, you received a stool collection kit. This kit, similar to the fecal occult blood test kit, consisting of a cylindrical container with a screw cap equipped with a small scoop for stool collection. Use the kit as follows: after defecation, open the container by unscrewing the cap, taking care not to drop it and avoiding touching the scoop. Holding the cap, collect a stool sample using the scoop and place it into the container. Close the container by inserting the scoop with the collected stool sample and screw the cap back on. Wrap the securely closed container thoroughly with aluminum foil or plastic wrap.

It is essential that the collected sample is kept in the fridge until delivery and that delivery occurs within 2 days from the collection to ensure the validity of the test result. If the collection occur a few hours before sample delivery (e.g., the morning), it is sufficient to keep the sample in the refrigerator for a few minutes or a couple of hours.

- **DELIVERY OF THE CONTAINER**

The container should be delivered on Monday, Tuesday, Wednesday, or Thursday (not on Friday) between 8:00 AM and 2:00 PM at PAVILION 9, FIRST FLOOR. Therefore, avoid collecting the sample on Thursday and Friday, as it cannot be delivered before the following Monday, which would be 3–4 days after collection.

- **TEST RESULT**

The test result will be provided in approximately 14 days, depending on the workload of the analysis laboratory.

The test results will be the only communication of the outcome for healthcare workers who test negative for Hp. Workers who test positive for Hp will be contacted by the researchers by phone and will receive appropriate information regarding possible diagnostic-therapeutic pathways; a Hp positivity record will be sent following the phone call.

C- Consent form

CONSENT FORM

Protocol for screening for **Helicobacter pylori screening among hospital workers – Prospective observational study conducted on a population of Hospital Workers**

I, the undersigned,
born on ..... in .....
residing at ....., ...
telephone ....., email .....,

hereby declare:

- I have received thorough explanations regarding the request to participate in the study, particularly concerning its objectives and the procedures.
- I was informed of the opportunity to ask questions and that I received satisfactory answers.
- I have read and understood the information provided to me and I was given sufficient time to consider it.
- I understand that participation is voluntary and I may withdraw from the study at any time, without needing to provide an explanation and without it affecting my future medical care.
- I am aware that if I withdraw my consent, the data collected until the withdrawal will be retained and used in accordance with the research protocol.
- I am also aware of the possibility that if the test result is positive, the medical doctor will contact me with a letter regarding the result.

Consequently, based on these declarations:

- I voluntarily agree to participate in the study.
- I agree to be contacted in the future to provide follow-up information.

Name & Surname: .....
Date .....
Signature: .....

Name of the person collecting the consent: .....
Date .....
Signature: .....

D- BASELINE QUESTIONNAIRE

GENERAL AND GASTROENTEROLOGICAL HEALTH STATUS ASSESSMENT QUESTIONNAIRE

HPOS study: *Prospective observational study conducted on a population of healthcare professionals.*

The following questionnaire is aimed at collecting sociodemographic, behavioral and clinical information.
Please clearly indicate your answers, whether positive or negative, by entering a cross or another sign in the corresponding box. If you are uncertain about an answer, please leave it blank or indicate 'I don't know'.
When ***you find written "specify", write down your answer in the space marked by ellipsis.***

Identification number (assigned by the researcher; also to be reported on the second page)

.....

NAME AND SURNAME .....

ID CODE

Mobile phone number.....

DATE OF COMPILATION.....

TIME……

N identifier .....

GENERAL AND EMPLOYMENT DATA

A1 Date of birth ..... A2 Place of birth.....
A3 Height ..... A4 Weight .....

A5 Current municipality of domicile ..... A6 from the year.....

A7 Level of education:
1. Elementary/Middle School (or Lower) |____|
2. Technical/professional high school |____|
3. High School |____|
4. Graduation |____|
5. Doctorate/Master/ Postgraduate Qualifications |____|

A8 Employment qualification
6. Doctor/MFS. |____|
7. Nurse |____|
8. Technician |____|
9. Administrative |____|
10. OSS |____|
11. Other (please specify) .....

A9 Department (please specify) .....

A10 Specific tasks...

A11 Start of work in the University Hospital S.Orsola-Malpighi (year) .....

A12 Previous occupations and their period (specify type of work and years during which it was carried out)

.....

.....

A13 In your work, do you regularly perform or assist investigative/interventional and invasive procedures that may cause contact with the oral cavity or anogenital organs? (examples: intubation, patient hygiene, bladder catheterization, removal of bladder catheter, gynecological examination...)
YES |____|
NO |_____|

A14 Do you ever work/have you worked for at least 1 month in a digestive or respiratory endoscopy department?
YES |____|
NO |_____|

A15 You perform your activities mainly in:
CLINICAL WARD |_____|
OUTPATIENT CLINIC |_____|
LABORATORY |_____|
SERVICES (e.g. canteen, bar, transport) |_____|
OFFICE |_____|

A16 Marital status
MARRIED OR COHABITING |____|
SEPARATE |____|
SINGLE |____|
WIDOWER |____|

A17 Do you have children?
NO |___

YES |_____| How many? ..... What sex? .....

A18 What are your habits with respect to cigarette smoking?
NEVER SMOKED |__|

EX SMOKER |__| Specify for how many years ..... How many years ago did he stop.....

SMOKER |__| Please specify how many years..... How many cigarettes a day.....

A19 Do you do sports?
NONE OR ALMOST NONE |__|
LIGHT (e.g. walks) |__|
MODERATE (e.g. sport 1-2 times a week) |__|
INTENSE (e.g. sport 3 or more times a week) |__|

KNOWLEDGE ABOUT HELICOBACTER PYLORI

B1 Have you ever heard or read about helicobacter pylori?
NO |____| □ go to the next section (Diet)
YES |____| □ Continue with this section.

B2 If you know about Helicobacter pylori, in what context did you first learn about it?
DURING STUDIES OR IN A WORK ENVIRONMENT |_____|
FROM THE ATTENDING PHYSICIAN |____|
FAMILY |_____|
ON THE INTERNET |_____|
ON TELEVISION |_____|
ON BOOKS/MAGAZINES/NEWSPAPERS |_____|

B3 In your opinion, how well known is Helicobacter pylori infection in the general population?
RATHER UNKNOWN |____|
VERY LITTLE KNOWN |____|
FAIRLY KNOWN |____|
WELL KNOWN |____|
IT IS KNOWN TO MOST PEOPLE |____|

B4 Have you ever tested for Helicobacter pylori infection?
NO |____|
YES |____|

B5 Have you ever been treated for Helicobacter pylori infection?
NO |____|YES |____| How many days did it last?
7 DAYS |____|
14 DAYS |____|
OTHER (please specify).....

DIET

	Food Unit		*Number of units per week?* (if not at all, enter 0)
E1	1 cup	Milk |__	|__|
E2	1 portion	Yoghurt|__|	__|
E3	1 portion	Pasta/rice|__|	__|
E6	1 serving	Red meat|__|	__|
E7	1 serving	Chicken |__|	__|
E7	1 serving	Fish (not canned) |__	|__|
E8	1 serving	Canned fish/in oil |__|	__|
E9	1 serving	Sausages |__|	__|
E10	1 plate	Vegetable|__|	__|
E11	1 medium fruit, 2 small fruits	Fruit |__|	__|
E12	1 serving	Biscuits/sweets/dessert |__	|__|
E13	1 unit	Coffee |__|	__|
E14	1 glass	Wine |__	|__|
E15	1 can (33 cl)	Beer |__|	__|

Does E16 Generally add salt to food?
NO |__|
YES |__|

E17 Are there any foods you usually avoid? Specify.....…

PHARMACOLOGICAL HISTORY

Q1 Do you usually use probiotics (generally prescribed for seasonal cycles, e.g. Prolactis, Enterolactis, Reuterin, Lactoflorene, Prolife, VSL3...)?
No |__|
Yes |__|

Q2 Do you use antithyroid drugs (e.g. Levothyroxine)?
No |__|
Yes |__|

Q3 Do you use iron supplements?
No |__|
Yes |__|

Q4 Do you use corticosteroids or other immunosuppressants in chronic?
No |__|
Yes |__|

D5 in the last year, how many times have you used antibiotics (eg. For respiratory or urinary infections)?
Never |__|
1-2 |__|
3 or more |__|

Q6 in the previous 5 years, how many times do you estimate you have used antibiotics in a year?
Never |__|
Less than 1 time per year |__|
1-2 times a year |__|
3 or more times a year |__|

GENERAL PATHOLOGICAL HISTORY

P1 Do you suffer from thyroid disease?
NO |__|YES |__|

P2 Do you suffer from iron deficiency anemia?
NO |__|YES |__|

P3 Do you suffer from dermatitis?
NO |__|
YES |__| specify.....

P4 Do you have allergies?
NO |__|
YES |__| specify.....

P5 Do you suffer from headache/migraine?
NO |__|YES |__|

P6 Do you suffer from inflammatory bowel disease (Chron's disease, ulcerative colitis)?
NO |__|YES |__|

P7 Have you been diagnosed with celiac disease?
NO |__|
YES |__|

P8 Have you been diagnosed with diabetes?
NO |__|
YES |__|

P9 Have you been diagnosed with hypertension?
NO |__|
YES |__|

P10 Do you suffer from hematological diseases?
NO |__|
YES |__| specify.....

P10 Do you suffer from other chronic diseases? Specify.....

PATHOLOGICAL HISTORY SPECIFIC TO THE GASTROINTESTINAL TRACT

G1 Do you Suffer/have you ever suffered from gastro-oesophageal reflux?
NO |__|
YES |__|

G2 Do you ever suffer/have you suffered from gastritis?
NO |__|
YES |__|

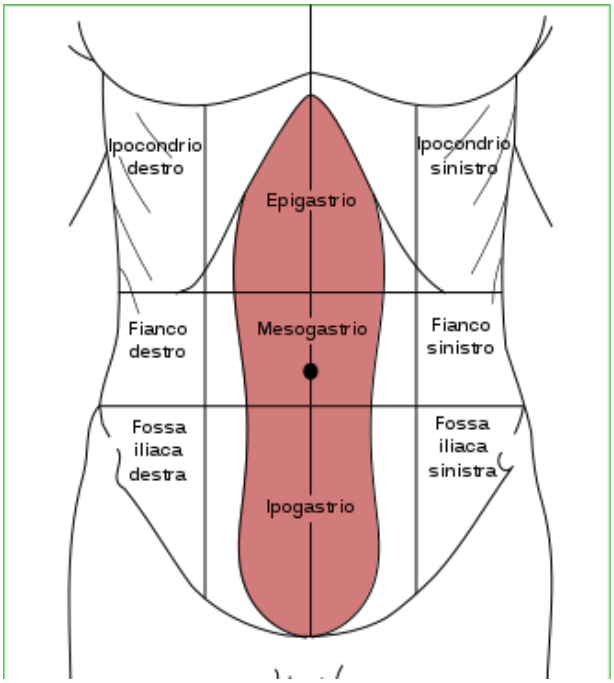
G3 Have you ever been diagnosed with peptic ulcer?
NO |__|
YES |__|

G4 Have you ever had a gastroscopy?
NO |__|
YES |__| Have you underwent gastroscopy in the last 5 years?
NO |__|
YES |__|
What diagnostic outcome? Specify.....

G5 In the last 3 months, have you had abdominal pain?
NO |__|YES |__| How often?
DAILY |__|
ABOUT 1 TIME PER WEEK |__|
ABOUT 1 TIME PER MONTH |__|

How intense was the abdominal pain?
MILD |__|
MODERATE |__|
INTENSE |__|

Marks in the image in which quadrants he had pain



Which of the following characteristics does abdominal pain have?
APPEARS AT MEALS |__|
RELIEVES MEALS |__|
RELIEVES WITH EVACUATION |__|
NONE ABOVE |__|

What foods favor the appearance of abdominal pain you feel?
Specify.....
.....
....
.....
.....

G6 How often you have had each of the following symptoms in the past 3 months

1. Epigastric pain/discomfort:
   never |__|

   <1 time per month |__|

   1 time per month |__|

   1 time per week |__|

   1 time per week-1 time per day |__|

   1 or more times a day |__|

2. Retrosternal burning
   never |__|

   <1 time per month |__|

   1 time per month |__|

   1 time per week |__|

   1 time per week-1 time per day |__|

   1 or more times a day |__|

3. Regurgitation
   never |__|

   <1 time per month |__|

   1 time per month |__|

   1 time per week |__|

   1 time per week-1 time per day |__|

   1 or more times a day |__|

4. Nausea
   never |__|

   <1 time per month |__|

   1 time per month |__|

   1 time per week |__|

   1 time per week-1 time per day |__|

   1 or more times a day |__|

5. Which of these symptoms has been most disturbing in the last 2 months?
   None |__|

   Epigastric pain/discomfort |__|

   Retrosternal burning |__|

   Regurgitation |__|

Nausea |__|

G7. Do you have at least one first-degree relative with a history of gastric cancer?

NO |__|

I DON'T KNOW |__|

YES |__|Specify how many and the type of kinship.....

G8. Do you have at least one first-degree relative who has been diagnosed with Helicobacter pylori infection?

NO |__|

I DON'T KNOW |__|

YES |__| Specify how many and the type of kinship .....

E- Follow-up questionnaire

FOLLOW-UP QUESTIONNAIRE

The following questionnaire includes follow-up questions regarding the fecal test for Helicobacter pylori (Hp) antigens, which you took as part of the HPOS study – a screening study on Helicobacter pylori among healthcare workers.

The questions aim to investigate the diagnostic and therapeutic path you may have undertaken after the detection of Hp infection, as well as your opinions on this process and your participation in the study.

Full name:

Date of birth:

Did you contact your general practitioner after receiving the Hp test result?

- ☐ NO
- ☐ YES
- ☐ Researchers from the team contacted them for me
- ☐ I consulted another doctor (e.g., gastroenterologist)

Were you prescribed antibiotic therapy for Hp eradication?

- ☐ NO
- ☐ OTHER NON-ANTIBIOTIC MEDICATIONS (please specify): _____
- ☐ YES – Which one?
  - 14-day triple therapy
  - 10-day sequential therapy
  - 10-day concomitant/quadruple therapy with bismuth
  - _____

Did you experience any discomfort or symptoms related to the therapy?

- ☐ NO / VERY MILD
- ☐ YES, MILD TO MODERATE
- ☐ YES, MODERATE TO SEVERE
- ☐ YES, SEVERE ENOUGH TO DISCONTINUE THE TREATMENT

If yes, what kind of symptoms did you experience?

- ☐ Diarrhea
- ☐ Discoloration of stool
- ☐ Headache / dizziness
- ☐ Altered taste
- ☐ Nausea / loss of appetite / heaviness
- ☐ Severe allergy / severe diarrhea / other complications
- ☐ Other (please specify): _____

When did the symptoms occur?

- ☐ DURING THE THERAPY
- ☐ DURING AND AFTER THE THERAPY (up to 7 days later)
- ☐ ONLY AFTER THE THERAPY

How long did the symptoms last?

- ☐ 1–3 days
- ☐ 4–7 days
- ☐ 7–14 days

Were you informed by your doctor about possible side effects?

- ☐ NO
- ☐ YES

Did your doctor explain the importance of strictly following the prescribed therapy?

- ☐ NO
- ☐ YES

Were you prescribed any other medications along with the therapy?

- ☐ NO
- ☐ YES, TO TAKE PROBIOTICS (please specify): _____
- ☐ YES, OTHER (please specify): _____

Did you ever forget to take a pill (e.g., missed doses or skipped a day)?

- ☐ NO
- ☐ YES – How many? _____

Did you find the therapy burdensome?

- ☐ NO
- ☐ A LITTLE
- ☐ QUITE
- ☐ VERY MUCH

Did you undergo a second test for Helicobacter pylori to confirm eradication?

- ☐ NO – Did your doctor advise against repeating it (or did you refuse)? _____
- ☐ YES – When? (date if possible): _____
  Which test? _____

Did you notice any changes in your gastrointestinal health after the therapy?

- ☐ NO
- ☐ YES, IMPROVEMENT
- ☐ YES, BUT NOT AN IMPROVEMENT

What was your general practitioner's attitude toward your process?

- ☐ NOT VERY INTERESTED OR AVAILABLE
- ☐ QUITE INTERESTED AND AVAILABLE
- ☐ VERY INTERESTED AND AVAILABLE

How useful do you think this path has been for you?

- ☐ NOT MUCH
- ☐ QUITE
- ☐ VERY MUCH

Overall, how would you rate the experience you had through this study, from 1 (poor) to 10 (excellent)?

Do you have any notes or suggestions about the proposed process?

Would you recommend this pathway to your acquaintances?

Some of your first-degree relatives (adult children, siblings up to 65 years old, parents up to 65 years old – note: not your partner due to lack of transmission risk) can be included in this study and take the same diagnostic test (fecal test for Hp) through occupational health services. Would you be interested in offering this to any of them?

Who?

_____

Definition	Composition	Duration
Standard triple therapy	PPI + clarythromycin+amoxycillin	10-14 days
Concomitant therapy	PPI + metronidazole+clarythromycin+amoxycillin	7-10 days
Sequential therapy	PPI + amoxicyllin 5-7 days Followed by PPI+metronidazole+clarithromycin 5-7 days	10-14 days
Modified triple therapy	PPI + levofloxacin+amoxycillin	10 days
Quadruple therapy with bismuth	PPI + metronidazole+tetracyclin+bismuth	10 days
Ibrid therapy	PPI+amoxycillin 7 days Followed by PPI+amoxycillin+metronidazole+clarythromycin for 7 days	14 days

Helicobacter pylori infection in hospital workers: sociodemographic, occupational, lifestyle and clinical factors – the HPOS study

Running head: Factors associated with Helicobacter pylori in hospital workers

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Data availability: The data will be made available upon reasonable request.

Abstract

Background: *Helicobacter pylori* (Hp) prevalence is highly dynamic. We investigated Hp epidemiology in a population of hospital workers (HW) participating to a workplace-based screening for gastric cancer prevention.

Materials and methods: The study targeted HW aged 40-65 employed at S. Orsola University Hospital in Bologna, Italy. HW were recruited between 2023 and 2025 during occupational health surveillance. Current Hp infection was assessed through stool antigen test (SAT) while past Hp infection was self-reported. Ever Hp infection was defined as SAT positivity or self-reported history of Hp treatment. We conducted analyses adjusted for sex and age to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of the determinants of current and ever Hp infection.

Results: Of 419 HW with available information, current Hp infection was 17.2% and ever Hp infection was 29.4%. High educational level (OR=0.39, 95% CI=0.17-0.88), 2-3 portions of yoghurt per week (OR=2.17, 95% CI=1.02-4.62), regular use of probiotics (OR=0.17, 95% CI=0.04-0.71), hypertension (OR=1.99, 95% CI=1.02-3.89), reflux (OR=0.55, 95% CI=0.32-0.94) and gastroscopy in the last 5 years (OR=0.52, 95% CI=0.29-0.95) were associated with Hp positive SAT. Age 56-65 (OR=1.81, 95% CI=1.01-3.26), working as health assistant (OR=1.84, 95% CI=1.06-3.21), high education (OR=0.47, 95% CI=0.25-0.87), predominant lab working (OR=0.43, 95% CI=0.19-0.94), invasive procedures (OR=1.58, 95% CI=1.02-2.45), gastritis (OR=1.99, 95% CI=1.29-3.09), peptic ulcer (OR=3.63, 95% CI=1.25-10.5), gastroscopy in the last 5 years (OR=2.07, 95% CI=1.33-3.23) were associated with ever Hp infection.

Conclusions: In a population of Italian HW, current Hp prevalence by SAT is about half that of ever infection, suggesting that a large proportion of infections has been eradicated. This gap highlights a potential window for targeted screening strategies focused on identifying and managing active infections to support gastric cancer prevention.

Key words: Helicobacter pylori; screening; epidemiology; stool antigen test; hospital workers; workplace health promotion

Introduction

Helicobacter pylori (Hp) infection is one of the most widespread chronic infections worldwide (1). Hp is the main responsible of gastritis, peptic ulcer and gastric cancer, representing the leading cause of infectious-related cancer worldwide (1), with an estimated 810,000 cases of gastric cancer in 2018 (2). The epidemiology of Hp infection is highly dynamic, and shaped by sociodemographic, environmental and healthcare factors, including birth cohort, education, hygienic levels, crowding, sanitation, use of antibiotics, and water source (3). Despite marked geographical heterogeneity, Hp prevalence has been declining globally over the recent decades (1,4). This decline, however, has been uneven across populations and age groups, making up-to-date information on Hp epidemiology essential to understand evolving trends of infection and of related gastric cancer (5).

Large body of evidence on Hp epidemiology derives from hospital-based studies conducted among dyspeptic patients (4). While informative, these studies are limited in their generalizability to asymptomatic populations and to prevention-oriented settings. Moreover, available evidence largely derives from *Asian countries and relies predominantly on serological testing, which does not distinguish between past exposure and active infection* (4). This limitation is particularly relevant for cancer prevention strategies, as only active Hp infection represents a modifiable target for screening and eradication.

Workers represent a large and generally healthy segment of the population, yet Hp epidemiology is poorly investigated in occupational settings (6). Previous studies reported higher Hp prevalence in certain working categories, including agricultural workers, fishermen, dentists and gastroenterologists, suggesting occupational exposure to the bacterium (6). Beyond exposure assessment, occupational health surveillance (OHS) offers a unique opportunity to implement population-based prevention strategies.

According to Chen et al., the pooled prevalence of Hp among Italian adult population between 2010 and2022 was 29.1% (4).
In the framework of an intervention for gastric cancer prevention integrated into routine OHS, we implemented a screening program for Hp infection among hospital workers (HW) employed at S. Orsola University Hospitalin Bologna – the HPOS study (7).
In this paper, we investigated the determinants of current (active) and ever Hp infection in Italian HW who participated to the HPOS study.

Materials and methods

The HPOS study is a cross-sectional study conducted in Bologna, Italy, within HW from the IRCSS Azienda Ospedaliero-Universitaria di S.Orsola. The study received approval from the Ethical Committee, 988/2021/Oss/AOUBo, and was carried out between March 2023 and March 2025. Detailed information has been provided elsewhere (7).

As part of the intervention, a screening for Hp infection was incorporated into the routine morning operations of the Occupational Medicine unit for hospital workers (HW). The screening process utilised the stool antigen test (SAT) method, which enabled non-invasive detection of current Hp infection status among participants. By embedding this screening within established OHS, the intervention aimed to facilitate efficient participation and minimise disruption to the daily workflow of HW. This approach ensured that Hp screening became a seamless component of regular OHS activities within the institution.

Inclusion criteria were age 40-65, employees of either S. Orsola University Hospital or University of Bologna, and provision of written consent form. We excluded HW who declared chronic use of proton pump inhibitors (PPI), pregnant women and those severely ill (eg., organ failure, active cancer). Workers who were short-time users of PPI or antibiotics were temporarily excluded, and considered for enrollment after four weeks from the end of the therapy; similarly, those using antiacid were considered for enrollment after 10 days from stopping the treatment.
HW who had recently used PPI or antibiotics for a short period were temporarily excluded from the initial screening. These individuals became eligible for enrolment in the study four weeks after completing their therapy. Similarly, workers who were using anti-acid medications were considered for participation after a washout period of 10 days following the cessation of their treatment. This approach was implemented to avoid potential interference of these medications with the accuracy of the Hp detection tests.
HW who volunteered as participants were also included and distinguished from those actively enrolled in the study.

A detailed written questionnaire including 8 sections (sociodemographic; occupational; lifestyle; dietary; Hp history and awareness; gastric disease history; other clinical history; gastrointestinal symptoms) was delivered to the HW, who could either compile it at the time of enrollment or bring it at home for simplicity and return it with the stool sample (Appendix A) (7).

The Curian® HpSA® test (Meridian Bioscience Europe, Milan, Italy) was used for Hp infection diagnosis. HW were given a stool container with an ID code and written instructions for sample collection, storage, and return. Samples were to be returned within 48 hours and kept refrigerated until then. Returned fecal samples were stored in a fridge at the OM Unit before transfer to the laboratory.

Data analysis

We considered three variables for Hp status: (i) current Hp infection, based on the SAT positive result collected in the screening process; (ii) ever Hp infection, combining self-reported history of Hp treatment with current Hp infection assessed with SAT. These variables were considered the outcomes of our analyses.

We distinguished three age groups, namely 40-45, 46-55, and 45-65. Job titles were coded as follow: nurse, health assistant, physicians/researchers (including resident physicians and PhD students), technicians and other health professional and non-healthcare workers (including office workers, maintenance workers, cooks, and gardeners). Based on the evidence of association between Hp infection and working in hospital Departments with high contact with patients (8), we defined as "high-risk Departments" the digestive and respiratory endoscopies. High-risk working practices included invasive procedures, referred to medical interventions implying manipulation of the oral cavity, oral and perineal hygiene, surgical and endoscopic procedures, aerosol-generating activities, catheter insertion, dialysis, and any other procedures potentially involving exposure to biological fluids of the patients.

Descriptive analyses were performed by Hp status. Multivariate logistic regression models adjusted for sex and age were run to investigate the determinants of current and ever Hp infection. Sensitivity analyses additionally adjusted by educational level and job title separately were considered when investigating associations with work-related factors (main working activity, high-risk department, invasive procedures). Strengths of association were expressed as odds ratio (OR) and 95% confidence interval (CI). The distribution of ever Hp infection by Hospital Department was also described.

All statistical analyses were conducted on Stata v16 (9).

Results

Figure 1 illustrates the flow chart of the study population. Overall, 435 HW were successfully tested for Hp. The comparative analysis of current and ever Hp infection included 419 HW with available information. Hp prevalence was respectively 17.2% and 29.4% based on the definition. Table 1 presents the characteristics of the study population according to sociodemographic, occupational and lifestyle factors, along with the results for the associations between these factors and the two definitions of Hp infection; data for clinical factors are shown in Table 2.

When considering current Hp infection, no clear sociodemographic pattern emerged, except for an inverse relationship with higher educational level (master/phd vs elementary/middle school/technical high school).
An inverse relationship was observed with reflux disease (OR=0.55, 0.32-0.94) and having had gastroscopy in the last 5 years (OR=0.52, 95% CI=0.29-0.95).
A positive association was observed for the consumption of 2-3 portions of yoghurt per week (OR=2.17, 95% CI=1.02-4.62), despite no clear dose-response trend (p=0.1); no association was observed for other dietary factors. An inverse relationship was identified with use of probiotics (OR=0.17, 95% CI=0.04-0.71). Hypertension was positively associated with Hp infection (OR=1.99, 95% CI=1.02-3.89).

When focusing on ever Hp infection, HW aged 56-65 had slightly higher likelihood of infection than those aged 40-45 (OR=1.81, 95% CI=1.01-3.26). Compared with nurses, health assistants had a higher risk of ever Hp infection (OR=1.84, 95% CI=1.06-3.21). An inverse relationship was observed for the highest educational level compared with the lowest (OR=0.47, 95% CI=0.25-0.87). Main working activity in laboratory settings was inversely associated with ever Hp infection (OR=0.43, 95% CI=0.19-0.94). While working in high-risk departments was not associated, performing invasive procedures was associated with the risk of ever Hp infection (OR=1.58, 95% CI=1.02-2.45). The latter association was attenuated after adjusting for educational level (OR=1.54, 95% CI=0.99-2.39) and was no longer evident after accounting for job title (OR=1.34, 95% CI=0.82-2.18), suggesting confounding by occupational role. Sensitivity analyses for work-related factors are shown in Supplementary table 1.
We did not observe associations with lifestyle and dietary factors.

Clinical variables showed opposite directions of association for current versus ever Hp infection.

For current Hp infection, inverse associations were observed with reflux (OR=0.55, 95% CI=0.32-0.94)), gastritis (OR=0.60, 95% CI=0.34-1.03), peptic ulcer (OR=0.70, 95% CI=0.15-3.21), and gastroscopy in the previous 5 years (OR=0.52, 95% CI=0.29-0.95). Ever Hp infection was positively associated with gastritis (OR=1.99, 95% CI=1.29-3.09), peptic ulcer (OR=3.63, 95% CI=1.25-10.5) and gastroscopy in the previous 5 years (OR=2.07, 95% CI=1.33-3.23), while no association was observed with reflux (OR=1.09, 95% CI=0.71-1.67). Statistical heterogeneity between current and ever Hp infection was observed for reflux (p-het=0.05), gastritis (p-het<0.001) and gastroscopy in the previous 5 years (p-het<0.001).

Departments with a higher prevalence of ever Hp infection included anesthesiology, digestive endoscopy, neurology and oncology, whereas the lowest prevalence was observed in research center, internal medicine, pharmacy, nephrology, ophthalmology, pediatrics, pneumology (non-interventional) and transplant units (Supplementary table 2).

Discussion

This study offers an overview on the epidemiology of Hp infection in a population of Italian HW participating to a workplace-based screening, according to different definitions of infection status. Current Hp infection assessed through SAT was almost half that observed when considering ever Hp infection, defined as either a positive SAT result or a self-reported history of Hp treatment. The prevalence of current infection was lower than previously reported in Italian population (4). Differences in study population, age structure, diagnostic methods, and increasing access to eradication therapies over time may partially explain these discrepancies.

We explored several associations, which can be broadly categorized according to their potential role in Hp epidemiology: factors possibly related to Hp acquisition (eg., occupation, educational level); factors potentially influencing persistence (eg., smoking, alcohol, diet); and factors likely representing consequences of Hp infection (eg., diseases and symptoms).

Occupational and educational factors

Occupation has emerged as a relevant but understudied determinant of Hp infection. Kheyre et al. found higher risk of Hp infection among workers in gastrointestinal units, agricultural, forestry, fishery, sewage workers, miners and institutional caregivers compared than in general population (6). Our data suggest that HW involved in invasive procedures—including those working in surgery

rooms or clinical wards—may have a higher risk of Hp infection compared to those employed in laboratory settings. This finding is consistent with a previous Italian study, which reported 4.3-time higher risk of Hp infection in nurses routinely exposed to patients and contaminated secretions compared than laboratory personnel after multiple adjustments (8). In fact, limited direct contact with patients and heightened adherence to biosafety protocols in laboratory environments might decrease the risk of Hp transmission through biological fluids (6,8).

We found a suggestive association between infection and health assistants, whose working activities often imply close patient contact, including oral hygiene, wound care, and personal assistance.
This pattern is consistent with findings from other Italian and European studies, which reported higher Hp prevalence among health assistants and nurses compared with physicians or administrative staff (11,12).

Overall, the occupational risk pattern emerging from our analysis support the hypothesis that close contact with patients and contaminated instruments may play a role in Hp transmission within hospital settings, as previously suggested (13).

As expected, educational level was associated with Hp infection, as well established in literature (3,14). This relationship is likely mediated by factors such as early-life early-life socioeconomic and environmental conditions, which are key determinants of Hp acquisition in early childhood (3).
The patterns described by hospital department likely reflect differences in workforce composition, age distribution, and occupational roles rather than direct departmental exposure to Hp infection.

Lifestyle factors

We did not find an association between smoking nor alcohol consumption with Hp infection, regardless of infection definition. Previous studies have reported heterogeneous findings. A large cross-sectional study of nearly 9,000 Japanese workers found inverse, dose-dependent associations between Hp seropositivity and both smoking and alcohol consumption (15). In contrast, a pooled analysis of 14 international case-control studies within the StoP Project (Stomach Cancer Pooling Project), restricted to controls**,** showed no relationship between smoking and Hp seropositivity (16). Some studies have suggested a protective effect of moderate alcohol consumption, possibly due to its bactericidal effect in the stomach. A dose–response meta-analysis of 12 observational studies reported a reduced risk of Hp infection among drinkers compared with non-drinkers (OR=0.78, 95% CI 0.69–0.89) (17).

A more recent meta-analysis of 24 studies (18) confirmed an inverse association. Conversely, a study restricted to Asian populations found a more than 3-folded risk of treatment failure in subjects with heavy alcohol consumption (> 40 g/day) (19).

No significant association was found with dietary factors except from yoghurt intake, which was associated with current Hp infection. This finding was counterintuitive, given that fermented foods such as yoghurt are known to exert probiotic effects which might contribute to Hp infection control (20,21). However, this association was not confirmed when considering ever Hp infection, nor was it supported by another Italian study (10). Residual confounding or reverse causation—where individuals with gastrointestinal symptoms preferentially consume yogurt—cannot be excluded.
Overall, large-scale prospective studies are needed to clarify the role of dietary factors in Hp persistence.

Clinical factors

Hp infection has been associated with several extra-gastric diseases, including
metabolic, cardiovascular, neurological, dermatological, and immunological disorders (1,22). We observed a positive association between hypertension and current Hp infection, but not with ever Hp infection. A meta-analysis of 6 studies identified a 34% increased risk of hypertension in Hp infected, hypothesizing eradication as beneficial for prevention of this condition (23). Metabolic or systemic inflammatory pathways may underlie this association (24,25).
Our findings also support the hygiene hypothesis, whereby Hp infection is inversely associated with allergic conditions such as asthma and eczema (26,27). Literature reports a lower risk of asthma in Hp positive individuals carrying CagA+ strains compared than Hp negatives (27). In addition, a meta-analysis of 11 observational studies found inverse relationship between eosinophilic esophagitis and Hp infection, supporting a role of Hp in immunomodulation (28).
However, conflicting evidence exists, with some studies reporting higher Hp prevalence among allergic individuals (29), underscoring the need for further investigation.

We did not observe any association with dermatitis or headache/migraine, in contrast with some previous reports (22,30,31).

Regular probiotic use was inversely associated with current Hp infection, whereas antibiotic use frequency did not influence infection status. While probiotics are effective in favoring Hp eradication (32), their beneficial effects outside eradication schemes seem scarce (33).

Abdominal pain was not associated with Hp infection in this study population, consistent with findings from other studies on HW (11). Studies which have reported higher infection rates in individuals with gastrointestinal symptoms may reflect a selection bias, as these patients are more likely to seek medical attention (1,4). Several studies showed that a substantial proportion of Hp infected people remain asymptomatic or experience only mild, non-specific and occasional symptoms (4,34,35). This may reflect host-pathogen equilibrium or variations in immune response, as well as infection with less pathogenic Hp strains, which mitigate clinical manifestations despite persistent colonization (36). Conversely, individuals with a history of Hp infection who have undergone eradication treatment often represent a selected, symptomatic population (4,34,35). Post-eradication symptoms are not uncommon: alterations in gastric acid secretion normalize in 6-12 months after eradication (34,37). Functional dyspepsia or persistent gastric discomfort may remain or develop after successful Hp eradication, potentially related to residual mucosal damage or altered gastric physiology (37,38).
This may partly explain the higher prevalence of symptoms observed among individuals which has ever been infected compared with those with current, asymptomatic colonization.

Similarly, the opposite associations observed for gastroscopy history and current vs ever Hp infection are plausible, given that symptomatic individuals are more likely to have undergone diagnostic evaluation and subsequent eradication (39).

Strengths and limitations

This study has several strengths. First, we provided and compared epidemiological data on Hp infection according to different definitions of infection status. This approach allowed us to disentangle determinants of current (active) versus past infection, which is particularly relevant for prevention-oriented screening strategies. We collected detailed information on occupational, lifestyle and clinical factors, which were investigated in relation to Hp infection. The study population consisted of healthy HW recruited through a workplace-based screening, reflecting a real-world occupational setting. Active Hp infection was assessed in all participants using SAT, representing an important methodological difference compared with many previous studies based on Hp seroprevalence (4), which cannot distinguish active from past infection.

Main limitations include self-reported information on past Hp treatment, which might be affected by recall bias, and the relatively low number of Hp infected, which limited the statistical power of some

analyses. Further, as eligibility criteria restricted enrollment to individuals aged 40-65, younger groups were not represented, limiting the generalizability of our findings.

CONCLUSIONS

Assessing Hp infection status and investigating its determinants is relevant for daily clinical practice, including OHS, as it allows a more comprehensive individual and population-level risk assessment. The identification of active infection is particularly important for prevention, as only active infection represents a modifiable target for intervention. The observed gap between current and ever infection prevalence highlights a window of opportunity in which workplace-based screening may support targeted strategies to reduce the burden of *H. pylori*–related diseases.

Additional studies are needed to elucidate which factors are associated with Hp infection in healthy individuals across different populations.

References

1- Malfertheiner P, Camargo MC, El-Omar E, Liou JM, Peek R, Schulz C, Smith SI, Suerbaum S. Helicobacter pylori infection. Nat Rev Dis Primers. 2023 Apr 20;9(1):19.
2- de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020 Feb;8(2):e180-e190.
3- Boffetta P. Infection with Helicobacter pylori and parasites, social class and cancer. IARC Sci Publ. 1997;(138):325-9.
4- Chen YC, Malfertheiner P, Yu HT, Kuo CL, Chang YY, Meng FT, et al. Global Prevalence of Helicobacter pylori Infection and Incidence of Gastric Cancer Between 1980 and 2022. Gastroenterology. 2024 Apr;166(4):605-619.
5- Collatuzzo G, Dajti E, Secco M, Bazzoli F, Boffetta P, Zagari RM. Burden of gastric cancer attributable to Helicobacter pylori in 27 countries from seven geographic regions in 2022. Gastric Cancer. 2025 Oct 20.
6- Kheyre H, Morais S, Ferro A, Costa AR, Norton P, Lunet N, Peleteiro B. The occupational risk of Helicobacter pylori infection: a systematic review. Int Arch Occup Environ Health. 2018 Aug;91(6):657-674.
7- Submitted - Workplace-based Helicobacter pylori Screening for Prevention of Gastric Cancer: the HPOS study
8- Mastromarino P, Conti C, Donato K, Strappini PM, Cattaruzza MS, Orsi GB. Does hospital work constitute a risk factor for Helicobacter pylori infection? J Hosp Infect. 2005 Jul;60(3):261-8.
9- StataCorp (2019) Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX.
10- Monno R, De Laurentiis V, Trerotoli P, Roselli AM, Ierardi E, Portincasa P. Helicobacter pylori infection: association with dietary habits and socioeconomic conditions. Clin Res Hepatol Gastroenterol. 2019 Oct;43(5):603-607.

11- Gasbarrini A, Anti M, Franceschi F, Armuzzi A, Cotichini R, Ojetti V, et al. Prevalence of and risk factors for Helicobacter pylori infection among healthcare workers at a teaching hospital in Rome: the Catholic University Epidemiological Study. Eur J Gastroenterol Hepatol. 2001 Feb;13(2):185-9.

12- Triantafillidis JK, Gikas A, Hyphantis T, Cheracakis P, Rokkas T, Konstantellou E, Antoniou A, Mallas H, Androulakis G. Helicobacter pylori infection in hospital workers over a 5-year period: correlation with demographic and clinical parameters. J Gastroenterol. 2002;37(12):1005-13.

13- Parsonnet J, Shmuely H, Haggerty T. Fecal and oral shedding of Helicobacter pylori from healthy infected adults. JAMA. 1999 Dec 15;282(23):2240-5.

14- Zhou Y, Deng Y, You Y, Li X, Zhang D, Qi H, et al. Prevalence and risk factors of *Helicobacter pylori* infection in Ningxia, China: comparison of two cross-sectional studies from 2017 and 2022. Am J Transl Res. 2022 Sep 15;14(9):6647-6658.

15- Ferro A, Morais S, Pelucchi C, Aragonés N, Kogevinas M, López-Carrillo L, et al. Smoking and Helicobacter pylori infection: an individual participant pooled analysis (Stomach Cancer Pooling-StoP Project). Eur J Cancer Prev. 2019 Sep;28(5):390-396.

16- Ogihara A, Kikuchi S, Hasegawa A, Kurosawa M, Miki K, Kaneko E, Mizukoshi H. Relationship between Helicobacter pylori infection and smoking and drinking habits. J Gastroenterol Hepatol. 2000 Mar;15(3):271-6.

17- Liu SY, Han XC, Sun J, Chen GX, Zhou XY, Zhang GX. Alcohol intake and Helicobacter pylori infection: a dose-response meta-analysis of observational studies. Infect Dis (Lond). 2016 Apr;48(4):303-309.

18- Du P, Zhang C, Wang A, Ma Z, Shen S, Li X. Association of Alcohol Drinking and Helicobacter pylori Infection : A Meta-analysis. J Clin Gastroenterol. 2023 Mar 1;57(3):269-277

19- Yu J, Lv Y, Yang P, Jiang Y, Qin X, Wang X. Alcohol increases treatment failure for Helicobacter pylori eradication in Asian populations. BMC Gastroenterol. 2023 Oct 25;23(1):365.

20- Collatuzzo G, Negri E, Pelucchi C, Bonzi R, Turati F, Rabkin CS, et al. Yoghurt Intake and Gastric Cancer: A Pooled Analysis of 16 Studies of the StoP Consortium. Nutrients. 2023 Apr 13;15(8):1877.

21- Yang YJ, Sheu BS. Probiotics-containing yogurts suppress Helicobacter pylori load and modify immune response and intestinal microbiota in the Helicobacter pylori-infected children. Helicobacter. 2012 Aug;17(4):297-304.

22- Pellicano R, Ianiro G, Fagoonee S, Settanni CR, Gasbarrini A. Review: Extragastric diseases and Helicobacter pylori. Helicobacter. 2020 Sep;25 Suppl 1:e12741.

23- Fang Y, Xie H, Fan C. Correction: Association of hypertension with helicobacter pylori: A systematic review and meta-analysis. PLoS One. 2022 Oct 24;17(10):e0276919.

24- Aramouni K, Assaf RK, Azar M, Jabbour K, Shaito A, Sahebkar A, et al. Infection with *Helicobacter pylori* may predispose to atherosclerosis: role of inflammation and thickening of intima-media of carotid arteries. Front Pharmacol. 2023 Oct 13;14:1285754.

25- Kountouras J., Papaefthymiou A., Polyzos S. A., Deretzi G., Vardaka E., Soteriades E. S., et al. (2021). Impact of Helicobacter pylori-related metabolic syndrome parameters on arterial hypertension. Microorganisms 9 (11), 2351. 10.3390/microorganisms9112351

26- Chen Y, Blaser MJ. Inverse associations of Helicobacter pylori with asthma and allergy. Arch Intern Med. 2007 Apr 23;167(8):821-7.

27- Reibman J, Marmor M, Filner J, Fernandez-Beros ME, Rogers L, Perez-Perez GI, et al. Asthma is inversely associated with Helicobacter pylori status in an urban population. PLoS One. 2008;3(12):e4060.

28- Shah SC, Tepler A, Peek RM Jr, Colombel JF, Hirano I, Narula N. Association Between Helicobacter pylori Exposure and Decreased Odds of Eosinophilic Esophagitis-A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2019 Oct;17(11):2185-2198.e3.

29- Akiner U, Yener HM, Gozen ED, Kuzu SB, Canakcioglu S. Helicobacter pylori in allergic and non-allergic rhinitis does play a protective or causative role? Eur Arch Otorhinolaryngol. 2020 Jan;277(1):141-145.

30- Guarneri C, Ceccarelli M, Rinaldi L, Cacopardo B, Nunnari G, Guarneri F. Helicobacter pylori and skin disorders: a comprehensive review of the available literature. Eur Rev Med Pharmacol Sci. 2020 Dec;24(23):12267-12287.
31- Sethia S, Batool T, Bambhroliya Z, Sandrugu JS, Lowe M, Okunlola O, et al. Association Between Helicobacter pylori Infection and Migraine: A Systematic Review. Cureus. 2023 Jul 31;15(7):e42747.
32- Yang Z, Zhou Y, Han Z, He K, Zhang Y, Wu D, Chen H. The effects of probiotics supplementation on Helicobacter pylori standard treatment: an umbrella review of systematic reviews with meta-analyses. Sci Rep. 2024 May 2;14(1):10069.
33- Penumetcha SS, Ahluwalia S, Irfan R, Khan SA, Rohit Reddy S, Vasquez Lopez ME, et al. The Efficacy of Probiotics in the Management of Helicobacter Pylori: A Systematic Review. Cureus. 2021 Dec 17;13(12):e20483. doi: 10.7759/cureus.20483.
34- Zullo A, Hassan C, De Francesco V, Repici A, Manta R, Tomao S, Annibale B, Vaira D. Helicobacter pylori and functional dyspepsia: an unsolved issue? World J Gastroenterol. 2014 Jul 21;20(27):8957-63.
35- Thrift AP, Dinarvand P, Juarez L, Brown J, Avila D, Zafiro Garcia-Villanueva JM, et al. Seroprevalence of Helicobacter pylori Infection Among Asymptomatic Patients Served by a Safety-Net Healthcare System. Clin Gastroenterol Hepatol. 2025 Oct 14:S1542-3565(25)00890-0.
36- Sundquist M, Quiding-Järbrink M. Helicobacter pylori and its effect on innate and adaptive immunity: new insights and vaccination strategies. Expert Rev Gastroenterol Hepatol. 2010 Dec;4(6):733-44.
37- Walker MM, Potter MD, Talley NJ. Tangible pathologies in functional dyspepsia. Best Pract Res Clin Gastroenterol. 2019 Jun-Aug;40-41:101650.
38- Ford AC, Tsipotis E, Yuan Y, Leontiadis GI, Moayyedi P. Efficacy of *Helicobacter pylori* eradication therapy for functional dyspepsia: updated systematic review and meta-analysis. Gut. 2022 Jan 12:gutjnl-2021-326583.
39- Palli D, Vaira D, Menegatti M, Saieva C. A serologic survey of Helicobacter pylori infection in 3281 Italian patients endoscoped for upper gastrointestinal symptoms. The Italian Helicobacter Pylori Study Group. Aliment Pharmacol Ther. 1997 Aug;11(4):719-28.

Table 1. Distribution of sociodemographic, occupational and lifestyle factors and results of the associations with current and ever Helicobacter pylori infection – The HPOS study.

Characteristic* (N=419)	**Current Hp - screened with SAT**		**Ever Hp – screened with SAT + self-reported treatment in the past**	
	Hp % (N)‡	**OR (95% CI)**	**Hp % (N)†**	**OR (95% CI)**
Overall	17.2 (72)		29.4 (123)	
Sex				
Men	11.0 (11)	Ref	23.3 (23)	Ref
Women	19.1 (61)	0.54 (0.27–1.08)	31.3 (100)	0.69, 0.41–1.17
Age				
40-45	16.5 (17)	Ref	23.3 (24)	Ref
46-55	15.3 (29)	0.90 (0.46–1.73)	28.0 (53)	1.27 0.73–2.21
56-65	20.5 (26)	1.24 (0.63–2.45)	36.2 (46)	1.81 1.01–3.26
Job title				
-nurse	17.1 (31)	Ref	30.4 (55)	Ref
-health assistant	27.3 (21)	1.79, 0.95-3.39	44.2 (34)	1.84 (1.06–3.21)
-physician/researcher	10.6 (5)	0.62, 0.22-1.71	21.3 (10)	0.70 (0.32-1.53)
-technicians and other health professionals	12.6 (11)	0.69, 0.33-1.47	19.5 (17)	0.57 (0.31–1.06)
-non-healthcare professionals	14.8 (4)	0.83, 0.26-2.61	25.9 (7)	0.73 (0.29–1.86)
Education				
Elementary/middle school/technical high school	22.3 (35)	Ref	36.3 (57)	Ref
High school	19.0 (4)	0.89, 0.28-2.86	33.3 (7)	0.94, 0.35-2.50
University degree	15.9 (22)	0.71, 0.37-1.34	28.3 (39)	0.83, 0.49-1.41
Master/phd	9.2 (9)	0.39, 0.17-0.88	18.4 (18)	0.47, 0.25-0.87
Marital status				
Married/couple	15.1 (43)	Ref	29.1 (83)	Ref
Single	16.2 (12)	1.16 (0.57–2.34)	24.3 (18)	0.81, 0.45-1.47
Separated/widowed	26.8 (15)	1.93 (0.96–3.87)	35.7 (20)	1.17, 0.63-2.17
Siblings				
No	17.3 (22)	Ref	30.7 (39)	Ref
Yes	16.3 (47)	0.84 (0.48–1.48)	28.1 (81)	0.80 (0.50–1.27)
Family history of Hp				
No	19.4 (44)	Ref	29.1 (66)	Ref
I do not know	13.3 (14)	0.61 (0.31-1.17)	30.5 (32)	1.03 (0.62-1.72)
Yes	15.8 (12)	0.73 (0.36-1.48)	29.0 (22)	0.96 (0.54-1.73)
Smoking				
Never	16.7 (17)	Ref	33.0 (73)	Ref
Former	11.7 (11)	0.85 (0.46–1.60)	26.5 (27)	0.73 (0.43–1.23)
Current	19.0 (42)	0.61 (0.30–1.25)	22.3 (21)	0.61 (0.34-1.07)
Main working activity				
-clinical department/surgery	20.5 (35)	Ref	32.2(55)	Ref
-clinical consultancy	16.9 (21)	0.69 (0.38–1.28)	29.8 (37)	0.81 (0.48–1.34)
-laboratory	9.6 (5)	0.38 (0.14–1.04)	17.3 (9)	0.43 (0.19–0.94)
-office/other	16.4 (9)	0.69 (0.30–1.58)	29.1 (16)	0.76 (0.38–1.51)
High-risk Department				
No	16.9 (59)	Ref	27.8 (97)	Ref
Yes	15.6 (10)	0.90 (0.43–1.89)	35.9 (23)	1.44 (0.81–2.54)

Invasive procedures				
No	15.9 (39)	Ref	26.0 (64)	Ref
Yes	18.6 (31)	1.28 (0.75–2.16)	33.9 (57)	1.58 (1.02–2.45)
Alcohol				
No	18.3 (24)	Ref	30.5 (40)	Ref
1-4 unit/week	19.7 (27)	1.26 (0.67–2.35)	32.9 (45)	1.28 (0.75–2.18)
5+ unit/week	11.3 (6)	0.65 (0.25–1.73)	24.5 (13)	0.85 (0.41–1.80)
Physical activity				
None	16.9 (14)	Ref	26.5 (22)	Ref
Low	14.2 (16)	0.85, 0.39-1.87	23.0 (26)	0.83 (0.43–1.61)
Moderate	19.3 (37)	1.23, 0.62-2.45,	34.9 (67)	1.46 (0.82–2.61)
Intense	12.5 (3)	0.86, 0.22-3.35	20.8 (5)	0.86 (0.28–2.63)
Yoghurt**				
0	12.0 (13)	Ref		Ref
1	11.8 (9)	0.87 (0.35–2.19)	25.9 (28)	1.04 (0.53-2.06)
2-3	23.7 (23)	2.17 (1.02–4.62)	27.6 (21)	1.66 (0.91-3.03)
4-7	21.9 (14)	1.91 (0.82–4.40)	37.1 (36)	0.98 (0.48-1.99)
8+	17.9 (10)	1.46 (0.59–3.62)	26.6 (17)	1.06 (0.51-2.20)
Coffee (continuous)**		1.01 (0.98-1.04)		0.99 (0.96-1.01)
Milk (continuous)**		1.06 (0.98-1.15)		0.99 (0.93-1.06)
Biscuits or dessert**				
0-2	17.4 (19)	Ref	33.9 (37)	Ref
3-6	16.3 (22)	0.89 (0.45-1.76)	29.6 (40)	0.81 (0.47-1.41)
7+	17.2 (27)	0.91 (0.47-1.75)	26.1 (41)	0.65 (0.38-1.12)
Added salt				
No	15.9 (23)	Ref	25.5 (37)	Ref
Yes	17.4 (46)	1.05 (0.60-1.83)	31.4 (83)	1.31 (0.83-2.08)
Red meat**				
0	19.1 (12)	Ref	28.6 (18)	Ref
1	9.9 (13)	0.54 (0.23–1.27)	27.5 (36)	1.08 (0.54-2.13)
2	22.2 (24)	1.43 (0.65–3.15)	29.6 (32)	1.21 (0.60-2.44)
3+	19.0 (19)	1.20 (0.53–2.74)	32.0 (32)	1.38 (0.68-2.80)
Processed meat**				
No	13.1 (11)	Ref	25.0 (21)	Ref
1	17.8 (24)	1.51 (0.69–3.29)	304 (41)	1.40 (0.75-2.61)
2	21.0 (16)	1.80 (0.77–4.20)	35.5 (27)	1.67 (0.84-3.33)
3	17.0 (8)	1.49 (0.55–4.05)	29.8 (14)	1.34 (0.60-3.01)
4+	13.8 (8)	1.11 (0.43–3.07)	24.1 (14)	1.01 (0.46-2.21)
Vegetables**				
<=7	17.9 (50)	Ref	31.1 (87)	Ref
>7	15.8 (22)	0.80 (0.46–1.39)	25.9 (36)	0.74 (0.46-1.18)
Fruit**				Ref
<=5	17.3 (24)	Ref	28.8 (40)	
>5	17.1 (48)	0.92 (0.53–1.60)	29.6 (83)	0.95 (0.60-1.49)
Pasta/rice**				
<4	17.0 (29)	Ref	31.0 (53)	Ref
4-7	16.4 (34)	1.76 (0.61–1.86)	28.0 (58)	0.96 (0.61-1.51)
>7	22.0 (9)	1.45 (0.62–3.38)	29.3 (12)	0.97 (0.45-2.05)

*Numbers might not sum up because of missing values **Portions per week ‡Prevalence of Helicobacter pylori based on SAT †Prevalence of Helicobacter pylori based on SAT, plus self-reported history of Hp treatment

Models adjusted for sex and age

Table 2. Distribution of clinical factors and results of the associations with current and ever Helicobacter pylori infection – The HPOS study.

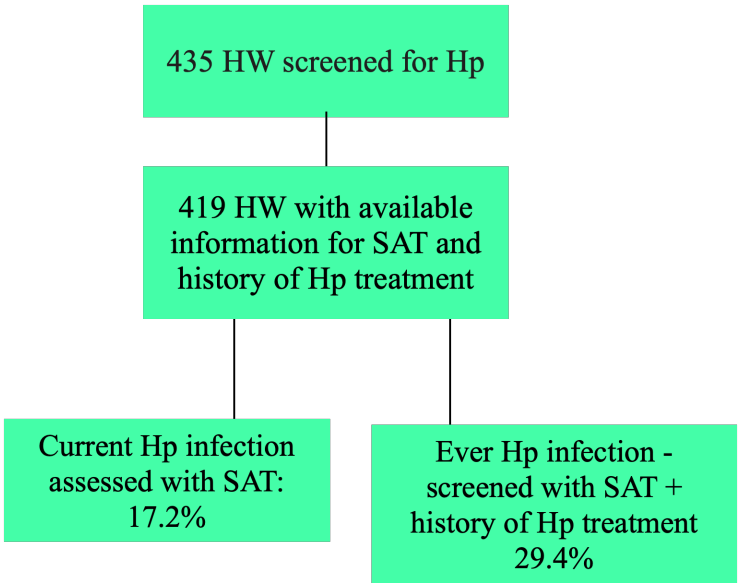
	Current Hp - screened with SAT		**Ever Hp – screened with SAT + self-reported treatment in the past**	
Variable*	**Hp % (N) ‡**	**OR (95% CI)**	**Hp % (N)†**	**OR (95% CI)**
Probiotics				
No	19.2 (69)	Ref	31.0 (112)	Ref
Yes	3.9 (2)	0.17 (0.04–0.71)	19.2 (10)	0.52 (0.25-1.07)
p-het=0.174				
Antibiotics				
<2/year	16.3 (23)	Ref	27.7 (39)	Ref
2+/year	17.1 (47)	1.06 (0.61–1.84)	29.9 (82)	1.13 (0.72-1.79)
Iron supplements				
No	16.8 (65)	Ref	29.0 (112)	Ref
Yes	18.5 (5)	1.03 (0.37-2.84)	33.3 (9)	1.18 (0.51-2.74)
Sideropenic anemia				
No	17.1 (66)	Ref	29.0 (112)	Ref
Yes	14.3 (4)	0.75 (0.25-2.26)	32.1 (9)	1.18 (0.51-2.74)
Anti-thyroid medications				
No	17.1 (62)	Ref	28.7 (104)	Ref
Yes	15.7 (8)	0.80 (0.36-1.80)	33.3 (17)	1.11 (0.59-2.10)
Thyroid disease				
No	16.1 (53)	Ref	27.3 (90)	Ref
Yes	20.5 (17)	1.19 (0.63–2.22)	37.3 (31)	1.38 (0.82-2.33)
Hypertension				
No	15.1 (53)	Ref	28.2 (99)	Ref
Yes	25.8 (16)	1.99 (1.02-3.89)	33.9 (21)	1.15 (0.64-2.09)
p-het=0.229				
Diabetes				
No	16.4 (66)	Ref	28.6 (115)	Ref
Yes	33.3 (4)	2.33 (0.67-8.09)	50.0 (6)	2.26 (0.70-7.24)
Allergy				
No	18.8 (N=46)	Ref	29.8 (73)	Ref
Yes	13.9 (N=23)	0.68 (0.39–1.17)	28.3 (47)	0.89 (0.58-1.39)
Dermatitis				
No	16.7 (N=56)	Ref	28.9 (97)	Ref
Yes	18.2 (N=14)	1.10 (0.58–2.12)	31.2 (24)	1.11 (0.64-1.91)
Headache/migraine				
No	16.2 (N=45)	Ref	27.8 (77)	Ref
Yes	18.4 (N=25)	1.11 (0.64–1.93)	32.3 (44)	1.27 (0.80-2.00)
Reflux				
No	20.7 (N=44)	Ref	28.6 (61)	Ref
Yes	12.8 (N=25)	0.55 (0.32–0.94)	30.3 (59)	1.09 (0.71-1.67)
p-het=0.05				
Gastritis				
No	19.6 (N=46)	Ref	23.0 (54)	Ref
Yes	13.4 (N=23)	0.60 (0.34–1.03)	38.4 (66)	1.99 (1.29-3.09)
p-het<0.001				
Peptic ulcer				
No	17.3 (N=68)	Ref	28.5 (112)	Ref
Yes	13.3 (N=2)	0.70 (0.15–3.21)	60.0 (9)	3.63 (1.25-10.5)
p-het=0.08				

Gastroscopy in the last 5 years				
No	19.9 (N=53)	Ref	24.0 (64)	Ref
Yes	12.1 (N=17)	0.52 (0.29–0.95)	40.7 (57)	2.07 (1.33-3.23)
P<0.001				
Abdominal pain in the last 3 months				
No	18.0 (N=42)	Ref	29.9 (70)	Ref
Yes	16.6 (N=28)	0.86 (0.51–1.47)	30.2 (51)	1.00 (0.64-1.55)

*Numbers might not sum up because of missing values ‡Prevalence of Helicobacter pylori based on SAT †Prevalence of Helicobacter pylori based on SAT, plus self-reported history of Hp treatment

Models adjusted for sex and age

Figure 1. Flow chart of the study population -The HPOS study.



HW, hospital workers; Hp, Helicobacter pylori; SAT, stool antigen test

Supplementary table 1. Results of the sensitivity analyses between current and ever Helicobacter pylori infection with work-related variables, accounting for job title and for educational level separately– The HPOS study.

Work-related variable	**Current Hp - screened with SAT**	**Ever Hp – screened with SAT + self-reported treatment in the past**
	OR (95% CI)	**OR (95% CI)**
Main working activity		
-clinical department/surgery	Ref	Ref
-clinical consultancy	0.72 (0.39-1.35) ϕ	0.83 (0.49-1.40) ϕ
-laboratory	0.46 (0.14-1.45) ϕ	0.64 (0.26-1.61) ϕ
-office/other	0.73 (0.26-2.08) ϕ	0.85 (0.36-2.02) ϕ
-clinical department/surgery	Ref	Ref
-clinical consultancy	0.68 (0.37-1.26) μ	0.79 (0.47-1.33) μ
-laboratory	0.45 (0.16-1.25) μ	0.49 (0.22-1.09) μ
-office/other	0.66 (0.28-1.52) μ	0.74 (0.37-1.47) μ
High-risk department		
No	Ref	Ref
Yes	0.91 (0.42-1.95) ϕ	1.43 (0.79-2.60) ϕ
No	Ref	Ref
Yes	0.92 (0.44-1.95) μ	1.51 (0.84-2.69) μ
Invasive procedures		
No	Ref	Ref
Yes	1.11 (0.62-1.99) ϕ	1.34 (0.82-2.18) ϕ
No	Ref	Ref
Yes	1.21 (0.71-2.07) μ	1.54 (0.99-2.39) μ

ϕ Models adjusted for sex, age and job title

μ Model adjusted for sex, age and educational level

Supplementary table 2. Distribution of ever Helicobacter pylori infection by Hospital Department – The HPOS study.

Department	Hp negative	Ever Hp positive	%
Anatomy	6	4	40,0
Anesthesiology	2	3	60,0
Administrartive, non-healthcare staff	17	4	19,0
Cardiology	18	8	30,8
Surgery	22	16	42,1
Research center	3	0	0
Internal medicine	36	14	28
Dermatology	7	1	12,5
Emergency room	13	8	38,1
Digestive endoscopy	2	3	60,0
Pharmacy	9	1	10,0
Gastroenterology	2	1	33,3
Ginecology	10	7	41,2
Laboratory and microbiology and genetics	18	5	21,7
Occupational medicine	9	5	35,7
Physical and rehabilitative medicine and orthopedics	16	4	20,0
Nuclear medicine	18	6	25,0
Nephrology	13	2	13,3
Neurology	1	3	75,0
Ophtalmology	9	1	10,0
Oncology	3	3	50,0
Pediatrics	14	2	12,5
Pneumology	10	0	0
Radiology	18	13	41,9
Transplants	4	0	0

Hp, Helicobacter pylori

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Helicobacter pylori screening integrated to occupational health surveillance - the HPOS Study

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INTRODUCTION

Eradication of Helicobacter pylori (Hp) infection can prevent cancer development(1-5). However, there are still no standardized screening protocols(6).

AIM

We aimed at testing an occupational-based Hp screening in a population of Italian healthcare workers (HCW).

METHOD

The study, approved by the Ethical Committee, started in January 2023 and completed in March 2025. The population includes HCW employed at the S.Orsola University Hospital, Bologna, aged 40-65. Detailed occupational, lifestyle and clinical information were collected through a written questionnaire.

Hp infection was tested with stool antigen test (SAT). Hp positives were referred to the general practitioner (GP) for treatment; they were followed-up at 3 months by phone interview on health status, management of the infection and feedback around the implemented screening.

RESULTS

Up to July 2024, 567 HCW were contacted, 379 agreed to participate and 278 returned the SAT for analyses. Of these, 213 (76.9%) were women and 64 (23.1%) were men, mean age 51 years old. Overall, 46 (16.6%) were Hp positive and 232 (83.4%) Hp negative. Family history of Hp infection was reported by 46 HCW (17.1%), while 152 (56.5%) did not report any history and 71 (26.4%) did not know; 34 HCW (12.7%) reported family history of gastric cancer. Most participants were nurses (N=123, 45.4%), and worked in medical units (N=107, 42.7%); 118 (43.5%) performed invasive practices during their activity; 36 (13.3%) worked in gastroenterology units; 115 HCW (42.9%) reported gastritis and 110 (41.5%) abdominal pain; 91 (34.0%) had undergone upper endoscopy. Surprisingly, 16 HCW (5.9%) reported to have no knowledge on Hp infection.

To date, 39 of the 46 Hp positives were followed-up: 25 contacted the GP,11 referred to another physician, the remaining did not report any contact. Of the 36 referring to a doctor, 30 were prescribed antibiotics (14: 10-day sequential; 12: 10-day concomitant therapy; 3:14-day triple therapy; 1: triple therapy modified; 2: not prescribed any therapy). Feedback on the study were very good: 27 HCW would suggest this screening to their families; 18 HCW involved their families in Hp screening; 22 HCW reported 9-10 points at the experience quality score. Figure 1 shows the HPOS study Hp screening protocol, Figure 2 shows the screening outcome, and Table 1 shows findings of variables.

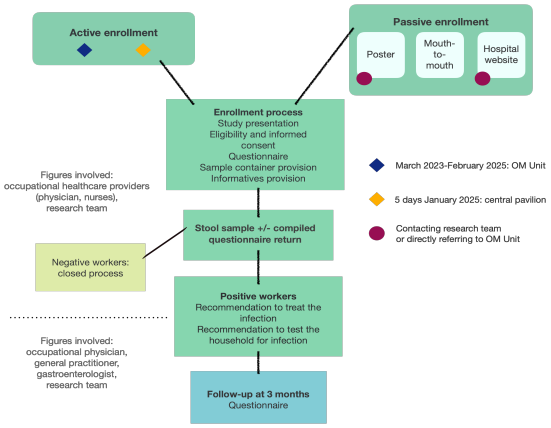

Figure 1: HPOS Study HP Screening Protocol

Acceptance rate: **67.5%** (400/593)
Dropout rate: 16.9% (93/551)

433 participants tested, 99 men (23.0%)

Hp prevalence= 16.4%
women: 18.0%; men: 11.0%

Figure 2: Screening Outcome

Variables	%
Medical contact	82.4
Type of medical contact	
- General practitioner	63.5
- Gastroenterologist	26.5
Therapy	95.7
Second Hp test	89.5
Probiotics	41.9
Difficult therapy	
– No	16.3
– Small difficulties	37.2
– Moderate difficulties	39.5
– High difficulties	7.0
Side effects	
– No/small	42.9
– Moderate	47.6
– Intense	9.5

Table 1: Findings of Variables

CONCLUSIONS

We implemented an occupational-based Hp screening program for gastric cancer prevention within HCW in Italy obtaining good compliance and feedback. Prevalence of infection was lower than expected. Replication in other populations of workers is needed.

REFERENCES

(1) Moss SF, Shah SC, Tan MC, El-Serag HB. Evolving Concepts in Helicobacter pylori Management. Gastroenterology. 2024 Feb;166(2):267-283.

(2) Ford AC, Yuan Y, Moayyedi P. Helicobacter pylorieradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut. 2020 Dec;69(12):2113-2121.

(3) Lee YC, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS et al. Association Between Helicobacter pylori Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis. Gastroenterology. 2016 May;150(5):1113-1124.e5.

(4) Yan L, Chen Y, Chen F, Tao T, Hu Z, Wang J, et al. Effect of Helicobacter pylori Eradication on Gastric Cancer Prevention: Updated Report From a Randomized Controlled Trial With 26.5 Years of Follow-up. Gastroenterology. 2022 Jul;163(1):154-162.e3.

(5) Chiang TH, Cheng HC, Chuang SL, Chen YR, Hsu YH, Hsu TH, et al. Mass screening and eradication of Helicobacter pylori as the policy recommendations for gastric cancer prevention. J Formos Med Assoc. 2022 Dec;121(12):2378-2392.

(6) Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, et al. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. Gut. 2022 Aug 8:gutjnl-2022-327745.

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5. Conclusions

Helicobacter pylori (Hp) remains one of the main modifiable carcinogens, yet a standardized and systematic approach to its management is suboptimal, representing an important area for further intervention. The occupational setting has emerged as a promising framework for the implementation of cancer prevention interventions. In particular, screening of Hp infection at the workplace might represent an important contributor to control the burden of Hp-related disease, through health education and identification of infected workers for the management of the infection. The HPOS study is the first which has demonstrated the feasibility and acceptability of a workplace-based Hp screening in Italy integrated into occupational health surveillance, obtaining high engagement of hospital workers as well as of occupational healthcare providers involved in the program.

Furthermore, this study has had broader impact by inspiring further research and the development of the European Cancer Prevention at Work (CPW) project, which extends the features and design of the HPOS study to Spain, Romania, and Slovakia. In these settings, workplace-based screening programs targeting Hp have been implemented, increasing awareness and fostering a culture of prevention of carcinogenic infections among workers, employers, occupational health professionals and occupational physicians themselves, therefore reaching a significant portion of the general population.

The high participation rates observed among workers and the reproducibility of the HPOS study, which is currently tested within the CPW context, highlight the potential for further research on workplace-based Hp screening across different occupational settings. This approach may provide valuable contributions to public health, informing policy development, guiding evidence-based strategies for cancer prevention, and ultimately supporting the proactive control of gastric cancer in Italy and across Europe.

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Andrea Farioli is in my soul and this thesis is dedicated to him