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RADIAZIONI IONIZZANTI COME FATTORE DI RISCHIO PER L'INSORGENZA DEL MESOTELIOMA MALIGNO: REVISIONE DELLA LETTERATURA SCIENTIFICA E ANALISI DEI REGISTRI "SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS" (SEER)

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Abstract

Il lavoro di dottorato presentato in questo progetto di tesi è stato caratterizzato da un doppio filone: quello riguardante lo studio dell'esposizione alle radiazioni ionizzanti come fattore di rischio per l'insorgenza del mesotelioma e quello dell'approccio alla ricerca nell'ambito della Medicina del Lavoro.

La tesi si compone di un capitolo di introduzione sulla materia complessa dello studio delle radiazioni ionizzanti in ambito radioprotezionistico e sulla presentazione delle conoscenze attuali in ambito epidemiologico e in ambito clinico del mesotelioma maligno. La parte di clinica è stata presentata solo marginalmente, poiché lo scopo di questo lavoro è quello di mettere in evidenza i fattori di rischio, da quelli più noti ai meno studiati, per l'insorgenza di questa neoplasia purtroppo ancora poco o quasi per niente trattabile.

I capitoli centrali sono caratterizzati dalla presentazione del lavoro di revisione della letteratura scientifica sull'argomento con l'analisi quantitativa dei risultati trovati e da uno studio e analisi dei dati dei registri dei tumori americani afferenti al SEER (*Surveillance, Epidemiology, and End Results*).

Per effettuare la revisione della letteratura scientifica è stata ideata una stringa di ricerca utilizzata prima per il database *Pubmed* e successivamente adattata anche per *Scopus* ed *Embase*.

I termini utilizzati nel campo *dell'exposure* (esposizione a radiazioni ionizzanti in ambito lavorativo e in seguito a radioterapia) sono stati: "radiotherapy", "external beam radiotherapy", "radionuclides", "nuclear industry/nuclear worker", "Thorium Dioxide", "Thorotrast"; per ciò che riguarda invece l'*outcome* (diagnosi di mesotelioma pleurico, peritoneale o di qualsiasi altra sede) abbiamo usato: "mesothelioma", "pleural cancer/neoplasm", "peritoneal cancer/neoplasm". Gli articoli ottenuti da tale ricerca sono stati analizzati in modo indipendente da due revisori, sulla base di titolo, *abstract* e full text; l'eventuale disaccordo tra gli autori è stato risolto mediante discussione o in alternativa attraverso l'intervento di un terzo revisore. In seguito, è stato effettuato un lavoro di *back-searching*, andando a ricercare nelle bibliografie degli articoli selezionati eventuali lavori scientifici non intercettati dalla nostra stringa di ricerca. Tutti i lavori scientifici selezionati sono stati riassunti in una tabella. Ogni articolo è stato poi analizzato secondo una *check list* ideata per gli scopi della revisione per poter ottenere uno *score* della qualità degli articoli. La stringa di ricerca utilizzata ha

identificato 4104 articoli: 19 articoli sono stati compresi nella analisi qualitativa e 16 per l'analisi quantitativa. Il lavoro di *back searching* non ha invece portato ad alcun articolo di rilievo che non fosse già stato incluso nella stringa di ricerca. È stata dapprima condotta una meta-analisi includendo tutti gli studi, sia quelli che prevedevano un'esposizione all'EBRT sia gli studi dei *nuclear workers*: la stima di rischio è pari a 1,87 con IC 95% compresi tra 1,44 e 2,29. Successivamente abbiamo selezionato separatamente gli articoli che mettevano in evidenza un'esposizione a EBRT e quelli che indagavano l'esposizione nella classe dei *nuclear workers* ottenendo rispettivamente una stima pari a 1,51 con IC 95% compresi tra 1,05, 1,98 e 2,10 con IC 95% compresi tra 1,45 e 2,76. Non siamo riusciti a dimostrare una relazione dose-risposta tra dose di radiazioni e rischio di mesotelioma. L'analisi della letteratura mostra che l'esposizione a radiazioni ionizzanti potrebbe essere un fattore determinante del mesotelioma. Sia l'esposizione a dosi elevate per brevi periodi (EBRT), sia a basse dosi per durate temporali superiori (esposizione lavorativa) sembrerebbero aumentare il rischio di sviluppare mesotelioma rispetto alla popolazione generale.

L'analisi di coorte retrospettiva, presentata nel terzo capitolo, è stata condotta utilizzando il database del SEER e si è concentrata ai soli adenocarcinomi diagnosticati dopo il quarantesimo anno di vita a partire dal 1973. Dopo l'esclusione dei soggetti con informazioni incomplete, sono stati inclusi nell'analisi primaria 853.447 maschi con diagnosi primaria di tumore della prostata. Il tempo-persona di questi pazienti è stato considerato fino all'incidenza di un secondo tumore, alla morte o alla fine del follow-up (31 dicembre 2015). Il primo anno dalla diagnosi di tumore alla prostata è stato censurato in considerazione del possibile *ascertainment bias* (diagnostica differenziale in base al trattamento scelto); in aggiunta, è stata applicata una censura del follow-up all'ottantacinquesimo anno di vita a causa della nota sotto-notifica dei casi di tumore ai registri dopo questa soglia di età. Le analisi sono state condotte adattando modelli di regressione di Cox multivariabili, specificando l'età anagrafica quale asse temporale principale. Per tenere conto dell'ipotizzabile aumento del rischio relativo di secondo tumore all'aumentare del tempo intercorso dall'irradiazione, è stata condotta una serie di analisi inserendo nei modelli di regressione dei termini di interazione tra la EBRT e la latenza (1-4 anni, 5 anni). Sono stati considerati quali possibili confondenti dell'associazione tra EBRT e mesotelioma peritoneale: l'età e l'anno di calendario alla diagnosi del tumore alla prostata, la razza

(bianco, afroamericano, altro), la chirurgia radicale (no/sì) e un indicatore ecologico di esposizione ad amianto (tasso di incidenza di mesotelioma pleurico primario tra i maschi adulti nella contea di residenza). Su 853.447 casi di tumore primario alla prostata, 264.005 (30.9%) sono stati tratti con EBRT. Come atteso, la scelta terapeutica è stata guidata anche dall'età del paziente, più elevata tra i soggetti che hanno ricevuto EBRT (mediana 69, intervallo interquartile 63-74) rispetto ai non irradiati (66, 59-72). 38 mesoteliomi peritoneali (17 tra i pazienti precedentemente trattati con EBRT) sono stati diagnosticati nel periodo di follow-up (6.587.508 anni persona). L'*Hazard Ratio* (HR) per l'EBRT, confrontata con i non irradiati, è risultato essere 1,72, con intervallo di confidenza (IC) al 95% di 0,90-3,29. Aggiustando per l'eventuale chirurgia radicale per tumore alla prostata, l'HR era di 2,22 (IC95% 1,03-4,78). All'analisi stratificata per latenza, il rischio relativo per l'EBRT è risultato crescere all'aumentare del tempo trascorso dall'irradiazione: 1-4 anni, 1,38 (95%IC 0,43-4,42) e pari a 2,92 (95%IC 1,17-7,27) per latenza superiore a 5 anni.

L'incidenza complessiva di mesotelioma peritoneale osservata nella coorte è stata estremamente bassa. I risultati dello studio supportano la possibile associazione tra esposizione a radiazioni ionizzanti e rischio di mesotelioma; in particolare, l'irradiazione del peritoneo che si verifica durante l'EBRT per tumori primitivi della prostata potrebbe aumentare il rischio di mesotelioma peritoneale con l'aumentare della latenza.

Dall'analisi dei dati dei registri SEER e della letteratura scientifica sia su esposizioni ad alte dosi (EBRT) che a basse dosi e frazionate (esposizione lavorativa) si evidenzia che esiste un aumento del rischio di sviluppo di questo tumore in seguito ad esposizione a radiazioni ionizzanti.

L'altro filone presente soprattutto nell'ultimo capitolo è la presentazione dei lavori di ricerca portati avanti e pubblicati durante il periodo novembre 2017- dicembre 2020.

Introduzione

Il lavoro di questo dottorato nasce con lo scopo di studiare una correlazione che storicamente è ritenuta non plausibile: l'esposizione a radiazioni ionizzanti e l'insorgenza di mesoteliomi.

Nonostante i mesoteli siano costituiti da cellule epiteliali e tessuto connettivo, si ritiene che questi siano poco sensibili alle radiazioni ionizzanti, quindi si classificano come tessuti non radio inducibili.

Recenti evidenze come la revisione di Goodman et al. (Goodman et al, 2009) ed alcuni studi effettuati su registri di tumori (Farioli et al, 2013; Farioli et al,2016) tendono a smentire tale ipotesi e classificano le radiazioni ionizzanti come possibile fattore di rischio anche per i mesoteliomi. Questa ipotesi andrebbe a confermare ciò che è noto per gli altri organi e apparati: le radiazioni ionizzanti sono un fattore di rischio per i tumori e per tale motivo sono state inserite dalla IARC nel gruppo 1 (cancerogeni certi per l'uomo).

A completamento del lavoro di tesi, nell'ultimo capitolo sono presentati tutti i lavori di ricerca che ho svolto in questi anni in campi della medicina del lavoro oltre a quelli dell'epidemiologia occupazionale ed ambientale.

Questo lavoro di tesi si compone di cinque capitoli:

1) un'introduzione dove verranno descritte le proprietà delle radiazioni ionizzanti e vi saranno dei brevi cenni sul mesotelioma;
2) una revisione sistematica della letteratura scientifica sulla correlazione tra esposizione a radiazioni ionizzanti e sviluppo di mesotelioma;
3) un'analisi della coorte derivante dai registri SEER (*US Surveillance, Epidemiology, and End Results cancer registries*) e il rischio di sviluppare mesoteliomi peritoneali;
4) una sintesi e confronto dei risultati dei capitoli 2 e 3;
5) una raccolta dei lavori di ricerca portati avanti e ultimati durante gli anni del dottorato.

È doveroso inserire nell'introduzione di questo lavoro un sentito ringraziamento ad un Ricercatore geniale nel campo dell'epidemiologia occupazionale e dalla forte personalità poliedrica, il Dott. Andrea Farioli, che purtroppo ci ha lasciati troppo presto. È stato lui a spronare il mio interesse per la ricerca e per gli studi epidemiologici. È stato un ottimo Maestro ma soprattutto un ottimo Amico.

Un ringraziamento particolare va anche al Prof. Boffetta che ha coadiuvato le mie attività di ricerca in Italia e negli U.S.A e mi ha permesso di sviluppare gli argomenti trattati in questa tesi, soprattutto quelli presenti nell'ultimo capitolo. Infine vorrei anche menzionare i colleghi che mi hanno permesso di portare a termine questo lavoro: Dott.ssa Ilaria Denti Pompiani e Dott. Giovanni Visci.

Capitolo 1. Radiazioni Ionizzanti e Mesotelioma Maligno

Definizione

Le radiazioni ionizzanti si dividono in corpuscolate ed elettromagnetiche: possono essere costituite o da particelle sub-atomiche (particelle alfa, beta, neutroni) che si muovono con velocità elevate, spesso prossime alla velocità della luce (radiazioni corpuscolate), o da fotoni che si propagano alla velocità della luce (raggi X e raggi gamma, radiazioni elettromagnetiche).

Gli effetti sull'individuo esposto

Quando le radiazioni ionizzanti interagiscono con la materia possono trasferire energia alle molecole delle strutture cellulari, causando dei danni in maniera temporanea o permanente alle cellule stesse (WHO, 2016).

Gli effetti delle radiazioni sull'uomo vengono solitamente classificati in effetti somatici ed ereditari (IRCP 118).

Gli effetti somatici sono quelli che interessano l'individuo, mentre gli effetti ereditari interessano il corredo genetico delle cellule riproduttive.

Gli effetti delle radiazioni ionizzanti si possono classificare anche in deterministici e stocastici.

Gli effetti deterministici possiedono una dose soglia, il cui superamento comporta l'insorgenza dell'effetto in tutta la popolazione esposta, e sono dovuti in gran parte alla morte o a disfunzioni delle cellule, conseguenti ad irradiazioni acute (forte intensità e breve durata). Con l'aumentare della dose l'effetto assume un carattere di maggiore gravità sul piano sintomatologico, clinico e prognostico.

Gli effetti stocastici consistono in neoplasie ed effetti genetici che possono comportare lo sviluppo di un tumore negli individui esposti a causa della mutazione di cellule somatiche, o malattie ereditarie nella loro progenie, a seguito di mutazione di cellule germinali. Essi sono caratterizzati dall'assenza di una dose-soglia (assunzione di linearità senza soglia) e dal carattere probabilistico con cui avvengono: secondo la teoria maggiormente seguita in campo radioprotezionistico, ad una dose di radiazione, per quanto piccola, è sempre associata una probabilità diversa da zero che l'effetto si verifichi. All'aumento di dose corrisponde un aumento della probabilità che un determinato effetto (cancro o mutazione genetica) possa verificarsi.

L'international Agency for Research on Cancer (IARC) ha classificato tutte le radiazioni ionizzanti nel GRUPPO 1, Cancerogeni certi per l'uomo (IARC volume 100D).
Infine, bisogna sottolineare che le caratteristiche dei tumori radioindotti sono identiche a quelle dei tumori di eziologia differente.

Grandezze usate in radioprotezione

Gli effetti delle radiazioni ionizzanti si manifestano ogni qualvolta si verifica una cessione di energia al mezzo attraversato.
In particolare, la quantità misurata in dosimetria è la "dose assorbita", D, definita come il rapporto tra l'energia media ceduta dalle radiazioni ionizzanti alla materia in un certo elemento di volume e la massa di materia contenuta in tale elemento di volume.
L'unità di misura della dose assorbita nel Sistema Internazionale di misura è il gray (Gy). Un gray corrisponde all'assorbimento di un joule in un kilogrammo di materia (1 Gy = 1 J/kg).
Nel caso di contaminazioni si utilizza anche dose assorbita per unità di tempo, ovvero l'intensità o rateo (tasso) di dose assorbita, che si misura in Gy/s.
La dose assorbita non tiene conto della diversità degli effetti indotti a parità di dose, a seconda della qualità della radiazione incidente, e non è da sola sufficiente a predire l'entità degli effetti dannosi.
Il rischio derivante dall'esposizione alle radiazioni ionizzanti non è, Infatti, solo proporzionale alla dose assorbita, ma è anche strettamente legato al tipo di radiazione incidente e alla radiosensibilità dei vari organi e tessuti irradiati.
Per considerare la diversa potenzialità di indurre un danno ai tessuti biologici delle varie tipologie di radiazioni incidenti si introduce il fattore di ponderazione della radiazione (W_R): parametro che tiene conto della differente pericolosità delle varie radiazioni - a parità di dose assorbita - rispetto alla radiazione di riferimento (fotoni) alla quale viene assegnato un coefficiente uguale a 1. Il prodotto della dose assorbita in un tessuto, D, per il fattore di ponderazione della radiazione, W_R prende il nome di dose equivalente, Ht. In formula: $Ht= W_R D$.
La dose equivalente si misura in sievert (Sv), e rappresenta la grandezza usata nell'ambito della legislazione italiana e degli standard protezionistici per definire i valori limite, nel caso di esposizioni omogenee del corpo.

Tipologia di radiazione	W_R		
Fotoni	1		
Elettroni e muoni	1		
Protoni e pioni carichi	2		
Particelle alfa, frammenti di fissione, nuclei pesanti.	20		
Neutroni		En < 1 Mev	2,5+18,2 $e^{-[\ln(En)]^{**}2/6}$
		1 Mev ≤ En ≤ 50 keV	5,0 + 17,0 $e^{-[\ln(2\,En)]^{**}2/6}$
		En > 50 MeV	2,5 + 3,25 $e^{-[\ln(0,04\,En)]^{**}2/6}$

TABELLA 1: fattori di ponderazione delle diverse tipologie di radiazioni

A parità di dose assorbita, le particelle alfa con energia di alcuni MeV, producono un danno biologico 20 volte superiore a quello prodotto dai fotoni.
Si parla di intensità o rateo (tasso) di dose equivalente quando ci si riferisce alla dose equivalente ricevuta nell'unità di tempo.
Per valutare la radiosensibilità dei diversi organi e tessuti del corpo umano per gli effetti stocastici, si introduce il concetto di dose equivalente efficace, E, somma delle dosi equivalenti efficaci nei diversi organi e tessuti, H_T, ciascuno moltiplicato per un fattore di ponderazione, W_T, che considera la diversa radiosensibilità degli organi irraggiati. Questa grandezza è stata definita per identificare il diverso effetto sui vari tessuti o organi della radiazione, tramite un fattore che tiene conto della risposta di ciascun organo (o tessuto) alla determinata radiazione (detrimento).

Anche l'equivalente di dose efficace, per mezzo del quale si stabiliscono i limiti per le esposizioni non omogenee, si esprime in Sv.

Le applicazioni delle radiazioni ionizzanti

Le attività umane e le applicazioni che implicano l'utilizzo diretto o indiretto delle radiazioni ionizzanti di origine artificiale sono molteplici.

Le più significative riguardano la medicina, la produzione di energia, la ricerca scientifica e tecnologica, l'industria in senso lato, l'agricoltura e l'industria alimentare, la geologia, la prospezione mineraria e le applicazioni ambientali.

Dal punto di vista dell'interesse del tema di ricerca trattato possiamo suddividere l'utilizzo delle radiazioni per scopi medici e per coloro che lavorano nel campo della produzione di energia (*nuclear workers*).

Attualmente gli usi medici costituiscono la maggiore fonte di esposizione dell'uomo alle radiazioni artificiali. Le dosi individuali variano enormemente: da zero, per coloro che non sono mai stati sottoposti ad esami radiologici, a un valore pari a migliaia di volte la radiazione annuale media derivante da radiazioni naturali.

Va ricordato che la probabilità di danno per il paziente nel caso dei comuni esami radiologici è relativamente bassa (Hall et al, 2008). Per quanto bassi essi siano, sono comunque valori da rapportare al beneficio indotto dalla possibile risoluzione del quesito diagnostico: infatti una probabilità di danno, per quanto piccola, è indebita se non correttamente giustificata.

Le applicazioni mediche delle radiazioni appartengono a due categorie fondamentali: la radiodiagnostica e la radioterapia.

In ambito diagnostico sono usati i raggi X nella diagnostica radiologica e nella TAC; nella MOC si utilizzano o tubi RX o sorgenti radioattive sigillate.

Sono invece utilizzati radiocomposti somministrati al paziente (sorgenti non sigillate) per la visualizzazione delle immagini di organi e tessuti in scintigrafia nucleare e nella PET. Con le tecniche diagnostiche multimodali (PET/CT, PET/MR e SPECT/CT) si utilizzano radiofarmaci per aggiungere alle informazioni anatomiche e morfostrutturali proprie delle indagini radiologiche (TC e RM), informazioni legate al metabolismo cellulare, alla modulazione di recettori specifici consentendo di definire le malattie non più per la disfunzione di organi o apparati o singole linee cellulari ma documentando a livello molecolare l'alterazione che induce un processo patologico.

In campo nucleare il potenziale rischio radiologico può essere rappresentato da diversi fattori. Nell'esposizione dei lavoratori in miniere uranifere è dovuto principalmente alla presenza del radon e dei suoi discendenti (contaminazione interna per inalazione) e ad una quota di esposizione esterna dovuta a radionuclidi γ emettitori.
I rischi connessi con l'esercizio di un impianto di fabbricazione di elementi di combustibile ad uranio sono principalmente legati alla contaminazione radioattiva (per inalazione e/o ingestione del radionuclide) ed in forma più limitata all'irradiazione esterna.
Nel normale esercizio di un reattore nucleare i lavoratori addetti sono esposti a rischi radiologici di modesta entità in quanto la maggior parte dell'impianto può essere agevolmente controllata in remoto mediante la strumentazione installata in sala controllo o comunque in locali dove esiste un basso livello di radiazione; le zone cui è necessario accedere durante il normale esercizio dell'impianto sono protette da schermi in generale più che sufficienti a ridurre i livelli di radiazione a valori trascurabili.
Gli impianti che trattano il combustibile nucleare irraggiato presentano per gli addetti rischi sia di irraggiamento esterno che di contaminazione radioattiva.
Le attività volte allo smantellamento (*decommissioning*) degli impianti nucleari rappresentano l'insieme delle operazioni necessarie e richieste per la chiusura definitiva, la disattivazione e l'eventuale smantellamento di un impianto nucleare: nelle fasi di disattivazione dell'impianto seguita dalla demolizione e rimozione di componenti attivi esistono rischi significativi. Si tratta di operazioni spesso non codificate, da pianificare e da valutare sotto il profilo radioprotezionistico caso per caso e in occasione delle quali può verificarsi l'esposizione dei lavoratori addetti sia al rischio di irraggiamento esterno (da materiali attivati) sia di contaminazione radioattiva (Linee guida AIRM, 2013).

Ipotesi lineare senza soglia

Il modello lineare senza soglia (LNT) presuppone una relazione diretta e proporzionale tra l'esposizione alle radiazioni ionizzanti e il rischio di sviluppare un tumore a qualsiasi dose. Il modello, così come è stato concepito, fornisce una spiegazione dei rischi per la salute da radiazioni e informa circa la definizione di limiti di dose e i regolamenti che limitano l'esposizione a un livello accettabile.

I rischi derivanti dalle radiazioni sono stati in gran parte derivati da studi sui sopravvissuti alla bomba atomica, in cui l'incidenza della malattia (principalmente cancro) è stata studiata rispetto alla dose di radiazioni ricevute (Grant et al, 2017; Siegel et al, 2017). Tuttavia, al di sotto di una determinata esposizione, l'incidenza naturale della malattia ha mascherato gli effetti che potrebbero essere stati causati dalle radiazioni. Per questo motivo, il modello LNT (*linear no threshold*) presume che l'incidenza dei tumori in relazione alla dose di radiazioni si comporti allo stesso modo sia per le dosi basse che per le dosi più elevate, cioè in modo lineare. Questo aspetto è ancora da dimostrare (Preston R et al, 2003).

I rapporti della Commissione internazionale sulla protezione radiologica (ICRP, 2006) e del *National Research Council* (BEIR VII, 2006) affermano che il modello LNT fornisce la migliore soluzione complessiva per scopi di protezione dalle radiazioni.

Nonostante la diffusa accettazione del modello LNT, esistono diverse teorie alternative per spiegare la relazione tra l'esposizione alle radiazioni e il rischio di cancro basate su modelli di risposte cellulari e subcellulari alle radiazioni a dosi molto basse per affrontare i risultati di studi che non seguono il modello LNT. La Figura 1 illustra diversi modelli di rischio da radiazioni che stimano il rischio di cancro al di sotto della dose più bassa in cui sono stati osservati tumori in eccesso (~ 100 mSv) (Prasad KN et al ,2004).

Esistono vari modelli di rischio da radiazioni: di seguito verranno illustrati alcuni esempi. Il modello di ipersensibilità suggerisce un rischio maggiore a dosi inferiori. Il modello LNT è rappresentato dalla linea retta che viene estrapolata a zero, il che significa che il rischio di cancro aumenterà con l'aumentare della dose.

Il modello soglia implica che al di sotto di una certa dose, non vi è alcun rischio.

Il modello dell'ormesi suggerisce che basse dosi di radiazioni possono persino essere protettive e benefiche. Numerosi studi su animali hanno dimostrato che le radiazioni causano un aumento nell’incidenza di quasi tutti i tipi di tumori cosiddetti spontanei, cioè degli stessi tumori che compaiono nella popolazione non esposta a radiazioni ionizzanti. Nel caso dei tumori umani i dati epidemiologici evidenziano come il tempo di latenza risulti differente per i diversi tipi di tumore. I casi di leucemia ed osteosarcoma radioindotti si manifestano non prima di 2-5 anni dall’irradiazione e raggiungono il loro picco entro i primi 10 anni (Gilbert ES et al, 2009). La maggior parte dei tumori solidi non si manifesta invece prima di 10 anni e possono presentare tempi

di latenza anche di 30-40 anni, nel corso dei quali possono mancare del tutto alterazioni cliniche a carico dei tessuti ove si manifesterà la neoplasia.

Le Radiazioni Ionizzanti ad elevato LET, ossia ad alta energia di trasferimento (radiazioni α e protoni), sono dotate in genere di una capacità di induzione neoplastica superiore rispetto a quelle a basso LET (β, γ). Le popolazioni esposte ad alte dosi hanno un'incidenza più alta di tumori.

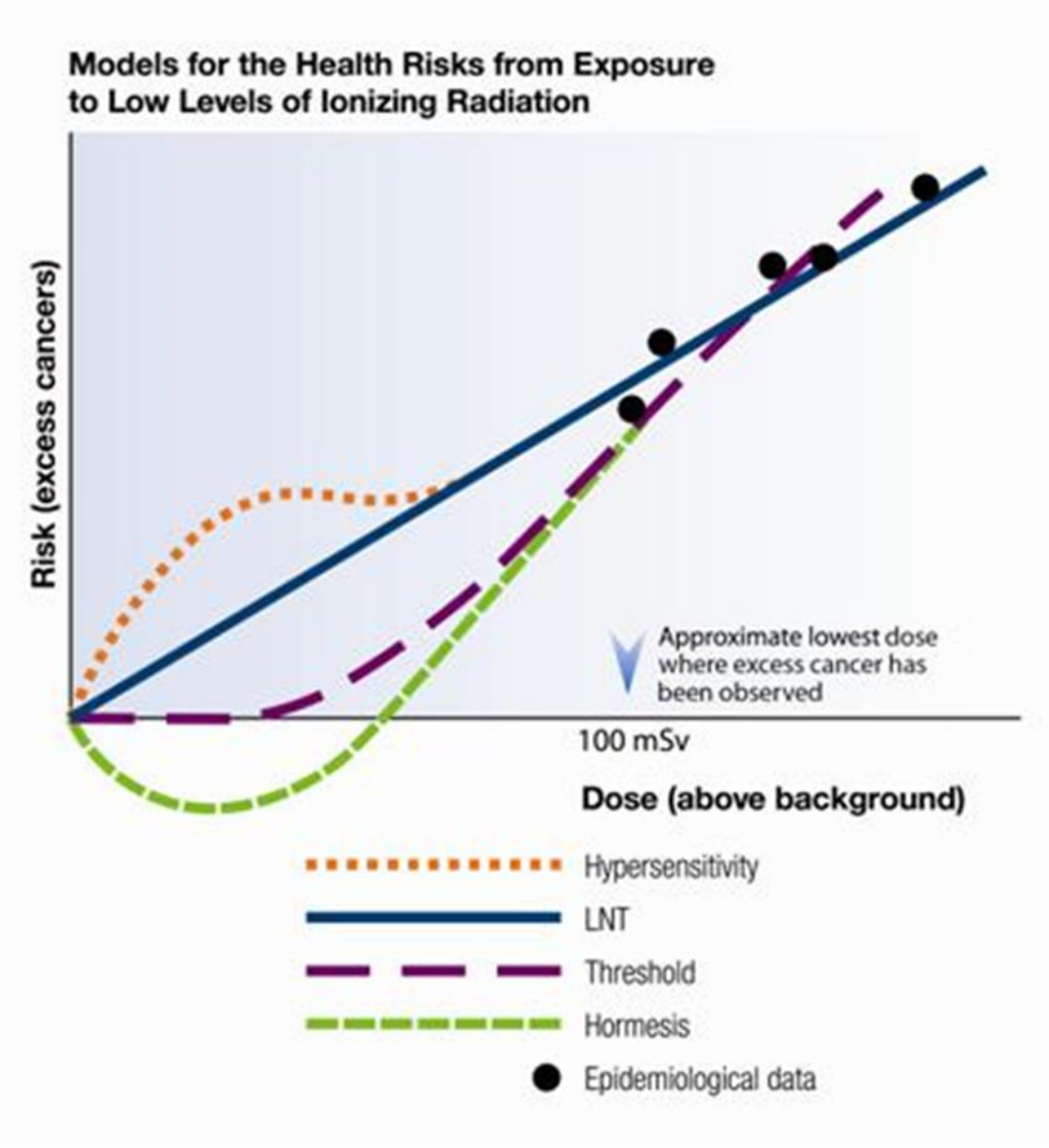

FIGURA 1. Modelli di rischio da radiazioni

La relazione dose-effetto lineare senza soglia (*Linear no-threshold model* - LN-T model) è un'ipotesi pensata per un'applicazione in ambito prevenzionistico, tesa a ridurre al massimo l'esposizione a radiazioni ionizzanti sia in ambito diagnostico-terapeutico, sia in ambito professionale. Si tratta pertanto di un'ipotesi conservativa, adottata ai fini preventivi della radioprotezione, la mancanza di una soglia deve quindi essere intesa come un'ipotesi prudenziale, scientificamente accettabile ma non dimostrata.

La stessa *International Commission on Radiological Protection* (ICRP), che ha elaborato tale ipotesi, sottolinea come verosimile che la frequenza reale degli effetti per unità di dose sia più bassa di quella così stimata quando l'esposizione comporti dosi basse o ratei di dose bassi e quindi "quanto più cautelativa è l'ipotesi di linearità tra dose ed effetti, tanto più diventa importante riconoscere che ciò può portare ad una sovrastima dei rischi da radiazioni" (ICRP 26, 1977). Nonostante queste chiare indicazioni fornite proprio dall'ente che ha formulato l'ipotesi dell'assenza di soglia, il modello radioprotezionistico definito LNT model è spesso divenuto un assunto di realtà e come tale considerato, mentre il suo razionale era, ed è, quello di essere una chiave interpretativa semplificata e vantaggiosamente approssimata per gli scopi preventivi della radioprotezione (Sinclair, 1992; Tubiana, 1998).

Mesotelioma Maligno: definizione e cenni di epidemiologia

Il mesotelioma maligno è un tumore che origina dal mesotelio, tessuto costituito da cellule che rivestono le cavità sierose della pleura, del peritoneo, del pericardio e della tonaca vaginale. Tra tutte le sierose citate precedentemente quella sicuramente più colpita da questa tipologia di tumore è la pleura.

Sebbene il mesotelioma sia un tumore raro, la sua incidenza è aumentata dal 1970 sino a metà degli anni Novanta (Price B et al, 2004). I primi Paesi che hanno promulgato il bando dell'utilizzo dell'asbesto stanno assistendo ad un decremento dell'incidenza, mentre quei Paesi che hanno messo a bando l'asbesto nella seconda metà degli anni '90 ancora risentono dell'incremento o della stabilità dell'incidenza di questo tumore (Abdel-Rahman O, 2018)

Colpisce più frequentemente gli uomini e in Italia rappresenta lo 0,4 per cento di tutti i tumori diagnosticati nell'uomo e lo 0,2 per cento di quelli diagnosticati nelle donne. Secondo l'Associazione Italiana Registro Tumori (AIRTUM, 2020) si stimano, per il 2020, 1.500 casi tra gli uomini e 500 tra le donne. Il numero dei casi è in lieve crescita tra le donne, probabilmente perché negli ultimi anni prima del bando dell'amianto del 1992 era aumentata la quantità di lavoratrici impiegate nella produzione industriale di materiali contenenti amianto, causa principale di questo tumore.

Nel dicembre 2016 il ReNaM (registro nazionale dei mesoteliomi) ha raccolto 27.356 casi di mesotelioma maligno, riferiti al periodo di incidenza tra il 1993 e il 2015. Le modalità di esposizione all'amianto sono state accertate per 21.387 (78%) ed è stata definita un'esposizione professionale per circa il 70% dei casi (14.818) (Marinaccio et al, 2020).

L'esposizione professionale ad asbesto non è l'unica possibile, infatti tra i 15.845 casi di mesotelioma registrati tra il 1993 e il 2008, l'esposizione a fibre di amianto è stata riscontrata per 12.065 individui (76,1%), identificando 530 (4,4%) con esposizione familiare (vivevano con un convivente professionalmente esposto), 514 (4,3%) con esposizione ambientale all'amianto (vivevano vicino a fonti di inquinamento da amianto e non sono mai stati esposti professionalmente) e 188 (1,6%) esposti attraverso attività legate all'hobby o ad altre attività ricreative. I cluster di casi dovuti all'esposizione ambientale sono principalmente legati alla presenza di stabilimenti dell'industria del cemento-amianto, alle attività di cantieristica e riparazione e alla contaminazione del suolo (Marinaccio et al, 2015).

Il mesotelioma è un tumore solitamente raro prima dei 50 anni e presenta un picco massimo attorno ai 70 anni; la sopravvivenza a 5 anni dalla diagnosi è inferiore al 20 per cento nella fascia di età compresa tra i 45 e i 54 anni e diminuisce progressivamente con l'aumentare dell'età (AIRTUM, 2020).
Come precedentemente descritto, l'esposizione occupazionale, para-occupazionale e non occupazionale all'asbesto costituiscono il principale fattore di rischio.
Altri fattori di rischio potrebbero essere, con vari gradi di evidenza, le fibre minerali non asbestiformi (erionite, fluoro-edinite), microtubuli di carbonio, virus (SV40, MC29 avian leukosis virus), metalli, infiammazione cronica delle sierose, le radiazioni ionizzanti (Jasani B et al, 2012), fattori ereditari come la mutazione dei geni che codificano per la proteina BAP1 (Pastorino S et al, 2018) nonché in passato l'esposizione a Thorotrast, un mezzo di contrasto a base di torio radioattivo utilizzato nella prima metà del 1900.

Cenni di clinica

Dal punto di vista istologico si distinguono diversi tipi di mesotelioma:

- sarcomatoide
- fibroso
- epitelioide
- epiteliomorfo (mesotelioma maligno epitelioide – mesotelioma pleurico epitelioide)
- benigno (in rari casi abbiamo un mesotelioma fibroso benigno – mesotelioma cistico benigno).

Clinicamente, la malattia si presenta in base alla sede interessata: pleurica, pericardica, peritoneale o testicolare. Per tale motivo i sintomi e i segni possono essere i più disparati: dalla tosse persistente e versamento pleurico, al senso di gonfiore addominale e comparsa di ascite.
La diagnosi si basa sul tipo istologico corredato da tecniche di immunoistochimica: la colorazione immunoistochimica per citocheratina 5/6, calretinina e WT-1 (marcatori positivi per mesotelioma) e CEA, Ber-Ep4, LeuM1 e Bg8 (negativi nel mesotelioma) rappresenta il pannello più utile di marcatori per mesotelioma maligno (Husain AN et al,2017)

Le terapie a disposizione sono quella chirurgica, chemioterapica e radioterapica. Tuttavia, come enunciato precedentemente la sopravvivenza è molto bassa e la prognosi è purtroppo sfavorevole (8% per i maschi e 10% per le femmine a 5 anni, e il 14% in totale per i successivi 5 anni) (AIRTUM,2020).

Capitolo 2. Relazione tra esposizione a radiazioni ionizzanti e rischio di Mesotelioma: revisione sistematica della letteratura scientifica e meta-analisi

Introduzione

Il mesotelioma maligno è un tumore raro che origina dalle cellule di rivestimento delle cavità pleuriche e peritoneali. Come risaputo, l'amianto è il più importante fattore di rischio per il mesotelioma (Alpert et al, 2020; Yang H et al, 2008). Tuttavia, è stata stimata una probabilità di base nella vita, cioè il rischio di contrarre la malattia in assenza di esposizione all'amianto, pari a circa 3 su 10.000 (AIRTUM). Recenti studi epidemiologici si sono concentrati su altri potenziali fattori causali del mesotelioma, tra cui: fibre minerali non asbestiformi (erionite; fluoro - edenite); nanotubi di carbonio; virus (ALV, MC29, SV40); metalli; infiammazione sierosa cronica; radiazioni ionizzanti (Goodman JE et al,2009).

Le radiazioni ionizzanti hanno un ruolo nella cancerogenesi, sono infatti riportate all'interno del gruppo I della IARC (IARC, Volume 75). I mesoteli sono considerati tessuti poco radiosensibili, tuttavia alcuni studi mettono in evidenza l'incremento del rischio di sviluppare un mesotelioma se esposti a radiazioni ionizzanti (Goodman JE et al,2009; Metz-Flamant et al, 2011).

L'associazione tra radiazioni ionizzanti e mesotelioma è stata studiata tra i lavoratori delle centrali nucleari e tra i pazienti esposti al mezzo di contrasto "Thorotrast" o alla radioterapia a fasci esterni (EBRT). Le prove disponibili sull'associazione sono ancora controverse per diversi motivi: la maggior parte degli studi si basa su un numero limitato di casi di mesotelioma e vi è mancanza di conoscenza sulla possibile relazione dose-risposta per basse dosi (Gilbert ES et al, 2009).

Lo scopo di questa revisione è quello di valutare e aggiornare le evidenze disponibili in letteratura riguardo la relazione tra l'esposizione a radiazioni ionizzanti e l'incidenza di mesotelioma e, successivamente, di effettuare una sintesi quantitativa di quanto riscontrato per valutare la forza di tale associazione.

Metodi

Selezione degli studi

Gli articoli inclusi nella revisione sistematica sono stati identificati utilizzando i database Pubmed, Scopus e Embase. La ricerca bibliografica è stata condotta a marzo 2020.

È stata ideata la seguente stringa utilizzata in Pubmed e poi adattata per Scopus ed Embase (riportate alla fine del capitolo):

(Radiotherapy OR EBRT OR "external beam radiotherapy" OR "stereotactic radiotherapy" OR (peritoneal AND irradiation) OR radionuclides OR "therapeutic ionizing radiation") OR ((Nuclear AND (industry OR work OR worker* OR job)) OR (Radiation AND (industry* OR work OR worker* OR job)) OR* "Radiography/adverse effects"[Mesh] OR (hiroshima[tiab] OR (nagasaki[tiab] OR atomic bomb survivors OR life span study) OR Thorium Dioxide"[Mesh] OR Thorotrast

AND

("etiology" [Subheading] OR etiologic OR Neoplasm, Radiation-induced[MH] OR Neoplasms, Radiation-Induced* OR Neoplasms, Second Primary[MH] OR Neoplasms, Second Primary* OR etiology[MH] OR aetiologic* OR aetiology OR Cohort Studies[MH])))*

AND

"*mesothelioma" OR "pleural cancer/neoplasm" OR "peritoneal cancer/neoplasm"*

Criteri di Inclusione

Nella revisione sono stati inclusi articoli che soddisfacevano i seguenti criteri: studi di coorte o caso-controllo, che contenevano informazioni circa l'esposizione a radiazioni ionizzanti, che avevano tra gli *outcome* il mesotelioma. Non sono state applicate restrizioni né per l'anno di pubblicazione né per la lingua in cui sono stati pubblicati.

Processo di selezione degli articoli

Due revisori [ER e GV], dopo aver impostato la ricerca attraverso le stringhe indipendentemente, hanno esaminato gli elenchi dei titoli e degli *abstract* per escludere articoli irrilevanti; gli articoli che risultavano duplicati sono stati eliminati. In caso di disaccordo o dubbio, è stato consultato un terzo revisore [AF]. Successivamente, gli articoli potenzialmente rilevanti sono stati analizzati in modo

indipendente e sono stati identificati gli studi che soddisfacevano i criteri di inclusione. È stata condotta una ricerca utilizzando il metodo di *back searching,* attraverso l'analisi delle *references* presenti negli articoli selezionati. La *flow chart* del processo di selezione è mostrata nella Figura 1.

Estrazione dei dati

Per poter condurre la meta-analisi sono state estratte dal testo le seguenti informazioni: anno di pubblicazione, paese, disegno dello studio, informazioni su età e sesso, periodo di studio, perdita al follow-up o tasso di risposta (nel caso di studi caso controllo), dimensione della coorte o numero dei casi e dei controlli, fonte di dati su esposizione ed *outcome*, tipologia di *outcome* (mortalità o incidenza), misura dell'associazione (rischio relativo (RR) o *standandized mortality ratio o standardized incidence ratio* (SMR/SIR) e corrispondente intervallo di confidenza (CI)).
In caso di risultati stratificati, ad esempio per gruppo di età o periodo storico di esposizione, sono state presi in considerazioni tutti i dati.

Valutazione della qualità degli studi

È stata utilizzata una *check list* per la valutazione della qualità degli studi redatta sulla base delle indicazioni NIH ed adattata per una migliore valutazione degli articoli oggetto della revisione sistematica (*https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools*). La *check list* è stata ideata per l'analisi di studi di coorte e caso controllo. In particolare, sono stati enfatizzati: la presenza di esposizione nota ad asbesto, un periodo di *follow up* superiore ai dieci anni e gli studi che prendevano in esame un'età media superiore ai sessant'anni (la *check list* è reperibile alla fine del capitolo). Per permette un confronto della qualità degli studi di coorte e caso controllo è stata calcolata la media ottenuta per ciascun articolo ed è stato riportato lo *score* totale in percentuale.

Analisi statistica

È stata condotta una meta-analisi degli effetti causali (DerSimonian e Laird, 1986), utilizzando il pacchetto Stata14 (StataCorp). Nell'analisi primaria sono stati combinati i risultati derivati sia da esposizioni mediche che da esposizioni lavorative. Il nostro scopo era valutare se un'esposizione di qualsiasi tipo potesse aumentare il rischio di sviluppare mesotelioma. Successivamente, abbiamo effettuato analisi secondarie

stratificate per esposizione (EBRT ed esposizione lavorativa). L'eterogeneità dei RR di sintesi è stata valutata utilizzando le statistiche I2 (Higgins e Thompson, 2002). Il *bias* di pubblicazione è stato valutato graficamente attraverso i *funnel plot* e formalmente testato con il test di Egger (Egger et al,1997).

Risultati

La stringa di ricerca utilizzata ha identificato 4104 articoli (2974 su *Pubmed*, 592 su S*copus*, 538 su E*mbase*), da cui sono stati sottratti i risultati duplicati. Dei rimanenti 2799 studi potenzialmente rilevanti, 2656 sono stati esclusi sulla base del titolo e 101 sulla base dell'*abstract*. Gli studi inclusi erano tutti presenti su Pubmed, non sono stati aggiunti articoli rilevanti da Scopus ed Embase.

42 articoli sono stati valutati per l'ammissibilità rispetto ai criteri di inclusione, ma una lettura del full text ha portato all'esclusione di 23 articoli:13 sono stati esclusi perché non erano studi di coorte o caso controllo, 4 non avevano dettagli dell'esposizione, 6 non avevano informazioni sul mesotelioma come *outcome*.

Quindi 19 articoli sono stati compresi nell'analisi qualitativa (Tabella 1 e Tabella 2). Tutti gli articoli inclusi sono studi di coorte, 9 sono relativi ad esposizione a radioterapia post-neoplastica, 10 riguardano invece esposizione lavorativa di operatori in centrali nucleari.

Il lavoro di *back searching* non ha portato ad alcun articolo di rilievo che non fosse già stato analizzato.

È stata condotta una valutazione qualitativa degli studi attraverso la *check-list* precedentemente illustrata e i risultati sono stati riportati come *quality score* (Tabella 1 e Tabella 2). Tale valutazione ha mostrato punteggi più elevati per gli studi che analizzavano EBRT come fattore di rischio rispetto a quelli che analizzavano l'esposizione lavorativa (Tabella 2).

Le Tabelle 3 e 4 riassumono le stime di rischio per l'insorgenza di mesotelioma negli studi selezionati rispettivamente per esposizione a EBRT e per esposizione lavorativa.

Per l'analisi quantitativa 2 studi non avevano informazioni disponibili per la meta-analisi (Tom Pickles et al, 2002; Metayer et al,2000) e uno studio è stato escluso perché analizzava la stessa corte di un altro studio incluso in analisi (Habib et al, 2005) (Figura 2). Per gli studi come Carpenter et al, 1998; Metz-Flamant C et al, 2011; Matanoski et al, 2008; Atkinson WD et al, 2004; Chang et al,2017, che presentavano

diverse stime di rischio, si è deciso di sintetizzare il dato al fine di calcolare una stima per ciascuno studio che fosse rappresentativa dello stesso. Nel caso dell'articolo di Farioli et al 2013 è stata scelta la stima di rischio derivante dall'analisi multivariata.

È stata dapprima condotta una meta-analisi includendo tutti gli studi, sia quelli che prevedevano un'esposizione all'EBRT che gli studi che prevedevano un'esposizione lavorativa (*nuclear workers):* la stima di rischio scaturita è pari a 1,87 con IC 95% compresi tra 1,44 e 2,29 (I^2 =74,8 %, P=0,000) (Figura 2).

Successivamente abbiamo selezionato separatamente gli articoli che mettevano in evidenza un'esposizione a EBRT e quelli che indagavano l'esposizione nella classe dei *nuclear workers* ottenendo rispettivamente una stima pari a 1,51 con IC 95% compresi tra 1,05 e 1,98 (Figura 4) e 2,10 con IC 95% compresi tra 1,45 e 2,76 (Figura 6).

È stata anche condotta un'ulteriore analisi per indagare la stima negli studi che sono stati classificati con un punteggio di *quality score* maggiore del 50% sia per l'esposizione a EBRT che per gli studi con esposizione lavorativa (1,51 con IC 95% compresi tra 1,05 e 1,98 e 2,76 con IC 95% compresi tra 1,81 e 3,71).

La presenza di *publication bias* è stata messa in evidenza dall'asimmetria presente all'interno del Funnel plot (Figura 3) ed è stata formalmente indagata attraverso il test di Egger (P=0,001). Ciò, probabilmente, è dovuto all'eterogeneità degli articoli selezionati.

In ultimo abbiamo analizzato i valori della meta-analisi escludendo uno studio per volta (Tabella 6).

Discussione

La nostra analisi ha dimostrato che l'esposizione a radiazioni ionizzanti può determinare un aumento del rischio di sviluppare mesotelioma. Negli anni molti sono stati molti i case report che avevano messo in evidenza questa associazione, soprattutto per quei casi in cui i pazienti sviluppano un tumore dei mesoteli dopo essere stati sottoposti a trattamenti di radioterapia per tumori primitivi in altre sedi (Deutsch M et al, 2007; Antman KH et al, 1983). Quando il tumore primitivo è situato in sede addomino-pelvica, vista la più stretta vicinanza al sito di irradiazione, l'associazione è più forte per il mesotelioma peritoneale, mentre per patologie come

linfomi di Hodgkin o non Hodgkin radiotrattati si ha la possibilità di sviluppare mesoteliomi pleurici (Farioli et al, 2013; Farioli et al, 2016; Metayer C et al, 2000).
Precedentemente è stata messa in evidenza anche un'associazione tra Thorothrast e mesotelioma (Boffetta, 2006; van Kaick G et al, 1999): in questa revisione non si sono analizzati studi su tale associazione poiché quelli riscontrati non rientravano nei criteri di inclusione.
Come evidenziato da Goodman et al (Goodman et al, 2009) la rarità del mesotelioma e la sua non precisa classificazione pongono dei limiti importanti anche per gli studi epidemiologici.
I principali limiti di questo lavoro sono rappresentati infatti dalla *missclassification* del mesotelioma all'interno dei vari studi presenti in letteratura scientifica, come si nota dalla stringa di ricerca sono state utilizzate sia le parole "*mesothelioma"* che *"pleural cancer/neoplasm"* o *"peritoneal cancer/neoplasm"*.
Le scarse, se non assenti, informazioni della co-esposizione all'amianto non hanno permesso di correggere la stima per questa variabile: in tutti gli studi esaminati veniva citato come possibile confondente ma nessuno aveva una stima puntuale della misura dell'esposizione.
Le coorti occupazionali non dispongono di informazioni su terapie effettuate o su radioterapie e molti interrogativi restano tuttora irrisolti, come ad esempio la forma della funzione di rischio (con riferimento alla dose e al tempo intercorso dall'esposizione), la quantificazione del rischio assoluto di mesotelioma maligno e la possibile interazione tra esposizione a radiazioni ionizzanti ed amianto nel determinare il rischio di mesotelioma maligno. Le poche informazioni a nostra disposizione circa una stima precisa e puntuale dell'esposizione a radiazioni ionizzanti (sia sulle irradiazioni esterne che sulle contaminazioni) non ci hanno permesso di studiare la relazione dose risposta.
Tuttavia, il numero di studi permette di confermare l'ipotesi iniziale: le radiazioni ionizzanti sono un fattore di rischio per il mesotelioma. L'eterogeneità geografica delle coorti mette in evidenza che tale ipotesi non risente di particolari caratteristiche di popolazione o di un territorio. Sono state però evidenziate differenze di distribuzione dei dati tra gli studi con esposizione a radioterapia (Nord America per la maggior parte) e quelli che studiavano le esposizioni lavorative (UK, Francia, Australia)

È risaputo, soprattutto da studi condotti sulle popolazioni di Hiroshima e Nagasaki o di altri disastri nucleari, che l'effetto cancerogeno non è studiato per dosi di piccola intensità e costante nel tempo (Grant et al, 2017; Siegel et al,2017).
Gli studi che hanno come esposizione la radioterapia sono tratti dalla coorte del SEER per la maggior parte, tuttavia il mesotelioma viene studiato come secondo tumore e il tumore primario preso in esame colpisce vari distretti: per tali ragioni si possono considerare come studi con coorti di popolazioni differenti.
Si deve ricordare che essendo il mesotelioma maligno un tumore raro, il numero dei casi esaminati considerando il numero degli studi e il numero dei soggetti è sempre molto basso. Questo va a condizionare la precisione della stima dell'associazione.
È da mettere in evidenza, infine, che le stime ottenute per esposizione a EBRT e per le esposizioni lavorative sono risultate simili. In realtà queste ultime sono risultate superiori alle precedenti. Questo risultato appare in contraddizione rispetto ad altri lavori precedenti (Metz Flamant et al, 2011) anche se è il primo che mette in relazione due tipi di esposizione differenti a radiazioni ionizzanti. Le motivazioni possono essere sempre ricercate nella co-esposizione ad amianto: si può ipotizzare che coloro che sono stati esposti a EBRT abbiano avuto una esposizione ad amianto inferiore rispetto ai soggetti esposti a radiazioni ionizzanti in ambito lavorativo. Sfortunatamente rimane solo un'ipotesi data la carenza delle informazioni di esposizione ad amianto in entrambi i *setting.*

Conclusioni

Il nostro studio dimostra che l'esposizione a radiazioni ionizzanti potrebbe essere un fattore di rischio per il mesotelioma: sia per l'esposizione a dosi elevate per brevi periodi (EBRT), sia per l'esposizione a basse dosi per una durata temporale prolungata (esposizione lavorativa). Nonostante il basso numero di mesoteliomi nella popolazione generale, il rischio costantemente aumentato tra individui esposti alle radiazioni è comunque da prendere in considerazione.
Studi più dettagliati sulla co-esposizione asbesto - radiazioni ionizzanti sarebbero necessari e dovrebbero essere condotti per capire il ruolo di entrambi nella cancerogenesi del mesotelioma.
A ciò si dovrebbe aggiungere una maggiore dettaglio sul *coding* del mesotelioma, con una precisa (e attualmente disponibile) classificazione della patologia.

Considerando le stime ottenute, i casi clinici e la modalità d'azione plausibile, si può concludere che le prove supportano una probabile associazione tra l'esposizione alle radiazioni ionizzanti e il rischio di mesotelioma, ma non siamo in grado di capire qual è il peso degli altri elementi confondenti (asbesto, altri cancerogeni, etc.)
Nei prossimi studi, ulteriori indagini dovrebbero migliorare la precisione e il dettaglio dell'esposizione all'amianto e dare una misura coerente dell'esposizione a radiazioni ionizzanti, considerando il rischio di mesotelioma maligno.

Contributo degli autori

Il presente studio è stato portato avanti con la collaborazione del Dott. Andrea Farioli, del Prof. Paolo Boffetta e del Dott. Giovanni Visci.

Figure e tabelle

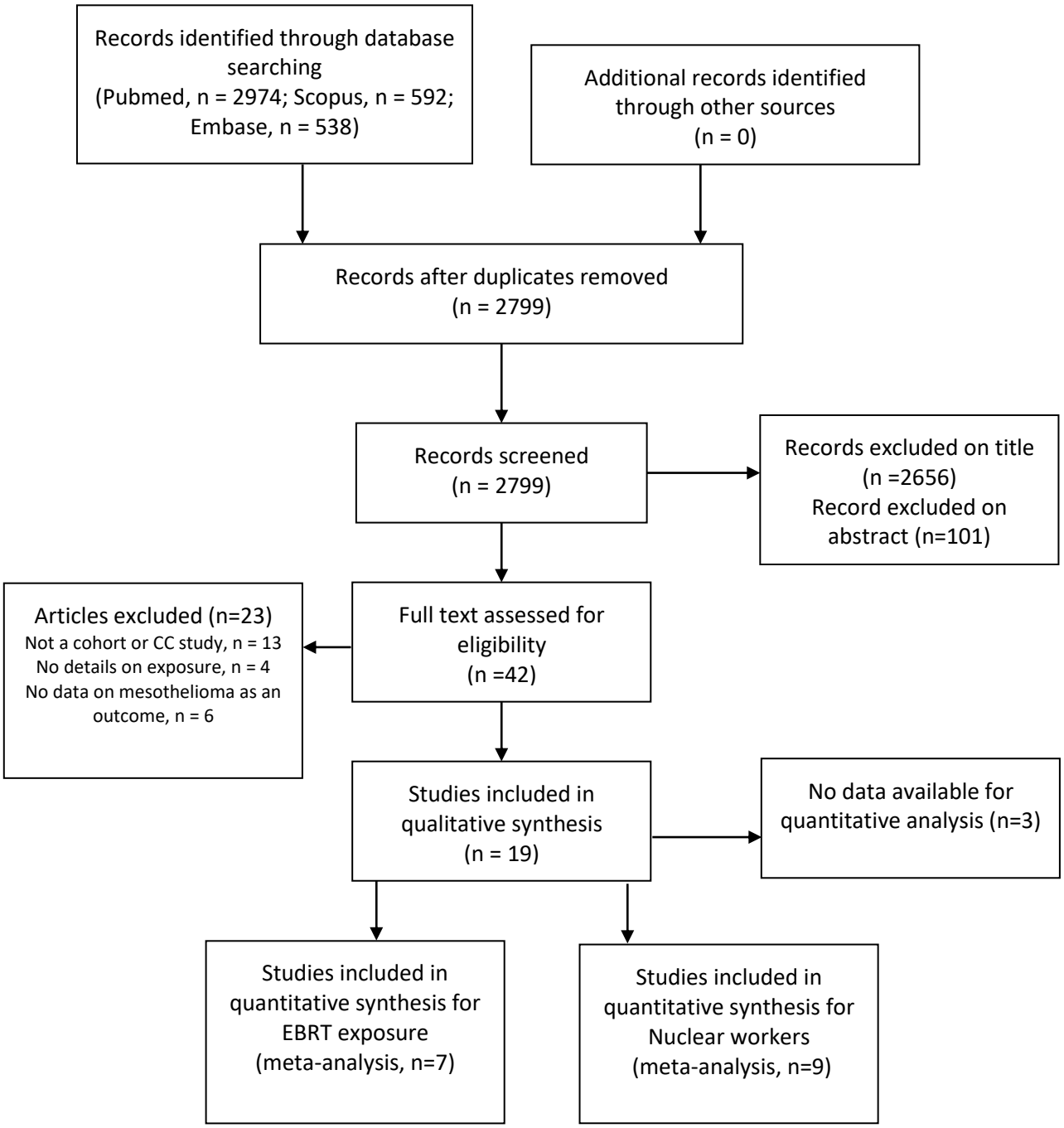

FIGURA 1. Prisma 2009 *flow diagram* della selezione degli studi

TABELLA 1. Caratteristiche degli studi selezionati per la revisione sistematica per esposizioni a radioterapia

Reference	Country	Sex (%M)	Study period	Cohort Size	Person years	Source of Data on exposure	Exposure	Source of Data on outcome	Outcome	Age	Quality score (%)
Chang et al. (2017)	USA	54	1973-2014	299309	2010600	SEER 18	RT	SEER 18	Incidence	NA	61
Farioli et al. (2016)	USA	33	1973-2012	935637	NA	NA	RT	NA	Incidence	59.7	78
Farioli et al. (2013)	USA	100	1973-2009	570883	3985991	SEER 9 and SEER 13	RT	SEER	incidence	NA	84
Berrington de Gonzalez et al. (2009)	USA	0	1978-2005	182057	2366741	SEER	RT	SEER	incidence	NA	61
ML De Bruin et al. (2009)	NETHERLANDS	56	1965-1995	2567	46462,7	5 cancer centers/Universitary hospitals in Netherlands	RT	5 cancer centers/Universitary hospitals in Netherlands	Incidence	NA	83
MJ Teta et al. (2007)	USA	55	1973-2003	122882	503100	SEER	RT	SEER	Incidence	54.2 M 58.9 F	62
Tom Pickles et al. (2002)	CANADA	100	1984-2000	39261	142983	BC Cancer Registry	RT	British Columbia Tumor registry	incidence	71,5	61
Metayer et al (2000)	NORTH AMERICA AND EUROPE	54	1935-1994	5925	19748	SEER and cancer registries of Connecticut, Ontario, Sweden, Denmark and Finland	RT	SEER and cancer registries of Connecticut, Ontario, Sweden, Denmark and Finland	Incidence	NA	57
Neugut et al. (1997)	USA	3	1973-1993	265493	1145203,5	SEER	RT	SEER	Incidence	NA	51

SEER= Surveillance, Epidemiology, and End Results; NA not available, RT: radiotherapy

TABELLA 2. Caratteristiche degli studi selezionati per la revisione sistematica per esposizioni a radiazioni ionizzanti in ambito lavorativo

Reference	Country	Sex (% M)	Study period	Cohort Size	Person years	Source of Data on exposure	Exposure	Source of Data on outcome	Outcome	Age	Quality score (%)
Samson et al (2016)	France	87.9	1968-2008	12649	342258	TRACY	Uranium	CépiDC-INSERM and National Vital Status registry	Mortality		51,1
Schubauer Berigan MK et al (2015)	U.S.A	80.4	up to 2015	119196	4019065	Hanford, INL,ORNL, PNS, SRS	γ ray, neutrons and tritium	National Death Index	Mortality		55,6
Metz-Flamant C et al (2011)	France	81.8	1968-2004	36769	1014556	CEA and AREVA Nucler cycle	nuclear industry	INSERM	Mortality		55,6
Matanoski et al (2008)	U.S.A	100	1957-1982	71815	920907	US Shipyard Workers	nuclear industry	Social security administration files, civil service administration files, HCFA files, Virginia mortality files and national Death Index	Mortality		61,1
Habib R et al (2006)	Australia	72.3	1972-1996	4523	73413	LHSTC	nuclear industry	NCSCH	Incidence		61,1
Habib R et al (2005)	Australia	74.2	1972-1998	7023	128036,1	LHSTC	nuclear industry	INSERM	Mortality		55,6
Atkinson WD et al (2004)	U.K.	71	1946-1997	51367	1371153	UKAEA	nuclear industry	NHSCRs	Mortality		44,4
Telle-Lamberton et al (2004)	France	76.7	1946-1994	58320	1327479,5	CEA	nuclear industry	INSERM	Mortality	NA-	33,3
RZ Omar et al (1999)	U.K.	NA	1947-1993	14385	415431,6	BNFL (Sellafield plant)	plutonium	NHSCRs	Mortality		50,0
Carpenter et al (1998)	U.K.	100	1946-1988	75006	NA	AEA establishment at Harwell, AWE and Sellafield	plutonium, tritium and other radionuclides	NHSCRs	Mortality		45,6

TRACY (Travailleurs du Cycle), INL (Idaho National Laboratory), Oak Ridge National Laboratory (ORNL), Partsmouth Naval Shipyard (PNS), Savannah River Site (SRS) CEA (Commissariat à l'Energie Atomique), AREVA Nucler cycle, US Shipyard Workers, LHSTC (Lucas Heights Science and Technology Centre), UKAEA (United Kingdom Atomic Energy Authority), BNFL (Sellafield plant), French National Health and Medical research Institute (INSERM), Social security administration files, civil service administration files, Health Care Financing Administration (HCFA) files, National Cancer Statistics Clearing House (NCSCH), National Health service central registers (NHSCRs); NA Not available

TABELLA 3. Stime di rischio per l'insorgenza di mesotelioma negli studi selezionati per la revisione sistematica per esposizioni a radioterapia

Reference	Country	Person years	Number of Mesothelioma	RR/IRR/SIR	index	LbCI	UbCI	Note
Chang (2017)	USA	2010600	28	RR	1,64	1,05	2,57	NA
Chang (2017)	USA	2010600	28	SIR	1,78	1,18	2,58	NA
Farioli (2016)	USA	NA	301	RR	1,34	1,04	1,74	NA
Farioli (2013)	USA	3985991	471	IRR	1,28	1,05	1,55	(multi)
Farioli (2013)	USA	3985991	471	IRR	1,39	1,15	1,69	(uni)
Berrington de Gonzalez (2009)	USA	2366741	2	SIR	9,14	1,11	33,02	NA
ML De Bruin (2009)	NETHERLANDS	46462,7	13	SIR	25,7	13,7	44	NA
MJ Teta (2007)	USA	503100	9	SIR	2,24	1,07	4,12	tutti
Tom Pickles (2002)	CANADA	142983	28	SIR	2,28	NA	NA	p=0.003
Tom Pickles (2002)	CANADA	142983	28	SIR	2,55	NA	NA	(<5y)
Tom Pickles (2002)	CANADA	142983	28	SIR	1,55	NA	NA	(5-10y)
Tom Pickles (2002)	CANADA	142983	28	SIR	3,06	NA	NA	(>10y)
Metayer (2000)	NORTH AMERICA AND EUROPE	19748	1	NA	NA	NA	NA	NA
Neugut (1997)	USA	1145203,5	6	RR	1,56	0,18	5,63	NA

RR: relative risk, SIR: standardized incidence ratio, SMR: standardized mortality ratio, LbCI, lower bounder confidence interval, UbCI, upper bounder confidence interval, NA Not available.

TABELLA 4. Stime di rischio per l'insorgenza di mesotelioma negli studi selezionati per la revisione sistematica per esposizioni a radiazioni ionizzanti in ambito lavorativo

Reference	Country	Person years	Number of Mesothelioma	RR/SMR/SIR	index	LbCI	UbCI	Note
Samson et al (2016)	France	342258	17	SMR	2,04	1.19	3.27	NA
Schubauer Berigan MK et al (2015)	U.S.A	4019065	96	SMR	2,8	2.27	3.42	NA
Metz-Flamant C et al (2011)	France	1014556	36	RR	0.48	0.12	1.19	NA
Metz-Flamant C et al (2011)	France	1014557	36	SMR	1.67	1.17	2.32	NA
Matanoski et al (2008)	U.S.A	920907	36	SMR	5.11	3.03	8.08	>5 mS
Matanoski et al (2008)	U.S.A	920907	36	SMR	5.75	2.48	11.33	<5 mS
Habib R et al (2006)	Australia	73413	6	SIR	17.71	7.96	39.43	NA
Habib R et al (2005)	Australia	128036,1	5	SMR	21.11	8.79	50.72	NA
Atkinson WD et al (2004)	U.K.	1371153	5	SMR	1,32	0,43	3,08	internal monitored workers
Atkinson WD et al (2004)	U.K.	1371154	10	SMR	1,04	0,49	1,91	radiation workers
Atkinson WD et al (2004)	U.K.	1371155	10	RR	5,35	1,36	infinito	NA
Telle-Lamberton et al (2004)	France	1327479,5	28	SMR	1.79	1.27	2.45	NA
RZ Omar et al (1999)	U.K.	415431,6	14	SMR	3,51	1,92	5,89	NA
Carpenter et al (1998)	U.K.	NA	1	RR	0,48	0.03	2.69	tritium
Carpenter et al (1998)	U.K.	NA	1	SMR	1,15			tritium
Carpenter et al (1998)	U.K.	NA	9	RR	1,97	0.71	5.49	plutonium
Carpenter et al (1998)	U.K.	NA	9	SMR	3,57			plutonium
Carpenter et al (1998)	U.K.	NA	4	RR	1,62	0.38	6.27	other radionuclides
Carpenter et al (1998)	U.K.	NA	4	SMR	2			other radionuclides

RR: relative risk, SIR: standardized incidence ratio, SMR: standardized mortality ratio, LbCI, lower bounder confidence interval, UbCI, upper bounder confiden NA Not available

TABELLA 5. Stime di rischio per analisi di sensibilità con l'esclusione di uno studio per volta (esposizione a radioterapia)

Reference	Risk Estimate	95% CI	I^2 (%)
NO Chang (2017)	1,46	(0,90 - 2.02)	59.7
NO Farioli (2016)	1,75	(0,86 - 2,64)	64
NO Farioli (2013)	1,78	(0,89 - 2,67)	61.5
NO Berrington de Gonzalez (2009)	1,51	(1,04 - 1,97)	61.5
NO ML De Bruin (2009)	1,35	(1,16 - 1,54)	0
NO MJ Teta (2007)	1,46	(0,97 - 1,94)	60.4
NO Neugut (1997)	1,56	(1,03 - 2,02)	64

TABELLA 6. Stime di rischio per analisi di sensibilità con l'esclusione di uno studio per volta (esposizione lavorativa)

Reference	Risk Estimate	95% CI	I2
NO Samson et al (2016)	2,14	(1,40 - 2,88)	80
NO Schubauer Berigan MK et al (2015)	1,94	(1,27 - 2,60)	69,8
NO Metz-Flamant C et al (2011)	2,24	(1,43 - 3,04)	79,5
NO Matanoski et al (2008)	1,89	(1,29 - 2,48)	72,9
NO Habib R et al (2006)	2,07	(1,43 - 2,70)	77,5
NO Atkinson WD et al (2004)	2,28	(1,58 - 2,99)	74,2
NO Telle-Lamberton et al (2004)	2,22	(1,41 - 3,02)	79,9
NO RZ Omar et al (1999)	2,00	(1,33 - 2,67)	78,4
NO Carpenter et al (1998)	2,27	(1,56 - 2,97)	77,9

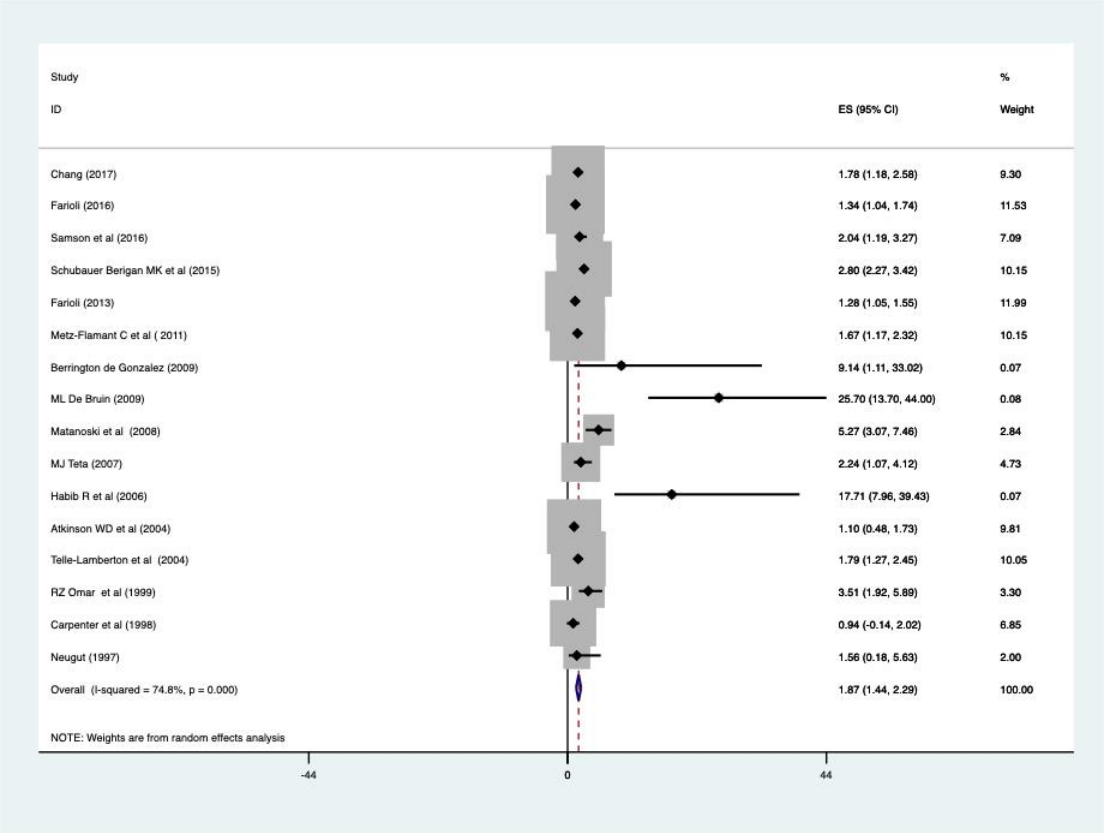

FIGURA 2. Forrest plot per metanalisi delle stime di rischio per l'insorgenza di mesotelioma negli studi selezionati per esposizioni a radioterapia ed esposizione lavorativa

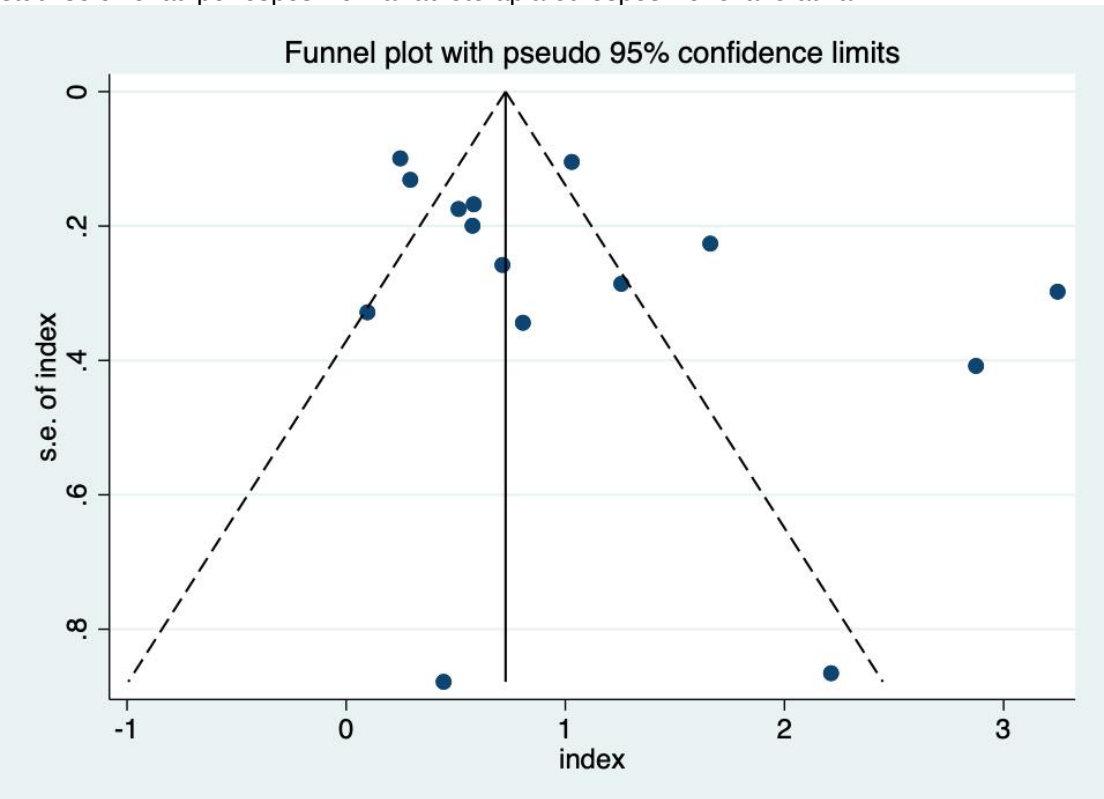

FIGURA 3. Funnel plot per metanalisi delle stime di rischio per l'insorgenza di mesotelioma negli studi selezionati per esposizioni a radioterapia ed esposizione lavorativa

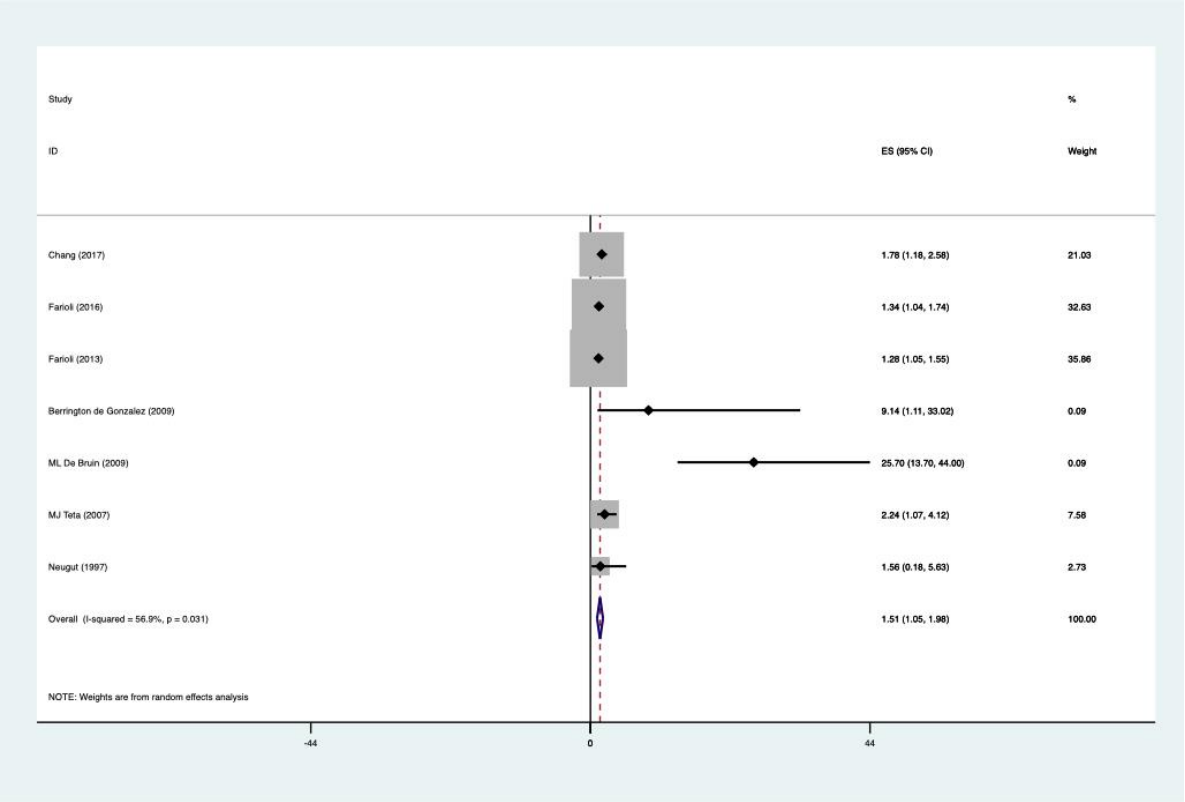

FIGURA 4. Forrest plot per metanalisi delle stime di rischio per l'insorgenza di mesotelioma negli studi selezionati per la revisione sistematica per esposizioni a radioterapia

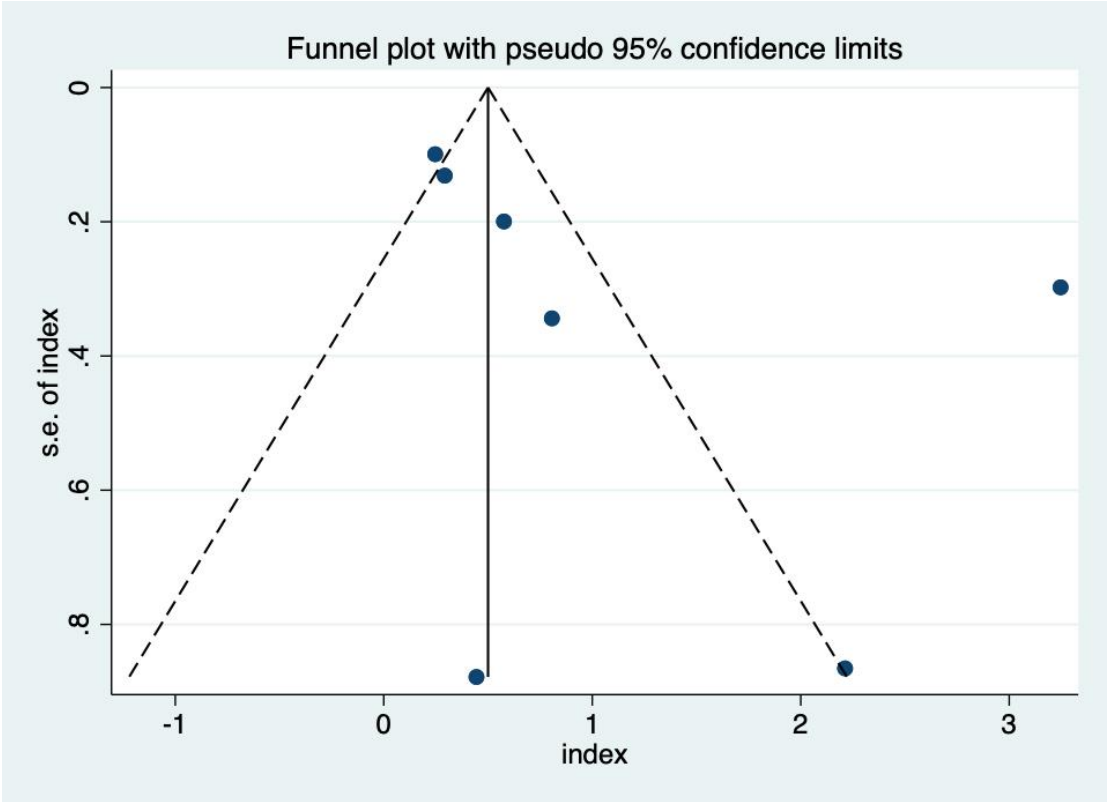

FIGURA 5. Funnel plot per metanalisi delle stime di rischio per l'insorgenza di mesotelioma negli studi selezionati per la revisione sistematica per esposizioni a radioterapia

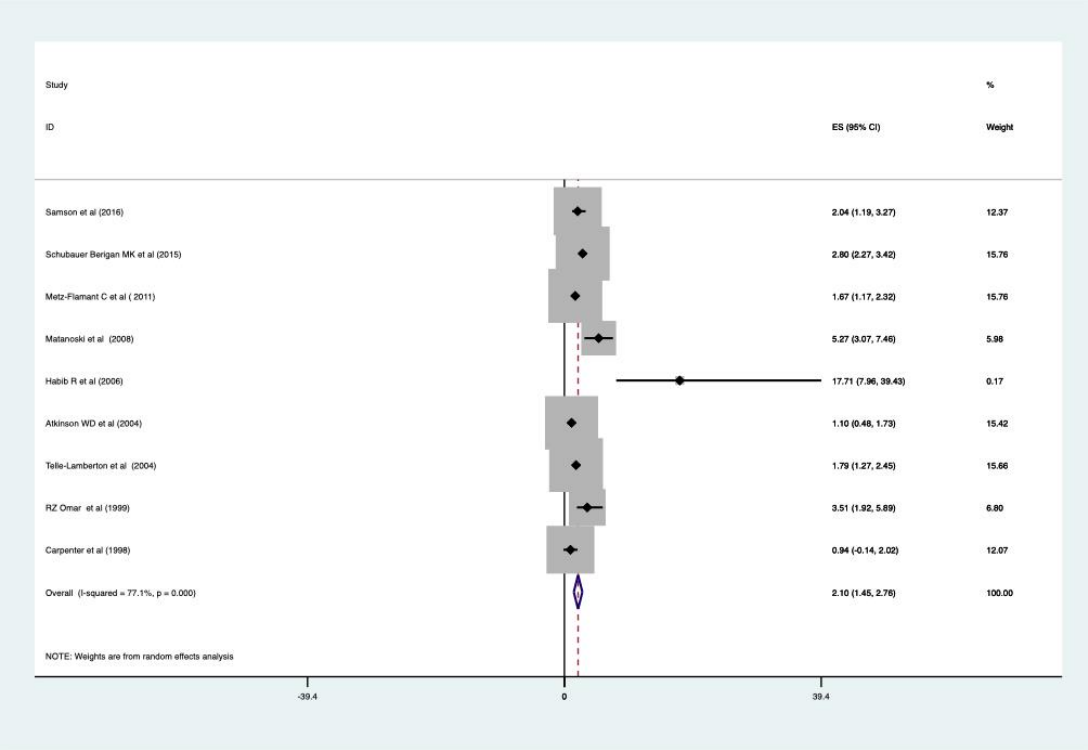

FIGURA 6. Forrest plot per metanalisi delle stime di rischio per l'insorgenza di mesotelioma negli studi selezionati esposizioni a radiazioni ionizzanti in ambito lavorativo

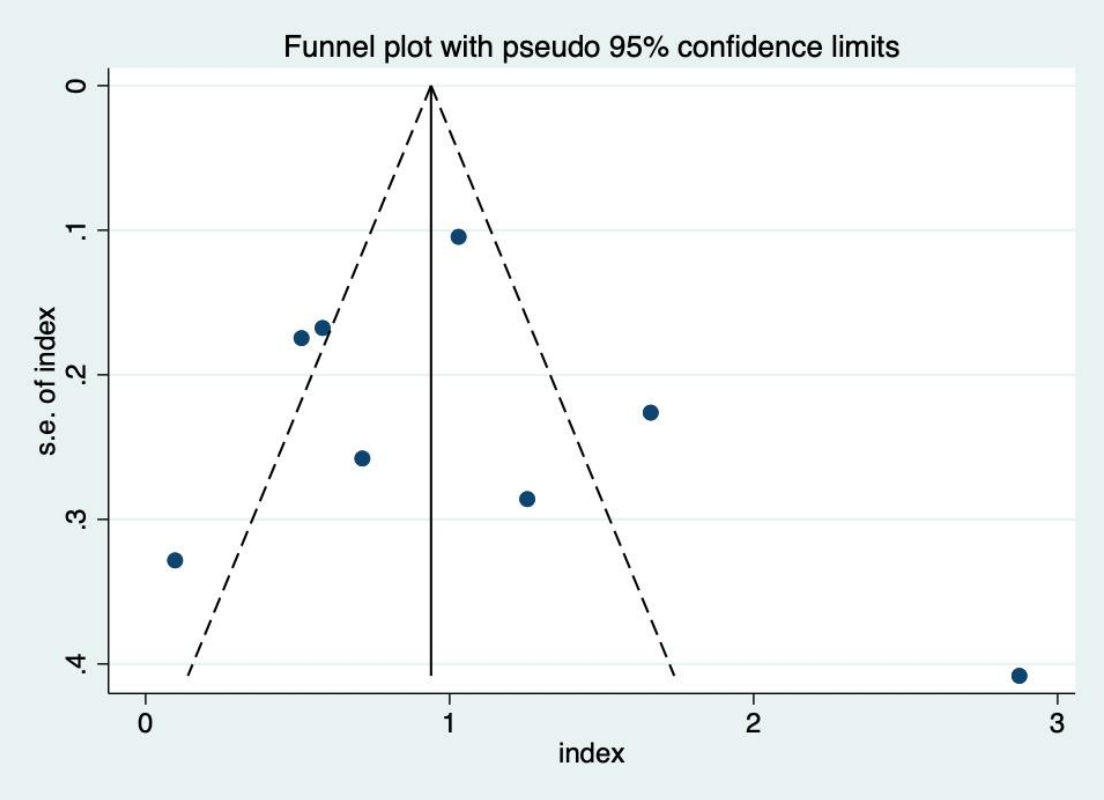

FIGURA 7. Funnel plot per metanalisi delle stime di rischio per l'insorgenza di mesotelioma negli studi selezionati per esposizioni a radiazioni ionizzanti in ambito lavorativo

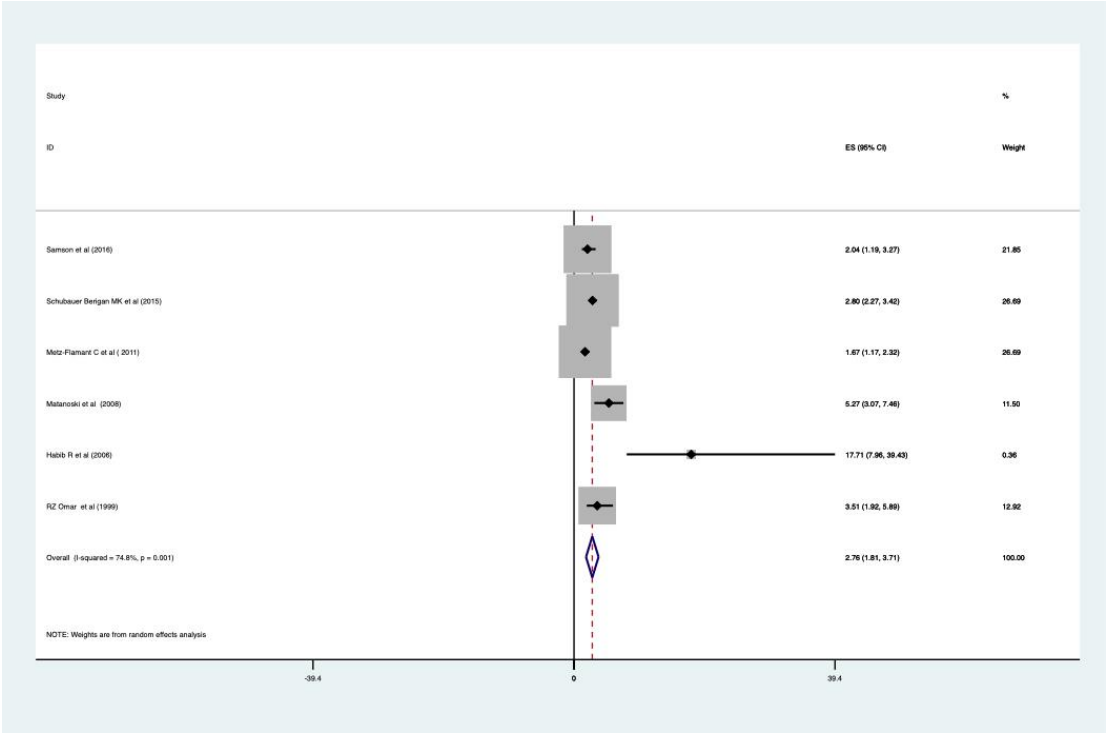

FIGURA 8. Forrest plot per metanalisi delle stime di rischio per l'insorgenza di mesotelioma negli studi selezionati, con *quality score* superiore al 50% per esposizioni a radiazioni ionizzanti in ambito lavorativo

Research strings

1) **Pubmed**

(((((((Radiotherapy OR EBRT OR “external beam radiotherapy” OR “stereotactic radiotherapy” OR (peritoneal AND irradiation) OR radionuclides OR “therapeutic ionizing radiation”)) OR ((Nuclear AND (industry* OR work OR worker* OR job)) OR (Radiation AND (industry* OR work OR worker* OR job))))) OR (''Radiography/adverse effects''[Mesh]) OR (Hiroshima[tiab] OR Nagasaki[tiab] OR atomic bomb survivors OR life span study) OR (''Thorium Dioxide''[Mesh] OR Thorotrast)

AND

(“etiology”[Subheading] OR etiologic* OR Neoplasm, Radiation-Induced[MH] OR Neoplasms, Radiation-Induced* OR Neoplasms, Second Primary[MH] OR Neoplasms, Second Primary* OR etiology[MH] OR aetiologic* OR aetiology OR Cohort Studies[MH])))

AND

(Mesothelioma OR Pleural cancer OR Pleural neoplasm OR Peritoneal cancer OR Peritoneal neoplasm OR “Mesothelioma”[MH] OR Mesothelioma/etiology* OR Pleural Neoplasms/mortality OR(Asbestos* AND (Cancer AND Neoplasm)))))

2) **Scopus**

((TITLE-ABS-KEY (industry* OR work OR worker* OR job)) AND (TITLE-ABS-KEY (radiation))) OR ((nuclear) AND (TITLE-ABS-KEY (industry* OR work OR worker* OR job))) OR (radiotherapy OR ebrt OR "external beam radiotherapy" OR "stereotactic radiotherapy") OR (radionuclides OR "therapeutic ionizing radiation") OR (peritoneal AND irradiation) OR ((Radiography AND adverse effects) OR ((hiroshima OR nagasaki OR (atomic AND bomb AND survivors) OR (life AND span AND study)) OR ((Thorium AND Dioxide) OR Thorotrast))

AND

etiolog* OR aetiolog* OR (neoplasm AND radiation-induced) OR (neoplasms AND second) OR (neoplasm AND primary)

AND

((cancer OR neoplasm) AND (asbestos)) OR (mesothelioma OR pleural AND cancer OR pleural AND neoplasm OR peritoneal AND cancer OR peritoneal AND neoplasm OR "Mesothelioma" [mh] OR mesothelioma/etiology* OR pleural AND neoplasms/mortality)

3) Embase

1) exp radiotherapy/ or exp external beam radiotherapy/ or exp adjuvant radiotherapy/ or exp "patient history of radiotherapy"/ or exp cancer radiotherapy/
2) exp radioisotope/
3) exp radiation exposure/ or exp ionizing radiation/
4) exp nuclear industry/
5) exp nuclear energy/
6) exp "Radiography adverse effects"/
7) exp Hiroshima/ or exp Nagasaki/ or exp atomic bomb survivors/ or exp life span study
8) exp Thorium Dioxide/ or exp Thorotrast
9) exp radiation carcinogenesis/ or exp second cancer/ or exp radiation induced neoplasm/
10) exp etiology/
11) exp pleura mesothelioma/ or exp mesothelioma/ or exp peritoneum mesothelioma/
12) 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
13) 9 or 10
14) 12 and 13 and 14

Quality assessment tool for papers

1 **Approach used to identify the study population and the potential for selection bias:**

a. Case-control studies:
   i. Representativeness of the cases:
      1. Representative cases of study base (1)
      2. Potential for selection biases or not stated (0)
   ii. Selection of controls:
      1. Community controls (1)
      2. Hospital controls (0.5)
      3. No description (0)
   iii. Have historical controls or proxies been used?
      1. No (1)
      2. Yes (0)

b. Cohort studies:
   i. Selection of exposed cohort:
      1. Cohort comprises all eligible subjects (1)
      2. Cohort comprises only a selected group from all eligible subjects (0.5)
      3. No description of the derivation of the cohort (0)
   ii. Selection of the non-exposed cohort:
      1. Drawn from the same study base (1)
      2. Drawn from a different source or no description (0)

2 **Approach used for exposure assessment and the potential for information bias, whether differential (non-random) or non-differential (random):**

a. Ascertainment of EBRT (or nuclear workers):
   i. Measure of dose received (or of dose absorbed in case of nuclear workers) (1)
   ii. Structured interview/job title collected from employment records (0.6)
   iii. Self-reported (0.3)

iv. No description (0)

b. Information about follow up:
    i. FU ≥ 10 years (1)
    ii. FU< 10 years (0)

c. Ascertainment of asbestos-exposure:
    i. Self-reported (1)
    ii. From other sources (0.5)
    iii. No description (0)

d. Mean age of study population
    i. At least 60 years old or older (1)
    ii. Younger than 60 years old (0)

3 **Approach used for outcome identification and any potential bias:**

a. Is the outcome selection adequate?
    i. Yes, with independent validation (1)
    ii. Yes, e.g. record linkage or based on self-reports (0.5)
    iii. No description (0)

b. In case of cancer, the outcome is:
    i. Incidence (1)
    ii. Mortality (0)

4 Potential for confounding to have influenced the findings:

a. Results adjusted for other carcinogens (e.g. asbestos) (1)
b. Results adjusted for basic confounders (e.g. age, sex, SES) (0.5)
c. No adjustment (0)

TOTAL SCORE FOR CASE-CONTROL STUDIES: _____ /10

TOTAL SCORE FOR COHORT STUDIES: _____/9

PROSPERO Protocol

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Ionizing radiation exposure and Mesothelioma risk: systematic review and meta- analysis

Emanuele Rizzello, Giovanni Visci, Andrea Farioli, Paolo Boffetta

Citation

Emanuele Rizzello, Giovanni Visci, Andrea Farioli, Paolo Boffetta. Ionizing radiation exposure and Mesothelioma risk: systematic review and meta- analysis. PROSPERO 2020 CRD42020166892 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020166892

Review question

Does exposure to ionizing radiation increase the risk to develop mesothelioma? If it is possible to assess this, how much the risk increments?

Searches

PubMed, Scopus, Embase with no restrictions of period or language

Types of study to be included

cohort studies, case control studies

Condition or domain being studied

Mesothelioma OR pleural/peritoneal cancer

Participants/population

People who were employed in nuclear industries; people who underwent radiotherapy for a cancer in another primary site, people who received X-ray for diagnostic procedures or people who received thorotrast as colloid solution contrast medium; nuclear bomb survivors.

Intervention(s), exposure(s)

Exposure to different sources of Ionizing radiation

Comparator(s)/control

People/workers who were not exposed

Main outcome(s)

Incidence/mortality due to mesothelioma in people exposed to ionizing radiation

* Measures of effect

none

Additional outcome(s)

None

* Measures of effect

none

Data extraction (selection and coding)

Two reviewers (GV, ER) will screen independently titles and abstracts to identify potentially relevant studies. The full texts of potentially relevant articles will be assessed for eligibility against the inclusion criteria. In cases of disagreement or doubts, results will be discussed with a third reviewer (AF). A PRISMA Flow Chart will be used to show search and selection process. The meta-analysis will be performed according to the PRISMA-statement [Mohrer et al., 2009].The following study characteristics will be extracted for the meta-

analysis: publication year, country, study design, age, sex, lost to follow-up (or response rate of cases and controls), cohort size (or number of cases and controls), irradiation source, confounders (exposition to asbestos, other carcinogenic, etc..), number of mesothelioma cases, main results (relative risk, SMR, SIR, IRR, OR and 95% confidence interval). Among other confounders, asbestos is certainly the most important one. As it is known, mesothelioma is a very rare tumor and asbestos effect on carcinogenesis of mesothelioma is very important. Between 70% to 80% of people diagnosed with mesothelioma have been exposed to asbestos.

Risk of bias (quality) assessment
Every included article will be scored for its quality according to a standardized checklist.

The quality of the studies included in the meta-analysis was independently evaluated by two authors (GV, ER) through tools for observational cohort and cross-sectional studies (NIH). Moreover we will adapt this quality assessment tool to explore the co-exposure with asbestos, particular importance will be given to study with a median age older than 60 years and with follow up in the study of at least 10 years

Strategy for data synthesis
The meta-analysis will be based on random effects models [DerSimonian & Laird, 1986], and will aim to calculate summary relative risks and 95% confidence intervals. The results of the tests for heterogeneity will be reported.

Analysis of subgroups or subsets
Study design; Ionizing radiation type; publication period, duration and completeness follow up

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Assistant/Associate Professor Andrea Farioli. University of Bologna
Professor Paolo Boffetta. University of Bologna

Type and method of review
Epidemiologic, Meta-analysis, Systematic review

Anticipated or actual start date
27 January 2020

Anticipated completion date
31 May 2020

Funding sources/sponsors
No founding sources/sponsors

Conflicts of interest
Professor Paolo Boffetta acted as expert witness in litigation involving mesothelioma.
Yes

Language
English

Country
Italy

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
MeSH headings have not been applied to this record

Date of registration in PROSPERO
28 April 2020

Date of first submission
05 February 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
28 April 2020

Capitolo 3. Mesotelioma maligno: valutazione dell'incidenza del mesotelioma peritoneale come secondo tumore in pazienti con tumore alla prostata trattati con EBRT

Introduzione

I pazienti che hanno subito un trattamento radioterapico per un tumore possono sviluppare, nel tempo, una seconda neoplasia indotta dalle radiazioni ionizzanti (Wallis CJ, 2016).

Dallo studio di Baxter sappiamo che le neoplasie indotte da radiazioni ionizzanti si manifestano all'interno del campo di irradiazione (Baxter et al, 2005); tuttavia si possono manifestare anche in organi distanti dal campo irradiato che risentono degli effetti della radiazione diffusa (Kry SF et al, 2005; Francois P, 1998).

Una dei nostri obiettivi è studiare l'incidenza del mesotelioma, come secondo tumore, comunemente non considerato come neoplasia indotta da radiazioni, in pazienti che sono stati esposti alla radioterapia a fasci esterni (EBRT) per il cancro alla prostata.

Per comprendere bene le dimensioni del problema di seguito saranno riportati alcuni cenni di epidemiologia e clinica del cancro della prostata.

Il cancro alla prostata (PCa) rappresenta il secondo tumore più comunemente diagnosticato negli uomini, con 1.276.106 milioni di nuove diagnosi in tutto il mondo nel 2018, pari al 13,5% di tutti i tumori diagnosticati (Bray et al, 2018).

L'incidenza del tumore alla prostata, tuttavia, varia ampiamente tra le diverse aree geografiche, essendo più alta in Australia / Nuova Zelanda e Nord America (tassi di incidenza standardizzati per età [ASR]rispettivamente di 86,4 e 73,7 per 100.000) e nell'Europa occidentale e settentrionale (ASR 85,7 e 75,8). L'incidenza è bassa nell'Asia centro-orientale e meridionale (ASR 12,7 e 5), mentre i tassi nell'Europa orientale e meridionale, che erano bassi, hanno mostrato un aumento costante (Bell KJ et al, 2015).

Secondo le linee guida più recenti circa la gestione di questa malattia, il rischio principale per la forma di basso grado è un trattamento eccessivo. Le raccomandazioni aggiornate prevedono allo stesso modo sia la sorveglianza attiva sia il trattamento attivo con prostatectomia radicale o radioterapia. La decisione di optare per una delle soluzioni proposte dovrebbe essere basata sulle probabilità di

progressione clinica, sugli effetti collaterali, sul potenziale beneficio per la sopravvivenza e sulle preferenze individuali di ciascun paziente. (Mottet N et al, 2020). Poiché la malattia di basso grado ha una prognosi notevolmente favorevole, in questi pazienti esiste il rischio di sviluppare un secondo tumore dopo trattamento con radioterapia.

Lo scopo del nostro lavoro è studiare l'incidenza del mesotelioma peritoneale come secondo tumore: in particolare, l'obiettivo è capire se il rischio di sviluppare il mesotelioma è maggiore nelle persone che hanno ricevuto un trattamento con radioterapia rispetto ai pazienti che non sono statti sottoposti a questa forma di terapia.

Metodi

Popolazione e *Follow up*

La coorte è definita da pazienti a cui è stato diagnosticato un cancro alla prostata primitivo segnalato in uno dei registri SEER (*Surveillance, Epidemiology, and End Results*).

Poiché i registri SEER sono cambiati nel corso del tempo, abbiamo consultato il SEER9 per il periodo compreso tra il 1 ° gennaio 1973 e il 31 dicembre 1991, mentre il database dei registri SEER 13 per il periodo tra il 1 ° gennaio 1992 e il 31 dicembre 2015. In questo modo abbiamo potuto analizzare anche il database dei registri di Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound e Utah, San Jose Monterey, Los Angeles, Alaska Natives e Rural Georgia.

I record individuali sono stati ottenuti da MP-SIR (*Multiple Primary-Standardized Incidence Ratio*) del software SEER * Stat.

La nostra analisi non ha considerato il registro dei pazienti dell'Alaska perché non è presente alcun caso di interesse nella sessione MP-SIR; l'unico caso presente è stato inserito dopo la morte sulla base del certificato di morte / autopsia ed è stato escluso dalla popolazione in studio.

Sono stati esclusi dall'analisi i soggetti di età inferiore ai 40 anni a causa dell'esiguo numero di tumori alla prostata, così come abbiamo escluso persone di età superiore agli 85 anni perché vi possono essere problemi di sotto notifica della malattia. Inoltre, poiché la maggior parte dei Pca sono degli adenocarcinomi, abbiamo escluso tumori con istologia diversa.

Per evitare diagnosi sincrone con altri tumori, il *follow-up* per ogni individuo è iniziato un anno dopo la data della diagnosi del tumore alla prostata e si è concluso alla data della diagnosi di mesotelioma, alla data della morte o alla fine dello studio (31 dicembre 2015). Per ridurre la possibilità di un'errata classificazione dell'esposizione a EBRT, i pazienti già presenti nel database prima della diagnosi di cancro alla prostata sono stati esclusi dallo studio. Abbiamo anche escluso i pazienti con informazioni mancanti sulla radioterapia o sulla contea di residenza così come sono state escluse le persone senza informazioni sulla terapia di tipo chirurgico a causa della sua correlazione con la possibilità di ricevere un trattamento EBRT (la Figura1 riassume la popolazione dello studio).

Esposizioni e variabili covariate

I pazienti sono stati classificati in tre gruppi, utilizzando le informazioni presenti nei registri SEER:

1.pazienti che non hanno ricevuto nessuna radioterapia;

2.pazienti che sono stati sottoposti a EBRT o ad EBRT in combinazione con la brachiterapia;

3.pazienti che sono stati trattati con impianti radioattivi, radioisotopi, altre forme di radiazioni quando il metodo o la fonte non erano specificati.

Gli *incidence rate ratio* (IRR) del mesotelioma per i pazienti trattati con radioterapia (gruppi 2 e 3 sopra) sono stati stimati prendendo come gruppo di riferimento i pazienti che hanno ricevuto radioterapia. Abbiamo anche eseguito un'ulteriore analisi di sensibilità in cui sono stati stimati gli IRR rispetto ai pazienti non irradiati che hanno ricevuto un trattamento chirurgico.

Le covariate utilizzate nell'analisi multivariata sono state selezionate a priori e includevano: età (anni compiuti), anno e razza (bianco, nero, altro).

L'esposizione all'amianto è nota per essere la principale causa di mesotelioma e poiché potrebbe potenzialmente rappresentare un fattore di confondimento per l’associazione tra EBRT e il tumore, abbiamo cercato di considerarla nei nostri modelli.

Le informazioni sull'amianto che abbiamo utilizzato sono state derivate da un'analisi geografica, come variabile ecologica, perché nel SEER non è disponibile alcuna storia lavorativa o altre informazioni sull'esposizione.

Come in uno studio precedente (Farioli et al, 2013), è stata creata una variabile a tre livelli (rischio relativo basso, medio e alto di mesotelioma tra gli uomini in base

all'esposizione all'amianto) utilizzando terzili di distribuzione dei rischi relativi del mesotelioma nella contea. Ogni soggetto è stato classificato in base alla contea di residenza al momento della diagnosi di cancro alla prostata.

Tra i possibili modificatori dell'effetto della relazione tra EBRT e mesotelioma è stata considerata la latenza. Per latenza si intende il tempo trascorso dalla prima esposizione a EBRT.

Da studi precedenti, è noto che è necessario un minimo di 5 anni per l'induzione di tumori solidi dopo l'esposizione a radiazioni (Preston DL, 2007). La latenza è stata calcolata con riferimento alla data della diagnosi di cancro alla prostata (presumibilmente poco prima dell'esposizione a EBRT). Poiché il basso numero di mesoteliomi limitava la nostra capacità di indagine, abbiamo scelto di suddividere la latenza in due categorie.

Il principale *outcome* è rappresentato dall'*Hazard Ratio* (HR) del mesotelioma peritoneale nei pazienti esposti a EBRT rispetto ai pazienti non esposti alla radioterapia dopo carcinoma prostatico primario in base al periodo di latenza. Inoltre, è stata condotta un'analisi sensibile per i pazienti che sono stati trattati con terapia chirurgica studiando l'HR in ciascuna classe di latenza (0-5, > 5 anni).

Analisi statistica

Nelle tabelle descrittive, le variabili continue sono state espresse attraverso la media e la sua deviazione standard mentre le variabili categoriche sono state rappresentate da numeri assoluti e percentuali.

È stato utilizzato un modello di regressione di Cox per lo studio degli *Hazard Ratio* utilizzando il tempo di sopravvivenza come asse temporale principale. Un' ulteriore analisi è stata condotta includendo il prodotto tra l'esposizione di interesse (EBRT) e il periodo di latenza categorizzandolo in due gruppi (1-5 anni, > 5 anni). È stata calcolata la differenza in percentuale del coefficiente β per età, età alla diagnosi, razza, trattamento con chirurgia e sono state utilizzate le variabili che presentavano una differenza percentuale maggiore del 10%.

È stata anche calcolato, tramite la stima di Nelson-Aalen, il tasso di rischio cumulativo di incidenza del mesotelioma peritoneale per esposizione a radioterapia a fasci esterni sulla base dell'età e degli anni dalla diagnosi di cancro alla prostata.

Il rischio relativo di sviluppare mesotelioma in ciascuna contea è stato calcolato utilizzando il modello di Besag–York–Mollie (BYM), sulla base delle informazioni sull'amianto in ciascuna delle Contee presenti nel registro. Sono state elaborate delle immagini che rappresentano la distribuzione della SIR e del RR di sviluppare il mesotelioma in soggetti di età compresa tra i 25 e gli 84 anni (Besag et al,1991) (Figure 3,4).

I dati sul cancro e i singoli record sono stati ottenuti utilizzando il software SEER * Stat 8.2.1. mentre per le analisi principali è stato utilizzato il software Stata 14 SE (Stata Corporation, Texas, TX).

Risultati

Analizzando i registri SEER sono stati riscontrati 1.138.292 casi di cancro alla prostata durante il periodo di studio. Dopo l'esclusione di pazienti con cancro alla prostata diverso da adenocarcinoma (52581), di soggetti di età inferiore a 40 anni alla prima diagnosi (497), di età superiore a 85 anni alla prima diagnosi (39793), di pazienti sopravvissuti meno di un anno dalla diagnosi di tumore alla prostata e dall'esclusione *left and right censoring* abbiamo ottenuto 934.231 casi, abbiamo anche escluso pazienti che hanno ricevuto RT diversa da EBRT (39793), soggetti le cui informazioni sulla contea di provenienza non erano complete (290) e coloro senza informazioni sulla terapia chirurgica. La popolazione finale dello studio includeva 38 casi di mesotelioma peritoneale da una popolazione di 853.447 pazienti. Su 853.447 casi di tumore primario alla prostata, 264.005 (30,9%) sono stati trattati con EBRT.

Come atteso e come mostrato nella tabella 1, la scelta terapeutica è stata guidata da diversi fattori, tra cui l'età del paziente, più elevata tra i soggetti che hanno ricevuto EBRT (mediana 69, intervallo interquartile 63-74) rispetto ai non irradiati (66, 59-72).

L'uso della radioterapia a fasci esterni è risultato più frequente tra i pazienti neri (34,2%) rispetto ai pazienti bianchi (30,5%). Inoltre, è interessante notare la differenza tra le persone che hanno ricevuto un intervento chirurgico e coloro che hanno ricevuto una terapia combinata (EBRT + chirurgia solo nel 9,8%).

Confrontando i dati sulla contea, possiamo osservare una differenza tra le persone che hanno ricevuto RT e le persone che non sono state sottoposte a tale trattamento (Test qui quadrato di Pearson inferiore a 0,001).

Secondo i dati ottenuti, è stata rappresentata la stima dei tassi di incidenza aggregati con il modello di Nelson Aalen. L'incidenza di mesotelioma peritoneale, considerando l'esposizione alla radioterapia a fasci esterni rispetto all'età e rispetto agli anni trascorsi dalla diagnosi del tumore alla prostata, risulta essere lievemente differente tra chi è stato sottoposto a radioterapia e i pazienti che non lo sono stati (Figura 2).
Nel periodo di follow-up (6.587.508 anni-persona), sono stati diagnosticati 17 mesoteliomi tra i pazienti precedentemente trattati con EBRT. L'*Hazard Ratio* (HR) per l'EBRT, confrontato con i non irradiati, è risultato essere 1,72, con intervallo di confidenza (IC) al 95% di 0,90-3,29. Aggiustando per l'eventuale chirurgia radicale del tumore alla prostata, l'HR era di 2,22 (IC 95% 1,03-4,78).
All'analisi stratificata per latenza, il rischio relativo per l'EBRT è risultato crescere all'aumentare del tempo trascorso dall'irradiazione: 1-4 anni pari a 1,38 (IC 95% 0,43−4,42); oltre i 5 anni HR pari a 2.92 (IC 95% 1,17–7,27) (Tabella 2).

Discussione

Sebbene i mesoteli non vengano considerati tessuti radiosensibili è stato riscontrato un aumentato rischio di sviluppare mesotelioma peritoneale nei soggetti che sono stati sottoposti all'EBRT rispetto ai soggetti che non hanno eseguito questo trattamento. Tale risultato è condiviso anche da altri studi (Farioli et al, 2013; Ohya M et al,2019; Baxter et al,2005).
Quanto finora descritto potrebbe essere spiegato da un meccanismo di promozione della cancerogenesi da parte delle radiazioni ionizzanti, note già per i loro effetti cancerogeni. I danni al DNA cellulare possono essere prodotti direttamente dalle radiazioni incidenti o indirettamente generati dall'interazione delle radiazioni con le molecole di acqua contenute nei tessuti. L'interazione con il DNA può provocare alterazioni a carico delle basi azotate attraverso fenomeni di ossidazione o di metilazione. Quando si ha un errore a livello del DNA non riparato correttamente possono verificarsi aberrazioni cromosomiche, perdita di materiale genetico e mutazioni che aumentano la probabilità di una trasformazione in senso tumorale (Prise KM et al, 2009). Si consideri che la sopravvivenza dei soggetti con un tumore alla prostata di basso grado permette di verificare queste ipotesi menzionate.
L'utilizzo dei registri SEER ci ha permesso di analizzare un enorme numero di casi di tumore alla prostata arrivando ad aver un buon numero di mesoteliomi peritoneali che

difficilmente sarebbe stato possibile ottenere in altro modo, sia per la bassa incidenza del mesotelioma sia per il fatto che si sta studiando il mesotelioma come secondo tumore.

Inoltre, sappiamo che per la storia naturale del mesotelioma questo è caratterizzato da una lunga latenza (fino a circa 40 anni) e l'aver eliminato dalla nostra analisi pazienti con età superiore agli 85 anni potrebbe aver influito negativamente sul reale numero di mesoteliomi. Tuttavia, per la distribuzione dei dati in nostro possesso è stato necessario effettuare questo tipo di esclusione.

L'aver comunque osservato questo numero di mesoteliomi potrebbe, anche se in modo blando, valorizzare l'idea che l'esposizione a radiazioni ionizzanti rappresenta un'azione di "facilitazione" allo sviluppo del mesotelioma facendolo manifestare con periodi di latenza più brevi.

Come noto dai lavori dagli studi *Life Span* (Siegel et al, 2017; Gant et al, 2017) e dagli studi dei sopravvissuti ai disastri di Chernobyl, etc. (Kamiya K et al, 2015) la forma della curva che descrive meglio la relazione di dose risposta è una relazione lineare. Non siamo riusciti ad aggiungere nessun tipo di informazione a quanto era già noto. Uno degli obiettivi da raggiungere in futuro sarà la comprensione della relazione dose risposta alle basse dosi (situazione che potrebbe interessare sia i lavoratori in campo sanitario che nel campo della produzione energetica).

Un altro limite del nostro studio è la mancanza di informazioni dirette circa l'esposizione ad asbesto. Infatti, come enunciato precedentemente, abbiamo attribuito a ciascun paziente una *proxy* dell'esposizione basata sulla contea di residenza al momento della diagnosi del tumore alla prostata. Avendo delle informazioni più precise su questo parametro si potrebbe meglio studiare la co-esposizione tra amianto e radiazioni ionizzanti. Come si evince dalla revisione del precedente capitolo, in letteratura pochi sono gli studi che affrontano questo tema.

Con i dati a nostra disposizione abbiamo notato che l'unico fattore di confondimento era rappresentato dalla chirurgia (Δ% β *coefficient*= 46,8%). Aggiustando per le altre variabili prese in considerazioni (età, razza e contea di provenienza) non abbiamo ottenuto informazioni aggiuntive (Tabella 3).

Altro fattore da tenere in considerazione è la possibilità di una scorretta assegnazione di terapia con EBRT all'interno dei registri SEER, tuttavia questa classificazione errata non porterebbe ad una variazione sostanziale poiché interessa tutti i soggetti presenti.

Infine, il nostro studio prende in considerazione due gruppi di latenza differenti: 1-5 anni e un tempo superiore ai 5 anni dopo l'esposizione a radioterapia. Sarebbe interessante poter suddividere il tempo di latenza in più gruppi per studiare cosa succede in ciascun gruppo e verificare se in quelli con maggiore latenza il rischio di avere un mesotelioma peritoneale aumenta oppure rimane stabile. Sfortunatamente i dati a nostra disposizione non ci hanno permesso di indagare questo aspetto.

Conclusioni

Come atteso, l'incidenza complessiva di mesotelioma peritoneale osservata nella coorte è stata estremamente bassa (38 casi). I risultati del nostro studio supportano la possibile associazione tra esposizione a radiazioni ionizzanti e rischio di mesotelioma; in particolare, l'irradiazione del peritoneo che si verifica durante l'EBRT per tumori primari della prostata potrebbe aumentare il rischio di mesotelioma peritoneale a 5 o più anni dell'irradiazione.

Nel complesso, i nostri dati suggeriscono che il rischio di mesotelioma peritoneale non possa rappresentare in assoluto una controindicazione alla radioterapia in quanto per i limiti descritti precedentemente non si può escludere che l'aumento del rischio sia determinato da altri fattori (ad es. asbesto) e per il fatto che la radioterapia, come stabilito dalle principali linee guida internazionali, rappresenta una valida alternativa alla chirurgia negli stadi iniziali del tumore alla prostata.

Futuri studi dovranno concentrarsi sull'eventuale interazione tra amianto e radiazioni ionizzanti nel determinare il rischio di mesotelioma: ulteriori analisi potranno essere informative se sarà disponibile una misura di esposizione individuale sia per le radiazioni ionizzanti che per l'amianto.

Se in futuro si provasse un'interazione più che additiva tra radiazioni ionizzanti ed esposizione ad amianto nel determinare il rischio di mesotelioma, l'EBRT potrebbe diventare un'opzione terapeutica di seconda scelta per il trattamento del tumore prostatico localizzato tra gli ex lavoratori la cui storia lavorativa di esposizione ad asbesto è ben nota.

Contributo degli autori

Il presente studio è stato portato avanti con la collaborazione del Dott. Andrea Farioli e del Dott. Giovanni Visci.

Figure e Tabelle

FIGURA 1. *Flow diagram* della popolazione in studio. Pazienti affetti da adenocarcinoma prostatico primario seguiti per mesotelioma peritoneale maligno. Abbreviazioni: EBRT, radioterapia a fasci esterni; ICD-O, international classification of diseases for oncology; SEER, Statistics, Epidemiology And End Results

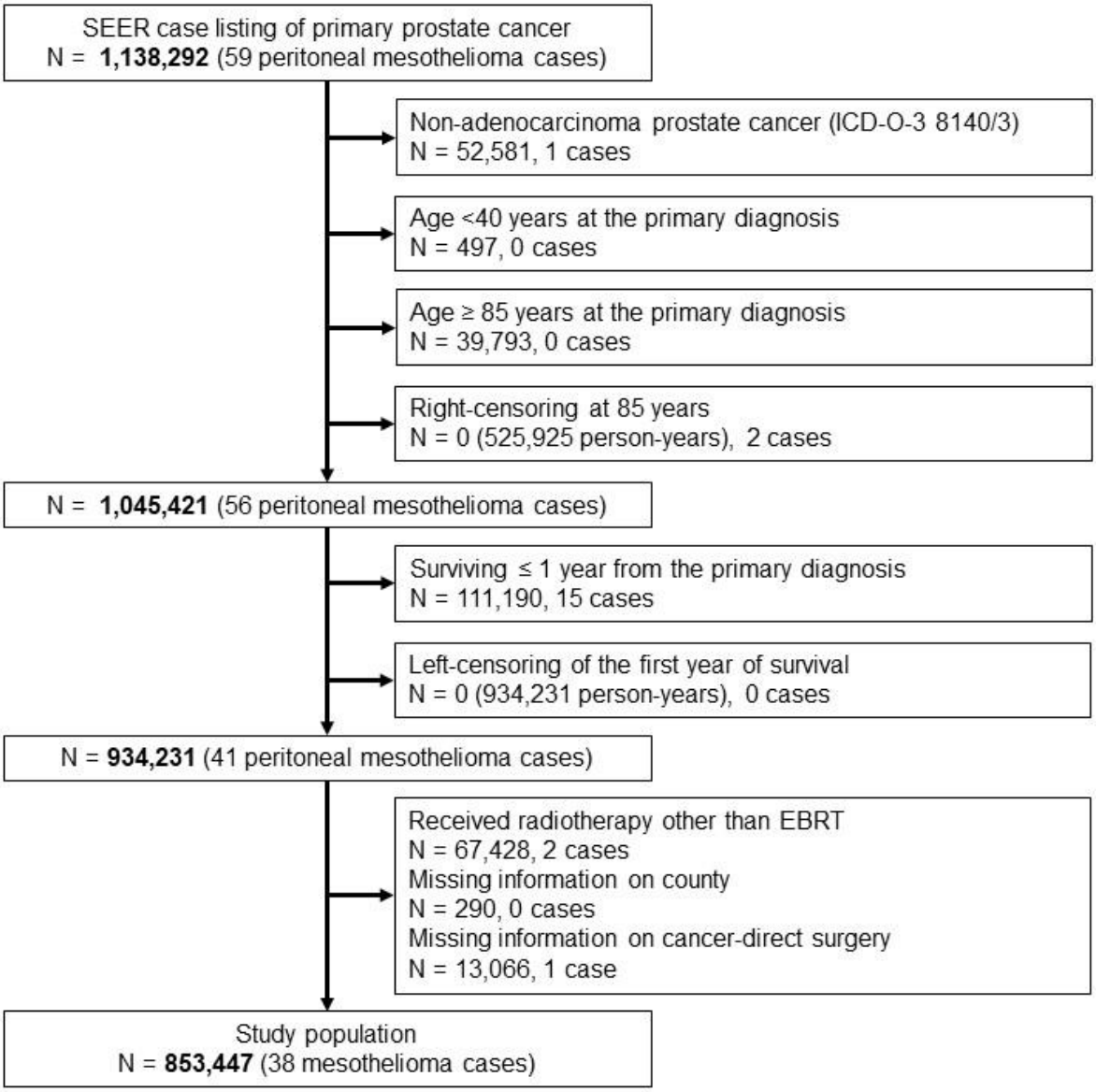

TABELLA 1. Caratteristiche della popolazione in studio alla diagnosi di adenocarcinoma prostatico primario.

	External beam radiotherapy				
	No (N= 589,442)		Yes (N=264,005)		P value
Age (years), median (IQR)	66	(59−72)	69	(63−74)	<0.001[a]
Race					
White, n (%)	470,309	(69.5)	206,030	(30.5)	
Black, n (%)	78,798	(65.8)	41,037	(34.2)	
Other/unknown	40,335	(70.4)	16,938	(29.6)	<0.001[b]
Year of diagnosis, median (IQR)	2004	(1997−2009)	2004	(1998−2009)	<0.001[a]
Cancer-direct surgery					
No, n (%)	213,742	(48.9)	223,063	(51.1)	
Yes, n (%)	375,700	(90.2)	40,942	(9.8)	<0.001[b]
County's mesothelioma RR					
≤0.74, n (%)	105,665	(68.4)	48,739	(31.6)	
0.75−0.99, n (%)	262,711	(71.7)	103,795	(28.3)	
1.00−1.24, n (%)	154,139	(79.1)	79,090	(33.9)	
>1.25, n (%)	66,927	(67,4)	32,391	(32.6)	<0.001[b]
Peritoneal mesothelioma					
No, n (%)	589,421	(69.1)	263,988	(30.9)	
Yes, n (%)	21	(55.3)	17	(44.7)	0.066

Abbreviation: RR, relative risk.

[a] Mann-Whitney U test.

[b] Pearson's chi square test.

FIGURA 2. Stime di sopravvivenza di Nelson-Aalen. Incidenza del mesotelioma peritoneale per esposizione a radioterapia a fasci esterni e (A) per età o (B) per anni dalla diagnosi di cancro alla prostata (analisi limitata a pazienti con sopravvivenza di almeno un anno).

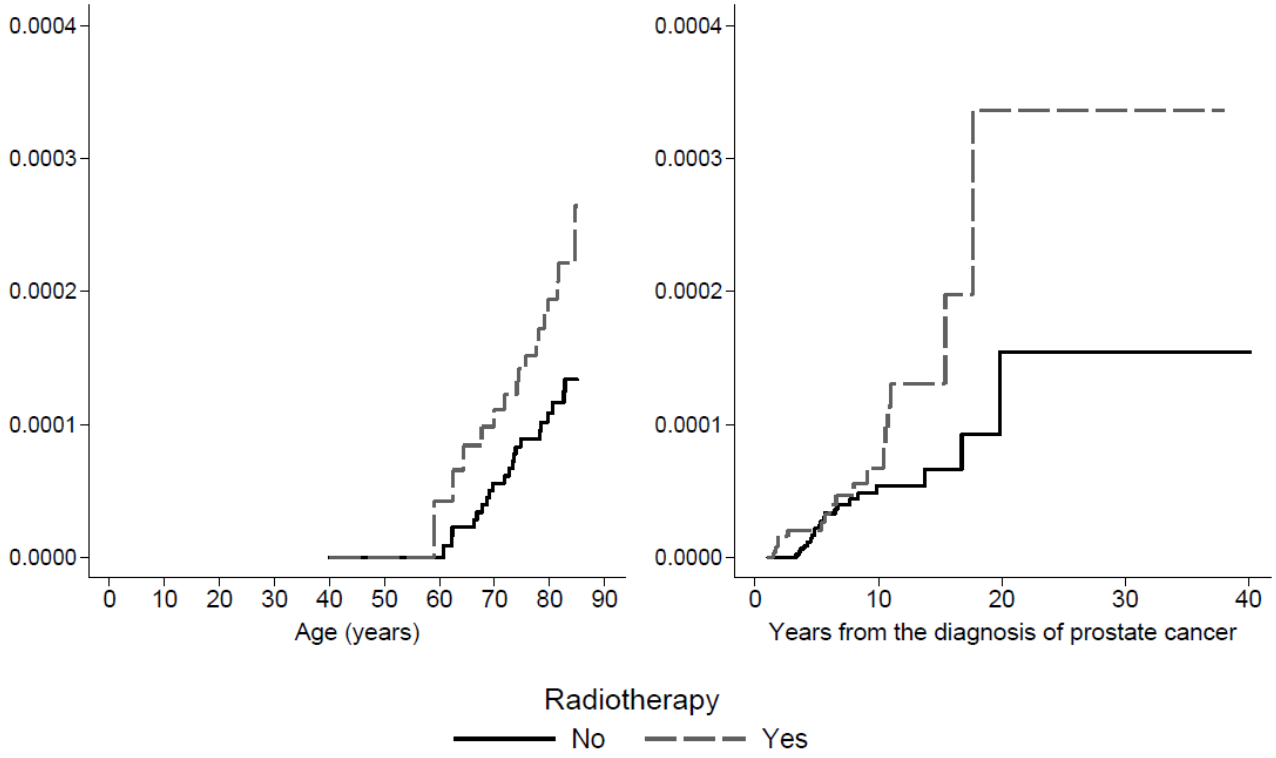

TABELLA 2. Associazione tra radioterapia a fasci esterni e rischio di mesotelioma peritoneale. Stime derivati da modelli di regressione di Cox.

All latency periods					
		Crude estimates		**Surgery adjusted estimates[a]**	
EBRT	**Events**	*HR*	*(95%CI)*	*HR*	*(95%CI)[b]*
No	21	1.00	Ref.	1.00	Ref.
Yes	17	1.72	(0.90−3.29)	2.22	(1.03−4.78)
Latency period between 1 and 5 years[b]					
		Crude estimates		**Surgery adjusted estimates[a]**	
EBRT	**Events**	*HR*	*(95%CI)*	*HR*	*(95%CI)[b]*
No	9	1.00	Ref.	1.00	Ref.
Yes	5	1.11	(0.37−3.34)	1.38	(0.43−4.42)
Latency period of more than 5 years[b]					
		Crude estimates		**Surgery adjusted estimates[a]**	
EBRT	**Events**	*HR*	*(95%CI)*	*HR*	*(95%CI)[b]*
No	12	1.00	Ref.	1.00	Ref.
Yes	12	2.30	(1.03−5.15)	2.92	(1.17–7.27)

Abbreviations: CI, confidence interval; EBRT, external beam radiotherapy; HR, hazard ratio; Ref., reference category.

[a] Estimates adjusted by cancer direct surgery for prostate cancer.

[b] Estimates from regression models including an interaction term between latency and exposure to external beam radiotherapy.

FIGURA 3. Rapporti di incidenza standardizzati (SIR) del mesotelioma primario tra i maschi di età compresa tra 20 e 84 anni. Registri SEER 18 (escluso registro nativi dell'Alaska), 2000-2015.

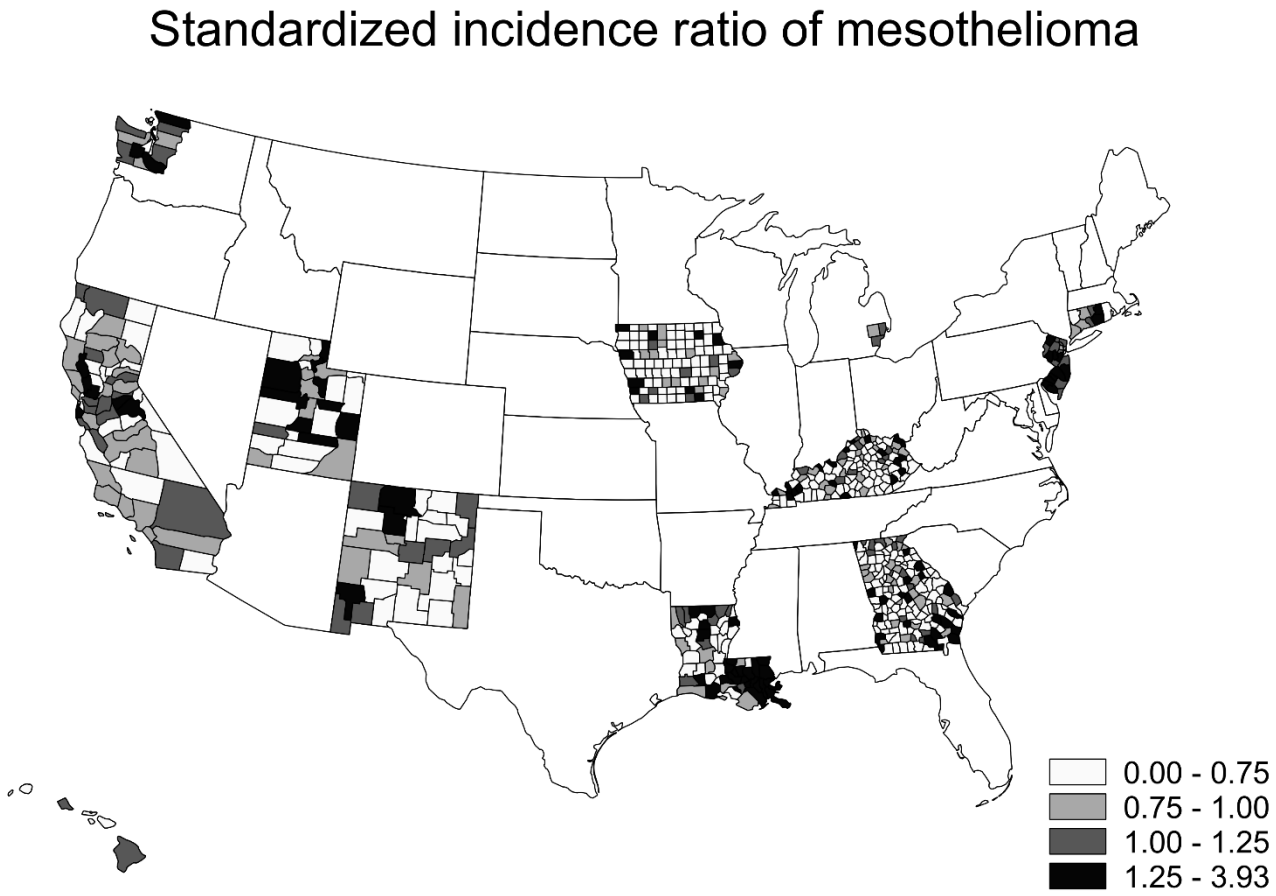

FIGURA 4. Rischio relativo (RR) di mesotelioma primario in soggetti di sesso maschile di età compresa tra 20 e 84 anni stimato con modelli Besag - York - Mollie. Registri SEER 18 (escluso registro nativi dell'Alaska), 2000-2015.

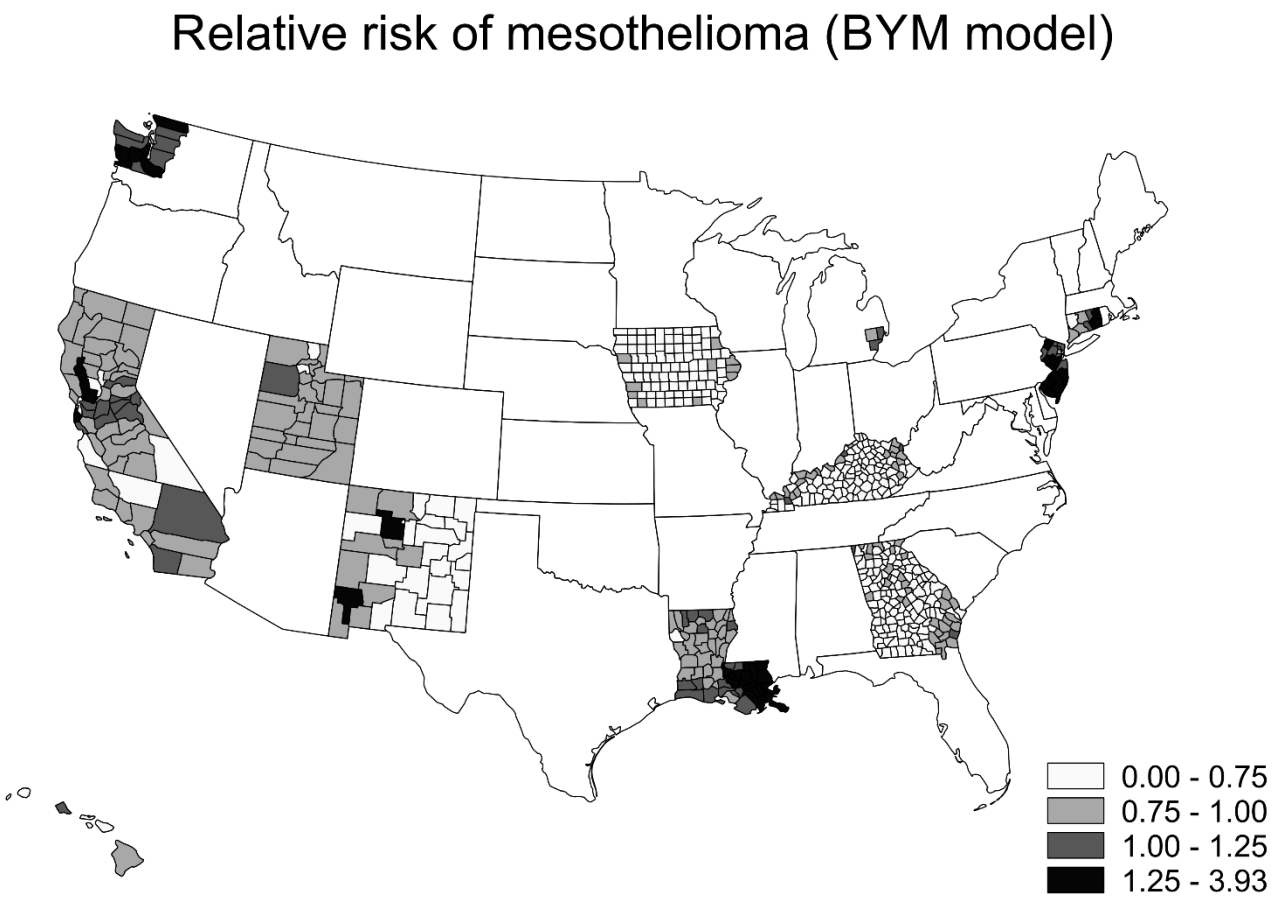

TABELLA 3. Modifica della stima per l'effetto della radioterapia a fasci esterni indotta dall'aggiustamento per potenziali covariate (una per una).

Covariate	**HR**	**(95% CI)**	**Δ% β coefficient[a]**
Crude	1.72	(0.903.29)	
Adjusted by age at the diagnosis of prostate cancer (years)	1.79	(0.94–3.44)	+7.4
Adjusted by race	1.77	(0.93–3.39)	+5.2
Adjusted by surgery	2.22	(1.03–4.78)	+46.8
Adjusted by year of diagnosis of prostate cancer	1.78	(0.93–3.39)	+5.7
Adjusted by county's mesothelioma RR	1.71	(0.90–3.27)[a]	-1.3

[a] $\Delta\% = (\beta_{adjusted}-\beta_{crude})/\beta_{crude}*100$

[b] Robust standard error

Capitolo 4. Mesotelioma Maligno e Radiazioni Ionizzanti: sintesi e confronto dei risultati

Come si è potuto evincere nei due capitoli precedenti, i risultati della revisione della letteratura sulla relazione tra radiazioni ionizzanti e mesotelioma e quelli dello studio sul rischio di mesotelioma peritoneale in pazienti sottoposti a EBRT sono sostanzialmente coerenti relativamente al rischio correlato alle radiazioni.

Essendo il mesotelioma maligno un tumore raro, il numero dei casi esaminati è sempre molto basso.

La revisione della letteratura e la successiva meta-analisi, presentate nel secondo capitolo, hanno dimostrato che l'esposizione a radiazioni ionizzanti può determinare un aumento del rischio di sviluppare mesotelioma.

Il rischio scaturito è pari a 1,51 con IC 95% compresi tra 1,05 e 1,98 nei pazienti trattati con EBRT e pari a 2,10 con IC 95% compresi tra 1,45 e 2,76 nei *nuclear workers*.

Il lavoro di analisi dei registri SEER mette in evidenza che il rischio di sviluppare mesotelioma peritoneale nei pazienti trattati con EBRT rispetto ai pazienti non trattati con radioterapia è pari 2,22 (IC 95% 1,03-4,78), indipendentemente dal periodo di latenza considerato, nonostante le due metodiche abbiamo dimostrato la stessa efficienza nel trattamento del tumore alla prostata localizzato.

Utilizzando approcci diversi per studiare lo stesso aspetto, questo lavoro di tesi ha messo in evidenza come vi sia un aumento del rischio determinato dall'esposizione a radiazioni ionizzanti. Tuttavia, come evidenziato nella revisione di Goodman del 2009, la rarità del mesotelioma e la sua non precisa classificazione pongono dei limiti importanti anche per gli studi epidemiologici.

A ciò si deve aggiungere che le scarse, se non assenti, informazioni circa la co-esposizione all'amianto non hanno permesso di correggere la stima per questa variabile. Sono state ricercate in maniera approfondita le informazioni riguardanti l'asbesto in tutti gli studi inclusi nella revisione, nella maggior parte dei casi queste risultava incomplete. Nei registri SEER mancava l'informazione circa l'anamnesi lavorativa. Come descritto precedentemente, questo aspetto è stato superato considerando l'esposizione ambientale ad asbesto, utilizzando una classificazione in base alla contea di residenza al momento della diagnosi di cancro alla prostata. Ma l'informazione così applicata a ciascun caso è di tipo ecologico e di conseguenza non permette ulteriori riflessioni.

Un punto di forza degli studi esaminati è rappresentato, come evidenziato nel secondo capitolo, dall'eterogeneità geografica delle coorti che mette in evidenza come tale ipotesi non risenta di particolari caratteristiche di popolazione o di territorio.
L'aver comunque osservato, nel capitolo 3, questo numero di mesoteliomi potrebbe valorizzare l'idea che l'esposizione a radiazioni ionizzanti rappresenta un'azione di "facilitazione" allo sviluppo del mesotelioma facendolo manifestare con periodi di latenza più brevi.
Se in futuro si provasse un'interazione più che additiva tra radiazioni ionizzanti ed esposizione ad amianto nel determinare il rischio di mesotelioma, l'EBRT potrebbe diventare un'opzione terapeutica di seconda scelta per il trattamento del tumore prostatico localizzato tra i pazienti la cui storia lavorativa di esposizione ad asbesto è ben nota. Considerando le stime ottenute, i casi clinici e la modalità d'azione plausibile, si può concludere che le prove supportano un probabile nesso causale tra l'esposizione alle radiazioni ionizzanti e il rischio di mesotelioma, ma non siamo in grado di capire qual è il peso degli altri elementi confondenti (asbesto, altri cancerogeni, etc.).
Nonostante il basso numero di mesoteliomi nella popolazione generale, il rischio costantemente aumentato tra individui esposti alle radiazioni è comunque da prendere in considerazione.
Futuri spunti di ricerca potranno essere caratterizzati da studi più dettagliati sulla co-esposizione asbesto - radiazioni ionizzanti. A ciò si dovrebbe aggiungere una maggiore dettaglio sul *coding* del mesotelioma, con una precisa (e attualmente disponibile) classificazione della patologia.
Una valutazione ulteriore potrebbe esser fatta analizzando le banche dati *Comprehensive Epidemiologic Data Resource* (CEDR) che includono le informazioni raccolte in 76 studi epidemiologici sugli effetti delle radiazioni ionizzanti nei *nuclear workers*. Sarebbe interessante effettuare un'analisi longitudinale della mortalità per mesotelioma in questo gruppo di coorti storiche di lavoratori radioesposti costituito da più di un milione di *nuclear workers*. Questo potrebbe essere lo spunto di studio per un'attività di ricerca ed una sfida futura poiché il dataset da analizzare è molto complesso ed eterogeneo tenuto conto della varietà di fonti di dati.

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Multisite musculoskeletal pain in migrants from the Indian subcontinent to the UK: a cross-sectional survey

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Abstract

Background: Recent findings indicate that wide international variation in the prevalence of disabling regional musculoskeletal pain among working populations is driven by unidentified factors predisposing to pain at multiple anatomical sites. As a step towards identification of those factors, it would be helpful to know whether the prevalence of multisite pain changes when people migrate between countries with differing rates of symptoms; and if so, whether the change is apparent in first generation migrants, and by what age it becomes manifest.

Methods: To address these questions, we analysed data from an earlier interview-based cross-sectional survey, which assessed the prevalence of musculoskeletal pain and risk factors in six groups of workers distinguished by the nature of their work (non-manual or manual) and their country of residence and ethnicity (UK white, UK of Indian subcontinental origin and Indian in India). Prevalence odds ratios (ORs) with 95% confidence intervals (CIs) were estimated by logistic regression.

Results: Among 814 participants (response rate 95.4%), 20.6% reported pain at ≥3 anatomical sites. This outcome was much less frequent in Indian manual workers than among white non-manual workers in the UK (adjusted OR 0.06, 95%CI 0.01–0.36), while rates in Indian non-manual workers were intermediate (OR 0.29, 95%CI 0.12–0.72). However, within the UK, there were only small differences between white non-manual workers and the other occupational groups, including those of Indian sub-continental origin. This applied even when analysis was restricted to participants aged 17 to 34 years, and when second and later generation migrants were excluded.

Conclusions: The observed differences in the prevalence of multisite pain seem too large to be explained by healthy worker selection or errors in recall, and there was no indication of bias from differences in understanding of the term, pain. Our findings suggest that whatever drives the higher prevalence of musculoskeletal pain in the UK than India is environmental rather than genetic, affects multiple anatomical sites, begins to act by fairly early in adult life, and has impact soon after people move from India to the UK.

Keywords: Multisite pain, Migrant, India, UK, Worker, Risk factor

Background

Regional musculoskeletal pain, especially in the low back, neck and upper limb, is a major cause of morbidity and disability in adults of working age [1]. However, its prevalence varies substantially between countries, even among people with similar jobs [2]. Data from a longitudinal investigation in 18 countries (the CUPID study) indicate that this variation is not explained by known mechanical and psychosocial risk factors, and appears to be driven more by other, unidentified causes which predispose to pain at multiple anatomical sites [3, 4]. Across 45 occupational groups that were studied in the CUPID investigation, the prevalence of disabling low back pain at follow-up correlated with the mean number of sites other than the low back that had been painful in the 12 months before baseline (correlation coefficient = 0.58) [3]. For disabling pain in the wrist/hand, the

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pattern was similar, but with an even higher correlation coefficient (0.86) [4].

These findings suggest that much of the global burden of musculoskeletal pain and disability will be impervious to interventions aimed at risk factors specific to only one or two anatomical sites (e.g. heavy lifting, forceful repetitive arm movements), and that greater scope for prevention may lie in understanding what drives propensity to pain across multiple body regions, and its variation between countries. As a first step towards the identification and characterisation of underlying causes, it would be helpful to know: a) whether the prevalence of multisite pain changes when people migrate between countries with differing rates of symptoms (which would indicate that the determinants are environmental rather than genetic); and if so, b) whether the change is apparent in first generation migrants (which would imply that the drivers act soon after migration and do not depend on a long period of acculturation); and c) by what age it becomes manifest (if the change is apparent at young ages, then its causes must operate relatively early in life).

To address these three questions, we analysed data from an earlier cross-sectional survey, which assessed the prevalence of musculoskeletal pain across five anatomical sites in samples of workers from the UK and India, including some UK workers whose families came originally from the Indian subcontinent [5]. That study had already shown that rates of pain in the back, neck and arm were much lower in Indian manual workers than among manual and non-manual workers in the UK, and that office workers in India had lower rates of pain in the wrist and hand than office workers in the UK. However, it had not examined the occurrence of pain at multiple anatomical sites in the same individuals.

Methods

The methods of data collection have been reported previously [5]. The survey focused on six groups of workers - defined by the nature of their work (non-manual or manual) and their country of residence and ethnicity (UK white, UK of Indian subcontinental origin and Indian in India). In the UK, all workers were employed by Royal Mail, either in offices (non-manual) or sorting mail by hand (manual). The non-manual workers in India were recruited from offices, including at a call centre and software house, while the Indian manual workers were employed on production lines in engineering and in the manufacture of soap and pharmaceuticals.

In each place of work, employees in relevant jobs were identified by their managers, and invited to take part in the study. Those who agreed were interviewed using a structured questionnaire, which was originally drafted in English and then translated into Marathi (with checks for accuracy by independent back-translation). The translated version was used for a subset of the Indian manual workers who preferred to be interviewed in their local language. Among other things, the questionnaire asked about demographic characteristics, mental health, occupational physical activities, psychosocial aspects of work (incentives, time pressures, support from colleagues and choice), and the occurrence in the past year of pain (lasting at least a day) at each of five anatomical sites (low back, neck, shoulder(s), elbow(s) and wrist/hand(s)).

The items about mental health were derived from the SF-36 questionnaire (with exclusion of one question that could not be translated satisfactorily) [6], and scores were graded to three levels (good, intermediate or poor) corresponding to approximate thirds of the overall distribution of scores in all subjects (i.e. with cut-points at approximate tertiles).

Physical exposures at work were ascertained by asking whether an average working day involved certain specified activities (listed in Table 1).

Regarding psychosocial aspects of work, participants were classed as being exposed to incentives if they indicated that an average working day involved either "piecework in which you are paid according to the number of articles or tasks you or your team make or finish in the day" or "payment of a bonus if you make or finish more than an agreed number of articles/tasks in the day". Work under time pressure was defined by report that an average working day entailed "working under pressure to complete tasks by a fixed time". Participants were deemed to receive support at work if they responded that when they had difficulties with their work, they received help and support (often or sometimes) from at least one of their colleagues, immediate superior or a trade union representative. And choice at work was defined by responses that there was often or sometimes choice in any of: "deciding how you do your work"; "deciding what you do at work"; or "deciding your work timetable or breaks".

The questions on musculoskeletal symptoms were adapted from the modified Nordic questionnaire on musculoskeletal complaints [7], and used diagrams to illustrate the relevant parts of the body.

Participants in the UK were also asked how they would best describe their ethnic origin (White; Bangladeshi; Indian; Pakistani; Black African/Caribbean; Chinese; or other), and if non-white British, whether they were first generation, second generation, or third or more generation. Those who described themselves as Bangladeshi, Indian or Pakistani were classed as being of Indian subcontinental origin.

Full copies of the questionnaires that were used to collect data in India and the UK can be found as Additional files 1 and 2.

Statistical analysis was carried out with Stata v.12.1 software (Stata Corp LP 2012, Stata Statistical Software:

Table 1 Characteristics of participants by study group

Characteristic	UK white		UK of Indian subcontinental origin		India	
	Non-manual (*n* = 172)	Manual (*n* = 159)	Non-manual (*n* = 67)	Manual (*n* = 73)	Non-manual (*n* = 165)	Manual (*n* = 178)
Age (years)						
17–24	34 (20%)	13 (8%)	20 (30%)	19 (26%)	70 (42%)	5 (3%)
24–34	37 (22%)	42 (26%)	34 (51%)	21 (29%)	75 (45%)	23 (13%)
35–44	44 (26%)	51 (32%)	7 (10%)	24 (33%)	19 (12%)	46 (26%)
45–63	57 (33%)	53 (33%)	6 (9%)	9 (12%)	1 (1%)	104 (58%)
Sex						
Male	93 (54%)	82 (52%)	53 (79%)	45 (62%)	118 (72%)	177 (99%)
Female	79 (46%)	77 (48%)	14 (21%)	28 (38%)	47 (28%)	1 (1%)
Mental health						
Good	48 (28%)	28 (18%)	15 (22%)	18 (25%)	50 (30%)	85 (48%)
Intermediate	57 (33%)	58 (36%)	27 (40%)	18 (25%)	56 (34%)	68 (38%)
Poor	67 (39%)	73 (46%)	25 (37%)	37 (51%)	59 (36%)	25 (14%)
Occupational activities in an average working day						
Use keyboard ≥4 h	137 (80%)	4 (3%)	44 (66%)	0 (0%)	163 (99%)	3 (2%)
Other repeated movements of wrist/hand ≥4 h	4 (2%)	147 (92%)	0 (0%)	69 (95%)	23 (14%)	171 (96%)
Repeated bending/straightening of elbow for > 1 h in total	81 (47%)	140 (88%)	40 (60%)	68 (93%)	88 (53%)	163 (92%)
Work with hand above shoulder height > 1 h in total	2 (1%)	60 (38%)	1 (1%)	27 (37%)	8 (5%)	68 (38%)
Work with neck twisted > 30 min in total	19 (11%)	67 (42%)	11 (16%)	31 (42%)	40 (24%)	82 (46%)
Lifting ≥5 kg one-handed	5 (3%)	53 (33%)	4 (6%)	30 (41%)	8 (5%)	136 (76%)
Psychosocial aspects of work						
Incentives	103 (60%)	8 (5%)	50 (75%)	5 (7%)	16 (10%)	4 (2%)
Time pressure	69 (40%)	118 (74%)	23 (34%)	54 (74%)	129 (78%)	170 (96%)
Support	166 (97%)	157 (99%)	65 (97%)	72 (99%)	162 (98%)	175 (98%)
Choice	89 (52%)	112 (70%)	27 (40%)	53 (73%)	145 (88%)	32 (18%)

Release 12.1, College Station TX, USA). We first summarised patterns of pain in the sample as a whole. Next, we compared the crude one-year prevalence of pain at different numbers of anatomical sites across the six occupational groups. We then used logistic regression to adjust the comparisons for sex, age, and other potential confounders, results being summarised by odds ratios (ORs) with 95% confidence intervals (CIs). In addition, we performed subsidiary analyses: a) restricted to participants aged < 35 years, and b) focusing on the subsets of UK workers who were first generation migrants from the Indian subcontinent. In most of the logistic regression analyses, we took UK white non-manual workers as the reference, since they provided a good representation of potentially confounding covariates. However, we also made several direct, pairwise, comparisons between other groups, in each case taking as our reference the group that had the better representation of covariates.

Ethical approval for data collection in the UK was provided by the Health and Safety Executive Research Ethics Committee. In India, the protocol for data collection was approved by the chairman of the ethics committee at the PD Hinduja National Hospital and Medical Research Centre, Mumbai, who judged that it did not need to be reviewed by the full committee.

Results

Interviews were completed by 855 (95.4%) of the 896 workers who were invited to take part in the study, but 41 from the UK were excluded from the current analysis because they were neither white nor of Indian subcontinental origin. Table 1 summarises the distribution of the remaining 814 participants according to occupational group, demographic variables, and various potential risk factors for musculoskeletal pain. All but one of the 178 Indian manual workers were men, and they tended to be older than participants in the other occupational groups. In contrast, the non-white, non-manual workers, both in India and the UK were relatively young. As expected, prolonged use of keyboards was more frequent among the non-manual workers in both countries, while manual workers were more exposed to other

sources of mechanical loading. Among the UK participants of Indian subcontinental origin, 18 (25%) of 73 manual workers and 41 (61%) of 67 non-manual workers were first generation migrants.

Table 2 shows the one-year prevalence of pain at each anatomical site in the study sample as a whole, and the frequency with which pain was reported at different numbers of sites. The highest prevalence of pain was in the low back (40.5%) followed by the neck (30.6%). Moreover, multi-site pain was common, 20.6% of participants reporting pain at ≥3 sites.

Figure 1A) illustrates the crude prevalence of pain at multiple anatomical sites in each of the six occupational groups. Multisite pain was consistently least frequent among Indian manual workers, intermediate in Indian non-manual workers, and highest in the four occupational groups from the UK. A similar pattern was observed when analysis was restricted to participants aged 17–34 years (Fig. 1B)).

Table 3 summarises the risk of pain at different numbers of anatomical sites by occupational group, firstly after adjustment for sex and age, and then with adjustment also for the other potential risk factors listed in Table 1. For each outcome, odds ratios are relative to no pain at any site. Multisite pain was confirmed as being substantially less frequent in Indian manual workers than among white non-manual workers in the UK (fully adjusted OR for pain at ≥3 sites 0.06, 95%CI 0.01–0.36), while rates in Indian non-manual workers were intermediate, the corresponding OR being 0.29 (95%CI 0.12–0.72). Within the UK, however, there were only small and non-significant differences between white non-manual workers and the other three occupational groups, including those of Indian sub-continental origin. In direct, fully adjusted comparisons, the risk of pain at ≥3 sites in Indian manual workers was significantly lower than that among UK workers of Indian subcontinental origin, in both manual (OR 0.04, 95%CI 0.01–0.015) and non-manual (OR 0.06, 95%CI 0.01–0.39) jobs.

Table 2 One-year prevalence of pain by anatomical site and frequency with which participants reported pain at different numbers of sites

Location of pain	Number (%) of participants	
Low back	330	(40.5)
Neck	249	(30.6)
Shoulder(s)	211	(25.9)
Elbow(s)	87	(10.7)
Wrist/hand(s)	229	(28.1)
Number of anatomical sites with pain		
0	280	(34.4)
1	214	(26.3)
2	152	(18.7)
3	104	(12.8)
4	44	(5.4)
5	20	(2.5)

This pattern was maintained when analysis was restricted to younger participants (aged 17 to 34 years), with fully adjusted ORs for pain at ≥3 sites of 0.02 (95%CI 0.001–0.35), 1.15 (95%CI 0.39–3.43) and 0.44 (95%CI 0.05–3.81) respectively in Indian manual workers, UK non-manual workers of Indian subcontinental origin and UK manual workers of Indian subcontinental origin, as compared with white non-manual workers in the UK. In direct comparisons restricted to this younger age group, the risk in Indian manual workers was significantly lower than that both in UK non-manual workers of Indian subcontinental origin (fully adjusted OR 0.01, 95%CI 0.001–0.29) and in UK manual workers of Indian subcontinental origin (OR 0.04, 95%CI 0.003–0.42).

Furthermore, the similarity of risk in UK workers of Indian subcontinental origin to that in white UK workers was still apparent when second and later generation migrants were excluded (ORs for pain at ≥3 sites relative to UK white non-manual workers 1.80, 95%CI 0.27–11.96 for first generation migrants in manual work and 0.80, 95%CI 0.28–2.31 for first generation migrants in non-manual work). In direct comparisons, the risk of pain at ≥3 sites in Indian manual workers was significantly lower than that of first generation migrant workers in the UK, both in manual (fully adjusted OR 0.04, 95%CI 0.01–0.23) and non-manual jobs (fully adjusted OR 0.09, 95%CI 0.01–0.65).

Discussion

Our analysis indicates that in the working populations studied, multisite musculoskeletal pain was substantially more common in the UK than in India. However, among workers in the UK of Indian sub-continental origin, including first generation migrants and those aged < 35 years, rates of pain were close to those of their white colleagues. These results suggest that whatever drives the much higher prevalence of musculoskeletal pain in the UK than India is environmental rather than genetic, affects multiple anatomical sites, begins to act by early in adult life, and has impact fairly soon after people move from India to the UK.

Our study benefited from a high response rate among those eligible to take part. Moreover occupational exposure to physical activities was (by design) much the same among the three groups of manual workers, and rather lower among the three groups of non-manual workers [5]. Differences in the physical demands of work are therefore unlikely to explain the lower prevalence of pain in Indian manual workers.

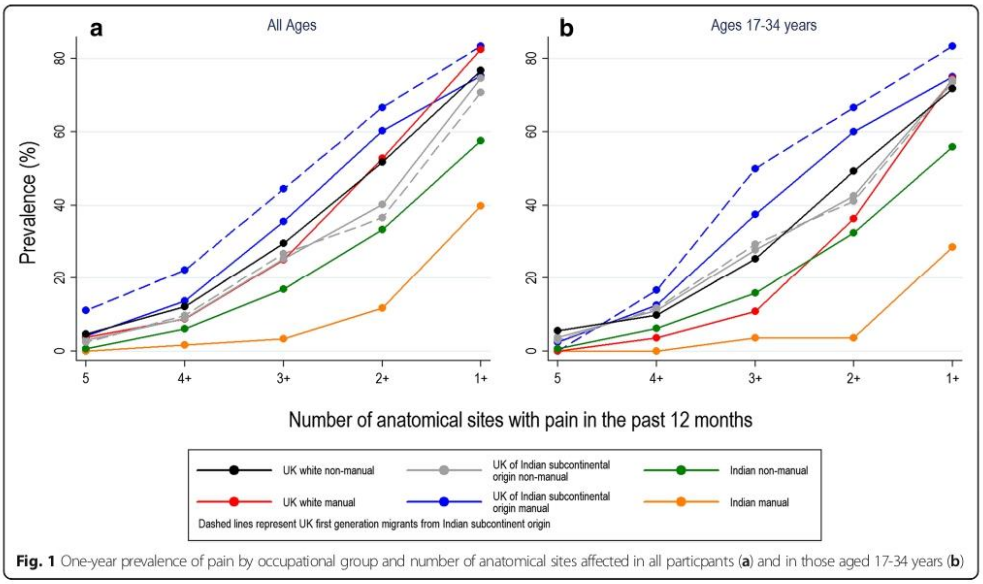

Fig. 1 One-year prevalence of pain by occupational group and number of anatomical sites affected in all particpants (**a**) and in those aged 17-34 years (**b**)

It is possible that some workers with disabling musculoskeletal pain were excluded from the sampling frame because they were absent from work at the time of the survey or had been forced to leave their jobs, and that this healthy worker selection was stronger in India than in the UK. However, we think it is unlikely that any resultant bias could explain such large differences in pain prevalence as were observed. For that to occur, well over half of all men taken on to work in the Indian manual jobs would have to leave their jobs because of musculoskeletal pain.

An earlier report, based on the same study, described the prevalence of pain in the past month at specific anatomical sites [5]. However, in the current analysis, we focused on the one-year prevalence of symptoms since it was expected to provide a more sensitive measure of general propensity to pain, and for that reason had been used previously in the CUPID study [3, 4]. For this purpose it did not matter whether the pain at different anatomical sites had occurred simultaneously – only the number of sites that had been affected at some time during the period of interest. Recall of

Table 3 Risk of pain in past year by occupational group according to number of anatomical sites affected

Occupational group	Number of anatomical sites with pain									
	0	≥1			≥2			≥3		
	n	N	[a]OR	(95% CI)	n	[a]OR	(95% CI)	N	[a]OR	(95% CI)
UK white – non-manual	40	132	1		89	1		51	1	
UK white – manual	28	131	[b]1.31	(0.75,2.28)	84	[b]1.24	(0.68,2.24)	40	[b]1.09	(0.56,2.11)
			[c]1.70	(0.62,4.66)		[c]1.63	(0.51,5.17)		[c]1.28	(0.30,5.42)
UK of Indian subcontinental origin – non-manual	17	50	[b]1.24	(0.63,2.45)	27	[b]1.10	(0.52,2.33)	17	[b]1.18	(0.51,2.75)
			[c]1.08	(0.52,2.23)		[c]0.90	(0.39,2.06)		[c]1.02	(0.40,2.63)
UK of Indian subcontinental origin – manual	18	55	[b]1.10	(0.57,2.11)	44	[b]1.34	(0.68,2.67)	26	[b]1.36	(0.64,2.92)
			[c]1.31	(0.44,3.93)		[c]1.70	(0.49,5.90)		[c]1.48	(0.33,6.75)
Indian – non-manual	70	95	[b]0.59	(0.36,0.98)	55	[b]0.54	(0.31,0.95)	28	[b]0.49	(0.25,0.94)
			[c]0.40	(0.21,0.77)		[c]0.37	(0.17,0.79)		[c]0.29	(0.12,0.72)
Indian – manual	107	71	[b]0.20	(0.12,0.33)	21	[b]0.09	(0.04,0.17)	6	[b]0.05	(0.02,0.12)
			[c]0.28	(0.10,0.83)		[c]0.14	(0.04,0.52)		[c]0.06	(0.01,0.36)

[a]Odds ratio (95% confidence interval) relative to no pain at any anatomical site. [b]Adjusted for sex and age. [c]Adjusted for all of the variables in Table 1

pain over the longer period may not have been as accurate as that for the past month. However, we know from the earlier analysis that in comparison with participants in the UK, the Indian workers, and especially those in manual jobs, also had a lower one-month prevalence of pain in both the low back and arm [5]. It therefore seems unlikely that the differences we observed in the one-year prevalence of multisite pain can be attributed to errors in recall.

Ideally, as in the CUPID study, our assessment of the extent of pain would have distinguished between upper limb pain affecting the right and left sides of the body. However, the questionnaire that had been used when interviewing workers in India had not asked about the laterality of pain in the elbow and wrist/hand, and therefore it could not be done.

Another possible source of bias was differences in understanding of the term, pain, especially when the questionnaire was translated into Marathi. However, among the Indian manual workers, the prevalence of pain was much the same, whether interviews were in Marathi or English (data available on request).

In the logistic regression analyses for Table 3, we took UK white, non-manual workers as our reference since they provided reasonable representation across the distribution of covariates. However, we did also make direct pairwise comparisons between other groups of workers. Importantly, the risk of pain at ≥3 sites among Indian manual workers was significantly lower, not only than that in the main reference group, but also than that in UK manual and non-manual workers of Indian subcontinental origin. The subsidiary analyses for younger workers and those who were first generation migrants to the UK included fewer participants, and were therefore subject to greater statistical uncertainty. Nevertheless, again with pain at ≥3 sites as the outcome, the risk for Indinan manual workers was significantly lower than that in UK manual and non-manual workers who were first generation migrants from the Indian subcontinent. And among participants aged < 35 years, risk among Indian manual workers was significantly lower than for UK manual and non-manual workers of Indian subcontinental origin.

The levels of pain prevalence that we found in our study cannot be compared directly with those in other surveys that have been based in the general population rather than workers in employment, covered different age ranges, and used different outcome measures (e.g. chronic widespread pain). However, our finding that rates of pain were lower in India than in the UK is consistent with the CUPID study, in which prevalence was lower in Pakistan and Sri Lanka than in the UK [2–4]. Moreover, as in the CUPID investigation, the differences applied to musculoskeletal pain in general and were not limited to just one or two anatomical sites. It is striking, however, that rates of pain among UK workers of Indian subcontinental origin were close to those of their white colleagues. Furthermore, this appeared to apply also to the subset of first generation migrants, and when analysis was restricted to younger ages (< 35 years).

We have been unable to identify any other studies that used standardised methods to compare the prevalence of musculoskeletal pain in migrant populations with those both in their country or region of origin and in the country to which they had moved. However, a survey in the North-West of England found that pain in the past month lasting > 1 week was slightly more common among migrants from South Asia than in the local white population, while "pain in most joints" lasting > 1 week in the past month was substantially more frequent [8]. A second study, which recruited also in the West Midlands, similarly found a higher prevalence of widespread pain ("all over the body in the past month") in South Asian ethnic groups than in white Europeans [9]. And in a more recent survey carried out in the Tower Hamlets district of London, the prevalence of chronic widespread pain (in two contralateral quadrants of the body and also the axial skeleton and present for at least three months) was greater among people of Bangladeshi origin than in white British/Irish participants [10]. While these investigations differed from ours in the pain outcomes that were examined and the demographics of the populations studied, they support the view that rates of pain in South Asian migrants to the UK are at least as high as in the indigenous white population.

The pattern of results in our study implies that the drivers of the large differences in musculoskeletal pain between workers in India and the UK are environmental, and predispose to pain at multiple anatomical sites. It suggests, moreover, that they act early in the lifecourse, and begin to affect migrants fairly soon after they move from India to the UK. Beyond this, our data do not indicate what the drivers might be, but one possibility is that awareness of musculoskeletal pain and responses to it are importantly influenced by a person's social environment, in the same way that a number of other illnesses appear to be culturally determined [11]. If so, rates of musculoskeletal pain would be expected to decline when people migrate from countries with high prevalence (e.g. in South and Central America) to places where it is less frequent (e.g. in Europe) – a hypothesis that would be worth testing in future research.

Conclusions

Whatever drives the much higher prevalence of musculoskeletal pain in the UK than the Indian subcontinent is environmental rather than genetic, affects multiple anatomical sites, and appears to act by early in adult life, with impact fairly soon after people move from the subcontinent to the UK.

Additional files

Additional file 1: India Questionnaire. **Description of data:** Copy of questionnaire used to collect data in India (DOCX 307 kb)

Additional file 2: UK Questionnaire. **Description of data:** Copy of questionnaire used to collect data in UK (DOCX 336 kb)

Abbreviations
CI: confidence interval; CUPID: Cultural and psychosocial influences on disability; OR: odds ratio; SF-36: Short Form-36

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Availability of data and materials
The database used in this study is available from the corresponding author on reasonable request.

Authors' contributions
ER carried out the initial statistical analysis, and wrote the first draft of the manuscript. GN supervised the statistical analysis. IM organised and carried out the original data collection. DC oversaw all stages of the research. All authors contributed to revision and finalisation of the manuscript, and all read and approved its final version.

Ethics approval and consent to participate
Ethical approval for data collection in the UK was provided by the Health and Safety Executive Research Ethics Committee. In India, the protocol for data collection was approved by the chairman of the ethics committee at the PD Hinduja National Hospital and Medical Research Centre, Mumbai, who judged that it did not need to be reviewed by the full committee. No further approval was needed for the analysis presented in this report since it did not involve any new data collection, and it fell within the scope of the objectives of the original investigation (to compare the prevalence of musculoskeletal pain and associated disability in the occupational groups surveyed, and their association with risk factors). All participants provided informed consent, having been given a written information sheet about the study one week earlier. Consent in the UK was written, but in India, verbal consent was considered culturally more acceptable, and that was approved as part of the protocol.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References
1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the global burden of disease study 2013. Lancet. 2015;386:743–800. https://doi.org/10.1016/S0140-6736(15)60692-4.
2. Coggon D, Ntani G, Palmer KT, Felli VE, Harari R, Barrero LH, et al. Disabling musculoskeletal pain in working populations: is it the job, the person or the culture? Pain. 2013;154:856–63. https://doi.org/10.1016/j.pain.2013.02.008.
3. Coggon D, Ntani G, Palmer KT, Felli VE, Harari F, Quintana LA, et al. Drivers of international variation in prevalence of low back pain: findings from the Cultural and Psychosocial Influences on Disability study. Eur J Pain. 2019;23:35–45.
4. Coggon D, Ntani G, Walker-Bone K, Felli VE, Harari F, Barrero LH, et al. Determinants of international variation in the prevalence of disabling wrist and hand pain: Submitted for publication. https://doi.org/10.1007/s10728-018-0362-1.
5. Madan I, Reading I, Palmer KT, Coggon D. Cultural differences in musculoskeletal symptoms and disability. Int J Epidemiol. 2008;37:1181–9. https://doi.org/10.1093/ije/dyn085.
6. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Med Care. 1992;30:473–83. https://doi.org/10.1097/00005650-199206000-00002.
7. Kuorinka I, Jonsson B, Kilbom A, Vinterberg H, Biering-Sørensen F, Andersson G, et al. Standardised Nordic questionnaires for the analysis of musculoskeletal symptoms. Appl Ergon. 1987;18:233–7. https://doi.org/10.1016/0003-6870(87)90010-X.
8. Allison TR, Symmons DPM, Brammah T, Haynes P, Rogers A, Roxby M, et al. Musculoskeletal pain is more generalised among people from ethnic minorities than among white people in greater Manchester. Ann Rheum Dis. 2002;61:151–6.
9. Palmer B, Macfarlane G, Afzal C, Esmail A, Silman A, Lunt M. Acculturation and the prevalence of pain amongst south Asian minority ethnic groups in the UK. Rheumatol. 2007;46:1009–14. https://doi.org/10.1093/rheumatology/kem037.
10. Choudhury Y, Bremner SA, Ali A, Eldridge S, Griffiths CJ, Hussain I, et al. Prevalence and impact of chronic widespread pain in the Bangladeshi and white populations of Tower Hamlets, East London. Clin Rheumatol. 2013;32:1375–82. https://doi.org/10.1007/s10067-013-2286-3.
11. Malleson A. Whiplash and other useful illnesses. Montreal and Kingston: McGill-Queen's University Press; 2002.

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RESEARCH ARTICLE Open Access

Correlations between pain in the back and neck/upper limb in the European Working Conditions Survey

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Abstract

Background: Recent research has suggested that wide international variation in the prevalence of disabling regional pain among working populations is driven largely by factors predisposing to musculoskeletal pain in general and not specific to individual anatomical sites. We sought to confirm this finding, using data from an independent source.

Methods: Using data from the fifth (2010) and sixth (2015) European Working Conditions Surveys, we explored correlations between the one-year prevalence of pain in the back and neck/upper limb among people of working age across 33 European countries, and between changes in pain prevalence at the two anatomical sites from 2010 to 2015.

Results: Each survey recruited ≥1000 participants per country, response rates ranging from 11 to 78%. In 2010, the estimated one-year population prevalence of back pain ranged from 23% in Ireland to 66% in Portugal, and that of pain in the neck/upper limb from 25% in Ireland to 69% in Finland, the prevalence of pain at the two anatomical sites being correlated across the 33 countries ($r = 0.42$). A similar pattern was apparent in 2015. For back pain, the percentage change in prevalence from 2010 to 2015 varied from − 41.4% (Hungary) to + 29.6% (Ireland), with a mean across countries of − 3.0%. For neck/upper limb pain, the variation was from − 41.0% (Hungary) to + 44.1% (Romania), with an average of − 0.1%. There was a strong correlation across countries in the change in pain prevalence at the two anatomical sites ($r = 0.85$).

Conclusions: Our findings accord with the hypothesis that international variation in common pain complaints is importantly driven by factors that predispose to musculoskeletal pain in general.

Keywords: Low back pain, Upper limb pain, Prevalence, International variation

Background

The Cultural and Psychosocial Influences on Disability (CUPID) study has demonstrated wide international variation in the prevalence of disabling regional pain among working populations [1–3]. This appeared to be driven largely by unidentified causes that predispose to musculoskeletal pain in general rather than being specific to only one or two anatomical sites [2, 3]. Thus, across 45 occupational groups from 18 countries, the prevalence of disabling low back pain (LBP) correlated with the mean number of anatomical sites other than low back that had earlier been reported as painful [2]. And after allowance for occupation and potentially confounding psychosocial risk factors, individual risk of disability and sickness absence from LBP was predicted by the number of other anatomical sites which the person had previously reported as painful [2, 4]. Moreover, similar associations were apparent for pain in the wrist/hand [3].

If major international differences in disabling musculoskeletal pain are truly a consequence of factors promoting musculoskeletal pain in general, there could be important implications for preventive strategies. It would suggest a need to look beyond conventional ergonomic

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approaches, which tend to focus on localised mechanical loading of structures such as the spine or wrist/hand. Thus, it would be helpful to know whether correlations between the prevalence of pain in different bodily regions are apparent in other datasets covering multiple countries. The European Working Conditions Survey (EWCS) [5, 6] offered an opportunity to examine this for pain in the low back and neck/upper limb, and also to explore whether there were correlations across countries in the extent to which the prevalence of pain at these anatomical sites changed over time.

We therefore analysed data from two successive rounds of the European Working Conditions Survey (EWCS) [5, 6], aiming to assess: a) differences between countries in the prevalence of pain in the back and neck/upper limb at each of two time points; b) differences between countries in changes over time in the prevalence of back and neck/upper limb pain; and c) the extent to which prevalence rates and changes in prevalence for the two anatomical regions correlated across countries.

Methods

The EWCS is a periodic survey conducted by the European Foundation for the Improvement of Living and Working Conditions (Eurofound) to provide information about the occupational circumstances and health of employees and self-employed workers across Europe. Detailed descriptions of its design and methods have been published elsewhere [5, 6].

We used data from the fifth and sixth surveys, which were conducted during January to August 2010, and February to December 2015. In each survey, the target population was all residents of participating countries, who were aged 15 years or older (16 or older in Spain, the UK and Norway) and currently in employment. Those eligible to take part were sampled with stratification by geographical region and level of urbanisation, either from population or address registers, or by a random route method with a screening procedure to select the eligible respondent within each household. Information was collected through face-to-face interviews, using a standardised questionnaire, which had been drafted originally in English and then translated into local languages (with checks for accuracy by independent back-translation). The subject matter was wide-ranging, but included two questions on experience in the past year of pain in the back and neck/upper limb ("Over the last 12 months did you have any of the following health problems … C - backache … D - muscular pains in shoulders, neck and/or upper limbs (arms, elbows, wrists, hands etc.)?").

To render them more representative of the intended target population, prevalence estimates for each country had been corrected by Eurofound for differences in selection probabilities that were inherent in the sampling strategy, and also by post-stratification weighting for sex, age, region, occupation and sector of economic activity to allow for differences in willingness and ability to take part in the survey [7, 8].

Statistical analysis was carried out with Stata v.12.1 software (Stata Corp LP 2012, Stata Statistical Software: Release 12.1, College Station TX, USA). We focused on the 33 countries for which data were available from both surveys. Spearman rank correlation coefficients (r) were used to summarise correlations across countries between the prevalence of pain in the back and in the neck/upper limb, and between changes over time in the prevalence of pain at the two sites. The approximate statistical significance of correlation coefficients was determined based on reported total sample sizes by country, but without adjustment for the stratification that was applied in sampling and the use of post stratification weighting (on which we did not have sufficient data).

The data that we accessed from the EWCS surveys were retrospective anonymized summary statistics, and ethical approval was not therefore required.

Results

Each survey recruited at least 1000 individuals per country (Table 1). In 2010, interviews were completed by 42,798 participants, with an overall response rate of 44% (ranging from 31% in Spain to 74% in Latvia). In 2015, 41,811 participants answered the questionnaire, the response rate varying from 11% in Sweden to 78% in Albania, with an average across all countries of 43%.

In 2010, the one-year prevalence of back pain ranged from 23% in Ireland to 66% in Portugal, while that of pain in the neck/upper limb varied from 25% in Ireland to 69% in Finland (Table 1). Moreover, the prevalence of pain at the two anatomical sites was correlated across the 33 countries ($r = 0.42$, $p = 0.015$). A similar pattern was apparent in 2015. The prevalence of back pain ranged from 27% (Hungary) to 60% (France), and that of pain in the neck/upper limb from 30% (Hungary) to 69% (Finland), with a correlation coefficient of 0.56 ($p = 0.001$).

Figure 1 plots the percentage change in the one-year prevalence of neck/upper limb pain from 2010 to 2015 against that for back pain. For back pain, the percentage change varied from − 41.4% (Hungary) to + 29.6% (Ireland), with a mean across countries of − 3.0%. For neck/upper limb pain, the variation was from − 41.0% (Hungary) to + 44.1% (Romania), with an average of − 0.1%. Again, there was a strong correlation across countries ($r = 0.85$, $p < 0.001$).

Discussion

Our analysis shows moderate to strong correlations across 33 European countries between the prevalence of

Table 1 Response rates and prevalence of musculoskeletal pain by country and year of survey

Country	2010				2015			
	Number interviewed	Response rate (%)	One-year prevalence of pain (%)		Number interviewed	Response rate	One-year prevalence of pain (%)	
			Back	Neck-upper limb			Back	Neck-upper limb
Albania (AL)	1000	58	39	43	1002	78	31	39
Austria (AT)	1003	32	46	43	1028	47	47	44
Belgium (BE)	4001	34	44	40	2587	36	46	45
Bulgaria (BG)	1014	66	34	33	1064	64	38	41
Croatia (CR)	1100	43	49	46	1012	50	50	51
Cyprus (CY)	1000	66	46	45	1003	69	45	49
Czech Republic (CZ)	1000	47	55	44	1002	63	40	31
Denmark (DK)	1069	58	40	50	1002	26	45	58
Estonia (EE)	1000	56	56	61	1015	59	48	57
Finland (FI)	1028	47	50	69	1001	33	48	69
France (FR)	3046	34	53	50	1527	37	60	57
FYROM[a]	1100	68	45	49	1011	75	43	42
Germany (DE)	2133	56	51	43	2093	51	42	35
Greece (GR)	1037	40	43	39	1007	64	38	39
Hungary (HU)	1006	47	47	50	1023	58	27	30
Ireland (IE)	1003	50	23	25	1057	54	30	30
Italy (IT)	1500	34	51	48	1402	61	41	35
Latvia (LV)	1001	74	58	53	1004	62	51	46
Lithuania (LT)	1004	54	52	39	1004	62	51	40
Luxembourg (LU)	1000	40	43	42	1003	43	53	50
Malta (MT)	1000	52	45	37	1004	46	41	43
Montenegro (ME)	1041	59	49	46	1005	71	48	40
Netherlands (NL)	1017	37	36	43	1028	37	37	41
Norway (NO)	1085	32	41	53	1028	51	40	51
Poland (PL)	1500	44	46	40	1203	56	47	42
Portugal (PT)	1000	44	66	56	1037	55	42	39
Romania (RO)	1017	59	48	37	1063	55	57	53
Slovakia (SK)	1002	57	54	39	1000	65	50	36
Slovenia (SI)	1404	42	53	49	1607	47	48	42
Spain (ES)	1008	31	44	43	3364	32	46	45
Sweden (SE)	1004	35	39	52	1002	11	41	54
Turkey (TR)	2100	56	41	47	2000	36	46	49
United Kingdom (UK)	1575	37	34	33	1623	42	35	37
All countries	42,798	44	46	44	41,811	43	45	44

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reported pain in the back and neck/upper limb, and between changes over time in the prevalence of pain in the two anatomical regions. These findings are consistent with the hypothesis that international variation in common pain complaints is importantly driven by factors that predispose to musculoskeletal pain in general.

The investigation was based on more than 1000 participants per survey in each participating country, and the large differences in the prevalence of symptoms between countries (more than two-fold), and within countries over time (up to 40%), are unlikely to have occurred simply by chance. For example, in a sample of 1000, the 95% confidence interval around a prevalence of 40% would be 37 to 43%.

The average response rate to the surveys was less than 50%, and that in Sweden in 2015 was as low as 11%.

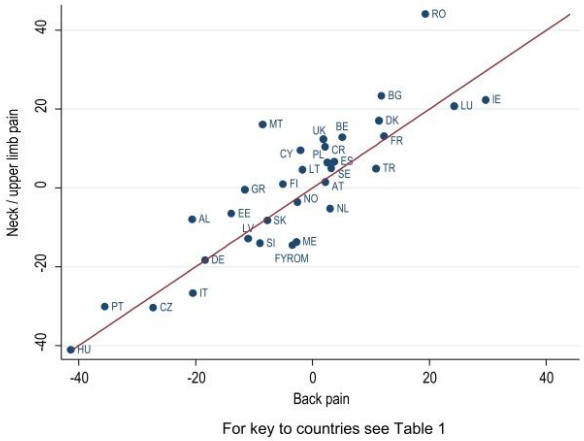

Fig. 1 Percentage change from 2010 to 2015 in one-year prevalence of back and neck/upper limb pain by country

Adjustments were made for differences in participation by sex, age, region, occupation and sector of economic activity. Moreover, the questions about pain were only a small component of a wide-ranging questionnaire. Nevertheless, it is possible that those who took part were unrepresentative in their experience of pain. There was no systematic difference in the prevalence of pain by response rate (overall correlation coefficients across all countries and both surveys = − 0.02, $p = 0.89$ for back pain and − 0.30 $p = 0.015$ for neck/upper limb pain), but for both anatomical regions, within-country changes in prevalence from 2010 to 2015 correlated with changes in response rate between the two surveys ($r = -0.42$, $p = 0.014$ for back pain and $r = -0.43$, $p = 0.013$ for neck/upper limb pain). Thus, while within-survey correlations in the prevalence of pain at the two anatomical sites are unlikely to have been influenced by differences in response rate, the correlation between changes over time in the prevalence of pain at the two sites may have been somewhat inflated.

Another possible source of bias might be differences in understanding of terms for pain when questionnaires were translated into local languages. However, that could not account for the changes in prevalence that were observed within countries over time, or for the strong correlation in such changes between pain in two distinct anatomical regions.

It could be that pain in the neck/shoulder renders people more prone to pain also in the back, or vice versa. For example, pain in one region might cause individuals to modify their postures or activities in a way that predisposes to pain elsewhere, or it might make them more aware of, and willing to report pain at other sites. We do not know what proportion of participants in the EWCS surveys reported pain in both the back and neck/upper limb, but in the CUPID study, multisite pain was common [9].

Alternatively, the observed correlations could reflect the effects of shared causes for pain at multiple anatomical sites. Our analysis does not indicate what those causes might be, but the relationship between pain at different sites in the CUPID study was present in people carrying out similar occupational activities, and after adjustment for established risk factors such as low mood, somatising tendency, fear-avoidance beliefs and psychosocial aspects of work [2, 3]. The shared causes could be unrecognised biomechanical factors, or perhaps more likely, physiological or psychological determinants of pain perception.

Whatever the nature of the causes, our results suggest that their impact can change importantly over time periods as short as five years, and that it has been going up in some European countries (e.g. Ireland, Romania and Luxembourg) while declining in others (e.g. Portugal, Czech Republic and Italy). If so, they may be amenable to preventive interventions, with potentially major benefits. Research is now needed to identify and characterise those unidentified causes, focusing on factors that could predispose to musculoskeletal pain in general rather than being site-specific.

Conclusions

Our findings provide independent corroboration that major differences in the prevalence of musculoskeletal pain in different anatomical regions correlate across countries. As such, they support the hypothesis that international variation in common pain complaints is importantly driven by factors that predispose to musculoskeletal pain in general.

Abbreviations
CUPID: Cultural and Psychosocial Influences on Disability; Eurofound: European Foundation for the Improvement of Living and Working Conditions; EWCS: European Working Conditions Survey; LBP: Low back pain; r: Spearman rank correlation coefficient

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Availability of data and materials
The datasets analysed in this study are available at: https://www.eurofound.europa.eu/surveys/about-eurofound-surveys/data-availability#datasets

Authors' contributions
ER carried out the abstraction of data and statistical analysis, and wrote the initial draft of the manuscript. GN supervised the statistical analysis. DC supervised the design and conduct of the study and revised the initial draft of the manuscript. All authors contributed to revision and finalisation of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The data that we accessed from the EWCS surveys were retrospective anonymized summary statistics, and ethical approval was not therefore required.

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Not applicable.

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The authors declare no competing interests.

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References
1. Coggon D, Ntani G, Palmer KT, et al. Disabling musculoskeletal pain in working populations: is it the job, the person or the culture? Pain. 2013;154:856–63.
2. Coggon D, Palmer KT, Ntani G, Felli VE, Harari F, Quintana LA, et al. Drivers of international variation in prevalence of disabling low back pain: findings from the cultural and psychosocial influences on disability study. Eur J Pain. 2019;23:35–45.
3. Coggon D, Ntani G, Walker-Bone K, Felli VE, Harari F, Barrero LH, et al. Determinants of international variation in the prevalence of disabling wrist and hand pain. Submitted for publication.
4. Coggon D, Ntani G, Walker-Bone K, Felli VE, Harari R, Barrero LH, et al. Associations of sickness absence for pain in the low back, neck and shoulders with wider propensity to pain. Submitted for publication.
5. Eurofound. Fifth European Working Conditions Survey – 2010. https://www.eurofound.europa.eu/surveys/european-working-conditions-surveys/fifth-european-working-conditions-survey-2010. Accessed 11 Jan 2018.
6. Eurofound. Sixth European Working Conditions Survey: 2015. https://www.eurofound.europa.eu/surveys/european-working-conditions-surveys/sixth-european-working-conditions-survey-2015. Accessed 11 Jan 2018.
7. Eurofound. 5th European Working Conditions Survey, 2010: Weighting report. https://www.eurofound.europa.eu/sites/default/files/ef_files/surveys/ewcs/2010/documents/weighting.pdf. Accessed 11 Jan 2018.
8. Eurofound. 6th European Working Conditions Survey: Weighting report. https://www.eurofound.europa.eu/sites/default/files/ef_survey/field_ef_documents/6th_ewcs_2015_-_weighting_report.pdf. Accessed 11 Jan 2018.
9. Coggon D, Ntani G, Palmer KT, Felli VE, Harari R, Barrero LH, et al. Patterns of multi-site pain and associations with risk factors. Pain. 2013;154:1769–77.

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Application of epidemiological findings to individuals*

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Key words: Epidemiology; external validity; clinical medicine

Parole chiave: Epidemiologia; validità esterna; medicina clinica

Summary

Three types of issues need to be considered in the application of epidemiology results to individuals. First, epidemiology results are subject to random error, and can be applied only to an ideal subject with average values of all variables under study, including potential confounders included in the regression models. Second, the observational nature of epidemiology makes it susceptible to systematic error, and any extrapolation to individuals would mirror the validity of the original results. Quantitative bias analysis has been proposed to assess the likelihood, direction and magnitude of bias, but this has not yet become part of the normal practice of epidemiology. Finally, external validity of the results (i.e., their application to individuals and populations other than those included in the underlying studies) needs to be addressed, including population-based factors, such as heterogeneity in exposure or disease circumstances, and individual-based factors, such as interaction of the risk factors of interest with other determinants of the disease. Similar considerations apply to the application of results of clinical trials to individual patients, although in these studies sources of systematic error are better controlled.

Riassunto

***«Applicazioni di risultati epidemiologici al singolo individuo»**. Quando si attribuiscono i risultati dell'epidemiologia al singolo individuo bisogna considerare tre differenti aspetti. In primo luogo, i risultati dell'epidemiologia sono soggetti a errori casuali e possono essere applicati solo ad un soggetto ideale con valori medi per tutte le variabili studiate, compresi i potenziali fattori di confondimento inclusi nei modelli di regressione. In secondo luogo, la natura osservazionale dell'epidemiologia la rende suscettibile di errori sistematici (bias) e qualsiasi attribuzione dei risultati agli individui rispecchierebbe la validità dei risultati originali. Sono stati proposti modelli di analisi quantitativa dei bias per valutare la probabilità, la direzione e l'entità dell'errore, ma queste metodologie non sono di uso comune. Infine, deve essere considerata anche la validità esterna dei risultati (ossia la loro applicabilità a individui e popolazioni diverse da quelle incluse negli studi originali), includendo fattori caratteristici della popolazione, come l'eterogeneità delle condizioni di esposizione o di malattia, e fattori caratteristici dell'individuo, come l'interazione dei fattori di rischio di interesse con altri determinanti della malattia. Considerazioni simili si applicano all'attribuzione dei risultati da trial clinici ai singoli pazienti, sebbene in questi studi le fonti di errore sistematico siano meglio controllabili.*

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Introduction

It is customary to consider a separation between clinical medicine, aimed at improving the health of individuals through prevention or treatment, and public health, aimed at improving health at the population level. Epidemiology provides research tools to both public health and clinical medicine: the implications of epidemiology results oftentimes clearly address one of these two domains, but in numerous instances they are applicable to both. Moving from these considerations, Rogawski et al. (23) distinguish between public health epidemiology, which "*informs interventions that are applied to populations or that confer benefits beyond the individual*" and medical epidemiology, which "*informs interventions that improve the health of treated individual*". Based on this distinction, they argue in favor of public health epidemiology, which, in their opinion, has been neglected in favor of individual-oriented approaches. We would like to opine that such dichotomy is epistemologically incorrect, and to provide a framework to apply epidemiology results to both populations and individuals. It has been a long time since Rose highlighted the link between "sick individuals and sick populations" (24).

The nature of epidemiologic results

Epidemiology measures health-related conditions and events in groups of individuals, and compares them to derive inferences on possible determinants. They therefore represent averages of the likelihood that the condition or event occur (or, in case of continuous variables, that they take a particular value or range) in the different groups under study: at the individual level, the corresponding likelihood is just zero or one. For example, a measure of incidence indicates the number of individuals in which the event of interest (e.g., diagnosis of a disease) occurs over the person-time of observation: while the measure can be interpreted as a hypothetical average likelihood that the event occurred in each individual under study, the actual individual likelihood of occurrence was one for cases and zero for non-cases. Analogously, a comparative measure such a ratio of incidences between two groups would indicate the ratio of the average likelihoods of the individuals in the two groups.

The application of group-based likelihoods, and their comparative measures, to individuals is particularly helpful to make prediction regarding individuals outside the population-time under study: in practice, we predict the risk of an individual to die over a given period of time based on the most recent mortality rates of their population, or, if these are not available, of a similar population, and we apply comparative measures to predict the risk of an individual with a given characteristics relative to their counterfactual without that characteristics.

It is important to note that these considerations apply to results of studies based on both observational (epidemiology studies) and experimental design (so called clinical trials), although there are differences in their interpretation as discussed below.

Issues in the application of group-derived measures to individuals

Precision

All biological variables are subject to random error, which is operationalized using probability distribution models derived from frequentist statistics: measures aimed at quantifying the variability, such as the standard error and the confidence interval, are customarily reported in clinical and epidemiological studies. The notion of random error and its quantification are familiar to most medical researchers: a simple interpretation is that the central measure of the parameter represents the value in the "average" individual or patient, and that the distribution of all individuals and patients in real life is described by the measures of variability. If the measures of interest are conditional to the distribution of other variables, as in the case of adjustment for potential confounders in stratified or regression analysis, the latter will also be considered in determining the evasive "average" subject.

In this context, a multivariable relative risk of lung cancer among smokers equal to 10 can be interpreted as the ratio of the likelihood to develop lung cancer of the "average" smoker in the study population to that of their non-smoking counter-

factual, where "average" refers not only to the variables capturing the carcinogenic effect of tobacco smoking (amount, duration, time since quitting, age at start, etc.), but also to other variables included in the regression models. Such ideal average individual, and their counterfactual, are useful simplifications to explain the implications of group-based results (in the example above, "Our study shows that the risk of lung cancer of a smoker is 10-times higher than that of a non-smoker"); these results, however, cannot be applied with certainty to any real individual.

Internal validity

Random error is not the only factor complicating the application of group-derived results of epidemiology studies to individuals. Well-designed and conducted epidemiologic studies provide the best risk estimates when experimental approaches are not applicable. The observational nature of epidemiologic research, however, makes it susceptible to systematic error. Complete control of bias and confounding can seldom be achieved due to:

- residual and unmeasured confounding;
- selection and information bias;
- publication bias.

Although the effect of known and measurable confounders can be controlled – at least in part – by including appropriate terms in regression models, control of bias requires appropriate provisions in the design, conduct and analysis of the study (25). In addition, quantitative bias analysis has been increasingly used to assess the possible effect of selected sources of bias (14). This represents a formal approach to provide a quantitative estimate of the likelihood, direction, and magnitude of the error introduced by one or multiple sources of bias. Several types of quantitative bias analysis have been described, depending on whether one or multiple types of bias are addressed, and whether a fixed value or a range of values are assigned to the bias parameter (15). Steps in the bias analysis include (i) to identify potential source of bias, (ii) to identify sources of information on bias parameters, (iii) to derive alternative values to the original study variables, and (iv) to quantify their effect on the original results. Recommendations have been developed, that quantitative bias analysis should accompany any presentation of results of observational studies (7), however, most investigators simply ignore them, resulting in an unknown amount of bias affecting results of such studies.

External validity

External validity concerns the applicability of the results of a study to a population other than that under study. It is also referred to as 'generalizability' of the results. Lack of external validity does not reduce the ability of a study to contribute to causal inference, and failure to recognize this fact is one of the most common mistakes in the interpretation of clinical and epidemiological studies. However, external validity becomes an important issue in the context of use of group-based results to individuals.

The considerations made above on the need to identify the "average" study subject to account for random error, and to control sources of bias to generate valid results apply only to the populations from which the results were generated. Any application of results of epidemiological or clinical research to individuals outside the populations under study should address factors that may differ between the two. These factors can be operationally divided in two groups.

The first group comprises factors external to the individuals to whom results are to be applied. Differences in exposure circumstances is one such factor. Table 1 illustrates this phenomenon in the case of the lower risk of lung cancer from tobacco smok-

Table 1 - Levels of cotinine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in urine samples of smoking lung cancer cases from Shanghai and Singapore (28)
Tabella 1 *- Livelli di cotinina e di 4-(metilnitrosamino)-1-(3-piridil)-1-butanolo (NNAL) in campioni di urine di soggetti fumatori con tumore del polmone urine nelle città di Shanghai e Singapore (28)*

	Shanghai (N=155)	Singapore (N=91)
Cotinine (ng/mg creat.)	3,033	2,873
NNAL (pmol/mg creat.)	0.23	0.89

ing in Chinese smokers compared to European and American smokers (13). In a series of elegant studies conducted in two populations of Chinese smokers from Shanghai and Singapore, Yuan et al. (28) showed that the lower risk was likely due to the characteristics of the cigarettes consumed in China vs. Singapore: although the level of urinary cotinine (a marker of amount of tobacco smoking) was comparable in the two groups, the levels of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a tobacco-specific nitrosamine and a markers of carcinogenicity of tobacco smoke, was significantly lower in smokers from Shanghai, likely due to differences in curing and manufacturing processes of traditional local Chinese cigarettes smoked in Shanghai compared to standard industrial cigarettes smoked in Singapore.

Most occupational epidemiological studies are of retrospective design, and address the health effects of exposure that occurred in the past. In many industries there have been changes in technology and industrial hygiene, which have resulted in important changes in exposure circumstances and levels. Although in some cases detailed dose-response and other data are available, that help transferring results of these studies to other populations of workers in the same industries or jobs, in many instances these data are not available. Use of results of studies conducted in other countries, where technological and industrial hygiene conditions might differ, is another potential source of lack of generalizability.

Another factor is the need to consider absolute, rather than relative measures of occurrence. Exposure to a risk factor increases the number of cases of the disease of interest in the population, i.e., its incidence; however, the relative measure of incidence depends also on the incidence in the unexposed group. In the absence of effect modification, the relative measure of incidence will therefore be lower in a population with higher incidence in the unexposed compared to a population with lower incidence, as shown in table 2. A well-known example of this phenomenon is the apparent stronger association between tobacco smoking and lung cancer in women compared to men: although various explanations have been proposed, such as a role of hormonal factors (21), the most likely explanation is the higher rate of lung cancer among men for causes other than tobacco smoking (e.g., occupational exposures): a reduction of the role of these other factors in men explain why the gender gap in relative risks observed in the past has disappeared in recent studies (22). The presence of interaction between the risk factor of interest and the determinants of the incidence among the unexposed would further affect the relative risk.

Characteristics of the individuals represent the second group of factors that may affect external validity. The simplest form they can take is that of modifiers of the effect of the exposure of interest (interaction), which is presented (in the form of a positive interaction) in table 3. The incidence among those unexposed to either factor is 10/1000. In the absence of factor B, exposure to factor A increases the incidence by 10/1000; in the absence of factor A, exposure to factor B increases the incidence by 20/1000. In the absence of interaction, the incidence among those exposed to both factors should

Table 2 - Effect of incidence in unexposed on the relative risk – Hypothetical example of two populations with 1000 exposed and 1000 unexposed subjects each, and higher incidence in the unexposed in one population. The incidence due to the exposure is set to 40/1000 in both populations
Tabella 2 *- Effetto di incidenza tra i non esposti sul rischio relativo – esempio ipotetico di due popolazioni di soggetti con 1000 esposti e 1000 non esposti con una maggiore incidenza nei non esposti in una delle popolazioni. L'incidenza dovuta all'esposizione è fissata a 40/1000 in entrambe le popolazioni*

	Population 1	Population 2
Incidence rate in unexposed	10/1000	20/1000
Incidence rate in exposed	50/1000	60/1000
Rate ratio	5	3

Table 3 - Hypothetical example of positive interaction between two risk factors on the incidence of a disease
Tabella 3 *- Esempio ipotetico di interazione positiva tra due fattori di rischio sull'incidenza della malattia*

	Incidence of the disease	
	Unexposed to A	Exposed to A
Unexposed to B	10/1000	20/1000
Exposed to B	30/1000	50/1000

be (10+10+20) = 40/1000; in the example in the table, the incidence among those exposed to both is 50/1000, suggesting a positive interaction between the two exposures (for sake of simplicity no consideration is given to the statistical significance of the interaction term). When rate ratios are used instead of incidence rates, and the group unexposed to both factors is taken as reference, the interaction is described by the formula:

$$RRab \neq RRa + RRb - 1.$$

Interaction is conceptually similar to the problem of difference in background incidence across populations described above; however, it applies to the characteristics of the individuals, irrespective of the distribution of the two risk factors in the population. Several examples of interaction have been identified among causes of chronic diseases, both genetic and environmental (in broad sense). Although their effect on the risk of disease at the individual level can in principle be accounted for, a precise estimate of their magnitude is available only for a fraction of them, such tobacco smoking and asbestos for lung cancer (20) and tobacco smoking and alcohol drinking for head and neck cancer (9).

Adequacy of statistical models aimed at measuring associations

In current epidemiological practice, observational studies are designed to identify or confirm an association between an exposure and the occurrence of a certain disease. The focus is posed on the measures of association (such as relative risk, when measuring on the multiplicative scale, or risk difference, when quantifying the absolute risk); little attention is devoted to the overall performance of the regression model. Sometimes researchers present direct comparison between two or more regression models by applying statistical testing (e.g. maximum likelihood ratio test (11)) or information criteria which are largely based on the likelihood function of the model (e.g. Bayesian Information Criterion or Akaike Information Criterion) (2, 3, 26). Of note, such comparisons inform whether a specific model adapts to sample data better than a few others; however, they do not convey information on the absolute goodness-of-fit of the models. A perhaps even worse practice is testing the goodness-of-fit (for instance, through the Hosmer-Lemeshow goodness-of-fit test (10)) and interpreting a low *p-value* as an indication that the model is performing well; in fact, these tests only inform that introducing a specific variable in the regression model contributes to improving the goodness-of-fit, but do not provide a meaningful measure of the overall performance of the regression model.

People with a quantitative background (e.g., industrial hygienists) should be familiar with measuring and reporting the proportion of the variance in the dependent variable (disease status) that is predictable from the independent variable (exposure); in the context of simple linear regression, this can be achieved by the coefficient of determination (usually reported as R^2). Outside linear regression, similar measures have bene proposed, like the McFadden pseudo-R^2 for logistic regression (17, 18). This index assumes a value of 0 in the empty model (no predictive value) and a value of 1 in case of perfect prediction. A conceptually similar index is the Harrel's C index of concordance estimated after fitting a Cox proportional hazards regression models (8). Describing the properties and the (several) limitations of these indices goes beyond the intents of this paper. However, a consideration is worthwhile: how often is the reader of an epidemiological paper informed about the absolute goodness of fit of a regression model whose results are reported in the classic form of one or several relative risks (and corresponding confidence intervals and *p-values*)? It has been shown that in most observational studies the absolute goodness of fit of regression models is usually rather low (e.g. odds ratios from case-control studies with a McFadden pseudo-R^2 not higher than 0.3) (19). This circumstance might not a limitation if the purpose of the analysis is to demonstrate the effect of a certain exposure in increasing (or decreasing) the risk relative or absolute risk of a specific condition; indeed, estimates of association will be valid as far as bias, including confounding, can be excluded (see above), independent from the overall goodness of fit of the regression model. Conversely, knowledge of the overall model performance

measured through an absolute goodness-of-fit index is fundamental if the goal is to answer to the following questions:

1) Did a specific subject in the study population develop the condition under investigation due to a specific exposure (*in-sample prediction*)?
2) Will a specific subject develop the condition under investigation, and when (*out-of-sample prediction*)?

To be answered, these questions need an extremely high predictive value from the underlying regression models. Outside the clinical context (e.g. prediction of tumor response based on treatment protocols), this condition is seldom achieved. A worthwhile example is the calculation of the risk of cardiovascular events based on the few strong determinants highly prevalent in the general population. The most known example is the so called "Framingham score", which consists in a series of formulas derived from Cox proportional hazards regression models applied to a prospective population-based cohort study (4). The authors were able to adapt models with an Harrel's C >0.7 – a conventional, somehow questionable, threshold that identifies models with good predictive value – based on a few variables: gender (the models were actually gender-specific), age, diabetes status, tobacco smoking, treated and untreated systolic blood pressure, total and high-density lipoprotein cholesterol (or body mass index, as a surrogate measure). Knowledge of these few data is used in current clinical practice to predict the 10-year risk of cardiovascular disease. However, a large body of literature suggested that the external validity of the formula might be limited (e.g. (27)); in particular, an overestimation of the risk has been observed in certain populations (5). This could occur because of improvements in the treatment and control of predisposing conditions (such as hypertension and diabetes) or due to a different baseline risk determined by lifestyle (including diet) and genetic factors.

In synthesis, the use of estimates from observational studies to predict individual events is a complex process often hampered by the lack of fundamental knowledge on the disease process and, hence, a limited predictive value of the multivariable regression models used to generate the results.

Considerations about clinical trials

The above discussion was formulated with respect to observational research. One can argue that these considerations do not apply to experimental studies, in which the determinant under investigation (exposure) is assigned to study subjects. In this respect, the results of trials, and in particular clinical trials, are directly applicable to individual patients with the same conditions as those included in the trials. After all, when clinicians prescribe a new drug to their patients based on the results of a trial, they do so because they expect in the patients the same effect shown in the trial.

If clinical and other medical trials are well designed and executed, they can prevent bias from affecting their results. However, the other two sources of error in applying results from populations to individuals, that were described above for observational studies, also apply to trials. Results of trials are affected by random error, and their results would precisely apply only to a hypothetical "average" patient. In practice, the clinicians mentioned in the previous paragraph would not be so naïve to expect in each of their patients exactly the result reported in the trial: they prescribe the new drug with the expectation to see in their patients, on average, the effect observed in the trial, but they recognize that there might be plenty of individual variation in the response.

More important, however, is the issue of external validity of results of experimental studies. The problem that trials, in particular treatment trials, include selected samples of patients who might in principle benefit from the treatments under has been increasingly recognized in the medical literature, in particular with respect to sociodemographic characteristics such as age (e.g., underrepresentation of elderly patients in clinical trials (16)) and race/ethnicity (e.g., overrepresentation of non-Hispanic Whites (6)).

Conclusions

Considerations about the applicability of results of epidemiology studies to individuals are analogous to those developed within the framework of personalized medicine. The goal of personalize medicine

is to describe all individual characteristics that determine the response of the individual patient to a given treatment, and select the most effective one (1). An analogous approach can be invoked for epidemiology, although issues of internal validity would complicate the process, as discussed above. Although an exhaustive description of all relevant individual factors remains elusive, steps can be taken in this direction.

Systematic reviews, meta-analyses and umbrella reviews (12) help improving the precision of risk estimates and offer opportunity for stratified analysis to address sources of heterogeneity of results across populations. Routine application of quantitative bias analysis (15), as discussed above, would improve the validity of inferences at the individual level. Integration of biology and epidemiology would contribute to reducing uncertainties on the external validity of the results.

In conclusion, epidemiology results can be applied to individuals under the stringent framework we outlined here. As in most instances sources of random error, internal validity, and external validity are only partially controlled, extrapolation to individuals remains tentative at best. One case in which extrapolation to individuals may be justified is that of high-penetrance susceptibility genes: in which results of clinical or epidemiological have shown such a high risk in carriers that consideration about random and systematic have less relevance, and it may be justified to assume external validity even in the absence of direct evidence supporting it.

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PB is an associate editor of the journal, but this article was reviewed by an anonymous reviewer, who provided useful suggestions to improve it

References

1. Academy of Medical Sciences: Stratified, Personalised or P4 Medicine: A New Direction for Placing the Patient at the Centre of Healthcare and Health Education (Technical Report). London: Academy of Medical Sciences, 2015
2. Akaike H: A new look at the statistical model identification. IEEE Transactions on Automatic Control. 1974; 19: 716-723
3. Clayton D, Hills M: Statistical Models in Epidemiology. Oxford, UK: Oxford University Press, 1993
4. D'Agostino RB, Vasan RS, Pencina MJ, et al: General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008; 117: 743-753
5. Damen JA, Pajouheshnia R, Heus P, et al: Performance of the Framingham risk models and pooled cohort equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis. BMC Med. 2019; 17: 109
6. Ford JG, H M, Lai GY, et al: Barriers to recruiting underrepresented population to cancer clinical trials: a systematic review. Cancer 2008; 112: 228-242
7. Fox MP, Lash TL: On the need for quantitative bias analysis in the peer-review process. Am J Epidemiol 2017; 185: 865-868
8. Harrell FE, Califf RM, Pryor DB, et al: Evaluating the yield of medical tests. JAMA 1982; 247: 2543-2546
9. Hashibe M, Brennan P, Chuang SC, et al: Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev 2009; 18: 541-550
10. Hosmer DW Jr, Lemeshow SA: Goodness of fit tests for the multiple logistic regression model. Communications in Statistics—Theory and Methods 1980; 9: 1043-1069
11. Hosmer DW Jr, Lemeshow SA, Sturdivant RX: Applied Logistic Regression. 3rd ed. Hoboken, NJ: Wiley, 2013
12. Ioannidis JP: Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. CMAJ 2009; 181: 488-493
13. Jung KJ, Jeon C, Jee SH: The effect of smoking on lung cancer: ethnic differences and the smoking paradox. Epidemiol Health 2016; 38: e2016060
14. Lash TL, Fox MP, Fink AK: Applying quantitative bias analysis to epidemiologic data. New York, NY: Springer, 2009
15. Lash TL, Fox MP, MacLehose RF, et al: Good practices for quantitative bias analysis. Int J Epidemiol 2014; 43: 1969-1985
16. Le Saux O, Falandry C, Gan HK, et al: Inclusion of elderly patients in oncology clinical trials. Ann Oncol 2016; 27: 1799-1804
17. Lemeshow S, Hosmer DW: A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol 1982; 115: 92-106
18. Mc Fadden D: Conditional logit analysis of qualitative choice behavior. In: Zarembka P, Ed. Frontiers in Econometrics. Cambridge, MA: Academic Press, 1974, p. 105-142

19. Menard S: Coefficients of determination for multiple logistic regression analysis. Am Stat 2000; 54: 17-24
20. Ngamwong Y, Tangamornsuksan W, Lohitnavy O, et al: Additive synergism between asbestos and smoking in lung cancer risk: A systematic review and meta-analysis. PLoS One 2015; 10: e0135798
21. O'Keeffe LM, Taylor G, Huxley RR, et al: Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis. BMJ Open 2018; 8: e021611
22. Pauk N, Kubík A, Zatloukal P, Krepela E: Lung cancer in women. Lung Cancer 2005; 48: 1-9
23. Rogawski ET, Gray CL, Poole C: An argument for renewed focus on epidemiology for public health. Ann Epidemiol 2016; 26: 729-733
24. Rose G: Sick individuals and sick populations. Int J Epidemiol 1985; 14: 32-38
25. Rothman KJ, Greenland S, Lash TL: Design strategies to improve study accuracy. In: Rothman KJ, Greenland S, Lash TL. Modern Epidemiology, Third Ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2008, pp. 168-182
26. Schwarz G: Estimating the dimension of a model. Annals of Statistics 1978; 6: 461-464
27. Siontis GC, Tzoulaki I, Siontis KC, Ioannidis JP: Comparisons of established risk prediction models for cardiovascular disease: systematic review. BMJ 2012; 344: e3318
28. Yuan JM, Koh WP, Murphy SE, et al : Urinary levels of tobacco-specific nitrosamine metabolites in relation to lung cancer development in two prospective cohorts of cigarette smokers. Cancer Res 2009; 69: 2990-2995

Interaction between Occupational Exposure to Diesel Exhaust and Tobacco Smoking in Determining Lung Cancer Risk: A Meta-Analysis

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Short title

Diesel exhaust - smoking interaction and lung cancer risk

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Abstract

Background: While an association between exposure to diesel exhaust (DE) and risk of lung cancer has been reported in several studies, its interaction with tobacco smoking in determining lung cancer risk is not well characterized. This study aims at performing a systematic review and meta-analysis of results of epidemiology studies on this.

Methods: Studies included in the systematic review were identified from PubMed, Scopus and Embase, without limitation of year of publication or language. Two reviewers independently reviewed the studies and abstracted relevant data from selected studies, applied a customized quality assessment tool and calculated the relative risks (RR) and 95% confidence intervals (CI) for the interaction between DE exposure and tobacco smoking on a multiplicative scale. Next, a random-effects meta-analysis of the interaction RR was conducted.

Results: Seven studies were included in the meta-analysis, of which two were cohort and five case-control studies. Results on the interaction were heterogeneous (I^2=45.6%). The summary RR for interaction was 0.79 (95% CI 0.42, 1.46). There was no indication of publication bias. There was no increased risk of lung cancer among non-smoking workers exposed to DE.

Conclusions: This meta-analysis suggested a less-than-multiplicative effect between DE exposure and tobacco smoking in determining lung cancer risk, but the hypothesis of multiplicative interaction cannot be rejected. The small number of relevant studies and the high heterogeneity among them prevent from definite conclusions.

Introduction

Diesel engine (DE) exhaust is a complex and variable mixture of particulate matter and gases that include several carcinogenic and mutagenic agents, including polycyclic aromatic hydrocarbons [1]. The relative fractions of the specific constituents vary according to engine characteristics, such as size, period of manufacture, age, and maintenance status [2]. Diesel engines are widely used in many different occupational settings, including into off-road activities (e.g. mining, railroad, construction) and on-road vehicle operations (e.g. transportation industry, automobile driving). It has been estimated that 3 million workers in Europe and 1.4 million workers in the USA are occupationally exposed to DE [1, 3]. DE has been classified as human carcinogen [1, 4], although some authors disagree with this conclusion [5, 6].

We aimed at performing a systematic review and meta-analysis of results of epidemiology studies on the interaction between DE exposure and tobacco smoking in determining the risk of lung cancer, as a contribution to the elucidation of the potential carcinogenic hazard of DE exposure on the human lung, and to the consideration of tobacco smoking as effect modifiers in DE-related lung cancer risk assessment. A secondary aim was to derive an estimate of the effect of DE exposure in non-smokers.

Methods

We followed the PRISMA guidelines to conduct a systematic review and meta-analysis [7]. The PRISMA checklist is reported in Appendix 1. The study protocol is available from the authors.

Study selection

The articles included in the systematic review were identified using the databases, Pubmed, Scopus and Embase. The bibliographic search was conducted in October 2019. The following string was used in Pubmed: *("Lung Neoplasms" [Mesh] OR "Carcinoma, Non-Small-Cell Lung" [Mesh] OR "Carcinoma, Small Cell" [Mesh] OR ((lung OR pulmonary) AND (cancer OR cancers OR neoplasm* OR carcinoma* OR adenocarcinoma*))) AND ("Gasoline" [Mesh] OR "diesel" OR "diesel engine exhaust" OR" Vehicle Emissions" [Mesh] OR Vehicle Emission* OR transportation [mh] OR truck driver*).* We adapted the same string to Scopus and Embase (available from the authors upon request).

Inclusion criteria

Articles which met the following criteria were included in the review: reports of human studies, studies published in peer-reviewed journals, cohort or case control studies presenting results for different combinations of DE exposure and tobacco smoking, without restriction on either year of publication or language. We selected only studies where the smoking data was derived from the same population included in the study. We did not consider any differences in diesel mixtures.

Article selection

Two authors [ER and IDP] independently reviewed the lists of titles and abstracts, to screen out irrelevant articles, that were eliminated together with duplicates. In case of disagreement or doubt, a third reviewer was consulted [PB]. Next, the full text of potentially relevant articles was reviewed by the two authors independently, and the studies fulfilling the inclusion criteria were identified. In case of multiple reports from the same study, the most complete results (i.e., those based on largest number of cases) were used. A backward research of missing articles was conducted by checking the reference lists of the articles retained for the review. The flowchart of the selection of articles is shown in Figure 1.

Data abstraction

The following study characteristics were extracted for the meta-analysis by two authors [ER, IDP]: publication year, country, study design, information on age and sex, study period, loss to follow up or response rate, cohort size or number and cases/controls, source of data on exposure and outcome, outcome (mortality or incidence), DE exposure assessment and categories, tobacco smoking assessment and categories, measure of association (relative risk [RR]) and corresponding confidence interval (CI). Information on other known or suspected risk factors for lung cancer was also abstracted, including exposure to occupational carcinogens such as radon decay products, asbestos and crystalline silica. Since categories of DE exposure and tobacco smoking were not consistent across studies, we reclassified the relevant variables to obtain comparable categories.

In case of stratified results, e.g., by age group or historical period of exposure, multiple entries were abstracted. From all eligible studies, relevant data were collected using a standardized data extraction sheet. Data extraction was performed by two authors [ER, IDP] and checked by a third author [PB].

Quality assessment

A customized checklist was used to score the quality of the studies selected for the analysis. The checklist was derived from the Newcastle- Ottawa Quality Assessment Scale [8] and from the National Research Council's Review of EPA's Integrated Risk Information System [9]. We added specific items based on the scope of our review, with a focus on combined exposure to DE and tobacco smoking, the representativeness of cases and controls or of cohort members, the potential for confounding, and the appropriateness of analytic methods used. Scores were expressed as percentages. The checklist is available at Appendix 2.

Statistical analysis

For each study, we abstracted or calculated, based on the data reported in the publication, the RR and the 95% CI in the four categories defined by exposure to DE and tobacco smoking, both categorized as dichotomous variables. We abstracted the RR from two studies [10, 11], and calculated the RR from data reported in the publication of five studies [12-16]. Next, we derived the term of interaction, following three different approaches. In one study [11] we extrapolated the estimates for DE exposure, tobacco smoking, and both agents, as we did not have access to crude data for each of these categories. In another study [14] we abstracted the term of interaction directly

from the publication. For all other studies, we calculated the term for the interaction on a multiplicative scale according to the formula:

$$\beta_{Interaction\ smoking \times DE} = \beta_{smoking+DE+} - \beta_{smoking+DE-} - \beta_{smoking-DE+}$$

and we estimated its 95% CI through a via Monte-Carlo simulation assuming a normal distribution for the β coefficients, and independence among them. Then, we conducted 100,000 simulations and we calculated the 2.5th percentile and the 97.5th percentile of the distribution after a burn-in of 90,000 simulations. Of note, the assumption of independence of the β coefficients probably determined an overestimation of the variance of the interaction term.

Finally, we conducted a random-effects meta-analysis [17] of the terms for interaction obtained from each study. We also conducted a sensitivity analysis on the contribution of each study to the summary result, by eliminating one study at a time. We evaluated publication bias by visually inspecting the funnel plot of the results and by applying the test proposed by Egger and colleagues [18]. Finally, we assessed a possible effect of study quality score by conducting a meta-regression with the score as independent variable. We used for the meta-analysis the Stata commands *metan*, *metabias*, *metafunnel*, and *metareg*.

Results

The flowchart of the selected studies is shown in Figure 1. From a total of 1,246 articles identified in the search, we eliminated 126 duplicates and 1016 articles were judged to be irrelevant after consideration of the title and the abstract. The full texts of the remaining 104 articles were reviewed, leading to the exclusion of 81 of them, which did not contain the relevant information. A careful examination of the remaining 23 articles resulted in the exclusion of 14 because they did not include information on tobacco smoking from the same population in which DE exposure was studied, of two because they did not report sufficient data to calculate the term of interaction, and of one study [19], 1994) because of inconsistencies in the data reported in the publication. Finally, one study [10] was identified from the reference lists of the other studies and was included in the systematic review. Details on the seven studies retained in the systematic review, which included two cohort studies, two case controls studies nested in cohorts, and three community-based case-control studies, comprising two pooled analyses, are presented in Table 1, which also includes information on the reclassification of DE exposure and tobacco smoking to obtain consistent categories across studies. Four studies reported results on incidence of lung cancer, while three analyzed mortality.

Table 2 reports the study-specific RR of lung cancer for each category of DE exposure and tobacco smoking, and Figure 2 shows the study-specific RR for the DE-tobacco smoking interaction and the summary RR. The study-specific RR for interaction were heterogenous (I^2 = 78.4%, p value <0.001), ranging from 0.16 [10] to 1.36 [14]. The summary RR was 0.71 (95% CI 0.08, 1.35). The summary RR for the interaction was 0.79 (95% CI 0.42, 1.46), which is compatible with both an under-multiplicative and a multiplicative model of interaction between DE exposure and tobacco smoking. In the sensitivity analysis, reported in Table 4, with one study removed at a time, the summary RR ranged from 0.32 (exclusion of [14] to 0.94 (exclusion of [10]). These were also the studies that contributed most to the heterogeneity: they were removed the I^2 was reduced to 0%, while the summary RR was 0.57 (95% CI 0.06, 1.08). However, in all cases the 95% CI included the value of 1. There was some evidence of publication bias (p of Egger test = 0.10), although the test had low power because of the small number of studies available. There was no effect of quality score on the result of the meta-analysis (p = 0.95).

The summary RR for DE exposure among non-smokers was 0.83 (95% CI 0.69, 0.98), with no heterogeneity (I^2 = 0%). Since 97% of the weight in the meta-analysis was provided by one study

[14], we repeated the meta-analysis after excluding it: the summary RR was 1.29 (95% CI 0.47, 2.11; $I^2 = 0\%$).

Discussion

The results of our meta-analysis do not allow to distinguish between an additive and a multiplicative interaction between tobacco smoking and exposure to DE in the genesis of lung cancer. In addition, the small number of studies and the heterogeneity between their results prevent a definite conclusion.

El Zoghbi and colleagues [20] reviewed the data on the interaction between DE exposure and tobacco smoking and concluded for the absence of multiplicative interaction. We expanded on this review by including a larger number of studies and conducting a meta-analysis of the results on interaction. In addition, El Zoghbi and colleagues [20] did not provide details about their research string, excluded several potentially relevant studies, and provided no information about the source of the smoking data.

There heterogeneity in the results included in our meta-analysis can be explained by difference in DE exposure. First, these studies covered a period of nearly 60 years (1947-2005), during which changes occurred in the composition of DE. The introduction of novel technology and more stringent regulations on emissions led to a decrease of the content of polycyclic aromatic hydrocarbons (PAH) and other potential carcinogens [21, 22]. This hampers the comparison between results from different study-periods, leading probably to an overestimate of the potential effect of current DE emissions. Second, there were methodological differences in the approaches used for DE exposure assessment in the selected studies, that used questionnaires, structured interviews, employment records, and measurement of total carbon. Third, both for DE and tobacco smoking assessment, the retrospective collection of data could be a potential source for recall bias. Fourth, potential confounders such as low socioeconomic status, which was not adjusted in the available studies. Finally, workers exposed to DE emissions may be employed in jobs, such as mining, in which tobacco smoking may have been regulated in the past for safety reasons.

The limited number of included studies, resulting from our strict inclusion criteria, represents a limitation of our meta-analysis. Furthermore, in a number of studies the data required for the meta-analysis were not available, and we had to derive them from data reported in the publications to calculate crude risk estimates. The fact that most available studies were of retrospective case-control design, and therefore less protected from bias than prospective cohort studies, is a reason of further caution in the interpretation of the data. Furthermore, the absence of a stratification in

exposure levels, both for DE and tobacco smoking, prevented our ability to conduct a dose-response meta-analysis.

The fact that the interaction between DE exposure and tobacco smoking is closer to an additive than a multiplicative model may be explained by an overlap of relevant carcinogens in the two mixtures [23], and of their effects. PAH and volatile organic chemicals are the two main groups of potential lung carcinogens present both in DE and tobacco smoking [1, 24].

The meta-analysis of results on DE exposure in non-smokers did not provide evidence of an independent effect of the former. This is similar to what has been detected for other lung carcinogens such as chrysotile asbestos [25] and silica [26], that appears to entail a minimal, if any, risk in the absence of tobacco smoking, probably because of low exposure levels.

More results from well-designed prospective studies would be needed to better understand the interaction between tobacco smoking and DE exposure in the genesis of lung cancer. Anyway, in the absence of conclusive evidence on the pattern of interaction, reducing exposure to both agents should contribute to reducing the risk of lung cancer among exposed workers.

Authors' contribution

PB, FV and ER conceived and designed the study; ER and IDP conducted the literature search and data abstraction, with supervision by PB. EM and PB conducted the statistical analysis and drafted the manuscript. All authors reviewed and approved the manuscript.

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References

1. International Agency for Research on Cancer. Diesel and gasoline engine exhaust. In: In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 105. Diesel and Gasoline Engine Exhaust and Some Nitroarenes. Lyon, France: IARC, 2013, p. 39-486.
2. Bassig BA, Dai Y, Vermeulen R, Ren D, Hu W, Duan H, et al. Occupational exposure to diesel engine exhaust and alterations in immune/inflammatory markers: a cross-sectional molecular epidemiology study in China. Carcinogenesis 2017;38:1104-11.
3. Lewtas J, Silverman DT. Diesel exhaust. In: International Agency for Research on Cancer. Identification of Research Needs to Resolve the Carcinogenicity of High-Priority IARC Carcinogens. IARC Tech Publ. 42. Lyon, France: International Agency for Research on Cancer, 2010, pp. 53 – 62
4. Silverman D. Diesel exhaust and lung cancer—aftermath of becoming an IARC Group 1 carcinogen. Am J Epidemiol 2018;187:1149-52.
5. Möhner M, Wendt A. A critical review of the relationship between occupational exposure to diesel emissions and lung cancer risk. Crit Rev Toxicol 2017;47:185-224.
6. Chang ET, Lau EC, Van Landingham C, Crump KS, McClellan RO, Moolgavkar SH. Re: "Diesel Exhaust and Lung Cancer-aftermath of Becoming an IARC Group 1 Carcinogen". Am J Epidemiol 2019;188:489-91.
7. Moher D, Liberati A; Tetzlaff J, Altmann DG. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Ann Intern Med 2009;151:264-69.
8. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
9. National Research Council. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press, 2014.
10. Damber L, Larsson LG. Professional driving, smoking, and lung cancer: a case referent study. Br J Ind Med 1985;42:246-52.
11. Neumeyer-Gromen A, Razum O, Kersten N, Seidler A, Zeeb H. Diesel motor emissions and lung cancer mortality--results of the second follow-up of a cohort study in potash miners. Int J Cancer 2009;124:1900-6.
12. Boffetta P, Stellman SD, Garfinkel L. Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. Am J Ind Med 1988;14:403-15.

13. Emmelin A, Nyström L, Wall S. Diesel exhaust exposure and smoking: a case-referent study of lung cancer among Swedish dock workers. Epidemiology 1993;4:237-44.
14. Olsson AC, Gustavsson P, Kromhout H, Peters S, Vermeulen R, Brüske I, et al. Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from case-control studies in Europe and Canada. Am J Respir Crit Care Med 2011;183:941-8.
15. Pintos J, Parent ME, Richardson L, Siemiatycki J. Occupational exposure to diesel engine emissions and risk of lung cancer: evidence from two case-control studies in Montreal, Canada. Occup Environ Med 2012;69:787-92.
16. Silverman DT, Samanic CM, Lubin JH, Blair AE, Stewart PA, Vermeulen R, et al. The Diesel Exhaust in Miners study: a nested case-control study of lung cancer and diesel exhaust. J Natl Cancer Inst 2012;104:855-68.
17. Der Simonian R, Laird N. (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177-88.
18. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997;315:1533-7.
19. Hall NE, Wynder EL. Diesel exhaust exposure and lung cancer: a case—control study. Environ Res 1984;34:77-86.
20. El Zoghbi M, Salameh P, Stücker I, Brochard P, Delva F, Lacourt A. Absence of multiplicative interactions between occupational lung carcinogens and tobacco smoking: a systematic review involving asbestos, crystalline silica and diesel engine exhaust emissions. BMC Public Health 2017;17:156.
21. Hesterberg TW, Long CM, Bunn WB, Lapin CA, McClellan RO, Valberg PA. Health effects research and regulation of diesel exhaust: an historical overview focused on lung cancer risk. Inhal Toxicol 2012;24 Suppl 1:1-45.
22. McClellan RO, Hesterberg TW, Wall JC. Evaluation of carcinogenic hazard of diesel engine exhaust needs to consider revolutionary changes in diesel technology. Regul Toxicol Pharmacol 2012;63:225-58.
23. Rothman KJ. The estimation of synergy or antagonism. Am J Epidemiol 1976; 103: 506-11.
24. International Agency for Research on Cancer. Tobacco smoking. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 83. Tobacco Smoking and Involuntary Smoking. Lyon, France: IARC, 2004, p. 51-1188.
25. Klebe S, Leigh J, Henderson DW, Nurminen M. Asbestos, Smoking and Lung Cancer: An Update. Int J Environ Res Public Health 2019;17:258.

26. Ge C, Peters S, Olsson A, Portengen L, Schüz J, Almansa J, et al. Respirable Crystalline Silica Exposure, Smoking, and Lung Cancer Subtype Risks: A Pooled Analysis of Case-control Studies. Am J Respir Crit Care Med 2020;202:412-21.

Table 1. Selected characteristics of the studies included in the meta-analysis

Ref	Country	Design	Sex	Study period	N	Exposure data	Outcome data	Outcome	DE exposure	Tobacco smoking
[10]	Sweden	CC	M	1972-1979	604/1114	Questionnaires on job titles*	CR	Inc	Drivers	Current and former smokers (<10 yrs)
[12]	USA	Co	M	1982-1988	476648	Questionnaires on DE exposure	National registry	Mor	Self-reported DE exposure	Current and former smokers
[13]	Sweden	NCC	M	1960-1982	50/154	Assessment of DE exposure among dock workers based on tasks	CR	Inc	Medium and high exposure	Current and former smokers (<5 yrs)
[11]	Germany	Co	M	1970-2001	5646	Dust measurements in potash mine	Local registries	Mor	High exposure	Ever smokers
[14]	Europe, Canada	CC†	PM	1985-2005	13304/16282	Questionnaires on job titles and job exposure matrix	Hospitals, CR	Inc	Ever DE exposure	Current and former smokers
[15]	Canada	CC‡	M	1979-1986 1996-2001	I 857/533 736/894	Questionnaires on job titles and tasks and expert assessment	Hospitals	Inc	Substantial exposure (medium/high for 10+ yrs)	Current and former smokers
[16]	USA	NCC	PM	1947- 1997	198/562	Dust measurements in the mines	National registries	Mor	Ever underground miners	Current and former smokers

CC: community-based case-control study, Co: cohort study; NCC, case-control study nested in a cohort; CR, cancer registry; Inc, incidence; Mort, mortality; Ref, reference; N, number of cohort members (cohort studies), number of cases/controls (case-control studies); DE, diesel exposure; M, men only; PM, predominantly men
* Next-of-kin of deceased cases and controls and alive controls
† Pooled analysis of 11 case-control studies
‡ Pooled analysis of two case-control studies

Table 2: RR for lung cancer in categories of combined DE exposure and tobacco smoking

Ref	DE -; smoking -		DE -; smoking +		DE +; smoking -		DE +; smoking	
	N	RR	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)
[10]	28	1	365	7.8 (5.4, 11.2)	3	5.4 (0.8, 26.6)	32	6.8 (3.9, 11.6)
[11]	25	1	633	12.17 (9.64, 15.36)	7	1.73 (0.60, 4.95)	163	14.78 (9.88, 22.11)
[12]	2	1	10	3.7 (0.7, 19.5)	4	2.01 (0.30, 13.64)	34	17.03 (3.04, 95.30)
[13]	NA	1	NA	21.09 (2.85, 156.21)	NA	4.21 (0.26, 67.35)	NA	22.25 (2.68, 185.05)
[14]	614	1	7062	5.87 (5.35, 6.43)	187	0.82 (0.69, 0.98)	5441	6.61 (6.01, 7.26)
[15]	22	1	1006	9.23 (5.7, 14.8)	9	1.37 (0.89, 3.19)	454	13.63 (9.33, 19.92)
[16]	5	1	9	9.34 (5.42, 16.12)	64	0.90 (0.26, 3.09)	103	3.04 (1.95, 4.78)

DE, diesel exhaust; NA, not available; N, number of cases; RR, relative risk; CI, confidence interval

Figure 1: Flow chart of selection of studies

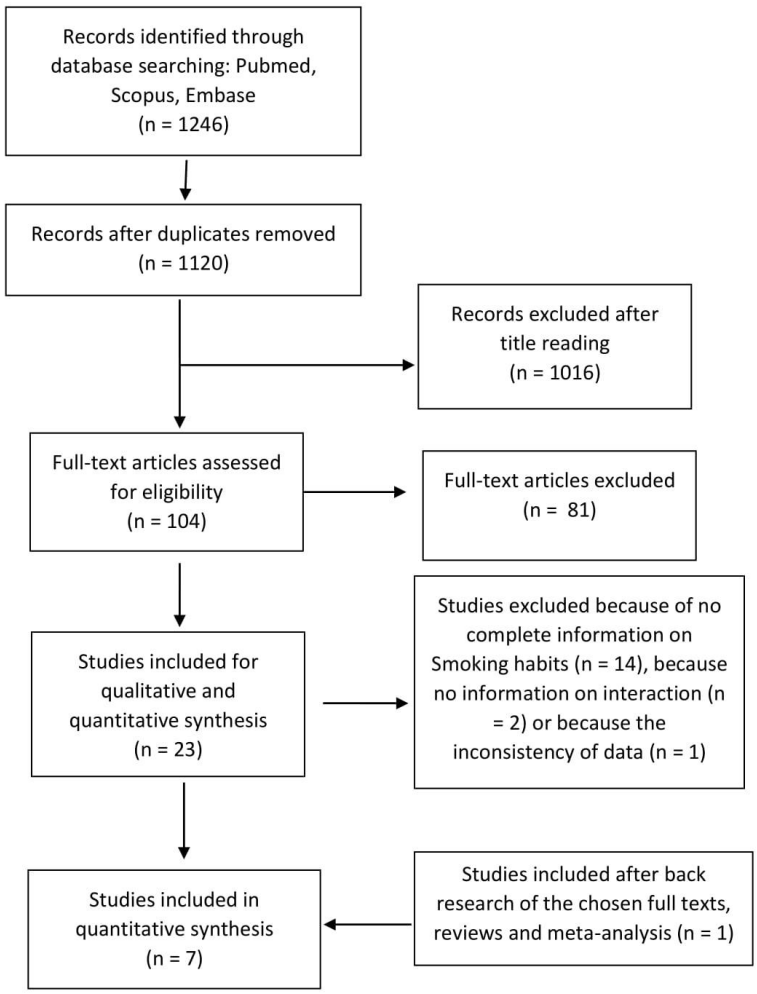
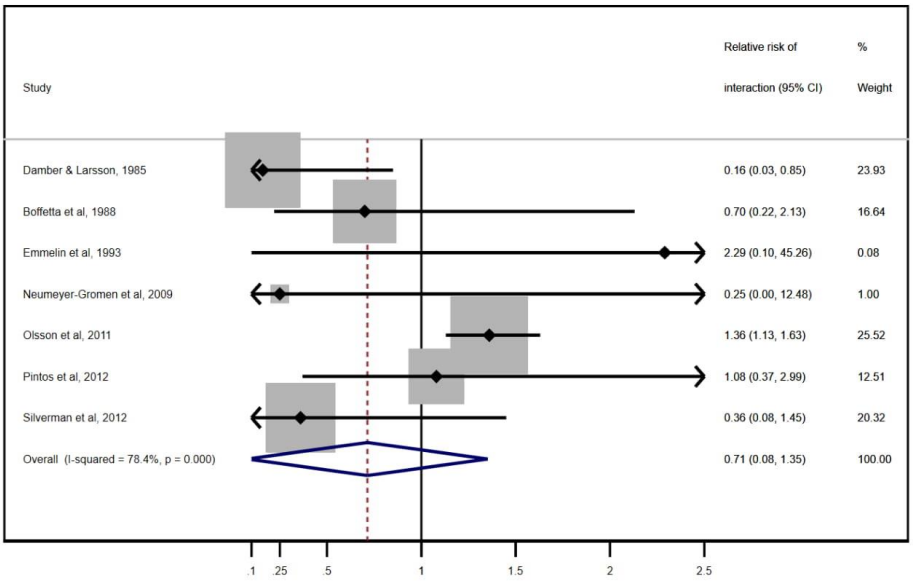


Figure 2. Meta-analysis of relative risks of interaction between DE exposure and tobacco smoking



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Systematic review and meta-analysis of recent high-quality studies on exposure to particulate matter and risk of lung cancer

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ABSTRACT

Background: Several aspects of the association between exposure to air pollution and risk of lung cancer remain unclear.
Objective: We aimed at performing a meta-analysis of high-quality cohort studies on exposure to particulate matter (PM) 10 and PM2.5 and risk of lung cancer.
Methods: We identified cohort studies published since 2004, that reported risk estimates of lung cancer for exposure to PM2.5 and PM10 adjusted for tobacco smoking and socioeconomic status, and conducted a meta-analysis based on random-effects models, including stratification by outcome, sex, country, tobacco smoking, and age.
Results: Results on PM2.5 exposure were available from 15 studies; the summary relative risk (RR) for an increase of 10 μg/m^3 was 1.16 (95% confidence interval [CI] 1.09, 1.23). The corresponding RR for PM10 exposure was 1.23 (95 CI 1.05, 1.40; seven studies). A higher risk was suggested in studies based on lung cancer mortality and in studies conducted in East Asia, while no difference was shown according to sex, smoking status or age. There was no suggestion of publication bias.
Conclusions: Our meta-analysis supported the hypothesis of an association between exposure to PM2.5 or PM10 and risk of lung cancer, and provided evidence that the magnitude of the risk might be higher than previously estimated, and might be modified by outcome and geographic region.

1. Introduction

Particulate matter (PM) is a mixture of solids and liquid droplets floating in the air. Some particles are released from a specific source, while others are generated through chemical reactions in the atmosphere. The chemical properties of PM vary depending on sources of particles; PM is not one particular chemical agent but a complex mixture whose components are classified by size in addition to chemical properties.

The two most commonly studied categories of fine PM are PM10, comprising PM 10 μm or less in aerodynamic diameter, and PM2.5, whose upper limit of the aerodynamic diameters is 2.5 μm (IARC, 2016).

A large number of studies have investigated the association between exposure to PM and human health, particularly short-term effects on cardiovascular and respiratory diseases (Dominici et al., 2006). Results of these studies are heterogeneous (Beelen et al., 2015), likely reflecting methodological aspects of the design (e.g., exposure assessment), the effect of bias, as well as differences in the chemical composition of PM due to season and location.

Long-term health effects of air pollution are more difficult to investigate than short-term effects, because of the need for longitudinal studies with valid assessment of exposure, data on potential confounders, adequate latency between exposure and outcome, and sufficient number of events. Lung cancer is prominent among diseases potentially affected by air pollution exposure (Ming et al., 2017) because it is the leading cause of cancer mortality worldwide, with an estimated 1.2 million deaths and 25.4 million disability-adjusted lost years in 2016 (GBD, 2018). In 2013, the International Agency for Research on Cancer classified air pollution as human carcinogen, based on sufficient evidence of an association with lung cancer (IARC, 2016), but this

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evaluation did not address the quantitative aspects of the association.

Several meta-analyses have been reported on the association between exposure to air pollution and occurrence of cancer, but none of these was restricted to studies that were adequately adjusted for potential confounders. Hamra et al. (2014) performed a meta-analysis of 18 studies, mainly conducted in the United States (US) and Europe, that resulted in summary relative risks (RR) for lung cancer mortality of 1.09 (95% confidence interval [CI]: 1.04, 1.14) and 1.08 (95% CI: 1.00, 1.17) for an increase in exposure to PM2.5 and PM10 equal to 10 $\mu g/m^3$, respectively. However, several of the studies were not adjusted for potential confounders (for example, smoking habits) and the result on the risk associated with PM10, while quantitative similar to that for PM2.5, was less robust. Cui et al. (2015) reviewed 19 prospective cohort: the summary adjusted RR for lung cancer mortality were 1.09 (95% CI: 1.06, 1.11) for 10 $\mu g/m^3$ increase in the concentration of PM2.5 (12 studies), and 1.05 (95% CI: 1.03, 1.07) for a comparable increase in the concentration of PM10 (seven studies).

Kim et al. (2018) reported a new meta-analysis on exposure to ambient air pollution and cancer mortality, including 30 cohort studies. The summary RR for 10 $\mu g/m^3$ increase in the concentration of PM2.5 was 1.17 (95% CI: 1.11, 1.24) for all cancers, 1.14 (95% CI: 1.07, 1.21) for lung cancer.

Our aim was to conduct a systematic review of the scientific literature reported in the last 15 years, and to perform a quantitative synthesis of the data through a meta-analysis, in order to evaluate the association between environmental exposure to PM10 and PM2.5 and risk of lung cancer, with emphasis on results adjusted by tobacco smoking and income or education. We decided to restrict the review to studies published in the last 15 years to take into account qualitative and quantitative changes in air pollution that occurred in more developed countries during the last decades, whose effects are likely addressed in recent studies.

2. Methods

We followed the PRISMA guidelines to conduct a systematic review and meta-analysis (Moher et al., 2009). The PRISMA checklist is reported in Appendix 1.

A literature search of the databases, PubMed/MEDLINE, Embase, and Scopus was carried out to identify relevant peer-reviewed articles of prospective studies evaluating the association between exposure to PM2.5 or PM10 and lung cancer incidence or mortality. The search was restricted to studies published between January 1st, 2004 and November 1st, 2019, details on the search strings can be found in Appendix 2.

All prospective cohort studies which reported results on the association between level of exposure to PM2.5 or PM10 and incidence or mortality from lung cancer (ICD10 codes C33–C34) in adults, in which the results were adjusted for sex, age, tobacco smoking (smoking status as a minimum) and socio-economic status (expressed either as education or income) were eligible for inclusion.

The following exclusion criteria were used: cross-sectional and retrospective (case-control) studies, case reports and case series, prospective studies without measures of association and confidence intervals (or data enabling to calculate them), studies measuring short-term effects (less than one year of follow-up), studies reporting results on incidence or mortality from broad groups of diseases (e.g. lung or respiratory diseases) or results not adjusted for tobacco smoking and socioeconomic status, abstracts with no full text available, and studies reporting results that have been superseded by subsequent reports from the same study population.

Two authors (ER and MC) independently reviewed the titles and the abstracts of the articles identified in the searches, applying the inclusion and exclusion criteria mentioned above. The same two researchers then independently reviewed the full-text articles to confirm their inclusion.

Disagreements were resolved by consensus with a third author (FL). Duplicate publications were carefully identified and excluded.

For each included study, information was abstracted independently by two authors (ER and MC) on details of the publication (author names, journal, year of publication, country of origin), characteristics of the cohort (gender, age, follow-up period, loss to follow-up, size), exposure definition and pollutant concentration assessment methods, study outcome (lung cancer incidence or mortality), details on the regression model, as well as RR and corresponding 95% CI.

The main outcome measure was the RR of lung cancer incidence or mortality associated with an increase of 10 $\mu g/m^3$ exposure to PM2.5 or PM10. If results were reported for an increase in exposure different from 10 $\mu g/m^3$, we calculated the corresponding RR for 10 $\mu g/m^3$ as proposed by Shah et al. (2013).

The quality of the studies included in the meta-analysis was independently evaluated by three authors (ER, FL, MC) using the NIH study quality assessment tools for observational cohort studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). The tool included 14 quality criteria, that were summarized in an overall score (good, fair, poor quality), based on consensus among the three scorers.

We conducted random effects meta-analysis (DerSimonian and Laird, 1986), using Stata package (StataCorp, 2019). In the primary analysis we combined results on lung cancer incidence and mortality, based on the poor survival from lung cancer and the assumption that PM exposure does not affect it. We then carried out secondary analyses stratified by outcome (lung cancer incidence, mortality), gender, smoking status, and median age at enrolment in the cohort. Heterogeneity of summary RRs was evaluated using the I^2 statistics (Higgins and Thompson. 2002). Publication bias was graphically evaluated trough funnel plots and formally tested (Egger et al., 1997) for meta-analyses which included at least 10 risk estimates. Two sensitivity analyses were conducted: first, we excluded one study at the time from the meta-analysis; next, we stratified the studies according to quality score.

3. Results

We identified 843 articles for abstract screening; 55 of them were selected for full text review, and 18 articles were retained for the meta-analysis (Fig. 1). They referred to 17 cohort studies (the articles by Laden et al., 2006 and Lepeule et al., 2012 were based on the same cohort). One of the studies (Raaschou-Nielsen et al. (2016)) consisted of

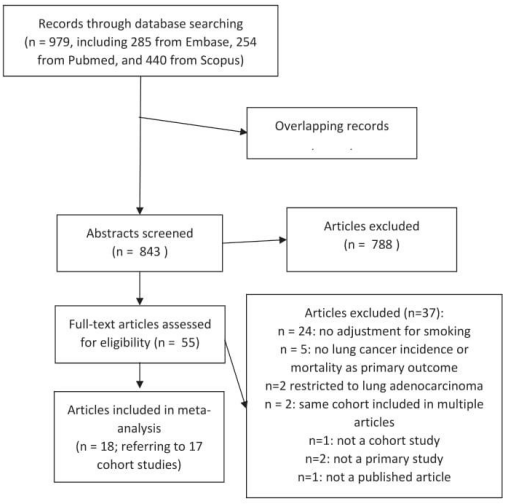

Fig. 1. Flow-chart for the identification of studies to include the meta-analysis.

a pooled analysis of 14 European cohorts, and was treated as a single study in our meta-analysis.

Selected characteristics of the 17 studies retained in the analysis are presented in Table 1. The total population included in these cohorts amounted to more than 30 million individuals, that contributed more than 274 million person years of observation. Thirteen studies considered lung cancer mortality as the outcome, while four measured lung cancer incidence. Eleven studies evaluated only exposure to PM 2.5, two only exposure to PM10 and five exposure to both mixtures. The majority of the studies assessed the risk of lung cancer for an increase of 10 μg/m^3 PM2.5 or PM10, while one study each measured the risk for an increase of 3, 3.2, 5, or 7 μg/m^3. Twelve studies were scored 'good' and four studies 'fair' (Table 1).

The meta-analysis of 15 studies on PM2.5 exposure resulted in a summary RR equal to 1.16 (95% CI 1.09, 1.23, $I^2 = 89\%$) for an increase of 10 μg/m^3 (Fig. 2). Among these studies, 11 reported results for mortality from lung cancer (RR 1.17; 95% CI 1.10, 1.25; $I^2 = 90\%$) and four on lung cancer incidence (RR 1.11; 95% CI 0.85, 1.37; $I^2 = 85\%$). The p-value of the test for heterogeneity between the two groups of studies was 0.05. The meta-analysis of seven studies with results on exposure to PM10 resulted in a summary RR of 1.23 (95 CI 1.05, 1.40, $I^2 = 93\%$; Fig. 3). Five of these studies were based on lung cancer mortality (RR 1.28; 95% CI 1.04, 1.52; $I^2 = 94\%$) and two on incidence (RR 1.11; 95% CI 0.91, 1.29; $I^2 = 62\%$); p-value of the test for heterogeneity between the two groups of studies < 0.001. The exclusion of one study at a time did not reduce the heterogeneity in either meta-analysis (results not shown in detail).

The results of the meta-analyses stratified by smoking status are reported in Table 2. For exposure to PM2.5, the summary RR of lung cancer was higher for former and never smokers than for current smokers, while the opposite pattern was detected for exposure to PM10. None of the differences between stratum-specific summary RR was statistically significant.

Stratification for geographic region (Table 3) suggested a stronger association in studies conducted in East Asia and North America than in studies conducted in Europe for exposure to PM2.5 (p of

Test for heterogeneity across regions < 0.001); corresponding results for PM10 were hampered by the small number of studies.

Only two studies of PM2.5 exposure reported separate results for men and women (Katanoda et al., 2011; Wong et al., 2016) the summary RR were 1.27 (95% CI 1.19, 1.39) in men and 1.09 (95% CI 0.92, 1.27) in women (p-value of test of heterogeneity between groups = 0.08). No studies of PM10 exposure reported separate results according to gender. The analysis by median age at enrolment was feasible only for studies of PM2.5 exposure: the summary RR were 1.63 (95% CI 0.62, 2.65) for two studies with median age lower than 50, 1.11 (95% CI 1.03, 1.18) for seven studies with median age between 50 and 64, and 1.15 (95% CI 1.11, 1.18) for three studies with median age 65 or higher.

Two sensitivity analyses were conducted. When we excluded one study at a time, the summary RR for PM2.5 exposure ranged from 1.12

Table 1
Selected characteristics of studies included in the meta-analysis.

Reference	Country	% men	Study period	Cohort size	Person years	Source of data on exposure	Out-come	Source of outcome data	Exposure	Age group	Quality score
Laden et al. (2006)‡	USA	45	1977–1998	8096	158978	Centrally located air-monitoring stations	Mor	NDI	PM 2.5	2	G
Beelen et al., (2008)	Netherlands	48	1986–1997	111816	1053330	National Air quality monitoring network	Inc	National registries	PM 2.5	2	F
Lipsett et al. (2011)	USA	0	1995–2005	124614	1370754	Models based on air monitoring stations	Mor	Active follow-up	PM 2.5; PM 10	NA	G
Katanoda et al. (2011)	Japan	47	1985–1995	63520	550338	Ambient air monitoring stations	Mor	Local registries	PM 2.5	2	G
Cao et al. (2011)	China	51	1991–2000	70947	638523	National monitoring data	Mor	Active follow-up	PM 2.5	2	G
Pope et al. (2011)	USA	39	1982–1988	794784	4768704	EPA Air Quality System	Mor	Active follow-up	PM 2.5	2	G
Lepeule et al. (2012)‡	USA	45	1977–2009	8096	212067	Centrally located air monitoring stations	Mor	NDI	PM 2.5	NA	G
Carey et al. (2013)	UK	NA	2003–2007	836557	4154210	Air dispersion models	Mor	National database	PM 2.5; PM 10	NA	F
Heinrich et al. (2013)	Germany	0	1985–2008	4752	109296	Air monitoring stations	Mor	State registries	PM 10	NA	G
Puett et al. (2014)	USA	0	1994–2010	103650	1510027	GIS-based models	Inc	Active follow-up	PM 2.5; PM 10	3	G
Fischer et al. (2015)	Netherlands	48	2004–2011	7218363	50528541	Air monitoring network	Mor	National registries	PM 10	NA	F
Raaschou-Nielsen et al., 2015[a]	9 European countries	NA	NA	245782	3229220	Models based on air monitoring stations	Inc	National registries	PM 2.5; PM 10	NA	NA
Wong et al. (2016)	Hong Kong	NA	1998–2011	60273	620812	Environmental Protection Department	Mor	National registries	PM2.5	3	G
Chen et al. (2016)	China	NA	1998–2009	39054	468648	Local air monitoring centres	Mor	Next to kin	PM 2.5	1	G
Pun et al. (2017)	USA	NA	2000–2008	18937461	170437149	EPA Air Quality System	Mor	Medicare	PM 2.5	3	G
Weichenthal et al. (2017)	Canada	55	2001–2012	1039128	12116232	Satellite observations	Inc	National registries	PM 2.5	2	F
Yin et al. (2017)	China	100	1996–2006	189793	3226481	Satellite-based models and ground measurements	Mor	National registries	PM 2.5	2	G
Pope et al. (2019)	USA	45	1986–2016	635539	19066170	Regulatory monitoring data	Mor	NDI	PM 2.5	1	G

Mor, mortality; Inc, incidence; NDI, National Death Index; NA, not available.
[a] Pooled analysis of 14 cohorts.

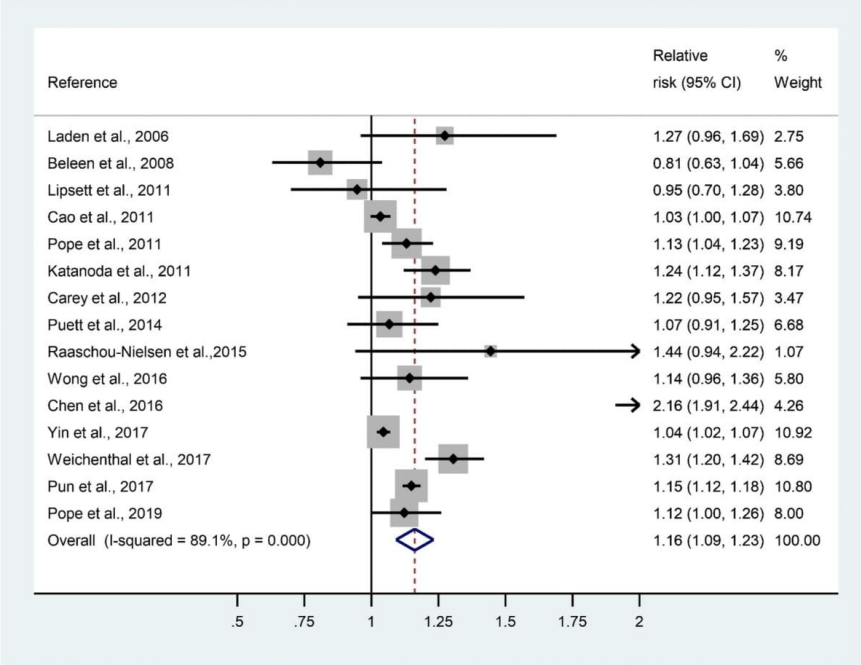

Fig. 2. Meta-analysis of studies on exposure to PM2.5 and risk of lung cancer.

to 1.18 (all statistically significant), and the summary RR from PM10 ranged from 1.13 (excluding Chen et al., 2016, $p > 0.05$) to 1.28. When we stratified the analysis by quality score, the meta-analyses for both exposure to PM2.5 and PM10 resulted in higher summary RR for good-quality studies (RR 1.16, 95% CI 1.09, 1.23, 12 studies; and RR 1.29; 95% CI 0.91,1.67, four studies, respectively) than for fair-quality studies (RR 1.11; 95% CI 0.78, 1.45, three studies; and RR 1.20, 95% CI 1.05, 1.35, two studies, respectively). The p-value of the test of heterogeneity between the two groups of studies was 0.02 for PM2.5 exposure studies and 0.07 for PM10 exposure.

The funnel plot for the analysis of exposure to PM2.5 is shown in Fig. 4. There was no evidence of publication bias ($p = 0.18$). The corresponding analysis of results on exposure to PM10 was hampered by small number, but provided no evidence of publication bias ($p = 0.81$).

4. Discussion

Previous reviews and meta-analyses of studies on risk of lung cancer from environmental exposure to PM2.5 or PM10 have concluded on the presence of an association (Cui et al. (2015); Hamra et al., 2014; Kim et al., 2018). However, this conclusion did not fully account for potential limitations in the underlying studies, including exposure misclassification, inconsistencies of subgroup results (e.g., tobacco smoking and sex) (Boffetta et al., 2015). We aimed at addressing these potential shortcomings by restricting our review to studies reported since 2004, that adjusted for potential confounders. Our meta-analysis confirmed the presence of an association between estimated exposure to PM2.5 and PM10 and risk of lung cancer, with a relative risk of 1.16 for an increase of 10 $\mu g/m^3$ in PM2.5 exposure and of 1.23 for a comparable increase in PM10 exposure.

These risk estimates are higher than those derived in previous meta-analysis. For example, in the meta-analysis by Hamra et al. (2014) the estimated relative risk for an increase of 10 $\mu g/m^3$ exposure was 1.09 for PM2.5 and 1.08 for PM10. The difference can be explained by several factors: (i) a higher quality of more recent studies, in particular in terms of reduced exposure misclassification, (ii) a lower absolute risk of lung cancer among those with low or no exposure to air pollutants because of decline in tobacco smoking and occupational exposures, (iii) a higher risk in studies from East Asia, which provided a larger share of the overall data compared to previous meta-analysis.

Despite our efforts to select the most valid results, several sources of bias might have still operated in the underlying studies. First, exposure to both PM2.5 and PM10 was assessed at the ecologic level, typically the place of residence, measured with variable level of precision. As discussed by previous authors, this bias would have likely caused non-differential misclassification resulting in underestimate of the risk.

Second, exposure levels might have been measured in a period of time not relevant for development of lung cancer in the study subjects. This is particularly relevant because most cohorts included in the review had a relatively short follow-up: only in the studies by Heinrich et al. (2013), Puett et al. (2014), and Pope et al. (2019) were the subjects followed up for more than 15 years. Given the secular decline in air pollution in all the countries where these studies were conducted, with the possible exception of China, using a recent exposure estimate would lead to an overestimate of the dose-response (Boffetta et al., 2015).

Third, residual confounding remains possible, since in many studies only broad categories of tobacco smoking were used in the statistical adjustment, and several risk factors of lung cancer, such as occupational exposure and diet, were mostly excluded from the adjustment. The direction and magnitude of the resulting bias are unclear, but if a positive correlation is present between tobacco smoking and air pollution exposure, the bias would have led to an overestimate of the association.

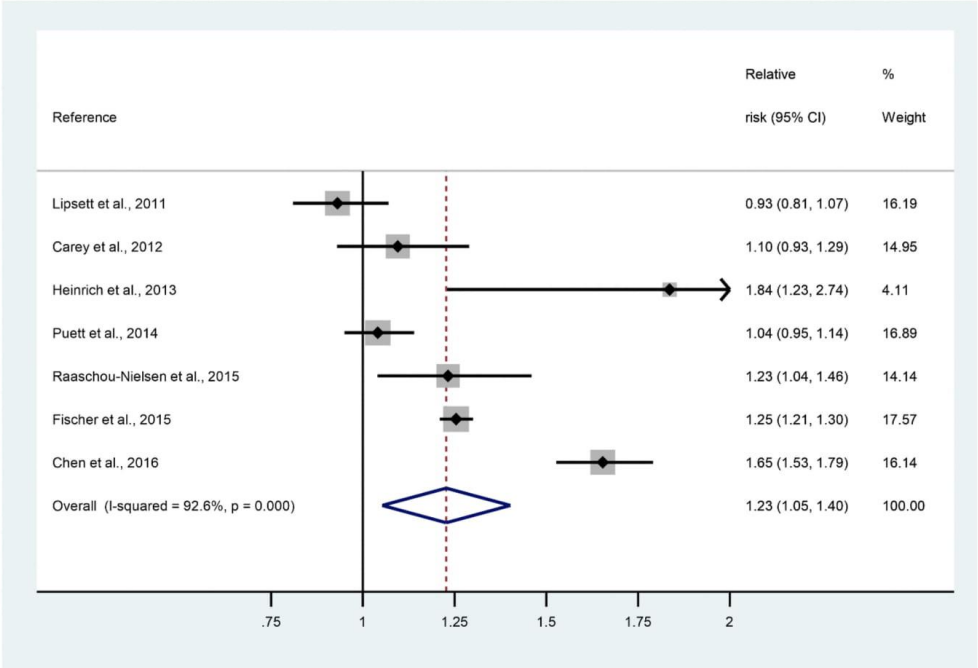

Fig. 3. Meta-analysis of studies on exposure to PM10 and risk of lung cancer.

Table 2
Meta-analysis of RR of lung cancer for exposure to PM2.5 and PM10, stratified by tobacco smoking.

Exposure	Smoking status	RR	95% CI	p het
PM2.5[a]	Current smoker	1.04	0.89–1.19	0.4
	Former smoker	1.30	0.90–1.70	0.05
	Never smoker	1.27	1.04–1.50	1.0
PM10[b]	Current smoker	1.18	0.91–1.46	0.04
	Former smoker	1.03	0.87–1.19	0.1
	Never smoker	1.07	0.98–1.16	0.5

RR, relative risk; CI, confidence interval; p het,p-value of test for heterogeneity.
[a] Lipsett et al. (2011); Lepeule et al. (2012); Puett et al. (2014); Raaschou-Nielsen et al., 2015
[b] Lipsett et al.(2011); Puett et al. (2014); Raaschou-Nielsen et al., 2016

Table 3
Meta-analysis of RR of lung cancer for exposure to PM2.5 and PM10, stratified by geographic region.

Exposure	Region	N studies	RR	95% CI	p het
PM2.5	North America	7	1.16	1.09–1.22	0.08
	Europe	3	1.09	0.72–1.46	0.03
	East Asia	5	1.23	1.11–1.36	<0.001
PM10	North America	2	0.99	0.89–1.10	0.18
	Europe	4	1.23	1.11–1.34	0.16
	East Asia	1	1.65	1.52–1.79	–

RR, relative risk; CI, confidence interval; p het, p-value of test for heterogeneity.

In addition to providing an updated and more valid estimate of the association between exposure to PM2.5 and PM10 and risk of lung cancer, our meta-analysis explored different factors that may explain the heterogeneity of results and modify the risk. Tobacco smoking is of primary importance, given its prominent role as risk factor of lung cancer. The results of our meta-analysis (Table 2) suggest a stronger association for never and former smokers than for current smokers, which can be interpreted as negative interaction or antagonism. Such effect, if real, can be explained by an overlap in the carcinogenic mechanisms underlying the two risk factors (Saracci and Boffetta, 1994). There is some evidence that a similar pattern operates in the interaction between diesel exhaust and tobacco smoking (Silverman et al., 2012).

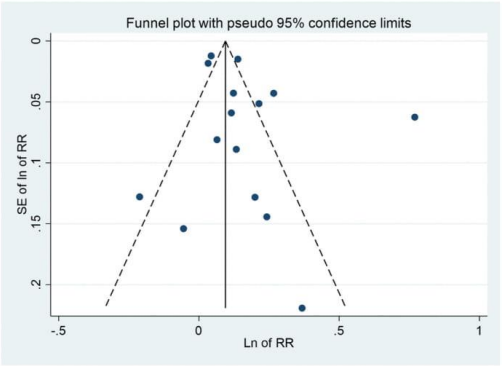

Fig. 4. Funnel plot of results on exposure to PM2.5 and risk of lung cancer.

An interesting and novel aspect of our results is the higher risk for exposure to both PM2.5 and PM10, detected in studies based on lung cancer mortality compared to studies on incidence. If real, this difference might indicate a possible effect of air pollutants on severity of the disease or response to therapy. An alternative explanation might be confounding by factors, such as socioeconomic status, that might be associated with both exposure to air pollution and outcome after lung cancer. Interestingly, this difference is not apparent for other risk factors of lung cancer, notably tobacco smoking (IARC, 2004).

As mentioned above, stratification by geographic area provided evidence of a stronger association in studies from East Asia and – to a less extent – North America compared to studies from Europe (Table 3). Assuming comparable validity of the underlying studies, this might result from differences in individual susceptibility, composition of air pollution, or interaction with other risk factor of lung cancer. Limited empirical data are available, however, to test each of these hypotheses.

The analysis of the interaction with sex was hampered by the small number of studies with relevant results. However, a stronger association between PM2.5 exposure and lung cancer was suggested in

Men compared to women, which might be explained by residual confounding by tobacco smoking or occupational exposure in the underlying studies.

In conclusion, our meta-analysis of high-quality cohort studies on PM exposure and risk of lung cancer support the hypothesis of an association that was proposed in previous studies. Our meta-analysis contributed to clarify several aspects of the association.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.110440.

References

Beelen, R., Hoek, G., Raaschou-Nielsen, O., et al., 2015. Natural-cause mortality and long-term exposure to particle components: an analysis of 19 European cohorts within the multi-center ESCAPE project. Environ. Health Perspect. 123, 525–533.
Beelen, R., Hoek, G., van den Brandt, P.A., et al., 2008. Long-term exposure to traffic-related air pollution and lung cancer risk. Epidemiology 19, 702–710.
Boffetta, P., La Vecchia, C., Moolgavkar, S., 2015. Chronic effects of air pollution are probably overestimated. Risk Anal. 35, 766–769.
Cao, J., Yang, C., Li, J., et al., 2011. Association between long-term exposure to outdoor air pollution and mortality in China: a cohort. J. Hazard Mater. 186, 1594–1600.
Carey, I.M., Atkinson, R.W., Kent, A.J., van Staa, T., Cook, D.G., Anderson, H.R., 2013. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am. J. Respir. Crit. Care Med. 187, 1226–1233.
Chen, X., Zhang, L.W., Huang, J.J., et al., 2016. Long-term exposure to urban air pollution and lung cancer mortality: a 12-year cohort study in Northern China. Sci. Total Environ. 571, 855–861.
Cui, P., Huang, Y., Han, J., Song, F., Chen, K., 2015. Ambient particulate matter and lung cancer incidence and mortality: a meta-analysis of prospective studies. Eur. J. Publ. Health 25, 324–329.
DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Contr. Clin. Trials 7, 177–188.
Dominici, F., Peng, R.D., Bell, M.L., et al., 2006. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. J. Am. Med. Assoc. 295, 1127–1134.
Egger, M., Smith, G.D., Phillips, A.N., 1997. Meta-analysis: principles and procedures. BMJ 315, 1533–1537.
Fischer, P.H., Marra, M., Ameling, C.B., et al., 2015. Air pollution and mortality in seven million adults: the Dutch environmental longitudinal study (DUELS). Environ. Health Perspect. 123, 697–704.
GBDCC (Global Burden of Disease Cancer Collaboration), 2018. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability- adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the global burden of disease study. JAMA Oncol 4, 1553–1568.
Hamra, G.B., Guha, N., Cohen, A., et al., 2014. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environ. Health Perspect. 122, 906–911.
Heinrich, J., Thiering, E., Rzehak, P., et al., 2013. Long-term exposure to NO2 and PM10 and all-cause and cause-specific mortality in a prospective cohort of women. Occup. Environ. Med. 70, 179–186.
Higgins, J.P., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21, 1539–1558.
IARC (International Agency for Research on Cancer), 2004. Tobacco smoking. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 83. IARC, Lyon, France, pp. 51–1188. Tobacco Smoking and Involuntary Smoking.
IARC (International Agency for Research on Cancer), 2016. Outdoor Air Pollution. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 109. IARC, Lyon, France.
Katanoda, K., Sobue, T., Satoh, H., et al., 2011. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. J. Epidemiol. 21, 132–143.
Kim, H.B., Shim, J.Y., Park, B., Lee, Y.J., 2018. Long-term exposure to air pollutants and cancer mortality: a meta-analysis of cohort studies. Int. J. Environ. Res. Publ. Health 21, 2608.
Laden, F., Schwartz, J., Speizer, F.E., Dockery, D.W., 2006. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. Am. J. Respir. Crit. Care Med. 173, 667–672.
Lepeule, J., Laden, F., Dockery, D., Schwartz, J., 2012. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. Environ. Health Perspect. 120, 965–970.
Lipsett, M.J., Ostro, B.D., Reynolds, P., et al., 2011. Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. Am. J. Respir. Crit. Care Med. 184, 828–835.
Ming, L., Jin, L., Li, J., et al., 2017. PM(2.5) in the Yangtze River Delta, China: chemical compositions, seasonal variations, and regional pollution events. Environ. Pollut. 223, 200–212.
Moher, D., Liberati, A., Tetzlaff, J., Altmann, D.G., 2009. The PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann. Intern. Med. 151, 264–269.
Pope 3rd, C.A., Burnett, R.T., Turner, M.C., et al., 2011. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure- response relationships. Environ. Health Perspect. 119, 1616–1621.
Pope 3rd, C.A., Lefler, J.S., Ezzati, M., et al., 2019. Mortality risk and fine particulate air pollution in a large, representative cohort of U.S. Adults. Environ. Health Perspect. 127, 77007.
Puett, R.C., Hart, J.E., Yanosky, J.D., et al., 2014. Particulate matter air pollution exposure, distance to road, and incident lung cancer in the nurses' health study cohort. Environ. Health Perspect. 122 (9), 926–932. https://doi.org/10.1289/ehp.1307490, 2014.
Pun, V.C., Kazemiparkouhi, F., Manjourides, J., Suh, H.H., 2017. Long-term PM2.5 exposure and respiratory, cancer, and cardiovascular mortality in older US adults. Am. J. Epidemiol. 186, 961–969.
Raaschou-Nielsen, O., Beelen, R., Wang, M., et al., 2016. Particulate matter air pollution components and risk for lung cancer. Environ. Int. 87, 66–73.
Saracci, R., Boffetta, P., 1994. Interactions of tobacco smoking with other causes of lung cancer. In: Samet, J.M. (Ed.), Epidemiology of Lung Cancer. Marcel Dekker, New York, pp. 465–493.
Shah, A.S., Langrish, J.P., Nair, H., et al., 2013. Global association of air pollution and heart failure: a systematic review and meta-analysis. Lancet 382, 1039–1048.
Silverman, D.T., Samanic, C.M., Lubin, J.H., et al., 2012. The Diesel Exhaust in Miners Study: a nested case–control study of lung cancer and diesel exhaust. J. Natl. Cancer Inst. 104, 855–868.
StataCorp, 2019. Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX.
Weichenthal, S., Bai, L., Hatzopoulou, M., et al., 2017. Long-term exposure to ambient ultrafine particles and respiratory disease incidence in in Toronto, Canada: a cohort study. Environ. Health 16, 64.
Wong, C.M., Tsang, H., Lai, H.K., et al., 2016. Cancer mortality risks from long-term exposure to ambient fine particle. Cancer Epidemiol. Biomark. Prev. 25, 839–845.
Yin, P., Brauer, M., Cohen, A., et al., 2017. Long-term fine particulate matter exposure and nonaccidental and cause-specific mortality in a large national cohort of Chinese men. Environ. Health Perspect. 125, 117002.

Bibliografia

- "Ionizing radiation, health effects and protective measures". World Health Organization. 29 April 2016.
- AA.VV. Linee guida A.I.R.M. Sorveglianza medica dei lavoratori esposti a radiazioni ionizzanti, 2013
- AIRTUM, 2020. I numeri del Cancro in Italia
- Abdel-Rahman O. Global trends in mortality from malignant mesothelioma: Analysis of WHO mortality database (1994-2013). Clin Respir J. 2018 Jun;12(6):2090-2100.)
- Alpert, Naomi, Maaike van Gerwen, and Emanuela Taioli. "Epidemiology of mesothelioma in the 21st century in Europe and the United States, 40 years after restricted/banned asbestos use." Translational Lung Cancer Research 9.Suppl 1 (2020): S28.
- Andersson M, Carstensen B, Storm HH. Mortality and cancer incidence after cerebral arteriography with or without Thorotrast. Radiat Res. 1995 Jun;142(3):305-20.
- Atkinson WD, Law DV, Bromley KJ, Inskip HM. Mortality of employees of the United Kingdom Atomic Energy Authority, 1946-97. Occup Environ Med. 2004 Jul;61(7):577-85.
- Attanoos RL, Churg A, Galateau-Salle F, Gibbs AR, Roggli VL. Malignant Mesothelioma and Its Non-Asbestos Causes. Arch Pathol Lab Med. 2018 Jun;142(6):753-760.
- Baxter NN, Tepper JE, Durham SB, Rothenberger DA, Virnig BA. Increased risk of rectal cancer after prostate radiation: a population-based study. Gastroenterology. 2005 Apr;128(4):819-24.
- Bell KJ, Del Mar C, Wright G, Dickinson J, Glasziou P. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. Int J Cancer. 2015 Oct 1;137(7):1749-57
- Berrington de Gonzalez A, Curtis RE, Gilbert E, Berg CD, Smith SA, Stovall M, Ron E. Second solid cancers after radiotherapy for breast cancer in SEER cancer registries. Br J Cancer. 2010 Jan 5;102(1):220-6.

- Besag, J. , York J., and Mollie A.. 1991. Bayesian image restoration, with two applications in spatial statistics (with discussion). Ann. Inst. Stat. Math. 43:1–59
- Boffetta P. Epidemiology of peritoneal mesothelioma: a review. Ann Oncol. 2007 Jun;18(6):985-90.
- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.
- Carpenter LM, Higgins CD, Douglas AJ, Maconochie NE, Omar RZ, Fraser P, Beral V, Smith PG. Cancer mortality in relation to monitoring for radionuclide exposure in three UK nuclear industry workforces. Br J Cancer. 1998 Nov;78(9):1224-32.
- Chang ET, Lau EC, Mowat FS, Teta MJ. Therapeutic radiation for lymphoma and risk of second primary malignant mesothelioma. Cancer Causes Control. 2017 Sep;28(9):971-979. doi: 10.1007/s10552-017-0929-4. Epub 2017 Jul 28. PMID: 28755241.
- De Bruin ML, Burgers JA, Baas P, van 't Veer MB, Noordijk EM, Louwman MW, Zijlstra JM, van den Berg H, Aleman BM, van Leeuwen FE. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. Blood. 2009 Apr 16;113(16):3679-81.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. doi: 10.1016/0197-2456(86)90046-2.
- Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ. 1997 Dec 6;315(7121):1533-7. doi: 10.1136/bmj.315.7121.1533.
- Farioli A, Ottone M, Morganti AG, Compagnone G, Romani F, Cammelli S, Mattioli S, Violante FS. Ron-induced mesothelioma among long-term solid cancer survivors: a longitudinal analysis of SEER database. Cancer Med. 2016 May;5(5):950-9.
- Farioli A, Violante FS, Mattioli S, Curti S, Kriebel D. Risk of mesothelioma following external beam radiotherapy for prostate cancer: a cohort analysis of SEER database. Cancer Causes Control. 2013 Aug;24(8):1535-45.
- Francois P, Beurtheret C, Dutreix A. Calculation of the dose delivered to organs outside the radiation beams. Med Phys. 1988 Nov-Dec;15(6):879-83
- Gilbert ES. Ionising radiation and cancer risks: what have we learned from epidemiology? Int J Radiat Biol. 2009 Jun;85(6):467-82.
- Goodman JE, Nascarella MA, Valberg PA. Ionizing radiation: a risk factor for mesothelioma. Cancer Causes Control. 2009 Oct;20(8):1237-54.

• Grant, Eric J., et al. "Solid cancer incidence among the life span study of atomic bomb survivors: 1958–2009." Radiation Research 187.5 (2017): 513-537.
• Guidelines for Pathologic Diagnosis of Malignant Mesothelioma 2017 Update of the Consensus Statement From the International Mesothelioma Interest Group. Husain AN, Colby TV, Ordóñez NG, Allen TC, Attanoos RL, Beasley MB, Butnor KJ, Chirieac LR, Churg AM, Dacic S, Galateau-SalléF, Gibbs A, Gown AM, Krausz T, Litzky LA, Marchevsky A, Nicholson AG, Roggli VL, Sharma AK, Travis WD, Walts AE, Wick MR Arch Pathol Lab Med. 2018;142(1):89.
• Habib RR, Abdallah SM, Law M, Kaldor J. Cancer incidence among Australian nuclear industry workers. J Occup Health. 2006 Sep;48(5):358-65.
• Habib RR, Abdallah SM, Law M, Kaldor J. Mortality rates among nuclear industry workers at Lucas Heights Science and Technology Centre. Aust N Z J Public Health. 2005 Jun;29(3):229-37.
• Hall EJ, Brenner DJ. Cancer risks from diagnostic radiology. Br J Radiol. 2008 May;81(965):362-78.
• Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539-58.
• ICRP 118 “Statement on Tissue Reactions and Early and Late Effects of Radiation in Normal Tissues and Organs – Threshold Doses for Tissue Reactions in a Radiation Protection Context”
• ICRP, 1977. Recommendations of the ICRP. ICRP Publication 26. Ann. ICRP 1 (3).
• ICRP, 2005. Low-dose Extrapolation of Radiation-related Cancer Risk. ICRP Publication 99. Ann. ICRP 35 (4).
• IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Radiation. IARC Monogr Eval Carcinog Risks Hum. 2012;100(Pt D):7-303. PMID: 23189752; PMCID: PMC4781534.• Jasani, Bharat, and Allen Gibbs. "Mesothelioma not associated with asbestos exposure." Archives of pathology & laboratory medicine 136.3 (2012): 262-267.
• Kamiya K, Ozasa K, Akiba S, Niwa O, Kodama K, Takamura N, Zaharieva EK, Kimura Y, Wakeford R. Long-term effects of radiation exposure on health. Lancet. 2015 Aug 1;386(9992):469-78.

• Kry SF, Salehpour M, Followill DS, Stovall M, Kuban DA, White RA, Rosen II. Out-of-field photon and neutron dose equivalents from step-and-shoot intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2005 Jul 15;62(4):1204-16.
• Marinaccio A, Binazzi A, Bonafede M, Corfiati M, Di Marzio D, Scarselli A, Verardo M, Mirabelli D, Gennaro V, Mensi C, Schallemberg G, Merler E, Negro C, Romanelli A, Chellini E, Silvestri S, Cocchioni M, Pascucci C, Stracci F, Ascoli V, Trafficante L, Angelillo I, Musti M, Cavone D, Cauzillo G, Tallarigo F, Tumino R, Melis M; ReNaM Working Group. Malignant mesothelioma due to non-occupational asbestos exposure from the Italian national surveillance system (ReNaM): epidemiology and public health issues. Occup Environ Med. 2015 Sep;72(9):648-55.
• Marinaccio A, Corfiati M, Binazzi A, Di Marzio D, Bonafede M, Verardo M, Migliore E, Gennaro V, Mensi C, Schallemberg G, Mazzoleni G, Fedeli U, Negro C, Romanelli A, Chellini E, Grappasonni I, Pascucci C, Madeo G, Romeo E, Trafficante L, Carrozza F, Angelillo IF, Cavone D, Cauzillo G, Tallarigo F, Tumino R, Melis M; ReNaM Working Group. The epidemiological surveillance of malignant mesothelioma in Italy (1993-2015): methods, findings, and research perspectives. Epidemiol Prev. 2020 Jan-Feb;44(1):23-30.
• Matanoski GM, Tonascia JA, Correa-Villaseñor A, Yates KC, Fink N, Elliott E, Sanders B, Lantry D. Cancer risks and low-level radiation in U.S. shipyard workers. J Radiat Res. 2008 Jan;49(1):83-91.
• Metayer C, Lynch CF, Clarke EA, Glimelius B, Storm H, Pukkala E, Joensuu T, van Leeuwen FE, van't Veer MB, Curtis RE, Holowaty EJ, Andersson M, Wiklund T, Gospodarowicz M, Travis LB. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. J Clin Oncol. 2000 Jun;18(12):2435-43
• Metz-Flamant C, Guseva Canu I, Laurier D. Malignant pleural mesothelioma risk among nuclear workers: a review. J Radiol Prot. 2011 Mar;31(1):9-23.
• Metz-Flamant C, Samson E, Caër-Lorho S, Acker A, Laurier D. Solid cancer mortality associated with chronic external radiation exposure at the French atomic energy commission and nuclear fuel company. Radiat Res. 2011 Jul;176(1):115-27.
• Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, Fanti S, Fossati N, Gandaglia G, Gillessen S, Grivas N, Grummet J, Henry AM, van der Kwast TH, Lam TB, Lardas M, Liew M, Mason MD, Moris L, Oprea-Lager DE, van der Poel HG, Rouvière O, Schoots IG, Tilki D, Wiegel T, Willemse PM,

Cornford P. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2020 Nov 7:S0302-2838(20)30769-7.

- National Research Council. 2006. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2. Washington, DC: The National Academies Press.
- Neugut AI, Ahsan H, Antman KH. Incidence of malignant pleural mesothelioma after thoracic radiotherapy. Cancer. 1997 Sep 1;80(5):948-50.
- Ohya M, Kobayashi M, Sozuki T, Kanno H, Nakazawa K. Malignant peritoneal mesothelioma diagnosed 50 years post-radiotherapy for ovarian cancer in a patient with a history of multiple malignancies: An autopsy case. Mol Clin Oncol. 2019;11(4):397-400. doi:10.3892/mco.2019.1906
- Pastorino S, Yoshikawa Y, Pass HI, Emi M, Nasu M, Pagano I, Takinishi Y, Yamamoto R, Minaai M, Hashimoto-Tamaoki T, Ohmuraya M, Goto K, Goparaju C, Sarin KY, Tanji M, Bononi A, Napolitano A, Gaudino G, Hesdorffer M, Yang H, Carbone M. A Subset of Mesotheliomas With Improved Survival Occurring in Carriers of BAP1 and Other Germline Mutations. J Clin Oncol. 2018
- Pickles T, Phillips N. The risk of second malignancy in men with prostate cancer treated with or without radiation in British Columbia, 1984-2000. Radiother Oncol. 2002 Dec;65(3):145-51.
- Prasad KN, Cole WC, Hasse GM. Health Risks of Low Dose Ionizing Radiation in Humans: A Review. Experimental Biology and Medicine. 2004;229(5):378-382.
- Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat Res. 2007 Jul;168(1):1-64.
- Preston, R. Julian. "The LNT model is the best we can do—today." Journal of Radiological Protection 23.3 (2003): 263.
- Price, Bertram, and Adam Ware. "Mesothelioma trends in the United States: an update based on Surveillance, Epidemiology, and End Results Program data for 1973 through 2003." American Journal of Epidemiology 159.2 (2004): 107-112.
- Prise KM, O'Sullivan JM. Radiation-induced bystander signalling in cancer therapy. Nat Rev Cancer. 2009 May;9(5):351-60.

• Samson E, Piot I, Zhivin S, Richardson DB, Laroche P, Serond AP, Laurier D, Laurent O. Cancer and non-cancer mortality among French uranium cycle workers: the TRACY cohort. BMJ Open. 2016 Apr 5;6(4):e010316.
• Schubauer-Berigan MK, Daniels RD, Bertke SJ, Tseng CY, Richardson DB. Cancer Mortality through 2005 among a Pooled Cohort of U.S. Nuclear Workers Exposed to External Ionizing Radiation. Radiat Res. 2015 Jun;183(6):620-31.
• Siegel, Jeffry A., Bill Sacks, and Yehoshua Socol. "The LSS Cohort of Atomic Bomb Survivors and LNT. Comments on ‘‘Solid Cancer Incidence among the Life Span Study of Atomic Bomb Survivors: 1958–2009” (Radiat Res 2017; 187: 513–37)
• Sinclair, W.K., Recent estimates of cancer risk from low-LET ionizing radiation and radiation protection limits. Adv Space Res, 1992. 12(2-3): p. 375-8.
• Telle-Lamberton M, Bergot D, Gagneau M, Samson E, Giraud JM, Néron MO, Hubert P. Cancer mortality among French Atomic Energy Commission workers. Am J Ind Med. 2004 Jan;45(1):34-44.
• Teta MJ, Lau E, Sceurman BK, Wagner ME. Therapeutic radiation for lymphoma: risk of malignant mesothelioma. Cancer. 2007 Apr 1;109(7):1432-8.
• Tubiana, M., The report of the French Academy of Science: 'Problems associated with the effects of low doses of ionising radiation'. J Radiol Prot, 1998. 18(4): p. 243-8.
• van Kaick G, Dalheimer A, Hornik S, Kaul A, Liebermann D, Lührs H, Spiethoff A, Wegener K, Wesch H. The german thorotrast study: recent results and assessment of risks. Radiat Res. 1999 Dec;152(6 Suppl):S64-71.
• Wallis CJD, Saskin R, Choo R, Herschorn S, Kodama RT, Satkunasivam R, Shah PS, Danjoux C, Nam RK. Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol. 2016 Jul;70(1):21-30.
• Wyllie FS, Haughton MF, Rowson JM, Wynford-Thomas D. Human thyroid cancer cells as a source of iso-genic, iso-phenotypic cell lines with or without functional p53. Br J Cancer. 1999 Mar;79(7-8):1111-20.
• Yang H, Testa JR, Carbone M. Mesothelioma Epidemiology, Carcinogenesis and Pathogenesis. Curr Treat Options Oncol 2008;9:147-57.
survivors: a longitudinal analysis of SEER database.