Prostate Cancer and Asbestos: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Asbestos-related diseases and cancers represent a major public health concern.

Objective: To conduct a systematic review and meta-analysis to demonstrate that asbestos exposure increases the risk of prostate cancer.

Methods: The PubMed, Cochrane Library, Embase, and ScienceDirect databases were searched using the keywords (*prostate cancer* OR *prostatic neoplasm*) AND (*asbestos** OR *crocidolite** OR *chrysotile** OR *amphibole** OR *amosite**). To be included, articles needed to describe our primary outcome: Risk of prostate cancer after any asbestos exposure.

Results: We included 33 studies with 15,687 cases of prostate cancer among 723,566 individuals. Asbestos exposure increased the risk of prostate cancer (effect size = 1.10, 95% confidence interval [CI] = 1.05-1.15). When we considered mode of absorption, respiratory inhalation increased the risk of prostate cancer (1.10, 95% CI = 1.05-1.14). Both environmental and occupational exposure increased the risk of prostate cancer (1.25, 95% CI = 1.01-1.48; and 1.07, 1.04-1.10, respectively). For type of fibers, the amosite group had an increased risk of prostate cancer (1.12, 95% CI = 1.05-1.19), and there were no significant results for the chrysotile/crocidolite group. The risk was higher in Europe (1.12, 95% CI = 1.05-1.19), without significant results in other continents.

Discussion: Asbestos exposure seems to increase prostate cancer risk. The main mechanism of absorption was respiratory. Both environmental and occupational asbestos exposure were linked to increased risk of prostate cancer.

Conclusion: Patients who were exposed to asbestos should possibly be encouraged to complete more frequent prostate cancer screening.

INTRODUCTION

Asbestos is a major occupational risk factor for workers, because it causes various asbestos-related cancers such as lung, laryngeal, and ovarian cancers, and pleural and peritoneal mesothelioma.[1] However, the influence of asbestos exposure on the risk of prostate cancer is still under debate.[2,3] Prostate cancer is the most frequent cancer in men in France[4] and the second most common in the world[5]; therefore, the influence of asbestos exposure on prostate cancer is a public health issue. Most studies demonstrate an increased risk of asbestos-related diseases owing to respiratory exposure.[6,7] Regarding oral ingestion of asbestos, animal studies have failed to demonstrate an increased risk,[8] whereas results of human studies suggest an increased risk of some cancers after drinking asbestos-contaminated water.[9,10] For prostate cancer, some studies demonstrated a particular risk both after respiratory[11,12] and oral ingestion of specific agents,[13-15] but comparisons between modes of absorption of asbestos on the risk of prostate cancer were never investigated. Last, even in countries prohibiting asbestos, asbestos remains widespread at workplaces and in public spaces. For example, some studies stated that nonoccupational exposure is the main cause of some asbestos-related cancers.[16] Therefore, the influence of the type of asbestos exposure (occupational or environmental) on prostate cancer also needs to be further investigated.

In view of these elements, we conducted a systematic review and meta-analysis to evaluate whether asbestos exposure increases the risk of prostate cancer. Secondary objectives were to evaluate the influence of the mode of absorption (respiratory or oral ingestion), the type of exposure (occupational or environmental), and other factors such as occupational role,[17] use of personal protective equipment,[18] quantification of asbestos exposure,[7] type of asbestos fibers,[19] or country.[20,21]

METHODS

Literature Search

We reviewed all published studies involving asbestos exposure, professional or not, and prostate cancer incidence and/or mortality. The inclusion criterion for the search strategy was asbestos exposure. For the literature search, we used the following keywords: (*prostate cancer* OR *prostatic neoplasm*) AND (*asbestos** OR *crocidolite** OR *chrysotile** OR *amphibole** OR *amosite**). The following databases were searched on September 1, 2019: PubMed,

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Keywords: amosite, asbestos, chrysolite, crocidolite, environmental asbestos exposure, occupational asbestos exposure, prostate cancer, work asbestos exposure

Cochrane Library, ScienceDirect, and Embase. The search was not limited to specific years, and no language restrictions applied. To be included, articles needed to describe our primary outcome: Risk of prostate cancer after asbestos exposure. More specifically, we included all articles with data on incidence of, or mortality from, prostate cancer, or articles with crude data allowing such calculation. In addition, reference lists of all publications meeting the inclusion criteria were manually searched to identify any further studies not found through electronic searching. The search strategy is described in Figure 1.

Four authors (LZ-C, VN, FD, and MM) separately conducted all literature searches, collated and reviewed the abstracts, and, on the basis of the selection criteria, decided the suitability of the articles for inclusion. A fifth author (BP) was asked to review the articles when consensus on suitability was debated. Then all authors reviewed the eligible articles.

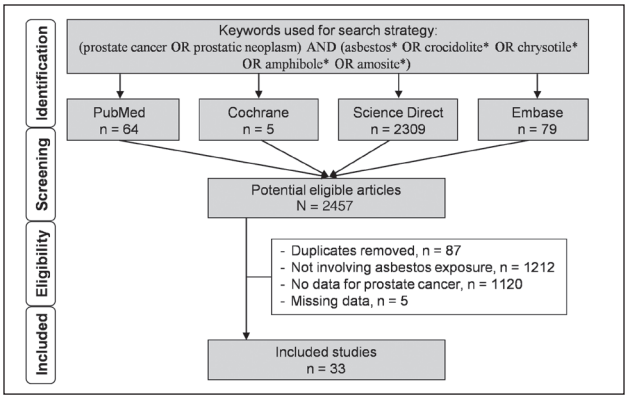

Figure 1. Search strategy.

Quality of Assessment

Although not designed for quantifying the integrity of studies,[22] the "STrengthening the Reporting of OBservational studies in Epidemiology" (STROBE) criteria were used for checking the quality of reporting.[23] The 22 items identified in the STROBE criteria were evaluated for a maximal score of 34 for each study. The methodologic quality of the studies was further evaluated by 3 authors (LZ-C, VN, and FD) using the Newcastle-Ottawa Quality Assessment Scale model.[24] The following 9 items were assessed in all cohort studies: 4 items on selection bias (representativeness of the exposed, selection of the nonexposed cohort, ascertainment of exposed, outcome of interest was not present at start), 2 items on comparability bias (design and analysis), and 3 items on outcome bias (assessment of outcome, longer follow-up, and adequacy of follow-up). Similar items were used to evaluate case-control studies. Each item was assigned a judgment of "yes," "no," "cannot say," or "not applicable." Disagreements were addressed by obtaining a consensus with a third author (BP), shown in Figures 2 and 3.

Statistical Analysis

Statistical analysis was conducted using software (Stata version 13, StataCorp, College Station, TX).[7,25-31] Characteristics of asbestos exposure, prostate cancer, individuals, or other variables were summarized for each study sample and reported as mean (standard deviation [SD]) and number (percent) for continuous and categorical variables, respectively. Heterogeneity in the study results was evaluated by examining forest plots, determining confidence intervals (CIs), and using formal tests for homogeneity based on the I^2 statistic, which is the most common metric for measuring the magnitude of between-study heterogeneity and is easily interpretable. The I^2 values range between 0% and 100% and are typically considered low for less than 25%, modest for 25% to 50%, and high for more than 50%. This statistical method generally assumes heterogeneity when the p value of the I^2 test is less than 0.05. For example, a significant heterogeneity may be caused by the variability between the characteristics of the studies, such as the mode of absorption of asbestos (respiratory or oral ingestion), the type of exposure (occupational or environmental), characteristics of individuals (age, sex, etc), or type of statistics retrieved in the included articles (odds ratio [OR], standardized incidence ratio [SIR], standardized mortality ratio [SMR], standardized rate ratio [SRR], and hazard ratio [HR]). Random-effects meta-analyses (DerSimonian and Laird approach) were conducted when data could be pooled.[32] All p values less than 0.05 were considered statistically significant.

We conducted meta-analyses on the risk of prostate cancer after asbestos exposure. We stratified these meta-analyses on the mode of absorption of asbestos (respiratory or oral ingestion), the type of exposure (occupational or environmental), type of fibers (amosite and others, chrysotile/crocidolite and nonspecified), type of risk (SMR, SIR, SRR, and HR), and by continent (Europe, North America, Asia, and Oceania). When data were pooled, results were expressed as effect size (ES) of the risk of prostate cancer after asbestos exposure.[32] An ES is defined as a unitless measure of the effects of asbestos exposure on the risk of prostate cancer centered at 1. An ES greater than 1 denoted an increased risk.[33] For thoroughness, funnel plots of these meta-analyses were used to search for potential publication bias.

To verify the strength of the results, we conducted further meta-analyses, excluding studies that were not evenly distributed around the base of the funnel.[34] We further performed a meta-analysis excluding studies with multiple exposures for sensitivity analysis. When possible (sufficient sample size), meta-regressions were proposed to study the relationship between the risk of prostate cancer after asbestos exposure and putatively to explain variables such as characteristics of the population (sex, age, etc),[1] working or environmental characteristics,[7] or details on asbestos exposure. Results were expressed as regression coefficients and 95% CI.

RESULTS

An initial search produced 2457 articles (Figure 1). Removal of duplicates (n = 87) and application of selection criteria (1212 studies did not involve asbestos exposure, 1120 studies did not report data on prostate cancer, and 5 studies had missing data) reduced these articles to 33 studies.[2,3,35-65] All identified articles were written in English.

Quality of Articles

Quality assessment of the 33 included studies, as outlined by the STROBE criteria, varied from 70.6[44,49,55,64] to 97%,[37] with a mean (SD) score of 81.8 (7.94). Overall, the studies performed best for quality in their discussion section and worst in the methods section. With use of the Newcastle-Ottawa Quality Assessment Scale models, included studies varied from 67[35,49] to 100%,[61] with a mean (SD) score of 82.5 (8.79). Detailed characteristics of methodologic quality assessment of each included study are available in Figures 2 and 3.

	Selection bias				Comparability bias		Outcome bias		
	Representativeness of the exposed	Selection of the nonexposed	Ascertainment of exposed	Outcome of interest was not present at start	Study controls for the most important factor	Study controls for any important factor	Assessment of outcome	Follow-up long enough	Adequacy of follow-up
Amstrong 1988 [40]	+	NA	+	+	+	+	+	+	+
Berry 2000 [41]	+	+	+	+	+	?	+	+	+
Clemmesen 1981 [42]	+	NA	+	+	+	+	+	+	?
Enterline 1987 [43]	+	NA	+	-	+	+	+	+	+
Franklin 2012 [44]	+	NA	+	?	+	+	+	+	?
Howe 1989 [35]	+	NA	+	-	+	+	+	+	?
Hughes 1987 [45]	+	NA	+	?	+	+	+	+	+
Ilíc 1996 [36]	+	+	+	-	+	+	+	+	+
Korda 2017 [37]	+	NA	+	+	+	+	+	+	+
Koskinen 2003 [38]	+	NA	-	+	+	+	-	+	+
Kovalevskiy 2016 [46]	+	+	+	+	+	?	+	+	+
Krstev 2007 [47]	+	NA	+	+	+	+	+	+	+
Meurman 1994 [48]	+	NA	+	+	+	+	+	+	+
Parent 2019 [49]	+	NA	+	-	+	+	+	+	?
Pesch 2010 [50]	+	NA	+	+	+	+	+	+	+
Pira 2007 [51]	+	NA	+	+	+	+	+	+	+
Pira 2009 [39]	+	NA	+	+	+	+	+	+	+
Pukkala 2014 [65]	+	NA	+	+	+	?	-	+	+
Puntoni 1979 [53]	+	NA	+	+	+	+	+	+	+
Puntoni 2001 [52]	+	NA	+	+	+	?	+	+	+
Raffn 1989 [54]	+	NA	+	+	+	+	+	+	+
Reid 2012 [2]	+	NA	+	+	+	-	+	+	+
Selikoff 1979 [55]	+	NA	+	-	+	+	+	+	+
Sorahan 2019 [56]	+	+	+	+	+	?	+	+	+
Szeszenlia-Dabrowska 2002 [57]	+	NA	+	+	+	+	+	+	+
Tomioka 2011 [59]	+	NA	+	+	+	?	+	+	+
Tola 1988 [58]	+	NA	+	+	+	?	+	+	+
Tsai 1996 [60]	+	NA	+	+	+	+	+	+	+
Van den Borre 2015 [61]	+	+	+	+	+	+	+	+	+
Wang 2012 [62]	+	NA	+	+	+	?	+	+	+
Wilczyńska 2005 [63]	+	NA	+	+	+	+	+	+	+
Wu 2014 [3]	-	NA	+	+	+	+	+	+	+
Zhivin 2013 [64]	+	NA	+	+	+	+	+	+	+

Figure 2. Methodologic quality of included articles using Newcastle-Ottawa Quality Assessment Scale.[a]

[a] The articles by Reid[2] and Wang[62] were published initally online in 2012 and in print in 2013.
+ = yes; - = no; ? = cannot say; NA = not applicable.

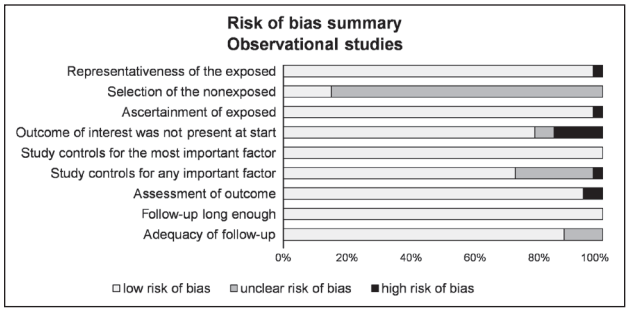

Figure 3. Risk of bias of included articles using Newcastle-Ottawa Quality Assessment Scale.

Inclusion Criteria for Asbestos Exposure

Asbestos exposure was the shared inclusion criterion of the 33 studies.[2,3,35-65] Eligibility for asbestos exposure varied: asbestos in drinking water,[35] residential airborne exposure,[2,37,44,49] and work exposure.[a] Studies without estimation of duration[b] or quantity[c] of asbestos exposure were also included.

Population

Population sizes ranged from 101[36] to 1,033,869.[37] In total 1,282,066 individuals were included in this meta-analysis.

Regardless of whether age was expressed as a median or a mean value, only 7 studies[2,36-38,44,50,57,62] reported age. The age of individuals ranged from 40 years[62] to 70.5 years.[36] Fifteen studies included only men.[d] A total of 723,566 men were included in this meta-analysis, ranging from 101[36] to 504,660.[37] Ten studies reported data on smoking[e]; no studies reported on alcohol or gave adjusted results taking into account those parameters (Table 1, available online at: www.thepermanentejournal.org/files/2020/19.086Table1.pdf).

Asbestos Exposure

Mode of Absorption

A total of 32 studies concerned respiratory inhalation,[2,3,36-65] and 1 study concerned oral ingestion from drinking asbestos-contaminated water[35] (Table 1, available online at: www.thepermanentejournal.org/files/2020/19.086Table1.pdf).

Type and Quantification of Exposure

Twenty-eight studies concerned work exposure,[3,36,38-43,45-48,50-65] and 5 studies concerned environmental exposure.[2,35,37,44,49] Seven studies were linked with an asbestos mine: 5 on miners (occupational exposure)[39,40,46,48,51] and 2 on adults who had an environmental asbestos exposure during childhood by living near a crocidolite mine.[2,44] The other studies on occupational asbestos exposure included shipbreaking and shipyards workers,[3,38,47,52,53,58,59] workers from the construction industry and asbestos industry,[38,45,50,51,54-57,60-64] and firefighters,[65] and occupation was unspecified in 1 study.[36] The 3 last studies with environmental exposure were on individuals exposed to drinking asbestos-contaminated water[35] and individuals with a residential exposure to asbestos insulation[37,49] (Table 1, available online at: www.thepermanentejournal.org/files/2020/19.086Table1.pdf).

Twelve studies estimated asbestos exposure from measurements on-site.[f] However, the method of estimation and units of estimation differed between studies: Number of fibers per milliliter of air per year,[2,48,50,54,55,57,62] fiber-years,[39,40] millions of fibers per liter of water,[35] and a unitless number categorizing asbestos exposure.[3,51] Therefore, the heterogeneity of quantification of asbestos exposure precluded further analysis.

Type of Asbestos

Twenty-six studies reported type of asbestos: Amosite and others fibers in 15 studies,[g] chrysotile/crocidolite in 12 studies,[h] anthophyllite in 1 study,[48] and nonspecified in 7 studies[3,36,38,56,57,59,64] (Table 1, available online at: www.thepermanentejournal.org/files/2020/19.086Table1.pdf).

Country of Exposure

As shown in Table 1 (available online at: www.thepermanentejournal.org/files/2020/19.086Table1.pdf), a total of 18 studies were in Europe (Belgium,[61] Denmark,[42,54] Finland,[38,48,58,65] France,[64] Germany,[50] Italy,[39,51-53] Poland,[57,63] Serbia,[36] and the UK[41,56]), 4 studies were in Asia (China,[3,62] Japan,[59] and Russia[46]), 7 studies were in North America (Canada[49,55] and US[35,43,45,47,55,60]), and 4 studies were in Oceania (Australia[2,37,40,4]).

Chronology or Duration of Exposure

The date of the beginning of exposure was retrieved in 18 studies[i] and ranged from 1920[45] to 1980.[37] However, duration of exposure was retrieved in only 2 studies as a mean[38] or a median.[2] Similarly, periods of exposure was retrieved in only 11 studies[j] and covered a long period without further details: From 20 years (1946-1966)[2] to 45 years (1930-1975).[39] Therefore, meta-regressions were possible only on the basis of the date of beginning exposure.

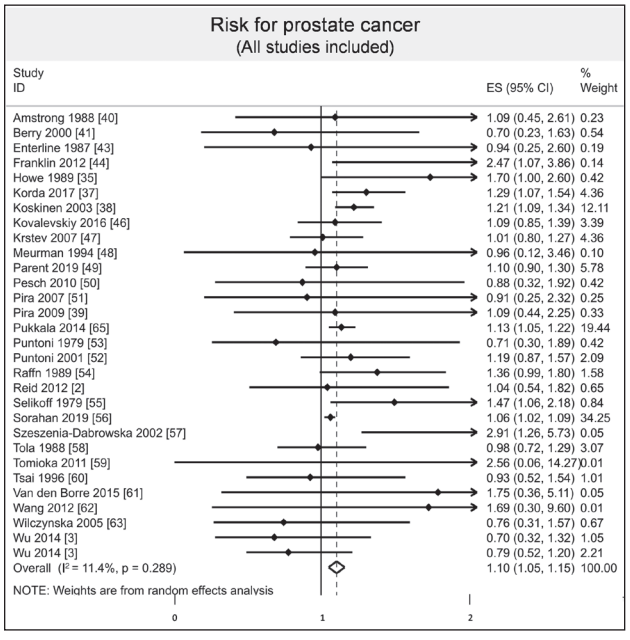

Figure 4. Meta-analysis of risk of prostate cancer after asbestos exposure.[a]

[a] Each horizontal black line represents the 95% confidence interval for the risk (represented by small solid diamond) of prostate cancer of each individual study. Open diamond represents overall risk (result of meta-analysis) considering all included studies. The articles by Reid[2] and Wang[62] were published initally online in 2012 and in print in 2013.

CI = confidence interval; ES = effect size; ID = identification.

Outcome and Aim of Studies

Nine studies shared similar outcomes: To evaluate the incidence of several cancers after any asbestos exposure.[3,3,35,37,38,44,48,58,65] Twenty-four studies evaluated mortality from cancer, and 1 other evaluated both incidence and mortality from cancer after asbestos exposure.[k] One study aimed to determinate risk factors for prostate cancer, inter alia, and specific occupational exposure as asbestos.[36]

Study Designs and Other Exposure

Thirty-two studies described a cohort follow-up design, analysing incidence and/or mortality of all cancer in population exposed,[2,3,35,37-65] and also giving results for prostate cancer. One was a case-control study of risk factors for prostate cancer, with 1 variable consisting of a broad category of occupational exposures

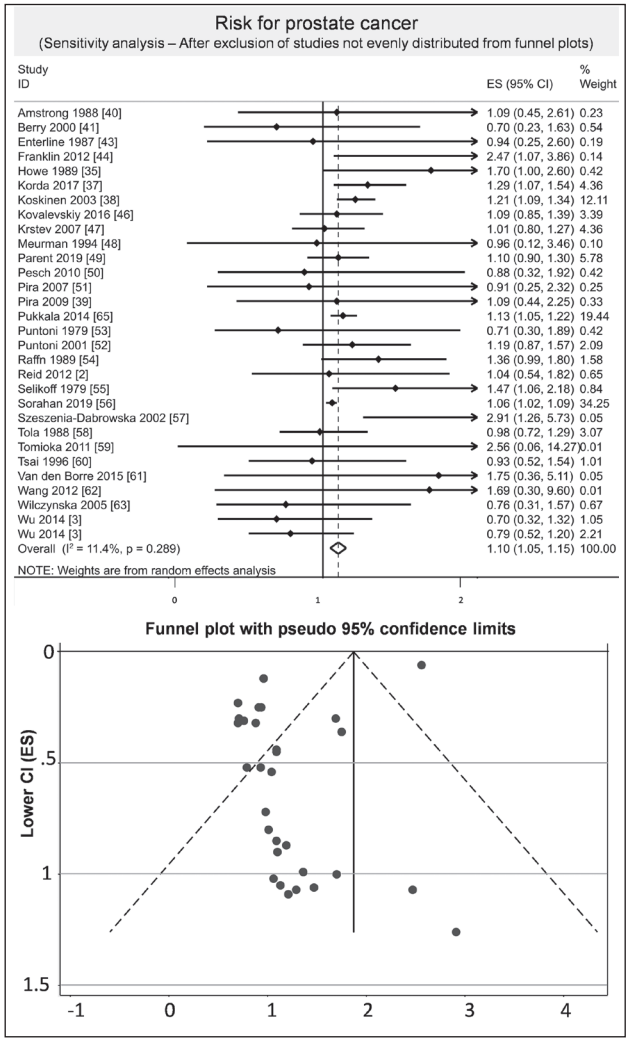

Figure 5. Sensitivity analysis of prostate cancer risk after exclusion of studies out of funnel plot.[a]

[a] Each horizontal black line represents the 95% confidence interval for the risk (represented by small solid diamond) of prostate cancer of each individual study. Open diamond represents overall risk (result of meta-analysis) considering all included studies. The articles by Reid[2] and Wang[62] were published initally online in 2012 and in print in 2013.

CI = confidence interval; ES = effect size; ID = identification.

without focusing only on asbestos.[36] Eighteen studies described an exposure to multiple agents without focusing only on asbestos exposure[l] (Table 1, available online at: www.thepermanentejournal.org/files/2020/19.086Table1.pdf).

Incidence of Prostate Cancer

Among 723,566 male participants, 15,687 cases of prostate cancer were diagnosed. Results were expressed with SIR in 9 studies,[2,3,35,37,38,44,48,58,65] ranging from 0.70[3] to 2.47[44]; with SMR in 19 studies[m]; with SRR in 1 study[56]; and with HR in 1 study.[3] Eight studies found an increased risk of prostate cancer,[35,37,38,44,55-57,65] with a risk from 1.06 (95% CI = 1.02-1.09)[56] to 2.91 (95% CI = 1.26-5.73).[57] Twenty-five studies did not retrieve an increased risk of prostate cancer,[2,3,36,38-43,45-54,58-63] with a nonsignificant risk from 0.70 (95% CI = 0.23-1.63)[41] to 2.56 (95% CI = 0.06-14.27).[59]

Meta-Analysis

We included 30 studies.[2,3,35-41,43,44,46-63,65] The overall result of the meta-analysis including all the studies was that asbestos exposure could possibly increase the risk of prostate cancer (ES = 1.10, 95% CI = 1.05-1.15, I^2 = 11.4%; Figure 4). After exclusion of studies not evenly distributed from funnel plots, we found an overall risk of 1.12 (95% CI = 1.07-1.18, I^2 = 20.9%; Figure 5).

Stratified results by mode of absorption demonstrated an increased risk of prostate cancer by respiratory inhalation (ES = 1.10, 95% CI = 1.05-1.15, I^2 = 7.90%), whereas there was no evidence of an increased risk of prostate cancer by oral ingestion (ES = 1.70, 95% CI = 0.90-2.50). Stratified results by type of exposure demonstrated that both environmental and occupational exposure slightly increased the risk of prostate cancer (ES = 1.25, 95% CI = 1.01-1.48, I^2 = 37.9%; and 1.07, 1.04-1.10, I^2 = 0.0%, respectively; Figure 6). Stratified results by type of fibers demonstrated an increased risk of prostate cancer with the amosite group (ES = 1.12, 95% CI = 1.05-1.19, I^2 = 0.0%), whereas there was no evidence of an increased risk with chrysotile/crocidolite and nonspecified groups (ES = 1.13, 95% CI = 0.98-1.28, I^2 = 0.0%; and 1.05, 0.90-1.21, I^2 = 60.3%, respectively; Figure 7). Stratification by continent demonstrated an increased risk of prostate cancer in Europe (ES = 1.12, 95% CI = 1.05-1.19, I^2 = 35.0%), whereas there was no evidence of an increased risk in North America, Asia, and Oceania (ES = 1.11, 95% CI = 0.94-1.28, I^2 = 17.1%; 1.09, 0.82-1.36, I^2 = 0.0%; and 1.28, 0.99-1.58, I^2 = 13.3%, respectively; Figure 8). Stratified results by type of risk demonstrated an increased risk of prostate cancer with SIR (ES = 1.16, 95% CI = 1.04-1.27, I^2 = 35.2%) and with SRR (ES = 1.06, 95% CI = 1.04-1.27), whereas there was no evidence of an increased risk with SMR and HR (ES = 1.09, 95% CI = 0.98-1.19, I^2 = 0.0%; and 0.79, 0.45 to 1.13, respectively).

We performed a sensitivity analysis by stratifying results and, after exclusion of studies out of the funnel plot, the

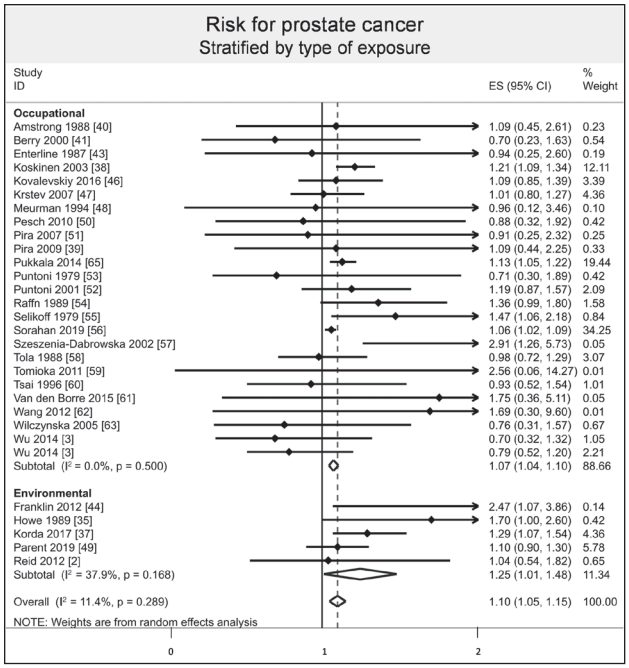

Figure 6. Risk of prostate cancer after asbestos exposure, stratified by type of exposure.[a]

[a] Each horizontal black line represents the 95% confidence interval for the risk (represented by small solid diamond) of prostate cancer of each individual study. Open diamond represents overall risk (result of meta-analysis) considering all included studies. The articles by Reid[2] and Wang[62] were published initally online in 2012 and in print in 2013.

CI = confidence interval; ES = effect size; ID = identification.

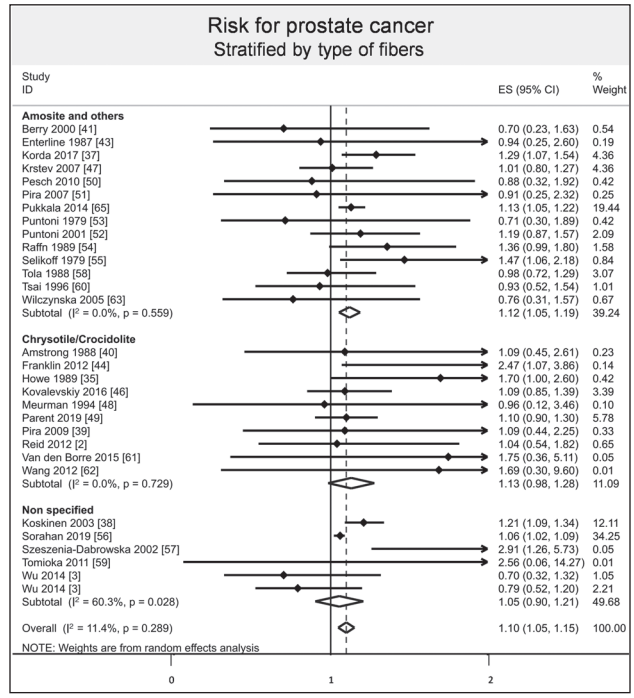

Figure 7. Risk of prostate cancer after asbestos exposure, stratified by type of fibers.[a]

[a] Each horizontal black line represents the 95% confidence interval for the risk (represented by small black diamond) of prostate cancer of each individual study. Blue diamond represents overall risk (result of meta-analysis) considering all included studies. The articles by Reid[2] and Wang[62] were published initally online in 2012 and in print in 2013.

CI = confidence interval; ES = effect size; ID = identification.

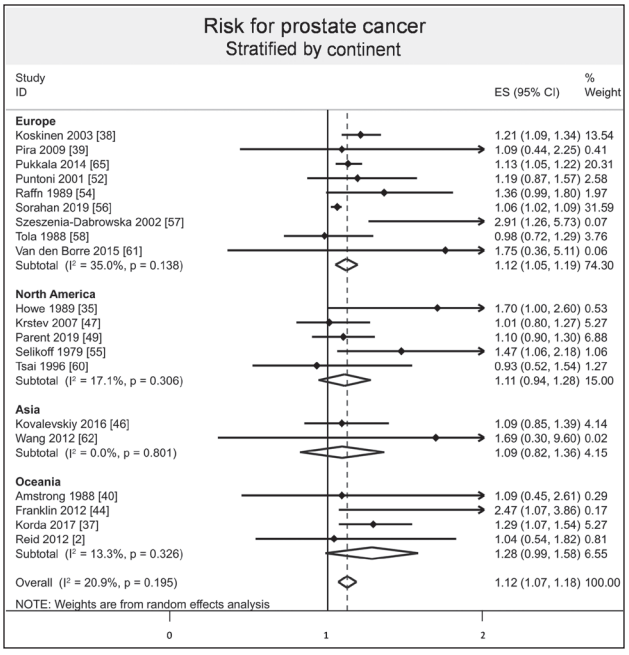

Figure 8. Risk of prostate cancer after asbestos exposure, stratified by continent.[a]

[a] Each horizontal black line represents the 95% confidence interval for the risk (represented by small solid diamond) of prostate cancer of each individual study. Open diamond represents overall risk (result of meta-analysis) considering all included studies. The articles by Reid[2] and Wang[62] were published initally online in 2012 and in print in 2013.

CI = confidence interval; ES = effect size; ID = identification.

meta-analysis demonstrated similar results. We then conducted a meta-regression including sex, age, cohort size, lifestyle, toxic exposures, duration of follow-up, type of absorption, type of exposure, type of fibers, type of risk, and geographic zone. They did not influence the risk of prostate cancer (Figure 9). Insufficient data on quantity and during of exposure as well as use of personal protective equipment precluded further analysis.

DISCUSSION

The main finding of this study was that asbestos exposure could potentially lead to an increased risk of prostate cancer; however, prospective studies are warranted to confirm this finding. The main mode of asbestos absorption was respiratory, whereas oral ingestion was not found to be statistically significant. Both occupational and environmental exposures increased the risk of prostate cancer. We demonstrated that the risk remained prevalent in Europe and did not decrease over time.

Asbestos Exposure and Increased Risk of Prostate Cancer

In 2012, the International Agency for Research on Cancer of the World Health Organization classified all types of asbestos causing lung, laryngeal, and ovarian cancers, and pleural and peritoneal mesothelioma, and possibly other cancers and diseases.[6] Our results suggest that asbestos exposure also may increase the risk of prostate cancer. Screening prostate cancer at an early stage is commonly done by the measurement of serum prostate-specific antigen (PSA)[66]; however, screening remains controversial because of overdiagnosis (up to 40%-50%) and adverse effects of overtreatment.[67-69] Indeed, no country has yet introduced a national PSA-based screening program.[70] Two recent studies have contradictory results. Results of the European Randomized Study of Screening for Prostate Cancer show a relative reduction of mortality of 21% after 13 years of follow-up.[71] In the US, the randomized Prostate, Lung, Colorectal and Ovarian screening trial concluded an absence of benefit on mortality.[72] However, this US trial had a major bias, because nearly 90% of the control group had at least 1 PSA test. Even the US Preventive Services Task Force changed its recommendations, recommending that clinicians inform men aged 55 to 69 years about the potential benefits and harms of PSA-based screening for prostate cancer.[73] In France, several national recommendations propose measuring PSA and performing rectal examination after clear information about benefits and harms to patients age 50 to 75 years. The implication of the present study is that asbestos-exposed male workers older than age 50 years should be encouraged even more to engage in the screening.

Mode of Absorption

Our results showed that respiratory inhalation could increase the risk of prostate cancer, whereas there was no increased risk of oral ingestion of asbestos-contaminated water. The effects of oral ingestion of asbestos on the risk of other cancers are discordant between studies.[74] Whereas several studies did not reveal an excess cancer mortality after oral asbestos exposure,[75-78] some studies demonstrated an increased risk of some cancers such as gastrointestinal[9] or stomach cancer.[10] The presence of fibers in organs such as the colon or gastrointestinal tract, kidney, spleen, and liver[79-81] is not necessarily linked to the development of a disease.[8] However, the inhalation of asbestos undoubtedly has lung and pleural toxicity.[82] The key mechanisms of carcinogenesis include oxidative stress, chronic inflammation, and genetic and

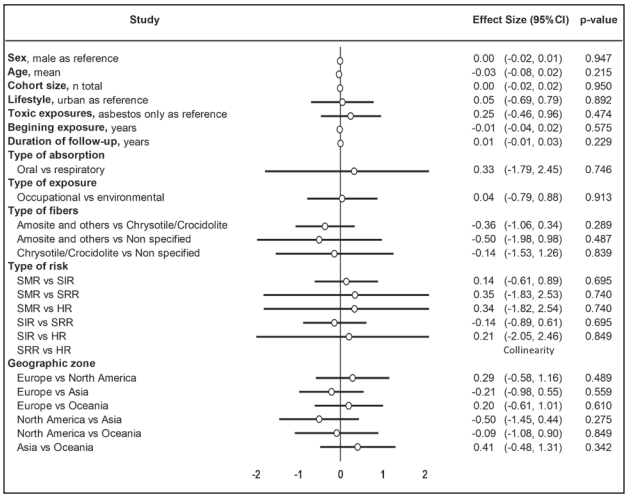

Figure 9. Meta-regression.

CI = confidence interval; HR = hazard ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRR = standardized rate ratio.

epigenetic alterations as well as cellular toxicity and fibrosis.[83] The asbestos fibers can pass the alveolar barrier and reach the lung interstitium, activating several pathways in alveolar and interstitial macrophages and inducing the release of pro-inflammatory cytokines.[84] The fibers accumulate at the site of pleural drainage, passing into the pleural space, which results in chronic damage and inflammation of several cells.[85] Then the genotoxic initiation process and/or epigenetic mechanisms mediate the carcinogenic activity of asbestos.[83,86] Asbestos fibers are phagocytosed by dividing cells and induce DNA breaks, leading to the presence of fiber-associated iron and reactive oxygen species.[87,88] Asbestos has been found in the kidney, brain, and liver but not in the prostate,[89] but the translocation pathways for inhaled asbestos fibers are unclear. One hypothesis is that fibers, drained by the pulmonary lymphatic system, could reach the blood and then potentially translocate to all organs.[90] A population-based case-control study in 4 Nordic countries concluded that exposure to asbestos might be a risk factor for intrahepatic cholangiocarcinoma.[91] For prostate cancer, the mechanism remains unknown.

Type of Exposure

In our study, both environmental and occupational exposures were risk factors for prostate cancer. The World Health Organization estimates that more than 100 million people could be exposed to asbestos in the workplace, resulting in more than 100,000 preventable deaths per year.[20] All forms of asbestos are now banned in 63 countries.[92] However, a large number of countries still use, import, and export asbestos and asbestos-containing products,[21] especially in some new industrial countries.[20,21] Attempts to understand the implications of asbestos exposure are ongoing.[93,94] Although the risk of occupational asbestos exposure is salient, environmental exposure is also a public health concern.[6] In our study, the environmental exposures were by drinking contaminated water or by residential airborne contamination. However, asbestos is also present in geologic formations in several countries, in various forms: Crocidolite in southern Africa, tremolite in Cyprus and Corsica, and erionite in Turkey.[95] The International Agency for Research on Cancer classified erionite as a group 1 known human carcinogen and concluded that erionite is the cause of the malignant mesothelioma epidemic in Cappadocia, Turkey.[96,97] Other cases of malignant mesothelioma have been reported after environmental exposure, in particular, in the family of asbestos workers.[16,98-100] The risk of prostate cancer has never been studied in this population, to our knowledge, and further studies are warranted.

Limitations

There are limitations to this study. Meta-analyses inherit the limitations of the individual studies of which they are composed and therefore are subjected to the bias of included studies. Our meta-analyses included studies suffering from confounding bias that precluded our results. Moreover, the meta-analysis is based on a moderate number of studies; however, a previous meta-analysis with fewer studies contributed to effective preventive strategies in asbestos-exposed workers.[7] Only 1 study reported an oral ingestion; therefore, stratified results for mode of absorption are inconclusive for oral absorption.[35] The difference in screening procedures for prostate cancer between countries[101] may have led to bias in the incidence of prostate cancer.

Surprisingly, studies in the European population demonstrated the greater risk without significant results for other continents, whereas it is known that health-related issues caused by asbestos exposure will be a public health problem in new industrial countries.[102,103] This finding may be related to a lack of epidemiologic monitoring surveillance.[104]

One study did not report sex in the total number of participants,[37] which can appear problematic in a meta-analysis for prostate cancer. However, this study gave risks of prostate cancer, and calculations in our meta-analysis did not require the number of individuals. Therefore, this study did not alter the quality of the results of the meta-analysis.

Another limitation is the absence of meta-regression based on quantification of asbestos exposure.[105] We included several studies[2,3,35,39,40,48,62] that estimated exposure on the basis of the address of individuals or job characteristics. Even if such an approach is interesting, heterogeneity of reporting measures between studies precluded further analyses. The last recommendations on measurements of real exposure from the International Labour Organization are more than 30 years old (1986) and do not precisely limit value. Even if the present commonly used limit of 100,000 fibers for 1 cubic meter[6] is applied, the recommendations need to be updated in accordance with evidence-based medicine.

Another limitation of our study is scarce information about type of fibers to which individuals were exposed. Indeed, asbestos fibers are divided in 2 groups: Serpentine fibers such as chrysotile and amphibole fibers with crocidolite and amosite, the most used in the past.[106] Their toxicity is associated with physicochemical properties of the material, such as length diameter and biopersistence.[107-109] We demonstrated that amosite exposure increased the risk of prostate cancer the most; nonetheless, the amosite group also included chrysotile/crocidolite and the percentage of each type of fibers was not reported in the included studies. Thus, incomplete classification precluded robust conclusions on the specific effect of each type of fiber.

Another limitation is the existence of other sources of exposure in addition to asbestos in some included articles.[n] However, there was no statistical influence of additional exposure on the risk of prostate cancer. Some articles also did not control for addictive behavior such as smoking and alcohol[o]; nevertheless, associations with prostate cancer incidence are unlikely but still a matter of debate.[110-113]

Some ecological studies[2,35,37,44] in our meta-analysis determined an asbestos environmental exposure based on the patient's address at the time of the study and did not account for patients who migrated in or out of the area, thus potentially leading to a misclassification of exposure to asbestos. However, sensitivity analyses did not modify our findings (ES = 1.08; 95% CI = 1.05-1.10, I^2 = 0.0%). Finally, no studies gave details on the use of personal protective equipment.

CONCLUSION

Asbestos exposure seems to increase the risk of prostate cancer. Considering mode of absorption, the main mechanism was

respiratory, without significant results for oral asbestos ingestion. Both environmental and occupational asbestos exposure were linked with increased risk of prostate cancer. Insufficient data did not permit us to analyze the influence of age and the use of protective equipment. The findings of this study imply that people who were exposed to asbestos should possibly be encouraged to complete more frequent prostate cancer screening. ❖

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[d] References 3, 36, 42, 45, 49-53, 55, 58-61, 65.
[e] References 2, 36, 38, 42, 48, 50, 55, 59, 62, 63.
[f] References 2, 3, 35, 39, 40, 48, 50, 51, 54, 55, 57, 62.
[g] References 37, 41-43, 47, 50-55, 58, 60, 63, 65.
[h] References 2, 35, 39, 40, 44-46, 49, 61, 62.
[i] References 2, 3, 35-38, 42, 45, 47, 48, 50, 51, 54, 56, 58-60, 62, 63.
[j] References 2, 38, 43, 44, 47, 50, 57, 59, 60.
[k] References 2, 38-43, 45-47, 49-57, 59-64.
[l] References 2, 3, 36, 38, 42, 47, 48, 50, 52, 53, 55, 56, 58, 59, 62-65.
[m] References 39-41, 43, 46, 47, 49-55, 57, 59-63.
[n] References 2, 3, 36, 38, 42, 47, 48, 50, 52, 53, 55, 56, 58, 59, 62-65.
[o] References 2, 36, 38, 42, 48, 50, 55, 59, 62, 63.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Author Contributions

Frédéric Dutheil, MD, PhD, conceived, designed, and performed the experiments; analyzed the data; contributed reagents, materials, and analysis tools; helped write the article; and is responsible for integrity of the data analysis. Laetitia Zaragoza-Civale, MD, and Valentin Navel, MD, performed the experiments; analyzed the data; contributed reagents, materials, and analysis tools; helped write the article; and are responsible for integrity of the data analysis. Bruno Pereira, PhD, and Julien S Baker, PhD, analyzed the data and contributed reagents, materials, and analysis tools. Martial Mermillod, PhD; Jeannot Schmidt, MD; and Fares Moustafa, MD, PhD, helped write the article; participated in the literature review; and contributed reagents, materials, and analysis tools. All authors have given final approval to the manuscript.

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