Cancer Causes Control (2013) 24:1535–1545
DOI 10.1007/s10552-013-0230-0

ORIGINAL PAPER

Risk of mesothelioma following external beam radiotherapy for prostate cancer: a cohort analysis of SEER database

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Received: 26 November 2012 / Accepted: 8 May 2013 / Published online: 24 May 2013

Abstract
Purpose To investigate the association between external beam radiotherapy (EBRT) for prostate cancer and mesothelioma using data from the US Surveillance, Epidemiology, and End Results (SEER) cancer registries.
Methods We analyzed data from the SEER database (1973–2009). We compared EBRT versus no radiotherapy. Incidence rate ratios (IRR) and 95 % confidence intervals (95 % CI) of mesothelioma among prostate cancer patients were estimated with multilevel Poisson models adjusted by race, age, and calendar year. Confounding by asbestos was investigated using relative risk of mesothelioma in each case's county of residence as a proxy for asbestos exposure.
Results Four hundred and seventy-one mesothelioma cases (93.6 % pleural) occurred in 3,985,991 person-years. The IRR of mesothelioma was increased for subjects exposed to EBRT (1.28; 95 % CI 1.05, 1.55) compared to non-irradiated patients, and a population attributable fraction of 0.49 % (95 % CI 0.11, 0.81) was estimated. The IRR increased with latency period: 0–4 years, IRR 1.08 (95 % CI 0.81, 1.44); 5–9 years, IRR 1.31 (95 % CI 0.93, 1.85); ≥10 years, IRR 1.59 (95 % CI 1.05, 2.42). Despite the fairly strong evidence of association with EBRT, the population attributable rate of mesothelioma was modest—3.3 cases per 100,000 person-years. The cumulative incidence of mesothelioma attributable to EBRT was 4.0/100,000 over 5 years, 24.5/100,000 over 10 years, and 65.0/100,000 over 15 years.
Conclusions Our study provides evidence that EBRT for prostate cancer is a small but detectable risk factor for mesothelioma. Patients should be advised of risk of radiation-induced second malignancies.

Keywords Mesothelioma · EBRT · SEER · Cohort study · Neoplasms · Radiation-induced

Introduction

Malignant mesothelioma is a cancer originating from the lining cells of the pleural and peritoneal cavities, as well as the pericardium and the tunica vaginalis. Although mesothelioma is a rare cancer, its incidence has increased steeply from the 1970s through the mid-1990s [1].

Mesothelioma is primarily a disease of adults and usually presents in the fifth to seventh decades, and 70–80 % of cases occur in men [2]. Occupational, para-occupational, and non-occupational environmental exposures to asbestos are the major risk factor for mesothelioma [2]. In Western countries, the proportion of mesothelioma cases with an identified asbestos exposure have been found to be around 80–90 % in men and 50–60 % in women [3, 4]. The fraction of mesothelioma attributable to occupational or para-occupational exposure in Britain was estimated as 97.0 % (95 % CI 96.0, 98.0 %) for males and 82.5 % (95 % CI 75.0, 90.0 %) for females [5]. Even though

Electronic supplementary material The online version of this article (doi:10.1007/s10552-013-0230-0) contains supplementary material, which is available to authorized users.

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asbestos is the main risk factors for mesothelioma and some authors have speculated that "virtually all mesotheliomas are due to asbestos exposure, and most exposure is related to work" [6], a background lifetime probability (i.e., the probability that would be expected in the absence of exposure to asbestos) of about 3 per 10,000 has been estimated [1, 7]. Additional exposures that have been hypothesized, with varying degrees of evidence, to be causal factors of mesothelioma include non-asbestiform mineral fibers (erionite; fluoro-edenite); carbon nanotubes; viruses (MC29 avian leukosis virus; SV40); metals; chronic serosal inflammation; and ionizing radiation [8].

Ionizing radiation sources linked (again with varying amounts of evidence) to mesothelioma are exposure to the diagnostic X-ray contrast medium "Thorotrast," working in nuclear power plants, and external beam radiotherapy (EBRT) [9]. The association between radiotherapy and mesothelioma was initially hypothesized after numerous case reports of mesotheliomas occurring after irradiation of nearby organs [9]. Goodman and colleagues reviewed the evidence linking EBRT to mesothelioma; all available studies were retrospective cohort analyses of cancer registry data. Most studies used data from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program database and studied primary neoplasms characterized by long survival and treatment with EBRT (cancers of the breast and testis as well as Hodgkin's and non-Hodgkin's lymphomas). Positive associations between EBRT and mesothelioma were reported in most of the studies reviewed by Goodman, but the findings were limited by a high degree of variability due to the small number of mesothelioma cases analyzed (maximum 40 cases, often <15) [9].

Prostate cancer is the most common cancer among males in the USA with more than 240,000 diagnoses expected in 2012 [10]. EBRT has long been the standard option for the treatment for locally advanced prostate cancer [11]. As many men are exposed every year to EBRT for the treatment for prostate cancer, considerable attention has been paid to the risk of radiation-induced second malignancies; with most of the emphasis understandably placed on risks of second cancers in sites proximal to the irradiated area (e.g., colorectal and bladder cancer). There have, however, been three studies linking EBRT for prostate cancer to increased risk of lung cancer [12–14]. To our knowledge, no study has been conducted on the association between EBRT for the treatment for prostate cancer and the risk of mesothelioma.

The aim of this study was to investigate the possible association between EBRT for primary prostate cancer and the risk of malignant mesothelioma using data from the SEER registries.

Methods

Population and follow-up

We defined the cohort as patients who were diagnosed with a first primary invasive prostate cancer reported to one of the SEER registries. The SEER 9 Registries database (including Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah) was consulted for the period between 1 January 1973 and 31 December 1991, while the SEER 13 Registries database (which further includes San Jose-Monterey, Los Angeles, Alaska Natives, and Rural Georgia) was used for the period between 1 January 1992 and 31 December 2009. Individual records were obtained from MP-SIR (Multiple Primary-Standardized Incidence Ratios) session of SEER*Stat software. The Alaska Natives registry was excluded from our analysis as no cancer record is present in the MP-SIR session.

One case diagnosed after death on the grounds of death certificate/autopsy was excluded from the study population. The follow-up time for each individual started at the date of the diagnosis of prostate cancer and ended at the date of the diagnosis of mesothelioma, at last known vital status, death, or the end of the study (31 December 2009). To reduce the misclassification of exposure to EBRT, patients with another record in the SEER database before the one bearing the diagnosis of prostate cancer were excluded from the study. We also excluded patients with missing information on radiotherapy or on county of residence (Fig. 1 summarizes the study population).

Exposure and covariates

Available information on the first course of treatment allowed us to classify patients according to whether or not they had received radiotherapy as a part of their initial treatment for prostate cancer. Hence, using the information from SEER registries, the patients were classified into three groups as follows:

1. no radiotherapy;
2. EBRT alone or in combination with brachytherapy;
3. radioactive implants, radioisotopes, other forms of radiation when the method or source was not specified.

The incidence rate ratios (IRR) of mesothelioma for patients treated with radiotherapy (groups 2 and 3 above) were estimated with reference to patients who did not undergo radiotherapy. We also performed a sensitivity analysis in which the IRRs were estimated with respect to the subset of non-irradiated patients who received surgical treatment for their cancer.

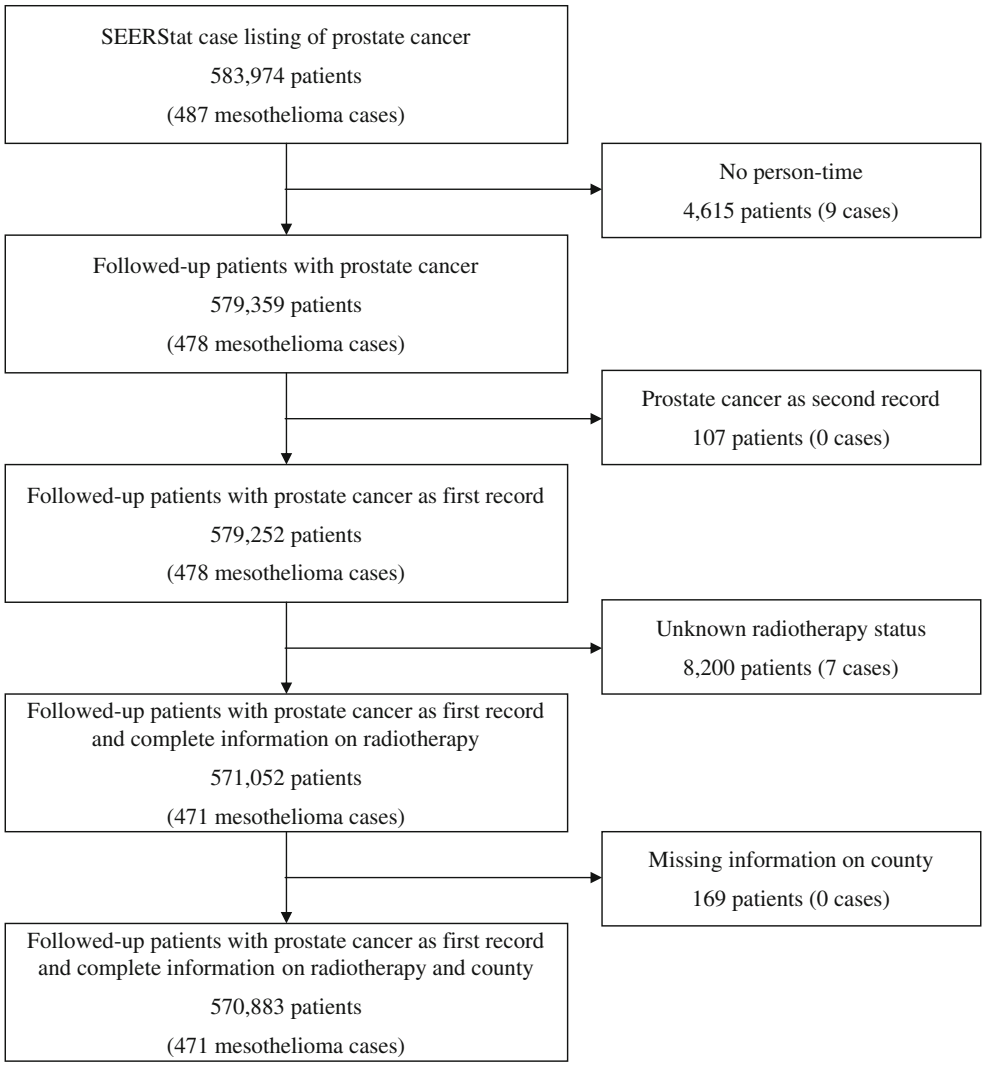

Fig. 1 Flow chart of the study population. Patients affected by primary prostatic cancer followed up for malignant mesothelioma

Covariates to be considered in multivariate analysis were selected a priori and included age (completed years), calendar year, and race (white, black, other). As noted, asbestos exposure is known to be the major cause of mesothelioma, and as such might potentially represent a confounder of the association between EBRT and the tumor. Unfortunately, no individual work history or other exposure information is available in SEER, and so we used a geographic analysis to investigate possible confounding by asbestos exposure. Many important industrial uses of asbestos tended in the past to be clustered (e.g., shipyards, asbestos textile plants), and as a result, mesotheliomas have been observed to cluster as well [15]. Moreover, the authors of a recent Italian study of municipal clusters of mesothelioma concluded that "pleural mesothelioma mortality at population level is a suitable indicator of previous asbestos exposure" [16]. We conducted an analysis of mesothelioma rates by county in the USA using the SEER 13 Registries data (1992–2009), and then linked each case's county of residence to that county's relative risk of mesothelioma as a proxy for county-level asbestos exposure. A three-level variable (low, medium, and high relative risk of mesothelioma among men) was created using tertiles of the distribution of the county mesothelioma relative risks. Each subject was classified according to the county of residence at the time of the diagnosis of prostate cancer.

In previous studies on radiation-induced second malignancies, tumor grade and stage have sometimes been included among the covariates (e.g., Moon et al. [13]). However, prostate cancer grade and stage are unlikely to be associated with the risk of mesothelioma; furthermore, the information on stage is often unavailable for SEER records [17]. Hence, we excluded tumor grade and stage from the covariates; nevertheless, we performed a sensitivity analysis restricted to subjects with full information to explore the role of grade and stage in the causal pathway between EBRT and mesothelioma.

Latency (time since first exposure to EBRT) was considered as a possible effect modifier of the relationship between EBRT and mesothelioma: based on current knowledge of carcinogenesis, it is likely that a minimum period of 5 years is necessary for the induction of solid cancers after exposure to radiation [18]. Latency was calculated with reference to the date of the diagnosis of prostate cancer (presumed to be shortly before EBRT exposure). Our ability to investigate particularly long latencies was limited by our data: only 30 cases of mesothelioma in 120,731 person-years were observed 15 or more years after the primary diagnosis of prostate cancer. Consequently, latency was grouped into three categories: 0–4 years; 5–9 years; and 10 or more years.

Outcome measures and case definitions

The main outcome measure was the incidence rate ratio (IRR) of mesothelioma in patients exposed to EBRT compared to patients unexposed to radiotherapy after primary prostate cancer. We also estimated the incidence rate difference (IRD, sometimes called attributable rate) of mesothelioma to provide perspective on the absolute magnitude of the risk from EBRT. Due to the small number of extrapleural mesotheliomas in the study population, we focused our main analysis on all cases of mesothelioma, irrespective of cancer site.

We estimated the population attributable fraction (PAF), that is, the proportion by which the incidence rate of the outcome in the entire population would be reduced if the exposure was eliminated, [19] to evaluate the role of EBRT in the global mesothelioma epidemic.

Statistical analysis

The IRRs of mesothelioma and 95 % confidence intervals (95 % CIs) were estimated using Poisson regression models. Temporal variables (i.e., age, calendar year, and latency) were analyzed as time-varying variables. We performed analysis stratified by latency categories. Based on preliminary analysis, two parameters were introduced in the multivariate models for age (completed years): age and squared age. Calendar year was introduced in the models with one degree of freedom.

When adjusting for county of residence RR of mesothelioma, we used multilevel random intercept Poisson regression models accounting for the within-county variance component. The models assumed a γ distribution of the county-level random intercept, accounting also for within-county dependence [20].

The relative risks of mesothelioma were calculated for the counties covered by the 13 SEER registries using the Besag–York–Mollie (BYM) model [21]. Briefly, the BYM model allows for both heterogeneous and spatially structured random effects; additional details on the model are presented in Web Appendix 1 along with the results of the analysis summarized in maps of the standardized incidence ratios and RRs (Web Figures 1 and 2).

We estimated the adjusted incidence rate difference (IRD) of mesothelioma (and 95 % CIs) for different treatments (EBRT, other radiation, and none) and for tertiles of county mesothelioma RR by applying the model proposed by Xu and colleagues [22]. The method consists of an ordinary least-squares regression of transformed variables, together with a robust variance estimator for inference; the calculated coefficients are an unbiased estimate of the IRDs at the group level [22]. As the method by Xu and colleagues was presented for analyzing categorical variables, we aggregated ages and calendar years in categories (as presented in Table 1) when estimating IRDs.

The population attributable fraction (PAF) was calculated for EBRT as$\mathrm{PAF} = P_c * (\mathrm{RR} - 1)/\mathrm{RR}$where P_c is the proportion of exposed among cases (here, the proportion of mesotheliomas following prostate cancer who received EBRT). The confidence interval for the PAF was estimated via Monte Carlo simulation assuming a binomial distribution for the P_c and lognormal for the RR.

Figures on cancer and individual records were obtained using SEER*Stat software version 7.0.9. We used WinBugs 1.4.3 to fit the BYM model and Stata 11.2 SE (Stata Corporation, Texas, TX, USA) software package for the main analysis.

Equations developed by Kry and colleagues were used to estimate the equivalent absorbed radiation doses at two pleural sites following two different standard EBRT techniques for prostate cancer [23]. Information needed to apply the equations is as follows: (1) distance from the treatment field; (2) depth of the tissue; and (3) treatment strategy. We assumed a distance ranging between 27.5(lung edge) and 35 cm (lung center) and a depth of 3 cm [24]. We estimated the equivalent adsorbed radiation dose for exposure to three-dimensional conformal radiation therapy (18 megavolt, 78.0 Gray) or to intensity-modulated radiation therapy (6 megavolt, 75.6 Gray; 18 megavolt, 75.6 Gray).

Results

There were 583,974 cases of primary prostate cancer reported to one of the consulted SEER registries during the study period. After the exclusion of patients without follow-up (4,615), with another record before the one bearing the diagnosis of prostate cancer (107), or with missing information on radiotherapy (8,200) or county (169), we identified a cohort of 570,883 subjects diagnosed with primary prostate cancer (Fig. 1). The final study population

Table 1 Distribution of person-years according to radiotherapy and selected characteristics

Characteristics	Radiotherapy					
	None		External beam radiotherapy		Other[c]	
	Person-years $n = 2{,}651{,}827$	%	Person-years $n = 1{,}137{,}411$	%	Person-years $n = 196{,}752$	%
Race						
White	2,195,335	82.8	924,165	81.2	169,732	86.3
Black	283,311	10.7	136,300	12.0	16,698	8.5
Other[a]	173,181	6.5	76,947	6.8	10,322	5.2
Age						
Below 65 years	530,740	20.0	152,792	13.4	46,137	23.5
Between 65 and 69 years	419,717	15.8	161,787	14.2	37,496	19.1
Between 70 and 74 years	504,808	19.0	243,718	21.4	43,927	22.3
Between 75 and 79 years	493,662	18.6	279,351	24.6	39,416	20.0
Between 80 and 84 years	389,054	14.7	196,897	17.3	21,485	10.9
At least 85 years	313,846	11.8	102,777	9.0	8,255	4.2
Calendar period						
1973–1989	351,286	13.2	125,797	11.1	10,785	5.5
1990–1999	838,046	31.6	369,021	32.4	27,228	13.8
2000–2009	1,462,495	55.2	642,594	56.5	158,739	80.7
Latency						
Between 0 and 4 years	1,446,343	54.5	621,351	54.6	124,382	63.2
Between 5 and 9 years	754,166	28.4	340,870	30.0	55,079	28.0
At least 10 years	451,318	17.0	175,191	15.4	17,291	8.8
County's mesothelioma relative risk[b]						
Low	270,989	10.2	115,907	10.2	24,972	12.7
Medium	1,169,166	44.1	494,654	43.4	72,336	36.8
High	1,211,671	45.7	526,851	46.3	99,444	50.5

SEER 9 Registries (1973–1991) and SEER 13 Registries (1992–2009)

[a] Other includes American Indian/AK Native; Asian/Pacific Islander; other unspecified; unknown

[b] Mesothelioma relative risks at the county level were estimated with a Besag–York–Mollier model

[c] Other includes radioactive implants; radioisotopes; radiation, method, or source not specified; other radiation

included 3,985,991 person-years and 471 cases of mesothelioma (441 localized to the pleura, 21 to the peritoneum, and 9 to other or unspecified sites).

Diagnostic techniques used for the identification of mesothelioma were as follows: histology ($n = 391$); exfoliative cytology (57); direct visualization (3); radiography (11); and clinical diagnosis (7). Quality of diagnosis was unknown for 2 cases.

A summary of the cohort (Table 1) reveals important differences in use of radiotherapy for prostate cancer among races, age groups, and over time. The use of other radiotherapy techniques (including radioactive implants) increased within the study period and was more frequent among white patients; 5.2 % of white patients received other radiotherapy techniques, compared to 3.8 % of black patients and 4.0 % of other non-white, non-black patients. Patients aged between 70 and 85 were more likely to be exposed to EBRT than to other forms of radiation.

An increased risk of mesothelioma was observed for patients exposed to EBRT compared to those who received no radiotherapy (adjusted IRR 1.28, 95 % CI 1.05, 1.55), while no increase in risk was seen from other radiotherapies (Table 2). Compared to white men, blacks, and other races had a substantially lower risk of mesothelioma following prostate cancer, independent of the risk from radiotherapy. Men with prostate cancer and residing in a county with a mesothelioma incidence rate in the highest tertile had about a threefold increased risk of mesothelioma (IRR 2.98; 95 % CI 1.76, 5.03), again independent of the choice of radiotherapy. A dose–response relationship across the tertiles of county mesothelioma risk was apparent (p for trend <0.001). Although the county's mesothelioma RR was able to predict the individual resident's risk of mesothelioma, it was not a confounder of the relationship between EBRT and mesothelioma: the IRR for EBRT in the multivariate model in Table 2 was unchanged to 3 decimal places after removing the county mesothelioma risk (data not shown). As expected, age was a strong determinant of mesothelioma incidence (Web Figure 3). Also, the risk of mesothelioma increased with calendar year (adjusted IRR 1.01; 95 % CI 1.00, 1.03).

As shown in Table 3, the adjusted IRD of mesothelioma for patients exposed to EBRT was 3.31 per 100,000 person-years (95 % CIs 0.72, 5.90). This figure can be compared

Table 2 Incidence rate ratios of mesothelioma after primary prostate cancer

Exposure	Cases $n = 471$	Pyrs 3,985,991	Univariate analysis			Multivariate analysis[c,d]		
			IRR	(95 % CIs)	p value	IRR	(95 % CIs)	p value
Radiotherapy								
None	281	2,651,827	1.00	(Ref.)		1.00	(ref.)	
EBRT alone or in combination	168	1,137,412	1.39	(1.15, 1.69)	0.001	1.28	(1.05, 1.55)	0.013
Other[a]	22	196,752	1.06	(0.68, 1.63)	0.808	1.04	(0.67, 1.62)	0.856
Race								
White	430	3,289,232	1.00	(ref.)		1.00	(ref.)	
Black	22	436,309	0.39	(0.25, 0.59)	<0.001	0.47	(0.30, 0.74)	0.001
Other[b]	19	260,450	0.56	(0.35, 0.88)	0.013	0.48	(0.29, 0.78)	0.003
County of residence mesothelioma relative risk								
Lowest tertile	20	411,868	1.00	(Ref.)		1.00	(ref.)	
Median tertile	171	1,736,156	2.03	(1.28, 3.22)	0.003	1.94	(1.12, 3.38)	0.019
Highest tertile	280	1,837,966	3.14	(1.99, 4.94)	<0.001	2.98	(1.76, 5.03)	<0.001

SEER 9 Registries (1973–1991) and SEER 13 Registries (1992–2009)

EBRT external beam radiotherapy, *IRR* incidence rate ratios, *Pyrs* person-years, *ref.* reference category; 95 % CIs 95 % confidence intervals

[a] Other includes radioactive implants; radioisotopes; radiation, method, or source not specified; other radiation

[b] Other includes American Indian/AK Native; Asian/Pacific Islander; other unspecified; unknown

[c] Model additionally adjusted by age, age^2, and calendar year, introduced in the model as time-varying covariates

[d] Multilevel Poisson regression model with random intercept on county (likelihood ratio test versus Poisson regression: χ^2 (2 df) = 29.25, $p < 0.001$)

to the incidence rate increase of 9.69 per 100,000 person-years (95 % CI 6.91, 12.47) for subjects resident in counties with an RR of mesothelioma in the top third, compared to those in the lowest third.

Complete information on tumor grade and stage were available for only 321,041 prostate cancers recorded between 1988 and 2009. The IRR of mesothelioma for subjects exposed to EBRT increased only by 2 % after adjusting by tumor stage and grade and neither of these two classifications showed any evidence of association with mesothelioma risk (see Web Table 1). The IRR of mesothelioma for EBRT estimated in the sensitivity analysis conducted using non-irradiated patients who received surgery as the comparison group was identical to that obtained when using all the non-irradiated patients as the reference category (Web Table 2).

The strength of the association between EBRT and mesothelioma increased with increasing latency period (Fig. 2). For latency from zero to 4 years, the IRR was 1.08 (95 % CI 0.81, 1.44) and the IRD was 0.9 per 100,000 pyrs (95 % CI −2.4, 4.2); for latency from 5 to 9 years, the IRR was 1.31 (95 % CI 0.93, 1.85) and the IRD was 4.0 per 100,000 pyrs (95 % CI −0.8, 8.9); and for latency of ten or more years, the IRR was 1.59 (95 % CI 1.05, 2.42) and the IRD was 8.1 per 100,000 pyrs (95 % CI 0.6, 15.7). Based on the observed IRDs, we estimated a cumulative incidence of mesothelioma attributable to EBRT of 4.0/100,000 over 5 years, of 24.5/100,000 over 10 years, and of 65.0/100,000 over 15 years.

Only 21 of the 471 mesothelioma cases considered in the present analysis were localized at the peritoneum; hence, we did not perform multivariate analysis separately for peritoneal mesothelioma. Univariate analyses like those shown in Table 2 but limited to peritoneal mesothelioma showed very similar patterns, albeit with wide confidence intervals. The incidence rate ratio for those exposed to EBRT was (IRR 1.75, 95 % CI 0.74, 4.15). Risk appeared to rise with increasing latency as well, although again the confidence intervals were wide (Fig. 2). The IRR of peritoneal mesothelioma was 1.16 (95 % CI 0.35, 3.87) for latency periods shorter than 5 years, 2.21 (95 % CI 0.31, 15.71) for latency periods between 5 and 9 years, and 3.87 (95 % CI 0.65, 23.14) for latency periods of 10 years or more.

We estimated the population attributable fraction (PAF) for EBRT contributing to mesothelioma using data for the 7,450 cases of mesothelioma among males recorded in the SEER 9 Registries or in the SEER 13 Registries (excluding the Alaska Natives registry). For the same time period, we identified 168 mesothelioma cases that had been exposed to EBRT for treating prostate cancer, yielding an exposure prevalence among cases of 2.3 % (95 % CIs 1.9, 2.6 %). Assuming a causal association, the PAF can be calculated from this exposure prevalence and from the IRR of mesothelioma for exposure to EBRT after prostate cancer

Table 3 Incidence rate differences of mesothelioma after primary prostate cancer

Exposure	Cases $n = 471$	Pyrs 3,985,991	Univariate analysis			Multivariate analysis[c,d]		
			IRD Per 100,000 pyrs	(95 % CIs)	*p* value	IRD Per 100,000 pyrs	(95 % CIs)	*p* value
Radiotherapy								
None	281	2,651,827	0.00	(Ref.)		0.00	(Ref.)	
EBRT alone or in combination	168	1,137,412	4.17	(1.62, 6.73)	0.001	3.31	(0.72, 5.90)	0.012
Other[a]	22	196,752	0.85	(−4.25, 5.42)	0.786	0.78	(−4.06, 5.63)	0.751
Race								
White	430	3,289,232	0.00	(Ref.)		0.00	(ref.)	
Black	22	436,309	−8.03	(−10.47, −5.59)	<0.001	−5.10	(−7.60, −2.61)	<0.001
Other[b]	19	260,450	−5.78	(−9.28, −2.27)	0.007	−6.54	(−10.10, −2.99)	<0.001
County of residence mesothelioma relative risk								
Lowest tertile	20	411,868	0.00	(ref.)		0.00	(Ref.)	
Median tertile	171	1,736,156	4.99	(2.40, −7.58)	0.001	4.88	(2.30, 7.47)	<0.001
Highest tertile	280	1,837,966	10.38	(7.60, −13.16)	<.0001	9.69	(6.91, 12.47)	<0.001

SEER 9 Registries (1973–1991) and SEER 13 Registries (1992–2009)

EBRT external beam radiotherapy, *IRR* incidence rate ratios, *Pyrs* person-years, *ref.* reference category, 95 % CIs 95 % confidence intervals

[a] Other includes radioactive implants; radioisotopes; radiation, method or source not specified; other radiation

[b] Other includes American Indian/AK Native; Asian/Pacific Islander; other unspecified; unknown

[c] Model additionally adjusted by age class and calendar period, introduced in the model as time-varying covariates

[d] Incidence rate difference and relative 95 % confidence intervals estimated according to Xu et al. [22]

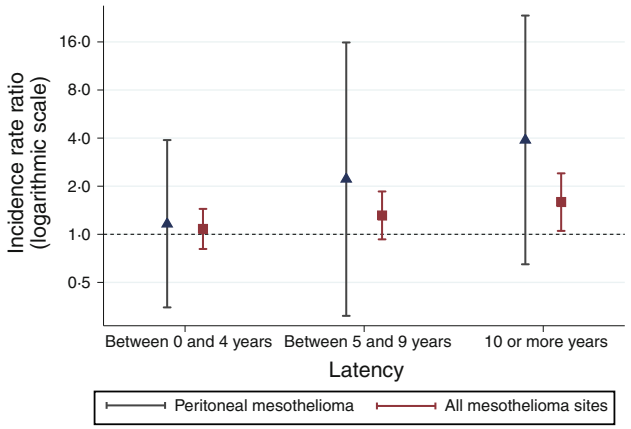

Fig. 2 Incidence rate ratios (95 % confidence intervals) of mesothelioma for subjects exposed to external beam radiotherapy compared to subjects not exposed to radiotherapy after prostate cancer. Analysis stratified by latency period. SEER 9 Registries (1973–1991), SEER 13 Registries (1992–2009). Incidence rate ratios for all mesothelioma sites were estimated with multilevel Poisson regression model adjusted by race, age, age^2, year, and county's mesothelioma relative risk

(IRR 1.28, 95 % CIs 1.05, 1.55) in Table 2. We estimated that 0.49 % (95 % CI 0.11, 0.81 %) of mesothelioma cases resulted from EBRT after primary prostate cancer.

Using the equations of Kry and colleagues, the estimated equivalent absorbed radiation doses to the pleura from EBRT ranged from about 7–25 milliSeverts (Web Table 3).

Discussion

We found an increased risk of mesothelioma in subjects that were previously irradiated to treat prostate cancer. The risk appeared to increase with latency. Based on the closer proximity to the site of irradiation, one might expect the risk to be higher for peritoneal mesotheliomas. Within the limits of the small number of such cases, this hypothesis appears to be supported—the point estimate for peritoneal mesothelioma risk and EBRT exposure was higher albeit with wide confidence intervals, and the IRRs stratified according to latency presented the same pattern found when analyzing all mesotheliomas combined.

Previous evidence and biological plausibility

Our findings support an association between exposure to EBRT and risk of mesothelioma. This observation is predominantly based on pleural mesotheliomas (accounting for more than 93 % of the cases) which occur distant from the irradiation field for prostate cancer.

Radiation-induced malignancies are usually expected to occur within the irradiated field (e.g., Baxter et al. [25]). However, even organs far from the irradiated field can still be significantly exposed due to scattered radiation, as well as leakage from the radiation source [23, 26, 27]. Three-dimensional conformal radiation therapy of the prostate (a frequent treatment during the 1990s

[28]) can expose the pleura to an equivalent absorbed radiation dose up to 25 mSv (Web Table 3); this value is far from being insignificant if we consider that the effective dose for a standard chest radiograph ranges between 0.05 and 0.24 mSv [29]. When interpreting this value, we should consider that 0.6–1.8 % of the cumulative risk of cancer to age 75 years could be attributable to diagnostic X-rays [30].

Findings from registry-based studies on second cancers provided inconsistent evidence. On the one hand, previous studies highlighted a possible association between EBRT for prostate cancer and risk of lung cancer [12–14]. On the other hand, a study on second neoplasms after invasive breast cancer did not identify any increase in risk for medium (0.5–1.0 Gy) or low (below 0.5 Gy) doses of radiation [31]. However, it is interesting to note that among sites receiving high radiation doses, pleural cancers presented the highest point estimate, although based on only two cases [17].

Our study period was limited (1973–2009), and we studied latencies shorter than those usually reported for asbestos-related mesothelioma [32]. Nevertheless, previous studies of the latency period of radiation-induced solid tumors suggest an average latency period of 5–15 years, in line with our analysis [14, 18]. Furthermore, several case reports on EBRT and mesothelioma have described cases occurring after latency periods in the range of 5–41 years [9].

Epidemiologic evidence that might support an association between exposure to ionizing radiation and mesothelioma is inconsistent. On the one hand, many studies on Thorotrast or EBRT and risk of mesothelioma do report increased risk of mesothelioma among subjects exposed to radiation [9]. On the other hand, studies among occupational cohorts working in the nuclear industry have not observed increased risk of mesothelioma, at least not that can be confidently attributed to radiation exposure rather than to confounding by asbestos [9, 33].

Study strength and limitations

Our study was based on a large number of mesothelioma cases, in contrast with previous studies on EBRT and mesothelioma [9]. Hence, we were able to detect a small increase in risk (about 30 %) and to conduct an analysis stratified according to latency.

The main limitation of our study is the potential for unmeasured confounding as information on personal characteristics and individual exposures was lacking. Confounding due to exposure to asbestos is always a concern when studying mesothelioma. In the present analysis, we were unable to adjust our estimates according to the personal history of exposure. Instead, we used the RR of mesothelioma among males in the county of residence as a proxy measure of exposure to asbestos. Although certainly affected by a high degree of misclassification, this measure of exposure to asbestos was able to capture at least part of the individual risk of mesothelioma, as shown by the well-shaped dose–response relationship. It is important to note that the estimate of interest, that is, the IRR for exposure to EBRT, did not change after the introduction in the multivariate models of the variable for the county's RR of mesothelioma. This finding suggests that the association between EBRT and mesothelioma was not highly confounded by asbestos in our study population.

It is possible that receiving radiotherapy rather than surgery might in some way be associated with determinants of mesothelioma, although aside from asbestos, there are no established personal risk factors for mesothelioma that could represent a contraindication for surgery. It is possible that there was a higher prevalence of chronic cardiac and pulmonary diseases among people occupationally exposed to asbestos because the asbestos exposure tends to occur more often in lower socioeconomic classes where poorer overall health might increase the aforementioned chronic conditions [34–36]. Treatment decision making in prostate cancer is influenced by the presence of comorbidities; patients affected by chronic diseases have a higher probability of receiving radiotherapy instead of surgery [37]. Hence, our findings could be at least partially explained by a higher tendency for former asbestos workers to receive EBRT (although we have no direct evidence to suggest this). To explore this possible source of selection bias, we performed a supplemental analysis in which only patients who had received neither surgery nor radiotherapy were used as the comparison group (Web Table 2). This change did not alter the point estimates of the risk associated with EBRT, although the smaller comparison group necessarily resulted in larger standard errors. Reports on the distribution of socioeconomic factors (i.e., level of education and income) highlighted that patients from lower socioeconomic status were less likely to receive any treatments, whereas the percentage of patients receiving radiation was usually independent from socioeconomic status or even showed a positive association [38–42]. Therefore, while the comparison between surgery and radiotherapy could be affected by a bias away from the null hypothesis (i.e., showing a risk greater than the real one), the comparison between patients who received surgery and patients who did not receive therapies should be biased toward the null hypothesis (i.e., showing a risk smaller than the real one). It is also interesting that the IRR for patients who received only surgery compared to untreated patients was 1.00 (Web

Table 2); this observation suggests that the distribution of previous occupational exposure to asbestos according to treatment status is not likely to be importantly unbalanced.

We also repeated this analysis after excluding stage I cancers, a subpopulation in which active surveillance has been proposed in the absence of comorbidities [43]. The risk for patients treated with EBRT compared to patients who did not receive any therapy was still close to that estimated in the main analysis (IRR = 1.28, data not shown). Taken together these findings suggest that selection bias introduced by comorbidities associated with asbestos exposure is not a major concern in our study. Another element supporting the absence of confounding by asbestos exposure is the increase in risk with latency (Fig. 2). Our estimates were adjusted by age and squared age, which were introduced in the models as time-varying covariates; under these conditions, residual confounding by age is unlikely. Moreover, almost no increased risk was observed in the first 5 years after the irradiation. Hence, the latency period from the diagnosis of prostate cancer is unlikely to reflect an age-dependent latency from the first occupational exposure to asbestos. To produce the observed pattern of estimates, confounding by asbestos should act differently in each latency period.

We also performed a target-adjustment sensitivity analysis to explore the difference in prevalence of occupational exposure to asbestos by EBRT status that would have been necessary to explain the observed associations (see Web Appendix 1). In order to completely explain the IRR observed for EBRT, the prevalence of occupational exposure to asbestos would have to have been 30 % higher in subjects exposed to EBRT compared to unexposed subjects (see Web Table 4). And, when applying a more plausible assumption of a latency of 10 or more years, the EBRT group would have to have had 63 % higher asbestos exposure than the comparison group in order to fully explain the observed association between EBRT and mesothelioma. Such large differences, with no evident explanation, are implausible.

Registry-based studies of cancer might be affected by detection bias (also called surveillance bias). Detection bias occurs when there are systematic differences between the study groups in the assessment of the outcome [19]. This kind of bias is often a serious threat when studying cancers that can be clinically silent for a long period (e.g., prostate cancer or breast cancer). Indeed, clinical follow-up of the primary cancer may elicit the identification of secondary neoplasms that otherwise would have gone undetected. The risk of mesothelioma for subjects treated with EBRT observed in our study increased with latency period; the higher risk was found for latency of 10 years or more. A substantial difference in health monitoring among the studied groups is unlikely to have occurred so far from the primary treatment for prostate cancer. Also, an analysis restricted to patients aged up to 85 years, a subpopulation in which under-ascertainment is less likely in SEER data [44], produced estimates similar to those obtained when studying the entire population (IRR of mesothelioma 1.24, 95 % CI 1.01, 1.53—data not shown). On balance, we believe that detection bias was not likely to have been a major limitation in our study.

As in some previous analyses of SEER data, we did not adjust by tumor stage and grade. However, a sensitivity analysis confirmed our a priori hypothesis that grade and stage of prostate cancer did not appear to be confounders of the association between EBRT and mesothelioma.

We do not believe that the quality of diagnosis is a serious limitation. Most of the mesothelioma cases were diagnosed with histology or exfoliative cytology which are effective in the differential diagnosis with peripheral lung cancer. On the other hand, no information was provided in SEER on results of an immunohistochemical panel, which has been recommended to distinguish benign from malignant mesothelial proliferations [45]. We cannot therefore exclude the possibility that the incidence of mesothelioma may have been slightly over-diagnosed; however, this misdiagnosis is unlikely to have been differential with respect to the exposure of interest (beam radiotherapy).

Exposure to EBRT was studied as a dichotomous variable as no detailed information on radiation doses or treatment type was available; therefore, we were not able to study a dose–response relationship. Also, it is likely that there was a certain degree of exposure misclassification because some subjects classified as unexposed at the baseline may have undergone EBRT later in the study period. This source of non-differential misclassification of exposure is likely to have biased estimate toward the null hypothesis.

When modeling on the absolute scale, we found that the increase in risk was modest (3.31 per 100,000 person-years); as a point of comparison, we note that it is smaller than that determined by living in a county at high risk of mesothelioma. This perspective and the very small population attributable fraction (0.49 %) suggest that the contribution of EBRT to the worldwide mesothelioma epidemic has been negligible.

Conclusions

Our study provides evidence that EBRT for prostate cancer is a risk factor for mesothelioma. However, we found a small absolute increase in risk and a small population attributable fraction; hence, we believe that EBRT is unlikely to have played any significant role in the global mesothelioma epidemic. Our findings corroborate the hypothesis that EBRT

could be a risk factor not only for cancer sites proximal to the primary treated tumor, but also for radiogenic cancers throughout the body [46].

Conflict of interest The authors declare that they have no conflict of interest.

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