Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE

To determine the association between exposure to radiotherapy for the treatment of prostate cancer and subsequent second malignancies (second primary cancers).

DESIGN

Systematic review and meta-analysis of observational studies.

DATA SOURCES

Medline and Embase up to 6 April 2015 with no restrictions on year or language.

STUDY SELECTION

Comparative studies assessing the risk of second malignancies in patients exposed or unexposed to radiotherapy in the course of treatment for prostate cancer were selected by two reviewers independently with any disagreement resolved by consensus.

DATA EXTRACTION AND SYNTHESIS

Two reviewers independently extracted study characteristics and outcomes. Risk of bias was assessed with the Newcastle-Ottawa scale. Outcomes were synthesized with random effects models and Mantel-Haenszel weighting. Unadjusted odds ratios and multivariable adjusted hazard ratios, when available, were pooled.

MAIN OUTCOME MEASURES

Second cancers of the bladder, colorectal tract, rectum, lung, and hematologic system.

RESULTS

Of 3056 references retrieved, 21 studies were selected for analysis. Most included studies were large multi-institutional reports but had moderate risk of bias. The most common type of radiotherapy was external beam; 13 studies used patients treated with surgery as controls and eight used patients who did not undergo radiotherapy as controls. The length of follow-up among studies varied. There was increased risk of cancers of the bladder (four studies; adjusted hazard ratio 1.67, 95% confidence interval 1.55 to 1.80), colorectum (three studies; 1.79, 1.34 to 2.38), and rectum (three studies; 1.79, 1.34 to 2.38), but not cancers of the hematologic system (one study; 1.64, 0.90 to 2.99) or lung (two studies; 1.45, 0.70 to 3.01), after radiotherapy compared with the risk in those unexposed to radiotherapy. The odds of a second cancer varied depending on type of radiotherapy: treatment with external beam radiotherapy was consistently associated with increased odds while brachytherapy was not. Among the patients who underwent radiotherapy, from individual studies, the highest absolute rates reported for bladder, colorectal, and rectal cancers were 3.8%, 4.2%, and 1.2%, respectively, while the lowest reported rates were 0.1%, 0.3%, and 0.3%.

CONCLUSION

Radiotherapy for prostate cancer was associated with higher risks of developing second malignancies of the bladder, colon, and rectum compared with patients unexposed to radiotherapy, but the reported absolute rates were low. Further studies with longer follow-up are required to confirm these findings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Management of prostate cancer has been fraught with concerns regarding overtreatment because of the considerable complications related to the treatment

Secondary malignancies related to treatment represent perhaps the most serious of all complications

A previous meta-analysis of this subject lacked important recent publications

WHAT THIS STUDY ADDS

There is a possible association between radiotherapy for the treatment of prostate cancer and an increased risk of bladder, colorectal, and rectal cancers

These findings were consistent after adjustment for baseline patient and tumor factors as well as lag time restrictions

Introduction

Treatment options for patients with a diagnosis with clinically localized prostate cancer can include surgery or radiotherapy.[1] Each option is associated with side effects including urinary incontinence and erectile dysfunction.[2 3] Recently, other complications related to treatment and resulting in hospital admissions, genitourinary and recto-anal procedures, and major surgeries have been described.[4-6] A unique complication for patients undergoing radiotherapy is the possibility of development of a secondary malignancy (second primary cancer).

Studies assessing the risk of secondary cancers after radiotherapy for prostate cancer have reported either an increased risk of secondary malignancies[7 8] or no association between radiotherapy and secondary malignancies.[9 10] One previous review concluded a negligible risk of secondary malignancies after radiotherapy,[11] whereas other reviews concluded that this is an important risk for both patients and physicians to consider.[12-14] A previous meta-analysis lacked data from several important recent publications.[15]

While direct radiation carcinogenesis has long been accepted,[16] there is evidence that irradiation of the prostate might contribute to carcinogenesis outside the irradiated area through radiation scatter and radiation induced genetic alterations without direct exposure because of increased reactive oxygen species[17-19] and

changes in gene expression in what has been termed the "bystander effect."[20] We therefore carried out a systematic review and meta-analysis of available data on the association between radiotherapy and the development of secondary malignancies of the bladder, colorectal tract, lung, and hematological system in patients with prostate cancer compared with other treatments.

Methods

Participants and exposure

We reviewed studies reporting on patients with confirmed adenocarcinoma of the prostate treated with commonly used forms of radiotherapy including conformal external beam, intensity modulated, brachytherapy, or a combination of types. We included studies irrespective of dose and duration of radiotherapy. Controls were patients who did not undergo radiotherapy, including those who were treated with surgery, other treatments for prostate cancer, or received no treatment. We conducted a subgroup analysis using only controls treated with surgery. When the comparator group was unclear, we excluded the study.

Outcome

Our primary outcome was the development of one or more histologically unique secondary cancers of the bladder, colorectal tract, rectum, lung, and hematologic system, excluding metastatic tumors. Studies reporting on rectal cancer were included in the analysis of colorectal cancer as well as in the analysis of rectal cancer.

It is argued that time (lag period) must elapse between the date of exposure to radiation and the development of a secondary cancer for that tumor to be considered induced by radiation.[13] Historically, this has been defined as five years.[13 21-23] There were differences in the use and application of the length of the lag period from the time of treatment to diagnosis of secondary cancer among included studies. To deal with differences in how studies handled the lag period, we conducted separate analyses stratified by inclusion without respect to lag period to only those using a five year lag period and to only those using a 10 year lag period.

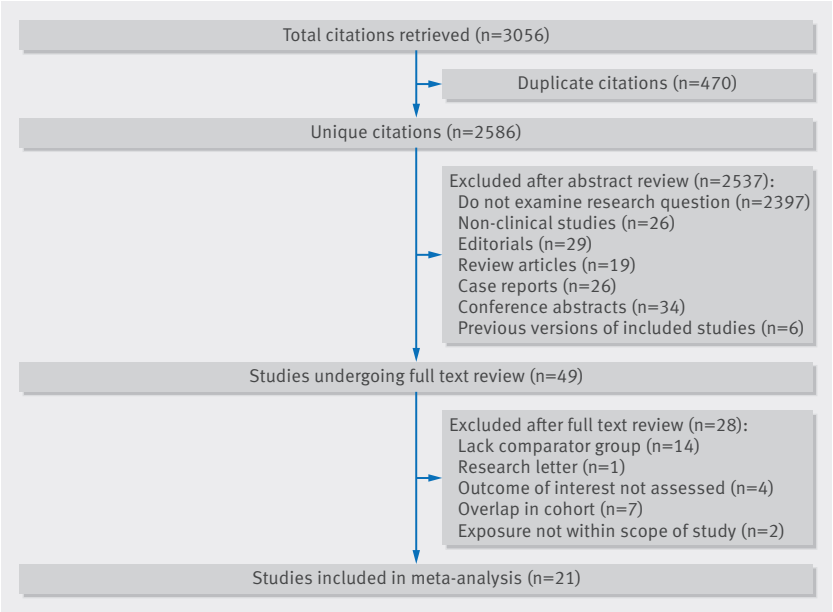

Fig 1 | Search strategy and final included and excluded studies of secondary malignancies after radiotherapy for prostate cancer

Types of studies

We included cohort and case control studies. We excluded case series that lacked comparator patients who did not undergo radiotherapy. Other publications on the topic, including basic science papers, review articles, editorials, articles not dealing with radiation induced malignancy, conference abstracts, early versions of data later published, and non-standard treatment (such as cryotherapy) were excluded (fig 1). When there was more than one publication resulting from the same cohort of patients, to prevent the duplication of patients from one cohort, for each of our analyses we selected one study based on a hierarchical assessment of comparability of study groups, definition of radiation exposure, time period of study (preference for more recent), and number of patients (appendix 1).

Methods of review

We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational studies in Epidemiology (MOOSE) guidelines for reporting of this systematic review and meta-analysis.[24 25]

Search strategy

With the help of a professional librarian we searched Medline and Embase databases using the OvidSP search platform for studies indexed up to 6 April 2015. Appendix 2 shows the detailed search strategy for each database. References from review articles, editorials, and included studies were reviewed and cross referenced to ensure completeness. Studies in any language were included. Conference abstracts were excluded.

Selection and data extraction

Two authors (CJDW and ALM) performed study selection. Titles and abstracts were screened for initial study inclusion, with full text review when the abstract was insufficient to determine if the study met the inclusion or exclusion criteria. Final agreement on study inclusion was made by discussion and consensus with other authors. Two reviewers performed all data extraction including evaluation of study characteristics, risk of bias, and outcome measures. Key variables were selected based on clinical and methodological relevance. Two authors pilot tested the data abstraction form to ensure completeness. Discrepancies were resolved through consensus (with PSS and RKN). Study authors were contacted when suitable data were not available.

Assessment of risk of bias

We used the Newcastle-Ottawa scale to assess risk of bias. This scale assesses risk in three domains:[26] selection of

the study groups, comparability of groups, and ascertainment of exposure and outcome.[27] Studies that scored >7 were considered as having low risk of bias, scores of 5-7 indicated moderate risk of bias, and scores of <5 indicated high risk of bias.

Statistical analysis

Meta-analysis was performed with Review Manager 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, 2014) software. We assessed the adjusted hazard ratio and unadjusted odds ratio of developing a secondary malignancy between participants treated with radiotherapy and controls. We first analyzed studies including any form of radiotherapy, stratified by studies that used controls groups comprising patients who did not undergo radiotherapy and patients treated with surgery.

Because of the clinical heterogeneity inherent in our data, we used random effects models for all meta-analyses. Given the relatively rare nature of our events, we used Mantel-Haenszel weighting.[28] For adjusted hazard ratios, we used the inverse variance technique. Statistical heterogeneity was assessed with I^2 values.[29]

As a post hoc analysis, we assessed the absolute risk difference between patients treated with radiotherapy and controls. We expressed this as the difference per 100 patients.

Subgroup analysis and exploration of heterogeneity

We performed a priori subgroup analyses by examining studies that used only external beam radiotherapy and those that used only brachytherapy. For each of these analyses, we stratified by control group (no radiation and surgery). To further explore heterogeneity, we conducted meta-regression using the Newcastle-Ottawa risk of bias score as a continuous variable in random effects models for all comparisons comprising five or more studies.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of results.

Results

We retrieved 3056 references from our literature search (fig 1). After full text review of 49 manuscripts, we selected 21 reports for inclusion (table 1). Twenty eight studies were excluded; figure 1 lists the reasons. Of note, we identified 24 reports derived from the United States Surveillance, Epidemiology, and End Results (SEER) cohort in our literature search. These studies overlapped in their inclusion criteria, study intervals, patient selection, and outcome measures. To prevent the duplication of patients from the SEER cohort, we selected a single study to represent the SEER cohort for each comparison as outlined in appendix 1. The studies used in each of the analyses are outlined in appendix 3.

We obtained unpublished data from the principal author of one study we included.[30] In a second case, we were unable to obtain necessary information for inclusion in a subgroup analysis, but the published data were adequate for our primary analysis.[31]

Study description

Table 1 shows characteristics of included studies. Eighteen were large multi-institutional reports, and three were single centre studies.[10 32 33] Conformal external beam radiotherapy was the most commonly assessed type of radiotherapy. There were insufficient data to distinguish between two dimensional, three dimensional, and intensity modulated radiotherapy, though most included studies assessed three dimensional conformal external beam radiotherapy. There were considerable differences in the definition and use of a lag period before outcome ascertainment (table 1). Length of follow-up also varied significantly between included studies (table 1). Thirteen studies (62%) included patients treated with surgery as the comparator, and eight studies (38%) used "no radiation" or "no radiation and no surgery" control groups (table 1). Crude incidence of individual secondary cancers ranged from 0.2% to 2.3% for patients treated with external beam radiotherapy, 0.1% to 2.1% for patients treated with brachytherapy, 0.2% to 1.7% for patients treated with brachytherapy and external beam boost, and 0.3% to 2.3% for patients not exposed to radiotherapy; however, these rates varied significantly between studies (table 1). Most studies did not specify whether the reported bladder cancers were superficial or invasive. For studies reporting adjusted hazard ratios, covariates included in the model varied significantly between studies though all included age at diagnosis (table A, appendix 4).

Assessment of risk of bias

Most studies were deemed to be of moderate risk of bias (table B, appendix 4). Commonly identified concerns include a lack of explicit demonstration that the outcome was not present at the start of the study, the length of follow-up, and attrition bias.

Bladder cancer

On unadjusted analysis with no restriction to lag period, we found an increased odds of bladder cancer (nine studies, 555 873 participants; unadjusted odds ratio 1.39, 95% confidence interval 1.12 to 1.71; I^2=56%; fig 2). The results were similar when we restricted analysis to studies with a five year lag period (three studies, 397 416 participants; 1.30, 1.19 to 1.42; I^2=0%; table 2, fig 2) or a 10 year lag period (two studies, 99 362 patients; 1.89, 1.65 to 2.16; I^2=0%). After multivariable adjustment, we found an increased risk for bladder cancer in those treated with radiotherapy (four studies; adjusted hazard ratio 1.67, 95% confidence interval 1.55 to 1.80; I^2=0%; fig 3). Absolute differences in risk of bladder cancer between patients exposed and unexposed to radiotherapy ranged from 0 to 0.6 cancers per 100 patients, depending on type of radiotherapy, comparator group, and lag period (table C, appendix 4).

Table 1 | Characteristics of included studies in systematic review of secondary malignancies after radiotherapy for prostate cancer

Author	Data source (study interval)	Follow-up	Lag time	Study size	Type of radiation	Control group	Crude incidence rate of secondary cancers, by treatment (%)				
							Bladder	Colorectal	Rectal	Lung	Hematologic
Abdel-Wahab (2008)[34]	SEER (1972-2002)	median 4.3-4.7 years	1 year	108 452	EBRT, brachytherapy, brach+	No radiation and no surgery	RT: 1.2, EBRT: 1.5, Brach: 0.5, Brach+: 0.8, Ctrl: 0.9	RT: 1.7 EBRT: 2.0, Brach: 0.8, Brach+: 1.0, Ctrl: 1.6	RT: 0.3 EBRT: 0.4, Brach: 0.2, Brach+: 0.2, Ctrl: 0.3	RT: 1.9 EBRT: 2.3, Brach: 0.9, Brach+: 1.1, Ctrl: 1.7	RT: 1.0 EBRT: 1.2, Brach: 0.6, Brach+: 0.6, Ctrl: 0.9
Abern (2013)[35]	SEER (1988-2007)	median 65 months	1 year	275 200	EBRT, brachytherapy, brach+, XRT NOS	Surgery	RT: 1.4, EBRT: 1.6, Brach: 0.9, Brach+: 1.3, Ctrl: 0.7	NR	NR	NR	NR
Baxter (2005)[36]	SEER (1973-99)	mean > 9 years	5 years	85 815	EBRT	Surgery	NR	RT: 1.7, Ctrl: 1.0	RT: 0.4, Ctrl: 0.3	NR	NR
Berrington de Gonzales (2011)[7]	SEER (1973-2002)	mean 12 years	5 years	200 163	EBRT, brachytherapy, brach+	No radiation	RT: 1.3, Ctrl: 0.9	RT: 1.3, Ctrl:1.2	RT: 0.5, Ctrl: 0.4	RT: 1.9, Ctrl: 1.7	NR
Bhojani (2010)[37]	Quebec (1983-2003)	NR	Multiple	17 845	EBRT	Surgery	RT: 2.3, Ctrl: 2.1	NR	RT: 1.1, Ctrl: 0.7	RT: 3.5, Ctrl: 2.9	NR
Boorjian (2007)[38]	CaPSURE (1989-2003)	median 39 months	30 days	9681	EBRT, brachytherapy	Surgery, other	RT: 1.3, Ctrl: 0.9	NR	RT: 0.4, Ctrl: 0.3	NR	NR
Brenner (2000)[8]	SEER (1972-93)	median 4 years	2 month	122 123	"Radiation"	Surgery	RT: 0.9, Ctrl: 0.9	RT: 1.4, Ctrl: 1.6	RT: 0.4, Ctrl: 0.4	RT: 1.6, Ctrl: 1.5	RT: 0.2, Ctrl: 0.2*
Davis (2014)[39]	SEER (1992-2010)	NR	10 years	106 879	EBRT	No radiation	RT: 1.3, Ctrl: 0.9	RT: 1.2, Ctrl: 0.8	RT: 0.4, Ctrl: 0.2	RT: 1.3, Ctrl: 1.1	RT: 1.0, Ctrl: 0.9
Hinnen (2011)[40]	Utrecht, Netherlands (1989-2005)	median 7.5 years	0	1888	Brachytherapy	Surgery	RT: 1.4, Ctrl: 1.4	RT: 2.1, Ctrl: 2.3	RT: 0.8, Ctrl: 1.2	RT: 1.4, Ctrl: 1.3	RT: 0.7, Ctrl: 0.7
Huang (2011)[32]	William Beaumont, MI and SEER (1984-2005)	mean 7.4 years	NR	17 264	EBRT (2D/ 3DCRT, IMRT), brachytherapy, brach+	Surgery	NR	NR	NR	NR	NR
Huo (2009)[41]	SEER (1973-2005)	NR	NR	635 910	EBRT, brachytherapy	No radiation	NR	RT: 1.2, Ctrl: 1.2	RT: 0.4, Ctrl: 0.4	NR	NR
Margel (2011)[31]	Israel Cancer Registry (1982-2005)	median 11.2 years	6 months	29 593	"Radiation"	Surgery, other/ none	NR	NR	RT: 1.2, Ctrl: 0.6	NR	NR
Moon (2006)[42]	SEER (1973-99)	median 10.0 years	5 years	140 767	EBRT, brachytherapy, brach+, XRT NOS	No radiation	RT: 1.4, EBRT: 1.4, Brach: 1.2, Brach+: 1.1, Ctrl: 0.9	RT: 1.7, EBRT: 1.7, Brach: 0.6, Brach+: 1.6, Ctrl: 1.4	RT: 0.4 EBRT: 0.4, Brach: 0.1, Brach+: 0.5, Ctrl: 0.3	RT: 2.0 EBRT: 2.0, Brach: 1.2, Brach+: 1.7, Ctrl: 1.6	RT: 1.0 EBRT: 1.0, Brach: 0.3, Brach+: 0.9, Ctrl: 0.9
Nam (2014)[6]	Ontario (2002-09)	NR	5 years	32 465	EBRT	Surgery	RT: 0.1, Ctrl: 0.1	RT: 0.3, Ctrl: 0.1	NR	RT: 0.2, Ctrl: 0.04	RT: 0.1, Ctrl: 0.1
Nieder (2008)[43]	SEER (1973-90)	median 49 months	6 month	243 082	EBRT, brachytherapy, brach+	Surgery	RT: 1.1, EBRT: 1.3, Brach: 0.5, Brach+: 0.8, Ctrl: 0.7	NR	RT: 0.4, EBRT: 0.4, Brach: 0.2, Brach+: 0.3, Ctrl: 0.3	NR	NR
Pickles (2002)[30]	BC Tumor Registry (1984-2000)	median 3.1-5.3 years	2 months	39 261	EBRT	No radiation	RT: 0.6, Ctrl:0.5	RT: 2.4, Ctrl: 1.1	NR	RT: 2.1, Ctrl: 1.2	RT: 0.9, Ctrl: 0.6
Rapiti (2008)[44]	Geneva Cancer Registry (1980-98)	median 7.4 years	5 years	1134	EBRT	No radiation	RT: 1.1, Ctrl: NR	RT: 4.2, Ctrl: 0.9	RT: 0.8, Ctrl: 0.5	RT: 1.1, Ctrl: NR	RT: 1.5, Ctrl: NR
Singh (2008)[33]	Syracuse VA Center (1996-2003)	NR	6 months	626	EBRT, brachytherapy, brach+	No radiation	RT: 3.8, Ctrl: 1.7	NR	NR	NR	NR
Singh (2010)[45]	SEER (1973-2005)	median 48.4-93.6 months	Multiple	555 337	EBRT	Surgery, none	RT: 1.5, Ctrl: 1.2	NR	NR	NR	NR
Van Hemelrijck (2014)[46]	Zurich Cancer Registry (1980-2010)	NR	0	20 559	Radiation	Surgery, ADT, other	RT: 1.5, Ctrl: 1.2	RT: 1.5, Ctrl: 1.8	RT: 0.4, Ctrl: 0.5	RT: 1.1, Ctrl: 1.6	RT: 1.4, Ctrl: 1.0
Zelefsky (2012)[10]	MSKCC (1998-2001)	median 90-113 months	NR	2658	EBRT (IMRT), brachytherapy	Surgery	RT: 1.2, EBRT: 1.3, Brach: 1.0, Ctrl: 1.2	RT: 1.5, EBRT: 1.2, Brach: 1.9, Ctrl: 0.7	RT: 0.5, EBRT: 0.6, Brach: 0.5, Ctrl: 0.7	RT: 1.2, EBRT: 1.3, Brach: 0.7, Ctrl: 1.6	RT: 1.2, EBRT: 1.2, Brach: 1.2, Ctrl:1.1†

SEER=Surveillance, Epidemiology and End Results; CaPSURE=Cancer of the Prostate Strategic Urologic Research Endeavor; VA=Veterans Administration; MSKCC=Memorial Sloan Kettering Cancer Center; EBRT=external beam radiotherapy; NR=not reported; XRT NOS=radiotherapy not otherwise specified; 2DCRT=two dimensional conformal radiotherapy; 3DCRT=three dimensional conformal radiotherapy; IMRT=intensity modulated radiotherapy; brach+=brachytherapy and EBRT; brach = brachytherapy; Ctrl=control.
*Restricted to leukemias.
†Restricted to lymphoma.

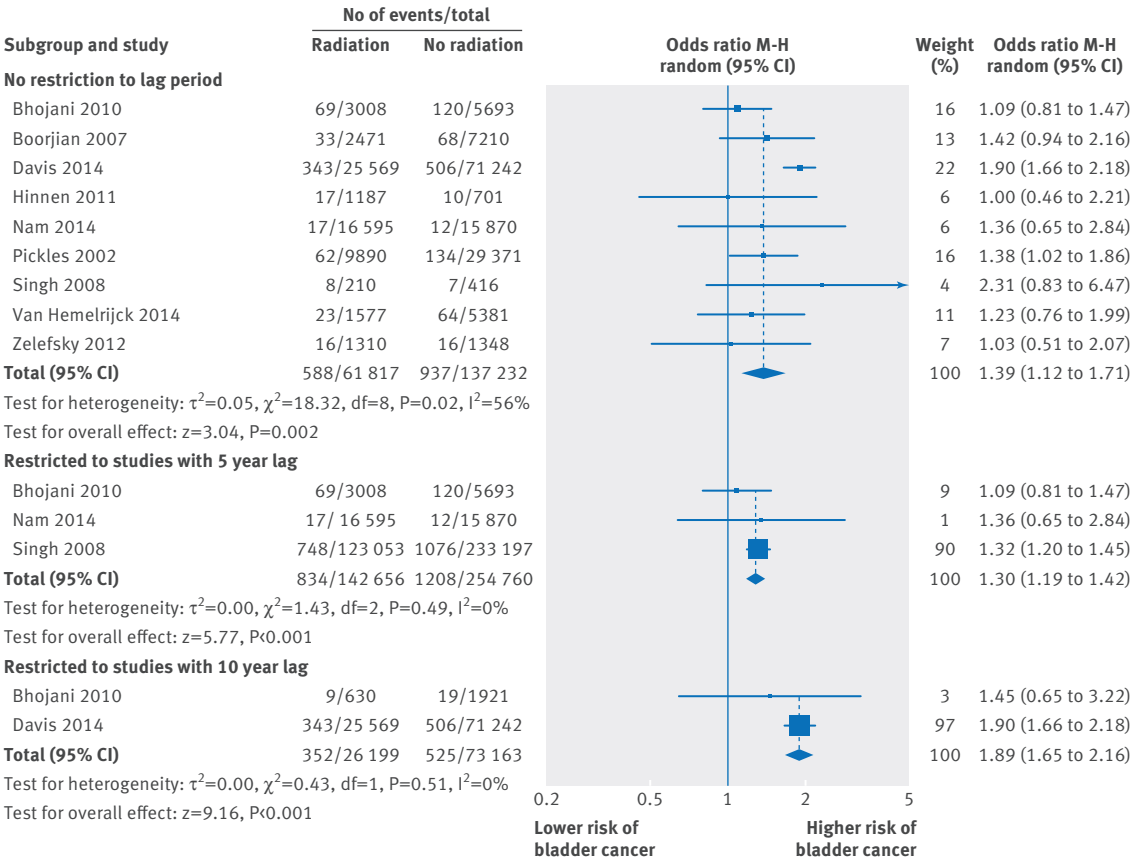

Fig 2 | Risk of bladder cancer after any radiotherapy compared with no radiation in studies with no restriction to lag period, studies with five year lag period, and studies with 10 year lag period

Colorectal cancer

On unadjusted analysis with no lag period, we found an increased odds of colorectal cancers after any form of radiotherapy compared with no radiation (10 studies; 228 965 participants; unadjusted odds ratio 1.68, 95% confidence interval 1.33 to 2.12; I^2=72%; fig 4). Again, results were similar after we restricted analysis to studies with a five year lag period (four studies, 242 878 patients; 1.94, 1.07 to 3.50, I^2=86%; table 2, fig 4) or a 10 year lag period (two studies, 99 578 patients; 1.56, 1.36 to 1.80; I^2=0%). Pooled multivariable adjusted hazard ratios showed an increased risk for colorectal cancer in those treated with radiotherapy (three studies; adjusted hazard ratio 1.79, 95% confidence interval 1.34 to 2.38; I^2=28%; fig 3). The absolute difference in colorectal cancers ranged from 0.2 to 1.4 cases per 100 patients for those treated with radiotherapy and controls, depending on type of radiotherapy, comparator, and lag period (table C, appendix 4).

Rectal cancer

When we restricted analysis to cases of rectal cancer after radiotherapy, we identified an increased odds associated with radiotherapy in unadjusted analysis without restriction to lag period (eight studies, 157 239 participants; unadjusted odds ratio 1.62, 95% confidence interval 1.26 to 2.08; I^2=33%; fig 5). Restriction of analysis to those studies with a five year lag period showed no significant association (three studies, 204 064 patients; 1.68, 0.90 to 3.15, I^2=76%; table 2, fig 5), while restriction to those studies with a 10 year lag period showed an association similar to the primary analysis (two studies, 99 578 patients; 2.20, 1.72 to 2.81, I^2=0%). Pooling of multivariable adjusted hazard ratios showed an increased risk similar to our primary analysis (three studies; adjusted hazard ratio 1.79, 95% confidence interval 1.34 to 2.38; I^2=28%; fig 3). The absolute difference in risk between radiotherapy exposed and unexposed patients ranged between −0.2 and 1.0 cases of rectal cancer per 100 patients (table C, appendix 4).

Lung cancer

Unadjusted analysis of studies without restriction to lag period showed no association between radiotherapy and lung cancer (seven studies, 188 911 participants; unadjusted odds ratio 1.31, 95% confidence interval 0.97 to 1.76; I^2=84%; fig A, appendix 5). Restriction of analysis to studies with a five year lag period showed marginal significance (three studies, 241 298 participants; 1.55, 1.00 to 2.40; I^2=88%; table 2), while there was no association in those studies with a 10 year lag period (two studies, 99 478 patients; 1.58, 0.89 to 2.83, I^2=76%). There was also no association when we pooled multivariable adjusted hazard ratios (two studies; adjusted

Table 2 | Pooled odds/hazard estimates for secondary tumor sites after treatment for prostate cancer stratified by type of radiotherapy and comparator group

	No lag restriction			5 year lag			Adjusted HR	
	Studies	No of patients	OR (95% CI)	Studies	No of patients	OR (95% CI)	Studies	HR (95% CI)
Bladder cancer								
Versus no radiotherapy:								
Any radiotherapy	9	555 873	1.39 (1.12 to 1.71)*	3	397 416	1.30 (1.19 to 1.42)*	4	1.67 (1.55 to 1.80)*
EBRT	6	186 854	1.37 (1.05 to 1.77)*	3	397 416	1.30 (1.19 to 1.42)*	2	1.62 (1.20 to 2.20)*
Brachytherapy	3	161 889	1.25 (1.10 to 1.42)*	1	95 826	1.45 (0.88 to 2.39)	2	1.04 (0.52 to 2.09)
Versus surgery:								
Any radiotherapy	6	692 487	1.37 (1.02 to 1.84)*†	2	41 166	1.12 (0.85 to 1.48)	2	1.62 (1.38 to 1.91)*
EBRT	5	259 521	1.39 (0.93 to 2.07)†	2	41 166	1.12 (0.85 to 1.48)	2	1.63 (0.90 to 2.96)
Brachytherapy	2	160 001	1.26 (1.11 to 1.43)*	NA	NA	—	1	0.66 (0.11 to 3.96)
Colorectal cancer								
Versus no radiotherapy:								
Any radiotherapy	10	228 965	1.68 (1.33 to 2.12)*	4	242 878	1.94 (1.07 to 3.50)*†	3	1.79 (1.34 to 2.38)*
EBRT	8	217 396	1.78 (1.38 to 2.29)*	4	177 061	1.93 (1.04 to 3.57)*†	2	1.41 (0.78 to 2.56)†
Brachytherapy	3	135 716	0.99 (0.39 to 2.53)†	1	95 826	0.15 (0.02 to 1.07)	1	0.96 (0.43 to 2.13)
Versus surgery:								
Any radiotherapy	7	332 953	1.45 (1.07 to 1.96)*	3	127 396	1.57 (0.91 to 2.70)†	2	1.41 (0.78 to 2.56)†
EBRT	6	282 014	1.52 (1.14 to 2.03)*	3	127 396	1.57 (0.91 to 2.70)†	2	1.41 (0.78 to 2.56)†
Brachytherapy	2	133 828	1.12 (0.19 to 6.66)†	NA	NA	—	NA	—
Rectal cancer								
Versus no radiotherapy:								
Any XRT	8	157 239	1.62 (1.26 to 2.08)*	3	204 064	1.68 (0.90 to 3.15)†	3	1.79 (1.34 to 2.38)*
EBRT	6	145 670	1.64 (1.21 to 2.21)*	3	144 596	1.56 (1.31 to 1.86)*	2	1.74 (1.45 to 2.08)*
Brachytherapy	3	135 716	0.65 (0.36 to 1.19)	1	95 826	0.28 (0.04 to 1.99)	NA	—
Versus surgery:								
Any radiotherapy	6	300 488	1.30 (0.99 to 1.71)	2	94 931	1.56 (1.26 to 1.93)*	2	1.74 (1.45 to 2.08)*
EBRT	5	249 549	1.38 (1.12 to 1.70)*	2	94 931	1.56 (1.26 to 1.93)*	2	1.74 (1.45 to 2.08)*
Brachytherapy	2	133 828	0.49 (0.35 to 0.67)	NA	NA	—	NA	—
Lung cancer								
Versus no radiotherapy:								
Any radiotherapy	7	188 911	1.31 (0.97 to 1.76)†	3	241 498	1.55 (1.00 to 2.40)*†	2	1.45 (0.70 to 3.01)†
EBRT	6	187 023	1.33 (0.97 to 1.82)†	3	175 681	1.60 (1.06 to 2.42)*†	2	1.38 (0.74 to 2.56)
Brachytherapy	3	54 605	0.62 (0.39 to 0.97)	1	95 826	0.71 (0.43 to 1.19)	1	0.70 (0.22 to 2.23)
Versus surgery:								
Any radiotherapy	5	173 074	1.16 (0.81 to 1.68)†	2	41 335	2.66 (0.52 to 13.64)†	2	1.45 (0.70 to 3.01)†
EBRT	5	172 661	1.19 (0.83 to 1.71)†	2	41 335	2.66 (0.52 to 13.64)†	2	1.37 (0.71 to 2.61)
Brachytherapy	1	1761	0.44 (0.13 to 1.48)	NA	NA	—	1	0.70 (0.22 to 2.23)
Hematological cancers								
Versus no radiotherapy:								
Any radiotherapy	6	180 032	1.33 (1.05 to 1.69)*	2	173 232	1.30 (0.79 to 2.13)	1	1.64 (0.90 to 2.99)
EBRT	5	177 740	1.36 (1.05 to 1.77)*	2	173 232	1.30 (0.79 to 2.13)	1	2.09 (0.15 to 29.75)
Brachytherapy	3	54 605	1.08 (0.80 to 1.46)	1	95 826	0.36 (0.13 to 0.92)	1	0.50 (0.09 to 2.78)
Versus surgery:								
Any radiotherapy	4	164 195	1.16 (0.78 to 1.72)	1	32 465	1.91 (0.96 to 3.83)	1	1.64 (0.90 to 2.99)
EBRT	4	272 093	1.08 (0.98 to 1.19)	1	32 465	1.91 (0.96 to 3.83)	1	2.09 (0.15 to 29.75)
Brachytherapy	1	1761	1.09 (0.39 to 3.01)	NA	NA	—	1	0.50 (0.09 to 2.78)

EBRT = external beam radiotherapy; NA=no data available for meta-analysis.
*Significant at P<0.05.
†I^2>75%, indicating significant heterogeneity.

hazard ratio 1.45, 95% confidence interval 0.70 to 3.01; I^2=86%). For lung cancers, the absolute difference between patients treated with radiotherapy and those not exposed ranged from −0.9 to 1.1 cancers per 100 patients (table C, appendix 4).

Hematologic cancers

We found an increased odds of hematologic cancers after radiotherapy in studies without restriction to lag period (six studies, 180 032 participants; unadjusted odds ratio 1.33, 95% confidence interval 1.05 to 1.69; I^2=50%; fig B, appendix 5), but this was not confirmed in studies with a five year lag period (two studies, 172 232 patients; 1.30, 0.79 to 2.13; I^2=57%; table 2), a 10 year lag period (one study, 96 811 patients; 1.09, 0.94 to 1.27), or multivariable adjusted hazard ratios (one study; adjusted hazard ratio 1.64, 95% confidence interval 0.90 to 2.99). The absolute difference in risk ranged between −0.6 and 0.2 cases per 100 patients for patients treated with radiotherapy and controls, depending on type of radiotherapy, comparator, and lag period (table C, appendix 4).

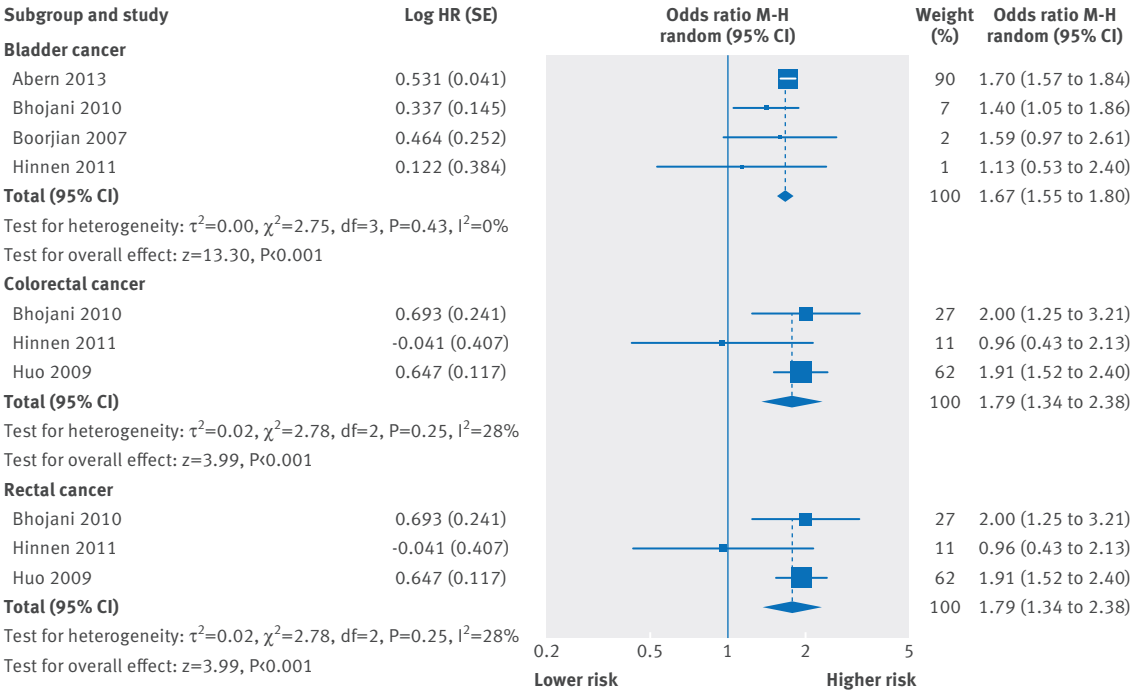

Fig 3 | Risk of cancer after any radiotherapy compared with no radiation in studies reporting adjusted hazard ratios

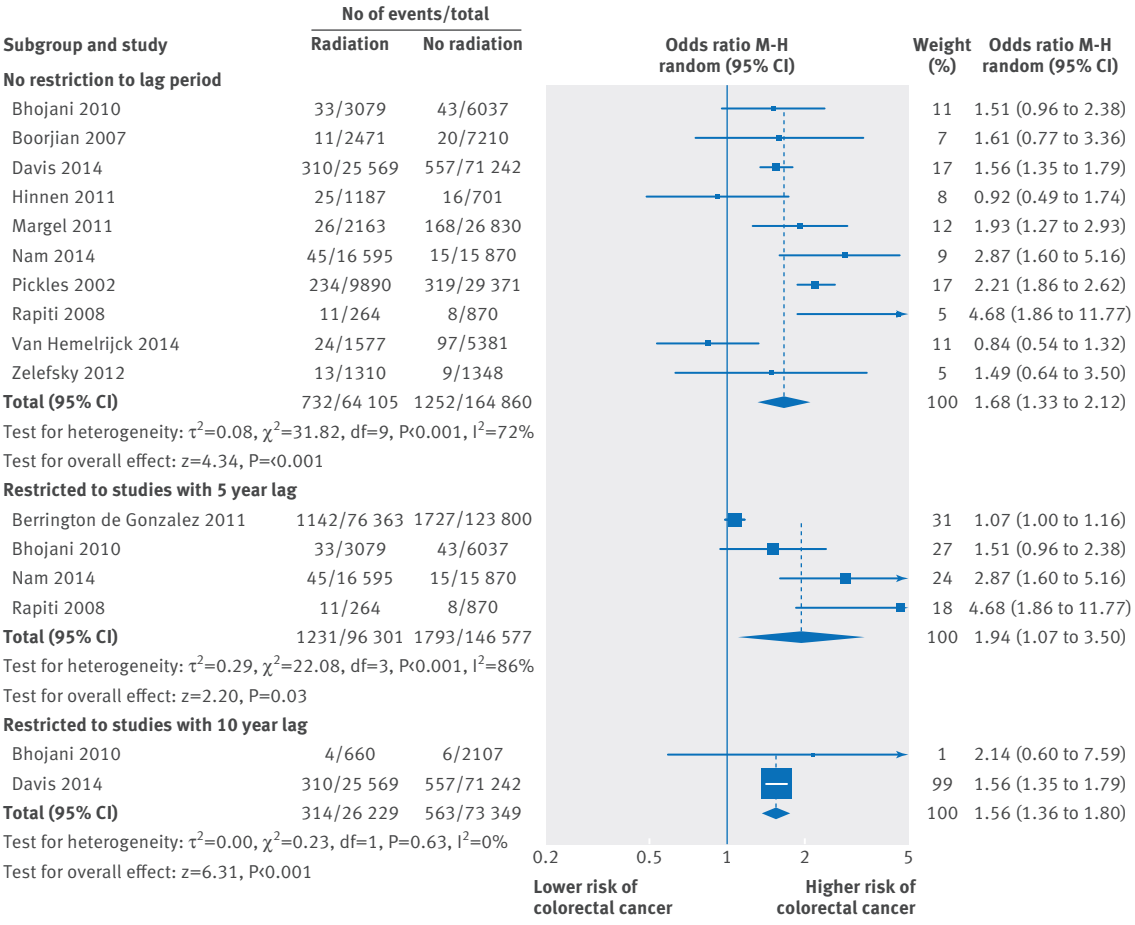

Fig 4 | Risk of colorectal cancer after any radiotherapy compared with no radiation in studies with no restriction to lag period, studies with five year lag period, and studies with 10 year lag period

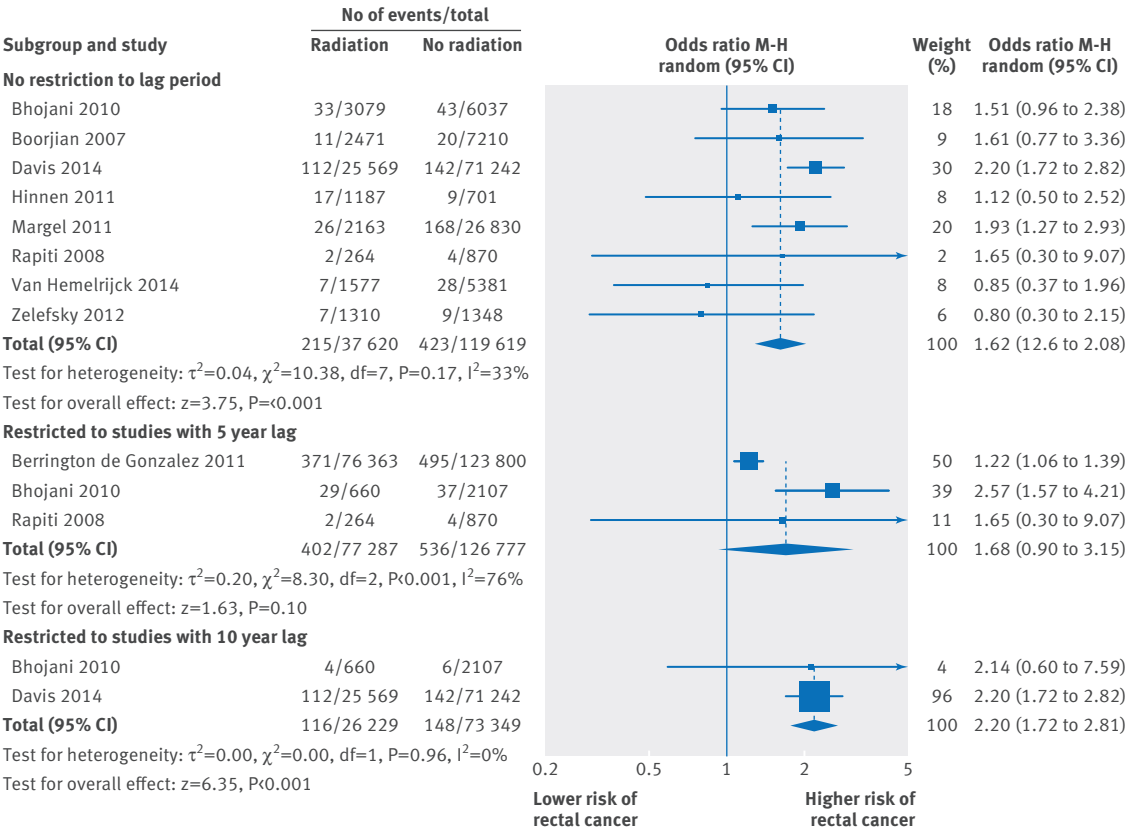

Fig 5 | Risk of rectal cancer after any radiotherapy compared with no radiation in studies with no restriction to lag period, studies with five year lag period, and studies with 10 year lag period

Subgroup analysis and exploration of heterogeneity

Studies limited to external beam radiotherapy predominately reported an increased odds of secondary malignancy after radiotherapy, whereas those limited to brachytherapy did not show this association (figs C and D, appendix 5; table 2). We conducted meta-regression using risk of bias score as a continuous variable in a random effects model when more than five studies were included in the meta-analyses. None of the analyses showed a significant effect of risk of bias score (all P>0.05) as a covariate on observed associations.

Discussion

In this comprehensive review and meta-analysis of 21 studies with moderate risk of bias, we identified an association between radiotherapy for prostate cancer and the development of secondary cancers of the bladder, colorectal tract, and rectum, compared with no radiotherapy or surgery. These results were consistent when we pooled multivariable adjusted hazard ratios and restricted analyses to studies using five or 10 year lag periods between treatment and outcome ascertainment. In particular, it is notable in our analysis that odds ratios for bladder and rectal cancer increased with a longer lag time (odds ratio at five year lag *v* 10 year lag: 1.3 *v* 1.89 for bladder cancer and 1.68 *v* 2.2 for rectal cancer). It is important to note, however, that the differences in absolute risks between cases and controls were low (table 1). In post hoc analyses, the absolute risk difference for patients treated with radiotherapy compared with those not treated with radiotherapy ranged from –0.9 to 1.9 cancers per 100 patients, with differences observed based on type of radiotherapy, comparator group, and lag time duration indicating that absolute risk for these secondary cancers is low.

Given the current understanding that the risk of secondary malignancy related to radiation increases over time, the progressive increase in odds ratio over time seen in our study supports a potential association between radiotherapy and the development of a secondary malignancy of the bladder and rectum. We did not find an association between radiotherapy and lung or hematologic cancers. It must be noted that many of the results were obtained from a small number of studies (between two and 10 in each analyses), and the absolute risk of secondary malignancy remains low. Variation in the crude incidence of secondary cancers is, at least in part, due to differences in follow-up between the included studies.

There was a trend across all analyses for lower odds ratios or hazard ratios in the pooled analysis resulting from studies using surgically treated patients as the control group rather than those using patients unexposed to radiotherapy. This could reflect a selection bias, with lower outcome ascertainment in those patients not treated with a definitive local therapy. Similarly, as patients treated with radiotherapy might experience increased bowel urgency and other recto-anal symptoms, including bleeding, as a result of

their treatment,[3] there is a potential for detection bias for colorectal and rectal cancers.

There was significant heterogeneity between studies for many of our outcomes, likely in large part because of the differences in control groups used and specific types of radiation delivered. Some studies used a surgery group[6 10 31 37 38] while others used a "no radiation" group[7 30 42 44] and yet others used a "no radiation, no surgery" group.[34] We sought to diminish the influence of these differences by providing stratified subgroup analyses. Further, within the external beam radiotherapy category, there was heterogeneity in radiotherapy techniques used (two dimensional[6 47] and three dimensional[6] conformational radiotherapy, external beam radiotherapy without further specification,[7 30 31 34 37 38 44] and intensity modulated radiotherapy[10]). Differences in the length of follow-up could contribute further to the heterogeneity. We also explored the role of study risk of bias in the observed heterogeneity. Meta-regression, however, failed to show a significant effect of risk of bias on the observed estimates.

Comparison with other studies

To our knowledge, there is only one other meta-analysis on this subject in addition to non-systematic reviews of the literature.[11 12 13 14 15] Our review differs from the previous meta-analysis[15] on this topic, which included only four studies. We identified significantly more studies and even among them we had to select studies from SEER cohort. In addition, most of their analyses relied on a single publication.[40] Further, they did not assess different radiotherapy techniques separately. Ours is the first attempt to quantify available knowledge on the subject in the most comprehensive, reproducible, and methodologically appropriate fashion.

Secondary primary cancers can arise because of common etiologic factors, including genetic predispositions, or effects related to treatment. Further, there might be issues of diagnostic bias when comparisons are made between treated patients and the general population. Considering that the comparison between patients treated with radiotherapy and those treated with surgery showed similar results to the main analysis, however, our data suggest that secondary cancers are largely because of effects related to treatment.

Several studies have shown differences in the risk of secondary cancer by specific type of radiation treatment. In our analysis, the association between radiotherapy and secondary cancers was much weaker for patients treated with brachytherapy than for those treated with external beam radiotherapy, in keeping with others' work.[48] Notably, when we assessed crude absolute incidence rates, patients treated with brachytherapy not infrequently had rates of secondary cancer lower than the control group; this likely represents selection of younger and healthier patients for brachytherapy. In a study of a single centre case series compared with the SEER population registry, Huang and colleagues showed no difference in rates of secondary malignancies between those men treated with brachytherapy and radical prostatectomy.[32] Moon and colleagues found that treatment with brachytherapy was associated with an increased odds of bladder cancer compared with treatment with surgery but that this risk did not apply to other tumor sites.[42] It can be speculated that brachytherapy could pose a lower risk of secondary malignancy related to radiation than external beam radiotherapy because it delivers much less integral radiation to normal tissues (outside the prostate) than external beam radiotherapy. While we did not examine intensity modulated radiotherapy separately from other types of external beam radiotherapy, it has supplanted conformal external beam radiotherapy in many jurisdictions.[49] To date, only a single study, by Zelefsky and colleagues, has independently examined the effect of intensity modulated radiotherapy on secondary cancers, and they reported no increased risk.[10]

Strengths and limitations of study

Major strengths of our review include the comprehensive search, careful selection of studies, critical appraisal of studies, planned subgroup analyses, analyses accounting for time lag in different methods (dichotomous and time incorporated hazards), and inclusion of adjusted estimates for hazard ratio. We must, however, acknowledge the limitations. First, given the number of studies derived from the SEER registry, we had to select a representative study. We used an explicit and transparent method. To ascertain whether study selection affected the results, however, we undertook a sensitivity analysis using the Newcastle-Ottawa risk of bias score as the primary determinant and sample size as the second. This resulted in the selection of a different study in 24 out of 83 comparisons (28.9%; appendix 6). For these 24 comparisons, the change in selected study resulted in an average change of −3.5% in the odds ratio estimates. As a result, the use of different selection criteria resulted in an average change of −1.02% when we considered all 83 comparisons. Therefore, we consider the study selection was robust. Second, we lacked important information on confounders and comorbidities and other risk factors associated with cancers other than prostate cancer, which might be higher in patients who are treated with radiotherapy. Of particular note is the lack of information on smoking for the ascertainment of risk of lung and bladder cancer, and obesity, which could predispose patients to colon[50] and prostate cancer.[51] This might bias the increased risk attributed to radiotherapy. Third, the small numbers of studies in individual subgroup analyses limited power in our conclusions. Finally, included studies had moderate risk of bias, and there is an ongoing need for high quality and minimally biased studies.

Conclusions and implications for practice and research

In view of the limited number of studies and limited adjustment for confounders, we identify an important need for future studies assessing the risk of secondary malignancy after radiotherapy for prostate cancer. This can be undertaken either as large prospective cohort

studies or multinational prospective registries. Implications of our results for clinical practice include use of these results in discussion with patients for decision making. In particular, for patients with a long life expectancy of 20 years or more, the possibility of secondary malignancy related to radiation needs to be included in management discussion. We acknowledge, however, that further studies are required before conclusive implication of the association between radiotherapy and secondary malignancy in these patients.

In conclusion, we identified a possible association between radiotherapy and an increased odds of secondary cancers compared with no radiotherapy or with surgery. We identified consistent evidence of an increased risk of bladder, colorectal, and rectal cancers in men treated with radiotherapy. We did not find consistent evidence for an association between radiotherapy and secondary lung and hematologic cancers. Although there was an increase in risk, the absolute rates of these secondary cancers remain low, particularly compared with other rates of complications associated with treatment for prostate cancer. This information could be helpful in the decision making process regarding such treatment.

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Contributors: CJDW and RKN designed the study, formulated the clinical question, and identified the PICOS components. CJDW performed the literature search and, with ALM, reviewed the search results for study inclusion. CJDW and ALM designed the data extraction form and extracted the data. CJDW and PSS performed the statistical analyses. CJDW wrote the paper and all other authors critically revised subsequent drafts. All authors approved the final manuscript for submission. CJDW and RKN are guarantors.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with organizations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work. SH, RTK, SAN, and RKN were authors of one of the included studies.

Ethical approval: This study was approved by the University of Toronto health research ethics board (No 31250). As aggregate data were used, patient consent was not deemed necessary.

Transparency: CJDW and RKN affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: Data extracted from published manuscripts is available from the senior author at Robert.Nam@utoronto.ca. Informed consent was not obtained from individual patients but aggregate, previously published data were used in this analysis and all data are fully anonymized.

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Appendix 1: Selection of representative SEER study for each outcome
Appendix 2: Literature search strategy **Appendix 3:** Studies included for each outcome **Appendix 4:** Supplementary tables A-C **Appendix 5:** Supplementary figures A-D **Appendix 6:** Sensitivity analysis