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Critical Review

Second Solid Cancers After Radiation Therapy: A Systematic Review of the Epidemiologic Studies of the Radiation Dose-Response Relationship

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Rapid innovations in radiation therapy techniques have resulted in an urgent need for risk projection models for second cancer risks from high-dose radiation exposure, because direct observation of the late effects of newer treatments will require patient follow-up for a decade or more. However, the patterns of cancer risk after fractionated high-dose radiation are much less well understood than those after lower-dose exposures (0.1-5 Gy). In particular, there is uncertainty about the shape of the dose-response curve at high doses and about the magnitude of the second cancer risk per unit dose. We reviewed the available evidence from epidemiologic studies of second solid cancers in organs that received high-dose exposure (>5 Gy) from radiation therapy where dose-response curves were estimated from individual organ-specific doses. We included 28 eligible studies with 3434 second cancer patients across 11 second solid cancers. Overall, there was little evidence that the dose-response curve was nonlinear in the direction of a downturn in risk, even at organ doses of ≥60 Gy. Thyroid cancer was the only exception, with evidence of a downturn after 20 Gy. Generally the excess relative risk per Gray, taking account of age and sex, was 5 to 10 times lower than the risk from acute exposures of <2 Gy among the Japanese atomic bomb survivors. However, the magnitude of the reduction in risk varied according to the second cancer. The results of our review provide insights into radiation carcinogenesis from fractionated high-dose exposures and are generally consistent with current theoretical models. The results can be used to refine the development of second solid cancer risk projection models for novel radiation therapy techniques.

Introduction

Rapid innovations in radiation therapy in the past decade, including the widespread introduction of intensity modulated radiation therapy treatment (IMRT) and the proliferation of proton therapy centers, have resulted in an urgent need for robust methods to project second cancer risks from radiation therapy. Risk projection models are a critical first step because direct observation of the potential solid cancer risks will require patient follow-up for many years, given that most radiation-related cancers do not develop until at least a decade after exposure. These newer treatments aim to reduce the amount of healthy tissue

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exposed to high doses of radiation (>5 Gy), but this may be at the expense of increasing the amount of normal tissue exposed to lower doses (1). Thus, risk projection models for novel radiation therapy techniques need to be able to model the cancer risks from a wide spectrum of radiation doses. Compared with the cancer risks from lower-dose radiation exposures (<5 Gy), the patterns of risk after fractionated high-dose exposure (>5 Gy) are less well understood. In particular, there is uncertainty about the shape of the dose-response curve at high doses and the magnitude of the reduction in cancer risk caused by fractionation and cell killing (1). Although theoretical models have been developed to predict the dose-response at these high dose levels (2, 3), until the past decade there have been relatively few direct human studies, and to our knowledge, no systematic evaluation of these studies has been conducted to date.

We conducted a systematic review of the epidemiologic studies that have evaluated the dose-response relationship for second solid cancer risks after high-dose fractionated radiation therapy. First, we reviewed the shape of the dose-response relationship for each second cancer site to assess whether the data support a linear relationship, a plateau, or a downturn in risk at high doses. Second, we compared the magnitude of the risk per unit dose from the high-dose fractionated exposures with age-matched and sex-matched risk estimates from the Japanese atomic bomb survivors, who received an acute lower-dose radiation exposure (<2 Gy) (4). It is well known that fractionation and cell killing will reduce the risk per unit dose; however, uncertainty remains about the magnitude of the reduction and whether the reduction is similar for all cancer sites. The comparison provides direct estimates of this reduction based on the available human data. In 2001, Little (5) assessed cancer risks after radiation therapy for benign and malignant conditions and compared them with risks in age-matched and sex-matched subsets of the Japanese atomic bomb survivor data. To our knowledge, the current review is the first to specifically focus on higher-dose (>5 Gy) studies that estimated the shape and magnitude of the dose-response relationship. Most of the eligible studies have been published since 2001 and therefore were not included in the earlier review. The results from our review provide insights into radiation carcinogenesis at high doses and can be used to refine the development of models for projecting second solid cancer risks from fractionated high-dose exposure. They can also be used to assess the validity of the theoretical models. The implications of the findings for the assessment of second cancer risks after newer radiation therapy techniques are also discussed.

Methods

Epidemiologic studies with an outcome of a second (or subsequent) solid cancer that had collected detailed data on radiation therapy, specifically the estimated dose delivered to the second cancer site for each patient, were eligible for inclusion in this review. Potentially eligible studies were identified from searching PubMed (search terms "radiotherapy," "dose," and "subsequent malignancy"), from review articles, and from references in identified studies. The search was limited to human studies and to peer-reviewed articles. No language or date restrictions were applied.

Studies were required to have published age-adjusted odds ratios or relative risks for at least 3 categories of estimated absorbed radiation dose to the second cancer site. Because we were evaluating the risks from high-dose radiation, we excluded studies with maximum absorbed organ doses of <5 Gy to the second cancer site of interest. Studies of high-dose radiation exposure for the treatment of nonmalignant conditions (eg, peptic ulcers) were not included because the fractionation patterns of the treatment are often quite different from those used to treat cancer.

For each eligible study, we extracted the following data: number of cases and controls (or cohort size), average (mean or median) and range of age at first cancer diagnosis, average (mean or median) age at second cancer diagnosis, average (mean or median) and range of estimated absorbed dose to the second cancer site in the controls (or the cohort), the relative risk (or odds ratio) and 95% confidence interval for the second cancer in relation to each category of radiation dose, and the estimated continuous dose-response relationship usually expressed as the excess relative risk per Gray (ERR/Gy) and its 95% confidence interval. We also recorded whether there had been an evaluation of the consistency of the dose-response relationship with nonlinear dose-response curves such as linear-exponential or linear-quadratic, and any associated tests of statistical significance. If the specific value for a variable (eg, mean absorbed dose) was not available, we attempted, wherever possible, to derive it from other values available in the publication.

To estimate the magnitude of the impacts of cell killing at high doses and fractionation on the second solid cancer risk, we compared the dose-response estimates from these radiation therapy studies with estimates from acute lower-dose radiation exposure using the risk models developed by the National Academy of Science Biological Effects of Ionizing Radiation (BEIR) VII committee (4). Although developed originally for low-dose radiation exposures (<0.1 Gy) the BEIR VII risk models have been used to compare lifetime cancer risk estimates for high-dose exposures from radiation therapy in some studies (6-8). The standard summary statistic for a linear dose-response relationship in studies of radiation-related cancer is the ERR/Gy. To maximize the comparability of the risk estimates, we estimated the ERR/Gy from the BEIR VII models for the average age at exposure and average attained age of the patients in each radiation therapy study. For studies that included men and women, we calculated the average of the sex-specific BEIR VII estimates. We then calculated the ratio of the ERR/Gy from the high-dose fractionated exposure to the low-dose exposure ERR/Gy estimate. The comparison was restricted to the ERR/Gy because most of the second cancer studies eligible for the current review are of case-control design, and therefore estimates of the excess absolute risk (EAR)/Gy were not available. The BEIR VII report included risk models for 10 solid cancer sites. We used additional risk models for brain tumors (including benign and malignant tumors) and esophageal cancer that we previously developed according to the BEIR VII method (9). For all cancer sites, except breast and thyroid, the BEIR VII models are based on the Life Span Study (LSS) of the Japanese atomic bomb survivors who received a single acute exposure (97% were exposed to <2 Gy). The BEIR VII breast and thyroid cancer models, however, were developed from pooled analyses that included fractionated low-dose exposures to medically exposed cohorts. Since the BEIR VII models are aimed primarily at exposures <0.1 Gy, the committee recommended that risk coefficients be divided by a dose and dose rate reduction effectiveness factor (DDREF) of 1.5 to account for a potential curvilinear dose-response curve in the very-low-dose range (<0.1 Gy). For the current analysis we did not apply the

Table 1 Study characteristics for the 28 eligible epidemiologic studies of high-dose fractionated radiation therapy, dose-response relationships and comparison with BEIR VII estimates of the ERR/Gy for lower-dose radiation exposure

Ref no.	Reference	2nd cancer	1st cancer	Cases	Controls
10	Travis et al, 2003*	Breast	Hodgkin disease	105	266
11	Guibout et al, 2005	Breast	Childhood	16	NA
12	Inskip et al, 2009	Breast	Childhood	107	389
13	Neglia et al, 2006	Glioma	Childhood	35	123
14	Taylor et al, 2010	Glioma/PNET	Childhood	68	68
13	Neglia et al, 2006	Meningioma	Childhood	58	196
14	Taylor et al, 2010	Meningioma	Childhood	109	109
15	Little et al, 1998	Brain	Childhood	22	282
16	Inskip et al, 1994	Lung	Breast	61	120
17	Gilbert et al, 2003	Lung	Hodgkin disease	227	455
18	Tucker et al, 1991	Thyroid	Childhood	22	82
19	de Vathaire et al, 1999	Thyroid	Childhood	14	NA
20	Bhatti et al, 2010†	Thyroid	Childhood	115	NA
21	Tucker et al, 1987	Bone sarcoma	Childhood	64	204
22	Boice et al, 1988	Bone sarcoma	Cervix	15	155
23	Hawkins et al, 1996	Bone sarcoma	Childhood	59	220
24	Le Vu et al, 1998	Bone sarcoma	Childhood	32	160
22	Boice et al, 1988	Soft tissue sarcoma	Cervix	46	598
25	Wong et al, 1997	Soft tissue sarcoma	Retinoblastoma	31	89
26	Menu-Branthomme et al, 2004	Soft tissue sarcoma	Childhood	23	113
27	Rubino et al, 2005	Sarcoma	Breast	14	98
28	Henderson et al	Sarcoma	Childhood	105	422
29	Morton et al	Esophagus	Breast	252	488
30	van den Belt-Dusebout 2009	Stomach	Testes & Hodgkin disease	42	126
22	Boice et al, 1988	Colon	Cervix	409	759
22	Boice et al, 1988	Rectum	Cervix	488	901
22	Boice et al, 1988	Uterine corpus	Cervix	313	469
22	Boice et al, 1988	Ovary	Cervix	309	560
22	Boice et al, 1988	Bladder	Cervix	273	520

Abbreviations: DOSE = estimated absorbed dose to the tumor site (except for Inskip et al, 1994, and Boice et al, 1988, where average absorbed dose to the whole organ was estimated); ERR/Gy = excess relative risk per Gray; MAX = maximum; NA = not available; NS = not significant; PNET = Primitive Neuroectodermal Embriogenic Tumor.

* ERR/Gy from Travis et al (2003) excludes patients who received alkylating agents or radiation of 5 Gy or more delivered to the ovaries.

† For Bhatti et al, the fitted dose-response is based on the linear term of the linear quadratic regression model.

‡ ERR/Gy for these studies was taken from UNSCEAR (51).

low-dose and low-dose-rate correction factor because we were interested in a direct comparison between the ERR/Gy from fractionated exposures >5 Gy with a lower acute exposure (<2 Gy).

Results

Our search identified 28 eligible studies (10-30) that included 3434 patients who experienced a second cancer, with average absorbed organ doses in the non-cases ranging from 5 to 165 Gy (Table 1). The majority of the studies were case-control studies (n=25), many of which were nested case-control studies within a cohort such as the Childhood Cancer Survivor Study (12, 13, 20, 28). More than half (n=16) of the studies were of childhood cancers. The study results are reviewed according to the 11 different second solid cancer sites, and common patterns across different second cancer sites are then evaluated.

Breast cancer

Three studies evaluated second breast cancers after radiation therapy. The average age at exposure was between 6 years and 22 years, and the maximum absorbed organ doses to the breast were 60 to 80 Gy (10-12). All 3 studies found approximately linear dose-response relationships with breast cancer risk and no evidence of a downturn in risk even at doses of 30 Gy or more (Fig. 1). The ERR/Gy varied from 0.13 to 0.27, 5-fold to 16-fold lower than the risk estimates observed in the pooled analysis of lower-dose studies by Preston et al (31) for similar age at exposure and attained age (Table 1). An important effect modifier was radiation therapy to the ovary of at least 5 Gy, which significantly reduced the risk of radiation-related breast cancer in both studies where such treatment was common (10, 12), most likely because the ablation of ovarian function suppresses the hormonal stimulation of the breast tissue. The use of alkylating agents also had a similar effect in reducing the risk of breast cancer after Hodgkin lymphoma (10).

Table 1 (*Continued*)

	Age 1st cancer	Age 2nd cancer	Dose (controls)		ERR/Gy		
Ref no.	Average (range)	Average	Average	Max	Study (& 95% CI)	BEIR VII	Ratio
10	22 y (13-30 y)	41 y	25 Gy	61 Gy	0.15 (0.04-0.73)	1.10	7.34
11	6 y (0-16 y)	30 y	5 Gy	80 Gy	0.13 (<0-0.75)	2.06	15.81
12	16 y (0-20 y)	36 y	14 Gy	60 Gy	0.27 (0.10-0.67)	1.43	5.29
13	0-4 y (0-20 y)	15 y	10 Gy	50 Gy	0.33 (0.07-1.71)	2.75	8.33
14	5-9 y (0-14 y)	24 y	9 Gy	40+ Gy	0.08 (0.02-0.23)	1.23	15.51
13	5-9 y (0-20 y)	26 y	9 Gy	50 Gy	1.06 (0.21-8.15)	1.10	1.03
14	5-9 y (0-14 y)	30 y	14 Gy	40+ Gy	5.10 (0.7-107.7)	0.90	0.18
15	6 y 0-17 y	20 y	6 Gy	83 Gy	0.19 (0.03-0.85)	1.52	8.01
16	50 y (35-72 y)	68 y	6 Gy	23 Gy	0.20 (-0.62-1.03)	1.17	5.87
17	49 y (9-81 y)	59 y	24 Gy	60+ Gy	0.15 (0.057-0.39)	1.43	9.56
18	7 y (0-18 y)	21 y	13 Gy	76 Gy	4.50 (3.1-6.4)	3.58	0.79
19	6 y (0-16 y)	24 y	7 Gy	75 Gy	4.00 NA	3.88	0.97
20	10 y (0-20 y)	28 y	11 Gy	40+ Gy	1.38 (0.74-2.69)	2.79	2.02
21	7 y (0-18 y)	17 y	27 Gy	60+ Gy	0.06 (0.01-0.20)	NA	-
22	45-54 y (<45-65+ y)	67 y	22 Gy	10+ Gy	0.02 (-0.03-0.21)‡	NA	-
23	NA NA	NA	20 Gy	55 Gy	0.16 (0.07-0.37)	NA	-
24	8 y (0-16 y)	15 y	8 Gy	83 Gy	1.40 (0.1-21.8)	NA	-
22	45-54 y (<45-65+ y)	67 y	7 Gy	10+ Gy	-0.05 (-0.11-0.13)‡	NA	-
25	<2 y (0-7 y)	15 y	11 Gy	112 Gy	0.17 (0.025-16.3)	NA	-
26	8 y (0-16 y)	21 y	12 Gy	50 Gy	NA NA	NA	-
27	55 y (35-77 y)	62 y	19 Gy	80 Gy	0.05 (<0-1.18)	NA	-
28	9 y (0-20 y)	21 y	7 Gy	76 Gy	1.32 (0.44-4.22)	NA	-
29	59 y (28-88 y)	74 y	7 Gy	45 Gy	0.08 (0.04-0.16)	0.61	7.64
30	34 y (20-50+ y)	51 y	11 Gy	40 Gy	0.84 (0.12-15.6)	0.43	0.52
22	45-54 y (<45-65+ y)	68 y	24 Gy	40+ Gy	0.00 (-0.01-0.02)‡	0.36	-
22	45-54 y (<45-65+ y)	68 y	30-60 Gy	60+ Gy	0.02 (0-0.04)‡	0.10	5.04
22	45-54 y (<45-65+ y)	68 y	165	200+ Gy	NA NA	NA	-
22	45-54 y (<45-65+ y)	68 y	32	60+ Gy	0.01 (-0.02-0.14)‡	0.32	31.89
22	45-54 y (<45-65+ y)	68 y	30-60 Gy	60+ Gy	0.07 (0.02-0.17)&‡	1.38	19.78

Brain cancer

All 3 studies of brain cancer or benign brain tumors (largely composed of meningioma) were in childhood cancer survivors with an average age of exposure <10 years (13-15). In 2 of the 3 studies, the results were reported separately for glioma and meningioma (13, 14). There was no evidence of significant curvature in the dose-response relationship in any of the studies even at doses of 50 Gy or higher (Fig. 2). The ERR/Gy was higher for meningioma than for glioma (Table 1) (13, 14). Detailed dose-response relationships for the LSS have been estimated only for all brain cancers combined (9). The ERR/Gy for all brain cancers combined in the LSS was about 5-fold to 10-fold higher than the estimate from the high-dose studies of glioma (13,14) and the study of all brain cancers after childhood cancer (15). The ERR/Gy in the 2 studies of meningioma was similar to, or even greater than, the risk for all brain cancers combined in the LSS. However, an analysis of the risks in the LSS by histology showed that the high ERR/Gy is driven by the risk of schwannomas rather than the meningiomas. The ERR/Gy for meningiomas and gliomas in the LSS was similar and about half the overall ERR/Gy (32).

Lung cancer

Two studies of second lung cancer were identified with similar average age at exposure (49-50 years) (16, 17). In the study of lung cancer after breast cancer (n=61), there was some evidence of an increasing risk with increasing dose, and the ERR/Gy was 0.2 at an average attained age of 68 years (16) (Fig. 3). In the larger study of 227 lung cancer cases after Hodgkin lymphoma, the ERR/Gy was similar in magnitude (0.15). The maximum doses were more than 60 Gy, but there was no evidence of departure from a linear dose-response relationship ($P>.5$) (17). Overall, the ERR/Gy was 5 to 10 times smaller than in the LSS for a similar age at exposure and attained age (4). There was evidence that the joint effect of chemotherapy and radiation therapy was approximately additive, whereas smoking and

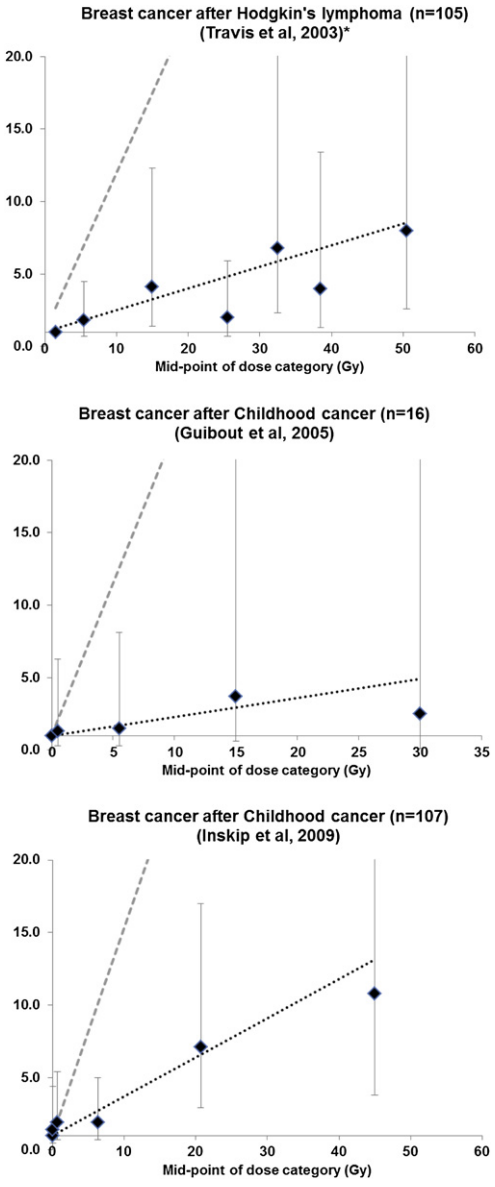

Fig. 1. Relative risk and 95% confidence interval for subsequent breast cancer according to the estimated absorbed radiation dose (Gy). Dotted black line indicates fitted linear dose-response for that study. Dashed grey line indicates relative risk for similar age at exposure and attained age based on the pooled excess relative risk model from Preston et al (31). *Travis et al (10) the reference dose category was 0-3 Gy, and the fitted linear dose-response was for women who did not receive alkylating agents or ovarian radiation (5+ Gy).

radiation therapy acted multiplicatively with respect to lung cancer risk (17).

Thyroid cancer

In the 3 studies of second thyroid cancer after various childhood cancers, the maximum dose to the thyroid was 76 Gy (18-20). In the largest study (20) there was clear evidence of a downturn in risk at doses above 20 Gy (Fig. 4), and a linear-exponential dose-response model fitted significantly better than the purely linear model ($P<.05$) (Fig. 4). The number of cases was small in the other 2 studies (n = 22 and n = 14), and 1 study also found evidence that a linear-exponential model fit better than the purely linear model ($P=.04$) (19), whereas in the other study, there was no evidence of significant curvature ($P=.09$) (20). The linear term of the dose-response models for the ERR/Gy varied from 1.4 to 4.5, which was reasonably consistent with the ERR/Gy of 3 to 4 in the pooled analysis of thyroid cancer studies that was the basis for the BEIR VII model for similar age at exposure and attained age (33). As noted earlier, some of the studies in that pooled analysis involved fractionated exposure, and there was some evidence that the ERR/Gy after fractionated exposure was about 1.5 times lower than after a single acute exposure, but this difference was not statistically significant ($P=.18$) (33). The estimated ERR/Gy for thyroid cancer after acute childhood exposure in the Japanese atomic bomb survivors was 4.2 (34).

Sarcoma

Second bone cancers after childhood cancer and cervical cancer have been evaluated (21-24). In the studies of childhood cancer, there was clear evidence of increasing risks with increasing doses and no evidence of a downturn even at doses of >60 Gy (21, 23, 24) (Fig. 5). In the 1 small study of exposure in adulthood (cervical cancer, n = 15) there was no clear relationship with dose (22). The number of bone sarcomas in the LSS is currently too small to enable the development of a detailed dose-response model for this outcome (34). After childhood cancer there was a significant dose-response relationship also for soft tissue sarcoma, but the ERR/Gy was lower than for bone sarcoma (25, 26), and there was no clear association with dose among the cervical cancer patients (22) (Fig. E1). In a small study of sarcomas after breast cancer (n = 14), there was an increased risk with increasing dose (27). The largest study to date examined all sarcomas combined after childhood cancer (28). About 40% of the cases in that study were bone sarcomas, and there was no evidence of a differential dose-response from soft tissue sarcomas. The ERR/Gy was higher than observed in the other soft tissue and bone sarcoma studies (1.38 [95% confidence interval, 0.44-4.22]). Heterogeneity in risk according to the primary cancer was suggested as a possible explanation for this higher risk (28).

Other sites

Several other second cancer sites after radiation therapy for cervical cancer were studied (22). The risks were generally linear with dose but with a much lower ERR/Gy than expected based on the Japanese atomic bomb survivors (5-30 fold) (Fig. E2). Two recent studies also found clear dose-response relationships for second esophageal and stomach cancer in adulthood cancer survivors (29, 30). In the large study of esophageal cancer after breast cancer, risk increased consistently over the range 20 to 60 Gy. Although there was modest evidence that a linear-quadratic dose-response function fitted the data better than a linear one ($P=.08$), the coefficient for the quadratic term was positive, that is, an upturn rather than a downturn in risk at very high doses. The ERR/Gy was nearly 10 times smaller than in the Japanese atomic bomb survivors (9). The analysis of stomach cancer after testicular cancer and Hodgkin lymphoma did not find evidence of curvature (30). Although the ERR/Gy was similar in magnitude to the

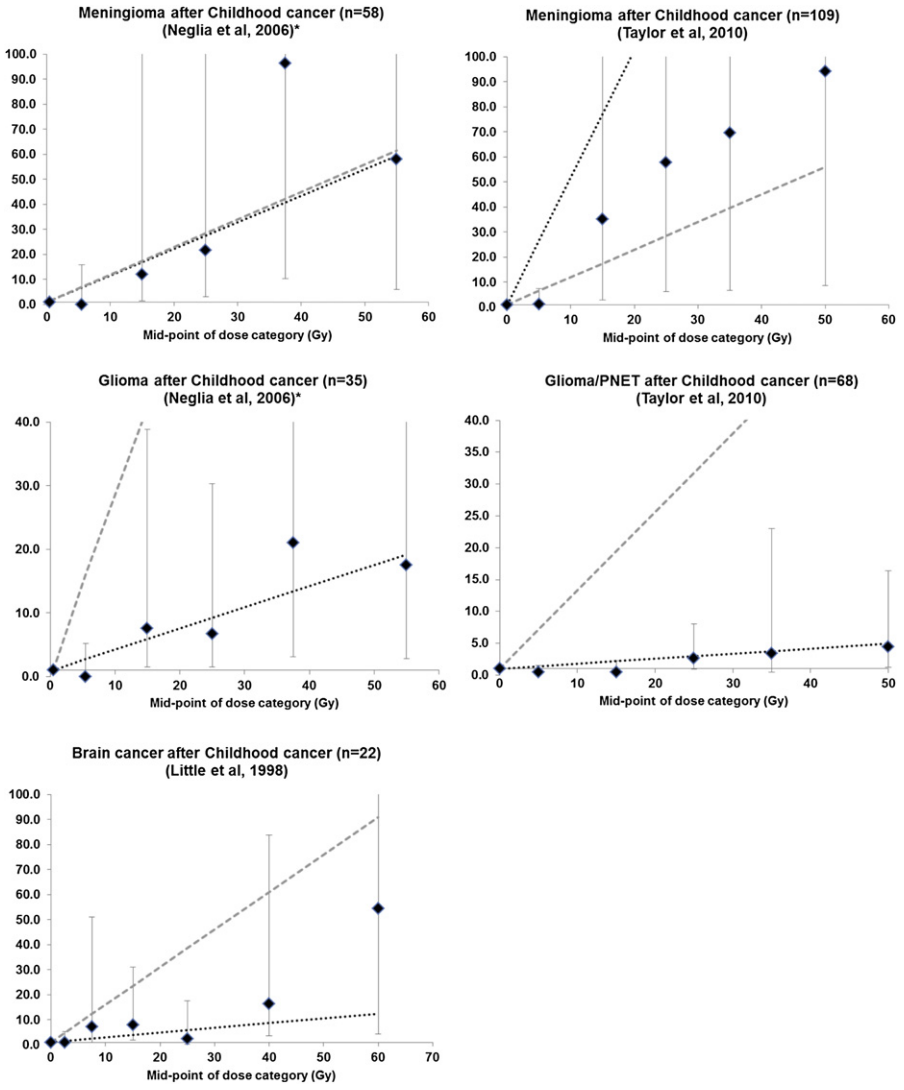

Fig. 2. Relative risk and 95% confidence interval for subsequent brain cancer according to the estimated absorbed radiation dose (Gy). Dotted black line indicates fitted linear dose-response for that study. Dashed grey line indicates relative risk for similar age at exposure and attained age based on the Biological Effects of Ionizing Radiation VII risk models (4, 9). *Reference categories for Neglia et al (13) were <1 Gy rather than 0 Gy, which is used for the fitted dose-response, and this accounts for any apparent discrepancy between the categoric estimates and fitted line.

estimate from the LSS, the confidence intervals were very wide because of the small number of cases (n = 42).

Results summary

Overall, when all second solid cancer sites were considered, there was no clear evidence of nonlinearity in the dose-response in the direction of a reduction in risk at high doses even at doses of 60 Gy or higher. The exception was thyroid cancer, for which there was a plateau in risk in 1 study (20) and a clear downturn in another above 20 Gy (18). The ERR/Gy was generally considerably lower after fractionated high-dose radiation therapy than after the acute lower-dose exposure experienced by the Japanese atomic bomb survivors, in the range of 5-fold to 10-fold lower for most second solid cancer sites. Confidence intervals for the ERR/Gy in the second cancer studies were often wide, and the lower bound was, on average, consistent with risks that were about 2-fold lower than the acute low-dose estimate. Although there were a couple of sites for which the ERR/Gy from the high-dose radiation therapy was nearly equivalent to the acute low-dose estimate, there are qualifications or possible alternative explanations. For example, the stomach cancer finding was based on only 1 small study (n = 42), and the BEIR VII thyroid cancer risk model included several studies of fractionated exposure (33). Although the results for meningioma were also consistent with the risk model for all brain tumors combined in the LSS, as noted earlier the high ERR/Gy for brain tumors in the LSS is driven by schwannomas, not by meningiomas (32). For most cancer sites, the relative risk at 40 Gy for the development of a second solid cancer was typically in the region of 5 to 10 times higher than the risk in the patients who did not receive radiation therapy or those who received very low doses.

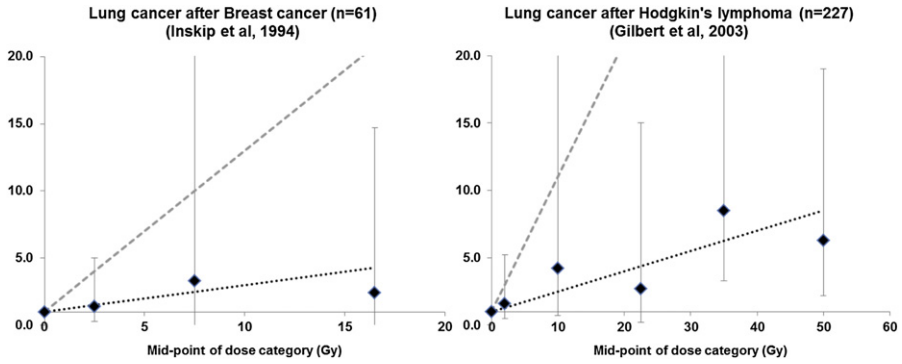

Fig. 3. Relative risk and 95% confidence interval for subsequent lung cancer according to the estimated absorbed radiation dose (Gy). Dotted black line indicates fitted linear dose-response for that study. Dashed grey line indicates relative risk for similar age at exposure and attained age based on the Biological Effects of Ionizing Radiation VII risk models (4).

Discussion

The rapid evolution of current radiation therapy techniques requires appropriate methods to estimate the potential risk of second solid cancers without having to wait a decade or more to study the risks directly. To date, most dose-response modeling efforts for IMRT and other newer therapies have assumed that, for all cancer sites, either (a) the BEIR VII risk models can be applied directly or (b) the BEIR VII risk models can be applied but adjusted with a plateau or a downturn above some dose level, as in, for example, Fontenot et al (6). Although this approach allows for rough comparisons of different treatments or treatment plans, it could give misleading results if the shape of the dose-response curve varies by cancer site and/or the reduction in risk due to fractionation and cell killing varies by cancer site. In this study, we conducted a systematic review of the available human dose-response data and found that, in general, there is little support for a plateau or a downturn in solid cancer risk at high doses with the exception of second thyroid cancer. As expected, the ERR/Gy is lower than from acute lower-dose exposures in the Japanese atomic bomb survivors or other lower-dose studies, often as much as 5 to 10 times lower. However, the exact magnitude of the reduction in risk varied according to second cancer, and even by cancer subtype (eg, meningioma, glioma), although some of this variation may be due to chance. This suggests that uniform adjustment factors for cell killing and fractionation effects for all solid cancer sites may result in misleading risk projections and comparisons for second cancer risks from high-dose fractionated radiation therapy.

Little (5) previously conducted an extensive review of all studies of cancer after medical radiation exposure, including studies of radiation therapy for benign conditions (5). This earlier review focused on the impact of fractionation and did not evaluate the shape of the dose-response curve at high doses. This was largely because few studies published at that time included individual dosimetry; indeed, only 5 of the 28 studies in the current review were included in that previous review. The finding by Little (5) that the magnitude of the dose-response was generally lower in the studies of high-dose radiation therapy than after the acute lower-dose exposure to the Japanese atomic bomb survivors was similar to the finding in the current review, and this is consistent with theoretical predictions.

Suit et al (35) also conducted a broad review of second cancer risks from radiation therapy that assessed both animal and human data. The human data were largely composed of several registry-based cohort studies that had very limited data on radiation therapy exposure (typically yes/no and external beam therapy/brachytherapy). Dose-response relationships were therefore constructed by combining different summary results from various studies, with each study contributing a single point estimate to the dose-response curve based on a typical organ dose. This approach is prone to many additional biases, given that there will likely be a wide variation in doses within each study and many differences between the studies that limit comparability in this manner. Dose-response assessment within a single study with accurate dose reconstruction to the tumor site is a much more powerful, less biased approach for assessing the shape of the dose-response relationship. Doi et al (36) conducted a meta-analysis combining the estimated ERR/Gy for any second cancer after radiation therapy for benign or malignant disease. Unsurprisingly, given the variation in second cancer sites, age at exposure, and sex, they found significant heterogeneity between studies. Overall, they found that the ERR/Gy for all cancers combined was about 3-fold lower than in the Japanese atomic bomb survivors. Our study shows that this ratio is likely to vary by cancer site and, therefore, that combining all cancer sites may conceal important differences in the radiosensitivity of different tissues.

Several additional factors other than the effect of cell killing and fractionation can affect the magnitude or the shape of the dose-response curve after high-dose radiation therapy, which could not always be taken into account and may have affected our results. Baseline cancer risks differ between the general population in the United States and Japan, and the BEIR VII committee recommended that radiation risks be transferred from the Japanese to the United States population using a weighted average of the ERR and the excess absolute risk models (4). For breast cancer, BEIR VII recommended use of the excess absolute risk model because this model has been found to vary less between the United States and Japan than the ERR model (31). Unfortunately, for most of the second cancer studies here, only ERR models are available because they are estimated from case-control studies. Furthermore, baseline cancer risks differ between cancer survivors and the general population, likely because of genetics and lifestyle factors. In addition, few studies provided a formal assessment of the potential interaction between radiation therapy and concomitant therapies. In those few studies where there was an individual and high quality assessment of chemotherapy, the joint effect was generally additive (13, 17, 29), but data are limited on this issue. Furthermore, these effects are tissue

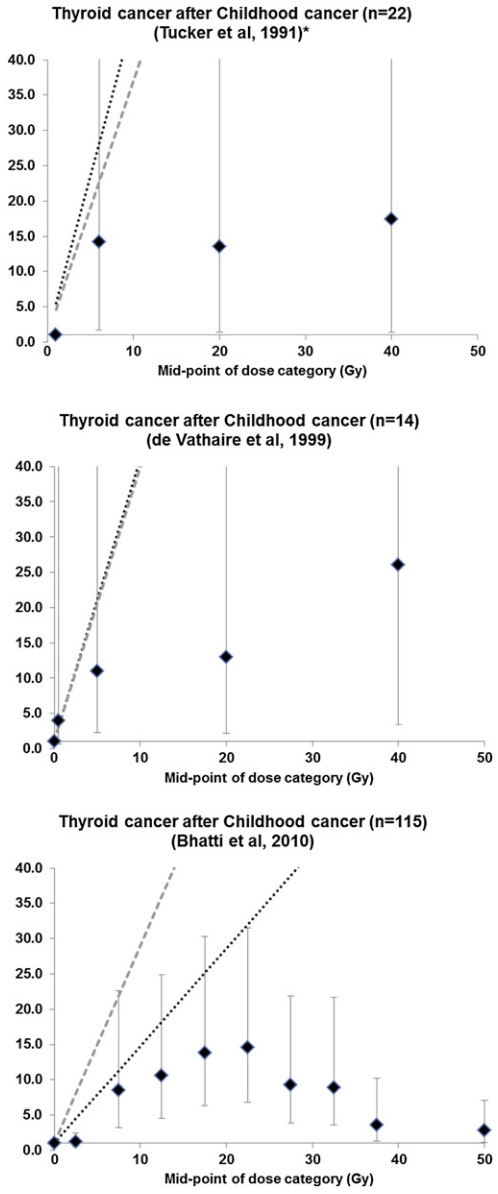

Fig. 4. Relative risk and 95% confidence interval for subsequent thyroid cancer according to the estimated absorbed radiation dose (Gy). Dotted black line indicates fitted linear dose-response for that study. Dashed grey line indicates relative risk for similar age at exposure and attained age based on the Biological Effects of Ionizing Radiation VII risk models (4). *For Tucker et al (18) the reference category was <2 Gy rather than 0 Gy, which is used for the fitted dose-response, and this accounts for any apparent discrepancy between the categoric estimates and fitted line. The fitted linear dose-response model for Bhatti et al (20) is based on the linear term from the linear-quadratic model.

specific because chemotherapy can also reduce second cancer risks, as has been shown for breast cancer (10, 12). The risk of radiation-related cancer also varies strongly with age at exposure (4). A limitation of the current available evidence on the dose-response relationship for second cancer risks after high-dose fractionated radiation therapy is that for brain, thyroid, and bone cancers, the studies are exclusively of radiation therapy to children and for lung cancer only radiation therapy exposure to adults. Therefore, some of the results may not be generalizable to other age groups.

Although the data reviewed here provide little indication of departure from a linear dose-response over the full dose range, statistical power for detecting such departures and for estimating the ERR/Gy was likely limited in many of the studies, as can be seen from the wide confidence intervals in Figs. 1 through 5, Figs. e1 and e2, and Table 1, where these intervals often cover more than an order of magnitude. Some studies had few participants who did not receive radiation therapy and/or lacked adequate data over the full dose range. Furthermore, the dose estimates used in these studies are subject to several uncertainties, including misspecification of the tumor location in relation to the treatment fields (37). Dose errors, which have not been taken into account in analyses of data from these studies, can further reduce power, potentially bias estimated risk coefficients, and distort the shape of the dose-response (38). The problem of random errors in the Japanese atomic-bomb dosimetry and their impact on inferences with respect to the cancer dose-response has been comprehensively investigated by many researchers (39-41). In general, the errors in individual dose estimates for the atomic bomb survivors are of classic form; upward corrections of 15% to 20% in the unadjusted risk coefficients are required (39-42). It is probable that the magnitude of dosimetric errors for the relevant organ doses in the various medical series considered here would be somewhat larger than those in the LSS, because doses are extremely heterogeneous within an organ (particularly when the organ is on the margins of the treatment field or when organ blocks are used), so that very slight uncertainties in estimated beam position can result in large errors in organ dose. Set against that, dose reconstruction is often based on individual treatment records. To the best of our knowledge, there has been no detailed evaluation of such errors in the datasets considered here. In summary, much work remains to be done to evaluate dosimetric uncertainty in second cancer studies, accounting for heterogeneity in dose within an organ, and assessing the effect on regression risk estimates. The majority of the studies reviewed here evaluated the risk in relation to the dose to the tumor site, and these models do not take account of dose inhomogeneity across the organs; more research is warranted on this important question. For risk projection models developed from human data, it will be necessary to consider the average dose to the organ until a better understanding of the impact of dose inhomogeneity is available from the human data.

The results from these human data do not support the traditional cell killing/inactivation model or the animal data, which predict a downturn in the dose-response relationship at doses as low as 5 Gy (43). Although the confidence intervals were often wide in the studies we reviewed, especially for the highest dose categories, additional strength for this conclusion can be drawn from the fact that across 26 of the 28 studies there was no clear evidence of a downturn or plateau in the risk, even at doses of 40 Gy or more. Although for thyroid cancer there was such a downturn, this was not evident until at least 20 Gy, vastly in excess of the level suggested by in vitro measures of cell killing, which imply that about half of the irradiated cells would be inactivated by a dose of 1 Gy (44). Lack of a downturn in the dose-response is consistent with theoretical models that incorporate both repopulation and cell killing after high-dose radiation therapy (2, 3, 45). Formal statistical comparison of the theoretical models with the entirety of the human data presented here would be an important next step. These comparisons should take account of the various additional uncertainties in the human data that may influence the shape of the dose-response curve

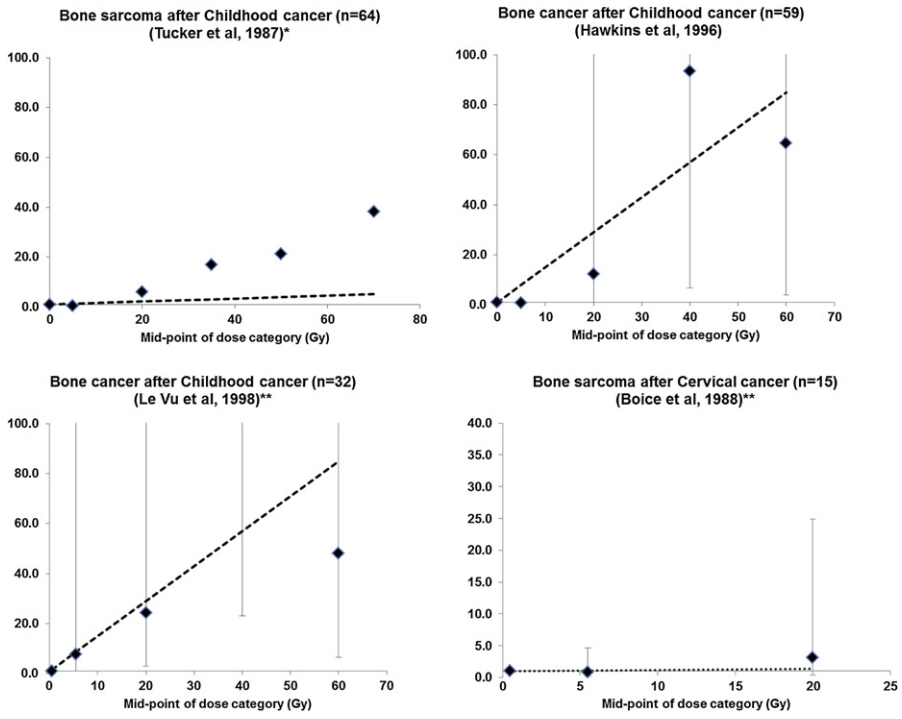

Fig. 5. Relative risk and 95% confidence interval for subsequent bone sarcoma according to the estimated absorbed radiation dose (Gy). Dotted black line indicates fitted linear dose-response for that study. Biological Effects of Ionizing Radiation VII risk models not available. *No confidence intervals were available for Tucker et al. **Reference category for Le Vu et al (24) and Boice et al (22) was <1 Gy rather than 0 Gy, which is used for the fitted dose-response, and this accounts for any apparent discrepancy between the categoric estimates and fitted line. Relative risk for Le Vu et al: 40 Gy dose category = 184.

that were described earlier. Hybrid risk prediction modeling that incorporates radiobiological (linear-quadratic cell repopulation) models and human data (46) is also an interesting approach that warrants further evaluation, but it also requires a formal assessment of the fit of the models to all relevant human data. For leukemia there is a clear downturn in the dose-response relationship after moderate-dose and high-dose radiation exposure in most studies at levels above 3 to 5 Gy (47, 48), and the review by Little (5) suggested that second leukemia excess risk was generally much lower than would be expected from the LSS. Theoretical mechanisms have been suggested that account for these observations, taking account of the known transfer of hematopoietic stem cells between bone marrow compartments (49, 50). Detailed dosimetry to the bone marrow is more complex than for solid cancer, and therefore these studies will be reviewed separately.

To date, no observational studies have directly assessed the second cancer risks after IMRT or proton therapy. Until sufficient follow-up is available to conduct such studies, assessment of the risks relies on risk projection studies or theoretical models. The results from our review, which are consistent with current theoretical models that combine cell killing and repopulation, can be used to refine the development of the second solid cancer risk projection models for evaluating novel radiation therapy techniques. We also highlight the limitations of the human data, in particular the large uncertainties at high dose levels. Pooled analyses of individual patient data constitute an important next step for a more robust assessment of the shape of the dose-response relationship and the impact of cell killing and fractionation for each second cancer site. Efforts for thyroid and brain cancer are already under way or are planned.

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