Research Article

Cancer Epidemiology, Biomarkers & Prevention

Patterns of Bone Sarcomas as a Second Malignancy in Relation to Radiotherapy in Adulthood and Histologic Type

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Abstract

Background: Radiotherapy decreases cancer mortality, but is associated with an increased incidence of second primary cancers, including osteosarcomas, especially after exposure in childhood. It remains uncertain whether radiation is related to other histologic types of bone sarcomas such as chondrosarcomas that are more common in adulthood.

Methods: Using data from 1973 to 2008 Surveillance Epidemiology and End Results registries, we evaluated long-term risk of bone cancer in 1,284,537 adult 5-year cancer survivors. We used standardized incidence ratios (SIR) to compare second bone sarcoma rates to the general population for each histologic type. We also used multivariate Poisson regression to estimate the relative risk (RR) associated with radiotherapy for the most common subtypes, osteosarcoma and chondrosarcoma.

Results: By the end of 2008, 159 second bone sarcomas were reported. Compared with the general population, the risk of developing any bone sarcoma was increased by 25% in patients with no history of radiotherapy [Observed (O) = 89, SIR = 1.25 (1.00–1.54)] and by 257% in patients with a history of radiotherapy [O = 70, SIR = 3.57 (2.78–4.50)]. For each histologic subtype, SIRs were higher among patients who had previously received radiotherapy than among those who had not. The RR for radiotherapy for osteosarcoma ($n = 63$) was 5.08 (3.05–8.59) and for chondrosarcoma ($n = 69$) was 1.54 (0.88–2.59), and these risks were even greater for second sarcomas that arose in the radiotherapy field used to treat the first cancer [osteosarcoma, RR = 10.35 (4.96–23.66); chondrosarcoma RR = 8.21 (2.09–39.89)].

Conclusions: Our findings provide the first evidence of a likely association between radiation exposure and chondrosarcoma.

Impact: These results further our understanding of radiotherapy-related cancer risks and will potentially direct practices in long-term surveillance of cancer survivors. *Cancer Epidemiol Biomarkers Prev; 21(11); 1993–9.* ©*2012 AACR.*

Introduction

Radiotherapy reduces cancer mortality and recurrence, but it has been associated with an increased risk of subsequent primary cancers. Bone sarcomas were one of the first tumors associated with radiation, first by Beck (1) and several years later by Martland in his famous report of increased osteosarcoma rates in watch dial painters who ingested radium (2). More recently, cohort and cancer registry studies have found that medical radiotherapy increases the risk of subsequent bone sarcoma from about 2-fold after the treatment in adults to more than 100-fold after the treatment in some pediatric populations (3). These studies most clearly show that osteosarcoma and malignant fibrous histiocytoma are caused by radiation, but it is unclear whether radiation is a risk factor for other histologic types such as chondrosarcoma, the most common primary bone sarcoma in adults (4, 5). Notably, the incidence of chondrosarcoma is currently increasing in U.S. women (6). Most studies of radiation-related bone sarcomas by histology have been case series and to date there has been no formal analysis of radiation-related risks for each histologic type of bone sarcoma.

The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program cancer registries, which contain information about cancer histology and radiotherapy treatments, now cover nearly 30% of the U.S. population and contain records with over 3 decades of follow-up. In this study, we used the SEER cancer registries to examine the patterns of bone sarcoma in adult cancer survivors in relation to prior radiotherapy. The large sample size and long-term follow-up afforded the power needed to assess radiation risks by histology, and

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enabled a more detailed evaluation of the 2 most common histologic subtypes: osteosarcoma and chondrosarcoma.

Materials and Methods

Study population

The cohort included adult patients ages 20 to 84 who were diagnosed with a first invasive cancer reported to 1 of 9 SEER registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah) between 1973 and 2008. Our aim was to evaluate radiotherapy risks specifically for adult patients, as these risks are relatively understudied compared with risks in children (3), and as children may have different susceptibility to radiation-related sarcoma because of age and underlying genetic syndromes (7). Because there is typically at least a 5-year latency period between radiation exposure and the onset of radiation-related solid cancers (8), we only included patients who survived without any subsequent malignancies for at least 5 years after the diagnosis of their first cancer. We excluded patients whose initial cancer was bone cancer to minimize the likelihood that the second cancer was a misclassified recurrence of the first ($n = 9$), and also excluded those whose history of radiotherapy was unknown ($n = 2$). Because cancers are often underdiagnosed in the very elderly patients, we excluded patients whose attained age was greater than 85 ($n = 6$).

Variable definitions

We defined the event of second bone sarcoma as any second invasive cancer reported to SEER that was classified as a sarcoma originating in the anatomic site "bone and joint" (ICD-O topography codes C41.0–C41.9). We used cancer sequence numbers based on diagnoses reported to SEER, and results were unchanged when we limited the analysis to patients whose first cancer reported to SEER was specified to be their first lifetime cancer (analysis not shown). We used International Classification of Diseases (ICD)-O3 morphology codes to further classify each bone sarcoma by histologic type: chondrosarcoma (ICD-O-3 codes 9220–9221, 9230–9231, 9240–9243), osteosarcoma (9180–9186, 9192–9194, 9200), fibrosarcoma/malignant fibrous histiocytoma (8810–8815, 8823–8825, 8830), Ewing sarcoma (9260), spindle cell sarcoma (8801), and giant cell sarcoma/malignant giant cell tumor of the bone (8802/9250). We included malignant giant cell tumor of the bone because clinically and histologically, it is considered a high-grade sarcoma and can be difficult to distinguish from giant cell sarcoma (9). We excluded second sarcomas with unspecified histologies ($n = 9$) and rare histologic types (synovial sarcoma and myxoid liposarcoma, both $n = 1$).

Patients were classified according to whether or not they received any type of radiotherapy (including external beam, brachytherapy, radioisotopes, and combination radiotherapy) in the first course of treatment for their first malignancy. Other variables used in the analyses include the latency period (time interval between the first and second cancer diagnoses, categorized as 5–9 years or 10+ years), gender, the age at first cancer diagnosis, the anatomic site of the first cancer, and the location of the bone sarcoma in relation to the radiotherapy field most commonly used to treat the first cancer. We classified the bone sarcomas as likely to be "in field" or not. We did not have data on the specific radiotherapy fields used to treat each patient, therefore, we used standard treatment fields for each first cancer that is routinely treated with radiotherapy (10). The locations defined as "in field" for each first cancer are shown in Appendix S1. If the bone sarcoma location was likely on the border of the typical radiation field, overlapping between 2 sites, or not recorded, the case was classified as "not in field." For some first cancers, the typical radiotherapy field could not be clearly mapped to an anatomic site of bone. For this reason, we excluded patients from the analysis of "in field" sarcomas if their first cancer was a lymphatic or hematopoietic cancer (other than localized non-Hodgkin lymphoma), or cancer of the thyroid, skin, soft tissue, stomach, or biliary system.

Statistical analysis

Standardized incidence ratios (SIR), defined as the number of observed events (O) divided by the number of expected events (E), were used to compare incidence rates of second bone sarcomas according to previous radiotherapy and histologic type to incidence rates in the general population. Expected rates were calculated for each histologic type of bone sarcoma using age-, gender-, race-, and calendar-year–specific rates from the 9 SEER registries. These rates were multiplied by the person-years at risk for each stratum and then summed across all strata to estimate the total expected number of second cancers (using SEER*Stat, version 7.0.5). Person-years at risk were calculated for each individual beginning at 5 years after initial cancer diagnosis and ending at the date of diagnosis of a second primary invasive cancer, date of last follow-up, death, or end of the study (December 31, 2008), whichever occurred first. Confidence intervals (CI) were computed using the Byar approximation based on the Poisson distribution (11), and 95% CIs that did not contain one were considered statistically significant.

In addition, we used multivariate Poisson regression to estimate the relative risks (RR) related to radiotherapy for osteosarcoma and chondrosarcoma separately (using Epicure, version 1.8; ref. 12), adjusting for the potential confounding factors including stage of the first cancer, age and year at first cancer diagnosis, latency, and gender. Other histologic groups of bone sarcomas had insufficient numbers of cases ($n \leq 12$) for multivariate analysis. The expected number of second bone sarcomas was used as an offset to adjust for potential confounding by attained age, attained calendar period, race, and gender (13). CIs at the 95% level were calculated on the basis of likelihood profiles.

For Poisson regression analyses, we also investigated effect modification of the radiotherapy risks for osteosarcoma and chondrosarcoma by gender, latency, age at first

Table 1. Descriptive statistics of 1,284,537 five-year adult cancer survivors[a] according to previous radiotherapy and development of bone sarcoma as a second malignancy (SEER 9 registries: 1973–2008)

	Cases of second bone sarcomas		Cohort	
Characteristic	**RT**	**No RT**	**RT**	**No RT**
N	70[b]	89	327,532	957,005
Mean latency, y	10.7	11.8	NA	NA
Mean age at first cancer, y	54.1	54.0	58.2	55.7
Stage of first cancer				
% Local/regional	64	73	75	80
% Distant	11	2	3	4
% Unknown[c]	24	25	22	16
Gender				
% Male	33	45	44	40
% Female	67	55	56	60

Abbreviations: NA, not applicable; RT, radiotherapy.

[a]All analyses excluded patients whose first cancer was bone cancer, whose history of radiotherapy was unknown, or who had attained age >85.

[b]Of the 70 patients who developed a bone sarcoma after radiotherapy, 59 received beam radiation, 2 received brachytherapy, 5 received a combination of beam radiation and brachytherapy, 1 received radioisotopes, and 3 received an unspecified type of radiotherapy.

[c]Includes cancers that are unstaged (including all lymphomas) and those for which a stage was not recorded (mostly prostate cancer).

cancer diagnosis, and location of sarcoma in relation to the radiation field.

Results

There were 1,284,537 adult cancer patients in the cohort who survived for 5 years or longer, with an average follow-up time of 13 years after the first cancer diagnosis. About 25% of cancer survivors received radiotherapy as part of the initial treatment of their first cancer, and more than 90% of these received some form of external beam radiation. Few patients had a first cancer that was staged as distant (3–4%), and this proportion was similar in both radiotherapy and nonradiotherapy groups (Table 1). Compared with the overall cohort, patients who developed second bone sarcomas ($n = 159$) were slightly younger at initial cancer diagnosis and were more likely to have previously received radiotherapy. Furthermore, in the group of patients who developed a second bone sarcoma after previous radiotherapy, there was a higher percentage of females (67%) and distant-staged first cancers (11%) than in the cohort as a whole.

Overall a 75% increase in rates of second primary bone sarcoma was observed compared with rates in the general population (O = 159, SIR = 1.75, 95% CI = 1.49–2.04%). The risk was elevated by 25% in patients who did not receive radiotherapy (O = 89, SIR = 1.25, 95% CI = 1.00–1.54%) and by 257% in those who received radiotherapy (O = 70, SIR = 3.57, 95% CI = 2.78–4.50; Table 2). For each histologic type of sarcoma, the SIRs were significantly elevated in all cancer survivors and were higher among patients who had previously received radiotherapy than among those who had not. SIRs in the radiotherapy group were 1.66 (95% CI, 1.00–2.60%) for chondrosarcoma ($n = 69$), 6.61 (4.69–9.07) for osteosarcoma ($n = 63$), 4.52 (1.66–9.84) for malignant fibrous histiocytoma ($n = 12$), and 7.11 (1.47–20.77) for spindle cell sarcoma ($n = 7$). Risks also varied depending on the type of the first cancer, but these SIRs should be interpreted with caution as they were based on small numbers for many first cancer sites (Appendix S2). We repeated our analyses by histology (Table 2) and first cancer site (Appendix S2) after excluding the 7% of patients who received brachytherapy or radioisotopes as their sole form of radiotherapy, and saw no difference in our results other than slightly widened CIs.

For second osteosarcoma and chondrosarcoma, we directly compared the risks in the radiotherapy and nonradiotherapy groups and calculated the RR associated with radiotherapy. Adjustment for confounding factors had a small effect on the RR estimates, generally reducing the RR in relation to radiotherapy for osteosarcoma and increasing the RR for chondrosarcoma. In the final model with adjustments for stage, age, and year at diagnosis of the first cancer, the RR for radiotherapy was 5.08 for osteosarcoma (95% CI, 3.05–8.59%) and 1.54 for chondrosaroma (95% CI, 0.88–2.59%; Table 3). The RR estimates were higher and statistically significant when restricted to osteosarcomas [RR = 10.35 (4.96–23.66)] and chondrosarcomas [RR = 8.21 (2.09–39.89)] that arose in the radiotherapy field typically used to treat the first cancer.

We assessed effect modification by gender, latency, and age at first cancer diagnosis (Table 3). Relative risk estimates for chondrosarcoma suggested higher risks in

Table 2. Standardized incidence ratio of bone sarcomas as a second malignancy in 5-year adult cancer survivors, according to previous radiotherapy and histologic type (SEER 9 registries: 1973–2008)

	Radiotherapy			No radiotherapy			Total		
Sarcoma histologic type	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
Chondrosarcoma	19	1.66[a]	(1.00–2.60)	50	1.19	(0.89–1.57)	69	1.29[a]	(1.01–1.64)
Osteosarcoma	38	6.61[a]	(4.68–9.07)	25	1.23	(0.79–1.81)	63	2.41[a]	(1.85–3.08)
Fibrosarcoma/MFH	6	4.52[a]	(1.66–9.84)	6	1.25	(0.46–2.71)	12	1.95[a]	(1.01–3.41)
Spindle cell sarcoma	3	7.11[a]	(1.47–20.77)	2	3.01	(0.82–7.71)	7	4.00[a]	(1.61–8.24)
Ewing sarcoma	2	6.52	(0.79–23.56)	2	1.52	(0.18–5.48)	4	2.46	(0.67–6.31)
Giant cell tumor	2	4.95	(0.6–17.87)	2	1.36	(0.16–4.9)	4	2.13	(0.58–5.45)
Total	70	3.57[a]		89	1.25*		159	1.75[a]	

[a]Significantly elevated compared with general population at $P < 0.05$. Individual P values for the radiotherapy group were: chondrosarcoma $P = 0.05$; osteosarcoma $P < 0.001$; MFH $P = 0.006$; spindle cell $P = 0.02$; Ewing $P = 0.08$; giant cell $P = 0.13$.

females [RR for females = 2.46 (1.25–4.67) vs. RR for males = 0.63 (0.18–1.64), $P = 0.02$] and after a longer latency (RR for 5–9 years latency = 0.87 (0.34–1.92) vs. RR for 10+ years latency = 2.49 (1.19–4.90), $P = 0.06$], but these findings are not conclusive as they are based on very small numbers. There was no evident relationship between age at exposure and radiotherapy risk for osteosarcoma or chondrosarcoma.

By 15 years after the first cancer diagnosis, there were an estimated 36 excess second bone sarcomas diagnosed in the 327,532 five-year cancer survivors who were treated with radiotherapy. This corresponds to an excess absolute risk of about 1 bone sarcoma for every 10,000 adult patients treated with radiotherapy.

Discussion

To our knowledge, this is the first cohort study of radiation-related bone sarcomas in adults to evaluate risks by histologic subtype, and our results provide the first evidence of a possible association between radiation exposure and chondrosarcoma. The RRs of developing bone cancer in the standard radiation field were substantial at 10.35 (4.96–23.66) for osteosarcoma and 8.21 (2.09–39.89) for chondrosarcoma. Risks of other less common bone sarcoma histologies also seem to be higher after the radiotherapy.

Previous studies of radiation-related bone sarcomas by histology have mostly been descriptive case series. Those reports have primarily focused on the predominance of osteosarcoma and malignant fibrous histiocytoma occurring in previously irradiated fields after both childhood and adult cancers, with the only mention of chondrosarcoma being its low rate in these series (making up 3–5% of all postradiation sarcomas; refs. 14–17). However, these studies all lack a formal control group; to date, controlled studies have only been conducted for osteosarcoma after childhood cancers (18) and for all bone cancers combined (19, 20). Still, several case reports have been published describing chondrosarcomas arising in a previously irradiated area (21–24) and Newton and colleagues noted that in childhood cancer survivors, chondrosarcoma has been seen "almost exclusively" in patients who had previously received radiation at the site of the sarcoma (25).

Our results for all bone sarcomas are consistent with previous registry-based studies, yielding SIRs slightly higher than those calculated by Virtanen and colleagues using data from the Finnish Cancer Registry (19). Our calculated 15-year excess absolute risk (1/10,000) is slightly smaller than the 1 in 10,000 increase in 10-year cumulative incidence Virtanen observes among patients who received radiotherapy, but the discrepancy is likely explained in part by our focus on bone sarcomas versus all sarcomas. In addition, our calculation probably underestimates the true excess risk, as many patients (66%) have not yet been followed up for 15 years in our SEER dataset. Earlier work also supports our findings of effect modification for the risk of bone sarcoma after radiotherapy by latency time and gender (19). We extended these prior analyses (which analyze trends using SIRs) by estimating RRs, which allowed for direct comparison of radiotherapy and nonradiotherapy groups with control for potential confounding factors.

Our results suggest that radiation-related chondrosarcoma may have a longer latency period than radiation-related osteosarcoma. This may be because of the typical behavior of sporadic chondrosarcomas, which are much slower growing than osteosarcomas and have a low metastatic potential, leading to delayed symptoms and hence clinical diagnosis. It is unclear why women might have a higher risk of chondrosarcoma after radiotherapy than men, although data from the Finish Cancer Registry also found a higher risk of second bone sarcoma females (but not males) who received radiotherapy for their first cancer compared with those who did not (19). Differences in the typical radiation dose to bone or cartilage for different gender-specific first cancers could be a partial explanation for these findings.

The observed pattern of radiation-related osteosarcoma by age at exposure did not clearly show the inverse

Table 3. Risk of second osteosarcoma (a) and chondrosarcoma (b) in 5-year adult cancer survivors, according to previous radiotherapy and histologic type (SEER 9 registries: 1973–2008)

	Radiotherapy		No radiotherapy				
Characteristic	**Observed**	**SIR**	**Observed**	**SIR**	**RR[a]**	**(95% CI)**	***P* value for heterogeneity**
(a) Osteosarcomas							
All osteosarcomas	38	6.61	25	1.23	5.08	(3.05–8.59)	
Latency							
5–9 years	21	6.48	12	1.21	5.37	(2.65–11.40)	
10+ years	17	6.79	13	1.24	4.78	(2.28–10.19)	>0.50
Age at first cancer diagnosis							
20–54	15	8.14	13	1.60	4.10	(1.90–8.92)	
55–84	23	5.89	12	0.98	6.05	(3.05–12.69)	0.46
Gender							
Male	14	5.46	10	1.25	3.93	(1.73–9.23)	
Female	24	7.54	15	1.21	5.99	(3.14–11.83)	0.43
Location of sarcoma[b]							
In radiation field	26	33.41	7	2.58	10.35	(4.96–23.66)	
Not in field	4	0.93	13	0.90	1.30	(0.40–3.66)	
(b) Chondrosarcoma							
All chondrosarcomas	19	1.66	50	1.19	1.54	(0.88–2.59)	
Latency							
5–9 years	7	1.09	25	1.30	0.87	(0.34–1.92)	
10+ years	12	2.40	25	1.10	2.49	(1.19–4.90)	0.06
Age at first cancer diagnosis							
20–54	9	1.96	22	1.08	2.13	(0.92–4.55)	
55–84	10	1.46	28	1.30	1.21	(0.55–2.42)	0.30
Gender							
Male	4	0.80	24	1.46	0.63	(0.18–1.64)	
Female	15	2.34	26	1.02	2.46	(1.25–4.67)	0.02
Location of sarcoma[b]							
In radiation field	6	3.91	3	0.58	8.21	(2.09–39.89)	
Not in field	11	1.27	37	1.26	1.07	(0.51–2.05)	

[a]RR is relative risk calculated using Poisson regression with stratification by stage, age at radiation exposure, and year at exposure.
[b]Analysis according to whether or not the second cancer arose within the typical radiation field used to treat the first cancer excludes patients if their first cancer was a lymphatic or hematopoietic cancer (other than non-Hodgkin lymphoma), or cancer of thyroid, skin (including Kaposi sarcoma), soft tissue, stomach, or biliary system. In total, 1,067,153 patients in the cohort were included in this analysis.

relationship that has been suggested in the past (26). However, more recent reports suggest that radiation risks may actually increase again with age in the elderly after an initial decrease, potentially because of actions of radiation as a promoter rather than an initiator of cancer (27, 28). Moreover, Paget disease of the bone is an additional risk factor for osteosarcoma in older adults, which could possibly add to the radiation susceptibility in this population (29).

Risk factors for chondrosarcoma are largely unknown (6); a possible relationship with ionizing radiation has been suggested, but as described earlier has not been formally assessed previously (14). Chondrosarcomas are a heterogenous group of tumors, and ongoing work to reveal the complex cytogenetics of each has not pointed toward a common underlying mechanism (30). Recently, Anfinsen and colleagues found increasing incidence rates of chondrosarcoma in the United States for females but not males, and hypothesize that this may be because of a relationship between estrogen and chondrosarcoma risk (6). However, more work in the form of both *in vitro* studies and large, long-term epidemiologic studies is needed to formally evaluate this association. Although the pathogenesis of osteosarcoma is also unclear, it has been shown to be associated with periods of rapid bone growth or remodeling and there are several established risk factors for the disease (including previous radiation, chemotherapy, and Paget's disease) (29, 31).

One of the main limitations to using data from the SEER registries is incomplete treatment information. Importantly, data on chemotherapy was not available for our cohort.

Because chemotherapy has also been associated with subsequent osteosarcoma (18) and bone sarcoma in general (32, 33), lack of adjustment for chemotherapy could lead to overestimation of radiotherapy risks if patients who received radiotherapy were also more likely to receive chemotherapy. However, chemotherapy would be unlikely to confound the analysis of bone sarcomas arising in the typical radiation field. Furthermore, radiotherapy may also be underreported because only information about the initial treatment is available in SEER, potentially resulting in underestimation of the relative risk for radiotherapy. As we do not know the exact radiotherapy fields used for any particular patient and because SEER only uses broad classification of the site of the bone sarcomas, there will certainly be misclassification in the in-field analysis. However, this misclassification would most likely be nondifferential with respect to radiotherapy treatment and therefore would be expected to bias the relative risk toward the null.

Other biases common to second cancer research may also be present. Surveillance bias could be another possible or partial explanation for our findings for chondrosarcoma if patients who underwent radiotherapy were more likely to undergo long-term surveillance imaging, leading to earlier diagnosis of this indolent cancer. There is also potential for loss to follow-up if a patient moves from the SEER registry area, but unless outmigration is greater in one treatment group than another, this should not affect the relative risk estimates for radiotherapy.

The strengths of this study include the large sample size of the population-based cohort, which provided the statistical power needed to investigate the risks for radiation-related bone sarcomas by histologic type. We also conducted multivariate regression to ensure that the available potential confounding factors (including latency, gender, and stage, age, and year at the first cancer diagnosis) were controlled for. In addition, the large numbers allowed us to evaluate patterns of effect modification by gender and latency.

Dramatic advancements in effective cancer therapies and screening over the last few decades have greatly improved the prognosis among cancer survivors, and as of 2011, second or multiple primary cancers in cancer survivors represented 18% of all new primary cancer diagnoses in SEER (10). To reduce the late effects related to cancer therapies and improve the long-term surveillance of cancer survivors, full understanding of treatment risks is necessary. Radiation-related sarcomas are associated with poorer prognoses than sporadic sarcomas (15). Although chondrosarcoma generally carries a better prognosis than osteosarcoma (34), investigation of whether radiation-related chondrosarcomas are more likely to be of the high grade, aggressive variety than sporadic chondrosarcomas may be worthwhile. Our study provides additional insights into the patterns of bone sarcomas after radiotherapy in adulthood including the first evidence of a likely association between radiation exposure and chondrosarcoma that warrants further investigation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L C. Wu, A. Berrington de González
Development of methodology: L C. Wu, A. Berrington de González
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R. E. Curtis, A. Berrington de González
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L C. Wu, R A. Kleinerman, R. E. Curtis, S. A. Savage, A. Berrington de González
Writing, review, and/or revision of the manuscript: L C. Wu, R A. Kleinerman, R. E. Curtis, S. A. Savage, A. Berrington de González
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