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Relationship between Radiation Exposure and Risk of Second Primary Cancers among Atomic Bomb Survivors

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Abstract

Radiation exposure is related to risk of numerous types of cancer, but relatively little is known about its impact on risk of multiple primary cancers. Using follow-up data through 2002 from 77,752 Japanese atomic bomb survivors, we identified 14,048 participants diagnosed with a first primary cancer, of whom 1,088 were diagnosed with a second primary cancer. Relationships between radiation exposure and risks of first and second primary cancers were quantified using Poisson regression. There was a similar linear dose-response relationship between radiation exposure and risks of both first and second primary solid tumors [excess relative risk (ERR) per Gray = 0.65, 95% confidence interval (CI): 0.57–0.74 and ERR/Gy=0.56, 95% CI: 0.33–0.80, respectively] and risk of both first and second primary leukemias (ERR/Gy=2.65, 95% CI: 1.78–3.78 and ERR/Gy=3.65, 95% CI: 0.96–10.70, respectively). Background incidence rates were higher for second solid cancers, compared to first solid cancers, until about age 70 years for men and 80 years for women ($p<0.0001$), but radiation-related ERRs did not differ between first and second primary solid cancers ($p=0.70$). Radiation dose was most strongly related to risk of solid tumors that are radiation sensitive including second primary lung, colon, female breast, thyroid, and bladder cancers. Radiation exposure confers equally high relative risks of second primary cancers as first primary cancers. Radiation is a potent carcinogen and those with substantial exposures who are diagnosed with a first primary cancer should be carefully screened for second primary cancers, particularly for cancers that are radiation sensitive.

Keywords

Radiation; second primary cancer; atomic bomb survivors

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INTRODUCTION

Numerous studies, most notably research on Japanese atomic bomb survivors,(1) have documented dose-response relationships between radiation exposure and risks of several types of cancers, including both leukemia and numerous solid tumors. An understudied aspect of the relationship between radiation dose and cancer risk is radiation's impact on the incidence of second primary cancers. Few populations are suitable for assessing this relationship given the difficulties in measuring or estimating radiation dose and the relative rarity of second primary cancers. While the decreasing rates of histologically diagnosed multiple primary cancers have been associated with increasing distance from the hypocenter in Nagasaki atomic bomb survivors,(2) there has not been any quantitative estimate of the radiation-related risk of second cancer in the survivors. The Life Span Study (LSS) cohort of Japanese atomic bomb survivors in Hiroshima and Nagasaki has been followed for a sufficient amount of time offering a unique opportunity to evaluate how radiation dose is related to the occurrence of multiple primary cancers. Given the clear evidence that several types of cancers are radiation sensitive, we hypothesize that radiation dose will be associated with an elevated risk of second primary cancer. In addition, given the considerable differences in risk associated with radiation dose by cancer type, we hypothesize that elevated risks of second primary cancers will be concentrated in the most radiation-sensitive types. Those include bladder, breast, colon, esophageal, lung, and thyroid cancers as well as leukemia.(1,3–17)

The primary goal of this study was to evaluate the relationship between radiation dose and risk of second primary cancers among atomic bomb survivors. Estimation of the frequency of second primary cancers within the cohort, and particularly types of first and second primary cancer organ sites, is of both scientific and clinical interest since such an investigation will further our understanding of the impact radiation exposure has on cancer incidence. The magnitude of the radiation-related excess risk of second cancer compared with that of first primary cancer is of special interest in radiation risk assessment. In particular, by exploring both the impact of age at radiation exposure and relative timing between first and second primary cancers we assessed both the short-term and long-term sequelae of radiation exposure with respect to cancer risk.

METHODS

We utilized data from participants in the Life Span Study (LSS), the prospective cohort of Japanese atomic bomb survivors, with follow-up through December 2002. Enrollment and follow-up of the 111,951 LSS cohort members who were alive and cancer free as of 1958 (when cancer registries were established in both Hiroshima and Nagaskai) began in October 1950, just over five years after the bombings in August 1945. The study is described in detail elsewhere.(18) We excluded cohort members who were temporarily outside of Hiroshima and Nagasaki at the time of the bombings (n=25,247), those with missing radiation dose (n=6,525), first primary cancer cases identified only from death certificate data (n=2,264), and first primary cancer cases diagnosed outside of either Hiroshima or Nagasaki (n=163). The latter two exclusions were made because person-time at risk could not be accurately determined for either group. This left a total of 77,752 cohort members upon which our analyses of first primary cancer risk were based.

In this report, cohort follow-up for diagnoses of first primary cancer begins on January 1, 1958 for all cohort members (though LSS follow-up was first initiated in October 1, 1950, the Hiroshima and Nagasaki population-based cancer registries were not established until 1957 and 1958, respectively) and ends in December 31, 2002, the most recent date through which Hiroshima and Nagasaki cancer registry data were complete. Participants diagnosed

with both first and second primary invasive cancers were identified from the Hiroshima and Nagasaki tumor registries. A total of 14,048 first primary invasive cancers have been diagnosed among LSS participants included in our study, of which 13,366 were solid tumors, 275 were leukemias and 407 were lymphomas or myelomas. Second primary invasive cancers were defined as those that occurred in an organ or site different from the first primary cancer, those that clearly had different morphologies (based on histology) compared to the first primary but occurred within the same organ or site, and those that occurred in the side opposite to the first cancer for paired organs such as the breast. In addition, to address the possibility of second primary cancers representing a metastasis of the first primary cancer, we only considered tumors to be second primaries if they were diagnosed at least 180 days after the first primary cancer was diagnosed. This approach is consistent with, or more conservative than several recent studies of second primary cancers that used the same interval, a shorter interval, or no interval.(19–22) Subjects who died (n=3,402), had another cancer diagnosis (n=365) or lost to follow-up (n=250) within 180 days after their first diagnoses were excluded from the analysis of second cancer risk. For each of the remaining 10,031 cancer survivors, follow-up for diagnosis of second primary cancer began 180 days after the first cancer diagnosis. A total of 1,088 second primary cancer cases (1,031 solid tumors, 23 leukemias, and 34 lymphomas or myelomas) were diagnosed in this cohort.

In the analyses of first primary cancers, the total number of person-years was adjusted to reflect migration of LSS cohort members from the tumor catchment area. Details regarding the migration adjustment in research on the atomic-bomb survivors have been published previously.(1) No adjustment for migration was made to the person-years in the analyses of second primary cancers because survivors of a first cancer were rigorously followed for the occurrence of a second cancer even if they migrated out of the catchment area. Furthermore, the information used to generate the migration adjustment probabilities was based from interviews with members of the Adult Health Study cohort of Japanese atomic bomb survivors and may not generalize to those diagnosed with a first cancer.

Estimates of absorbed radiation organ doses were calculated using the DS02 dosimetry system.(23) This system is based on refined estimates of the bomb yields and source terms (gamma ray dose plus ten times the neutron dose) and takes better account of the impact of shielding from both buildings and the environment. For solid tumors estimated dose to the colon was used as our primary exposure because colon dose has previously been used as a proxy for radiation exposure of internal organs in other research on this population.(1) For leukemia, estimated dose to the bone marrow was used as our primary exposure. Dose estimates are reported in units of Gray (Gy) without including tissue weighting factors.

Statistical Analysis

The overall strategy for this analysis was to fit models similar to those that have previously been applied to solid tumor incidence(1) and leukemia mortality,(23) and test whether the background and/or radiation-related excess risk components of those models differed between first and second cancers. Person-years (PY) at risk and counts of first and second primary cancer cases were cross-classified by the following variables: estimated radiation doses to the colon and marrow (21 categories each: 0–4, 5–24, 25–49, 50–74, 75–99, 100–124, 125–149, 150–174, 175–199, 200–249, 250–299, 300–499, 500–749, 750–999, 1000–1249, 1250–1499, 1500–1749, 1750–1999, 2000–2499, 2500–2999, and ≥3000 mGy), city ($c = -1/2$ for Hiroshima, +1/2 for Nagasaki), sex ($s = -1/2$ for males, +1/2 for females), age at the time of the bombing (15 categories: 0–4, 5–9, …, 65–69, ≥70), attained age (17 categories: 5–9, 10–14, …, 80–84, ≥85), calendar time (10 categories: 1958–60, 1961–65, …, 1991–96, and 1997–2002), follow-up period ($p = 1$ or 2 for before first primary cancer diagnosis or >180 days after first diagnosis, respectively), and follow-up time (9 categories:

0–4, 5–9, …, 35–39, and ≥40 years since beginning of follow-up period). In addition, the follow-up period for second cancers was further cross-tabulated by age at first cancer diagnosis (15 categories: 0–4, 5–9, …, 65–69, ≥70) and, for analyses of second primary cancers following specific first cancer types, by type of first cancer (stomach, lung, colon, liver, breast, non-Hodgkin lymphoma, leukemia, thyroid, bladder and other). 145,526 of the resulting cells had PY>0. For each of these cells the numbers of primary cancers of different types were calculated, along with the mean values of estimated colon and marrow doses (generically denoted *d*), age at the time of the bombing (*e*), attained age (*a*), follow-up time (*t*) and, for the second cancer follow-up period, mean age at first diagnosis (*f*) and mean time since first diagnosis (*m*).

Poisson regression analysis was used to estimate and compare the radiation dose responses for first and second primary cancers. The number of cases for a given cancer type was assumed to be a Poisson variate with mean $\mu_{d,c,s,a,e,t,p,f,m} = PY_{d,c,s,a,e,t,p,f,m}\,\lambda_{d,c,s,a,e,t,p,f,m}$, where *PY* denotes person years (PY) at risk and λ the incidence rate. Risk was represented by linear excess relative risk (ERR) models of the form

$$\lambda_{d,c,s,a,e,t,p,f,m}=\lambda_0(c,s,a,e,t,p,f,m)[1+ERR(d,c,s,a,e,t,p,f,m)]$$

or excess additive risk (EAR) models of the form

$$\lambda_{d,c,s,a,e,t,p,f,m}=\lambda_0(c,s,a,e,t,p,f,m)+ERR(d,c,s,a,e,t,p,f,m)$$

where $\lambda_0(.)$ is the background cancer incidence rate for subjects with zero dose, and *ERR(.)* and *EAR(.)* are the ERR and EAR associated with dose *d*.

Analyses of solid cancer incidence were based primarily on linear ERR models, although EAR models were also fit. Background rates for solid tumors were modeled as sex-specific parametric functions of city, attained age, and age at exposure (equivalent to birth cohort). For each sex the log rate was described using city, logarithm of attained age divided by 70, and piecewise quadratic functions of age at exposure joining smoothly at ages 30 and 50. A smooth piecewise quadratic function with knots at e_1 and e_2 can be written as $Q(e) = \eta_1 e + \eta_2 e^2 + \eta_3 \max(e\text{-}e_1,0)^2 + \eta_3 \max(e\text{-}e_2,0)^2$. To compare first and second primary cancers, coefficients of the terms in the background model were allowed to differ according to follow-up period, and an additional term was included for age at diagnosis of first primary cancer (centered at age 55). The general model for background incidence rates in the analysis of all solid tumors was therefore

$$\lambda_0(c,s,a,e,p,f)=\exp[\alpha_{s,p}+\alpha_{c,s,p}c+\alpha_{a,s,p}\ln(a/70)+Q_{s,p}(e)+\alpha_{f,s,p}I(p=3)(f-55)]$$

where $I(.)$ is the indicator function and $Q_{s,p}(.)$ denotes different piecewise quadratic functions for each (s,p). Analyses of specific solid tumors such as stomach or lung cancer were based on smaller numbers of cases, especially for second primary cancers; therefore these analyses used a simpler background model in which the effect of age at exposure was represented by terms of the form $\alpha_{e,s,p}\ln(e/30)$ rather than the piecewise quadratic terms $Q_{s,p}(e)$. Differences in background rates of first and second primary cancers were tested by comparing parameter values for p=1 and p=2.

ERR(d) was modeled as $\rho(d)\gamma(c, s, a, e, t, p, f, m)$ where $\rho(d)$ describes the shape of the dose response and $\gamma(.)$ represents the modifying effects of the covariates. The analyses presented here for solid tumors considered the linear ERR model $\rho(d) = \beta d$. The general model for the modifying effect of the covariates was

$$\gamma(c, s, a, e, p, f)=\exp\{\theta_p+\theta_{c,p}c+\theta_{s,p}s+\theta_{a,p}\ln(a/70)+\theta_{e,p}(e-30)+I(p=2)[\theta_{f,p}(f-55)+\theta_{m,p}(m-10)]\}.$$

As for the background model, differences between first and second cancers in β and the modifying effects of the other factors were tested by comparing parameter values for p=1 and p=2.

Leukemia incidence rates were investigated using additive models of the form

$$\lambda_{d,c,s,a,e,t,p,f,m}=\lambda_0(c, s, a, e, t, p, f, m)+EAR(d, c, s, a, e, t, p, f, m),$$

where *EAR(.)* is the excess additive risk (EAR). The background rates were modeled using the same general model as for solid tumors. Following the approach of BEIR VII.,(23) $EAR(d) = \rho_s(d)\gamma(c, a, e, t, p, f, m)$ was modeled using a sex-specific linear-quadratic function of dose $\rho_s(d) = \beta_s d(1 + \kappa d)$ where κ, the curvature of the dose-response function, was assumed to be the same for both sexes. Dose effect modification was modeled as

$$\gamma(c, a, e, t, p, f, m)=\exp\{\theta_p+\theta_{c,p}c+F_p(e)+G_p(e, t)+I(p=2)[\theta_{f,p}(f-55)+\theta_{m,p}(m-10)]\}.$$

Defining $F_p(e) = \theta_{e,p}(e\text{-}30)$ or $F_p(e) = \Sigma_j\theta_{e,p,j}I(e_j \leq e < e_{j+1})$ for exposure age categories (0–19, 20–39, and 40+) permitted age at exposure to modify the radiation dose effect in a continuous or categorical manner. Similarly $G_p(e, t) = \theta_{e,t,p}\,(e\text{-}30)\text{x}(t\text{-}25)$ or $G_p(e, t) = \theta_{e,t,p}(t\text{-}25)\Sigma_j\theta_{e,p,j}I(e_j\ e < e_{j+1})$ allowed the EAR to vary with time since exposure in an age at exposure-dependent manner.

The Poisson regression models defined above were fit using the Epicure software package. Differences between background models and dose-response models of first and second malignancies were tested using likelihood ratio tests. 95% confidence intervals (CIs) were calculated by Wald's method for parameters in exponential terms, and from profile likelihoods for dose response parameters β and β_s.

Ethical considerations

The conduct of the LSS was approved by the Human Investigation Committee of Radiation Effects Research Foundation (RERF). The use of death certificates of the LSS subjects was approved by the Ministry of Internal Affairs and Communications. The respective committees of Hiroshima City Cancer Registry, Hiroshima Prefecture Tissue Registry and Nagasaki Prefecture Cancer Registry approved the use of cancer registry data for the present study.

RESULTS

There were proportionally fewer women among both the participants diagnosed with a first cancer and with a second cancer compared to the study cohort (Table 1). Stomach, lung, colon, liver, and female breast cancers were the five most commonly diagnosed first and

second primary cancers. The incidence rate for second solid tumors was 1,656 per 10^5 PY (1,031 cases in 6.23 $\times 10^4$ PY), which is 57% higher than the corresponding rate of 1,067 per 10^5 PY for first primary cancers (13,336 cases, 2.14×10^6 PY, standardized to the age and sex distribution of PY for second cancers). The analogous leukemia incidence rates showed a similar difference, with rates of 37 per 10^5 PY (23 cases) and 19 per 10^5 PY (275 cases) for second and first leukemia, respectively.

Solid tumors

The overall linear excess relative risk relationships between radiation exposure and incidence of first primary solid invasive cancer and second primary solid invasive cancer were similar (ERR/Gy=0.65, 95% CI: 0.57–0.74 and ERR/Gy=0.56, 95% CI: 0.35–0.81, respectively) (Table 2). While data on radiation therapy and chemotherapy were not uniformly collected by the Nagasaki registry until 1986 and by the Hiroshima registry until 1993, information on whether or not patients received radiation therapy or chemotherapy was available for 67% and 68% of participants, respectively. Among those with known radiation therapy data, 89% did not receive radiation for their first cancer and 11% did. The ERR/Gy of second primary solid cancer was 0.54 (95% CI: 0.29–0.84) among those who did not receive radiation and 0.27 (95% CI: −0.21–1.08) among those who did (p-value for heterogeneity of these two risk estimates = 0.48). Among those with known chemotherapy data, 63% did not receive radiation for their first cancer and 37% did. The ERR/Gy of second primary solid cancer was 0.53 (95% CI: 0.26–0.88) among those who did not receive chemotherapy and 0.42 (95% CI: 0.06–0.92) among those who did (p-value for heterogeneity of these two risk estimates = 0.68). Thus, the relationship between atomic bomb radiation exposure and risk of second primary solid cancer did not appear to be modified by treatment of first primary cancers with either radiation therapy or chemotherapy.

The radiation-related risks for first and second cancers were comparable when results were stratified by gender and age at time of the bombing (Table 3). However, the ERRs of first and second solid tumors were larger among women (ERR/Gy=1.09, 95% CI: 0.94–1.24 and ERR/Gy=1.03, 95% CI: 0.64–1.49, respectively) compared to men (ERR/Gy=0.51, 95% CI: 0.40–0.63 and ERR/Gy=0.37, 95% CI: 0.11–0.70, respectively). Additionally, radiation was more strongly related to risk of both first and second solid tumors among those who were younger at the time of the bombing. Given those differences, radiation effects were further investigated using linear ERR models with dose effect modification by sex, age at exposure, attained age, and, for second cancers, time since first cancer diagnosis. When these models were fit to the data, the background incidence rates of first and second primary solid cancer differed significantly ($p<0.0001$). The age at exposure specific background rates were higher for second solid cancers, compared to first solid cancers ($p<0.0001$), up to attained age of about 70 years for men and 80 years for women. After accounting for this difference in background rates, the radiation-related excess relative risks modified by age at exposure and attained age did not differ significantly between first and second primary solid cancers ($p=0.70$). Additionally, the effect of radiation on second solid cancer risk did not vary significantly with age at first cancer diagnosis ($p=0.69$) or with time since first cancer diagnosis ($p=0.57$). Specifically, the ERR/Gy was 0.38 (95% CI: 0.10–0.74) for second primary tumors diagnosed between 180 days and 5 years of the first primary, 1.40 (95% CI: 0.74–2.33) for 5 to 10 years after, and 0.59 (95% CI: 0.23–1.07) for more than 10 years after (Table 4).

The overall EAR of solid cancer was 264 cases per 10^5 PY-Gy (95% confidence interval 227–304 cases/10^5 PY-Gy) for first primary cancers, and about three-fold higher for second primaries: 814 per 10^5 PY-Gy (537–1120 cases/10^5 PY-Gy). However for both first and second primary solid cancers the radiation-related EAR decreased with increasing age at

exposure and increased with increasing age. In particular the EAR for second primary solid cancers was higher than for first primaries for younger ages at exposure and decreased more rapidly with increasing age at exposure (45% and 42% per decade for men and women, respectively) compared to first primaries (23% per decade for either men or women). The greater EAR for second primary cancers was concentrated primarily in those of age <30 at exposure.

Risks of selected types of first and second primary solid cancers were also similar with respect to radiation dose. Table 5 summarizes the effects of radiation on risk of six types of solid tumors. Elevations in risk of similar magnitude for both first primary and second primary cancer associated with radiation were observed for lung, colon, and female breast cancers. Alternatively, the ERR/Gy for first primary thyroid cancer was more than twice the ERR/Gy for second primary thyroid cancer (ERR/Gy=2.31, 95% CI: 1.56–3.24 and ERR/Gy=0.97, 95% CI: 0.06–2.58, respectively), the ERR/Gy for second primary bladder cancer was 1.75-fold higher than the ERR/Gy for first primary bladder cancer (ERR/Gy=1.71, 95% CI: 0.20–5.29 and ERR=0.96, 95% CI: 0.46–1.61, respectively), and radiation appeared to be associated with risk of first primary stomach cancer but not second primary stomach cancer (ERR/Gy=0.42, 95% CI: 0.28–0.58 and ERR=0.05, 95% CI: −0.23–0.50, respectively). However, none of these differences between first and second cancer risk estimates were statistically significant.

The association between radiation exposure and risk of second primary solid cancer varied somewhat across survivors of these six types of first primary solid cancer (Table 6). While radiation was significantly associated with risk of second primary cancer among survivors of female breast cancer, thyroid, and bladder cancers, it was not significantly associated with risk among survivors of either first primary lung or colon cancer (though there were relatively few survivors of these cancers exposed to higher radiation doses limiting our statistical power), and had a nearly statistically significant effect among stomach cancer survivors (ERR/Gy = 0.39, 95% CI −0.01–0.97, p=0.057).

Leukemia

Among the 77,752 members of the cohort, 275 were diagnosed with leukemia as their first primary cancer, and only 23 of the 10,031 survivors of a first cancer investigated for second cancers were subsequently diagnosed with leukemia. The estimated linear ERR/Gy for second primary leukemia was somewhat higher than for first leukemia, although the confidence intervals for the two estimates overlapped considerably (ERR/Gy=3.65, 95% CI: 0.96–10.70 and ERR=2.65, 95% CI: 1.78–3.78, respectively) suggesting the dose-responses are similar (Table 2). This was confirmed in the analysis of the sex-specific linear-quadratic EAR dose-response model with dose effect modification by age at exposure and attained age (or, equivalently, time since exposure), as this model did not differ significantly between first and second primary leukemias (p=0.41). Due to the small number of second leukemias and the inability to more precisely model dose effect modification by age, attained age and/or time since exposure, further analyses of leukemia were not pursued.

DISCUSSION

In the cohort of Japanese atomic bomb survivors the dose response relationships between radiation dose and cancer risk are similar for both first primary cancer among the study cohort and second primary cancer among the cohort of cancer survivors. This similarity held across both solid tumors and leukemias, both women and men, and age at the time of the bombing. The relationship was somewhat stronger among women compared to men, and this difference is likely driven by female breast cancer since it is a particularly radiation sensitive site. The background risk of any second primary solid cancer was generally higher

than the risk of first solid tumor for men and women up to about age 70 and 80, respectively. This might reflect an inherently higher risk of cancer among those who suffer second solid cancers, although the possibility that treatment for the first solid tumor might contribute to increased risk of second cancer cannot be excluded. An increased ascertainment of second cancers through closer medical follow-up of cancer patients should also be considered.

Consistent with previous literature,(1,3–17) we did observe that certain first and second primary cancer types were more radiation sensitive. Specifically, radiation was related to risk of both first and second primary lung, colon, female breast, thyroid, and bladder cancers in addition to leukemia. Interestingly, among survivors of the most radiation sensitive types of first primary solid tumors, survivors of female breast, thyroid, and bladder cancers, radiation was strongly related to risk of any type of second primary solid cancer, but among lung and colon cancer survivors it was not (Table 6). It may be that individuals exposed to radiation who are diagnosed with a particularly radiation sensitive cancer may have a particularly elevated risk of second primary cancer, possibly as a result of carrying particular genetic variants. This is consistent with the idea that certain individuals are more susceptible to radiation induced cancer than others. Further research is needed to clarify what genetic or other factors may potentially convey an increased susceptibility

Given that radiation is one of the few exposures that has been clearly established to be involved in the etiology of numerous types of cancer and also that the radiation-related risks of cancer have been shown to be persistent, it is not surprising that atomic bomb radiation exposure is similarly related to risk of both first primary and second primary cancer among exposed individuals. The atomic bombings resulted in essentially full body exposure for the majority of LSS participants, and so given the nature of this type of exposure radiation could exert its carcinogenic effects in multiple parts of an individual’s body. Our results suggest that the influence of radiation dose on risk of a second primary cancer is generally the same as it is for first primary cancer risk, and that this holds across the major radiation-related sites, for both sexes, by age at exposure, and regardless of duration between first and second primary cancers. Thus, the diagnosis of first primary cancer in and of itself does not appear to influence the relationship between radiation dose and risk of second primary cancer.

While no prior studies have been able to assess the quantitative relationship between this type of radiation exposure and risk of second primary cancer, it is important to acknowledge the limitations of our study. Despite utilizing a large cohort, given the relative rarity of second primary cancers many of our stratified analyses were based on small numbers of cases making it difficult to discern differences across groups. As a result, our statistical power to detect associations specific to particular cancer sites was limited. We lacked information on exposures that are related to risk of different types of cancer (e.g., smoking, alcohol use, reproductive factors, and family history of cancer), and thus could not evaluate these exposures as either confounders or effect modifiers of the observed relationships. However, we did observe that treatment of first cancers with either radiation or chemotherapy did not alter our risk estimates. In addition, it is possible that some of the second primary cases represent recurrences or metastases of first primary cancers rather than true second primaries. This number is likely limited though given the various strategies (detailed in the methods section) we utilized beyond those already utilized by the cancer registries to guard against this to increase our certainty that cases identified as second primaries were true second primaries. Even though we utilized the latest dosimetry developed for this cohort, which is the result of cumulative efforts to improve quantitated estimates of radiation exposure on the individual level based on numerous considerations, (23,24) there remains inherent uncertainty in estimating radiation dose among cohort participants. The degree of uncertainty in dose is likely to be non-differential resulting in a bias of our results toward the null. Lastly, while this population was a generally healthy one

prior to the atomic bombings, LSS members have been carefully followed clinically through their identification as atomic bomb survivors and their participation in the cohort. Thus, there are limitations to extrapolating the results of this study to other populations. However, the extent of the biases present may be limited as consistent with available literature we observed that radiation dose was related only to risk of second primary cancers known to be radiation sensitive, and not to those that are not.

In summary, radiation dose is associated with risk of both first primary and second primary cancer, with similar dose-response relationships for both solid tumors and leukemia. This is the first study with sufficient size and follow-up to evaluate the risk of second primary cancers related to this type of radiation exposure. The results suggest that individuals exposed to radiation who develop cancer should be followed carefully for the occurrence of a second primary cancer. They also suggest that some people may be more susceptible to radiation induced cancers than others, but further research is needed to characterize what defines a susceptible individual. Conversely though, the similar dose-response relationships seen for first and second cancers suggests that most patients who were diagnosed with two cancers developed them independently given the nature of the whole body exposure this cohort experienced and the potency of radiation as a human carcinogen to multiple organ sites.

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Table 1

Demographic characteristics of the study cohort, those diagnosed with a first cancer, and those diagnosed with a second cancer

	Study cohort (n=77,752)		Participants diagnosed with a first cancer* (n=14,048)		Participants diagnosed with a second cancer* (n=1,088)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Age at time of atomic bombing, years						
≤14	25,867	33.2	2,788	19.9	215	19.8
15–19	8,204	10.5	1,666	11.9	186	17.1
20–29	10,296	13.2	2,505	17.8	267	24.5
30–39	11,299	14.5	3,096	22.0	242	22.2
40–49	11,843	15.2	2,618	18.6	138	12.7
≥50	10,243	13.1	1,375	9.8	40	3.7
Gender						
Female	46,456	59.6	7,692	54.8	608	55.9
Male	31,296	40.2	6,356	45.2	480	44.1
City						
Hiroshima	52,488	67.4	9,973	71.0	801	73.6
Nagasaki	25,264	32.4	4,075	29.0	287	26.4
Age at cancer diagnosis, years						
≤49			1,305	9.3	30	2.8
50–59			2,468	17.6	119	10.9
60–69			4,051	28.8	288	26.5
70–79			4,056	28.9	409	37.6
≥80			2,168	15.4	242	22.2
Year of cancer diagnosis						
1958–1968			2,564	18.3	57	5.2
1969–1979			3,124	22.2	124	11.4
1980–1990			3,754	26.7	283	26.0
1991–2002			4,606	32.8	624	57.4
Cancer site						
Stomach			3,536	25.2	187	17.2
Lung			1,335	9.5	135	12.4

	Study cohort (n=77,752)		Participants diagnosed with a first cancer* (n=14,048)		Participants diagnosed with a second cancer* (n=1,088)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Colon			1,109	7.9	124	11.4
Liver			1,072	7.6	85	7.8
Female Breast			970	6.9	61	5.6
Cervix			650	4.6	12	1.1
Rectum			642	4.6	50	4.6
Thyroid			429	3.1	61	5.6
Gallbladder			410	2.9	28	2.6
Bladder			391	2.8	30	2.8
Pancreas			363	2.6	27	2.5
Prostate			355	2.5	48	4.4
Esophagus			291	2.1	25	2.3
Non-Hodgkin’s lymphoma			283	2.0	19	1.8
Leukemia			275	2.0	23	2.1
Oral			240	1.7	21	1.9
Kidney			235	1.7	24	2.2
Ovary			192	1.4	11	1.0
Other/Unknown			1,270	9.0	117	10.8

*Cancers diagnosed only from death certificates are excluded.

Table 2

Relationship between estimated radiation dose and risk of first and second primary cancers

Solid Tumors								
Colon dose, Gy	**Person years for time to 1st cancer**	**Number of 1st primary cases**	**RR***	**95% CI**	**Person years for time to 2nd cancer**	**Number of 2nd primary cases**	**RR***	**95% CI**
<0.005	943,630	5,580	1.00	ref	25,227	401	1.00	ref
0.005–0.49	1,056,910	6,424	1.03	0.99–1.07	30,045	475	1.01	0.88–1.15
0.50–0.99	82,759	700	1.42	1.31–1.54†	3,757	55	1.01	0.76–1.33
1.00–1.99	41,770	474	1.92	1.74–2.10†	2,146	62	1.98	1.51–2.59†
≥2.00	13,923	188	2.53	2.19–2.93†	1,078	38	2.47	1.77–3.46†
ERR/Gy*			0.65	0.57–0.74†			0.57	0.36–0.82†
Leukemias								
Marrow dose, Gy	**Person years for time to 1st cancer**	**Number of 1st primary cases**	**RR***	**95% CI**	**Person years for time to 2nd cancer**	**Number of 2nd primary cases**	**RR***	**95% CI**
<0.005	917,052	95	1.00	ref	24,482	7	1.00	ref
0.005–0.49	1,062,570	117	1.16	0.88–1.53	30,031	6	0.75	0.25–2.26
0.50–0.99	90,912	19	2.08	1.27–3.41†	3,671	4	4.35	1.26–15.01†
1.00–1.99	48,913	21	4.07	2.53–6.53†	2,644	4	6.33	1.83–21.90†
≥2.00	19,550	23	12.57	7.94–19.88†	1,424	2	6.09	1.24–29.88†
ERR/Gy*			2.65	1.78–3.78†			3.70	0.99–10.80†

*Relative risk (RR) and excess RR per Gray (ERR/Gy) are adjusted for sex, city, attained age, age at time of bombing, and age at first cancer diagnosis (second primary cancer risk estimates only).

†p<0.05.

Table 3

Relationship between colon radiation dose and risk of first and second primary solid cancers by gender and age

Colon dose, Gy	# of 1st primary cases	HR	95% CI	# of 2nd primary cases	HR	95% CI
GENDER						
Men						
<0.005	2,608	1.00	ref	189	1.00	ref
0.005–0.49	2,827	1.25	1.18–1.32†	203	1.15	0.93–1.42
0.50–0.99	309	1.53	1.36–1.72†	21	0.96	0.61–1.51
1.00–1.99	218	1.82	1.58–2.09†	25	1.81	1.18–2.77†
≥2.00	83	2.13	1.71–2.66†	16	2.08	1.24–3.49†
ERR/Gy		0.51	0.40–0.63†		0.37	0.11–0.71†
Women						
Colon dose, Gy	**# of 1st primary cases**	**HR**	**95% CI**	**# of 2nd primary cases**	**HR**	**95% CI**
<0.005	2,972	1.00	ref	212	1.00	ref
0.005–0.49	3,597	1.31	1.24–1.38†	272	1.33	1.09–1.61†
0.50–0.99	391	1.78	1.60–1.98†	34	1.42	0.99–2.06
1.00–1.99	256	2.67	2.35–3.04†	37	3.11	2.18–4.44†
≥2.00	105	3.92	3.22–4.76†	22	3.42	2.18–5.37†
ERR/Gy		1.09	0.94–1.24†		1.03	0.64–1.51†
AGE AT TIME OF BOMBING						
Age at time of bombing ≤14 years						
Colon dose, Gy	**# of 1st primary cases**	**HR**	**95% CI**	**# of 2nd primary cases**	**HR**	**95% CI**
<0.005	1,070	1.00	ref	65	1.00	ref
0.005–0.49	1,249	1.04	0.96–1.14	93	1.31	0.95–1.81
0.50–0.99	139	1.78	1.49–2.13†	15	1.62	0.92–2.87
1.00–1.99	116	2.92	2.41–3.54†	15	2.64	1.50–4.66†

GENDER

Men

Colon dose, Gy	# of 1st primary cases	HR	95% CI	# of 2nd primary cases	HR	95% CI
≥2.00	63	4.17	3.23–5.38†	16	5.61	3.22–9.76†
ERR/Gy		1.28	1.04–1.54†		1.20	0.63–2.00†

Age at time of bombing* 15–19 *years

Colon dose, Gy	# of 1st primary cases	HR	95% CI	# of 2nd primary cases	HR	95% CI
<0.005	641	1.00	ref	63	1.00	ref
0.005–0.49	689	1.04	0.93–1.16	68	0.88	0.62–1.25
0.50–0.99	124	1.53	1.26–1.85†	18	1.38	0.82–2.34
1.00–1.99	89	2.19	1.75–2.74†	15	1.67	0.95–2.94
≥2.00	39	2.45	1.77–3.40†	12	2.31	1.23–4.36†
ERR/Gy		0.74	0.53–0.97†		0.59	0.19–1.15†

Age at time of bombing* 20–29 *years

Colon dose, Gy	# of 1st primary cases	HR	95% CI	# of 2nd primary cases	HR	95% CI
<0.005	1,015	1.00	ref	101	1.00	ref
0.005–0.49	1,114	1.01	0.93–1.11	118	0.97	0.74–1.28
0.50–0.99	134	1.40	1.17–1.68†	12	0.86	0.47–1.57
1.00–1.99	84	1.79	1.43–2.23†	14	2.11	1.20–3.70†
≥2.00	29	2.05	1.42–2.96†	8	2.14	1.03–4.43†
ERR/Gy		0.64	0.45–0.85†		0.52	0.12–1.07†

Age at time of bombing* ≥30 *years

Colon dose, Gy	# of 1st primary cases	HR	95% CI	# of 2nd primary cases	HR	95% CI
<0.005	2,854	1.00	ref	172	1.00	ref
0.005–0.49	3,372	1.03	0.98–1.09	196	0.98	0.79–1.21
0.50–0.99	303	1.27	1.13–1.44†	10	0.59	0.31–1.11

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GENDER

Men

Colon dose, Gy	# of 1st primary cases	HR	95% CI	# of 2nd primary cases	HR	95% CI
1.00–1.99	185	1.55	1.34–1.80†	18	1.87	1.15–3.05†
≥2.00	57	1.97	1.51–2.56†	2	0.58	0.14–2.32
ERR/Gy		0.40	0.29–0.52†		0.16	−0.14—0.57

*Relative risks (RR) and excess RR per Gray (ERR/Gy) are adjusted for sex, city, attained age, age at time of bombing, and age at first cancer diagnosis (second primary cancer risk estimates only).

†p<0.05.

Table 4

Relationship between radiation dose and risk of second primary solid tumors by time since the first primary cancer diagnosis

Colon dose, Gy	Number of 2nd primary cases	RR*	95% CI
Second primary diagnosed 180 days to 5 years after the first primary cancer			
<0.005	194	1.00	ref
0.005–0.49	238	1.08	0.89–1.31
0.50–0.99	28	1.12	0.75–1.67
1.00–1.99	30	1.88	1.28–2.76†
≥2.00	10	1.44	0.76–2.73
ERR per gray		0.37	0.10–0.71†
Second primary diagnosed 5 to 10 years after the first primary cancer			
<0.005	62	1.00	ref
0.005–0.49	104	1.40	1.02–1.93†
0.50–0.99	11	1.18	0.62–2.25
1.00–1.99	17	3.19	1.85–5.49†
≥2.00	13	5.25	2.86–9.65†
ERR per gray		1.25	0.64–2.09†
Second primary diagnosed >10 years after the first primary cancer			
<0.005	145	1.00	ref
0.005–0.49	133	0.73	0.57–0.92
0.50–0.99	16	0.76	0.45–1.29
1.00–1.99	15	1.48	0.84–2.53
≥2.00	15	2.59	1.49–4.41†
ERR per gray		0.45	0.13–0.87†

*Relative risks (RR) and excess RR per Gray (ERR/Gy) are adjusted for sex, city, attained age, age at time of bombing, and age at first cancer diagnosis.

†$p<0.05$.

Table 5

Relationship between colon radiation dose and risk of site specific first primary cancers within the LSS cohort and site specific second primary cancer among cancer survivors

Stomach Cancer

	Risk of first primary stomach cancer in the LSS cohort			**Risk of second primary stomach cancer among cancer survivors**		
Colon dose, Gy	**# of cases**	**HR**	**95% CI**	**# of 2nd primary**	**HR**	**95% CI**
<0.005	1468	1.00	ref	87	1.00	ref
0.005–0.49	1761	1.04	0.97–1.12	81	0.78	0.57–1.06
0.50–0.99	160	1.23	1.04–1.44†	10	0.90	0.46–1.73
1.00–1.99	105	1.58	1.30–1.93†	4	0.63	0.23–1.71
≥2.00	42	2.11	1.56–2.87†	5	1.65	0.67–4.09
ERR per gray		0.42	0.28–0.58†		0.05	−0.23—0.50

Lung Cancer

	Risk of first primary lung cancer in the LSS cohort			Risk of second primary lung cancer among cancer survivors		
Colon dose, Gy	# of cases	HR	95% CI	# of 2nd primary cases	HR	95% CI
<0.005	554	1.00	ref	49	1.00	ref
0.005–0.49	629	1.05	0.94–1.18	60	1.10	0.75–1.62
0.50–0.99	72	1.51	1.18–1.94†	6	0.98	0.42–2.28
1.00–1.99	65	2.64	2.04–3.41†	11	3.08	1.60–5.94†
≥2.00	15	2.11	1.26–3.52†	9	5.61	2.73–11.51†
ERR per gray		0.88	0.60–1.20†		1.28	0.55–2.33†

Colon Cancer

	Risk of first primary colon cancer in the LSS cohort			Risk of second primary colon cancer among cancer survivors		
Colon dose, Gy	# of cases	HR	95% CI	# of 2nd primary cases	HR	95% CI
<0.005	472	1.00	ref	55	1.00	ref
0.005–0.49	538	1.05	0.93–1.20	51	0.80	0.54–1.19
0.50–0.99	50	1.24	0.93–1.66	7	0.97	0.44–2.13

Stomach Cancer

	Risk of first primary stomach cancer in the LSS cohort			Risk of second primary stomach cancer among cancer survivors		
Colon dose, Gy	**# of cases**	**HR**	**95% CI**	**# of 2nd primary**	**HR**	**95% CI**
1.00–1.99	34	1.70	1.20–2.41†	5	1.20	0.48–3.01
≥2.00	15	2.57	1.54–4.31†	6	3.28	1.40–7.68†
ERR per gray		0.53	0.26–0.83†		0.53	0.04–1.28†

Female Breast Cancer

	Risk of first primary breast cancer in the LSS cohort			Risk of second primary breast cancer among cancer survivors		
Colon dose, Gy	# of cases	HR	95% CI	# of 2nd primary	HR	95% CI
<0.005	357	1.00	ref	14	1.00	ref
0.005–0.49	450	1.10	0.96–1.27	32	1.88	1.00–3.54
0.50–0.99	82	2.54	2.00–3.23†	2	0.78	0.18–3.46
1.00–1.99	45	3.18	2.33–4.33†	8	5.53	2.30–13.28†
≥2.00	29	6.42	4.40–9.39†	5	7.33	2.61–20.59†
ERR per gray		2.15	1.66–2.72†		1.72	0.56–3.85†

Thyroid Cancer

	Risk of first primary thyroid cancer in the LSS cohort			Risk of second primary thyroid cancer among cancer survivors		
Colon dose, Gy	# of cases	HR	95% CI	# of 2nd primary cases	HR	95% CI
<0.005	144	1.00	ref	20	1.00	ref
0.005–0.49	213	1.27	1.03–1.58†	27	1.07	0.60–1.93
0.50–0.99	36	2.76	1.91–3.98†	7	2.27	0.96–5.40
1.00–1.99	24	3.92	2.54–6.03†	6	3.23	1.27–8.20†
≥2.00	12	6.25	3.47–11.28†	1	1.10	0.15–8.24
ERR per gray		2.31	1.56–3.24†		0.97	0.06–2.60†

Bladder Cancer

	Risk of first primary bladder cancer in the LSS cohort	Risk of second primary bladder cancer among cancer survivors
Colon dose, Gy		

Stomach Cancer

	Risk of first primary stomach cancer in the LSS cohort			Risk of second primary stomach cancer among cancer survivors		
Colon dose, Gy	**# of cases**	**HR**	**95% CI**	**# of 2nd primary**	**HR**	**95% CI**
	# of cases	HR	95% CI	# of 2nd primary cases	HR	95% CI
<0.005	145	1.00	ref	6	1.00	ref
0.005–0.49	198	1.18	0.95–1.47	18	2.73	1.07–6.99†
0.50–0.99	25	1.96	1.28–2.99†	0	0.00	NE‡
1.00–1.99	16	2.37	1.41–3.97†	4	8.06	2.27–28.64†
≥2.00	7	3.43	1.61–7.33†	2	8.28	1.66–41.40†
ERR per gray		0.96	0.46–1.61†		1.71	0.20–5.29†

*Relative risk (RR) and excess RR per Gray (ERR/Gy) are adjusted for sex, city, attained age, age at time of bombing, and age at first cancer diagnosis (second primary cancer risk estimates only).

†p<0.05

‡The confidence interval could not be estimated (NE) by the statistical model.

Table 6

Relationship between colon radiation dose and risk of second primary solid cancer among survivors of various types of cancer within the LSS cohort

Stomach cancer survivors			
Colon dose, Gy	**Number of 2nd primary cases**	**RR***	**95% CI**
<0.005	101	1.00	ref
0.005–0.49	93	0.78	0.58–1.04
0.50–0.99	8	0.80	0.39–1.65
1.00–1.99	8	1.28	0.62–2.64
≥2.00	6	2.34	1.02–5.39†
ERR/Gy*		0.39	−0.01—0.96
Colon cancer survivors			
Colon dose, Gy	**Number of 2nd primary cases**	**RR***	**95% CI**
<0.005	39	1.00	ref
0.005–0.49	51	1.23	0.79–1.91
0.50–0.99	5	1.31	0.51–3.38
1.00–1.99	4	1.52	0.53–4.30
≥2.00	1	1.16	0.16–8.55
ERR/Gy*		0.27	NE‡-1.27
Thyroid cancer survivors			
Colon dose, Gy	**Number of 2nd primary cases**	**RR***	**95% CI**
<0.005	15	1.00	ref
0.005–0.49	19	0.80	0.40–1.59
0.50–0.99	9	2.05	0.87–4.87
1.00–1.99	7	3.36	1.32–8.57†
≥2.00	5	2.79	0.99–7.85
ERR/Gy*		1.24	0.27–3.10†
Lung cancer survivors			
Colon dose, Gy	**Number of 2nd primary cases**	**RR***	**95% CI**
<0.005	15	1.00	Ref
0.005–0.49	24	1.38	0.69–2.75
0.50–0.99	1	0.33	0.04–2.62
1.00–1.99	3	1.95	0.55–6.96
≥2.00	1	3.42	0.43–27.04
ERR/Gy*		0.12	NE‡-1.36

Stomach cancer survivors			
Colon dose, Gy	**Number of 2nd primary cases**	**RR***	**95% CI**
Female breast cancer survivors			
Colon dose, Gy	**Number of 2nd primary cases**	**RR***	**95% CI**
<0.005	35	1.00	Ref
0.005–0.49	59	1.30	0.85–1.99
0.50–0.99	9	1.12	0.54–2.34
1.00–1.99	10	2.45	1.21–4.95†
≥2.00	11	4.17	2.08–8.35†
ERR/Gy*		1.05	0.42–2.01†
Thyroid cancer survivors			
Colon dose, Gy	**Number of 2nd primary cases**	**RR***	**95% CI**
<0.005	17	1.00	Ref
0.005–0.49	24	0.87	0.46–1.63
0.50–0.99	3	1.24	0.36–4.29
1.00–1.99	5	3.80	1.34–10.75†
≥2.00	3	3.40	0.97–11.93
ERR/Gy*		1.25	0.21–3.26†

*Relative risk (RR) and excess RR per Gray (ERR/Gy) are adjusted for sex, city, attained age, age at time of bombing, and age at first cancer diagnosis (second primary cancer risk estimates only).

†p<0.05

‡The lower bound of the confidence interval could not be estimated (NE) by the statistical model.