Radiation Risk of Ovarian Cancer in Atomic Bomb Survivors: 1958–2009

Authors: Utada, Mai, Brenner, Alina V., Preston, Dale L., Cologne, John B., Sakata, Ritsu, et al.

Source: Radiation Research, 195(1) : 60-65

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RADE-20-00170.1

RADIATION RESEARCH **195**, 60–65 (2021)
0033-7587/21 $15.00

DOI: 10.1667/RADE-20-00170.1

Radiation Risk of Ovarian Cancer in Atomic Bomb Survivors: 1958–2009

Mai Utada,[a,1] Alina V. Brenner,[a] Dale L. Preston,[b] John B. Cologne,[a] Ritsu Sakata,[a] Hiromi Sugiyama,[a] Naohiro Kato,[a] Eric J. Grant,[a] Elizabeth K. Cahoon,[c] Kiyohiko Mabuchi[c] and Kotaro Ozasa[a]

[a] *Radiation Effects Research Foundation, Hiroshima and Nagasaki, Japan;* [b] *Hirosoft International, Eureka, California; and* [c] *Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland*

Utada, M., Brenner, A. V., Preston, D. L., Cologne, J. B., Sakata, R., Sugiyama, H., Kato, N., Grant, E. J., Cahoon, E. K., Mabuchi, K. and Ozasa, K. Radiation Risk of Ovarian Cancer in Atomic Bomb Survivors: 1958–2009. *Radiat Res.* 195, 60–65 (2021).

There is limited evidence concerning the association between radiation exposure and ovarian cancer. We evaluated radiation risk of ovarian cancer between 1958 and 2009 among 62,534 female atomic bomb survivors in the Life Span Study cohort, adding 11 years of follow-up from the previously reported study. Poisson regression methods were used to estimate excess relative risk per Gy (ERR/Gy) for total ovarian cancer and according to tumor type. We assessed the modifying effect of follow-up period and other factors on the radiation risk. We ascertained 288 first primary ovarian cancers including 77 type 1 epithelial cancers, 75 type 2 epithelial cancers, 66 epithelial cancers of undetermined type and 70 other cancers. Radiation dose was positively, although not significantly, associated with risk of total ovarian cancer [ERR/Gy = 0.30, 95% confidence interval (CI): –0.22 to 1.11]. There was a suggestion of heterogeneity in radiation effects ($P = 0.08$) for type 1 (ERR/Gy = –0.32, 95% CI: <–0.32 to 0.88) and type 2 cancers (ERR/Gy = 1.24, 95% CI: –0.08 to 4.16). There were no significant trends in the ERR with time since exposure or age at exposure. Further follow-up will help characterize more accurately the patterns of radiation risk for total ovarian cancer and its types.

INTRODUCTION

Ovarian cancer is a relatively rare gynecological malignancy, composed of several tumor types differing in histologic origin, pathogenesis, and risk factors (*1*). Ovarian cancer incidence rates in Japan are lower than those in Western countries, but rates of clear-cell and endometrioid types have rapidly increased in recent years (*2*). Worldwide, serous carcinoma is the dominant histological type of ovarian cancer but it occurs less frequently in Japan (28%) compared to the international average (45%) (*2*).

The most consistent associations with risk of ovarian cancer are age, family history of ovarian cancer and lower parity (*1*). Available evidence on the effects of ionizing radiation is inconclusive, as findings from a limited number of studies are inconsistent (*3*). Significantly elevated ovarian cancer risk was found in one published study of women who received radiation treatment for benign gynecological disorders (*4*), but not in other studies (*5–7*). Increased ovarian cancer rates have not been seen among women treated with radiation for cervical cancer (*8, 9*), or in studies of radiation workers (*10–13*). In the Life Span Study (LSS) cohort of atomic bomb survivors, significantly increased risk of ovarian cancer has previously been observed in both incidence and mortality studies (*14, 15*).

As part of the new LSS solid cancer incidence studies (*16*), we evaluated radiation risk of ovarian cancer, adding 11 years of observation since the previously reported work (*14*) using revised dose estimates and incorporating information on lifestyle and reproductive factors. We also evaluated radiation risks according to type of ovarian cancer linked to different morphological and clinical features (*17, 18*).

MATERIALS AND METHODS

Ethical Considerations

This study was approved by the Institutional Review Board of the Radiation Effects Research Foundation. The Hiroshima and Nagasaki Prefectures approved the linkage between LSS cohort and data from the Cancer Registries.

Study Population

The LSS is a cohort of 120,321 atomic bomb survivors who were residents of Hiroshima and Nagasaki, including those who were not in either city of at the time of the bombings (NIC) (*16*). The subjects of this study were 62,534 women with estimated radiation doses who were alive and had not been diagnosed with any cancer as of January 1, 1958.

Editor's note. The online version of this article (DOI: https://doi.org/10.1667/RADE-20-00170.1) contains supplementary information that is available to all authorized users.

[1] Address for correspondence: Department of Epidemiology, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan; e-mail: utada@rerf.or.jp.

Follow-up, Case Ascertainment and Cancer Subtypes

Incident cancers were ascertained through linkage with the cancer registries in Hiroshima and Nagasaki. Incidence follow-up began on January 1, 1958 and ended on the earliest date of any cancer diagnosis, date of death, 110th birthday or December 31, 2009. Cancers diagnosed outside of cancer registry catchment areas were not treated as cases and the observed person-years (PY) of follow-up were adjusted for probability of migration (*16*).

Cases were first primary ovarian cancers, which were defined by the International Classification of Diseases, 10th revision code (ICD-10), as reported elsewhere (*14*). Borderline tumors classified as malignant by the International Classification of Disease for Oncology, second revision (ICD-O-2), between the late 1990s and early 2000s, though not by ICD-O-1 or ICD-O-3, were treated as cases. Two ovarian cancers diagnosed solely at autopsy (''autopsy only'') were excluded because of selection bias concerns (*16*).

Based on morphological and clinical characteristics (*17, 18*), we classified epithelial ovarian cancers into type 1 (including mucinous, clear cell, endometrioid, squamous, transitional cell or Brenner carcinomas) and type 2 (including serous and undifferentiated carcinomas) (see Supplementary Table S1; https://doi.org/10.1667/RADE-20-00170.1.S1). Since local cancer registries do not routinely collect information on tumor grade necessary for classifying endometrioid and serous carcinomas into type 1 and type 2 cancers, we followed the approach used by another cancer registry-based study (*19*) and classified all endometrioid carcinomas into type 1 and all serous carcinomas into type 2.

Radiation Dose and Other Covariates

Individual ovarian dose (Gy) was estimated using the Dosimetry System 2002 Revision 1 (DS02R1) (*20*). We used weighted absorbed ovarian dose defined as the sum of gamma dose and 10 times the neutron dose. Information on lifestyle and reproductive factors was obtained by several questionnaire surveys. In the analysis, we used information on reproductive factors (age at menarche, parity, number of full-term pregnancies and age at first pregnancy), body mass index (BMI) and smoking history. Detailed descriptions of these risk factors are given elsewhere (*16, 21*).

Statistical Analysis

To evaluate the effects of radiation on rates of ovarian cancer, we used Poisson regression methods to estimate excess relative risk per Gy (ERR/Gy) (*16*). The ERR model can be summarized as λ_0*[1 + ERR], where λ_0 is the background rate for unexposed (zero dose) individuals described as a function of city (*c*), birth year (*b*), attained age (*a*), an indicator of NIC status (*nic*), an indicator of whether the subjects were between 3,000 m to 10,000 m from the hypocenter at the time of bombings (*dis*), and other factors (*f*), e.g., reproductive factors (see Supplementary Information; https://doi.org/10.1667/RADE-20-00170.1.S1).

The ERR was modeled as $\rho(d)$*$\varepsilon(a, e, t)$, where $\rho(d)$ describes the shape of the dose response and $\varepsilon(.)$ describes effect modification. We considered several forms of the dose-response function, including linear (βd), linear-quadratic ($\beta d + \gamma d^2$) and categorical functions of dose. Departure from linearity was assessed by testing $\gamma = 0$. Effect modification by attained age (*a*), age at exposure (*e*) or time since exposure (*t*) was modeled using a log-linear function and each factor was tested individually. The ERRs by categories of these factors were also computed to examine non-monotonic effect modification patterns. We also evaluated radiation effects by cancer type. Heterogeneity in radiation effects on type 1 and type 2 cancers was tested using a joint analysis comparable to the analysis of competing risks (*22*). In the above test, we assumed asymptotic normality of the estimators. However, estimation of the ERR was on the boundary. To avoid the asymptotic normality assumption, we also employed a permutation test based on the same model as in the joint analysis (*23*).

To compare the radiation risk estimates for ovarian cancer with those reported in the previously published study, including cases diagnosed at ''autopsy only'' with a follow-up through 1998 (*14*), we estimated ERR/Gy using the current data with a follow-up restricted through 1998.

Maximum-likelihood parameter estimates and 95% (or 90% where indicated) profile-likelihood confidence intervals (CIs) were computed using the AMFIT program of Epicure version 2.00.02 (*24*) and the permutation test was conducted using R version 3.5.3 (*25*). Statistical tests were two-sided and considered significant when $P < 0.05$, unless stated otherwise.

RESULTS

We ascertained 288 first primary ovarian cancers for the follow-up period between 1958 and 2009. Histological confirmation was available for 236 cases (82%). The 21 cases (7%) were ascertained based on death certificate only (DCO). Overall, ovarian carcinomas made up two thirds of the cases (218 cases, 76%), 17 cancers (6%) were of non-epithelial or mixed origin and 53 (18%) had ''not otherwise specified'' (NOS) morphology (Supplementary Table S1; https://doi.org/10.1667/RADE-20-00170.1.S1). Of the 218 ovarian carcinomas, 77 cases (35%) were classified as type 1, 75 cases (34%) were classified as type 2 and 66 cases (30%) could not be classified due to limited information (other epithelial cancers). More than one half of type 1 cancers were mucinous carcinomas (43 cases, 56%) while 17 clear cell, 11 endometrioid and 6 squamous/transitional/Brenner carcinomas comprised 22%, 14% and 8%, respectively. The majority of type 2 cancers were serous carcinomas (70 cases, 93%) and all the remaining cases were undifferentiated epithelial carcinomas (five cases, 7%). There were six cases of borderline malignancies, including four type 1 and two type 2 cancers which were registered as malignancy only in the ICD-O-2.

The crude incidence rate (per 10,000 PY) was 1.5 for total ovarian cancers combined and 0.4 for both type 1 and type 2 cancers (Table 1 and Supplementary Table S2 for other cancers; see Supplementary Fig. S1 for fitted age-specific rates by birth cohort; https://doi.org/10.1667/RADE-20-00170.1.S1). The rates of total ovarian cancer did not apparently differ between Hiroshima and Nagasaki and increased monotonically with attained age. Crude rates for type 1 and type 2 cancers also increased with attained age, peaking around ages 60–69 and 70–79 years, respectively. The rates of total ovarian cancer increased with increasing age at exposure, i.e., older birth cohorts. The rate of total ovarian cancer was high in women who received ovarian dose of 1 Gy or higher, but there was little increase at lower doses. No increase in rate with dose was observed for type 1 cancers, but the rate appeared to increase with dose for type 2 cancers.

In the analyses including lifestyle and reproductive factors, none of the factors were significantly associated with background rate of total ovarian cancer or its type.

TABLE 1
Incidence Rate of Total Ovarian Cancer and Subtypes in the LSS Cohort, 1958–2009

			Total ovary		Type 1		Type 2	
	Subjects	Person-year	Case	Rate[a]	Case	Rate[a]	Case	Rate[a]
City								
Hiroshima	43,903	1,385,640	200	1.4	47	0.3	58	0.4
Nagasaki	18,631	551,734	88	1.6	30	0.5	17	0.3
Attained age (years)								
0–19	9,540	31,693	0	0.0	0	0.0	0	0.0
20–39	23,325	321,626	8	0.2	3	0.1	2	0.1
40–49	10,371	298,891	30	1.0	9	0.3	7	0.2
50–59	9,841	385,393	63	1.6	18	0.5	18	0.5
60–69	6,030	413,009	76	1.8	25	0.6	20	0.5
70–79	2,775	313,288	65	2.1	14	0.4	21	0.7
80+	652	173,479	46	2.7	8	0.5	7	0.4
Age at exposure (years)								
0–9	11,495	418,691	40	1.0	18	0.4	11	0.3
10–19	12,704	482,769	68	1.4	17	0.4	19	0.4
20–29	10,950	416,643	49	1.2	13	0.3	17	0.4
30–39	10,614	333,271	69	2.1	14	0.4	18	0.5
40–49	9,157	199,778	45	2.3	7	0.4	8	0.4
50+	7,614	86,226	17	2.0	8	0.9	2	0.2
DS02R1 weighted absorbed ovary dose (Gy)								
NIC	14,751	473,774	69	1.5	18	0.4	21	0.4
<0.005	21,545	658,153	103	1.6	28	0.4	22	0.3
0.005–0.1	16,358	506,797	66	1.3	21	0.4	17	0.3
0.1–0.2	3,431	105,360	18	1.7	4	0.4	5	0.5
0.2–0.5	3,625	108,922	15	1.4	4	0.4	4	0.4
0.5–1	1,785	54,475	9	1.7	1	0.2	3	0.6
1+	1,039	29,897	8	2.7	1	0.3	3	1.0
Total	62,534	1,937,380	288	1.5	77	0.4	75	0.4

[a] Incidence rate per 10,000 person-years.

Abbreviation: DS02R1 = dosimetry system 2002 revision 1; NIC = not in the city of Hiroshima or Nagasaki at the time of the bombings; LSS = Life Span Study.

Therefore, these factors were not included in the final models.

The ERR/Gy for total ovarian cancers combined was not significantly different from zero (0.30, 95% CI: –0.22 to 1.11, Table 2). The ERR/Gy changed little when the six borderline malignancies were excluded (0.29, 95% CI: –0.22 to 1.10). The ERR/Gy for type 1 cancers was not increased (–0.32, 95% CI: <–0.32 to 0.88) whereas the ERR/Gy for type 2 cancers was elevated (1.24, 95% CI: –0.08 to 4.16). A test for heterogeneity of the ERR/Gy estimates indicated borderline significance ($P = 0.08$). A similar result was obtained with the permutation test ($P = 0.096$). There was no indication of a quadratic departure from linearity for total ovarian cancer or either cancer subtype (all P values > 0.7).

We found no significant modification of the ERR for total ovarian cancer by age at exposure, attained age or time since exposure (Table 3). However, some patterns were noteworthy. The ERR/Gy appeared to be higher in women exposed before age 10 and between age 10 and 19 years compared to women exposed after age 20. There was no clear trend in the ERR with attained age. The radiation risk appeared to be higher during the early follow-up period (1958–1985) than in the later period (1986–2009). The effect modification patterns for type 2 cancers by age at exposure, attained age or time since exposure were similar to those for total ovarian cancer. The results for type 1 cancers were not shown because of its low ERR/Gy.

The ERR/Gy for other epithelial cancers was close to zero (0.05, 95% CI: <–0.27 to 1.76, Supplementary Table S3).

TABLE 2
Excess Relative Risk per Gy (ERR/Gy) for Total Ovarian Cancer and Subtypes

			95% CI			
	Cases	ERR/Gy	Lower	Upper	*P* for ERR	*P* for heterogeneity
Ovary	288	0.30	–0.22	1.11	0.31	-
Type 1	77	–0.32	<–0.32	0.88	0.38	0.08
Type 2	75	1.24	–0.08	4.16	0.08	

Notes. Type 1 includes mucinous, clear cell, endometrioid, squamous cell, transitional cell and Brenner carcinomas. Type 2 includes serous and undifferentiated carcinomas. CI = confidence interval.

TABLE 3
Excess Relative Risk per Gy (ERR/Gy) of Total Ovarian Cancers and Type 2 Cancers According to Age at Exposure, Attained Age and Follow-up Period

	Total ovary				Type 2			
			95% CI				95% CI	
	Case	Estimate	Lower	Upper	Case	Estimate	Lower	Upper
Age at exposure (years)								
0–9	40	0.56	<–0.27	3.25	11	1.18	<0	11.35
10–19	68	0.82	–0.18	2.65	19	2.42	0.03	8.35
20+	180	–0.02	<–0.34	0.91	45	0.28	<–0.26	3.30
P heterogeneity[a]		0.471				0.494		
P trend[b]		0.723				0.283		
Attained age (years)								
0–54	67	0.51	<–0.26	2.30	18	3.68	0.08	13.33
55–74	140	0.15	<–0.22	1.13	38	0.48	<–0.25	3.19
75+	81	0.55	<–0.30	2.88	19	1.00	<0	10.19
P heterogeneity[a]		0.831				0.386		
P trend[b]		0.317				0.082		
Follow-up period								
1958–1985	163	0.55	–0.20	1.78	41	3.02	0.35	8.98
1986–2009	125	0.04	<–0.30	1.10	34	0.01	<–0.17	2.40
P heterogeneity[a]		0.409				0.072		
P trend[b]		0.498				0.564		

Notes. Each modifier was tested individually. CI = confidence interval.
[a] *P* value for heterogeneity in ERRs by categories of age at exposure, attained age, or follow-up period
[b] *P* value of log-linear age at exposure, attained age or time since exposure.

We did not perform dose-response analysis for cancers of non-epithelial or mixed origin because no cases were exposed to more than 0.2 Gy (Supplementary Table S2; https://doi.org/10.1667/RADE-20-00170.1.S1).

The ERR/Gy for cancers with NOS morphology appeared to be elevated (1.75, 95% CI: –0.07 to 5.85, Supplementary Table S3). This group included 21 DCO cases (40%) and 32 non-DCO cases (60%) that were ascertained on the basis of histological, cytological, radiological or clinical information without further specification. The ERR/Gy for DCO cases was 2.58 (95% CI: <0 to 14.93), while the ERR/Gy for non-DCO cases was 1.32 (95% CI: <0 to 6.40).

To evaluate the influence of case definition in the current study (i.e., exclusion of two ''autopsy only'' cases) compared with the previously reported study (*14*), we estimated the ERR/Gy for total ovarian cancer restricting follow-up to 1958–1998. The ERR/Gy (0.55, 90% CI: –0.02 to 1.38) was similar to that reported previously (0.61, 90% CI: 0.00 to 1.5) (*14*), and higher than that for the current follow-up results (ERR/Gy = 0.30).

DISCUSSION

In the current study of ovarian cancer incidence among atomic bomb survivors, extending previous follow-up by 11 years, radiation dose appeared to be positively, although not significantly, associated with risk of total ovarian cancer and there was a suggestion of heterogeneity in the radiation effects for type 1 and type 2 cancers.

A significant positive association between radiation dose and incidence of ovarian cancer in the LSS was seen in previously published analyses (*14, 26*). The first cancer incidence study reported the ERR/Sv of 1.0 (95% CI: 0.12 to 2.34) for the 1958–1987 period (*26*); subsequently the ERR/Gy was reported as 0.61 (90% CI: 0.00 to 1.5) for the period of 1958–1998 (*14*). With the current follow-up through 2009, the ERR/Gy decreased to 0.30 (95% CI: –0.22 to 1.11). Sensitivity analyses under the same conditions as reported by Preston *et al*. (*14*) suggested that the difference between current and previously reported risk estimates was not due to different case definitions, but mainly due to the extended follow-up period.

As the LSS includes women exposed to radiation at all ages, opportunity exists to evaluate variation in radiation risk by age at exposure. The previously reported pathology-based study, with follow-up from 1950 through 1980, showed a significantly decreasing trend in relative risk (exposed to 100 rad or more versus unexposed) of ovarian cancer with increasing age at exposure, with the highest risk estimated for women exposed before age 20 (*27*). In the current study, radiation dose appeared to be positively associated with risk of total ovarian cancer among women exposed before age 10 and between age 10 and 19, but the age-at-exposure trend was not significant. High radiation risks of breast cancer and uterine corpus cancer among the LSS women exposed at ages near menarche were recently reported, suggesting increased sensitivity to radiation during a period of increased tissue proliferation (*21, 28*). However, the age-at-exposure pattern for ovarian cancer remains unclear with the current data.

Evidence concerning radiation effects on ovarian cancer risk is inconsistent. Elevated risk of mortality from ovarian

cancer was reported in women after radiotherapy for benign gynecologic disorders (ERR/Gy = 0.31, 95% CI: 0.12 to 0.68) (*4*). In that study, patients received high radiation doses (median 3.1 Gy) and were mostly adults at time of treatment (average 46 years). However, other published studies of patients who received high-dose radiotherapy indicated no elevated risks of ovarian cancer (*5–8*). Furthermore, among radiation workers exposed to low doses at low dose rates, no significant associations with ovarian cancer risk were found (*10–13*). The risk estimates for ovarian cancer mortality, while positive, were not significant in either the International Nuclear Workers Study (INWORKS) (*13*) or the UK National Registry for Radiation Workers (NRRW) cohort (*10*).

Ovarian cancer is a mixture of various histological types (*1*). Type 1 cancers (mostly mucinous, clear cell and endometrioid) arise in a stepwise manner from precursors, showing genetic stability and indolent behavior, whereas type 2 cancers (predominately serous) develop *de novo*, exhibiting chromosomal instability and aggressive clinical behavior (*17, 18*). Heterogeneity of the associations with established risk factors for type 1 and type 2 cancers reported in recent epidemiological studies support different etiologic origins (*17*). In our study, the radiation risk estimates for type 1 and type 2 cancers indicated borderline heterogeneity; the association between radiation dose and risk for type 2 but not for type 1 cancers appeared to be positive. Previous LSS studies based on histological review with shorter follow-up and smaller number of cases did not clearly show differential radiation risks by ovarian cancer type (*27, 29*).

The suggestion of heterogeneity in radiation effects for type 1 and type 2 cancers must be interpreted cautiously as an ovarian cancer type could not be assigned for 66 epithelial cancers and 53 cases with NOS morphology from a total of 288 cases. The distribution of dose among type 1 and type 2 cancers combined, and among cases with unassigned histological type, was comparable (see Supplementary Table S4 https://doi.org/10.1667/RADE-20-00170.1.S1); however, it is unknown whether the ratio of type 1 and type 2 cancers among cases with assigned and unassigned type was comparable as well. Because type 2 cancers tend to be diagnosed at an advanced stage due to their aggressive behavior (*17*), therapeutic surgery which also enables histological verification may not be chosen if risk of surgery outweighs survival benefit. Thus, the proportion of type 2 cancers among cases with NOS morphology is thought to be high. In addition, metastatic cancer from other sites may be included in the category of ovarian cancer NOS, especially among DCO cases. However, because the ERR/Gy was increased for both DCO cases and non-DCO cases ascertained on the basis of clinical information without further specification, metastatic cancers cannot fully explain the elevated ERR/Gy for all cases with NOS morphology. No association between radiation dose and incidence of epithelial cancers without detailed histological information was observed. As the proportion of such cases decreased over time (34% prior to 1970 and 16% after 1990), likely reflecting the growing importance of detailed histological diagnosis in clinical practice, further follow-up should help clarifying the difference in radiation effects on type 1 and type 2 cancers.

The strengths of our study include a large, well-defined cohort with long follow-up, improved radiation dose estimates, and ascertainment of cancers from population-based cancer registries. Weaknesses, in addition to the incomplete histological information for a sizable fraction of ovarian cancers as discussed above, include the limited number of radiation-related excess cases, reducing the power for assessing effect modification. Moreover, we could not correct person-years at risk for the effect of oophorectomy because such information was unavailable and could not be estimated for most women. In the LSS, the fraction of women who reported a history of any ovarian surgery was 4.2% among approximately 20,000 respondents to the 1969 mail questionnaire. This is broadly comparable to the fraction of women with a self-reported history of unilateral oophorectomy in the Japan Nurses' Health Study (3.4%) (*30*). As there was no clear trend in the proportion of LSS women reporting ovarian surgery with radiation dose, the most likely consequence of unaccounted oophorectomy might be a slight overestimation of person-years at risk and underestimation of the ERR/Gy due to non-differential misclassification.

In conclusion, the atomic bomb radiation appeared to be positively associated with risk of type 2 ovarian cancer but not type 1 ovarian cancer. The current risk estimate for total ovarian cancer that was somewhat lower than in the previously reported study indicated a decreasing trend over time. Further follow-up of atomic bomb survivors is needed to more accurately characterize the patterns of radiation risk by time since exposure, age and type of ovarian cancer.

SUPPLEMENTARY INFORMATION

Background model.

Table S1. Classification of ovarian cancer into histological groups.

Table S2. Incidence rate of subtypes other than type 1 or 2 in the LSS cohort, 1958–2009.

Table S3. Excess relative risk per Gy (ERR/Gy) for other subtypes of ovarian cancer.

Table S4. Distribution of assigned and unassigned histological types by radiation dose (Gy).

Fig. S1. Background incidence rates for total ovarian cancer, type 1 and type 2 cancers by attained age and year of birth. The dotted line is fitted background incidence rate among women born prior to 1915, the dashed line is that among women born between 1915 and 1929, and the solid line is that among women born after 1930. Panel A: Total ovarian cancer. Panel B: Type 1 cancers. Panel C: Type 2 cancers.

ACKNOWLEDGMENTS

The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan, is a public-interest incorporated foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE). This research was also funded in part through DOE award no. DE–HS0000031 to the National Academy of Sciences and contract no. HHSN261201400009C from the U.S. National Cancer Institute (NCI), with additional support from the Division of Cancer Epidemiology and Genetics in the NCI Intramural Research Program. This publication was supported by RERF Research Protocol 1–75 and 18–61. The views of the authors do not necessarily reflect those of the two governments. We thank the LSS cohort members for their longstanding cooperation. We also gratefully acknowledge the support of the Hiroshima and Nagasaki cancer registries. We are grateful to Dr. Munechika Misumi for helpful statistical advice.

Received: July 8, 2020; accepted: September 18, 2020; published online: November 12, 2020

REFERENCES

1. Tworoger SS, Shafrir AL, Hankinson SE. Ovarian cancer. In: Thun MJ, Linet MS, Cerhan JR, Haiman C, Schottenfeld D, editors. Cancer epidemiology and prevention. New York: Oxford University Press; 2018. p. 889–907.
2. Coburn SB, Bray F, Sherman ME, Trabert B. International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. Int J Cancer 2017; 140:2451–60.
3. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Effects of ionizing radiation. UNSCEAR 2006 Report to the General Assembly, with Scientific Annexes. New York: United Nations; 2008.
4. Sakata R, Kleinerman RA, Mabuchi K, Stovall M, Smith SA, Weathers R, et al. Cancer mortality following radiotherapy for benign gynecologic disorders. Radiat Res 2012; 178:266–79.
5. Darby SC, Reeves G, Key T, Doll R, Stovall M. Mortality in a cohort of women given X-ray therapy for metropathia haemorrhagica. Int J Cancer 1994; 56:793–801.
6. Ryberg M, Lundell M, Nilsson B, Pettersson F. Malignant disease after radiation treatment of benign gynaecological disorders. A study of a cohort of metropathia patients. Acta Oncol 1990; 29:563–7.
7. Ron E, Auvinen A, Alfandary E, Stovall M, Modan B, Werner A. Cancer risk following radiotherapy for infertility or menstrual disorders. Int J Cancer 1999; 82:795–8.
8. Boice JD, Jr., Engholm G, Kleinerman RA, Blettner M, Stovall M, Lisco H, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat Res 1988; 116:3–55.
9. Kleinerman RA, Boice JD, Jr., Storm HH, Sparen P, Andersen A, Pukkala E, et al. Second primary cancer after treatment for cervical cancer. An international cancer registries study. Cancer 1995; 76:442–52.
10. Muirhead CR, Goodill AA, Haylock RG, Vokes J, Little MP, Jackson DA, et al. Occupational radiation exposure and mortality: second analysis of the National Registry for Radiation Workers. J Radiol Prot 1999; 19:3–26.
11. Cardis E, Gilbert ES, Carpenter L, Howe G, Kato I, Armstrong BK, et al. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. Radiat Res 1995; 142:117–32.
12. Atkinson WD, Law DV, Bromley KJ, Inskip HM. Mortality of employees of the United Kingdom Atomic Energy Authority, 1946–97. Occup Environ Med 2004; 61:577–85.
13. Richardson DB, Cardis E, Daniels RD, Gillies M, Haylock R, Leuraud K, et al. Site-specific Solid Cancer Mortality After Exposure to Ionizing Radiation: A Cohort Study of Workers (INWORKS). Epidemiology 2018; 29:31–40.
14. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat Res 2007; 168:1–64.
15. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950–2003: an overview of cancer and noncancer diseases. Radiat Res 2012; 177:229–43.
16. Grant EJ, Brenner A, Sugiyama H, Sakata R, Sadakane A, Utada M, et al. Solid Cancer Incidence among the Life Span Study of Atomic Bomb Survivors: 1958–2009. Radiat Res 2017; 187:513–37.
17. Kurman RJ, Shih I-M. The dualistic model of ovarian carcinogenesis: Revisited, revised, and expanded. Am J Pathol 2016; 186:733–47.
18. Shih Ie M, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol 2004; 164:1511–8.
19. Matz M, Coleman MP, Sant M, Chirlaque MD, Visser O, Gore M, et al. The histology of ovarian cancer: worldwide distribution and implications for international survival comparisons (CONCORD-2). Gynecol Oncol 2017; 144:405–13. Erratum-ibid 2017; 147:726.
20. Cullings HM, Grant EJ, Egbert SD, Watanabe T, Oda T, Nakamura F, et al. DS02R1: Improvements to atomic bomb survivors' input data and implementation of Dosimetry System 2002 (DS02) and resulting changes in estimated doses. Health Phys 2017; 112:56–97.
21. Brenner AV, Preston DL, Sakata R, Sugiyama H, de Gonzalez AB, French B, et al. Incidence of breast cancer in the Life Span Study of atomic bomb survivors: 1958–2009. Radiat Res 2018; 190:433–44.
22. Pierce DA, Preston DL. Joint analysis of site-specific cancer risks for the atomic bomb survivors. Radiat Res 1993; 134:134–42.
23. LaFleur BJ, Greevy RA. Introduction to permutation and resampling-based hypothesis tests. J Clin Child Adolesc Psychol 2009; 38:286–94.
24. Preston D, Lubin J, Pierce DA, McConney M. Epicure users guide. Seattle, Washington: Hirosoft International Corporation; 1993.
25. R Core Team. R: A language and environment for statistical computing. Vienna: Foundation for Statistical Computing; 2019.
26. Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, et al. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. Radiat Res 1994; 137:S17–67.
27. Tokuoka S, Kawai K, Shimizu Y, Inai K, Ohe K, Fujikura T, et al. Malignant and benign ovarian neoplasms among atomic bomb survivors, Hiroshima and Nagasaki, 1950–80. J Natl Cancer Inst 1987; 79:47–57.
28. Utada M, Brenner AV, Preston DL, Cologne JB, Sakata R, Sugiyama H, et al. Radiation risks of uterine cancer in atomic bomb survivors: 1958–2009. JNCI Cancer Spectrum 2018; 2:pky081.
29. Inai K, Shimizu Y, Kawai K, Tokunaga M, Soda M, Mabuchi K, et al. A pathology study of malignant and benign ovarian tumors among atomic-bomb survivors–case series report. J Radiat Res 2006; 47:49–59.
30. Yasui T, Hayashi K, Mizunuma H, Kubota T, Aso T, Matsumura Y, et al. Factors associated with premature ovarian failure, early menopause and earlier onset of menopause in Japanese women. Maturitas 2012; 72:249–55.