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ARTICLE

Radiation Risks of Uterine Cancer in Atomic Bomb Survivors: 1958–2009

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Abstract

Background: Ionizing radiation is known to be capable of causing cancer of many organs, but its relationship with uterine cancer has not been well characterized.
Methods: We studied incidence of uterine cancer during 1958–2009 among 62 534 female atomic bomb survivors. Using Poisson regression analysis, we fitted excess relative risk (ERR) models to uterine cancer rates adjusted for several lifestyle and reproductive factors. Person-years at risk were also adjusted for the probability of prior hysterectomy, because it could affect the subsequent risk of uterine cancer. We assessed the modifying effect of age and other factors on the radiation risk. For analysis of the modifying effect of age at radiation exposure around menarche, we compared the radiation risk for several exposure-age categories as well as using parametric models.
Results: There were 224 uterine corpus cancers and 982 cervical cancers. We found a significant association between radiation dose and risk of corpus cancer (ERR per Gray [ERR/Gy] = 0.73, 95% confidence interval [CI] = 0.03 to 1.87) but not for cervical cancer (ERR/Gy = 0.00, 95% CI = −0.22 to 0.31). For corpus cancer, we found statistically significant heterogeneity in ERR/Gy by age ($P_{heterogeneity}$ = .001) with elevated risk for women exposed to radiation between ages 11 and 15 years (ERR/Gy = 4.10, 95% CI = 1.47 to 8.42) and no indication of a radiation effect for exposures before or after this exposure-age range.
Conclusions: The current data suggest that uterine corpus is especially sensitive to the carcinogenic effect of radiation exposure occurring during the mid-pubertal period preceding menarche. There is little evidence for a radiation effect on cervical cancer risk.

Uterine cancer is the most common gynecological malignancy among women, responsible for approximately 850 000 new cases worldwide each year (1), and involves two major types with differring etiology and pathology. Uterine corpus cancers have been increasing globally (2) whereas uterine cervical cancers have been decreasing in many developed countries (3). Similar patterns are seen in Japan, except for a recent rising trend for cervical cancers (4). Most corpus cancers are adenocarcinomas arising from the endometrial epithelium. Increased estrogen exposure is believed to play an important role in their pathogenesis (5). Cervical cancers are predominantly squamous cell carcinomas that develop from the squamocolumnar junction of the cervix and are primarily attributed to infection with high-risk strains of human papilloma virus (HPV) (6).

Ionizing radiation is an established carcinogen, and epidemiological characteristics of radiation-related cancer risk have been well characterized for many organs. However, the association between radiation and uterine cancer has been less well understood, largely due to the limited amount of informative data available to date (7). Although several studies of cervical cancer point to an absence of radiation effect (7–9), increased corpus cancer risk has been reported from several studies of

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high-dose radiotherapy patients (10–12) and one study of radiation workers (13).

Although previous studies of cancer risk in the Life Span Study (LSS) of Japanese atomic bomb survivors have provided no indication of radiation effects on cervical cancer rates (9), there is suggestive evidence of a radiation-related increase in corpus cancer rates among women who were exposed to the bombs before age 20 years (9). The latter finding as a heightened radiation effect of exposure at young ages is consistent with changes occurring in the uterine endometrium during the period preceding menarche (14–16) and suggests that more detailed analysis of the risk following exposure around puberty may be warranted (17,18).

We report results from the latest analysis of uterine cancer incidence among Japanese atomic bomb survivors with a focus on age at exposure, especially around menarchal age, taking into consideration possible effects of lifestyle and reproductive risk factors.

Materials and Methods

Study Population

The LSS cohort and methods for cancer incidence ascertainment are described in detail elsewhere (17). Briefly, the LSS cohort includes 120 321 atomic bomb survivors who were registered residents of Hiroshima or Nagasaki, including 26 580 who were not present in either city at the times of the bombings (defined as beyond 10 km from the hypocenter) (see Supplementary Material, available online, for further details) (17). The cohort includes 62 534 women with estimated radiation doses who were alive and did not have a cancer diagnosis as of January 1, 1958. This study was reviewed and approved by the Institutional Review Board of the Radiation Effects Research Foundation. Linkage to data from the Hiroshima and Nagasaki cancer registries was approved by the relevant Hiroshima and Nagasaki Prefectural and Hiroshima City authorities.

Follow-up and Cancer Ascertainment

Incident cancers in the LSS cohort are ascertained through linkage with local cancer registries in Hiroshima and Nagasaki, which became operational in 1957 and 1958, respectively (see Supplementary Material, available online) (17). Incidence follow-up for these analyses began on January 1, 1958 and ended on the earliest of the date of any cancer diagnosis, date of death, 110th birthday, or December 31, 2009. Cancers diagnosed outside of the cancer registry catchment areas are incompletely ascertained and thus were not treated as cases and, as in (17), the observed person-years (PY) of follow-up were adjusted for probability of residence within the cancer registry areas using information from the Adult Health Study (AHS), a subset of the LSS cohort undergoing biennial clinical examinations (see Supplementary Material, available online) (17). Study outcomes included first primary cancers of the uterine corpus and cervix, excluding in situ cases, which were not treated as cases. Uterine cancer was defined by the International Classification of Diseases, 10th revision topography codes: C53 for cervical cancer, C54 for corpus cancer, and C55 for uterine cancer not otherwise specified (NOS). As in earlier analyses (9), cervical and NOS cancers were combined in the analysis because it was common practice for Japanese physicians to report cervical cancers as “uterine cancers.” We excluded sarcomas (20 corpus and 25 cervical) because of the different cell type and cancers diagnosed only at autopsy (1 corpus and 7 cervical) (17).

Radiation Dose and Covariates

Individual uterine doses (DS02R1) were estimated on the basis of detailed dose reconstruction (18). We used weighted absorbed uterine dose defined as the sum of gamma dose and 10 times the neutron dose. Information on lifestyle and reproductive factors was obtained from mail surveys conducted in the LSS cohort in 1969, 1978, and 1991, and from AHS clinical questionnaires administered in 1963, 1965, and 1968. In the analysis, we used information on reproductive factors (age at menarche, parity, number of full-term pregnancies, age at first pregnancy, age at menopause, and whether menopause was natural or artificial), body mass index (BMI), and smoking history. Age at menarche was known for 47% and menopausal status for 50% of the cohort members. Details about the handling of other factors are presented in (17,19).

Statistical Analysis

To evaluate the association between radiation dose and uterine cancer, we used Poisson regression to estimate excess relative risks (ERR) as in (17). The ERR model may be summarized as λ_0*[1+ ERR], where λ_0 is the background rate for unexposed (zero dose) individuals. The background rate is typically assumed to be a function of city, birth year, attained age, and location at the time of the bombings (distal [≥3 km but <10 km]) to avoid a potential confounding by geographical variation (20,21). We call this model “conventional background.” We also considered an “extended background” rate model that included effects of reproductive factors, BMI, and smoking (see Supplementary Material, available online). The ERR was modeled as $\rho(d)$*$\varepsilon(a, e, f)$, where $\rho(d)$ describes the shape of the dose-response and $\varepsilon(.)$ describes effect modification as a log-linear function of attained age (a), age at exposure (e), and other factors (f) (eg, reproductive factors). We considered several forms of dose-response function: linear (βd), linear-quadratic (βd + γd^2), and categorical. Departure from linearity was assessed by testing $\gamma = 0$.

To examine modification of radiation risk of corpus cancer by exposure period around puberty, we used age-at-exposure windows denoting pre-, peri-, and postpuberty periods, with the peri-puberty window width set to 5 years. We considered six sets of such windows with peri-puberty intervals centered at ages from 10 to 15 years (median age at menarche = 15 years; see Supplementary Figure 1, available online). We also examined effect modification using a quadratic spline function in age at exposure with a knot at age 15 years (see Supplementary Material, available online).

Because removal of the uterus precludes the future occurrence of uterine cancer, standard analytic methods ignoring the hysterectomy may underestimate the risk of uterine cancer and could bias the radiation risk estimates if hysterectomy is radiation dose related. Not having individual data on hysterectomy, we used self-reported artificial menopause, reported by 10% of the responders, as a surrogate. We adjusted for observed PY, assuming that 80% of women reporting artificial menopause had their corpus removed (22) including 50% who underwent total hysterectomy (both corpus and cervix removed) and 30% who underwent supra-cervical hysterectomy (corpus removed while cervix preserved) (see Supplementary Material, available online).

Analyses were carried out both with and without PY adjustment for probability of hysterectomy. We present the hysterectomy-adjusted rates and risk estimates in the main tables.

Maximum likelihood parameter estimates and 95% Wald or profile-likelihood confidence intervals (CIs) were computed with the AMFIT program of Epicure (version 2.00.02) (23). All statistical tests were two-sided and considered statistically significant when P was less than .05.

Results

There were 1206 first primary uterine cancers including 224 corpus cancers and 982 cervical cancers (including 97 cases of uterine cancer, NOS). Histological verification was obtained for 96% of the corpus cancers and 96% of the cervical cancers excluding NOS; proportions of those diagnosed solely based on death certificates were 2% and 1%, respectively. Adenocarcinoma was the main histological type of corpus cancer (93%), and squamous cell carcinoma was the main type of cervical cancer excluding NOS (86%).

Baseline Rates, Lifestyle, and Reproductive Factors

The overall hysterectomy-adjusted rate for corpus cancer was 1.3 per 10 000 PY and that for cervical cancer was 5.4 per 10 000 PY (Table 1). These rates are, respectively, 8% and 6% higher than the corresponding unadjusted rates. Crude rates for both cancers were somewhat higher in Hiroshima than Nagasaki and increased with attained age up to 60–70 years. Corpus cancer rates increased with calendar year, whereas cervical cancer rates decreased. The rates for corpus cancer were highest among women exposed as teenagers, and for cervical cancer, among women exposed in their 40s. In relation to dose, the highest rate for corpus cancer was observed for women who received doses of 1–2 Gray (Gy) and for cervical cancer, doses 2 or more Gy, but there was little indication of a radiation effect at the lower doses for either cancer.

Fitted corpus cancer background rates increased with increasing year of birth and attained age up to around 70 years (see Supplementary Figure 2, available online). The fitted cervical cancer background rates decreased with increasing year of birth. The rates increased with attained age depending on year of birth, with the peak incidence age becoming younger in more recent birth years. In analyses with lifestyle and reproductive factors (see Supplementary Material and Supplementary Table 1, available online), fitted corpus cancer background rates increased with each year approaching menopause and high BMI and decreased with each additional pregnancy for parous women and each year past menopause. The fitted cervical cancer background rates were higher in ever-smokers than never-smokers, increased with each year approaching menopause, and decreased with older age at first pregnancy.

Radiation and Corpus Cancer

Based on a simple linear dose response model with conventional background and without effect modification, the estimated ERR was 0.67 per Gy ($P = .05$; Table 2). With adjustment for BMI, parity, number of full-term pregnancies, time to menopause, and time from menopause, the estimated ERR per Gy (ERR/Gy) increased slightly to 0.73 per Gy ($P = .04$). The fitted linear dose response with the extended background model is shown in Figure 1 and the dose category-specific ERRs in Supplementary Table 2 (available online). There was no indication of a statistically significant departure from linearity ($P = .08$), suggesting that statistical significance of the dose response was not caused by only the highest dose category with high ERR; otherwise, a liner-quadratic dose-response model should have fit better. ERR estimates unadjusted for probability of hysterectomy were somewhat lower: 0.51 per Gy (95% CI = −0.09 to 1.47, $P = .1$) with the conventional background model and 0.58 per Gy (95% CI = −0.05 to 1.60, $P = .08$) with the extended background model.

The ERR/Gy did not vary statistically significantly with attained age ($P = .3$). Although there was no statistically significant trend in the ERR with log-linear age at exposure ($P = .09$), there was statistically significant nonmonotonic heterogeneity in the ERRs across pre-, peri-, and postpuberty age-at-exposure groups. Under the age-at-exposure-window model with the smallest Akaike's Information Criteria, there was statistically significant ($P = .001$) heterogeneity in the risks for the three windows (see Supplementary Table 3, available online) and the risk was statistically significantly increased for the 11–15 peripuberty exposure group (ERR/Gy = 4.10, 95% CI = 1.47 to 8.42, $P < .001$), but not for the 0–10 prepuberty exposure group (ERR/Gy = −0.03, 95% CI = −1.45 to 1.38, $P = .9$) or 16+ postpuberty exposure group (ERR/Gy = −0.15, 95% CI = −0.86 to 0.56, $P = .7$). This heterogeneity was also well described by a model in which effect modification was characterized using a log quadratic spline function in age at exposure with a knot at age 15 years (Figure 2, see Supplementary Material, available online). Under this model, the largest ERR at 1 Gy was seen for exposures at age 12.5 years.

There was no indication of independent modification of the radiation risk by any of reproductive factor, BMI, or smoking (see Supplementary Table 4, available online).

Radiation and Cervical Cancer

There was no indication of a radiation effect for cervical cancer in either the conventional model (ERR/Gy = 0.08, $P = .6$, Table 2) or the extended background (ERR/Gy = 0.00, $P = .9$), both adjusted for probability of hysterectomy. The ERR/Gy changed little when the uterus NOS cases were excluded (ERR/Gy = 0.04, 95% CI = −0.20 to 0.37, $P = .8$). There was no evidence of radiation risk modification for cervical cancer by reproductive and lifestyle factors (see Supplementary Table 4, available online). Unadjusted for probability of hysterectomy, an ERR/Gy was 0.05 (95% CI = –0.19 to 0.38, $P = .7$) with the conventional background.

Discussion

Earlier analyses of cancer incidence from the LSS cohort of atomic bomb survivors provided no evidence of a radiation effect on overall rates of corpus cancer but suggested an effect among those exposed before age 20 years (9). The current study adds 11 years of follow-up through 2009, mainly among those exposed in childhood and adolescence. Approximately 55% of women with corpus cancer in the current study were exposed before age 20 years, providing us with increased precision in describing the radiation risks for this age group. Our findings indicate a marked, statistically significant radiation effect on uterine corpus cancer rates for exposure occurring in mid-puberty, but not for either early-childhood or adult exposures. For

Table 1. Incidence rate of uterine corpus and cervical cancer by selected characteristics of subjects in the LSS cohort, 1958–2009

			Corpus				Cervix			
					Hysterectomy-adjusted†				Hysterectomy-adjusted‡	
Characteristic	Women	PY	Cases	Rate*	PY	Rate*	Cases	Rate*	PY	Rate*
City										
Hiroshima	43 903	1 385 080	175	1.3	1 266 020	1.4	726	5.2	1 310 670	5.5
Nagasaki	18 631	551 325	49	0.9	503 510	1	256	4.6	521 441	4.9
Attained age, y										
0–39	32 865	352 174	6	0.2	349 609	0.2	76	2.2	350 571	2.2
40–49	10 371	298 927	13	0.4	282 518	0.5	165	5.5	288 672	5.7
50–59	9841	385 511	67	1.7	344 869	1.9	229	5.9	360 110	6.4
60–69	6030	413 022	76	1.8	363 648	2.1	237	5.7	382 163	6.2
70–79	2775	313 288	46	1.5	275 060	1.7	186	5.9	289 396	6.4
80+	652	173 479	16	0.9	153 831	1	89	5.1	161 199	5.5
DS02R1 weighted absorbed uterine dose, Gy										
NIC	14 751	473 547	54	1.1	433 269	1.2	253	5.3	448 373	5.6
<0.005	21 533	657 385	70	1.1	602 022	1.2	313	4.8	622 783	5
0.005–0.1	16 348	506 054	62	1.2	464 016	1.3	267	5.3	479 780	5.6
0.1–0.2	3450	105 645	11	1.0	96 885	1.1	53	5	100 170	5.3
0.2–0.5	3604	108 783	14	1.3	99 706	1.4	58	5.3	103 110	5.6
0.5–1	1789	54 427	5	0.9	47 561	1.1	23	4.2	50 136	4.6
1–2	837	24 342	8	3.3	21 415	3.7	9	3.7	22 513	4
2+	222	6 219	0	0	4661	0	6	9.6	5 245	11.4
Age at exposure, y										
0–9	11 495	417 942	49	1.2	391 726	1.3	69	1.7	401 557	1.7
10–19	12 704	482 541	74	1.5	435 200	1.7	169	3.5	452 953	3.7
20–29	10 950	416 643	50	1.2	376 629	1.3	225	5.4	391 634	5.7
30–39	10 614	333 271	30	0.9	306 058	1	229	6.9	316 263	7.2
40–49	9157	199 779	17	0.9	181 896	0.9	216	10.8	188 602	11.5
50+	7614	86 226	4	0.5	78 025	0.5	74	8.6	81 100	9.1
Year of diagnosis										
1958–1970	—	673 034	32	0.5	643 389	0.5	417	6.2	654 506	6.4
1971–1980	—	429 640	31	0.7	398 383	0.8	271	6.3	410 104	6.6
1981–1990	—	359 555	59	1.6	321 855	1.8	166	4.6	335 993	4.9
1991–2000	—	283 198	52	1.8	244 873	2.1	101	3.6	259 245	3.9
2001–2009	—	190 975	50	2.6	161 034	3.1	27	1.4	172 262	1.6
Total	62 534	1 936 400	224	1.2	1 769 530	1.3	982	5.1	1 832 110	5.4

*DS02R1= dosimetry system 2002 revision 1; NIC = not in Hiroshima or Nagasaki city at the time of the bombings; Gy = Gray; LSS = Life Span Study; PY = person-years. Incidence rate per 10 000 PY.

†Hysterectomy-adjusted PY at risk used for analysis of corpus cancer.

‡Hysterectomy-adjusted PY at risk used for analysis of cervical cancer.

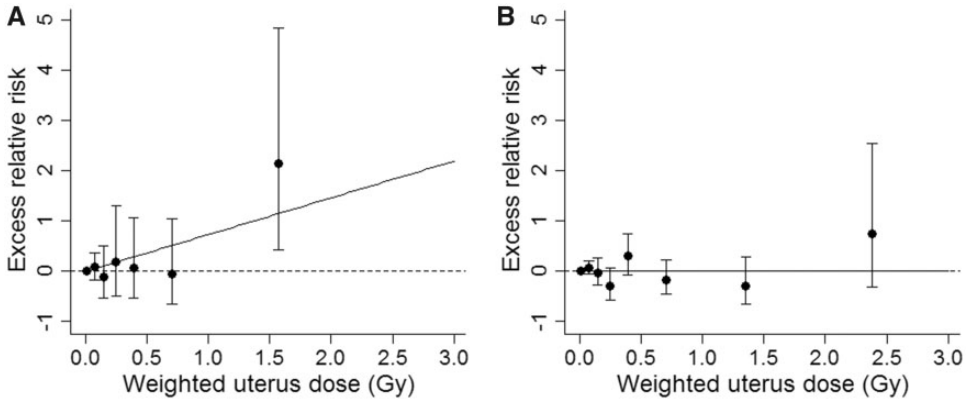

Figure 1. Excess relative risk (ERR) for uterine corpus and cervical cancer in relation to radiation dose. The solid line is fitted linear dose response from a model without effect modification. The black points (vertical lines) are categorical ERR estimates (95% confidence intervals). The categorical and parametric estimates are derived from a model with extended background and adjusted for probability of hysterectomy. **A**) Corpus cancer. **B**) Cervical cancer.

Table 2. Excess ERR/Gy of radiation for uterine corpus and cervical cancer adjusted for probablity of hysterectomy

Model	Corpus	Cervix
ERR/Gy using conventional background model* (95% CI)	0.67 (−0.01 to 1.75)	0.08 (−0.17 to 0.42)
ERR/Gy using extended background model† (95% CI)	0.73 (0.03 to 1.87)	0.00 (−0.22 to 0.31)

*CI = confidence interval; ERR/GY = excess relative risk per Gray. Includes city, birth year, attained age, and location at the time of the bombings. See Supplementary Material (available online), (3) background model.
†Includes lifestyle and reproductive factors as well as conventional factors. See Supplementary Table 1 (available online) for selected lifestyle and reproductive factors.

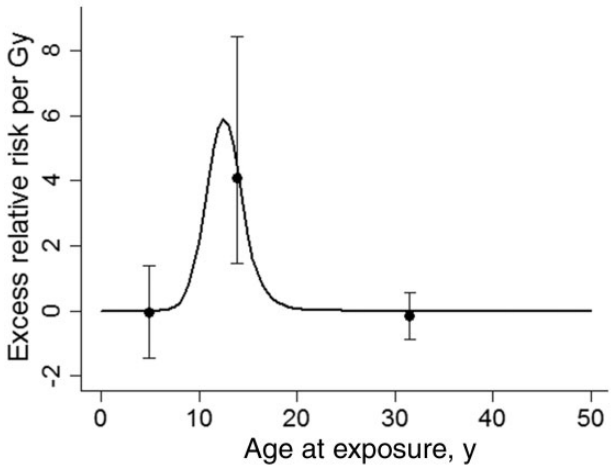

Figure 2. Excess relative risk per Gy (ERR/Gy) for uterine corpus cancer by age at exposure. The **black points** (vertical lines) are categorical ERR/Gy estimates (95% confidence intervals) from the best fitting age-at-exposure window model. The age ranges for three windows are from 0 to 10 years (person-years weighted mean = 4.9 years), 11 to 15 years (13.9 years), and 16 years or older (31.5 years). The **fitted solid curve** is based on a quadratic spline function with a knot at age 15 years (see Supplementary Material, available online). The categorical and parametric ERR/Gy estimates for different ages at exposure are derived from a model with extended background and adjusted for probability of hysterectomy.

uterine cervical cancer, as in previous LSS cancer incidence analysis (9), the present data provided no indication of a radiation effect.

An important methodological improvement in the present study is consideration of the effect of hysterectomy in assessing cancer risks. Previous studies in the AHS found that the frequency of uterine myoma increased with radiation dose, and a substantial proportion of women had undergone hysterectomy precluding subsequent occurrence of uterine cancer (24,25). Consequently, not considering hysterectomy would lead to underestimation of the uterine cancer risk; the effect would be greater for corpus than cervical cancer, because total hysterectomy involves the removal of the uterine corpus and the cervix, whereas subtotal hysterectomy does not involve the removal of the cervix. As expected, radiation risk estimates for corpus cancer corrected for probability of hysterectomy were somewhat higher than unadjusted estimates.

Epidemiological data on the radiation risk of uterine corpus cancer are limited, and previously published data have largely concerned radiation exposure at adult ages. Elevated risk was reported in patients treated with radiation for cervical cancer (10) and benign gynecological disorders (11,12); these patients were mostly adults (52 and 46 years [mean], respectively) at the time of treatment and received high therapeutic doses (165 [mean] and 34 [median] Gy, respectively). It seems unlikely that the observed increased risk is comparable with our result because the radiation dose was quite high and gynecologic conditions for which these patients were irradiated may have influenced the corpus cancer risk. Besides, no statistically significant dose response was found in either study. Increased mortality from corpus cancer was reported among UK radiation workers, who were exposed to low-dose radiation (mean cumulative dose = 18 mSv) as adults, but the result was based on only 10 deaths in radiation workers and there was no association with dose (13). The present finding on lack of dose-related increase in corpus cancer risk after adult exposure is consistent with the available data. To our knowledge, virtually no data on corpus cancer risk following exposures at young ages are available beyond the LSS (8).

In the absence of other informative epidemiological data, biological plausibility of the observed pattern of risk is an important consideration. Based on understanding of stem cell biology and its role in radiation carcinogenesis (26), one may hypothesize that exposure to radiation during a period of increased proliferation of endometrial tissue might be associated with increased risk of uterine corpus cancer. Morphological and clinical studies suggest that endometrial thickness and uterine volume increase dramatically during puberty prior to menarche (14–16). Our findings for the corpus cancer risk based on age-at-exposure window and quadratic-spline analyses suggest that mid-puberty (11–15 years) is the period of highest susceptibility to radiation. Interestingly, the highest radiation ERRs for breast cancer reported in the recent LSS analyses (19) were estimated for exposures at menarche (median age 15 years). So the window of heightened radio-susceptibility for endometrial epithelium suggested by the present data seems to coincide with increased size of the uterus indicating increased rates of cell proliferation, which occur on average 2–3 years earlier than the respective window for the breast (27). Further study is indicated for validating our findings in other irradiated populations.

As in earlier analyses of the LSS data (ERR/Gy = 0.06, 90% CI = –0.41 to 0.31) (9) and studies of other radiation-exposed populations (7), we found that cervical cancer risk was not associated with radiation exposure regardless of whether the uterus NOS cases (10%) were included or excluded from the analysis. Although factors related to differences in magnitude and pattern of radiation risks are not completely understood, the difference in radiation effect on uterine corpus and cervix may relate to histologic origin and developmental processes.

The strengths of our study include a large, well-defined cohort with long-term follow-up, application of improved individual dose estimates, ascertainment of incident cancers from population-based cancer registries, and a high rate of histological verification. We corrected PYs for the probability of hysterectomy using available information on artificial menopause as a surrogate. Adjustment for hysterectomy corrects, albeit only slightly, for underestimation of the previously reported uterus risk data, and thus the current data tend to strengthen the negative finding on cervical cancer. The primary limitation of our study concerns incomplete data on reproductive and lifestyle factors. Overall, such data were missing for approximately one-half of the women, with higher proportions among those born earlier (because they had to be alive at the time of the first mail survey in 1969). Missing data were treated as unknown in the analyses of background rate adjustment and modification of

radiation risk. However, previous analyses with this cohort have not shown a difference in radiation risk estimates between women with known and missing data (19). The questionnaire information was self-reported. However, reproductive information is considered to be reliable due to high reproducibility (28). We did not have information on HPV infection, the major risk factor for cervical cancer (6), but radiation risk is unlikely to be confounded by an association with prior HPV status because survivors were nonselectively (randomly, with regard to HPV status) exposed to atomic bomb radiation (17,29).

We found an increased risk of uterine corpus cancer with radiation from atomic bombs among women exposed in mid-puberty with no apparent radiation effect for exposures before or after this period. Such pattern is consistent with increased radio-susceptibility of endometrial epithelium during a period of increased cell proliferation. There was no evidence for radiation effect on risk of cervical cancer. Adjustment for hysterectomy is important in obtaining unbiased estimates of radiation risk for uterine cancer in exposed populations.

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Notes

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