Published in final edited form as:
Radiat Res. 2012 October ; 178(4): 266–279.

Cancer Mortality Following Radiotherapy for Benign Gynecologic Disorders

Ritsu Sakata[a,b], **Ruth A. Kleinerman**[a], **Kiyohiko Mabuchi**[a], **Marilyn Stovall**[c], **Susan A. Smith**[c], **Rita Weathers**[c], **Jean Wactawski-Wende**[d], **Diane L. Cookfair**[e], **John D. Boice Jr.**[f], and **Peter D. Inskip**[a]

[a]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland [b]Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Japan [c]Department of Radiation Physics, University of Texas M.D. Anderson Cancer Center, Houston, Texas [d]Department of Social and Preventive Medicine, University at Buffalo, State University of New York, Buffalo, New York [e]Department of Neurology, School of Medicine, University at Buffalo, State University of New York, Buffalo, New York [f]Department of Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee and International Epidemiology Institute, Rockville, Maryland

Abstract

The purpose of this study is to quantify cancer mortality in relationship to organ-specific radiation dose among women irradiated for benign gynecologic disorders. Included in this study are 12,955 women treated for benign gynecologic disorders at hospitals in the Northeastern U.S. between 1925 and 1965; 9,770 women treated by radiation and 3,186 women treated by other methods. The average age at treatment was 45.9 years (range, 13–88 years), and the average follow-up period was 30.1 years (maximum, 69.9 years). Radiation doses to organs and active bone marrow were reconstructed by medical physicists using original radiotherapy records. The highest doses were received by the uterine cervix (median, 120 Gy) and uterine corpus (median, 34 Gy), followed by the bladder, rectum and colon (median, 1.7–7.2 Gy), with other abdominal organs receiving median doses ≤1 Gy and organs in the chest and head receiving doses <0.1 Gy. Standardized mortality rate ratios relative to the general U.S. population were calculated. Radiation-related risks were estimated in internal analyses using Poisson regression models. Mortality was significantly elevated among irradiated women for cancers of the uterine corpus, ovary, bladder, rectum, colon and brain, as well as for leukemia (exclusive of chronic lymphocytic leukemia) but not for cancer of the cervix, Hodgkin or non-Hodgkin lymphoma, multiple myeloma, or chronic lymphocytic leukemia. Evidence of a dose-response was seen for cancers of the ovary [excess relative risk (ERR) 0.31/Gy, $P < 0.001$], bladder (ERR = 0.21/Gy, $P = 0.02$) and rectum (ERR = 0.23/Gy, $P = 0.05$) and suggested for colon (ERR = 0.09/Gy, $P = 0.10$), but not for cancers of the uterine corpus or brain nor for non-chronic lymphocytic leukemia. Relative risks of mortality due to cancers of the stomach, pancreas, liver and kidney were close to 1.0, with no evidence of dose-response over the range of 0–1.5 Gy. Breast cancer was not significantly associated with dose to the breast or ovary. Mortality due to cancers of heavily irradiated organs remained elevated up to 40 years after irradiation. Significantly elevated radiation-related risk was seen for cancers of organs proximal to the radiation source or fields (bladder, rectum and ovary), as well as for non-chronic lymphocytic

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

leukemia. Our results corroborate those from previous studies that suggest that cells of the uterine cervix and lymphopoietic system are relatively resistant to the carcinogenic effects of radiation. Studies of women irradiated for benign gynecologic disorders, together with studies of women treated with higher doses of radiation for uterine cancers, provide quantitative information on cancer risks associated with a broad range of pelvic radiation exposures.

INTRODUCTION

Radiation formerly was used to treat many benign conditions for which radiotherapy (RT) no longer is considered appropriate (1). Those conditions include benign gynecologic disorders (BGD) associated with dysfunctional uterine bleeding, also referred to as metropathia hemorrhagica (2–4). In the U.S., use of radiation to treat these disorders peaked in the 1930s and 1940s, and typical patients were in their mid-40s at the time of treatment (5, 6). The underlying cause for the abnormal bleeding in many cases was thought to be excessive secretion of estrogen relative to progesterone with associated anovulatory cycles, and radiation was administered to eliminate, suspend, or otherwise alter ovarian endocrine function (7–9). For women in their 40s, the intent often was to induce menopause. Both intracavitary radium and external-beam X rays were used. Radiation doses were lower than those associated with treatment for cervical or endometrial cancer (10–12), but still substantial, with doses to organs in the pelvic region in the tens or hundreds of Gy, and doses to abdominal organs in the tenths of Gy to upward of 1 Gy (3, 6). The availability of RT records allows for detailed organ-specific dose reconstruction for individual patients. Survival after the treatments was high, but most women now have died. Therefore, long-term studies of irradiated BGD patients can provide quantitative information concerning lifetime cancer risks after exposure to moderate to high-doses of radiation.

We conducted a large retrospective cohort study of cancer mortality among women treated for BGD in four states in the Northeastern U.S. (Massachusetts, Rhode Island, Connecticut and New York). A key feature of the study is that it included a subgroup of BGD patients who did not receive radiation, allowing for an internal comparison group. We previously reported on solid cancer mortality among women treated with radium in Massachusetts or Rhode Island (6), and leukemia, lymphoma and multiple myeloma mortality for the entire cohort (5). An earlier study of the women treated in Connecticut and Massachusetts focused on leukemia and uterine sarcoma (13). Here, we broaden the analysis to include all cancer mortality for the entire cohort with follow-up extended by 11 years, which substantially increased the number of solid cancer outcomes available for study.

METHODS

Study Subjects

Details concerning the study population have been described previously (5, 13). The cohort consisted of 12,955 women who were treated for BGD at any one of eight hospitals in Eastern Massachusetts, six in Connecticut, two in Rhode Island and one in Western New York between 1925 and 1965. The cohort is a composite of women first ascertained for study during the 1980s (5, 6) and previously studied women first ascertained prior to 1970 (13) or 1960 (8) for whom follow-up was extended in the present study. The study was approved by the institutional review boards at each hospital.

Ascertainment was conducted through searches of RT records, surgical logbooks and medical records at participating hospitals, as well as physician records. Women known to have had gynecologic cancer diagnosed prior to or at the time of treatment for BGD were excluded. Of the 12,955 women enrolled, 5,981 (46%) received brachytherapy with

intrauterine radium (^{226}Ra) capsules or needles, 1,947 (15%) were treated by external-beam X rays, 1,841 (14%) received both types of radiation treatment, and 3,186 (25%) were not irradiated for BGD. The 3,186 women who did not receive RT were all from the hospital in Western New York and were usually treated by dilatation and curettage, hysterectomy (with or without oophorectomy) or hormonal therapy. The histopathological diagnoses most commonly associated with the baseline visit for BGD were myoma (23%), hyperplasia or dysplasia of the endometrium (14%), chronic cervicitis (13%) and endometrial or cervical polyp (8%).

Radiation Dose Reconstruction

Procedures for estimating organ doses were described previously (5, 6) and resemble those used for a large international study of patients treated for cancer of the uterine cervix (10, 14, 15). Briefly, photocopies of RT reports describing radium implant procedures and external X-ray treatments were sent to medical physicists at the University of Texas M.D. Anderson Cancer Center in Houston. Physicists simulated representative radium and X-ray treatment configurations with anthropomorphic phantoms. Approximately 300 thermoluminescent dosimeters were positioned throughout the phantom for each irradiation to obtain the range of dose as well as the average dose to the organ. Organ doses for each woman were estimated based on the results of these simulations and treatment data. Average or typical configurations and placements of radium applicators were assumed, and filtration, typically with 1 mm platinum or 1 mm brass plus 0.5 mm silver, was taken into account. An average dose to the entire active (red) bone marrow was estimated as a weighted average of dose to each of 14 bone marrow compartments, using weights believed to correspond to the percentage of active marrow in each compartment (5, 16).

Radium treatments typically were administered over a period of 12 to 48 h. X-ray treatments usually were delivered in 2–4 fractions, ranging from 150–300 cGy per fraction. Doses from these fractions were summed. For 1,729 women known to have received RT for BGD more than once in the same year, estimated organ doses from these treatments were summed. Doses from RT for diseases other than BGD given after the RT for BGD, mainly for cancer, were not included because of incomplete RT information or knowledge of such treatments. There were 357 women known to have received subsequent RT for cancer (289 irradiated for BGD and 68 not irradiated for BGD).

Follow-Up and Cause of Death Coding

Vital status of women was determined as described previously (5) using the following information sources: state vital records, the National Death Index (NDI), the Social Security Administration Death Master File, municipal directories, driver license registries, credit bureaus, U.S. Postal Service address correction service, and Health Care Financing Administration files of past and present Medicare recipients. For 1,066 of the 4,324 women included in a previous study of irradiated women in Massachusetts or Connecticut (13), follow-up was closed on January 1, 1967, because personal identifiers were lost during a flood in a storage facility and no additional follow up was possible. This subgroup accounts for 8.2% of the study population included in the present analysis.

Ninety-two percent of the subjects were successfully traced: 72% were known to have been deceased and 20% were alive as of the end of follow-up (January 1, 1995 or January 1, 1967), leaving 8% lost to follow-up. Cause of death on death certificates was coded by trained nosologists according to the International Classification of Disease (ICD) revision in effect when the woman died and then was recoded to ICD-8 (17). Copies of death certificates or causes of death from NDI could not be obtained for 131 irradiated women

(2% of all deaths) and for 61 nonirradiated women (3.6%) with known dates (or years) of death. These women were included in the analysis as deceased due to unknown cause.

Analysis

For irradiated women, the entry date was the later of the dates of RT for BGD or the date of first BGD diagnosis at the participating hospital. For nonirradiated women, the date of BGD diagnosis at the participating hospital was used as the entry date. Person years (PY) were counted from the date of entry until the earliest of date of death, close of follow-up (January 1, 1995 or January 1, 1967), date of 90th birthday or date lost to follow-up. There were 2,222 women whose follow up time stopped when they reached their 90th birthday. Observed deaths from a particular cause and PY were tabulated in a cross-classification defined by race (white, non-white), attained age (5-year categories from 10–90), birth cohort (5-year categories beginning with 1849–1854), attained calendar year (5-year categories, from 1925–1995), estimated organ dose in 4 or 5 categories (different intervals were used for different organs) and modality of therapy (no radiation, brachytherapy only, external X-ray therapy only, both brachytherapy and external X ray). Women of unknown race were assumed to be white and those of other races to be non-white.

Standardized mortality rate ratios (SMRs) were calculated as the ratio of the number of observed deaths to the number of expected deaths. Numbers of expected deaths were computed by multiplying the age-, race-, and calendar year-specific U.S. population mortality rate for each stratum or cell in the cross-classification matrix by the observed number of PY. The 95% confidence intervals (CI) for SMRs were calculated assuming that the number of observed deaths was distributed as a Poisson random variable. For early years of follow-up, cause-specific U.S. mortality data were not available for certain disease categories. In that case, we extrapolated the earliest available age-, race-, cause-specific mortality rates to the preceding years. Categories of cause of death for which backward extrapolation of mortality rates was necessary and periods over which extrapolation occurred include: (1) 1925–1949: all solid cancers combined, cancers of the breast, all uterus, uterine cervix, uterine corpus, ovary, stomach, esophagus, thyroid, brain, non-Hodgkin lymphoma (NHL), multiple myeloma, lymphocytic leukemia, myeloid leukemia; and (2) 1925–1969: leukemia exclusive of chronic lymphocytic leukemia (non-CLL leukemia). We evaluated the sensitivity of findings to the extrapolations by repeating analyses with follow-up beginning in the year for which mortality rates for that category first became available. The estimated SMRs did not vary appreciably (data not shown). Internal analyses (see below) were not sensitive to this issue.

Poisson regression methods for rates (18) were used for estimation of radiation-related risk. The mortality rate (R) was assumed to be the product of a background hazard term and a relative risk term that was a function of modality of treatment (t). The mortality rate for nonirradiated women was taken to represent the background rate and depended on attained age (a) and calendar year (y). The general form of the model was as follows:

$$R(a, y, t) = R_0(a, y) \exp\{\beta_1 t\}.$$

The relative risks (RRs) associated with radiation treatment were calculated using nonirradiated women as the reference group. We estimated excess relative risk (ERR) per unit of radiation dose, Gy, (d) under the assumption of linear dose-response. The general form of the model was as follows:

$$R(a, y, d) = R_0(a, y)[1 + ERR(d)].$$

We also estimated excess absolute rates (EARs) per unit of radiation dose. The general form of the EAR model was:

$$R(a, y, d) = R_0(a, y) + EAR(d).$$

EARs were expressed per 100,000 PY per Gy.

Because numbers of cancer deaths were small for certain types of lymphopoietic and hematopoietic cancer, SMR (S) regressions were used. For type of treatment (t), models were of the form:

$$S(t) = S_o \exp\{\beta_1 t\}$$

where S_0 is the SMR for nonirradiated women. The general forms of the ERR model and the EAR model were as follows:

$$S(d) = S_0[1 + ERR(d)]$$

$$R(r, a, y, d) = U + EAR(d),$$

where U is the race-, age-, and calendar year-specific U.S. female population mortality rate.

Dose-response analyses for solid cancers were based on follow-up beginning 10 years after the entry date, and those for lymphopoietic and hematopoietic cancers based on follow-up starting 2 years after the entry date, because cancer deaths that occurred during earlier years were unlikely to have been caused by this RT. Parameter estimation was carried out using the Amfit program of the Epicure software package (19). RR estimates were not presented when the number of cases among nonirradiated women was three or fewer.

RESULTS

Demographic characteristics of the study population are shown in Table 1. The usual modality of RT differed according to the state where treatment for BGD occurred. Approximately half of the 1,959 subjects in Connecticut received external beam X-ray therapy, and almost all of the remaining half received brachytherapy. Most of the subjects from Massachusetts (2,365 women) or Rhode Island (2,118 women) received brachytherapy. Subjects from New York (6,513 women) were the largest group. Approximately half of them did not receive RT for BGD, and approximately half of the women who received any RT had both brachytherapy and external X rays. The nonirradiated subjects were all from the New York hospital and tended to enter the study in more recent years compared to the irradiated groups. The external X-ray treatment group had the youngest average age at entry, but ages were similar among groups (nonirradiated: 45.4 years; X rays: 43.8 years; brachytherapy: 46.5 years; both modalities: 47.2 years). Average years of observation also were similar among groups, ranging from 29 to 32 years, with a maximum of 69.9 years. More than 95% of women for whom information on race was available were white, and the proportion of white women did not differ appreciably by type of treatment.

Excessive or irregular bleeding was a presenting complaint among 92% of the irradiated women and 60% of the nonirradiated women for whom information about symptoms was

available. Information about symptoms was unavailable for the 1,086 women in the earlier study by Wagoner (13) for whom records had been destroyed. The reason for treatment for BGD among irradiated women involved an abnormality of the endometrium more often than among nonirradiated women: disorders of the uterine cervix or myometrium were relatively more common among nonirradiated women (data not shown). The mean body mass index (BMI) for irradiated women was significantly higher than that for nonirradiated women ($P < 0.001$, nonirradiated: 25.4 ± 5.5; irradiated: 26.5 ± 5.9).

Table 2 provides organ dose estimates by modality of RT. The uterine cervix and corpus were the most heavily irradiated organs, with median doses of 120 and 34 Gy, respectively. The extremely high doses received by the uterus, especially the uterine cervix, were primarily from brachytherapy. The bladder, rectum, ovary and colon also were heavily exposed, with median doses ranging between 1.7–7.2 Gy. Within the colon, doses were highest for the descending and ascending segments (data not shown). Doses decreased with increasing distance from the treatment site, more sharply for brachytherapy than for X rays. As a result, several organs at intermediate distance from the treatment site, such as the ovary, colon, liver, and stomach, received higher doses from X rays than from brachytherapy. The liver (including the biliary system), stomach, kidney, pancreas and active bone marrow received median doses between 0.1–1 Gy. Dose to different bone marrow compartments was extremely heterogeneous, with the highest doses to marrow in the pelvis, lumbar vertebrae and upper femurs (data not shown).

By the end of the follow-up, 9,353 (or 72.2%) of the subjects were known to have died, including 1,748 deaths from solid cancers. Among the cancer deaths, breast cancer was the most frequent cause of death (269 deaths), followed by colon cancer (254 deaths) and uterine corpus cancer (232 deaths).

As in the previous analysis (6) and in other studies of women treated for BGD (3, 4, 20), solid cancer sites of interest were grouped into those organs that were heavily irradiated (median dose >1 Gy), lightly irradiated (0.1–1 Gy) and very lightly irradiated (< 0.1 Gy) (Table 3). Among the nonirradiated women, SMRs for death due to all causes (SMR = 0.9) and all solid cancers (SMR = 0.8) were significantly low but, for most specific cancer sites, were not significantly different from 1.0. No cancer cause of death was significantly increased. Significant deficits were seen for cancer of the rectum (O = 4) and non-CLL leukemia (O = 3) based on small numbers of observed deaths. Cancers of the uterine cervix (SMR = 0.7) and uterine corpus (SMR = 0.7) occurred below population expectation but not significantly. Among the irradiated women, the SMR for all cause mortality (SMR = 0.9) was similar to that for nonirradiated women. However, mortality due to solid cancers was significantly increased. SMRs were significantly higher than 1.0 for cancers of the uterine corpus, bladder, ovary, brain and non-CLL leukemia. Deficits of borderline significance were seen for cancers of the liver, stomach, and breast.

Relative risks (RR) of mortality due to cancer based on internal analyses contrasting irradiated and nonirradiated women are also shown in Table 3. For all RT modalities combined, irradiated women had significantly increased RRs for cancers of most heavily irradiated organs. Sites with significantly elevated RRs included uterine corpus, bladder, rectum, ovary and colon. The RRs for cancers of the uterine cervix (1.2) and genital organs other than ovary (0.6) were not significantly different from 1.0. Relative risks for cancers of lightly or very lightly irradiated organs generally were close to unity and not significantly elevated. Regarding lymphopoietic and hematopoietic cancers, the irradiated women showed a significantly increased RR for leukemia, which was due to non-CLL leukemia. Lymphocytic leukemia (CLL and lymphocytic leukemia not otherwise specified) was not associated with irradiation (RR = 0.9; 95% CI: 0.4–2.3). In the age range covered by this

study, most of the unspecified lymphocytic leukemias can be assumed to have been CLL. Relative risks for non-Hodgkin lymphoma (RR = 0.9), Hodgkin lymphoma (RR = 0.7) and multiple myeloma (RR = 0.9) were not increased. In general, RRs for site-specific cancers showed very similar patterns regardless of the radiation treatment modality (Appendix 1).

Relative risks of mortality by time since radiation exposure are presented for all causes and selected cancers in Fig. 1. For cancers of the uterine corpus, bladder and ovary, the RRs remained elevated up to 40 years after RT, with little or no indication of a decline with time since exposure (Fig. 1). There were too few cases of rectal cancer in the non-exposed group to assess variation in the RR with time. The RR for colon cancer increased after irradiation but dropped in the 30–40 year interval. Relative risks for cancers of lightly irradiated sites (liver, stomach, pancreas, kidney) were consistent with stable patterns over time. For leukemia, the RRs were highest during the first 10 years after the first RT. The RRs for non-CLL leukemia with respect to time since irradiation could not be calculated, because there were no deaths due to these causes among nonirradiated women within the first 20 years after first irradiation.

Relationships between organ dose and RRs of mortality due to cancers of selected sites are shown in Fig. 2. The RR for cancer of the uterine corpus was elevated significantly in all non-zero dose groups based on comparisons with the nonirradiated women. However, there was no significant gradient in risk among exposed women ($P = 0.42$). The RR for cancer of the uterine cervix was not significantly increased in any dose category. A significant dose-related increase in the RR was found for cancers of the bladder ($P = 0.02$), rectum ($P = 0.05$) and ovary ($P < 0.001$). The RR for colon cancer tended to increase slightly with an increasing colon dose, but not significantly ($P = 0.10$). No significant trends with dose were seen for cancers of lightly irradiated sites (exposed up to 1.5 Gy), notably, the liver, stomach, kidney and pancreas. Among cancers of very lightly irradiated sites, lung cancer did not show a dose-related increase or decrease (data not shown). The RR of breast cancer did not vary significantly in relation to dose to the breast ($P = 0.39$) or ovary ($P > 0.50$), although the RRs for breast cancer mortality were below 1.0 for all categories of ovarian dose. While data in Table 3 indicated a significantly high SMR for brain cancer in irradiated women, doses to the brain were negligible (Table 2), and there was no evidence of association of risk with dose to the brain (data not shown). We explored a possible intermediary role of ovarian irradiation by examining the relationship with ovarian doses (see Discussion). The RR for brain cancer showed an inverted U-shaped pattern in relationship to ovarian dose (data not shown).

The risk of non-CLL leukemia, but not CLL, was elevated in all categories of average bone marrow dose that we evaluated, with a greater increase in risk per Gy occurring at lower rather than higher dose categories (Fig. 2). There were no significant associations between lymphomas (Hodgkin or non-Hodgkin) or multiple myeloma and bone marrow dose, which was assumed to be a crude surrogate for dose to lymphopoietic tissue (data not shown).

Excess relative risks (ERR) per Gy and excess absolute rates (EAR) per 100,000 PY per Gy were estimated using a linear dose-response model (Table 4). When nonirradiated women were included, the ERR estimate for cancer of uterine corpus was highly significant ($P < 0.001$), however, there was no gradient in risk among irradiated women (ERR = 0.005/Gy, $P = 0.42$). ERR estimates were significantly greater than 0.00 for ovary, bladder and rectum, and nonsignificantly greater for colon. EAR estimates were significantly elevated for ovary and rectum and nonsignificantly elevated for stomach, bladder and colon.

DISCUSSION

The previous analysis of solid cancer mortality data in this cohort included patients treated by radium at hospitals in Massachusetts and Rhode Island (6). The additional 11 years of follow up of the patients treated at Massachusetts and Rhode Island hospitals, and the addition of patients treated in New York and Connecticut hospitals, doubled the number of solid cancer deaths (1,395) among irradiated women, which allowed for the analyses of several specific cancer sites that were not possible in the previous study. The expanded study included a large number of BGD patients who were treated by methods other than radiation, which provided a more appropriate comparison group than the general U.S. population, as was used in the previous solid cancer study.

Mortality due to cancer of the uterine corpus and other organs proximal to the treatment area (bladder, rectum, ovary and colon) was significantly increased among women who received RT compared with women treated by other means. A significant dose-related increase was found for cancer of the bladder, as previously reported. In addition, significant dose-response relationships were found for cancers of the ovary and rectum with the updated mortality data. Colon cancer mortality showed a non-significant positive association with dose. Mortality due to cancer of the uterine corpus was increased in the RT group, but was not associated with radiation dose, and interpretation of the findings for this cancer is complex (see below). In contrast, increased RRs were not observed for most cancers of sites distant from the treatment area. Although most distant organs generally received low radiation doses, doses up to 1.5 Gy were delivered to the pancreas, liver, kidney and stomach. There was no indication of a dose-response for any of those cancer sites. Among very lightly irradiated sites, brain cancer was the only site with a significantly elevated SMR 2.3 (O = 20 deaths). However, the increased SMR was unlikely due to radiation, as the brain dose was quite low (median, 0.004 Gy), and a radiation dose-response was not observed.

The present study includes 28 additional deaths due to hematopoietic and lymphopoietic cancers compared to our previous report (5). Seventy-one percent of the additional deaths were from cancers of lymphopoietic tissue (15 non-Hodgkin lymphoma and 5 multiple myeloma). Mortality due to non-CLL leukemia remained elevated, with the greatest increase occurring during the first 10 years following irradiation. This is consistent with patterns observed in other studies of women irradiated for metropathia (3), and in large international studies of leukemia following cervical (21) and endometrial cancer (11). With additional follow-up and increased numbers of deaths, neither lymphoma nor multiple myeloma was found to be radiation-related despite the high local radiation dose to bone marrow in the pelvic region.

Gynecologic Cancers

In the present study, we were able to assess the associations of radiation and cancers of the uterine corpus and uterine cervix separately. The two types of cancer have quite different etiologies (22, 23). Cervical cancer is well known to be strongly related to infection with the human papillomavirus (24) and with cigarette smoking (25), whereas uterine corpus cancer has been more strongly linked with hormonal factors (22). Evidence from the literature of a radiation-related risk is weaker for cancer of the uterine cervix than for cancer of the uterine corpus (26), and the low RR for mortality due to cervical cancer in the present study is consistent with that of previous studies (27, 28).

Several issues complicate interpretation of findings for cancer of the uterine corpus. Although risk for cancer of the uterine corpus was significantly elevated among irradiated women, there was no evidence of dose-response among the exposed women over a broad range of dose up to 60 Gy. Some of the gynecologic conditions that led to the radiation

treatments, such as hyperplasia or dysplasia of the endometrium, have been associated with endometrial cancer, possibly due to their common link with estrogenic stimulation (22). Further, the mean BMI was higher for irradiated women than for nonirradiated women, and BMI was associated with uterine cancer. Among women with known BMI, the RR of uterine corpus cancer was higher among women who were obese (BMI ≥ 30) at BGD diagnosis relative to women who were under weight or normal weight (BMI < 25) (RR = 2.5; 95% CI: 1.3–5.0). We did not adjust for BMI in the main analysis, because the proportion of irradiated women with known BMI was small (34%). However, among women with known BMI, adjustment for BMI lowered the ERR/Gy estimate by 29%. Comparisons between irradiated and nonirradiated women might be artificially biased upward if a greater proportion of nonirradiated women had their uteri removed, whether at the time of treatment for BGD or subsequently. We lacked information about subsequent hysterectomies unless they were performed at the hospital where the woman was treated for BGD. It is a comparison based on limited information, but the proportion of women who had hysterectomies among nonirradiated women was 1.7 times higher than that among irradiated women. Given the possible problems involved in comparison of irradiated and nonirradiated women with respect to uterine corpus cancer, the most convincing evidence from this study to support the radio-resistance (for cancer) of the uterine corpus is the lack of a radiation dose-response. Few studies have found significant increases of uterine cancer following irradiation except at therapeutic doses (26), though there was a suggestion of radiation-related risk only for exposures occurring before age 20 (27) among atomic bomb survivors.

Cancer of the ovary showed an association with radiation dose, and the pattern of excess risk over time is consistent with a radiation effect. Studies of atomic bomb survivors also indicated that the ovary is a radiosensitive organ (27). The ERR estimate of 0.31 per Gy (95% CI: 0.12–0.68) in the present study was lower than, but not significantly different from, that of 0.61 (90% CI: 0.00–1.5) for the atomic bomb survivors (27). In other studies, ovarian cancer was not significantly increased among women irradiated for BGD (3, 4) or cervical cancer (10).

Colorectal Cancer

We observed a significantly elevated RR for mortality due to cancer of the rectum based on internal analysis, which is a new finding not seen in our previous analysis based on general population comparisons (6). However, the elevated RR was driven by a lesser than expected occurrence of deaths due to rectal cancer among nonirradiated women (SMR = 0.3) rather than a greater than expected occurrence among irradiated women (SMR = 1.0). Studies of cervical cancer survivors also found increased risk of rectal cancer associated with RT (10, 29). Irradiated cervical cancer patients received a very high rectal dose of the order of tens of Gy (10). Dose to the rectum was considerably lower for BGD patients, but the data nonetheless suggest a dose-response relationship. In a study of 2,067 women treated with X rays for metropathia hemorrhagica (3), death due to rectal cancer occurred about as often as expected based on general population mortality rates. The study of atomic bomb survivors, most of whom received comparatively low doses, did not show a significantly increased risk for incident cases of rectal cancer in an analysis for both sexes combined (27), with an ERR estimate of 0.19 per Gy (90% CI: −0.04–0.47), which did not vary with age at exposure, attained age or gender. The ERR estimate of 0.23 per Gy from the present study is similar to this estimate.

Colon doses in the present study were intermediate between those for cervical cancer patients and atomic bomb survivors, and so were the risk estimates. The dose-response, though not significant, was suggestive, as was the pattern of excess risk over time. Whereas studies of cervical cancer patients indicated an increased risk of rectal cancer, an increase

was not seen for colon cancer, even though doses were high (mean, 24 Gy) (10). A dose-related risk of colon cancer was seen at much lower doses among female atomic bomb survivors (27). Boice *et al.* (10) suggested that the high rate of turnover of cells in the colon might make them more susceptible to the cell killing effect of radiation compared to cells in the rectum, resulting in lesser risk of colon cancer at high doses.

Bladder Cancer

We observed a significant dose-response for bladder cancer. A study of metropathia patients treated with X rays in the UK (3) reported a relative risk for bladder cancer (SMR = 3.0; 95% CI: 1.8–4.6), which was very similar to the RR that we observed, and both studies found high RRs for later follow up intervals. Bladder cancer has been associated with radiation among cervical cancer patients (10) and atomic bomb survivors (27). The ERR estimate of 0.21 per Gy (95% CI: 0.02–0.85) from the present study was smaller than that of 1.9 per Gy (90% CI: 0.79–3.4) estimated for female atomic bomb survivors (27).

Cancers of the Stomach, Pancreas, Liver and Kidney

Doses to the stomach, pancreas, liver and kidneys were relatively low compared with doses to pelvic organs. Not only was there no overall excess mortality due to these cancers among irradiated women, there also was no indication of dose-response for doses up to 1.5 Gy. Mortality due to these cancers was not significantly elevated in a previous study of metropathia patients (3). Stomach and liver cancer were significantly associated with dose among atomic bomb survivors, whereas cancers of the pancreas and kidney were not (27). Stomach cancer, but not pancreatic cancer, was increased among irradiated cervical cancer patients, and kidney cancer was increased 15 or more years after treatment, but was evident only for cancers of the renal pelvis and ureter, which have similar transitional cell types as the bladder, for which a radiation effect also was apparent (10).

Breast Cancer

Several studies have reported decreased risk of breast cancer among women who received high doses of radiation (>5 Gy) to their ovaries (3, 30, 31). Overall, a decreased RR was not seen in the present study. This is consistent with the previous study of a subset of the population treated with radium (6). However, in the present study, the SMR for breast cancer in the combined modality RT group was significantly low (SMR = 0.62, 95% CI: 0.41–0.87). Radiation dose to the ovary for women who received combined modality therapy (median, 5.5 Gy) was higher than that for the much larger group of women treated with radium alone (2.8 Gy). A significantly reduced risk of breast cancer was observed among women irradiated for metropathia hemorrhagica who received ovarian doses ≥5 Gy (3) and among women irradiated for cervical cancer with ≥6 Gy to the ovaries (30). Radiation dose to the ovaries among most women in the present study may have been insufficient to detectably reduce the risk of breast cancer (32).

Brain Cancer

The increased mortality due to brain cancer is unexplained but unlikely to be due to radiation. The radiation dose to the brain was very low, and brain cancer mortality was not associated with radiation dose. Previous studies have indicated increased risk of brain cancer (glioma) among women with later ages at menarche (33). We hypothesized that irradiation of the ovaries might indirectly influence risk of brain cancer through suppression of circulating of estrogen or other hormones but saw no association between brain cancer risk and radiation dose to the ovaries (Appendix 2). If our brain cancer finding stood in isolation, it might be dismissed as likely to have been due to chance. However, previous studies of women treated for metropathia also reported elevated rates of brain cancer: SMR = 1.84 (n =

9 deaths) in the Scottish series (3) and SMR = 1.67 (4 deaths) in the Swedish Radiumhemmet series (4). Possible non-radiation-related hypotheses include: (1) pre-existing brain cancers caused some instances of uterine bleeding, or (2) women irradiated for BGD were under more intense medical care than the general population, leading to more complete or accurate recording of brain cancer on their death certificates. Arguing against these hypotheses is the observation that a large proportion of brain cancer deaths in the present study occurred many years after irradiation for BGD (median, 25.2 years), and most gliomas are not believed to remain clinically silent for this long of a time. It is possible that some of the brain cancers were metastases, though this seems unlikely when specific histopathologic diagnoses for brain cancer (e.g., glioblastoma or astrocytoma) were given.

Hematopoietic and Lymphopoietic Cancers

The number of leukemia deaths in our previous report (5) increased from 71 to 80 in the present analysis, adding 5 deaths due to CLL and 4 deaths from non-CLL leukemia. As with various previous studies (3, 11, 21, 29), we observed increased risk for leukemia among women who received RT, derived primarily from the increased risk for non-CLL that occurred during early years of follow-up. Mortality due to lymphocytic leukemia (CLL) was not increased, which was consistent with nearly all studies of radiation exposed populations (26). The average marrow dose for BGD patients was well below that received by cervical cancer (21) or endometrial cancer (11) patients; yet, the overall RRs were similar among studies, and, in no case did the RR increase monotonically with bone marrow dose. Most likely, there was radiation-related killing of hematopoietic stem cells in marrow of the pelvis, lumbar vertebrae and femurs, and this partially offset a leukemogenic effect (21, 34). Even though the average dose to the active bone marrow for BGD patients was not large (median, 0.7 Gy), marrow in the pelvis would have received threefold higher doses.

Positive associations between non-Hodgkin lymphoma risk and radiation exposure have been reported at high doses among survivors of cancers of the uterine cervix (10) and uterine corpus (12), but not among BGD patients (3) or female atomic bomb survivors (35). More recently, a parallel analysis of non-Hodgkin lymphoma mortality among male atomic bomb survivors and U.S. nuclear facility workers suggested a long latency (35 or more years after exposure) for radiation-related lymphoma (36). In the present study, in which mortality follow-up extended well over 40 years, there was no indication of increased risk of non-Hodgkin lymphoma following radiation exposure.

Studies of the relationship between multiple myeloma and radiation have been inconsistent. Some studies using mortality as the end point reported a positive relationship (3, 28, 37), while studies of incidence have not reported elevated risks (38, 39). We did not observe elevation of risk of death due to multiple myeloma among women irradiated for BGD.

Strengths and Limitations

Strengths of the present study include its large size, inclusion of an internal nonirradiated comparison group, individual radiation dosimetry and long-term follow up. Limitations include use of cancer mortality rather than incidence, small numbers of deaths for uncommon cancers, possible effects of indications for treatment (radiation versus no radiation), incomplete information about hysterectomies and oophorectomies, uncertainty in dose estimates for heterogeneous radiation exposures and incomplete information about subsequent RT. We used mortality as an outcome due to the unavailability of cancer registry data. Mortality data are suboptimal for evaluating effects of radiation for types of cancer that have a good prognosis (e.g., thyroid or breast). However, for most cancers, mortality findings are consistent with incident findings, with differences mainly being in precision and statistical power. Not only the type of BGD condition, but also other patient characteristics,

may have influenced whether a woman was treated with radiation. For example, textbooks and journal articles from the era indicate that women who were poor candidates for surgery (e.g., due to obesity or circulatory or renal disease) were more likely to be treated with radiation (9, 40). All of the nonirradiated women in the present study came from a single hospital in Western New York. We assumed that they were a suitable comparison group for the cohort as a whole. We did not take into account RT other than RT for BGD, including pelvic RT for subsequent uterine cancer, as we only had knowledge of such treatments if given at the same hospital at which the treatment for BGD occurred. We did not take into account hysterectomies, oophorectomies or cervical amputations because of limited knowledge of such treatments in the years following treatment for BGD.

CONCLUSIONS

Evidence of significantly elevated radiation-related risk was seen for cancers of organs proximal to the radiation source or fields (bladder, rectum and ovary), as well as for non-CLL leukemia. Mortality due to cancer of the uterine corpus was increased among irradiated women, but the role of radiation in explaining this increase is unclear. No significant increase was seen for organs that received between 0.1 Gy up to 1.5 Gy (i.e., pancreas, kidney, stomach and liver), and ovarian doses appeared insufficient to significantly lower breast cancer risk. Our results corroborate those from previous studies in suggesting that cells of the uterine cervix and lymphopoietic system are relatively resistant to the carcinogenic effects of radiation. Studies of women irradiated for BGD complement studies of women treated with higher doses of radiation for cancers of the cervix and endometrium. Together, they provide quantitative information about lifetime cancer risks over a broad range of pelvic radiation exposures.

Acknowledgments

This study was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health. We are grateful for the substantial contributions made by Dr. Joseph K. Wagoner (deceased) in developing cohorts of women treated for benign gynecological disease in Connecticut and Massachusetts, and by Drs. Richard R. Monson and George B. Hutchison who, when at the Harvard School of Public Health, provided valuable guidance and advice during the early years of study development and conduct. We are also grateful for the support provided to Dr. Ritsu Sakata by the Radiation Effects Research Foundation while she was a Visiting Scientist at the National Cancer Institute. The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan, is a private, non-profit foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE), the latter in part through DOE Award DE-HS0000031 to the National Academy of Sciences. The views of the authors do not necessarily reflect those of the two governments.

Appendix

APPENDIX 1:

Relative Risks of Mortality Due to Selected Cancers by Modality of Treatment

			X ray			Brachytherapy			Both
Cause of death	***n*[a]**	**RR[b]**	**95% CI[c]**	***n*[a]**	**RR[b]**	**95% CI[c]**	***n*[a]**	**RR[b]**	**95% CI[c]**
Number of women:	1,947			5,981			1,841		
Person-years:	59,096			175,086			54,408		
All causes	1,342	1.1	1.0–1.2	4,391	1.1	1.1–1.2	1,429	1.1	1.0–1.1
All solid cancers	253	1.3	1.1–1.5	853	1.3	1.2–1.5	289	1.4	1.2–1.6
Heavily-irradiated sites (>1 Gy)	125	1.9	1.5–2.5	410	1.9	1.5–2.3	155	2.0	1.6–2.6
Uterine cervix	12	1.3	0.6–2.9	35	1.1	0.6–2.1	18	1.4	0.7–3.0
Uterine corpus	30	3.2	1.8–6.1	129	3.7	2.2–6.6	58	4.1	2.4–7.6
Bladder	9	3.3	1.1–10.7	32	3.5	1.5–10.2	7	2.1	0.7–7.3
Rectum	10	4.3	1.4–15.6	27	3.7	1.4–12.6	14	5.9	2.0–21.3
Ovary	24	2.1	1.1–3.7	53	1.5	0.9–2.6	28	2.6	1.4–4.7
Other genital organs	1	0.3	0.0–1.8	5	0.5	0.1–1.6	4	1.2	0.3–4.5
Colon	40	1.4	0.9–2.2	134	1.5	1.1–2.2	30	1.1	0.7–1.7
Lightly-irradiated sites (0.1–1 Gy)									
Liver, gallbladder and bile ducts	4	0.5	0.1–1.4	23	0.9	0.4–1.7	15	1.6	0.7–3.4
Stomach	13	1.1	0.6–2.3	40	1.0	0.6–1.8	15	1.0	0.5–2.1
Kidney	6	1.1	0.4–3.2	13	0.7	0.3–1.8	5	0.8	0.2–2.4
Pancreas	10	0.8	0.3–1.5	52	1.3	0.8–2.2	12	1.1	0.5–2.1
Very lightly-irradiated sites (<0.1 Gy)									
Lung	20	1.1	0.6–1.8	49	1.0	0.7–1.6	15	1.2	0.6–2.3
Breast	39	0.9	0.6–1.4	127	1.0	0.8–1.4	28	0.7	0.5–1.2
Esophagus	0	0.0	—[d]	6	—[e]	4	—[e]		
Thyroid	1	0.8	0.0–8.7	2	0.5	0.1–4.5	2	1.5	0.2–14.6
Buccal cavity and pharynx	3	1.3	0.3–6.0	6	0.8	0.2–3.4	2	0.9	0.1–4.9
Brain	4	—[e]	13	—[e]	3	—[e]			
Bone and connective tissue cancers									
Bone	4	—[e]	0	0.0	—d	0	0.0	—d	
Connective tissues	1	—[e]	2	—[e]	3	—[e]			

APPENDIX 2:

			X ray			Brachytherapy			Both
Cause of death	***n*[a]**	**RR[b]**	**95% CI[c]**	***n*[a]**	**RR[b]**	**95% CI[c]**	***n*[a]**	**RR[b]**	**95% CI[c]**
Lymphatic/Hematopoietic cancers									
Non-Hodgkin lymphoma	11	1.0	0.5–2.1	29	0.9	0.5–1.6	8	0.8	0.3–1.8
Hodgkin lymphoma	2	0.8	0.1–4.1	7	0.9	0.3–3.4	0	0.0–	
Multiple myeloma	4	0.9	0.3–3.0	10	0.8	0.3–2.1	4	1.1	0.3–3.4
Leukemia	9	1.6	0.6–3.9	47	2.6	1.4–5.5	14	2.4	1.1–5.6
Non-CLL[f] leukemia	5	—[e]	35	—[e]	11	—[e]			
Myeloid leukemia	3	—[e]	19	—[e]	6	—[e]			
Lymphocytic leukemia	4	1.0	0.3–3.5	12	0.9	0.4–2.4	3	0.7	0.2–2.7

[a] Number of deaths.

[b] Relative risk.

[c] 95% confidence interval (relative risks and 95% confidence intervals for Lymphatic/Hematopoietic cancers were calculated based on standardized mortality rate regression).

[d] Not applicable.

[e] Relative risk and 95% confidence intervals were not presented due to small number of deaths among no RT group.

[f] Chronic lymphocytic leukemia.

Mean Organ Dose, Number of Deaths and Relative Risks of Mortality Due to Selected Cancers by Dose Categories

Categories	Mean Organ dose (Gy)	n^a	Pyrs^b	RR^c	95% CI^d	Categories	Mean organ dose (Gy)	n^a	Pyrs^b	RR^c	95% CI^d
Uterine cervix						Uterine corpus					
No RT^e	0	7	71,392	1.00		No RT^e	0	8	71,392	1.00	
0–44	13	11	47,155	1.98	0.77–5.42	0–12.4	7	26	41,758	4.70	2.22–11.12
45–89	78	5	30,024	1.09	0.31–3.59	12.5–25.4	17	19	19,091	6.04	2.69–14.86
90–134	119	19	68,459	2.11	0.90–5.52	25.5–37.4	31	44	61,777	4.32	2.12–10.02
135–179	151	8	20,412	2.84	0.99–8.38	37.5–49.0	40	40	43,029	6.10	2.99–14.14
≥180	205	4	21,535	1.51	0.39–5.11	≥50.0	58	18	21,930	5.53	2.47–13.57
Bladder						Rectum					
No RT^e	0.00	5	71,395	1.00		No RT^e	0.00	4	71,395	1.00	
0.0–5.9	4.28	5	3,306	1.69	0.47–6.10	0.0–2.24	1.39	1	11,538	1.59	0.08–10.86
6.0–7.9	6.89	15	43,124	4.21	1.63–13.00	2.25–4.4	3.25	9	58,183	2.22	0.71–8.30
≥8.0	10.31	12	59,784	2.35	0.86–7.49	4.5–6.74	5.70	13	47,563	3.80	1.31–13.75
						6.75–8.69	7.90	4	16,126	3.56	0.83–15.25
						≥9.0	12.99	3	12,951	3.29	0.64–15.24
Ovary						Colon					
No RT^e	0.00	15	71,392	1.00		No RT^e	0.00	44	71,392	1.00	
0.0–1.9	1.43	10	40,544	1.35	0.57–3.05	0.0-0.9	0.59	15	24,144	1.10	0.59–1.95
2.0–3.9	2.90	35	76,592	2.31	1.26–4.45	1.0–1.9	1.37	79	79,592	1.53	1.05–2.26
4.0–5.9	5.29	20	35,393	2.96	1.47–6.08	2.0–2.9	2.55	40	40,793	1.47	0.94–2.28
6.0–7.9	6.95	9	16,589	2.76	1.14–6.30	3.0–3.9	3.49	17	19,803	1.30	0.72–2.26
≥8.0	10.56	14	18,467	3.87	1.81–8.23	≥4.0	5.54	25	23,254	1.64	0.98–2.69
Liver, gallbladder and bile ducts						Stomach					
No RT^e	0.00	11	71,395	1.00		No RT^e	0.00	16	71,392	1.00	
0–0.224	0.15	15	93,709	0.93	0.42–2.13	0–0.24	0.16	17	65,037	0.86	0.42–1.74
0.225–0.44	0.31	5	32,453	0.88	0.28–2.42	0.25–0.4	0.31	18	62,422	1.02	0.52–2.03
0.45–0.674	0.54	10	31,808	1.70	0.68–4.20	0.5–0.74	0.62	7	30,196	0.70	0.27–1.67
0.675–0.89	0.77	4	11,611	1.88	0.51–5.67	0.75–0.9	0.86	3	12,834	0.71	0.16–2.16
≥0.9	1.30	1	16,545	0.35	0.02–1.81	≥1.0	1.37	8	17,097	1.47	0.59–3.38
Kidney						Pancreas					

Categories	Mean Organ dose (Gy)	n^a	Pyrs^b	RR^c	95% CI^d	Categories	Mean organ dose (Gy)	n^a	Pyrs^b	RR^c	95% CI^d
No RT^e	0.00	6	71,392	1.00		No RT^e	0.00	23	71,392	1.00	
0–0.24	0.17	9	86,061	1.25	0.43–3.88	0–0.24	0.15	41	100,722	1.43	0.84–2.49
0.25–0.4	0.33	3	40,745	0.81	0.17–3.13	0.25–0.4	0.31	9	23,926	1.11	0.48–2.32
0.5–0.74	0.66	4	28,208	1.62	0.40–6.02	0.5–0.74	0.66	11	29,969	1.27	0.58–2.63
0.75–0.9	0.91	1	11,425	1.01	0.05–6.17	0.75–0.9	0.87	5	5,872	3.07	1.02–7.58
≥1.0	1.47	3	21,147	1.61	0.33–6.40	≥1.0	1.48	3	27,097	0.37	0.09–1.09
Breast (dose for breast)						Breast (dose for ovary)					
No RT^e	0.00	67	71,392	1.00		No RT^e	0.00	67	71,392	1.00	
0–0.024	0.02	22	25,439	1.00	0.60–1.62	0.0–1.9	1.43	34	40,544	0.95	0.61–1.46
0.025–0.04	0.04	69	85,248	0.85	0.60–1.22	2.0–3.9	2.90	62	76,592	0.84	0.59–1.21
0.05–0.074	0.06	40	47,925	0.89	0.57–1.30	4.0–5.9	5.29	27	35,393	0.81	0.50–1.27
0.075–0.09	0.08	8	13,397	0.63	0.27–1.24	6.0–7.9	6.95	16	16,589	1.00	0.56–1.71
≥0.10	0.13	14	15,577	0.94	0.50–1.65	≥8.0	10.56	14	18,467	0.80	0.43–1.39
Brain (dose for ovary)						Non-Hodgkin lymphoma					
No RT^e	0.00	2	71,392	1.00		No RT^e	0.00	20	92,397	1.00	
0–2.9	1.85	8	86,936	6.21	1.41–43.63	0.0–0.7	0.50	28	133,723	1.04	0.59–1.87
3.0–5.9	4.41	8	65,593	8.18	1.84–57.95	0.8–1.5	1.13	7	48,527	0.64	0.25–1.44
≥6.0	8.90	1	35,056	1.78	0.08–19.44	1.6–2.3	1.82	5	39,864	0.62	0.21–1.53
						≥2.4	3.33	3	25,463	0.56	0.13–1.63
Hodgkin lymphoma						Multiple myeloma					
No RT^e	0.00	4	92,397	1.00		No RT^e	0.00	8	92,397	1.00	
0.0–0.7	0.50	3	133,723	0.45	0.09–2.04	0.0–0.7	0.50	8	133,723	0.77	0.28–2.08
0.8–1.5	1.13	4	48,527	1.64	0.39–6.91	0.8–1.5	1.13	6	48,527	1.40	0.46–4.03
1.6–2.3	1.82	1	39,864	0.48	0.03–3.25	1.6–2.3	1.82	3	39,864	0.96	0.21–3.32
≥2.4	3.33	1	25,463	0.77	0.04–5.21	≥2.4	3.33	0	25,463	0.00	—^{f}
Leukemia						Non-CLL^g leukemia					
No RT^e	0.00	10	92,397	1.00		No RT^e	0.00	3	92,397	1.00	
0.0–0.7	0.50	35	133,723	2.33	1.20–4.97	0.0–0.7	0.50	25	133,723	5.66	1.99–23.75
0.8–1.5	1.13	17	48,527	2.89	1.35–6.55	0.8–1.5	1.13	12	48,527	6.97	2.21–30.56
1.6–2.3	1.82	10	39,864	2.13	0.87–5.18	1.6–2.3	1.82	6	39,864	4.32	1.14–20.44
≥2.4	3.33	5	25,463	1.67	0.52–4.69	≥2.4	3.33	5	25,463	5.62	1.38–27.37

Note. Relative risks and 95% confidence intervals for Lymphatic/Hematopoietic cancerswere calculated based on standardized mortality rate regression.

[a] Number of deaths.

[b] Person-years.

[c] Relative risk.

[d] 95% confidence interval.

[e] Radiotherapy.

[f] Not applicable.

[g] Chronic lymphocytic leukemia.

REFERENCES

1. Boice, JD, Jr. Ionzing Radiation. In: Schottenfeld, D.; Fraumeni,, JF., Jr., editors. Cancer epidemiology and prevention. Oxford University Press; New York: 2006. p. 259-93.
2. Alderson MR, Jackson SM. Long term follow-up of patients with menorrhagia treated by irradiation. Br J Radiol. 1971; 44:295–8. [PubMed: 4994676]
3. 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. [PubMed: 8119768]
4. 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. [PubMed: 2206566]

5. Inskip PD, Kleinerman RA, Stovall M, Cookfair DL, Hadjimichael O, Moloney WC, et al. Leukemia, lymphoma, and multiple myeloma after pelvic radiotherapy for benign disease. Radiat Res. 1993; 135:108–24. [PubMed: 8327655]
6. Inskip PD, Monson RR, Wagoner JK, Stovall M, Davis FG, Kleinerman RA, et al. Cancer mortality following radium treatment for uterine bleeding. Radiat Res. 1990; 123:331–44. [PubMed: 2217730]
7. Novak ER. The problem bleeder after thirty-five. Trans N Engl Obstet Gynecol Soc. 1960; 14:163–77. [PubMed: 13729717]
8. Palmer JP, Spratt DW. Pelvic carcinoma following irradiation for benign gynecological diseases. Am J Obstet Gynecol. 1956; 72:497–505. [PubMed: 13354658]
9. Waterman GW, Reid WA. End results of radium treatment of nonmalignant conditions of the uterus. Trans N Engl Obstet Gynecol Soc. 1948:101–9.
10. 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. [PubMed: 3186929]
11. Curtis RE, Boice JD Jr. Stovall M, Bernstein L, Holowaty E, Karjalainen S, et al. Relationship of leukemia risk to radiation dose following cancer of the uterine corpus. J Natl Cancer Inst. 1994; 86:1315–24. [PubMed: 8064889]
12. Lonn S, Gilbert ES, Ron E, Smith SA, Stovall M, Curtis RE. Comparison of second cancer risks from brachytherapy and external beam therapy after uterine corpus cancer. Cancer Epidemiol Biomarkers Prev. 2010; 19:464–74. [PubMed: 20142245]
13. Wagoner, JK. Leukemia and other malignancies following radiation therapy for gynecological disorders. In: Boice, JD., Jr.; Fraumeni, JF., Jr., editors. Radiation Carcinogenesis: Epidemiology and Biological Significance. Raven Press; New York: 1984. p. 153-9.
14. Stovall M, Smith SA, Rosenstein M. Tissue doses from radiotherapy of cancer of the uterine cervix. Med Phys. 1989; 16:726–33. [PubMed: 2509867]
15. Stovall M, Weathers R, Kasper C, Smith SA, Travis L, Ron E, et al. Dose reconstruction for therapeutic and diagnostic radiation exposures: use in epidemiological studies. Radiat Res. 2006; 166:141–57. [PubMed: 16808603]
16. Cristy M. Active bone marrow distribution as a function of age in humans. Med Phys. 1981; 26:389–400.
17. International Classification of Diseases, adapted for use in the United States. U.S. Department of Health and Human Services; Washington, D.C.: 1967.
18. Frome EL, Checkoway H. Epidemiologic programs for computers and calculators. Use of Poisson regression models in estimating incidence rates and ratios. Am J Epidemiol. 1985; 121:309–23. [PubMed: 3839345]
19. Preston, DL.; Lubin,, JH.; Pierce, DA.; McConney, ME. Epicure User' s Guide. Hirosoft International Corporation; Seattle: 1993.
20. Brinkley D, Haybittle JL. The late effects of artificial menopause by X-radiation. Br J Radiol. 1969; 42:519–21. [PubMed: 5788062]
21. Boice JD Jr. Blettner M, Kleinerman RA, Stovall M, Moloney WC, Engholm G, et al. Radiation dose and leukemia risk in patients treated for cancer of the cervix. J Natl Cancer Inst. 1987; 79:1295–311. [PubMed: 3480381]
22. Cook LS, Kmet LM, Magliocco AM, Weiss NS. Endometrial cancer survival among U.S. black and white women by birth cohort. Epidemiology. 2006; 17:469–72. [PubMed: 16755263]
23. Schiffman, MH.; Hildesheim,, A. Cervical Cancer. In: Boice, JD., Jr.; Fraumeni, JF., Jr., editors. Cancer Epidemiology and Prevention. Oxford University Press; New York: 2006. p. 1044-67.
24. Lowy DR, Solomon D, Hildesheim A, Schiller JT, Schiffman M. Human papillomavirus infection and the primary and secondary prevention of cervical cancer. Cancer. 2008; 113:1980–993. [PubMed: 18798536]
25. Deacon JM, Evans CD, Yule R, Desai M, Binns W, Taylor C, et al. Sexual behaviour and smoking as determinants of cervical HPV infection and of CIN3 among those infected: a case-control study nested within the Manchester cohort. Br J Cancer. 2000; 83:1565–72. [PubMed: 11076670]

26. UNSCEAR. UNSCEAR 2006 Report to the General Assembly with Scientific Annexes, Effects of Ionizing Radiation. Vol. Vol 1: Report and Annexes A and B. United Nations; New York, NY: 2008.
27. 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. [PubMed: 17722996]
28. Weiss HA, Darby SC, Doll R. Cancer mortality following X-ray treatment for ankylosing spondylitis. Int J Cancer. 1994; 59:327– 38. [PubMed: 7927937]
29. 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. [PubMed: 8625126]
30. Boice JD Jr. Blettner M, Kleinerman RA, Engholm G, Stovall M, Lisco H, et al. Radiation dose and breast cancer risk in patients treated for cancer of the cervix. Int J Cancer. 1989; 44:7–16. [PubMed: 2744900]
31. Inskip PD, Robison LL, Stovall M, Smith SA, Hammond S, Mertens AC, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. J Clin Oncol. 2009; 27:3901–7. [PubMed: 19620485]
32. Inskip PD. Pelvic radiotherapy, sex hormones, and breast cancer. Cancer Causes Control. 1994; 5:471–8. [PubMed: 7999969]
33. Hatch EE, Linet MS, Zhang J, Fine HA, Shapiro WR, Selker RG, et al. Reproductive and hormonal factors and risk of brain tumors in adult females. Int J Cancer. 2005; 114:797–805. [PubMed: 15609304]
34. Hutchison GB. Leukemia in patients with cancer of the cervix uteri treated with radiation. A report covering the first 5 years of an international study. J Natl Cancer Ins. t; 1968:40–951.
35. Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, et al. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. Radiat Res. 1994; 137:S68–97. [PubMed: 8127953]
36. Richardson DB, Sugiyama H, Wing S, Sakata R, Grant E, Shimizu Y, et al. Positive associations between ionizing radiation and lymphoma mortality among men. Am J Epidemiol. 2009; 169:969–76. [PubMed: 19270049]
37. Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. Radiat Res. 1996; 146:1–27. [PubMed: 8677290]
38. Damber L, Larsson LG, Johansson L, Norin T. A cohort study with regard to the risk of haematological malignancies in patients treated with x-rays for benign lesions in the locomotor system. I. Epidemiological analyses. Acta Oncol. 1995; 34:713–9. [PubMed: 7576736]
39. Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. Radiat Res. 1990; 123:275–84. [PubMed: 2217725]
40. Hunter RM, Ludwick NV, Motley JF, Oaks WW. The use of radium in the treatment of benign lesions of the uterus; a critical twenty-year survey. Am J Obstet Gynecol. 1954; 67:121–9. [PubMed: 13114295]

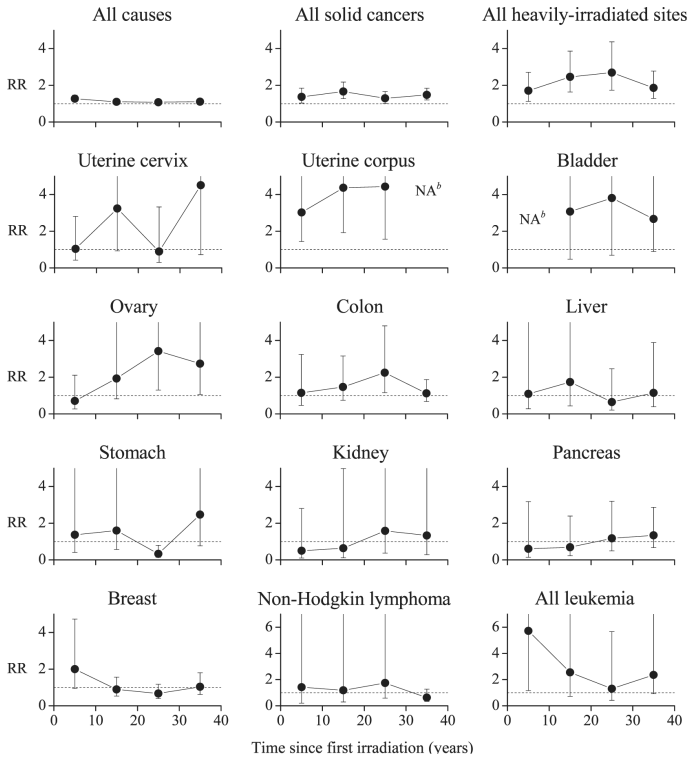

FIG. 1.

Relative risks (RR[a]) of mortality and 95% confidence interval associated with radiotherapy for selected cancers by time since first irradiation. [a]Relative risk were calculated by using the no radiotherapy group as the referent. Relative risks for lymphatic/hematopoietic cancers were calculated based on standardized mortality rate regression. [b]Not available, could not be calculated due to small numbers in reference group.

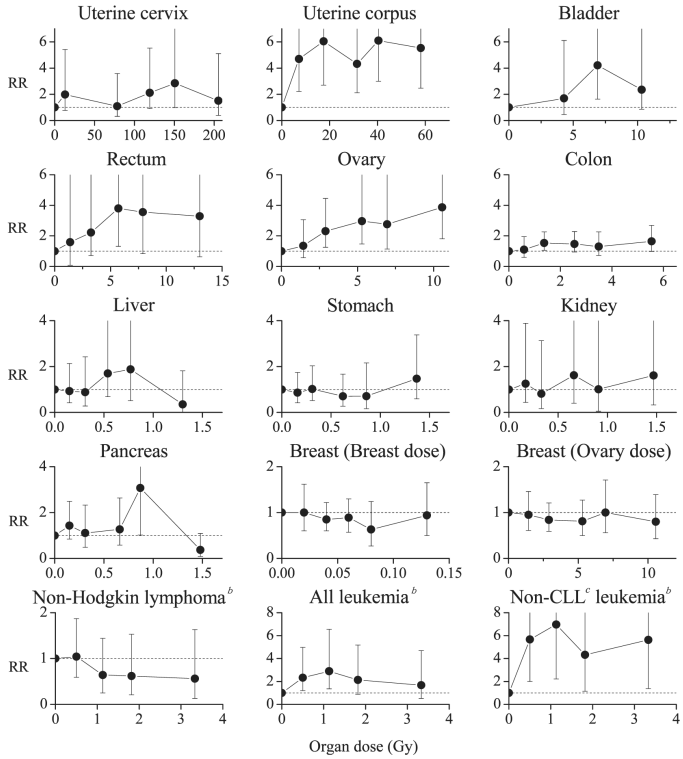

FIG. 2.

Relative risks (RR[a]) of mortality and 95% confidence intervals for selected cancers in relationship to organ dose. The dose scales vary by cancer site. [a]Relative risks were calculated by using the no radiotherapy group at the referent, relative risks for lymphatic/hematopoietic cancers were calculated based on standardized mortality rate regression. [b]Average bone marrow dose was used for leukemia and lymphomas. [c]Chromic lymphocytic leukemia.

TABLE 1

Demographic Characteristics of 12,955 Patients Treated for Benign Gynecologic Disorders

			Modality of radiotherapy		
Characteristic	**No RT[a]**	**Any RT**	**External X ray**	**Brachytherapy**	**Both**
Subjects (%[b])	3,186 (24.6)	9,769 (75.4)	1,947 (15.0)	5,981 (46.2)	1,841 (14.2)
Type of exit					
Deceased	2,191 (68.77)	7,162 (73.3)	1,342 (68.9)	4,391 (73.4)	1,429 (77.6)
Alive as of the end of follow-up	758 (23.79)	1,786 (18.3)	336 (17.3)	1,047 (17.5)	403 (21.9)
Lost to follow-up	237 (7.4)	821 (8.4)	269 (13.8)	543 (9.1)	9 (0.5)
Location of treatment					
Connecticut	0 (0.0)	1,959 (20.1)	1,035 (53.2)	898 (15.0)	26 (1.4)
Massachusetts	0 (0.0)	2,365 (24.2)	263 (13.5)	2,068 (34.6)	34 (1.8)
New York	3,186 (100.0)	3,327 (34.1)	631 (32.4)	932 (15.6)	1,764 (95.8)
Rhode Island	0 (0.0)	2,118 (21.7)	18 (0.9)	2,083 (34.8)	17 (0.9)
Year of entry					
1925–1939	788 (24.7)	5,223 (53.5)	839 (43.1)	2,953 (49.4)	1,431 (77.7)
1940–1949	1,589 (49.9)	3,865 (39.6)	934 (48.0)	2,526 (42.2)	405 (22.0)
1950–1965	809 (25.4)	681 (7.0)	174 (8.9)	502 (8.4)	5 (0.3)
Age at entry, years					
<40	1,054 (33.1)	1,706 (17.5)	453 (23.3)	988 (16.4)	265 (14.4)
40–49	1,094 (34.3)	5,404 (55.3)	1,156 (59.4)	3,238 (54.1)	1,010 (54.9)
50–59	566 (17.8)	2,036 (20.8)	290 (14.9)	1,332 (22.3)	414 (22.5)
≥60	472 (14.8)	626 (6.4)	48 (2.5)	426 (7.1)	152 (8.3)
Years of observation					
0–19	710 (22.3)	2,465 (25.2)	473 (24.3)	1,506 (25.2)	486 (26.4)
20–39	1,420 (44.6)	4,856 (49.7)	897 (46.1)	3,096 (51.8)	863 (46.9)
≥40	1,056 (33.2)	2,448 (25.1)	577 (29.6)	1,379 (23.1)	492 (26.7)
Race					
White	2,999 (95.0)	8,110 (98.8)	1,386 (98.6)	4,934 (98.6)	1,790 (99.2)
Black	152 (4.8)	95 (0.1)	19 (1.4)	63 (1.3)	13 (0.7)
Other	7 (0.2)	6 (0.01)	0 (0.0)	5 (0.1)	1 (0.1)

Characteristic	No RT[a]	Any RT	Modality of radiotherapy		
			External X ray	Brachytherapy	Both
Unknown	28	0.88	1,558	16 542	979 37
Dysfunctional uterine bleeding[c]					
No	1,256 (39.6)	647 (7.8)	193 (12.9)	267 (5.4)	187 (10.2)
Yes	1,919 (60.4)	7,618 (92.2)	1,306 (87.1)	4,661 (94.6)	1,651 (89.8)
Unknown	11	1,504	448	1,053	3
Hysterectomy					
No	2,618 (83.5)	6,493 (90.4)	969 (88.1)	3,848 (89.9)	1,676 (93.1)
Yes	516 (16.5)	689 (9.6)	131 (11.9)	433 (10.1)	125 (6.9)
Unknown	52	2,607	867	1,700	4
Oophorectomy					
No	2,585 (85.9)	5,101 (84.6)	876 (82.4)	2,649 (82.3)	1,576 (89.9)
Unilateral	205 (6.8)	471 (7.8)	102 (9.6)	267 (8.3)	102 (5.1)
Bilateral	199 (6.6)	433 (7.2)	75 (7.1)	289 (9.0)	69 (3.9)
NOS[d]	22 (0.7)	28 (0.5)	10 (0.9)	12 (0.4)	6 (0.3)
Unknown	175	3,736	884	2,764	88

[a] Radiotherapy.

[b] Percentages are shown, with exception of unknown.

[c] Dysfunctional uterine bleeding at the time of benign gynecologic diagnosis.

[d] Not otherwise specified.

Radiat Res. Author manuscript; available in PMC 2013 October 01.

TABLE 2

Median and 10th to 90th Percentiles of Organ Doses (Gy) Among Women Irradiated for Benign Gynecologic Disorders, by Modality of Radiotherapy

	Organ dose (Gy)							
	Modality of RT							
	Any RT[a]		X ray		Brachytherapy		Both	
Organ	Median	P_{10}–P_{90}[b]	Median	P_{10}–P_{90}[b]	Median	P_{10}–P_{90}[b]	Median	P_{10}–P_{90}[b]
Uterus	38	8–58	7.1	4.4–11	43	19–58	41	35–61
Uterine cervix	120	8–180	7.1	4.4–11	130	59–180	120	98–180
Uterine corpus	34	7–50	7.1	4.4–11	38	17–50	37	31–53
Bladder[c]	7.2	4.7–12	6.5	3.8–10	7.2	4.0–9.6	9.1	8.3–15
Rectum[d]	4.8	2.4–9.0	7.2	4.2–11	3.6	2.0–4.8	6.1	5.7–12
Ovary	3.1	1.6–8.1	7.1	4.4–11	2.8	1.2–3.7	5.5	4.5–9.4
Colon (entire)[e]	1.7	0.8–4.4	3.9	2.5–7.4	1.5	0.7–2.0	3.0	2.4–5.1
Sigmoid colon	3.8	1.9–7.9	7.0	4.4–10	3.4	1.5–4.6	5.7	4.8–9.6
Liver	0.2	0.1–0.9	0.7	0.3–1.2	0.2	0.1–0.3	0.5	0.5–1.2
Stomach	0.3	0.1–0.9	0.8	0.4–1.4	0.3	0.1–0.3	0.6	0.5–1.1
Kidney	0.3	0.1–1.1	1.0	0.4–1.6	0.2	0.1–0.3	0.7	0.5–1.3
Pancreas	0.2	0.1–1.1	1.1	0.5–1.7	0.2	0.1–0.3	0.7	0.5–1.3
Lung	0.05	0.0–0.1	0.1	0.0–0.1	0.04	0.0–0.1	0.1	0.1–0.1
Breast	0.04	0.0–0.1	0.1	0.0–0.1	0.04	0.0–0.1	0.1	0.1–0.1
Thyroid	0.01	0.0–0.0	0.01	0.0–0.0	0.01	0.0–0.0	0.02	0.0–0.0
Brain	0.004	0.0–0.0	0.004	0.0–0.0	0.004	0.0–0.0	0.005	0.0–0.0
Total active bone marrow[f]	0.7	0.4–2.0	3.3	1.1–3.3	0.6	0.3–0.9	1.6	1.2–2.8

[a] Radiotherapy.

[b] 10th and 90th percentiles of the dose.

[c] Average bladder dose among women who received brachytherapy was assumed to equal 4.0 Gy/1000 mg · h (range within bladder = 1.0 to 15.0 Gy/1000 mg · h).

[d] Average dose to rectum among women who received brachytherapy was assumed to equal 2.0 Gy/1000 mg · h (range within rectum = 0.9 to 5.5 Gy/1000 mg · h).

[e] An average dose for entire colon was calculated by first averaging estimates for 2 subsites of the ascending and descending colon, respectively, and then taking an equally weighted average of doses to the ascending, descending, transverse and sigmoid segments.

[f] The dose to the total active bone marrow was a weighted average of the dose to each of 14 anatomic compartments, with weights given by the presumed percentage contributions of each compartment to the total active bone Marrow (Cristy 1981).

TABLE 3

Numbers of Deaths Due to Cancer of Selected Organs and Lymphatic/Hematopoietic Cancers, Standardized Mortality Ratios (External Comparisons), by Treatment and Relative Risks (Internal Comparisons)

		No radiotherapy			Any radiotherapy				
ICD8	**Cause of death**	***n*** [a]	**SMR** [b]	**95% CI** [c]	***n*** [a]	**SMR** [b]	**95% CI** [c]	**RR** [d]	**95% CI** [c]
	Number of women:	3,186			9,769				
	Person-years:	101,816			288,589				
10–999	All causes	2,191	0.9	0.8–0.9	7,162	0.9	0.9–0.9	1.1	1.1–1.2
140–199	All solid cancers	353	0.8	0.8–0.9	1,395	1.1	1.1–1.2	1.3	1.2–1.5
Heavily-irradiated sites (>1 Gy)		109	0.7	0.6–0.8	690	1.4	1.3–1.5	1.9	1.6–2.4
180–180	Uterine cervix	14	0.7	0.4–1.2	65	0.9	0.7–1.1	1.2	0.7–2.3
181–182	Uterine corpus	15	0.7	0.4–1.2	217	2.9	2.6–3.3	3.7	2.3–6.5
188	Bladder	5	0.5	0.2–1.1	48	1.6	1.2–2.1	3.2	1.4–9.2
154	Rectum	4	0.3	0.1–0.6	51	1.0	0.7–1.3	4.1	1.7–13.8
183	Ovary	21	0.8	0.5–1.1	105	1.3	1.1–1.6	1.8	1.1–3.0
184	Other female genital organs	6	2.0	0.8–4.1	10	1.1	0.5–1.9	0.6	0.2–1.7
153	Colon	50	0.8	0.6–1.0	204	1.1	0.9–1.2	1.4	1.1–2.0
Lightly-irradiated sites (0.1–1 Gy)									
155–156	Liver, gallbladder and bile ducts	14	0.9	0.5–1.4	42	0.7	0.5–1.0	0.9	0.5–1.8
151	Stomach	19	0.8	0.5–1.2	68	0.8	0.6–1.0	1.0	0.6–1.8
189	Kidney	9	1.2	0.6–2.2	24	1.2	0.8–1.7	0.8	0.4–1.9
157	Pancreas	26	1.0	0.7–1.5	74	1.0	0.8–1.3	1.1	0.7–1.9
Very lightly-irradiated sites (<0.1 Gy)									
162	Lung	42	1.0	0.7–1.3	84	1.0	0.8–1.3	1.1	0.7–1.6
174	Breast	75	0.9	0.7–1.1	194	0.8	0.7–1.0	1.0	0.7–1.3
150	Esophagus	1	0.2	0.0–1.0	10	0.8	0.4–1.4	— [e]	
193	Thyroid	2	0.9	0.2–2.8	5	0.7	0.2–1.5	— [e]	
140	Buccal cavity and pharynx	4	0.7	0.2–1.6	11	0.7	0.4–1.2	1.0	0.3–3.6
191	Brain	3	0.6	0.2–1.6	20	2.3	1.4–3.5	— [e]	
Bone and connective tissue cancers									
170	Bone	1	0.5	0.0–2.3	4	0.6	0.2–1.3	— [e]	

		No radiotherapy			Any radiotherapy				
ICD8	**Cause of death**	***n*** [a]	**SMR**[b]	**95% CI**[c]	***n*** [a]	**SMR**[b]	**95% CI**[c]	**RR**[d]	**95% CI**[c]
171	Connective tissues	1	0.6	0.0–2.5	6	1.4	0.5–2.8	— [e]	
Lymphatic/Hematopoietic cancers									
200, 202	Non-Hodgkin lymphoma	20	1.4	0.9–2.2	48	1.3	1.0–1.7	0.9	0.5–1.6
201	Hodgkin lymphoma	4	1.6	0.5–3.8	9	1.1	0.5–2.0	0.7	0.2–2.6
203	Multiple myeloma	8	1.2	0.5–2.2	18	1.0	0.6–1.6	0.9	0.4–2.1
204–207	Leukemia	10	0.6	0.3–1.1	70	1.5	1.1–1.8	2.4	1.3–4.9
204.0, 205–207	Non-CLL[f] leukemia	3	0.2	0.1–0.6	51	1.4	1.1–1.8	— [e]	
205	Myeloid leukemia	3[g]	0.5	0.1–1.3	28[h]	1.6	1.1–2.3	— [e]	
204.1, 204.9	Lymphocytic leukemia	7	1.8	0.8–3.7	19	1.6	1.0–2.5	0.9	0.4–2.3

[a] Number of deaths.

[b] Standardized mortality ratio.

[c] 95% confidence interval.

[d] Relative risk of mortality (relative risks and 95% confidence intervals for lymphatic/hematopoietic cancers were calculated based on standardized mortality rate regression).

[e] Relative risk and 95% confidence intervals were not presented due to small number of deaths among no RT group.

[f] Chronic lymphocytic leukemia.

[g] Two acute myeloid leukemia and 1 not other specified.

[h] Twelve acute myeloid leukemia, 12 chronic myeloid leukemia and 4 not other specified.

TABLE 4

Excess Relative Risks (ERRs)/Gy and Excess Absolute Rates (EARs)/Gy · 100,000 Person-Years of Mortality Due to Selected Cancers

Cause of death		Risk	95% CI[a]	p [b]
Uterine cervix	ERR[c]	0.003	−0.003[d]–0.01	0.29
	EAR[e]	0.04	−0.05d–0.13	0.45
Uterine corpus[f]	ERR	0.00	−0.008[d]–0.03	0.42
	EAR	0.18	−0.53[d]–1.00	>0.5
Bladder	ERR	0.21	0.02–0.85	0.02
	EAR	0.75	−0.09[d]–1.87	0.09
Rectum	ERR	0.23	−0.11[d]–1.07	0.05
	EAR	1.83	0.09[d]–3.70	0.04
Ovary	ERR	0.31	0.12–0.68	<0.001
	EAR	6.06	3.22–9.11	<0.001
Colon	ERR	0.09	−0.01–0.24	0.10
	EAR	5.33	−1.05–12.87	0.11
Liver	ERR	–0.01	−0.80[d]–0.77[d]	>0.50
	EAR	–0.64	−12.00[d]–10.73[d]	>0.50
Stomach	ERR	0.21	−0.54[d]–1.14	0.46
	EAR	12.79	−0.43–30.75	0.06
Kidney	ERR	0.50	−0.91[d]–3.30	0.41
	EAR	–0.52	−7.47[d]–12.36	>0.50
Pancreas	ERR	–0.18	−0.35[d]–0.003[d]	0.16
	EAR	–1.13	−9.90[d]–7.64[d]	0.46

[a] 95% confidence interval.

[b] Likelihood ratio test of ERR(EAR) > 0 versus ERR (EAR) ≤ = 0.

[c] Excess relative risk (/Gy)

[d] Likelihood-based estimation algorithm failed to identify an interval. A Wald-type CI was calculated.

[e] Excess absolute rate (/Gy · 100,000 person-years) at attained age 60 for a women who was born in 1900.

[f] ERR and EAR for cancer of uterine corpus were analyzed after excluded nonirradiated women.