TABLE 28
Observed and Fitted[a] Female Breast Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Subjects	Person years	Cases	Background	Fitted excess	Attributable fraction
<0.005	35,883	994,838	546	531	0	0.1%
0.005–0.1	15,508	425,835	217	230	10	4.3%
0.1–0.2	3,396	94,634	57	52	11	16.9%
0.2–0.5	3,918	108,307	103	59	29	33.2%
0.5–1	2,036	53,190	53	29	27	48.5%
1–2	1,262	34,331	61	18	37	67.2%
2–4	522	13,318	36	7	32	82.0%
Total	62,525	1,724,453	1,073	926	147	27.1%[c]

[a] Estimates of background and fitted excess cases are based on an ERR model with a linear dose response and effect modification by age at exposure and attained age. All not-in-city subjects were used in the modeling, but the baseline risk model allows for city-specific differences in the level of the baseline risks for the not-in-city group.
[b] Weighted breast dose in Gy.
[c] Attributable fraction among cohort members with dose greater than 0.005 Gy.

was described by a birth cohort effect in which age-specific rates increased by about 45% per decade increase in year of birth.

2. Dose response and excess cases

As the crude rates in Table A11 suggest, there was strong evidence of a breast cancer dose response. Table 28 provides estimates of the background and fitted excess cases based on the standard linear dose–response model with allowance for effects of age at exposure and attained age on the ERR.

About 27% (147) of the 527 cases among cohort members with doses of at least 5 mGy were associated with the radiation exposure. There was a statistically significant ($P < 0.001$) dose response with the estimated standardized ERR_{1Gy} of 0.87 and EAR of 9.2 (Table 29, Fig. 14). There was no statistically significant non-linearity on the dose response on either the full dose range ($P > 0.5$) or when the test was limited to the 0–2 Gy-dose range ($P > 0.5$).

It is widely believed that age at exposure is an important modifier of the breast cancer ERR [e.g. the recent review paper by Ronckers *et al.* (*95*)]. It has also been suggested, on the basis of LSS data (*8, 96*), that radiation might have an especially large "early-onset" effect on the risk of breast cancer diagnosed prior to age 35. The following text describes the magnitude and evidence for a simple log-linear age-at-exposure effect in modeling the breast cancer risk, while early-onset risks are discussed later in this section.

As shown in Tables 11, 12 and 29 and the upper panel of Fig. 15, when adjusted for attained age, there was no indication of a significant age-at-exposure effect on the breast cancer ERR in the LSS. Without allowance for the attained-age effect, there was a statistically significant age-at-exposure effect of −19% per decade increase in the ERR (90% CI −33%; −4%), but the addition of attained age to this model led to a significant ($P = 0.002$) improvement in fit and reduced the age-at-exposure effect estimate to 0. Addition of age at exposure to an attained-age-only ERR model did not significantly improve the fit ($P > 0.5$).

TABLE 29
Female Breast Cancer Radiation-Risk-Model Parameter Estimates

Model	Risk per Gy[a]	Age at exposure[b] (percentage change per decade increase)	Attained age[b] (power)
ERR	0.87	0%	−2.3
	(0.55; 1.3)[c]	(−19%; 24%)	(−3.5; −1.1)
EAR	9.2[d]	−37%	1.7
	(6.8; 12)	(−48%; −24%)	(1.0; 2.5)

[a] At age 70 after exposure at age 30 per Gy weighted breast dose.
[b] Models include both attained-age and age-at-exposure effects.
[c] 90% confidence interval.
[d] Excess cases per 10,000 per PY Gy.

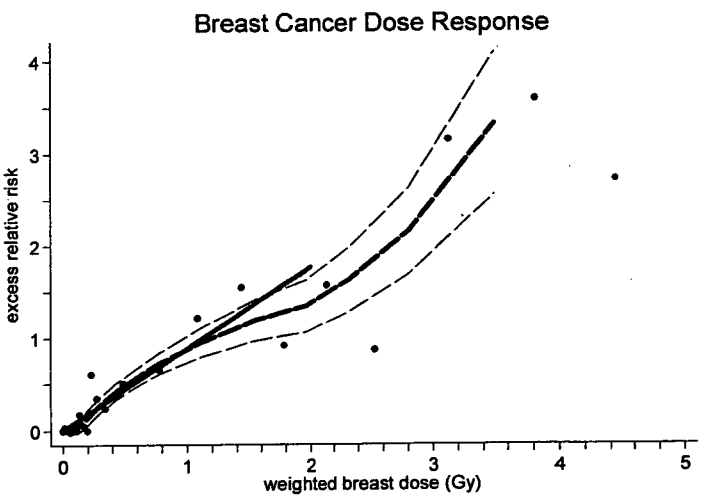

FIG. 14. Female breast cancer dose–response function. The thick solid line is the fitted excess relative risk (ERR) dose response at age 70 after exposure at age 30 based on data in the 0- to 2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The solid line is a non-parametric smooth of the category-specific estimates and the dotted lines are one standard error above and below this smooth.

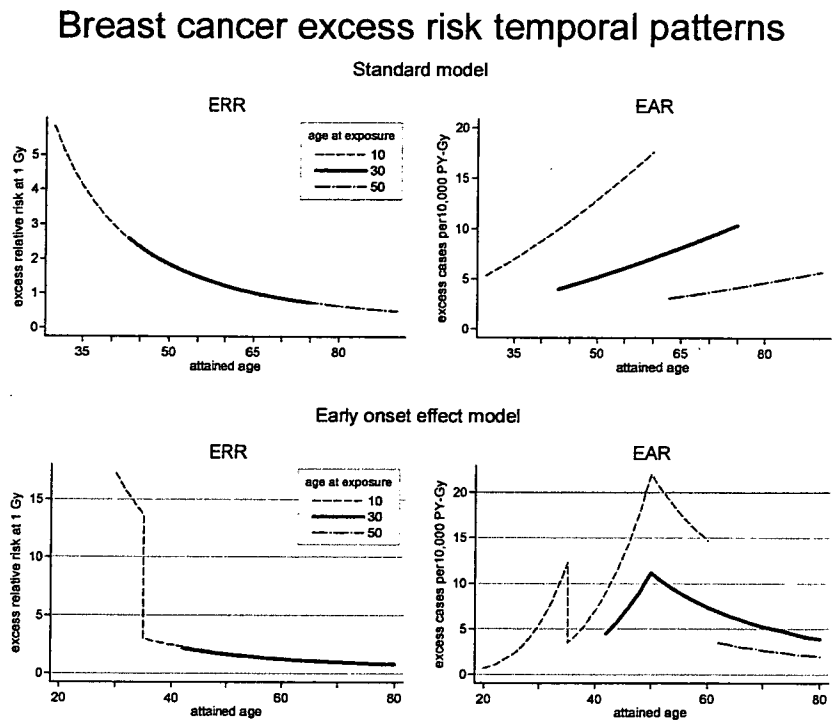

FIG. 15. Temporal patterns and age-at-exposure variation in the radiation-associated excess breast cancers risks for the standard effect modification model in which excess risks is proportional to a log-linear function of age-at-exposure and a power of attained age (top row) and a model that includes an additional multiplicative effect for early onset (prior to 35 years of age) cancer (bottom row). The panels in the left column compare variation in the excess relative risk (ERR) at 1 Gy with attained age for ages at exposure of 10, 30 and 50 years. The panels in the right column compare variation in the excess absolute risk (EAR) at 1 Gy with attained age for ages at exposure of 10, 30 and 50 years.

The top row of plots in Fig. 16 contrasts the baseline birth-cohort effect for breast cancer with the age-at-exposure effects in the standard ERR and EAR models (Table 29). The plots highlight the fact that despite the large increase in risk for more recent birth cohorts, there was virtually no indication of a significant age-at-exposure effect on the breast cancer ERR, whereas both attained age and age at exposure had significant joint effects on the EAR. The large age-at-exposure effect on the EAR together with the lack of an age-at-exposure effect on the ERR suggests that the factors (such as reproductive history) responsible for the changes in baseline rates in this population may act multiplicatively with respect to radiation.

The standard EAR model used for the above analyses (which included log-linear effects of age at exposure and log attained age) did not describe the data as well as an ERR model with similar form. However, allowing the EAR to vary with age in a manner similar to that seen for the baseline rates (described in terms of a quadratic spline in log age with a knot at age 50) led to a marked improvement in fit ($P = 0.001$) but had little impact on the age-at-exposure effect estimate. There were no indications of more complicated attained-age effects on the ERR ($P > 0.5$).

As mentioned earlier, Land and colleagues (*8, 96*) have previously noted remarkably large breast cancer ERR estimates among cases diagnosed before age 35. We found the magnitude and statistical significance of this effect to be highly dependent on the nature of the baseline risk model and the estimated baseline rates for young women. In particular, under a simple power-of-age (Armitage-Doll-like) model that allowed the power to change at age 50, the "early-onset" effect on the radiation-associated ERR was not statistically significant. A generalization of the standard effect modification model (see Eq. 1) was used for these analyses. This model can be written as $\varepsilon(e, a) = \exp\{\gamma I_{(a<35)} + \alpha e + \omega_1 \log(a) + \omega_2 \log(a/50) I_{a>50}\}$, where $I_{a<x}$ is defined as 1 if attained age is less than x and is 0 for ages of x or more. The first term in the model captures the early-onset effect while the last term allows for changes in risk associated with menopause.

However, when baseline rates for women less than 35 years of age were allowed to be lower than the predictions of the simple model, there appeared to be an early-onset effect. In particular, the excess risks for radiation-associated breast cancer prior to age 35 was estimated to be about 4.5 times greater ($P = 0.01$) than predicted by the standard ERR model and 3.5 times higher ($P = 0.08$) in the EAR model (Table 30).

The bottom panels in Fig. 15 display the age–time patterns of the ERR and EAR in models with an early-onset effect and, in the case of the EAR model, allowance for a different attained-age slope before and after age 50.

Uterus (ICD10: C53–C54)

Two major types of cancer of the uterus, i.e., cancers of the corpus and cervix, present different entities in terms of

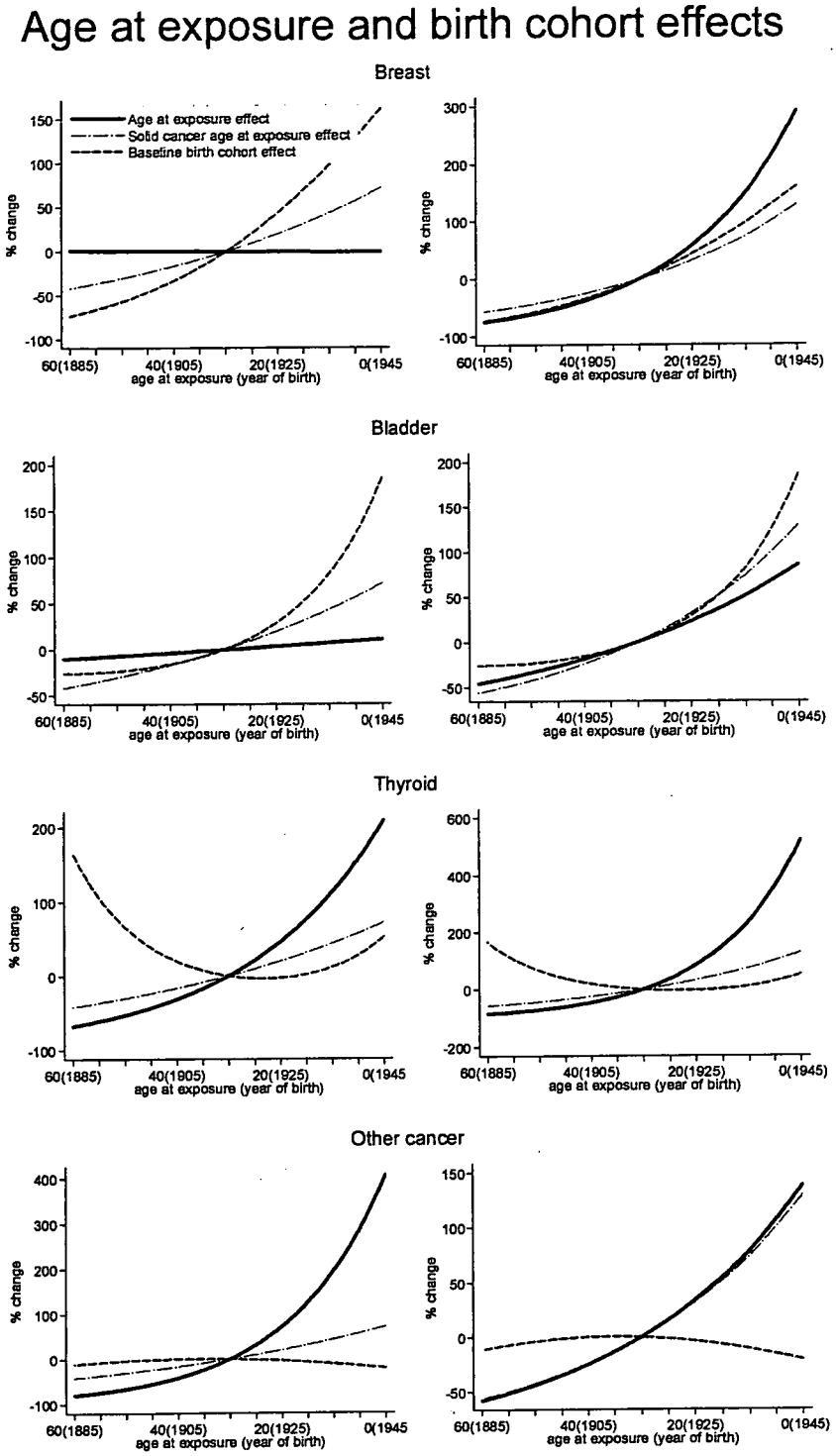

FIG. 16. Comparison of age-at-exposure effects on the excess risk (thick solid line) and birth cohort effects on baseline rates (thick dashed line) for cancers of the breast, bladder, thyroid and other sites (see text for definition). Age-at-exposure effects for all solid cancers (thin dash-dot line) are also shown. The left-hand panels are for excess relative risk (ERR) estimates while the right-hand panels are for excess rate (EAR) estimates. Age-at-exposure effects on the radiation-associated excess risk are measured relative to the risk for a cohort member who was 30 years old at the time of exposure. Birth cohort effects on age-specific baseline rates are measured relative to people born in 1915.

histology and etiology. While excess estrogenic stimulation is considered to be the principal risk factor for cancer of the uterine corpus (*97*), oncogenic subtypes of human papillomavirus are the major etiological factor for squamous cell carcinoma of the cervix (*98*). Mortality rates are a poor measure of uterine cancer risk because cervix and corpus cancer patients both have a high 5-year survival of about 70% (*49*). In Japan, as in many other populations, incidence rates for cervical cancer have decreased steadily, while corpus cancer rates have increased. Cervical cancers, however,

TABLE 30
Female Breast Cancer Radiation-Risk-Model Parameter Estimates with Early Onset and Menopause Effects[a]

Model	Attained age range	Risk per Gy[b]	Age at exposure[c] (percentage change per decade increase)	Attained age[c] (power)	Early-onset effect[c] (age under 35)
ERR	any	0.98 (0.64; 1.40)[d]	−3% (−22%; 20%)	−1.55 (−2.8; −0.3)	4.5 (1.8; 11)
	0–49			5.2 (2.9; 7.8)	3.5 (1.1; 12)
EAR	50+	5.3[e] (2.5; 8.6)	−29% (−41%; −14%)	−2.2 (−5.1;−0.01)	

[a] Menopause effect only included in excess absolute rate (EAR) model. The menopause effect on the EAR was modeled by fitting a log-linear spline in log(age) with a single knot at age 50.
[b] Risk at age 70 after exposure at age 30 per Gy weighted breast dose.
[c] Models include attained-age, age-at-exposure and early-onset effects. The early onset effect is modeled as a multiplicative factor associated with attained age less than 35.
[d] 90% confidence interval.
[e] Excess cases per 10,000 per PY Gy.

are still about twice as frequent as corpus cancers (*99*). The incidence rate of cancer of the uterus—cervix and corpus cancers together—ranks fourth in Japanese women in the most recent years (*33*).

In our previous analysis of the LSS cancer incidence data, we found a non-significant reduction in radiation risk (ERR less than 0) for cancer of the uterus (*2*). The ERR estimate for uterine cancer in the latest LSS mortality data was positive but considerably lower than that for all solid cancers (*20*). Elsewhere, excess risk of uterine corpus cancer has been linked to high-dose radiation therapy administered for medical reasons (benign gynecological conditions, cervical cancer, or breast cancer) (*56, 62, 100, 101*). Few occupational studies provide risk estimates for uterine cancer, largely because the study populations are predominantly male. The latest study of the employees of the UK Atomic Energy Authority showed significantly higher mortality from uterine cancer among radiation workers compared to non-radiation workers, although there was no indication of a dose response (*102*). In contrast, in a large study of U.S. female X-ray technologists, the standardized incidence rate for uterine cancer was significantly reduced in comparison to U.S. population rates (*103*).

The world-population age-standardized rate for all uterine cancers among Japanese women in 1999 was estimated as 12.8 cases per 100,000 women per year (*33*). This rate includes contributions of 6.6 cervical cancer cases, 5.4 cancers of the uterine corpus, and 0.8 cases in which the nature of the tumor was not specified. As can be seen in Table 5, world-population age-standardized cervical cancer rates are slightly less than those in the U.S. or Sweden, while cancers of the uterine corpus are considerably less common.

We analyzed all cancers of the uterus as a group as well as cervical cancer and uterine corpus cancer as specific sites. Most cancers of the uterus reported on death certificates lack histology or site information and are coded as "uterine cancer, NOS"; however, these are likely to be cancers of the cervix in Japan, because it is common practice for Japanese physicians to report cervical cancer as "uterus cancer" in death certification. In this analysis, we therefore included the 119 uterine cancers, NOS in the cervical cancer group.

There were a total of 1,162 incident cases of uterus cancer including 978 with cervix cancer or uterus cancer NOS and 184 with uterine corpus cancer. Almost all (97%) of the cases explicitly identified as cervical or corpus cancers were confirmed histologically, and only 1% of these cases were identified solely on the basis of death certificates. However, for the 119 uterine cancers of unspecified location, only 55% were confirmed histologically and 30% were ascertained solely from death certificates (Table 3).

1. Baseline rates and birth cohort effects

The age-specific rates for cancer of the uterus as a whole increased with increasing age at exposure, largely reflecting the trends for cancer of the cervix since they account for most of the cases (Table A12). Based on the baseline rate models fitted in our analyses, uterine cancer rates increased rapidly with increasing attained age until about age 55 and then decreased. The data also exhibited a striking birth cohort effect, with age-specific rates increasing by about 25% (90% CI 19%; 30%) for each decade increase in the year of birth. Cervical cancer baseline rates followed a similar pattern. Rates for cancer of the body of the uterus also tended to increase with age until around the time of menopause and then declined; however, the birth cohort effect was in the opposite direction, with age-specific rates decreasing by about 30% (90% CI 20%; 36%) for each decade increase in the year of birth.

2. Dose response and excess cases

The crude rates in Table A12 showed a dose related increase for all uterus, cervix and corpus cancers among those exposed at young ages, especially as children, but dose-related patterns were not clear for those exposed at older ages. The data did not support detailed modeling of the

TABLE 31
Observed and Fitted[a] Uterine Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Subjects	Person years	Cases	Background	Fitted excess	Attributable fraction
<0.005	35,883	994,845	658	662.8	0.0	0.0%
0.005–0.1	16,535	454,537	318	302.8	0.9	0.3%
0.1–0.2	3,379	92,983	59	64.6	0.9	1.4%
0.2–0.5	3,643	99,048	73	67.9	2.2	3.1%
0.5–1	1,908	52,009	30	34.4	2.4	6.4%
1–2	895	23,746	15	15.4	2.1	11.8%
2–4	282	7,285	9	4.5	1.0	18.9%
Total	62,525	1,724,452	1,162	1,152.5	9.5	1.9%[c]
ERR per Gy[c]			0.10 (90% CI −0.09; 0.33)			
EAR per Gy			0.56 (90% CI < −0.01; 1.9)			

[a] Estimates of background and fitted excess cases are based on an ERR model with a linear dose response without effect modification. All not-in-city subjects were used in the modeling, but the baseline risk model allows for city-specific differences in the level of the baseline risks for the not-in-city group.

[b] Weighted uterine dose in Gy.

[c] Estimated time-constant ERR at 1 Gy with 90% confidence interval with estimated EAR and confidence limits derived from this value. The EAR has units of excess cases per 10,000 person years per Gy.

effect modification due to the small estimated numbers of radiation-associated cases.

As indicated in Table 31, under a simple linear dose–response model without effect modification, we estimated that there were 9.5 radiation-associated cases of uterine cancers as a group. We estimated that there were 4.2 radiation-associated cancers of uterine corpus, and 4.7 radiation-associated cervical cancers (Table 32). These cases represented 1.9%, 5.1% and 1.1% of the cancers in those exposed to >5 mGy for all uterus, uterine corpus and cervix cancer, respectively.

The ERR_{1Gy} estimates for all uterine cancers, corpus cancers, and cervical cancers were 0.10 (90% CI −0.09; 0.33), 0.3 (90% CI −0.14; 0.95), and 0.06 (90% CI −0.14; 0.41), respectively. The corresponding EAR estimates are 0.56 (90% CI <0; 1.9), 0.33 (90% CI <0; 1.6), and 0.30 (90% CI < 0; 0.92) for all uterine cancers, cervical cancers, and corpus cancers, respectively.

For all uterine cancers as a group, there was a suggestion ($P = 0.15$) of an effect of young age at exposure (under 20) on the ERR. The estimated ERR for this group was 0.37 (90% CI 0.001, 0.86). The evidence for this effect came primarily from the uterine corpus cancer data, for which the ERR_{1Gy} for those exposed under age 20 years was 1.00 (90% CI 0.14; 2.4). There also was significant heterogeneity between the risks for women exposed before

TABLE 32
Observed and Excess[a] Cancers of the Uterine Corpus and Cervix by Dose Category with Attributable Risks

	Uterine corpus			Cervix and NOS		
Dose category[b]	Cases	Fitted excess	Attributable fraction	Cases	Fitted excess	Attributable fraction
<0.005	110	0.0	0.0%	548	0.0	0.0%
0.005–0.1	46	0.4	0.9%	272	0.5	0.2%
0.1–0.2	10	0.4	3.9%	49	0.5	0.8%
0.2–0.5	8	1.0	8.3%	65	1.1	1.8%
0.5–1	4	1.0	16.2%	26	1.2	3.9%
1–2	4	0.9	27.5%	11	1.0	7.2%
2–4	2	0.5	39.5%	7	0.5	12.0%
Total	184	4.2	5.1%[c]	978	4.7	1.1%[c]
ERR per Gy[d]	0.29 (90% CI −0.14; 0.95)			0.06 (90% CI −0.14; 0.31)		
EAR per Gy	0.30 (90% CI −0.16; 0.92)			0.33 (90% CI −0.79; 1.7)		

[a] Estimates of the fitted excess cases are based on an ERR model with a linear dose response without effect modification. All not-in-city subjects were used in the modeling, but the baseline risk model allows for city-specific differences in the level of the baseline risks for the not-in-city group.

[b] Weighted uterus dose in Gy.

[c] Attributable fraction among cohort members with dose greater than 0.005 Gy.

[d] Estimated time-constant ERR at 1 Gy with 90% confidence interval with estimated EAR and confidence limits derived from this value. The EAR has units of excess cases per 10,000 person years per Gy.

and after age 20 ($P = 0.04$). There was no evidence of an age-at-exposure effect on cervical cancer. The cervical cancer ERR estimates were 0.15 and 0.02 for those exposed at ages <20 and 20 or over, respectively (P for heterogeneity >0.5).

As with the previous LSS incidence and mortality findings (*2*), despite the relatively large number of cases, the data provided no indication of radiation effects on cancers of the uterus as a group or on cervical cancer. However, there was a suggestion of a radiation effect on the risk of cancer of the uterine corpus among women exposed before age 20. In the AHS, a dose-related increase in the occurrence of uterine myoma was found (*104–106*). The suggestion of an increased risk of uterine corpus cancer among the survivors exposed at young ages is of interest in view of the fact that uterine myoma and corpus cancer share a common etiology, i.e., estrogenic stimulation. The present finding is based on a very small number of excess cases and needs to be interpreted with caution.

Ovary (ICD10: C56)

Ovarian cancers are relatively common in Western populations but are rather infrequent in Japan. The world-population age-standardized ovarian cancer rate among Japanese women in 1999 has been reported as 7.0 (*33*). This is about half of the rates seen in the U.S., Sweden (Table 5) or other European countries (*67*). Incidence rates have been slowly increasing in Japan and many Western countries (*67, 107*). The etiology of ovarian cancer is poorly understood, but pregnancy and oral contraceptive use are known to decrease the risk of ovarian cancer, possibly by affecting the lifetime number of ovulations (*108*). The increasing Japanese rates have been attributed to declining parity but may be due in part to improvements in diagnosis and reporting (*108, 109*).

An increased risk of ovarian cancer has been found among 10-year survivors of high-dose radiotherapy for cervical cancer (average ovary dose of 35 Gy) (*56*). Studies of other medically irradiated populations at moderate doses have yielded varying results. At moderate doses, a higher than expected incidence of cancer of the female genital organs (mainly ovary and uterine corpus) was found among women irradiated for benign gynecological diseases in Connecticut (*110*); studies of other populations irradiated for similar conditions in the U.S. and Scotland (mean ovary doses were 5.3 and 2.3 Gy, respectively) found only insignificantly increased ERRs (*62, 111*). Mortality from ovarian cancer in patients irradiated for ankylosing spondylitis (mean ovary dose of 5.5 Gy) was not higher than expected (*112*). The LSS incidence data were the first to provide evidence of a dose response for ovarian cancer after radiation exposure at doses less than several Gy (*2, 113*).

There were 245 cases of ovarian cancer, which represented 2.6% of total female solid cancer cases in the LSS. The histological verification rate of 88% and the DCO rate of 5% suggest relatively good data quality (Table 3).

1. Baseline rates and birth cohort effects

The crude rates for ovarian cancer (Table A13) suggested that baseline rates did not increase rapidly with attained age and did not suggest marked birth cohort effects. This impression was borne out by our baseline rate models in which rates increased roughly in proportion to age squared before age 60 and less rapidly after that. Our models also suggested that birth cohort effects were not large, with age-specific rates decreasing by less than 4% for each decade decrease in the year of birth.

2. Dose response and excess cases

The ovarian cancer rates in Table A13 suggested that, for all exposure ages, risks in the highest dose category are increased relative to those in the lowest category considered. A simple linear dose–response model without effect modification provided a standardized ERR_{1Gy} estimate of 0.61 (90% CI 0.00; 1.5), which was similar in magnitude to that for total solid cancers for women (Table 33). The EAR estimate was 0.56 (90% CI 0.02; 1.3) per 10,000 PY Gy. Under a linear dose–response model, it was estimated that 11.4 cases were associated with the radiation exposure—an attributable fraction of 10.3% among those exposed at >0.005 Gy. Further analysis of modifying effects was not possible due to the small number of excess cases and the moderate radiation effect.

Prostate (ICD10: C61)

While prostate cancer is the most common cancer among men in the U.S., Japanese men have one of the lowest incidence rates in the world. Data from the last few decades indicate, however, that both incidence and mortality are increasing in Japan. Incidence rates jumped about 66% from 1960 to 1980, but the increase was strikingly higher from 1970 to 1980 (*114*). By 1999, the world-population age-standardized incidence rate was 14.1 per 100,000 population (*33*). These rates are about one-eighth of those in the U.S. and less than one-quarter of those in Sweden (Table 5). Increased detection as a result of the introduction and swift adoption of new diagnostic technologies as well as the incidental diagnosis of prostate cancer during transurethral resection for benign prostatic hyperplastic disease appear to be the principal reasons for this worldwide leap in reported incidence rates.

In the previous LSS cancer incidence evaluation, Thompson and colleagues (*2*) reported an ERR per Gy of 0.29 with a negative lower 95% confidence bound. Studies of patients receiving radiotherapy for benign diseases have not yielded convincing evidence of an association between radiation exposure and risk of prostate cancer; however, few of these studies had individual organ dose estimates and several included people who were young at exposure and

TABLE 33
Observed and Fitted[a] Ovarian Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Subjects	Person years	Cases	Background	Fitted excess	Attributable fraction
<0.005	35,883	994,845	142	135.0	0.0	0.0%
0.005–0.1	16,529	454,505	56	61.4	1.1	1.8%
0.1–0.2	3,385	93,094	15	12.8	1.1	7.9%
0.2–0.5	3,640	98,950	13	13.4	2.6	16.1%
0.5–1	1,910	52,022	9	7.0	2.9	29.2%
1–2	897	23,809	9	3.1	2.5	44.4%
2–4	281	7,227	1	0.9	1.2	58.3%
Total	62,525	1,724,453	245	233.6	11.4	10.3%[c]
ERR per Gy[d]			0.61 (90% CI 0.00; 1.5)			
EAR per Gy			0.56 (90% CI 0.02; 1.3)			

[a] Estimates of background and fitted excess cases are based on an ERR model with a linear dose response without effect modification. All not-in-city subjects were used in the modeling, but the baseline risk model allows for city-specific differences in the level of the baseline risks for the not-in-city group.

[b] Weighted dose to the ovaries in Gy.

[c] Attributable fraction among cohort members with dose greater than 0.005 Gy.

[d] Estimated time-constant ERR at 1 Gy with 90% confidence interval with estimated EAR and confidence limits derived from this value. The EAR has units of excess cases per 10,000 person years per Gy.

had not experienced long enough follow-up to reach the usual age to develop prostate cancer (*55, 112*).

Prostate cancers comprised about 2% of the total malignancies ascertained among members of the LSS cohort and 4.9% of malignancies occurring among males. Of the 387 prostate cancers included in this study, the diagnosis was based on histological verification for 342 (88%), whereas less than 5% of the cancers were identified based on DCO (Table 3).

1. Baseline rates and birth cohort effects

Prostate cancer is a disease of old age and, as in most populations, the LSS baseline incidence rates for prostate cancer increased rapidly among older men. Rates also rose with each succeeding birth cohort, so that the incidence rate for 70-year-olds who were born in 1885 was about one-third of that observed among 70-year-old males born 40 years later, i.e. in 1925. The LSS baseline rates, which increase in proportion to age to the ninth power, reflect this. There was a large birth cohort effect, with age-specific rates increasing by about 30% per decade increase in the year of birth.

2. Dose response and excess cases

The crude incidence rates for prostate cancer (Table A14) clearly indicated the upsurge in rates with increasing age at diagnosis but did not provide much of a suggestion of a dose response except possibly for men who were very young (0–9) at the time of exposure. Analysis of the data using a simple model without effect modification provided little evidence of dose response ($P > 0.5$). Less than four excess cases, or an attributable fraction of 2%, were predicted among survivors exposed >0.005 Gy (Table 34).

The standardized ERR_{1Gy} was 0.11 (90% CI, −0.10; 0.54) and the EAR was 0.34 (90% CI, −0.64; 1.60). Because of the small number of radiation-associated cases, it was not possible to make useful inferences about effect modification for this site.

Renal Cell (ICD10: C64)

Renal cell cancers are by far the most common type of kidney cancers, usually comprising about 70%, whereas the other cancers of the urinary tract generally are transitional (urothelial) cell carcinomas. Cancers of the kidney are more common among men than women, and over the last few decades the incidence has been increasing in many parts of the world (*115, 116*). In 1999, the world-population age-standardized incidence rates were 6.4 and 2.5 per 100,000 Japanese males and females, respectively (*33*). Based on data from a number of population-based cancer registries in Japan, the world-population age-standardized incidence rates for cancers of the kidney and renal pelvis more than doubled between 1975 and 1998 (Table 6).

In the previous LSS cancer incidence report, the ERR_{1Gy} estimates were 0.71 for cancers of the renal parenchyma and 1.66 for cancers of the renal pelvis and ureter; however, the number of cases was small (115 total kidney cancers) and the 95% confidence bounds were extremely wide (−0.11, 2.25 and −0.21, 6.57, respectively), indicating the instability of the estimates (2). Data regarding radiation effects on the kidney are sparse, but a few studies of patients receiving radiotherapy suggest an association (*56, 112*). The associations are weak and in general they have been noted when exposures were high.

Since the etiology for the various kidney cancers differs, we restricted our analysis to renal cell cancers, which accounted for 68% of the kidney cancers and about 1% of the total cancers diagnosed in the study cohort (Table 2).

TABLE 34
Observed and Fitted[a] Prostate Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Subjects	Person years	Cases	Background	Fitted excess	Attributable fraction
<0.005	24,909	604,098	231	225.7	0.0	0.0%
0.005–0.1	11,262	275,096	87	96.8	0.4	0.4%
0.1–0.2	2,143	52,830	22	20.5	0.3	1.5%
0.2–0.5	2,289	54,915	25	21.7	0.8	3.4%
0.5–1	1,282	29,579	13	10.9	0.8	7.2%
1–2	751	17,662	7	6.3	0.9	12.8%
2–4	266	6,099	2	1.6	0.4	20.8%
Total	42,902	1,040,279	387	383.4	3.6	2.2%[c]
ERR per Gy[d]			0.11 (90% CI −0.10; 0.54)			
EAR per Gy			0.34 (90% CI −0.64; 1.6)			

[a] Estimates of background and fitted excess cases are based on an ERR model with a linear dose response without effect modification. All not-in-city subjects were used in the modeling, but the baseline risk model allows for city-specific differences in the level of the baseline risks for the not-in-city group.

[b] Weighted bladder dose in Gy.

[c] Attributable fraction among cohort members with dose greater than 0.005 Gy.

[d] Estimated time-constant ERR at 1 Gy with 90% confidence interval with estimated EAR and confidence limits derived from this value. The EAR has units of excess cases per 10,000 person years per Gy.

The diagnosis for 82% of the 167 renal cell cancers was confirmed histologically, whereas the diagnosis was based on DCO for almost 7% (Table 3).

1. Baseline rates and birth cohort effects

As suggested by the low-dose crude rates in Table A15, baseline renal cell cancer rates in the LSS tend to increase with attained age for men but did not increase very much for women. At age 70, the baseline rate for women was about one-third of that for men. The baseline rate models suggested that age-specific renal cancer baseline rates in the LSS have increased by about 20% per decade increase in year of birth.

2. Dose response and excess cases

Although the number of cases was not large, the crude rates in Table A15 suggested that renal cell cancer incidence rates increase with dose; however, a simple linear ERR model without effect modification provided no indication of a significant dose response ($P > 0.5$). The estimated ERR_{1Gy} was 0.13 (90% CI −0.25; 0.75), which was less than that in the previous incidence report (*2*). Under this model it was estimated that only about two of the cases were associated with radiation exposure (Table 35).

Score tests suggested that the ERR may decrease with either age at exposure ($P = 0.005$) or attained age ($P < 0.001$). Another way to look at this issue is to fit a time-

TABLE 35
Observed and Fitted[a] Renal Cell Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Subjects	Person years	Cases	Background	Fitted excess	Attributable fraction
<0.005	60,792	1,598,944	97	92.8	0.0	0.0%
0.005–0.1	27,789	729,603	44	44.6	0.2	0.4%
0.1–0.2	5,527	145,925	8	9.2	0.2	1.9%
0.2–0.5	5,935	153,886	9	9.9	0.4	4.1%
0.5–1	3,173	81,251	3	5.1	0.5	8.6%
1–2	1,647	41,412	5	2.6	0.5	15.2%
2–4	564	13,711	1	0.8	0.2	24.3%
Total	105,427	2,764,732	167	165.0	2.0	2.7%[c]
ERR per Gy[d]			0.13 (90% CI −0.25; 0.75)			
EAR per Gy			0.08 (90% CI −0.16; 0.44)			

[a] Estimates of background and fitted excess cases are based on a constant ERR model with a linear dose response without effect modification. All not-in-city subjects were used in the modeling, but the baseline risk model allows for city-specific differences in the level of the baseline risks for the not-in-city group.

[b] Weighted bladder dose in Gy.

[c] Attributable fraction among cohort members with dose greater than 0.005 Gy.

[d] Estimated time-constant ERR at 1 Gy with 90% confidence interval with estimated EAR and confidence limits derived from this value. The EAR has units of excess cases per 10,000 person years per Gy.

constant EAR model, which, in view of the increase in baseline rates with increasing attained age, implicitly assumes that the ERR decreases with attained age. Under this model the dose response was statistically significant ($P = 0.002$). The estimated EAR estimate was 0.25 cases per 10,000 PY per Gy (90% CI 0.07; 0.53) with an estimate of six radiation-associated cases. In view of the small number of radiation-associated renal cell cancers, it is difficult to come to any firm conclusions regarding radiation effects; however, if radiation increased the renal cell cancer rates, the magnitude of the ERR has decreased over time.

Bladder (ICD10: C67)

Bladder cancer is a disease that occurs at older ages and is about three times more common among males than females. In the U.S. the incidence among whites is more than two times that among Japanese living in California or Hawaii (*117*). Thus it may not be surprising that in Japan, bladder cancer accounts for less than 3% of all cancer, a percentage that is lower than in other industrialized nations. The incidence of bladder cancer is about four times more common among Japanese men than women. Incidence rises steeply with age, with the large majority (almost 75%) of cancers occurring after age 65 years (*33*). Understanding the temporal trends for bladder cancer incidence over the last few decades is complicated by accompanying changes in medical practice, including the increase in diagnosis of early-stage disease. Nonetheless, incidence has increased until fairly recently when rates started to level off. Over the last half-decade, large improvements in survival have resulted in a decrease in mortality (*117*). In 1999, the world-population age-standardized incidence rates for bladder cancer among Japanese men and women were 9.7 and 2.2, respectively.

Several risk factors for bladder cancer have been identified. Cigarette smoking, occupational exposure to aromatic amines, and ionizing radiation have clearly been linked to bladder cancer, while shistosomiasis, analgesics containing phenacetin, and cyclophosphamide have a high likelihood of being related (*117*). Previous incidence (*2*) and mortality (*20*) studies of the A-bomb survivors have reported strong and significant associations between radiation dose from the bombings and bladder cancer with ERRs of over one. These studies, however, were based on a relatively small number of cases (210 incidence cases and 150 deaths) and a very small number of excess cancers, so not much attention was focused on this site. Radiation also has been linked to an elevated risk of bladder cancer in several patient populations (*37*). A dose-related increase in the incidence of bladder cancer was reported after high-dose radiotherapy (mean dose 45 Gy) for cervical cancer (*56*). Significant and larger ERRs were observed for patients receiving radiotherapy for benign diseases that resulted in mean bladder doses of between 2 and 6 Gy (*62, 111, 112*).

The current evaluation included 469 cases of bladder cancer, which accounted for about 3% of all solid cancer cases and 71% of urinary tract cancer cases. Eighty-eight percent of the cases had histologically confirmed diagnosis, whereas only 5% of the cases were identified through death certificates (Table 3). The cases used in these analyses included 185 cases that were diagnosed after 1987 and 66 cases diagnosed prior to 1988 among people who were not in the cities at the time of the bombings.

1. Baseline rates and birth cohort effects

Prior to about age 80, the increase in bladder cancer baseline rates for both men and women in the LSS was roughly proportional to age to the sixth power. However, after age 80 the rates appeared to level off or even decrease slightly. A highly significant ($P < 0.001$) birth cohort effect was seen for men, with age-specific rates increasing by about 33% for each decade increase in year of birth (Fig. 16). However, there was no indication ($P > 0.5$) of a birth cohort effect on baseline rates for women.

2. Dose response and excess risks

Table A16 presents the crude bladder cancer incidence rates and numbers of cases by dose category and age at exposure. These rates provided a strong suggestion of a dose response. Estimates of background and fitted excess cases from our standard ERR model with effect modification and a linear dose response are shown in Table 36.

Allowing for effects of gender, age at exposure and attained age, we estimated that there were 35 radiation-related bladder cancers. The attributable fraction was 16% for survivors exposed to over 0.005 Gy. For persons exposed to 1 Gy or more, almost 60% of the cancers could be attributed to their radiation exposure.

Based on our standard linear dose–response model with effect modification, there was statistically significant evidence of a dose response with the gender-averaged estimated ERR per Gy of 1.23 (Table 37 and Fig. 17). This was the largest gender-averaged, attained-age-70 ERR estimate for any organ. The linear ERR model fit the data well, and there was no evidence of non-linearity ($P = 0.5$) (Fig. 17).

The ERR estimate of 0.61 for men was one-third of that (1.86) for women (Table 37). Among the sites considered in these analyses, this ERR gender ratio was second only to that for lung cancer. With only 35 excess bladder cancer cases, the effect estimates were uncertain; however, the patterns seen in this analysis very closely mirror those observed in the first cancer incidence report (2). There was no indication that the ERR per Gy varied with either age at exposure or attained age (Tables 11, 12 and 37 and Figs. 16 and 18). It should be noted that bladder cancer was the only site for which the ERR did not decrease with increasing attained age.

The gender-averaged EAR per 10,000 PY for bladder cancer was 3.2 (Table 37), with estimates of 3.8 for males

TABLE 36
Observed and Fitted[a] Bladder Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Subjects	Person years	Cases	Background	Fitted excess	Attributable fraction
<0.005	60,792	1,598,944	247	256	0.1	0.1%
0.005–0.1	27,792	729,598	120	110	3.5	3.1%
0.1–0.2	5,519	145,695	30	23	3.3	12.8%
0.2–0.5	5,938	154,102	32	24	7.9	24.6%
0.5–1	3,174	81,307	20	12	8.4	40.7%
1–2	1,649	41,330	16	7	7.9	54.6%
2–4	563	13,756	4	2	3.8	68.0%
Total	105,427	2,764,732	469	434	34.9	16.4%[c]

[a] Estimates of background and fitted excess cases are based on an ERR model with a linear dose response and effect modification by gender, age at exposure and attained age. All not-in-city subjects were used in the modeling, but the baseline risk model allows for city-specific differences in the level of the baseline risks for the not-in-city group.
[b] Weighted bladder dose in Gy.
[c] Attributable fraction among cohort members with dose greater than 0.005 Gy.

and 2.6 for females (male:female ratio of 0.7). Considering the much higher male background rates of bladder cancer, the relatively small gender difference in the EAR suggests that the effect of radiation may be additive with respect to factors leading to the gender difference in baseline rates (such as smoking). The results from the current study as well as others suggest that the bladder is quite sensitive to radiation. In contrast to other solid cancers, our results also show that both the ERR and EAR are increasing with time. Further studies taking smoking into account are needed.

Brain and Other Nervous System (ICD10: C70–C72)

The Hiroshima and Nagasaki tumor registries routinely ascertain all tumors of the brain and other nervous system because clinical behavior and treatment of benign and uncertain tumors is quite similar to that for malignant tumors at these sites. Thus, as in earlier LSS reports, we elected to include malignant, benign and tumors of uncertain behavior in our analyses of tumors of the nervous system. Gliomas are the most common malignant brain tumor, whereas meningiomas and schwannomas are the most common benign tumors (*118*). The distribution by gender differs by histology, with gliomas occurring more frequently among men and meningiomas having a much higher incidence among women. The incidence of malignant nervous system tumors has been increasing in many parts of the world, including Japan (*33, 34*), partly due to better methods of diagnosis, especially among the elderly. Based on data from 12 population-based cancer registries in Japan, the 1999 world-population age-standardized incidence rate was 2.7 and 2.0 per 100,000 Japanese males and females, respectively, and the rates for both men and women rose over 50% between 1975 and 1999 (*33*).

A significant dose–response relationship between brain tumors and external radiation has been reported in many cohorts of patients receiving radiotherapy for either benign or malignant diseases (*37, 119–121*). The most recent study of incident nervous system tumors in the LSS included a detailed pathology review with follow-up through 1995 (*14, 15*). Thus, because the current analyses did not add much additional information, the presentation is brief. The earlier detailed pathology review (*14, 15*) allowed evaluation of radiation risks by histological type. Elevated risks of borderline statistical significance were observed for glioma (ERR/Sv = 0.56, 95% CI: −0.2−2.0) and meningioma (ERR/Sv = 0.64, 95% CI: −0.01−1.8), while the risk for schwannoma was unusually high (ERR/Sv = 4.5, 95% CI: 1.9–9.2). Other studies of radiation effects on the nervous

TABLE 37
Bladder Cancer Radiation-Risk-Model Parameter Estimates

Model	Risk per Gy[a] Male	Female	Sex-averaged	Sex ratio (F:M)	Age at exposure[b] (percentage change per decade increase)	Attained age[b] (power)
ERR	0.61 (0.11; 1.2)[c]	1.9 (0.79; 3.4)	1.23 (0.59; 2.1)	3.1 (0.17; 1.0)	−3% (−42%; 56%)	0.33 (−2.8; 4.4)
EAR	3.8[d] (0.2; 8.0)	2.6 (1.1; 4.4)	3.2 (1.1; 5.4)	0.7 (0.21; 10)	−19% (−54%; 41%)	6.3 (3.2; 10.2)

[a] At age 70 after exposure at age 30 per Gy weighted bladder dose.
[b] Models include both attained-age and age-at-exposure effects.
[c] 90% confidence interval.
[d] Excess cases per 10,000 per PY Gy.

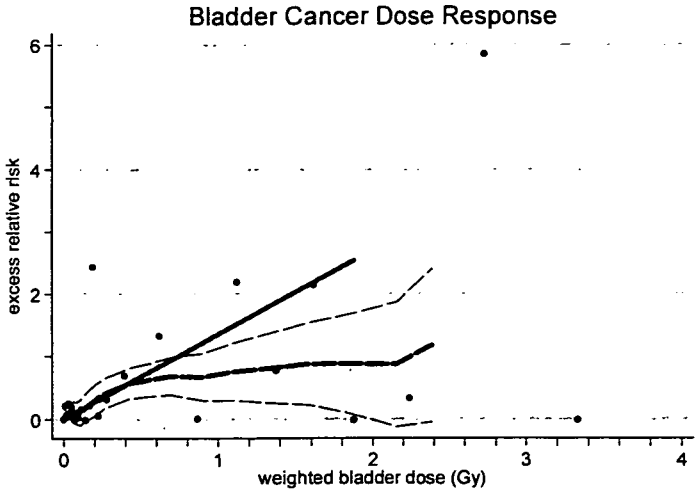

FIG. 17. Bladder cancer dose–response function. The thick solid line is the fitted linear gender-averaged excess relative risk (ERR) dose response at age 70 after exposure at age 30 based on data in the 0- to 2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The thick dashed line is a non-parametric smooth of the category-specific estimates and the thin dashed lines are one standard error above and below this smooth.

system support an association; however, the relationship is not as strong as for many other tumors and has been observed primarily after childhood exposure. Risks also appear to be higher for benign tumors, especially schwannomas, than malignant tumors.

All together there were 281 nervous system tumors, accounting for less than 2% of the tumors considered in these analyses. The histological breakdown was 56 gliomas, 110 meningiomas, 64 schwannomas, and 51 other types of tumors. The diagnosis for 81% of the nervous system tumors was confirmed histologically, whereas the diagnosis was based on DCO for 6% (Table 3).

1. Baseline rates and birth cohort effects

LSS nervous system tumor baseline rates for both men and women increased in proportion to attained age cubed. In contrast to most other solid tumors, nervous system tumor rates were somewhat higher for women than for men except late in life, when rates for women seemed to reach a peak whereas those for men continue to rise. As noted previously (*15*), there was an indication of a secular trend in baseline rates that appeared to be correlated with the introduction of CT and MRI examinations. Much of the evidence for this effect, however, could be captured by a birth cohort effect in which age-specific rates increase rapidly with year of birth for those born after about 1920. Rates for those born in 1940 were estimated to be almost three times those for people born in 1920.

2. Dose response and excess cases

Crude rates (Table A17) do not provide a clear indication of a dose response, partly because there were very few female cases in the high-dose category. Because the number of excess cases was small, we fit the data using a simple linear model without any effect modification. This analysis indicated a statistically significant ($P = 0.03$) dose response with an estimated ERR of 0.62 (90% CI 0.21, 1.17). There was no indication of significant non-linearity in the response ($P = 0.4$). These results were consistent with those presented previously (*14, 15*). Of the 281 nervous system tumors, 19 were estimated to be in excess (Table 38). Among the exposed, the attributable risk was about 13%, but among those who received doses above 1 Gy it reached 52%.

With only 19 excess cases, the data did not support detailed modeling of the effect modification, but there was an indication that the ERR for men was higher than that for women ($P = 0.02$) and that the ERR may decline with increasing age at exposure ($P = 0.1$) or attained age ($P = 0.01$). Using a constant EAR model, the EAR was 0.51 (90% CI 0.17, 0.95). Again there was a suggestion of a marked decline in risk with increasing age at exposure and attained age.

Thyroid (ICD10: C73)

Thyroid cancer incidence is relatively high in Japan compared with many other industrialized countries. As in many Western nations, incidence has been increasing, especially papillary carcinoma among women, over the last few decades. Improved medical diagnosis explains part of the increase (*122*). In Japan, over 90% of thyroid cancers are papillary carcinomas (*34*), possibly related to the iodine-rich diet. Worldwide, thyroid cancer incidence is substantially more common among women than men, and this pattern is clearly seen in Japan (1999 world-population age-Japanese incidence rate for females and males is 6.6 and 1.6 per 100,000 population, respectively) (*33*). Thyroid cancer generally has a relatively young age distribution, with a median age at diagnosis in the mid-50s.

External radiation exposure during childhood is the major known risk factor for thyroid cancer. The strong link between thyroid cancer and radiation has been observed in numerous populations exposed to medical radiation (*37*), but early studies of the atomic bomb survivors played a central role in demonstrating this association (*123*). Age at exposure is the most important modifier of risk (*37, 125*), and it also was noted among the survivors (*124*). To better understand the patterns of radiation risk, seven studies of thyroid cancer and radiation were pooled, and a joint analysis was conducted (*125*). With about 700 thyroid cancers, this large series clearly demonstrated a linear dose–response relationship, as well as the impact of young age at exposure on excess relative risk. While females had a two-fold greater risk, the difference was not statistically significant and was not consistent in all of the studies. Since the Chernobyl accident, it has become evident that childhood

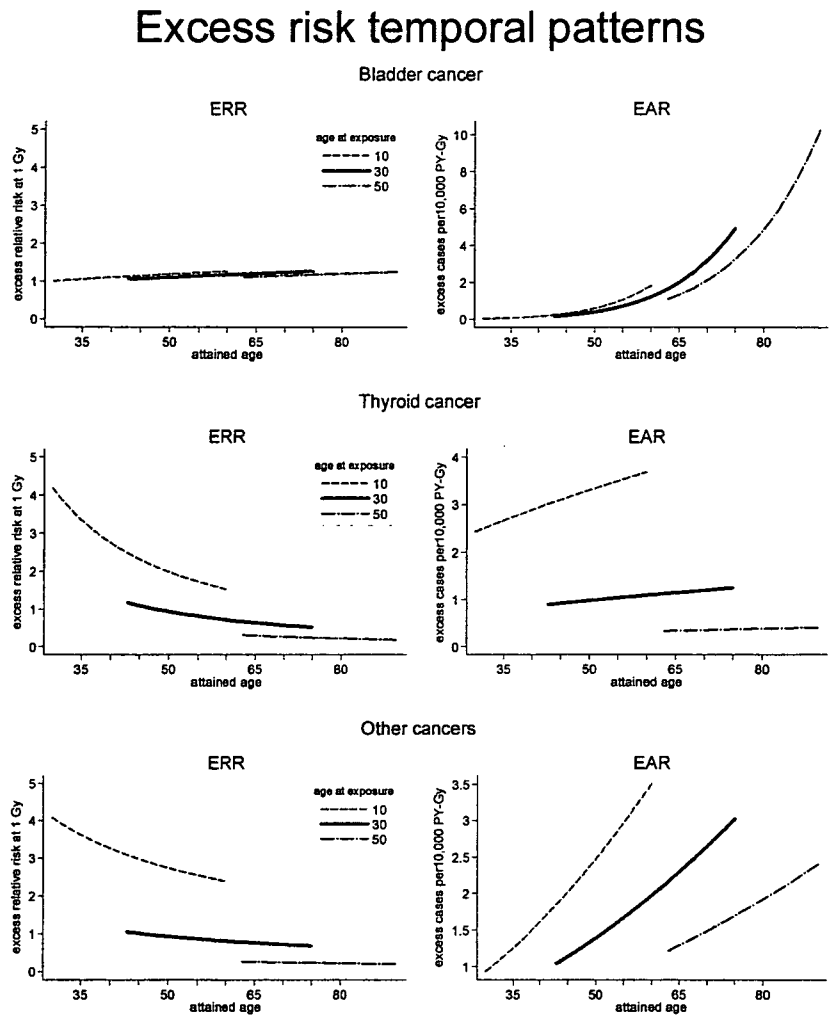

FIG. 18. Temporal patterns and age-at-exposure variation in the radiation-associated excess risk for cancers of the lung, bladder, thyroid and other sites (see text for definition). The panels in the left column compare variation in the gender-averaged excess relative risk (ERR) at 1 Gy with attained age for ages at exposure of 10, 30 and 50 years. The panels in the right column compare variation in the gender-averaged excess absolute risk (EAR) at 1 Gy with attained age for ages at exposure of 10, 30 and 50 years.

TABLE 38
Observed and Fitted[a] Brain and Other Nervous System Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Subjects	Person years	Cases	Background	Fitted excess	Attributable fraction
<0.005	60,792	1,598,935	144	135.7	0.1	0.0%
0.005–0.1	26,186	689,474	66	74.4	1.5	1.9%
0.1–0.2	6,018	156,993	19	17.8	1.6	8.3%
0.2–0.5	6,820	179,898	21	19.9	4.4	18.1%
0.5–1	2,529	62,294	15	6.7	3.1	31.8%
1–2	2,194	55,703	14	5.6	4.7	45.7%
2–4	888	21,434	2	2.1	3.5	63.4%
Total	105,427	2,764,731	281	262.1	18.9	13.0%[c]
ERR per Gy[d]			0.62 (90% CI 0.21; 1.2)			
EAR per Gy			0.51 (90% CI 0.17; 0.95)			

[a] Estimates of background and fitted excess cases are based on an ERR model with a linear dose response without effect modification. All not-in-city subjects were used in the modeling, but the baseline risk model allows for city-specific differences in the level of the baseline risks for the not-in-city group.

[b] Weighted brain dose in Gy.

[c] Attributable fraction among cohort members with dose greater than 0.005 Gy.

[d] Estimated time-constant ERR at 1 Gy with 90% confidence interval with estimated EAR and confidence limits derived from this value. The EAR has units of excess cases per 10,000 person years per Gy.

TABLE 39
Observed and Fitted[a] Thyroid Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Cases	Background	Fitted excess	Attributable fraction
<0.005	206	215	0	0.1%
0.005–0.1	115	106	4	3.9%
0.1–0.2	36	27	4	14.1%
0.2–0.5	51	31	12	28.5%
0.5–1	24	14	12	46.1%
1–2	24	11	16	60.5%
2–4	15	4	13	78.1%
Total	471	408	63	24.5%[c]

[a] Estimates of background and fitted excess cases are based on an ERR model with a linear dose response with effect modification by gender, age at exposure and attained age. All not-in-city subjects were used in the modeling, but the baseline risk model allows for city-specific differences in the level of the baseline risks for the not-in-city group.

[b] Weighted thyroid dose in Gy.

[c] Attributable fraction among cohort members with dose greater than 0.005 Gy.

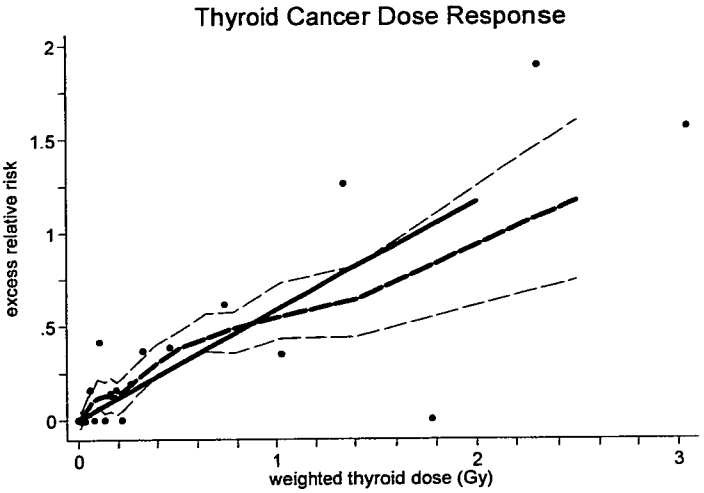

FIG. 19. Thyroid cancer dose–response function. The thick solid line is the fitted linear gender-averaged excess relative risk (ERR) dose response at age 70 after exposure at age 30 based on data in the 0- to 2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The thick dashed line is a non-parametric smooth of the category-specific estimates and the thin dashed lines are one standard error above and below this smooth.

^{131}I exposure increases the risk of thyroid cancer substantially (*126*).

In the first comprehensive LSS cancer incidence report (*2*), a pronounced radiation risk was apparent for thyroid cancer. The risk decreased rapidly with increasing age at exposure, so that it was no longer elevated among persons exposed after age 30. Little gender difference was observed, although the risk was slightly higher among women.

The present series included 471 thyroid cancers, 381 among females and 90 among males. Based on a population comparable to the one evaluated in the first incidence report, the number of cases increased more than 50% during the extended follow-up period. It can be seen from Table 3 that 95% of the thyroid cancers considered here were verified microscopically while only 1% were identified solely from death certificates.

1. Baseline rates and birth cohort effects

Thyroid cancer accounted for less than 3% of the cancers diagnosed among LSS cohort members. Modeling of the background rates demonstrated a high female-to-male ratio (slightly over 2). The median age at diagnosis for thyroid cancer was 60.4 years compared with 67.4 years for all solid cancers combined. After allowing for birth cohort effects, the increase with age in thyroid cancer baseline rates was less rapid than what was seen for other solid cancers. Prior to age 70, incidence rates increased roughly proportional to attained age to power 1.5 for men and proportional to age squared for women. For both men and women, the baseline rate estimates tend to peak around age 75 and appear to decline markedly after that.

Baseline thyroid cancer incidence rates for AHS participants were estimated to be about 40% higher than those for other cohort members (90% CI 16%; 70%, $P = 0.003$). Because of this difference, all of the dose–response analyses were adjusted for AHS participation.

Baseline thyroid cancer rates in the LSS exhibited birth cohort effects, which were complicated by microcarcinomas diagnosed during the autopsy program conducted at RERF until about 1970. Overall rates were about three times higher for persons born in 1885 compared with those born in 1915. Rates remained fairly stable until the 1930 birth cohort began to experience a rapid rise in rates. A better description of the baseline rates that excludes thyroid cancer cases diagnosed at autopsy suggested that age-specific rates increased steadily with increasing year of birth.

2. Dose response and excess risks

The crude rates exhibited a strong pattern of increasing incidence with increasing dose (Table A18). The standard linear dose–response model with effect modification predicted 63 radiation-associated thyroid cancers among survivors receiving over 0.005 Gy; i.e., about 25% of cases could be attributed to their radiation exposure (Table 39). The attributable fraction increased sharply with increasing dose categories, so that among persons exposed to 1 Gy or more, it was estimated that approximately two-thirds of the cancers were radiation-related.

As seen in Fig. 19, the dose response appeared to be linear. However, over the dose range from 0 to 2 Gy there was a suggestion of downward curvature ($P = 0.10$). At doses below 0.1 Gy, the risk estimates from the linear-quadratic model were about 70% greater than those for the linear model, and for doses of 1.5 Gy, the fitted ERRs for a linear-quadratic dose–response model with effect modification were 50% larger than those for the linear model.

The gender-averaged ERR_{1Gy} estimate was 0.57, with fe-

TABLE 40
Thyroid Cancer Radiation-Risk-Model Parameter Estimates

Model	Risk per Gy[a]			Sex ratio (F:M)	Age at exposure[b] (percentage change per decade increase)	Attained age[b] (power)
	Male	Female	Sex-averaged			
ERR	0.49 (0.15; 1.15)[c]	0.65 (0.27; 1.25)	0.57 (0.24; 1.1)	1.3 (0.56; 3.9)	−31% (−59%; 4%)	−1.5 (−2.9; 0.0)
EAR	0.5[d] (0.3; 1.5)	1.9 (1.3; 4.2)	1.2 (0.48; 2.2)	3.6 (1.78; 9.5)	−46% (−68%; −12%)	0.60 (−0.58; 1.8)

[a] At age 70 after exposure at age 30 per Gy weighted thyroid dose.
[b] Models include both attained-age and age-at-exposure effects.
[c] 90% confidence interval.
[d] Excess cases per 10,000 per PY Gy.

males having a 30% higher risk than males (Table 40). In a model that allows for the effects of both age at exposure and attained age, the parameter estimate for the age-at-exposure effect was high (31% decrease in risk with increasing decade of age at exposure), but the estimate did not reach statistical significance. It can be seen, however, that persons exposed early in life had a very high risk of thyroid cancer (Fig. 18). Indeed, for survivors aged 70, the fitted ERR model suggests that the excess risk of thyroid cancer for those exposed at age 30 was about twice as large as that for survivors exposed at age 50 and predicts that the excess for those exposed at age 10 will be about twice that for those exposed at age 30 (Tables 11 and 12). Risk also decreased with attained age and the parameter estimate of the attained age effect was of borderline significance; thus it appears that there is a joint effect of both age at exposure and attained age on the ERR. After allowing for the effect of AHS participation on the baseline rates, there was no evidence ($P > 0.5$) that the excess risk varies with AHS participation.

Due to the relatively few persons diagnosed with thyroid cancer, the EAR per 10,000 PY was not large (1.2), but it was significantly elevated (Table 40). The gender-specific EAR estimates were 1.9 for females and 0.5 for males, reflecting the high female-to-male gender ratio in the background rates and resulting in the largest female:male ratio (3.6) in the cohort. The EAR for thyroid cancer decreased significantly with age at exposure and increased slightly with attained age.

Other Sites

The tumor registry included information on 836 cases with cancer at sites other than those discussed thus far among the LSS subjects. The location was ill-defined for 213 (25%) of these cases. The remaining cases included 61 cancers of the small intestine or other parts of the digestive tract, 82 nasal cavity tumors, 133 cancers of the larynx, 12 cancers of the thymus, 27 respiratory tract cancers, 53 cancers of the bone and connective tissues, 17 melanomas, 9 male breast cancers, 50 cancers of the female genital organs, 33 cancers of the male genital organs, 105 cancers of the urothelial system (renal pelvis, ureter and urethra), and 41 cancers of the endocrine organs other than the thyroid. In view of the high proportion of cancers with ill-defined site, it was not surprising that the histological verification rate was rather low (75%) while the proportion of cases ascertained solely from death certificates (13%) was relatively high (Table 3).

1. Baseline rates and birth cohort effects

Table A19 presents the numbers of cases and crude rates for this collection of cancers stratified by gender, age at exposure (birth cohort), and dose category. The crude rates, together with more formal analyses of the baseline rates, indicated that males had about twice the rates of females and that the rates increased markedly with age. As with all solid cancers combined, this increase was roughly proportional to age to the 5th power with estimated rates appearing to plateau after age 80. There was little evidence of a birth cohort effect for either men or women.

2. Dose response and excess risks

As suggested by crude rates in Table A19, there was a statistically significant radiation dose response for this disparate group of cancers ($P < 0.001$). The dose–response data are shown in Fig. 20. There was no evidence of nonlinearity over the 0–2-Gy range. Under a linear dose–response model with allowance for effect modification by gender, age at exposure and attained age, we estimated that 65 of the cancers in this group are associated with the radiation exposure (Table 41). This excess made up 16% of the 392 cases among cohort members with dose estimates in excess of 0.005 Gy.

The gender-averaged standardized ERR_{1Gy} estimate was 0.91 (Table 42). There were no indications of statistically significant variation in the ERR with gender, age at exposure, or attained age, but the point estimates of the gender and age-at-exposure effects were quite similar to those for all solid cancers.

The gender-averaged standardized EAR estimate was 5.0 excess cases per 10,000 PY per Gy. While the EAR increased significantly with increasing attained age, the gender ratio was not significantly different from one.

The bottom panel in Fig. 18 displays the fitted age–time patterns from the ERR and EAR models for these data, while the bottom row in Fig. 16 compares the birth-cohort

TABLE 41
Observed and Fitted[a] Cancers at Sites Not Included in Other Analyses by Dose Category with Attributable Fraction Estimates

Dose category[b]	Cases	Background	Fitted excess	Attributable fraction
<0.005	436	441.6	0.3	0.1%
0.005–0.1	208	203.8	6.1	2.9%
0.1–0.2	53	42.2	5.6	11.7%
0.2–0.5	62	45.0	13.4	23.0%
0.5–1	37	23.3	15.8	40.4%
1–2	26	11.8	15.4	56.6%
2–4	14	3.3	8.4	71.8%
Total	836	771.0	65.0	16.4%[c]

[a] Estimates of background and fitted excess cases are based on an ERR model with a linear dose response with effect modification by gender, age at exposure and attained age. All not-in-city subjects were used in the modeling, but the baseline risk model allows for city-specific differences in the level of the baseline risks for the not-in-city group.
[b] Weighted colon dose in Gy.
[c] Attributable fraction among cohort members with dose greater than 0.005 Gy.

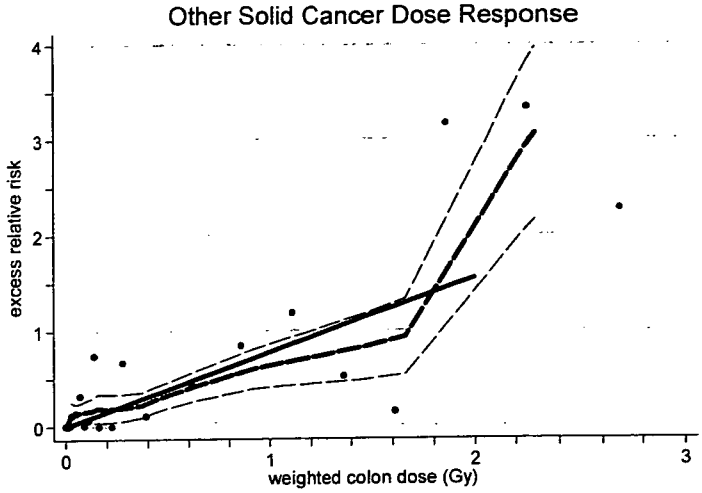

FIG. 20. Dose–response function for cancers at sites not considered in other analyses in this paper. The thick solid line is the fitted linear gender-averaged excess relative risk (ERR) dose response at age 70 after exposure at age 30 based on data in the 0- to 2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The thick dashed line is a non-parametric smooth of the category-specific estimates and the dotted lines are one standard error above and below this smooth.

and age-at-exposure effects. Since the birth cohort effects on baseline rates were rather small, the patterns of the ERR and EAR by age at exposure were similar.

The two largest subgroups of this collection of cancers are cancers of the larynx and cancers of the urothelial system. In analyses of these sites using simple ERR models without effect modification there was no indication of a dose response for cancers of the larynx ($P > 0.5$). However, there was a significant ($P < 0.001$) dose response for the urothelial group, with an estimated ERR of 2.8 (90% CI 1.2; 5.5). These sites will be considered in more detail in a special study of bladder and other urinary tract cancers. If larynx and urothelial tumors are removed from the other cancer group, the dose response remains statistically significant ($P < 0.001$) and the ERR estimate and temporal patterns are similar to those seen for all cancers in this group.

Risks by Histological Type

The results presented in the previous section focused on cancers of specific organs or functionally related groups of organs (i.e. *sites*). As discussed later, our analyses revealed considerable variability in the estimated levels and patterns of the ERRs among sites. While some of this variability reflects statistical uncertainties that would be seen even if the level and patterns of risk were the same across sites, real biological differences also would be expected for cancers originating from different cells and tissues. To explore such differences in a relatively systematic manner, we classified tumors into five broad histological groups: squamous cell carcinoma, adenocarcinoma, other epithelial malignancies, sarcoma and other non-epithelial cancer. This grouping recognizes differences in germinal cell layers from which the tumor originated and morphological expression of the tumor. The definition of these groups in terms of ICDO morphology codes and the number of cases in each group are given in Table 43. Over 96% of the solid tumors were epithelial tumors with adenocarcinoma accounting for about 60% of the epithelial tumors (Table 44).

The standard ERR and EAR models with effect modification were fitted to the data for the five histological groupings. As indicated in Table 45, there was a statistically significant dose response for each of the epithelial subtypes

TABLE 42
Radiation-Risk-Model Parameter Estimates for Cancers at Sites Not Included in Other Analyses

Model	Risk per Gy[a] Male	Risk per Gy[a] Female	Risk per Gy[a] Sex-averaged	Sex ratio (F:M)	Age at exposure[b] (percentage change per decade increase)	Attained age[b] (power)
ERR	0.75 (0.31; 1.33)[c]	1.08 (0.56; 1.80)	0.91 (0.50; 1.4)	1.5 (0.70; 3.3)	−26% (−51%; 4%)	−0.79 (−2.4; 1.0)
EAR	6.1[d] (2.8; 9.3)	4.0 (2.1; 6.4)	5.0 (2.7; 7.7)	0.7 (0.37; 1.58)	−19% (−44%; 9%)	2.8 (1.3; 4.7)

[a] At age 70 after exposure at age 30 per Gy weighted colon dose.
[b] Models include both attained-age and age-at-exposure effects.
[c] 90% confidence interval.
[d] Excess cases per 10,000 per PY Gy.

TABLE 43
Histology Group Definitions and Distribution of LSS Solid Cancer Cases

Histology group[a]	Definition (ICD-O morphology codes)	Cases
Adenocarcinoma	8140–8381; 8290–8420; 8430; 8440–8490; 8500–8543	10,384
Squamous cell carcinoma	8050–8082	2,097
Other epithelial malignancies	8010–8045; 8090–8110; 8120–8130; 8550; 8560–8580; 8590–8671; 8680–8790	4,307
Sarcoma	8800–8804; 8810–8833; 8840–8841; 8850–8881; 8890–8920; 8930–8933; 8940; 8950–8951; 8963; 8980–8991; 9020–9040; 9120–9161; 9170–9175; 9180–9241; 9250–9251; 9260–9262; 9580–9581	149
Other non-epithelial malignancies	9050–9055; 9060–9091; 9100–9104; 9110; 9270–9340; 9350–9370; 9380–9481; 9490–9523; 9530–9539; 9540–9570;	302
Unknown	8000–8005	209
Total		17,448

[a] Cancers of the lympho-hematopoietic system (leukemia, lymphoma, myeloma) ICDO-M 9590–9999 are excluded.

and, despite the small number of cases, for sarcomas and other non-epithelial cancers. Plots of the fitted temporal patterns in the ERR and EAR by histology groups are presented in Fig. 21. There were some striking differences in the patterns shown.

For adenocarcinoma, which included almost 60% of all solid cancers and over 75% of stomach cancers, the magnitude of gender-specific ERR estimates (0.31 for men and 0.62 for women) were similar to those for all solid cancers (Table 45). The ERR and EAR estimates were both significantly higher for women than men. There was no significant effect of age at exposure or attained age on the ERR. The EAR increased significantly with decreasing age at exposure and also with increasing attained age. These patterns roughly resembled those seen for all solid cancers and largely reflect the patterns observed for breast, stomach and colon cancers, which make up 57% of total adenocarcinomas. Given the recent increase in the background rates for adenocarcinomas, which was slightly more pronounced than for all solid cancer rates (data not shown), the temporal patterns of ERR and EAR were consistent with multiplicative effects of radiation and factors affecting background rates.

The gender-averaged ERR estimate of 0.43 for squamous

TABLE 44
Distribution of LSS Cancer Cases by Site and Histology Group

	Histology group						
Site[a]	Squamous	Adenocarcinoma	Other epithelial	Sarcoma	Other non-epithelial	Unknown	Total
Oral cavity	201	33	24	9	3	7	277
Esophagus	266	3	82	1	0	0	352
Stomach	7	3,596	1,083	19	0	25	4,730
Colon	1	1,354	156	2	0	3	1,516
Rectum	12	735	89	1	0	1	838
Liver	0	1,097	379	2	1	15	1,494
Gallbladder	11	327	208	0	0	3	549
Pancreas	3	242	263	0	0	4	512
Lung	362	631	752	1	0	13	1,759
Non-melanoma skin	133	11	178	7	0	1	330
Female breast	4	1,005	49	5	0	10	1,073
Uterus	761	198	155	26	15	7	1,162
Uterine Corpus	*2*	*143*	*23*	*16*	*0*	*0*	*184*
Cervix	*759*	*55*	*132*	*10*	*15*	*7*	*978*
Ovary	4	174	55	1	7	4	245
Prostate	1	327	56	0	0	3	387
Bladder	34	13	416	1	0	5	469
Renal Cell	1	136	24	1	0	5	167
CNS	0	0	0	11	238	32	281
Thyroid	47	379	42	0	0	3	471
Other sites	249	123	296	62[b]	38	68	836
Total	2,097	10,384	4,307	149	302	209	17,448

[a] The groups considered here correspond to the groups considered in this paper. As discussed in the text, the *other sites* group includes cancers for specific sites as well as cancers for which the site is unknown or uncertain.

[b] Includes 35 cancers of the bone and connective tissue.

TABLE 45
Radiation-Risk-Model Parameter Estimates for Selected Histology Groups

Model	Risk per Gy[a] Male	Female	Sex-averaged	Sex ratio (F:M)	Age at exposure[b] (percentage change per decade increase)	Attained age[b] (power)
			Squamous cell carcinoma			
ERR	0.38 (0.13; 0.68)[c]	0.48 (0.21; 0.84)	0.43 (0.21; 0.68)	1.3 (0.54; 3.5)	−18% (−50%; 21%)	−0.52 (−2.4; 1.7)
EAR[d]	3.6 (0.4; 8.5)	6.0 (3.3; 9.1)	4.8 (2.2; 7.9)	1.7 (0.7; 13)	5% (−32%; 57%)	1.7 (0.00; 3.9)
			Adenocarcinoma			
ERR	0.31 (0.22; 0.40)	0.62 (0.50; 0.75)	0.46 (0.38; 0.55)	2.0 (1.5; 2.8)	−8% (−20%; 4%)	−2.3 (−2.9; 0.2)
EAR	22 (15; 31)	40 (33; 48)	31 (25; 38)	1.8 (1.3; 2.6)	−30% (−38%; −20%)	2.4 (1.9; 3.0)
			Other epithelial cancers			
ERR	0.38 (0.21; 0.58)	0.82 (0.54; 1.12)	0.60 (0.41; 0.79)	2.2 (1.3; 3.9)	−40% (−55%; 22%)	−0.05 (−1.2; 1.3)
EAR	14 (7.4; 21)	14 (9.4; 18)	14 (9.2; 19)	1.0 (0.6; 1.8)	−11% (−30%; 11%)	3.3 (2.1; 4.6)
			Sarcomas			
ERR	0.76 (0.08; 2.3)	0.20 (0.02; 0.80)	0.49 (0.07; 1.4)	0.27 (0.03; 1.5)	−19% (−68%; 60%)	−2.8 (−6.0; −0.1)
EAR	0.60 (0.10; 1.7)	0.19 (0.03; 0.67)	0.39 (0.08; 1.04)	0.31 (0.05; 0.99)	−13% (−63%; 80%)	−0.56 (−2.8; 1.5)
			Other non-epithelial cancers			
ERR	1.5 (<0;3.2)	0.30 (−0.52; 1.0)	0.91 (<−0.3; 1.6)	0.19 (−0.15; 0.76)	−6% (−73%; 57%)	−1.0 (−3.0; 1.2)
EAR	0.65 (<0; 3.1)	0.00 (<−01; 1.1)	0.33 (<−0.1; 1.2)	0.00 (<−0.1; 0.8)	−62% (−85%; 7%)	1.3 (−0.7; 3.6)

[a] At age 70 after exposure at age 30 per Gy weighted colon dose.
[b] 90% confidence interval.
[c] Excess cases per 10,000 per PY Gy.
[d] Models include both attained-age and age-at-exposure effects.

cell carcinomas was also similar in magnitude to the all-solid ERR estimate (Table 45). There was no gender difference in either the ERR or EAR. The ERR did not vary significantly with increasing attained age. The gender-averaged ERR estimate (0.60) for other or unspecified epithelial tumors was slightly higher than for adenocarcinomas or squamous cell carcinomas. The ERRs and EARs for the group of other and unspecified tumors were both higher for women than men, but the gender difference in EAR was not significant. The EAR increased significantly with increasing attained age; no other modifying age effects were found.

Because data for sarcomas as a histological group had not been presented before, we provide risk information in some detail even though there were only 149 cases. Tumors of the connective tissues (32 cases), bones, joints, etc. (11), and uterus (26) together comprised 46% of the sarcomas. An estimated 11.7 cases were related to radiation exposure, with an attributable fraction of 17% among those exposed to >5 mSv. The ERR estimate of 0.76 for men was non-significantly higher than that of 0.20 for women. The EAR for men (0.60) was significantly higher than for women (0.19), with a female:male ratio of 0.31 (Table 45). The ERR increased with decreasing age at exposure and attained age, with the effect of attained age being marginally significant. The EAR also increased with decreasing attained age, but neither effect was statistically significant at the 0.05 level.

SUMMARY AND DISCUSSION

Changes in Risk Estimates since the Last Major Analysis

Since we are using richer models in the current analyses than had been used in the analyses presented in the first comprehensive report on LSS cancer incidence (*2*), it is not possible to compare the results by contrasting summary risk estimates given in this paper to those in the earlier paper. However, it is interesting to investigate how well models of the form considered here, with attained age, age at exposure, and gender, describe data for the earlier period. In other words, have there been any marked changes in the nature of the dose response and effect modification?

We made such comparisons by first fitting the standard solid cancer model to the current incidence data, fixing the parameters at their current estimates, and fitting the constrained model to the site-specific data for the 1958–1987 period. For sites for which it was possible to fit the full (unconstrained) model, we examined the change in deviance between the constrained and unconstrained ERR and EAR models. For sites for which the data were insufficient to fit the full model, we used score tests to identify lack of fit for individual constrained parameters. The results do not suggest that there has been any statistically significant change in the level or patterns of the excess risk for all solid cancers as a group as a result of the extended follow-up period.

Under an ERR model, the change in deviance associated with fitting the 1958–1987 data using the current ERR parameters (Table 10) and estimating the four ERR-related parameters (linear dose response, attained age, age at exposure, and gender) is 1.73 (4 *df* $P > 0.5$). Looking at the parameter estimates, the age-at-exposure trend is slightly less pronounced and the attained-age effect is somewhat sharper with the extended follow-up data; however, score tests for the individual ERR-related parameters in this model do not suggest any significant differences ($P > 0.5$ for each parameter).

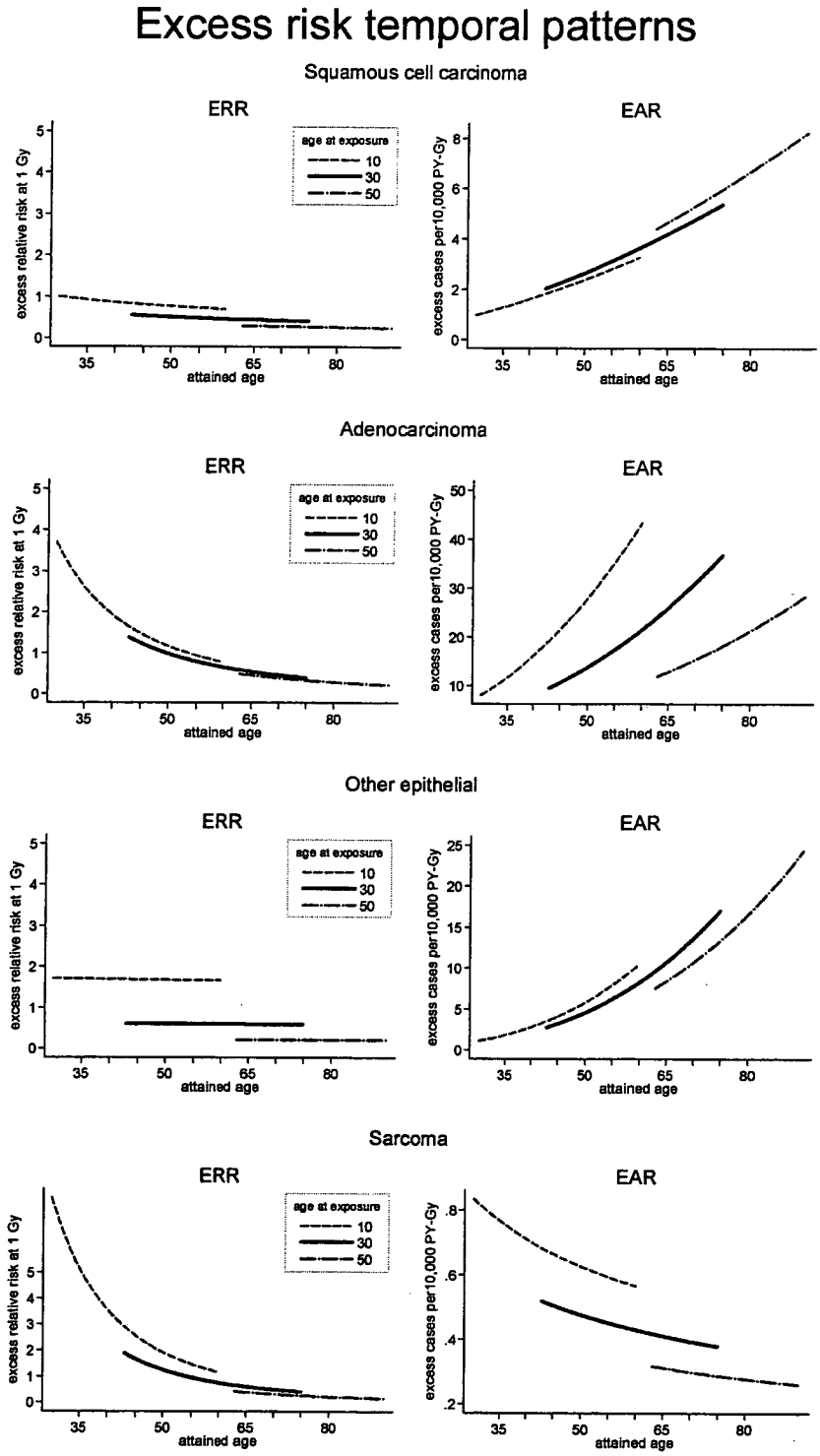

FIG. 21. Temporal patterns and age-at-exposure variation in the radiation-associated excess risk for selected histology groups: squamous cell carcinoma, adenocarcinoma, other epithelial cancers, and sarcomas. The panels in the left column compare variation in the gender-averaged excess relative risk (ERR) at 1 Gy with attained age for ages at exposure of 10, 30 and 50 years. The panels in the right column compare variation in the gender-averaged excess absolute risk (EAR) at 1 Gy with attained age for ages at exposure of 10, 30 and 50 years.

Results for the EAR model were similar. The deviance difference between the constrained and unconstrained models was 2.68 ($P > 0.5$), and score tests for each of the individual parameters other than gender were not statistically significant ($P > 0.5$), while the score test ($P = 0.15$) for a common gender effect suggested a slightly larger gender difference with the more recent data, i.e., increased male:female ratio.

Effect of Inclusion of the NIC Group

Follow-up for the NIC group was used in the current analyses, whereas members of the NIC group were not in-

cluded in the earlier solid cancer incidence analyses. As noted in the Material and Methods section, the baseline rate models used here allow baseline rates for the NIC to differ from those for other cohort members. Baseline rates for the Hiroshima NIC group were significantly lower (SIR 0.93, 90% CI, 0.89; 0.97, $P < 0.001$) than those for other Hiroshima cohort members. Rates for the Nagasaki NIC group were slightly lower (SIR 0.97) than those for other Nagasaki cohort members, but the SIR was not significantly different from 1 (90% CI 0.89; 1.04, $P = 0.3$). The dose–response parameter estimates are virtually unchanged when the NIC group is excluded from the analyses. When the NIC group was included in analyses without adjustment of the baseline rates, the point estimate of the standardized ERR was increased by about 8% relative to those given in Table 10 with almost no change in the effect modification estimates.

Comparison of Site-Specific Excess Risk Patterns

As has been noted in reports on cancer mortality risks in the LSS (*20, 21*), one must be careful in interpreting the variation in the levels and patterns of excess risk across sites. With follow-up through 1990, Pierce *et al.* (*21*) show that the hypothesis of a common standardized ERR value for all solid cancer sites could not be rejected. With 7 years of additional follow-up, Preston and colleagues (*20*) report significant variation in the site-specific standardized ERR estimates but also note that formal statistical tests provide little evidence of variation in the gender effects or temporal patterns of the ERRs for deaths from different types of solid cancer. In this report, we considered temporal patterns and gender effects on radiation-associated excess cancer incidence risks for a large number of organs and groups of organs. Despite the lack of well-developed methods and the limited power to detect significant variation, we offer some comments on variation in excess risk patterns across cancer sites.

Figure 22 summarizes the variation in site-specific ERR estimates by gender, age at exposure, and attained age for sites with an appreciable number of radiation-associated cancers. These comparisons are illustrated by presenting ERR estimates for two values of the factor of interest. The upper panel presents gender-specific standardized ERR estimates (at age 70 after exposure at age 30). The middle panel contrasts the gender-averaged ERR at age 70 for exposure at age 10 with that for exposure at age 40, while the lower panel gives gender-averaged ERR estimates at age 50 and 75 after exposure at age 30. The all-solid-cancer estimates are also included in the figure along with a group of cancers that consists of the 5,936 cancers in sites not otherwise considered. Within each panel, sites are ordered by the magnitude of the ratio of the two values.

The largest gender effects are seen for lung and bladder cancers for which female ERRs are three to five times those for men. It is noteworthy that because smoking is an important risk factor for both of these cancers, baseline rates in women, who have lower smoking rates, are typically about one-third of those for men. Colon cancer is notable because the ERR for men is considerably greater than that for women.

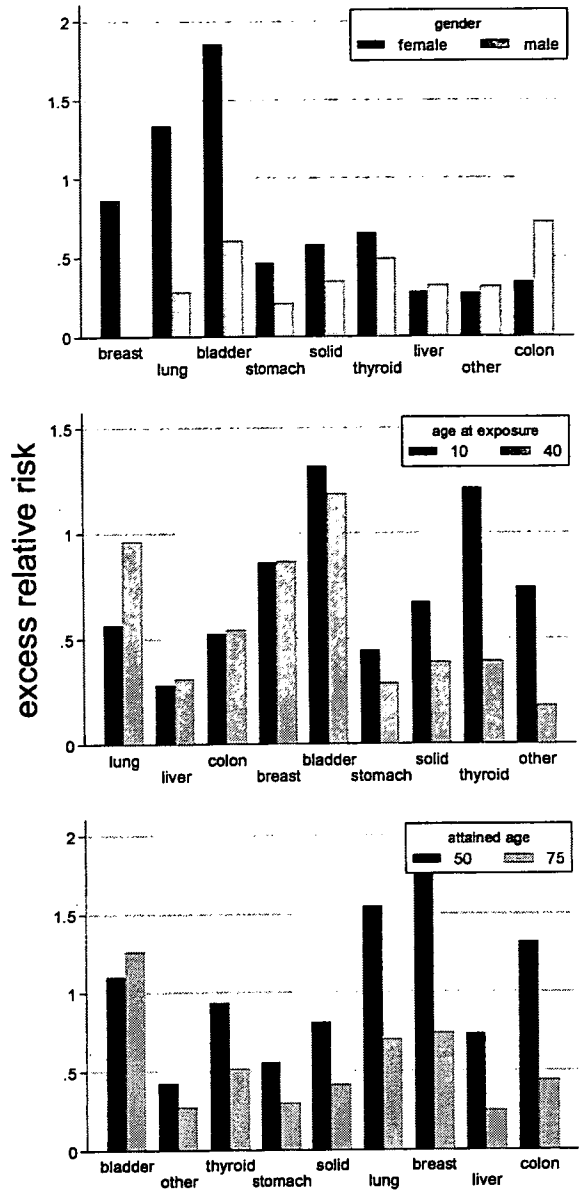

FIG. 22. Comparison of site-specific gender (top panel), age-at-exposure (middle panel), and attained-age (bottom panel) effects on standardized ERR_{1Gy} estimates for selected sites and all solid cancers. The ERR estimates for the *other* category are based on the results of analyses of the 5,396 cancer cases not included in the sites explicitly considered here. The gender-specific estimates correspond to the fitted ERR per Gy at age 70 for a person exposed at age 30. The age-at-exposure specific estimates are gender-averaged ERR estimates at age 70 after exposure at age 10 (left bar) or age 40 (right bar). Attained-age-specific estimates are gender averaged ERR estimates at ages 50 (left bar) and 75 (right bar) after exposure at age 30. Within each panel the sites are ordered based on the magnitude of the ratio of the effect pairs.

With regard to age-at-exposure effects, shown in the middle panel, lung cancer is the only site for which the ERR increased with increasing age at exposure. As noted earlier,

TABLE 46
Tests for Heterogeneity in Site-Specific Excess Relative-Risk Levels and Effect Modification Patterns

Site	Cases	Excess cases	ERR_{1Gy}[b]	ERR effect modification[c]			
				Age at exposure	Attained age	Gender	Global[d]
Oral cavity	277	16	0.5[a]	0.4[a]	0.18[a]	>0.5[a]	>0.5[a]
Esophagus	352	16	>0.5	0.4	0.5	>0.5	0.5
Stomach	4,730	151	**0.01**	>0.5	>0.5	0.4	>0.5
Colon	1,516	78	>0.5	>0.5	0.4	**0.006**	**0.04**
Rectum	838	14	**0.006**	>0.5	0.11	>0.5	0.34
Liver	1,494	54	0.18	>0.5	>0.5	0.3	>0.5
Gallbladder	549	−2	**0.003**	>0.5	>0.5	>0.5	>0.5
Pancreas	512	11	>0.5	0.14	>0.5	0.2	0.2
Lung	1,759	117	**0.06**	**0.02**	0.25	**0.005**	**0.002**
Non-melanoma skin	330	40	**<0.001**	**<0.01**	0.4	>0.5	**<0.001**
Breast	1,073	147	**0.015**	0.25	>0.5	—	0.4
Uterus	1,162	12	**<0.001**	0.36	0.16	—	0.37
Ovary	245	11	0.3	>0.5	>0.5	—	>0.5
Prostate	387	4	>0.5	>0.5	0.5	—	>0.5
Renal cell	167	2	>0.5	0.29	**0.006**	0.37	**0.04**
Bladder	469	35	0.14	0.16	**0.10**	0.4	0.27
CNS	281	19	0.375	0.41	0.44	**0.005**	**0.03**
Thyroid	471	63	0.2	0.4	>0.5	>0.5	>0.5
Other	836	65	**0.04**	>0.5	>0.5	>0.5	>0.5
Total	17,448	853[e]					

[a] Two-sided *P* values for tests of hypotheses that the solid cancer effect estimates apply to specific sites.

[b] The test for level is made by fixing the other effect modifiers at the solid cancer estimates. Information on the direction of the difference is given in the text, Table 11, and Figs. 22 and 23. *P* values of 0.1 or less are printed in bold.

[c] The effect modification tests are made assuming that the level can vary.

[d] The global test is a test that all three (two for gender-specific cancers) parameters have the same value as those for solid cancer.

[e] The estimated number of radiation-associated solid cancers from the pooled all-solid-cancer model is 853 (see Table 9).

this pattern is primarily a consequence of the large smoking-related birth cohort effect on lung cancer baseline rates and the apparent independence of smoking and radiation effects on lung cancer risks in the LSS. The large ERR for thyroid cancer among persons exposed to the bombings at a young age is clearly seen in this figure. The lack of an age-at-exposure effect for the breast cancer ERR reflects the fact that temporal variation for this site appears to be captured more effectively by decreases in the ERR with attained age.

With the exception of bladder cancer, the fitted ERRs decrease with increasing attained age. These decreases are most marked for liver, colon and breast cancer, sites for which there is little evidence of variation in the ERR with age at exposure despite fairly marked birth cohort effects (increased risks for later birth cohorts) on the baseline rates.

Figure 22 highlights the considerable inter-site variability in ERR effect modification parameters. As noted earlier in the discussion and indicated by the broad confidence intervals for many of the site-specific risks and effect modification parameters, there is considerable uncertainty in these site-specific results. To provide a rough guide to which sites differ from the level or pattern of the ERR observed for all solid cancers, we formally tested the hypothesis that the level of radiation risk (standardized ERR_{1Gy}) did not differ from that for all solid cancers, and for both ERR and EAR models we considered whether individual effect modification parameters (gender, age-at-exposure, and attained age effects) differed from those for all solid cancers combined.

Table 46 provides information on the results of these tests (*P* values) along with summary information on the total number of cases and estimated number of radiation-associated cases for each site. Tests that provide some suggestion of a difference (*P* values ≤ 0.1) between the site-specific parameter and that for the full model are highlighted.

The site-specific standardized ERR_{1Gy} was significantly lower than that for all solid cancers for stomach, rectum, gallbladder, uterus and non-melanoma skin cancers when using a linear-spline dose–response model. The standardized ERR_{1Gy} estimates for cancers of the lung, breast and other sites were significantly higher than that for all solid cancers. The non-melanoma skin cancer ERR decreased more rapidly with increasing age at exposure than that for