TABLE 6
Temporal Trends in Age-Standardized Incidence Rates per 100,000 People for Selected Solid Cancers in Japan between 1975 and 1999[a]

Site	ICD-10	Year				
		1975–1979	1980–1984	1985–1989	1990–1994	1995–1999
		Men				
All solid cancers	C00–C89	193.1	214.9	243.0	249.8	253.6
Oral cavity	C00–14	3.3	4.2	4.8	5.1	5.8
Esophagus	C15	8.2	8.2	9.3	9.6	10.6
Stomach	C16	80.5	77.2	79.1	70.9	64.1
Colon	C18	9.3	13.4	18.9	28.3	30.4
Rectum	C19–21	9.1	11.9	14.1	16.4	18.4
Liver	C22	14.1	19.6	25.0	26.0	24.3
Gallbladder	C23–24	4.4	5.6	6.8	6.7	6.6
Pancreas	C25	6.8	7.7	9.1	8.9	8.9
Lung	C33–34	25.0	30.5	35.7	36.5	37.4
Prostate	C61	5.2	6.5	7.9	9.2	12.1
Kidney	C64–C66, C68	2.7	3.4	4.9	5.6	6.3
Bladder	C67	5.7	7.8	7.6	8.0	8.7
Brain, CNS	C70–72	2.0	2.6	2.9	2.4	2.4
Thyroid	C73	0.7	1.3	1.6	1.3	1.5
Other solid cancers		16.2	15.0	15.3	14.9	16.1
		Women				
All solid cancers	C00–C89	134.0	141.5	152.3	152.8	155.1
Oral cavity	C00–14	1.3	1.9	2.0	1.8	2.0
Esophagus	C15	1.8	1.7	1.5	1.4	1.4
Stomach	C16	38.6	35.9	35.0	29.3	25.3
Colon	C18	7.7	10.1	13.1	16.9	17.7
Rectum	C19–C21	6.2	6.8	7.7	8.5	8.7
Liver	C22	5.3	5.7	6.7	7.2	7.4
Gallbladder	C23–24	4.7	6.0	6.7	6.0	5.3
Pancreas	C25	3.8	4.5	5.2	5.0	5.1
Lung	C33–34	7.5	9.2	10.3	10.1	11.4
Breast	C50 D05	17.5	21.4	26.6	28.8	32.8
Cervix uteri	C53	13.8	12.5	10.1	7.8	7.6
Corpus uteri	C54	1.6	2.9	3.2	3.9	4.6
Uterus, NOS	C55	4.1	1.1	0.9	1.2	0.6
Ovary	C56	3.8	4.3	5.7	5.9	6.6
Kidney	C64–C66, C68	1.0	1.5	1.7	2.0	2.3
Bladder	C67	1.5	1.8	1.8	2.0	2.0
Brain, nervous system	C70–72	1.4	1.8	2.2	1.8	1.9
Thyroid	C73	2.4	3.4	5.2	6.4	5.9
Other solid cancers		9.9	8.9	6.7	6.9	6.7

[a] World-population age-standardized rates from ref. (*34*).

exposure would be about 34% higher than for someone age 30 at exposure (Table 10).

As noted earlier, age-specific baseline rates have changed over time (see Fig. 2), complicating interpretation of the effects of age at exposure on the excess risk, particularly for the ERR. Figure 5 compares the age-at-exposure effect on the excess risk to the birth cohort effect on baseline rates.

For both the ERR and the EAR, the attained-age-specific risks increase with decreasing age at exposure. This trend was in the same direction as the change in baseline rates with birth cohort. This suggests that for all solid cancers as a group, factors affecting the age-at-exposure effect are unlikely to be acting in either a simple additive or multiplicative manner with respect to the factors responsible for the birth cohort effects.

When age-at-exposure and attained-age effects were assessed separately without taking the effect of the other age variable into account, the effects were larger; i.e., risk decreased by about 32% per decade increase in age at exposure and risk deceased in proportion to attained age to the power −2.2.

3. Gender differences

As indicated in Table 10, the standardized EAR per 10,000 PY at 1 Gy was 52 (90% 43; 60). Similar to the gender pattern for the ERR, the EAR was higher for women than men, but the magnitude of the gender ratio was smaller than for the ERR. As illustrated in the right panel of Fig. 4, and unlike the pattern observed for the ERR, the EAR increased in proportion to attained age to the power 2.4 but decreased by 24% per decade increase in age at exposure.

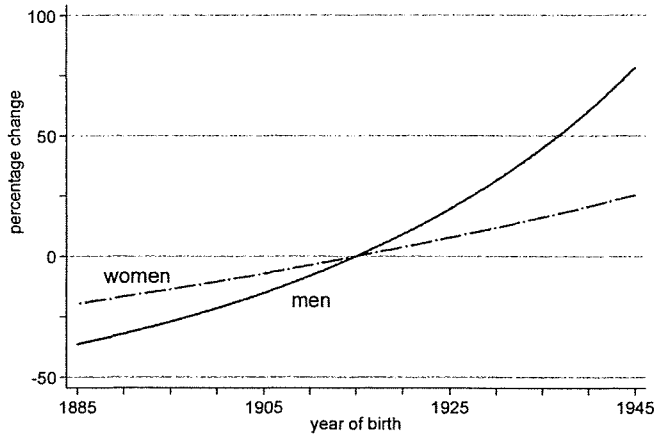

FIG. 1. Solid cancer gender-specific birth cohort effects in the Life Span Study in terms of changes in incidence rates at 70 years of age born in different years to those for people who were born in 1915.

The results in Table 10 also suggest that both ERR and EAR estimates are significantly higher for women than for men for all solid cancers as a group. While apparent gender effects on the ERR may reflect differences in background cancer rates and/or possible gender differences in radiosensitivity, gender differences in the EAR, which is not influenced by background rates, might be thought to be a more direct indication of gender differences in radiosensitivity. While information on gender differences in site-specific cancer risks are presented below, we also carried out an analysis of the ERR and EAR for all non-gender-specific solid cancers, i.e. excluding cancer of the breast, prostate and other male or female genital organs. This restriction reduced the number of cases by 2,950 to 14,498. The lower portion of Table 10 summarizes the parameter estimates for the standardized ERR and EAR models.

The ERR gender ratio for non-gender-specific cancers was essentially the same as for all solid cancers, but the gender ratio in the EAR was significantly less than that for the EAR for all solid cancers ($P < 0.001$) and was not significantly different ($P > 0.5$) from one, i.e. no gender difference. These results suggest that the greater ERR for women than men largely reflects gender differences in the background rates.

4. Attained-age and age-at-exposure effects on excess risks

As was seen in Table 10 and Fig. 4, the excess risks varied with both age at exposure and attained age. For persons exposed to the bombings at young ages, the ERR declined over time, but the EAR increased rapidly and showed no sign of abating. The pattern of the excess risk indicated that radiation exposure is associated with a lifelong elevation of the natural age-specific risk. Indeed, at the end of the last follow-up in 1987, it was estimated that about 11% of all cancers among survivors exposed to doses above 0.01 Gy were associated with exposure to radiation from the bombs. Eleven years later, radiation-associated cancers accounted for about 11% of the cancers among LSS cohort members exposed to doses in excess of 0.005 Gy and about 13% of the 6,783 cases among survivors with doses in excess of 0.01 Gy. Thus it seems clear that the excess risks are not disappearing as the cohort ages (Fig. 4).

To investigate the adequacy of the simple monotonic attained-age effect modification trend, the standard ERR and EAR models were extended to describe the variation with attained age using a quadratic spline in log age with a single knot at age 70. This more complex model did not significantly improve the fit of the standard power-of-age effect modification model for either the ERR ($P > 0.5$) or the EAR ($P > 0.5$). Furthermore, under this richer model, the age dependence of the gender-averaged excess risk was virtually the same as that for the simpler ERR and EAR models.

Additional analyses provided no indication that either the addition of an interaction between age and age at exposure on the ERR or EAR ($P > 0.5$ in both cases) or allowing the power of age to vary with age-at-exposure category led

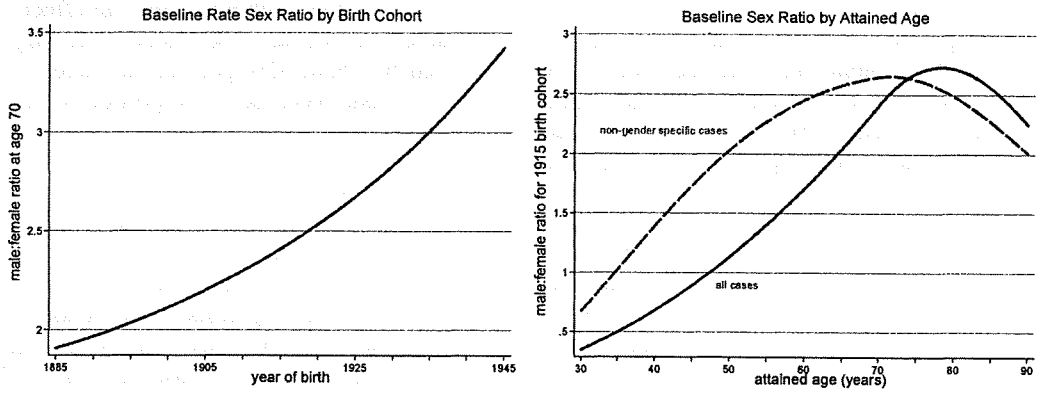

FIG. 2. Male:female rate ratios as a function of attained age for all solid cancers (solid line) and all solid cancers except gender-specific cancers (breast, prostate and reproductive organs) (dashed line). The results shown are those for the 1915 birth cohort.

TABLE 7
Crude Incidence Rates (Cases Per 10,000 Person Years) for All Solid Cancers by Age-at-Exposure and Dose Categories, 1958–1998

Age at exposure (years)		Male				Female			
		<0.005[a]	−0.5	−1	1–4	<0.005	−0.5	−1	1–4
0–9	Rate	19	19	21	74	16	18	47	73
	Cases	353	247	15	43	323	261	38	42
	Person-years	182,290	132,655	7,017	5,849	196,591	142,103	8,058	5,727
	Subjects	6,300	4,447	241	211	6,464	4,549	270	199
10–19	Rate	53	60	78	109	35	36	57	102
	Cases	942	638	77	94	857	480	89	96
	Person-years	179,333	106,670	9,881	8,646	243,259	134,612	15,666	9,371
	Subjects	6,115	3,603	344	310	7,629	4,217	518	323
20–29	Rate	95	87	149	130	51	59	67	117
	Cases	569	288	45	33	1,089	772	82	82
	Person-years	59,872	33,150	3,017	2,530	213,448	131,400	12,199	7,002
	Subjects	1,987	1,115	111	88	6,388	3,965	375	237
30–39	Rate	123	124	140	161	71	80	86	130
	Cases	979	549	59	47	1,262	1,003	63	70
	Person-years	79,424	44,405	4,207	2,913	178,022	124,654	7,358	5,369
	Subjects	3,157	1,765	178	121	5,939	4,200	254	203
40–49	Rate	154	153	187	185	89	94	121	140
	Cases	1,090	674	70	49	1,019	740	75	43
	Person-years	70,788	44,063	3,746	2,643	113,939	78,769	6,217	3,079
	Subjects	4,020	2,499	226	167	5,126	3,590	293	157
50+	Rate	186	200	218	248	103	122	173	209
	Cases	603	439	38	28	511	427	37	18
	Person-years	32,392	21,909	1,747	1,131	49,587	35,023	2,138	863
	Subjects	3,330	2,265	185	117	4,337	3,036	178	78
All ages	Rate	75	74	103	124	51	57	74	112
	Cases	4,536	2,835	304	294	5,061	3,683	384	351
	Person-years	604,099	382,852	29,615	23,712	994,846	646,561	51,636	31,411
	Subjects	24,909	15,694	1,285	1,014	35,883	23,557	1,888	1,197

[a] Weighted colon dose in Gy.

to a significant improvement in the fit ($P > 0.5$ for both the ERR and EAR models).

Consideration of models that include more complex age-at-exposure effects suggested that the standard log-linear age-at-exposure model may not adequately describe age-at-exposure dependence of either the ERR and EAR. We initially tested the standard models for lack of fit by adding a seven-level age-at-exposure category variable to the standard model. The age-at-exposure categories used corresponded to decades from 0 to 59 and a seventh category that included everyone who was 60 years old or more at the time of the bombings. Adding age-at-exposure category parameters to the standard model provided some indication of the inadequacy of the standard model. P values for the six-degree of freedom lack-of-fit tests were 0.06 for the ERR model and 0.05 for the EAR model. For both the ERR and EAR models, the inadequacy of the standard description was primarily due to higher than predicted risks for the 60+ age-at-exposure group (Fig. 7). The standardized, gender-averaged ERR and EAR estimates for those exposed late in life are comparable to those for the youngest survivors and are considerably greater than those for people exposed as young adults.

TABLE 8
Solid Cancer Crude Relative Risks[a] by Age at Exposure, Gender and Dose Category

Age at exposure (years)	Male			Female		
	0.005–0.5[b]	−1	1–4	0.005–0.5	−1	1–4
0–9	0.96	1.10	3.80	1.12	2.87	4.46
10–19	1.14	1.48	2.07	1.01	1.61	2.91
20–29	0.91	1.57	1.37	1.15	1.32	2.30
30–39	1.00	1.14	1.31	1.14	1.21	1.84
40–49	0.99	1.21	1.20	1.05	1.35	1.56
50+	1.08	1.17	1.33	1.18	1.68	2.03

[a] Computed from the crude rates in Table 7. Relative risks are defined relative to the <0.005-Gy category.
[b] Weighted colon dose in Gy.

For a more powerful test of the adequacy of the standard model, we allowed the risks to vary with age at exposure as either a log-quadratic or log-quadratic spline with a single knot at age 40. Log-quadratic functions of age did not significantly improve the fit of the log-linear model ($P = 0.14$ for the ERR and $P = 0.07$ for the EAR). However, splines described the age-at-exposure variation in the excess risk significantly better than the simple log-linear trend models ($P = 0.015$ for the ERR model and $P = 0.02$ for the EAR model) and, as indicated in Fig. 6, capture the variability seen in the category-specific risk estimates.

TABLE 9
Observed and Fitted[a] Solid Cancer Cases by Dose Category and Attributable Fraction

Dose category[b]	Subjects	Person years	Cases	Background	Fitted excess	Attributable fraction
<0.005	60,792	1,598,944	9,597	9,537	3	0.0%
0.005–0.1	27,789	729,603	4,406	4,374	81	1.8%
0.1–0.2	5,527	145,925	968	910	75	7.6%
0.2–0.5	5,935	153,886	1,144	963	179	15.7%
0.5–1	3,173	81,251	688	493	206	29.5%
1–2	1,647	41,412	460	248	196	44.2%
2–4	564	13,711	185	71	111	61.0%
Total	105,427	2,764,732	17,448	16,595	853	10.7[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 people with dose greater than 0.005 Gy.

Additional details on the age-at-exposure pattern for all solid cancers are given later in the discussion of the BEIR VII report (*35*).

5. Solid cancer risks during adolescence and young adulthood

Because the tumor registries were established in 1958, cancer incidence could not be evaluated for the first 13 years after the bombings, thus precluding a full evaluation of radiation risks related to childhood cancers. However, we were able to examine risks for persons diagnosed during adolescence and young adulthood. Eight survivors developed solid cancers (one each of stomach, bone, connective tissue, non-melanoma skin, brain, and other nervous system, and two with thyroid cancer) between the ages of 13 and 19. Five of these cancers occurred among survivors exposed to over 1 Gy. The ERR_{1Gy} for cancers diagnosed before age 20 was 19.8 (90% CI 6; 77). As the age of diagnosis increased, the ERR dropped, so that when the 20 cases diagnosed between the ages of 20 and 24 years were included in the analysis, the ERR_{1Gy} was reduced to 7.2 (90% CI 3.2; 15), and when the 37 cases diagnosed between the ages of 24 and 29 were included, the ERR_{1Gy} was reduced further to 5.7 (90% CI 3.1; 9.7). These limited data suggest that if early follow-up had been available, the risks for childhood cancer would have been extremely high.

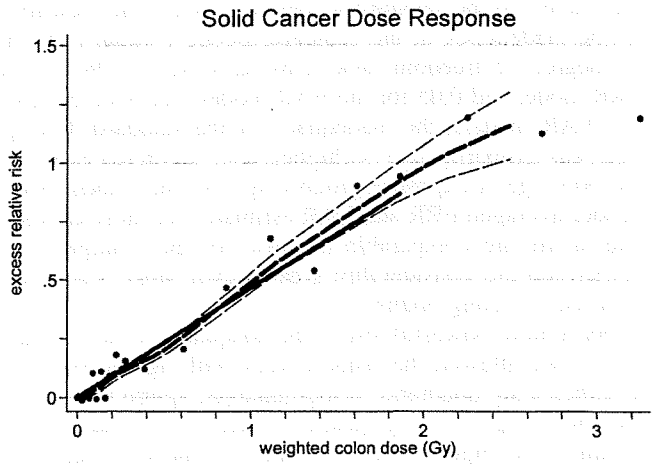

FIG. 3. Solid cancer dose–response function. The thick solid line is the fitted linear gender-averaged excess relative risk (ERR) dose response at age 70 after exposure at age 30 based on data in the 0- to 2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The thick dashed line is a nonparametric smooth of the category-specific estimates and the thin dashed lines are one standard error above and below this smooth.

Site-Specific Cancer Risks

Consideration of site-specific risk estimates is important both for radiation protection and for better understanding of how radiation affects cancer incidence rates. However, because of the limited number of radiation-associated cases for any specific malignancy, inferences about radiation effects are imprecise. The following presentations of specific cancer sites begin with a brief description of the modeled baseline (background) incidence rates and birth cohort effects, since, as discussed in the section on solid cancer, these patterns and trends have a bearing on how to interpret the effects of age at exposure and attained age on excess relative risks and absolute rates. These discussions often refer to crude rate tables given in the Appendix but also make use of the results of the explicit modeling of baseline rates that was carried out for each site (detailed results of this modeling are not given). This section is followed by a description of radiation effects. The depth of these discussions varies depending on the amount of information available for inference about the excess rates. In particular, for the eight sites (stomach, colon, liver, lung, bladder, female breast, non-melanoma skin and thyroid) for which the estimated number of radiation-associated cancers is relatively large (35 or more), we provide detailed results for both ERR and EAR models including information on the nature

TABLE 10
Solid 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)
			All solid cancers			
ERR	0.35	0.58	0.47	1.6	−17%	−1.65
	(0.28; 0.43)[c]	(0.43; 0.69)	(0.40; 0.54)	(1.31; 2.09)	(−25%; −7%)	(−2.1; −1.2)
EAR	43[d]	60	52	1.4	−24%	2.38
	(33; 55)	(51; 69)	(43; 60)	(1.10; 1.79)	(−32%; −16%)	(1.9; 2.8)
			Non-gender-specific solid cancers[e]			
ERR	0.34	0.61	0.48	1.8	−10%	−2.09
	(0.27; 0.42)[c]	(0.50; 0.73)	(0.39; 0.56)	(1.31; 2.09)	(−20%; −1%)	(−2.6; −1.5)
EAR	48[d]	44	46	0.9	−19%	2.52
	(36; 61)	(37; 52)	(38; 55)	(0.72; 1.20)	(−29%; −9%)	(2.0; 3.1)

[a] At age 70 after exposure at age 30.
[b] Models include both attained-age and age-at-exposure effects.
[c] 90% confidence interval.
[d] Excess cases per 10,000 per PY Gy.
[e] Excludes cancers of the breast, prostate and reproductive organs.

of the dose response and effect modification by gender, age at exposure and attained age. Less detailed results are given for sites with an estimate of fewer than 30 radiation-associated cases. At a minimum the results include the linear ERR estimate computed without allowance for effect modification, score-test P values for the basic effect modifiers (gender, attained age and age at exposure), and an estimate of the EAR computed directly from the estimated number of radiation-associated cases estimated from the linear ERR model. This group of sites includes two cancer groups (cancers of the oral cavity and pharynx and tumors of the brain and nervous system) and eight individual cancer sites (cancers of the esophagus, rectum, gallbladder, pancreas, uterus, ovary, prostate and renal cell).

Before presenting the results for specific sites or groups of sites, we provide a summary of risk estimates and how they vary with age at exposure for all solid cancers and for the specific sites discussed later in this report (Table 11). The table compares estimates of the gender-averaged ERR and EAR at attained age 70 for ages 10, 30 and 50 years at exposure. The site-specific estimates were based on the models in which the ERR varies as a log-linear function of age at exposure (see Eq. 1). In interpreting these statistics, it should be kept in mind that 59% of the cohort members are women and that they contribute 62% of the total person years (Table 4). In addition, the age-at-exposure distributions for male and female cohort members differ markedly with relatively few men between the ages of about 18 and 40 at the time of the bombings.

Table 12 presents gender-averaged ERR estimates at attained age 70 for four age-at-exposure groups for all solid cancers and for selected major sites. Comparing estimates in Tables 11 and 12 indicates that the parametric models provide a good description of the age-at-exposure specific

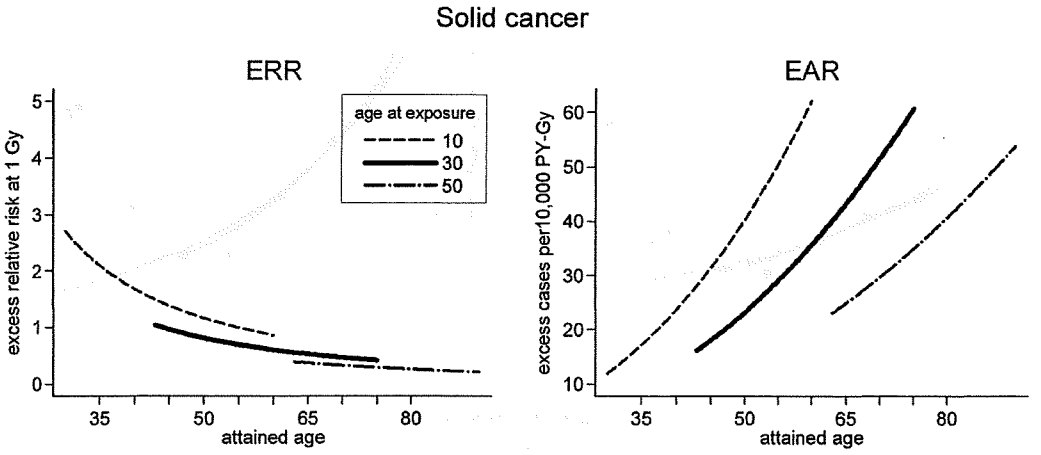

FIG. 4. Variation in solid cancer excess risks at 1 Gy with attained age for ages at exposure of 10, 30 and 50 years. The left panel presents the fitted excess relative risk (ERR) estimates while the right panel indicates excess rate (EAR) estimates. The curves are gender-averaged risks after exposure to 1 Gy.

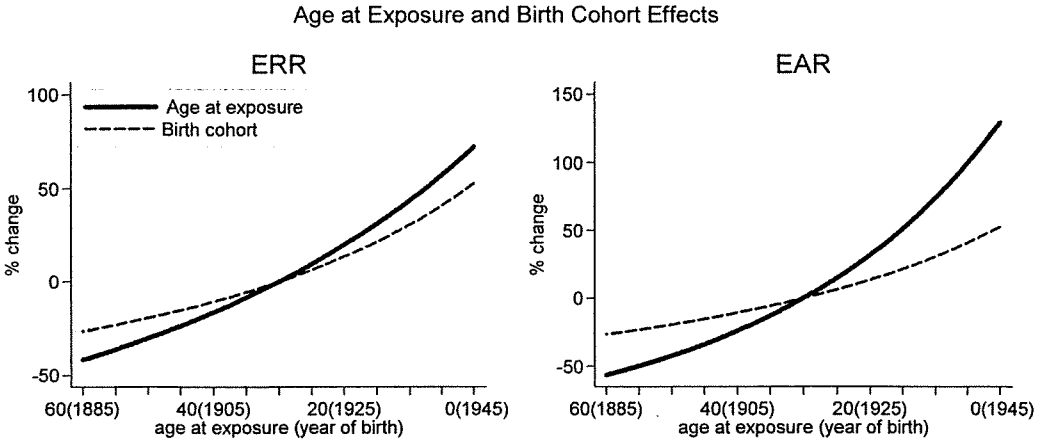

FIG. 5. Comparison of age-at-exposure effects on the excess risk (solid lines) with birth cohort effects on baseline rates for ERR (left panel) and EAR (right panel) models. Age-at-exposure effects on the radiation-associated excess risk are measured relative to the risk for a cohort member who was 30 years of age at the time of exposure. Birth cohort effects on age-specific baseline rates are measured relative to people born in 1915. In ERR models, when baseline rates vary with birth cohort, the age-at-exposure effect is confounded with the birth cohort effect, which complicates generalization of the age-at-exposure effect to other populations. There is less likelihood of such confounding in EAR models.

ERRs. Confidence intervals for the fully parametric models of Table 11 were narrower than those for the semiparametric models used for Table 12.

Oral Cavity and Pharynx (ICD10: C00–C14)

Cancers of the oral cavity and pharynx are a diverse group of malignancies that vary substantially in their etiology. In recent years the world-population age-standardized incidence among Japanese men (6.2 per 100,000 population) has been about three times that for women (2.0 per 100,000 population) (*38*). This difference is largely explained by the fact that smoking and alcohol are the major risk factors for cancers of the tongue, mouth and pharynx. Several epidemiological studies have suggested that diets low in fruits and vegetables and poor oral hygiene also may increase the risk of developing cancers of the tongue, mouth and pharynx (*39*). Cancers of the lip and salivary glands are less common and exhibit different incidence and risk patterns. Lip cancers are predominately squamous cell carcinomas and are very rare in Japan. UV-radiation exposure and tobacco use are the main risk factors that have been identified for this malignancy (*40, 41*). The causes of salivary gland cancers are, for the most part, unknown, although exposure to ionizing radiation is associated with an elevated risk (*2, 7, 42–45*). Earlier studies of atomic bomb survivors have provided important insights into the rela-

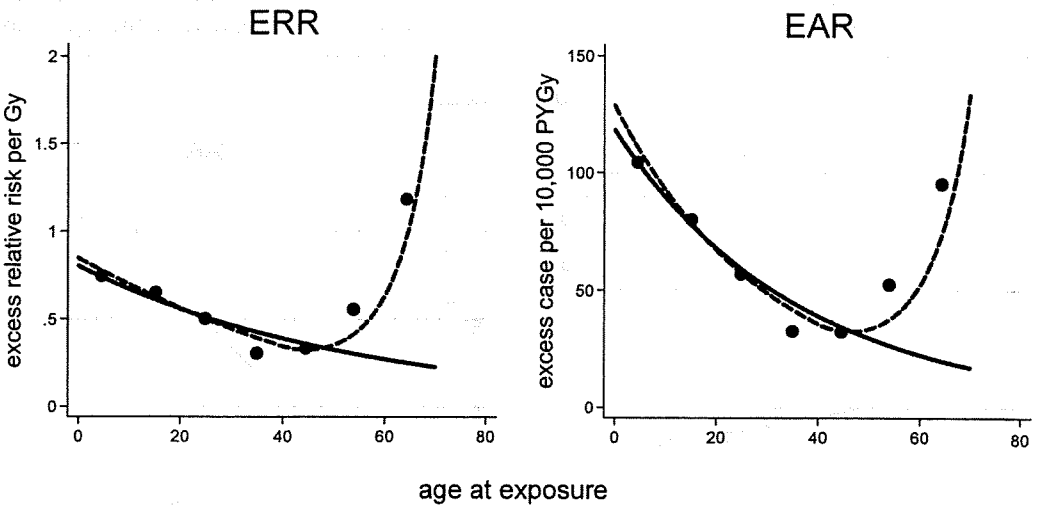

FIG. 6. Alternative descriptions of age-at-exposure effects on solid cancer risks. The points are non-parametric category-specific estimates of the gender-averaged excess risk at age 70 after a dose of 1 Gy. The solid lines show the simple log-linear trend commonly used in description of age-at-exposure effects on LSS cancer risks. The dashed lines are fitted log-quadratic splines with a single knot at an exposure age of 40 years. As described in the text, these splines describe the age-at-exposure pattern significantly better than the commonly used log-linear trends.

TABLE 11
Site-Specific Gender-Averaged Excess Relative Risk and Excess Absolute Rate Estimates at Attained Age 70 after Exposure at Ages 10, 30 and 50 Years

Site	Attributable fraction (%)[a]	Excess relative risk[b]			Excess absolute rate[c]		
		Age at exposure					
		10	30	50	10	30	50
All solid	10.7	0.67 (0.52; 0.85)	0.47 (0.40; 0.54)	0.32 (0.24; 0.42)	90 (68; 113)	52 (43; 60)	30 (22; 39)
Oral cavity	11.4		0.39 (0.11; 0.76)			0.56 (0.20; 1.2)	
Esophagus	10.2		0.52 (0.15; 1.0)			0.58 (0.18; 1.1)	
Stomach	7.2	0.44 (0.20; 0.83)	0.34 (0.22; 0.47)	0.25 (0.12; 0.44)	9.9 (4.5; 18)	9.5 (6.1; 14)	9.2 (4.2; 16)
Colon	11.4	0.52 (0.21; 1.2)	0.54 (0.30; 0.81)	0.55 (0.15; 1.2)	41 (17; 91)	8.0 (4.4; 12)	1.6 (0.3; 3.9)
Rectum	3.7		0.19 (−0.04; 0.47)			0.56 (−0.13; 1.4)	
Liver	8.1	0.28 (0.06; 0.78)	0.30 (0.11; 0.55)	0.32 (0.07; 0.85)	6.8 (0.0; 22)	4.3 (0.0; 7.2)	2.6 (0.5; 6.4)
Gallbladder	−1.0		−0.05 (<−0.3; 0.3)			−0.01 (<−0.1; 0.51)	
Pancreas	4.8		0.26 (<−0.07; 0.68)			0.46 (−0.13; 1.5)	
Lung	14.7	0.56 (0.26; 1.1)	0.81 (0.56; 1.1)	1.15 (0.69; 1.8)	7.3 (3.4; 14)	7.5 (5.1; 10)	7.8 (4.6; 12)
Non-melanoma skin	23.2	2.28 (0.04; 7.8)	0.17 (0.003; 0.55)	0.01 (0.00; 0.08)	2.3 (0.2; 7)	0.35 (0.03; 1.1)	0.05 (0.00; 0.29)
Female breast	27.1	0.86 (0.47; 1.5)	0.87 (0.55; 1.3)	0.87 (0.44; 1.5)	23 (15; 34)	9.2 (6.8; 12)	3.7 (2.1; 5.9)
Uterus	1.9		0.10 (−0.09; 0.33)			0.56 (<0; 1.9)	
Ovary	10.3		0.61 (0.00; 1.5)			0.56 (0.02; 1.3)	
Prostate	2.2		0.11 (−0.10; 0.54)			0.34 (−0.64; 1.6)	
Renal cell	2.7		0.13 (−0.25; 0.75)			0.08 (−0.16; 0.44)	
Bladder	16.4	1.32 (0.28; 4.1)	1.23 (0.59; 2.1)	1.15 (0.34; 2.5)	4.8 (0.7; 16)	3.2 (1.1; 5.4)	2.1 (0.5; 4.5)
Brain, CNS	13.0		0.62 (0.21; 1.2)			0.51 (0.17; 0.95)	
Thyroid	24.5	1.21 (0.43; 2.9)	0.57 (0.24; 1.1)	0.27 (0.05; 0.77)	4.0 (1.7; 7.8)	1.2 (0.5; 2.2)	0.4 (0.0; 1.3)
Other solid	16.4	1.65 (0.69; 3.5)	0.91 (0.50; 1.4)	0.51 (0.14; 1.1)	7.7 (3.3; 16)	5.0 (2.7; 7.7)	3.3 (1.1; 6.5)

[a] Estimated percentage of cases among those exposed to at least 0.005 Gy that are associated with atomic bomb radiation exposure.

[b] Estimated gender-averaged excess relative risk at 1 Gy for attained age 70 after exposure at the indicated ages. The estimates are based on the models described in the text. If no values are shown for ages 10 or 50, the final model did not include age at exposure, so the ERR is the same for all exposure ages. The values in parentheses are 90% confidence intervals.

[c] Estimated gender-averaged excess absolute rate at 1 Gy for attained age 70 after exposure at the indicated ages with units of excess cases per 10,000 PY Gy. The estimates are based on the models described in the text. If no values are shown for ages 10 or 50 the final model did not include age at exposure, so the ERR is the same for all exposure ages. The values in parentheses are 90% confidence intervals.

tionship between radiation and histological type (7) for salivary gland tumors, especially a strong dose response for mucoepidermoid carcinoma.

Cancers of the oral cavity and pharynx accounted for less than 2% of the cancers diagnosed among members of the LSS cohort. Almost one-third of the 277 malignancies of the oral cavity and pharynx were cancers of the tongue. Cancers of the mouth and pharynx each accounted for about 25% of the cancers in this group. The diagnoses for 263 (95%) of the cases were verified histologically (Table 3).

1. Baseline rates and birth cohort effects

As in most populations, the LSS baseline incidence rates for cancers of the oral cavity and pharynx increased with

TABLE 12
Age-at-Exposure Category Specific ERR Estimates[a] for All Solid Cancers and Selected Sites

Site	Age-at-exposure group			
	0–9	10–19	20–39	40+
All solid	0.72 (0.52; 0.98)	0.64 (0.51; 0.79)	0.41 (0.33; 0.50)	0.41 (0.29; 0.53)
Stomach	0.63 (0.23; 1.4)	0.38 (0.19; 0.68)	0.38 (0.22; 0.56)	0.23 (0.06; 0.42)
Colon	0.45 (0.13; 1.3)	0.54 (0.25; 1.0)	0.54 (0.23; 0.92)	0.51 (−0.06; 1.3)
Liver	0.06 (<−0.1; 0.63)	0.61 (0.18; 1.3)	0.18 (<−0.07; 0.44)	0.44 (<−0.14; 1.1)
Lung	0.66 (<−0.02; 2.0)	0.57 (0.23; 1.1)	0.79 (0.48; 1.2)	1.2 (0.71; 1.7)
Breast	0.78 (0.38; 1.5)	1.2 (0.69; 1.9)	0.83 (0.48; 1.3)	0.54 (−0.02; 1.4)
Bladder	−0.09 (<−0.1; 5.1)	1.3 (0.16; 3.9)	1.1 (0.33; 2.2)	1.4 (0.47; 2.8)
Thyroid	1.5 (0.47; 3.9)	1.2 (0.50; 2.5)	0.46 (0.11; 1.1)	0.31 (−0.1; 0.92)

[a] Gender-averaged ERR estimates at 1 Gy in age-at-exposure categories. These estimates were computed without the assumption that the ERR varies as a log-linear function of exposure age (as was done in Table 12). Estimates were standardized to attained age 70 by assuming that the within each age-at-exposure group the ERR varies as a power of attained age.

age. This increase was roughly proportional to age cubed with a slightly less rapid increase after age 70. Age-specific rates among men roughly doubled with each decade increase in year of birth, but there was little indication of a birth cohort effect for women. Background rates were about three times greater among males than females.

2. Dose response and excess cases

Crude incidence rates are shown by gender, age at exposure (birth cohort), and dose category in Table A1. Rates were higher for men (1.6 per 10,000 PY) than women (0.4 per 10,000 PY) and increased with advancing age at all dose levels.

TABLE 13
Observed and Fitted[a] Oral Cavity and Pharynx Cancers by Dose Category and Attributable Fraction

Dose category[b]	Cases	Background	Fitted excess	Attributable fraction
<0.005	152	149.4	0.0	0.0%
0.005–0.1	56	61.3	0.8	1.3%
0.1–0.2	20	14.8	0.8	5.1%
0.2–0.5	18	15.8	1.9	10.5%
0.5–1	12	10.9	2.9	21.2%
1–2	12	6.6	3.6	35.1%
2–4	7	3.6	4.5	55.7%
Total	277	262.4	14.6	11.4%[c]
ERR per Gy[d]	0.39 (90% CI 0.11; 0.76)			
EAR per Gy	0.56 (90% CI 0.20; 1.2)			

[a] Estimates of background and fitted excess cases are based on an ERR model with a simple linear dose–response model 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 skin 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.

There was a statistically significant linear dose response ($P = 0.01$) in an ERR model without effect modification, with no indication of non-linearity ($P = 0.4$) over the 0- to 2-Gy dose range. As of the end of follow-up, about 15 of the 277 cancers of the oral cavity or about 11% of the cases among cohort members with doses in excess of 0.005 Gy, were associated with exposure to radiation from the bombs (Table 13). The estimated ERR_{1Gy} was 0.39 (90% CI 0.11; 0.76) corresponding to excess rate of 0.6 radiation-associated cases per 10,000 PY Gy (90% CI 0.19; 1.2).

Because of the relatively small number of radiation-associated cases, it was not possible to compute useful effect-modification estimates. Score tests for age-at-exposure ($P > 0.5$), attained-age ($P > 0.5$), or gender ($P = 0.1$) effects on the ERR were not statistically significant.

A previous analysis of salivary gland cancer incidence in the LSS for the period through 1987 (*7*) revealed a large and statistically significant dose response for salivary gland tumors. Based on 42 salivary gland tumors in the current analyses, we continued to see strong evidence of a radiation dose response. The ERR_{1Gy} estimate was 1.8, (90% CI 0.6; 4.0, $P < 0.001$). Approximately nine salivary gland cancers were attributable to radiation, i.e. more than half of the total estimated number of radiation-associated oral cavity cancers in the cohort. There was a suggestion that salivary gland cancer risk decreased with age at exposure ($P = 0.05$) or attained age ($P = 0.08$), but there was no indication of a statistically significant gender difference in the ERR ($P = 0.4$).

The ERR_{1Gy} estimate for tumors of the oral cavity other than salivary gland was only 0.16 (90% CI −0.06; 0.50). As the lower confidence bound suggests, this risk was not significantly elevated ($P = 0.28$)

Esophagus (ICD10: C15)

The incidence of cancer of the esophagus varies widely throughout the world and is generally higher among men than women. Over the last few decades, incidence has been

increasing in many regions, but the temporal trends can differ by histological type and gender (*34, 46*). In Japan, the world-population age-standardized incidence rates for men rose from 8.3 per 100,000 in 1975 to 11.0 in 1999, whereas during the same period they declined from 1.9 to 1.6 for women. Squamous cell carcinoma is the predominant histological type, often comprising as much as 90% of all esophageal malignancies (*47, 48*). Although survival from esophageal cancer has improved over time, it remains quite poor, with recent 5-year survival rates of about 20% in Japan (*49*).

The etiology of esophageal cancer is quite well described (*46, 48, 50*). In one multi-centered case-control study, close to 90% of the squamous cell carcinomas were attributed to tobacco and alcohol use and low consumption of fresh fruits and vegetables, while nearly 80% of the adenocarcinomas were attributed to smoking, elevated BMI, gastrointestinal reflux, and low consumption of fresh fruits and vegetables (*50*). Increased risks of esophageal cancer have been associated with medical irradiation in some individual cohorts, but the increased risk was not statistically significant in a large meta-analysis (*51*). A moderately elevated risk of squamous cell carcinoma was observed in a recent study of breast cancer patients receiving radiotherapy after mastectomy (*52*).

In the current study, there were 352 cases of esophageal cancer, the great majority of which were squamous cell carcinomas. The diagnoses for 80% of the cancers were confirmed histologically, whereas the diagnosis was based solely on death certificates (DCO) for 7% (Table 3).

1. Baseline rates and birth cohort effects

The crude incidence rates for esophageal cancer (Table A2) were about seven times higher for men (2.73 per 10,000 PY) than women (0.39 per 10,000 PY), and they increased markedly with increasing attained age. This increase was roughly proportional to age to the fifth power. For men, baseline rates for esophageal cancer appeared to peak around age 80, while for women there was no indication of downturn in the rates at older ages. This gender difference is consistent with the important etiological role of smoking for these cancers.

2. Dose response and excess cases

The crude rates suggested that risk increased with increasing radiation dose (Table A2). Sixteen excess cases were observed, suggesting that about 10% of the cases occurring among survivors exposed to over 0.005 Gy were related to the radiation exposure (Table 14).

In a simple ERR model without effect modification, there was a statistically significant linear dose response. The point estimate of the ERR per Gy was 0.52 (90% CI 0.15; 1.01). While the data do not support detailed modeling of effect modification, the addition of attained-age, age-at-exposure or gender effects did not improve the model fit. In the previous incidence report the ERR per Gy for esophageal cancer was 0.28 (90% CI −0.21; 1.04) based on only 185 cases, and was considerably, albeit not significantly, higher for women than men (*2*).

TABLE 14
Observed and Fitted[a] Esophagus Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Cases	Background	Fitted excess	Attributable fraction
<0.005	200	195.6	0.1	0.0%
0.005–0.1	88	86.6	1.5	1.7%
0.1–0.2	17	17.5	1.3	7.0%
0.2–0.5	22	19.3	3.3	14.7%
0.5–1	11	9.9	3.8	27.5%
1–2	6	5.3	3.7	41.6%
2–4	8	1.8	2.3	56.5%
Total	352	336.0	16.0	10.2%[c]
ERR per Gy[d]	0.52 (90% CI 0.15; 1.0)			
EAR per Gy	0.58 (90% CI 0.18; 1.1)			

[a] Estimates of background and fitted excess cases are based on an ERR model with a simple linear dose–response model 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 stomach 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.

Using a constant EAR model, the excess risk was 0.58 cases per 10,000 PY per Gy (90% CI 0.15; 1.01). No significant effect modification by gender or age was observed.

Stomach (ICD10: C16)

Stomach cancer is the most common malignancy in Japan (*38*). In 1998, the world-population age-standardized incidence rates for males and females were 61.8 and 23.8 per 100,000, respectively. Stomach cancer incidence and mortality rates have been declining in many countries, including Japan, due in part to dietary changes. The decline in the prevalence of *H. pylori* infection may also have played a role in reducing stomach cancer incidence (*53, 54*). Despite this marked decline in Japanese stomach cancer incidence rates over time, rates in Japan are still almost 10 times those in the U.S. or Europe (Table 5). Stomach cancer mortality is decreasing even more rapidly than incidence in Japan as result of both early-detection screening programs and improvements in treatment.

Stomach cancer has been linked to radiation in a few studies of patients receiving radiotherapy (*55, 56*), but these studies provide little detailed or quantified information on the risk per unit dose, the shape of the dose response, or effect modification. Most information on radiation-associated stomach cancer has come from studies of the atomic bomb survivors. In past incidence and mortality analyses

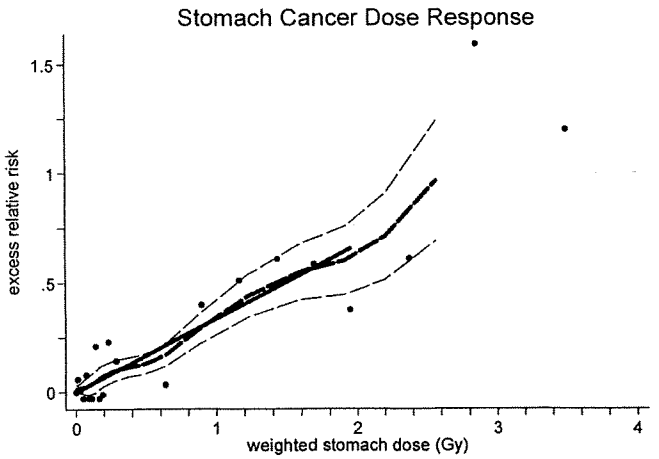

FIG. 7. Stomach cancer dose–response function. The thick dashed line is the fitted linear gender-averaged excess relative risk (ERR) dose response at age 70 after exposure at age 30 based on data in the 0- to 2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The 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.

TABLE 15
Observed and Fitted[a] Stomach Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Cases	Background	Fitted excess	Attributable fraction
<0.005	2,635	2,628	1	0.0%
0.005–0.1	1,226	1,203	14	1.2%
0.1–0.2	251	249	13	5.0%
0.2–0.5	308	274	33	10.7%
0.5–1	158	135	36	21.0%
1–2	108	67	33	33.0%
2–4	44	22	21	48.5%
Total	4,730	4,579	151	7.2%[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 stomach dose in Gy.

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

of the LSS cohort, a linear dose response was reported (*2, 20*). A total of 4,730 stomach cancers, accounting for 27% of all solid cancers and 47% of gastrointestinal cancers, were identified in the LSS cohort. Stomach cancer was three times more frequent than any other individual cancer site. About 80% of the cancer diagnoses were verified microscopically, whereas only 10% of the cancers were identified only through death certificates (Table 3).

1. Baseline rates and birth cohort effects

In the LSS, both year of birth and gender influenced the background stomach cancer incidence rates, with rates increasing with advancing age and higher rates consistently observed for men than women, in part due to differences in smoking rates and dietary patterns (*57, 58*). The fitted baseline rates suggested that at younger ages stomach cancer incidence increased in proportion to attained age to the power 4 for men and slightly less rapidly for women. Age-specific stomach cancer incidence has been decreasing steadily, with the most pronounced decreases among women. For women born in 1900, the stomach cancer incidence rate was 26 cases per 10,000 PY at age 70 compared with 17 cases for a 70-year-old woman who was born in 1930, a drop of approximately 35%. The comparable incidence rates were 64 and 56 cases per 10,000 PY for men born in 1900 and 1930, respectively, a reduction of only about 13%. These differences in temporal patterns resulted in an increase in the male-female ratio from 2.5 to 3.4 over a 35-year period. The strong birth cohort and period effects on baseline rates and the fact that stomach cancer rates for Japan are considerably greater than those in many other countries complicate the interpretation and generalization of estimates of radiation effects based on the LSS stomach cancer data.

2. Dose response and excess risks

The crude incidence rates for stomach cancer (Table A3) clearly showed gender differences in rates and provided an indication of a dose effect. Using our standard model with effect modification a significant linear dose–response relationship was demonstrated ($P < 0.001$) (Fig. 7) with no indication of non-linearity ($P < 0.5$).

Among survivors exposed to 0.005 Gy or more, approximately 150 (7%) could be attributed to radiation, but among survivors exposed to ≥1 Gy, we estimated that over one-third were related to radiation exposure (Table 15).

The gender-averaged point estimate of the ERR at 1 Gy for a person aged 70 years exposed at age 30 years was 0.34 (Table 16). Risks for women were 2.3 times those for men.

The ERR decreased about 13% per decade increase in age at exposure (Table 16 and Fig. 8), but this trend was not statistically significant ($P = 0.4$). The influence of attained age was statistically significant ($P = 0.05$), with the excess relative risk decreasing in proportion to attained age to the power −1.5 for any age at exposure.

The gender-averaged standardized EAR was 9.5 cases per 10,000 PY per Gy (Table 16). The EAR was similar for men (9.4) and women (9.7). The stomach cancer EAR increased in proportion to age squared, and this increase was highly significant. As seen from the panels for stomach cancer in Fig. 8, age at exposure did not modify the EAR, suggesting that radiation may be acting additively with respect to the factors leading to the decline in baseline rates.

This suggestion of additivity can be seen more clearly from the comparison of birth cohort trends in baseline rates to age-at-exposure effects on stomach cancer risks in the

TABLE 16
Stomach 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	0.21 (0.10; 0.34)[c]	0.47 (0.29; 0.68)	0.34 (0.22; 0.47)	2.3 (1.2; 4.5)	−13% (−35%; 15%)	−1.5 (−2.7; −0.3)
EAR	9.4[d] (4.4; 16)	9.7 (6.4; 14)	9.5 (6.1; 14)	1.0 (0.5; 2.1)	−2% (−26%; 29%)	1.9 (0.8; 3.1)

[a] At age 70 after exposure at age 30 per Gy weighted stomach 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.

first row of Fig. 9. The (non-significant) increase in the stomach cancer ERR with decreasing age at exposure was similar to that seen for all solid cancers, while the age at exposure effect on the EAR was flat.

Colon (ICD10: C18)

Colon cancer incidence and mortality rates in Japan have increased rapidly over the past 25 years. This increase has been more rapid for men than women (*59*). The current world-population age-standardized rates for men are about twice those for women (Table 6). The higher rates for men and the more rapid increase in these rates over time may partially reflect gender differences in food and nutrient consumption or other lifestyle factors, but in general the reasons for these differences are unknown (*60, 61*). Colon cancer is currently the third most common cancer in Japan (*33*), following stomach and lung cancers in men and breast and stomach cancers in women. In 1999 (*33*), the world-population age-standardized colon cancer rates in Japan were 31.2 for men and 18.5 for women. These rates are greater than those seen in Sweden and similar to those in the U.S. (Table 5).

The increase in colon cancer rates in the Hiroshima and Nagasaki tumor registries (and possibly other registries in Japan) has been especially dramatic since the mid-1980s. This increase is likely to reflect, at least in part, more emphasis on surveillance and screening, better diagnostic tools, and the recent marked increase in the likelihood of identifying mucosal colon cancers (coded as stage 0). Prior to 1980, less than 5% of the cancers with some stage information were coded as stage 0. Despite the increase in screening during the 1980s, this percentage remained relatively low (about 7%) until the 1990s when the Hiroshima and Nagasaki tumor registries began systematic coding of cancer stage and about 35% of all staged colon cancers were coded as stage 0. Since the majority of mucosal colon cancers were invasive and not in situ lesions, they were included in the current analysis.

Colon cancer data from other populations exposed to low-LET radiation are limited. While the lack of an excess risk of colon cancer in patients treated for cervical cancer may be due to cell killing effects of extremely high doses (*56*), there is little evidence of increased colon cancer risks from studies of patients receiving low to moderately high doses (several grays) for treatment of peptic ulcer (*55*), benign gynecological disease (*62*), and skin hemangioma (*63*).

Colon cancer was the third most common solid cancer in the LSS. The 1,516 colon cancer cases accounted for 9% of all solid cancer cases (Table 2). The relatively high histological verification rate of 90% and the low DCO rate of 5% (Table 3) indicate the reliability of the incidence data for this cancer.

1. Baseline rates and birth cohort effects

An important feature of the background rates for colon cancer was the striking increase in age-specific rates with birth cohort (second row in Fig. 9). This increase was more pronounced in men than in women. Age-specific rates for the oldest (pre-1885) birth cohort were similar for men and women. For men, age-specific rates for the 1930 birth cohort were nine times those for the 1900 birth cohort; however, for women, the 1930 birth cohort rates were six times the 1900 birth cohort rates. As a result, the 1900 birth cohort rates for men were about twice as high as for the rates for women. Colon cancer baseline rates in this cohort increased quite rapidly with attained age, with the increase for either gender proportional to about age to the 8th power. For both men and women the increase with attained age was less rapid after reaching age 80, but the rates did not appear to reach a peak.

2. Dose response and excess cases

The crude rates for colon cancer in the LSS (Table A4) reflect the gender and birth cohort effects discussed above. These rates generally appeared to increase with increasing dose for various ages at exposure for both men and women.

As suggested by Fig. 10, there was a significant linear dose response ($P < 0.001$) in the standard ERR model with effect modification with no evidence of non-linearity ($P > 0.5$) over the 0- to 2-Gy dose range. Based on the linear ERR model, 78 of the 1,516 colon cancer cases were estimated to be associated with radiation exposure, accounting for 11.4% of the 671 cancers among subjects with doses of 0.005 Gy or more (Table 17).

The ERR per Gy (at age 70 after exposure at age 30) of

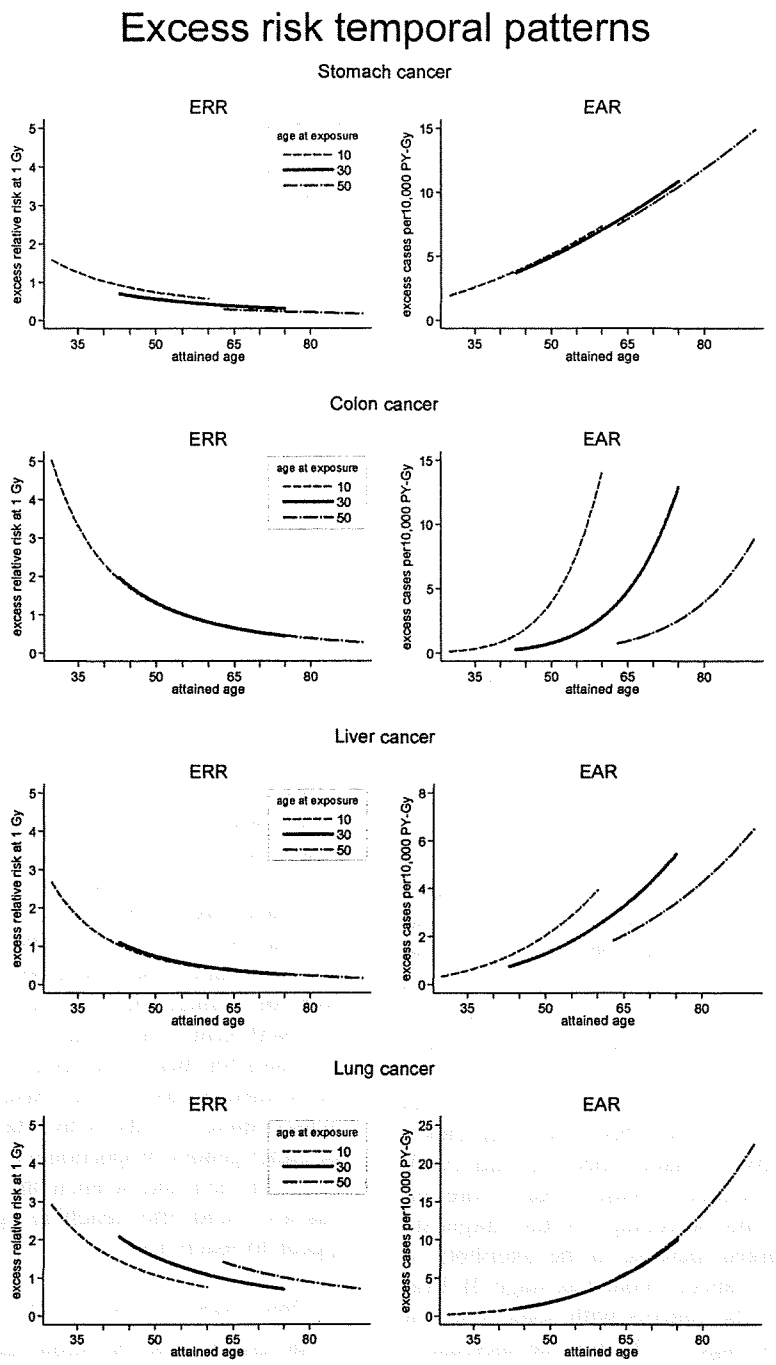

FIG. 8. Temporal patterns and age-at-exposure variation in the radiation-associated excess risk for cancers of the stomach, colon, liver and lung. The panels in the left column compare variation in the gender-averaged excess relative risk (ERR) at 1 Gy with attained age for ages at exposure of 10, 30 and 50 years. The panels in the right column compare variation in the gender-averaged excess absolute risk (EAR) per 10,00 person years at 1 Gy with attained age for ages at exposure of 10, 30 and 50 years.

0.34 for women was about half that for men, 0.73 (Table 18). While the ERR gender ratio was not significantly different from 1, it was significantly ($P = 0.006$) lower than that for all solid cancers. Age at exposure had a negligible effect on the ERR (Tables 11 and 12, Fig. 8). The ERR decreased, though not significantly, with increasing attained age.

The EAR estimate of 13.0 for men was significantly higher than that of 3.0 for women, which resulted in a female:male ratio of 0.2. There was a marked and highly significant decrease in the EAR with increasing age at exposure, with the EAR decreasing by 56% per decade increase in age at exposure (Table 18, Fig. 8). The EAR also increased significantly with attained age (Table 18).

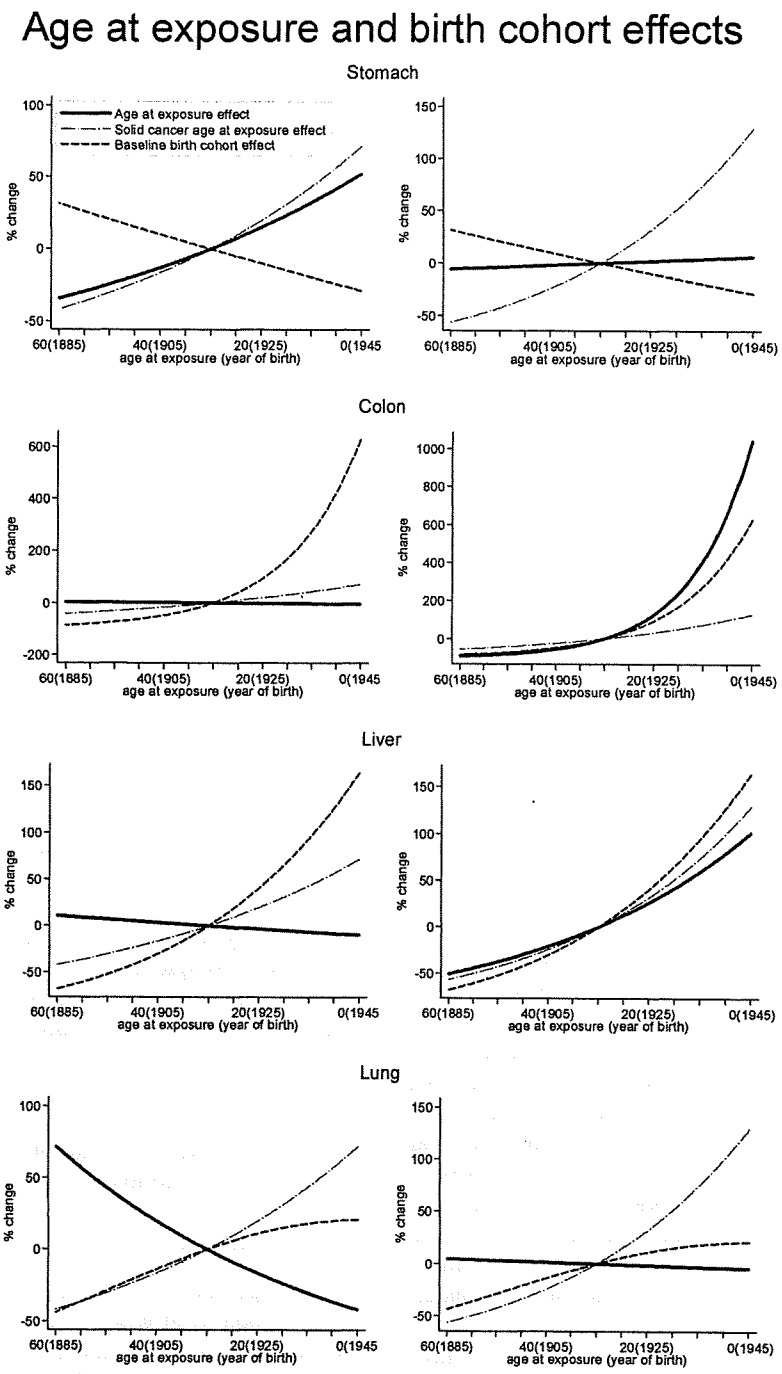

FIG. 9. Comparison of age-at-exposure effects on the excess risk (thick solid line) and birth cohort effects on baseline rates (thick dashed line) for cancers of the stomach, colon, liver and lung. The age-at-exposure effects for all solid cancers (thin dash-dot line) are also shown. The left-hand panels are for excess relative risk (ERR) estimates while the right-hand panels indicate 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.

The contrast between the age-at-exposure effects and the baseline birth-cohort effects illustrated in Fig. 9 suggests that radiation may be acting multiplicatively with respect to the factors responsible for the dramatic increase in colon cancer background rates over time.

Because, as noted earlier, information on stage is available only for recent years, the primary colon cancer risk analyses were based on cases regardless of stage. However, additional analyses were carried out to investigate the impact of the screening effects on ERR estimates. In the first

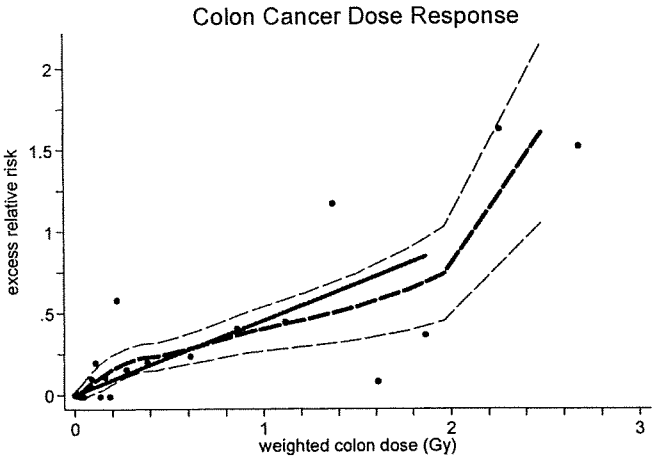

FIG. 10. Colon cancer dose–response function. The thick solid line is the fitted linear gender-averaged excess relative risk (ERR) dose response at age 70 after exposure at age 30 based on data in the 0- to 2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The thick 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.

TABLE 17
Observed and Fitted[a] Colon Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Cases	Background	Fitted excess	Attributable fraction
<0.005	845	832	0	0.0%
0.005–0.1	367	378	8	2.0%
0.1–0.2	90	77	7	7.9%
0.2–0.5	103	81	16	16.2%
0.5–1	53	42	18	30.4%
1–2	37	21	19	47.2%
2–4	21	6	11	64.0%
Total	1,516	1,438	78	11.4%[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 colon dose in Gy.

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

of these analyses the baseline rate model was stratified on three periods (1958–1980, 1981–1990 and 1991–1999). This resulted in a significant (P = 0.01) improvement in model fit, with baseline rates in the most recent period being almost 40% higher than those in the earliest period. The birth cohort effect on the baseline rates was still significant, but the change per decade increase in year of birth was reduced. Allowing for screening effects on the baseline rates had little impact on the level or pattern of the ERR. The standardized ERR per Gy was 0.53 (90% CI 0.29; 0.80). The age at exposure effect was −3.5% per decade, while the ERR decreased in proportion to attained age to the −2.4th power of age. The ERR for women was estimated to be half that for men. Analyses were also carried out excluding known *in situ* (stage 0) cases. In these analyses, the standardized ERR was reduced to 0.44 (90% CI 0.21; 0.72), the female-to-male ERR ratio was increased slightly (0.57) and both the age-at-exposure (−7.75% per decade) and attained-age effects (proportional to age to the power −3.3) were somewhat larger than in the standard model (Table 18).

The LSS data continue to be the major source of information on radiation-related risk of colon cancer. In view of the recent marked changes in Japanese baseline colon cancer rates (*64*) and the somewhat unusual way in which colon cancer excess risks vary with gender and age at exposure, continued analyses of the LSS colon cancer data will be important in further elucidation of the nature of radiation effects.

Rectum (ICD10: C20)

Baseline incidence rates for rectal cancer increased in the past several decades in Japan but at a slower pace than those for colon cancer (*33*). The effects of changes in lifestyle and environmental factors may differ by location in the large intestine (*59*). Rectal cancers are the fifth and sixth most common malignancies in Japanese men and women, respectively (*33*). Data from Japanese cancer registries for 1999 (*33*) provide world-population age-standardized rate estimates of 18.7 cases per 100,000 men and 8.7 per 100,000 women.

In the clinical literature, high-dose radiotherapy for treatment of gynecological malignancies has been associated with the subsequent development of rectal cancer (*65*), but previous analyses of the LSS incidence and mortality data did not demonstrate a radiation effect for this cancer (*2, 20, 66*).

There were 838 cases of rectal cancer (5% of all solid cancer cases) in this cohort. The DCO rate of 5% and histological confirmation rate of 90% (Table 3) indicate a relatively high reliability of the data.

1. Baseline rates and birth cohort effects

The age-specific baseline rates were roughly twice as high in men as in women and were considerably higher for people born in the years shortly before the bombings than those for those born earlier (Table A5). The LSS data suggested that baseline rates for rectal cancer increase roughly in proportion to age to the power of 5 or 6.

2. Dose response and excess cases

Under a simple linear ERR model without effect modification, only 14 of the 838 cases, or less than 4% of the cases seen among cohort members with doses in excess of 0.005 Gy, were estimated to be attributable to radiation exposure (Table 19). The ERR_{1Gy} estimate of 0.19 (90% CI −0.04; 0.47) was not significantly elevated, and there was

TABLE 18
Colon 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	0.73 (0.38; 1.17)[c]	0.34 (0.13; 0.63)	0.54 (0.30; 0.81)	0.5 (0.17; 1.01)	1% (−36%; 45%)	−2.68 (−5.1; 0.4)
EAR	13.0 (4.4; 16)[c]	3.0 (6.4; 14)	8.0 (4.4; 12)	0.2 (0.06; 0.52)	−56% (−74%; −34%)	6.9 (4.5; 10)

[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.

no indication of significant variation in the ERR with age at exposure ($P = 0.4$), attained age ($P > 0.5$) or gender ($P = 0.3$).

Liver (ICD10: C22)

The liver is a frequent site of metastasis for tumors originating in other organs. Mortality data based on death certificates, which often do not distinguish primary from secondary tumors, are less reliable than incidence data based on information obtained from hospital records. Reported incidence rates of liver cancer vary widely in different countries and populations, and Japan is among those with the high rates (*67*). Hepatocellular carcinoma is the major histological type of liver cancer in many populations and is principally caused by hepatitis B (HBV) and C (HCV) viruses. Cholangiocarcinomas and other histological types are less frequent and show little international variations.

Liver cancer incidence rates in Japan have increased sharply since around 1975 in both men and women (*33, 68*), and it is currently the fourth most common cancer in men and seventh in women. The world-population age-standardized incidence rate of 23.5 per 100,000 for Japanese men and that of 7.5 for women (*38*) are higher than the U.S. white and European rates, which range from 3 to 12 for men and from 1 to 5 from women (*34*). The high liver cancer rates in Japan are generally attributed to the high prevalence of HCV infection among the population currently 40 years or older (*68, 69*). The higher rates among men than women are due mostly to the differences in prevalence of HCV and HBV infection and other risk factors such as alcohol consumption and smoking (*70*). It is estimated that about 80% of the liver cancers in Japan are related to HCV infection and 16% to HBV infection (*68*). Evidence of an association between radiation and liver cancer, especially hepatocellular carcinoma, was first presented in the previous incidence report (*2*) and then in a more detailed study based on pathology reviews of hepatocellular carcinoma cases (*9, 11*). Subsequently, a case-control study nested in this cohort found HCV-infected individuals to have a higher radiation-related risk of hepatocellular carcinoma than uninfected persons (*71*).

TABLE 19
Observed and Fitted[a] Rectum Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Cases	Background	Fitted excess	Attributable fraction
<0.005	462	469	0	0.0%
0.005–0.1	230	221	1	0.6%
0.1–0.2	48	45	1	2.6%
0.2–0.5	45	48	3	5.7%
0.5–1	31	25	3	11.7%
1–2	16	13	3	20.1%
2–4	6	4	2	31.1%
Total	838	824	14	3.7%[c]
ERR per Gy[d]		0.19 (90% CI −0.04; 0.47)		
EAR per Gy		0.56 (90% CI −0.13; 1.4)		

[a] Estimates of background and fitted excess cases are based on an ERR model with a linear dose response and no 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.

With 1,494 cases, liver cancer was the fourth most common solid cancer in this cohort, accounting for 9% of all solid cancer cases (Table 2). The low histological verification rate (41%), the high proportion of DCO cases (21%) (Table 3), and the fact that the liver is a common metastatic site are indicative of the difficulties faced in obtaining high-quality data on liver cancer.

1. Baseline rates and birth cohort effects

The age-specific rates were three to four times higher in men than women (Table A6). As with many other solid cancers, liver cancer rates increase with age and the age-specific baseline rates were higher in more recent birth cohorts. The birth cohort effect, however, was somewhat more pronounced for liver cancer than for all solid cancers as a group, especially for males. For both men and women the increase in baseline rates was roughly proportional to age to the power of 4.

2. Dose response and effect modification

There was a significant linear dose response ($P = 0.01$) with no indication of non-linearity ($P > 0.5$) for curvature

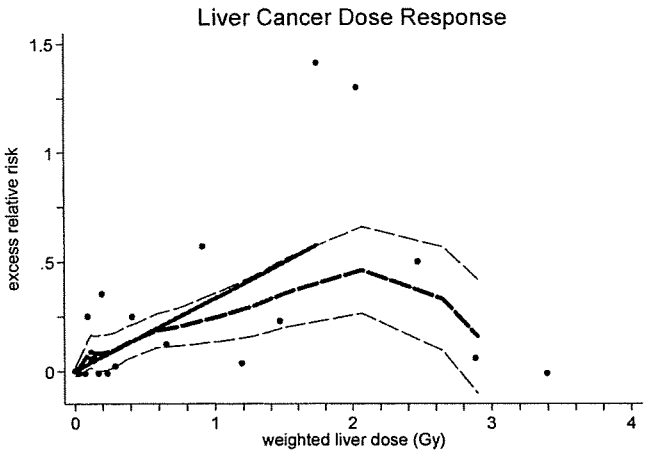

FIG. 11. Liver cancer dose–response function. The thick solid line is the fitted linear gender-averaged excess relative risk (ERR) dose response at age 70 after exposure at age 30 based on data in the 0- to 2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The thick 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.

TABLE 20
Observed and Fitted[a] Liver Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Cases	Background	Fitted excess	Attributable fraction
<0.005	849	830	0	0.0%
0.005–0.1	358	378	5	1.3%
0.1–0.2	79	73	4	5.4%
0.2–0.5	102	86	11	11.3%
0.5–1	61	42	12	22.7%
1–2	30	22	12	36.0%
2–4	15	8	9	52.5%
Total	1,494	1,440	54	8.1%[c]

[a] Estimates of background and fitted excess cases are based on an ERR model with a linear dose response and effect modification by 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 liver dose in Gy.

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

on the 0- to 2-Gy dose range (Fig. 11). Among the 645 survivors with doses of >0.005 Gy, 54 (8%) were estimated to be related to radiation exposure (Table 20).

Using our standard model with effect modification, the ERR_{1Gy} estimate was 0.30 (Table 21). Despite the large gender difference in baseline rates, ERR estimates for men and women were virtually the same, with an estimated female:male ratio of 0.9. The point estimate of the change in the ERR per decade increase in age at exposure was only 3%. An unusual age-at-exposure pattern, i.e. very low increased risks for those exposed under age 10 or after age 45, was noted previously in a detailed analysis of the LSS liver cancer incidence (*9*) for the period through 1987. When we considered models with a non-monotonic age-at-exposure effect, we found little evidence of any increase in the risk with dose for those exposed under age 10 (ERR = 0.02, $P > 0.5$), while the risk was significantly increased for older ages at exposure ($P = 0.02$). The ERR did not vary significantly with age at exposure ($P = 0.2$) among those exposed after age 10. Table 11 presents point estimates and confidence bounds for the risk at age 70 for ages 10, 30 and 50 at exposure in the ERR model described in Table 21. Table 12 gives estimates based on a model that did not assume that the ERR varied log-linearly with age at exposure. Although the modifying effect of attained age was not statistically significant, the ERR decreased with increasing attained age as was seen for many other solid cancers (Table 21).

The standardized EAR estimate was 4.3 cases per 10,000 PY per Gy (Table 21). The EAR estimate was about three times higher in men (6.4) than in women (2.1). This resulted in an estimated female:male EAR ratio of 0.3. Given that baseline rates for men are three to four times those for women, the smaller EAR for women suggests that radiation may act multiplicatively with respect to the factors responsible for the gender difference in baseline rates. The point estimate of the age-at-exposure effect on the EAR (a 21% decrease in the excess rate per decade increase in age at exposure) was large relative to those seen for many other sites, which may reflect the impact of the rapid increase in baseline rates for more recent birth cohorts. The liver cancer panels in Figs. 7 and 8 illustrate the age and age-at-exposure effects for the liver cancer excess risk.

Almost 85% of primary liver cancers were hepatocellular carcinomas, with the remainder being mostly cholangiocarcinomas (*9, 11*). There were too few cases in this and previous series to assess the radiation effects on cholangiocarcinomas, which have been linked to Thorotrast exposure (*37*).

Gallbladder Including Other or Unspecified Parts of Biliary Tract (ICD10: C23 and C24)

Carcinoma of the gallbladder and other or unspecified parts of biliary tract are relatively rare diseases, although the incidence does vary markedly by geographic region and is high in Japan [6.7 and 5.0 per 100,000 male and female world-population age-standardized rates, respectively, in 1999 (*33*)] relative to the U.S. and most European countries (*72, 73*). Gallbladder cancer is highly fatal, and it differs from other gastrointestinal malignancies in that in most countries, it is more common in women than in men (*74*). Risk factors for gallbladder carcinoma include a history of gallstones and other benign diseases of the gallbladder, obesity, estrogens and multiple pregnancies. In Japan, there are several notable features of cancer of the gallbladder: It is more common in the northern part of Japan, survival is better than in most other countries, and the incidence increased rapidly from 1975 until the late 1980s when the

TABLE 21
Liver 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	0.32 (0.12; 0.60)[c]	0.28 (0.05; 0.63)	0.30 (0.11; 0.55)	0.9 (0.16; 2.4)	3% (−37%; 68%)	−2.7 (−5.8; 0.5)
EAR	6.4[d] (0.2; 12)	2.1 (0.6; 4.3)	4.3 (0.2; 7.2)	0.3 (0.10; 3.2)	−21% (−57%; 378%)	3.6 (−3.5; 6.1)

[a] At age 70 after exposure at age 30 per Gy weighted liver 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.

rates for females began to decline steadily while those for men remained stable, resulting in the current male-to-female ratio of slightly over one (*75*).

In the 1994 cancer incidence report (*2*), there was no evidence of a dose–response relationship between radiation from the bombings and malignancies of the gallbladder. Few studies of irradiated populations have provided risk estimates for carcinoma of the gallbladder; however, patients exposed to radioactive Thorotrast were found to have a large excess relative risk (*76*).

The 549 gallbladder cancers (176 in males and 373 in females) represented about 3% of the total malignancies ascertained among members of the LSS cohort and 5.5% of gastrointestinal malignancies. Only 65% of the cases were verified histologically, which was a lower proportion than for many other cancer sites. Twelve percent of the cancers were ascertained through death certificates (Table 3).

TABLE 22
Observed and Fitted[a] Gallbladder Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Cases	Background	Fitted excess	Attributable fraction
<0.005	331	327.8	0.0	0.0%
0.005–0.1	135	139.3	−0.2	−0.2%
0.1–0.2	33	28.5	−0.2	−0.7%
0.2–0.5	25	30.3	−0.5	−1.7%
0.5–1	16	15.9	−0.6	−3.7%
1–2	8	7.5	−0.5	−7.4%
2–4	1	2.0	−0.2	−13.9%
Total	549	551.3	−2.3	−1.0%[c]
ERR per Gy[d]	−0.05 (90% CI < −0.3; 0.3)			
EAR per Gy	−0.01 (90% CI < 0. 1; 0.51)			

[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 pancreas 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.

1. Baseline rates and birth cohort effects

The LSS baseline incidence rates for cancers of the gallbladder increased over time. Rates also rose with each succeeding birth cohort, but an overall increase was seen only among males. Among females, the incidence rate for 70-year-olds increased and then decreased, so that cohorts who were born in 1885 had about the same incidence rate as those born 60 years later, i.e. in 1945. As was the case for many other solid cancers, the increase in gallbladder cancer rates with attained age was roughly proportional to the 5th and 6th power of age with a less rapid increase at older ages. There was little evidence for a gender difference in baseline rates except beyond age 70, where women may have somewhat higher rates than men.

2. Dose response and excess cases

The crude incidence rates of gallbladder carcinoma gave no indication of a dose–response relationship for men or for women (Table A7). Using simple excess risk models with no effect modification, no excess cases were predicted (Table 22), the ERR_{1Gy} estimate was negative (−0.05) and the EAR was estimated to be 0.0 cases per 10,000 PY per Gy. The apparent lack of a radiation effect on gallbladder cancer risks was notable, especially since the upper confidence bound of the ERR was lower than the lower bound for solid cancers.

As discussed in the later section on the comparison of site-specific risks, if one assumes that the gallbladder ERR follows the same gender and temporal patterns as all solid cancers, it is possible to reject ($P = 0.003$) the hypothesis that the standardized gallbladder ERR is equal to that for all solid cancers. While such a comparison is not an ideal way to address this issue, it does suggest that the gallbladder may be less radiosensitive than many other organs.

Pancreas (ICD10: C25)

Cancer of the pancreas is a relatively rare but highly fatal malignancy that is difficult to diagnose because of its inaccessibility. Cigarette smoking has been the most consistently reported risk factor for this cancer (*77*), whereas the relationships with other possible risk factors, such as diet, coffee and alcohol, are unclear (*78*). An increased risk of

pancreatic cancer has been found in some patient populations receiving radioactive Thorotrast (*76*) and among long-term cancer survivors receiving cancer radiotherapy (*79*). An increased risk of pancreatic cancer was also reported from a follow-up of patients who received a mean dose of 13.5 Gy in the pancreas from radiotherapy for peptic ulcer (*55*). Despite a relatively large number of pancreatic cancer cases, previous analyses of the LSS data did not provide evidence of a radiation effect on pancreatic cancer rates (*2, 66*).

Recent data indicated that pancreatic cancers are the eighth and tenth most common malignancies in Japanese men and women, respectively [Table 5 and (*33*)] with world-population age-standardized rates of 9.0 per 100,000 PY among men and 5.2 for women. It has been noted (*80*) that age-specific pancreatic cancer mortality rates in Japan increased with year of birth for people born before 1920, but there was little change for later birth cohorts. Pancreatic cancer rates are somewhat higher for men than for women.

The 512 cases of pancreatic cancer available for the current analyses (223 among men and 289 among women) accounted for about 3% of the solid cancer cases in the cohort. The histological verification rate of 52% for pancreatic cancer was among the lowest for any cancer site in the Hiroshima and Nagasaki registries, while the proportion of DCO cases, 20% (Table 3), was one of the highest rates, reflecting the short survival time of pancreatic cancer patients.

1. Baseline rates and birth cohort effects

As suggested by the crude rates (Table A8) and our modeling of the baseline rates, age-specific rates were higher in men than in women and increased with increasing age in a manner similar to that for all solid cancer as a group. Our descriptive modeling of the baseline rates did not provide evidence of birth cohort effects. Pancreatic cancer baseline rates increased roughly in proportion the 5th or 6th power of age prior to the mid-70s, at which time the rates appeared to level off or even decrease slightly with attained age. Baseline rates for men tended to be about twice those for women except for ages in excess of 80, where they appeared to be similar.

2. Dose response and excess cases

Under a simple linear dose–response model without effect modification, it was estimated that there were 11 radiation-associated cases (Table 23). Neither the ERR_{1Gy} estimate of 0.26 nor the EAR estimate of 0.46 excess cases per 10,000 PY per Gy was statistically significant.

TABLE 23
Observed and Fitted[a] Pancreatic Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Cases	Background	Fitted excess	Attributable fraction
<0.005	283	287.8	0.0	0.0%
0.005–0.1	142	132.2	1.1	0.8%
0.1–0.2	30	28.1	1.0	3.5%
0.2–0.5	18	29.4	2.4	7.6%
0.5–1	25	14.8	2.6	15.1%
1–2	14	7.1	2.4	25.4%
2–4	—	1.9	1.2	37.7%
Total	512	501.2	10.8	4.8%[c]
ERR per Gy[d]	0.26 (90% CI −0.07; 0.68)			
EAR per Gy	0.46 (90% CI −0.13; 1.5)			

[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 pancreas 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.

Lung (ICD10: C34)

Lung cancer is the most common cancer worldwide, with the highest incidence rates reported in North America and Europe (*67*). It is currently the second most common cancer in men and the fifth in women in Japan (*33*). There has been a steady increase in Japanese lung cancer rates for both men and women during the past several decades (*33*), mostly due to changes in smoking habits. The prevalence of smoking in Japan males increased from 76% in 1955 to a peak of 82% in 1965 before declining to 50% in 1992 (*81*). The prevalence of smoking in women, though still lower than in men, has increased recently among young women (*82*). In 1999, the world-population age-standardized lung cancer rates per 100,000 person years were 37.6 and 22.5 for men and women, respectively (*33*). Lung cancer is highly fatal, with 5-year survival of about 15% in the U.S. and 20% in Japan (*49, 67*).

The present series included 1,759 lung cancer cases. It was the second most common cancer in the cohort accounting for 10% of all solid cancer cases and almost 90% of the respiratory cancer cases. Diagnoses were verified histologically for 73% of the lung cancer cases, while 15% of the cases were identified solely from death certificates (Table 3). Comparison with the 69% histological verification and 18% DCO rates seen in the pre-1987 data considered in the last LSS incidence report (*1*) indicated improvements in the quality of tumor registry data obtained over the last decade.

1. Baseline rates and birth cohort effects

Crude lung cancer rates stratified by gender, dose category and age at exposure (Table A9) suggest that that baseline lung cancer rates among men were three to four times higher than those for women. The rates increased markedly with age at exposure, reflecting the effects of both increasing attained age and birth cohort. Our analyses of the LSS

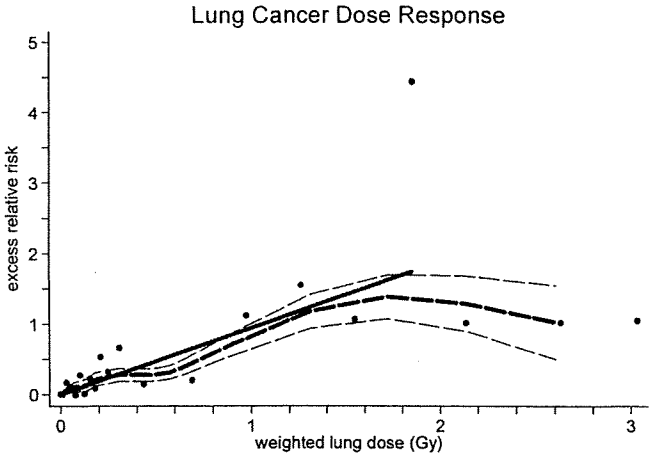

FIG. 12. Lung cancer dose–response function. The thick solid line is the fitted linear gender-averaged excess relative risk (ERR) dose response at age 70 after exposure at age 30 based on data in the 0- to 2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The thick dashed is a nonparametric smooth of the category-specific estimates and the thin dashed lines are one standard error above and below this smooth.

TABLE 24
Observed and Fitted[a] Lung Cancer Cases by Dose Category with Attributable Fraction Estimates

Dose category[b]	Cases	Background	Fitted excess	Attributable fraction
<0.005	970	964	0	0.0%
0.005–0.1	405	393	9	2.3%
0.1–0.2	101	99	11	9.8%
0.2–0.5	135	104	28	21.5%
0.5–1	64	43	24	36.3%
1–2	64	29	27	47.8%
2–4	20	10	17	63.9%
Total	1,759	1,642	117	14.7%[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 lung dose in Gy.

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

baseline rates suggested that age-specific LSS baseline lung cancer rates have increased by about 20% per decade increase in year of birth for both men and women. The male: female ratio of the baseline rates was about four for people in the earliest birth cohorts but was closer to three for later birth cohorts. The estimated baseline lung cancer rates (per 10,000 PY) at age 70 for people born in 1900 were 23 for men and 6 for women, while the corresponding baseline rate estimates for men and women in the 1930 birth cohort were 33 and 9, respectively, an increase of about 50% for this 30-year birth-cohort difference.

The increase in lung cancer baseline rates with attained age was proportional to the sixth power of age for both men and women, a rate of increase that is larger than that for most other solid cancers. Lung cancer baseline rates appeared to peak between 75 and 80 years of age.

2. Dose response and excess cases

As suggested by the crude rates in Table A9 and the dose–response summaries shown in Fig. 12, there was a statistically significant linear dose response ($P < 0.001$), with no evidence of non-linearity over the 0- to 2-Gy dose range ($P = 0.2$).

With allowance for the effects of gender, age at exposure, and attained age on the radiation-associated ERR, the linear model predicted 117 excess cases, or an attributable risk of almost 15% among those exposed to more than 0.005 Gy (Table 24).

The standardized gender-averaged ERR per was 0.81 (Table 25). The ERR estimate of 0.28 for men was much lower than that for 1.33 for women. Indeed, as will be discussed later in this report, the female:male gender ratio of 4.8 (90% CI 2.6; 11) (Table 25) was the highest of all organ-specific ERR gender ratios.

In contrast to most other solid cancers, the lung cancer ERR appeared to be increasing with increasing age at exposure (Tables 11, 12 and 25, Figs. 8 and 9). The point estimate suggested that the ERR increased by about 20% per decade increase in age at exposure. While this was not significantly different from no increase ($P = 0.2$), the age-at-exposure trend for lung cancer was significantly different ($P = 0.02$) from the 17% per decade decrease seen for all solid cancers.

The standardized, gender-averaged lung cancer EAR was 7.5 cases per 10,000 PY per Gy (Table 25). The EAR did not vary significantly with gender ($P = 0.3$) or age at exposure, but it did increase significantly with attained age (Table 25 and Figs. 7 and 8).

Although we could not explicitly adjust for smoking in these analyses, comparison of the effects of gender and age at exposure on the ERR and EAR together with knowledge of smoking prevalence in Japan suggests that smoking and radiation may have independent (additive) effects on lung cancer risks in the LSS. Smoking is considerably less prevalent among women than men in Japan, and for the birth cohorts in this population, both the prevalence of smoking and the cumulative amount smoked by a given age tend to be higher for later birth cohorts. If radiation and smoking act additively, then the ERR per unit radiation dose should be much higher for women than for men in analyses that do not explicitly adjust for the effect of smoking, while EAR estimates for men and women would be similar. This was the pattern observed here. Similarly, if radiation and smoking have independent effects on lung cancer risks, the marked increase in the prevalence of smoking would elevate lung cancer risks for later birth cohorts and thus dampen or even reverse the typical pattern in which the ERR for

TABLE 25
Lung 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	0.28 (0.12; 0.49)[c]	1.33 (0.91; 1.8)	0.81 (0.56; 1.1)	4.8 (2.6; 12)	20% (−7%; 54%)	−1.94 (−3.7; −0.2)
EAR	6.0[d] (2.3; 11)	9.1 (6.4; 12)	7.5 (5.1; 10)	1.5 (0.82; 3.9)	2% (−20%; 28%)	4.23 (2.8; 5.7)

[a] At age 70 after exposure at age 30 per Gy weighted lung 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.

radiation effects tend to increase with decreasing age at exposure, while attained-age specific EAR estimates would vary little with age at exposure. As indicated in the bottom panel of Fig. 9, these patterns result in age-at-exposure effects on the radiation-associated ERR that are the opposite of those seen for solid cancers as a group.

Joint effects of radiation and smoking on lung cancer incidence were recently analyzed among LSS members for whom individual information on smoking history was available (*13*), and it was found that adjustment for smoking reduced the female:male ERR ratio for radiation effects from 5.8 to 1.6. Not surprisingly the unadjusted gender ratio was similar to the ratio of 4.8 seen in our ERR analyses, while the smoking-adjusted estimate of 1.6 was similar to that (1.5) obtained in our EAR analysis as would be implied by additivity.

The LSS findings on radiation and smoking effects differ from those found for lung cancer related to radon exposure (*83*) or radiotherapy (*84*). The radon effects were significantly greater than additive and were closer to multiplicative, and the effects of moderate to heavy smoking and radiotherapy for Hodgkin lymphoma were compatible with a multiplicative relationship. It should be noted that mechanisms involving high-LET or high-dose therapeutic exposures may be different from those at low dose of low-LET radiation.

Non-melanoma Skin Cancer (ICD10: C44)

Non-melanoma skin cancer is very common in Caucasian populations, especially among the elderly. In Japan and other Asian countries, non-melanoma skin cancer incidence is quite low (world-population age-standardized rates of 3.4 per 100,000 PY for men and 2.2 for women) (*33*). Moreover, the rates of basal cell carcinoma and squamous cell carcinoma are quite similar, whereas among Caucasian populations, basal cell carcinoma is far more common than squamous cell carcinoma. Basal cell carcinoma has been increasing in Japan over the last few decades, but squamous cell carcinoma rates are largely stable (*17, 85*). In Western countries, because the number of non-melanoma skin cancers is overwhelming and most of the cancers can be treated in an outpatient setting, cases are not routinely collected by most tumor registries. Japanese tumor registries routinely ascertain cases of non-melanoma skin cancer partly because non-melanoma skin cancer is relatively rare. Thus it is feasible to use the Hiroshima and Nagasaki tumor registries to evaluate radiation risks associated with non-melanoma skin cancers in the atomic bomb survivors (*1, 17*).

There is clear evidence that non-ionizing ultraviolet (UV) radiation increases the risk of non-melanoma skin cancer, but the picture is less clear for low-dose ionizing radiation (*37*). The effects of ionizing radiation on non-melanoma skin cancer risks have been considered in a number of irradiated populations, and in general, elevated risks of basal cell carcinoma have been observed (*86–88*) most frequently among people exposed to relatively high doses of radiation as children. In contrast, there is little evidence of an association between squamous cell carcinoma and ionizing radiation at low doses (*37*).

Non-melanoma skin cancer risks in the atomic bomb survivors have been considered in detail in two reports (*6, 17*) published since the last general review of LSS cancer incidence (*2*). The results of these analyses clearly demonstrate the existence of radiation effects on skin cancer incidence rates for skin doses in excess of about 1 Gy. As in other populations, the excess risk was largely due to a radiation-associated increase in basal cell carcinoma, with no excess seen for squamous cell carcinoma. Further analyses that incorporated a pathology review of all cases did not show an interaction between ionizing radiation and UV radiation, with the EAR being similar in the UV-radiation-exposed and -shielded areas of the body. There was no indication that ionizing radiation exposure influenced melanoma risks; however, since the number of melanoma cases diagnosed among LSS cohort members during several decades of incidence follow-up is small (*17*), there is little power to detect radiation-associated changes in melanoma risks.

The current analyses were based on 330 non-melanoma skin cancers (166 basal cell carcinoma, 131 squamous cell carcinoma, 33 other), somewhat less than 2% of all solid cancers. This is considerably more cases than the 208 considered in earlier analyses (*6*) due to the longer follow-up and inclusion of 55 cases diagnosed among people who were not in the cities at the time of exposure. Because there were only 17 melanoma cases, melanomas could not be