Table 2 shows hazard ratios (95% confidence intervals [CIs]) of mortality from all causes of death, as well as all cancers, and the major sites of cancer. We have tested the assumption of proportional hazard, and a proportionality of hazards of education was not confirmed for female breast cancer. When an interaction term with a time-dependent variable was included in the model, the results did not change materially. For all causes of death, age- and multivariate-adjusted mortality data showed a statistically significant inverse association with educational achievement (i.e., an increasing trend with decreasing levels of educational level) for both men and women. For all sites combined, age-adjusted cancer mortality showed a statistically significant inverse association with educational achievement in both men and women, but the trend was not significant after adjustment in the multivariate model. Among the factors used for multivariate adjustment, smoking was significantly associated with cancer of all sites combined; past and current smokers showed significantly higher hazard ratios compared with those who had never smoked (never smokers): 1.52 (95% CI: 1.25–1.85) for ex-smokers and 2.33 (95% CI: 1.96–2.77) for current smokers in men and 1.41 (95% CI: 1.15–1.73) for ex-smokers and 1.69 (95% CI: 1.49–1.93) for current smokers in women.

Among the major sites of cancer, mortality from male liver and prostate cancers showed a significantly increasing trend with decreasing education achievement in multivariate-adjusted model. For male liver cancer, when alcohol drinking habits were added in the multivariate model, hazard ratios for liver cancer mortality changed relatively little (i.e., from 1.49 [95% CI: 1.10–2.03] to 1.52 [95% CI:1.12-2.06]) for those with 9 years or less of education compared with those with 13 years of education. For female lung cancer, a significant inverse trend with educational achievement was observed in the age-adjusted model. After multivariate adjustment, the trend was not significant, whereas BMI, current smoker status, and estimated lung radiation dose all showed significant hazard ratios: 0.96 (95% CI: 0.93–0.99) for BMI, 4.28 (95% CI: 3.19–5.73) for current smokers, and 1.80 (95% CI: 1.40–2.31) for lung dose (Gy).

The percentages of DCO cases and cases of localized clinical stage by education are shown for all sites combined and major sites of cancer in Table 3. The percentages of DCO cases were significantly different by education for cancer of all sites combined and stomach cancer in men, with those having ≥13 years of education being the highest. The percentages of cases of localized clinical stage were not significantly different by education for all sites combined or any site of cancer.

Table 4 shows hazard ratios (95% CIs) of incident cancer of all sites combined and major sites. We have tested the assumption of proportional hazard, and a proportionality of hazards of education was not confirmed for cancer incidence of all sites combined and liver cancer incidence. When an interaction term with time-dependent variable

TABLE 2. Hazard ratios (95% confidence intervals) for deaths from all causes and major sites of cancer by education, followed up until 2003 among 32,883 respondents, 74 years of age or younger, of mail survey in 1978 in the Life Span Study cohort, Hiroshima and Nagasaki

		Age-adjusted				Multivariate-adjusted*			
		Education				Education			
	No. of deaths	≥13 yr	10–12 yr	≤9 yr	*p* for trend	≥13 yr	10–12 yr	≤9 yr	*p* for trend
Men (N = 12,747; 256,258 person-years)									
All causes	4,670	1.00	1.16 (1.06–1.27)	1.28 (1.18–1.40)	<0.001	1.00	1.13 (1.04–1.24)	1.23 (1.13–1.35)	<0.001
Cancer									
All sites	1,824	1.00	0.98 (0.86–1.12)	1.12 (0.98–1.28)	0.03	1.00	0.95 (0.83–1.09)	1.07 (0.94–1.23)	0.14
Stomach	363	1.00	1.06 (0.79–1.43)	1.03 (0.77–1.40)	0.90	1.00	1.04 (0.77–1.40)	1.00 (0.74–1.36)	0.94
Colorectal	159	1.00	1.04 (0.68–1.61)	0.88 (0.56–1.38)	0.47	1.00	1.03 (0.67–1.60)	0.88 (0.56–1.39)	0.48
Liver	372	1.00	1.05 (0.78–1.43)	1.48 (1.10–2.00)	0.002	1.00	1.05 (0.77–1.42)	1.50 (1.11–2.04)	0.002
Lung	387	1.00	0.94 (0.70–1.27)	1.21 (0.91–1.61)	0.08	1.00	0.87 (0.65–1.17)	1.04 (0.78–1.39)	0.49
Prostate	56	1.00	1.88 (0.63–5.55)	3.14 (1.11–8.89)	0.01	1.00	1.89 (0.64–5.59)	3.21 (1.13–9.15)	0.01
Women (N = 20,126; 409,646 person-years)									
All causes	5,516	1.00	1.17 (1.01–1.37)	1.35 (1.16–1.57)	<0.001	1.00	1.15 (0.99–1.34)	1.31 (1.12–1.53)	<0.001
Cancer									
All sites	1,680	1.00	1.11 (0.87–1.42)	1.22 (0.95–1.55)	0.04	1.00	1.09 (0.85–1.39)	1.16 (0.90–1.48)	0.15
Stomach	262	1.00	0.85 (0.49–1.48)	0.83 (0.47–1.46)	0.63	1.00	0.83 (0.48–1.45)	0.83 (0.47–1.45)	0.70
Colorectal	189	1.00	1.43 (0.63–3.28)	1.42 (0.62–3.28)	0.67	1.00	1.43 (0.62–3.28)	1.40 (0.61–3.23)	0.75
Liver	247	1.00	1.49 (0.70–3.21)	1.81 (0.84–3.90)	0.06	1.00	1.42 (0.66–3.06)	1.70 (0.79–3.66)	0.09
Lung	214	1.00	1.10 (0.53–2.27)	1.56 (0.75–3.23)	0.02	1.00	1.08 (0.52–2.23)	1.30 (0.63–2.70)	0.19
Breast	122	1.00	1.29 (0.59–2.82)	1.14 (0.50–2.57)	0.85	1.00	1.28 (0.59–2.81)	1.16 (0.51–2.63)	0.94

*Adjusted for age, body mass index, smoking category, radiation dose, and city.

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TABLE 3. Percentage of cases by death certificate only cases and clinical stage (localized) in major sites of cancer, identified until 2001 among 32,883 respondents of mail survey in 1978, aged 74 years or younger in the Life Span Study cohort, Hiroshima and Nagasaki

Site	% DCO and % localized*	Total	Education			p Value†
			≥13 yr	10–12 yr	≤9 yr	
Men						
All	% DCO (n = 2,682)	11.9	16.9	10.5	11.3	0.001
	% Localized (n = 1,822)	44.2	46.2	44.7	43.0	0.63
Stomach	% DCO (n = 660)	7.0	12.9	4.8	6.6	0.02
	% Localized (n = 524)	51.5	52.7	49.8	52.9	0.79
Colorectal	% DCO (n = 358)	7.8	11.9	7.1	6.9	*0.48*
	% Localized (n = 301)	52.5	53.2	56.6	46.8	0.30
Liver	% DCO (n = 388)	22.7	27.1	22.9	20.9	0.62
	% Localized (n = 179)	55.3	52.2	57.9	53.8	0.83
Lung	% DCO (n = 377)	19.4	23.6	16.1	20.8	0.39
	% Localized (n = 245)	18.4	25.7	16.5	17.8	0.47
Prostate	% DCO (n = 161)	4.3	4.8	7.4	2.3	*0.29*
	% Localized (n = 98)	40.8	53.8	30.6	44.9	0.24
Women						
All	% DCO (n = 2,751)	10.9	11.4	10.6	11.1	0.91
	% Localized (n = 2,067)	48.0	52.6	48.3	47.1	0.56
Stomach	% DCO (n = 485)	6.2	11.8	7.9	3.8	0.06
	% Localized (n = 406)	53.0	55.6	52.4	53.1	0.95
Colorectal	% DCO (n = 403)	5.2	7.1	7.4	2.7	*0.07*
	% Localized (n = 354)	46.0	50.0	44.6	47.3	0.85
Liver	% DCO (n = 241)	22.0	9.1	21.1	24.0	*0.57*
	% Localized (n = 119)	66.4	100.0	66.7	63.3	*0.31*
Lung	% DCO (n = 228)	20.6	30.0	20.5	20.0	*0.68*
	% Localized (n = 158)	31.0	66.7	26.2	32.2	*0.12*
Breast	% DCO (n = 393)	5.1	4.3	5.2	5.1	*1.00*
	% Localized (n = 356)	58.7	42.9	58.0	62.6	0.23

DCO = death certificate only.
*Cases of unknown stage were excluded.
†Chi-square test and Fisher exact test (in italics).

was included in the models, the results did not change materially. Subjects with a history of cancer (218 men and 683 women) were excluded. For all sites combined, an inverse trend with educational achievement was observed in the multivariate-adjusted model ($p < 0.001$) in men but not in women. Liver cancer incidence in men showed a significant, inverse trend with educational achievement. When alcohol drinking habits were added in the

TABLE 4. Hazard ratios (95% confidence interval) for cancer incidence of major sites, identified until 2001 among 31,982 respondents of mail survey in 1978, aged 74 years or younger without history of cancer in the Life Span Study cohort, Hiroshima and Nagasaki

		Age-adjusted				Multivariate-adjusted			
		Education				Education			
	No. of cases	≥13 yr	10–12 yr	≤9 yr	p for trend	≥13 yr	10–12 yr	≤9 yr	p for trend
Men (N = 12,529; 227,238 person-years)									
All sites	2,682	1.00	1.12 (1.004–1.25)	1.22 (1.09–1.37)	<0.001	1.00	1.10 (0.99–1.23)	1.20 (1.07–1.35)	0.001
Stomach	660	1.00	1.04 (0.84–1.30)	1.07 (0.86–1.34)	0.55	1.00	1.03 (0.83–1.28)	1.07 (0.86–1.34)	0.52
Colorectal	358	1.00	1.26 (0.93–1.69)	1.06 (0.78–1.45)	0.96	1.00	1.26 (0.94–1.70)	1.08 (0.79–1.48)	0.93
Liver	388	1.00	1.14 (0.85–1.54)	1.55 (1.15–2.09)	0.001	1.00	1.14 (0.85–1.54)	1.60 (1.18–2.17)	<0.001
Lung	377	1.00	1.18 (0.87–1.61)	1.41 (1.04–1.92)	0.02	1.00	1.09 (0.80–1.49)	1.24 (0.91–1.70)	0.13
Prostate	161	1.00	1.09 (0.66–1.80)	1.54 (0.95–2.49)	0.03	1.00	1.10 (0.67–1.83)	1.59 (0.98–2.58)	0.02
Women (N = 19,453; 354,448 person-years)									
All sites	2,751	1.00	1.11 (0.93–1.33)	1.16 (0.96–1.39)	0.13	1.00	1.10 (0.92–1.31)	1.14 (0.95–1.37)	0.18
Stomach	485	1.00	0.66 (0.46–0.95)	0.71 (0.49–1.03)	0.63	1.00	0.65 (0.45–0.94)	0.73 (0.51–1.06)	0.86
Colorectal	403	1.00	1.44 (0.84–2.48)	1.31 (0.76–2.28)	0.94	1.00	1.43 (0.83–2.46)	1.30 (0.75–2.26)	0.90
Liver	241	1.00	0.98 (0.53–1.82)	1.15 (0.62–2.15)	0.28	1.00	0.94 (0.51–1.75)	1.07 (0.57–2.02)	0.43
Lung	228	1.00	0.94 (0.49–1.82)	1.51 (0.78–2.91)	0.002	1.00	0.94 (0.49–1.81)	1.35 (0.70–2.59)	0.03
Breast	393	1.00	1.29 (0.84–1.98)	1.08 (0.69–1.70)	0.47	1.00	1.27 (0.83–1.95)	1.09 (0.69–1.71)	0.56

multivariate model, the hazard ratios changed relatively little (i.e., from 1.60 [95% CI: 1.18–2.17] to 1.61 [95% CI: 1.19–2.18]). For lung cancer, a significant inverse trend with educational achievement was observed in the multivariate-adjusted model in women but not in men. This may be because of a gender difference in strength of associations between cigarette smoking and lung cancer incidence; hazard ratios of current smoking were 7.52 (95% CI: 4.11–13.7) in men and 3.14 (95% CI: 2.36–4.19) in women. Overall, the gradient in cancer incidence appeared to be an increase as the educational level declined. The exception to the latter was the multivariate stomach cancer incidence data in women, and its agreement with the mortality data.

DISCUSSION

To our knowledge, this is the first study that examined cancer incidence and mortality in a Japanese population in relation to education achievement and as a surrogate measure of socioeconomic status. Prospective cohort data linked with cancer registries allowed adjustment for other potential confounding factors, such as BMI and smoking. The associations with educational level were generally stronger for incidence than for mortality. Subjects of our cohort were largely residents of smaller areas of the cities of Hiroshima and Nagasaki rather than larger administrative areas of Hiroshima Prefecture and Nagasaki Prefecture and were likely to be socioeconomically more homogeneous than residents of Osaka Prefecture (15). It is interesting to note that, even in this relatively homogeneous population, there may exist an association between level of educational achievement and cancer in general and for liver cancer in men and lung cancer in women.

Stomach cancer was the most common cancer in our cohort, although a declining trend in mortality has been observed in Japan (27). No significant trends were found in stomach cancer mortality or incidence in our data. In Japan, Fujino et al. have examined the associations between educational background and stomach cancer mortality in a prospective cohort study and found a gender difference (10). The risk of death was marginally significantly elevated among individuals with low levels of education in men but not in women (9). Our data also showed a contrast by gender, but the pattern was different from that reported by Fujino et al. (9). Hazard ratios for stomach cancer in men were not elevated at lower educational levels. However, the hazard ratios for stomach cancer in women tended to decrease among those with lower educational level.

Colorectal cancer incidence has increased recently, but the mortality has remained at the same level in Japan (20). According to the review by Faggiano et al. (1), colon cancer shows a positive trend with social class while cancer of the rectum does not. In our cohort, an education-related trend for colorectal cancer mortality and incidence was steeper in women than in men. This might be partly explained by the difference in cancer screening participation. Although socioeconomic differences in the participation rate have been reported among Japanese women (28), it is unlikely that comparable differences among Japanese men will be detected; this is due to the fact that Japanese working men usually undergo occult blood testing once a year with health check-ups ordained by the Occupational Health and Safety Law.

Incidence and mortality of liver cancer have been decreasing in Japan (20, 27). Hazard ratios for liver cancer mortality by educational level were higher in women than in men, but the trend was significant only in men. Alcohol drinking habits were significantly different by education level in men, and frequencies of habitual and occasional alcohol drinkers combined were positively associated with education in men: 74.5%, 80.7%, and 83.0% for those with 9 years or less, 10 to 12 years, and 13 years or more of education, respectively. As shown in the Results section, hazard ratios for liver cancer mortality changed relatively little when alcohol drinking was taken into account in the multivariate model. For liver cancer incidence, the trend was also significant only in men, and the hazard ratios changed relatively little as well when alcohol drinking was taken into account in the multivariate model. Therefore it would appear that alcohol drinking contributed little to the high hazard ratios for liver cancer mortality and incidence in men at lower educational levels.

Lung cancer incidence has increased, but associated mortality rates have remained at the same level in Japan (20). Hazard ratios were higher in women than in men with lower levels of education in both cancer mortality and incidence. This may have been due to gender differences in patterns of smoking prevalence. In our data, the percentage of smokers among those with 10 to 12 years and 9 years or less of education were both higher than among those with 13 years or more of education in both men and women. As shown in the results, a hazard ratio of current smoking for lung cancer incidence was higher in men than in women, and this seemed to have resulted in the attenuation of hazard ratios of education in men.

Breast cancer incidence has been increasing in Japanese women, but still remains very low (27) compared with Western countries. Female breast cancer has been reported to follow a consistent gradient, rising from lower to higher social classes in many Western countries (1). Our data showed no gradient in incidence, whereas hazard ratios for mortality slightly increased with decreasing educational level. As the incidence rate continues to rise, socioeconomic

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differences might become more evident, as in the Western countries.

Prostate cancer incidence has been increasing in Japanese, but still remains very low (27) compared with the Western countries. Inverse associations with education were observed in both mortality and incidence as opposed to the results reported from Finland (3).

Some limitations are present in our study. First, as our cancer cases were recorded in cancer registries in the Hiroshima and Nagasaki prefectures, incident cases occurring outside of these areas were largely ascertained only as DCO cases. However, no inverse education-related associations were observed in the percentages of DCO cases (a significant "positive" association was observed for all sites of cancer in men), it seems unlikely that DCO cases contributed to the inverse education-related associations observed for all sites combined in men, or for liver cancer in men for the cancer incidence analyses; therefore this effect seems to have been minimized. In addition, when we excluded DCO cases in cancer mortality analyses, the results did not change substantially. Second, we used dummy variables for missing observations of the variables other than education in which subjects without information on educational achievement were excluded because it was a main factor of the study. When multiple imputation was used for the variables other than education, the results did not change substantially (29, 30). Third, we used education instead of occupation as an indicator of socioeconomic status because education applies to both working and nonworking people. It also does not change during adult life, so it can be equally used for our subjects 34 to 74 years of age. Thus education appears to be a good socioeconomic indicator in our cohort.

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ARTICLE

Solid Cancer Incidence in Atomic Bomb Survivors Exposed In Utero or as Young Children

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Background In utero exposure to radiation is known to increase risks of childhood cancers, and childhood exposure is associated with increased risks of adult-onset cancers. However, little is known about whether in utero exposure to radiation increases risks of adult-onset cancers.

Methods Solid cancer incidence rates were examined among survivors of the atomic bombings of Hiroshima and Nagasaki who were in utero (n = 2452) or younger than 6 years (n = 15388) at the time of the bombings. Poisson regression was used to estimate and compare the levels and temporal patterns of the radiation-associated excess risks of first primary solid cancers among these survivors at ages 12–55. All statistical tests were two-sided.

Results There were 94 eligible cancers in the in utero group and 649 in the early childhood group. The excess relative risk (ERR) increased with dose for both in utero (age 50, ERR = 1.0 per Sv, 95% confidence interval [CI] = 0.2 to 2.3 per Sv) and early childhood (age 50, ERR = 1.7 per Sv, 95% CI = 1.1 to 2.5 Sv) exposures. The ERR declined ($P = .046$) with increasing attained age in the combined cohort. Excess absolute rates (EARs) increased markedly with attained age among those exposed in early childhood but exhibited little change in the in utero group. At age 50, the estimated EARs per 10000 person-years per Sv were 6.8 (95% CI = <0 to 49) for those exposed in utero and 56 (95% CI = 36 to 79) for those exposed as young children.

Conclusions Both the in utero and early childhood groups exhibited statistically significant dose-related increases in incidence rates of solid cancers. The apparent difference in EARs between the two groups suggests that lifetime risks following in utero exposure may be considerably lower than for early childhood exposure, but further follow-up is needed.

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The Radiation Effects Research Foundation (RERF) tracks the mortality and cancer incidence among survivors of the 1945 atomic bombings of Hiroshima and Nagasaki. Observations of those exposed in utero have been analyzed and periodically reported since 1970. A dose-related increase in cancer mortality before age 15 (ie, childhood cancer mortality) could not be demonstrated in this group due to the small numbers of cancers (1–4). However, as the cohort has aged and cancers have accumulated, so has evidence of a dose-related increase in cancer mortality (5–7).

People who were in utero or young children at the time of the bombings are now attaining ages at which background cancer rates begin to rise sharply. A previous analysis considered solid cancer and leukemia mortality over the age range 15–46 years in these groups (7). Because the in utero cohort is small and follow-up time was limited, the data included only eight deaths from solid cancers and two from leukemia among those exposed to at least 0.01 Sv. However, it was possible to show a statistically significant excess relative risk (ERR) of solid cancers (ERR = 2.4 per Sv, 95% confidence interval [CI] = 0.3 to 6.7 per Sv) (7). The magnitude of this excess did not differ from that of those exposed during the first 6 years of life (ERR = 1.4 per Sv, 95% CI = 0.4 to 3.1). The number of leukemia deaths was too small for a dose–response analysis.

In this report, we consider solid cancer incidence in the age range of 12–55 years for the period 1958–1999 among a cohort of atomic bomb survivors who were either in utero or in the first 6 years of life at the time of the bombings. We pay particular attention to differences in the temporal pattern of the radiation-associated excess risk of solid cancers following exposure in utero or during early childhood. Analyses of the risk of leukemia and other malignant

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neoplasms of the lymphohematopoietic system will be presented in a separate paper because the case ascertainment methods and follow-up period differ from those used for solid cancers.

Subjects and Methods

Study Cohorts

This study was reviewed and approved by the human subjects study review committees of the RERF and the Hiroshima and Nagasaki Tumor registries.

The study population consisted of a cohort of 3268 people who were in utero at the time of the bombings (August 6, 1945, in Hiroshima; August 9, 1945, in Nagasaki) and an early childhood cohort including the 15 899 members of the RERF Life Span Study (LSS) who were younger than 6 years at the time of bombings. Individuals in both groups were alive and had no documented history of cancer before January 1, 1958, when tumor registries were established in each city. Follow-up for analyses of mortality in the LSS cohort began on October 1, 1950. Between this date and the end of 1957, there was only one cancer death among those exposed in utero and none among those exposed in early childhood. Individual radiation doses were determined using the Dosimetry System 2002 (DS02) (8–10). The gamma dose was combined with the neutron dose, which was weighted (ie, multiplied by 10) to reflect the greater biologic effect of neutron radiation. Because DS02 does not provide fetal dose estimates, the mother's uterine dose was used as a surrogate for fetal dose in persons who were exposed in utero (11–13). The DS02-weighted colon dose was used for persons who were exposed as children. DS02 estimates could not be computed for 738 persons (227 exposed in utero, 511 exposed in early childhood) who were exposed within 3 km of the hypocenter and for whom the effects of shielding by buildings or terrain could not be adequately characterized. These people were excluded from the analyses.

The in utero cohort also included 589 people born to women whose exposure status is unknown. Because it is believed that these women were not exposed to radiation from the bombs, it has been customary to treat their children as having received zero dose. However, rather than make that assumption, we excluded the children of these women from the current analyses. Interestingly, age- and sex-adjusted solid cancer incidence rates in this group appear to be lower (RR = 0.35, 95% CI = 0.15 to 0.67) than those for the cohort members who received little or no radiation dose, suggesting that they differed from others with regard to some factors affecting their baseline cancer rates.

Follow-up began on January 1, 1958, when the tumor registries started, except, as described in (7), for 468 (14%) of the in utero cohort members who were identified after 1958, largely through a supplement to the 1960 Japanese national census. Follow-up for these 468 cohort members began on October 1, 1960. Follow-up ended on the date of the first primary cancer diagnosis, the date of death from any cause, the date of loss to follow-up, the date of reaching age 55, or December 31, 1999, whichever occurred first. A total of 35 cohort members (12 in utero) were lost to follow-up due to migration from Japan. The age 55 cutoff was used to ensure compatibility because all in utero cohort members were younger than this at the end of follow-up on December 31, 1999.

CONTEXT AND CAVEATS

Prior knowledge

Exposure to ionizing radiation in utero and in childhood is associated with increased risks of cancers in childhood and in adulthood, respectively.

Study design

Excess risks of solid cancers at ages 12–55 among survivors of the atomic bombings of Hiroshima and Nagasaki who were in utero and young children at the time of the bombings were determined.

Contributions

Excess relative risks of solid cancers increased with radiation dose for both groups of survivors; they declined with increasing attained age in the combined cohort. Excess absolute rates increased with attained age among those who were exposed in childhood but remained steady among those exposed in utero.

Implications

The difference in excess absolute rates between the two groups of survivors suggests that lifetime risks after exposure may be lower for those exposed in utero than those exposed in childhood, but additional follow-up is necessary.

Limitations

Due to the limited population size available for analysis, data regarding temporal patterns and risks of site-specific cancers were not available.

After exclusions, 2452 survivors who were in utero and 15 388 who were young children at the time of the bombings were included in the study (Table 1). People whose mothers normally resided in the city and met the other cohort eligibility criteria but were "not in city" at the time of the bombing were included in the study population because they contribute to the estimation of background rates and, hence, to the precision of the estimated excess rate per Sv of radiation exposure. The not-in-city group for the LSS was identified on the basis of special censuses conducted in Hiroshima and Nagasaki cities in 1950, 1951, and 1953. As noted elsewhere (14), in view of the way in which the group was selected, it seems that members of the not-in-city group were more likely to have been residents of areas near the hypocenters than more distal residents.

Incident cancers were ascertained by linkage to the Hiroshima and Nagasaki tumor registries, which provide relatively complete population-based case ascertainment for residents of Hiroshima and Nagasaki and the surrounding areas. Complete mortality follow-up data for both the in utero and early childhood cohorts are available from the mandatory national family registry system *(koseki)*. Tumor registry case ascertainment and data quality were discussed in (15), and mortality follow-up procedures have been described in many reports [including (16,17)]. In view of the incomplete ascertainment among nonresidents, it would be ideal to limit analyses of cancer incidence to periods when cohort members were residents of the Hiroshima and Nagasaki tumor registry catchment areas. However, such detailed individual residence history information is not available. Therefore, as in analyses of cancer incidence in the LSS (18,19), migration-adjusted person-years at risk were estimated using city-specific, calendar year–specific, age-specific, and

Table 1. Study population size by cohort, city, sex, and dose category

Characteristic	Cohort, No. (%)	
	In utero	Early childhood (0–5 y)
Total	3268 (100)	15899 (100)
City		
Hiroshima	2654 (81)	10488 (66)
Nagasaki	614 (19)	5411 (34)
Sex		
Male	1612 (49)	7783 (49)
Female	1656 (51)	8116 (51)
Dose category*, Sv		
0.0 (not in city)†	586 (18)	3384 (21)
>0.0 to <0.005	961 (29)	5165 (32)
0.005 to <0.1	435 (13)	4528 (28)
0.1 to <0.5	330 (10)	1712 (11)
0.5 to <1.0	92 (3)	325 (2)
≥1	48 (1)	274 (2)
Unknown dose‡	227 (7)	511 (3)
Unknown exposure status§	589 (18)	0 (0)

* Individual radiation doses were determined using the Dosimetry System 2002 (8–10). Weighted dose was computed as gamma dose + 10 × neutron dose. For those exposed in utero, the mother's uterine dose was used. For children aged 0–5 years, colon dose was used. Percentages may not add to 100% due to rounding.

† Mothers (in utero cohort) or subjects (early childhood cohort) who were residents of Hiroshima or Nagasaki but who were farther than 10 km from the hypocenter at the time of the explosion. People in this group were included in the risk analyses with an assigned dose of 0.

‡ Mothers (in utero cohort) or subjects (early childhood cohort) who were within 3 km of the hypocenter. People in this group were excluded from the risk analyses.

§ There is no information on the exposure status of mothers of these cohort members. These people were excluded from the risk analyses.

sex-specific residence probability estimates that were derived from a subset of individuals who were contacted biennially for RERF's clinical follow-up study (18,20). Additional information on residence probabilities is included online (Supplementary Figure 1, available online). It should also be noted that participation in the RERF clinical examination program has little impact on cancer ascertainment because this examination is not the primary source of medical care for cohort members and is not, with the exception of some short-term programs concerned with thyroid disease (21) and skin neoplasms (22), a cancer screening exam. Few cancers were initially diagnosed in the RERF clinical study.

Statistical Analysis

Analyses included first primary solid cancers [International Classification of Disease for Oncology (*ICD-O*) version 3 (23) topography codes C00–C76 and C80 and behavior code 3] and first primary tumors of the brain, central nervous system, and meninges (*ICD-O* topography codes C70–C72), including benign tumors or tumors of uncertain behavior (*ICD-O* behavior codes 0 and 1, respectively). In situ tumors (behavior code 2) were not included. Like most major registries (24), the Hiroshima and Nagasaki registries routinely collect and report information on the incidence of tumors of the brain and central nervous system with benign or uncertain behavior. As in other analyses of cancer incidence among the atomic bomb survivors (25), all tumors of the brain and central nervous system were included in these analyses. Approximately 90% of the cancers were histologically confirmed. Cancers among cohort members who lived outside Hiroshima or Nagasaki prefecture at the time of diagnosis were not included in the analyses.

Analyses were based on simple parametric ERR and excess absolute rate (EAR) models fit to a detailed stratification of cancers and person-years using Poisson regression methods (26,27). The person-year table was stratified on city, sex, in utero vs childhood exposure, age at exposure (trimester for in utero and 0–2 years and 3–5 years for children), attained age (2-year categories from age 12 to 53, with an additional category for age 54), maternal distance from the hypocenter or exposure status (<1500, 1500–2999, 3000–10000 m, and not in city), and 13 adjusted DS02 dose categories (with cut points at weighted doses of 0.005, 0.02, 0.05, 0.1, 0.2, 0.5, 0.75, 1, 2, 2.5, and 3 Sv). The dose-error–adjustment method (28,29) was used, assuming 35% random error in individual dose estimates to allow for the impact of uncertainty in individual dose estimates on risk estimates. The resulting table had nonzero person-years in 7361 of the 84480 potential cells. In addition to person-years and the number of solid cancers, each cell also contained information on the numbers of several specific types of cancer and person-year–weighted means of attained age, age at exposure, year, distance, and dose.

ERR analyses were based on models using the form

$$\lambda_0(a,s)(1 + \rho(d)\varepsilon(z)),$$

for which λ_0 is a parametric model for the baseline rates that depends, as described below, on attained age (a) and sex (s) and $\rho(d)\varepsilon(z)$ describes the shape of the dose response ($\rho(d)$) and radiation effect modification ($\varepsilon(z)$). The dose response was generally found to be linear in dose, with a slope that may differ for those exposed in utero and those in early childhood. Effect modification was described using a log-linear function of factors of interest, such as sex, attained age, or age at exposure. The primary effect modifiers considered in these analyses were log attained age and sex.

The EAR or excess rate models used the form

$$\lambda_0(a,s) + \rho(d)\varepsilon(z),$$

in which the second term describes the excess rate. The dose response and effect modification terms were the same as those considered for the ERR models.

The logarithms of the sex-specific baseline rates were described as quadratic functions of log attained age, which implies that baseline rates are proportional to a power of age that varies with logarithm of age. This model can be written as

$$\lambda_0(a,s) = e^{\beta_s + \alpha_1 \ln(a) + \alpha_2 \ln(a)^2} = e^{\beta_s}(a)^{\alpha_1 + \alpha_2 \ln(a)}. \quad [1]$$

City, being in utero, and location at the time of the bombs (proximal defined as being within 3 km of the hypocenter, distal defined as being 3–10 km from the hypocenter, and not in city defined as being more than 10 km from the hypocenter) were considered as potential modifiers of the baseline rates. The 10 km cutoff has been used previously to define the not-in-city (unexposed) group (16). The 3 km cut point, which has been used in other reports on the LSS (8,17,25), was chosen because the estimated maximum possible

dose at this distance is low, that is, less than annual natural background radiation levels.

Age effects on the ERR and EAR were modeled as log-linear in log age and hence can be described as proportional to age to a (constant) power. In models that include age effects on the excess risk, the dose–response slope is the sex-averaged risk for a 50 year old who received 1 Sv. Although age 50 is near the upper end of the age range used in these analyses, most of the cancers in these cohorts were diagnosed among participants between the ages of 45 and 55.

The shape of the dose–response curve was examined using methods described in several recent reports on cancer incidence and mortality in the LSS (8,17,30). These methods make use of both linear quadratic and nonparametric (dose category–specific) descriptions of the dose response. The extent of nonlinearity in the linear quadratic model was described in terms of the curvature, which was defined as the ratio of the quadratic coefficient to the linear coefficient. The curvature is zero in a linear model; it is negative if the dose response is concave downward and positive if it is upward, becoming infinite for a pure quadratic dose response. Because radiation protection is concerned with curvature at low doses, we focused on the 0 to 2 Sv dose range to reduce the effects that high-dose exposures might have (due, eg, to cell killing or dose error) on inference about the nature of the dose response at lower doses.

In the linear quadratic models, we allowed the coefficient of the linear term in dose to differ for in utero and childhood exposures but constrained the curvature to be the same for the two groups. The nonparametric descriptions of the dose response assumed that in utero and childhood exposure risks were proportional, with the same constant of proportionality over all dose categories. These rather strong assumptions were necessary because of the small size of the in utero–exposed cohort.

Hypothesis tests and confidence intervals were based on likelihood ratio tests applied to the profile likelihood (31). Ninety-five percent CIs were used for specific model parameters. All statistical tests were two-sided, and P values less than .05 were considered statistically significant.

Results

Descriptive Statistics and Crude Rates

In the full cohort, 1216 solid cancers were recorded during the follow-up period (January 1, 1958, to December 31, 1999), including 901 first primary cancers that were diagnosed before age 55. A total of 34 of these first primary tumors occurred among people whose exposure status or DS02 dose was unknown, and 124 occurred among people who did not reside in the catchment area at the time of diagnosis (Table 2). Dose–response analyses were based on the remaining 743 cancers.

The 743 eligible first primary solid cancers included 336 cancers among men and 407 among women. Cancers of the digestive system were the most common, accounting for 70% of male and 30% of female cancers, and nearly half of the cancers were stomach cancers. Cancers of the breast and reproductive organs accounted for 48% of the cancers among women. Thyroid cancers accounted for 3% of male and 11% of female cancers. Only eight of the solid cancers were diagnosed during adolescence (ie, between ages 14 and 19), of which seven were among the early childhood exposure group (including cancers of the stomach, bone, soft tissue, skin, and thyroid and two central nervous system tumors) and one in the in utero group (a Wilms tumor diagnosed at age 14). In large part, the types of cancers in these cohorts seem consistent with what one would expect in an unexposed young adult Japanese population. Additional information on the distribution of types of cancer by sex is available as supplementary material (Supplementary Table 1, available online).

Background Rate Models

Because the members of these study cohorts were born within a few years of each other and all were exposed at the same time, there is little likelihood of birth cohort effects on the baseline rates. Thus, the primary factors considered in modeling baseline rates were attained age and sex. However, we also looked for evidence of differences in the baseline rate level with exposure cohort (in utero, childhood), city, and location at the time of the bombs (proximal, distal, not in city, or unknown exposure status). These analyses were carried out with allowance for separate dose effects for in utero and childhood exposure.

Baseline rates and the nature of their variation with age differed by sex. For both men and women, the log age-specific rates were well described by a linear quadratic function in log age. The quadratic term in log age was statistically significant for men (P = .008) but not for women (P = .10). No difference in the Hiroshima and Nagasaki baseline rates was observed (P = .13, Nagasaki to Hiroshima rate ratio = 1.0, 95% CI = 0.85

Table 2. Numbers of eligible and ineligible solid cancers by cohort (1958–1999)*

		Ineligible first primary cancers		Unused cancers		
Cohort	Eligible cancers	Nonresident	Unknown dose†	Not first primary tumor	Age >54	Total
In utero	94	15	17	14	0	140
Early childhood	649	109	17	98	203	1076
Total	743	124	34	112	203	1216

* First primary solid cancers diagnosed before age 55 in the tumor registry catchment area and between January 1, 1958, and December 31, 1999, among cohort members with dose estimates were eligible in the analyses. First primary cancers for cohort members who were not catchment area residents at the time of diagnoses or whose dose was unknown were ineligible. Second primary cancers and cancers diagnosed after age 54 were not used.

† Includes cohort members with unknown maternal exposure status and known maternal exposure status but unknown maternal dose. Because of the way in which the cohort was chosen, exposure status, but not necessarily dose, was known for all members of the early childhood group. However, exposure status was unknown for 18% of the in utero cohort.

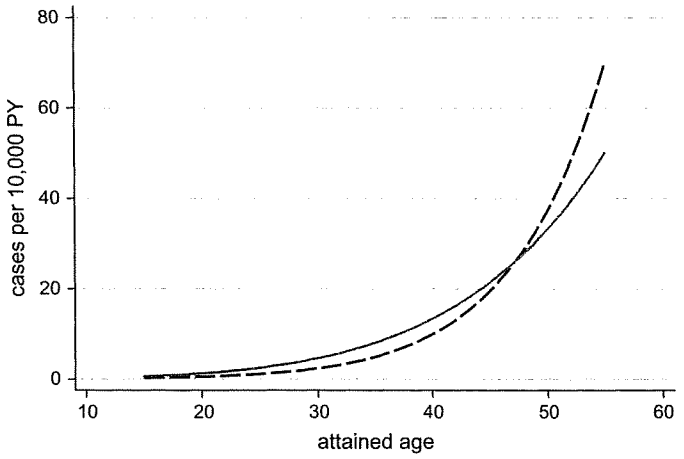

Figure 1. Solid cancer baseline rates for the combined in utero and childhood exposure cohorts by sex. The curves (**dashed curve** for men and **solid curve** for women) are based on the full dataset with separate dose effects for the in utero and childhood exposure groups. PY = person-years.

to 1.2), nor was there any indication of differences between the baseline rates for the in utero and childhood exposure groups ($P > .5$).

Age-specific baseline rates of solid cancer incidence were estimated for men and women after allowance for a linear radiation dose response (Figure 1). The pattern was typical of many populations in that women had higher rates of solid cancers than men before age 50, and rates for both men and women began to increase dramatically after age 40. The increase in rates between ages 40 and 55 was roughly proportional to age to the fourth power for men and to age to the third power for women.

There was statistically significant heterogeneity in the baseline rates for the proximal, distal, and unexposed groups ($P < .001$). Baseline rates for the distal exposure group were about 50% greater than those for the proximal exposure group (RR = 1.46, 95% CI = 1.20 to 1.77), whereas rates for the not-in-city group were virtually the same as those for the proximal exposure group (RR = 0.99, 95% CI = 0.80 to 1.2). The difference between rates in the distal and proximal group exposure groups was in the same direction as, but considerably larger than, the difference noted in (14,30) for the full LSS cohort. As in most LSS analyses, we included the distal survivors without any special adjustments. Adjusting for possible proximal–distal differences in baseline rates increased risk estimates by about 25% but had little impact on the estimates of temporal patterns that are described below.

Dose Response and Effect Modification

We examined the dose distribution of solid cancers by cohort (Table 3) and calculated crude rates and crude relative risks for three dose categories stratified by sex and attained age (Table 4). Although the number of cancers was not large, especially for the in utero group, the results suggested that risks were elevated among those exposed to doses in excess of 0.2 Sv and that radiation-associated risks for the in utero cohort may have a somewhat different temporal pattern than those for the childhood exposure cohort. These patterns will be explored more formally below.

Excess Relative Risk Models

In a model with the same time-constant ERR for in utero and childhood exposures, the estimated ERR per Sv (ERR_{1Sv}) was 1.9 (95% CI = 1.4 to 2.6; $P < .001$). Allowing the dose response for in utero and childhood exposures to differ, the ERR_{1Sv} estimates were 1.3 (95% CI = 0.2 to 2.8) for in utero exposure and 2.0 (95% CI = 1.4 to 2.8) for childhood exposure. The difference between these ERR estimates was not statistically significant ($P = .3$). Allowing for different ERRs, the estimated numbers of radiation-associated cancers were nine in the in utero group and 87 in the early childhood group.

Using the effect modification model described in equation 1 to describe variation in the ERR with attained age, the ERR decreased with increasing age ($P = .046$). This decrease was proportional to age to the -1.3 power (95% CI = -2.4 to -0.06). As indicated in the upper portion of Table 5, allowing for this temporal trend, the ERR_{1Sv} estimates at age 50 for in utero and early childhood exposure were 1.0 (95% CI = 0.20 to 2.3) and 1.7 (95% CI = 1.1 to 2.5), respectively. Radiation effect parameter estimates were also determined from a more general model that included a sex effect and allowed different attained age effects for in utero and childhood exposure (Table 5). In this model, the ERR decreased in proportion to age to the power -2.8 for those exposed in utero and to the power -1.1 for early childhood exposure (Figure 2). The difference in the decrease between the two groups was not statistically significant ($P = .3$). Using this model, the ERR_{1Sv} estimates at age 50 were 0.42 (95% CI = <0.00 to 2.0) and 1.7 (95% CI = 1.1 to 2.5) for in utero and childhood exposures, respectively. There was a weak suggestion of a sex difference in the ERRs ($P = .13$).

Table 3. Number of patients with solid cancers, person-years, and solid cancers by DS02-weighted dose category*

	In utero exposure			Early childhood exposure		
Dose category, Sv	**No. of patients**	**Person-years**	**No. of cancers**	**No. of patients**	**Person-years**	**No. of cancers**
<0.005	1547	49326	54	8549	247744	318
0.005 to <0.1	435	14005	16	4528	134621	173
0.1 to <0.2	158	5041	6	853	25802	38
0.2 to <0.5	172	5496	8	859	25722	51
0.5 to <1.0	92	2771	7	325	9522	21
≥1	48	1404	3	274	7620	48
Total	2452	78043	94	15388	451031	649

* DS02 = Dosimetry System 2002. Individual radiation doses were determined using the DS02 (8–10). Weighted dose was computed as gamma dose + 10 × neutron dose. For those exposed in utero, the mother's uterine dose was used. For those exposed in early childhood (0–5 years), colon dose was used.

Table 4. Crude rates of solid cancer and RRs by cohort, sex, attained age, and dose categories*

Dose category, Sv	In utero exposure				Early childhood exposure			
	No. of cancers	Person-years	Crude rate	Crude RR (95% CI)†	No. of cancers	Person-years	Crude rate	Crude RR (95% CI)†
Male, ages 12–29‡								
<0.005	1	10883	0.9	(Referent)	5	48630	1.0	(Referent)
0.005 to <0.2	0	4247	0.0	0.0 (0 to 15)	3	31278	1.0	0.9 (0.2 to 3.8)
≥0.2	1	2168	4.6	5.0 (0.2 to 127)	2	8302	2.4	2.3 (0.3 to 11)
Male, ages 30–54								
<0.005	23	12882	17.9	(Referent)	147	69759	21.1	(Referent)
0.005 to <0.2	12	5008	24.0	1.3 (0.6 to 2.6)	90	45645	19.7	0.9 (0.7 to 1.2)
≥0.2	9	2521	35.7	2.0 (0.9 to 4.2)	43	11957	36.0	1.7 (1.2 to 2.4)
Female, ages 12–29								
<0.005	1	11600	0.9	(Referent)	12	52638	2.3	(Referent)
0.005 to <0.2	0	4458	0.0	0.0 (0 to 15)	8	33743	2.4	1.0 (0.4 to 2.5)
≥0.2	2	2270	8.8	10.2 (1.0 to 220)	6	9257	6.5	2.8 (1.0 to 7.3)
Female, ages 30–54								
<0.005	29	13962	20.8	(Referent)	154	76717	20.1	(Referent)
0.005 to <0.2	10	5333	18.8	0.9 (0.4 to 1.8)	110	49758	22.1	1.1 (0.9 to 1.4)
≥0.2	6	2712	22.1	1.1 (0.4 to 2.4)	69	13347	51.7	2.6 (1.9 to 3.4)

* RR = relative risk; CI = confidence interval. Crude rates are given as cancers per 10000 person-years.

† Ratio of the crude rate to that for the <0.005-Sv dose category.

‡ Attained age at diagnosis.

Excess Absolute Rate Models

EAR models with effects for attained age and sex described the data as well as the ERR models discussed above. The EAR for childhood exposure (at age 50, EAR = 56 cancers per 10000 person-years per Sv, 95% CI = 36 to 79) increased statistically significantly with increasing attained age ($P < .001$), with the increase estimated to be proportional to age cubed (Table 5 and Figure 2, B). However, there was no evidence of a statistically significant change in the EAR with attained age ($P > .5$) among those exposed in utero (at age 50, EAR = 6.8 cancers per 10000 person-years per Sv, 95% CI = <0 to 49). Because of the small number of radiation-associated cancers in the in utero group, this difference in temporal risk patterns, although striking, was not statistically significant ($P = .14$).

A statistically significant difference in the EAR estimates of men and women was observed (Table 5). Excess rates for women were about twice those for men.

Shape of Dose–Response Curve

For doses in the 0 to 2 Sv range, there was a suggestion of upward curvature in the dose–response curve ($P = .09$), with a curvature

Table 5. Parameter estimates (and 95% CIs) for solid cancer excess risks in the in utero and childhood exposure cohorts from three models*

Cohort	Risk per Sv at age 50			Ratio of females to males	Power of attained age†
	Male	Female	Sex averaged		
ERR with common attained age dependence and no sex effect					
In utero	1.00 (0.20 to 2.3)			1‡	−1.3 (−2.4 to −0.06)
Childhood	1.70 (1.1 to 2.5)				
ERR with separate attained age dependence and a common sex effect					
In utero	0.31 (0.00 to 2.0)‡	0.53 (0.00 to 2.4)	0.42 (0.00 to 2.0)	1.7 (0.9 to 3.8)§	−2.8 (−9.3 to 2.8)
Childhood	1.3 (0.6 to 2.2)	2.2 (1.3 to 3.4)	1.7 (1.1 to 2.5)		−1.1 (−2.3 to 0.2)
EAR (cancers per 10000 person-years per Sv) at age 50					
In utero	4.3 (0.001 to 36)	9.2 (0.002 to 65)	6.8 (0.002 to 48)	2.1 (1.1 to 4.7)§	0.0 (−6.9 to 4.3)
Childhood	36 (16 to 63)	76 (49 to 100)	56 (36 to 79)		2.9 (1.8 to 4.3)

* CI = confidence interval; ERR = excess relative risk; EAR = excess absolute rate.

† In the effect modification model used (see equation 1), the change in the ERR and EAR is taken to be proportional to a power of attained age, which was estimated as the coefficient of the log of age in the model.

‡ Model assumes the same ERR for men and women.

§ The ratio of females to males was assumed to be the same for both in utero and childhood exposures. The difference was not statistically significant for the ERR ($P = .13$) but was for the EAR ($P = .02$). P values were calculated using two-sided maximum-likelihood tests.

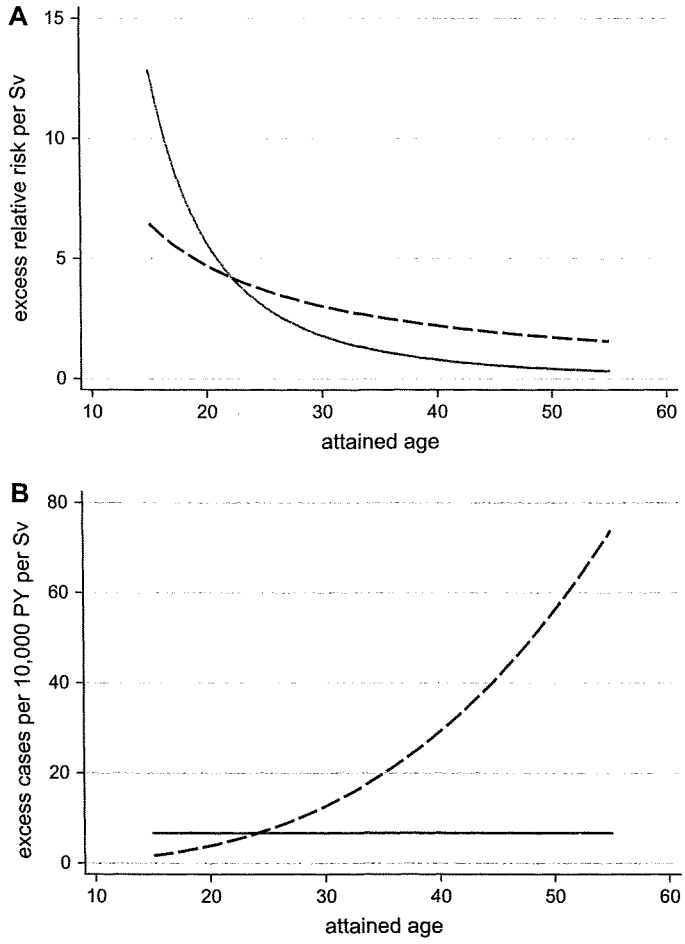

Figure 2. Temporal patterns of radiation-associated solid cancer incidence risks among atomic bomb survivors exposed in utero or as young children. The plots describe variation in the fitted excess risk following exposure to a radiation dose of 1 Sv. **A)** Excess relative risks. **B)** Excess absolute rates. No statistically significant differences in temporal trends between in utero (**solid lines**) and early childhood (**dashed lines**) exposure were observed for either the excess relative risks (P = .30) or the excess absolute rates (P = .14). P values were calculated using two-sided maximum likelihood tests. PY = person-years.

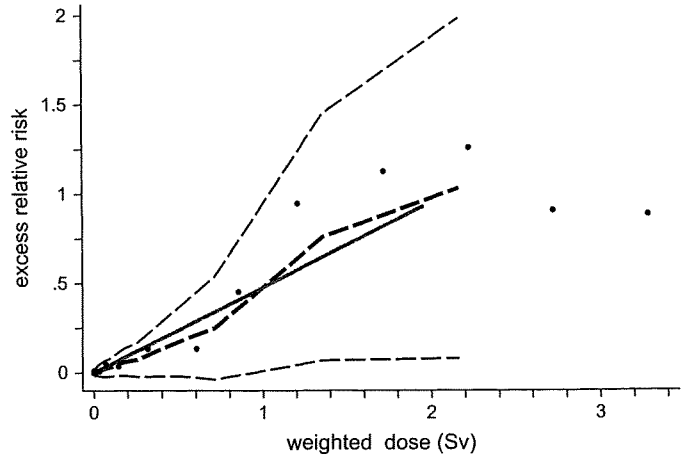

Figure 3. Fitted parametric and nonparametric dose–response functions for solid cancer incidence adjusted to reflect in utero cohort risks. Dose category–specific estimates of the excess relative risk at age 50 are shown as **points**. The smoothed nonparametric dose response (**thick dashed line**) with 95% confidence intervals (**thin dashed lines**) and the fitted linear dose response (**solid line**) are shown. Both the parametric and nonparametric fits were based on descriptions in which the in utero and early childhood risks were assumed to be proportional with a common attained age trend.

estimate of 1.0 (95% CI = −0.07 to 212). Assuming the same curvature for in utero and early childhood exposures, the low-dose slope in the linear quadratic model for in utero exposure was about 50% of that for the linear model, but this ratio was quite uncertain (95% CI = 0.06% to 300%). A nonparametric dose–response function that was computed by smoothing dose category–specific ERR estimates was similar to the simple linear dose–response function (Figure 3).

Variation in Risk by Trimester or Age at Exposure

No variation in the ERR by trimester of exposure was observed for those exposed in utero (P > .5), and the point estimates (at age 50 in a model that allows for effect modification by attained age) were virtually identical: 1.1 (95% CI = <0 to 3.4) for the first trimester, 0.9 (95% CI = <0 to 2.8) for the second trimester, and 1.0 (95% CI = −0.06 to 3.7) for the third trimester. In addition, no variation in risks with age at exposure was observed for those with early childhood exposure (P > .5). The ERR_{1Sv} estimates (at age 50) were 1.8 (95% CI = 1.1 to 2.8) for those exposed before age 3 and 1.5 (95% CI = 0.8 to 2.5) for those exposed at ages 3–5.

Discussion

This study provides direct evidence that radiation exposure is associated with increased risks of adult-onset solid cancers in atomic bomb survivors exposed in utero or in early childhood. For those exposed in early childhood, the ERRs may decrease with time. The absolute risks among those exposed in utero are therefore likely to be considerably lower than simple projections based on studies of childhood cancers in other in utero–exposed populations [which have been estimated to be approximately 6% per Sv by age 15 (19)] and may be lower than absolute risks among those exposed early in life. However, additional follow-up of this cohort is necessary before definitive conclusions can be made about the nature of the risks for those exposed in utero.

This study is one of the only cohort studies of in utero exposure with long-term, continuous active follow-up. This study also provides a unique opportunity to compare effects of in utero and early childhood exposures. However, the power of the study to characterize temporal patterns is limited by the small number of cohort members who received appreciable radiation exposures (eg, >100 mSv), especially among those exposed in utero, and by the fact that the oldest surviving in utero exposed cohort members were only 55 years of age at the end of follow-up. Because of these limitations, site-specific analyses are not yet feasible. However, the types of cancers seen to date (ie, primarily stomach, lung, and breast cancer) appear to be typical of what is seen in Japanese populations (24). Furthermore, because comprehensive data on solid cancer incidence are unavailable for the period from 1945 to 1957, this study cannot provide information on the effect of radiation on the incidence of childhood cancers.

Cancer incidence in the early childhood cohort with 1 year less follow-up than in this study was considered in the recently published analyses of cancer incidence in the full LSS cohort of atomic bomb survivors (25) (which includes the early childhood cohort considered here). In those analyses, simple parametric models were used to describe variation in the excess risks with attained age and age at exposure and the early childhood exposure risk estimates are similar to those obtained directly from the analyses of the early childhood performed in this study.

This study of atomic bomb survivors is one of the few human studies that have specifically examined adult-onset cancers following in utero exposure. Earlier analyses of solid cancer mortality in this cohort (7) provided some indication of elevated rates among those exposed in utero but no evidence of differences in excess rates for in utero and early childhood exposures. Although follow-up for the current analyses began more than 7 years after the start of follow-up for the mortality analyses, the number of cancers used in the current analyses (n = 94) is considerably greater than the number of deaths considered in the mortality analyses (n = 57). This increase is due to the inclusion of follow-up at older ages and because less fatal types of cancer, such as breast and thyroid cancer, account for a relatively high proportion of cancers seen in young adults. We are aware of only one other relevant study in a different population, in which cancer mortality to age 49 was examined among 3097 residents near the Techa River who were exposed to radiation in utero and/or postnatally before the age of 5 (32). In that study, prenatal total body doses ranged from 0 to 0.2 Gy and postnatal doses ranged from 0 to 0.46 Gy and a non–statistically significant excess of solid cancers (30 observed, 25.4 expected) was found. The combined prenatal and postnatal bone marrow dose, which averaged 0.3 Gy and ranged up to 2.0 Gy, was nearly statistically significantly associated with leukemia incidence ($P = .09$).

Little or no apparent dose response was found for chromosome aberrations among in utero atomic bomb survivors (33), and mouse experimental data (34) suggest that chromosome aberrations do not persist after in utero exposure. The lack of a chromosome aberration dose response among the in utero exposed group may be related to the differences in excess risks for the in utero and early childhood exposure groups. Excess mammary tumors have been seen in rats (35) and excess liver tumors have been observed in mice (36) after in utero irradiation, primarily after doses of greater than 2 Gy. Fetal exposure of beagles to either 0.16 or 0.8 Gy led to increases in lymphoma incidence and in total lifetime fatal malignancies (37). However, other studies of mice and dogs (38–43) suggest that cancer risks associated with in utero exposure may be lower than those associated with postnatal exposures. Notably, Upton et al. (43) found no excess leukemia or cancer risk in RF mice after in utero exposure to 3 Gy, Di Majo et al. (36) found no excess cancer in BC3F1 mice after in utero exposure to 300 mGy, and Ellender et al. (44) reported no excess of intestinal tumors in *Apc/Min+* mice after acute in utero exposure to 2 Gy x-rays. However, each of these studies showed increased risks following comparable doses administered postnatally.

Thousands of pregnant women are exposed to radiation each year, either occupationally or as patients, and in utero exposure is still a public health concern (45,46). Several reviews (19,47,48) have summarized the numerous studies on fetal x-ray exposures and childhood cancer with general support for an association between fetal exposure and childhood leukemia. However, there is less consensus regarding fetal radiation exposure and solid cancer risk, ranging from doubts about whether such an effect even exists (47) to being generally positive but with caveats (48) and to a conclusion that the total childhood cancer risk is large (19)—an absolute risk on the order of 6% per Gy. Much less is known about the long-term health consequences of in utero radiation exposure.

The present data suggested that increases in risks of adult-onset cancer among those exposed to radiation in utero may be smaller than for those exposed in early childhood. Moreover, we found a statistically significant decrease in the ERR for adult-onset solid cancer with increasing attained age for in utero as well as for early childhood exposures to radiation, and this decrease may be more marked for those exposed in utero than as children. The difference in temporal patterns for in utero and early childhood exposures was most striking when the radiation effects were described in terms of the EAR, with the estimated EAR for in utero exposure being virtually constant over the age range considered here and that for postnatal exposure increasing markedly with age. This apparent difference suggests that lifetime risks following in utero exposure may be considerably lower than for early childhood exposures. Further follow-up is needed to determine whether this is the case. Whether or not differences in the level and temporal pattern of excess risks for in utero and early childhood exposures to radiation prove to be statistically significant in future analyses, the finding of a decrease in the ERR with increasing age for both in utero and early childhood exposures in the atomic bomb survivor data indicates that lifetime risks of cancer in those exposed in utero are likely to be considerably less than projections based on relative risks derived from studies of childhood cancer incidence (19).

Atomic bomb survivors who were exposed to radiation in utero are just reaching ages at which baseline cancer rates increase markedly. Thus, further follow-up of this cohort is needed to provide new information on risks of adult-onset cancers following in utero radiation exposure.

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Risk Factors for Hepatocellular Carcinoma in a Japanese Population: A Nested Case-Control Study

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Abstract

Background: **Epidemiologic studies have shown effects of lifestyle-related factors on risk for hepatocellular carcinoma. However, few cohort studies have incorporated, in a strict and in-depth manner, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections or investigated synergism between such factors.**

Methods: **We conducted a nested case-control study using sera stored before hepatocellular carcinoma diagnosis in the longitudinal cohort of atomic bomb survivors. The study included 224 hepatocellular carcinoma cases and 644 controls that were matched to the cases on gender, age, city, time of serum storage, and method of serum storage, and countermatched on radiation dose.**

Results: **Univariate analysis showed that HBV and HCV infections, alcohol consumption, smoking habit, body mass index (BMI), and diabetes mellitus were associated with increased hepatocellular carcinoma risk, whereas coffee drinking was associated with decreased hepatocellular carcinoma risk. Multivariate relative risks of hepatocellular carcinoma (95% confidence interval) were 45.8 (15.2-138), 101 (38.7-263), 70.7 (8.3-601), 4.36 (1.48-13.0), and 4.57 (1.85-11.3), for HBV infection alone, HCV infection alone, both HBV and HCV infections, alcohol consumption of ≥40 g of ethanol per day, and BMI of >25.0 kg/m^2 10 years before diagnosis, respectively. HBV and HCV infection and BMI of >25.0 kg/m^2 remained independent risk factors even after adjusting for severity of liver fibrosis. Among HCV-infected individuals, the relative risk of hepatocellular carcinoma for a 1 kg/m^2 increase in BMI was 1.39 (P = 0.003).**

Conclusions: **To limit the risk for hepatocellular carcinoma, control of excess weight may be crucial for individuals with chronic liver disease, especially those with chronic hepatitis C.** (Cancer Epidemiol Biomarkers Prev 2008;17(4):846–54)

Introduction

Hepatocellular carcinoma is one of the most common cancers worldwide. Chronic infections with hepatitis B virus (HBV) or with hepatitis C virus (HCV) are recognized as critically important risk factors for hepatocellular carcinoma. In addition, a large number of epidemiologic studies have shown that environmental factors such as dietary aflatoxin, smoking, alcohol consumption, and oral contraceptive intake are associated with increased risk for hepatocellular carcinoma (1, 2). It is generally considered that effects of these environmental factors are modified by gender, age, and race of patients (2-4).

Obesity and diabetes mellitus have recently received increased attention as risk factors for hepatocellular carcinoma (5-9). A large number of epidemiologic studies have shown that obesity and diabetes mellitus increase risks of a variety of cancers, including colon, renal, prostate, postmenopausal breast, and ovarian, in Asian and Western countries (7, 10, 11). Several recent epidemiologic studies indicated that obesity might be associated with an increased risk for hepatocellular carcinoma, but few cohort studies have incorporated HBV and HCV infection status in a strict and in-depth manner. A recent study of liver cirrhosis showed that, although obesity [body mass index (BMI), >30 kg/m^2] is an independent risk factor for hepatocellular carcinoma among patients with alcoholic cirrhosis or cryptogenic cirrhosis, it is not a significant risk factor for hepatocellular carcinoma in patients with chronic HBV and/or HCV infections (12).

Compared with viral etiologic factors, alcohol consumption, smoking, obesity, and diabetes mellitus may have less effect on hepatocellular carcinoma occurrence (13, 14); however, most epidemiologic studies have indicated that such factors promote development from chronic hepatitis to hepatocellular carcinoma (6, 8). Alcohol consumption, obesity, and diabetes mellitus have been shown to be involved in the progression of liver fibrosis; it is possible that liver fibrosis results from advanced oxidative stress due to hepatic steatosis and iron overload (15-17). Liver cirrhosis characterized by severe liver fibrosis may underlie the occurrence of hepatocellular carcinoma, specifically in the presence of chronic hepatitis C, nonalcoholic steatohepatitis, and

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alcoholic liver diseases (3, 8). On the other hand, several recent large-scale studies have indicated that coffee drinking suppressed the progression of liver fibrosis and inhibited the development of hepatocellular carcinoma (18, 19).

The fact that liver cirrhosis is not a necessary condition for hepatocellular carcinoma occurrence was already known, not only from clinical findings but also from genetic findings. Among hepatocellular carcinoma cases with HBV, a part of the HBV genome has been shown to be integrated into the host's intracellular DNA, thereby causing hepatocellular carcinoma (20). Among hepatocellular carcinoma cases with HCV, the HCV core protein seems to directly contribute to the mechanism of carcinogenesis by elevating oxidative stress (21). In light of the aforementioned findings, for the purpose of determining independent risk factors for hepatocellular carcinoma, careful analyses are needed controlling for severity of liver fibrosis, as well as for viral etiologic factors.

With the aim of determining whether HBV or HCV infections, alcohol consumption, smoking, coffee drinking, BMI, and diabetes mellitus are independent risk factors for hepatocellular carcinoma, and how the effects of these factors might change after adjusting for severity of liver fibrosis, we conducted a nested case-control study among the Adult Health Study longitudinal cohort using stored sera. We also evaluated whether viral etiology and increase of BMI exert synergistic effects on the risk for hepatocellular carcinoma.

Materials and Methods

Cohorts. The Atomic Bomb Casualty Commission and its successor, the Radiation Effects Research Foundation, established the Adult Health Study longitudinal cohort in 1958, in which 20,000 age-, gender-, and city-matched proximal and distal atomic bomb survivors and persons not present in the cities at the time of bombings have been examined biennially in outpatient clinics in Hiroshima and Nagasaki.

Study Population. Serum samples obtained from the study participants on each occasion of visiting outpatient clinics have been collected and stored systematically since 1969 (22). Incident cancer cases were identified through the Hiroshima Tumor and Tissue Registry and Nagasaki Cancer Registry, supplemented by additional cases detected via pathologic review of related diseases (23). There were 359 primary hepatocellular carcinoma cases among Adult Health Study participants diagnosed between 1970 and 2002, who visited our outpatient clinics before their diagnosis. Of these, 130 cases were excluded because of nonavailability of stored serum or having only one stored sample. The other 229 cases had serum samples obtained within 6 years before hepatocellular carcinoma diagnosis. After excluding five cases with inadequate stored serum, 224 cases remained for our study. For each case, three controls were selected from the cohort in nested case-control fashion. Nested control selection was random among those who matched the case on gender, age (±2 years), city, time of serum storage (±2 years), and method of serum storage, and countermatched on radiation exposure (24). Although the total number of potential matched control serum samples is 672, because of occasional lack of subjects with stored sera who met the matching and countermatching criteria, the total number of control serum samples actually used was 644.

Laboratory Tests. HBV surface antigen and antibody to hepatitis B core antigen were measured by enzyme immunoassay, and anti-HCV antibody was measured by second-generation enzyme immunoassay as previously described (22, 25). Qualitative detection of HCV RNA among anti-HCV–positive samples was done using a thermocycler (Whatman Biometra) with two sets of PCR primers corresponding to the 5′-untranslated region, as previously described (25). Qualitative detection of HCV RNA was conducted at least twice. HBV infection (HBV+) status was defined as positive for HBV surface antigen or having a high titer of the antibody to hepatitis B core antigen. HCV infection (HCV+) status was defined as positive for HCV RNA (25). Hyaluronic acid and type IV collagen as liver fibrosis markers were measured using an autoanalyzer (Hitachi 7180, Hitachi, Ltd.) and latex agglutination–turbidimetric immunoassay (Fujirebio, Inc., Daiichi Pure Chemicals Co. Ltd.). Ferritin was measured using an autoanalyzer (Hitachi 7180, Hitachi) and colloidal gold immunoassay (Alfresa Pharma Corporation). Platelet count was measured using an automatic blood cell counter at the time of serum storage.

Information on Covariates. Self-administered questionnaires on various lifestyle factors were given to participants in 1965 during attendance at the Adult Health Study examination and in 1978 by mail survey. Information from the 1978 survey was obtained before hepatocellular carcinoma diagnosis for all but 19 (15%) of the cases. Information on alcohol consumption was obtained from the 1965 questionnaire when available, with missing data complemented using the 1978 survey. Alcohol consumption per volume of each type of alcoholic beverage was quantified as previously described (26), and mean ethanol amounts were calculated as grams per day. Information on smoking habits was obtained from the 1965 questionnaire; subjects were divided into the following categories: never, prior, and current smoker. Information on coffee drinking was obtained from the 1978 survey; subjects were divided into the following categories of frequency of coffee consumption: never, 1 day per week, 2 to 4 days per week, and almost daily. Disease diagnoses were based on the International Classification of Diseases (ICD) codes: diabetes mellitus was defined by ICD-7 code 260, ICD-8 code 250, ICD-9 code 250, and ICD-10 codes E10 through E14. BMI (kg/m^2) was calculated from height and weight measured at the Adult Health Study examination.

Subjects were classified based on BMI quintiles with cut points of 19.5, 21.2, 22.9, and 25.0. The number of hepatocellular carcinoma cases with BMI of >30.0 kg/m^2 was too small to be analyzed in detail. Following the recommendations for Asian people by the WHO, the International Association for the Study of Obesity, and the International Obesity Task Force (27), 21.3 to 22.9 kg/m^2 was considered as normal, 23 to 25 kg/m^2 as overweight, and >25.0 kg/m^2 as obese in the present study. We used information on diabetes mellitus and BMI obtained 10 years before the time of hepatocellular

Table 1. Characteristics of hepatocellular carcinoma cases and controls

Study variables	Hepatocellular carcinoma cases (n = 224)			Controls (n = 644)		
	Complete data (%)	n (%)	Mean (SD)	Complete data (%)	n (%)	Mean (SD)
Matched variables						
Gender	100			100		
Male		136 (60.7)			387 (60.1)	
Female		88 (39.3)			257 (39.9)	
Age at hepatocellular carcinoma diagnosis (y)	100		67.6 (10.1)	—		—
City	100			100		
Hiroshima		155 (69.2)			444 (68.9)	
Nagasaki		69 (30.8)			200 (31.1)	
Age at serum storage (y)	100		66.4 (10.2)	100		63.7 (9.8)
Unmatched variables						
Etiology (HBV/HCV status)	94.2			99.4		
HBV−/HCV−		45 (21.3)			579 (90.5)	
HBV+/HCV−		29 (13.7)			18 (2.8)	
HBV−/HCV+		132 (62.6)			41 (6.4)	
HBV+/HCV+		5 (2.4)			2 (0.3)	
Fibrosis markers	94.2			99.4		
Hyaluronic acid (ng/mL)			288.6 (284.6)			69.1 (108.3)
Type IV collagen (ng/mL)			245.2 (136.9)			148.8 (122.1)
Platelet count ($\times 10^4/\mu L$)	67.4		13.0 (6.0)	70.0		22.4 (6.2)
Ferritin (ng/mL)	92.0		250.5 (278.6)	98.6		136.7 (151.0)
Alcohol consumption (g of ethanol per day)	88.8			89.6		
>0 and <20		37 (18.6)			130 (22.5)	
≥20 and <40		20 (10.1)			64 (11.1)	
≥40		45 (22.6)			68 (11.8)	
Current smoking		107 (53.8)			262 (45.3)	
Prior smoking	88.8	12 (6.0)		89.8	33 (5.7)	
Daily coffee drinking	62.1	38 (27.3)		73.3	175 (37.1)	
BMI (kg/m^2) 10 y before diagnosis	93.8			98.3		
≤19.5		38 (18.1)			122 (19.3)	
19.6-21.2		33 (15.7)			136 (21.5)	
21.3-22.9		36 (17.2)			142 (22.4)	
23-25		49 (23.3)			124 (19.6)	
>25		54 (25.7)			109 (17.2)	
Diabetes 10 y before diagnosis	100	18 (8.0)		100	33 (5.1)	
Radiation dose to the liver (Gy)	91.1		0.46 (0.69)	94.1		0.34 (0.56)

carcinoma diagnosis or control matching because these conditions are subject to change because of disease progression in the later stages before diagnosis of hepatocellular carcinoma. Atomic bomb radiation dose was estimated for each subject according to the Dosimetry System DS02 (28).

Ethical Consideration. This nested case-control study was based on RERF Research Protocol 1-04 and approved by the Human Investigation Committee of Radiation Effects Research Foundation.

Statistical Analyses. The nested case-control design is analyzed using a partial likelihood method analogous to that used for cohort follow-up studies (29), which is, in practice, the same as the conditional binary data likelihood for matched case-control studies (30) except that the subjects (cases and controls) in the study are not completely independent because of the possibility of repeated selection. All factors other than radiation were analyzed using relative risks estimated by a log-linear model. The population attributable fraction was estimated for individual factors that increased the risk for hepatocellular carcinoma in the present study. Population attributable fraction was calculated as $pd \times [(mRR - 1) / mRR]$, where mRR is the multivariate adjusted relative risk for the covariates and pd is the proportion of cases exposed to the risk factor. Statistical interaction between viral infection and BMI was tested by adding the product of the two factors to the log-linear model, which tests departure from a multiplicative relationship. Reported P values and confidence limits are based on Wald statistics. Although radiation exposure could have been adjusted by matching on radiation dose as an additional matching factor in the control selection (31), in addition to assessing effects of lifestyle factors and viral hepatitis, another purpose of the present study was to examine effects of radiation exposure after adjustment for possible confounding and interaction by these factors, so matching on radiation, which prevents analysis of radiation risk, was not desirable; rather, we countermatched on radiation (29, 32). Radiation risk was analyzed by using an excess relative risk model as has been done previously (33).

Results

Characteristics of Study Population. Characteristics of the 224 hepatocellular carcinoma cases and 644 comparison subjects are shown in Table 1. The mean age of the cases was 67.6 years, and 61% were men. Cases and controls were comparable with respect to gender, age, city, time of serum storage, and method of serum storage by design. Virological and biochemical assays were done on 211 case and 640 control sera because 13 case samples and 4 control samples had insufficient stored sera for these assays. Hepatocellular carcinoma

case sera evidenced a higher prevalence of HBV or HCV infection status, higher values of fibrosis markers and ferritin, and lower platelet counts compared with control sera. Greater proportions of hepatocellular carcinoma cases had a history of alcohol consumption of ≥40 g of ethanol per day, were current smokers, were obese, had diabetes mellitus, and received high radiation doses compared with the controls. In addition, hepatocellular carcinoma cases were less likely than controls to be daily coffee drinkers. There were no important differences in characteristics such as gender, age at hepatocellular carcinoma diagnosis, city, or BMI between hepatocellular carcinoma cases excluded because of nonavailability of stored serum and those included in this study.

Risk Factors for Hepatocellular Carcinoma Development. Table 2 shows the results of univariate and multivariate analyses using HBV and HCV infection status, alcohol consumption, smoking habit, coffee drinking, BMI, diabetes mellitus, and radiation dose. Strong association was found between hepatocellular carcinoma and hepatitis virus infection, resulting in unadjusted relative risks of 33.7 [95% confidence interval (95% CI), 12.7-89.6] for HBV+/HCV− status and 64.5 (95% CI, 29.1-143) for HBV−/HCV+ status. As expected, the risk for hepatocellular carcinoma for alcohol consumption was significant, with an unadjusted relative risk of 1.34 (95% CI, 1.12-1.60) per 20 g of ethanol per day using continuous alcohol consumption and 2.66 (95% CI, 1.55-4.55) at ≥40 g of ethanol per day using grouped alcohol consumption. Although the grouped results suggest that a simple log-linear model in continuous alcohol consumption may not be adequate, a quadratic term did not significantly improve the model (data not shown). Current smoking was significantly associated with hepatocellular carcinoma risk, with an unadjusted relative risk of 1.87 (95% CI, 1.14-3.07). Daily coffee drinking was associated with decreased risk for hepatocellular carcinoma, with an unadjusted relative risk of 0.51 (95% CI, 0.29-0.90). The presence of obesity and diabetes mellitus 10 years before diagnosis were statistically associated with increased risk for hepatocellular carcinoma, resulting in unadjusted relative risks of 1.88 (95% CI, 1.13-3.13) and 1.88 (95% CI, 1.01-3.50), respectively. The relative risk for a 1-unit difference in BMI was 1.04 (95% CI, 0.99-1.09). Radiation exposure was marginally significantly associated with increased risk for hepatocellular carcinoma ($P = 0.055$).

The risks for viral infection in multivariate analysis did not meaningfully differ from those obtained in the univariate analysis. Alcohol consumption of ≥40 g of ethanol per day and obesity remained significant risk factors for hepatocellular carcinoma even after adjusting for viral infection status and the other factors, whereas the effects of current smoking and diabetes mellitus became nonsignificant after adjustment. Daily coffee drinking was marginally significantly associated with decreased risk for hepatocellular carcinoma after adjustment for viral infection and the other factors. The adjusted relative risk for a one unit difference in BMI, 1.12 (95% CI, 1.03-1.22), was statistically significant, but a quadratic term was not significant.

Table 3 shows the estimated population attributable fraction based on the multivariate adjusted relative risks in the present study. The proportion of hepatocellular

Table 2. Relative risks of hepatocellular carcinoma for individual factors

Variables	Unadjusted		Multivariate adjusted	
	RR (95% CI)	*P*	RR (95% CI)*	*P*
Etiology (HBV/HCV status)				
HBV−/HCV−	1	—	1	—
HBV+/HCV−	33.7 (12.7-89.6)	<0.001	45.8 (15.2-138)	<0.001
HBV−/HCV+	64.5 (29.1-143)	<0.001	101 (38.7-263)	<0.001
HBV+/HCV+	42.4 (6.2-291)	<0.001	70.7 (8.3-601)	<0.001
Alcohol consumption (g of ethanol per day)				
Never	1	—	1	—
>0 and <20	1.11 (0.69-1.78)	>0.5	1.27 (0.56-2.87)	>0.5
≥20 and <40	1.07 (0.57-1.99)	>0.5	1.02 (0.34-3.05)	>0.5
≥40	2.66 (1.55-4.55)	<0.001	4.36 (1.48-13.0)	0.008
Continuous (per 20-g ethanol per day)	1.34 (1.12-1.60)	<0.001	1.73 (1.19-2.52)	0.004
Smoking habit				
Never	1	—	1	—
Current smoking	1.87 (1.14-3.07)	0.014	2.03 (0.82-4.98)	0.13
Prior smoking	1.80 (0.81-3.99)	0.15	1.12 (0.25-5.07)	>0.5
Coffee drinking				
Never	1	—	—	—
Daily	0.51 (0.29-0.90)	0.016	0.40 (0.16-1.02)	0.055
BMI (kg/m^2) 10 y before diagnosis				
≤19.5	1.24 (0.73-2.11)	0.43	1.31 (0.51-3.34)	>0.5
19.6-21.2	0.97 (0.55-1.70)	>0.5	1.24 (0.43-3.54)	>0.5
21.3-22.9	1	—	1	—
23-25	1.61 (0.96-2.70)	0.074	2.51 (0.99-6.37)	0.053
>25	1.88 (1.13-3.13)	0.016	4.57 (1.85-11.3)	<0.001
Continuous (+1 kg/m^2 difference)	1.04 (0.99-1.09)	0.087	1.12 (1.03-1.22)	0.010
Diabetes 10 y before diagnosis	1.88 (1.01-3.50)	0.047	1.98 (0.63-6.27)	0.24

Abbreviation: RR, relative risk.
*Adjusted for hepatitis virus infection, continuous alcohol consumption, smoking habit, coffee drinking, BMI, diabetes mellitus, and radiation dose to the liver.

Table 3. Estimated population attributable fraction of hepatocellular carcinoma for risk factors in this study population

Variables*	Proportion of cases exposed (%)	Multivariate-adjusted RR	Population attributable fraction (%)
Etiology (HBV/HCV status)			
HBV+/HCV−	13.7	45.8	13.4
HBV−/HCV+	62.6	101	62.0
HBV+/HCV+	2.4	70.7	2.4
Alcohol consumption			
≥40-g ethanol per day	22.6	4.36	17.4
BMI 10 y before diagnosis			
>25 kg/m^2	25.7	4.57	20.1

*Population attributable fraction was estimated only for the significant hepatocellular carcinoma risk factors.

carcinoma cases that is attributable to HBV+/HCV−, HBV−/HCV+, HBV+/HCV+, alcohol consumption of ≥40 g of ethanol per day, and obesity were 13.4%, 62.0%, 2.4%, 17.4%, and 20.1%, respectively. These values are not mutually exclusive because some cases were exposed to more than one risk factor.

Analyses with Adjustment for Variables Associated with Severity of Liver Fibrosis. Table 4 shows results for univariate analyses incorporating biomarkers associated with progression of liver fibrosis, such as hyaluronic acid and type IV collagen of fibrosis markers, platelet count, and ferritin. Large statistically significant differences in the mean values of these variables were observed between hepatocellular carcinoma cases and controls. Figure 1 shows a comparison of multivariate analysis results with or without adjustment for ln(type IV collagen) and platelet count using HBV and HCV infection status, alcohol consumption, smoking habit, coffee drinking, BMI, diabetes mellitus, and radiation dose as adjustment variables. We evaluated type IV collagen and platelet count as surrogate markers associated with severity of liver fibrosis. Hepatocellular carcinoma risk for hepatitis virus infection status after adjusting for liver fibrosis meaningfully decreased compared with the results indicated in the previous multivariate analysis, with relative risks of 20.8 (95% CI, 4.8-90.3) and 37.8 (95% CI, 12.4-115) for HBV+/HCV− status and HBV−/HCV+ status, respectively (Fig. 1A). Effects of ≥40 g of ethanol per day and daily coffee drinking decreased and disappeared, respectively, so that adjustment for liver fibrosis decreased the effect of these factors on risk for hepatocellular carcinoma. Current smoking became marginally significantly associated with increased risk for hepatocellular carcinoma after adjusting for liver fibrosis. Obesity remained a significant risk factor independent of adjustment for severity of liver fibrosis, and the relative risk for diabetes mellitus did not meaningfully differ from that without such adjustment (Fig. 1B).

Interaction between Hepatitis Virus Infection Status and Increase of BMI. Table 5 shows the joint effects of hepatitis virus infection status and BMI, with adjustment for alcohol consumption, smoking habit, coffee drinking, diabetes mellitus, and radiation dose. Although being obese was clearly a risk factor for hepatocellular carcinoma subjects with adjustment for viral factors, it was not a significant risk factor in those with HBV−/HCV− status. However, despite the appearance of a trend with BMI, only 15 hepatocellular carcinoma cases were identified among HBV−/HCV− individuals with obesity. Among hepatocellular carcinoma subjects with HBV−/HCV+ status, the relative risk increased dramatically with increasing BMI. Linear (P = 0.003) and quadratic (P = 0.013) terms in continuous BMI were

Table 4. Relative risks of hepatocellular carcinoma for variables associated with severity of liver fibrosis: unadjusted relative risk and 95% CI

Variables	Hepatocellular carcinoma cases/controls	Unadjusted	
		RR (95% CI)	P
Liver fibrosis markers	211/640		
Hyaluronic acid (+per 10 ng/mL)		1.10 (1.08-1.12)	<0.001
ln(hyaluronic acid) (+per 1 unit)		5.43 (4.04-7.30)	<0.001
Type IV collagen (+per 10 ng/mL)		1.14 (1.10-1.17)	<0.001
ln(type IV collagen) (+per 1 unit)		80.9 (35.8-183)	<0.001
Platelet count	151/448		
+Per 10^4/μL		0.75 (0.71-0.80)	<0.001
≥25.0 (×10^4/μL)	4/133	1	
20.0-24.9 (×10^4/μL)	19/163	4.5 (1.3-1.6)	0.02
15.0-19.9 (×10^4/μL)	26/105	11.8 (3.2-43)	<0.001
10.0-14.9 (×10^4/μL)	52/42	61 (16-232)	<0.001
<10.0 (×10^4/μL)	50/5	822 (125-5400)	<0.001
Ferritin	206/635		
+ Per 10 ng/mL		1.03 (1.02-1.04)	<0.001
ln(ferritin) (+per 1 unit)		1.51 (1.25-1.82)	<0.001

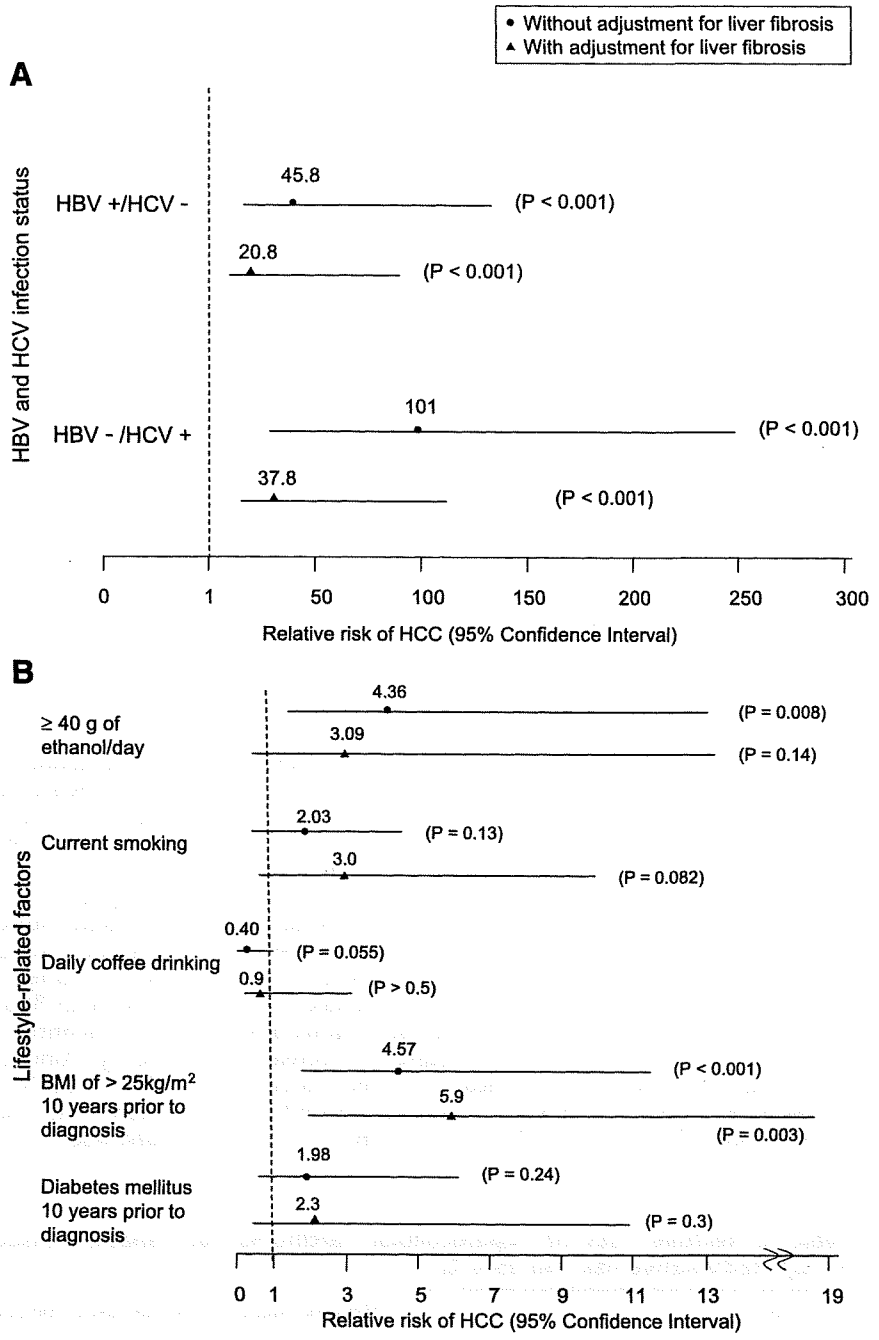

Figure 1. Multivariate relative risk for hepatocellular carcinoma for individual risk factors, with and without adjustment for variables associated with severity of liver fibrosis. Each relative risk was analyzed with and without adjustment for ln(type IV collagen) and platelet count, using HBV and HCV infection status, continuous alcohol consumption, smoking habit, coffee drinking, BMI, diabetes mellitus, and radiation dose as adjustment variables. **A.** HBV and HCV infection status. **B.** Lifestyle-related factors. *HCC*, hepatocellular carcinoma.

significant among HBV−/HCV+ individuals. Among hepatocellular carcinoma subjects with HBV+/HCV− status, the relative risk for hepatocellular carcinoma did not show evidence of an increase with increased BMI, although the examination of a joint effect of HBV infection and BMI was based on only one hepatocellular carcinoma case out of three subjects who were HBV+/HCV− and obese. The reason for the relatively small unadjusted relative risk for obesity (Table 2) might have been due to the small number of cases and controls with HBV+/HCV− status, which apparently offset the increase observed in HBV−/HCV+ status individuals.

Discussion

This nested case-control study indicated that HBV and HCV infection, alcohol consumption of ≥40 g of ethanol per day, and obesity 10 years before hepatocellular carcinoma diagnosis were independent risk factors for hepatocellular carcinoma, and that obesity as well as hepatitis virus infection remained independent risk factors for hepatocellular carcinoma after taking into account the severity of liver fibrosis. Furthermore, significant multiplicative interaction in hepatocellular carcinoma risk between viral etiology and increased BMI was observed in HCV-infected individuals. The