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Radiation and Risk of Liver, Biliary Tract, and Pancreatic Cancers among Atomic Bomb Survivors in Hiroshima and Nagasaki: 1958–2009

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The Life Span Study (LSS) of atomic bomb survivors has consistently demonstrated significant excess radiation-related risks of liver cancer since the first cancer incidence report. Here, we present updated information on radiation risks of liver, biliary tract and pancreatic cancers based on 11 additional years of follow-up since the last report, from 1958 to 2009. The current analyses used improved individual radiation doses and accounted for the effects of alcohol consumption, smoking and body mass index. The study participants included 105,444 LSS participants with known individual radiation dose and no known history of cancer at the start of follow-up. Cases were the first primary incident cancers of the liver (including intrahepatic bile duct), biliary tract (gallbladder and other and unspecified parts of biliary tract) or pancreas identified through linkage with population-based cancer registries in Hiroshima and Nagasaki. Poisson regression methods were used to estimate excess relative risks (ERRs) and excess absolute risks (EARs) associated with DS02R1 doses for liver (liver and biliary tract cancers) or pancreas (pancreatic cancer). We identified 2,016 incident liver cancer cases during the follow-up period. Radiation dose was significantly associated with liver cancer risk (ERR per Gy: 0.53, 95% CI: 0.23 to 0.89; EAR per 10,000 person-year Gy: 5.32, 95% CI: 2.49 to 8.51). There was no evidence for curvature in the radiation dose response ($P = 0.344$). ERRs by age-at-exposure categories were significantly increased among those who were exposed at 0–9, 10–19 and 20–29 years, but not significantly increased after age 30 years, although there was no statistical evidence of heterogeneity in these ERRs ($P = 0.378$). The radiation ERRs were not affected by adjustment for smoking, alcohol consumption or body mass index. As in previously reported studies, radiation dose was not associated with risk of biliary tract cancer (ERR per Gy: –0.02, 95% CI: –0.25 to 0.30). Radiation dose was associated with a nonsignificant increase in pancreatic cancer risk (ERR per Gy: 0.38, 95% CI: <0 to 0.83). The increased risk was statistically significant among women (ERR per Gy: 0.70, 95% CI: 0.12 to 1.45), but not among men.

INTRODUCTION

Although incidence rates of liver cancer are decreasing in areas of the world with high and intermediate rates, liver cancer remains the fourth-most common cause of cancer death globally (*1*) and the sixth-most common in Japan (*2*). One of the most common risk factors for liver cancer is chronic infection with hepatitis virus (*3*), the prevalence of which varies by geographical region (*4, 5*). In Japan, the incidence of liver cancer increased from the 1970s to the mid-1990s, reportedly due to an increased prevalence of hepatitis C virus (HCV) infection, particularly among individuals who were born between the mid-1920s and mid-1930s (*6, 7*). There is sufficient evidence that high-linear energy transfer (LET) radiation, such as plutonium (*8*) and thorium (*9, 10*), causes liver cancer. However, there is much less evidence that exposure to low-LET radiation causes liver cancer (*11*), even in a large-scale international pooled analysis of nuclear worker cohorts (*12*). To our knowledge, the Life Span Study (LSS) of atomic bomb survivors in Hiroshima and Nagasaki is the only study that has consistently reported a significantly increased risk of liver cancer associated with exposure to low-LET radiation (*13–17*). Because liver cancer is largely linked to chronic infection with HCV in Japan (*18*), the possibility of confounding and effect modification by HCV has been investigated extensively in studies of the atomic bomb survivors (*19, 20*).

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Pancreatic and biliary tract cancers are often diagnosed at advanced stages when there is little chance of curative treatment. There are established risk factors (*21, 22*) (e.g., smoking and obesity for pancreatic cancer, gallstones and anomalies of the pancreaticobiliary duct for biliary tract cancer), but whether radiation exposure is associated with these cancers is unclear (*11*). To date, no evidence of a radiation-related risk of pancreatic or biliary tract cancer has been found in the LSS. Several other studies have reported increased risks of pancreatic cancer among those who received radiotherapy for benign or malignant diseases, although a dose-response relationship has not been established (*11*). Recently, however, some published studies of cancer survivors have indicated a dose-response relationship between doses from radiotherapy and risk of pancreatic cancer (*23, 24*).

The primary objective of the current study was to estimate radiation risks for liver, biliary tract and pancreatic cancers in the LSS. Our analyses extend the cohort follow-up 11 years beyond that used in the most recent LSS incidence report, make use of improved dose estimates and account for the effects of alcohol consumption, smoking and body mass index (BMI) in radiation risk assessment.

METHODS

Design and Participants

This study was conducted as part of an ongoing series of analyses regarding radiation risks for solid cancer in aggregate (*25*) and at major anatomical sites (*26–29*). The study design and eligibility criteria were identical to those for the all-solid-cancer analysis (*25*). In brief, potentially eligible participants were members of the LSS cohort (n = 120,321): survivors of the atomic bombings who were within 10 km of the hypocenter in Hiroshima or Nagasaki (n = 93,741) and city residents who were not in either city (not-in-city; NIC) at the time of the bombings (n = 26,580). We excluded participants who died between 1950 and 1958 or had a documented history of cancer before the start of cancer incidence follow-up (n = 8,317), who could not be traced using koseki (family registry) records (n = 86), and one person who was enrolled in duplicate. We also excluded participants whose dose of atomic bomb radiation was unknown (n = 6,473). The resulting number of eligible participants was 105,444.

Follow-up and Case Ascertainment

Cancer incidence follow-up of the LSS began on January 1, 1958, when the cancer registries in Hiroshima and Nagasaki were established. Follow-up continued until December 31, 2009 for the current analysis. Vital status and causes of death were confirmed from nationwide records of koseki and death certificates. Information about incident cancer cases was obtained through linkage with the cancer registries in Hiroshima and Nagasaki, supplemented by Adult Health Study (AHS) health examinations and ABCC-RERF pathology programs. Cancer cases were classified using International Classification of Diseases for Oncology, Third Edition codes (ICD-O-3). The outcomes of interest were first primary malignant tumors of the liver, including liver (ICD-O-3 topography: C22.0) or intrahepatic bile ducts (IHBD) (C22.1); biliary tract, including gallbladder (C23) or other and unspecified parts of biliary tract (C24); and pancreas (C25). Censoring events were: a first primary cancer or death due to a cause other than liver, biliary tract or pancreatic cancer; loss to follow-up due to emigration; end of follow-up when the participants reached 110 years of age; and the end of the study period.

Eligible cases were first primary liver, biliary tract or pancreatic cancers diagnosed within the Hiroshima and Nagasaki cancer registry catchment areas during the follow-up period. Person-years were adjusted for expected migration out of the Hiroshima and Nagasaki catchment areas, with estimated migration rates stratified by city, sex, birth year and calendar year. Cases diagnosed only by autopsy under the ABCC-RERF program (autopsy-only) were not included as eligible cases and were censored at death; the numbers of cases were 46, 20 and 15 for liver, biliary tract and pancreatic cancers, respectively. Because such autopsies were intensively performed largely among survivors with higher radiation doses and only during the early years of follow-up, inclusion of autopsy-only cases could result in distorted radiation risk estimates among those who were older at the time of the bombings (*25*).

Irradiation

Dosimetry System 2002 (DS02) was used to estimate revised DS02R1 radiation doses (*30, 31*), which were adjusted for implausibly high dose estimates (>4 Gy) and random measurement errors (*32*). DS02R1 weighted absorbed liver doses, which were the sum of gamma ray and 10 times neutron doses, were used in all analyses of liver and biliary tract cancers. Weighted absorbed pancreas doses were used in analyses of pancreatic cancer.

Information regarding smoking, alcohol consumption, body height and body weight was collected through a series of LSS mail surveys (1965, 1969, 1978, 1991) and AHS questionnaires (1963, 1965, 1968) (*33*). We examined the consistency of responses across time and created summary variables for smoking (non-smoker, current smoker, former smoker or unknown) and drinking (non-drinker, current drinker, former drinker or unknown) status. We also calculated pack-years of cigarette smoking as cumulative smoking intensity. Initial pack-years was total pack-years at the time of the first questionnaire and pack-years accumulated as follow-up proceeded. Change in smoking status was incorporated into the computed pack-years by using information about age at starting and quitting smoking. Amount of alcohol intake (grams per day) was averaged over periods when a person was a drinker. For former drinkers, intake was assigned the value of their former intake amount. We calculated BMI as the weight in kilograms divided by the square of the height in meters using the earliest height and weight.

Statistical Analysis

Case counts and accrued person-years of follow-up were stratified by city, sex, age at exposure, attained age, calendar time, NIC status, DS02R1 weighted absorbed liver (or pancreas) dose and an indicator of total shielded kerma >4 Gy. We used Poisson regression methods to estimate radiation risks of liver, biliary tract and pancreatic cancers. The risks were presented as the excess relative risk (ERR) and excess absolute risk (EAR) using:

$$\lambda = \lambda_0(1 + ERR_{rad}); \quad (1)$$

$$\lambda = \lambda_0 1 + EAR_{rad}, \quad (1)$$

where λ_0 represents the baseline (or background) rate for individuals without radiation exposure, and ERR_{rad} and EAR_{rad} represent the ERR and EAR for radiation exposure, respectively. EARs were estimated only when ERRs were statistically significant.

Exploratory data analysis, along with known trends in cancer in Japan, was used to inform modeling strategies. Sex-specific baseline rates were modeled using birth cohort categories (1914 or earlier, 1915–1924, 1925–1934, 1935–1945) for liver cancer or linear birth cohort effect for biliary tract and pancreatic cancers, and quadratic regression splines for log-attained age with a knot at age 70 years. For

liver cancer, due to heterogeneity within and between cities in liver cancer rates by distance from the hypocenter (*17*), the model included an interaction between city and NIC status and an interaction between city and distal location (i.e., $\geq$3 km from the hypocenter), such that only zero-dose proximal (i.e., $<$3 km from the hypocenter) survivors were included in the reference group (*34*). For biliary tract and pancreatic cancers, because there was no evidence of heterogeneity by location, all zero-dose survivors and NIC residents were included in the reference group. However, the background models for biliary tract and pancreatic cancers included an interaction between sex and city to describe differences in incidence rates between men and women in Hiroshima and Nagasaki.

The shape of the radiation dose response was determined by comparing the fit of linear versus linear-quadratic dose-response models, for which comparisons were made using likelihood ratio tests and the Akaike information criterion (AIC). Curvature was defined as the ratio of the linear to quadratic dose-response coefficients. For all analyses, an indicator variable for total shielded kerma $>$4 Gy was included as an effect modifier. For liver cancer, effect modification of the ERR and EAR by sex, age at exposure and attained age was evaluated. The ERR and EAR were therefore presented as sex-averaged risks among individuals who were exposed at an age of 30 years and who attained an age of 70 years. We also computed radiation ERRs of liver cancer by categories of age at exposure to determine whether there was non-monotonic effect modification by age at exposure, as was observed in previously published studies (*15–17*). For biliary tract and pancreatic cancers, we considered effect modification on the ERR and EAR by sex, but lack of an overall dose response precluded consideration of effect modification by age at exposure and attained age in multivariable models. Instead, descriptive analyses compared crude incidence rates across dose groups, stratified by categories of age at exposure and attained age.

For liver and pancreatic cancers, joint effects of radiation with smoking, alcohol consumption and BMI were estimated using both additive and multiplicative ERR models and using EAR models (only for liver cancer). In the multiplicative ERR model, radiation risks are estimated relative to those who had the same smoking status, drinking status and BMI, whereas in the additive model, radiation risks are estimated relative to non-smoking non-drinkers with BMI $<$25.0 kg/m^2. The fit of additive versus multiplicative models was compared using AIC. For smoking, the models included cumulative pack-years, with a corresponding ERR (ERR_{smk}). For liver cancer, sex-specific ERRs of smoking were estimated because of a better model fit. For alcohol consumption, the model included average intake amount, with a corresponding ERR (ERR_{alc}), as well as an indicator variable for former drinkers. Thus, the model allowed for risk differences between current and former drinkers with the same amount of (current or former) alcohol consumption. For BMI, the model included indicator variables for BMI $\geq$25.0 kg/m^2 (ERR_{BMI}) and unknown BMI, because the association between BMI and risk of liver or pancreatic cancers appeared to be J-shaped. For pancreatic cancer, sex-specific indicator variable for unknown BMI was used. Smoking and alcohol EARs (EAR_{smk} and EAR_{alc}) for liver cancer were computed using models with the same terms as those for ERR_{smk} and ERR_{alc} with effect modification by attained age. Indicator variables for BMI $\geq$25.0 kg/m^2 and unknown BMI were included in the baseline model in the EAR model.

We performed several sensitivity analyses for liver and biliary tract cancers. Because liver and IHBD cancers, as well as gallbladder and other and unspecified parts of biliary tract (e.g., extrahepatic bile duct, EHBD) cancers, differ with respect to their cell of origin, risk factors (*35–37*), and possibly radiation-induced carcinogenesis, we estimated radiation ERRs separately for liver and IHBD cancers and for gallbladder and EHBD cancers. The ERRs for liver, IHBD, gallbladder and EHBD cancers were calculated from ERR models fit to separate person-year datasets, as well as from joint analyses (*38*), which accommodated heterogeneity in background rates and radiation effects between liver and IHBD cancers, between gallbladder and EHBD cancers and between IHBD and EHBD cancers. First, person-year datasets for liver and IHBD cancers were combined, and the fitted model included interaction of an indicator variable for liver versus IHBD cancer with sex-specific attained age and birth cohort in baseline rate model, radiation dose, and effect modification by sex, age at exposure and attained age. Second, person-year datasets for gallbladder and EHBD cancers were combined, and the fitted model included interaction of an indicator variable for gallbladder versus EHBD cancer with sex-specific attained age and birth cohort in baseline rate model and radiation dose. Third, person-year datasets for IHBD and EHBD cancers were combined, and the fitted model included interaction of an indicator variable for IHBD versus EHBD cancer with sex-specific attained age and birth cohort in baseline rate model and radiation dose.

Ethical Considerations

This study was approved by the RERF Institutional Ethical Review Board (research protocols 1-75 and 18-61). Use of data on causes of death and cancer incidence was approved by relevant authorities.

RESULTS

The number of eligible participants was 105,444, including 80,205 in-city survivors and 25,239 NIC residents.

Liver Cancer

During the follow-up period of 1958–2009, we ascertained 2,016 first primary liver cancer cases, comprised of 1,885 liver and 131 IHBD cancer cases, over 3,079,460-person years (Table 1); 522 cases (25.9%) were identified during the 11 years of follow-up since the last reported study. Dominant histological types were hepatocellular carcinoma and cholangiocarcinoma for liver and IHBD cancers, respectively (Table 2). The relatively low proportion of cases with histological verification and the high proportion of cases identified solely from death certificates reflects the relative inaccessibility to this organ and indicates poor diagnostic accuracy for this cancer.

The crude (unadjusted) liver cancer incidence rate was 6.5 per 10,000 person-years. The crude incidence rate among men (10.2 per 10,000 person-years) was more than twice that among women (4.4 per 10,000 person-years) (Table 1). Unadjusted rates exhibited a non-monotonic pattern across birth cohorts among men, with the 1925–1934 birth cohort having the highest rate, while the rates tended to decrease with increasing birth year among women. These patterns reflected birth-cohort-related differences in liver cancer incidence in the general Japanese population. Unadjusted rates increased with increasing attained age and radiation dose among both men and women. Rates among those exposed to $<$5 mGy in Hiroshima varied by location at the time of the bombing. In particular, the rate among distal survivors was higher than that among proximal survivors and NIC residents; the adjusted relative risk for distal survivors compared to proximal and NIC residents was 1.34

TABLE 1
The Numbers of Participants, Person-Years of Follow-up, Liver Cancer Cases and Crude Incidence Rate by Sex, City, Birth Cohort, Attained Age and DS02R1 Weighted Absorbed Liver Dose: 1958–2009

	Participants		Person-years		Liver cancer[a]			
					Men		Women	
	Men	Women	Men	Women	Cases	Rates[b]	Cases	Rates[b]
City								
Hiroshima	29,498	43,903	807,742	1,385,520	829	10.3	634	4.6
Nagasaki	13,412	18,631	334,495	551,704	337	10.1	216	3.9
Birth cohort (year)								
–1914 (≥30 years at exposure)	18,021	27,385	309,066	619,334	321	10.4	347	5.6
1915–1924 (20–29 years at exposure)	3,301	10,950	105,328	416,660	140	13.3	210	5.0
1925–1934 (10–19 years at exposure)	10,375	12,704	347,894	482,698	495	14.2	238	4.9
1935–1945 (0–9 years at exposure)	11,213	11,495	379,950	418,528	210	5.5	55	1.3
Attained age (years)								
<50	28,681	43,236	480,132	652,232	68	1.4	14	0.2
50 to <60	6,796	9,841	229,608	385,182	269	11.7	89	2.3
60 to <70	5,228	6,030	238,163	413,001	428	18.0	237	5.7
70 to <80	1,874	2,775	143,794	313,313	292	20.3	303	9.7
≥80	331	652	50,540	173,492	109	21.6	207	11.9
DS02R1 weighted absorbed liver dose (Gy)								
NIC[c]	10,488	14,751	287,797	473,753	287	10.0	183	3.9
<0.005 (distal)[d]	9,639	13,526	251,453	416,291	265	10.5	212	5.1
<0.005 (proximal)[e]	4,799	7,624	124,179	230,129	109	8.8	95	4.1
0.005 to <0.1	11,159	16,326	301,842	505,454	295	9.8	195	3.9
0.1 to <0.2	2,153	3,478	57,914	106,747	56	9.7	47	4.4
0.2 to <0.5	2,304	3,629	60,491	109,469	66	10.9	54	4.9
0.5 to <1.0	1,307	1,974	32,422	60,061	46	14.2	38	6.3
1.0 to <2.0	772	916	19,300	26,618	30	15.5	17	6.4
≥2.0	289	310	6,840	8,699	12	17.5	9	10.3
Total	42,910	62,534	1,142,240	1,937,220	1,166	10.2	850	4.4

[a] Liver (C22.0) (n = 1,885) and intrahepatic bile duct (C22.1) (n = 131) cancers.
[b] Per 10,000 person-years.
[c] Not in either city at the time of the bombings.
[d] ≥3km from the hypocenter.
[e] <3km from the hypocenter.

TABLE 2
Characteristics of Eligible Cases

Topography (ICD-O-3)	No. of cases	Percentage histological confirmation	Percentage DCO[a]	Dominant histological type (%)[b]
Malignant tumors of the liver				
Liver (C22.0)	1,885	37%	20%	Hepatocellular carcinoma (94%)
Intrahepatic bile duct (C22.1)	131	64%	3%	Cholangiocarcinoma (83%)
Malignant tumors of the biliary tract				
Gallbladder (C23)	354	61%	12%	Adenocarcinoma, NOS (54%) Papillary adenocarcinoma, NOS (19%) Tubular adenocarcinoma, NOS (14%)
Other and unspecified parts of biliary tract (C24)	340	56%	14%	Adenocarcinoma, NOS (57%) Tubular adenocarcinoma, NOS (19%) Papillary adenocarcinoma, NOS (12%)
Malignant tumors of the pancreas				
Pancreas (C25)	723	43%	21%	Adenocarcinoma, NOS (51%) Tubular adenocarcinoma, NOS (24%)

[a] Ascertained only by death certificate (death certificate only: DCO).
[b] Among cases with histological confirmation.
NOS: not otherwise specified

TABLE 3
Excess Relative Risks (ERRs) and Effect Modification by Sex, Age at Exposure and Attained Age of Liver (C22.0) and Intrahepatic Bile Duct (C22.1) Cancers as a Group with or without Adjustment for Smoking, Alcohol Consumption and BMI

	ERR per Gy			Effect modification		
	Sex-averaged	Men	Women	F:M ratio	Age at exposure (percentage change per decade increase)	Attained age (power)
Unadjusted						
Estimates	0.53	0.44	0.63	1.43	-23%	–1.1
(95% CI)	(0.23 to 0.89)	(0.17 to 0.81)	(0.24 to 1.14)	(0.63 to 3.12)	(–48% to 4%)	(–3.3 to 1.3)
Adjusted for smoking, alcohol consumption and BMI[a]						
Estimates	0.58	0.46	0.70	1.51	–23%	–1.1
(95% CI)	(0.27 to 0.95)	(0.19 to 0.83)	(0.29 to 1.25)	(0.69 to 3.20)	(–47% to 2%)	(–3.3 to 1.3)

[a] Multiplicative joint effects model was used.

(95% CI: 1.17 to 1.52). In Nagasaki, there was no such difference.

There was no evidence of non-linearity in the radiation dose response ($P = 0.344$). When both the linear and quadratic dose-response terms were allowed to vary by sex, the curvature estimate was 0.05 for men ($P > 0.50$) and 2.16 for women ($P = 0.180$). Therefore, we focused on the linear dose-response model for both sexes. Sex-averaged ERRs per Gy estimated from the linear dose-response model with effect modification by sex, age at exposure and attained age are shown in Table 3 and Fig. 1. The sex-averaged ERR was significantly increased, with no significant difference between men and women ($P = 0.371$). There was no evidence of effect modification by age at exposure ($P = 0.168$) or attained age ($P = 0.370$). We also computed radiation ERRs among categories of age at exposure (Table 4). The ERRs were significantly increased among those who were 0–9 years (ERR per Gy 0.81), 10–19 years (ERR per Gy 0.66) and 20–29 years (ERR per Gy 0.92) at exposure, and decreased and became non-significant thereafter, although the difference in ERRs between age categories was not statistically significant ($P = 0.378$). There was also no evidence of non-linearity in the interaction between radiation and age at exposure on the log-linear scale: addition of a quadratic term for the age-at-exposure effect modifier to a model with a linear term did not improve model fit ($P = 0.287$). Therefore, we selected a log-linear model for effect modification by age at exposure.

The sex-averaged EAR per 10,000 person-year Gy was 5.32 overall, 6.90 among men and 3.74 among women, but the difference between sexes was not statistically significant ($P = 0.107$) (Table 5). The EAR significantly decreased with increasing age at exposure ($P = 0.011$). EARs within categories of age at exposure exhibited a similar pattern to those for the ERR. The EARs increased among those who were 0–9 years (10.34, 95% CI: 2.31 to 23.57), 10–19 years (12.90, 95% CI: 5.90 to 21.70) and 20–29 years (10.47, 95% CI: 2.82 to 21.05) at exposure, but decreased after 30 years old. In contrast to the ERR, the EAR increased with increasing attained age ($P < 0.001$).

We modeled joint effects of radiation with smoking, alcohol consumption and BMI using both additive and multiplicative ERR and EAR models. Although the fit of the additive ERR model was better than that of the multiplicative ERR model (AIC difference of 15.8), we preferred the multiplicative ERR model because of its simpler interpretation. The radiation ERR was essentially unchanged after adjustment for smoking, alcohol consumption and BMI (Table 3). These lifestyle factors were associated with liver cancer risk. The smoking ERR was

TABLE 4
Age-at-Exposure Category-Specific Excess Relative Risks (ERRs) of Liver Cancer in the Current Study and Previous LSS Cancer Incidence Reports

			Age at exposure (years)				
	Follow-up	No. cases	0–9	10–19	20–29	30–39	≥40
Current study[a]	1958–2009	2016	0.81 (0.19 to 1.95)[c]	0.66 (0.28 to 1.17)[c]	0.92 (0.31 to 1.77)[c]	0.45 (–0.05 to 1.20)[c]	0.09 (<0 to 0.76)[c]
Thomson *et al.* (*15*)[b]	1958–1987	585	–0.25	0.85	0.92		0.44
Preston *et al.* (*16*)[a]	1958–1998	1494	0.06 (<–0.1 to 0.63)[d]	0.61 (0.18 to 1.3)[d]	0.18 (<–0.07 to 0.44)[d]		0.44 (<–0.14 to 1.1)[d]

[a] Sex-averaged ERRs at 1 Gy.
[b] ERRs at 1 Gy in both sexes. Confidence intervals were not reported.
[c] 95% confidence intervals.
[d] 90% confidence intervals.

TABLE 5
Excess Absolute Risks (EARs) and Effect Modification by Sex, Age at Exposure and Attained Age of Liver (C22.0) and Intrahepatic Bile Duct (C22.1) Cancers as a Group with or without Adjustment for Smoking, Alcohol Consumption and BMI

	EAR per 10,000 person-year Gy			Effect modification		
	Sex-averaged	Men	Women	F:M ratio	Age at exposure (percentage change per decade increase)	Attained age (power)
Unadjusted						
Estimates	5.32	6.90	3.74	0.54	–37%	4.4
(95% CIs)	(2.49 to 8.51)	(2.60 to12.28)	(1.60 to 6.41)	(0.24 to 1.48)	(–56% to –15%)	(2.8 to 6.4)
Adjusted for smoking, alcohol consumption, and BMI						
Estimates	5.36	6.64	4.07	0.61	–40%	5.0
(95% CIs)	(2.36 to 8.35)[a]	(1.85 to 11.43)[a]	(1.70 to 6.43)[a]	(0.25 to 1.27)[a]	(–57% to –16%)[a]	(3.1 to 6.9)[a]

[a] Wald 95% CIs were computed because likelihood-based CIs were difficult to compute.

0.36 per 50 pack-years (95% CI: 0.16 to 0.60) among men and 1.20 per 50 pack-years (95% CI: 0.54 to 2.01) among women. The alcohol ERR was 0.09 per 20 g of ethanol intake per day (95% CI: 0.03 to 0.17). The ERR for former drinkers was significantly elevated (0.86, 95% CI: 0.52 to 1.25), possibly due to reverse causality: drinkers ceased their alcohol consumption due to health problems related to liver cancer. The ERRs for BMI $\geq$25 kg/m^2 were 0.46 (95% CI: 0.27 to 0.67). As noted with the ERR, adjustment for smoking and alcohol consumption did not affect the estimated EAR (Table 5).

There were 107 (75.0 plus 32.2; see Table 6) excess cases attributable to exposures to atomic bomb radiation including interaction with smoking, alcohol consumption and BMI (Table 6). The attributable fraction for those with $\geq$5 mGy of radiation was 11.6%.

Site-specific ERRs for liver and IHBD cancers were calculated (Supplementary Table S1; http://dx.doi.org/10.1667/RR15341.1.S1). The ERRs per Gy estimated from separate models (without effect modification) were 0.57 for liver and 0.70 for IHBD cancers. Similar ERRs per Gy were estimated by the joint model (without effect modification), and there was no significant difference between the ERRs for liver and IHBD cancer ($P > 0.50$). The inclusion of effect modifiers had little impact on the radiation ERRs obtained from separate and joint analyses.

Biliary Tract Cancer

There were 694 incident biliary tract cancer cases including 354 gallbladder and 340 other and unspecified parts of biliary tract (EHBD) cancers. The crude incidence rate was 2.3 per 10,000 person-years and was 1.9 among men and 2.4 among women (Table 7). Differences in fitted baseline rates between men and women differed between cities ($P < 0.001$); in Hiroshima, the adjusted relative risk between men and women was 0.70 (95% CI: 0.56 to 0.88), but in Nagasaki, the adjusted relative risk was 1.31 (95% CI: 0.73 to 2.36). The ERR per Gy estimated from a model

TABLE 6
The Numbers of Participants, Person-Years, Liver Cancer Cases and Expected Numbers of Cases, Background and Excess Due to Radiation or Lifestyle Factors by Dose Category

DS02R1 weighted absorbed liver dose (Gy)	Participants	Person-years	Observed cases	Expected cases[a]	Background[a]
<0.005 and NIC	60,827	1,783,600	1,151	1,157.3	781.1
0.005 to <0.1	27,485	807,296	490	482.9	317.3
0.1 to <0.2	5,631	164,660	103	102.8	64.1
0.2 to <0.5	5,933	169,960	120	119.4	66.7
0.5 to <1.0	3,281	92,482	84	80.7	37.8
1.0 to <2.0	1,688	45,917	47	53.5	18.9
$\geq$2.0	599	15,539	21	19.3	6.1
Total	105,444	3,079,460	2,016	2,016.0	1,292.0

[a] Estimated by a multiplicative ERR model with effect modification and joint effects with smoking, alcohol consumption and BMI.
[b] Proportion of cases estimated to be attributable to radiation exposure over expected number of cases.
[c] Proportion of cases estimated to be attributable to interaction of radiation exposure with smoking, alcohol consumption and BMI over expected number of cases.
[d] Proportion of cases estimated to be attributable to smoking, alcohol consumption, BMI and interaction with each other over expected number of cases.
[e] Among those with $\geq$0.005 Gy.

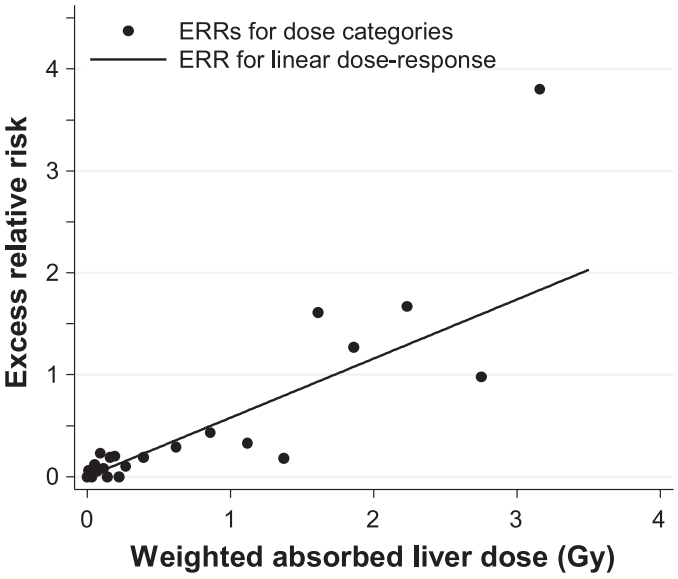

FIG. 1. Dose-response relationship between liver dose and excess relative risk (ERRS) for liver cancer. Sex-averaged ERRS at the age 70 years and after exposure at age 30 years estimated by models with joint effects with alcohol consumption, smoking and body mass index are plotted. Points are ERRs for 22 dose categories. Solid line is a linear dose-response functions.

without effect modification was –0.02. Sex-specific ERRs were 0.17 among men and –0.14 among women (Table 8), with no evidence of difference between sexes ($P = 0.284$). Crude incidence rate ratios by dose group did not differ across strata of age at exposure or attained age.

The ERR for gallbladder cancer was negative, while the ERR for EHBD cancer was positive (Supplementary Table S2; http://dx.doi.org/10.1667/RR15341.1.S1). However, neither were statistically significant, and the difference between the ERRs was not statistically significant ($P = 0.183$). The ERRs for IHBD and EHBD were both positive (Supplementary Table S2), but the difference between ERRs was not statistically significant ($P = 0.379$).

Pancreatic Cancer

We ascertained 723 incident cases of pancreatic cancer (Table 9), of which 219 cases (30.3%) occurred during the 11 years of additional follow-up. Accuracy of diagnosis for pancreatic cancer was considered poor as suggested by the relatively high proportion of cases reported only by death certificate and the low proportion of cases diagnosed by histology (Table 2). The crude incidence rate of pancreatic cancer was 2.3 per 10,000 person-years and was 2.7 among men and 2.2 among women. Differences in fitted baseline rates between men and women differed between cities ($P = 0.065$); in Hiroshima, the adjusted relative risk between men and women was 0.48 (95% CI: 0.38 to 0.59), while in Nagasaki, the adjusted relative risk was 0.65 (95% CI: 0.38 to 1.15). Radiation risk estimates of pancreatic cancer are shown in Table 10. The sex-averaged ERR per Gy estimated by a model without effect modification by age at exposure or attained age was 0.38. Although the sex difference was not statistically significant ($P = 0.193$), women had a numerically higher ERR compared to men. Among women, the ERR for pancreatic cancer was significantly increased. Crude incidence rate ratios by dose group did not differ across strata of age at exposure or attained age. A model with multiplicative joint effects between radiation, smoking, alcohol consumption and BMI revealed a significantly increased sex-averaged ERR (0.45; 95% CI: 0.07 to 0.92). In addition, the ERR was significantly elevated among women, but not among men. The ERR for smoking was 0.83 per 50 pack-years (95% CI: 0.37 to 1.44), but the ERRs for alcohol consumption and BMI ≥ 25.0 kg/m^2 were not significantly increased.

TABLE 6
Extended.

Radiation only		Radiation-lifestyle interaction		Lifestyle factors only	
Excess cases[a]	Attributable fraction (%)[b]	Excess cases[a]	Attributable fraction (%)[c]	Excess cases[a]	Attributable fraction (%)[d]
0.3	0.0	0.1	0.0	375.8	32.5
7.5	1.6	3.6	0.7	154.5	32.0
6.6	6.4	3.0	2.9	29.2	28.4
15.4	12.9	6.9	5.8	30.4	25.5
19.5	24.2	7.7	9.5	15.7	19.4
18.4	34.4	7.8	14.6	8.4	15.7
7.3	37.8	3.1	16.1	2.9	14.7
75.0	8.7[e]	32.2	3.7[e]	616.8	28.1[e]

TABLE 7
The Numbers of Participants, Person-Years of Follow-up, Biliary Tract Cancer Cases and Crude Incidence Rate by Sex, City, Age at Exposure, Attained Age and DS02R1 Weighted Absorbed Liver Dose: 1958–2009

	Participants		Person-years		Biliary tract cancer[a]			
					Men		Women	
	Men	Women	Men	Women	Cases	Rates[b]	Cases	Rates[b]
City								
Hiroshima	29,498	43,903	807,742	1,385,520	163	2.0	295	2.1
Nagasaki	13,412	18,631	334,495	551,704	57	1.7	179	3.2
Age ATB (years)								
0 to <10	11,213	11,495	379,950	418,528	27	0.7	13	0.3
10 to <20	10,375	12,704	347,894	482,698	53	1.5	68	1.4
20 to <30	3,301	10,950	105,328	416,660	29	2.8	116	2.8
30 to <40	5,224	10,614	133,214	333,300	42	3.2	148	4.4
40 to <50	6,917	9,157	119,503	199,805	49	4.1	98	4.9
≥50	5,880	7,614	56,349	86,228	20	3.5	31	3.6
Attained age (years)								
<50	28,681	43,236	480,132	652,232	9	0.2	15	0.2
50 to <60	6,796	9,841	229,608	385,182	21	0.9	36	0.9
60 to <70	5,228	6,030	238,163	413,001	71	3.0	85	2.1
70 to <80	1,874	2,775	143,794	313,313	80	5.6	170	5.4
≥80	331	652	50,540	173,492	39	7.7	168	9.7
DS02R1 weighted absorbed liver dose (Gy)								
NIC[c]	10,488	14,751	287,797	473,753	61	2.1	107	2.3
<0.005	14,438	21,150	375,632	646,420	77	2.0	170	2.6
0.005 to <0.1	11,159	16,326	301,842	505,454	48	1.6	130	2.6
0.1 to <0.2	2,153	3,478	57,914	106,747	10	1.7	27	2.5
0.2 to <0.5	2,304	3,629	60,491	109,469	9	1.5	21	1.9
0.5 to <1.0	1,307	1,974	32,422	60,061	8	2.5	13	2.2
1.0 to <2.0	772	916	19,300	26,618	6	3.1	4	1.5
≥2.0	289	310	6,840	8,699	1	1.5	2	2.3
Total	42,910	62,534	1,142,240	1,937,220	220	1.9	474	2.4

[a] Cancers of the gallbladder (C23) (n = 354) and unspecified parts of biliary tract (C24) (n = 340).
[b] Per 10,000 person-years.
[c] Not in either city at the time of the bombings.

DISCUSSION

The updated liver cancer incidence data in the LSS continued to provide evidence of a linear relationship between radiation dose and liver cancer risk, regardless of whether joint effects with smoking, alcohol consumption and BMI were considered. We analyzed liver and IHBD cancers combined and separately, and found a suggestion of an excess risk of IHBD cancer, although there was no evidence that radiation ERRs differed between liver and IHBD cancers. We also tested for differences in radiation risks between gallbladder and EHBD cancers, as well as between IHBD and EHBD cancers, and again there was no evidence of a difference. Analyses considering IHBD and EHBD, which were grouped with liver and gallbladder, respectively, were not typically performed in the LSS, with one exception (*17*). The extended follow-up increased the number of cases of biliary tract cancer (23.6%), but there was no evidence of radiation-associated excess risk. Pancreatic cancer (30.3%) also increased during the 11-year extended follow-up period, and there was a suggestion of excess risk among women.

TABLE 8
Sex-Averaged and Sex-Specific Excess Relative Risks (ERRs) of Biliary Tract Cancer

	ERR per Gy		
	Sex-averaged	Men	Women
Estimates (95% CI)	–0.02 (–0.25 to 0.30)	0.17 (–0.23 to 0.80)	–0.14 (<0 to 0.25)

In the current study, the estimated ERR (0.53 per Gy) and EAR (5.32 per 10,000 PY per Gy) for liver cancer, unadjusted for smoking, alcohol consumption and BMI, were higher than those in the previously published study by Preston *et al*. (ERR per Gy = 0.30 and EAR per 10,000 PY per Gy = 4.3) (*16*). We investigated whether revised doses (*31*), extension of the follow-up period or change in statistical models explained the difference by comparing ERRs estimated based on both previous and current data and statistical models. Both extension of the follow-up and change in statistical model (described below) increased the estimated ERRs, but the revised doses did not have a substantial effect (data not shown). In the current study, we selected zero-dose proximal survivors (<3 km from the hypocenter) as the reference group, while Preston *et al*., selected all zero-dose survivors (<10 km from the hypocenter) as the reference group. Because the <5 mGy proximal survivors had a lower incidence of liver cancer

TABLE 9
The Numbers of Participants, Person-Years of Follow-up, Pancreatic Cancer Cases and Crude Incidence Rate by Sex, City, Age at Exposure, Attained Age and DS02R1 Weighted Absorbed Pancreas Dose: 1958–2009

	Participants		Person-years		Pancreas[a]			
					Men		Women	
	Men	Women	Men	Women	Cases	Rates[b]	Cases	Rates[b]
City								
Hiroshima	29,498	43,903	807,745	1,385,510	234	2.9	298	2.2
Nagasaki	13,412	18,631	334,495	551,707	72	2.2	119	2.2
Age ATB (years)								
0 to <10	11,213	11,495	379,951	418,529	49	1.3	24	0.6
10 to <20	10,375	12,704	347,896	482,698	82	2.4	77	1.6
20 to <30	3,301	10,950	105,327	416,659	22	2.1	105	2.5
30 to <40	5,224	10,614	133,214	333,301	57	4.3	111	3.3
40 to <50	6,917	9,157	119,504	199,805	58	4.9	68	3.4
≥50	5,880	7,614	56,349	86,230	38	6.7	32	3.7
Attained age (years)								
<50	28,681	43,236	480,133	652,233	11	0.2	11	0.2
50 to <60	6,796	9,841	229,608	385,181	37	1.6	30	0.8
60 to <70	5,228	6,030	238,163	413,001	113	4.7	73	1.8
70 to <80	1,874	2,775	143,795	313,314	94	6.5	164	5.2
≥80	331	652	50,541	173,492	51	10.1	139	8.0
DS02R1 weighted absorbed pancreatic dose (Gy)								
NIC[c]	10,488	14,751	287,797	473,753	82	2.8	92	1.9
<0.005	14,647	21,512	380,720	657,020	100	2.6	154	2.3
0.005 to <0.1	11,175	16,353	302,359	506,594	85	2.8	93	1.8
0.1 to <0.2	2,138	3,418	57,839	105,244	13	2.2	27	2.6
0.2 to <0.5	2,277	3,622	59,152	108,533	9	1.5	20	1.8
0.5 to <1.0	1,276	1,818	32,027	55,516	10	3.1	23	4.1
1.0 to <2.0	687	822	17,106	23,874	4	2.3	8	3.4
≥2.0	222	238	5,240	6,688	3	5.7	0	0
Total	42,910	62,534	1,142,240	1,937,220	306	2.7	417	2.2

[a] Pancreatic cancer (C25) (n = 723).
[b] Per 10,000 person-years.
[c] Not in either city at the time of the bombings.

compared to the <5 mGy distal survivors (3 to <10 km from the hypocenter), perhaps due to urban-rural differences in socioeconomic or lifestyle factors associated with liver cancer, change in reference group could have resulted in an increased ERR (*34*). In fact, after fitting a model with all zero-dose survivors as the reference group, the ERR decreased from 0.53 (95% CI: 0.23 to 0.89) to 0.39 (95% CI: 0.14 to 0.70).

Previous LSS liver cancer incidence studies reported a non-monotonic age at exposure effect (Table 4). The ERRs were shown to be higher among those exposed between 10 and 39 years, peaking among those exposed between 10 and 19 years, with no or small risk among the youngest and the oldest age-at-exposure groups (*15–17*). In the current study, both absolute and relative risks by categorical ages at exposure were significantly increased for exposure under age 9 years, 10–19 years and 20–29 years, with no significant risks after age 30 years (Table 4). However, these risk differences between groups were not statistically significant. In the current study, the baseline liver cancer rates were relatively low among those who were 0–9 years at exposure (Table 1). This lower baseline rate might reflect a lower prevalence of HCV infection among this birth cohort, which was observed among general populations in Japan (*7*) as well as among the Adult Health Study (AHS) participants, a clinical subset of the LSS, in Hiroshima (*39*). Additional follow-up of this youngest birth cohort might provide useful information on how the prevalence of HCV infection influences radiation risk estimates of liver cancer.

TABLE 10
Sex-Averaged and Sex-Specific Excess Relative Risks (ERRs) of Pancreatic Cancer

	ERR per Gy		
	Sex-averaged	Men	Women
Unadjusted			
Estimates	0.38	0.07	0.70
(95% CI)	(<0 to 0.83)	(–0.29 to 0.63)	(0.12 to 1.45)
Adjusted for smoking, alcohol consumption, and BMI[a]			
Estimates	0.45	0.13	0.77
(95% CI)	(0.07 to 0.92)	(–0.26 to 0.74)	(0.16 to 1.56)

[a] Multiplicative joint effects model was used.

Excess risks of radiation-associated liver cancer have been consistently reported in the LSS. However, outside the LSS cohort studies, there has been no clear evidence of excess liver cancer risks from populations with medical (*40, 41*) or occupational (*12, 42*) exposures to low-LET radiation. One of the few studies that found excess risk of

radiation-associated liver cancer is a cohort study of physicians in China (*43*). Radiologists had elevated risk of developing incident liver cancer compared to physicians not engaged in radiological procedures. Nevertheless, a dose-response relationship was not demonstrated. In addition, radiation risk estimates could have been influenced by a higher prevalence of hepatitis virus infection among those who started radiological practice in earlier periods, as well as by diagnostic inaccuracies for primary liver cancer, which was also noted in a study in high natural background radiation areas in China (*44*).

In published studies on the effects of high-LET radiation such as thorium or plutonium, excess risks of liver cancer have been demonstrated. Patients who were chronically exposed to alpha particles from Thorotrast (contrast material containing colloidal thorium dioxide) (*9, 10*) and workers at the Mayak nuclear facility who were exposed to both inhaled plutonium and external gamma radiation (*8, 45, 46*) had elevated risks for liver cancer. Of note, the dominant histological type is hepatocellular carcinoma among the LSS participants (Table 2) and Mayak workers with relatively lower plutonium doses (*46*), while it is cholangiocarcinoma and/or hemangiosarcoma among Thorotrast patients, reflecting the fact that intravenously administered Thorostast is more likely to deposit in periportal areas than in hepatic cord areas of the liver (*47*). In the Mayak workers cohort, hemangiosarcoma was also observed, exclusively among workers exposed to higher plutonium doses ($\geq$4 Gy) (*46*).

In the current study, radiation risk of pancreatic cancer was significantly increased among women, but not among men. Whether there is a sex difference in radiation risks of pancreatic cancer remains unknown. Studies among female patients who received radiotherapy for uterine bleeding (*48*) or cervical cancer (*49*) reported excess risks of pancreatic cancer associated with radiotherapy, but studies including both sexes (*23, 41, 50*) did not assess sex difference in risks. Although significant dose-response relationship was rarely demonstrated by earlier studies, more recently published studies reported that there was a significant dose-response relationship between doses from radiotherapy and risk of pancreatic cancer among survivors of Hodgkin lymphoma (*23*) or testicular cancer (*24*) while accounting for effects of chemotherapy. Reported excess odds ratio per Gy (0.12; 95% CI 0.03 to 0.42) among 5-year survivors of testicular cancer (*24*) was comparable with the ERR per Gy among male LSS participants (0.07; 95% CI –0.29 to 0.63). Studies among patients who received Thorotrast suggested that exposure to thorium might be associated with increased risks for pancreatic and gallbladder cancers (*10*), but there is no clear evidence of increased risk in other populations exposed to high-LET radiation. More studies with precise dosimetry and outcome information are required to further elucidate radiation risks of pancreatic or biliary tract cancers.

Although we did not have data on hepatitis virus infection, how infection with hepatitis virus affects radiation risk estimates of liver cancer in atomic bomb survivors is important, because Japan is an area where the prevalence of HCV infection is high and large proportions of liver cancer cases are attributable to HCV (*3, 18*). To date, there has been no indication of confounding by hepatitis virus infection. Studies in the AHS found that radiation dose was not associated with HCV infection (*39*). Moreover, estimated radiation risks were essentially unchanged after adjustment for infection with HCV in the AHS (*20*). A radiation dose-related increase in prevalence of chronic HBV infection was observed (*51–53*). However, this was limited to atomic bomb survivors who received blood transfusions between 1945 and 1972 when screening for blood product was not performed in Japan (*53*). Adult-onset persistent infection with HBV was established perhaps due to impaired immune function caused by radiation exposure (*53*). This suggests that HBV infection might be a mediator of the association between exposure to atomic bomb radiation and occurrence of liver cancer. A possibility that HCV might synergistically work with radiation to increase excess risks of liver cancer was reported elsewhere in a study of the LSS (*19*), although a more recently published analysis in the AHS did not provide support for this study (*20*). The role of hepatitis virus infection in the etiology of radiation-associated liver cancer should be more definitively demonstrated in future studies by developing a biologically plausible mechanistic framework.

A strength of our study is the large sample size with a sufficient number of cases over a long follow-up period, between 1958 and 2009. Because the LSS participants are comprised of both sexes and a wide range of ages at exposure, we were able to evaluate effect modification by these factors. We adjusted for effects of major non-radiation risk factors such as smoking, alcohol consumption and BMI, and demonstrated that radiation risk estimates of liver cancer were not influenced by these factors.

We acknowledge the following limitations. Information about infections with HBV and HCV was not available, although, as mentioned above, there has been no convincing evidence that HBV and HCV could confound radiation risk estimates for liver cancer, according to previously reported studies among atomic bomb survivors. Also, we considered joint effects with major risk factors for cancer such as smoking, alcohol consumption and BMI, which were collected after exposures to atomic bomb radiation. It might be possible that survivors with higher doses were more likely to change lifestyle habits because of health concerns, although survivors generally are unaware of their radiation dose. In addition, we accounted for reported changes in smoking and alcohol consumption over time, but we were unable to account for changes between the last questionnaire survey in 1991 and the end of follow-up in 2009, when older survivors might have decreased their smoking and alcohol consumption. Because approximately 76% of

all person-years were accumulated before 1990 and because it takes many years for changes in these exposure levels to translate into appreciable changes in cancer risk (*26*), we do not expect that misclassification of lifestyle habits in recent calendar years would have a meaningful impact on the results. Another limitation is that a larger proportion of liver and pancreatic cancer cases were ascertained only by death certificates (DCs). Sharp *et al*. found a substantial impact of misclassification of primary liver cancer in DCs on estimated baseline liver cancer rate (*54*). The extent to which the DC misclassification affects radiation dose-response analysis remains unclear.

In conclusion, this study provided consistent evidence of a dose-response relationship between atomic bomb radiation and risk of liver cancer. Further follow-up is essential to clarify age-at-exposure effect on radiation risks of liver cancer. Our findings continue to suggest the lack of excess radiation-related risks for biliary tract cancer. There was a suggestion that radiation risk of pancreatic cancer was increased among women.

SUPPLEMENTARY INFORMATION

Table S1. Site-specific ERRs of liver (C22.0) and intrahepatic bile duct (C22.1) cancers.

Table S2. Site-specific ERRs of gallbladder (C23), extrahepatic bile duct (C24) and intrahepatic bile duct (C22.1) cancers.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68:394–424.
2. Vital statistics Japan. Ministry of Health, Labour, and Welfare, Japan; 2016.
3. Tanaka K, Hirohata T, Koga S, Sugimachi K, Kanematsu T, Ohryohji F, et al. Hepatitis C and hepatitis B in the etiology of hepatocellular carcinoma in the Japanese population. Cancer Res 1991; 51:2842–7.
4. London WT, Petrick JL, McGlynn K Liver cancer. In: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, editors. Cancer epidemiology and prevention. 4th ed. New York: Oxford University Press; 2018. p. 635–60.
5. Yoshizawa H. Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. Oncology 2002; 62:S8–17.
6. Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 1993; 328:1797–801.
7. Tanaka H, Imai Y, Hiramatsu N, Ito Y, Imanaka K, Oshita M, et al. Declining incidence of hepatocellular carcinoma in Osaka, Japan, from 1990 to 2003. Ann Intern Med 2008; 148:820–6.
8. Sokolnikov ME, Gilbert ES, Preston DL, Ron E, Shilnikova NS, Khokhryakov VV, et al. Lung, liver and bone cancer mortality in Mayak workers. Int J Cancer 2008; 123:905–11.
9. Mori T, Kido C, Fukutomi K, Kato Y, Hatakeyama S, Machinami R, et al. Summary of entire Japanese thorotrast follow-up study: updated 1998. Radiat Res 1999; 152:S84–7.
10. Travis LB, Hauptmann M, Gaul LK, Storm HH, Goldman MB, Nyberg U, et al. Site-specific cancer incidence and mortality after cerebral angiography with radioactive thorotrast. Radiat Res 2003; 160:691–706.
11. Effects of ionizing radiation : United Nations Scientific Committee on the Effects of Atomic Radiation : UNSCEAR 2006 Report to the General Assembly, with scientific annexes. New York: United Nations; 2008.
12. Richardson DB, Cardis E, Daniels RD, Gillies M, Haylock R, Leuraud K, et al. Site-specific Solid Cancer Mortality After Exposure to Ionizing Radiation: A Cohort Study of Workers (INWORKS). Epidemiology 2018; 29:31–40.
13. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. Radiat Res 2003; 160:381–407.
14. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950–2003: an overview of cancer and noncancer diseases. Radiat Res 2012; 177:229–43.
15. Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, et al. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. Radiat Res 1994; 137:S17–67.
16. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat Res 2007; 168:1–64.
17. Cologne JB, Tokuoka S, Beebe GW, Fukuhara T, Mabuchi K. Effects of radiation on incidence of primary liver cancer among atomic bomb survivors. Radiat Res 1999; 152:364–73.
18. Inoue M, Sawada N, Matsuda T, Iwasaki M, Sasazuki S, Shimazu T, et al. Attributable causes of cancer in Japan in 2005–systematic assessment to estimate current burden of cancer attributable to known preventable risk factors in Japan. Ann Oncol 2012; 23:1362–9.
19. Sharp GB, Mizuno T, Cologne JB, Fukuhara T, Fujiwara S, Tokuoka S, et al. Hepatocellular carcinoma among atomic bomb survivors: significant interaction of radiation with hepatitis C virus infections. Int J Cancer 2003; 103:531–7.
20. Ohishi W, Fujiwara S, Cologne JB, Suzuki G, Akahoshi M, Nishi N, et al. Impact of radiation and hepatitis virus infection on risk of hepatocellular carcinoma. Hepatology 2011; 53:1237–45.
21. Antwi SO, Jansen RJ, Petersen GM. Cancer of the pancreas. In: Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, editors. Cancer epidemiology and prevention. 4th ed. New York: Oxford University Press; 2018. p. 611–34.
22. Koshiol J, Ferreccio C, Devesa SS, Roa JC, Fraumeni JF, Jr. Biliary tract cancer. In: Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D editors. Cancer epidemiology and prevention. 4th ed. New York: Oxford University Press; 2018. p. 661–70.
23. Dores GM, Curtis RE, van Leeuwen FE, Stovall M, Hall P, Lynch

CF, et al. Pancreatic cancer risk after treatment of Hodgkin lymphoma. Ann Oncol 2014; 25:2073–9.

24. Hauptmann M, Borge Johannesen T, Gilbert ES, Stovall M, van Leeuwen FE, Rajaraman P, et al. Increased pancreatic cancer risk following radiotherapy for testicular cancer. Br J Cancer 2016; 115:901–8.

25. Grant EJ, Brenner A, Sugiyama H, Sakata R, Sadakane A, Utada M, et al. Solid cancer incidence among the Life Span Study of atomic bomb survivors: 1958–2009. Radiat Res 2017; 187:513–37.

26. Cahoon EK, Preston DL, Pierce DA, Grant E, Brenner AV, Mabuchi K, et al. Lung, laryngeal and other respiratory cancer incidence among Japanese atomic bomb survivors: An updated analysis from 1958 through 2009. Radiat Res 2017; 187:538–48.

27. Brenner AV, Preston DL, Sakata R, Sugiyama H, Berrington de Gonzalez A, French B, et al. Incidence of breast cancer in the Life Span Study of atomic bomb survivors: 1958–2009. Radiat Res 2018; 190:433–44.

28. Utada M, Brenner AV, Preston DL, Cologne JB, Sakata R, Sugiyama H, et al. Radiation risks of uterine cancer in atomic bomb survivors: 1958–2009. JNCI Cancer Spectrum 2019; 2:1–6.

29. Sugiyama H, Misumi M, Brenner A, Grant EJ, Sakata R, Sadakane A, et al. Radiation risk of incident colorectal cancer by anatomical site among atomic bomb survivors: 1958–2009. Int J Cancer 2019; Epub ahead of print.

30. Cullings HM, Fujita S, Funamoto S, Grant EJ, Kerr GD, Preston DL. Dose estimation for atomic bomb survivor studies: its evolution and present status. Radiat Res 2006; 166:219–54.

31. Cullings HM, Grant EJ, Egbert SD, Watanabe T, Oda T, Nakamura F, et al. DS02R1: Improvements to Atomic Bomb Survivors' Input Data and Implementation of Dosimetry System 2002 (DS02) and resulting changes in estimated doses. Health Phys 2017; 112:56–97.

32. Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. Radiat Res 1990; 123:275–84.

33. Sakata R, McGale P, Grant EJ, Ozasa K, Peto R, Darby SC. Impact of smoking on mortality and life expectancy in Japanese smokers: a prospective cohort study. BMJ 2012; 345:e7093.

34. French B, Cologne J, Sakata R, Utada M, Preston DL. Selection of reference groups in the Life Span Study of atomic bomb survivors. Eur J Epidemiol 2017; 32: 1055–63.

35. Palmer WC, Patel T. Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. J Hepatol 2012; 57:69–76.

36. Ishiguro S, Inoue M, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Risk factors of biliary tract cancer in a large-scale population-based cohort study in Japan (JPHC study); with special focus on cholelithiasis, body mass index, and their effect modification. Cancer Causes Control 2008; 19:33–41.

37. Welzel TM, Graubard BI, El-Serag HB, Shaib YH, Hsing AW, Davila JA, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. Clin Gastroenterol Hepatol 2007; 5:1221–8.

38. Pierce DA, Preston DL. Joint analysis of site-specific cancer risks for the atomic bomb survivors. Radiat Res 1993; 134:134–42.

39. Fujiwara S, Kusumi S, Cologne J, Akahoshi M, Kodama K, Yoshizawa H. Prevalence of anti-hepatitis C virus antibody and chronic liver disease among atomic bomb survivors. Radiat Res 2000; 154:12–9.

40. Darby SC, Doll R, Gill SK, Smith PG. Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br J Cancer 1987; 55:179–90.

41. Carr ZA, Kleinerman RA, Stovall M, Weinstock RM, Griem ML, Land CE. Malignant neoplasms after radiation therapy for peptic ulcer. Radiat Res 2002; 157:668–77.

42. Cardis E, Gilbert ES, Carpenter L, Howe G, Kato I, Armstrong BK, et al. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. Radiat Res 1995; 142:117–32.

43. Wang JX, Zhang LA, Li BX, Zhao YC, Wang ZQ, Zhang JY, et al. Cancer incidence and risk estimation among medical x-ray workers in China, 1950-1995. Health Phys 2002; 82:455–66.

44. Tao Z, Akiba S, Zha Y, Sun Q, Zou J, Li J, et al. Cancer and non-cancer mortality among inhabitants in the high background radiation area of Yangjiang, China (1979–1998). Health Phys 2012; 102:173–81.

45. Gilbert ES, Koshurnikova NA, Sokolnikov M, Khokhryakov VF, Miller S, Preston DL, et al. Liver cancers in Mayak workers. Radiat Res 2000; 154:246–52.

46. Labutina EV, Kuznetsova IS, Hunter N, Harrison J, Koshurnikova NA. Radiation risk of malignant neoplasms in organs of main deposition for plutonium in the cohort of Mayak workers with regard to histological types. Health Phys 2013; 105:165–76.

47. Dagle GE, Moen EP, Adee RR, Hui TE, James AC, Filipy RE, et al. Microdistribution and microdosimetry of thorium deposited in the liver. Health Phys 1992; 63:41–5.

48. Inskip PD, Monson RR, Wagoner JK, Stovall M, Davis FG, Kleinerman RA, et al. Cancer mortality following radium treatment for uterine bleeding. Radiat Res 1990; 123:331–44.

49. Boice JD, Jr., Engholm G, Kleinerman RA, Blettner M, Stovall M, Lisco H, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat Res 1988; 116:3–55.

50. Weiss HA, Darby SC, Doll R. Cancer mortality following X-ray treatment for ankylosing spondylitis. Int J Cancer 1994; 59:327–38.

51. Kato H, Mayumi M, Nishioka K, Hamilton HB. The relationship of hepatitis B surface antigen and antibody to atomic bomb radiation in the Adult Health Study sample, 1975–1977. Am J Epidemiol 1983; 117:610–20.

52. Neriishi K, Akiba S, Amano T, Ogino T, Kodama K. Prevalence of hepatitis B surface antigen, hepatitis B e antigen and antibody, and antigen subtypes in atomic bomb survivors. Radiat Res 1995; 144:215–21.

53. Fujiwara S, Sharp GB, Cologne JB, Kusumi S, Akahoshi M, Kodama K, et al. Prevalence of hepatitis B virus infection among atomic bomb survivors. Radiat Res 2003; 159:780–6.

54. Sharp GB, Cologne JB, Fukuhara T, Itakura H, Yamamoto M, Tokuoka S. Temporal changes in liver cancer incidence rates in Japan: accounting for death certificate inaccuracies and improving diagnostic techniques. Int J Cancer 2001; 93:751–8.