Gastrointestinal Cancer Survival and Radiation Exposure among Atomic Bomb Survivors: The Life Span Study

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ABSTRACT

Background: Radiation exposure is an established risk factor for the development of several forms of cancer, including gastrointestinal cancers. However, few studies have investigated the relationship between prediagnostic radiation exposure and survival after cancer diagnosis.

Methods: Participants in the Life Span Study (LSS) of atomic bomb survivors who were diagnosed with a first primary invasive stomach, colon, or rectal cancer between 1958 and 2009 were followed for mortality during 1958–2014. Cox regression models were used to calculate HRs and 95% confidence intervals (CI) for associations of radiation dose from atomic bomb exposure with survival (cancer-specific and overall) after cancer diagnosis. Analyses were adjusted for city of primary exposure, sex, age at diagnosis, and year of diagnosis.

Results: We identified 7,728 eligible patients with cancer for analysis. We observed no statistically significant associations between radiation dose and cancer-specific survival among LSS participants with a gastrointestinal cancer. Higher radiation doses (≥1 Gy) were suggestively, but not significantly, associated with modestly poorer cancer-specific survival for colon cancer only (HR, 1.38; 95% CI, 0.90–2.12), and were associated with poorer overall survival regardless of cancer site.

Conclusions: Although radiation exposure is associated with increased risk of gastrointestinal cancer incidence and mortality, study results are inconclusive about an association between prediagnostic radiation exposure and survival after gastrointestinal cancer diagnosis.

Impact: Radiation exposure from the atomic bomb before gastrointestinal cancer diagnosis was not associated with cancer survival, but should be evaluated in relation to survival for other cancer types.

Introduction

Exposure to ionizing radiation is an established risk factor for several forms of cancer, including stomach and colon cancers (1–3). In particular, exposure to radiation from the 1945 atomic bombings of Hiroshima and Nagasaki has been associated with increased incidence and mortality for stomach and colon cancers (4, 5).

In addition to cancer induction, radiation may also contribute to cancer outcomes–either via the effects of radiation exposure knowledge on cancer screening behavior, or via the effects of radiation on the biology and clinicopathology of tumors. For example, previous studies have noted differences in tumor-associated stromal cells (6) and in the involvement of double-stranded DNA breaks (7) in gastric cancers in persons exposed to radiation from the atomic bombings compared with those who were not exposed. Other studies have reported greater genomic instability, higher histologic grade (8), and increased copy-number alterations (9) in breast tumors for patients exposed to the atomic bombings. However, few studies have considered the extent to which past exposure to radiation is associated with survival after subsequent cancer diagnosis. One study from the Hiroshima Atomic Bomb Survivors Hospital found poorer gastric cancer survival among atomic bomb survivors relative to unexposed controls (10, 11), but did not investigate the association between survival and radiation dose.

To address this gap in knowledge, we undertook an analysis evaluating survival outcomes among atomic bomb survivors diagnosed with gastrointestinal cancers in relation to radiation dose received from the atomic bombings.

Materials and Methods

Study setting and data collection

The Life Span Study (LSS) is a cohort of 93,741 Japanese individuals who survived the atomic bombings of Hiroshima and Nagasaki in 1945 and who resided in these cities in 1950 (12); the LSS also includes 26,580 residents of Hiroshima or Nagasaki during 1950–1953 who were not in either city (or, NIC) at the time of the bombings. Details regarding the formation of the LSS, data collection within the cohort, and the lasting health effects of radiation exposure observed within this cohort are provided elsewhere (13). In brief, vital status was ascertained through the national family registration system followed by ascertainment of causes of death from death certificates (since 1950), while cancer incidence was ascertained through population-based cancer registries in Hiroshima and Nagasaki (since 1958). Additional demographic and lifestyle data, including alcohol intake and smoking status, have been collected from in-clinic questionnaires (1963, 1965, 1968) and mailed surveys (1965, 1969, 1978, 1991; ref. 13).

Revised DS02R1 organ-specific radiation doses received from the atomic bombs were estimated for each survivor, based on age, reported

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location, the amount and type of shielding between the survivor and the blast, and the orientation of the survivor relative to the direction of the blast according to Dosimetry System 2002 (DS02; refs. 14, 15). In the analyses, we used weighted absorbed stomach dose or colon dose calculated using a neutron weighting factor of 10.

Study inclusion

From among the 120,321 participants in the LSS, we identified 10,626 participants who were diagnosed with a first primary invasive stomach, colon, or rectal cancer during 1958–2009. After excluding participants who were diagnosed outside of the catchment areas for the Hiroshima or Nagasaki cancer registries, and those whose diagnosis was obtained only from an autopsy, our analytic dataset included a total of $n = 9{,}164$ participants. Individuals were also excluded from the current analysis for having a cancer ascertained only through a death certificate (without additional information in cancer registries, $n = 703$), or for having missing data on radiation dose ($n = 733$), resulting in a final analytic dataset of $n = 7{,}728$ participants.

Data elements

Study data pertaining to the cancers of interest included anatomic site of cancer [stomach; International Classification of Disease, 10th revision (ICD10): C16; colon: C18, and rectum: C19–21], stage at diagnosis (localized, invasive to lymph-node or regional organs, metastasis, and unknown), and age/date at diagnosis. Information on vital status and, as applicable, underlying cause and date of death were obtained via linkage with national death records.

Table 1. Characteristics of gastrointestinal cancer cases by specific cancer diagnosis, LSS.

	Cancer site			
	Stomach $n = 5{,}022$	**Colon** $n = 1{,}753$	**Rectal** $n = 953$	**Overall** $N = 7{,}728$
City				
Hiroshima	3,761 (74.9%)	1,225 (69.9%)	662 (69.5%)	5,648 (73.1%)
Nagasaki	1,261 (25.1%)	528 (30.1%)	291 (30.5%)	2,080 (26.9%)
Sex				
Male	2,792 (55.6%)	719 (41.0%)	479 (50.3%)	3,990 (51.6%)
Female	2,230 (44.4%)	1,034 (59.0%)	474 (49.7%)	3,738 (48.4%)
Age at exposure (birth year)				
<20 years (1926–1945)	1,627 (32.4%)	782 (44.6%)	433 (45.4%)	2,842 (36.8%)
20–39 years (1905–1925)	2,018 (40.2%)	737 (42.0%)	342 (35.9%)	3,097 (40.1%)
≥40 years (≤1904)	1,377 (27.4%)	234 (13.3%)	178 (18.7%)	1,789 (23.2%)
Age at diagnosis				
<60 years	1,149 (22.9%)	254 (14.5%)	192 (20.1%)	1,595 (20.6%)
60–69 years	1,541 (30.7%)	529 (30.2%)	320 (33.6%)	2,390 (30.9%)
70–79 years	1,551 (30.9%)	586 (33.4%)	301 (31.6%)	2,438 (31.5%)
≥80 years	781 (15.6%)	384 (21.9%)	140 (14.7%)	1,305 (16.9%)
Year of diagnosis				
1958–1968	924 (18.4%)	83 (4.7%)	102 (10.7%)	1,109 (14.4%)
1969–1978	1,019 (20.3%)	171 (9.8%)	122 (12.8%)	1,312 (17.0%)
1979–1988	1,070 (21.3%)	308 (17.6%)	187 (19.6%)	1,565 (20.3%)
1989–1998	1,039 (20.7%)	569 (32.5%)	274 (28.8%)	1,882 (24.4%)
1999–2009	970 (19.3%)	622 (35.5%)	268 (28.1%)	1,860 (24.1%)
Radiation dose (Gy)				
Not in city	1,213 (24.2%)	433 (24.7%)	216 (22.7%)	1,862 (24.1%)
<0.005	1,602 (31.9%)	558 (31.8%)	326 (34.2%)	2,486 (32.2%)
0.005–0.49	1,884 (37.5%)	642 (36.6%)	356 (37.4%)	2,882 (37.3%)
0.5–0.99	175 (3.5%)	67 (3.8%)	37 (3.9%)	279 (3.6%)
≥1	148 (2.9%)	53 (3.0%)	18 (1.9%)	219 (2.8%)
Smoking status[a]				
Never smoker	1,292 (39.2%)	699 (55.4%)	294 (46.7%)	2,285 (44.0%)
Former smoker	548 (16.6%)	191 (15.1%)	119 (18.9%)	858 (16.5%)
Current smoker	1,460 (44.2%)	372 (29.5%)	216 (34.3%)	2,048 (39.5%)
Unknown	1,722	491	324	2,537
Alcohol consumption[a]				
Never drinker	1,239 (44.7%)	611 (51.0%)	250 (41.9%)	2,100 (46.0%)
Former drinker	246 (8.9%)	101 (8.4%)	58 (9.7%)	405 (8.9%)
Current drinker	1,286 (46.4%)	485 (40.5%)	288 (48.3%)	2,059 (45.1%)
Unknown	2,251	556	357	3,164
Stage at diagnosis				
Localized	1,355 (50.0%)	714 (47.3%)	304 (45.9%)	2,373 (48.6%)
Regional	786 (29.0%)	520 (34.5%)	267 (40.3%)	1,573 (32.2%)
Metastatic	571 (21.1%)	274 (18.2%)	92 (13.9%)	937 (19.2%)
Unknown	2,310	245	290	2,845

[a]Smoking status and alcohol consumption recorded at the time of the questionnaire collected in closest proximity prior to cancer diagnosis.

Data analysis

We used Cox regression models to examine the association between prediagnosis exposure to radiation from the atomic bombings and survival after subsequent diagnosis of gastrointestinal cancer. In all analyses, the primary time scale was time since cancer diagnosis. We conducted separate analyses for each cancer site using organ-specific radiation dose in Gy (i.e., stomach dose for stomach cancer, colon dose for colon cancer and rectal cancer), and categorized into four exposure levels (<0.005, 0.005–0.49, 0.5–0.99, ≥1.0 Gy). NIC residents were included in a separate stratum, given prior evidence that their survival experience might differ from in-city survivors (16). In primary analyses, the outcome of interest was defined as cancer-specific mortality (e.g., stomach cancer death among patients with stomach cancer); individuals with deaths due to other causes were censored at the time of death. We also conducted secondary analyses evaluating all-cause mortality as the outcome of interest.

We adjusted for city (Hiroshima, Nagasaki), sex, age at cancer diagnosis (as a continuous variable), and calendar year of diagnosis (as a continuous variable). In sensitivity analyses, we removed age and year at cancer diagnosis from the model and instead controlled for age at time of bombing (as a continuous variable), which is equivalent to birth year since all survivors were exposed in 1945. In addition, we performed analyses restricted to participants with nonmissing smoking and alcohol data, and additionally controlled for smoking status (never, former, current) and alcohol consumption (never, former, current).

Although information regarding stage at diagnosis was available only for study participants with more recent cancer diagnoses (since 1985 for the Nagasaki Cancer Registry and 1992 for the Hiroshima Cancer Registry), using these data, we conducted stage-stratified analyses to assess potential differences in radiation-survival associations according to cancer stage.

Results

Of the gastrointestinal cancers under consideration ($n = 7{,}728$), the most common cancer was stomach cancer (65.0% of participants), followed by colon (22.7%) and rectal (12.3%) cancers. The study population had an even distribution of sex, with 51.6% of all patients documented as male; across included cancer sites, this proportion ranged from 41.0%–55.6%. Most patients in this study were under the age of 40 years at the time of the atomic bombings (76.9%; range, 72.6%–86.6%). Few patients were diagnosed before age 60 years (20.6%; range, 14.5%–22.9%), with the largest proportion of cases

Table 2. Association of atomic bomb radiation dose with survival after cancer diagnosis[a].

	Disease-specific survival		Overall survival	
	Deaths, *n*/ Total *N*	**HR (95% CI)**	**Deaths, *n*/ Total *N***	**HR (95% CI)**
Stomach cancer				
Radiation dose, Gy				
Not in city	659/1,213	0.97 (0.88–1.08)	1,083/1,213	0.99 (0.91 to 1.07)
<0.005	882/1,584	Reference	1,394/1,584	Reference
0.005–0.49	1,060/1,887	1.04 (0.95–1.14)	1,638/1,887	1.03 (0.96–1.11)
0.5–0.99	91/184	0.87 (0.70–1.08)	159/184	0.99 (0.84–1.17)
≥1.0	83/154	1.03 (0.82–1.29)	141/154	1.25 (1.05–1.49)
Nagasaki vs. Hiroshima	702/1,261	1.16 (1.06–1.26)	1,089/1,261	1.13 (1.06–1.22)
Female vs. male	1,218/2,230	0.91 (0.84–0.98)	1,974/2,230	0.84 (0.79–0.90)
Age at diagnosis	Per 10 years	1.31 (1.26–1.36)	Per 10 years	1.60 (1.55–1.65)
Year of diagnosis	Per 10 years	0.67 (0.65–0.69)	Per 10 years	0.70 (0.69–0.72)
Colon cancer				
Radiation dose, Gy				
Not in city	155/433	1.01 (0.82–1.25)	312/433	1.04 (0.89–1.20)
<0.005	200/558	Reference	420/558	Reference
0.005–0.49	223/642	0.96 (0.79–1.17)	504/642	1.04 (0.91–1.19)
0.5–0.99	20/67	0.81 (0.51–1.29)	46/67	0.92 (0.68–1.25)
≥1.0	24/53	1.38 (0.90–2.12)	49/53	1.35 (1.00–1.82)
Nagasaki vs. Hiroshima	185/538	1.04 (0.87–1.24)	401/538	1.09 (0.97–1.23)
Female vs. Male	375/1034	0.97 (0.82–1.14)	783/1,034	0.79 (0.70–0.88)
Age at diagnosis	Per 10 years	1.35 (1.24–1.46)	Per 10 years	1.74 (1.64–1.85)
Year of diagnosis	Per 10 years	0.78 (0.72–0.83)	Per 10 years	0.73 (0.69–0.76)
Rectal cancer				
Radiation dose, Gy				
Not in city	85/216	0.92 (0.69–1.21)	172/216	0.98 (0.80–1.20)
<0.005	129/326	Reference	249/326	Reference
0.005–0.49	141/356	0.89 (0.69–1.14)	274/356	0.93 (0.77–1.11)
0.5–0.99	15/37	0.86 (0.50–1.47)	30/37	0.86 (0.59–1.26)
≥1.0	7/18	1.06 (0.49–2.28)	15/18	1.56 (0.92–2.64)
Nagasaki vs. Hiroshima	102/291	0.84 (0.66–1.07)	217/291	0.94 (0.80–1.11)
Female vs. male	182/474	0.88 (0.72–1.08)	370/474	0.79 (0.68–0.92)
Age at diagnosis	Per 10 years	1.25 (1.13–1.38)	Per 10 years	1.73 (1.60–1.87)
Year of diagnosis	Per 10 years	0.68 (0.63–0.73)	Per 10 years	0.71 (0.67–0.75)

[a]All analyses were adjusted for city, sex, age at diagnosis, and year of diagnosis.

Table 3. Association of atomic bomb radiation dose with survival after cancer diagnosis by cancer site and stage at diagnosis (diagnosis years 1985–2009)[a].

	Disease-specific survival		Overall survival	
Radiation dose (Gy)	**Deaths, *n*/ Total *N***	**HR (95% CI)**	**Deaths, *n*/ Total *N***	**HR (95% CI)**
Localized stage				
Stomach cancer				
Not in city	31/297	0.66 (0.43–1.03)	218/297	0.93 (0.78–1.11)
<0.005	56/438	Reference	297/438	Reference
0.005–0.49	56/531	0.79 (0.54–1.16)	347/531	0.86 (0.74–1.01)
0.5–0.99	4/44	0.63 (0.23–1.75)	29/44	0.92 (0.63–1.35)
≥1.0	7/45	1.39 (0.63–3.08)	37/45	1.78 (1.26–2.50)
Colon cancer				
Not in city	23/173	0.94 (0.54–1.63)	102/173	0.99 (0.76–1.28)
<0.005	31/222	Reference	137/222	Reference
0.005–0.49	31/274	0.71 (0.43–1.18)	182/274	0.97 (0.77–1.21)
0.5–0.99	3/30	0.76 (0.23–2.50)	17/30	1.02 (0.61–1.69)
≥1.0	3/15	1.44 (0.44–4.71)	13/15	1.33 (0.75–2.35)
Rectal cancer				
Not in city	10/67	1.17 (0.50–2.72)	47/67	1.13 (0.77–1.68)
<0.005	15/106	Reference	68/106	Reference
0.005–0.49	12/114	0.80 (0.36–1.78)	63/114	0.82 (0.57–1.19)
0.5–0.99	3/13	1.32 (0.37–4.69)	8/13	0.93 (0.44–1.97)
≥1.0	3/4	10.9 (2.89–40.8)	4/4	6.99 (2.45–19.9)
Regional stage				
Stomach cancer				
Not in city	106/180	1.12 (0.87–1.45)	164/180	1.17 (0.96–1.44)
<0.005	148/259	Reference	231/259	Reference
0.005–0.49	173/284	1.21 (0.97–1.52)	247/284	1.12 (0.93–1.34)
0.5–0.99	15/31	0.72 (0.42–1.23)	24/31	0.79 (0.52–1.20)
≥1.0	21/32	1.29 (0.82–2.05)	29/32	1.37 (0.93–2.02)
Colon cancer				
Not in city	55/135	1.27 (0.87–1.85)	91/135	1.03 (0.78–1.36)
<0.005	55/159	Reference	118/159	Reference
0.005–0.49	70/184	1.22 (0.85–1.75)	147/184	1.24 (0.97–1.59)
0.5–0.99	4/19	0.61 (0.22–1.71)	13/19	0.93 (0.52–1.67)
≥1.0	10/23	1.15 (0.58–2.29)	21/23	1.14 (0.71–1.83)
Rectal cancer				
Not in city	23/55	1.06 (0.63–1.78)	41/55	0.96 (0.65–1.42)
<0.005	41/105	Reference	77/105	Reference
0.005–0.49	43/90	1.14 (0.74–1.78)	67/90	0.97 (0.69–1.36)
0.5–0.99	6/10	0.99 (0.39–2.47)	8/10	1.11 (0.52–2.35)
≥1.0	1/7	0.28 (0.04–2.07)	5/7	0.92 (0.37–2.29)
Metastatic stage				
Stomach cancer				
Not in city	137/144	1.07 (0.85–1.34)	143/144	1.06 (0.85–1.32)
<0.005	168/181	Reference	180/181	Reference
0.005–0.49	184/201	1.06 (0.86–1.31)	198/201	1.08 (0.88–1.33)
0.5–0.99	22/25	1.60 (1.02–2.50)	25/25	1.71 (1.12–2.61)
≥1.0	16/20	0.92 (0.55–1.55)	20/20	1.07 (0.67–1.71)
Colon cancer				
Not in city	56/73	0.83 (0.58–1.18)	70/73	0.95 (0.68–1.31)
<0.005	72/84	Reference	81/84	Reference
0.005–0.49	79/97	0.98 (0.70–1.36)	95/97	1.06 (0.78–1.43)
0.5–0.99	7/9	1.29 (0.59–2.86)	9/9	1.45 (0.72–2.93)
≥1.0	9/11	1.51 (0.74–3.08)	11/11	1.43 (0.75–2.74)
Rectal cancer				
Not in city	20/27	1.15 (0.62–2.13)	27/27	1.22 (0.71–2.09)
<0.005	24/35	Reference	31/35	Reference
0.005–0.49	17/23	1.15 (0.61–2.18)	22/23	1.19 (0.68–2.09)
0.5–0.99	2/3	0.87 (0.19–3.87)	3/3	1.16 (0.34–4.01)
≥1.0	2/4	0.61 (0.14–2.64)	3/4	0.71 (0.21–2.43)

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Table 3. Association of atomic bomb radiation dose with survival after cancer diagnosis by cancer site and stage at diagnosis (diagnosis years 1985–2009)[a]. (Cont'd)

	Disease-specific survival		Overall survival	
Radiation dose (Gy)	**Deaths, *n*/ Total *N***	**HR (95% CI)**	**Deaths, *n*/ Total *N***	**HR (95% CI)**
Unknown stage				
Stomach cancer				
Not in city	385/592	0.98 (0.78–1.23)	558/592	1.00 (0.83–1.21)
<0.005	510/706	Reference	686/706	Reference
0.005–0.49	647/871	1.04 (0.86–1.26)	846/871	1.05 (0.90–1.23)
0.5–0.99	50/84	0.73 (0.45–1.19)	81/84	0.80 (0.54–1.17)
≥1.0	39/57	0.72 (0.37–1.41)	55/57	1.00 (0.63–1.60)
Colon cancer				
Not in city	21/52	0.66 (0.38–1.15)	49/52	0.97 (0.66–1.21)
<0.005	42/93	Reference	84/93	Reference
0.005–0.49	43/87	0.99 (0.63–1.57)	80/87	0.92 (0.66–1.30)
0.5–0.99	6/9	0.91 (0.37–2.21)	7/9	0.66 (0.30–1.46)
≥1.0	2/4	1.19 (0.27–5.21)	4/4	2.25 (0.78–6.48)
Rectal cancer				
Not in city	32/67	1.02 (0.50–2.08)	57/67	1.30 (0.75–2.28)
<0.005	49/80	Reference	73/80	Reference
0.005–0.49	69/129	0.90 (0.49–1.63)	122/129	1.29 (0.81–2.04)
0.5–0.99	4/11	0.29 (0.07–1.23)	11/11	0.64 (0.28–1.46)
≥1.0	1/3	4.49 (0.51–39.25)	3/3	2.19 (0.27–17.48)

[a]All analyses were adjusted for city, sex, age at diagnosis, and year of diagnosis. Stage data were available from the Hiroshima Cancer Registry beginning in 1985, and from the Nagasaki Cancer Registry beginning in 1992.

being diagnosed between ages 70 and 79 years (31.5%; range, 30.9%–33.4%). Among those who were exposed to radiation from the atomic bombs, most were exposed to 0.005–0.49 Gy (37.3%; range, 36.6%–37.5%), with a small proportion exposed to a dose ≥1 Gy (2.8%; range 1.9%–3.0%; **Table 1**). Among those with known stage at diagnosis, almost half were diagnosed at a localized stage (range, 45.9%–50.0%), while 19.2% were diagnosed at a metastatic stage (range, 13.9%–21.1%). The proportion of patients diagnosed at a metastatic stage was highest among those with the highest levels of radiation exposure (28.3%; Supplementary Table S1).

Radiation dose was not significantly associated with disease-specific survival, regardless of cancer site. A dose of 0.5–0.99 Gy was associated with slightly, but not statistically significantly, more favorable disease-specific survival for stomach cancer [HR, 0.87 (95% confidence interval (CI), 0.70 - 1.08)], colon cancer (HR, 0.81; 95% CI, 0.51–1.29), and rectal cancer (HR, 0.86; 95% CI, 0.50–1.47) compared with those exposed to 0–0.005 Gy of radiation (**Table 2**). High doses of radiation (≥1.0 Gy) were suggestively associated with poorer disease-specific survival for colon cancer (HR, 1.38; 95% CI, 0.90–2.12), but again this association was not statistically significant. Doses of greater than 1.0 Gy were associated with poorer all-cause survival for stomach (HR, 1.25; 95% CI, 1.05–1.49) and colon cancer (HR, 1.35; 95% CI, 1.00–1.82), with a similar but not statistically significant association for rectal cancer (HR, 1.56; 95% CI, 0.92–2.64; **Table 2**).

Similar patterns were observed with adjustment for age at time of bombing instead of age and year at cancer diagnosis, and again associations were not statistically significant (Supplementary Table S2). Results from analyses restricted to those with nonmissing smoking and alcohol data and adjusted for smoking status and alcohol consumption and were very similar to those from analyses not including these factors (Supplementary Table S3).

In combined analyses of all cancer sites stratified by stage at diagnosis (**Table 3**), we found that high levels of radiation exposure (≥1 Gy) were suggestively associated with poorer survival for individuals with cancer diagnosed at a localized stage; however, this association was significant for rectal cancer only and were based on small numbers.

Discussion

In this large, prospective cohort study of atomic bomb survivors diagnosed with gastrointestinal cancers, we found that exposure to radiation from the atomic bombings of Hiroshima and Nagasaki was not statistically significantly associated with subsequent cancer survival. This study draws on the strengths of the data-rich LSS cohort, with more than 50 years of follow-up and nearly complete vital status ascertainment and high-quality cancer case ascertainment. Each individual in our study had an individually calculated radiation dose based on distance from the hypocenter and shielding.

Gastrointestinal cancer is the second leading cause of cancer-related deaths in the world, with the highest mortality rates observed in Eastern Asia. In Japan, deaths from stomach, colon, and rectal cancers account for almost 14% of all cancer-related deaths. Within the LSS cohort, radiation exposure has previously been found to be associated with increased incidence and mortality of stomach and colon cancers (4, 5). Thus, the burden of gastrointestinal cancers in the LSS is high: stomach cancer accounts for more than 25% of all cancer cases within the cohort (17), whereas colon and rectal cancers account for 9% and 5% of all cancer cases in the LSS, respectively. Given this high burden, any association between radiation dose and gastrointestinal cancer survival would be of considerable impact. However, our results suggest that if such an association exists, it is likely to be modest.

Our findings should be interpreted in the context of study limitations. In particular, some data elements in the LSS are incomplete. Data on stage at diagnosis were unavailable for earlier diagnosis years (Nagasaki: 1958–1984; Hiroshima: 1958–1991), because cancer registries did not obtain clinical stage information during this time. Analyses of disease-specific survival are subject to lower statistical power than analyses of overall survival and rely on accurate reporting of cause of death (18).

Lifestyle factors known to be associated with gastrointestinal cancer incidence and survival, such as smoking and alcohol consumption, could influence the results of this study. However, collection of these data in the LSS began in the late 1970s. As such, data completeness is highly dependent on an individual's survival and age at that time, with about 60% of LSS participants having ever completed a survey (3). However, adjustment for smoking and alcohol consumption status (where available) had minimal impact on study findings, suggesting that results of our primary analyses are unlikely to be biased due to missing smoking and alcohol data.

There is strong evidence that exposure to radiation increases cancer incidence and mortality rates, especially among survivors of the Hiroshima and Nagasaki atomic bombings. Atomic bomb survivors receive regular health checkups and may be more likely to receive routine cancer screening. Since 1983, stomach, colon, and rectal cancers have been routinely screened for in Japan via nationwide programs targeting individuals aged 40 years and older, with around 4 million people participating each year (19). Such screening efforts could, in theory, lead to earlier detection of cancer which, in turn, could contribute to better chances of cancer survival. However, among the LSS members included in the present study we observed that, if anything, those with higher radiation exposure levels were more likely to have been diagnosed with metastatic, advanced stage disease (Supplementary Table S1). This observation suggests an alternative possibility that prior radiation exposure may contribute to more aggressive, metastatic disease. Still, despite the fact that individuals with higher radiation exposure levels had, on average, more advanced stage at diagnosis, we did not observe statistically significant differences in survival by radiation dose in the current analysis.

In conclusion, the results of this study indicate no statistically significant association between gastrointestinal cancer survival and prediagnostic radiation dose from the atomic bombings. Very few studies have examined the relationship between radiation exposure preceding cancer diagnosis and subsequent cancer survival, and more studies involving different cancer sites are needed to improve our understanding of a potential relationship. In particular, future studies examining potential differences in tumor biology according to past radiation exposure could provide critical information.

Authors' Disclosures

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Authors' Contributions

B. Bockwoldt: Formal analysis, writing–original draft, writing–review and editing. **H. Sugiyama:** Conceptualization, resources, data curation, supervision, methodology, project administration, writing–review and editing. **K. Tsai:** Formal analysis, methodology, writing–original draft, writing–review and editing. **P. Bhatti:** Resources, supervision, project administration, writing–review and editing. **A.V. Brenner:** Conceptualization, data curation, methodology, writing–review and editing. **A. Hu:** Methodology, writing–review and editing. **K.F. Kerr:** Formal analysis, supervision, methodology, writing–review and editing. **E. Morenz:** Formal analysis, methodology, writing–review and editing. **B. French:** Conceptualization, resources, supervision, methodology, writing–review and editing. **A.I. Phipps:** Conceptualization, resources, supervision, methodology, writing–original draft, project administration, writing–review and editing.

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