Gastrointestinal Cancer Survival Among Atomic Bomb Survivors

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Abstract

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Radiation exposure is a strong, established risk factor for the development of several forms of cancer, including gastrointestinal cancers. However, few studies have investigated the relationship between pre-diagnostic radiation exposure and survival after cancer diagnosis. Using data from the Life Span Study (LSS) of atomic bomb survivors, we identified N=8,461 LSS participants diagnosed with a first primary invasive stomach or colorectal cancer (CRC) between 1958-2009. Cancer incidence data were linked with mortality data for years 1958-2014. Cox regression was used to calculate hazard ratios and 95% confidence intervals for associations of radiation dose due to atomic bomb exposure with overall survival (i.e., death from any cause) and gastrointestinal cancer-specific survival (i.e., death attributed to CRC or stomach cancer) after cancer diagnosis. Analyses were adjusted for age at diagnosis, year of diagnosis, and sex. Among LSS participants with a gastrointestinal cancer, data showed significantly more favorable survival for combined gastrointestinal cancers for individuals exposed to 0.50 – 0.99 Gy and modestly poorer survival among those exposed to higher levels of radiation (≥1 Gy) compared to those with no to very low exposure (<0.005 Gy), with associations differing across gastrointestinal cancer sites. Similar associations, although not statistically significant, were observed in stratified analyses restricted to those with stomach cancer and colon cancer. No associations were observed in analyses of LSS members with rectal cancer. In addition to the established increased risk of cancer, these results suggest that pre-diagnostic radiation exposure may affect survival after gastrointestinal cancer diagnosis for certain cancer sites.

Introduction

Exposure to ionizing radiation is an established risk factor for several forms of cancer, including gastrointestinal cancers (Schottenfeld & Fraumeni, 2006). In particular, exposure to radiation from the 1945 atomic bombs in Japan has been associated with increased incidence and mortality for stomach and colon cancers, but not for rectal cancers (Sugiyama et al. 2019).

In addition to its demonstrated effects on cancer development, radiation may also plausibly contribute to cancer outcomes – either via the effects of radiation on the biology and clinicopathology of tumors in those exposed to radiation, or via the effects of radiation exposure knowledge on cancer screening behavior. To date, however, few studies have considered the extent to which past exposure to radiation is associated with survival after subsequent cancer diagnosis. One prior study found poorer gastric cancer survival in patients who were atomic bomb survivors compared to gastric cancer patients who had not been exposed to the atomic bomb (Yamamoto et al. 2009; Yamamoto et al. 2013). Another study of prostate cancer observed no statistically significant difference in survival between cancer cases who were atomic bomb survivors and cancer cases not exposed to radiation from this event; however, there is mixed evidence for the sensitivity of prostate tissue to ionizing radiation (Shoji et al. 2017; Preston et al. 2007). To our knowledge, associations specific to other cancer sites have not been explored and associations with radiation dose have not been considered.

To address this gap in knowledge, we undertook an analysis comparing survival outcomes in atomic bomb survivors diagnosed with gastrointestinal cancers after the atomic bomb in relation to their past radiation exposure dose.

Methods and Materials

Study Setting:

The Life Span Study (LSS) is a cohort of 93,741 Japanese individuals who survived the atomic bombs of Hiroshima and Nagasaki in 1945 and who still resided within these cities in 1950 (Ozasa et al. 2018). This cohort also includes 26,580 participants who were residents of Hiroshima or Nagasaki during 1950-1952, but who were not in city (NIC) at the time of the bombings (Ozasa et al. 2018). 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 (Ozasa et al. 2018). Radiation dose received from the atomic bomb was estimated for each participant in this cohort, based on distance from the hypocenter at the time of the blast and shielding conditions according to DS0R2 (Preston et al. 2007). Data have been collected for this cohort through several surveys, dating back to 1950, and via ongoing linkage with cancer registries and death registries, since 1958 (Ozasa et al. 2018).

Study Inclusion:

To investigate the relationship between past radiation exposure and cancer survival, we identified LSS participants who were diagnosed with a first primary invasive cancer of the stomach, colon, or rectum during study follow-up, based on linkage with the Hiroshima and Nagasaki cancer registries (1958-2009). Cancer incidence data were then linked with national mortality data (1958-2014). LSS participants not identified as having experienced a cancer diagnosis at one of these anatomic sites were excluded from the present analysis. From among the 120,321 subjects in the LSS, we identified 10,626 subjects who were diagnosed with a first primary stomach or colorectal cancer. After excluding subjects who were not diagnosed between 1958 and 2009, those who were diagnosed outside of the catchment areas for the Hiroshima or Nagasaki cancer registries, those who were diagnosed by autopsy only, and those who were death certificate only cases, our analytic dataset included 8,461 subjects.

Study Data:

Study data pertaining to the cancers of interest were obtained from the Hiroshima and Nagasaki cancer registries, including information on cancer site, sequence number of the cancer, stage at diagnosis, confirmation of diagnosis (verified histologically, clinically, death certificate, etc.), date of diagnosis (year and month), age at diagnosis, and data source (abstraction of medical chart, tissue registry, report from hospitals, etc.). Information regarding vital status and, as applicable, cause and date (month and year) of death were obtained via linkage with national death records. Demographic data, including participant sex, year and month of birth, time of entry into the cohort (year and month), age and location at the time of the atomic bomb (city, distance from the hypocenter), as well as estimated organ-specific radiation doses were previously collected as part of the LSS (Ozasa et al. 2018). Information regarding other demographic and lifestyle factors was previously obtained from LSS questionnaires, including smoking history, alcohol intake, and socioeconomic factors (e.g., education level) (Grant et a. 2017).

Data Analysis:

Within this cohort of individuals who experienced a cancer diagnosis during follow-up, we conducted a series of survival analyses using Cox proportional hazards regression. Under these survival analysis models, the time axis was defined as time since cancer diagnosis with the exposure being radiation dose. We conducted analyses of all gastrointestinal cancers combined, as well as separate analyses of individuals diagnosed with stomach cancer, colon cancer, and rectal cancer. Each cancer site was linked to the estimated dosage of the specified organ (i.e., colon dose for colon cancer, stomach dose for stomach cancer, bladder dose for rectal cancer) and colon dose was used for analyses of combined gastrointestinal cancers. For each cancer site, we conducted analyses of disease-specific survival, in which the outcome of interest was defined as death from cancer at the analysis-specific site (e.g., stomach cancer death); in such analyses, individuals with deaths due to other causes were censored at the time of death. We also conducted secondary analyses using overall survival (OS), in which the outcome was death from any cause during study follow-up.

In all analyses, we adjusted for age at cancer diagnosis, year at diagnosis, and sex. Information regarding stage at diagnosis was available only for study participants with more recent cancer diagnoses (1985 for the Nagasaki Cancer Registry and 1992 for the Hiroshima Cancer Registry through 2014). However, using these limited data, we constructed stage-stratified analysis models to assess any differential associations according to stage. Based on our hypothesis that past radiation exposure may impact future cancer survival via an impact on tumor aggressiveness, we also examined differences in the distribution of cancer stage at diagnosis according to radiation exposure.

Results

Among the 8,461 participants included in the present study, the vast majority were in Hiroshima or Nagasaki at the time of the bombings (83.9%). Among those who were exposed to radiation from the atomic bombs, most were exposed to 0.005 – 0.49 Gy (32.2%) with a small proportion having experienced a dose ≥1 Gy (2.4%) (Table 1). This study population had an even distribution of sex, with 51.3% of all participants identifying as male. Most participants in this study were under the age of 40 years old at the time of the atomic bombs (73.1%). Among the participants for whom we had stage data available, for the majority were diagnosed at a localized stage (46.7%) while 19% were diagnosed at a metastatic stage. The proportion of patients diagnosed at a metastatic stage was highest among those with the highest levels of radiation exposure (25.2%).

With respect to age at cancer diagnosis, few participants were diagnosed before age 60 (19.6%) with the majority of cases being diagnosed between ages 70-79 (31.2%). Of the included gastrointestinal cancers, the most common cancer site within this study was stomach cancer (65.8% of participants), followed by colon (22.2%) and rectal (12%) cancers.

When comparing participants exposed to 0.5 – 0.99 Gy of radiation to those with 0-0.005 Gy of radiation in analyses of all gastrointestinal cancers combined, those with higher levels of radiation exposure had statistically significant better disease-specific survival [hazard ratio (HR):0.80, 95% Confidence Interval (CI): 0.67 – 0.96] (Table 2). Similar associations, although not statistically significant, were observed in stratified analyses restricted to those with stomach cancer [HR:0.83 (95% CI: 0.68 – 1.03)] and colon cancer [HR:0.72 (95% CI: 0.46 – 1.13)]. In contrast, high levels of radiation exposure (≥1.0 Gy) were suggestively associated with poorer survival in analyses of all gastrointestinal cancers combined [HR:1.11 (95% CI: 0.93-1.34)], but particularly for those with colon cancer [HR: 1.41 (95% CI: 0.95 – 2.09)]. No associations were observed in analyses of LSS members with rectal cancer; however, this was also the smallest case group.

In analyses of all cancer sites combined stratified by stage at diagnosis (Table 3), those with gastrointestinal cancer diagnosed at a localized stage who had moderate levels of radiation exposure (0.005 – 0.49 Gy) had statistically significant better disease-specific survival [HR:0.74 (95% CI: 0.59 – 0.94)] compared to those diagnosed at the same stage but with lower radiation dose; results were similar but not statistically significant for those with 0.5-0.99 Gy exposure within this stage strata. We also found that high levels of radiation exposure (≥1 Gy) were associated with poorer survival among those with gastrointestinal cancers classified as localized or invasive, NOS (i.e., not otherwise specified) at the time of diagnosis; however, these associations were not statistically significant (Table 3).

In our secondary analysis of overall survival, participants who were exposed to high levels of radiation (≥1.0 Gy) and survived long enough to be diagnosed with a gastrointestinal cancer had better subsequent survival when compared to participants with gastrointestinal cancer exposed to 0 - 0.005 Gy of radiation. This was true in analyses of stomach and colon cancers, but not in analyses restricted to those with rectal cancer (Table 4). In contrast, participants with gastrointestinal cancer who had been exposed to 0.005 – 0.49 Gy were observed to have worse overall survival when compared to participants who were exposed to 0-0.005 Gy of radiation. Those who experienced 0.5-0.99 Gy of radiation also had statistically significant poorer overall survival when compared to participants who experienced 0-0.005 Gy of radiation [HR: 2.64 (95% CI: 1.61 – 4.32)].

Discussion

In this large, prospective cohort study of atomic bomb survivors diagnosed with gastrointestinal cancers, we found that exposure to radiation from the atomic bombs of Hiroshima and Nagasaki was not statistically significantly associated with subsequent cancer survival. One exception to this overall finding was the observation of modestly more favorable cancer-specific survival among those exposed to 0.50 - 0.99 Gy of radiation; this association was similar, although not statistically significant, across included cancer sites. High (≥1.0 Gy) levels of radiation exposure were suggestively associated with poorer survival for colon and rectal cancers.

Gastrointestinal cancer is the second leading cause of cancer deaths in the world (Hamashima 2014). The highest mortality rates of gastrointestinal cancer are found in Eastern Asia (Hamashima 2014). Incidence rates are around three times higher for men than they are women (Hamashima 2014). In Japan, gastric cancer deaths account for almost 14% of all cancer deaths (Hamashima 2014).

Radiographic screening for gastrointestinal cancer was developed in Japan in the 1960’s (Hamashima 2014). However, nationwide cancer screening programs were not started until 1983. Screening technology has improved in the interim, and since the 2000’s screening has moved to digital imaging using high density barium (Hamashima 2014). Stomach, colon, and rectal cancers are routinely screened through nationwide screening programs with one-year intervals (Hamashima 2014). These nationwide screening programs target individuals 40 years and older (Hamashima 2014). Around 4 million people participate in Japan's nationwide screening program every year. Endoscopic screening was not recommended by the Japanese nationwide screening program until recent years, and studies have reported higher detection rates and earlier diagnosis for endoscopic screening than radiographic screening (Hamashima 2014).

Within the LSS cohort, radiation exposure has been found to be associated with increased incidence and mortality for stomach and colon cancers, but not for rectal cancers (Sugiyama et al. 2019, Ozasa 2018). Previous studies have found that the incidence of colon cancer increased with increased dosage of radiation levels, along with the mortality rates (Sugiyama 2019). Stomach cancer is the most common cancer in the LSS cohort, accounting for more than 25% of all cancer cases within the cohort (Preston 2007). Colon and rectal cancers are other common cancers among survivors with 9% of all cancer cases being colon cancer and 5% of all cases being rectal cancer. Incidence rates for colorectal cancers are comparable in Hiroshima and Nagasaki (Sugiyama 2019).

Our findings should be interpreted in the context of study limitations. In particular, some data elements in the LSS are incomplete (Sugiyama et al. 2019). Data on stage at diagnosis were systematically missing for earlier diagnosis years (Nagasaki: 1958-1985, Hiroshima: 1958-1992). Analyses of disease-specific survival rely on accurate reporting of cause of death and are subject to lower statistical power (Takamori et al. 2016). There is also a known stigma around cancer for atomic bomb survivors. It has been documented that people may have listed the primary cause of death on official documents (e.g., death certificates) as a cause other than cancer to avoid this stigma (Takamori et al. 2016). With this knowledge, we know that this study is prone to misclassification and some cancer deaths may not be captured in this study. Associations with overall survival are not subject to this misclassification; however, associations with overall survival are likely to be less sensitive than those with disease-specific survival, given the relationship of radiation exposure to numerous potential causes of death. Furthermore, analyses of overall survival within the present study cohort were contingent on study participants having survived long enough to have been diagnosed with a gastrointestinal cancer, thus limiting their interpretability due to competing risks. Those who have survived long enough to be diagnosed with gastrointestinal cancer may be biologically different than those who died from other causes before having the opportunity to be diagnosed with such cancers.

This study draws on the strengths of the rich LSS cohort. The LSS has more than 50 years of follow-up with nearly complete vital status ascertainment and high-quality cancer case ascertainment. This cohort has more than 120,000 participants, including the 8,461 included in the present study. Each individual in our study had an individually calculated radiation dose estimate based on their distance from the hypocenter and shielding mechanism (Ozasa et al. 2018).

There is strong evidence that exposure to radiation increases cancer incidence and mortality rates, especially among survivors of the Hiroshima and Nagasaki atomic bombs. With the known concern of cancer and other health effects, atomic bomb survivors receive regular health checkups and may be more likely to receive routine cancer screening. Such screening efforts could 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.

Very few studies have looked at the relationship between pre-diagnosis radiation exposure and subsequent cancer survival, and more studies involving different cancer sites are needed to improve our understanding of this potential relationship. In particular, future studies examining potential differences in tumor biology according to past radiation exposure could provide critical information.

In conclusion, results from this study suggest modest differences in gastrointestinal cancer survival according to levels of pre-diagnosis radiation exposure within the Life Span Study of atomic bomb survivors. Data show significantly more favorable survival for combined gastrointestinal cancers among individuals exposed to 0.50 – 0.99 Gy and modestly poorer survival among those exposed to higher levels of radiation, with associations differing across gastrointestinal cancer sites. The results of this study are subjected to limitations of competing risk, as all analyses of disease-specific survival are based on the assumption of independent censoring. In future studies it may be worthwhile to investigate the effects competing risk have on this analysis.

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Appendix:

Table 1: Characteristics

	Dose Category						
	Total **(N=8,461)**	<0.005 **(N=2,781)**	0.005 – 0.49 **(N=3206)**	0.50 – 0.99 **(N=303)**	≥1.0 **(N=241)**	Unknown **(N=567)**	Not in City **(N=2066)**
City:							
Hiroshima	6642 (72.5)	1707 (61.4)	2610 (81.4)	204 (67.3)	174 (72.2)	300 (52.9)	1647 (79.7)
Nagasaki	2522 (27.5)	1074 (38.6)	596 (18.6)	99 (32.7)	67(27.8)	267 (47.1)	419(20.3)
Sex:							
Male	4705 (51.3)	1419 (51.0)	1591 (49.6)	156 (51.5)	126 (52.3)	321 (56.6)	1092 (52.9)
Female	4459(48.7)	1362 (49.0)	1615 (50.4)	147 (48.5)	115 (47.7)	246 (43.4)	974 (47.1)
Age at exposure:							
<20	3118 (34.0)	955 (34.3)	1058 (33.0)	124 (40.9)	93 (38.6)	199 (35.1)	689 (33.3)
20-39	3577 (39.0)	1043 (37.5)	1245 (38.8)	107 (35.3)	99 (41.1)	246 (43.4)	837 (40.5)
≥40	2469 (26.9)	783 (28.2)	903 (28.2)	72 (23.8)	49 (20.3)	122 (21.5)	540 (26.1)
Age at cancer diagnosis:							
<60	1793 (19.6)	511 (18.4)	635 (19.8)	77 (25.4)	67 (27.8)	120 (21.2)	383 (18.5)
60-69	2704 (29.5)	811 (29.2)	961 (30.0)	87 (28.7)	67 (27.8)	150 (26.5)	628 (30.4)
70-79	2942 (32.1)	944 (33.9)	992 (30.9)	91 (30.0)	71 (29.5)	189 (33.3)	655 (31.7)
≥80	1725 (18.8)	515 (18.5)	618 (19.3)	48 (15.8)	36 (14.9)	108 (19.0)	400 (19.4)
Cancer site:							
Stomach	6026 (65.8)	1821 (65.5)	2131 (66.5)	193 (63.7)	162 (67.2)	365 (64.4)	1354 (65.5)
Colon	2037 (22.2)	615 (22.1)	694 (21.6)	71 (23.4)	59 (24.5)	123 (21.7)	475 (23.0)
Rectal	1101 (12.0)	345 (12.4)	381 (11.9)	39 (12.9)	20 (8.3)	79 (13.9)	237 (11.5)
Stage at diagnosis:							
Localized	2558 (46.7)	771 (47.6)	920 (50.2)	87 (47.0)	64 (39.3)	177 (50.1)	539 (48.6)
Invasion to lymph nodes and adjacent organs	1530 (27.9)	476 (29.4)	502 (27.4)	59 (31.9)	51 (31.3)	112 (31.7)	272 (24.5)
Metastatic	1040 (19.0)	315 (19.4)	341 (18.6)	33 (17.8)	41 (25.2)	57 (22.8)	253 (22.8)
Invasive, NOS	354 (6.5)	59 (3.6)	68 (3.7)	6 (3.2)	7 (4.3)	7 (2.0)	45 (4.1)
Unknown	1693	626	542	56	26	12	322

Table 2. Association of atomic bomb radiation dose with survival after gastrointestinal cancer*

Dose category	Gastrointestinal Cancer Specific Survival	
All gastrointestinal cancer sites:	**N deaths / total N**	**HR (95% CI)‡**
<0.005	2145/2781	1.00
0.005 – 0.49	2487/3206	0.98 (0.91 – 1.05)
0.5 – 0.99	226/303	0.80 (0.67 – 0.96)*
≥1.0	206/241	1.11 (0.93 – 1.34)
Unknown	468/567	0.98 (0.86 – 1.11)
Not in city	1611/2066	0.98 (0.90 – 1.06)
Stomach cancer cases:		
<0.005	1453/1643	1.00
0.005 – 0.49	1692/1940	1.00 (0.91 – 1.09)
0.5 – 0.99	149/177	0.83 (0.68 – 1.03)
≥1.0	139/150	1.03 (0.83 – 1.28)
Unknown	314/346	0.97 (0.83 – 1.13)
Not in city	1110/1240	0.95 (0.86 – 1.04)
Colon cancer cases:		
<0.005	437/575	1.00
0.005 – 0.49	514/652	0.96 (0.80 – 1.14)
0.5 – 0.99	46/67	0.72 (0.46 – 1.13)
≥1.0	51/55	1.41 (0.95 – 2.09)
Unknown	93/121	1.04 (0.76 – 1.41)
Not in city	324/445	1.07 (0.88 – 1.29)
Rectal cancer cases:		
<0.005	255/332	1.00
0.005 – 0.49	281/363	0.91 (0.73 – 1.13)
0.5 – 0.99	31/38	0.91 (0.56 – 1.48)
≥1.0	16/19	1.01 (0.56 – 2.16)
Unknown	61/77	0.93 (0.65 – 1.34)
Not in city	177/221	1.01 (0.79 – 1.29)

*All analyses were adjusted for age at diagnosis, year at diagnosis, and sex

Table 3. Association of cancer stage on atomic bomb radiation dose with survival after gastrointestinal cancer*

Dose category	Gastrointestinal Cancer Specific Survival	
Localized:	**N deaths / total N**	**HR (95% CI)‡**
<0.005	507/771	1.00
0.005 – 0.49	593/919	0.74 (0.59 – 0.94)*
0.5 – 0.99	52/87	0.65 (0.35 – 1.19)
≥1.0	55/64	1.59 (0.95 – 2.67)
Unknown	127/177	1.01 (0.70 – 1.46)
Not in city	369/539	0.88 (0.68 – 1.14)
Invasive to regional lymph nodes and adjacent organs:		
<0.005	379/475	1.00
0.005 – 0.49	404/501	1.06 (0.88 – 1.27)
0.5 – 0.99	44/59	0.94 (0.66 – 1.41)
≥1.0	44/51	1.01 (0.67 – 1.52)
Unknown	92/112	1.36 (0.85 – 1.52)
Not in city	257/330	1.05 (0.86 – 1.29)
Invasive, NOS:		
<0.005	56/57	1.00
0.005 – 0.49	63/63	1.27 (0.84 – 1.92)
0.5 – 0.99	5/5	1.02 (0.38 – 2.73)
≥1.0	7/7	1.34 (0.51 – 3.48)
Unknown	7/7	2.87 (1.25 – 6.55)*
Not in city	42/43	1.00 (0.64 – 1.56)
Metastasis:		
<0.005	302/310	1.00
0.005 – 0.49	327/333	1.10 (0.93 – 1.30)
0.5 – 0.99	33/33	1.31 (0.88 – 1.94)
≥1.0	29/40	1.06 (0.73 – 1.52)
Unknown	57/57	1.26 (0.93 – 1.71)
Not in city	246/250	1.04 (0.87 – 1.24)

*All analyses were adjusted for age at diagnosis, year at diagnosis, and sex

Table 4. Association of atomic bomb radiation dose with survival after gastrointestinal cancer*

Dose category	Overall Survival	
All gastrointestinal cancer sites:	**N deaths / total N**	**HR (95% CI)‡**
<0.005	2145/2560	1.00
0.005 – 0.49	2487/2955	1.28 (1.11 – 1.46)
0.5 – 0.99	226/282	1.27 (0.95 – 1.70)
≥1.0	206/224	0.56 (0.35 – 0.91)
Unknown	468/544	0.97 (0.75 – 1.25)
Not in city	1611/1906	1.40 (1.20 – 1.64)
Stomach cancer cases:		
<0.005	1435/1625	1.00
0.005 – 0.49	1692/1941	1.10 (0.90 – 1.34)
0.5 – 0.99	163/188	0.86 (0.56 – 1.33)
≥1.0	143/156	0.56 (0.31 – 1.01)
Unknown	314/346	1.28 (0.86 – 1.90)
Not in city	1110/1240	1.26 (0.99 – 1.59)
Colon cancer cases:		
<0.005	437/575	1.00
0.005 – 0.49	514/652	1.44 (1.12 – 1.86)*
0.5 – 0.99	46/67	2.64 (1.61 – 4.32)*
≥1.0	51/55	0.30 (0.11 – 0.85)*
Unknown	93/121	0.51 (0.34 – 0.79)*
Not in city	324/445	1.38 (1.06 – 1.80)*
Rectal cancer cases:		
<0.005	255/332	1.00
0.005 – 0.49	281/363	0.91 (0.73 – 1.13)
0.5 – 0.99	31/38	0.91 (0.56 – 1.48)
≥1.0	16/19	1.01 (0.56 – 2.16)
Unknown	61/77	0.93 (0.65 – 1.34)
Not in city	177/221	1.01 (0.79 – 1.29)

*All analyses were adjusted for age at diagnosis, year at diagnosis, and sex

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