Effects of Radiation on the Incidence of Prostate Cancer among Nagasaki Atomic Bomb Survivors

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Running title: Prostate cancer among atomic bomb survivors

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SUMMARY

Atomic bomb survivors have been reported to have an increased risk of some cancers, especially leukemia. However, the risk of prostate cancer in atomic bomb survivors is not known to have been examined previously. This study examined the association between atomic bomb radiation and the incidence of prostate cancer among male Nagasaki atomic bomb survivors. The subjects were classified by distance from the hypocenter into a proximal group (<2 km), a distal group (≥2 km), and an early entrance group (those who entered the region <2 km from the hypocenter within 2 weeks after the explosion). Between 1996 and 2009, 631 new cases of prostate cancer were identified among approximately 18,400 male Nagasaki atomic bomb survivors who were alive in 1996. The Cox proportional hazard model was used to estimate the risk of prostate cancer development, with adjustment for age at atomic bomb explosion, attained age, smoking status, and alcohol consumption. Compared with the distal group, the proximal group had significant increased risks of total, localized, and high-grade prostate cancer (relative risk [RR] and 95% confidence interval [CI]: 1.51 and [1.21, 1.89]; 1.80 and [1.26, 2.57]; and1.88 and [1.20, 2.94], respectively). This report is the first known to reveal a significant relationship between atomic bomb radiation and prostate cancer.

Keywords: prostate cancer; atomic bomb survivors; ionizing radiation

Introduction

Prostate cancer incidence rates are much lower in Japan than in Western Europe and the USA. However, because of rapid aging, increasing “Westernization,” and the frequent use of the serum prostate-specific antigen test for prostate cancer, the age-adjusted incidence rate of prostate cancer has increased approximately 6.5 times from 1975 to 2008 and remains high today. The number of new cases was estimated to account for 51,500 in 2008 in Japan.[1]

Atomic bomb survivors have been reported to have an increased risk of many solid cancers, including lung cancer and colon cancer.[2-3] However, the risk of prostate cancer in atomic bomb survivors has not been previously reported, although the risks for bladder cancer, which involves the same urinary organ, and breast cancer, which is considered to share some biological and epidemiological features, are reported.[2-3] The small number of prostate cancer cases detected is a plausible reason for these inconsistent results.[3]

In this study, we examined whether atomic bomb radiation affected the incidence of prostate cancer among Nagasaki atomic bomb survivors. To our knowledge, this report is the first to examine the association between atomic bomb radiation and prostate cancer after its incidence began to increase.

Materials and Methods

Study group

The subjects were Nagasaki atomic bomb survivors registered since 1973 at the Atomic Bomb Disease Institute, Nagasaki University, which was established in 1972. In the present study, an “atomic bomb survivor” was defined as a person who received the “Atomic Bomb Survivor’s Health Handbook” authorized by Nagasaki City. The Atomic Bomb Disease Institute maintains computerized records of data on the handbook holders. Information on

these survivors, including changes in address and date of death, has been updated monthly with the cooperation of the Department for Atomic Bomb Survivors' Affairs, Nagasaki City Hall. The registered cases include directly exposed persons, those not present in Nagasaki City at the time of bombing but entering the city soon after the bomb (within 2 weeks), those in the rescue services, and fetuses. In this study, the incidence of prostate cancer was evaluated in residents of Nagasaki City who were directly exposed or who entered the city soon after the bomb explosion, those who were confirmed alive in 1996, and those whose smoking and alcohol consumption habits were recorded during an interview at a health examination (data on approximately three-quarters of subjects were available in 1996 and data on the rest were available subsequently). Of the 50,229 male atomic bomb survivors, 15,223 died, 9,619 moved out of the city before 1996, 49 had prostate cancer before the start of the follow-up period, and 6,929 had undocumented smoking and alcohol consumption habits. Thus, the analytical cohort consisted of 18,409 male atomic bomb survivors. The distance from the hypocenter was determined from information on exposure status given in the application forms of the Atomic Bomb Survivors' Health Handbook at Nagasaki City Hall.

Cohort follow-up and identification of cancer cases

To examine the development of prostate cancer (International Classification of Diseases for Oncology, Third Edition, code C619) in atomic bomb survivors, we used the data from the Nagasaki Prefecture Cancer Registries (NPCR),[(4)] which was established in 1985. The NPCR database included data on patient age, gender, tumor site, histological diagnosis, diagnostic method, motivation for consultation, clinical stage, pathological grade and date of diagnosis. These data have been linked to the survivors' database since 1996 to identify survivors having suffered from prostate cancer. In this study, 700 cases of primary incident prostate cancer

were identified in our cohort from 1996 to 2009. After exclusion of 69 cancer cases that were diagnosed by screening, 631 incident prostate cancer cases were considered eligible for this study. Information on disease stage and grade were available for 391 (62%) and 454 (72%) men, respectively. Tumors were classified as localized (clinical stage, ≤2; n = 231) or advanced (clinical stage, 2–8; n = 160). In addition, the tumors were categorized according to Gleason score as follows: 2–6, low grade (n = 193); 7, middle grade (n = 123), and ≥8, high grade (n = 138).

Statistical methods

We used the Cox proportional hazard model [(5)] with person-years as the underlying metric to estimate relative risks (RRs) and 95% confidence intervals (CIs) for prostate cancer in the proximal group and early entrance group compared with the distal group. Person-years of follow-up were calculated from the date from which information on cigarette smoking and alcohol consumption were available until the date of prostate cancer diagnosis, death, moving out of Nagasaki City, or the end of follow-up, whichever occurred first. Men for whom information on either cigarette smoking or alcohol consumption was not available were excluded from the analysis. In the analysis, RRs were adjusted for age at bombing, attained age, cigarette smoking, and alcohol consumption. Attained age was defined as the age when the survivor was diagnosed with prostate cancer, died, moved out of Nagasaki City, or censored on the December 31, 2009, whichever came first. The proportional hazards assumptions for each covariate were evaluated by a Kolmogorov-type supremum test and were upheld for all covariates. Analyses were carried out for total cases and separately for less- and more-aggressive tumors, on the basis of stage and grade information, to compare with the results of others.

All statistical tests were two-sided and $P \leq 0.05$ was considered statistically significant. The PHREG procedure in the SAS software package (version 9.3; SAS Institute, Inc., Cary, NC, USA) was used for the calculations.

Approval

This study was approved by the Ethics Review Committee of Nagasaki University Graduate School of Biomedical Sciences, Japan (Protocol No.12073028), and the use of data from the Nagasaki Prefectural Cancer Registry was approved by the Ethics Committee of the Nagasaki Prefectural Cancer Registry.

Results

Comparisons of baseline characteristics are presented according to exposure status (i.e., proximal survivors, distal survivors, and early entrance survivors) in Table 1. Of the 18,409 male survivors, 1,874 (10.2%) belonged to the proximal group, 12,112 (65.8%) belonged to the distal group, and 4,423 (24.0%) belonged to the early entrance group. The mean follow-up time for all the subjects was 11.5 years. The crude prostate cancer incidence rate was highest among the proximal survivors, followed by early entrance and distal survivors. Survivors in the distal group were a little younger than were those in the proximal and early entrance groups. The early entrance survivors were less likely to be current smokers than were proximal and distal survivors; however, the proportion of never smokers did not differ significantly between the groups. Early entrance survivors were also less likely to be everyday drinkers than were proximal and distal survivors; however, the proportion of everyday drinkers did not differ significantly between proximal and distal survivors

The proximal survivors had significantly higher risks for total and localized prostate

cancer than the distal survivors (Table 2). Compared with the distal survivors, the proximal survivors had an adjusted RR of 1.51 for total prostate cancer (95% CI:1.21, 1.89) and 1.80 for localized prostate cancer (95% CI:1.26, 2.57). A statistically insignificant association was observed for advanced prostate cancer (adjusted RR, 1.05; 95%CI:[0.65, 1.69]). The incidence of prostate cancer decreased significantly as the age at atomic bombing increased (Tables 2 and 3). Except for high-grade cancer, the risk of prostate cancer was significantly lower in the current smokers than in the never smokers (Tables 2 and 3). In former smokers, the risk was only slightly attenuated. With regard to alcohol consumption, everyday drinkers had a significantly high risk for total prostate cancer but an insignificantly high risk for localized, advanced, low-grade, moderate-grade, and high-grade prostate cancers. In the occasional drinkers, the risk was only slightly attenuated (Tables 2 and 3).

The proximal survivors also had a high risk for high-grade prostate cancer (Table 3). Compared with the distal survivors, the proximal survivors had an adjusted RR of 1.88 (95% CI:1.20, 2.94). For low- and middle-grade prostate cancers, insignificantly high risks were observed in the proximal survivors (adjusted RR and 95% CI: low-grade cancer, 1.31 and [0.85, 2.02]; middle-grade cancer, 1.31 and [0.80, 2.30]).

Discussion

We used exposure distance from the hypocenter as a substitute for the estimated irradiated dose and found a significant increase in prostate cancer risk among proximal survivors. This result supports the hypothesis that atomic bomb radiation is a risk factor for prostate cancer. To our knowledge, this is the first report to reveal an association between atomic bomb radiation and prostate cancer. Several unique epidemiological studies on Nagasaki survivors have already been documented according to the exposure distance.[6-11] In general, survivors

who were less than 2.0 km from the hypocenter were exposed to a significant dose of radiation. The estimated doses in Nagasaki survivors who were not shielded at the time of explosion were 924.7 cGy at 1.0 km, 120.7 cGy at 1.5 km, 17.9 cGy at 2.0 km, and 2.9 cGy at 2.5 km from the hypocenter.[8]

Thompson et al.[2] and Preston et al.[3] investigated cancer incidence among Nagasaki and Hiroshima atomic bomb survivors and reported no evidence of a radiation dose response for prostate cancer, with excess RRs per Gy of 0.29 and 0.11, respectively, and negative lower 95% confidence bounds. However, these studies were carried out from 1958 until 1987 or 1998, when the number of detected prostate cancer cases was relatively low (140 among 32,309 male survivors and 387 among 42,902 male survivors, respectively). Furthermore, the effects of cigarette smoking and alcohol consumption were not considered in these studies. We believe that the large number of prostate cancer cases followed-up in our study together with consideration of the effects of smoking and alcohol consumption provide more precise estimates of risk. Accordingly, we found that the elevated radiation-associated RR of prostate cancer reached statistical significance.

In this study, the follow-up period of each subject was calculated from 1996 or later; therefore, a substantial number of prostate cancer cases might have been missed, although the incidence rate of prostate cancer is not so high in younger men. The possible exclusion of prostate cancer cases from the analysis was a potential source of bias that might have affected the assessment of the association between atomic bomb radiation and prostate cancer. In consideration of this issue, we included in our analysis male survivors who were alive in 1973. In this cohort (approximately 44,000 subjects), 922 cases of prostate cancer were identified from 1973 to 2009. Compared with the distal survivors, the proximal survivors had a significantly increased RR of prostate cancer (adjusted for age at bombing and attained age,

1.47 [95% CI: 1.23, 1.76]). This result indicates that the above-mentioned possible exclusion of prostate cancer cases could not have influenced our findings.

Preston et al.[3] reported a birth cohort effect in which age-specific incidence rates increased with the year of birth (that is, in younger survivors) in many cancers including prostate cancer. In our analysis, the RR with a 1-year increment in the age at atomic bombing was 0.83 (95% CI: 0.81, 0.85), which corresponded to the findings of Preston et al.

A few well-established risk factors for prostate cancer incidence are known: increasing age, race/ethnicity; and a positive family history.[12]

Smoking is an important risk factor for many cancers. However, the majority of the previous cohort studies[13-18] found no significantly elevated risk of prostate cancer in current smokers, and some studies[13-16] reported that current smokers had a decreased risk of prostate cancer. In our analysis, the RR for current smokers compared with never smokers was 0.70 (95% CI: 0.58, 0.86), which was in agreement with previous results.

Alcohol consumption is also an established risk factor for some cancers, including esophagus, liver, colon, and breast cancers.[19] The findings of different studies with regard to the association between alcohol consumption and prostate cancer are inconsistent[20-24]; some studies[23-24] report an elevated risk in heavy drinkers compared with never drinkers. In our analysis, the RR for everyday drinkers (heavy drinkers) compared with never drinkers was 1.32 (95% CI: 1.08, 1.61), in accordance with previous findings.

We did not consider the effects of diet in our analysis; however, many previous studies found no association between diet and prostate cancer,[25-26] and our results are therefore unlikely to be affected.

At present, the actual reason for proximal survivors having a higher incidence of prostate cancer than distal and early entrance survivors is not known. However, genetic injuries

including DNA double-strand breaks were certainly induced by exposure to atomic bomb radiation,[27] which resulted in an increase in the incidence of cancer among atomic bomb survivors.[3] Hence, the same phenomena quite likely contributed to the development of prostate cancer.

In conclusion, we found that the proximal survivors had an increased risk for prostate cancer, especially for localized and high-grade ones, compared with the distal and early entrance survivors. These findings from a prospective cohort provide evidence that high dose radiation exposure may influence the development of prostate cancer.

Acknowledgements

This study was based on the database of the Atomic Bomb Disease Institute, Nagasaki University, which has been collecting administrative and medical data on Nagasaki atomic bomb survivors since 1973 with the support of Nagasaki City Government and the Nagasaki Atomic Bomb Casualty Council Health Management Center. The authors are grateful for their tremendous support.

Disclosure Statement

The authors have no conflict of interest.

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Table 1. Baseline characteristics of 18,409 male survivors according to exposure status

Characteristic	Exposure status		
	Proximal	Distal	Early Entrance
No. of subjects	1,874 (10.2%)	12,112 (65.8%)	4,423(24.0%)
Mean follow-up years*	11.2 (4.1)	11.7 (3.8)	10.8 (4.2)
No. of person-years	20,987	142,189	47,735
No. of prostate cancer cases	98	378	155
Crude incidence rate†	467.0	265.8	324.7
Mean age in years at bombing*	13.9 (8.5)	11.2 (8.1)	16.3 (8.5)
Mean attained age in years*	75.9 (7.9)	73.8 (7.6)	78.2 (7.9)
Smoking			
Current smoker	772 (41.2%)	5,324 (44.0%)	1,686 (38.1%)
Former smoker	435 (23.2%)	2,642 (21.8%)	1,174 (26.5%)
Never smoker	667 (35.6%)	4,146 (34.2%)	1,563 (35.4%)
Alcohol consumption			
Everyday drinker	881 (47.0%)	5,843 (48.2%)	1,989 (45.0%)
Occasional drinker	310 (16.5%)	2,153 (17.8%)	713 (16.1%)
Never drinker	683 (36.5%)	4,116 (34.0%)	1,721 (38.9%)

* parentheses show standard deviation
† per 100,000 person-years

Table 2. Multivariate relative risk and 95% confidence interval of prostate cancer among male atomic bomb survivors in Nagasaki, 1996–2009, according to exposure status, age at atomic bombing, cigarette smoking, and alcohol consumption, and extent of disease

Variable	Total cancer			Localized cancer			Advanced cancer‡		
	Cases	Relative risk*	95% CI†	Cases	Relative risk*	95% CI†	Cases	Relative risk*	95% CI†
Exposure status									
Proximal	98	1.51	1.21, 1.89	40	1.80	1.26, 2.57	20	1.05	0.65, 1.69
Distal	378	1.00		144	1.00		106	1.00	
Early entrance	155	0.91	0.75, 1.10	47	0.89	0.63, 1.26	34	0.66	0.44, 0.98
Age at atomic bombing (For every 1-year increment)	631	0.88	0.86, 0.89	231	0.81	0.78, 0.84	160	0.91	0.88, 0.94
Cigarette smoking									
Never smoker	272	1.00		106	1.00		71	1.00	
Current smoker	209	0.72	0.60, 0.87	72	0.57	0.42, 0.77	60	0.85	0.60, 1.20
Former smoker	150	0.80	0.66, 0.98	53	0.74	0.53, 1.03	29	0.60	0.39, 0.93
Alcohol consumption									
Never drinker	214	1.00		72	1.00		53	1.00	
Everyday drinker	318	1.24	1.04, 1.48	125	1.29	0.96, 1.72	78	1.29	0.90, 1.84
Occasional drinker	99	1.02	0.80, 1.30	34	0.91	0.60, 1.37	29	1.28	0.81, 2.02

* adjusted for attained age, exposure status, age at atomic bombing, cigarette smoking, and alcohol consumption
†Confidence Interval
‡Advanced prostate cancer were defined as all cancers that were regional or metastatic (not in situ or localized)

Table 3. Multivariate relative risk and 95% confidence interval of prostate cancer among male atomic bomb survivors in Nagasaki, 1996–2009, according to exposure status, age at atomic bombing, cigarette smoking, and alcohol consumption, and grade of disease

Variable	Low grade cancer‖			Middle grade cancer¶			High grade cancer**		
	Cases	Relative risk*	95% CI†	Cases	Relative risk*	95% CI†	Cases	Relative risk*	95% CI†
Exposure status									
Proximal	25	1.31	0.85, 2.02	17	1.31	0.80, 2.30	26	1.88	1.20, 2.94
Distal	122	1.00		79	1.00		81	1.00	
Early entrance	46	1.01	0.71, 1.43	27	0.89	0.57, 1.41	31	0.89	0.58, 1.37
Age at atomic bombing (For every 1-year increment)	193	0.82	0.79, 0.85	123	0.77	0.73, 0.82	138	0.82	0.78, 0.86
Cigarette smoking									
Never smoker	80	1.00		57	1.00		58	1.00	
Current smoker	68	0.74	0.53, 1.02	41	0.64	0.42, 0.95	44	0.72	0.48, 1.07
Former smoker	45	0.83	0.58, 1.20	25	0.65	0.41, 1.04	36	0.91	0.60, 1.39
Alcohol consumption									
Never drinker	58	1.00		41	1.00		45	1.00	
Everyday drinker	106	1.37	0.99, 1.90	64	1.18	0.79, 1.75	67	1.18	0.81, 1.73
Occasional drinker	29	1.00	0.64, 1.57	18	0.87	0.50, 1.52	26	1.22	0.75, 1.98

* adjusted for attained age, exposure status, age at atomic bombing, cigarette smoking, and alcohol consumption
†Confidence Interval
‖ Low-grade prostate cancer was based on a Gleason score of ≦6, categorized as highly differentiated
¶ Middle-grade prostate cancer was based on a Gleason score of 7
** High-grade prostate cancer was based on a Gleason score of ≧8, categorized as poorly differentiated