Research Article for Cancer Science

Incidence of Multiple Primary Cancers in Nagasaki Atomic Bomb Survivors: Association with Radiation Exposure

Short title: multiple primaries in atomic-bomb survivors

Masahiro Nakashima[1], Hisayoshi Kondo[2], Shiro Miura[3], Midori Soda[5], Tomayoshi Hayashi[6], Takeshi Matsuo[7], Shunichi Yamashita[4], Ichiro Sekine[1,3]

[1]Tissue and Histopathology Section and [2]Biostatistics Section, Division of Scientific Data Registry, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, 852-8523, Japan
[3]Department of Tumor and Diagnostic Pathology, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, 852-8523, Japan
[4]Department of Molecular Medicine, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, 852-8523, Japan
[5]Radiation Effects Research Foundation, Nagasaki, 850-0013, Japan
[6]Nagasaki University Hospital, Nagasaki, 852-8501, Japan
[7]Nagasaki Tumor Tissue Registries, Isahaya, 859-0401, Japan

Correspondence: Masahiro Nakashima, M.D. Ph.D.
Tissue and Histopathology Section
Division of Scientific Data Registry
Atomic Bomb Disease Institute
Nagasaki University Graduate School of Biomedical Sciences
1-12-4 Sakamoto, Nagasaki 852-8523, Japan
TEL : 81-95-849-7124
FAX : 81-95-849-7130
E-mail : moemoe@nagasaki-u.ac.jp

Key words: multiple primary cancers; atomic bomb; radiation; epidemiology

Abbreviations: MPC: multiple primary cancers; IR: incidence rate; RR: relative risk; CI: confidence interval; NTTR: Nagasaki Tumor Tissue Registries; LSS: life span study

Category: Epidemiology and Prevention

Brief statements: The significant finding of this study is that the atomic bomb survivors who had been exposed at a younger age still have a higher risk for a wide range of cancers, even at 62 years after the bombing. These results, on the associations between incidence of multiple primary cancers and atomic bombing, are described for the first time in this report.

Summary

To assess effects of atomic bomb radiation on incidence of multiple primary cancers (MPC), we analyzed the association between incidence of second primary cancers in the survivors of the atomic bombing of Nagasaki and exposure distance. The incidence rate (IR) of a second primary in MPC was calculated and stratified by the distance from the hypocenter and age at the time of bomb for the years 1968 through 1999. The IR of first primary was also calculated and compared with second primary to determine whether atomic bomb radiation was associated with the multiplicity of the tumors. There were 511 confirmed cases of MPC in the 7,572 cancer-bearing survivors. The crude IR was 27.6 per 100,000 person-years. The IR of second primaries significantly decreased with increasing distance from the hypocenter: relative risk (RR), 0.89 per 1.0 km; 95% confidence interval (CI), 0.84-0.94. A significant decrease was also noted for those of older ages at the time of the bombing based on the attained age of second primary: RR, 0.91 per 1 year; 95% CI, 0.90-0.92. These findings suggested the radiation effects on MPC. Furthermore, when compared with the first primary, a stronger distance effect was suggested on the occurrence of a second primary in the survivors. This study suggests the significance of atomic bomb radiation on MPC in the survivors. These results, on the incidence of MPC in the tumor-bearing survivors and its correlations with the atomic bombing of 62 years ago, are described for the first time in this report.

Introduction

Sixty-two years have now elapsed since two atomic bombs were exploded on Hiroshima and Nagasaki, Japan on August 6 and 9, 1945. The average age of the survivors has now reached 75 years. Several types of leukemia showed the highest incidence in the 5 to 10 year period after the atomic bomb explosions. Meanwhile, an increased risk of cancers has continued for decades, and the incidences of certain types of cancers are still higher than in controlled populations.[1-3] The occurrence of multiple primary cancers (MPC) is considered to be a reflection of systematic exposure to environmental carcinogens or of a predisposition to cancer. The association of radiation exposure from the atomic bomb and the development of MPC has not yet been studied, but is of interest in terms of learning more about the effects of whole-body irradiation on carcinogenesis. To elucidate the late carcinogenic effects of atomic bomb radiation on the survivors, the association between the incidence of MPC in survivors and exposure distance from the hypocenter has been analyzed. This study was conducted to provide insights into the etiology of cancer among the survivors and also to collect important information for medical care of the atomic bomb survivors and other victims of radiation-associated accidents around the world.

Subjects and Methods

Subjects

A series of clinical data were available on 91,890 subjects including 54,915 females and 36,975 males of the survivors registered at the Division of Scientific Data Registry, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, which was established in 1972. The registry of clinical data on Nagasaki survivors was started in 1968. This population was confined to residents in Nagasaki city who were directly exposed by the atomic bomb and used as a denominator. A survivor was defined in the present study as a person who received the "Atomic Bomb Survivor's Health Handbook" produced by Nagasaki city authorities since the establishment of the Atomic Bomb Survivors' Medical Treatment Law in April 1957. All information including exposure distance had been recorded before this study.

To examine malignancy cases in survivors, we used a database by the Nagasaki Tumor Tissue Registries (NTTR), which was established in 1974. This data base included 301,673 cases of tissue registration based on pathological reports of patients living in south Nagasaki prefecture including Nagasaki city since 1961 through 1999. The registered database included patient age, gender, tumor site, histological diagnosis, and date of diagnosis. These data were linked to the survivors' database since 1968 to identify survivors having suffered from malignancy. The experimental protocol was approved by the Ethics Review Committee of Nagasaki University Graduate School of Biomedical Sciences (Protocol No. 0305150036).

To identify MPC in atomic bomb survivors

A retrospective search of the database for MPC was conducted according to following criteria: i) multiple (two or more) primaries occurring in different organs, ii) multiple lesions of different histological types occurring in paired organs but apparently different sites (e.g. adenocarcinoma of left lung and small cell carcinoma of right lung, ductal carcinoma of left breast and lobular carcinoma of right breast), iii) multiple lesions of the same histological type occurring in paired organs are not counted as a MPC but as a single primary, iv) multiple primaries occurring in the colorectum but apparently different sites (e.g. ascending and sigmoid colon). A series of immunohistochemical studies were used with site-related antibodies, including cytokeratins 7 and 20, thyroid transcription factor-1, CA125, prostate specific antigen, estrogen receptor, progesterone receptor, etc., to carefully differentiate primary or metastatic cancers (e.g. colorectal and lung cancers, colon/gastric cancer and ovarian cancers, prostatic/uterine and rectal cancers).

To evaluate the association between MPC and atomic bomb radiation

In this study, an event of MPC in each survivor was considered to occur with a pathological diagnosis of two first primaries in synchronous case/second primary in metachronous case. Person-years of observation were cumulative from the date when the individual survivor's data was registered in our database until the earliest date at diagnosis of two first primaries in a synchronous case/second primary in a metachronous case, date of death, the end of follow-up (date when survivors moved outside of Nagasaki city), or the end of study (31 December 1999). Then, the incidence rate (IR) of MPC per 100,000 person-years among atomic bomb survivors including

healthy individuals was calculated by stratification of the distance from the hypocenter (0-1.0, 1.1-1.5, 1.6-2.0, 2.1-2.5, 2.6-3.0, >3.0km) and age at the time of bombing (0-9, 10-19, 20-29, 30-39, ≥40). Furthermore, the IR of second primaries per 100,000 person-years among atomic bomb survivors who had experienced the first primary was calculated exactly in the same way as mentioned above, and compared with the IR of first primaries to clarify whether atomic bomb radiation was associated with the multiplicity of tumors.

The exposure distance was used as a substitute for the estimated irradiated dose. Actually, several unique epidemiological studies on Nagasaki survivors have already been documented with exposure distances.[4-9] In general, survivors who were less than 1.5 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 are: 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.[7]

Statistical analyses

The effects of change in exposure distance, age at the time of bombing, and gender on the IR of second/first primary in survivors was evaluated using a Cox proportional hazard model. The Cox model is a robust, semiparametric method for modeling time-to-event data in the presence of censored cases to assess the effect of independent predictor variables. The following predictor variables were used in the model: exposure distance, age at the time of bombing, and gender. An event was considered to occur with the development of second/first primary. A comparison of IR between the two groups (younger vs. older attained age-range, first vs. second primary) was performed

by the relative risk (RR) with 95% confidence interval (CI). The PHREG procedure in the SAS 8.2 software (SAS Institute, Cary, NC, USA) was utilized for calculation. All tests were two tailed, and a p-value of <0.05 was considered statistically significant.

Results

The IR of MPC among atomic bomb survivors and its association with exposure distance/age at the time of bombing/gender

Overall 91,890 survivors have been followed for 1,850,046 person-years during which a total of 511 MPC cases comprised of 242 females and 269 males were confirmed. Of the 511 MPC cases, 473 (92.6%) were double, 29 (5.7%) were triple, 8 (1.6%) were quadruple, and 1 (0.2%) was quintuple. The crude IR of MPC was 27.6 per 100,000 person-years in the overall study population. Both person-years and crude IR of MPC by gender and exposure distance are shown in Table 1. The IR of MPC significantly decreased as distance increased from the hypocenter [RR per 1.0km increment: 0.89, 95% CI: 0.84-0.94]. Simultaneously, an age effect was observed in the IR of MPC, because the incidence significantly decreased with older age at the time of bomb based on respective attained-age range [RR per 1 year increment in the overall study population: 0.91, 95% CI: 0.90-0.92]. When analyses were stratified by gender, the IR of MPC was significantly higher in males than in females [overall RR vs. male: 0.40, 95% CI: 0.34-0.48]. However, contrary to that noted in the overall population, in younger attained-age range less than 50-yo, IR of MPC was significantly higher in females than in males [RR vs. male: 3.16, 95% CI: 1.04-9.60]. RRs for the IR of MPC in survivors by exposure distance, age at the time of bombing, and gender in respective

attained age-range are summarized in Table 2.

MPC can be divided into synchronous and metachronous groups depending on the interval between their diagnoses. The MPC cases determined by the interval between the first and second primaries are summarized in Table 3. Of the 511 MPC cases, 331 cases (64.8%) had two primaries within the 5-year interval (short-term). Of these, there were 82 synchronous cases (16.0%) and 249 short-term metachronous cases (48.8%). The IRs of short-term MPC by the exposure distance and age at the time of bombing were also calculated. The IR of short-term MPC significantly decreased with increased distance from the hypocenter [RR per 1.0km increment: 0.91, 95% CI: 0.85-0.98] and, simultaneously, significantly decreased with older age at the time of bombing based on the attained age of MPC [RR per 1 year increment: 0.92, 95% CI: 0.90-0.93].

Associations between the IR of second primary in metachronous cases and exposure distance/age at the time of bombing/gender, and their comparisons with first primary

In our cohort, 7,572 survivors were found who had suffered from a malignancy. Overall 7,572 survivors bearing a first primary were followed for 193,274 person-years during which a total of 429 second primary cases (in which 82 synchronous cases were excluded) that included 217 females and 212 males were confirmed. The crude IR of second primaries was 222.0 per 100,000 person-years in the survivors bearing first primary, whereas that of a first primary was 419.0 per 100,000 person-years in the overall study population (Table 4). The IRs of second and first primaries categorized by gender and exposure distance are presented in Table 4. The IRs of both second and first primaries significantly decreased as distance increased from the hypocenter [overall RR per 1.0km increment: 0.86 and 0.97, 95% CI: 0.80-0.92 and 0.96-0.98, respectively]

(Table 5). By compariing overall RR per 1.0km increment between the second and first primary, a stronger distance effect was suggested on the occurrence of second primary. Simultaneously, an age effect was observed in the IRs of both second and first primary, because the incidence significantly decreased with older age at the time of bombing based on the respective attained-age range [overall RR per 1 year increment: 0.96 and 0.96, 95% CI: 0.95-0.98 and 0.96-0.97, respectively] (Table 5). Furthermore, the IRs of both second and first primaries were significantly higher in males than in females [overall RR vs. male: 0.46 and 0.58, 95% CI: 0.38-0.56 and 0.55-0.60, respectively] (Table 5). However, contrary to that in the overall population, in the younger attained-age group less than 50-yo, the IRs of both second and first primaries were higher in females than in males [RR vs. male: 2.50 and 1.53, 95% CI: 0.80-7.87 and 1.31-1.79, respectively] (Table 5).

Sites of second and first primary

A wide range of cancers was observed in both second and first primaries. Sites of second primary (in which 82 synchronous cases were excluded) by gender and attained-age are presented in Table 6. The most prominent sites for second primary included the breast and lung (n=3, 21.4%, each) in younger attained-age group (n=14), while colon (n=84, 20.2%) and stomach (n=80, 19.3%) were followed by lung (n=50, 12.0%) in the older attained-age group (n=415). The most prominent sites for first primary included the stomach (n=162, 23.1%) following breast (n=121, 17.3%) and uterine cervix (n=111, 15.9%) in the younger attained-age group (n=700), while stomach (n=1713, 25.2%) and colon (n=917, 13.5%) were in the older attained-age group (n=6790).

DISCUSSION

In general, the population-based systematic studies on the incidence of MPC have been carried out by long standing cancer registries, because a huge cohort of cancer patients has to be followed to identify MPC cases. However, a previous report showed a modification of the risk of developing MPC in cancer patients in comparison with the general population.[10] The cohort studied showed an approximately 10% reduced risk of developing further cancers in comparison with the general population when only second metachronous cancers were considered. In contrast, the inclusion of synchronous cases resulted in an approximately 10% increased risk. MPC is defined as two or more independent primary cancers arising in the same individual, and their existence of does not depend on time. Therefore, synchronous MPC should be included in a study on MPC incidence, and could be diagnosed not only in cancer patients but could also be present in cancer-free patients before the diagnosis. We carefully reviewed each case with a series of immunohistochemistry to determine whether each malignancy is primary or metastatic and, finally, identified 82 synchronous cases (16.0%) from a total 511 MPC in Nagasaki survivors who suffered direct exposure. Because the main purpose of this study was to clarify the significance of atomic bomb radiation on the multiplicity of tumors, we could not exclude these synchronous cases in calculating the IR of MPC among overall survivors. Simultaneously, the IR of a second primary, excluding synchronous cases among survivors who had experienced a first primary, was calculated. This IR was then compared with that of the first primary to determine whether atomic bomb radiation was associated with the multiplicity of the tumors. This study points out the significance of atomic bomb radiation on the occurrence of MPC in the survivors. Furthermore, compared with first primary, the

higher increased risk for the development of a second primary was noted in the survivors who were exposed at a closer distance, again suggesting the association of atomic bomb radiation on the occurrence of MPC. These results dealing with the incidence of MPC and its associations with the atomic bombing of 62 years ago are described for the first time in this report.

In a previous Japanese report, the incidence of MPC in Nagasaki survivors was examined with cases registered at the NTTR during the period from 1973-1977.[4] These cases should be a part of the cohort in our present study, but no significance of atomic bomb radiation exposure in the incidence of MPC was found in those Nagasaki survivors.[4] The increased risk for MPC seems to begin more recently than that for single cancers. It is quite plausible that the survivors who had been exposed at younger ages have already reached the cancer-prone age to develop the cancers in multiple organs. Thus, the atomic bombing of 62 years ago is still increasing the cancer risks in survivors, particularly for those exposed at a closer distance and younger age.

We found a higher incidence for both second and first primaries in males than in females in the overall population. In contrast, RRs for both second and first primaries were significantly higher in females than in male among the younger attained-age group. This is quite likely because female-specific cancers such as breast and uterine cervix are most prominent in the younger attained-age group, while stomach and colon cancers, which are not gender specific but typically show higher risks for their incidences in males than in female, are most prominent in the older attained-age group.

Radiotherapy and chemotherapy for the first primary might be associated with an increased risk of developing a second primary.[11] Our analysis did not control for treatment differences. However, the effect of treatment on a subsequent primary would

be negligible in short-term MPC, because studies of treatment–associated risk for second primaries typically had at least a 10-15 year interval between the two tumors.[12,13] Reports on large populations of patients, who have been exposed to cancer treatments in childhood, have shown that the cumulative probability of a second cancer can be quite low.[14] Also, other reports suggested that only about 1% of the long-term follow-up patients developed a second malignancy after treatment for the first primaries with an interval of 82-136 months.[15,16] Thus, mechanisms other than those related therapy should be postulated for the development of the second primary in short-term MPC. In our study, 64.8% cases were short-term MPC, while only 16.4% cases were metachronous MPC with more than a 10-year interval. Our statistical analyses demonstrated a significant high incidence of short-term MPC in the survivors exposed at closer distance and younger age at the time of bombing. These results also provide evidence for the involvement of atomic bomb radiation in MPC among the survivors.

Our data suggest that the survivors, particularly for those who were exposed at a younger age, still have a high risk for cancers in multiple organs even at the present time. Although it is now 62 years since the atomic bomb explosions, we do not know the crucial mechanisms that can explain the continuously higher incidence of cancers in atomic bomb survivors for decades. It is noteworthy that according to our data base, the number of atomic bomb survivors living in Nagasaki city was 49,250 (39.4 % of Nagasaki A-bomb survivors) at the end of 2005. Furthermore, most of them were exposed as children in 1945. Thus, a higher risk of MPC, as a late effect of atomic bomb radiation, still persists in the survivors. We believe that further research on MPC in the survivors can contribute to an understanding of both radiation-associated carcinogenesis and a predisposition to cancers.

ACKNOWLEDGEMENTS

This work was supported in part through Nagasaki University 21st Century COE program, and by Grant for Research Project of Atomic Bomb Diseases from the Japanese Ministry of Health, Labour and Welfare. The authors are grateful to Prof. Tahara, Radiation Effects Research Foundation, and Dr. Saenko, Nagasaki University, for valuable comments in this study. We also thank Ms. Noguchi for her secretarial assistance in preparing this manuscript.

REFERENCES

1. 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.
2. Ron E, Lubin JH, Shore RE *et al*. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 1995; **141**: 259-77.
3. Carmichael A, Sami AS, Dixon JM. Breast cancer risk among the survivors of atomic bomb and patients exposed to therapeutic ionising radiation. *Eur J Surg Oncol* 2003; **29**: 475-9.
4. Murase K, Shimokawa I, Hayashida M, Matsuo T, Ikeda T. Epidemiological studies on multiple primary malignant tumors in Nagasaki city (in Japanese). *Gan No Rinsho* 1984; **30**: 871-9.
5. Sadamori N, Mine M, Hori M. Skin cancer among atomic bomb survivors. *Lancet* 1989; **1**: 1267.
6. Shibata S, Sadamori N, Mine M, Sekine I. Intracranial meningiomas among Nagasaki atomic-bomb survivors. *Lancet* 1994; **344**: 1770.
7. Sadamori N, Shibata S, Mine M *et al*. Incidence of intracranial meningiomas in Nagasaki atomic bomb survivors. *Int J Cancer* 1996; **67**: 318-22.
8. Honda S, Shibata Y, Mine M *et al*. Mental health conditions among atomic bomb survivors in Nagasaki. *Psychiatry Clin Neurosci* 2002; **56**: 575-83.
9. Yokota K, Mine M, Honda S, Tomonaga M. Cancer mortality in Nagasaki atomic bomb survivors with epilation. *Acta Med Nagasaki* 2005; **50**: 73-6.
10. Crocetti E, Buiatti E, Falini P, the Italian Multiple Primary Cancer Working Group. Multiple primary cancer incidence in Italy. *Eur J Cancer* 2001; **37**: 2449-56.

11. Kony SJ, de Vathaire F, Chompret A *et al*. Radiation and genetic factors in the risk of second malignant neoplasms after a first cancer in childhood. *Lancet* 1997; **350**: 91-5.
12. Travis LB, Holowaty EJ, Bergfeldt K *et al*. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. *N Engl J Med* 1999; **340**: 351-7.
13. Travis LB, Gospodarowicz M, Curtis RE *et al*. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst* 2002; **94**: 182-92.
14. Blatt J, Copeland DR, Bleyer WA. Late effects of childhood cancer and its treatment. In: Pizzo PA, Poplack DG, eds. *Principles and practice of pediatric oncology*. Philadelphia: JB Lippincott, 1993: 1091-114.
15. Dunst J, Ahrens S, Paulussen M *et al*. Second malignancies after treatment for Ewing's sarcoma: a report of the CESS-studies. *Int J Radiat Oncol Biol Phys* 1998; **42**: 379-84.
16. Craft AW, Cotterill SJ, Bullimore JA, Pearson D. Long-term results from the first UKCCSG Ewing's Tumour Study (ET-1). United Kingdom Children's Cancer Study Group (UKCCSG) and the Medical Research Council Bone Sarcoma Working Party. *Eur J Cancer* 1997; **33**: 1061-9.

Table 1. The crude incidence rates of multiple primary cancers in Nagasaki atomic-bomb survivors by gender and exposure distance by each factor.

Distance (km)	Female			Male			Total		
	PY	Cases	IR	PY	Cases	IR	PY	Cases	IR
Second primary									
≤1.0	24,516	18	73.4	17,274	6	34.7	41,790	24	57.4
1.1-1.5	54,688	22	40.2	43,027	35	81.3	97,715	57	58.3
1.6-2.0	98,570	18	18.3	62,712	24	38.3	161,282	42	26.0
2.1-2.5	121,270	28	23.1	73,444	18	24.5	194,714	46	23.6
2.6-3.0	148,996	36	24.2	86,980	30	34.5	235,976	66	28.0
3.0<	700,200	120	17.1	418,369	156	37.3	1,118,569	276	24.7
Overall	1,148,240	242	21.1	701,806	269	38.3	1,850,046	511	27.6

PY: person-years, IR: incidence rate

Table 2. Relative risks and 95% confidence intervals for the incidence rate of multiple primary cancers in Nagasaki atomic-bomb survivors by each factor in respective attained age-range.

Attained age*	Cases	Exposure distance		ATB		Female	
		RR[a]	95% CI	RR[b]	95% CI	RR[c]	95% CI
<50	18	0.82	0.59-1.14	0.96	0.88-1.04	3.16	1.04-9.60
50-59	73	0.91	0.79-1.05	0.91	0.88-0.94	0.55	0.35-0.88
60-69	182	0.89	0.81-0.98	0.91	0.89-0.93	0.43	0.32-0.57
70-79	148	0.86	0.76-0.96	0.90	0.88-0.92	0.35	0.25-0.48
80+	90	0.92	0.80-1.07	0.91	0.89-0.94	0.26	0.17-0.40
Overall	511	0.89	0.84-0.94	0.91	0.90-0.92	0.40	0.34-0.48

ATB: age at the time of bomb, RR: relative risk, CI: confidence intervals

a: per 1km increment, b: per 1-year increment, c: vs. male

*: The attained-age of multiple primary cancers was defined as age at a pathological diagnosis of two first primaries in synchronous case/second primary in metachronous case.

Table 3. Number of multiple primary cancers in Nagasaki atomic-bomb survivors by gender and interval between the first and second primary.

Interval (y)	Female	Male	Total
Synchronous	25 (4.9%)	57 (11.2%)	82 (16.0%)
<1	38 (7.4%)	42 (8.2%)	80 (15.7%)
1-2	22 (4.3%)	31 (6.1%)	53 (10.4%)
2-3	29 (5.7%)	23 (4.5%)	52 (10.2%)
3-4	11 (2.2%)	24 (4.7%)	35 (6.9%)
4-5	17 (3.3%)	12 (2.4%)	29 (5.7%)
Short-term*	142 (27.8%)	189 (36.9%)	331 (64.8%)
5-10	46 (9.0%)	50 (9.8%)	96 (18.8%)
10<	54 (10.6%)	30 (5.9%)	84 (16.4%)
Total	242 (47.4%)	269 (52.6%)	511 (100%)

*Synchronous and short-term metachronous multiple primary cancers which was defined as two primaries within 5-year interval.

Table 4. The crude incidence rates of second primary and first primary in Nagasaki atomic-bomb survivors in respective exposure distance.

Distance (km)	Female			Male			Total		
	PY	Cases	IR	PY	Cases	IR	PY	Cases	IR
Second primary									
≤1.0	2,654	18	678.3	2,624	5	190.5	5,278	23	435.8
1.1-1.5	6,704	21	313.2	7,643	32	418.7	14,347	53	369.4
1.6-2.0	9,287	16	172.3	7,361	17	230.9	16,648	33	198.2
2.1-2.5	11,660	23	197.2	8,985	13	144.7	20,646	36	174.4
2.6-3.0	13,586	29	213.5	10,904	26	238.5	24,490	55	224.6
3.0<	64,801	110	169.7	47,063	119	252.9	111,865	229	204.7
Overall	108,692	217	199.6	84,580	212	250.6	193,274	429	222.0
First primary									
≤1.0	23,762	112	471.3	16,818	109	648.1	40,580	221	544.6
1.1-1.5	52,772	245	464.3	416,78	325	779.8	94,450	570	603.5
1.6-2.0	96,178	354	368.1	61,349	294	479.2	157,527	648	411.4
2.1-2.5	118,289	454	383.8	71,780	347	483.4	190,069	801	421.4
2.6-3.0	145,638	532	365.3	84,991	474	557.7	230,629	1,006	436.2
3.0<	683,498	2,434	356.1	410,450	1,892	461.0	1,093,947	4,326	395.4
Oveall	1,120,137	4,131	368.8	687,066	3,441	500.8	1,807,202	7,572	419.0

PY: person-years, IR: incidence rate

Table 5. Comparisons of relative risks and 95% confidence intervals for the incidence of second primary and first primary in Nagasaki atomic-bomb survivors by each factor in respective attained age-range.

Attained age	Cases	Exposure distance		ATB		Female	
		RR[a]	95% CI	RR[b]	95% CI	RR[c]	95% CI
Second primary							
<50	15	0.79	0.55-1.14	0.94	0.86-1.04	2.50	0.80-7.87
50-59	59	0.85	0.72-1.00	0.89	0.86-0.93	0.69	0.41-1.15
60-69	151	0.84	0.75-0.94	0.91	0.88-0.93	0.49	0.35-0.67
70-79	126	0.86	0.75-0.97	0.89	0.86-0.91	0.39	0.27-0.56
80+	78	0.92	0.78-1.08	0.91	0.88-0.95	0.30	0.19-0.47
Overall	429	0.86	0.80-0.92	0.96	0.95-0.98	0.46	0.38-0.56
First primary							
<50	702	0.97	0.93-1.02	1.02	1.00-1.03	1.53	1.31-1.79
50-59	1,577	0.97	0.94-1.00	0.97	0.97-0.98	0.72	0.65-0.79
60-69	2,387	0.97	0.95-1.00	0.97	0.96-0.97	0.50	0.46-0.55
70-79	1,881	0.98	0.95-1.01	0.95	0.95-0.96	0.43	0.39-0.47
80+	1,025	0.94	0.90-0.98	0.95	0.94-0.95	0.51	0.45-0.58
Overall	7,572	0.97	0.96-0.98	0.96	0.96-0.97	0.58	0.55-0.60

ATB: age at the time of bomb, RR: relative risk, CI: confidence intervals
a: per 1km increment, b: per 1-year increment, c: vs. male
*: The attained-age of second/first primary was defined as age at the pathological diagnosis of second/first primary

Table 6. Sites of second primary by gender and attained-age

Sites	Female (%)			Male (%)			Overall (%)		
	Attained age		Total	Attained age		Total	Attained age		Total
	<49	>50		<49	>50		<49	>50	
Oral cavity & pharynx	0	2 (1.0)	2 (0.9)	1 (25.0)	2 (1.0)	3 (1.4)	1 (7.1)	4 (1.0)	5 (1.2)
Nose & larynx	0	0	0	0	5 (2.4)	5 (2.4)	0	5 (1.2)	5 (1.2)
Lung	3 (30.0)	22 (10.6)	25 (11.5)	0	28 (13.5)	28 (13.2)	3 (21.4)	50 (12.0)	53 (12.4)
Esophagus	0	3 (1.4)	3 (1.4)	0	10 (4.8)	10 (4.7)	0	13 (3.1)	13 (3.0)
Stomach	1 (10.0)	40 (19.3)	41 (18.9)	0	40 (19.2)	40 (18.9)	1 (7.1)	80 (19.3)	81 (18.9)
Colon	0	45 (21.7)	45 (20.7)	2 (50.0)	39 (18.8)	41 (19.3)	2 (14.3)	84 (20.2)	86 (20.0)
Rectum	1 (10.0)	16 (7.7)	17 (7.8)	0	20 (9.6)	20 (9.4)	1 (7.1)	36 (8.7)	37 (8.6)
Liver	0	4 (1.9)	4 (1.8)	1 (25.0)	12 (5.8)	13 (6.1)	1 (7.1)	16 (3.9)	17 (4.0)
Gallbladder & bile duct	0	2 (1.0)	2 (0.9)	0	3 (1.4)	3 (1.4)	0	5 (1.2)	5 (1.2)
Pancreas	0	2 (1.0)	2 (0.9)	0	1 (0.5)	1 (0.5)	0	3 (0.7)	3 (0.7)
Urinary tract & bladder	0	7 (3.4)	7 (3.2)	0	10 (4.8)	10 (4.7)	0	17 (4.1)	17 (4.0)
Kidney	0	1 (0.5)	1 (0.5)	0	2 (1.0)	2 (0.9)	0	3 (0.7)	3 (0.7)
Thyroid	0	5 (2.4)	5 (2.3)	0	0	0	0	5 (1.2)	5 (1.2)
Breast	3 (30.0)	15 (7.2)	18 (8.3)	0	0	0	3 (21.4)	15 (3.6)	18 (4.2)
Cervix	1 (10.0)	3 (1.4)	4 (1.8)				1 (7.1)	3 (0.7)	4 (0.9)
Endometrium	0	7 (3.4)	7 (3.2)				0	7 (1.7)	7 (1.6)
Ovary	1 (10.0)	4 (1.9)	5 (2.3)				1 (7.1)	4 (1.0)	5 (1.2)
Prostate				0	17 (8.2)	17 (8.0)	0	17 (4.1)	17 (4.0)
Testis				0	0	0	0	0	0
Skin	0	17 (8.2)	17 (7.8)	0	7 (3.4)	7 (3.3)	0	24 (5.8)	24 (5.6)
Hematopoietic	0	7 (3.4)	7 (3.2)	0	9 (4.3)	9 (4.2)	0	16 (3.9)	16 (3.7)
Brain	0	2 (1.0)	2 (0.9)	0	0	0	0	2 (0.5)	2 (0.5)
Others	0	3 (1.4)	3 (1.4)	0	3 (1.4)	3 (1.4)	0	6 (1.4)	6 (1.4)
Total	10	207	217	4	208	212	14	415	429

Figure 1

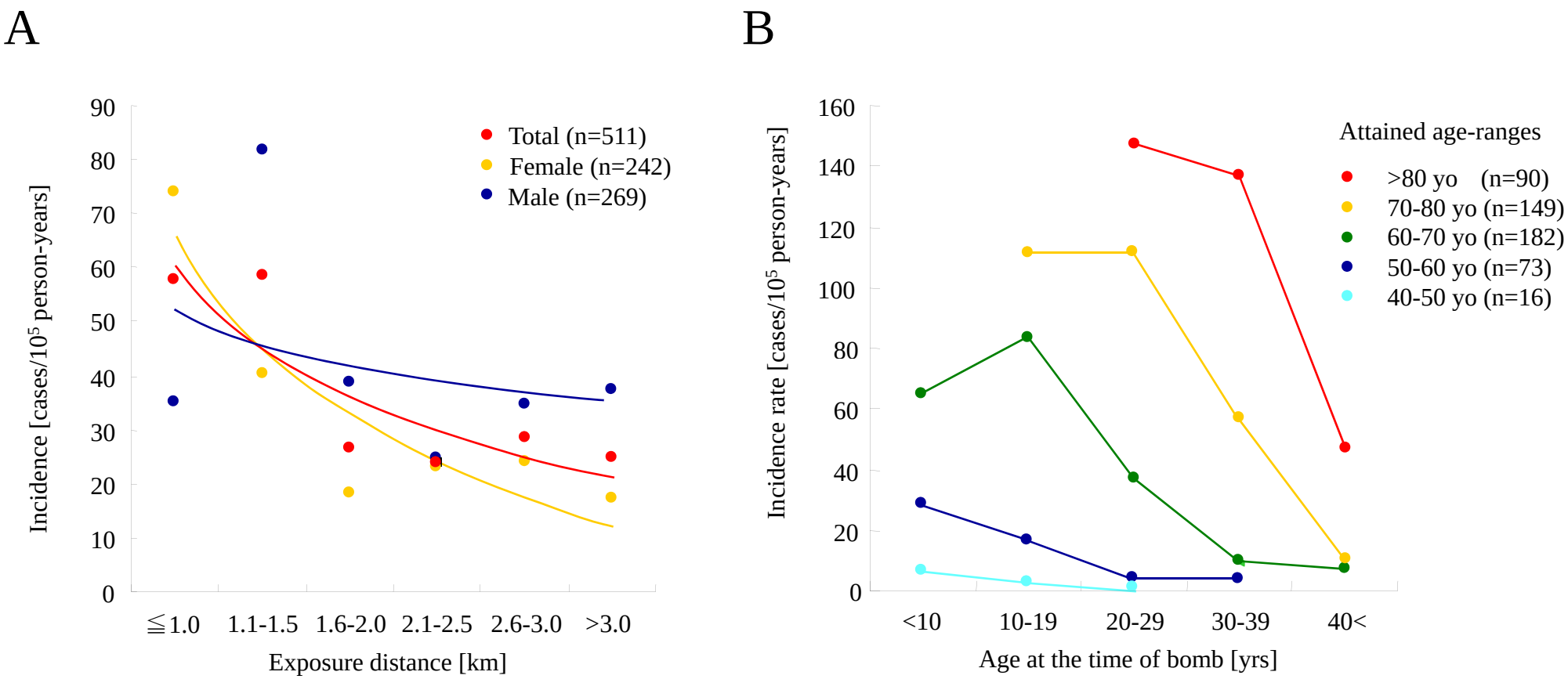
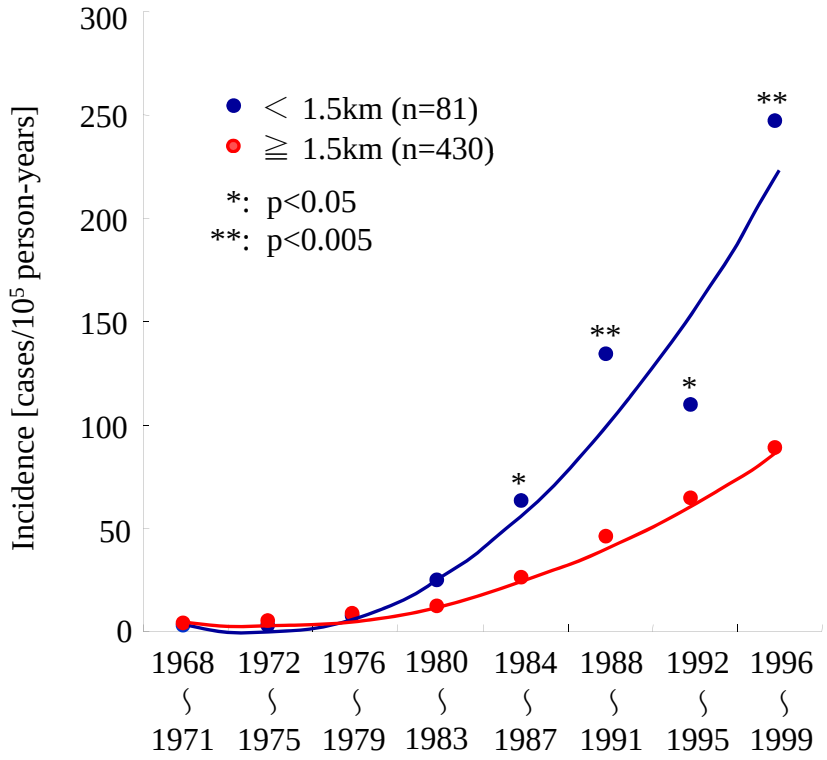

A
Incidence [cases/10^5 person-years]
90
80
70
60
50
40
30
20
10
0
Total (n=511)
Female (n=242)
Male (n=269)
≦1.0
1.1-1.5
1.6-2.0
2.1-2.5
2.6-3.0
>3.0
Exposure distance [km]
B
Incidence rate [cases/10^5 person-years]
160
140
120
100
80
60
40
20
0
Attained age-ranges
>80 yo (n=90)
70-80 yo (n=149)
60-70 yo (n=182)
50-60 yo (n=73)
40-50 yo (n=16)
<10
10-19
20-29
30-39
40<
Age at the time of bomb [yrs]

Figure 2


300
250
200
150
100
50
0
Incidence [cases/10^5 person-years]
< 1.5km (n=81)
≧ 1.5km (n=430)
*: p<0.05
**: p<0.005
*
**
*
**
1968 ~ 1971
1972 ~ 1975
1976 ~ 1979
1980 ~ 1983
1984 ~ 1987
1988 ~ 1991
1992 ~ 1995
1996 ~ 1999