Pathological and Epidemiologic Study of Gastric Cancer in Atomic Bomb Survivors, Hiroshima and Nagasaki, 1959-77

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A study to elucidate the effects of atomic bomb (A-bomb) radiation exposure on the incidence of stomach cancer was conducted on 79,856 A-bomb survivors included in the Life Span Study sample for whom dose estimates are available. From cases diagnosed during the period 1950-77 a total of 2,155 were accepted, following review of the clinical and pathologic records, as meeting the criteria for stomach cancer. 1. Evaluation of the effects of each dose group corrected for sex and age, showed a significant increase in the risk of stomach cancer only in the heavily exposed 200+ rad group. In the 200+ rad group, the increase in stomach cancer risk was remarkable in the under 30 years of age at the time of the bomb (ATB) group. 2. The dose-response relationship of the incidence of stomach cancer as followed over a period of 27 years is not quadratic, but linear. Based on this finding, the estimated risk of A-bomb radiation-induced stomach cancer is 1.24 per 1 million person years/rad. 3. Histologically, the differentiated type is frequently observed in the control and low dose groups,

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INTRODUCTION

It has been confirmed clinically as well as by animal experiments that radiation exposure induces tumors, especially malignant tumors. Increased incidence of tumors such as leukemia\(^1\textsuperscript{1}, \textsuperscript{2}, \textsuperscript{3}\), lung cancer\(^4\textsuperscript{4}, \textsuperscript{5}\), breast cancer\(^6\), thyroid cancer\(^7\), and salivary gland tumor\(^8\textsuperscript{8}, \textsuperscript{9}\) has been reported among the A-bomb survivors of Hiroshima and Nagasaki.

Among the malignant tumors developing in the Japanese, stomach cancer is the one with the highest incidence and mortality rates. It is of great interest to know what effect A-bomb exposure has on the incidence of stomach cancer. The issue concerning stomach cancer among A-bomb survivors has been studied in the Atomic Bomb Casualty Commission/Radiation Effects Research Foundation (ABCC/RERF), Life Span Study (LSS) and pathological studies. The results of studies conducted on the LSS, using information from death certificates, have indicated high stomach cancer mortality among heavily exposed survivors\(^10\textsuperscript{10}, \textsuperscript{11}, \textsuperscript{12}\). However, due to the low autopsy rate, the study using autopsy materials, has not demonstrated any statistically definite increase in stomach cancer incidence\(^13\textsuperscript{13}, \textsuperscript{14}, \textsuperscript{15}, \textsuperscript{16}\).

Remarkable increase in the rate of early detection of stomach cancer due to rapid progress in stomach diagnostics and the extensive use of mass stomach screening can be mentioned as changes occurring in stomach cancer clinics over the past three decades\(^17\). Among cases undergoing surgery, the frequency of stomach cancer detected at an early stage has increased to more than 30% of all cases since 1970, and the surgical treatment results have improved so that the 5-year survival rate now exceeds 90%. In order to review stomach cancer among A-bomb survivors in greater detail, it seemed appropriate, in view of such changes in the clinical situation regarding stomach cancer, to pursue the association between stomach cancer and A-bomb exposure using stomach cancer cases first detected at surgery, cases detected by biopsy and diagnosed histologically, clinically diagnosed cases, and cases first identified on death certificate or at autopsy.

MATERIALS AND METHODS

The stomach cancer cases used in the present study are those pertaining to the LSS extended sample\(^18\) during 1950–77 in Hiroshima and Nagasaki.

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and diagnosed clinically or histopathologically. In the LSS extended sample, composed of 108,912 subjects, 152 cases whose family register (Koseki) cannot be identified, and all stomach cancer cases with onset date prior to October 1950 were excluded from this study. Also excluded from the analysis were 26,518 subjects who were not in the city ATB, and 2,386 subjects whose dose estimates were not available. Therefore, this analysis relates to 79,856 A-bomb survivors (Hiroshima: 60,482; Nagasaki: 19,374) among whom 2,155 (Hiroshima: 1,720; Nagasaki: 435) were identified as stomach cancer cases during the 27 years from October 1, 1950 to December 31, 1977. Of these cases 1,148 or 53.3%, were histopathologically studied. However, it should be emphasized that, with in each city, the distribution of cases by dose category was not significantly different between death certificate (1,007 cases) and histopathological materials (autopsy 385 cases, surgical or biopsy 763 cases).

In collecting stomach cancer cases, reference was made to materials from the Tumor and Tissue Registries of the Hiroshima and Nagasaki Cities and Prefectural Medical Associations, and the RERF LSS. Further, efforts were made to collect cases which occurred prior to initiation of the Tumor Registry by checking existing clinical, surgical pathology, and autopsy data at Hiroshima and Nagasaki Universities and at hospitals located in the two cities. The clinical, surgical pathology, and autopsy records of each of the 2,155 cases identified were checked as extensive as possible in order to determine the time clinical symptoms became manifest, date and method of clinical diagnosis, date of histopathological diagnosis, and date of death.

The exposure dose estimates used here are the tentative 1965 radiation dose estimates as revised in accordance with the recent relocation of the Nagasaki epicenter and a standardized rounding off procedure for the calculation of individual doses (T65DR)\textsuperscript{19-20}. A review of the quantity and quality of radiation received by A-bomb survivors is continuing\textsuperscript{21}, and reassessment of the dose estimates will be made in the near future. Accordingly, in order to avoid biases which might occur from using erroneous estimates, based on T65DR neutrons and gamma rays separately, the relationship between stomach cancer incidence and radiation dose was reviewed using the estimated T65DR (total) received by each individual. It might be considered natural to evaluate the relationship of radiation dose to stomach cancer incidence using organ dose estimates, but since so many uncertain factors are involved in the estimates of neutron and gamma ray components of T65DR, it was decided to employ total kerma dose.

In the continued interest of accurately defining the late effects of the A-bombs, the qualitative and quantitative characteristics of the A-bomb radiation exposure doses are periodically refined. If warranted by future dose assessments, the data reported here will be reanalyzed and subsequently reported.

Statistical methods: It is assumed that \(X_{ijk}\), the observed number of stomach cancer cases indexed by sex (\(i = 1\) or 2), age (\(j = 1, \ldots, 6\)), and dose (\(k = 1, \ldots, 5\)) groups, follows the Poisson distribution with parameter \(\lambda_{ijk} = R_{ijk}P_{ijk}\). Here
$R_{ijk}$ indicates the person-years at risk in the $(i,j,k)$th category.

Two simple regression models were used in the analysis of stomach cancer incidence within city:

Model I: $P_{ijk} = \alpha_{ij} + \beta_1D_{ijk}$

Model II: $P_{ijk} = \alpha_{ij} + \beta_1D_{ijk} + \beta_2D_{ijk}^2$

where $\alpha_{ij}$ is the effect of sex and ATB age-groups (0–9, 10–19, 20–29, 30–39, 40–49, and 50+) at the control group level, $D_{ijk}$ is the average total kerma dose of the $(i,j,k)$th group, $D_{ijk}^2$ the squared average of total kerma dose, with index $k$ ranging over the five dose groups (0, 1–49, 50–99, 100–199, and 200+ rad), and where $\beta_1$ and $\beta_2$ are constants expressing dose-response characteristics common to sex or age categories. Each test statistic on two dose-response estimates of parameters are $\chi^2 = \hat{\beta}_1^2 / V(\hat{\beta}_1)$ or $\hat{\beta}_2^2 / V(\hat{\beta}_2)$, which has approximately a $\chi^2$ distribution with one degree of freedom under the hypothesis $H: \beta_1 = 0$ or $\beta_2 = 0$, where $V(\hat{\beta}_1)$ or $V(\hat{\beta}_2)$ denotes the asymptotic variance of the maximum likelihood (ML) estimate $\hat{\beta}_1$ or $\hat{\beta}_2$ of $\beta_1$ or $\beta_2$. A test statistic for the null hypothesis ($H_0 : \beta_1 - \beta_2 = 0$) of no difference in risk between two groups, say, males and females, is $\chi^2 = (\hat{\beta}_1 - \hat{\beta}_2)^2 / V(\hat{\beta}_1 - \hat{\beta}_2)$ which has approximately a $\chi^2$ distribution with one degree of freedom, where $V(\hat{\beta}_1 - \hat{\beta}_2)$ denotes the asymptotic variance of difference in two groups.

ML estimates of the parameters, based on the Poisson distribution, were obtained by the Newton-Raphson iteration method. Furthermore, a review was made of the relative risk for each dose group within strata defined by city, sex, and age, and at the same time, a risk analysis22, 23) adjusted for the effect of city, sex, or age, was conducted.

RESULTS

Stomach cancer incidence: Table 1 shows by age, the annual crude incidences and relative risks of stomach cancer during 1950–77 for Hiroshima and Nagasaki combined. Stomach cancer incidence per 100,000 persons observed shows a tendency by age for cancer frequency to increase with increase of dose in both cities and markedly so in the highest dose group. The average relative risk adjusted for city, sex, and age-group was significantly different ($P < .001$) only in the 200+ rad group, it being 1.6 times higher than the 0 rad group. When the risk was similarly observed by city (Fig. 1) and sex (Fig. 2), only the 200+ rad group revealed a highly significant excess risk, especially in Hiroshima. There is also evidence that the excess risk for the 200+ rad group is concentrated in the <30 ATB age-groups.
Table 1. Crude annual incidence rates and relative risks of stomach cancer among Hiroshima and Nagasaki A-bomb survivors by age ATB and dose, 1950–77

| Age ATB | Radiation dose (rad) | Total | 0 | 1—49 | 50—99 | 100—199 | 200+ |
|---------|----------------------|-------|---|------|-------|---------|------|
|         |                      |       |   |      |       |         |      |
| 0—9     | Stomach cancers      | 32    | 14| 12   | 1     | 1       | 4    |
|         | Annual incidence (x10^5) | 7.8 | 8.6| 5.8  | 5.2   | 9.4     | 36.4 |
|         | Relative risk        | —     | 1.0| .7   | .6    | 1.1     | 4.2* |
|         | Person-years (x10^3)  | 410.7 | 162.5| 207.0 | 19.5  | 10.7    | 11.0 |
| 10—19   | Stomach cancers      | 112   | 30 | 47   | 9     | 11      | 15   |
|         | Annual incidence (x10^5) | 24.8 | 17.5| 22.3 | 38.3  | 45.0    | 67.1 |
|         | Relative risk        | —     | 1.0| 1.3  | 2.2*  | 2.6**   | 3.8***|
|         | Person-years (x10^3)  | 452.4 | 171.3| 210.8 | 23.5  | 24.4    | 22.4 |
| 20—29   | Stomach cancers      | 147   | 50 | 65   | 11    | 8       | 13   |
|         | Annual incidence (x10^5) | 54.2 | 47.5| 51.6 | 70.2  | 66.5    | 104.7|
|         | Relative risk        | —     | 1.0| 1.1  | 1.5   | 1.4     | 2.2***|
|         | Person-years (x10^3)  | 271.3 | 105.2| 126.0 | 15.7  | 12.0    | 12.4 |
| 30—39   | Stomach cancers      | 417   | 176| 183  | 19    | 17      | 22   |
|         | Annual incidence (x10^5) | 143.9 | 149.8| 134.7 | 120.0 | 159.2   | 222.9|
|         | Relative risk        | —     | 1.0| .9   | .8    | 1.0     | 1.4  |
|         | Person-years (x10^3)  | 289.8 | 117.5| 135.9 | 15.8  | 10.7    | 9.9  |
| 40—49   | Stomach cancers      | 742   | 280| 358  | 36    | 33      | 35   |
|         | Annual incidence (x10^5) | 266.7 | 250.0| 273.9 | 235.2 | 298.3   | 384.2|
|         | Relative risk        | —     | 1.0| 1.0  | .9    | 1.1     | 1.4* |
|         | Person-years (x10^3)  | 279.2 | 112.0| 120.7 | 15.3  | 11.1    | 9.1  |
| 50+     | Stomach cancers      | 705   | 282| 345  | 37    | 22      | 19   |
|         | Annual incidence (x10^5) | 364.9 | 352.8| 373.9 | 348.3 | 380.8   | 410.4|
|         | Relative risk        | —     | 1.0| 1.1  | 1.0   | 1.1     | 1.1  |
|         | Person-years (x10^3)  | 193.2 | 79.9| 92.8  | 10.6  | 5.8     | 4.6  |
| Totals  | Stomach cancers      | 2155  | 832| 1010 | 113   | 92      | 108  |
|         | Annual incidence (x10^5) | 113.7 | 111.2| 111.9 | 112.5 | 123.2   | 155.6|
|         | Relative risk        | —     | 1.0| 1.0  | 1.0   | 1.1     | 1.6***|
|         | Person-years (x10^3)  | 1895.6| 748.3| 902.7 | 100.5 | 74.7    | 69.4 |

Relative risk values have been adjusted for city and sex and also for age in totals.
Significance levels: NS (P>.10), Sug (P<.10), * (P<.05), ** (P<.01), *** (P<.001)
Mean doses by dose group and city are 0, 10.4, 70.6, 141.9, 358.6 in Hiroshima, and 0, 10.8, 70.6, 143.0, 347.1 in Nagasaki, respectively.
Fig. 1. Stomach cancer incidence, by city and dose 1950–77, relative risk

** Fig. 1. Stomach cancer incidence, by city and dose 1950–77, relative risk **

Fig. 2. Stomach cancer incidence, by sex and dose 1950–77, relative risk

** Fig. 2. Stomach cancer incidence, by sex and dose 1950–77, relative risk **
Dose-response relationship: The average T65DR dose for each dose group by city is given in a footnote of Table 1. Table 2 summarized the dose-response coefficients of regression analysis using Model I and Model II, taking into consideration the effect of age by city and sex. Using the linear-quadratic (L-Q) dose response represented in Model II shows no significant or definite contribution to stomach cancer incidence, but only the linear response effect on induction of stomach cancer assumed in Model I gives a highly or definitely significant difference (P < .01). In Hiroshima, the dose-response relationship suggests a significant possibility of nonlinearity. But this significance is only for males. On the other hand, in Nagasaki a linear response model seems to give the best representation for both males and females. Therefore, from the standpoint of dose-response evaluation overall, it appears to be reasonable to conclude that radiation-induced stomach cancer response is adequately described by a linear function. Thus, the average risk of stomach cancer by sex is 1.46 per million PYR for males (1.25 in Hiroshima and 1.72 in Nagasaki), and 1.12 per million PYR for females (0.72 in Hiroshima and 1.66 in Nagasaki). The difference in risk between males and females by city is not statistically significant. The influence of age is very strong. Since there is a possibility that there are differences between younger and more advanced age-groups, in their respective sensitivities in dose-response effects, it may be useful to examine different effects using a linear dose-response relationship, stratified by sex and age. Review of the dose-response relationship for stomach cancer by ATB age-group is conducted here with respect to Model I only. The results of regression analysis show significant radiation effects greater than zero only in the <30 ATB age-groups for both city and sex adjusted, especially in the 10–19 and 20–29 ATB age-groups.

Average age at onset of stomach cancer: Table 3 shows average ages at onset of stomach cancer by age ATB and dose group. Little difference with increase of dose can be observed in average age at onset of stomach cancer. Moreover, for each of the ATB age-groups, comparison of the average age at onset of stomach cancer by dose shows no significant difference with increase of dose. this is similarly observed to hold for both sexes by city.

Average period until onset of cancer: Average period from A-bomb exposure to development of stomach cancer are shown in Table 4 by age and dose. When average periods until onset of stomach cancer are compared with the all age-group average and examined by dose group, the 50+ ATB age-group seems to be the only one consistent to fall short of the all age-group average for all dose groups. This appears to be a competing risk phenomenon, being due to reductions in the 50+ ATB age-group due to deaths resulting from other causes. However, comparing these average time period by dose groups, there is no suggestion whatsoever of a tendency for the average period to decrease with increase of dose. The average period in the 0–9 ATB age-group appears to decrease, it
Table 2. Dose-response coefficients estimated by city, sex and model

| Items                  | Both cities | Hiroshima | Nagasaki          |
|------------------------|-------------|-----------|-------------------|
|                        | Model I     | Model II  | Model I           | Model II          | Model I     | Model II          |
| Linear: $\beta_1 \times 10^6$ (SD) | 1.24*** (0.28) | 0.84NS (0.72) | 1.46** (0.50)     | 1.03NS (1.35)    | 1.12** (0.36) | 0.61NS (0.96)    |
| Quadratic: $\beta_2 \times 10^6$ (SD) | 1.23NS (2.09) | 1.27NS (3.69) | 1.58NS (2.77)     |                     |                     |                     |

The estimates of the nuisance parameters except for the linear and linear quadratic responses are not included here because they are of no importance in this study. The goodness of fit is due to Pearson's $\chi^2$ statistic with the corresponding degrees of freedom. Note that the two groups between 0–9 and 10–19 age ATB in Nagasaki males were combined. It is noted that all models applied here showed a good fit.

Significance levels are as in Table 1.

Table 3. Mean age at onset of stomach cancer by age ATB and dose

| Age ATB | Radiation dose (T65DR) |
|---------|------------------------|
|         | Total  | 0     | 1–49  | 50–99 | 100–199 | 200+ |
| 0–9     | 31.3   | 30.9  | 32.3  | 37.0  | 31.0    | 28.3 |
|         | (32)   | (14)  | (12)  | (1)   | (1)     | (4)  |
| 10–19   | 39.1   | 38.7  | 38.4  | 40.2  | 40.5    | 40.5 |
|         | (112)  | (30)  | (47)  | (9)   | (11)    | (15) |
| 20–29   | 48.6   | 49.1  | 48.7  | 47.0  | 47.6    | 48.4 |
|         | (147)  | (50)  | (65)  | (11)  | (8)     | (13) |
| 30–39   | 58.3   | 58.6  | 58.0  | 57.4  | 60.9    | 56.8 |
|         | (417)  | (176) | (183) | (19)  | (17)    | (22) |
| 40–49   | 65.9   | 66.5  | 65.5  | 65.5  | 64.3    | 65.9 |
|         | (742)  | (280) | (358) | (36)  | (33)    | (35) |
| 50+     | 75.0   | 74.4  | 75.5  | 74.2  | 75.0    | 76.3 |
|         | (705)  | (282) | (345) | (37)  | (22)    | (19) |
| Total   | 64.3   | 64.8  | 64.8  | 62.9  | 61.6    | 58.8 |
|         | (2155) | (832) | (1010)| (92)  | (108)   |       |

Parentheses indicate the number of stomach cancer cases in each category.
being 20 years in the 200+ rad group as compared with 25 years in the control (0 rad) group. Due to the paucity of cases, however, this results is not definite. The results of follow-up studies on the average periods compared here will naturally show large-scale changes as time passes, just as follow-up studies will show that the average ages at onset of stomach cancer change. Assuming that in future research an increase of stomach cancer cases will be observed hereafter in the youngest age-group that were exposed (in which few cases of 200+ rad were detected during the present study period), not only the average age at the time of onset of stomach cancer, but the average period until onset for this dose group, as well as other groups, will definitely increase.

Table 4. Average time period from A-bomb exposure to onset of stomach cancer by age ATB and dose

| Age ATB | Radiation dose (T65DR) |
|---------|-----------------------|
|         | Total  | 0   | 1—49 | 50—99 | 100-199 | 200+ |
| 0—9     | 25.1   | 25.1| 26.8 | 27.0   | 23.0    | 19.8 |
| 10—19   | 23.4   | 22.6| 23.0 | 25.2   | 24.6    | 23.9 |
| 20—29   | 23.0   | 23.8| 22.8 | 21.5   | 21.6    | 23.0 |
| 30—39   | 22.4   | 22.5| 22.3 | 21.0   | 24.6    | 21.8 |
| 40—49   | 20.6   | 21.1| 20.4 | 19.7   | 19.4    | 20.4 |
| 50+     | 17.8   | 17.7| 18.0 | 17.4   | 17.5    | 19.6 |
| Total   | 20.4   | 20.5| 20.2 | 19.9   | 20.7    | 21.3 |

The number of stomach cancer cases in each category is given in parentheses in Table 3.

Pathological observations: Of the present stomach cancer study material, 1,148 cases (53.3%) were diagnosed as having stomach cancer based on histopathological review. These cases can be classified roughly into two groups, namely, those in whom the primary focus was detected and those in whom only the infiltrative, metastatic, or local recurrent focus could be detected. Of these, the former, primary focus cases, account for 997 cases (86.8%) of the total. The total of 1,148 stomach cancer cases include 385 autopsy cases, 576 gastrectomy cases, 36 biopsy cases, and 151 cases in whom the primary focus could not be detected and only the infiltrative metastatic focus or local recurrent focus could be detected. Furthermore, these cases include 64 cases (6 autopsy cases, 13 gastrectomy cases, 42 biopsy cases, and 3 cases with only metastatic infiltrative focus) on whom histopathological specimens were not available for microscopic examination, and reference was made only to pathological diagnosis reports. Even among the primary focus cases detected, whole pathological specimens are not enough for each pathological observation. So, the number of pathological
observations varies according to the specimen available in each case. These cases are excluded from analysis, as are unexamined cases.

**Location of stomach cancer:** Tables 5 and 6 show the major locations of tumors in the stomach by four exposure dose groups. In Table 5, the locations are classified into three sites, i.e., upper part (C), middle part (M), and lower part (A), and in Table 6 into six sites, namely, lesser curvature (Min), greater curvature

| Location | Radiation dose (T65DR) | Total | 0 | 1—99 | 100—199 | 200+ |
|----------|------------------------|-------|---|------|---------|------|
| C (upper) | 135                    | 51    | 68 | 7    | 9       |      |
| %        | 13.3                   | 12.1  | 13.2 | 20.6 | 20.5    |      |
| M (medium)| 326                    | 143   | 161 | 9    | 13      |      |
| %        | 32.1                   | 33.9  | 31.3 | 26.5 | 29.5    |      |
| A (lower)| 553                    | 228   | 285 | 18   | 22      |      |
| %        | 54.5                   | 54.0  | 55.4 | 52.9 | 50.0    |      |
| **Total**| **1014**               | **422** | **514** | **34** | **44**  |      |
| **%**    | **100.0**              | **100.0** | **100.0** | **100.0** | **100.0** |      |

Test statistic is $\chi^2 = 4.71$ with 6 degrees of freedom (P > 0.10).

| Location | Radiation dose (T65DR) | Total | 0 | 1—99 | 100—199 | 200+ |
|----------|------------------------|-------|---|------|---------|------|
| Min      | 356                    | 143   | 180 | 17   | 16      |      |
| %        | 35.1                   | 33.9  | 35.0 | 50.0 | 36.4    |      |
| Maj      | 70                     | 25    | 39  | 0    | 6       |      |
| %        | 6.9                    | 5.9   | 7.6  | 0.0  | 13.6    |      |
| Ant      | 146                    | 54    | 77  | 4    | 11      |      |
| %        | 14.4                   | 12.8  | 15.0 | 11.8 | 25.0    |      |
| Post     | 178                    | 79    | 88  | 6    | 5       |      |
| %        | 17.6                   | 18.7  | 17.1 | 17.6 | 11.4    |      |
| Circ     | 79                     | 35    | 40  | 3    | 1       |      |
| %        | 7.8                    | 8.3   | 7.8  | 8.8  | 2.3     |      |
| Other    | 185                    | 86    | 90  | 4    | 5       |      |
| %        | 18.2                   | 20.4  | 17.5 | 11.8 | 11.4    |      |
| **Total**| **1014**               | **422** | **514** | **34** | **44**  |      |
| **%**    | **100.0**              | **100.0** | **100.0** | **100.0** | **100.0** |      |

Test statistic is $\chi^2 = 19.37$ with 15 degrees of freedom (P > 0.10).
First, observation of the frequency of cancers by site show the highest frequency in each dose group to be in the lower part of the stomach, followed by the middle part, while the frequency of the upper part is lowest for all dose groups. By exposure dose, the frequencies for the 100–199 rad group and that for the 200+ rad group are almost identical. On the other hand, when classifying by six sites, the frequency of cancer in the lesser curvature of the stomach shows up as highest, while that of all other sites is low. However, these particular findings are not related to radiation dose.

Histological type: On the basis of the General Rules for Gastric Cancer Studies in Surgery and Pathology, compiled by the Japanese Research Society for Gastric Cancer, the 997 cases in whom the primary focus of stomach cancer was detected in advance into the following 11 histological types: 1. papillary adenocarcinoma, 2. well-differentiated type tubular adenocarcinoma, 3. moderately differentiated type tubular adenocarcinoma, 4. poorly differentiated adenocarcinoma, 5. mucinous adenocarcinoma, 6. signet-ring cell carcinoma, 7. adenosquamous carcinoma, 8. squamous cell carcinoma, 9. carcinoid tumor, 10. undifferentiated carcinoma, and 11. type unknown. Of these, the type unknown group includes biopsy cases, autopsy cases with remarkable degeneration due to postmortem autolysis, autopsy and surgical resection cases for which repeat microscopic examination of histopathological samples was not possible, and the tumor histological types which could not be ascertained through pathological diagnosis reports.

Of the tumor histological types classified above, papillary adenocarcinoma, well-differentiated type tubular adenocarcinoma, and moderately differentiated type tubular adenocarcinoma were reclassified as differentiated type adenocarcinoma, and poorly differentiated type adenocarcinoma and signet-ring cell carcinoma were reclassified as poorly differentiated type adenocarcinoma, and adenosquamous carcinoma, squamous cell carcinoma, carcinoid tumor, and undifferentiated carcinoma were reclassified as other histological types. For analysis by exposure dose, the following five groups of histological type were employed: differentiated type adenocarcinoma, poorly differentiated type adenocarcinoma, mucinous adenocarcinoma, other histological types, and type unknown.

Table 7 shows histological types of all stomach cancer cases for both cities combined by exposure dose. The percentage of differentiated type adenocarcinoma are high in the 0 rad group and 1–99 rad group, showing 48.8% and 46.8%, respectively, which exceeds the 31.5% and 35.5% observed for poorly differentiated type adenocarcinoma. On the other hand, in the 100–199 and 200+ rad groups, the percentage of differentiated type adenocarcinoma is decreased to 17.1% and 25.9%, respectively, whereas those for poorly differentiated
type adenocarcinoma are increased to 46.3% and 40.7%, respectively. This finding suggests that the differentiated type of adenocarcinoma is frequently observed in the control and low dose groups whereas the poorly differentiated type is seen in the high dose group. Actually, a statistically significant difference can be observed between the histological type group and the dose group. As it may be assumed that the increase in the frequency of type unknown carcinoma cases in the 100+ rad group as compared with that in the 0 rad group brings about a decrease in frequency of differentiated type carcinoma cases, it is difficult to conclude that a significant increase can be recognized for the poorly differentiated type carcinoma.

It must be emphasized that the 997 cases confirmed by autopsy, gastrectomy, and biopsy were classified histopathologically without knowledge of exposure dose. Accordingly, the distribution of type unknown carcinoma cases under each histological classification is considered to be random, and was excluded from subsequent analyses.

Degree of extension of cells into the gastric wall: Cell extension into the gastric wall by exposure dose is classified into five stages: tunica mucosa (M), tela submucosa (SM), tunica muscularis propria (PM), tela subserose (SS), and tunica serosa (S). More than 70% of the cases in each dose group show extensions into the SS and S. Thus, no statistical differences by dose could be demonstrated between the degrees of extension into the gastric wall.

Volume of tumor stroma: Stomach carcinoma can be classified into three types: medullary, intermediate, and scirrhous types depending on the amount

| Table 7. Histological type by dose |
|-----------------------------------|
| Histological type                  | Radiation dose (T65DR) |
|                                   | Total  | 0     | 1—99  | 100—199 | 200+ |
|-----------------------------------|--------|-------|-------|---------|------|
| Differentiated adenocarcinoma      |        |       |       |         |      |
| Observed (%)                      | 451    | 189   | 241   | 7       | 14   |
| (45.2)                            | (48.8) | (46.8)| (17.1)| (25.9)  |
| Poorly differentiated              |        |       |       |         |      |
| Observed (%)                      | 346    | 122   | 183   | 19      | 22   |
| (34.7)                            | (31.5) | (35.5)| (46.3)| (40.7)  |
| Mucinous adenocarcinoma            |        |       |       |         |      |
| Observed (%)                      | 57     | 28    | 21    | 3       | 5    |
| (5.7)                             | (7.2)  | (4.1) | (7.3) | (9.3)   |
| Other                             |        |       |       |         |      |
| Observed (%)                      | 8      | 3     | 4     | 0       | 1    |
| (0.8)                             | (0.8)  | (0.8)| (0.0) | (1.9)   |
| Type unknown                      |        |       |       |         |      |
| Observed (%)                      | 135    | 45    | 66    | 12      | 12   |
| (13.5)                            | (11.6)| (12.8)| (29.3)| (22.2)  |
| Total                             | 997    | 387   | 515   | 41      | 54   |
| (%)                               | (100.0)| (100.0)| (100.0)| (100.0) | (100.0) |

Test statistics with and without the type unknown carcinoma are \( \chi^2 = 34.59 \) with 12 degrees of freedom (\( P<.001 \)) and \( \chi^2 = 23.44 \) with 9 degrees of freedom (\( P<.01 \)), respectively.
of stromal connective tissue. The tumor stroma volume can be classified by exposure dose into two histological types: differentiated type carcinoma and poorly differentiated type carcinoma. Most differentiated type carcinomas are either of the medullary type or the intermediate type, whereas poorly differentiated type carcinomas are mostly of the intermediate type or scirhous type, and the frequency of scirhous type is high in the 200+ dose group. There was a tendency in both histological types for the tumor stroma in the 200+ rad group to have increased in volume, but a statistical increase for linear trend was noted ($P < .05$) in the poorly differentiated type carcinoma only.

Infiltrative growth pattern of tumor: Infiltrative (INF) growth patterns (INF$\alpha$ — expansive growth of the cancerous focus, INF$\beta$ — intermediate growth between $\alpha$ and $\gamma$, and INF$\gamma$ — infiltrative growth of the focus) of tumor into its surrounding tissue by histological type (differentiated type or poorly differentiated type carcinoma) and exposure dose were examined.

Most of the differentiated type carcinoma were of either the INF$\alpha$ or INF$\beta$ pattern, while the poorly differentiated type carcinomas were most of the INF$\gamma$ pattern. Neither the differentiated type nor poorly differentiated type carcinomas showed a significant difference between INF growth pattern and radiation dose.

Invasion into lymph duct and vein, and metastasis: The degree of invasion in the lymph duct and vein was approximately the same and unrelated to exposure dose. Also, presence of metastasis to the lymph node and distant organ

Table 8. Mucosal intestinal metaplasia by dose

| Histological type | Mucosal intestinal metaplasia | Radiation dose (T65DR) | Linear trend $\delta$ (x10$^5$) | $SE$ (x10$^4$) |
|-------------------|------------------------------|------------------------|-------------------------------|---------------|
|                   |                              | Total                  | 0 | 1–99 | 100–199 | 200+ |
| Differentiated adenocarcinoma | None to mild (%) | 94 | 41 | 50 | 1 | 2 |
|                   | Observed                      | (30.1) | (30.8) | (30.3) | (20.0) | (22.2) | 4.00* | 1.85 |
|                   | Moderate to severe (%)        | 218 | 92 | 115 | 4 | 7 |
|                   | Observed                      | (69.9) | (69.2) | (69.7) | (80.0) | (77.8) |
| Total             | Observed (%)                  | 312 | 133 | 165 | 5 | 9 |
|                   | (100.0)                       | (100.0) | (100.0) | (100.0) | (100.0) |
| Poorly differentiated | None to mild (%) | 149 | 48 | 84 | 8 | 9 |
|                   | Observed                      | (62.9) | (64.9) | (64.6) | (57.1) | (47.4) | 7.46** | 0.78 |
|                   | Moderate to severe (%)        | 88 | 26 | 46 | 6 | 10 |
|                   | Observed                      | (37.1) | (35.1) | (35.4) | (42.9) | (52.6) |
| Total             | Observed (%)                  | 237 | 74 | 130 | 14 | 19 |
|                   | (100.0)                       | (100.0) | (100.0) | (100.0) | (100.0) |

The estimate of parameters from a linear trend model was obtained by a weighted least sequence approach. Significant level are as in Table 1.
was of the same rate and unrelated to exposure dose.

*Intestinal epithelial metaplasia of the gastric mucosa:* Intestinal epithelial metaplasia of the gastric mucosa, especially, in the gastric mucosa surrounding the tumor, classified by exposure dose, histological type, and degree of differentiation are given in Table 8. The frequency of moderate-to-severe cases in each dose group of the differentiated type was always higher than that of none-to-mild cases. The degrees of intestinal epithelial metaplasia of the gastric mucosa by histological type give a significant linear trend with increase of dose.

**DISCUSSION**

The LSS based on death certificate information and the pathological study of autopsy cases, have been heretofore employed in investigating the development of stomach cancer in A-bomb survivors. Epidemiologic studies of stomach cancer in A-bomb survivors in the LSS sample were conducted by Kato et al (1950—66), Nakamura (1950—73), and Beebe et al (1950—74). The results of all of these studies have indicated a significant increase in stomach cancer mortality in the heavily exposed survivors.

On the other hand, pathological research on stomach cancer includes a study by Murphy and Yasuda conducted during 1948—57 using autopsy and surgical materials in Hiroshima, and studies by Yamamoto et al conducted during 1961—68, 1961—69, and 1961—74 using autopsy material in Hiroshima and Nagasaki. However, none of these pathological studies revealed a significant correlation between stomach cancer incidence and exposure.

As described in the introduction, a remarkable increase in the rate of early stomach cancer detection due to advancements achieved in gastric diagnostics and the popularization of mass stomach screening in Japan during the past three decades has greatly changed the clinical picture of stomach cancer. It has now become almost impossible to adequately pursue the association between A-bomb exposure and the incidence of stomach cancer using the conventional procedures of the LSS and pathological study alone.

In this study, aiming to make up for deficiencies in research methods employed heretofore, the association between A-bomb exposure and stomach cancer was investigated using as study subjects all cases of stomach cancer including surgical and pathological cases and clinical cases as well as cases identified by death certificate or autopsy.

As a result, when the risk was corrected for the effects of sex and age, the effects of radiation were evident only in the 200+ rad group. When the effect of dose is reviewed in relation to age-group, a significant increase in risk is observed in all three age-groups under 30 ATB who were exposed to 200+ rad. However, the risk of those in the 50+ ATB age-group is not significant, it being 1.1, which is of the same level as the control group. Since those who are in the
under 30 ATB age-groups are now showing a higher incidence of stomach cancer, and are now approaching the age of greatest cancer risk (50–70), it will be of great interest to conduct follow-up studies of future trends in stomach cancer incidence.

So far, tumors which have been observed with an increased frequency among A-bomb survivors include leukemia, lung cancer, breast cancer, thyroid cancer, salivary gland tumor, malignant lymphoma, and multiple myeloma. The increase in incidence of these tumors is generally observed in the heavily exposed, 100+ rad groups. In the present study, significant increase in the incidence of stomach cancer was also evident in the 100+ rad groups, especially 200+ rad group. This tendency was similar to those for the other types of tumors mentioned above.

The finding that tumors develop at a high frequency in those exposed at a young age was pointed out by Jablon et al. based on their study of the 100+ rad group in Hiroshima and in Nagasaki who had been less than age 10 ATB. Also, similar findings have been reported subsequently for leukemia, salivary gland tumor, and breast cancer. More particularly, it has been reported that leukemia develops at the highest frequency in the heavily exposed group under age 15 ATB, and thyroid gland tumor in the proximally exposed group of age 0–19 ATB, and the highest risk of breast cancer is observed in the 100+ rad groups who were age 10–19 ATB.

Based on the dose-response relationship obtained using total kerma dose in conjunction with the present data on the incidence of stomach cancer, it must be stressed that the dose-response of stomach cancer development is definitely not quadratic, but linear, at least when results based on the T65DR are used. It should be noted, however, that only the results for males in Hiroshima suggest a quadratic dose response. Conducting observations by age-group, a significant linear response was observed in the 10–19 and 20–29 ATB age-groups. The 10–19 ATB age-group showed the most significant increase in risk, but their estimated risks of stomach cancer for both city and sex adjusted were 1.5 and 1.7 per million PYR, respectively. These values, as compared with 1.2, the average risk for all city-sex-age factors adjusted, indicate that the younger ATB age-groups have a higher risk per million PYR. Furthermore, the 0–9 ATB age-group, only a part of whom are now reaching the age of higher cancer risk, were still 32–41 years of age at the time of the 1974 survey, and a significant linear response could not be observed at that time. The dose response for this younger age-group will become known through follow-up studies continued on the fixed population.

Sites of stomach cancer focuses are similar regardless of dose, with the frequency being highest in the lower to middle portions, especially on the lesser curvature. The same finding had been reported by Yamamoto et al., and the above locations generally correspond with the main locations of tumors in typical
In the present analysis of stomach cancer by histological type, classification was made roughly into five types: differentiated type adenocarcinoma, poorly differentiated type adenocarcinoma, mucinous adenocarcinoma, other histological types, and type unknown. There was a tendency in the 200+ rad group for the frequency of poorly differentiated type adenocarcinoma to increase, while on the other hand, the differentiated type adenocarcinoma decreased. However, since there was a good agreement between the observed and expected numbers of the poorly differentiated type, it could not be concluded that there is a significant relationship between dose and histological type, because the possibility exists that the decrease in the frequency of differentiated type cases is due to the increase in the frequency of type unknown ones.

Generally, the radiation-induced cancers developing among A-bomb survivors have failed to exhibit predominance of any specific histological type for leukemia, breast cancer, and salivary gland tumor. The exception is lung cancer, in which there has been shown to be a high frequency of small cell carcinoma. Accordingly, it is considered necessary that a larger number of cases be accumulated in the future, so that more comprehensive review can be made of histological types of stomach cancer.

Intestinal epithelial metaplasia is considered important as the mother tissue of stomach cancer, especially in the case of differentiated type carcinoma. However, pathological studies of stomach cancer in A-bomb survivors conducted heretofore have made no mention of the degree of intestinal epithelial metaplasia. It is assumed that this is probably because the degree of intestinal epithelial metaplasia could not be determined due to the severe postmortem degeneration of the autopsy material.

The present study revealed that the degree of intestinal epithelial metaplasia is greater and its frequency is higher in the differentiated than poorly differentiated type carcinomas. This finding supports a theory that differentiated type carcinoma develops from intestinal epithelial metaplastic mucosa as its mother tissue. Review of cases of various histological types by exposure dose demonstrated a significant trend only in the degree of intestinal epithelial metaplasia. That is, there was an evidence that the degree in intestinal epithelial metaplasia increases with dose.

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