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Lung Cancer Incidence among Japanese A-Bomb Survivors, 1950-80

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A-bomb/Radiation/Human Lung Cancer/Patho-epidemiology Study

The incidence of lung cancer during 1950-80 in a cohort of Japanese A-bomb survivors and controls was investigated. A total of 1,057 cases were identified; 608 of these diagnoses were based on histopathological examination, and 442 were confirmed by the present investigators. The distributions of histologic types varied significantly between the sexes ($p < .001$), with adenocarcinoma more frequent among women and epidermoid and small cell carcinoma more frequent among men. The distributions of primary sites did not differ significantly between the sexes. The relative risk (RR) of lung cancer increased significantly with A-bomb radiation dose ($p < .0001$): based on tentative 1965 dose estimates as revised in 1978 (T65DR) and a linear RR model, the estimated RR at 100 rad (±s.e.) is 1.41 ± 0.09. Among Hiroshima survivors the women experienced radiation-related excess RR nearly twice as great as men ($p = .06$). RR increased with decreasing age at the time of bombing (ATB; $p = .07$), and after allowing for this effect, there was no significant evidence that RR varied systematically with attained age. Small cell carcinoma displayed somewhat greater sensitivity to radiation than did adenocarcinoma or epidermoid carcinoma; however the variation between the histology-specific RR functions was not statistically significant ($p = .44$).

INTRODUCTION

In recent years, increases in lung cancer have been reported in various countries throughout the world, and Japan is no exception[1,2]. Attention has been focused on lung cancer as well

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as other radiation-induced cancers among A-bomb survivors since shortly after the bombings of Hiroshima and Nagasaki. Reports have examined clinical cases and autopsy cases during 1950-70[3–6], and mortality during 1950-82[7]. The studies have shown that the risk of lung cancer is related to radiation dose, and that the association of anaplastic small cell carcinoma to radiation may be especially strong. The purpose of this report is to summarize the incidence rates and histopathological characteristics of lung cancer during 1950-80 among a cohort of A-bomb survivors and unexposed controls. As many cases as possible, including clinical, autopsy, and death certificate cases, were considered.

MATERIALS AND METHODS

Study Cohort

This study is based on the extended ST-100 cohort, which includes about 82,000 persons exposed to the atomic bombings of Hiroshima and Nagasaki and 27,000 unexposed controls who were in neither city (NIC) ATB. The selection of this cohort is described in detail elsewhere[8]. This is essentially the same cohort as that used in the analyses of mortality by Kato and Schull[9]. Follow-up of each member of the cohort commenced between 1 October 1950 and 1 October 1953.

The cohort was divided into categories by city (Hiroshima, Nagasaki), sex (male, female), and age ATB (0-9, 10-19, 20-29, 30-39, 40-49, 50+), data which are known for all members of the extended ST-100.

As in most analyses of A-bomb survivor data in the last two decades, radiation dose is here synonymous with tissue kerma in air (sum of neutron and gamma) adjusted for shielding by man-made structures or natural objects, calculated according to the tentative 1965 dosimetry system, as revised in 1978 (T65DR dose estimates)[9, 10]. Survivors for whom T65DR dose estimates cannot be calculated, due to complicated shielding situations or missing information, were excluded from analyses of the radiation dose-response, as was the NIC group. The remaining 79,940 survivors were divided into eight dose categories: 0 rad (meaning < 1/2 rad), 1-9, 10-49, 50-99, 100-199, 200-299, 300-399, and 400+.

It has become clear that T65DR dose estimates may be seriously in error for many subjects[11], although at the time of this writing (1986) an accepted alternative dosimetry system is not available. Revision of the dose estimates is likely to result in modification of estimates of risk of radiogenic cancer. In particular the difference between the two cities is expected to change, since dose estimates of Nagasaki survivors are likely to change much more than those of Hiroshima survivors. Therefore comparisons between the cities are not emphasized in this report, and some analyses are restricted to Hiroshima survivors. It is important to note that recent analyses of cancer mortality among A-bomb survivors[12] have indicated that, while estimates of radiogenic risk and intercity comparisons will be sensitive to the anticipated modification of dose estimates, other important features of the radiogenic risk such as sex differences and dependencies on age ATB or time will probably change very little.

Identification of Cases

An attempt was made to identify as many cases of lung cancer as possible using various sources available to Radiation Effects Research Foundation, including tumor and tissue registries in each city; records of autopsies performed at Atomic Bomb Casualty Commission-Radiation Effects Research Foundation (ABCC-RERF), at the Schools of Medicine of Hiroshima and Nagasaki Universities, and other medical facilities in the cities; and records of certified causes of death routinely obtained by ABCC-RERF as part of its program of active followup of the extended ST-100 cohort. Each person's followup began on 1 October 1950 or his/her 20th birthday, whichever was later. (No cases of lung cancer were diagnosed among persons aged less than 20 years.)

Tissue specimens or slides from autopsies, biopsies, and/or surgical procedures were obtained when possible for microscopic examination by a single pathologist (T.Y.). Autopsy protocols were reviewed, and reexamination of questionable cases were conducted from paraffin blocks. Mainly H-E stain was employed, although PAS and Alcian-Blue were used as well. Histological classification was based on the Japan Lung Cancer Society's criteria[13], which are similar and comparable to the World Health Organization's classification system[14]. In the event of even minor uncertainty, the diagnosis was established in conference with the coinvestigators.

Statistical Methods

Accumulation of person-years (PY) at risk commenced with the beginning of each person's followup, or on his/her 20th birthday, whichever was later, and ceased upon onset of lung cancer, death from any cause, or 31 December 1980, whichever was earliest. Because of the variety of sources from which cases were identified, no single event could be defined as a date of onset which was known for all cases. Therefore the recorded dates of onset for this study range between the date of first diagnosis and the date of death.

Age attained throughout the period of followup, 1950-80, was divided into six categories: 20-29, 30-39, ..., and 70+. The period of followup was also divided into four intervals ending on the last days of 1954, 1958, 1962 and 1980. For analyses of lung cancer risk, PY and cases were aggregated and crossclassified according to city, sex, age ATB, attained age, interval of followup, and radiation dose, using the categories defined above. For analyses as quantitative variables, the categories of age ATB and attained age were assigned as classmarks the values 5, 15, ..., 55 and 25, 35, ..., 80, respectively. The classmark values for the radiation dose categories were the average doses within each category.

For analyses of the radiation dose-response among the 79,940 exposed survivors with T65DR dose estimates, directly standardized incidence rates were calculated. These were adjusted for age ATB, attained age, interval of followup, and (when appropriate) city and/or sex using the distribution of PY in the 0 rad group. Further analyses of the effects of radiation were based on linear RR models. A detailed description of the use of such models is given elsewhere[7,15,16]. Let $i = 1, \ldots, 224$ be an index for strata defined by the combinations of city, sex, age ATB, attained age, and interval of followup. Let the classmark values of dose, d, index the radiation dose categories. The numbers of lung cancer cases in the various combinations

of strate and dose groups were assumed to be realizations of independent Poisson random variables with expected values PY (d;i)λ(d;i), where PY (·) denotes PY at risk and λ (·) denotes the specific incidence rate. Then RR (d;i) = λ (d;i)/λ(O;i) is the RR associated with dose d in stratum i. Under the linear RR model, the radiation-related excess RR is proportional to dose:

$$RR(d;i) - 1 = \beta_i d \quad . \qquad [1]$$

The coefficient β_i represents excess RR per unit of radiation dose. Notice that the excess RR in [1] may depend on i, which allows modification of the dose-response by factors such as sex, age ATB, etc. Because RR cannot be less than zero, the excess RR per 100 rad must be greater than $-100/d_{max}$, where d_{max} is the largest dose classmark, 526 rad. Thus a minimum feasible value of −.19 is set for the excess RR per 100 rad in [1] for analyses based on all dose categories.

Parameter estimation and significance testing were based on maximum likelihood analysis of the Poisson regression models described above, which requires that the background (spontaneous) incidence rates, λ (O;i), be estimated simultaneously with the parameters of excess risk. For most analyses the following parametric background model was used:

$$\log [\lambda(O;i)] = \alpha_0^{(k)} + \alpha_1 CITY + \alpha_2 SEX + \alpha_3 (ATB\text{-}30) + \alpha_4 \ell n(ATT/50) + \alpha_5 [\ell n(ATT/50)]^2 , \qquad [2]$$

where k indexes the four intervals of followup, CITY and SEX are indicator variables, and ATB and ATT denote the classmark values of age ATB and attained age, respectively, defined above. Allowing separate constant terms for the first three intervals of followup, $\alpha_0^{(1)}$, $\alpha_0^{(2)}$, and $\alpha_0^{(3)}$, was necessary to accommodate exceptionally low rates observed prior to 1963. For simplicity, estimates of the parameters in the background model [2] are not reported in the text of this report, but are summarized for selected models in Appendix Table 1. For certain analyses, which are explicitly identified below, [2] was not used; rather background rates were permitted to vary without restriction among the 224 strata. The latter approach, designated the nonparametric background model, was also used to test the goodness-of-fit for the parametric background model [2].

RESULTS

Description of Cases

A total of 1,057 cases of lung cancer among members of the Extended ST-100 cohort during the period 1950-80 were identified. Of these, 608 were based on histopathologic diagnosis (Table 1), including 442 which were confirmed by histopathological examination of tissue specimens in the current study (Table 1, Part A). For 615 cases no histopathological review was possible for this study. The majority of these diagnoses were based on death certificates

and/or tumor registry records (Table 1, Part B). The heavy reliance on death certificate diagnoses (257 cases) is a cause for concern, since the Autopsy Program recorded a confirmation rate of only 61% for death certificate diagnoses of lung cancer[17]. For 318 cases the Tumor Registries contained records of premortem diagnoses of lung cancer. None of these diagnoses were based solely on ultrasonographic, radiographic, or clinical examinations, and 46% (146) were based on cytological or microscopic examination of tumor cells. The false positive rates for those various kinds of premortem diagnoses are unknown.

Table 1. Summary of diagnostic data

A. Cases confirmed by microscopic examination for present study

Type of specimen(s)	Exposed survivors		NIC	Total
	T65DR known	T65DR unknown		
Autopsy only	293	7	76	376
Autopsy, plus surgical or biopsy	7	1	1	9
Surgical	24	1	10	35
Biopsy	19	0	3	22
Total	343	9	90	442

B. Cases not confirmed for the present study

Most definitive diagnosis of lung cancer	Exposed survivors		NIC	Total
	T65DR known	T65DR unknown		
	1. Histopathological diagnoses			
RERF Autopsy Program, but specimen not available	6	1	2	9
Tumor Registry Record				
– Autopsy	7	0	4	11
– Microscopic or cytological	105	3	38	146
Total	118	4	44	166
	2. Other diagnoses			
Tumor Registry Record – Surgical, endoscopic or radioisotopic	129	3	40	172
Death Certificate	183	5	69	257
No Autopsy Program, Tumor Registry, or Death Certificate Diagnosis	19	0	1	20
Total	331	8	110	449

The distribution of histologic types among the 442 confirmed cases are shown by sex and exposure status in Table 2. Adenocarcinoma was the most common diagnosis, accounting for 174 (40%) of 435 cases assigned a histologic type, followed by epidermoid carcinoma (148; 34%) and small cell carcinoma (72; 17%). The distributions differ significantly between the sexes ($p < .001$, based Pearson's χ^2 test with mucoepidermoid and unclassified cases

Table 2. Distribution of histologic types among 442 confirmed lung cancer cases; by T65DR status and sex (Ext. ST-100 cohort, both cities, all ages ATB, attained age 20+, 1950-1980)

Histologic type	Exposed survivors				NIC		Total	
	T65DR known		T65DR unknown					
	Male	Female	Male	Female	Male	Female	Male	Female
Adenocarcinoma	80 (35%)	60 (54%)	1 (17%)	2 (67%)	16 (25%)	15 (58%)	97 (33%)	77 (55%)
Epidermoid carcinoma	78 (35%)	28 (25%)	3 (50%)	1 (33%)	32 (51%)	6 (23%)	113 (38%)	35 (25%)
Small cell carcinoma	43 (19%)	13 (12%)	2 (33%)	0 (0%)	11 (17%)	3 (12%)	56 (19%)	16 (11%)
Large cell carcinoma	12 (5%)	7 (6%)	0 (0%)	0 (0%)	3 (5%)	2 (8%)	15 (5%)	9 (6%)
Mixed Epidermoid-adenocarcinoma	13 (5%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	13 (4%)	2 (1%)
Mucoepidermoid carcinoma	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (<1%)	1 (1%)
Total classified	226(100%)	111(100%)	6(100%)	3(100%)	63(100%)	26(100%)	295(100%)	140(100%)
Not classified	5 ---	1 ---	0 ---	0 ---	1 ---	0 ---	6 ---	1 ---
Total	231 ---	112 ---	6 ---	3 ---	64 ---	26 ---	301 ---	141 ---

omitted). Adenocarcinoma is relatively more frequent among women (55%) than among men (33%), while the opposite is true for epidermoid carcinoma (males 38%, females 25%) and small cell carcinoma (19% and 11%).

The primary site of the lung cancer was at least partially known for 445 cases (Table 3). Survivors without T65DR dose estimates and the NIC group are included in the table. Cancers

Table 3. Distribution of primary sites of lung cancer among 445 cases by sex (Ext. ST-100 cohort; both cities, all ages ATB, attained age 20+, 1950-1980)

Lobe	Sex		Total
	Male	Female	
1. Left lung			
Upper	68 (22%)	39 (28%)	107 (24%)
Lower	44 (14%)	19 (14%)	63 (14%)
Unknown	25 (8%)	9 (6%)	34 (8%)
Subtotal	137 (45%)	67 (48%)	204 (46%)
2. Right lung			
Upper	62 (20%)	34 (24%)	96 (22%)
Middle	11 (4%)	6 (4%)	17 (4%)
Lower	65 (21%)	22 (16%)	87 (20%)
Unknown	24 (8%)	9 (6%)	33 (7%)
Subtotal	162 (53%)	71 (51%)	233 (52%)
3. Bronchus			
Subtotal	6 (2%)	2 (1%)	8 (2%)
4. All sites			
Total	305 (100%)	140 (100%)	445 (100%)

were only slightly more frequent in the right lung, compared to the left, and this pattern did not differ significantly between males and females ($p = 0.60$, based on the χ^2 test for a 2×2 table without correction for continuity). Among 370 cancers arising in the lungs and for which the lobe of origin was known, 203 (55%) occurred in the upper lobes. This proportion was slightly higher among females (73/120; 61%) than males (130/250; 52%), but the difference was not statistically significant ($p = 0.11$).

Lung Cancer Incidence and Radiation Dose

The incidence of lung cancer among exposed survivors with T65DR dose estimates is sum-

Table 4. Lung cancer incidence among exposed survivors with T65DR doses; by city, sex, and T65DR radiation dose (Ext. ST-100 cohort, all ages ATB, attained age 20+, 1950-1980)

	T65DR Radiation Dose (rad)								
	0	1-9	10-49	50-99	100-199	200-299	300-399	400+	Total[1)]
1. All exposed survivors									
Number	31618	22614	14819	4187	3115	1370	635	1582	79,940
Mean dose	0	3	22	71	142	244	345	526	32
2. Males: Hiroshima									
Person-years	244305	153794	91507	22155	16584	6369	3147	5231	543,092
Cases	151	89	66	19	25	8	3	8	369
Rate (per 10^5PY)[2)]	63.3	62.6	68.5	75.8	131.2	132.3	96.9	167.1	---
Relative risk	1.00	0.99	1.08	1.20	2.07	2.09	1.53	2.64	---
3. Males: Nagasaki									
Person-years	41548	65496	36041	15338	15182	7697	2979	4018	188,298
Cases	30	34	15	7	13	7	3	4	133
Rate (per 10^5PY)[2)]	85.8	76.1	54.9	48.1	133.6	134.7	105.8	155.8	---
Relative risk	1.00	0.89	0.64	0.56	1.56	1.57	1.23	1.82	---
4. Females: Hiroshima									
Person-years	399982	220315	163914	42932	24415	9337	5578	6814	873,289
Cases	89	55	60	19	14	4	6	3	250
Rate (per 10^5PY)[2)]	21.0	23.8	33.4	39.9	56.7	39.8	95.9	47.9	---
Relative risk	1.00	1.14	1.60	1.90	2.70	1.90	4.57	2.29	---
5. Females: Nagasaki									
Person-years	54261	101935	56140	19853	20044	10541	3777	4606	271,158
Cases	11	27	9	2	6	3	1	1	60
Rate (per 10^5PY)[2)]	24.8	31.4	18.6	9.0	32.1	40.5	30.5	12.4	---
Relative risk	1.00	1.27	0.75	0.36	1.30	1.63	1.23	0.50	---

1. Person-years may not sum to "Total" due to rounding.
2. Directly standardized to adjust for age ATB, attained age, and time since exposure, using the distribution of PY in the 0 rad group for both cities and both sexes combined. Approximate standard errors for rates are shown in Figs. 1 and 2.

marized by city, sex, and radiation dose in Table 4, and the standardized incidence rates are illustrated in Fig. 1. Two remarkable features are apparent in the figure. The first is the relatively low rates among Nagasaki males exposed to 1-99 rad and Nagasaki females exposed to 10-99 rad. The second feature is the absence of any obvious increasing trend with dose above 100 rad. City-specific standardized incidence rates and RRs for both sexes combined are

Table 5. Standardized rates of lung cancer incidence among exposed survivors with T65DR doses; by city and T65DR radiation dose (Ext. ST-100 cohort, both sexes, all ages ATB, attained age 20+, 1950-1980)

	T65DR Radiation Dose (rad)							
	0	1-9	10-49	50-99	100-199	200-299	300-399	400+
				1. Hiroshima				
Rate(per 10^5PY)[1)]	36.4±2.4	37.8±3.2	45.7±4.1	53.1±8.7	84.3±13.9	76.1±22.1	97.6±33.4	91.9±28.2
Relative risk	1.00	1.04	1.25	1.46	2.32	2.09	2.68	2.52
				2. Nagasaki				
Rate(per 10^5PY)[1)]	48.3±7.7	48.0±6.2	32.5±6.7	24.5±8.3	68.5±17.7	73.0±24.1	61.2±31.7	69.7±33.2
Relative risk	1.00	0.99	0.67	0.51	1.42	1.51	1.27	1.44

1. Cases per 10^5 PY ± one approximate standard error; directly standardized to adjust for sex, age ATB, attained age, and time since exposure, using the distribution of PY in the 0 rad group for both cities pooled.

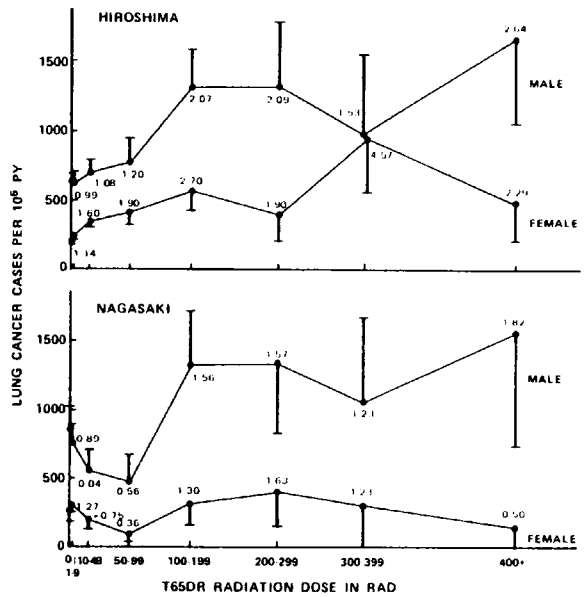

Fig. 1. Standardized lung cancer rates by city, sex, and T65DR radiation dose (all ages ATB, attained age 20+, 1950-1980)
Adjusted for age ATB, attained age, and time since exposure by direct standardization, based on the distribution of PY in the 0 rad group with both cities and both sexes combined. The numerical values shown in the figure are the ratios of rates in each dose category to the rate for the 0 rad group.

summarized in Table 5; the two features mentioned above are clearly seen in this sex-pooled data. The standardized incidence rates (± one approximate standard error) for all doses of 100+ rad are 87.8 ± 10.5 per 10^5 PY and 71.9 ± 12.9 per 10^5 PY for Hiroshima and Nagasaki, respectively. The corresponding standardized rate ratios (100+ rad vs. 0 rad) are 2.4 and 1.5, respectively.

Results of fitting linear RR models of the form [1] for the effect of radiation exposure are summarized in Table 6. The estimates in that table are adjusted for age ATB, attained age, followup interval, and, as appropriate, city and/or sex by the use of the parametric background model [2]. For both cities and both sexes combined, the estimated RR at 100 rad is 1.41 ± 0.09. For comparing dose-responses among subsets of the cohort, it is useful to consider the *excess* RR. Calculated as one less than the estimated RR at 100 rad, this gives the rate at which RR increases for each dose increment of 100 rad. As indicated in Table 6, the excess RR for Hiroshima (0.56 ± 0.12 per 100 rad) is nearly three times larger than that for Nagasaki (0.19 ± 0.11). Moreover, among Hiroshima survivors, the excess RR for females (0.83 ± 0.24 per 100 rad) is nearly twice that for males (0.43 ± 0.14), although the difference is only marginally significant (one-sided p = .06). The excess RR for Nagasaki females is slightly lower than that for Nagasaki males: 0.15 ± 0.19 vs. 0.20 ± 0.13 per 100 rad, respectively; however, due to the unusual shape of the Nagasaki dose-response, this was not analyzed in further detail. Appendix Table 1 gives the full set of parameter estimates for the model with city-by-sex-specific dose-responses.

The estimated number of excess cases induced by A-bomb radiation (calculated as described by Preston et al.[7]) is 76.2, which corresponds to an absolute excess risk of 1.5 cases per 10^6 PY-rad. Since these radiogenic cases are necessarily included among the 511 cases in survivors exposed to 1+ rad, the estimated attributable risk is 15% (76.2/511).

Figure 1 indicates that even for Hiroshima the RR may not increase linearly over the entire range of radiation doses. Since accurate estimation of risks associated with exposures to

Table 6. Radiation dose-response[1] for lung cancer incidence among exposed survivors with T65DR doses; by city, sex, and radiation dose range (Ext. ST-100 cohort, all ages ATB, attained age 20+, 1950-1980)

City	Sex		
	Male	Female	Both
	1. All radiation doses		
Hiroshima	1.43 ± .14[2]	1.83 ± .24	1.56 ± .12
Nagasaki	1.20 ± .13	1.15 ± .19	1.19 ± .11
Both	1.34 ± .10	1.56 ± .17	1.41 ± .09
	2. Only doses less than 100 rad		
Hiroshima	1.30 ± .37	2.59 ± .61	1.78 ± .33
Nagasaki	0.46 ± .36	0.18 ± .44	0.38 ± .29
Both	1.01 ± .28	1.90 ± .47	1.32 ± .25

1. Based on T65DR dose estimates.
2. Estimated RR at 100 rad ± one approximate standard error, based on linear RR model [1].

low doses is of particular importance, Table 6 also gives results based only on doses less than 100 rad. For both sexes combined, the excess RR for Hiroshima increases to 0.78 ± 0.33 per 100 rad, while the apparent dose-response is negative for Nagasaki. Also the difference between the sexes in Hiroshima becomes even more pronounced: 1.59 ± 0.61 for females vs. 0.30 ± 0.37 for males (p = 0.03).

Table 7 gives the radiation dose-response by categories of age ATB and/or attained age. The entires in Table 7 are based on the parametric background model [2], and common linear RR functions are estimated for both cities and both sexes. Categories with age ATB less than 9 years or attained age less than 40 years are excluded from Table 7. This was done to eliminate categories for which the dose-response cannot be estimated precisely; only 10 cases occurred in those categories. Notice that the overall estimated RR at 100 rad, when limited to persons 10+ years old ATB and after the 4th decade of life, is 1.42 ± 0.09, which is almost identical to the corresponding value in Table 6.

As shown in Table 7, RR tends to increase with decreasing age ATB, although the trend is only marginally significant (one-sided p = .04, based on a test for loglinear trend in age ATB). A similar effect is observed for attained age (p = .07) if age ATB is ignored. The two age variables are highly correlated in these data, however, so after allowing for the loglinear trend of excess RR in relation to age ATB, there is no significant additional effect of attained age (p = .46). Moreover, although the excess RR appears, very generally, to increase with attained age among the three youngest ATB groups and to decrease with attained age among the two oldest ATB groups, the interaction between the effects on the excess RR of age ATB and attained age is not statistically significant, after allowing for the effect of age ATB (p = .88).

The differences between Hiroshima and Nagasaki; between the sexes for Hiroshima survivors; and between the categories of age ATB are illustrated in Fig. 2. The estimated RR at 100 rad is consistently largest for Hiroshima females, and smallest for Nagasaki survivors. The RRs are also largest in each case for persons 10-29 years old ATB. There is also a suggestion

Table 7. Radiation dose-response[1] for lung cancer incidence among exposed survivors with T65DR; by age ATB and attained age (Ext. ST-100 cohort, both cities, both sexes, 1950-1980)

Age ATB	Attained age				
	40-49	50-59	60-69	70+	All 40+
10-19	1.99 ± .58 (19)[2]	2.37 ± .95 (8)			2.08 ± .50 (27)
20-29	1.74 ± .68 (8)	2.02 ± .48 (32)	1.67 ± .76 (9)		1.87 ± .36 (49)
30-39	0.81 (6)[3]	1.05 ± .22 (38)	1.29 ± .22 (83)	1.56 ± .50 (23)	1.23 ± .15 (150)
40-49	NE (0)[4]	1.95 ± .63 (21)	1.36 ± .20 (118)	1.27 ± .16 (178)	1.35 ± .12 (317)
50+		5.3 ± 6.1 (3)	1.56 ± .47 (30)	1.34 ± .16 (206)	1.38 ± .16 (239)
All 10+	1.70 ± .39 (33)	1.66 ± .24 (102)	1.37 ± .14 (240)	1.32 ± .12 (407)	1.42 ± .09 (782)

1) Based on T65DR dose estimates.
2) Estimated RR at 100 rad ± one approximate standard error, based on linear RR model [1]. Number of cases is given in parentheses.
3) Minimum feasible value of RR at 100 rad, based on linear RR model.
4) Not estimable, since no cases occurred.

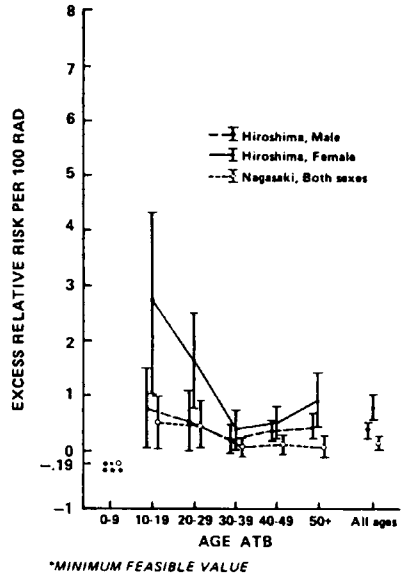

Fig. 2. Radiation dose-response by city, age ATB, and, for Hiroshima, sex (attained age 20+, 1950-1980)
Plotted points show estimated RR at 100 rad ± one approximate standard error, adjusted for attained age and interval of followup by the parametric background model [2]. Asterices indicate that RR or lower end of standard error bar is set at the minimum feasible value.

in Fig. 2 that the RRs increase slightly with increasing age ATB above the age of 30 years ATB, however the data are quite adequately fit by a loglinear model, according to which the RRs decrease monotonically with increasing age ATB. This loglinear effect of age ATB does not vary significantly among the three groups in Fig. 2 ($p = .47$). Parameter estimates for the model corresponding to Fig. 2, but with the loglinear effect of age ATB on excess RR, are given in Appendix Table 1.

Dose-Response by Histologic Type

To examine the effect of exposure to A-bomb radiation on the risks of specific histologic types of lung cancer, attention was restricted to the 343 *confirmed* cases among exposed survivors with T65DR dose estimates (Table 2). The proportion of cases which were confirmed for this study tended to be higher in the high radiation dose categories: 205/486 (42%), 110/255 (43%) and 28/51 (55%) for the 0-9, 10-199, and 200+ rad groups, respectively. Therefore, analyses based only on confirmed cases will be subject to bias in the estimation of the radiation dose-response. For example, the estimated RR at 100 rad based on the 343 confirmed cases is 1.56 ± 0.15, which is greater than the corresponding estimate, 1.41 ± 0.09, based on all 792 cases (Table 6).

If it is assumed that these biases affect all histologic types equally, then comparisons among histology-specific effects of radiation will be unbiased. Figure 3 displays the RRs as-

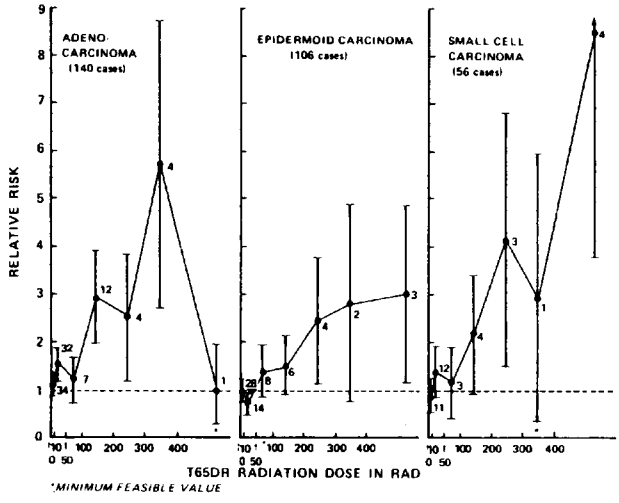

Fig. 3. Relative risk of lung cancer incidence by radiation dose category and histologic type (both cities, both sexes, all ages ATB, all attained ages, 1950-1980)
Adjusted for city, sex, age ATB, attained age, and interval of followup by use of the stratified background model [2]. Points are plotted at average doses given in Table 4. Bars indicate ± one approximate standard error; arrows indicate when error bars extend beyond the range of the RR axis. Numbers of cases in each dose category above 0 rad are indicated in the figure.

sociated with each dose category for the three major histologic types: adenocarcinoma, epidermoid carcinoma, and small cell carcinoma. These RRs are adjusted for city, sex, age ATB, attained age and interval of followup by the nonparametric background model, rather than [2]. Based on [1], the estimated RRs at 100 rad are 1.58 ± 0.25, 1.48 ± 0.26, and 2.14 ± 0.54 for these three types, respectively. Although the excess RR for small cell carcinoma is twice as large as that for adenocarcinoma, the dose-response does not differ significantly among the three histologic types ($p = .44$).

DISCUSSION

The purpose of this report is to provide an overview of lung cancer in the Extended ST-100 cohort during 1950-80. Examination of the histopathological features of the cancers in this cohort has necessarily been limited to less than half of the 1.057 cases detected, since tissue specimens were not available for 615 cases (Table 1). Among the 442 cases from which specimens were examined for this study, the pathological findings were generally consistent with those reported for other populations. For example, the predominance of adenocarcinoma among histologic types has been reported for Japanese in Tokyo[18] and for Japanese women in

Hawaii[19]. This contrasts with the predominance of epidermoid carcinoma in western populations. Ives et al.[20] summarized sex-specific distributions of histologic types of lung cancer in their Table 3 (derived from a review by Mondan[21] of studies done in 10 different nations, mostly European and not including Japan). The pattern of histologic types in their summary was similar to that shown here in Table 2. However, some variations between populations do exist. For example, Vincent et al.[22] in a review of lung cancer patients seen at Roswell Park Memorial Institute (RPMI) during 1962-75 found that small cell carcinoma was relatively more frequent among women than men, while the opposite is true for the Extended ST-100 cohort (Table 2). However, in the RPMI series, epidermoid carcinoma and adenocarcinoma were the predominant types among males and females, respectively[22], which is consistent with the present results (Table 2). Such variations may be attributable to genetic differences between Japanese and U.S. populations, to differences in patterns of etiology, and/or to differences in diagnostic criteria and practice (42% of the RPMI[20] series were based on confirmation of autopsy data, compared to 85% (376/442) in the present study). It is interesting that the overall relative frequencies of small cell carcinoma were roughly comparable between the two series (19% for RPMI, 17% for the Extended ST-100), although it has been suggested that small cell carcinoma is reported more frequently from autopsy diagnoses, compared to surgical, biopsy, or cytological diagnoses[20].

Exposure to A-bomb radiation significantly increased the risk of lung cancer among the 79,940 exposed survivors with T65DR dose estimates. This is consistent not only with other studies of A-bomb survivors[3-7], but with studies of patients with ankylosing spondilitis as well[23,24].

The differences between the radiation dose-responses of the two cities (Figs. 1 and 2) is partly attributable to the use of T65DR dose estimates. Preliminary results based on an interim set of revised dose estimates[12] suggest that such city differences will be largely eliminated by the eventual adoption of a revised dosimetry, upon completion of the U.S.-Japan dose reassessment project. Still the exceptionally low lung cancer rates among Nagasaki survivors exposed to 1-100 rad remains unexplained.

Among Hiroshima survivors, women experienced significantly greater RR of radiogenic lung cancer incidence than men. In a recent survey of cancer mortality, a similar sex effect was observed for lung cancer[7]. The effect was shown to arise because women experienced absolute (additive) excess risks similar to those of men, but background rates substantially lower than men[7]. This is also seen in the parameter estimates for [2] given in Appendix Table 1. The background rate for women is only about $\exp(-1.01) \times 100\% = 36\%$ of the background rate for men, a highly significant difference ($p < .0001$). This difference is most likely largely attributable to differences in smoking habits. Since smoking data were available for only a subset of the Extended ST-100 cohort, and analysis of the joint effects of smoking and A-bomb radiation on the incidence of lung cancer is given in a separate report[25].

Based on cases diagnosed during 1950-80, those exposed at young ages ATB have experienced greater RR of radiogenic lung cancer than those who were older. This pattern has been observed for mortality from several nonleukemic cancers[7]. Further followup of the cohort will be necessary in order to determine the effect that exposure in youth to radiation will have

on the full life-time risk of lung cancer: at the end of 1980, persons aged 0-20 ATB were no older than 56.

The radiation dose-responses of the three major histological types of lung cancer (Fig. 3) were not significantly different, although small cell carcinoma appeared to be slightly more radiosensitive than adenocarcinoma or epidermoid carcinoma. This lack of statistical significance may derive from the comparatively small numbers of cases of each type and the consequent lack of statistical power, a common weakness of studies seeking to compare the radiosensitivities of specific types of lung cancer[20]. The present data, while not conclusive in this regard, support a tentative conclusion that all three histological types are susceptible to induction by radiation.

In the continued interest of accurately defining the late effects of the atomic 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.

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Appendix Table 1. Maximum likelihood estimates for selected models of lung cancer incidence among exposed survivors with T65DR doses

Variable	Coefficient	Model	
		#1	#2
Background Incidence Rates: model [2]			
Constant (1950-54)	$\alpha_0(1)$	3.828 ± 0.281[1)]	3.791 ± 0.283
Constant (1955-58)	$\alpha_0(2)$	4.552 ± 0.200	4.516 ± 0.203
Constant (1959-62)	$\alpha_0(3)$	5.457 ± 0.137	5.422 ± 0.141
Constant (1963-80)	$\alpha_0(4)$	6.033 ± 0.094	5.999 ± 0.099
City (H = 0, N = 1)[2)]	α_1	0.163 ± 0.101	0.155 ± 0.100
Sex (M = 0, F = 1)[2]	α_2	−1.006 ± 0.085	−1.008 ± 0.082
ATB-30	α_3	0.020 ± 0.006	0.023 ± 0.006
ℓn (ATT/50)	α_4	5.098 ± 0.499	5.132 ± 0.503
$[\ell n (ATT/50)]^2$	α_5	−2.793 ± 0.803	−2.851 ± 0.810
Radiation-related excess RR: $RR(d;i) = \beta d \exp[\beta_1 (ATT-30)]$			
Dose (H, M)[2)]	β	0.427 ± 0.136	0.548 ± 0.199
Dose (H, F)[2)]	β	0.832 ± 0.236	1.056 ± 0.331
Dose (N, M)[2)]	β	0.197 ± 0.131	---[3)]
Dose (N, F)[2)]	β	0.149 ± 0.186	---[3)]
Dose (N, M+F)[2)]	β	---[3)]	0.256 ± 0.145
ATB-30	β_1	---[3)]	−0.026 ± 0.016

1) Parameter estimate ± one approximate standard error
2) H = Hiroshima, N = Nagasaki, M = Male, F = Female
3) Variable omitted from model

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