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Statistical Assessment on Cancer Risks of Ionizing Radiation and Smoking Based on Poisson Models

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In many epidemiological and medical studies, a number of cancer mortalities in categorical classification may be considered as having Poisson distribution with person-years at risk depending upon time. The cancer mortalities have been evaluated by additive or multiplicative models with regard to background and excess risks based on several covariances such as sex, age at the time of bombings, time at exposure, or ionizing radiation, cigarette smoking habits, duration of smoking habits, etc. An interest herein is to examine an additive, synergistic, or antagonistic relationship between radiation exposures and cigarette smoking habits for cancer mortalities. The results revealed a highly significant antagonistic influence for cancer mortalities from all nonhematologic findings, lung and respiratory system with negative interaction between radiation exposures and cigarette smoking amounts.

Keywords: Excess relative risks, cancer mortalities, antagonistic effects, prospective studies, atomic bomb survivors

1 Introduction

A positive relationship between radiation exposure and cancer induction has been established in human population exposed to medical x-rays, to occupational sources of ionizing radiation, and in the atomic bomb survivors (BEIR 1980). Among this latter group, Pierce et al. (1996) recently report a significant increase in the studies of the cancer mortalities in the relation to radiation exposure for leukemia and multiple myeloma, as well as cancers of all except leukemia, digestive organs and peritoneum, esophagus, stomach, colon, rectum, liver, respiratory system, lung, cervix uteri and uterus, ovary, urinary tract, and bladder. These specific sites of cancers are associated not only with ionizing radiation, but are also known to be related to smoking and other environmental factors such as drinking, occupational, marital status, education and other indicators of general socioeconomic conditions. In particular, interest has been focused on the joint effects of cigarette smoking habits and radiation exposure. Prentice et al. (1983) have examined the joint relationship to cancer mortality of atomic bomb radiation exposure and cigarette smoking habits, using data obtained from several epidemiologic surveys conducted between 1963 and 1970. Applying Cox regression method (Cox 1972), Prentice et al. have found that the relative risk due to joint exposure appeared generally not only to be submultiplicative for all nonhematologic cancer, stomach cancer and digestive cancer other than stomach, but to be subadditive as well. The relative risk function could not be distinguished from either a multiplicative or an additive form.

The radiobiological concerns herein are, therefore, to investigate specific sites of cancer mortalities, based upon relative risk models, to determine whether there is an additive, synergistic, or antagonistic relationship between radiation exposure and cigarette smoking history obtained from 1963 and 1985 cancer mortality data.

2 Material and Methods

Several epidemiologic questionnaire surveys have been conducted between 1963 and 1980 within subsets of the original Life Span Study (LSS) extended sample; a cohort composed of 110,000 persons in Hiroshima and Nagasaki (Beebe and Usagawa 1968). Therefore, cigarette smoking histories are not available for the LSS cohort as a whole.

2.1 Epidemiologic survey during 1963-1980

Of these surveys the Adult Health Study (AHS) sample (also see Beebe and Usagawa 1968), a subset of the LSS numbering nearly 20,000 persons, is an important source of smoking data. Epidemiologic questionnaires were administered to AHS participants, primarily during the 4th examination cycle (1964-1966). The AHS

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Table.1. The tabulations by site of cancer were prepared by 7th, 8th and 9th ICD Code Versions

Site	International Classification of Disease (ICD)		
	7th	8th	9th
1. All cancers	140-205	140-207	140-208
2. All nonhematologic	140-199	140-199	140-199
3. Buccal cavity and pharynx	140-148	140-149	140-149
4. Digestive organ and peritoneum	150-159	150-159	150-159
5. Lung	162,163	162	162
6. Respiratory system	160-165	160-163	160-163
7. Esophagus	150	150	150
8. Stomach	151	151	151
9. Buccal cavity, pharynx and	140-148	140-149	140-149
respiratory system	160-165	160-163	160-165
10. Leukemia	294	204-207	204-208

subjects received epidemiologic questionnaires between 1963 and 1964 and between 1964 and 1968. However, the instrument from the former time period uses different codes to classify the number of cigarettes smoked as compared to the latter instrument which records actual number of cigarettes smoked per day. The 1963-64 survey groups daily cigarette consumption, and uses the codes 0 (nonsmoker), 1 (less than 5 (cigarettes per day), 2 (5-9 cigarette per day), . . ., 5 (more than or equal to 20 cigarette per day). The third epidemiologic survey, conducted in 1968, uses actual number of cigarettes. In addition to these AHS surveys, all LSS males aged 40-69 were surveyed by mail in 1965 as part of a Cardio Vascular Disease (CVD) study. This survey used a rough code to classify smoking history, as follows: nonsmoker, about 5 cigarettes per day, about 10 cigarettes per day, about 20 cigarettes per day or about 30 cigarettes per day. In 1970, females in the remaining LSS sample excluding the AHS sample were administered an epidemiologic questionnaire. Smoking histories were coded in manner similar to the AHS surveys. In 1980 a large scale health and environmental living survey was conducted among males and females in the LSS extended sample. Recorded were the actual number of cigarettes smoked per day.

A flow-chart following a priority scheme of epidemiologic surveys has been used to develop a consistent smoking code for the same person who was included in number of different epidemiologic surveys between 1963 and 1980. In the 1963-1964 survey, their parts were 43 smokers of 20 cigarettes or more per day (31 in Hiroshima and 12 in Nagasaki) who had no information from any other surveys. There were 12 persons (11 in Hiroshima and 1 in Nagasaki) for whom the data were in consistent with those of the later surveys: these being from the groups less than 15 cigarettes per day, nonsmoker, "not recorded" or unknown. All of these inconsistencies were corrected on the bases of the results of a medical chart questionnaire review. In addition, those who belonged to the group coded as "about 5 cigarettes per day" in the 1965 CVD study were checked based on the flow-chart sequence and cigarette smoking histories were replaced by results from the later surveys. Specifically, in the CVD study there were 593 males with a code of "about 5 cigarettes." Of these cases, 35 (26 in hiroshima and 9 in Nagasaki) actually smoked 15 cigarettes or more per day, 10 were nonsmokers (9 in Hiroshima and 1 in Nagasaki) and 28 smoked on unknown number of cigarettes per day (21 in Hiroshima and 7 in Nagasaki). The 45 cases in the first two categories were reclassified into the 5-14 cigarettes group and the less than 5 cigarettes group, respectively. Thus a total of 548 cases could not be changed. Table 1 gives the tabulation of 7th, 8th and 9th ICD code version by site of cancer.

As a result of several epidemiological surveys during the period 1963-1985, 64097 LSS subjects were included in at least one or more questionnaires. Table 2(nextpage) gives by city and sex the number of subjects who were selected according to the sequence of priority. Of the total 64,097 cases, 26351 smokers (41.1%), 34,400 nonsmokers (53.7%) and 3,346 cases (5.2%) who were "not recorded" or unknown, are given in Table 3(nextpage). However, a high proportion of smoking population (92.3%) smokes cigarettes only. Only 6.9% of all smokers listed a mixture of tobacco sources, such as cigar, pipe or kizami (Japanese typical tobacco). Therefore, it will be not be a problem to use a data set consisting of nonsmokers and those smoke cigarettes only. Of 58,716 subjects (34,400 nonsmokers and 24,316 cigarette smokers only), 57 subjects (21 nonsmokers and 36 smokers) had already died prior to the time of the first epidemiologic mail survey and are, thus, excluded. The remaining cigarette only smokers are divided into three groups: 18515 cases who are still continuing to smoke, 436 cases who began to smoke after the first questionnaire survey, and 5,365 cases who stopped to smoke after that. The first two groups, 18915 smokers and 34,379 nonsmokers, would provide a potential data set. However, the analysis herein should also exclude in both groups the 1,216 subjects whose dose estimates were not available and the 947 additional cases whose duration of cigarette smoking since the age at which they first smoked could not be

Table.2. Number of subjects with smoking information according to priority order of survey by city and sex

Priority order	Years	Hiroshima			Nagasaki		
		Total	Females	Males	Total	Males	Females
1	1964-68	8398	2877	5446	3765	1521	2244
2	1963-64	687	283	404	363	163	200
3	1965	7520	7520	-	2167	2167	-
4	1968	319	124	195	158	68	90
5	1970	15164	-	15164	4475	-	4475
6	1980	7554	7552	2‡	2812	2812	-
6	1980	8288	-	8288	2504	-	2504
Total	-	47853	18354	29499	16244	6731	9513

Table 3. Distribution of smoking status by city and sex

Sex	Non-Smoker	Cig. only	Other Smoking habits					another	Unk.& Blank
			Subtot.	Cigar	Pipe	Kizami	Other		
				Hiroshima					
Total	25741	17882	1393	258	445	511	179	173	2664
%	59.0	41.0							
Mail	2455	13389	1243	258	444	377	164	89	1178
%	15.5	84.5							
Femail	23286	4493	150	-	1	134	15	84	1486
%	83.8	16.2							
				Nagasaki					
Total	8659	6434	431	81	134	175	41	38	682
%	57.4	42.6							
Male	998	4948	396	81	134	144	37	26	363
%	16.8	83.2							
Female	7661	1486	35	-	-	31	4	12	319
%	83.8	16.2							

calculated. Therefore, this analysis relates to 51,131 study subjects during 1963-1985.

2.2 Dosimetry

Individual radiation doses were assigned using of the Dosimetry System 1986 (DS86) (Roesch 1987). These individual DS86 doses were computed in two ways. For survivors expected within 1600 m of the hypocenter in Hiroshima and within 2000 m in Nagasaki, where the requisite shielding information is available, dose estimates were obtained by modeling the physical circumstances of an individual's exposure, including posture and orientation to survivors exposed beyond these distances, where the dose was low and detail shielding information is generally not available, individual doses have been estimated by regression methods employing average structural and body transmission factors derived from information obtained from survivors exposed between 1000 m and 1600 m in Hiroshima or between 1000 m and 2000 m in Nagasaki (Preston and Pierce 1988). Such estimates are called indirect. The DS86 cannot be applied to all A-bomb survivors. Persons to whom it cannot be applied were typically exposed in non-wooden structures or had shielding histories insufficiently detailed to allow their exposures to be modeled directly. In July of 1989 the DS86 dose estimates were updated to include more survivors at the greater distances from the epicenter who in the open ATB (both cities) and, in Nagasaki, who were either shielded by terrain or were in factories ATB. If the total (gamma ray + neutron) shielded karma exceeded 6 gray (Gy) (3 of 567 individuals in the complete data set and 4 of 821 individuals in the extended set), it was truncated to 6 Gy since these doses are so high as to raise concern about their validity. This same truncation has been used in various RERF Life Span Study (LSS) reports.

‡Note that two females (MF220062 and MF228581) were included in the 1980 mail survey. Note that number of subjects include individuals overlapped among several surveys.

3 Specific Sites of Cancers

The tabulated format makes use of the same groupcuts regarding city (Hiroshima and Nagasaki), sex (male and female), and continuous factors categorized with interval bounds as follows: Age at the time of bombings (ATB): 0-19, 20-34, and ≥35 years at exposure,

Dose groups (Sv: Sievert dose = gamma+10 × neutrons): 0-0.004, 0.005-0.494, 0.495-0.994, 0.995-1.994, 1.995-2.994, ≥ 2.995

Groups of cigarette numbers: 0 (nonsmoker), 1-4, 5-14, 15-24, and ≥ 25

Duration of smoking habits (periods): 0, 1-19, 20-34, and ≥ 35

Follow-up periods (years): 1963-1966, 1967-1970, 1971-1974, 1975-1978 and 1979-1985

The each average of subjects corresponding to these categories were respectively assigned as age ATB group, dose group, cigarette smoking group, and duration periods. This report has a great discrepancy for calculation of person-years at risk with regard to the follow-up period between report series of cancer mortality among atomic bomb survivors (Preston, et al. 1987, Shimizu, et al. 1987, Pierce, et al. 1996). Their reports have dealt with categorircal data analyses with regard to means in each cell devision. Our statistical analysis has been also depended on categorical data. The person-years in each epidemiologic survey are calculated from the time of the first survey of cigarette smoking habits to the end of 1985.

4 Statistical Methods

In many epidemiological studies and medical applications, the number of deaths, y_{ij}, may be regarded as Poisson rather than binomial variate. This approach, each subject contributes only many years of observation to the population at risk as he or she is actually observed; if he or she leaves after 1 year, he or she contributes 1 person-year; if after 10, 10 person-years. The method can be measure incidence over extended and variable time periods. In 1966, Armitage introduces an approach of Poisson distribution based on person-years at risk, PY_{ij}. The notation for the Poisson case is indicated below. Poisson statistical approaches are applied with additive and multiplicative models for rates. Most of the essential concepts involved in statistical modeling can be given by considering a simple table such as a two dimensional notation, but stratum $(1, ..., i, ..., k : 1, ..., j, ..., m)$ denote a constant term (c), sex (s), or age ATB groups (a), duration of smoking habits (h) or follow-up time period (t). In the models city difference is not modeling because doses used here are the organ dose equivalent in seiverts based on an assumed neutron RBE of 10.

Let a $k \times m$ contingency classification and notation with person years at risk be denoted by

	Dose classification	
Stratum	1,...,j,...,m	Total
1		
⋮		
i	Specific cancer deaths y_{ij} and Person-year PY_{ij}	$y_{i.} = \sum_{j=1}^{m} y_{ij}$ and $R_{i.} = \sum_{j=1}^{m} PY_{ij}$
⋮		
k		

where, $i = 1, 2, ..., k$, that is, stratification of k groups indicates sex (s), age ATB (a), or time (t), etc., and $j = 1, ..., m$, radiation dose groups. The y_{ij} and PY_{ij} denotes number of specific cancer deaths and person years at risk in (i, j) cell.

4.1 Hazard model based on distribution

The joint probability density function of independent Poisson distribution when we assume y_{ij} as poisson variate is expressed as a Poisson model with parameter $\mu_{ij} = PY_{ij} \times \lambda_{ij}(\Theta_{il})$ for $l = 1, ..., p$ by

$$\begin{aligned} L(\Theta) &= L(y_{i1}, ..., y_{im}|\Theta_{i1}, ..., \Theta_{ip}) = \lambda_{ij}(\Theta_{il}) \\ &= \prod_{i=1}^{k}\prod_{j=1}^{m}\prod_{l=1}^{p} \frac{\mu_{ij}^{y_{ij}}}{y_{ij}!} \exp(-\mu_{ij}) \end{aligned} \quad (1)$$

The logarithm m of (1) is expressed as

$$\log L(\Theta) = \prod_{i=1}^{k}\prod_{j=1}^{m}\prod_{l=1}^{p}(y_{ij} \log \lambda_{ij}(\Theta_{il}) - \lambda(\Theta_{il}) - \text{const}_{ij})$$

where $\text{const}_{ij} = \log PY_{ij} - PY_{ij} - y_{ij}!$ indicates a nuisance factor including other noncancer deaths than cancers. After derivative of parameter Θ_{il}, we obtain the maximum likelihood (ML) estimates of parameters by Newton-Raphson iterative procedure, namely,

$$\begin{bmatrix} \Theta_1(v+1) \\ \Theta_2(v+1) \\ \vdots \\ \Theta_p(v+1) \end{bmatrix} = \begin{bmatrix} \Theta_1(v) \\ \Theta_2(v) \\ \vdots \\ \Theta_p(v) \end{bmatrix}$$

$$- \begin{bmatrix} \frac{\partial^2 \log L(\Theta)}{\partial \Theta_1^2}|_{(v)} & \frac{\partial^2 \log L(\Theta)}{\partial \Theta_1 \partial \Theta_2}|_{(v)} & \cdots & \frac{\partial^2 \log L(\Theta)}{\partial \Theta_1 \partial \Theta_p}|_{(v)} \\ & \frac{\partial^2 \log L(\Theta)}{\partial \Theta_2^2}|_{(v)} & \cdots & \frac{\partial^2 \log L(\Theta)}{\partial \Theta_2 \partial \Theta_p}|_{(v)} \\ & & \ddots & \vdots \\ & & & \frac{\partial^2 \log L(\Theta)}{\partial \Theta_p^2}|_{(v)} \end{bmatrix}^{-1}$$

$$\times \begin{bmatrix} \frac{\partial \log L(\Theta)}{\partial \Theta_1}|_{(v)} \\ \frac{\partial \log L(\Theta)}{\partial \Theta_2}|_{(v)} \\ \vdots \\ \frac{\partial \log L(\Theta)}{\partial \Theta_p}|_{(v)} \end{bmatrix} \quad \text{for} \quad v = 1, 2, ..., r.$$

The methods analyzed for cancer risk used here take additive models

$$\begin{aligned}
\text{Model I} &: \lambda_{(\%con)sat} + ERR\ (d_1, d_2, ..., d_p), \\
\text{Model II} &: \exp\ (\lambda_{(\%con)sat}) + \exp\ (d_1, d_2, ..., d_p), \\
&\text{and} \\
\text{Model III} &: \exp\ (\lambda_{\%con} + s + a + t + d_1 + d_2 + ... \\
&+ d_p),
\end{aligned}$$

or multiplicative models, that is,

$$\begin{aligned}
\text{Model IV} &: \lambda_{(\%con)sat}[1 + ERR(d_1, d_2, ..., d_p)], \\
\text{Model V} &: \exp(\lambda_{(\%con)sat})[1 + ERR(d_1, d_2, ..., d_p)], \\
&\text{and} \\
\text{Model VI} &: \exp(\lambda_{(\%con)sat})\lambda_{(\%con)sat} \\
&\times[1 + \exp(ERR(d_1, d_2, ..., d_p))],
\end{aligned}$$

where $\lambda_{(\%con)sat}$denotes the background rate at zero dose and nonsmokers, indicating %con (constant term), s (sex), a (age ATB) and t (time), and excess absolute risk (EAR) and excess relative risk (ERR) are considered in the models, respectively. The background rate depends on constant value (%con), sex (s), age at risk (a), while excess relative risks depend on dose (d_1) classified by 6 dose groups, cigarette amounts (d_2) classified by 5 groups, interaction (d_3) between radiation doses and cigarette smoking amounts, age at exposure (d_4) classified by 3 age ATB groups, durations (d_5) classified by 4 groups, starting age of smoking (d_6) classified by 3 year periods, etc, respectively. Each mean value calculated by categorical groups corresponding to all group cuts were assigned here.

Stewart and pierce (1982) confirmed the efficiency of nonparametric survival analysis (Cox 1972) relative to parametric with grouped data. The results obtained are similar to published results for grouped data.Poisson regression methods for group survival data (Breslow and Day 1988) are available for examining the relationship of the dependence of risk on radiation dose and for evaluating the variation of the dose response with respect to sex, age ATB, time at exposure, and duration of smoking habits. The principal analytical method used herein was several relative risk or excess risk or attributable risk models fitted by maximum likelihood, using the EPICURE, Command Summary of statistical programs for analysis of atomic bomb survivor data (Preston, et al. 1993). In 1982 Prentice et al. analyzed cancer mortality in relation to total Tentative 1965 Dose Revised (T65DR) level and cigarette smoking habits using the Cox regression method (Cox 1972). The numbers of lung cancer cases in the various combinations of strata, dose groups and smoking categories are assumed to be realizations of independent Poisson random variables with expected values (Kopecky et al. 1986).

4.2 Smoking status

During the 22 years of follow-up study from 1963 to 1985, there are 2615 deaths from all malignant neoplasms (1294 males and 1321 females) were observed in the overall study population of 58,716 subjects with a smoking information at least, which were composed of 17,882 cigarette smokers (41%) and 25,741 nonsmokers (59%). Japanese were cigarette smokers with 24,316 (92.3%) of 26351 smokers (91.3% for males and 95.5% for females), showing in Table 3. Smokers other than cigarettes such as cigar, pipe, kizami, or others are small. These subjects have been excluded from statistical analysis because of more complexity for data analysis. Cigarette smoking habits among Japanese are quite different by sex. At that time about 84% of 21,790 males are cigarette smokers, whereas only 16% of 36,926 females are cigarette smokers.

4.3 Goodness of fit for Models

All models which specific cancer data of solid cancers and leukemia had convergence to the models applied herein have given well fitness with χ^2 values less than that of degrees of freedom. Table 4 gives the deviance values of goodness of fits from Model I to Model VI. Among these models, Models III and VI indicate stable and suitable fitness for all of specific cancer data set. Model III is an excess absolute risk method, Model VI is an excess relative risk approach. A relationship of goodness fits between Models III and VI is not so different from biological standpoints of view in Table 4(next page), but we employs an excess relative risk model for analysis of specific cancer data to compare the excess relative risks with those risks based on different models.

5 Results

The distribution of 10 classification and the cancer deaths were shown by city, sex and site in Table 5.(nextpage) The specific cancer deaths are revealed for those who are available for information of smoking habits.

All cancers (malignant neoplasms) : In Model VI, highly significant excess for all of mean dose ($p < 0.001$), cigarette smoking amounts ($p < 0.001$), age ATB ($p < 0.001$), and interaction ($p = 0.018$) between radiation doses and cigarettes are observed for 2,615 all cancers, using DS86 large intestine organ dose.

Table 4. Status of covergences and deviance values of fitted Models to specific cancer data

Items (Site of cancers)	Number of death	Degrees of freedom	Models I	II	III	IV	V	VI
1. All cancers	2615	3205	2386.38	1909.62	1881.51	2304.68	1882.77	1884.14
2. All nonhemat.	2468	3205	2321.54	1855.02	1826.09	2239.80	1827.33	1827.82
3. Buccal cavity and pharynx	1362	3205	Not Con.	1347.55	1343.11	Not Con.	1346.67	1347.72
4. Digestive organs and peritoneum	27	3326	Not Con.	Not Con.	145.710	Not Con.	Not Con.	145.707
5. Lung	378	3274	Not Con.	772.633	791.475	Not Con.	758.259	791.602
6. Respiratory	415	3274	Not Con.	833.514	850.116	Not Con.	817.926	849.811
7. Esophagus	69	3210	Not Con.	Not Con.	289.247	Not Con.	380.060	289.619
8. Stomach	790	3210	Not Con.	Not Con.	991.774	Not Con.	989.879	993.703
9. Buccal cavity, pharynx and respiratory	442	3317	Not Con.	850.160	857.171	Not Con.	835.313	856.452
10. Leukemia	60	3296	Not Con.	Not Con.	307.066	Not Con.	Not Con.	308.209

Note that Not Con. means not convergence for obtaining the estimates after several iterations of maximum likelihood techniqueiteratio.

Table 5. Distribution of specific cancer mortality for cigarette smokers by city and sex, 1963- 1985

Items (Site of cancers)	Death from cancers Hiroshima Total	Male	Female	Nagasaki Total	Male	Female
1. All cancers	2021	993	1028	594	301	293
2. All nonhemato.	1910	946	964	558	280	278
3. Buccal cavity and pharynx	20	12	8	7	5	2
4. Digestive organs and peritoneum	1059	559	500	303	154	149
5. Lung	285	181	104	93	59	34
6. Respiratory system	313	199	114	102	62	40
7. Esophagus	59	45	14	10	10	0
8. Stomach	614	348	274	176	100	76
9. Buccal cavity, pharynx and respiratory	333	211	122	109	67	42
10. Leukemia	51	29	22	9	4	5
Study subjects used	38191	12158	26033	12940	4499	8441
Person-years	462649	138705	323944	150017	47460	102557

The effects of backgrounds were significant for sex and time in follow-up study, but age ATB group was suggestive ($p = 0.064$). When starting age of smoking and duration of smoking habits were included in the excess risk model, the former starting age only was significant ($p = 0.034$), but the latter duration was not significant. The square of radiation dose shows about suggestively negative effect ($p = 0.010$). The dose-square effect is not so serious.

All nonhematologic cancers : An analysis of 2,468 nonhematologic cancer data has been performed by Model VI. A highly significant excess was noted for radiation dose ($p < 0.001$), and cigarette smoking amounts ($p < 0.001$), but an interaction between exposed doses and cigarette smoking amounts was significant ($p = 0.029$). The square of doses was significant negative effect at the level of $P = 0.016$.

The interaction of starting age and cigarettes smoking amounts ($p = 0.04$), and age ATB and cigarette smoking amounts ($p = 0.006$) was significant, but the relationship of smoking and duration of smoking time not significant.

Cancers from buccal cavity and pharynx : The cancers from buccal cavity and pharynx are only 27 cases in both city. The results in Model VI show significant excess for age ATB group ($p = 0.005$) and suggestive effect of cigarette smoking amounts ($p = 0.065$), using DS86 thyroid organ dose estimates. Other factors for radiation dose and interaction between radiation doses and cigarette smoking amounts are quite not significant. Background effects other than age group ($p = 0.031$) were all not significant.

Cancers from digestive organ and peritoneum : The

cancer deaths of the sites are 1362 during periods from 1963 to 1985. Statistical significant effects using DS86 intestine organ dose estimates were observed all for radiation dose, cigarette smoking amounts, and mean ages ($p < 0.001$), but the interaction of radiation doses and cigarette smoking amounts is not observed.

Lung cancer : An analysis of 378 lung cancer data has been performed by Model VI, using lung organ dose estimates. All background effects with regard to sex, and time were noted highly for significant difference, but age group was not significant. The excess relative risks were also significant for radiation dose ($p = 0.003$), amount of smoking habits ($p < 0.001$) and age ATB ($p = 0.013$) were observed, but an interaction between radiation dose and cigarette smoking amounts is around 4% level with negative effect of antagonistic relationship. Background effects other than age group ($p = 0.013$) were all significant at level of less than 1%.

Cancer from respiratory system : Respiratory system cancers have confirmed 415 deaths (See Table 3). The results were almost same as those of lung cancers with those of lung cancers. Excess relative risks were also significant for radiation dose ($p = 0.002$), cigarette smoking amounts ($p < 0.001$) and age means ($p = 0.005$) were observed, but an interaction between radiation dose and smoking amounts is significant with negative effect of antagonistic relationship ($p = 0.029$). All background effects with regard to city, sex, and time were noted highly for significant difference, but age group was not significant.

Esophagas : Analysis of 69 cancer deaths from esophagas was significant excess risks for cigarette smoking amounts and age ATB group, but not significant excess risks for radiation doses and interaction between radiation doses and cigarette smoking amounts. The effect of age ATB was highly significant.

Stomach cancer : In this study period, 790 deaths from stomach cancer were observed in both cities. Two items of dose and cigarette has been noted with a highly significant effects, but no significant excess for age ATB group and interaction between cigarette smoking amounts and radiation dose.

Cancers from buccal cavity, pharynx and respiratory system : Cancers including lung, and buccal cavity and pharynx gave a highly sensitive effects at less than 0.1% level for all sites of exposed dose, cigarette smoking amounts, and age ATB group, a significant negative effect of interaction between dose and cigarette (Table 6 nextpage).

Leukemia : A highly significant excess from leukemia was observed only for radiation dose. No significant difference was for cigarette smoking habits. Other effects of interaction between exposed doses and cigarette smoking amounts, and age were roughly suggestive. Another factors such as starting age of smoking habits, duration of smoking habits or interaction between age and cigarette were all nonsignificant.

6 Discussion

In site-specific cancer mortality, Shimizu et al. in 1991 have demonstrated that mortality from leukemia has long been known to be increased among A-bomb survivors, and mortality from malignant tumors other than leukemia has also increased. However, an increased risk has not been observed for all cancer sites based on the 90% confidence limits. The relative risk at 1 gray of cancer mortality by site with the 90% confidence limits for the period 1950-85 were shown. It will be noted that, in addition to leukemia, cancers of the esophagus, colon, stomach, lung, breast, ovary, urinary tract, and multimyeloma are also increased significantly. However, there has been no demonstrable increase as yet in mortality from cancers of the rectum, pancreas, uterus, prostate, or malignant lymphoma. Using the cancer mortality data based upon RBE 10 and with an increase of 2104 deaths of all neoplasms from 5936 cancer deaths in 1950-1985 to 8090 in 1950-1990, however, Pierce et al. (1996) have stated all a significant excess in mortality from cancers of the rectum, pancreas, uterus, prostate, or malignant lymphoma. Pierce et al. have emphasized that ERR descriptions for excess solid cancer must be considered specifically in relation to sex and age at exposure.

A cancer study by Prentice et al (1983) found that additive and multiplicative models for RR fit almost equally well to data from a respective study of lung cancer mortality among A-bomb survivors and non-exposed controls. In this paper, three additive and three multiplicative models have been applied for cancer mortality data. Log linear Model III as an additive model and Model VI as a multiplicative model were better deviances than those of all other models. These two models gave stable and suitable convergences, but others not so, and almost the same deviance values or goodness of fits. Being different from the extended LSS cohort cancer data from 1950 to 1990 (Pierce et al. 1996), the cancer mortalities which were available for information of smoking habits in the period from 1963 to 1980 were 2615 deaths only in 1963-1985. Therefore, 10 sites of cancer mortality groups have been evaluated in this study. Figure 1 shows the relationship of the ERR effects of radiation doses with 95% confidence intervals by 10 sites of cancer mortalities.

Table 6. Excess relative risks and 95% confidence limits by specific cancer, excluding for background effects such as constant term, city, sex, age group and time.

Specific cancer	Item	Estimate	Significant Level(Prob)	95% confidence limits Lower	Upper
1. All cancers	Dose	1.536	< 0.001	1.393	1.693
	Cigarette	1.032	< 0.001	1.026	1.038
	Dose × Cigarette	0.991	0.018	0.984	0.998
	Age	1.067	< 0.001	1.044	1.091
	Deviance(d.f.)		1884.14 d.f.=3205		
2. All nonhemat.	Dose	1.482	< 0.001	1.335	1.645
	Cigarette	1.033	< 0.001	1.027	1.039
	Dose × Cigarette	0.992	0.029	0.984	0.999
	Age	1.070	< 0.001	1.046	1.095
	Deviance(d.f.)		1827.82 d.f.=3205		
3. Buccal cavity and pharynx	Dose	1.448	< 0.001	1.257	1.668
	Cigarette	1.026	< 0.001	1.018	1.034
	Dose × Cigarette	0.994	N.S.	0.984	1.004
	Age	1.083	< 0.001	1.050	1.115
	Deviance(d.f.)		1347.72 d.f.=3205		
4. Digestive organs and peritoneum	Dose	0.638	N.S.	0.084	4.869
	Cigarette	1.047	0.065	0.997	1.099
	Dose × Cigarette	0.986	N.S.	0.857	1.134
	Age	1.308	0.005	1.086	1.575
	Deviance(d.f.)		145.707 d.f.=3326		
5. Lung	Dose	1.452	0.003	1.140	1.850
	Cigarette	1.069	< 0.001	1.056	1.083
	Dose × Cigarette	0.982	0.039	0.965	0.999
	Age	1.076	0.013	1.016	1.139
	Deviance(d.f.)		791.602 d.f.=3274		
6. Respiratory	Dose	1.442	0.002	1.148	1.812
	Cigarette	1.069	< 0.001	1.056	1.082
	Dose × Cigarette	0.983	0.029	0.967	1.000
	Age	1.080	0.005	1.023	1.141
	Deviance(d.f.)		849.811 d.f.=3274		
7. Esophagus	Dose	1.408	N.S.	0.739	2.684
	Cigarette	1.057	< 0.001	1.028	1.087
	Dose × Cigarette	0.986	N.S.	0.947	1.024
	Age	1.223	< 0.001	1.100	1.359
	Deviance(d.f.)		289.619 d.f.=3210		
8. Stomach	Dose	1.470	< 0.001	1.196	1.806
	Cigarette	1.022	< 0.001	1.010	1.034
	Dose × Cigarette	0.994	N.S.	0.981	1.008
	Age	1.027	N.S.	0.978	1.079
	Deviance(d.f.)		993.703 d.f.=3210		
9. Buccal cavity, pharynx and respiratory system	Dose	1.392	0.003	1.117	1.736
	Cigarette	1.068	< 0.001	1.056	1.081
	Dose × Cigarette	0.982	0.032	0.966	0.998
	Age	1.097	< 0.001	1.042	1.154
	Deviance(d.f.)		856.452 d.f.=3316		
10. Leukemia	Dose	2.139	< 0.001	1.656	2.768
	Cigarette	1.029	N.S.	0.990	1.061
	Dose × Cigarette	0.971	N.S.	0.934	1.011
	Age	1.197	0.105	0.978	1.260
	Deviance(d.f.)		308.209 d.f.=3296		

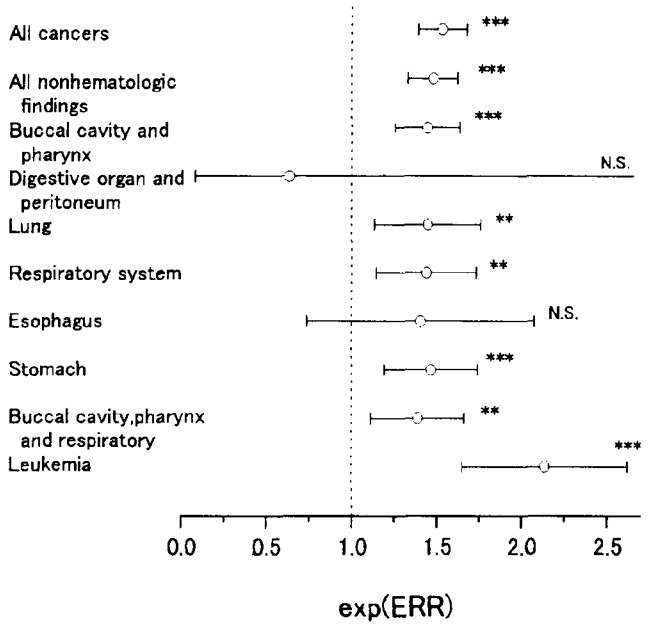

Figure 1. ERRs and the confidence limits with regard to radiation exposures by site of cancer mortalities. N.S. is not significant with $p > 0.10$,** $p < 0.01$ and *** $p < 0.001$.

Highly significant ERRs were noted for cancers from all nonhematologic findings, buccal cavity and pharynx, lung, respiratory system, stomach, and leukemia. Highly significant ERRs of time at exposure were observed for seven sites of other cancers than suggestive ERR of digestive organs and peritoneum, and nonsignificant ERR of leukemia, as shown the ERRs with 95% confidence limits in Figure 2.

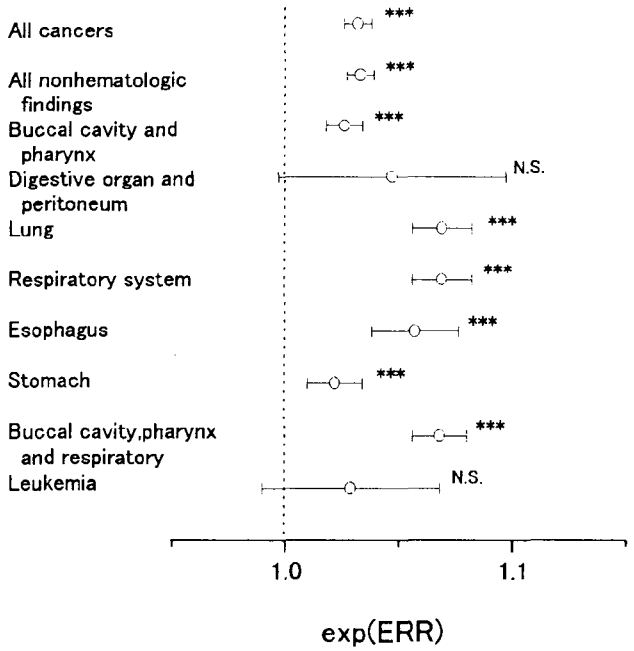

Figure 2. ERRs and 95% confidence limits with regard to cigarette smoking amounts by site of canser mortalities. N.S. is not significant with $p > 0.10$ and *** $p < 0.001$.

However, we are interested in an analysis of the effects of additive, synergistic or antagonistic relationship between radiation doses and cigarette smoking amounts for cancer mortalities data. Antagonistic effects were plotted in three dimensional risks of cancers from respiratory system in Figure 3. The maximum trend risk of cancers from respiratory system are plotted in this figure with regard to risks of the association of radiation

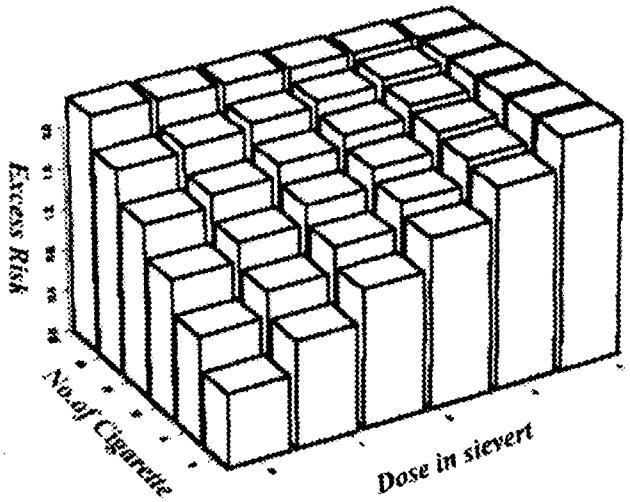

Figure 3. An tagonistic relationship of ERRs of Lung between radiation doses and cigarette smoking amounts.

effects are respectively indicated with the constant same upper risks with increase of excess risks of radiation doses and smoking habits. However, a decrement of two doses and smoking variables after each reaching the maximum risk begins to reduce for each risk. However, such a declined risk may be difficult to comprehend the phenomenon from a radiobiological standpoint. Significantly antagonistic effects in the negative interaction between radiation doses and cigarette smoking amounts has been detected for cancer mortality from respiratory system, and also significantly effects observed for cancer deaths from all nonhematologic findings and lung neoplasms. The antagonistic effect of negative interaction increases with radiation dose or with smoking amounts, but an increase reaches a largest limit of radiation dose or smoking risks and then gives flat or constant risk in the highest region regardless of that of another exposure . After the largest risk, these risk variations decrease with an increase of radiation doses and smoking amounts, but the risks of these doses with regard to radiation exposures or cigarette smoking exposure indicate values of unbelievably or inconsiderable limits. These trend in general aspect would be differed from a phenomenon of cell killing risk.

The comparison of the models for solid cancers and leukemia excess relative risks is given as goodness of fits in Section 4-3. As shown in Table 5, these analyses have been applied for multiplicative models and show a good fitness for log linear response relationship as an additive model. Highly significant excess radiation risks have been noted for all specific solid cancers other than those of digestive organs and peritoneum (27 cancer deaths), and esophagus (69 cancer deaths), and es-

pecially for leukemia (60 cases). However, a significant excess risk for smoking habits was observed for those of nonhematologic cancers (2468 deaths), lung cancer (378 deaths) and respiratory cancer (415 deaths). An interaction effect between doses and cigarettes gives significantly a negative response risk to nonhematologic cancers, lung cancer and respiratory system. The fact influence is not additive response risk, but we are interested in antagonistic response relationship, deceasing with an increase of doses and cigarette smoking. All cancers other than those solid cancers were not significant for interaction between doses and smoking.

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