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Excess Relative Risk of Solid Cancer Mortality after Prolonged Exposure to Naturally Occurring High Background Radiation in Yangjiang, China

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A study was made on cancer mortality in the high-background radiation areas of Yangjiang, China. Based on hamlet-specific environmental doses and sex- and age-specific occupancy factors, cumulative doses were calculated for each subject. In this article, we describe how the indirect estimation was made on individual dose and the methodology used to estimate radiation risk. Then, assuming a linear dose response relationship and using cancer mortality data for the period 1979–1995, we estimate the excess relative risk per Sievert for solid cancer to be –0.11 (95% CI, –0.67, 0.69). Also, we estimate the excess relative risks of four leading cancers in the study areas, i.e., cancers of the liver, nasopharynx, lung and stomach. In addition, we evaluate the effects of possible bias on our risk estimation.

INTRODUCTION

A cancer mortality study was started in 1972 in the high-background radiation areas (HBRA) of Yangjiang and neighboring control areas of Guangdong Province, China[1)]. In 1991, a collaborative study involving Chinese and Japanese scientists began to collect cancer mortality data

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starting from 1987[2]. Because data for 1970–1978 had not been computerized, we considered only cancer mortality data for 1979–1995 in our present analysis. The cancer mortality study accumulated 1.7 million person-years during the period 1979–1995 in a follow-up of 125,079 subjects and identified 1,003 cancer deaths. When compared with a nearby control area, the relative risks (RRs) of solid cancer and leukemia in HBRA were estimated to be 0.99 (95% CI, 0.87 to 1.14) and 1.12 (95% CI, 0.56 to 2.22), respectively[3]. Recently, Yuan et al[4] and Morishima et al[5] indirectly estimated individual doses on the basis of hamlet-specific average doses for indoor and outdoor radiation exposure and sex- and age- specific occupancy factors. Using this dosimetry system and cancer mortality data for the period 1979–1995, we estimated the cancer risk associated with high-background radiation assuming a linear dose response. In this article, we report the estimated excess relative risk of solid cancer and four leading cancers in the study areas for the period 1975–1995 and describe the methodology used to estimate risk. We also evaluate the effects of possible bias on our risk estimation.

MORTALITY FOLLOW-UP

In 1979, we established the Health Household Registry (HHR) in every village of our study areas in order to carry out an efficient and complete mortality survey. The details of this registry system were described elsewhere[3,6]. We determined the underlying causes of death and coded them according to the ninth revision of the International Classification of Diseases and Injuries (ICD-9)[7].

INDIVIDUAL DOSE CALCULATION

Migration

When estimating the individual dose of a subject, we summed doses received in the following places: birthplace, the registered hamlet where the subject lived when the cohort study began on 1 January 1987, and place of relocation. The formula can be written as follows:

$$Dose = \Sigma\ dose_{birthplace} + \Sigma\ dose_{registration\ place} + \Sigma\ dose_{subsequent-location}$$

However, this formula only applies to the fixed-cohort study conducted from 1987 to 1995. When following up a dynamic population from 1979 to 1986, we did not consider migration, assuming that every subject spent their whole life in the registered hamlet.

Indoor and outdoor doses

We estimated the dose received at each place by summing indoor and outdoor doses, taking into account the occupancy factors. In each hamlet, outdoor gamma exposure doses were measured in alleys, in open recreational areas, on main roads, in rice paddies, on dry land, on the banks of ponds, and in areas adjacent to wells[4]. More than 90% of subjects were adult farmers,

who spent about 8 hours a day on farmland. We divided outdoor places into two categories, i.e., public places in a hamlet and farmland. Doses received at public places in a hamlet or on farmland are relatively homogeneous. When estimating dose, we used arithmetic mean doses calculated for public places and for farmland in each hamlet. We measured indoor doses by sampling one-third of all houses in each hamlet[4]. When indoors, residents spent most of time in bed. However, the dose received while in bed differed somewhat from the doses received in other indoor places, including the kitchen and sitting room. Therefore, we used two indoor kerma doses, i.e., the dose received while in bed and the arithmetic mean dose received in the kitchen and sitting room. Indoor doses differed somewhat from house to house, being highly dependent on building materials and room size. We noted that most houses where the study subjects lived were built before the 1978 economic reform. Before this time, the structure and building materials of houses were roughly uniform within a hamlet.

Unfortunately, 8 percent of subjects who migrated outside HBRA moved to regions not covered in our survey, so we have no dosimetry data for them. Instead, we assigned them the arithmetic mean doses for the control areas: 16.99×10^{-8} Gy/h in bed, 16.29×10^{-8} Gy/h during other indoor activities, 10.33×10^{-8} Gy/h in public places, and 8.66×10^{-8} Gy/h in farmland.

Occupancy factor

Occupancy factors specific for sex and age used in dose estimation were obtained from a questionnaire survey conducted from 1991 to 1993 on 5,291 subjects (0–92 years old, 35.4 ± 22.3) living in over 88 hamlets[4]. Age was divided into 17 categories, i.e., 0, 1–4, 5–9, 10–14, ..., ≥ 75 year-old. The sex- and age-specific occupancy factors represented the time spent in bed, at other indoor places, and outside in public places or farmland [4,8].

External and internal doses, cosmic rays

The effective dose for each subject was calculated using the following formula:

$$H_{E,\mathrm{age}} = [f_{bedroom(sex,age} \times (K_{a,bedroom} - 2.59) + f_{other\ indoor(sex,age)} \times (K_{a,other\ indoor} - 2.59) + (24 - f_{bedroom(sex,age)} - f_{other\ indoor(sex,age)}) \times (K_{a,outdoor} - 2.88] \times \theta \times 365.25/1000 + 23.2 \quad \text{.....(1)}$$

, where $H_{E,\ age}$ is the effective dose for each age category, 10^{-5} Sv/a; $K_{a,\ bedroom}$ is the average free-air kerma dose on the bed in the subject's hamlet, 10^{-8}Gy/h; $K_{a,other\ indoor}$ is the average free-air kerma dose at other indoor places in 5 houses in the corresponding hamlet, 10^{-8}Gy/h; $K_{a,outdoor}$ is the average of free-air kerma doses in public places and farmland in a corresponding hamlet, 10^{-8}Gy/h; f is the time spent at each place, in hours; and θ is an age-dependent parameter to convert air kerma dose into effective dose. The values of θ for the subjects 0, 1–14, and ≥ 15 years old were assumed to be 0.93, 0.80, and 0.72, respectively[9]. The indoor and outdoor doses resulting from cosmic rays were assumed to be 2.59 and 2.88 10^{-8} Gy/h, respectively. The effective dose from cosmic rays per year was assumed to be 23.2 10^{-5} Sv/a.

Cumulative dose calculation

We calculated the cumulative dose from both external exposure and internal exposure doses by summing $H_{E,\,age}$ from age 0 to attained age or attained age minus latent period of radiation-induced cancer, the interactive computing program DATAB[10] was used. Thus, the dose can be expressed as follows:

$$Dose = \sum_{i=0}^{attained\_age-latency\_period} H_{E,age} + (attained\_age - latency\_period) \times dose_{ieternal,year} \quad \text{.....(2)}$$

, where $H_{E,\,age}$ is the dose per year from external exposure obtained from Eq.(1) and is sex- and age-dependent, 10^{-5}Sv/a; $dose_{internal,\,year}$ is dose per year from internal exposure, which was assumed to be 4.273 10^{-3}Sv/a and 1.651 10^{-3}Sv/a in the HBRA and the control area, respectively, regardless of sex and age; and *the latency period* of radiation-induced solid cancer was assumed to be 10 years.

STATISTICAL METHODS

Risk calculation was based on the tabulated data, cross-classified by the variables having the following categories: Sex; male or female, Age at risk; 0, 1, 2, 3, 4, ..., 89, ≥ 90 years, Follow-up year; 1979, 1980, 1981, ..., 1994, 1995, Cumulative dose (mSv) ; 0–, 100–, 200, 300, ≥ 400.

The number of cancer deaths, total person-years at risk, average cumulative doses, and mean age at risk for each cell of the cross-classification tables were calculated using the same DATAB program[10].

The excess relative risk (ERR) per dose in sievert resulting from exposure to the naturally occurring radiation was estimated using the following model:

$$r = r_0 [1 + ERR\ (dose)]$$

, where r is the mortality rate for given age, sex, and calendar period; r_0 is the background or baseline of cancer mortality rate in the population; and *dose* is the cumulative dose in sievert.

The background mortality was estimated using a model including gender, age at risk, and calendar year. The Poisson model was fitted to estimate excess relative risk per sievert dose using the interactive computing program AMFIT[10]. Significance tests and confidence intervals were calculated by χ^2 approximation to likelihood ratio methods.

RESULTS

Solid cancer deaths and person-years for the period 1979–1995 are presented in Table 1.

Table 1. Person-years (Pyr) and number of solid cancer deaths (Cases) by period of follow-up (1979–1995) and dose category

Follow-up	Attained age		Dose category (mSv)										Total
			0–99		100–199		200–299		300–399		≥ 400		
interval	(y)		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	
1979–86	0–34	Pyr	246074	213744	41674	34080	.	.	.	.	.	.	535573
		Cases	15	14	16	6	.	.	.	.	.	.	51
	35–44	Pyr	11240	7452	16943	11877	11812	10110	.	.	.	.	69434
		Cases	9	3	15	8	15	7	.	.	.	.	57
	45–54	Pyr	6225	6658	2867	3355	24028	23165	847	1165	.	.	68309
		Cases	15	6	8	6	37	18	1	1	.	.	92
	55–64	Pyr	.	.	8118	9240	2671	2996	13701	16052	.	.	52777
		Cases	.	.	18	23	6	4	35	20	.	.	106
	65–74	Pyr	.	.	4466	5786	.	.	7595	8739	2368	3561	32515
		Cases	.	.	14	5	.	.	32	19	8	7	85
	≥75	Pyr	.	.	1251	2446	7	.	.	.	3253	6522	13479
		Cases	.	.	0	7	0	.	.	.	13	9	29
	Sutotal	Pyr	263539	227854	75319	66784	38517	36271	22142	25956	5621	10083	772086
		Cases	39	23	71	55	58	29	68	40	21	16	420
1987–95	0–34	Pyr	248725	228321	65375	53837	.	.	.	.	.	.	596257
		Cases	20	13	10	4	.	.	.	.	.	.	47
	35–44	Pyr	20094	13098	28151	21010	17732	13089	.	.	.	.	113173
		Cases	20	6	18	7	19	8	.	.	.	.	78
	45–54	Pyr	8458	4950	2966	2279	30571	22461	906	1240	.	.	73830
		Cases	17	4	5	0	59	19	4	2	.	.	110
	55–64	Pyr	.	.	9674	10472	4090	3481	22321	22135	.	.	72174
		Cases	.	.	32	7	15	4	57	28	.	.	143
	65–74	Pyr	.	.	7064	8208	.	.	10661	12310	4040	5108	47390
		Cases	.	.	24	13	.	.	41	23	12	3	116
	≥75	Pyr	.	.	2633	4473	.	.	.	.	6102	10193	23401
		Cases	.	.	7	8	.	.	.	.	20	10	45
	Subtotal	Pyr	277277	246369	115863	100278	52393	39031	33888	35684	10142	15300	926226
		Cases	57	23	96	39	93	31	102	53	32	13	539
Total		Pyr	540816	474223	191182	167062	90910	75302	56030	61640	15763	25384	1698312
		Cases	96	46	167	94	151	60	170	93	53	29	959

Table 2 shows the results obtained from an analysis of solid-cancer mortality. The interaction term between gender and attained age ($p = 0.051$) and the quadratic term for age ($p < 0.001$) were included in the model to improve the fitness of our model. Including a quadratic term for radiation dose did not improve the fitness of our models to the cancer mortality data, and neither sex nor calendar year modified the radiation-related cancer risk significantly. In Table 2, the regression coefficient for radiation dose represents the excess relative risk of radiation exposure: −0.11 per dose in sievert. Table 3 shows the relative risk of solid cancer mortality for five dose categories. The slight decrease in risk in the highest dose category was not significant ($p = 0.172$).

We also estimated the excess relative risks for four common cancer sites: cancer of the liver, nasopharynx, lung, and stomach (see Table 4). None of which was found to be related to radia-

Table 2. Coefficient of modeling of solid cancer mortality risk

Variable	Coefficient	95% CI	P value
Dose (Sv)	−0.11	−0.67 to 0.69	0.752
Male	0.24	−0.24 to 0.73	0.329
Age(y)	0.17	0.15 to 0.19	<0.001
Age^2	−0.0012	−0.0014 to −0.00096	<0.001
Age × male	0.0084	−0.000041 to 0.017	0.051
Calendar year	−0.0054	−0.018 to 0.0076	0.416

Note: The model is written as follows: Solid cancer mortality = exp(constant + male + age + age^2 + male × age + year) (1 + dose), where *dose* is individual radiation dose estimate, and *age* is the attained age.

Table 3. Relative risk (RR) of solid cancer mortality by dose category

Dose (mSv)	No. of cases	RR	95% CI
0–99	142	1 (referent)	–
100–199	261	0.83	0.65 to 1.06
200–299	211	0.98	0.76 to 1.26
300–399	263	0.90	0.68 to 1.18
≥400	82	0.66	0.45 to 0.98

Table 4. ERR per dose in sievert for major cancer sites, all ages, and both sexes

Site of cancer	No. of cases	ERR[a] per Sv	95% CI
Liver	258	−0.99	−1.60 to 0.10
Nasopharynx	189	0.10	−1.21 to 3.28
Stomach	102	−0.27	−1.37 to 2.69
Lung	94	−0.68	−1.58 to 1.66

[a] Excess relative risk

tion dose.

In the risk estimation, we used a latency period of 10 years for solid cancers. This value is widely accepted for radiation-induced cancer resulting from acute exposure to a high radiation dose. For chronic exposure, there is no generally accepted latency period for cancer. We alternatively used latency periods of 0, 5, and 10 years, and then estimated the excess relative risk for all solid cancers. The estimated ERRs were −0.11 (95% CI, −0.58 to 0.54), −0.12 (95% CI, −0.62 to 0.60), and −0.11 (95% CI, −0.67 to 0.69), respectively. Within this limited range of latency periods, solid-cancer risk estimates in HBRA study did not vary greatly.

Because data from 1979–1986 and 1987–1995 were obtained by means of different types of studies, we were particularly concerned about the comparability of these two data sets. The risk of solid cancer estimated using the cohort data for 1979–1986 was 0.00041 (95% CI, −0.83 to 1.43), a somewhat higher value than the excess risk for 1987–1995, which was −0.20 (95% CI, −0.89 to 0.87). However, the difference was not significant ($p = 0.142$).

In the risk estimation presented above, we did not consider emigration from the study areas because this information was unavailable for the period 1979–1986. To evaluate the influence of emigration on radiation-related cancer risk estimates, we calculated two ERRs: one that took migration into account and another that did not. We used the cohort data for 1987–1995, and arrived at two similar estimates: with adjustment for migration, –0.19 (95% CI, –0.89 to 0.92) and, without adjustment, –0.20 (95% CI, –0.86 to 0.87).

Another concern was accuracy of diagnosis. Of the 959 solid cancer cases, 222 cases were diagnosed pathologically, 582 by X-ray/ultrasonic examinations, 131 clinical diagnosis, and 24 by verbal autopsy based on the information obtained from the task group. It should be pointed out that the proportion of cancer pathologically diagnosed varied according to the cancer site. Only 51 percent (96/189) of nasopharyngeal carcinomas and 2 percent (6/258) of liver cancers were diagnosed pathologically. These two cancers accounted for 45 percent of all cancer deaths in our mortality data. In addition, the accuracy of diagnosis for certain cancers may not be high enough for site-specific cancer risk analysis. Estimating risk on the basis of diagnosis methods revealed that cancer diagnosis may bias our risk estimates to some extent. When we restricted solid cancer deaths to those diagnosed pathologically, the ERR of solid cancer was –1.26 (95% CI, NA to –0.14). Using all solid cancer deaths but excluding unreliable diagnosis, (that is clinical diagnosis and verbal autopsy), we calculated the risk as –0.17 (95% CI, –0.75 to 0.66).

DISCUSSION

A cancer mortality study was carried out in the high-background radiation areas of Yangjiang, China. Based on hamlet-specific environmental doses and sex- and age-specific occupancy factors, we calculated cumulative doses for each study subject. Using this dose estimation system and cancer mortality data for 1979–1995, we estimated the excess relative risk of solid cancer. In this article, we describe how we indirectly estimated individual dose and conducted a statistical analysis, which also evaluated the effects of possible bias.

The major difficulty in radiation-induced cancer risk estimation arises from the fact that we cannot distinguish radiation-induced cancer from spontaneously occurring cancers. Radiation epidemiologists confront the enormous task of estimating radiation-related cancer risk by comparing exposed and control populations, which may differ in terms of their genetic backgrounds and environmental factors, including lifestyles. It should be noted here that the confounding effects of covariates in low-dose ranges are even greater than those in high-dose ranges. For example, the RR of lung cancer associated with cigarette smoking in average Chinese men ranges from 5 to 10[11], which is much greater than the RR one might expect to be associated with low-level radiation exposure. In certain studies, researchers assume that the distribution of lifestyle-related factors is not highly dependent on radiation levels, and, therefore, their confounding effects on radiation-related risk estimates can be ignored. Since most of the residents in the HBRA and the control area in this study were farmers, we assumed that the socioeconomic status and lifestyles in the two areas did not differ greatly. To date, surveys have revealed no distinct differences in lifestyles in the HBRA and the control area[12].

One major goal of radiation epidemiology is to accurately estimate the radiation dose received by study subjects. Although the ideal approach is to directly measure lifetime cumulative dose, this is possible only in exceptional situations. One such example is the follow-up study of radiation workers in Japan, in which all the information on radiation exposure in restricted areas is available to researchers[13]. The second approach is estimating dose on the basis of several parameters obtained from study subjects. One example is the dose estimation conducted among atomic-bomb survivors, for whom researchers know the distance from the hypocenter, shielding conditions, and postures at the time of the bombing[14]. Another approach is assigning a dose estimate. For example, among the atomic-bomb survivors exposed at 2.5 km or further from the hypocenter, a radiation dose estimate based on air kerma dose at the location of exposure has been assigned. The individual dose estimation approach we used for HBRA study is similar. We calculated cumulative doses for each study subject, using the hamlet-specific environmental doses and sex- and age-specific occupancy factors. We should point out that our individual dose estimates did not take into account occupancy factors obtained from each individual or indoor doses specific for each household. Our study used the occupancy factors obtained from a survey of 5,291 subjects and hamlet-specific indoor and outdoor doses. We compared the individual doses estimated by this indirect method with those obtained from direct measurements using thermoluminescent dosimeters (TLD). The TLD survey subjects numbered 5,204 in 88 hamlets, most of whom had also participated in the occupancy factor survey mentioned previously. Morishima et al[5] and Yuan et al[4] reported good correlation between the estimated and measured doses. We also wish to point out that we did not consider medical radiation exposure in our study. We have no evidence that suggests the level of medical exposure differed in HBRA and the control areas[12].

To consider internal exposure when calculating the individual effective dose, we used an average internal dose common to all sex and age groups. Although using sex- and age-specific internal doses is, at minimum, preferred, information on internal doses was limited, resulting in the use of an average internal dose in the present study. In the study areas, we are conducting further work on internal dose estimation. Thus, we hope to obtain more accurate estimates of internal dose in the near future.

Although there is no unequivocal definition of low-level radiation exposure, both the 1988 UNSCEAR report and the ICRP Publication 60 cite a dose of less than 200 mGy for a single exposure[15,16], primarily because no excess cancer risk had been observed below this dose among the atomic-bomb survivors until recently. However, a 1996 report on atomic-bomb survivors reported excess cancer deaths in much lower dose ranges[17]. In the Life Span Study of mortality for the period 1950–1990, exposures in a dose range of 0.005–0.02 Sv were assigned a significant ERR of 0.03 for solid cancer, which can be translated into 2.6 per sievert. Although low-dose-rate exposure is thought to be associated with a lower cancer risk than high-dose-rate exposure even when the total dose received is the same, such an effect is not yet well established in radiation epidemiology. For example, dose-rate effects have not been observed for radiation-related breast cancer, which is one of the most radiation-sensitive cancers[18]. Those spending 50 years in HBRA may receive a 320 mSv dose (6.4 mSv $\times$ 50 years), which is comparable to the average dose among the LSS cohorts of atomic-bomb survivors, for which the solid cancer ERR

is 0.40 (95% CI, 0.31 to 0.51)[17]. We did not observe any excess risk in HBRA (ERR = –0.11), although the confidence interval of our estimate (95% CI: –0.67 to 0.69) overlaps with the confidence interval of the atomic-bomb survivor estimate. Since 45 percent of all cancer deaths in our mortality data were accounted for by cancers of the liver and nasopharynx, in which viral infection plays a major etiological role, our relative risk estimate might have been diluted by cancers that are less sensitive to radiation. Excluding the cancers of the liver and nasopharynx from all solid cancers, the ERR is estimated to be 0.24 (95% CI, –0.53 to 1.49) per dose in sievert.

Epidemiological studies of low-level radiation effects are complicated by the need for a large sample. For example, to detect a RR of 1.1 requires 2.4 million person-years for both the exposed and control groups ($\alpha = 5\%$, $\beta = 20\%$). Since the number of exposed is usually fixed in most epidemiological studies, statistical accuracy can be improved only by increasing the number of control subjects. However, even by increasing the ratio of the exposed to unexposed to 1:10, the exposed group would need 1.3 million person-years. This translates to following up 130,000 subjects for 10 years. Another approach to increase statistical accuracy is to conduct pooled data analysis or meta-analysis using data from different studies. A collaborative study between Indian and Japanese research groups, started in 1999, improves the likelihood that such an approach may be possible using the Chinese and Indian data in the future.

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