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Cancer risks in a population with prolonged low dose-rate γ-radiation exposure in radiocontaminated buildings, 1983–2002

S.-L. HWANG[1,9], H.-R. GUO[2], W.-A. HSIEH[3], J.-S. HWANG[4], S.-D. LEE[5], J.-L. TANG[6], C.-C. CHEN[7], T.-C. CHANG[6], J.-D. WANG[8] & W. P. CHANG[1]

[1]*National Yangming University Medical School,* [2]*National Cheng Kung University,* [3]*Tzuchi University,* [4]*Academia Sinica,* [5]*National Taipei College of Nursing and National Taiwan University Hospital,* [6]*National Taiwan University Hospital,* [7]*Jenai Municipal Hospital, Taipei City,* [8]*National Taiwan University, and* [9]*Diwan College of Management, Taiwan*

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Abstract

Purpose: To assess cancer risks in a population that received prolonged low dose-rate γ-irradiation for about 10 years as a result of occupying buildings containing ^{60}Co-contaminated steel in Taiwan.

Materials and methods: The cancer risks were compared with those populations with the same temporal and geographic characteristics in Taiwan by standardized incidence ratios (SIR), adjusted for age and gender. The association of cancer risks with excess cumulative exposure was further evaluated for their relative risks by the Poisson multiple regression analysis.

Result: A total of 7271 people were registered as the exposed population, with 101,560 person-years at risk. The average excess cumulative exposure was approximately 47.8 mSv (range < 1–2,363 mSv). A total of 141 exposed subjects with various cancers were observed, while 95 developed leukemia or solid cancers after more than 2 or 10 years initial residence in contaminated buildings respectively. The SIR were significantly higher for all leukemia except chronic lymphocytic leukemia ($n = 6$, SIR = 3.6, 95% confidence interval [CI] 1.2–7.4) in men, and marginally significant for thyroid cancers ($n = 6$, SIR = 2.6, 95% CI 1.0–5.7) in women. On the other hand, all cancers combined, all solid cancers combined were shown to exhibit significant exposure-dependent increased risks in individuals with the initial exposure before the age of 30, but not beyond this age.

Conclusions: The results suggest that prolonged low dose-rate radiation exposure appeared to increase risks of developing certain cancers in specific subgroups of this population in Taiwan.

Keywords: *^{60}Co, low dose-rate, radiation, cancer risk, human population*

Introduction

Acute radiation exposure has been demonstrated to increase cancer risks in many studies including studies of Japanese atomic bomb survivors (ABS; Preston et al. 1994, Thompson et al. 1994), persons with medical exposure (Boice et al. 1991), and persons exposed in occupational settings (Ivanov et al. 1997). It remains uncertain whether chronic or protracted low dose-rate radiation exposure would incur increased cancer risks in a general public setting, as addressed in a recent review (Brenner et al. 2003). Studies of carcinogenic effects of low dose-rate ionizing radiation exposure have focused on nuclear workers (Cardis et al. 1995, Muirhead et al. 1999), and workers in the Mayak nuclear facility in the former Soviet Union with significant increases in the mortality rates of both solid cancers and leukemia (Shilnikova et al. 2003). Risk estimates from the Techa River cohort (TRC) also suggested that the risks of mortality from leukemia and other cancers increased with increasing radiation exposure (Kossenko et al. 1997). Furthermore, a Swedish study showed an elevated risk of acute lymphocytic leukemia among children and young adults living in uranium-containing alum shale concrete houses with high indoor radon concentrations (Axelson et al. 2002). Brenner et al. (2003) suggested that a protracted γ-radiation exposure of 50–100 mSv may be associated with increased cancer risks in humans.

Correspondence: Dr W. Peter Chang, Institute of Environmental Health Sciences, National Yangming University Medical School, 155, Sec. 2, Linong Street, Taipei 112, Taiwan. Tel: +886 2282 02837. Fax: +886 2282 07883. E-mail: wpc94@yahoo.com

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However, there are few studies concerning exposure of the general public, particularly including women and children at different ages of exposure.

In late 1982, several ^{60}Co orphan sources were recycled in the steel scrap industry in northern Taiwan resulting in more than 20,000 tons of various contaminated steel products employed in over 200 residential, industrial, and school buildings (Chang 1993, Chang et al. 1997a). It was not until August 1992 that these contaminated buildings started to be identified. The rates of exposure (0.5 – 270 μSv/hours) in these buildings, measured in 1994, have been estimated to be several to > 1,000 times the background radioactivity (0.08 – 0.1 μSv/hours) in general Taiwanese construction. Cytogenetic analysis in subgroups of the exposed population had shown increased micronucleus frequencies in peripheral lymphocytes (Chang et al. 1997b), increases in acentromeric and single or multiple centromeric cytogenetic damages (Chang et al. 1999a), and higher frequencies of chromosomal translocations, rings and dicentrics (Hsieh et al. 2002). Persistent depression in peripheral leucocytes and neutrophils (Chang et al. 1999b), increased eosinophils, altered distributions in lymphocyte subpopulations (Chang et al. 1999c), increased frequencies of lens opacities (Chen et al. 2001), delayed physical development in children (Wang et al. 2001), increased risk of thyroid abnormalities (Chang et al. 2001), as well as late consequences on haematopoietic adaptation in children were also observed (Wang et al. 2002). This follow-up study was designed to evaluate risks of developing cancers in these radiocontaminated buildings (RCB) exposed population more than 10 years after their initial exposure.

Materials and methods

Study population

In August 1992, radioactive contamination was brought to public attention by a local newspaper (Chang et al. 1997a). Upon the discovery of these radiocontaminated buildings (RCB), the Atomic Energy Council (AEC; the nuclear regulatory authority in Taiwan), the Department of Health, and a designated research team began to establish a registry for all residents and students who had stayed in these buildings by using household and school registration records. The household registration system in Taiwan has been maintained by the Ministry of Interior (MOI) since the 1950s and has been completely computerized since the 1990s. As the household registration was accessible by National Identification Numbers (NIN), we were able to trace all individuals with official residential occupancy in these contaminated buildings since 1982 when these individuals first moved in. Moreover, individuals identified by home owner records or reported by other registrants to have resided in those buildings, but not registered in the MOI residential registration, were further evaluated for details of their occupancy and exposure through extensive contacts and interviews. Those who left before the beginning of the registration in 1992 were also traced by household registration, police records, and other approaches.

After individuals moved out of contaminated buildings or after the contaminated steel materials were removed or shielded, they were designated as not having continuous additional excess cumulative exposure. Systematic questionnaire-based interviews were administered to each registered individual to obtain medical history, occupation, education, and detailed exposure history, including dates moved in and out, and lifestyles in these radiocontaminated buildings. Excess exposure to other radiation sources in these registrants, such as occupational and medical exposure, and radiotherapy, were also evaluated carefully. If registered individuals were deceased, interviews were conducted with their families, as well as teachers at school, and employers when necessary. The protocols for conducting the questionnaire survey were reviewed by the Internal Review Boards of the National Yangming University and further approved by Department of Health (DOH) and the National Health Research Institute, which had supported the research, to ensure confidentiality and quality. The interviews were conducted only after the contents were fully explained to the individuals and informed consent was acquired. These individuals were further periodically evaluated even after they relocated to non-contaminated buildings. Deaths amongst the study cohort were further matched by the National Mortality Registry of Taiwan, which had been maintained by the Bureau of Vital Statistics in Taiwan since early 1950s. At the end of 2002, some 7271 members (including 3461 men and 3810 women) were registered and most of them were followed up closely.

The duration of observation of each cohort member with radiation-related cancers at risk was from the date they moved into a contaminated building to the date of death, the date of cancer diagnosis, or 31 December 2002, whichever came first. The minimum latent period, according to the International Commission on Radiological Protection (ICRP) recommendations (ICRP 60, 1990), is the shortest period of time after which a radiation-inducible cancer is known to occur after exposure. Then, the ''person-years at risk'' of these cohort members were obtained by subtracting the minimum latent period from the duration of observation and were used in SIR and Poisson regression analyses.

Ascertainment of cancer cases

Cancer cases were identified through the National Cancer Registry of Taiwan (NCRT), which was established in 1979 by the Department of Health. The cases identified through the NCRT were coded by the International Classification of Disease for Oncology (ICD-O, First Edition). The NCRT is a population-based cancer registry that collects information on all newly diagnosed cancer patients from all health care sectors in Taiwan and had provided data to many nationwide and international cancer studies (Guo et al. 1997, Chien et al. 2001).

Exposure evaluation

An exposure assessment system, the Taiwan Cumulative Dose (TCD), had been established in the beginning of the cohort registration and applied to exposure reconstruction for the cohort on an individual basis. The TCD integrated the time-activity analysis recommended by the U.S. National Institute for Occupational Safety and Health advisory committee (Cardarelli et al. 1997) and the highly occupied zone (HOZ) model of this study group (Hwang et al. 1998), incorporating a detailed history of occupancy duration in each radioactive area of the buildings and area-specific radiation exposure to the whole-body of each individual. Each cohort member was asked to recall and provide as much detailed information as they could about previous occupancy, including daily regular durations in each HOZ. Environmental radioactivities of representative spots in each room were measured accordingly. Cumulative excessive exposures were corrected for the half-life of radioactive decay, i.e., 5.27 years for Co-60, and integrated with lifestyle patterns while residing in the contaminated buildings. The exposure assessment by the TCD has been employed in several related studies (Chen et al. 2001, Wang et al. 2002) and comparable to biodosimetric analysis by fluorescence in situ hybridization chromosomal translocation frequencies (Hsieh et al. 1999).

With the restriction of insufficient information for exposure assessment by the TCD, 6246 subjects were included for exposure-dependent risk analysis. A total of 1025 persons were not included due to TCD deficiency of occupancy durations in each radioactive area of the buildings. The average excessive cumulative exposure, i.e., above background radiation exposure, was 47.8 mSv (ranging from $<1-2363$ mSv), with 2285 (36.6%) with less than but close to 1 mSv, 3137 (50.2%) 1–50 mSv, and 824 (13.2%) more than 50 mSv. When the exact exposure duration for each individual was taken into consideration, the estimated dose-rate of excess exposure was 10.5 mSv/year on average ($<1-1413$ mSv/year), including 63% with less but close to 1 mSv/year, 16% with 1–5 mSv/year, and 21% with more than 5 mSv/year. Owing to large variations of occupancy durations in specific irradiated areas of these buildings and variations in the radioactivity in these areas, from slightly higher than 0.1 μSv/hour up to 500 μSv/hour, there was a wide range of cumulative exposures.

Statistical analysis

The cancer risks in the radiocontaminated buildings (RCB) exposed population were compared with a reference population with the same temporal and geographic characteristics in Taiwan; that is, Taipei City and Counties of Taipei, Keelong, Taoyuan, and Changhwa, where the radiocontaminated buildings were located (Chang et al. 1997a). The expected number of cancer cases was calculated by multiplying the number of "person-years at risk" with the average age-specific cancer incidence rates of the reference population during the period of 1983–2002. A standardized incidence ratio (SIR) adjusted for age and gender was calculated with the observed number of cancer cases as the numerator and the expected number of specific cancer cases as the denominator (Breslow & Day 1987). The 95% confidence interval (CI) for each SIR was constructed using the exact limits given by Pearson and Hartley (1976). There was no attempt to match economic factors related to residency, although residency was apparently influenced by economic factors.

Specific cancer risks associated with cumulative exposure were analysed by the Poisson regression models. We assumed that the numbers of cancer cases in the ith stratum denoted by y_i followed independent Poisson distributions with the mean equal to μ_i. The mean in the ith stratum was influenced by a set of 3 regressors via the model

$$\mu_i = P_i \times \exp\left(\beta_0 + \beta_1 I(X_{1i} = M) + \sum_{j=1}^{3} \beta_{2j} I(X_{2i} = j) + \sum_{j=1}^{2} \beta_{3j} I(X_{3i} = j)\right),$$

where P_i was the person-years at risk in the ith stratum, $I(.)$ is a indicator function, X_{1i} was a gender variable, $X_{2i} = 1$, 2, and 3 corresponding to the attained age 21–40, 41–60, or >60 years old, respectively, and $X_{3i} = 1$ and 2 corresponding to lagged of the excess cumulative exposure (Lag_TCD) 1–50 or >50 mSv, respectively. The models were fitted separately with those with age at initial exposure ≤ 30, >30 years old, or all age

combined. P_i was the person-years at risk and included those non-cancer individuals in the exposed cohort members.

The age at initial exposure was defined as the age when they first moved into the radiocontaminated buildings, while the attained age was the age of death, the date of cancer diagnosis, or 31 December 2002, whichever came first. When analysing gender-relative cancer (i.e., breast cancers, combination of thyroid and breast cancers), the regressor of sex was exclusive in the regression model. The excess cumulative exposure was lagged 2 years for leukemia and 10 years for other cancers to allow for a minimum latent period of cancer induction. The likelihood function for the Poisson regression can be expressed as:

$$L(\beta|y_1 \cdots y_m) = \prod_{i=1}^{m} \left[\frac{e^{-\mu_i} \left(\frac{\mu_i}{P_i}\right)^{y_i}}{y_i!} \right],$$

where m was the number of stratum in the Poisson regression model. The estimations of the parameters β, relative risks and 95% confidence intervals were obtained by fitting the data to the model with the GENMOD procedure via the software package SAS (version 8.0e; SAS Institute Inc., Cary, NC).

Results

These 7271 cohort members were followed-up for 16.1 ± 4.0 years on average ($<1-20$ years), with initial exposure at 17.2 ± 16.0 years of age (intrauterine to 80 years old) and a total of 101,560 person-years at risk (48,119 for men and 53,441 for women; Table I). A total of 141 cohort members were found to have developed cancers, and 46 of these cases (45 solid cancers and 1 multiple myeloma, Table II) developed in less than the minimal latent periods, as recommended by the ICRP 60. Therefore, 95 subjects who developed cancers with latent period more than the minimal latent periods were included for analysis of simple SIR and relative risks.

Simple SIR analyses without consideration of dose estimates revealed significantly elevated risks for thyroid cancers ($n=7$, SIR = 2.6, 95% CI 1.1–5.4) and non-Hodgkin's lymphoma ($n=5$, SIR = 5.4, 95% CI 1.8–12.6), and marginally significantly elevated risk for leukemia except chronic lymphocytic leukemia (leukemia except CLL; $n=7$, SIR = 2.2, 95% CI 0.9–4.6), for both genders combined.

Table I. Distribution of person-years at risk[†] and cancer cases by age at initial exposure, Taiwan Cumulative Dose and gender, Taiwan RCB, 1983–2002.

		Men		Women		Total			
Age at initial exposure	Cumulative exposure (TCD*; mSv)	Person-years at risk	Number of cancers[†]	Person-years at risk	Number of cancers	Person-years at risk	Number of cancers	Dose rate (mSv year^{-1})	Average follow-up time (years)
≤30 years									
	<1	10,851	1	12,404	2	23,255	3		
	1∼50	17,366	3	19,473	12	36,839	15		
	>50	4,598	2	4,569	5	9,167	7		
	40.0 (<1, 2,206)[‡]	32,815	6	36,446	19	69,261	25	11.0 (<1, 1,413)	
	missing	5,804	1	6,147	0	11,951	1		
Total		38,619	7	42,593	19	81,212	26		15.8 (<1, 20)
>30 years									
	<1	1,914	7	2,755	9	4,669	16		
	1∼50	4,941	19	4,780	17	9,721	36		
	>50	1,683	5	1,810	5	3,493	10		
	80.0 (<1, 2,363)	8,538	31	9,345	31	17,883	62	8.5 (<1, 469.5)	
	missing	962	4	1,503	3	2,465	7		
Total		9,500	35	10,848	34	20,348	69		17.2 (2, 20)
All age									
	<1	12,765	8	15,159	11	27,924	19		
	1∼50	22,307	22	24,253	29	46,560	51		
	>50	6,281	7	6,379	10	12,660	17		
	47.8 (<1, 2,363)	41,353	37	45,791	50	87,144	87	10.5 (<1, 1,413)	
	missing	6,766	5	7,650	3	14,416	8		
Total		48,119	42	53,441	53	101,560	95		16.1 (<1, 20)

*Taiwan Cumulative Dose; [†]Latent period considered, 2 years for leukemia and 10 years for other cancers; [‡]Mean (min, max).

Table II. Characteristics of 46 cancer cases with latent periods less than the minimal latent periods as recommended by the ICRP 60*.

Cancer site	Cases	Latent periods (years) Mean (min, max)	Cumulative exposure (TCD; mSv) Mean (min, max)	Age at initial exposure (years) Mean (min, max)
Nasopharynx	1	4.3	4.3	36.4
Stomach	3	5.9 (1.7, 8.2)	444.3 (378.8, 571.0)	52.7 (47.9, 61.4)
Colon	5	8.4 (5.1, 9.7)	41.1 (4.2, 177.9)	64.3 (54.2, 70.9)
Rectum	4	5.7 (3.8, 9.6)	0.7 (<1, 2.0)	38.8 (18.6, 55.8)
Liver	3	5.0 (4.2, 6.5)	50.3 (10.3, 105.1)	32.2 (27.6, 38.7)
Lung	3	8.4 (6.2, 9.6)	544.7 (2.5, 1,464.0)	62.3 (48.5, 71.4)
Breast	7	6.2 (1.1, 10.0)	97.9 (<1, 447.1)	40.1 (26.0, 59.0)
Cervix Uteri	8	6.9 (2.5, 9.9)	78.4 (1.3, 293.4)	41.2 (26.6, 64.5)
Corpus Uteri	2	9.0 (8.9, 9.1)	35.3 (7.9, 62.8)	54.9 (45.4, 64.3)
Ovary	2	9.6 (9.3, 9.8)	88.7 (1.6, 175.8)	28.6 (24.0, 33.2)
Urinary	2	7.5 (6.5, 8.4)	<1 (<1, <1)	61.6 (56.9, 66.2)
Kidney	1	2.3	34.7	70.0
Thyroid glands	4	8.6 (7.9, 9.8)	8.9 (0.3, 22.1)	27.5 (5.2, 41.0)
Multiple myeloma	1	1.3	43.1	61.3

*Latent periods: solid cancers and multiple myeloma less than 10 years or leukemia less than 2 years.

On the other hand, SIR was marginally significantly lower in both genders combined for all cancers (SIR = 0.8, 95% CI 0.7–1.0; Table III). There were significantly lower risks for all cancers except leukemia (SIR = 0.8, 95% CI 0.6–0.9), and all solid cancers combined (SIR = 0.7, 95% CI 0.6–0.9).

In men, there were significantly elevated risks for all leukemia combined ($n = 6$, SIR = 3.4, 95% CI 1.2–7.4) and leukemia except CLL ($n = 6$, SIR = 3.6, 95% CI 1.3–7.8). For all leukemia, the diseases were diagnosed 6–18 years (mean 13.3 ± 4.7 years) after initial exposure, while the ages at initial exposure were 5 (two cases), 15, 39, 52 and 70 years old, respectively. A case of papillary thyroid cancer was observed in a 47-year-old man, 10 years after initial exposure. There were significantly lower SIRs for all cancers except leukemia (SIR = 0.7, 95% CI 0.5–0.9) and all solid cancers combined (SIR = 0.6, 95% CI 0.4–0.8). In women, there were marginally significantly elevated risks for thyroid cancers ($n = 6$, SIR = 2.6, 95% CI 1.0–5.7). The ages at initial exposure were 9, 30, 32, 34, 51, and 67 years old, respectively, and the diagnoses made 10–16 years (mean 12.5 ± 2.4 years) after initial exposure. All thyroid cancers were of the papillary cell type.

According to the Life Span Study (LSS; Thompson et al. 1994, Preston et al. 1994), the top two solid cancers associated with radiation were breast cancers (excess relative risk per Sievert ERR_{1Sv} 1.74) and thyroid cancers (ERR_{1Sv} 1.50). Therefore, these two cancers were combined as the target cancer group to assess the exposure-response relationship. All cancers, solid cancers, leukemia except CLL, thyroid cancers, breast cancers, and thyroid/breast cancers combined were evaluated for exposure-dependent cancer risk, respectively (Table IV). Among those who received initial exposure before 30 years of age, those who were exposed to more than 50 mSv had significantly increased risk for all cancers combined (Relative risk; RR = 5.5, 95% CI 1.5–19.9), all solid cancers combined (RR = 9.0, 95% CI 2.0–40.8), breast cancers (RR = 16.0, 95% CI 1.4–179.8) and thyroid/breast cancers combined (RR = 8.1, 95% CI 1.1–59.0), as compared with those who had received less than 1 mSv of exposure. There was no significant exposure-dependent increase in those with initial exposure after age 30. For all ages combined, there was marginally significantly increased risk for breast cancers (RR = 4.3, 95% CI 1.0–19.8), and no significant exposure-dependent increase in leukemia (except CLL) (RR = 2.9, 95% CI 0.4–22.0), thyroid/breast cancers combined (RR = 2.8, 95% CI 0.7–11.3) among those with more than 50 mSv as compared with those who had received less than 1 mSv of exposure.

Discussion

This cohort in Taiwan with exposure to prolonged low dose-rate γ-irradiation in radiocontaminated buildings were shown with evidences of exposure-dependent increases in cancer risks, especially in individuals with initial exposure before age 30. The exposed cohort is unique because it consists of a general population (both genders and all ages), and has received relatively higher radiation exposure similar to those in the LSS studies. However, the exposed cohort differs from that of the LSS in that the exposure was protracted and primarily from gamma rays. In contrast to other occupational radiation exposure cohorts comprised primarily of men, this cohort population comprises similar numbers of both genders.

Table III. Standardized incidence ratios for the exposed population, 1983–2002*.

	Men			Women			All		
	Cases			Cases			Cases		
Cancer site	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
All cancers	42	53.8	0.8 (0.5, 1.0)	53	60.9	0.9 (0.7, 1.1)	95	114.9	0.8† (0.7, 1.0)
All cancers except Leukemia	36	52.0	0.7‡ (0.5, 0.9)	52	59.3	0.9 (0.7, 1.2)	88	111.6	0.8‡ (0.6, 0.9)
Solid cancers	32	50.9	0.6‡ (0.4, 0.8)	50	58.5	0.9 (0.6, 1.1)	82	109.5	0.7‡ (0.6, 0.9)
Tongue	0	1.1	– –	1	0.3	3.7 (0.1, 20.7)	1	1.5	0.7 (0.02, 3.7)
Oral	1	1.4	0.7 (0.02, 4.0)	0	0.2	– –	1	1.7	0.6 (0.02, 3.3)
Nasopharynx	1	2.0	0.5 (0.01, 2.7)	0	1.0	– –	1	3.1	0.3 (0.01, 1.8)
Esophagus	1	1.8	0.6 (0.01, 3.2)	1	0.3	3.6 (0.1, 20.3)	2	2.2	0.9 (0.1, 3.3)
Stomach	5	4.9	1.0 (0.33, 2.4)	2	3.1	0.6 (0.1, 2.3)	7	8.2	0.8 (0.3, 1.8)
Colon	2	4.0	0.5 (0.1, 1.8)	3	3.8	0.8 (0.2, 2.3)	5	7.9	0.6 (0.2, 1.5)
Rectum	3	3.1	1.0 (0.2, 2.8)	2	2.7	0.7 (0.1, 2.7)	5	5.9	0.8 (0.3, 2.0)
Liver	5	8.9	0.6 (0.2, 1.3)	3	3.7	0.8 (0.2, 2.3)	8	13.1	0.6 (0.3, 1.2)
Lung	7	7.6	0.9 (0.4, 1.9)	3	4.5	0.7 (0.1, 2.0)	10	12.5	0.8 (0.4, 1.5)
Connective	1	0.5	2.1 (0.1, 11.9)	1	0.4	2.3 (0.1, 12.6)	2	0.9	2.2 (0.3, 7.9)
Skin	2	1.5	1.4 (0.2, 4.9)	1	1.5	0.7 (0.02, 3.6)	3	3.0	1.0 (0.2, 2.9)
Melanoma skin	0	0.2	– –	1	0.2	5.4 (0.1, 30.1)	1	0.4	2.8 (0.1, 15.7)
Non melanoma skin	2	1.4	1.5 (0.2, 5.3)	0	1.4	– –	2	2.8	0.7 (0.1, 2.6)
Breast	0	0.0	– –	12	12.1	1.0 (0.5, 1.7)	12	11.2	1.1 (0.6, 1.9)
Cervix Uteri	0	0.0	– –	12	12.9	0.9 (0.5, 1.6)	12	11.9	1.0 (0.5, 1.8)
Corpus Uteri	0	0.0	– –	3	1.5	2.0 (0.4, 6.0)	3	1.4	2.2 (0.5, 6.4)
Prostate gland	1	3.4	0.3 (0.01, 1.7)	0	0.0	– –	1	3.8	0.3 (0.01, 1.5)
Kidney	2	1.3	1.5 (0.2, 5.5)	0	1.1	– –	2	2.4	0.8 (0.1, 3.0)
Thyroid glands	1	0.5	2.0 (0.1, 11.1)	6	2.3	2.6† (1.0, 5.7)	7	2.7	2.6‡ (1.1, 5.4)
Leukemia (all types)	6	1.8	3.4‡ (1.2, 7.4)	1	1.5	0.7 (0.02, 3.7)	7	3.3	2.1† (0.8, 4.3)
Leukemia except CLL	6	1.7	3.6‡ (1.3, 7.8)	1	1.5	0.7 (0.02, 3.8)	7	3.2	2.2† (0.9, 4.6)
Acute lymphocytic leukemia (ALL)	3	0.4	6.8‡ (1.4, 19.8)	0	0.4	– –	3	0.8	3.6† (0.7, 10.4)
Acute myelocytic leukemia (AML)	2	0.6	3.3 (0.4, 11.8)	1	0.5	1.8 (0.05, 10.1)	3	1.2	2.5 (0.5, 7.4)
Chronic myelocytic leukemia (CML)	1	0.3	3.9 (0.1, 21.9)	0	0.2	– –	1	0.5	2.2 (0.1, 12.1)
Multiple myeloma	1	0.3	3.9 (0.1, 21.5)	0	0.2	– –	1	0.5	2.2 (0.1, 12.3)
Malignant Lymphoma	3	0.9	3.3 (0.7, 9.7)	2	0.7	2.9 (0.04, 8.1)	5	1.6	3.1‡ (1.0, 7.2)
Non-Hodgkin's lymphoma	3	0.5	6.3‡ (1.3, 18.4)	2	0.4	4.6 (0.6, 16.5)	5	0.9	5.4‡ (1.8, 12.6)

*Latent period considered; †$0.05 < p < 0.1$; ‡$p \leq 0.05$; SIR, standardized incidence ratio; CI, confidence interval; –: not applicable.

Table IV. Relative risks (RR) of cancer by different categories of Taiwan Cumulative Dose (TCD) and age at initial exposure*.

	Cohort members	All cancers		All solid cancers		Leukemia Except CLL		Thyroid cancers		Breast cancers		Combination of Thyroid/Breast	
		N[§]	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)
Age at initial exposure													
≤30 years													
Gender													
Men	2,408	6	1	3	1	3	1	0	1				
Women	2,633	19	2.8[‡] (1.1, 7.0)	17	4.9[‡] (1.4, 16.7)	0	–	2	–	6		8	
Lag_TCD (mSv)[‖]													
<1	2,618	4	1	3	1	2	1	1	1	1	1	2	1
1∼50	1,944	15	3.4[‡] (1.1, 10.6)	13	3.9[‡] (1.1, 13.8)	0	–	1	–	3	3.3 (0.3, 31.9)	4	2.0 (0.4, 11.4)
>50	479	6	5.5[‡] (1.5, 19.9)	4	9.0[‡] (2.0, 40.8)	1	–	0	–	2	16.0[‡] (1.4, 179.8)	2	8.1[‡] (1.1, 59.0)
Total	5,041	25		20		3		2		6		8	
>30 years													
Gender													
Men	568	31	1	26	1	2	1	1	1				
Women	637	31	0.9 (0.6, 1.5)	30	1.1 (0.6, 1.8)	1	–	4	3.9 (0.4, 35.2)	6		10	
Lag_TCD (mSv)													
<1	354	18	1	22	1	0	1	1	1	3	1	4	1
1∼50	651	37	1.0 (0.6, 1.7)	31	0.9 (0.5, 1.6)	2	–	4	3.1 (0.3, 27.9)	2	0.5 (0.08, 3.0)	5	0.9 (0.2, 3.5)
>50	200	7	0.6 (0.3, 1.5)	3	0.5 (0.2, 1.8)	1	–	0	–	1	1.5 (0.2, 14.3)	1	1.1 (0.1, 10.0)
Total	1,205	62		56		3		5		6		10	
All age													
Gender													
Men	2,976	37	1	29	1	5	1	1	1				
Women	3,270	50	1.2 (0.8, 1.8)	47	1.4 (0.9, 2.3)	1	0.2 (0.02, 1.6)	6	–	12		18	
Lag_TCD (mSv)													
<1	2,972	22	1	25	1	2	1	2	1	4	1	6	1
1∼50	2,595	52	1.3 (0.8, 2.2)	44	1.2 (0.7, 1.9)	2	0.8 (0.1, 6.0)	5	–	5	1.1 (0.3, 4.0)	9	1.2 (0.4, 3.4)
>50	679	13	1.1 (0.6, 2.3)	7	1.2 (0.5, 2.9)	2	2.9 (0.4, 22.0)	0	–	3	4.3[†] (1.0, 19.8)	3	2.8 (0.7, 11.3)
Total	6,246	87		76		6		7		12		18	

*Poisson regression model: $\mu_i = P_i \times \exp(\beta_0 + \beta_1 I(X_{1i} = M) + \sum_{j=1}^{3} \beta_{2j} I(X_{2i} = j) + \sum_{j=1}^{2} \beta_{3j} I(X_{3i} = j))$, where P_i was the person-years in the ith stratum, $I(.)$ is a indicator function, X_{1i} was a gender variable, $X_{2i} = 1$, 2, and 3 corresponds to attained age 21–40, 41–60, and > 60 years old, respectively, and $X_{3i} = 1$ and 2 corresponds to lagged of the excess cumulative exposure 1–50 and > 50 mSv, respectively; All the relative risks were adjusted for attained age; [†]$0.05 < p < 0.1$; [‡]$p \leq 0.05$; [§]Numbers of cancer cases; [‖]excess cumulative exposure were lagged 2 years for leukemia and 10 years for other cancers; –: not applicable.

Lack of information on other confounding risk factors related to lifestyle, particularly socio-economic status, was one of the limitations in the current study. On the other hand, due to prolonged exposures, the excessive cumulative exposures discontinued to the date of death, the date of cancer diagnosis, or the date of moving out of the radio-contaminated buildings. As the result, the cumulative exposures for the cancer cases tend to be lower than exposed but healthy cohort members. The existence of such a bias in exposure estimation would lead to an underestimation of risks.

Leukemia was the first cancer to be noted with higher incidences among the atomic bomb survivors (Folley et al. 1952). This study was able to show that there were significantly elevated SIR for leukemia (except CLL) in men and significantly elevated risks for malignant lymphoma (especially for non-Hodgkin's lymphoma) in both genders combined (Table III), as reported by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2000). According to the ATB studies (Preston et al. 1994), there was an increased risk of leukemia in those receiving radiation exposures at a young age. Owing to the relatively small number of cancer cases, leukemia except CLL was not shown with significantly elevated risks in the exposed population (Table IV), with gender considered.

External exposure of the thyroid gland to ionizing radiation, even under 0.05 Gy, was shown to increase the risk of thyroid cancers for children and adolescents (Jacob et al. 1999). A previous study on this cohort indicated a significant exposure-dependent increase in thyroid abnormalities (Chang et al. 2001). The small number of cases in the exposed population and the relatively short follow-up could explain why we did not observe exposure-dependent increases in thyroid cancers in this cohort.

Breast cancers have been linked with radiation exposure in many studies (Preston et al. 2002). This study did not observe an elevated SIR for breast cancers (Table III), but there was marginally significant exposure-dependent increase in breast cancers in the exposed population (Table IV). Several other variables for breast cancers, including body mass, reproductive history and hormone use, were not considered in this analysis, and may affect different observations in SIR and RR. A case-control study has shown that early age at first full-term pregnancy, multiple births, and lengthy total lactation history were protective against breast cancer among A-bomb survivors, especially among women under 20 years of age (Land et al. 1994). A further nested case-control study for this cohort will help clarify the association between exposure and breast cancers.

It was shown that the excess relative risk decreased with increased age at exposure for combined gastrointestinal, stomach, non-melanoma skin, breast and thyroid cancers and leukemia in the atomic bomb survivors (Preston et al. 1994, Thompson et al. 1994). In this study, we were able to note significant exposure-dependent increased risks in individuals with initial exposure before age 30 but not beyond this age, especially for all cancers combined, all solid cancers combined. Due to relatively small numbers of cancer cases, it was difficult to observe exposure-dependent associations for these cancers.

According to the ICRP 60 report (ICRP 60, 1990), cancer risks associated with low-dose or low dose-rate exposures may be less than from acute high exposure. A reduction factor, termed the ''dose and dose rate effectiveness factor'' (DDREF) is used to allow for a reduced effectiveness of radiation in inducing cancer in human populations at both low doses and low dose rates. Studies in the Japanese atomic bomb survivors indicated DDREF as 2–2.5 for leukemia, about 1.4 for solid cancers, and 1.7 for leukemia and solid cancers combined. For solid cancers, DDREF were very similar. In the current prolonged low dose-rate radiation exposure study, a combination of thyroid/breast cancers was representative as the target radiation sensitive solid cancer for assessing the excess cumulative exposure-dependent relationship between radiation and cancer incidence. Further follow-up in this cohort population would provide better analysis on the related DDREF.

Compared to the reference population, the study population had lower incidences of all cancers combined, all cancers combined except leukemia and all solid cancers combined (Table III). Most study cohort members have resided in buildings constructed in the early 1980s, a period of rapid economic development in Taiwan. It was likely that the exposed population could have higher socio-economic status than the general population, with healthier lifestyles and consequently lower cancer risks, a situation that has been described in other population studies (Lowry et al. 1996, Lantz et al. 1998, Wardle & Steptoe 2003). Unfortunately, we were not able to closely match the economic status of these individuals with the reference population in this study. Since the exposure assessment was made without knowledge of the disease status of these exposed subjects, information bias was unlikely, even though there might be random measurement errors.

In this study, we used both external (simple standardized incidence ratio; SIR) and internal (relative risk; RR) comparisons to assess the cancer risks of the exposed population. We employed both SIR and RR as indicators for measurement of risks in this study, as it is more meaningful to present the results of SIR and RR analysis at the same time for

comparison. The results from the assessment of relative risk can further help clarify the relationship between excessive cumulative radiation exposure and cancer risks in this population.

Chen et al. (2004) reported a primitive analysis on a similar cohort population in Taiwan, while suggesting reduced cancer mortality. However, Chen apparently used group analysis for their exposure, and included only a portion of the exposed population mentioned in this study, based only on initial preliminary community registration by the AEC and not through detailed registration. Their analysis did not consider risk factors like attained age, sex, age at initial exposure et al. No further analyses on the exposure-dependent risks were conducted.

This study cohort was large enough to detect statistically significant cumulative exposure-dependent increases in various cancers in individuals with initial exposure before age 30. The average follow-up period since initial exposure was still too short to observe the development of the whole spectrum of cancers in this cohort. Further follow-up of the study cohort is necessary to corroborate our findings and identify other types of cancers that may also be related to the protracted and low dose-rate ionizing radiation.

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