SHORT COMMUNICATION

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30 years follow-up and increased risks of breast cancer and leukaemia after long-term low-dose-rate radiation exposure

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Background: The current study followed-up site-specific cancer risks in an unique cohort with 30 years' follow-up after long-term low-dose-rate radiation exposure in Taiwan.

Methods: 6242 Taiwanese people received extra exposure in residential and school buildings constructed with Co-60-contaminated steel from 1982 until informed and relocated in early 1990s. The additional doses received have been estimated. During 1983–2012, 300 cancer cases were identified through the national cancer registry in Taiwan, 247 cases with minimum latent periods from initial exposure. The hazard ratios (HR) of site-specific cancers were estimated with additional cumulative exposure estimated individually.

Results: Dose-dependent risks were statistically significantly increased for leukaemia excluding chronic lymphocytic leukaemia (HR_{100mSv} 1.18; 90% CI 1.04–1.28), breast cancers (HR_{100mSv} 1.11; 90% CI 1.05–1.20), and all cancers (HR_{100mSv} 1.05; 90% CI 1.0–1.08, $P = 0.04$). Women with an initial age of exposure lower than 20 were shown with dose response increase in breast cancers risks (HR_{100mSv} 1.38; 90% CI 1.14–1.60; $P = 0.0008$).

Conclusions: Radiation exposure before age 20 was associated with a significantly increased risk of breast cancer at much lower radiation exposure than observed previously.

The effects of acute radiation exposure on cancer risks have been well established in non-occupational exposed general populations (Preston *et al*, 1994, 2007; Ozasa *et al*, 2012; Hsu *et al*, 2013; Leuraud *et al*, 2015). Although occupational radiation hazards often involve long-term low-level exposure in adults, healthy worker effects cannot be neglected. Recent studies from protracted low-level radiation exposure have observed increased risks on leukaemia incidence, such as in the Techa River Cohort study (Krestinina *et al*, 2013; Richardson *et al*, 2015) and the International Nuclear WORKers Study (INWORKS; Krestinina *et al*, 2013). Similar to these results were solid cancer mortality (Schonfeld *et al*, 2013) and solid cancer incidence after adjusted smoking among the Techa Tiver Cohort study (Davis *et al*, 2015). The risks of prolonged low-level ionising radiation on site-specific cancers in the general population remain to be further examined.

In late 1982, over 200 schools and residential buildings constructed in Taiwan accidentally used >20 000 tons of steel rebar contaminated with cobalt-60 (Chang, 1993, 1997; Chang and Kau, 1993). It was not until early 1992 that residents and students who resided or studied in these buildings were identified and

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informed as exposed to excessive cumulative radiation. The governmental regulator conducted a nationwide survey of buildings suspected to contain contaminated steel, whereas a radiation-contaminated buildings (RCB) epidemiological study registered ~10 000 citizens having received protracted low-dose-rate radiation exposure since 1982. However, when the study started in late 1992, some of them and particularly students had already leaved and without adequate information for exposure assessment. Eventually, 6242 were with adequate information for cumulative exposure assessment system Taiwan Cumulative Dose (TCD) established on an individual basis. The TCD integrated the time activity analysis of each cohort members, with detailed history of occupancy duration in each radioactive area of the buildings and area-specific radiation exposure to the whole body. Cohort members recalled detailed information about previous occupancy on representative spots accordingly, with temporal exposures considering half-life of radioactive decay, that is, 5.27 years for Co-60. The TCD had been employed in several related studies (Wang *et al,* 2002; Hsieh *et al*, 2010) and comparable to biodosimetric analysis by fluorescence *in situ* hybridisation of stable chromosomal translocation frequencies (Hsieh *et al,* 1999). The average, median, and range of excess cumulative exposures above background radiation were 48 mGy, 6.3 mGy, and <1 ~ 2 363 mGy.

The initial age of exposure (IAE), when the exposed subjects moved into or were born in these buildings, was 16.9 ± 16.5 (mean ± 1 s.d.) years, ranging from 0 to 87 years old, and was much younger than most of the other radiation cohort studies. Significantly increased risks of leukaemia, excluding chronic lymphocytic leukaemia, were reported previously (Hwang *et al*, 2006, 2008). The current study further examined the magnitude of site-specific cancers risks, resulting from protracted radiation exposure and distinguished IAEs as contributing factor for cancer induction.

MATERIALS AND METHODS

A total of 300 cancer cases were reported between 1983 and the end of 2012 through the countrywide National Cancer Registration systems among the 6242 cohort members. These included 247 cancer cases incident after a minimum latent period of 2 years for leukaemia and 10 years for solid cancers (ICRP, 1990; Hwang *et al*, 2006, 2008). For solid cancers, an alternative minimum latent period of 5 years was also used for sensitive analysis.

The mandatory cancer case report with pathological proof had been established in Taiwan since 1979, with health data accessable by Center of Health Information Application in Taiwan's Ministry of Health and Welfare. The RCB cohort was linked by personal identification number with the Taiwan Cancer Registry (Taiwan Cancer Registry Center, 2017) and the national database of Causes of Death. The study received ethical approval by the TMU-IRB review board.

The attained age was defined when they were diagnosed with a cancer or their age at the last follow-up or at 31 December 2012. With the sparse data for specific cancers during the follow-up period, the analysis of excess relative risk (ERR) by Cox model (hazard ratios; HR) could be more conservative than by the more unstable Poisson linear relative risk model and Poisson model (rate ratios). The ERR_{100mSv} were then calculated by subtracting 1 from HR_{100mSv}, and the HRs from each 100 mSv, HR_{100mSv}, were estimated for the association between cumulative exposure (as continuous variables) and related cancer risks by Cox proportional hazard models, adjusting the IAE, individual exposure via TCD, and the 'attained age' as the time scale. To examine the contribution of IAE to risk of breast cancers, Cox models were stratified by IAE >or ⩽20 years of age. Firth's penalised likelihood estimator was further used for cancer types with less than 10 incidents (Lin *et al*, 2013). The confidence intervals for site-specific cancers were partial likelihood-based or Firth's penalised likelihood-based for small numbers of events. A test was considered statistically significant if its two-tailed *P*-value was <0.10; this was equivalent to a threshold for a one-sided *P*-value <0.05 to test for an increased risk.

RESULTS

The distribution of the subjects with the solid cancers and leukaemia excluding chronic lymphocitic leukaemia (CLL) or multiple myeloma (MM), sex and age at initial exposure, cumulative exposure (TCD, mSv) were shown in Table 1. A total of 236 solid cancers were reported and 11 leukaemia within 97 106 person years among the 6242 subjects. The crude solid cancer incidence rate in female ($25.38/10^4$ person-year) was higher than male ($23.1/10^4$ person-year), but reverse result observed in leukaemia (1 *vs* 0.51 $/10^4$ person-year). Increased incidence rate by age at initial exposure and TCD were observed. Assuming minimum latent period 10 years for solid cancer and 2 year for

Table 1. Characteristics of the cohort population in radio-contaminated buildings (RCB cohort) by solid cancers and leukaemia

			Solid cancers			Leukaemia		
Characteristics	**No. of subjects (%)**	**No. of cases**	**Cancer cases[a]**	**Person-years**	**Incidence rate[a]**	**Cancer cases[a]**	**Person-years**	**Incidence rate[a]**
Overall	6242 (100)	247	236	97 106	24.3	11	147984	0.74
Sex								
Male	2968 (47.5)	113	106	45 890	23.1	7	69 849	1.00
Female	3274 (52.5)	134	130	51 216	25.38	4	78 135	0.51
Age at initial exposure (years)								
<20	3907 (62.6)	43	40	58 778	6.81	3	90 191	0.33
20–39	1721 (27.6)	112	108	29 614	36.47	4	43979	0.91
⩾40	614 (9.8)	92	88	8714	100.99	4	13814	2.90
Mean; median (range)	16.9; 9.7 (<0–87)							
Cumulative exposure (Taiwan Cumulative Dose; mSv)								
<5	2932 (47.0)	79	79	41 671	18.96	0	65 448	0
5–99	2752 (44.1)	122	114	46 137	24.71	8	68 620	1.17
⩾100	558 (8.9)	46	43	9298	46.25	3	13 916	2.16
Mean; median (range)	47.7; 6.3 (<1 ~ 2363)							

[a]Cancers with assumed minimum latent periods (leukaemia: 2 years; solid cancers: 10 years); Incidence rates are per 10 000 person years accounting for assumed minimum latent periods.

Table 2. Adjusted hazard ratio associated with a 100-mSv increase in cumulative exposure

	Minimum latent period 10 years assumed for solid cancer and 2 years for leukaemia				Minimum latent period 5 years assumed for solid cancer and 2 years for leukaemia			
Cancer site	Case[a]	HR_{100mSv}[b]	90% CI[b]	*P*-value[b]	Case[a]	HR_{100mSv}[b]	90% CI[b]	*P*-value[b]
All cancers	249	1.05	(1.00, 1.08)	0.04	282	1.05	(1.00, 1.08)	0.03
All cancers excluding leukaemia	241	1.04	(1.00, 1.08)	0.08	274	1.04	(1.00, 1.08)	0.05
All solid cancers	236	1.04	(1.00, 1.08)	0.07	269	1.04	(1.01, 1.08)	0.04
Female breast	35	1.11	(1.05, 1.20)	0.008	40	1.12	(1.04, 1.17)	0.002
Cervix uteri	24	1.10	(0.96, 1.20)	0.10	28	1.09	(0.97, 1.17)	0.13
Lung	24	1.10	(1.00, 1.17)	0.05	27	1.12	(1.04, 1.18)	0.004
Thyroid gland	20	1.06	(0.83, 1.17)	0.52	25	1.03	(0.80, 1.15)	0.75
Liver	18	1.05	(0.88, 1.15)	0.52	19	1.04	(0.88, 1.14)	0.57
Stomach	13	1.08	(0.92, 1.19)	0.27	15	1.10	(0.97, 1.19)	0.10
Rectum	16	1.03	(0.73, 1.17)	0.78	17	1.02	(0.71, 1.16)	0.87
Leukaemia excluding MM&CLL	8	1.18	(1.04, 1.28)	0.006	8	1.18	(1.04, 1.28)	0.006
Leukaemia excluding CLL	11	1.15	(1.03, 0.24)	0.012	11	1.15	(1.03, 1.24)	0.012

Abbreviations: CLL = chronic lymphocitic leukaemia; MM = multiple myeloma.
[a]Cancers with minimum latent periods (leukaemia:2 years; solid cancers:10 years or 5 years).
[b]HR were adjusted for initial exposure age, 90% CI were partial likelihood-based, and *P*-values were two-sided.

Table 3. Relative hazards (HRs) of breast cancers by the initial age of exposure

Risk groups	Cases	Person years	Incidence (10 000 py)	HR	90% CI of HR	*P*-value
IAE >20 years old						
TCD <5 mSv	10	14131	7.1	1		
TCD 5–100 mSv	11	19816	5.6	0.88	0.43, 1.82	0.76
TCD ⩾100 mSv	7	5123	13.7	2.07	0.89, 4.62	0.14
TCD 100 mSv (test for linear trend)				1.07	0.98, 1.14	0.14
IAE ⩽20 years old						
TCD <5 mSv	1	27829	0.4	1		
TCD 5–100 mSv	4	26792	1.5	3.02	0.59, 31.82	0.33
TCD ⩾100 mSv	2	4321	4.6	10.91	1.55, 125.9	0.05
TCD 100 mSv (test for linear trend)				1.38	1.14, 1.60	0.0008

Abbreviations: CI = confidence interval; HR = Hazards ratio; IAE = initial age at exposure; TCD = Taiwan Cumulative Dose; person-years accounted for minimum latent periods as stated in Table 2. Breast cancers with minimum latent periods 10 years.

leukaemia and MM, significantly increased risks were observed for leukaemia excluding MM and chronic lymphocytic leukaemia (HR_{100mSv} 1.18; 90% CI 1.04–1.28, $P = 0.006$; Table 2), leukaemia excluding CCL (HR_{100mSv}1.15; 90% CI 1.03–1.24, $P = 0.012$), female breast cancers (HR_{100mSv} 1.11; 90% CI 1.05–1.20, $P = 0.008$), and all cancers (HR_{100mSv} 1.05; 90% CI 1.01–1.08, $P = 0.04$). In addition, assuming shorter latent period of 5 years for solid cancers, increased risk for all solid cancers and lung cancer were noted (Table 2). The HR_{100mSv} for site-specific cancers were all >1, with the relative hazards of female breast cancers in different exposure shown in Table 3. For individuals with IAE⩽20 years, a dose response increase on breast cancer risk was noted, with HR_{100mSv} 1.38 (90% CI 1.14–1.6; $P = 0.0008$). For those IAE >20 years, the linear trend was less significant, with HR_{100mGy} 1.07 (90% CI 0.98–1.14; $P = 0.14$).

DISCUSSION

The follow-up on the cancer risks of this unique cohort extended up to 30 years after their initial radiation exposure. A total 300 cancer cases were collected, with 135 newly reported since the previous report (Hwang *et al*, 2008). These were mainly consisted of solid cancers and leukaemia and MM.

The cohort population comprised of individuals with a wide range of excessive cumulative exposure, including very low (<1 mSv) and close to unexposed populations. Moreover, the incidence rates were weighted by various durations of observation. Therefore, no parallel appropriate unexposed cohort population was available for comparison. The HR_{100mSv} for leukaemia excluding CLL was 1.18 (ERR_{100mSv} 0.18, 90% CI 1.04–1.28), with a smaller standard error estimate than ERR_{100mSv} 0.19 in the previous report (Hwang *et al*, 2008). On the other hands, the risk estimates for leukaemia were similar to those of the Techa River study (ERR_{100mSv} 0.22, 95% CI 0.08–0.54; (Krestinina *et al*, 2010) and the multi-national nuclear workers study (ERR_{100mSv} 0.19, 95% CI <0–0.85 and 0.193; Cardis *et al*, 2005; Vrijheid *et al*, 2007), but smaller than the Japanese Life Span Study (LSS) with acute radiation exposure (ERR_{100mSv} 0.31; (Preston *et al*, 1994)) and leukaemia mortality in the INWORKS nuclear workers study (ERR_{100mSv} 0.30, 90% CI 0.12–0.52; (Cardis *et al*, 2005; Vrijheid *et al*, 2007)). This could be caused by much lower exposures of this cohort than those of the Techa River with marrow doses up to 9 Gy and a mean 0.42 Gy (Krestinina *et al*, 2013), the LSS cohort, and similar to those of the nuclear workers.

As the members of the exposed cohort in Taiwan were not aware of the radiation when they moved in or studied in these buildings, risk factors like cigarette smoking and hormone exposure were assumed randomly occurred and unlikely to

confound the causal effect of radiation. Moreover, most of these cohorts had relocated to these newly constructed buildings or schools during strong economic development in Taiwan in 1980s, and were likely more socio-economically favorite groups, with less probabilities in adverse health behaviors like cigarette and drinking, compared with the other general public in Taiwan. Therefore, there could be mild under-estimation of the risks incurred in this cohort population.

IAE in the Taiwanese female cohort was relatively young, 16.9 ± 16.5 (s.d.) years old (Table 1) and the ERR_{100mSv} for breast cancer was estimated at 0.11 (90% CI 1.05–1.20) for 10 years latent period (Table 2), similar to the ERR_{100mSv} 0.12 (90% CI 0.07–0.19) in the Japanese LSS cohort, whose ages at exposure were between 10 and 19 years (Preston *et al*, 2007). On the other hand, age at initial exposure had been demonstrated to be an important effect modifier in relation to the dose response in the LSS study (Land *et al*, 2003; Preston *et al*, 2007). In the present study, those who were exposed initially equal or <20 years old were shown with a statistically significant radiation dose response and breast cancer risks (HR_{100mSv} 1.38, 90% CI 1.14–1.6), but not those with IAE above 20 years old (HR_{100mSv} 1.07; 90% CI 0.98–1.14. This suggested that women exposed at younger age were more sensitive to radiation, especially before the age of 20 compared with unexposure population. In either groups of IAE, the incidence rates of breast cancer with exposure $\geqslant 100$ mSv were much higher than those <100 mSv. With cigarette smoking rate in women generally below 5% during the last three decades in Taiwan, and the average incident age of breast cancers 51.7 years old, confounding by smoking or hormonal effect was very unlikely.

The ERR100mSv of all solid cancers in this cohort was ~ 0.05, similar to the 0.06 (95% CI 0.004–0.127) of the Techa River study (Schonfeld *et al*, 2013) and 0.047 (90% CI 0.04–0.05; 95% CI 0.039–0.055; Preston *et al*, 2007; Grant *et al*, 2017) of the LSS. In the present study, all point estimates of HR_{100mSv} in site-specific cancers were consistently >1.

This suggested that when individuals were exposed at younger ages, the risks of developing breast cancers or solid cancers were similar for acute or chronic radiation exposure. Although the comparisons between protracted and acute exposure studies are a bit complicated. The exact magnitude of effects might not be fully comparable, however, the trends are noteworthy. A stronger dose response in breast cancer risks for the individuals with younger IEA ($P<0.001$) than those with older IEA ($P=0.14$) was noted, and was comparable with those by acute exposure.

With small numbers of leukaemia cases in this analysis, the sample size was not adequate to provide stratified analysis on their IAE. Although with relatively small numbers of cancer cases, as a relatively young study population, follow-up of this cohort will provide more results in the future.

In conclusion, the exposed cohort provided unique evidences of protracted, low-dose-rate radiation exposures, with cumulative exposure mostly <1 Sv. The estimates of the ERR for leukaemia were similar to the Techa River study, as well as to the 15-country nuclear workers' study, but are less than those of the LSS. On the other hand, the estimates of ERR for breast cancer were similar to the LSS among those exposed at ages 10–19. Those who were initially exposed before 20 years old had the highest relative risk of developing breast cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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