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Estimates of Relative Risks for Cancers in a Population after Prolonged Low-Dose-Rate Radiation Exposure: A Follow-up Assessment from 1983 to 2005

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Radiation effects on cancer risks in a cohort of Taiwanese residents who received protracted low-dose-rate γ -radiation exposures from ⁶⁰Co-contaminated reinforcing steel used to build their apartments were studied, and risks were compared to those in other radiation-exposed cohorts. Analyses were based on a more extended follow-up of the cohort population in which 117 cancer cases diagnosed between 1983 and 2005 among 6,242 people with an average excess cumulative exposure estimate of about 48 mGy. Cases were identified from Taiwan's National Cancer Registry. Radiation effects on cancer risk were estimated using proportional hazards models and were summarized in terms of the hazard ratio associated with a 100-mGy increase in dose (HR_{100mGy}). A significant radiation risk was observed for leukemia excluding chronic lymphocytic leukemia (HR_{100mGy} 1.19, 90% CI 1.01–1.31). Breast cancer exhibited a marginally significant dose response (HR_{100mGy} 1.12, 90% CI 0.99–1.21). The results further strengthen the association between protracted low-dose radiation and cancer risks, especially for breast cancers and leukemia, in this unique cohort population. © 2008 by Radiation Research Society

INTRODUCTION

The association between cancer rates and exposure to high-dose ionizing radiation is well documented. The most recent comprehensive report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2000) indicated significant radiation effects for leu-

kemia and cancers of breast, stomach, colon, lung, ovary, urinary bladder and thyroid (1). The UNSCEAR findings were based on epidemiological studies among atomic bomb survivors [Life Span Study; LSS (2–4)] and people who received medical diagnostics (5) or therapeutic (6) radiation exposures. However, the appropriate method for extrapolating from risk assessments for acute high-dose-rate exposures to those for low-dose-rate exposure remains to be determined.

In late 1982 an unknown amount of ⁶⁰Co was recycled into at least one steel mill in northern Taiwan and then reprocessed into steel billets (7) that were used for the manufacture of reinforcing rods. In 1983 and 1984, over 200 buildings in Taiwan, including dozens of school complexes, were constructed with these ⁶⁰Co-contaminated steel rods, resulting in the protracted low-dose-rate ionizing radiation exposure of more than 10,000 citizens and students (8–10). These radiocontaminated buildings were first identified in August 1992, and exposure rates of 0.5 to 270 μ Gy/h to the occupants were demonstrated. There have been several reports concerning the radiation effects on the exposed population, including cytogenetic analysis that showed increased micronucleus frequencies in peripheral lymphocytes in the exposed population (11), increases in acentromeric and single or multiple centromeric cytogenetic damages (12), and higher frequencies of chromosomal translocations, rings and dicentric (13). Other analyses have shown persistent depression of peripheral leucocytes and neutrophils (14), increased eosinophils, altered distributions of lymphocyte subpopulations (15), increased frequencies of lens opacities (16), delays in physical development among exposed children (17), increased risk of thyroid abnormalities (18), and late consequences in hematopoietic adaptation in children (19).

In a recent study employing standardized incidence ratio (SIR) analyses of the registered residents of radiocontaminated buildings for the period from 1983 to the end of 2002 (20), we reported significantly elevated SIR for leukemia

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in men (3.6) and thyroid cancers in women (2.6) compared to a reference population with the same temporal and geographic characteristics in Taiwan (20).

The purpose of the current study was to further assess the excess risks for various types of cancers in this cohort with follow-up extended to the end of 2005. With approximately 23,000 more person-years of follow-up and 34% more cancer cases than were available at the time of our previous study (20). Incident cases of cancer among cohort members were identified by means of computerized record linkage to the National Cancer Registry of Taiwan (NCRT). These data were used to assess the evidence for radiation effects on incidence rates for all cancers, all solid cancers, and selected sites. Radiation effects were modeled in terms of the hazard ratio associated with a 100-mGy increase in dose ($HR_{100\text{mGy}}$). Our estimates for this cohort were compared to those observed among atomic bomb survivors (2, 3) and in other exposed cohorts (21–24) that included large numbers of men and women with a wide age distribution who received a broad range of radiation doses.

MATERIALS AND METHODS

Study Population

The methods used to assemble the cohort are summarized briefly here; details can be found in ref. (20). The radioactive contamination event in Taiwan was brought to public attention by an article in a major local newspaper (9) in August 1992. After the discovery of these radiocontaminated buildings, 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 of all residents and students who had lived in these buildings from household and school registration records. A questionnaire survey was conducted through personal interview, which included questions on medical history, occupation, education and detailed exposure history with exact dates of residence and summaries of daily activities in the radiocontaminated buildings. The cohort includes 7,262 people who were registered as having lived in a radiocontaminated building. Follow-up began on the date an individual was registered as moving into a radiocontaminated building and continued until the earliest of the date of cancer diagnosis, death or the end of 2005. The study design was approved by the University IRB as well as the IRB of the National Health Research Institution in Taiwan, which had supported the program project during 1995–2000.

Ascertainment of Cancer Cases

Cancer cases were ascertained through computerized linkage with the National Cancer Registry of Taiwan (NCRT) that was established by the Department of Health since 1979 and has been continuously well maintained. For each registered case, the NCRT contained the individual's unique national identification number (NIN), name, gender and date of birth as well as the date of diagnosis, location and histology of the cancer. The NIN was used as the primary key for linking cohort members to the NCRT. These data have been used in several other cancer epidemiology studies (e.g. 25, 26). Topography, morphology and behavior coding are based on the International Classification of Disease for Oncology (ICD-O, First Edition).

The minimum latent period for radiation-associated cancers was taken as 2 years for leukemia and 10 years for solid cancers, in accordance with the International Commission on Radiological Protection (ICRP) recommendations (27). A total of 178 cancer cases were identified in the

cohort between 1983 and 2005; however, 128 of these cases occurred after the assumed minimum latent periods.

Exposure Evaluation

An exposure assessment system known as the Taiwan Cumulative Dose (TCD) was developed to reconstruct the exposures for individual cohort members. The TCD combined the time-activity analysis recommended by the U.S. National Institute for Occupational Safety and Health Advisory Committee (28) with a highly-occupied-zone (HOZ) model (29). Standardized interviews and questionnaires were used to reconstruct the amount of time spent in each room of the contaminated apartment in which a cohort member had stayed (29). This information was used to define time-dependent occupancy patterns in contaminated areas that were then combined with area-specific whole-body exposure-rate estimates to develop individual dose estimates throughout their residence in these radiocontaminated buildings. Exposure rates were estimated on the basis of measurements of representative locations in each room. Excess cumulative exposures were corrected for radioactive decay half-lives. In this study, the term excess cumulative exposure indicates exposure dose resulting from time spent in a radiocontaminated building excluding background radiation. In earlier reports we demonstrated a strong association between the exposure assessed by the biodosimetric measurements and TCD dose estimates (30). However, due to incomplete or missing occupancy pattern data, TCD exposure assessment and dose estimates were available for only 6,242 of the cohort members.

Statistical Methods

Relative risks of cancer associated with an increase of 100 mGy exposure were estimated using Cox proportional hazard models in which the radiation effect was taken as log-linear in dose. The results are summarized by the estimated hazard ratio for a 100-mGy increase in the excess cumulative dose ($HR_{100\text{mGy}}$). Thus, for example, an $HR_{100\text{mGy}}$ of 1.5 means that the risk associated with a cancer is 50% higher for individuals who received excess cumulative exposures of 100 mGy than those who received 0 mGy and that the risk increases by 50% for each 100-mGy increase in excess cumulative exposure (31). Many studies of radiation effects report results based on excess relative risk (ERR) estimates. To compare the risk estimates obtained in this study to those from studies presenting ERR estimates, we convert reported ERR estimates to the ERR for a dose of 100 mGy ($ERR_{100\text{mGy}} \sim HR_{100\text{mGy}} - 1$). Because of the low doses in this study and the non-linearity of HR model-based ERR estimates, we feel that this is more appropriate than comparison of HR and ERR estimates for a 1-Gy exposure.

The hazard function was modeled as

$$h(t|X_1, X_2, X_3) = h_0(t) \exp[\beta_1 I(X_1 = M) + \beta_2 X_2 + \beta_3 X_3],$$

where $h_0(t)$ is the baseline hazard function with the time scale being years since coming to stay in a radiocontaminated building, X_1 is a gender variable, X_2 indicates birth cohort, and X_3 is excess cumulative exposure (continuous; unit: 100 mGy). The function $I(X_1 = M)$ is defined as 1 for men and 0 for women. The $HR_{100\text{mGy}}$ estimate is given by $\exp(\beta_3)$ (31, 32).

Duration of follow-up was calculated from the date a person first came to stay in a contaminated building until the date of death, the date of cancer diagnosis, or December 31, 2005, whichever came first. The 90% confidence intervals (CI) for the $HR_{100\text{mGy}}$ and the P values were calculated on the basis of partial likelihood. A test was considered statistically significant if its two-tailed P value was less than 0.10; this was equivalent to a threshold for a one-sided P value less than 0.05 to test for an increased risk. All statistical analyses were carried out using SAS for Windows.

RESULTS

Information on the number of incident cancers and other characteristics of the cohort is presented in Table 1. Among

TABLE 1
Characteristics of the Radiocontaminated Building Cohort

	TCD ^a exposure estimates available			TCD exposure estimates unavailable (<i>n</i> = 1,020)
	Male (<i>n</i> = 2,967)	Female (<i>n</i> = 3,275)	Total (<i>n</i> = 6,242)	
Number of cancer cases	63	102	165	13
Cases with latent periods more than the minimal latent periods as recommended by ICRP ^b	50	67	117	11
Follow-up time (years)	18.8 ± 4.3 ^c (0–25)	18.9 ± 4.3 (0–25)	18.9 ± 4.3 (0–25)	19.7 ± 3.9 (4–23)
Attained age (years)	35.1 ± 17.9 (0–94)	36.5 ± 17.4 (0–103)	35.8 ± 17.7 (0–103)	32.1 ± 16.4 (<8–91)
Age at initial exposure (years)	16.2 ± 16.6 (Intrauterine –83)	17.6 ± 16.3 (Intrauterine –87)	16.9 ± 16.5 (Intrauterine –87)	12.6 ± 15.8 (Intrauterine –80)
Excess cumulative exposure (TCD; mGy)	48.8 (<1–2,206)	46.7 (<1–2,363)	47.7 (<1–2,363)	—

^a Estimates of exposure by Taiwan Cumulative Dose.

^b Minimum latent periods recommended in ICRP 60 (27): 2 years for leukemia, 10 years for other cancers.

^c Mean ± standard deviation (range in parentheses).

the 6,242 subjects with exposure estimates, the average excess cumulative exposure at the end of follow-up was 48 mGy (median 6.3 mGy, range from <1 to 2,363 mGy). The average length of follow-up was 19 years (median 21.3 years). The mean age of initial exposure and attained age at the end of follow-up were 17 ± 17 years (mean ± SD; range from intrauterine to 87 years old) and 36 ± 18 years (mean ± SD; range <1 to 103 years old), respectively. There were 128 cohort members who developed cancers with latent periods more than the minimum latent period for radiation-inducible cancers recommended by ICRP (27). Analyses were based on 117 cases diagnosed among the 6,242 cohort members with exposure history data.

The adjusted hazard ratios for all cancers and the specific cancers with more than five cases are shown in Table 2. There was no indication of a statistically significant increase in risk for all cancers as a group (*P* = 0.3) or for

all cancers other than leukemia (*P* > 0.5). However, a significant dose response was observed for leukemia excluding CLL (HR_{100mGy} = 1.19, 90% CI 1.01–1.31, *P* = 0.08) and a marginally significant dose response for breast cancer (HR_{100mGy} 1.12, 90% CI 0.99–1.21, *P* = 0.13). There were no indications of statistically significant increased risks for any of the other cancers considered (Table 2).

DISCUSSION

Cancer risk evaluation from low-dose radiation exposures is largely based on extrapolation from risks observed in populations with a significant number of people with acute high-dose radiation exposures. The radiocontaminated building cohort includes men and women of all ages who received protracted low-dose-rate radiation exposure between 1983 and 1992. The risks observed in this cohort

TABLE 2
Adjusted Hazard Ratios of Cancers for the Radiation-Contaminated Building Cohort

Cancer site	Number of cancers ^a	HR _{100mGy} ^b	90% CI of HR ^b	<i>P</i> value ^b
All cancers	117	1.04	(0.97, 1.08)	0.32
All cancers excluding leukemia	111	1.02	(0.95, 1.08)	0.57
All solid cancers	106	1.03	(0.96, 1.09)	0.50
Selected solid cancers (with case numbers >5)				
Female breast	17	1.12	(0.99, 1.21)	0.13
Cervix uteri	16	0.95	(0.64, 1.13)	0.70
Lung	12	1.09	(0.96, 1.19)	0.21
Thyroid glands	8	0.81	(0.21, 1.15)	0.52
Liver	8	1.03	(0.76, 1.19)	0.81
Stomach	8	1.10	(0.88, 1.25)	0.41
Rectum	6	0.48	(0.02, 1.10)	0.27
Leukemia excluding chronic lymphocytic leukemia	6	1.19	(1.01, 1.31)	0.08

^a Cases with latent periods more than the minimum latent period as recommendation in ICRP 60 [2 years for leukemia, 10 years for other cancers] (27).

^b Estimated relative risk (hazard ratio) of cancer with 100-mGy increase in exposure dose adjusting for gender and birth cohorts, using Cox models with the attained age as the time-scale. The confidence intervals and *P* values are partial likelihood-based.

provide useful estimates of low-dose, low-dose-rate radiation effects in a human population. It is also important to compare radiation risk estimates from the radiocontaminated building cohort with other cohorts with different environmental or occupational exposures.

Our previous study reported significantly elevated standardized incidence ratios (SIRs) for all leukemia in men (3.6), and thyroid cancers in women (2.6) and a suggestion of an increased SIR for breast cancer in comparison with Taiwan's population rates (20). In our current analyses with more cancer cases and extended follow-up, we were able to make use of individual dose estimates to test for evidence of a radiation dose response based on internal comparisons. As indicated above, the results suggest that prolonged low-dose-rate radiation exposure increased risks for leukemia excluding CLL and breast cancer.

For all solid cancers combined, the HR_{100mGy} estimate was 1.04 (90% CI 0.97, 1.08), which corresponds to an ERR_{100mGy} estimate of 0.04 (90% CI -0.03, 0.08). This estimate is slightly less than the estimated risks at 100 mGy based on studies of the atomic bomb survivors [$ERR_{100mGy} = 0.063$, 95% CI 0.052, 0.074 (3)], nuclear workers in 15 countries [$ERR_{100mGy} = 0.087$, 95% CI 0.003, 0.188 (22)], the Techa River Cohort [$ERR_{100mGy} = 0.092$, 95% CI 0.02, 0.17 (33)], and those in the Chernobyl accident [$ERR_{100mGy} = 0.113$, 95% CI 0.014, 0.213 (23)].

The hazard ratio for leukemia excluding CLL ($HR_{100mGy} = 1.19$, 90% CI 1.01–1.31) was statistically significant. This estimate is slightly less than an estimate of the risk at 100 mGy based on the LSS data in ref. (2), $ERR_{100mGy} = 0.31$ (90% CI 0.25, 0.38).

Exposure to high-dose ionizing radiation is associated with increased risk of breast cancer incidence in female atomic bomb survivors (3). Among atomic bomb survivors the ERR_{100mGy} estimate is 0.16 for all ages combined (3), with ERR_{100mGy} estimates of 0.32 for those less than 10 years old, 0.26 for those between 10 and 19 years old, 0.12 for those between 20 and 39, and 0.06 for those more than 40 years old. While it was widely believed that age at exposure was an important modifier of the risks of radiation-induced breast cancers, the recent results in cancer incidence in A-bomb survivors indicate that attained age may be more important than age at exposure (34). Studies from the Massachusetts TB fluoroscopy cohort (35, 36) also showed an increased risk in breast cancers, with particularly high risks when exposures occurred between the ages of 15 and 24.

In the present study, there was a marginally significant increase in risk for breast cancers ($HR_{100mGy} = 1.12$, 90% CI 0.99, 1.21). In view of the relatively young age at initial radiation exposure in the radiocontaminated building cohort (mean \pm SD 17 \pm 16.5 years old with 60% of the women initially exposure before age 20, 30% between 20 to 40, and only 10% after age 40), the risk estimate seems somewhat less than that for female atomic bomb survivors of a

similar ages. Further follow-up is necessary to clarify the risk of breast cancer among women in this cohort.

A radiation dose response for thyroid cancers was observed in the LSS (3). Individuals exposed at younger ages had significantly elevated risks, while there was no indication of an increase in risk for people who were over 40 years of age at exposure. Other studies have shown that the most sensitive group was in children less than age 15 at exposure, while the highest ERR was observed 15–29 years after their exposure (37). We reported previously that the prevalence of simple goiter was related to the exposure with an exposure-dependent relationship for males of all ages and for females aged ≤ 15 at examination (18), and significantly increased thyroid cancer incidence risk [SIR = 2.6 (20)]. However, there was no significant excess risk for thyroid cancers [$HR_{100mGy} = 0.81$, 90% CI 0.21, 1.15; an estimate of HR-based ERR -0.19 (90% CI -0.79, 0.15)] in the present analysis (Table 2).

The LSS study also indicated that there was significantly increased excess relative risk for cancers of the stomach ($ERR_{100mGy} = 0.032$, 95% CI 0.016, 0.05) and lung [$ERR_{100mGy} = 0.1$, 95% CI 0.06, 0.136 (3)]. A study of exposed workers at the Mayak plant also showed that there was an increased risk for lung cancer (38). The 15-country nuclear worker study indicated an increased lung cancer risk [$ERR_{100mGy} = 0.19$, 95% CI 0.026, 0.4 (22)] from protracted low-dose-rate exposures. On the other hand, the study of the Canadian fluoroscopy cohort did not show increased risk of lung cancer (39) after highly fractionated exposures. Smoking is the strongest risk factor for lung cancer and is responsible for approximately 90% of lung cancer cases (40). A joint analysis of smoking and radiation among atomic bomb survivors indicated that the effects of smoking and radiation on lung cancers were consistent with an additive model (41). While the point estimates of the stomach ($HR_{100mGy} = 1.10$) and lung ($HR_{100mGy} = 1.10$) cancer in these analyses of the radiocontaminated building cohort were generally consistent with the LSS and nuclear worker studies, these estimates were not statistically significant. Future analysis with additional follow-up will provide more precise estimates of the risk for these cancers. In addition, detailed information on smoking, alcohol consumption, and diet should help clarify the nature of the radiation risk at these sites in the radiocontaminated building cohort.

The strengths of the present study include being a population-based study, drawing cancer cases from a comprehensive cancer registration system with virtually complete follow-up, and the availability of individual exposure estimates based on information collected through detailed exposure assessment. The limitations are related to the small number of cases, which is a consequence of the relative youth and currently short follow-up time of the cohort. In conclusion, this quantitative analysis of cancer incidence using data from the Taiwan radiocontaminated building cohort provides limited evidence of a cumulative-exposure-

dependent association between cancer rates and low-dose, low-dose-rate ionizing radiation exposure for breast cancer and leukemia excluding CLL, for which other studies have suggested particularly high risks. Follow-up of this cohort is ongoing, and as the number of cancer cases increases, more stable and precise risk estimates will be expected.

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REFERENCES

1. UNSCEAR, *Sources and Effects of Ionizing Radiation*, 2000 Report to the General Assembly, with Scientific Annexes, Vol. II, *Effects*. United Nations, New York, 2000.
2. D. L. Preston, S. Kusumi, M. Tomonaga, S. Izumi, E. Ron, A. Kuramoto, N. Kamada, H. Dohy, T. Matsui and K. Mabuchi, Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. *Radiat. Res.* **137** (Suppl.), S68–S97 (1994).
3. D. E. Thompson, K. Mabuchi, E. Ron, M. Soda, M. Tokunaga, S. Ochikubo, S. Sugimoto, T. Ikeda, M. Terasaki and D. L. Preston, Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. *Radiat. Res.* **137** (Suppl.), S17–S67 (1994).
4. D. A. Pierce, Y. Shimizu, D. L. Preston, M. Vaeth and K. Mabuchi, Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. *Radiat. Res.* **146**, 1–27 (1996).
5. J. D. Boice, Jr., D. Preston, F. G. Davis and R. R. Monson, Frequent chest X-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. *Radiat. Res.* **125**, 214–222 (1991).
6. A. Mattsson, B. I. Ruden, J. Palmgren and L. E. Rutqvist, Dose- and time-response for breast cancer risk after radiation therapy for benign breast disease. *Br. J. Cancer* **72**, 1054–1061 (1995).
7. W. P. Chang and C. C. Chan, Radioactive contamination in Taiwan: An update. *Health Phys. Newsletter* **26**, 22 (1998).
8. W. P. Chang and J. Kau, Taiwan: exposure to high doses of radiation. *Lancet* **341**, 750 (1993).
9. W. P. Chang, C. C. Chan and J. D. Wang, ⁶⁰Co contamination in recycled steel resulting in elevated civilian radiation doses: causes and challenges. *Health Phys.* **73**, 465–472 (1997).
10. J. Y. Hwang, J. B. Chang and W. P. Chang, Spread of ⁶⁰Co contaminated steel and its legal consequences in Taiwan. *Health Phys.* **81**, 655–660 (2001).
11. W. P. Chang, B. F. Hwang, D. Wang and J. D. Wang, Cytogenetic effect of chronic low-dose, low-dose-rate gamma-radiation in residents of irradiated buildings. *Lancet* **350**, 330–333 (1997).
12. W. P. Chang, W. A. Hsieh, D. P. Chen, Y. P. Lin, J. S. Hwang, J. J. Hwang, M. H. Tsai and B. F. Hwang, Change in centromeric and acrocentric micronucleus frequencies in human populations after chronic radiation exposure. *Mutagenesis* **14**, 427–432 (1999).
13. W. A. Hsieh, C. Ni, J. J. Hwang, J. S. Fang, S. P. Lin, Y. A. Lin, T. W. Huang and W. P. Chang, Evaluation of the frequencies of chromosomal aberrations in a population exposed to prolonged low dose-rate ⁶⁰Co gamma-irradiation. *Int. J. Radiat. Biol.* **78**, 625–633 (2002).
14. W. P. Chang, Y. P. Lin, P. T. Hwang, J. L. Tang, J. Y. Chen and S. D. Lee, Persistent leukocyte abnormalities in children years after previous long-term low-dose radiation exposure. *Br. J. Haematol.* **106**, 954–959 (1999).
15. W. P. Chang, J. S. Hwang, M. C. Hung, T. H. Hu, S. D. Lee and B. F. Hwang, Chronic low-dose gamma-radiation exposure and the alteration of the distribution of lymphocyte subpopulations in residents of radioactive buildings. *Int. J. Radiat. Biol.* **75**, 1231–1239 (1999).
16. W. L. Chen, J. S. Hwang, T. H. Hu, M. S. Chen and W. P. Chang, Lenticular opacities in populations exposed to chronic low-dose-rate gamma radiation from radiocontaminated buildings in Taiwan. *Radiat. Res.* **156**, 71–77 (2001).
17. J. C. Wang, Y. P. Lin, J. S. Hwang, W. H. Hsieh, Y. J. Tsai and W. P. Chang, Physical heights of children with prolonged low dose-rate gamma-radiation exposure in radiocontaminated buildings. *Int. J. Radiat. Biol.* **77**, 117–125 (2001).
18. T. C. Chang, W. L. Chen, W. P. Chang and C. J. Chen, Effect of prolonged radiation exposure on the thyroid gland of residents living in ⁶⁰Co-contaminated rebar buildings. *Int. J. Radiat. Biol.* **77**, 1117–1122 (2001).
19. J. C. Wang, Y. P. Lin, S. L. Hwang, W. A. Hsieh, J. C. Chen, J. L. Tang, J. S. Hwang, W. J. Lu and W. P. Chang, Late haematological changes in population with chronic low dose-rate radiation exposure during childhood. *Br. J. Radiol.* **75**, 135–140 (2002).
20. S. L. Hwang, H. R. Guo, W. A. Hsieh, J. S. Hwang, S. D. Lee, J. L. Tang, C. C. Chen, T. C. Chang, J. D. Wang and W. P. Chang, Increased cancer risks in a population with prolonged low dose-rate γ -radiation exposure in radiocontaminated buildings, 1983–2002. *Int. J. Radiat. Biol.* **82**, 849–858 (2006).
21. W. N. Sont, J. M. Zielinski, J. P. Ashmore, H. Jiang, D. Krewski, M. E. Fair, P. R. Band and E. G. Letourneau, First analysis of cancer incidence and occupational radiation exposure based on the National Dose Registry of Canada. *Am. J. Epidemiol.* **153**, 309–318 (2001).
22. E. Cardis, M. Vrijheid, M. Blettner, E. Gilbert, M. Hakama, C. Hill, G. Howe, J. Kaldor, C. R. Muirhead and K. Veress, Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. *Br. Med. J.* **331**, 77–82 (2005).
23. V. K. Ivanov, E. M. Rastopchin, A. I. Gorsky and V. B. Ryvkin, Cancer incidence among liquidators of the Chernobyl accident: solid tumors, 1986–1995. *Health Phys.* **74**, 309–315 (1998).
24. V. K. Ivanov, A. F. Tsyb, A. I. Gorsky, M. A. Maksyutov, E. M. Rastopchin, A. P. Konogorov, A. M. Korelo, A. P. Biryukov and V. A. Matyash, Leukemia and thyroid cancer in emergency workers of the Chernobyl accident: estimation of radiation risks (1986–1995). *Radiat. Environ. Biophys.* **36**, 9–16 (1997).
25. H. Y. Lin, C. Y. Cheng, W. M. Hsu, W. H. Kao and P. Chou, Incidence of eyelid cancers in Taiwan: A 21-year review. *Ophthalmology* **113**, 2101–2107 (2006).
26. Y. C. Shen, C. J. Chang, C. Hsu, C. C. Cheng, C. F. Chiu and A. L. Cheng, Significant difference in the trends of female breast cancer incidence between Taiwanese and Caucasian Americans: Implications from age-period-cohort analysis. *Cancer Epidemiol Biomarkers Prev.* **14**, 1986–1990 (2005).
27. ICRP, *Recommendations on the International Commission on Radiological Protection*. Publication 60, *Annals of the ICRP*, Vol. 21, Pergamon Press, Oxford, 1990.
28. J. Cardarelli, 2nd, L. Elliott, R. Hornung and W. P. Chang, Proposed model for estimating dose to inhabitants of Co-60 contaminated buildings. *Health Phys.* **72**, 351–360 (1997).
29. J. S. Hwang, C. C. Chan, J. D. Wang and W. P. Chang, Radiation exposure modeling for apartments living spaces with multiple radioactive sources. *Health Phys.* **74**, 379–386 (1998).
30. W. A. Hsieh, J. N. Lucas, J. J. Hwang, C. C. Chan and W. P. Chang, Biodosimetry using chromosomal translocations measured by FISH in a population chronically exposed to low dose-rate ⁶⁰Co γ -irradiation. *Int. J. Radiat. Biol.* **77**, 797–804 (2001).

31. D. W. Hosmer and S. Lemeshow, *Applied Survival Analysis: Regression Modeling of Time to Event Data*. Wiley, New York, 1999.
32. P. W. Dickman, A. Sloggett, M. Hills and T. Hakulinen, Regression models for relative survival. *Stat. Med.* **23**, 51–64 (2004).
33. L. Y. Krestinina, D. L. Preston, E. V. Ostroumova, M. O. Degteva, E. Ron, O. V. Vyushkova, N. V. Startsev, M. M. Kossenko and A. V. Akleyev, Protracted radiation exposure and cancer mortality in the Techa River Cohort. *Radiat. Res.* **164**, 602–611 (2005).
34. D. L. Preston, E. Ron, S. Tokuoka, S. Funamoto, N. Nishi, M. Soda, K. Mabuchi and K. Kodama, Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat. Res.* **168**, 1–64 (2007).
35. J. D. Boice, Jr., D. L. Preston, F. G. Davis and R. R. Monson, Frequent chest x-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. *Radiat. Res.* **125**, 214–222 (1991).
36. G. R. Howe and J. McLaughlin, Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study. *Radiat. Res.* **145**, 694–707 (1996).
37. E. Ron, J. H. Lubin, R. E. Shore, K. Mabuchi, B. Modan, L. M. Pottern, A. B. Schneider, M. A. Tucker and J. D. Boice, Jr., Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat. Res.* **141**, 259–277 (1995).
38. N. S. Shilnikova, D. L. Preston, E. Ron, E. S. Gilbert, E. K. Vassilenko, S. A. Romanov, I. S. Kuznetsova, M. E. Sokolnikov, P. V. Okatenko and N. A. Koshurnikova, Cancer mortality risk among workers at the Mayak nuclear complex. *Radiat. Res.* **159**, 787–798 (2003).
39. G. R. Howe, Lung cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with lung cancer mortality in the atomic bomb survivors study. *Radiat. Res.* **142**, 295–304 (1995).
40. A. J. Alberg and J. M. Samet, Epidemiology of lung cancer. *Chest* **123** (Suppl.), 21–49 (2003).
41. D. A. Pierce, G. B. Sharp and K. Mabuchi, Joint effects of radiation and smoking on lung cancer risk among atomic bomb survivors. *Radiat. Res.* **159**, 511–520 (2003).