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Commentary

Circulatory Disease Risk after Low-level Ionizing Radiation Exposure

Suminori Akiba

Department of Epidemiology and Preventive Medicine, Kagoshima University Graduate School of Medical and Dental Sciences
8-35-1 Sakuragaoka, Kagoshima, 890-8544, Japan

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1. Introduction

This commentary conducts a critical review of the paper entitled"Systematic Review and Meta-analysis of Circulatory Disease from Exposure to Low-Level Ionizing Radiation and Estimates of Potential Population Mortality Risks", written by Little MP *et al.*[1)]

They conducted a systematic review and meta-analysis to summarize information on circulatory disease risks associated with moderate- and low-level whole-body ionizing radiation exposure. Studies eligible for their meta-analysis were those with cumulative mean doses less than 0.5 Sv or dose rates less than 10 mSv/day. They estimated an excess relative risk per sievert (ERR/Sv) for ischemic heart disease, using the ERR estimates per dose reported by mortality studies of i) the Life Span Study (LSS) cohort of atomic-bomb survivors[2)], ii) Eldorado uranium-mine workers[3)], iii) employees of the French National Electricity Company (Electricite de France-EDF)[4)], iv) nuclear workers in 15 countries (IARC 15-country study)[5)], and v) the UK cohort of the National Registry for Radiation Workers (NRRW)[6)], in addition to morbidity studies of i) the Adult Health Study (AHS) cohort of atomic-bomb survivors[7)], ii) Mayak Production Association (PA) workers[8)], and iii) Chernobyl emergency workers[9)]. Their meta-analysis gave a fixed effect estimate of 0.10 (95% CI=0.05, 0.15) and a random effect estimate of 0.10 (95% CI=0.04, 0.15)[1)]. For the meta-analysis of cerebrovascular disease (stroke) mortality, Little *et al.* used the study reported by German uranium-mine workers[10)] as well. For the analysis of stroke incidence, they used another study of Mayak workers[11)] in addition to the AHS[7)], and the Chernobyl emergency worker study[9)]. In the meta-analysis, the estimates obtained from a fixed effect model and a random effect model were 0.20 (95% CI=0.14, 0.25) and 0.21 (95% CI=0.02, 0.39), respectively[1)]. They also conducted meta-analyses for other (nonischemic) heart diseases, and circulatory diseases apart from heart diseases and stroke. Using those summary estimates and current mortality rates for nine major developed countries, they estimated excess population risks for all circulatory diseases combined.

Little *et al.* concluded as follows[1)]: "Our review supports an association between circulatory disease mortality and low and moderate doses of ionizing radiation."However, their study seems to have failed to present convincing evidence for the association of circulatory disease risk with low/moderate dose exposure (<0.5Sv by the definition of authors). This commentary reviews the studies which Little *et al.* used for their meta-analysis.

2. Critical review of epidemiological studies used in the meta-analysis conducted by Little *et al.*

1. Atomic-bomb survivors

Study population: The LSS cohort consists of about 94,000 survivors of the atomic bombings in Hiroshima and Nagasaki, Japan, in 1945[12)], who were identified by the supplementary schedules to the national census in 1950[2)]. It includes a large proportion of men and women with all ages who were within 2.5 km of the hypocenters at the time of the bombings and still resided

Suminori Akiba: Department of Epidemiology and Preventive Medicine, Kagoshima University Graduate School of Medical and Dental Sciences
8-35-1 Sakuragaoka, Kagoshima, 890-8544, Japan
E-mail: sumi.akb@gmail.com

in Hiroshima or Nagasaki in 1950, as well as a random age and sex matched sample of people 2.5 to 10 km from the hypocenter who were exposed to small to negligible amounts of radiation doses. In addition, this cohort includes 27,000 subjects who were not in city at the time of bombing[2]. The AHS is a longitudinal study that has conducted the biennial medical examination of the study subjects selected from among the LSS cohort. The meta-analysis of Little *et al*. used the results obtained from the mortality follow-up of the LSS cohort reported by Shimizu *et al*.[2], and the non-cancer disease incidence among the AHS cohort examined by Yamada *et al*.[7].

Radiation exposure: The study reported by Shimizu *et al*. examined the mortality of atomic-bomb survivors with individually estimated radiation doses (N=86,611)[2]. The survivors had mainly acute external exposure to a whole-body low-LET radiation. In the study of Shimizu *et al*., 86% of cohort members received doses less than 0.2 Gy, and the average dose was 0.1 Gy[2]. However, those features do not necessarily assure that this study gives information on low/moderate doses. Note that a low average dose will be obtained from a cohort consisting of subjects with the radiation dose of, for example, 2 Gy and the overwhelming majority of unexposed subjects. In this study medical exposure was not evaluated. In low/moderate dose ranges, however, radiation doses from diagnostic medical X-ray procedures, particularly from CT scans, can be substantial relative to atomic-bomb radiation.

Confounders: The hypocenters of Hiroshima and Nagasaki were in the center of downtown and in the area inhabited by many catholic people, respectively. Therefore, the lifestyles of proximally exposed survivors may be different from those who were more distally exposed in both cities. Indeed, distally exposed survivors, whose doses were estimated to be approximately zero, had about 5% higher cancer rates than the estimated cancer rates for zero dose from proximally exposed survivors[13]. The factors responsible for the observed difference are yet to be identified. The mortality analysis of circulatory disease is likely to be affected by this problem. The study by Shimizu *et al*. did not adjust for life-styles, including smoking, drinking and dietary habits[2], which are most important risk factors of circulatory diseases. It should be noted, however, that the prevalence of smoking among the LSS cohort is not significantly related to radiation dose. An exception is the group of women who were exposed to radiation dose of 2+ Gy. This group had a slightly higher prevalence of smoking than women with lower doses[14]. However, it is unlikely that smoking strongly confounds the dose-response relationship of circulatory diseases in this study.

Mortality follow-up: The LSS study has a long follow-up period (from 1950 to present). Since the establishment of this cohort was completed in the late 1950s, the mortality data in the early years of follow-up were collected in a retrospective manner. For the periods 1950-52, 1950-55, and 1950-60, the ERRs/Sv of solid cancer mortality, calculated using a stratified linear RR model, were 041 (90% CI=-0.01, 0.99), 0.38 (90% CI=0.07, 0.75), and 0.24 (90% CI=0.05, 0.45), respectively[15]. The estimates appear to be larger in early follow-up years. It is difficult to tell whether those findings indicate the presence of selection bias possibly involved in a retrospective follow-up of a cohort. It is unlikely, however, that the mortality of circulatory disease is affected by this problem since their risk started to increase in the late 1960s. The follow-up of this cohort is considered virtually complete.

Clinical studies: Yamada *et al*. examined the relationships between the incidence of non-cancer diseases and atomic-bomb radiation dose, using longitudinal data for about 10,000 AHS participants during the period 1958-1998[7]. They found a significant quadratic dose-response relationship for hypertension (P=0.028) among the entire AHS cohort, and a significant excess for myocardial infarction among survivors exposed at less than 40 years of age (P=0.049). Accounting for smoking and drinking did not evidently alter the results. Using the longitudinal data accumulated by the AHS study, Sasaki *et al*. demonstrated a small but statistically significant effect of ionizing radiation on the longitudinal trends of both systolic and diastolic blood pressures (BPs). They concluded that their observations can be explained by the degenerative effect of ionizing radiation on blood vessels[16]. The AHS also revealed that serum cholesterol levels were elevated among irradiated women. Among men, only the youngest birth cohort of 1935-1945 showed a notable increase[17]. Those findings on BPs and serum cholesterol levels might have been coincidental relationships between the distance from the hypocenter and lifestyles rather than a causal association of radiation exposure with BPs or serum cholesterol levels.

Weight of evidence: The meta-analysis of Little *et al*. used the ERR of 0.02 (95% CI=-0.10, 0.15) for ischemic heart disease mortality, and an ERR of 0.12 (95% CI=0.05, 0.19) for cerebrovascular disease (stroke) mortality among the LSS cohort[2] In the same meta-analysis, they also used the ERR estimates obtained from an incidence study[7] among the AHS cohort. The ERR estimates obtained from the incidence study were 0.05 (95% CI=-0.05, 0.16) for the ischemic heart disease, and 0.07 (-0.08, 0.24) for cerebrovascular disease (stroke). It should be noted that the risk estimates obtained from the LSS and the AHS are likely to be dependent on each other. Another problem is the fact that the excess risk of non-cancer diseases among the LSS and AHS studies is mainly from survivors with doses larger than 0.5 Gy. Neither the study of Shimizu *et al*. nor the study of Yamada *et al*. presents any convincing

evidence indicating an excess risk of circulatory diseases, including ischemic heart diseases and cerebrovascular attacks, among survivors with low/moderate radiation dose or low dose-rate radiation exposure. It should also be noted that the presence of biases from confounding factors such as lifestyles and socioeconomic status (SES) cannot be denied in those dose ranges.

2. Mayak study

Study population: Mayak PA is the first and largest nuclear weapons facility in the former Soviet Union, consisting of nuclear reactors and radiochemical and plutonium plants. This facility, located near the city of Ozyorsk in the Southern Urals in the Russian Federation, started its operations in 1948[8, 11]. The study cohort includes 8,658 male and 3,552 female workers first employed by one of the main Mayak plants from the start of operations until the end of 1958. The workers involved in incidents/accidents and developed acute radiation syndromes, and workers exposed to radionuclides other than plutonium-239, e.g. tritium, were excluded from the cohort. The mean age of starting work at Mayak PA was 25 years, and was not significantly different in men and women. The mean durations of work at the reactors, radiochemical and plutonium plants were 14 (standard deviation (SD)=13), 11 (SD=13) and 14 (SD=13) years, respectively.

Radiation exposure and dose: Workers at reactors had external radiation exposure. At radiochemical and plutonium plants, workers were exposed to alpha-particle radiation from internally deposited lutonium-239, in addition to external radiation exposure. Among workers monitored for plutonium exposure, the liver dose from alpha-particle was used as a surrogate for the muscle dose. Doses from other potential sources of exposure, including neutron and diagnostic medical X-ray examinations, were considered negligible. The average dose was 0.83 Sv. Note that this dose is much larger than 0.5 Sv, which is a maximum dose for studies eligible for the meta-analysis of Little *et al*.

Confounding: In this study, the effects of smoking and drinking were taken into account when estimating radiation-related risk. However, residual confounding by smoking/drinking cannot be denied since this study did not take into account the duration of smoking/drinking or the daily amounts of smoking/drinking.

Mortality follow-up: Less than a half of the cohort (46%) were living in Ozyorsk at the end of 2000 or had lived there until their death, whereas about 53% had migrated from the city during the follow-up. The follow-up of the cohort was virtually complete as long as study subjects lived in Ozyorsk City (vital status was unknown for only 0.03%) whereas the vital status was unknown for 11% of the entire cohort, indicating that the follow-up was not easy once cohort members left the city. Whether the completeness of mortality follow-up depends on the radiation dose or not is unclear. The cause of death is known for 95.7% of those deceased. It is difficult to tell the accuracy of cause of death in this study.

Morbidity follow-up: Morbidity data were available as long as the cohort members lived in Ozyorsk City. Up to 31 December 2000, morbidity data were collected from 94% of the entire cohort. The accuracy of diagnosis is not evaluated in the study of Azizova *et al*.[8, 11]

Weight of evidence: The meta-analysis of Little *et al*. used the results obtained from morbidity studies, which gave an ERR of 0.119 (95% CI=0.051, 0.186) for ischemic heart disease[8], and an ERR of 0.449 (95% CI=0.338, 0.559) for cerebrovascular disease (stroke)[11]. In this study, it is not entirely clear whether it was possible to distinguish the effects of external and internal radiation exposures. In addition, the average dose is much larger than 0.5 Gy. Taken together, this study does not seem to give any convincing evidence for an excess risk of ischemic heart disease or cerebrovascular attack attributable to low/moderate doses from external radiation exposure.

3. Chernobyl emergency workers

Study population: The number of liquidators (clean-up workers) involved in the clean-up work at the Chernobyl was 77,663 in 1986, 58,694 in 1987 and 31,565 during 1988-1990, giving a total of 167,862. Following the government decree, liquidators underwent annual medical examinations in state health institutions. The information obtained from those examinations was registered to the Russian National Medical and Dosimetric Registry (RNMDR). Nearly 700,000 persons have been registered in the RNMDR to date. A retrospective cohort established for risk analysis consists of male workers who were registered in the RNMDR up to 1 January 1992, and were living in the six regions of the European part of Russia (North-West, North-Caucasus, Volgo-Vyatsky, Povolzhsky, Central-Chernozemny and Ural regions)[18, 19]. The workers eligible for the analysis were those with information on health status, which was collected at least once during the period from the first entry to the Chernobyl zone to the end of 2000. Subjects having diseases of the circulatory system prior to entry to the zone were excluded from analysis.

Exposure: Dosimetry data for liquidators can be classified into three groups: i) an absorbed dose based on readings of an individual dosimeter; ii) a group dose assigned to members of a group performing an operation in the Chernobyl zone, which was determined on the basis of the readings of an individual dosimeter held by one member of the group; and iii) an itinerary dose for a group of workers estimated from the duration of their stay in the zone and the average dose rate of the zone.

Dose range: The largest number of workers belong to the dose group of 50–150 mGy. This group of workers mainly consists of the liquidators who arrived in the Chernobyl zone in 1987. The group with doses above 200 mGy mainly has liquidators who arrived in the zone in 1986.
Confounding: This study did not take into account lifestyles or socioeconomic factors.
Mortality follow-up: The completeness of mortality follow-up is not entirely clear. The SMR of all causes of death among 65,905 emergency workers during the period 1991–1998 was below 0.9 except for 1997. The observed mortality rates smaller than expected may be explained by healthy worker effects. However, the incompleteness of death ascertainment may also be involved.
Morbidity follow-up: Ivanov *et al*. stated that the studied cases of diseases of the circulatory system were confirmed by physicians during specialized examinations[9] using standard diagnostic criteria recommended by the World Health Organization for epidemiological studies. Cerebrovascular diseases among emergency workers were diagnosed mainly on the manifestations of cerebral circulatory insufficiency, transient disorders of cerebral circulation, discirculatory encephalopathy and arterial hypertension. The diagnoses of cerebrovascular diseases were confirmed by neurologists. If necessary, following examinations were performed: ultrasonic dopplerography, rheoencephalography, electroencephalography, thermoencephalography, computer tomography and magnetic resonance tomography.
Weight of evidence: The meta-analysis of Little *et al*. used the report on cerebrovascular disease morbidity during 1986-2000. The estimates of ERR/Sv used for the meta-analysis of ischemic heart disease and stroke (cerebrovascular disease) were 0.41 (95% CI=0.05, 0.78) and 0.45 (95% CI=0.11, 0.80), respectively[9]. An anomalous finding in this study is a decreasing trend of the cerebrovascular disease risk during the follow-up period of 1994-1999. Unless a reasonable explanation for such a time trend is given, the results obtained from this study cannot be regarded as convincing evidence to indicate an excess of circulatory disease risk. One of alternative explanations for such a time trend is the involvement of psychological stress related to emergency work. It is not unlikely that radiation dose is related to the magnitude of psychological strain.

4. German uranium mine workers

Study subjects: The study subjects were male uranium miners who were born after 1899, first employed by the Wismut Company during the period 1946-1989, and employed for at least 6 months. A random sample of 59,161 workers was selected from among approximately 130,000 workers identified in three personnel files, stratifying on the date of first employment (1946–1954, 1955–1970 and 1971–1989), place of work (underground or milling/processing or surface) and the location of mining facilities (Thuringia or Saxony). After exclusion of 160 people without information on radiation exposure or clear personal identity, the cohort had 59,001 workers[10, 20].
Exposure: The total duration of production for uranium mining by the Wismut company can be divided into three distinct periods (1946–1954, 1955–1970 and 1971–1989). During the first period (1946-1954), working conditions were characterized by dry drilling, the lack of forced ventilation, and an increasing exposure to radon. In the second period (1955-1970), radon concentrations decreased due to improved ventilation and the replacement of dry drilling with wet drilling. In the third period after 1970 up to the company closure in 1990, international radiation protection standards were introduced. Measurements of radon and long-lived alpha-emitters are available only from 1955. For the period 1946-1954, radon exposure was determined retrospectively on the basis of the first available radon measurements in 1955, taking into account previous working conditions, and historical data gathered from the Czech and French ore mining industries. Doses from exposure to radon, long-lived radionuclides and external gamma radiation were estimated by using a detailed job-exposure matrix for each year of employment between 1946 and 1989, each mining facility and each place of work. It is unclear whether it was able to distinguish the effect of internal exposure to alpha particle from that of external exposure to gamma ray. Note that in the review of Little *et al*., the radiation exposures had to be whole-body. Kreuzer *et al*. wrote as follows: "To date, there is no dosimetric model to determine the doses to the heart or arteries from either all three radiation sources combined or the single source[10].
Dose range: Among the study cohort, 8,244 workers (14%) had never been exposed to radiation. The mean cumulative dose from external gamma radiation was 41 mSv. Workers who were exposed to more than 500 mSv numbered 124[10].
Confounding: The risk analysis did not take into account lifestyles and socioeconomic factors.
Mortality follow-up: Information on vital status was collected through local registration offices and district archives, and copies of death certificates were obtained from local health authorities. For some cases, additional information on the causes of death before 1989 was available from the Wismut pathology archives.
Weight of evidence: The meta-analysis of Little *et al*. used the ERR estimate of 0.09/Sv (95% CI=-0.6, 0.8) for cerebrovascular disease (stroke), reported by Kreuzer *et al*.[10] In this study, we cannot deny the possibility of internal exposure affecting radiation-related risk

estimates. The possibility of confounding by smoking cannot be denied, either.

5. Eldorado uranium mine workers

Study population: Study subjects were workers at the Eldorado facilities owned by Eldorado Nuclear Ltd sometime between 1932 and 1980 during the ages of 15–75 years[3]. Most of them were i) uranium miners and mill workers employed at Port Radium in Northwest Territories, and Beaverlodge in Saskatchewan; and ii) workers at Port Hope, Ontario, which is a radium and uranium refining and processing plant. A small number of study subjects were workers employed at other sites, including head offices, and workers involved in aviation, research and development and exploration. The final cohort for mortality analysis consisted of 17,660 workers (89% of the original cohort). Since women made up only 8% of workers, the analysis was restricted to 16,236 male workers.

Radiation and Dose range: In this study, individual gamma-ray doses of a sizable number of workers were measured with film badges. For other individuals who had not been wearing a badge, personal gamma-ray doses were calculated from the average dose rates and time on the job.

Confounding: This study showed an increase of lung cancer incidence in relation to radon exposure, and the ERR/WLM (working level months) of lung cancer was 0.55% (95% CI=0.37, 0.78). This ERR estimate per exposure is similar to those reported by recent studies[21]. In this study, exposure to radon decay products was slightly but negatively related to the mortality of ischemic heart diseases (ERR/WLM=-0.01%) and stroke (ERR/WLM=-0.04%). On the other hand, gamma ray exposure was positively related to ischemic heart disease mortality (ERR/Gy=0.15, P=0.36). Those results suggest that the levels of radon decay products and gamma ray were not strongly related to each other.

Mortality follow-up: The Canadian Mortality Database (CMDB) contains records of all deaths in Canada registered by all provinces and territories. This database also keeps records of voluntarily reported deaths of Canadian residents in the United States. Deaths among the study cohort were identified through probabilistic record linkage with CMDB at Statistics Canada. This study followed workers who had their last contact after 1940 and were alive at start of follow-up in 1950 until the end of 1999. Since the CMDB does not contain cause of death (it has only the fact of death) during the period 1940-49, the subjects who were found dead during that period were eliminated from further analysis.

Weight of evidence: The meta-analysis of Little *et al*. used the ERR/Sv of 0.15 (95% CI=-0.14, 0.58) for ischemic heart disease, and the ERR/Sv of -0.29 (95% CI=<-0.29, 0.27) for cerebrovascular disease (stroke), reported by Lane *et al*.[3]In this study, the risk of neither leukemia nor solid cancer was significantly related to gamma ray exposure. Actually, the incidence of leukemia excluding chronic lymphocytic leukemia was negatively related to radiation dose (ERR/Sv=-0.34, P=0.73). In the analysis of solid cancer mortality, positive ERR estimates were obtained for cancers of the stomach (ERR/Sv=0.28, P=0.78), colon (ERR/Sv=0.82, 0.58) and prostate (ERR/Sv=0.19, P=0.8). In cancer incidence analysis, positive associations were found in cancers of the colon (ERR/Sv=0.31, P=0.59) and bladder (ERR/Sv=2.83, P=0.15). Since P values for those estimates were large, and, therefore, their confidence intervals were wide, this study does not present any significant evidence to indicate an excess risk of cancer or non-cancer diseases in relation to gamma ray exposure. In addition, wide confidence intervals make it difficult to evaluate the presence of confounding by smoking. For example, this study reported a relatively large estimate of ERR/Sv for bladder cancer, which is known to be related to smoking. However, it is difficult to tell whether this was caused by chance or caused by confounding factors such as smoking.

6. EDF study

Study population: The French National Electricity Company (Electricite de France-EDF) operates 58 nuclear power plants[4]. The mortality analysis conducted by Laurent *et al*. included all EDF permanent employees (N=22,393) who had worked for at least 1 year in the company and who had been monitored for exposure to ionizing radiation between 1961 and 2003.

Radiation exposure and dose range: External exposure to high-energy photon radiation (gamma rays, energy range 100–3,000 keV) was monitored using personal Kodak type 2 WLM badge dosimeters, which were worn on the chest. Estimated colon doses were used for risk analysis of non-cancer disease mortality. Data for exposure to neutrons have been available since 1967. However, since neutron dose estimates appeared to have uncertainties, the dose estimates of neutron exposure were primarily used to identify workers with potentially substantial exposure to neutrons. The mean cumulative dose of workers at the end of study was 21.5 mSv. The workers with doses less than 5 mSv accounted for 43% of the cohort. Less than 5% of workers had the cumulative doses larger than 100 mSv.

Confounding: This study did not take into account the effects of lifestyles or socioeconomic factors. RRs at 100 mSv for all cancers, lung cancer, smoking-related cancers and non-smoking-related cancers were estimated to be 0.68 (90% CI=0.43, 1.03), 0.67 (90% CI=0.28, 1.35), 0.85 (90% CI=0.50, 1.34) and 0.41 (90% CI=0.61, 0.91), respectively.

Although the RR estimate of lung cancer was similar to that of all cancers, the estimate for smoking–related cancers was larger than that for non-smoking-related cancers. Those differences may be explained by statistical errors. However, another possibility is the presence of a positive relationship between smoking and radiation dose. Such a correlation can confound the dose-response relationship between circulatory disease risk and radiation dose.

Follow-up: The mortality during the period 1968-2003 was examined. The starting date of follow-up was the date of first dosimetric monitoring, the date of initial employment plus 1 year or 1 January 1968, whichever comes first. Information on the vital status of workers was obtained through record linkage with the National Vital Status Registry (Repertoire National d'Identification des Personnes Physiques). An additional search using internal EDF sources was also conducted. For workers identified as deceased, causes of death coded according to the International Classification of Diseases (version 8 for period 1968–1978, 9 for period 1979–1999 and 10 for 2000–2003) were obtained from the National Causes of Death Registry (CepiDC-Inserm).

Weight of evidence: The estimates of RR at 100 mSv for all cancers, ischemic heart diseases and cerebrovascular diseases were 0.68 (90% CI=0.43, 1.03), 1.41 (90% CI=0.71, 2.37), and 2.74 (90% CI=1.02, 5.39), respectively[4]. While no excess risk was observed for cancer or ischemic heart disease, an excess was found in cerebrovascular disease risk (P=0.01). However, the estimate of ERR/Sv(=1.74) was much larger than those obtained from the study of atomic-bomb survivors. Those findings suggest a possibility that the estimates of ERR per dose were biased by non-radiation factors.

7. IARC 15 country study

Study population: The 15-Country Study pooled the mortality data of nuclear industry workers from 15 countries. The main analysis included workers who had been monitored for external radiation exposure and whose doses resulted predominantly from exposure to higher energy photon radiation (X and g-rays in the range 100–3000 keV). Workers who had been employed for less than one year in any study facilities were excluded from analysis[5]. Due to the lack of adequate SES information, US-Idaho National Laboratory and Canada-Ontario Hydro cohorts were excluded from the pooled analysis of non-cancer disease mortality. The Japanese cohort data, which lacked information on non-cancer diseases, were not included in that analysis, either[22].

Radiation exposure: For each worker monitored for external radiation exposure, an individual annual recorded radiation dose was obtained from facility records and/or national dose registries. For the analysis of circulatory disease mortality, estimated absorbed doses to the colon were used. The average cumulative dose was 20.7 mSv; and less than 0.1% of workers had received cumulative doses larger than 500 mSv. The anomalously high radiation-associated cancer risk for Canadian workers in the IARC 15-country study is suspected to be related to missing dosimetry information, including dates of hire. Apparently, the dosimetry data obtained from the records of Atomic Energy Canada Limited (AECL) workers were not properly transferred to the National Dose Registry[23]. It should be noted that approximately 75% of the Canadian workers used in the standard analysis were accounted for by AECL employees.

Confounding: The validity of the radiation risk estimates reported by the IARC 15-country study has been questioned[24, 25]. For example, smoking might have confounded the results. Adjustment for SES made in this study might have reduced the magnitude of potential confounding by smoking but it is unlikely to have eliminated it. Indeed, confounding by smoking is strongly suspected by the fact that the ERR estimate of all cancers excluding leukemia was 0.97/Sv while the estimate for all cancers excluding leukemia and lung cancer was 0.62/Sv (95% CI=-0.51, 2.20). It should also be pointed out that lung cancer was the only cancer site that had a significant excess in relation to radiation dose in cancer mortality analysis, and the ERR per dose was about two times higher than the corresponding value reported by the study of atomic-bomb survivors[26]. Cardis *et al.* (2005) acknowledged that residual confounding by smoking was present in the 15-country study[27].

Weight of evidence: The estimates of ERR/Sv for ischemic heart disease and cerebrovascular disease (stroke) were -0.01 (95% CI=-0.59, 0.69) and 0.88 (95% CI=-0.67, 3.16), respectively. The meta-analysis of Little *et al.* used those estimates reported by Vrijheid *et al.*[5] The risk estimates obtained by this study are suspected to be confounded by smoking. In addition, dosimetry data of Canadian study included in this pooled analysis are suspected to have serious problems.

8. the third analysis of National Registry for Radiation Workers (NRRW-3)

Study population: In the first analysis of NRRW[28], the data contained 95,217 radiation workers from the following five major employers in the nuclear industry: the Atomic Weapons Establishment (AWE), British Nuclear Fuels public limited company (BNFL), Ministry of Defense, Nuclear Electric, and the United Kingdom Atomic Energy Authority (UKAEA). Also included were employers monitored by the former Defense Radiological Protection Service (DRPS). The NRRW cohort for the second analysis (NRRW-2) was enlarged by adding about 30,000 extra workers, including new workers at

the organizations involved in the first analysis[29]. Newly added facilities were the Daresbury and Rutherford Appleton Laboratories of the Council for the Central Laboratory of Research Council, the Medical Research Council Radiobiology Unit (now MRC Harwell), National Radiological Protection Board (NRPB, now Radiation Protection Division of the Health Protection Agency (HPA)), Nycomed Amersham public limited company, Rolls-Royce and Associates, and Scottish Nuclear Ltd. Also added to the cohort were some groups of workers monitored by NRPB's Personal Monitoring Services (now HPA's Radiation Protection Division). The analysis incorporated updated dosimetry and personal data for those workers at UKAEA, AWE and BNFL Sellafield who were included in the Nuclear Industry Combined Epidemiology Analysis. ERRs per sievert of all malignant neoplasms in the first and second analyses were close to zero. Non-cancer disease mortality did not show any significant excess risk in relation to external radiation exposure in either analysis. The cohort for the third analysis contains about 50,000 more workers than before[6]. Those newly added were i) for most employers, persons who started radiation work during 1991–1999; ii) workers who ceased employment at BNFL Capenhurst and Springfields before 1976; iii) Ministry of Defense (MOD) radiation workers who ceased employment before 1977; and iv) workers at British Energy Generation/Magnox Electric's Dungeness A and B power stations during 1965–1990. As a result, the number of workers first employed by BNFL Capenhurst and Springfields increased from 8,079 in the NRRW-2 to 21,018 in the NRRW-3. MOD workers increased more evidently. The workers first employed by the MOD in the second and third NRRW analyses were 33,484 and 67,112, respectively.

Radiation exposure: The mean lifetime doses for the NRRW-2 and NRRW-3 cohorts were 30.5 mSv (3810 person Sv/124,743 workers) and 24.9 mSv, (4348 person Sv/174,541 workers), respectively, indicating that the newly added members of the NRRW-3 cohort had lower average doses than the NRRW-2 cohort. The proportion of workers with 100 mSv or more was small in this cohort. In the NRRW-3, such workers accounted for 6% of the entire cohort. Estimates of doses from internal emitters were not generally available and could not be used in the risk analysis. Muirhead *et al*. indicated that the doses received by workers monitored for internal exposure were likely to be lower than their external doses in most instances, and some of them may not have received any internal dose at all. They also pointed out, however, that doses of internal exposure to the lung from actinides such as plutonium may sometimes be substantial.

Mortality follow-up: The follow-up for the first analysis was up to the end of 1988 for most of instances. In the data used for the second analysis, follow-up was up to the end of 1992 for all workers. In the third analysis, mortality and cancer incidence were studied until the end of 2001. The average follow-up periods in the second and third analyses were 16.5 years (2,063,300 person-years/124,743 workers) and 22.3 years (3.9 million person-years/174,541 workers), respectively. The years of follow-up added to the original NRRW-2 cohort in the third analysis is unclear. It is probably in the range of 5-9 years on average.

The effect of internal exposure: In the second analysis, the estimate of ERR/Sv for all malignant neoplasms excluding leukemia was 0.086 (90% CI=-0.28, 0.52). Exclusion of about 22,000 workers ever monitored for internal exposure increased the estimate to 0.46 (90% CI=−0:24, 1.31). Interestingly, the corresponding estimate for the all cancers excluding leukemia and lung cancer was similar to the ERR estimate for all cancers excluding leukemia. Those findings suggest that the ERR/Sv of lung cancer, which was -0.11 (90% CI=-0.72, 0.72), was affected by internal exposure. In the third analysis, similar findings were made, and exclusion of workers ever monitored for internal exposure increased the estimate of ERR/Sv for all malignant neoplasms excluding leukemia from 0.275 (90% CI=0.02, 0.56) to 0.758 (90% CI=0.22, 1.38). Regarding the radiation exposure levels with workers monitored for internal exposure, Muirhead *et al*. wrote as follows[30]: "it should be born in mind that many of workers who had been internally monitored had also received relatively high external doses." Even if the relatively large ERR per dose for that group is attributable to radiation, that means that workers monitored for potential internal exposure had evidently larger ERRs per dose than other workers. The difference between those monitored for internal exposure and the rest can be explained by internal exposure or confounding by non-radiation factors. Either way, those findings suggest that the ERR estimates were affected by factors other than external radiation exposure.

ERRs/Sv for cancer in the second and third analyses: The estimate of ERR/Sv for all cancers excluding leukemia changed from 0.09 (90% CI=0.28, 0.52) in the second analysis to 0.275 (90% CI=0.02, 0.56) in the third analysis. The risk estimates were obtained from stratified analysis. In the third analysis, data were stratified for age (in 5-year groups), gender, calendar period (1955-, 1960-1995, 2000–2001), industrial classification (industrial/non-industrial/unknown) and first employer[30]. The third analysis for the first time presented evidence of an increasing trend with dose in mortality of all cancers (two-sided P=0.036). Cancer incidence analysis gave an estimate (=0.266; 90% CI=0.04, 0.51) similar to that obtained from mortality analysis. The determinants for the observed difference between the second and third analyses are unclear. In the third analysis, the follow-up period of was extended by 5-9 years. Since the NRRW-

2 had 16.5 years of follow-up on average, the addition of such a short follow-up period is unlikely to make such a large difference when estimating an ERR/Sv of cancer. Therefore, the most likely cause is the addition of new cohort members. Since the NRRW-3 cohort had a mean cumulative dose evidently smaller than the NRRW-2 cohort, the newly added cohort members of NRRW-3 had to have a relatively low mean cumulative dose and a relatively large ERR per unit dose than the rest of the cohort, suggesting the presence of heterogeneity in terms of ERR per among different sub-populations. Although radiation sensitivity may be involved in such heterogeneities, there is no evidence for such a factor to play a major role in risk estimation. Factors likely at work are lifestyle-related risk factors for circulatory diseases, which may confound radiation-related risk estimation.

Confounding by smoking: In the third analysis, the ERR/Sv for the mortality of cancer of the trachea, bronchus and lung (lung cancer) was 0.106 (95% CI=-0.43, 0.79), which was evidently lower than the one for all cancers excluding leukemia (=0.275). However, this finding does not necessarily indicate that smoking is negatively correlated to radiation doses since lung cancer risk may be affected by internal exposure. Interestingly, laryngeal cancer mortality had an ERR/Sv of 4.1 (95% CI=0.18, 14.46). This cancer is known to be more strongly related to smoking than lung cancer[31] whereas its association with radiation exposure is not considered stronger than lung cancer. Therefore, the significant association of laryngeal cancer with radiation dose suggests a possibility that smoking is positively related to radiation doses. It should be noted, however, the association is not significant after adjustment for multiple comparisons. On the other hand, the estimates of ERR/Sv for malignant and non-malignant diseases strongly related to smoking were 0.13 (95% CI=-0.28, 0.62) and 0.05 (95% CI=-0.22, 0.35), respectively. Those findings suggest that smoking is not strongly related to radiation dose. In contrast, the estimate of ERR/Sv for bronchitis, emphysema, and chronic obstructive disease was -1.04 (95% CI=-1.40, 0.48), suggesting a negative relationship between radiation dose and smoking. It should also be noted that the confidence intervals of those estimates were wide. Taken together, it is likely that the relationships between smoking and radiation doses are heterogeneous in this cohort: some subcohorts have a positive association; some, no association; and the rest, a negative association.

Weight of evidence: In this study, the estimates of ERR/Sv for ischemic heart disease and cerebrovascular attack were 0.259 (95% CI=-0.05, 0.61) and 0.161 (95% CI=-0.42, 0.91), respectively[6]. The meta-analysis of Little *et al*. used those estimates. It should be noted that a part of the data of the NRRW-3 were included in IARC 15-country study. Little *et al*. argued that the overlap can be ignored. However, the basis of their argument is not entirely clear. The NRRW-3 cohort seems to consist of sub-cohorts with different population characteristics and different estimates of ERR per dose. The estimates of ERR per dose in sub-cohorts may be confounded by factors different from sub-cohort to sub-cohort. Combining the data obtained from various cohorts does not eliminate biases specific to each cohort. Rather, consolidation makes it difficult to identify problems involved in each sub-cohort. The ERR estimate per dose of the consolidated cohort will be determined by a delicate balance between different sub-cohorts. The results of the NRRW-3 do not constitute convincing evidence for the presence of an excess risk of ischemic heart disease or cerebrovascular attack in relation to radiation exposure unless more detail information on each sub-cohort is presented.

3. Summary and conclusion

The studies of atomic-bomb survivors showed excess risks of ischemic heart disease and cerebrovascular attack in relation to acute external exposure to low-LET whole-body radiation. However, those results do not constitute convincing evidence for an excess risk of circulatory disease in relation to low-level radiation exposure. It should also be noted that the risk estimates per dose in low/moderate dose ranges are much smaller that the risks related to lifestyles and socioeconomic factors. In the studies of Mayak PA workers, and German and Canadian uranium mine workers, it seems not easy to distinguish the effects of external and internal radiation exposures. In addition, the average dose of Mayak PA workers was larger than 0.5 Gy. In the case of uranium mine workers, confounding by smoking cannot be denied. Taken together, those studies do not give any convincing evidence for an excess risk attributable to low/moderate doses of external whole-body radiation exposure. The studies of Chernobyl emergency workers and EDF workers have anomalous findings, making the validity of those studies doubtful. The risk estimates obtained from the IARC 15-country study is suspected to be confounded by smoking. In addition, dosimetry data of Canadian study included in this pooled analysis are suspected to have serious problems. The NRRW-3 cohort seems to consist of sub-cohorts with different population characteristics and different estimates of ERR per dose. The estimates of ERR per dose in sub-cohorts may be confounded by factors different from sub-cohort to sub-cohort. The results of the NRRW-3 do not constitute convincing evidence for the presence of an excess risk of ischemic heart disease or cerebrovascular attack in relation to radiation exposure unless more detail information on each sub-cohort is presented.

Taken together, the meta-analysis of Little *et al*. used studies with i) relatively high doses or dose rates, ii) possible internal exposures, iii) possible biases from lifestyles, socioeconomic factors and psychological factors, and iv) errors in radiation dose data. Although confounding by lifestyles and socioeconomic factors is suspected in most of studies, most of the studies included in their meta-analysis could not take into account those factors at all, and even the studies that had information on those factors could not take them into account satisfactorily. Note that meta-analysis can increase the precision of estimates but cannot eliminate biases. Overlaps of data may also be a problem. In conclusion, their meta-analysis does not give any convincing evidence for the relationship between circulatory disease risk and low-level exposure to external whole-body radiation.

United Nations Scientific Committee on the Effects of Atomic Radiation conducted an epidemiological evaluation of cardiovascular disease following radiation exposure, and concluded as follows[32]: "Given the relatively small increase in risk associated with radiation at doses less than 1-2 Gy, it is uncertain whether epidemiological studies of mortality alone will be able to make a significant contribution to understanding the potential for and the nature of any relationship between circulatory diseases and radiation at these levels of dose." The results obtained from the AHS of atomic-bomb survivors suggest a possibility that the development of atherosclerosis after exposure to ionizing radiation of approximately 0.5 Gy or larger. Such a hypothesis seems to be supported by the results obtained by the morbidity study of Mayak PA workers. Atherosclerosis is considered to have two major aspects: atherosis (fatty degeneration) and sclerosis (acceleration of arterial stiffness)[33]. Atherosis contributes to atherosclerotic disease development. There are several clinical indices based on non-invasive evaluation of arterial stenosis and occlusion. The most important index among them is intima-media thickness (IMT) of carotid arteries. Ultrasound scanning of carotid IMT can detect atherosclerotic disease in early and asymptomatic stages[34]. Until recently, sclerosis had been received less attention partially because of its difficulty to assess. However, aortic stiffness measured by aorta-iliac or carotid-femoral pulse wave velocity (PWV) is known to be able to predict cardiovascular disease risk[35]. Recently, a new method, termed the cardio-ankle vascular index (CAVI), has been proposed in Japan to overcome the disadvantages associated with measuring PWV[36].

In the AHS study of atomic bomb survivors, a cross-sectional study of approximately 4,000 subjects, including the expanded AHS group of younger subjects, is underway[37]. Parameters related to PWV are evaluated and the Framingham risk scores for arteriosclerosis will be calculated[38]. In Kerala, India, researchers of Regional Cancer Center, Trivandrum started a cross-sectional study of 300 men and 600 women living in high natural background radiation areas, in which PWV and carotid IMT are evaluated by CAVI and ultrasonography, respectively. Blood is drawn for analyses of blood lipid and lipoprotein profiles. A similar study of Mayak PA workers would provide us with invaluable insights into the association between ionizing radiation and atherosclerosis.

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