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Invited Commentary: Studies of Workers Exposed to Low Doses of Radiation

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Extensive studies of atomic bomb survivors in Hiroshima and Nagasaki and of persons exposed for medical reasons have resulted in a wealth of knowledge about the health effects resulting from radiation exposure at relatively high doses and dose rates. The availability of individual estimates of dose has made it possible to quantify dose-response relations and to estimate risks from exposure at low doses and dose rates. These estimates form the basis for setting radiation protection standards (1–3).

As Sont et al. (4) note, the primary reason for studying nuclear workers is to allow a direct assessment of risks resulting from exposure to radiation at low doses and dose rates. The atomic bomb survivor cohort and some of the medically exposed cohorts include persons exposed at low doses and have provided evidence of risk for doses as low as 0.1 Sv (5). However, estimates from these studies are generally driven by doses exceeding 0.5 Sv, whereas it is primarily doses of less than 0.1 Sv that are of interest for risk assessment. Obviously there are uncertainties in extrapolating not only from high to low doses and dose rates but also from a Japanese population exposed under special circumstances in 1945 to modern-day populations of other races and nationalities.

Table 1 summarizes data and results from the National Dose Registry of Canada (4, 6) and from two other large worker studies, and it supplements the comparisons in the report from Sont et al. (4). The three-country study (7, 8), which was coordinated by the International Agency for Research on Cancer, combined data from most nuclear worker studies that had been published prior to 1989 and included the following facilities: Hanford, Oak Ridge National Laboratory, and the Rocky Flats Plant in the United States; Atomic Energy Authority, Atomic Weapons Establishment, and the Sellafield Plant in the United Kingdom; and Atomic Energy of Canada Limited in Canada. The strengths of the three-country study were that a detailed evaluation of dosimetry practices and potential biases and uncertainties in dose estimates for each of the facilities was conducted (9) and that successful efforts were made to obtain a measure of socioeconomic status for all but the Canadian study. The National Registry for Radiation Workers in the United Kingdom was set up in 1976 for the purpose of studying the health effects of chronic low-dose radiation exposure (10). It differs from the National Dose Registry of Canada in that it includes only workers at selected nuclear facilities and does not include dental and medical workers. There is overlap in the studies. The National Registry for Radiation Workers includes most of the 38,494 subjects from the United Kingdom component of the three-country study, but the most recent analyses from the National Registry for Radiation Workers had 4 additional years of follow-up. The 11,355 Canadian workers in the three-country study cohort would also be in the National Dose Registry of Canada study. Estimates of the excess relative risk per sievert are presented for leukemia because this is the cancer that has been most strongly linked with radiation in high dose studies and for all cancers excluding leukemia.

Table 1 also shows data on the atomic bomb survivors. The excess relative risk estimates were taken from the report by Muirhead et al. (10) and based on analyses of male atomic bomb survivors who were exposed between the ages of 20 and 60 years using mortality data (11). In the worker studies, most exposure is to adults, and the atomic bomb survivor studies have demonstrated that excess relative risks depend on both age at exposure and sex. Even though the cohort of the National Dose Registry of Canada is about half female, table 1 of reference 4 shows few females in the higher cumulative dose categories. Estimates of the excess relative risk per sievert for solid cancers in female atomic bomb survivors are about twice those for males (11).

The atomic bomb survivor cohort has by far the largest doses and, primarily because of their older ages and longer follow-up, more cancer deaths than any of the worker cohorts. Risk estimates from the three-country study and the National Registry for Radiation Workers are similar. With their wide confidence intervals, both are compatible with those obtained from the atomic bomb survivor studies, although the latter are estimated more precisely. The atomic bomb survivor data also show clear evidence of increasing risk with increasing dose (11) (not shown in table 1).

The study of Sont et al. makes a potentially important addition to the body of data on workers exposed to low doses of radiation because it is a large study and because it provides cancer incidence data, whereas most other worker studies address only mortality. The National Dose Registry of Canada has the largest number of subjects of any of the worker cohorts, but the total person-sieverts and the number

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Abbreviation: CI, confidence interval.

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TABLE 1. Characteristics and excess relative risk (ERR) estimates for several studies of radiation workers and for the atomic bomb survivor study

Study (reference)*	No. of subjects	No. of cancer deaths or cases	No. of subjects with cumulative doses exceeding		Total person-sieverts	Mean dose (mSv)	ERR for leukemia excluding CLL†		ERR for all cancer excluding leukemia	
			100 mSv	400 mSv‡			ERR Sv^{-1}	90% CI†	ERR Sv^{-1}	90% CI
National Dose Registry of Canada (4)	191,333	3,737	2,948	236	1,267	6.6	2.7§	<0, 19	2.3	1.1, 3.9
National Dose Registry of Canada (6)	206, 620	1,632	2,926	234	1,293	6.3	0.4§	–4.9, 5.7	3.0¶	1.1, 4.9
IARC† three-country study (7, 8)	95,673	3,976	10,007	1,752	3,843	40.2	2.2	0.13, 5.7	–0.07	–0.4, 0.3
National Registry of Radiation Workers (10)	124,743	3,598	9,580	NA†	3,810	30.5	2.6	–0.03, 7.2	0.09	–0.3, 0.5
Atomic bomb survivors (11)	86,572	7,578	17,264	5,489‡	NA	NA	2.2#,**	0.4, 4.7	0.24#	0.12, 0.4

* All but the study by Sont et al. (4) are mortality studies.
† CLL, chronic lymphatic leukemia; CI, confidence interval; IARC, International Agency for Research on Cancer; NA, not available.
‡ For the atomic bomb survivors, this is the number of subjects with a dose exceeding 500 mSv.
§ These estimates are for leukemia excluding CLL in males.
¶ This estimate is for all cancer in males; the estimate for females was 1.5 Sv^{-1} (90% CI: –3.3, 6.3).
# Based on male atomic bomb survivors, aged between 20 and 60 years at exposure, as presented by Muirhead et al. (10).
** Adjusted for the effects of time since exposure and for nonlinearity in dose (10).

of subjects with cumulative doses exceeding 0.1 Sv (100 mSv) are about a third of those from either the three-country study or the National Registry for Radiation Workers study. The estimates of the excess relative risk per sievert for all cancers from the National Dose Registry of Canada, whether based on incidence or mortality data, are larger than those from any of the other studies and appear incompatible with other estimates. Other studies such as those of the UK Atomic Weapons Establishment (12) and Oak Ridge National Laboratory (13) cohorts (both included in the three-country study) and a recent study of Rocketdyne workers (14) have also produced large risk estimates, but these cohorts were much smaller than the National Dose Registry of Canada and the resulting estimates are less precise.

Although there are clearly advantages to the direct study of persons exposed at low doses, there are important limitations that must be considered in interpreting findings from the National Dose Registry of Canada and other worker studies. The most obvious is low statistical power, which may explain in part why individual worker studies have produced a wide range of risk estimates that have sometimes been viewed as contradictory. For example, in the three-country study, estimates of excess relative risk per sievert for all cancer excluding leukemia for the individual studies ranged from negative to several times higher than the estimate obtained from the atomic bomb survivors. Although this range might reflect real differences in the studies, a test for heterogeneity demonstrated that it could also be explained by statistical imprecision. A major objective in conducting combined analyses of data from several studies (three-country study) or of studying large cohorts of workers employed in many different facilities (National Registry for Radiation Workers and National Dose Registry of Canada) is to increase statistical precision.

A second limitation is the large potential for bias due to confounding when studying small risks. The excess relative risk for all cancer excluding leukemia from Sont et al. is 2.3 Sv^{-1}, whereas that based on the atomic bomb survivor data is 0.24 Sv^{-1} (table 1). These estimates lead to relative risks of only 1.023 and 1.002, respectively, at 0.01 Sv (10 mSv), which is about the 90th percentile of the dose distribution for the National Dose Registry of Canada. Can we realistically expect to distinguish risks at these levels? The small amount of bias required to bring about (or mask) a difference of this magnitude can probably never be ruled out in an epidemiologic study. Relative risks less than 1.5 are generally considered difficult to interpret.

Although the potential for bias is not unique to the National Dose Registry of Canada study, it may be more severe than in the three-country and National Registry for Radiation Workers studies because of the lower doses. In addition, certain findings from the National Dose Registry of Canada mortality study could suggest bias. Ashmore et al. (6) estimated that the excess relative risk per sievert for all causes of death in males (2.5 Sv^{-1}, 90 percent confidence interval (CI): 1.5, 3.5) was similar in magnitude to that for cancer alone (see table 1) and found significantly elevated excess relative risks for circulatory disease (2.3 Sv^{-1}, 90 percent CI: 0.9, 3.7) and for accidents (8.8 Sv^{-1}, 90 percent CI: 2.7, 15.0). Although recent data on atomic bomb survivors provide evidence for a dose-response for noncancer diseases, the estimated excess relative risk per sievert is much smaller than that for cancer (15). In addition, even though a healthy worker effect would be expected in the National Dose Registry of Canada cohort, the standardized mortality ratios were unusually low: 0.59 for all causes in males and 0.68 for all cancers in males. The noncancer findings and the low standardized mortality ratios for the National Dose Registry of Canada cohort could indicate bias, perhaps related to the ascertainment of deaths. Because there were common features of linkage methods used to obtain mortality and cancer incidence data, such bias might also affect the incidence findings of Sont et al. Caution would thus seem advisable when interpreting results from the National Dose Registry of Canada. To their credit, Sont et al. do not overemphasize differences in the results from their study and those obtained from the atomic bomb survivors.

An important strength of worker studies is the availability of dose estimates based on personal dosimeters worn by workers. However, these estimates are nevertheless subject to various sources of bias. In addition to the possible problems with reporting limits noted by Sont et al., monitoring programs were designed for radiation protection, and recorded dose estimates probably overestimate doses to bone marrow (relevant for leukemia) and to most other organs of the body (16). A drawback of the National Dose Registry of Canada may be that several thousand employers participated, making a detailed evaluation for each employer impractical. Although dosimetry was handled by a small number of processors, the employers would have some responsibility for ensuring that workers wore their dosimeters consistently and appropriately. Moreover, Sont et al. indicate that no information was available on doses received before 1951, which might be important for the medical workers.

The use of incidence (instead of mortality data) by Sont et al. is particularly advantageous for studying specific cancers, especially those with low fatality rates. The finding for testicular cancer, based on 75 cases, is intriguing. No evidence of a dose-response was found for this site in the three-country, National Registry for Radiation Workers, or National Dose Registry of Canada mortality studies, but few deaths were available for study (19, 8, and 6 deaths for the three respective studies). Sont et al. generally advise caution in interpreting the results for specific cancers. If bias is partly responsible for the large excess relative risk per sievert for all cancers, estimates for specific cancers are also likely to be biased upward. In addition, when a large number of cancer sites are evaluated, false positive results are likely; in the study by Sont et al., there is no a priori reason to think that cancers of the lung, colon, rectum, pancreas, or testis would have especially large excess relative risk estimates. In addition, because of the criteria used to determine whether risk estimates would be presented, cancers not shown in table 7 of reference 4 are likely to have negative associations with radiation.

In conclusion, radiation worker studies are the most informative epidemiologic studies of persons exposed at low doses of radiation that have been conducted. They have the major advantage of doses that have been objectively measured through the use of personal dosimeters and include persons exposed to a wide range of cumulative doses. Both the three-country and the National Registry for Radiation Workers studies generally confirm the appropriateness of estimates obtained through extrapolation from studies of persons exposed to high doses and dose rates. However, worker studies are subject to important limitations, including large statistical uncertainty and uncertainty resulting from potential confounding, making it unlikely that worker studies can replace atomic bomb survivors as the primary source of data for risk estimation.

Additional data on workers can be expected in the future. Only a small percentage of the workers in the studies included in table 1 were dead by the end of the follow-up period (17 percent for the three-country study, 10 percent for the National Registry for Radiation Workers, and 2.6 percent for the National Dose Registry of Canada). Thus, there is more that can be learned by continuing to follow these workers. A collaborative study of about 600,000 nuclear workers in 17 countries, including workers in earlier studies, is being conducted with the International Agency for Research on Cancer serving as the coordinating agency (17). This study, which includes an extensive evaluation of systematic and random errors in dose estimates, should lead to more precise estimates of risk based on a direct assessment at low doses and dose rates and thus provide important supplemental information to that obtained from high dose studies.

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