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Invited Editorial

The importance of radiation worker studies

A major unanswered question in radiation carcinogenesis revolves around the level of risk when exposures are received gradually over time. Radiation causes cancers and human studies have provided quantitative estimates of effects for over 100 years. But convincing and consistent evidence for effects arises at relatively high doses, greater than 100–200 mSv, following brief exposures such as received by the Japanese atomic-bomb survivors and patients treated for benign or malignant conditions, or among workers who had very high intakes of radionuclides, e.g. radium among dial painters and plutonium among Mayak plutonium workers. Animal studies are fairly consistent in implying that spreading dose over time (from radiations of low linear energy transfer) results in a lowering of the cancer risk, but human data are far less clear. Further, quantitative estimates of cancer risk following intakes of radioactive elements in human populations are few and far between. Thus the study of workers of the former British Nuclear Fuels plc (BNFL) by Gillies and Haylock (2014) is of interest and importance. As discussed below, however, interpretation is hindered by the relatively small number of workers, the likely influence of confounding factors (e.g. asbestos) and lifestyle factors, and most importantly the absence of organ doses from the intake of radionuclides. Monitoring for radionuclide intakes with urine samples says nothing about whether any radioactivity was detected in the urine, much less about whether any organs received dose from the intake.

But why should the public, politicians, scientists, regulators and health professionals care? It goes beyond the adequacy of the regulatory structure which has been fairly effective in controlling cumulative dose to workers and the public over the last many decades. Such studies are important because chronic exposures are what the population experiences in daily life and in the workplace (Simon and Linet 2014) and such exposures are increasing. Exposures today are from diagnostic imaging procedures in medicine, environmental exposures from nuclear reactor accidents such as at Fukushima and Chernobyl, from increased air travel, and among certain occupations such as non-destructive testing and interventional radiology and cardiology (Boice 2014a).

Better knowledge of chronic exposure is needed to assess more accurately the possible late effects of nuclear terrorism, so called ‘dirty bombs’ or improvised nuclear devices (Nisbet and Chen 2014), the possible late effects of low-level but increased levels of environmental radiation whether from natural sources or technologically-enhanced sources, and the possible late effects from increased levels of medical radiation. Better models could be developed to assist governments in compensation schemes for radiation workers, atomic veterans, or ‘downwinders’ from nuclear weapons tests. Better understanding ‘might’ alleviate the extraordinary fear that is associated with any exposure to radiation (González *et al* 2013), i.e. the fear of radiation has no threshold and is unrelated to dose.

The study of the Japanese atomic-bomb survivors is the single most important investigation to date and is used almost exclusively by protection committees that recommend guidance in radiation, by governments in providing compensation for prior exposures, and by modelers who wish to project forward in time the potential adverse effects of frequent computed tomography scans, of Fukushima exposures and of galactic cosmic ray exposures to astronauts. Wouldn’t it be preferred to make judgments based upon more representative populations, i.e. healthy individuals

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who are exposed over many years and not a few seconds of time in 1945? This again points to the importance of the BNFL worker study, and other investigations that can be identified with high-quality dosimetry, high-quality follow-up, and high-quality methodology.

Gillies and Haylock (2014) conducted an extended combined follow-up of 42 431 BNFL 'radiation workers' who were ever employed at Sellafield, Springfields, Capenhurst or Chapelcross nuclear sites. In contrast, the UK National Registry for Radiation Workers (NRRW) included 174 541 workers (Muirhead *et al* 2009), the UK component of the study by the International Agency for Research on Cancer included 87 322 workers after excluding 23 253 because of potential internal intakes of radionuclides (Vrijheid *et al* 2007), and the previous Sellafield plutonium worker study included 14 319 employees (Omar *et al* 1999). Gillies and Haylock differ in attempting to assess any modifying effect of internal intakes of radionuclides. However, their analysis is based only on whether a urine sample was taken, irrespective of whether any radioactivity was detected in the urine sample. The absence of organ dose determinations is an important limitation that tempers the strength of conclusions.

The authors evaluated 27 categories of cancer mortality and 33 categories of cancer occurrence. Dose-response evaluations covered seven categories of cumulative external dose (mean, 53.0 mSv). The follow-up for mortality began in 1946 and ended in 2005. Cancer incidence began in 1971 and ended in 2005. The follow-up for vital status was remarkably complete and reported to be 99.3%. External doses relied upon film-badge measurements but there was no accounting of organ doses associated with internal intakes of radionuclides which included plutonium, uranium and tritium. Comparisons of the cancer experience among those monitored for internal intake of radionuclides and workers only receiving external exposure were made. However, interpretations are challenging because external doses received by internal radiation workers were much greater than external doses received by external-only radiation workers.

The authors concluded that there was evidence of an increase in cancer risk associated with occupational exposure to external radiation and that the risk estimates were consistent with the values used by national and international authorities in setting radiation protection standards. Significant risks were reported for all cancers, all solid cancers, digestive cancers, and leukemia excluding chronic lymphocytic leukemia (CLL). They also concluded that lower cancer risks were associated with external exposure for workers who were also monitored for internal intakes of radionuclides. However, the sampling variation is such that the data are also consistent with values that are higher than currently considered valid for radiation protection purposes. Perhaps more importantly, because no assessment of equivalent dose or effective dose was made for workers with intakes of radioactive elements, the consistency with standards that are based on effective dose cannot be strictly addressed.

The authors should be commended for the clear exposition of their study results and discussions of potential confounding, lifestyle factors and other socioeconomic factors that could distort study findings. The following represents the limitations of low-dose epidemiologic studies in general, although focusing on the BNFL worker studies, where the influence of chance and confounding factors on cancer risk can overwhelm detection of a small radiation effect above a high background occurrence (ICRP 2005).

- The overall findings and conclusions are difficult to interpret because organ doses associated with internal intake of radionuclides were not taken into account. The external exposure received by the 'internal radiation workers' was three times greater than the external exposure received by the 'external-only radiation workers'. The comparisons between external-only workers with internal workers say little about the possible radiation effects of radionuclide intakes, but rather only about differences in the populations studied unrelated to internal doses. It is of interest that in previous studies where organ doses from plutonium were computed based on over 223 000 urine samples, there was little evidence for a dose response when plutonium doses were included with the external doses (Omar *et al* 1999). The previous study did indicate that comprehensive attempts had been made to assess and incorporate organ doses from the intake of plutonium (Riddell *et al* 2000).

- The classification of workers being monitored for intake of radionuclides provides little information on whether a worker actually inhaled or ingested the radionuclide. As previously reported, "Plutonium workers were defined as those who had ever provided a urine sample for plutonium assay. Some of these workers will never have been exposed to plutonium…" (Omar *et al* 1999). In a recent study of workers monitored for plutonium at the Mound facility in the US, only 55% had a positive urine sample (Boice *et al* 2014). In another study of workers monitored for primarily uranium at the Rocketdyne facility in the US, 87% of the workers were judged to have negligible intakes (Boice *et al* 2006, 2011). The fact of providing a urine sample does not mean that there was internal exposure to a radionuclide.
- The number of statistical comparisons was remarkable, several thousand, and interpretation is challenging based on the quantity of data presented and the differences in the comparisons made. Consider cancer of the rectum, a site that has not been consistently found to be related to radiation exposure (UNSCEAR 2008). For mortality, the standardised mortality ratio for non-radiation workers was significantly high, but no increase was seen among radiation workers. But for the radiation workers there was a positive dose response and a significant and very high ERR Sv^{-1} estimate of 5.74. In contrast, for cancer incidence the standardised incidence ratio was not increased among either non-radiation or radiation workers, the dose response was positive but not significant and the ERR Sv^{-1} estimate of 0.53 was a magnitude lower than the mortality estimate. This is challenging, to say the least, on how best to interpret, i.e. are these observations due to random variations in the data, choice of comparisons, multiple comparisons, real associations, and/or bias in the study design or confounding factors?
- The overall dose–response relations seemed to be driven by cancer sites that are not convincingly linked to radiation. Throughout, cancer of the pleura was significantly elevated whereas cancer of the lung was not. Cancer of the rectum was significantly elevated but not cancer of the stomach. Cancer of the prostate was increased, but cancer of the bladder was decreased. The combining of cancer sites of diverse etiology and baseline incidence can produce patterns that are not related to external radiation exposure, particularly when organ doses from radionuclides are not taken into account. Further, if organ doses from the intake of radionuclides were meaningful, then dose–response evaluations based only on external doses could be misleading if the internal doses from radionuclide intake differed over external dose categories.
- Following intakes of plutonium or uranium, the organs that would likely receive the highest dose would be the lung (if inhaled), the bone and liver. Among workers monitored for internal radiation, there were no significant increases in lung, bone or liver cancer across categories of external dose, or in comparisons with population rates. For liver cancer a negative ERR Sv^{-1} was presented. These observations suggest that that the internal exposures may not have been meaningful, but conclusions are limited because organ doses from the radionuclide intakes were not determined.
- The increased cancer risk was apparent only for doses greater than 200 mSv and only among the larger Sellafield workforce. None of the analyses were powerful enough to show significant trends up to 200 mSv, consistent with previous worker studies (Cardis *et al* 1995, 2007, Muirhead *et al* 2009) and due in part to small sample sizes. The excess

of leukemia excluding CLL, seen at Sellafield, has been previously reported and related, again, to workers who received greater than 200 mSv. This points to the value of large studies (or combined studies) to address the effects of chronic exposures over broad categories of cumulative dose.

- The consistent increase in cancer of the pleura points to confounding by asbestos (Omar *et al* 1999), likely associated with thermal insulation at nuclear facilities.
- It was somewhat surprising that the overwhelming proportion of the thousands of associations presented were positive, which would not be expected given the low doses overall. This had been raised as an issue for the previously reported associations seen for noncancers, i.e. "… the fact that most specific mortality endpoints of noncancer disease are elevated to a similar extent suggests that there may be bias" (Little *et al* 2008). This, coupled with the large increases in cancers not typically increased in radiation studies, suggests the possible confounding by lifestyle factors associated with socio-economic status or even other occupational factors (Preston *et al* 2013).
- Combining diverse study populations in either a meta-analysis or a pooled (combined) analysis is not straightforward. When combining low-dose studies, the statistical assumptions used in the analysis and the variables chosen for adjustment can make a difference in the statistical significance of the results (Boice 2010). The analytical approaches taken by the authors, similar to those taken in the NRRW study (Muirhead *et al* 2009), were clearly defined and appropriate. Nonetheless, the substantial difficulties in combining diverse worker studies and interpreting the results related to epidemiological (not just statistical) issues of bias and confounding should not be underestimated (Preston *et al* 2013, Wakeford 2014)
- It was informative to place the worker exposures in perspective by contrasting them with the dose received from natural background radiation once a worker reached 40 years of age (106 mSv) and then when he or she reached 70 years of age (182 mSv). The mean dose that the radiation workers received was about 53 mSv, or two to three times lower than the background dose. This doesn't include medical radiation, which is likely of the same magnitude as the background doses. This indicates the great difficulty in conducting low dose radiation studies where the background noise (non-occupational dose) is greater than the occupational dose, in addition to the baseline rates of cancer being much greater than the small excess to be detected.
- Increases of some malignancies in worker populations, such as prostate, might be related to selective screening of the population or even possibly slighter better healthcare for workers of long employment (and associated higher doses) (Preston *et al* 2013). Further, the inclusion of organs with low or no radiosensitivity clouds the inferences that can be made, e.g. cancers of the pancreas, pleura, rectum, prostate, uterus, brain and others are not consistently increased in epidemiologic studies.
- Finally, the difference in the dose response (based on external exposure) between workers monitored for internal radionuclides and workers monitored only for external radiation is noteworthy, though difficult to interpret. It might be of interest to compare the dose–response relationship for internal radiation workers whose intakes were determined to be negligible, i.e. little to no detection of radioactivity in the urine, with the external radiation workers. Perhaps there are lifestyle factors, confounding influences or other occupational exposures that are important.

In conclusion, the study of Gillies and Haylock (2014) was well conducted. Findings, however, are difficult to interpret in large part because of the inconsistencies between the mortality and incidence data, the inclusion of workers with known intakes of radionuclides but not accounting for their organ-specific doses, and the peculiar mix of significantly elevated cancers such as the prostate, pleura, testes, rectum related to radiation which is not seen in most other studies. There was little evidence for a significant radiation-related excess of cancer under 200 mSv. Part of the problem is that the signal-to-noise ratio is so very small, i.e. the small possible effect associated with radiation even at currently accepted risk coefficients is very small. When there is a small effect then small differences and potential confounding factors (e.g. cigarette smoking), biases (selection and surveillance) can have an inordinate influence on study findings (ICRP 2005). There is a need for combining studies with long-term follow-up like this one, ideally in one country with one system of follow-up and outcome ascertainment, consistent dosimetry and large numbers. Perhaps in the future there will be an enhancement of UK investigations with the other components of the National Registry for Radiation Workers taking into account organ-specific doses from the intake of radionuclides. This is something that we are attempting in the United States, where over a million US radiation workers and atomic veterans have been assembled, including the Manhattan Project workers of the 1940s, early nuclear utility workers of the 1950s and 1960s, atomic veterans at nuclear weapons tests in the 1940s and 1950s, industrial radiographers, and early medical workers in radiology, technology, nuclear medicine and oncology (Boice 2014a, 2014b). It is hoped that large studies with consistent methods of worker identification and follow-up, similar methods for outcome ascertainment, and comprehensive dosimetry taking into account organ-specific doses will be able to provide clarification to the major question in radiation epidemiology, “What is the level of risk when dose is received gradually over time?”

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