Invited Commentary: Are Low Radiation Doses or Occupational Exposures Really Risk Factors for Malignant Melanoma?

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Concerns about a possible association between melanoma and employment in the nuclear industry first surfaced in the early 1980s (1), and even earlier with regard to employment in other industries (2). Although occupationally related skin disorders were first observed in the 1700s (3), and although radiation-induced skin erythemas and skin cancers were observed among early radiation workers as well as among populations undergoing radiation therapy (4, 5), observations regarding the possible association between occupational exposures and melanoma have tended to receive little credence (6).

In 1981, Austin et al. (1) reported results from a retrospective cohort study, including a fourfold increase in the incidence of melanoma, among workers at the Lawrence Livermore National Laboratory (LLNL) in Livermore, California. These findings generated concern that other nuclear workers might be similarly subject to increased risk of melanoma, perhaps due to job-related exposures to low doses of ionizing radiation. Studies carried out at a sister laboratory, Los Alamos National Laboratory (LANL) (7, 8), indicated that increased melanoma incidence did not exist among LANL workers as a whole (7), and further that only increasing education level was clearly associated with the occurrence of incident melanoma within this cohort (8).

The case-control study reported by Austin and Reynolds (9) in this issue of the Journal continues the analysis of melanoma among LLNL workers that was originally reported in 1981 (1). The current investigation expands the total number of melanoma cases from the 19 reported in the 1981 study to 31. The study window for case ascertainment is also increased from 1972–1977 to 1969–1980. The new study adds to our understanding of risk factors for cutaneous malignant melanoma experienced by LLNL workers by considering a variety of occupational and nonoccupational exposures, as well as biologic, demographic, and other characteristics.

Data were collected by reviewing personnel and medical records obtained from LLNL, by means of mailed questionnaires, and by face-to-face interviews. Unfortunately, health physics records, which contained dosimetry information on individual workers, were not made available to Austin and Reynolds, even though they were allowed access to medical and personnel records. In my experience, medical records (and perhaps records having to do with security clearances) have always been considered to be more sensitive in terms of privacy issues than have radiation dosimetry records. The end result of this restriction of access to dosimetry data is that Austin and Reynolds were forced to rely on self-reports of work with radioactive materials rather than on individual dosimetry data. The availability of individual dosimetry for ionizing radiation is one of the strengths of research on effects of exposures to low radiation doses. Strangely, LLNL released the dosimetry data, after reviewing the findings reported by Austin and Reynolds, to a separate group of investigators. These investigators, with funding from LLNL, conducted an evaluation of Austin and Reynolds' finding of an association between melanoma and self-reports of ever having worked with ionizing radiation. The report by the other investigators, Schwartzbaum et al. (10), was published in another journal before the substantive findings reported in this issue of the Journal could be published. The findings of the Schwartzbaum et al. evaluation (10) do, however, essentially support the validity of the association between melanoma and self-reports of work with radioactive materials. The report by the other investigators, Schwartzbaum et al. (10), was published in another journal before the substantive findings reported in this issue of the Journal could be published. The findings of the Schwartzbaum et al. evaluation (10) do, however, essentially support the validity of the association between melanoma and self-reports of ever having worked with ionizing radiation reported by Austin and Reynolds, thereby decreasing concerns that this finding is due to random error, bias, or confounding. In fact, Schwartzbaum et al. (10) report an odds ratio considerably higher but with a wider confidence interval (odds ratio (OR) = 10.8, 95 percent confidence interval...
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interval (CI) 1.4–85.1) than do Austin and Reynolds (9) (OR = 3.7, 95 percent CI 1.6–8.6).

Restriction by Austin and Reynolds to cases diagnosed only while employed limits the investigation to early effects of radiation or other occupational exposures if such effects exist. If the average induction times for non-melanotic skin cancers among radiation-treated populations of 25–30 years (4) apply to the induction of radiation-induced melanoma, many melanomas may not yet have occurred among LLNL workers.

What are the findings of studies of similar populations, such as studies of other nuclear workers and of participants in nuclear tests? The results from mortality studies of three large nuclear worker cohorts in the United Kingdom (11, 12) have been inconsistent. The most recent of these studies (11), a combined analysis of three different cohorts, reported an elevated risk of melanoma and other skin cancers among employees of the Atomic Energy Authority (AEA), but not among employees of the Atomic Weapons Establishment (the facility most similar to LLNL and LANL) or British Nuclear Fuels. Results from a retrospective cohort mortality study of registrants of the National Registry of Radiation Workers in the United Kingdom, which included some workers reported in the above-mentioned studies, found neither evidence of excess melanoma mortality nor evidence of an association with cumulative radiation exposures (12).

Studies of US nuclear workers have reported inconsistent results. Furthermore, most of these studies have found no, or very small, overall increases in melanoma mortality or no evidence of associations with radiation exposure (13–19).

Increased mortality from melanoma was found among a cohort of all white male workers at the Mound Facility (20), and among workers at this same facility who were monitored for penetrating radiation (21), as well as among employees at a nuclear fabrication facility (22). But, again, no clear association was observed with exposure to ionizing radiation (21, 22).

Perhaps most relevant to the findings for LLNL workers are the results of studies conducted of employees at LLNL’s sister laboratory, Los Alamos National Laboratory (LANL). A study of melanoma incidence among LANL workers (7), which included follow-up from 1969 through 1978, concluded that no excesses were present among white male workers (standardized incidence ratio (SIR) = 68 based on 3 observed cases). Although an elevated risk (SIR = 200, 90 percent CI 49–569) was observed among white females of other than Hispanic descent, this finding was based on only 2 observed cases. A matched case-control study (8) expanded case ascertainment from 1969 through 1981. However, contrary to the results for the LLNL workers, no association was found between melanoma and employment as a chemist. An odds ratio of 1.7 (crude OR = 1.4, 95 percent CI 0.3–6.1) was found for physicists, however, and an odds ratio of 3.0 (crude OR = 2.0, 95 percent CI 0.7–6.5) was observed for workers defined as professionals. In regard to exposures to ionizing radiation, matched odds ratios of 1.1 for beta radiation and 1.4 for total penetrating radiation were observed among males. No exposed cases were observed among females, and no plutonium-exposed cases were seen among either males or females. The most interesting finding, however, was a trend between the relative risk of melanoma and increasing education. Compared with workers with less than a college degree, standardized rate ratios increased from 2.1 for workers with college degrees to 3.2 for those with a graduate degree (Mantel-Haenszel test for trend, p = 0.04).

Several studies of participants of nuclear tests and of civilians residing downwind of such tests (23–25) have reported interesting, but imprecise, findings. Johnson (23), found an increased incidence of melanoma among Utah residents, based on unconfirmed self-reports. This study, however, has proven to be controversial and may be flawed (26). Caldwell et al. (24) described small to moderate increases in both incidence and mortality from melanoma experienced by US military personnel who participated in the Smoky nuclear test. Darby et al. (25) reported a very small increase in relative risk of mortality from melanoma among participants in atmospheric nuclear tests conducted by the United Kingdom. However, in both the Smoky study (25) and the United Kingdom study (26), the lower confidence limits were well below unity.

When the results from all of these studies are considered together, they offer little support to hypotheses either of an excess of melanoma among all nuclear workers, of an association with low dose ionizing radiation, or of an association with job-related exposures. The findings do, however, suggest that either the increase in melanoma observed at LLNL is spurious, or, if the LLNL findings are real, the risk factors that contribute to this increase are not present at LANL or at most other nuclear facilities.

A range of occupations and some occupational exposures have been associated with increased risks of malignant melanoma (27). Unfortunately, with some exceptions, the relative risks found for melanoma are often not clearly related to specific exposures but rather are linked with broad categories of workers, such as chemists, physicists, scientists, petrochemical
workers, and electronics industry employees (8, 27). The exceptions appear to be workers exposed to polychlorinated biphenyls (2, 28), fluorescent lighting (29), organic chemicals (30), and perhaps ionizing radiation (1, 9–11, 21), although results are by no means consistent. This potpourri of occupations and potential exposures, which does not take into account the large number of negative studies among similar occupational groups, or of known nonoccupational risk factors, suggests to me that occupation is of less concern than the risk factors for melanoma that are more commonly recognized, i.e., ultraviolet (UV) sunlight exposure, and genetic, biologic, and life-style characteristics.

The paper by Austin and Reynolds (9) raises some issues concerning the conduct of epidemiologic research in the nuclear weapons complex and similar settings. One concern that needs to be addressed is the manner in which data on workers are sometimes restricted to certain investigators but released to other investigators under contract to the employer. Data-sharing, debate, replication, and open discussion of research results are necessary to enable the self-correcting process inherent to science to work. Furthermore, Austin and Reynolds report that their work was subjected to a tedious and overly extensive review. If the work of other epidemiologists is subjected to such a review, this may seriously impact on the timeliness of reporting results of epidemiologic research (31).

Issues of a scientific nature raised by Austin and Reynolds (9) include the manner in which life-style, genetic, and socioeconomic factors modify the effect that occupational exposures, including the possible role of ionizing radiation, exert on the occurrence of melanoma. That exposure to sunlight is the major etiologic factor for the development of melanoma cannot be denied (32). However, sunlight exposure is not the only risk factor (32). The interaction between UV exposure and other causal factors remains to be clarified, because the relation between malignant melanoma and UV sunlight is more complex than that for non-melanotic skin cancers (27, 32).

Austin and Reynolds’ characterization of the association between melanoma and ionizing radiation among LLNL workers as their “most notable” finding (9, p. 530) is arguable. It would seem to me that an odds ratio of almost 15 for more than 6 moles >1/2 cm is more notable than the risk implied by an odds ratio less than 4.0 for work with radioactive materials, especially when surrogate measures of exposure do not substantiate this result. The findings of Schwartzbaum et al. (10) do lend credence to Austin and Reynolds’ results of an association between melanoma and radiation exposure (9), a finding which at this time appears to be limited primarily to LLNL and perhaps Mound workers in the United States, and AEA workers in the United Kingdom. As described above, most studies of other nuclear worker populations have not found employment at these facilities or radiation exposures to be associated with increased risks of melanoma. Important caveats are that most studies have moderate average lengths of follow-up and that the most common health endpoint in these studies is mortality. Both of these characteristics may decrease chances of finding clear associations between these exposures and melanoma. Some studies that have considered both incidence and mortality have reported similar results for these two endpoints (25).

A related issue, also mentioned by Schwartzbaum et al. (10), concerns the excess of incident melanomas among LLNL workers in the absence of excesses for tumor sites that are well known to be related to ionizing radiation. Are we to accept that among LLNL workers, melanoma is induced by very low doses of ionizing radiation but leukemia is not? What are we to make of the absence of increased incidence for other well-known radiation-sensitive organ sites such as the female breast, thyroid gland, and bone?

Another statement with which I take issue is Austin and Reynolds’ conclusion that the results of their study provide “compelling evidence for an occupational component to risk for malignant melanoma” (9, p. 531). As evidenced by their own analyses of occupational and nonoccupational risk factors, the strongest associations that they report are for the presence of moles among the LLNL workers and for history of solar exposure, which are the most consistent types of risk factors found in other epidemiologic studies of melanoma occurrence. In the future, certain occupational exposures will probably be substantiated as risk factors for melanoma. Attention should be directed to identifying and estimating the amount of risk associated with such exposures, as well as the degree to which biologic and life-style characteristics modify the risk associated with those exposures. Nevertheless, genetic, racial, and life-style risk factors and their interactions with UV sunlight exposures will continue to be of far greater importance for understanding the etiology of the vast majority of malignant melanoma cases.

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REFERENCES