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Occupational Radiation Carcinogenesis (Overview)

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CLASSICALLY, RADIUM dial painters have been known for some time to be exposed to increased risk of those cancers caused as a result of the deposition of radium in bone. However, given that, in addition to the radon daughter exposure, there were other forms of external radiation exposure, there has been interest as to whether or not these workers have shown an increased risk of other forms of cancer. Baverstock and colleagues [1] studied a cohort of U.K. radium luminisers. They found no increase in all-cause mortality compared to that expected, though a slight but non-significant increase in mortality from all cancers was observed. For breast cancer, however, there appeared to be an excess related particularly to high estimated exposure to external radiation. Stebbings and colleagues [2] studied a cohort of radium dial painters in the U.S.A., concentrating particularly on those who entered the profession before 1930. There was a marginally significant excess of colon and breast cancer as well as a non-significant excess of stomach cancer and lung cancer. When they adjusted the SMRs for county rates and migration, the elevations for colon and breast cancer reverted to non-significance. They did, however, have an excess of multiple myeloma, five cases observed for an SMR of 333, with 95% confidence interval of 108–776.

Breast cancer is interesting in terms of the effects of radiation exposure. In medically irradiated cohorts and in the Atomic Bomb Commission data in Japan, excesses are not seen until the cohorts have been followed long enough for the expected natural increase in incidence of breast cancer to occur [3, 4]. However, perhaps more important is the fact that age at first exposure seems to be critical in terms of the degree of excess risk. The greatest risk appears to be experienced by those whose first exposure was around the time of menarche or earlier. With increasing age at first exposure, risk falls to reach a barely significant excess for those 35 years of age or more [4].

Turning to the effects of uranium on the incidence of lung cancer, a number of studies have clearly shown excess with a dose–response relationship, for example that of Whittemore and McMillan [5]. Whittemore and McMillan [5] were also able to collect data on cigarette smoking. There was a significant increase in risk for radiation exposure adjusted for smoking, but also a significant increased risk for cigarette smoking adjusted for radiation exposure. Both factors, therefore, seemed to be operating independently with a strong suggestion of a multiplicative relationship.

In the studies of uranium miners [6, 7] there were some rather striking differences between the estimated excess risk per unit of exposure in those who worked in the Beaverlodge Uranium Mine compared to those who worked in the older Port Radium Mine where doses were much higher. The effect per unit of exposure was greater in the more modern mine with lower exposures than in the cohort that worked in the older mine. This suggests a dose-rate effect that appears to be compatible with radiobiological theory [7].

The Committee for the Biological Effects of Ionizing Radiations [8] evaluated the excess relative risk per WLM for different cohorts: Ontario miners; the Beaverlodge cohort; a cohort in Sweden; and Colorado miners. Although there were differences in relative risks in each cohort, the confidence intervals around the estimates were large, and in fact compatible with similar effects.

Studies have continued on the effects in uranium miners; thus, Samet and associates [9] in a study on the New Mexico uranium miners again showed increasing risk with increasing exposure, which largely persisted following adjustment for cigarette smoking. Although cigarette smoking data were not available for the IDSP [10] study of Ontario uranium miners, a dose–response relationship again seemed to be present. However, a particular feature of the IDSP analysis was an attempt to fit regression models and estimate the risk according to the time exposure occurred. The best-fitting model for the cohort of miners who had not also been exposed to gold mining was:

$$SMR = 1.382 + 0.0364\ W2 + 0.004087\ W3$$

where W2 = WLM exposure 10–14 years prior to observation and death and W3 = WLM exposure 15+ years prior to observation or death. The model seems robust and indeed was largely replicated in the miners who had also been exposed to gold mining, suggesting that rather than the most significant exposure being that in the early years, the most significant exposure in terms of increase in risk was that encountered 10–14 years prior to observation or death. Although surprising this suggests an effect of radi-

ation at the late stages of carcinogenesis, as well as a lesser effect at early stages.

The question of what causes the excess lung cancer risk in Ontario gold miners has been investigated by a number of people. A recently reported study updating the experience of the cohort has confirmed that the risk is largely found in those whose first exposure occurred prior to 1945 [11]. Those who entered the industry after 1945 have so far not demonstrated any increase in risk. This study was able to make estimates of exposure to arsenic before 1946. A significant dose–response relationship was found for arsenic exposure lagged by 20 years. However, this was mirrored by a significant dose–response relationship by estimated exposure to radon decay products and in a multivariate model, an independent effect of years of exposure in a dusty gold mine that appears to be an index for exposure to silica. Thus, three factors appear to increase risk in Ontario gold miners, the analysis suggesting that any two of these are sufficient to explain the risk seen, though the most parsimonious model does not include exposure to radiation.

The interaction between cigarette smoking and radon daughter product exposure in uranium miners was explored by L'Abbe and associates [12] in a nested case-control study within the Beaverlodge cohort. This, like the study of Whittemore and McMillan [5], appeared to suggest an independent effect of cigarette smoking and exposure to radiation with no evidence of a significant interaction term. Once again, therefore, the relationship between the two appears to be most compatible with a multiplicative model.

It can be concluded that mining in hard rock is generally accompanied by exposure to radon daughter products. Thus, in addition to uranium and gold miners, excesses of lung cancer have been found in nickel and iron ore miners. A common exposure is certainly present, probably radon daughter products, although as for gold miners it is possible that other carcinogenic factors may also operate.

Turning to those occupationally exposed to radiation in the medical profession, a classic study is that of Court Brown and Doll [13]. In a group of British radiologists who entered the profession pre-1921, although there was no excess of all-cause mortality, there was an excess of mortality from cancer. A similar excess was, however, not seen in those who entered the profession post-1921. The cohort was too small to evaluate the effects of the radiation exposure on leukaemia. In fact there were only two observed deaths in the post-1921 cohort, 0.7 would have been expected from the rates from all doctors. Excess of leukaemia, multiple myeloma and aplastic anaemia have been reported in American radiologists [14], but not in U.S. Army X-ray technologists who served during World War II [15]. More recently, lesser effects in more recent entrants compared to earlier entrants have been shown in American radiologists [16].

A recent Danish study among staff of two radiotherapy departments, derived from record linkage with the Danish Cancer Registry, has shown non-significant excesses of respiratory cancer, breast cancer and multiple myeloma, and a significant excess of prostate cancer based on an observed number on five cases for a relative risk of 6.02, with 95% confidence intervals of 1.94–14.06 [17]. This is important in view of the fact that a suggestion of a similar excess has been found in at least one of the cohorts of nuclear workers [18]. However, in radiotherapists one has to be concerned with ascertainment bias as they can be expected to have more medical care than the general population.

Although in this paper the studies of nuclear workers (such as those of 18–24) have not been reviewed, it is nevertheless possible to draw some conclusions on the studies that have been reported. First, there are many relatively small cohort studies of nuclear workers. Secondly, the results of these studies usually suggest no major increase in risk for radiation-associated cancers. However, the power of these studies has been too low to exclude a small excess risk of some important cancers, for example leukaemia. Indeed, it is inconceivable, unless our theories of radiation carcinogenesis are wrong, that there is no risk, although of course it may be very difficult to demonstrate this conclusively. We can note that the reported excesses in cancers have been inconsistent, but concern remains about some, for example pancreas and prostate cancer. Confounding is unlikely, but chance probably explains these inconsistencies. A meta-analysis may clarify the situation, but given that cohort studies are being combined, and that different types of exposure, to both external and internal emitters of radiation are involved, concerns may remain that may require either a large nested case-control study to resolve them, or further research (including case-control studies specifically directed to cancers of concern as well as potential confounders).

In conclusion, time-related factors in radiation carcinogenesis have not yet been clarified fully, in spite of the study they have received in the radioepidemiologic literature. It is, however, already apparent that of the cancers induced by radiation lung cancer has approximately a ten-year latency, leukaemia has a short, around 5-year latency, thyroid 5–10 years, breast 10 or more years, and some other cancers have a long latency of approximately 20 years. However, these latent periods should not necessarily be interpreted as always a true latency, nor as indicating that radiation is always an initiator. Thus, radiogenic breast cancer only occurs at the time breast cancer normally occurs. Further, an important increase in risk is only seen for women irradiated before the age of 35 years, and the highest risk of breast cancer is seen in those irradiated before breast development is complete. As far as lung cancer is concerned, this appears to be induced in uranium miners at a relatively late stage of carcinogenesis. Finally, it can be concluded that, like many other circumstances where other factors are involved acting at different stages in carcinogenesis, the effects of smoking and radiation on lung cancer induction are in practice independent, i.e. statistically multiplicative or near multiplicative. This has implications when one is considering compensation of workers for radiation effects. It means essentially that radiation should be considered on its own without being particularly concerned as to whether or not the worker was exposed to other factors.

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