Published in final edited form as:
Expert Rev Hematol. 2010 June ; 3(3): 251–254. doi:10.1586/ehm.10.25.

Risk of childhood leukemia after low-level exposure to ionizing radiation

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Leukemia risk models

There is unambiguous epidemiological evidence that exposure to moderate and high doses of ionizing radiation increases the subsequent risk of leukemia [1,2]. This evidence is based upon studies of the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki in 1945, and groups exposed therapeutically or occupationally. Models of radiation-induced leukemia risk derived from leukemia mortality among the Japanese atomic bomb survivors adopt a linear dose–response relationship in the low-dose (<100 mGy) region, and assume that there is no threshold dose below which there is an absence of risk [1,2]. The implication of these models is that even low doses of radiation increase the risk of leukemia to some (albeit small) extent.

In the low-dose region, the excess relative risk (ERR) coefficient (the proportional increase in risk over background per unit radiation dose received by the red bone marrow) is predicted to increase after a minimum latent period of 2 years, and this increase is especially steep for those exposed as children, rising to a maximum of approximately 50 Gy^{-1} some 7 years after exposure. The ERR then attenuates, so that, at 25 years after exposure, it is approximately 2, which is the proportional increase in risk experienced this long after exposure by those irradiated as adults [3,4]. Therefore, for those exposed as children, the proportional increase in the risk of leukemia is expressed over time as a distinct ‘wave’.

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Financial & competing interests disclosure
Richard Wakeford carries out paid consultancy for a number of companies (including from the nuclear industry), government bodies and academic and research institutes, and occasionally gives paid expert advice in a legal and quasi-legal context. The work of Mark Little was funded partially by the European Commission under contract FP6-036465. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

Childhood leukemia & nuclear installations

Since it is established that childhood leukemia is especially sensitive to induction by ionizing radiation, reports of notably elevated incidence rates of leukemia among children living near certain nuclear installations (e.g., Sellafield in northwest England) [5], gave rise to concern that exposure to radiation as a consequence of operations at these installations could be responsible. Radiological risk assessments based upon conventional risk models inferred that the radiation doses received from radioactive material discharged from the installations were, in general, less (usually considerably less) than the doses received from natural background radiation, and much too small, by a factor of at least 100, to account for the excess cases of childhood leukemia [6]. Despite the dominance of doses from natural sources, this conclusion led to suggestions that the application of risk models based upon moderate-to-high acutely delivered doses to circumstances involving low-level exposures may be severely underestimating the risk [7].

Unfortunately, direct epidemiological evidence from studies of low-level exposures is not abundant, but the ERR coefficient for childhood leukemia, which may be derived from the largest case–control study of childhood cancer and exposure *in utero* of the third-trimester fetus to diagnostic radiography, does not differ greatly from that obtained from the Japanese atomic bomb survivors irradiated as young children [8,9], although the interpretation of the evidence from antenatal radiography remains somewhat controversial [10]. Nonetheless, from the available evidence, it does not appear that current risk estimates for childhood leukemia after the receipt of low doses of radiation are gross underestimates.

Internally deposited radionuclides

It has been further suggested that the risk coefficients derived from groups irradiated from external sources, such as the Japanese atomic bomb survivors and patients undergoing radiotherapy, are not appropriate for the radiation doses received from radioactive material taken into the body (‘internal emitters’) [7,11]. Some radionuclides emit short-range radiation (e.g., α-particles) that travels only a short distance in tissues, and essentially pose a risk to health only if deposited in the close vicinity of sensitive cells. Since much of the dose received by children as a result of discharges of radioactive material from nuclear installations is from internal emitters, it has been proposed that the leukemogenic effect of man-made radionuclides taken into the body has been seriously underestimated, and that this is the explanation for the excess incidence of childhood leukemia that has been observed near some nuclear installations [11]. It should be noted, however, that a significant component of the red bone marrow dose received from natural background radiation is owing to the intake of radionuclides, implying that anthropogenic radionuclides would have to pose a much greater risk than naturally occurring radionuclides, which is unlikely [11]. Further, studies of people exposed to α-particle-emitting thorium-232, as well as various other internal emitters, yield leukemia risks compatible with those observed in the Japanese atomic bomb survivors [12], although these studies relate to leukemia in adulthood rather than childhood.

Atmospheric nuclear weapons testing

Of some interest in this respect, is the program of atmospheric nuclear weapons testing, which was at its height in the late-1950s and early-1960s [13]; this led to worldwide contamination by radioactive fallout, consisting of a range of radionuclides very similar to those discharged from many nuclear installations. Since measurements of man-made radionuclides in the tissues of members of the general public residing near nuclear installations show levels that, in general, do not differ greatly from those found in people living distant from such installations [14], it is pertinent to enquire whether a wave of excess

cases of childhood leukemia occurred after the marked peak of atmospheric nuclear weapons testing, which would be a sign of serious underestimation of the leukemogenic risk from man-made radionuclides.

Such an investigation is not as straightforward as it might seem, since the number of large-scale cancer registries in existence during the 1960s was small and mortality data are not an acceptable alternative, given the increasingly successful treatment of childhood leukemia at this time. However, examination of the childhood leukemia incidence data from 11 registries on three continents has not revealed a discernible wave of cases subsequent to the peak of atmospheric nuclear weapons testing, rendering untenable an explanation of excess cases in the vicinity of some nuclear installations in terms of internal emitters [14].

Paternal preconceptional irradiation

The interest in raised incidence rates of childhood leukemia near nuclear installations also gave rise to another hypothesis that attracted appreciable media publicity at the time – male exposure to radiation increases the risk of childhood leukemia in their subsequently conceived offspring. The hypothesis arose from a case–control study conducted around the Sellafield (UK) nuclear complex, which found a statistically significant association between childhood leukemia and relatively high doses of radiation received by fathers while working at Sellafield before the conception of their children [15]. The authors suggested that the association could explain the notable excess of childhood leukemia in the nearby village of Seascale (UK).

However, the association was novel, and based upon just four cases. Nonetheless, a considerable volume of research was initiated by this study. However, little or no support for a cause-and-effect interpretation of the original statistical association between childhood leukemia and paternal preconceptional irradiation has been found, and the hypothesis has now been abandoned [16–18].

Natural background radiation

Despite the failure to find evidence for a gross underestimation of the risk of radiation-induced childhood leukemia after the receipt of low doses, conventional risk models do imply some risk at low levels of exposure, and this has implications in a number of areas. For example, ubiquitous natural background radiation gives rise to an annual equivalent dose to the red bone marrow of British children of approximately 1.3 mSv, consisting of penetrating external radiation from terrestrial and extraterrestrial sources, and internal radiation from naturally occurring radionuclides in food and drink, plus a small component from inhaled radon [19].

We have estimated that conventional risk models predict that 15–20% of childhood leukemia cases in Great Britain may be attributable to natural background radiation, although the uncertainties in this value are considerable [20,21]. For example, risk models derived from the experience of the Japanese atomic bomb survivors use data from a country during a period when the childhood leukemia rate was a factor of 2.5-times lower than the current rate in Great Britain, raising the question of whether it is more appropriate to transfer the ERR or the excess absolute risk (the additional risk above background) between populations [20,21].

Furthermore, the question naturally arises as to why, if it is real, such material contributions to the risk of childhood leukemia have not been detected by epidemiological studies conducted to date. Our investigations have shown that large studies involving several thousand cases would be required, in order to have a reasonable chance of discerning the

predicted risk from natural background radiation, and that previous studies, as well as potentially suffering from bias and uncontrolled confounding, have not included sufficient numbers of cases to detect the predicted risk with any reliability [22]. However, large (possibly international) and carefully designed studies should be capable of demonstrating whether or not a predicted level of risk is posed by natural background radiation.

Implications for radiography

Finally, current risk models for radiation-induced leukemia have implications for modern radiographic techniques, such as CT scans, which involve comparatively high doses [23]. A red bone marrow dose of a few tens of milligray received by a young child would be predicted to approximately double the risk of childhood leukemia and, although the absolute increase in risk is not great (for irradiation soon after birth, an approximate increase in the risk of leukemia before the 15th birthday is from one out of 1800 to one out of 900), it cannot be considered trivial, and behoves careful judgement to be applied when assessing the need for pediatric CT scans. That is not to say that pediatric CT scans should not be conducted, only that appropriate consideration should be given to the possible risks, as well as the benefits.

The effect of pediatric CT scans upon the risk of childhood leukemia should, if conventional predictions are correct, be capable of detection by sufficiently large case–control studies if the population prevalence of the procedures is high enough, and such studies are underway [24]. It is ironic that it is half a century since case–control studies of childhood leukemia and antenatal diagnostic x-rays found an association (when the population prevalence of such examinations was ~10%) and this association forms part of the evidence to support the application of risk models derived from moderate-to-high doses to the low-dose region – the region of CT scan exposure.

Biographies

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