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# Let's not relive the past: a review of cancer risk after diagnostic or therapeutic irradiation

Radiation was used in medicine almost immediately after X-rays were discovered by Roentgen in 1895 [1]. Since then, radiation has become one of the three main treatment modalities for cancer and a ubiquitous diagnostic tool. Radiotherapy also is occasionally used as a treatment for benign diseases. Epidemiologic studies of a wide variety of radiation exposures at different dose levels have demonstrated radiation-related long-term deleterious health effects [2]. These studies provide strong scientific evidence that radiation increases the risk of cancer, even at low doses.

The Life Span Study (LSS) of atomic bomb survivors has been the principal source of information on radiation-related health effects in humans for more than 50 years [3, 4, 5]. The original LSS cohort comprises slightly more than 120,000 people. Most analyses, however, include only the survivors who were in Hiroshima or Nagasaki at the time of the bombings, were alive in 1950, and for whom radiation dose estimates could be calculated. This more-defined cohort includes about 86,500 survivors. Approximately 40% of the cohort received doses of less than 5 mSv and about 3% received doses of more than 1 Sv. As the cancer mortality and morbidity follow-up of the survivors has lengthened, the quality and quantity of the information has improved. The most recent analysis of cancer mortality [4] has demonstrated a linear dose-response relation with no evidence of a threshold. An analysis of solid cancer incidence from 1958 through 1994 shows a linear dose-response with a statistically significant excess risk at very low doses, i.e., in the range of 0–0.1 Sv [5]. The direct evidence of risks at these low levels is particularly relevant to the higher dose diagnostic X-ray examinations such as CT scans. Studies of the LSS show a pattern of increasing risk with decreasing age at exposure [3, 6]. This finding bears directly on the risks associated with pediatric diagnostic examinations. Data from the atomic bomb survivors also reveal a twofold excess relative risk of developing radiation-related solid cancers among women and clearly show that the carcinogenic risks persist throughout life [3, 4, 5, 6].

Artificial (man-made) sources of radiation account for approximately 15% of the radiation exposure of the general public [7]. Almost all of this exposure comes from medical radiation and diagnostic procedures represent the main source of medical radiation exposure. Improvements in diagnostic accuracy and in ease of use have led to very large numbers of diagnostic X-ray examinations. Temporal trends indicate that worldwide frequency of diagnostic examinations per 1000 population has increased, as well as the mean effective dose per examination. Between 1985 and 1990, 800 diagnostic examinations were performed per 1000 people in the US; between 1991 and 1996, that number had risen to 962 [8]. That means that during the latter period, the US population had almost one examination per person per year. While the development of alternative diagnostic imaging modalities has provided new ways of reducing radiation exposure, X-ray examinations remain a mainstay of contemporary medicine. Concern about the long-term health effects of radiation has resulted in the reduction in dose for some procedures, but at the same time some relatively high-exposure diagnostic examinations have been introduced. For example, a pediatric CT scan results in about 30 mSv to the brain. If the scan

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settings are not adjusted properly for a child, the brain dose could be 60 mSv. Recent data from the LSS indicate that tumors of the nervous system, especially schwannomas, are associated with doses below 200 mSv [9]. Thus, exposure from several pediatric CT scans is in the dose range where an excess risk of neural tumors has been observed.

There is a large body of epidemiologic data on medically irradiated populations [10, 11]. Quantified assessments of carcinogenic risks in patients provide important data that complement those from the atomic bomb survivor studies. Studies of medically irradiated populations are singularly useful because, unlike the A-bomb survivors, they include heterogeneous populations with diverse ethnic, age and gender distributions, who have been irradiated with numerous types of radiation and a broad range of doses. Follow-up of these patients has shown that some radiation treatments and diagnostic procedures have had unexpected long-term harmful health outcomes.

Epidemiology is the study of the distribution and determinants of disease in humans [12]. The advantage of epidemiology is that it studies humans; one does not need to extrapolate from animal or cellular models. The disadvantages also largely stem from the fact that humans are studied directly. Events concerning people do not always occur as planned, individual memory is imperfect, and assembling a population of required size to assess low doses of radiation adequately is extremely challenging. For example, a doctor might recommend a diagnostic examination for a patient and could document that recommendation in the medical record. The patient, however, could decide not to have the examination, the examination could have been administered improperly so that a dose different than that prescribed could have resulted from the examination, or the patient could have had the examination but forgotten about it when queried about previous radiation exposure. Another problem is that of statistical power. To be sure there is sufficient statistical power to evaluate satisfactorily the radiation-related risk of developing a disease, factors such as disease prevalence, the length and quality of follow-up, the size of the population under study, the radiation dose, and the predicted level of risk must all be considered.

Because diagnostic examinations are extremely common, they are of special concern to the public. However, because doses from diagnostic examinations typically are low, the range of doses is narrow, and estimating individual doses from past exposure is complicated, it is difficult to study risks associated with diagnostic radiation using epidemiologic methods. Furthermore, when risks are small, they can easily be obscured or inflated by methodologic flaws in an epidemiologic study. Methodologic problems, such as incomplete follow-up, exposure or disease misclassification, multiple comparisons, and the potential for confounding can all result in incorrect results. If a significant part of a study population has had multiple examinations, radiologic records are retrieved for estimating doses, information regarding potential confounding factors is collected, and follow-up is complete and accurate, the study has a substantially better chance of being informative. Studying therapeutic exposure is somewhat easier in terms of epidemiologic methods because radiologic records are usually available and exposures typically are much higher. With these criteria in mind, this review focuses on epidemiologic investigations that have provided useful data for risk assessment. However, since risks associated with small diagnostic doses are of more interest to the public, data from low-dose studies will be highlighted. Furthermore, the data involving childhood exposure will be emphasized, since they are most relevant to the risks of pediatric CT scans.

Childhood cancer risk associated with postnatal diagnostic X-rays has been evaluated in a few case-control studies. However, since individual doses were not computed, quantified risk estimates could not be calculated (Table 1). In the studies of Shu et al. and Infante-Rivard et al., a history of diagnostic X-rays was more common among patients with childhood acute lymphocytic leukemia (ALL) than among controls [13, 14]. Although these studies obtained the data regarding past history of X-ray examinations during interviews conducted with mothers of the young cancer patients, recall bias does not appear to be a critical limitation. In one investigation, no case-control difference in the frequency of recalled ultrasound examinations was found, even though the data were collected using the same methods [13]. In the second investigation, the frequency of prenatal diagnostic X-ray examinations recalled by the mothers of the patients, population controls and hospital controls was validated against hospital medical records, and although mothers of all three groups under-reported examinations, the level of under-reporting did not differ significantly between the patients and controls [15]. In contrast, Meinert et al. observed no association between postnatal diagnostic examinations and childhood cancers in a large study conducted in Germany [16]. This study is complicated by differences in the two subgroups studied, with a particularly long time between diagnosis and interview in one subgroup. Shu et al. also did not find evidence of an association between childhood leukemia and diagnostic X-rays, except in a subgroup of children with pre-B-cell ALL, in a large follow-up study of childhood cancer survivors in the US [17]. This study also relied on mother's recall, but without any medical record validation. The inconsistent results from these investigations of childhood cancer and previous diagnostic radiation exposure make it impossible to draw firm conclusions about whether any association exists. Without dose information, it is not possible to determine

**Table 1.** Childhood cancer risks associated with diagnostic X-ray examinations (*ALL* acute lymphocytic leukemia, *NHL* non-Hodgkin's lymphoma)

| Reference | Location | Cases/controls | Year of diagnosis | Cancer outcome | No. of examinations | Odds ratio | 95% confidence interval |
|---|---|---|---|---|---|---|---|
| 13 | Shanghai | 642/642 | 1981–1991 | Childhood cancer | Any | 1.3 | 1.0–1.7[a] |
| | | | | | 1–2 | 1.2 | 0.9–1.6 |
| | | | | | 3+ | 1.8 | 1.2–2.9 |
| | | 166/166 | 1986–1991 | Acute leukemia | Any | 1.6[a] | 1.0–2.6[a] |
| | | | | | 1–2 | 1.5 | 0.9–2.5 |
| | | | | | 3+ | 2.0 | 0.8; 5.0 |
| | | 107/107 | 1981–1991 | Brain cancer | Any | 1.5[a] | 0.8–3.0[a] |
| | | | | | 1–2 | 1.5 | 0.7–3.1 |
| | | | | | 3+ | 1.5 | 0.5–4.5 |
| | | 87/87 | 1981–1991 | Lymphoma | Any | 1.3[a] | 0.6–2.7[a] |
| | | | | | 1–2 | 1.1 | 0.5–2.7 |
| | | | | | 3+ | 1.7 | 0.5–6.1 |
| 14 | Canada | 491/491 | 1980–1993 | ALL | 1 | 1.08[b] | 0.73–1.59[b] |
| | | | | | 2+ | 1.78 | 1.21–2.63 |
| 17 | US | 1842/1986 | 1989–1993 | ALL | Any | 1.1[c] | 0.9–1.2[c] |
| | | | | | 1–2 | 0.9 | 0.8–1.1 |
| | | | | | 3+ | 1.2 | 1.0–1.6 |
| | | 227/245 | 1989–1993 | Pre-B-cell ALL | Any | 1.7[c] | 1.1–2.7[c] |
| | | | | | 1–2 | 1.5 | 0.8–2.6 |
| | | | | | 3+ | 3.2 | 1.5–7.2 |
| 16 | Germany | 940/2588 | 1992–1994 | Solid childhood cancer | 1–4 | 0.8[e] | 0.55–0.98[e] |
| | | | | | 4+ | 0.8 | 0.48–1.3 |
| | | 1184/2588 | 1980–1994 and 1992–1994[d] | Leukemia | 1–4 | 0.8[e] | 0.65–0.93[e] |
| | | | | | 4+ | 1.0 | 0.65–1.55 |
| | | 234/2588 | 1980–1994 and 1992–1994 | NHL | 1–4 | 0.71[e] | 0.51–1.0[e] |
| | | | | | 4+ | 0.60 | 0.27–1.3 |

[a]Adjusted for maternal age, birth weight, paternal smoking prior to birth of index child
[b]Excludes x-ray exams occurring within 3 months before the reference date; adjusted for maternal age and maternal level of schooling; excluding dental X-rays
[c]Excludes x-ray exams occurring within 2 years before the reference date; excluding dental X-rays
[d]Altogether 634 cases and 688 controls were diagnosed in 1980–1994; 1867 cases and 2057 controls were diagnosed in 1992–1994, but no breakdown of cases by study years is given for individual cancer types
[e]Excludes x-ray exams occurring within 1 year before the reference date; adjusted for maternal education, family income, and race

whether the different results are due to differences in levels of exposure, study methods, or chance.

The results from a mortality follow-up of 5466 female scoliosis patients, 4822 of whom received multiple diagnostic X-rays during childhood or adolescence to monitor their scoliosis and 644 who were unexposed, were published recently [18]. Individual doses were computed for the irradiated patients based on the number of examinations and estimated doses for these examinations taken from the medical literature. The mean age at exposure was about 10.5 years and the mean breast dose was 0.11 Gy. The study revealed that 77 breast cancer deaths occurred compared with 45.6 expected. The excess radiation risk per Gray (ERR/Gy) was high (5.4; 95% confidence interval, CI, 1.2–14.1), but was not statistically inconsistent from the A-bomb survivor breast cancer mortality risk estimate of 3.16 (90% CI 1.6–5.0) for female survivors under the age 20 years at the time of the bombings [4, 18].

Evaluations of tuberculosis patients who received multiple fluoroscopies are especially informative because the dose to the chest area was relatively high, individual organ doses were carefully calculated based on review of the original medical records, phantom experiments, and computer simulations, follow-up was long, the study populations were large, and two different populations, in the US and Canada, were studied [19, 20, 21, 22, 23, 24]. The patients in these cohorts were adolescents or young adults and the average age at exposure was in the mid-twenties. The mean dose to the breast was 0.8–0.9 Gy, which is substantially higher than for the scoliosis patients or most patients receiving routine diagnostic examinations. The risk of developing breast cancer in these patients was significantly elevated, and there was a significant trend for the risk to decrease with increasing age at exposure [20, 22]. For women who received most of the fluoroscopies after menopause, the breast cancer risk was negligible. In contrast, although doses to the

lung were considerable there was no excess risk of lung cancer [23, 24]. The difference in the results suggests that highly fractionated exposure of the lung may be less carcinogenic than such exposure of the breast.

Assessment of cancer risks associated with more recent adult diagnostic examinations generally have been negative. Two case-control studies conducted in Sweden used computerized registries and medical records to evaluate the risk of thyroid cancer from exposure to diagnostic X-ray examinations [25, 26]. By using computerized registries to ascertain exposure to diagnostic X-rays, recall bias is essentially eliminated. Neither of these studies found an association, but most of the diagnostic X-ray exposure occurred during adulthood and adult radiation exposure has rarely been linked to thyroid cancer development even at substantially higher doses [3, 27]. In a case-control study conducted in Kaiser-Permanente in Oregon and California, record linkage was used to compare the frequency of past diagnostic X-ray examinations among 1091 adults with hematopoietic malignancies compared with 1390 controls [28]. Individual doses were not available, but the mean number of X-ray examinations was about 12 and about 12% of the diagnostic examinations were high-dose fluoroscopies or multifilms. The authors estimated that the dose from 5–14 X-ray examinations ranged from 0.1 to 50 mGy. No evidence of an association between diagnostic X-ray examinations and hematopoietic malignancies was observed. Relying on information about frequency of past radiographic examinations obtained from comprehensive and detailed patient interviews, Preston-Martin and colleagues have reported increased risks of leukemia and cancer of the parotid gland associated with adult exposure to dental and medical diagnostic X-rays performed many years ago, when exposure was presumed to be high [29, 30].

There have been several epidemiologic studies that have shown a link between diagnostic exposure in utero and the development of subsequent malignancies, particularly leukemia [31]. The Oxford Survey of Childhood Cancers, which was initiated by Dr. Alice Stewart and later expanded to include all British childhood cancers diagnosed between 1953 and 1981 was the first to show statistically significantly enhanced risks of childhood cancer and leukemia associated with diagnostic radiation to the fetus [9, 32]. Doll and Wakeford conducted a review of case-control and cohort studies and concluded that in utero radiation exposure of about 10 mGy increases the risk of childhood cancer by about 40% and that the excess risk is about 6% per Gray [33]. There has been controversy about whether this relationship is causal [34]. Nevertheless, although the magnitude of the risk is uncertain, in the aggregate the data indicate an enhanced risk at doses on the order of 10–20 mGy [2]. In utero diagnostic examinations performed more recently have not been linked to increased risk of childhood cancer [17, 35]. These investigations are reassuring and suggest that the lower doses currently used probably do not result in excess childhood cancers.

Irradiation of the head and neck was used, in the past, as treatment for several benign diseases and conditions. Investigations of the exposed populations have yielded important information on the carcinogenic effects of moderate-dose radiation, modification of these effects by age at exposure, and the effects of time since exposure. The large number of studies of therapeutic childhood irradiation to the head and neck, have all found increased risks of thyroid cancer. The studies that have individual organ doses demonstrate a linear dose-response relationship with no evidence of a threshold [36]. Results from a pooled analysis of five cohort studies (including the atomic bomb survivors) indicate that the elevated risk continues for more than 40 years, that there is a steep decline in risk with increasing age at exposure, and that differences in risk for males and females are not significant [27].

Radium plaques were used to treat infants with hemangiomas in Sweden. Two large cohorts of irradiated hemangioma patients have demonstrated that relatively low doses, given at a very young age, can increase the risk of cancers of the thyroid, other endocrine glands, breast, and central nervous system [37, 38, 39, 40]. These studies include individual estimated organ doses, and have long-term and complete follow-up based on the national computerized record-linkage system in Sweden. However, because the number of cases of a specific cancer was small, only limited analyses could be performed. Also in Sweden, a significantly raised excess relative risk of leukemia incidence and mortality was demonstrated in a cohort of about 20,000 adult patients treated with X-radiation for benign lesions in the locomotor system, mostly arthritis and spondylitis [41]. The mean bone marrow dose was estimated to be about 0.36 Sv. At a similar mean bone marrow dose, an excess risk was also observed among patients irradiated to the scalp for tinea capitis in Israel [42].

## Conclusions

The use of radiation in medicine is widespread and appears to be increasing. Much of the increase is due to diagnostic radiation. While the radiation dose from any one diagnostic examination is usually quite low, patients, including young children, often receive multiple diagnostic examinations. The rapid increase in the use of CT scans reflects their value as a diagnostic tool, as well as their ease of performance. Unfortunately, CT scans are relatively high-dose procedures. They contribute a large part of the collective radiation dose.

It is estimated that about 10% of CT scans are performed on children, which would mean that about 2.7 million pediatric CT scans are performed per year [7]. CT scans reportedly are being used to examine young scoliosis patients [43]. Given that multiple X-ray examinations to monitor scoliosis have been found to increase the risk of breast cancer mortality, Wagner [43] suggests that before ordering a CT examination, physicians should consider whether a simpler, lower-dose examination could be substituted or whether an older examination might still be useful enough to make a new examination unnecessary [18, 43].

The data summarized in this short review highlight several points: (1) the development of radiation-related cancer is a well-known, although rare, complication of radiation exposure, (2) previous uses of medical radiation that were thought harmless at the time are linked to increased risks of cancer, (3) radiation doses similar to the levels received from some pediatric CT scans are associated with enhanced cancer risks, and (4) children are at higher risk than adults of developing radiation-related cancers.

The decision to perform a pediatric CT examination should always be made considering the risks as well as the benefits. In most situations, the need for the examination will outweigh the minimal risk for an individual undergoing a single diagnostic examination. However, the large collective dose from the many millions of examinations is a public health concern. All efforts should be made to minimize the number of unnecessary examinations as well as to reduce exposure when a necessary examination is performed.

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