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# Childhood and Adult Cancer After Intrauterine Exposure to Ionizing Radiation

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**ABSTRACT** Since the reports in 1956 and 1958 that in utero radiation was associated with an increased risk of leukemia and solid cancers during childhood, this issue has been debated. Many epidemiological studies have been performed. Evidence for a causal association derives almost entirely from case-control studies, whereas practically all cohort studies find no association, most notably the series of atomic bomb survivors exposed in utero. Although it is likely that in utero radiation presents a leukemogenic risk to the fetus, the magnitude of the risk remains uncertain. The causal nature of the risk of cancers other than leukemia is less convincing, and the similar relative risks (RR = 1.5) for virtually all forms of childhood cancer suggests an underlying bias. Few studies have addressed the potential risk of adult cancer after intrauterine exposure. Radiotherapy given to newborns, however, has been linked to cancers of the thyroid and breast later in life. *Teratology 59:227–233, 1999.*


## PRENATAL EXPOSURE–CHILDHOOD CANCER

Stewart and colleagues first reported in 1956 an association between cancer in children less than 10 years of age and diagnostic x-ray exposures of their mother's abdomen during pregnancy (Stewart et al., '56). Children less than 15 years of age were included in subsequent reports which indicated that the frequency of each of the main childhood cancers was increased about 1.5-fold (Stewart et al., '58; Bithell and Stewart, '75). This same relative risk (RR = 1.5) has remained a puzzle for virtually all forms of childhood cancer after very low doses just before birth.

Most studies of medical exposure to diagnostic x-rays during pregnancy are consistent with a 40% increased risk of childhood leukemia and cancer (MacMahon and Hutchison, '64; UNSCEAR, 1994). The largest and most comprehensive study is the Oxford Survey of Childhood Cancer with more than 15,000 case-control pairs. These studies are important because of the possibility that the developing fetus may be more susceptible to the leukemogenic effects of radiation than the child, and because there are few investigations that provide direct evidence of risk at relatively low doses of 1–10 cGy. Extensive reviews have been published (NAS, '90; UNSCEAR, '72, '86, '94), with the most recent review by Doll and Wakeford ('97). The medical profession has acted on the assumption that the association is causal, and pelvimetry x-rays have been replaced in large part by ultrasound procedures. Certain diagnostic x-ray examinations, however, can result in relatively high radiation doses, such as computed tomography (CT) scans, which should not be used on pregnant women except on firm clinical grounds (NRPB, '98).

## EVIDENCE FOR CAUSALITY

The evidence for a causal association between low-dose irradiation of the human fetus and subsequent cancer in childhood is summarized in Table 1.

1. Meta-analysis of the many epidemiologic studies conducted on prenatal x-ray and childhood cancer are consistent with a relative risk of about 1.40, and there is little evidence for heterogeneity among studies; that is, while the risk estimates differ, statistically the variation might be due simply to chance (MacMahon and Hutchison, '64; UNSCEAR, '94; Doll and Wakeford, '97).
2. One report of a dose response shows an increase in risk of childhood cancer with increasing numbers of x-ray films (Bithell and Stewart, '75).
3. Circumstantial evidence indicates a reduction in exposure resulted in a reduction in the risk of childhood malignancies (Bithell and Stiller, '88; Doll and Wakeford, '97). Based on estimates of dose per x-ray film made by UNSCEAR ('72), a decrease in possible fetal dose during 1940–1970 was suggested. This decrease in assumed obstetric x-ray exposure apparently paralleled the decrease in the RR of childhood malignancies associated with obstetric radiology among corresponding birth cohorts of children born over these years. A slight increase in the relative risk of childhood cancer associated with obstetric x-rays after 1970 is inconsistent with this picture, but it might be attributable to chance.
4. Initial criticisms of the Oxford Survey of Childhood Cancer included the potential for recall bias, in that mothers of children with cancer might remember

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**TABLE 1. Arguments supporting a causal association between prenatal radiation and childhood leukemia and cancer**

1. *Consistency.* Practically all studies are statistically consistent, with a RR of 1.40 for leukemia (MacMahon and Hutchison, '64; UNSCEAR, '94; Doll and Wakeford, '97).
2. *Dose response.* Risk of childhood cancer was found to increase with number of X-ray films (Bithell and Stewart, '75).
3. *Coherence.* Apparent lower risk of childhood cancer in birth cohorts born in years when dose per film was lower (Bithell and Stiller, '88; Doll and Wakeford, '97).
4. Recall bias is unlikely to be a major factor (MacMahon, '62).
5. Confounding variables have been sought, but none has been found (Bithell and Stewart, '75; Monson and MacMahon, '84).
6. Selection bias related to reason for radiographic examination is not supported by case-control studies of twins (Mole, '74; Harvey et al., '85).
7. Risk estimates after intrauterine exposures are generally comparable to risks after childhood exposures for leukemia (UNSCEAR, '94; Muirhead and Kneale, '89).

their pregnancy experiences better than mothers of control children. These concerns were minimized with the publication of MacMahon's study (MacMahon, '62). His large series relied on medical records to determine x-ray examinations and not on mother's memory of events some years in the past. The initial MacMahon ('62) study confirmed Stewart's findings. An extended series published in 1984, however, no longer showed an excess of solid cancer related to prenatal x-ray (Monson and MacMahon, '84) (Table 2).

5. Confounding factors that might explain the associations have been sought, but no factors were found.
6. Case-control studies of twins are consistent with other studies of single births, minimizing the role of selection bias. Presumably, mothers of twins are x-rayed to determine fetal position before delivery, and not necessarily because of any illness or condition that might be associated with childhood cancer. The excess risk of childhood cancer was found to be as great among twins, for whom x-ray pelvimetry was far more frequent (55%), than among singletons (10%) (Mole, '74). This latter observation was confirmed in a small but comprehensive case-control study of twins born in Connecticut (Harvey et al., '85). Similar but nonsignificant findings were reported in a Swedish twin study (Rodvall et al., '90).
7. The improvements in risk estimates and exposure assessment have reduced the discrepancy between radiation risk estimates for in utero and childhood exposures, at least for leukemia. That is, the risk estimate associated with intrauterine radiation is not substantially greater than that seen following childhood irradiation (Muirhead and Kneale, '89; Mole, '90).

Based on the collected evidence to date, Doll and Wakeford ('97) conclude "that irradiation of the fetus in utero increases the risk of childhood cancer, that an increase in risk is produced by doses of the order of 10 mGy, and that in these circumstances the excess risk is approximately 6% per Gy."

## EVIDENCE FOR UNCERTAINTY

Despite the wealth of knowledge described above, uncertainties regarding causality, as well as the magnitude of the risk, remain (UNSCEAR, '94; Boice et al., '96) (Table 3).

1. It had been postulated that selection factors, related to the medical reasons why women receive prenatal x-ray studies, might be responsible for the increased leukemia and other cancer risk, and not the x-ray exposures themselves (Oppenheim et al., '75; Totter and MacPherson, '81). The absence of any childhood leukemia (and only one childhood cancer death, a liver cancer in a 6-year-old girl) in atomic bomb survivors exposed in utero supported the selection hypothesis (Jablon and Kato, '70). Stewart's data on obstetric x-rays, according to a calculation by Jablon and Kato ('70), led to an estimate of 5–14 extra deaths from childhood cancer among A-bomb survivors exposed in utero. Only one was observed, as anticipated from Japanese national rates. Subsequent studies of cancer incidence among atomic bomb survivors exposed in utero revealed a second cancer case (i.e., a 14-year-old girl with Wilms tumor) (Yoshimoto et al., '88). Among the 753 survivors exposed to >10 mGy, the mean uterine dose was about 310 mGy. The excess absolute risk associated with observing two cancer cases as opposed to less than 1 expected based on population rates is about 0.7% per Gy (95%CI = 0.1%, 2.6%) (Doll and Wakeford, '97), which remains considerably less than the estimate of 6% per Gy from the Oxford Survey. Radiation as a cause of Wilms tumor at age 14 years after in utero exposure is also questionable in that the Monson and MacMahon ('84) survey found no increase in risk among children who died after age 10, and the Oxford Survey (Bithell and Stewart, '75) relative risk for ages 12–14 at death was 1.08 (95%CI = 0.76, 1.54). Regardless, the numbers remain very small, only two cancers, and no cases of childhood leukemia occurred among A-bomb survivors exposed in utero, although the doses were larger than in the U.S. and U.K. studies of diagnostic x-ray pelvimetry examinations. Doubts about the causal nature of the prenatal x-ray findings and the possibility for recall bias were also raised when Graham et al. ('66) reported leukemia risks for exposure of either parent before conception that were similar to the leukemia risk for fetal exposures during pregnancy.
2. Miller ('69) argued that it was peculiar that diagnostic x-ray studies would increase all childhood malignancies by about the same percentage (40–50%) when there is such a remarkable degree of variabil-

**TABLE 2. New England studies of obstetric x-rays and childhood cancer**

| | Control sample | | Leukemia | | | Solid tumors | | |
|---|---|---|---|---|---|---|---|---|
| Study (yr) | No. of pregnancies | % X-ray | No. of children | % X-ray | RR | No. of children | % X-ray | RR |
| Initial (1962) | 7,230 | 10.6 | 292 | 16.1 | 1.48 | 246 | 15.4 | 1.45 |
| Extension (1984) | 7,046 | 8.2 | 305 | 12.8 | 1.58 | 261 | 8.4 | 1.06 |
| Both (1984) | 14,276 | 9.4 | 597 | 14.4 | 1.52* | 507 | 11.8 | 1.27** |

*95% confidence limits: (1.18–1.95).
**95% confidence limits: (0.95–1.70).
Modified from MacMahon ('62) and Monson and MacMahon ('84).

**TABLE 3. Grounds for uncertainty regarding the causal nature of the association between prenatal radiation and childhood cancer**

1. A-bomb in utero study finds no excess of childhood cancer deaths (Jablon and Kato, '70), whereas a lower limit of 5.2 extra cancer deaths was predicted from the risk model based on obstetric X-ray data (Stewart and Kneale, '70). The central estimate of excess cancer deaths predicted was about 10.*
2. All major cohort studies are negative (Court-Brown et al., '60; Diamond et al., '73; UNSCEAR, '94).
3. Biological implausibility; the equality of relative risks associated with obstetric X-rays for leukemia and solid tumors is perplexing given the variability in tissue radiosensitivity, dissimilar origins, and different incidence patterns (Miller, '69; NAS, '90). The extended MacMahon study did not find an increased risk for solid cancers (Monson and MacMahon, '84).
4. Risk estimates appear greater for in utero versus newborn exposures, for solid cancers (UNSCEAR, '94).
5. Twin cohorts have lower risk of childhood cancer than singletons despite more frequent X-rays (UNSCEAR, '94; Inskip et al., '91; Rodvall et al., '92).
6. Supporting animal evidence is weak (Upton et al., '60; UNSCEAR, '86; NAS '90).

*More recent incidence data revealed two childhood cancers diagnosed at 6 and 14 years of age, but no childhood leukemias and no significant excess overall (Yoshimoto et al., '88).

ity between tissues in their response to radiation at other ages (Pierce et al., '96) and because childhood cancers are known to have dissimilar origins. Similar RRs associated with obstetric x-ray were reported on the order of 1.5 (Bithell and Stewart, '75) for leukemia, lymphoma, CNS tumors, neuroblastoma, Wilms' tumor, and all other childhood cancers, with the exception of osteosarcoma, a cancer known to be increased after radiotherapy in childhood (Tucker et al., '87). The extended study by MacMahon (Table 3) failed to find an association for solid tumors (RR = 1.06) (Monson and MacMahon, '84).

3. Risk estimates based on obstetric x-ray studies still appear higher, on a relative scale, than those after childhood or adult exposure, especially for solid cancers. The excess relative risk per gray (ERR/Gy) derived from the various case-control studies are roughly 40 for leukemia and 40 for other cancers (UNSCEAR, '94). Biologic plausibility has been questioned because while children exposed under age 10 to the atomic bombs were at high risk of leukemia (ERR/Gy = 17), this was not the case for other cancers (ERR/Gy = 2) (Yoshimoto et al., '94). Although these excess relative risk coefficients refer to cancers that occur at all ages, and not just in childhood, the leukemia excess risk occurred early on and within 30 years of exposure, in contrast to the solid cancer excess risk, which occurred later and almost entirely 30 years after exposure (Pierce et al., '96). Doll and Wakeford ('97) suggest that "it is not to be expected, however, that the carcinogenic effects of irradiation of the fetus and child should be the same, because the cells that give rise to most of the typical childhood cancers, other than leukemia . . . persist and are capable of dividing for only a short time, if at all, after birth." They conclude, however, that existing data provide no justification for concluding that the Oxford Survey findings are anomalous. Nonetheless, the diversity in the origins and natural history of childhood cancers does not necessarily suggest that cell division just before birth can explain the 40–50% excess for virtually all forms of these neoplasms (Table 4). Development of lymphomas, for example, seems to have more to do with a change in immunity in mid-childhood than with cell division in late fetal development (Miller and Dalager, '74). At birth, the thymus is two-thirds its mature weight, which it attains at one year of age (Miller, '66). Involution begins just before puberty, and the frequency of Hodgkin's disease is near zero before age five. Neither Hodgkin's disease nor non-Hodgkin's lymphoma has been convincingly linked to ionizing radiation among atomic bomb survivors. Embryonal cancers account for about 25% of cancer before 15 years of age (Miller et al., '95). These tumors arise from embryonal tissue that persists into childhood. They have not been shown to be induced by radiation, and they involve different genes (three thus far have been identified in the genesis of Wilms' tumor). Neuroblastoma is believed to arise from microscopic foci of neuroblastoma cells, present in all fetuses—cells that normally regress spontaneously by three months of age (Brodeur and Castleberry, '93). The brain develops rapidly until two years of age, so increased susceptibility to radiogenic cancer is possible. There was no increase in neural cancer among atomic bomb survivors. Bone tumors increase in proportion to bone growth, reaching a peak soon

**TABLE 4. Incidence of childhood cancers under age 15**

| Childhood cancer | Relative % | Comments |
|---|---|---|
| Leukemia, all types | 31.5 | Induced by A-bomb, all ages except CLL |
| Lymphoma, all types | 13.1 | Not induced by A-bomb; very rare at 0–4 years in general population |
| CNS, all types | 17.9 | Cells seldom divide above 2 years (neural tissue) |
| Sympathetic nervous system | 8.3 | Early childhood only, due to nonregression of in situ lesions? |
| Retinoblastoma | 2.6 | Early childhood only |
| Wilms tumor | 6.0 | Rarely occurs after 7 years of age |
| Hepatoblastoma | 1.2 | Rarely occurs after 7 years of age |
| Osteosarcoma | 2.4 | Rises steadily with growth |
| Ewing's sarcoma | 2.2 | Rises steadily with growth. No cases after age 35 years, unlike osteosarcoma; not radiogenic |
| Soft tissue sarcomas | 6.8 | 3.7% are rhabdomyosarcoma, 60% of which are embryonal |
| Germ cell | 3.1 | Not radiogenic; adolescent peak |
| Carcinoma | 3.9 | Some types are radiogenic in adults |
| Other and unspecified | 0.5 | |

Data from Miller ('66), Brodeur and Castleberry ('93), and Miller et al. ('95, '96).

**TABLE 5. Studies of twin cohorts and risk of childhood cancer***

| Study (ref) | Year of birth | No. of twins | Cancer Obs | Cancer Exp** | RR |
|---|---|---|---|---|---|
| California (as presented by Inskip et al., '91) | 1940–1964 | 145,708 | 100 | 110.6 | 0.90 |
| Connecticut (Inskip et al., '91) | 1930–1969 | 30,925 | 31 | 46.4 | 0.67 |
| Norway (Windham et al., '85) | 1967–1979 | 14,504 | 14 | 15.6 | 0.96 |
| Sweden (Rodvall et al., '92) | 1952–1967 | 35,582 | 59 | 61.7 | 0.96 |
| Total: | | 226,719 | 204 | 234.3 | 0.87[1] |

*Actual exposure to pelvimetry x-rays is unknown but likely to be of the order of 30–55% of all pregnancies depending on country and calendar year.
**95%CI = 0.76–1.00. A deficit of childhood cancer (RR = 0.80) among twin births was also reported in the Oxford Survey of Childhood Cancer (121 cf. 151.6) (Hewitt et al., '66).

after the adolescent growth spurt (Miller et al., '96). Prenatal x-rays have not been linked to osteosarcoma, nor has exposure to the atomic bomb in Japan. Mesenchymal tissue, blood and lymph tissues, and epithelial tissues continue to divide throughout adulthood, and all give rise to childhood cancers, although epithelial cancer is rare. Experimental studies of animals irradiated before and after birth find a wide diversity of radiation-induced tumors consistent with the different developmental stages of the animals at exposure (UNSCEAR, '86), raising further doubt as to the causal nature of the peculiar finding that practically all childhood tumors would be increased by the same relative amount after intrauterine irradiation.

4. Animal experiments indicate a wide range of tumors induced by radiation before and after birth, and do not suggest an enhanced sensitivity to leukemia induction after irradiation during fetal stages (UNSCEAR, '86). Myelogenous leukemia has been reported to be increased in mice irradiated as adults, but not in mice irradiated as fetuses (Upton et al., '60).
5. Twin studies are puzzling. Case-control studies support an association between obstetric x-ray and childhood cancer, but cohort studies do not. Despite substantial population exposure to prenatal x-rays, cohort studies consistently find twins to be at low risk of childhood leukemia compared with single births (Inskip et al., '91; Rodvall et al., '92; UNSCEAR, '94) (Table 5).
6. It is somewhat peculiar that only case-control studies find significant increased leukemia and childhood cancer risks after prenatal exposure and all comprehensive cohort investigations are negative (Court Brown et al., '60; Diamond et al., '73; Oppenheim et al., '74; Jablon and Kato, '70), although once again the numbers are small (Table 6), and some groupings of cohort studies suggest positive overall results (Doll and Wakeford, '97).

Although there is no reason to believe that the fetus should be immune to the leukemogenic and carcinogenic effects of ionizing radiation, there also is little reason to believe that the risk should be greater for exposures just before birth than for exposures in early childhood. Further, the similarities in the relative risk estimates for leukemia and all solid tumors (except osteosarcoma) hint of an underlying bias in the case-control studies that has not been adequately explained. Thus, although it is established that prenatal x-irradiation is associated with an increased risk of childhood cancer, the magnitude of the hazard, and even the causal nature of the association, remain uncertain (MacMahon, '89; UNSCEAR, '94).

## PRENATAL EXPOSURE—ADULT CANCER

Only the study of atomic bomb survivors has evaluated adult-onset cancers after prenatal exposure. In 1988, the in utero cohort of 1,630 exposed survivors was 39 years old, and an increase in cancer mortality was

**TABLE 6. Major cohort studies of prenatal irradiation and childhood cancer***

| Study (ref) | Years of exposure | No. exposed | Dose (m Gy) | Cancer | |
|---|---|---|---|---|---|
| | | | | Obs | Exp |
| Atomic bomb survivors | | | | | |
| Mortality (Jablon and Kato, '70) | 1945 | 1,292 | ~138 (meant, fetal) | 1 | 0.8 |
| Incidence (Yoshimoto et al., '88) | 1945 | 1,263 | 184 (mean, uterine) | 2[a] | ~0.73 |
| London, Edinburgh[b,c] (Court-Brown et al., '60) | 1945–1956 | 39,166 | ~1–20 | 9 | 10.5 |
| Baltimore[b] (Diamond et al., '73) | 1943–1958 | 11,443 | ~1–20 | 13 | 12.8 |

*Major case-control studies of prenatal irradiation and childhood cancer have been tabulated in UNSCEAR ('94) and other sources.
[a]Liver cancer (6 years) and Wilms' tumor (14 years).
[b]Leukemia only.
[c]One of the authors subsequently questioned the reliability of this study (Doll and Wakeford, '97).

**TABLE 7. Cancer deaths among atomic bomb survivors exposed in utero**

| Case | Cancer | Dose (Sv) | Radiation-inducible?* | Age at death (yr) | Dose at >0.10 Sv? |
|---|---|---|---|---|---|
| 1 | Pancreas | 1.080 | No | 45 | Yes |
| 2 | Uterus | (2,194 m)** | No | 34 | No |
| 3 | Colon | (1,956 m)** | Yes | 21 | No |
| 4 | Myeloid leukemia | 0.023 | Yes | 18 | No |
| 5 | Lymphoid leukemia | 0.040 | Yes | 30 | No |
| 6 | Breast | 0.088 | Yes | 40 | No |
| 7 | Stomach | 0.238 | Yes | 25 | Yes |
| 8 | Stomach | 0.539 | Yes | 35 | Yes |
| 9 | Hepatocellular | 1.433 | Yes | 6 | Yes |
| 10 | Ovary | 2.237 | Yes | 35 | Yes |

*In A-bomb survivors (Preston et al., '94; Thompson et al., '94).
**Meters from the hypocenter, about the same in cases 4 and 5. Thus, dose likely <0.05 Sv.
Modified from Delongchamp et al. ('97) and Miller and Boice ('97).

suggested (Yoshimoto et al., '88). Five years later, the evidence for a radiation risk was diminished in that cancers in the lightly exposed occurred at a higher rate than in the heavily exposed (Yoshimoto et al., '94). A fuller account of the findings through age 46 was recently reported. Risks of prenatal exposure were compared with those of children exposed before age 6 (Delongchamp et al., '97). Interpretation remains equivocal, in large part because the sample size is small with only 10 cancer deaths occurring among the in utero exposed. While the radiation risks appear compatible between the prenatal exposed group and the children aged 0–5 years at exposure, there are several biological inconsistencies (Miller and Boice, '97). The risk of leukemia was inversely related to dose, two of the eight solid cancers are of types not known to be inducible by radiation, and two others followed very low dose, <0.10 Sv (Table 7). These observations thus far reveal only a small excess of adult tumors among atomic bomb survivors exposed in utero. Additional follow-up evaluation might be informative, however, because thyroid cancer and breast cancer have been linked to radiotherapy among newborns treated for enlarged thymus glands and followed into adulthood (Hempelmann et al., '75; Hildreth et al., '89).

## CONCLUSION

Learned debate continues as to the causal nature of low-level intrauterine radiation exposure and subsequent cancer risk. The association is not questioned, but the etiologic significance is. Different scientists interpreting the same data have different opinions as to the causal nature of the association and the possible level of risk (MacMahon, '85, '89; Mole, '74, '90; Boice and Inskip, '96; Boice et al., '96; Doll and Wakeford, '97).

Is there any possibility for sound epidemiologic study of this question, now that pelvimetry x-ray has apparently been largely replaced by ultrasound? Meaningful data from the Chernobyl accident appear unlikely to emerge; there is no evidence for an excess of leukemia among exposed children (Parkin et al., '96; Ivanov et al., '96), and ecologic surveys of in utero exposure are inconsistent (Petridou et al., '96; Michaelis et al., '97; see also Stevens et al., '90). In utero exposure to nuclear wastes released in the Techa River in Russia might

provide some new insights, although the numbers are likely to be small (Kossenko et al., '97). One population that has yet to be studied are the offspring of women who were treated for cancer with radiation while pregnant. The scatter radiation to the fetus after maternal radiotherapy for breast cancer, for example, could be meaningful, and large numbers of children might be assembled by combining registries from several countries over a period of several decades. If a 1.5-fold or greater excess of solid tumors in childhood is not observed after comparatively large exposures, there would be little reason why such an increase should occur after lower diagnostic exposures.

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