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.

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...
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).

| 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 (J ablon and Kato, '70). Stewart's data on obstetric x-rays, according to a calculation by J ablon 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-

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."
3. Risk estimates based on obstetric x-ray studies still and no significant excess overall (Yoshimoto et al., '88).

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).

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

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Control sample</th>
<th>Leukemia</th>
<th>Solid tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of pregnancies</td>
<td>No. of children</td>
<td>% X-ray</td>
</tr>
<tr>
<td>Initial (1962)</td>
<td>7,230</td>
<td>292</td>
<td>10.6</td>
</tr>
<tr>
<td>Extension (1984)</td>
<td>7,046</td>
<td>305</td>
<td>8.2</td>
</tr>
<tr>
<td>Both (1984)</td>
<td>14,276</td>
<td>597</td>
<td>9.4</td>
</tr>
</tbody>
</table>

**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 (J ablon 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).
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 extensive 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-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).

**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

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

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

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

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

<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>Year of birth</th>
<th>No. of twins</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>California (as presented by Inskip et al., '91)</td>
<td>1940–1964</td>
<td>145,708</td>
<td>110.6 0.90</td>
</tr>
<tr>
<td>Connecticut (Inskip et al., '91)</td>
<td>1930–1969</td>
<td>30,925</td>
<td>46.4   0.67</td>
</tr>
<tr>
<td>Norway (Windham et al., '85)</td>
<td>1967–1979</td>
<td>14,504</td>
<td>15.6    0.96</td>
</tr>
<tr>
<td>Sweden (Rodvall et al., '92)</td>
<td>1952–1967</td>
<td>35,582</td>
<td>61.7    0.96</td>
</tr>
</tbody>
</table>

Total: 226,719 204 234.3 0.87

*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).
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).

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

<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>Years of exposure</th>
<th>No. exposed</th>
<th>Dose (m Gy)</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomic bomb survivors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (A blon and Kato, '70)</td>
<td>1945</td>
<td>1,292</td>
<td>~138 (mean, fetal)</td>
<td>1 0.8</td>
</tr>
<tr>
<td>Incidence (Yoshimoto et al., '88)</td>
<td>1945</td>
<td>1,263</td>
<td>184 (mean, uterine)</td>
<td>2* ~0.73</td>
</tr>
<tr>
<td>London, Edinburgh&lt;sup&gt;h&lt;/sup&gt;c (Court-Brown et al., '60)</td>
<td>1945–1956</td>
<td>39,166</td>
<td>~1–20</td>
<td>9 10.5</td>
</tr>
<tr>
<td>Baltimore&lt;sup&gt;e&lt;/sup&gt; (Diamond et al., '73)</td>
<td>1943–1958</td>
<td>11,443</td>
<td>~1–20</td>
<td>13 12.8</td>
</tr>
</tbody>
</table>

*Major case-control studies of prenatal irradiation and childhood cancer have been tabulated in UNSCEAR ('94) and other sources.

<sup>h</sup>Leukemia only.

<sup>c</sup>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**

<table>
<thead>
<tr>
<th>Case</th>
<th>Cancer</th>
<th>Dose (Sv)</th>
<th>Radiation-inducible?</th>
<th>Age at death (yr)</th>
<th>Dose at &gt;0.10 Sv?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pancreas</td>
<td>1.080</td>
<td>No</td>
<td>45</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Uterus</td>
<td>(2.194 m)**</td>
<td>No</td>
<td>34</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Colon</td>
<td>(1.956 m)**</td>
<td>Yes</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Myeloid leukemia</td>
<td>0.023</td>
<td>Yes</td>
<td>30</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Lymphoid leukemia</td>
<td>0.040</td>
<td>Yes</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Breast</td>
<td>0.088</td>
<td>Yes</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Stomach</td>
<td>0.238</td>
<td>Yes</td>
<td>25</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Stomach</td>
<td>0.539</td>
<td>Yes</td>
<td>35</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Hepatocellular</td>
<td>1.433</td>
<td>Yes</td>
<td>6</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Ovary</td>
<td>2.237</td>
<td>Yes</td>
<td>35</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<sup>h</sup>In A-bomb survivors (Preston et al., '94; Thompson et al., '94).

<sup>**</sup>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).

**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.

LITERATURE CITED


CANCER AFTER INTRAUTERINE EXPOSURE


