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Review article

Risk of childhood cancer from fetal irradiation

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Abstract. The association between the low dose of ionizing radiation received by the fetus *in utero* from diagnostic radiography, particularly in the last trimester of pregnancy, and the subsequent risk of cancer in childhood provides direct evidence against the existence of a threshold dose below which no excess risk arises, and has led to changes in medical practice. Initially reported in 1956, a consistent association has been found in many case-control studies in different countries. The excess relative risk obtained from combining the results of these studies has high statistical significance and suggests that, in the past, a radiographic examination of the abdomen of a pregnant woman produced a proportional increase in risk of about 40%. A corresponding causal relationship is not universally accepted and this interpretation has been challenged on four grounds. On review, the evidence against bias and confounding as alternative explanations for the association is strong. Scrutiny of the objections to causality suggests that they are not, or may not be, valid. A causal explanation is supported by evidence indicating an appropriate dose–response relationship and by animal experiments. It is concluded that radiation doses of the order of 10 mGy received by the fetus *in utero* produce a consequent increase in the risk of childhood cancer. The excess absolute risk coefficient at this level of exposure is approximately 6% per gray, although the exact value of this risk coefficient remains uncertain.

Introduction

The evidence for an association between diagnostic exposure of the fetus to ionizing radiation *in utero* and the subsequent risk of cancer in childhood has resulted in major changes in medical practice, yet its interpretation is still controversial 40 years after it was first adduced. Radiologists have reacted on the assumption that a causal relationship has been established, without the loss of any material medical or economic benefit. It might, therefore, be thought that the correct interpretation of the evidence was unimportant. This is not the case. If the relationship that has been reported is in truth causal in character, it provides evidence that much smaller doses of radiation are carcinogenic than has been demonstrated in other situations and strengthens belief in the idea that there is no threshold dose below which no effect is produced.

The evidence

Evidence that diagnostic radiography might be carcinogenic for the fetus was initially reported by Stewart et al in 1956 [1]. It was obtained by means of a case-control study in which the mothers of the children who had died from cancer under 10 years of age in England and Wales from 1953 to 1955 and the mothers of control children were asked about the frequency with which they and their children had been examined radiographically, as well as many other aspects of the medical and social histories of both mother and child. The questionnaires were administered by doctors from the local departments of health. The control children were matched with those who developed cancer by date of birth and sex and were selected from live children on the birth register for the area in which the affected child had resided when he or she died. The results for irradiation *in utero* are summarized in Table 1.

The suggestion that radiographic examination of the mother's abdomen during pregnancy had approximately doubled the risk of the child developing cancer was received with scepticism. Many people thought that the reported difference was likely to be the result of recall bias, on the assumption that the mothers of the children who had died were more motivated than the mothers of living children to recall in detail the medical examinations they had had during their relevant pregnancies, which had mostly occurred several years before they were questioned. 2 years later, when similar results were reported in an extended series [2], the findings began to be taken more seriously; but it was not until 1962, when MacMahon [3] reported very similar findings in

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Table 1. Relative risk of cancer under 10 years of age associated with a radiographic examination of the pregnant mother, for deaths during 1953–1955 (after Stewart et al [1])

Maternal irradiation during relevant pregnancy	Leukaemia				Other malignant disease			
	No. of children		RR[a]	(95% confidence interval)	No. of children		RR[a]	(95% confidence interval)
	Affected	Control			Affected	Control		
Abdomen	42	24	1.92	(1.12, 3.28)	43	21	2.28	(1.31, 3.97)
Other	25	23	1.19	(0.65, 2.16)	33	32	1.15	(0.68, 1.94)
None	202	222	1.00	—	202	225	1.00	—

[a]RR, relative risk and 95% confidence interval (not cited by authors).

the northeastern United States based on contemporary hospital records of exposure that were not susceptible to bias, that the association began to be widely accepted. Subsequently, Hewitt et al [4] and Knox et al [5] showed that recall bias could have had relatively little effect on the results of the British study; maternal statements could be largely confirmed from antenatal records, irrespective of the child's fate, and similar associations were found whether maternal reports or clinical records were used in the analysis. In addition, the prevalence rate of abdominal X-rays during pregnancy recorded by Stewart et al was very similar to that recorded at corresponding periods in national surveys in 1957, 1958 and 1970 [6].

The study, now known as the Oxford Survey of Childhood Cancers (OSCC), was continued and expanded to cover all children dying from malignant disease in Great Britain under 16 years of age, and in 1981 included 15 276 case-control pairs [7]. The quantitative relationship has diminished with the passage of time [8], but so has the dose of radiation to which pregnant women have been exposed during an examination. The estimated relative risk is now almost identical with that obtained from the combined results of the many other studies that have been reported, as was shown in a meta-analysis carried out by Bithell in 1989 [9] and subsequently updated in 1993 [10]. The principal results of Bithell's review are summarized in Table 2. It is evident from Table 2, that nearly three-quarters of the total amount of information, worldwide, has been obtained by the OSCC, so that the quantitative conclusions about the risk of childhood cancer from irradiation *in utero* essentially depend on the validity of these data. Nevertheless, whether attention is restricted to the OSCC, to all other studies, or to the grand total, a highly significant relative risk of about 1.4 is seen.

Knox et al [5] suggested that the OSCC data showed the relative risk was highest for cancer deaths occurring between the ages of 4 and 7 years. This was supported by the finding (based upon small numbers) in the northeastern United States that no excess risk was detectable before the age of 2 years or after the age of 9 years [11]. However, no significant variation of relative risk with

Table 2. Relative risk of cancer in childhood associated with irradiation *in utero* found in different studies (after Bithell [10])

Study (period covered)	Amount of evidence[a]	Relative risk (unadjusted)	95% confidence interval
OSCC (1953–1981)	852.4	1.39	(1.30, 1.49)
NE United States (1947–1967)	114.7	1.47	(1.22, 1.77)
Inter-regional study, UK (1980–1982)	39.0	1.23	(0.90, 1.68)
Los Angeles (1950–1957)	23.9	1.34[b]	(0.90, 2.00)
Louisiana (1951–1955)	18.3	1.70	(1.08, 2.69)
Helsinki (1959–1968)	17.9	1.18	(0.74, 1.87)
California (1955–1956)	17.8	1.68[b]	(1.06, 2.67)
Tri-state (US) (1959–1962)	16.6	1.40[b]	(0.87, 2.27)
Swedish twins (1952–1983)	11.6	1.38	(0.78, 2.46)
Minnesota (1953–1957)	10.2	1.28[b]	(0.69, 2.37)
All other[c]	42.4	1.13	(0.84, 1.53)
All except OSCC	312.4	1.37	(1.22, 1.53)
All	1164.8	1.38	(1.31, 1.47)

[a]A measure of the statistical information contained in a study which is approximately the inverse of the variance of the logarithm of the relative risk [10].
[b]Leukaemia only.
[c]Includes cohort studies other than the Japanese atomic bomb survivor study.

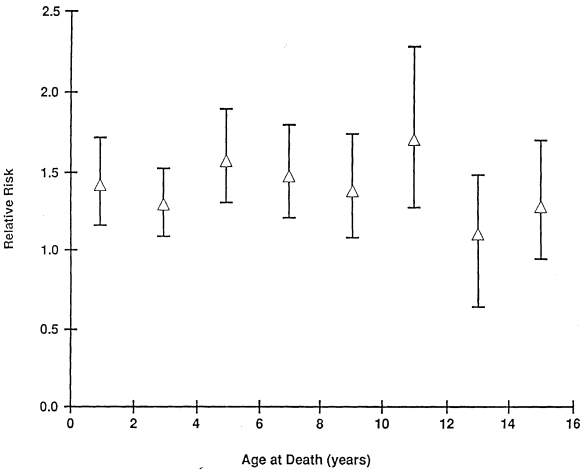

Figure 1. The variation in the relative risk of childhood cancer associated with radiation exposure *in utero* by successive 2 year groups of ages at death. Data are taken from the Oxford Survey of Childhood Cancers for deaths during 1953–1979 [6] with a 95% confidence interval calculated for each age group.

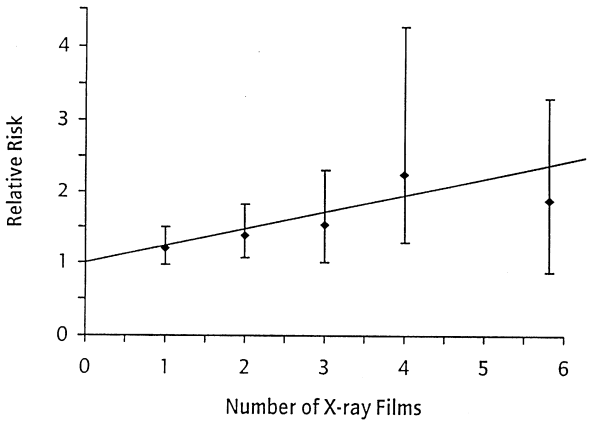

Figure 2. The variation of the relative risk of childhood cancer associated with radiation exposure *in utero* by the number of X-ray films used in a third trimester radiographic examination, based on hospital records. Data are taken from the Oxford Survey of Childhood Cancers for deaths during 1953–1972, the fitted linear trend having a slope of 0.194 excess relative risk per film (95% confidence interval 0.134–0.280) [9, 10].

attained age is seen in the OSCC data (shown in Figure 1) and the small decline beyond 12 years of age is not statistically significant [8].

Even a highly significant association is not necessarily causal and many thought that, if real, the relationship was due to confounding with some aspect of pregnancy that had given rise to the need for the radiographic examinations. No such factor has been identified [11, 12] and the idea that the relationship was due to confounding became unlikely when Mole [13] pointed out that quantitatively similar relationships were observed in both singleton and twin pregnancies within the OSCC, despite the fact that 55% of women bearing twins had had radiographic examinations of their abdomens during their pregnancy, while only 10% of those bearing singletons had done so. Mole's finding for twins has now been confirmed by others in the USA [14] and Sweden [15] and the idea that the association was due to confounding cannot be plausibly sustained.

The idea that the relationship is causal is, in contrast, supported by an appropriate increase in relative risk with the increase in the number of X-ray exposures—and hence, presumably, the dose of radiation—experienced by the fetus during examinations conducted in the third trimester, as shown in Figure 2 [9, 10], and the statistically significant decline in the relative risk with the year of birth that was demonstrated for the OSCC by Bithell [9, 10] and is illustrated in Figure 3. The decline closely parallels the exponential decline in fetal doses that, according to the United Nations Scientific Committee on the Effects of Atomic Radiation [16], occurred over the same period (Figure 4). Precisely what the fetal doses were between 1943 and 1965 is still uncertain; but, given

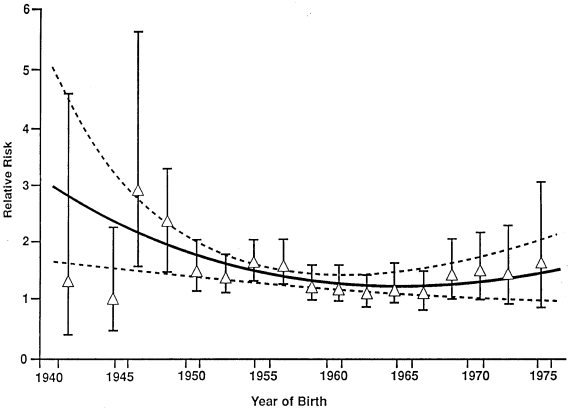

Figure 3. The variation of the relative risk of childhood cancer associated with radiation exposure *in utero* by successive birth cohorts within the Oxford Survey of Childhood Cancers for births during 1940–1976 and deaths during 1953–1979. Data are taken from Mole [6], with a 95% confidence interval calculated for each birth cohort. The curve and associated 95% confidence band are those derived by Bithell [10].

that the Committee's estimates were approximately correct, this compatibility between the temporal variation in risk and dose accords with a causal hypothesis. The apparent increase in relative risk in those born between 1968 and 1976 to 1.47 (95% confidence interval 1.20–1.80) may be an artefact, possibly due to data on cancer deaths having been available up to 1979 only. More recent data [7] for births during 1968–1976 give a relative risk of 1.28 (95% confidence interval 1.08–1.51) and it is unlikely that the upturn of the curve shown in Figure 3 will remain statistically significant.

Further support for a causal explanation of the relationship is provided by Monson and MacMahon's finding [11] that the raised risk of childhood mortality following diagnostic

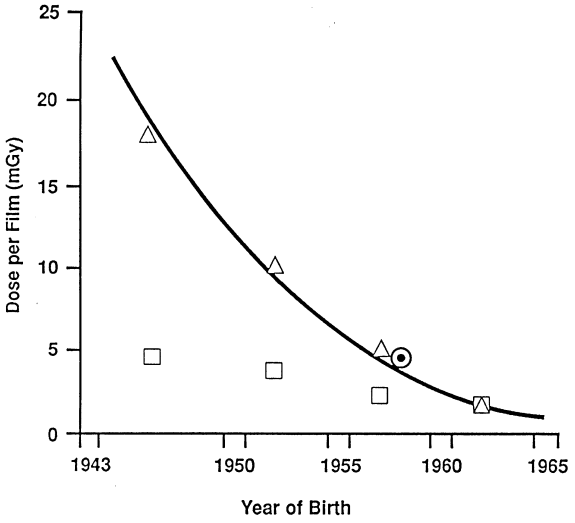

Figure 4. Estimates of average fetal doses per film exposed in obstetric X-ray examinations carried out during four successive periods (1943–1949, 1950–1954, 1955–1959 and 1960–1965). △, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) estimates [16]; □, Ardran estimates [17]; ⊙, Adrian Committee estimate for 1958 [6]. The curve is a fit to the UNSCEAR estimates done by Bithell and Stiller [18].

irradiation *in utero* was limited to cancer and did not extend to other causes of death beyond 3 months of age, and by the results of two animal experiments, although neither experiment addressed the issue of an effect from doses as low as 1 cGy. One found that rats exposed to 266 cGy *in utero* had an increased lifetime risk of cancer (particularly cancer of the brain and gonads) relative to a large series of historical unirradiated controls. This increased risk was greater than that for two groups of rats irradiated 3 months and, in particular, 9 months after birth [19, 20]. The other experiment found a small increase in cancer under 4 years of age in beagles exposed to a mean dose of 83 cGy *in utero*, when compared with an equal number of dogs receiving a mean dose of 16 cGy *in utero* and a control group, particularly if irradiated late in fetal life [21].

Grounds for controversy

Controversy, however, continues on four grounds. First, children exposed *in utero* to radiation from the atomic bomb explosions in Hiroshima and Nagasaki have not experienced any corresponding risk of cancer, nor has any increase been observed in the two other substantial studies that have investigated the relationship in predefined cohorts. Second, the case-control studies of childhood cancer and intrauterine exposure have shown an almost equal increase in relative risk for leukaemia and for all solid tumours, while the increased risk of cancer in childhood among the Japanese irradiated by the explosions when under 10 years of age has been limited to leukaemia. Third, the excess risk per gray estimated from the OSCC data, which mostly refer to exposure in the last month of pregnancy, is substantially higher than that derived for childhood cancer following the irradiation of young children, and the discrepancy is even greater for exposure in the first trimester. Fourth, twins have not been found to have a higher risk of cancer than singletons, despite the presumption of a higher than normal frequency of irradiation *in utero*. Taken together these observations appear to suggest that the estimates derived from the case-control studies are unreliable and may be qualitatively, as well as quantitatively, fallacious. They are considered in reverse order below.

Risk of childhood cancer in twins

That childhood cancer is not increased in twins [22, 23], and has actually been found to be decreased in some studies [13, 24], would be a sound reason for doubting a causal interpretation of the association, if the studies had been large enough to make chance an unlikely explanation and if twins were known to have the same risk as singletons in the absence of irradiation. In fact the studies were too small for the expected excess to be confidently detected. Even in Rodvall et al's study [23] of over 35000 twins with an overall frequency of X-ray exposure of 36%, the anticipated relative risk of childhood cancer would have been only 1.14, which was well within the 95% confidence limits of the observed risk relative to that in the general population (0.73, 1.24). Moreover, it is not known that twins should be expected to have the same risk as singletons in the absence of radiation exposure. With at least one of the mechanisms that have been proposed for the production of acute lymphoblastic leukaemia in children [25] they might be expected to have a lower risk.

Estimates of risk in utero *and after birth*

The objection that the excess risk per gray estimated from the case-control studies is unreasonably high depends on the estimates of the doses that are likely to have been received *in utero* by the children in the OSCC. Some early tentative estimates of fetal dose by Ardran, reported by Stewart and Kneale [17, 26] and shown in Figure 4, led to very high estimates of risk, notably an excess absolute risk of cancer mortality under 15 years of age of about 20% per Gy derived by Knox et al [5]. When, however, Muirhead and Kneale [8] corrected an error in this analysis and used the dose estimates given in the 1972 report

of the United Nations Scientific Committee on the Effects of Atomic Radiation [16], which have been referred to earlier and are also shown in Figure 4, they derived a risk coefficient for childhood cancer incidence of 6.4% per Gy (95% confidence interval 4.1–10.0). In Mole's view [6] neither set of dose estimates was reliable and the only fetal doses that could be used were those obtained from the investigations of the Adrian Committee in 1958. These led Mole to calculate an excess relative risk coefficient of 0.038 per mGy (95% confidence interval 0.007–0.079) from which an absolute risk coefficient of 6% per Gy (95% confidence interval 1.0–12.6) may be derived. Recently, Bithell [10] has used the Adrian Committee dose data with the time-dependent relative risk model shown in Figure 3 to obtain a relative risk coefficient of 0.051 per mGy (95% confidence interval 0.028–0.076), from which an absolute risk coefficient of 8% per Gy (95% confidence interval 4.4–12.0) may be derived. This last estimate makes use of all the available OSCC data rather than just the births during 1958–1961 employed by Mole in his analysis, but, like Mole's, does not rely on the assumptions needed to determine the temporal variation of fetal doses shown in Figure 4. Bithell's estimate is, however, likely to be too high because it is influenced by the upturn in the relative risk beyond 1967 (see Figure 3) which, as noted earlier, is probably artificial.

The National Radiological Protection Board has adopted an excess absolute risk coefficient for cancer incidence under 15 years of age following low dose irradiation *in utero* of 6% per Gy [27]. 40% of the risk was estimated to be due to leukaemia (2.5% per Gy) which is only slightly greater than the risk of 1.8% per Gy estimated by the Board for a 10 mGy dose received just after birth, based on the model derived from the Japanese bomb survivor data that was proposed by the US Committee on the Biological Effects of Ionizing Radiations [28]. On this basis the leukaemia data, at least, cannot be said to show any discrepancy at all.

More difficult questions arise from the distribution of the risk over different periods of gestation. The data based on medical records in the OSCC suggest [29] that the relative risk is essentially the same when exposure occurs in the second and third trimesters (1.29 and 1.30, respectively), but is appreciably higher when the exposure occurs in the first trimester (3.19) and is highest when it occurs in the first 8 weeks after conception (4.60). The greater relative risk in the first trimester is, moreover, statistically significant, even after allowing for the number of films taken, and Gilman et al [29] concluded that the embryo and first trimester fetus are particularly susceptible. They failed, however, to take into account the dose from non-obstetric radiographic examinations which, unlike exposures later in pregnancy, comprised most of the examinations performed in the first trimester and which showed a notable excess frequency in children who subsequently developed cancer only during the earliest period 1939–1949 [7] when doses would have been highest. In particular, the dose received from examinations using contrast media (such as urography and fluoroscopy), which were commonly associated with radiography only when exposure occurred in the first trimester, is likely to have so increased the fetal dose that the relative risks for the different periods cannot be compared [6]. More importantly, perhaps, Mole [6] showed that the excess relative risk associated with the 25 cases in children known to have been irradiated in the embryo stage (1.7% of the total with intrauterine exposure confirmed by medical records) was confined to those 22 cases in children whose mothers were examined for non-obstetric reasons, and that these exposures occurred almost entirely in the early years—before 1960 and extending back into the 1940s—when hospital records were less complete. No control children had first trimester X-ray exposures confirmed in the period 1939–1949 [7] and the recorded excess in the first 2 months of pregnancy may be an artefact resulting from the failure of some of the control mothers in the initial years of the study to recall their non-obstetric exposures early in pregnancy in adequate detail for their records to be identified. Organ specific cancers might not be produced before about the sixth week of pregnancy when organogenesis begins and the results of experimental irradiation of beagles *in utero* have suggested that the risk of cancer in young dogs is greater when exposure occurs late in pregnancy than when it occurs early (0 malignant tumours in 359 pooled controls, against (pooling the two exposure groups) 1 in 240 dogs irradiated 8 days post-coitus (a case in the low exposure group), 0 in 240 irradiated 28 days post-coitus, and 3 in 240 irradiated 55 days post-coitus (all three cases in the high exposure group)) [21]. However, the possibility cannot be excluded that pre-malignant changes may be induced in the primitive mesodermal and ectodermal stem cells before the sixth week, leading the National Radiological Protection Board to assume that some risk exists following irradiation during the first few weeks of pregnancy [27].

Another difficulty has been thought to be the concentration of the risk from irradiation for all the major types of childhood cancer in the period 13 weeks before birth, when the exposure occurred in over 90% of the children who developed cancer and had objective records of prenatal X-rays and exposure age [29]. This should not be surprising, however, as the primitive cells that give rise to all

the specific cancers apparently produced by fetal irradiation (shown in Table 3) continue to be active in the last few weeks of pregnancy.

Increased risk of solid tumours

The objection that there is a discrepancy between the findings of the case-control studies of the effects of fetal irradiation, which show a similar increase in relative risk for leukaemia and all other types of childhood cancer grouped together [11, 12], and the experience of the Japanese children who were irradiated after birth by the atomic bomb explosions, which does not [30, 31], depends on the assumption that the effects of irradiation at these two periods should be the same for all types of cancer produced. In the OSCC, the relative risk of leukaemia was almost exactly the same as that of solid tumours: 1.49 and 1.45, respectively (see Table 3) [12]. In contrast, no cancer other than leukaemia was seen under 15 years of age in the Japanese children who received a dose of at least 0.5 Gy during the atomic bombings while under 10 years of age, whereas there were 11 cases of leukaemia [30, 31]. The Japanese survivors irradiated as children did experience an increased relative risk of cancers other than leukaemia in adult life, but at a much lower level than that of childhood leukaemia [32]. It is not to be expected, however, that the carcinogenic effects of irradiation of the fetus and the child should be the same, because the cells that give rise to most of the typical childhood cancers, other than leukaemia (that is, the cells that give rise to Wilm's tumours, neuroblastoma, most of the central nervous system cancers, and nearly all the rarer types of cancer classed in the OSCC as "other") persist and are capable of dividing for only a short time, if at all, after birth. Moreover, animal experiments show that the tumour types produced in animals irradiated before or after birth differ [19,20,33]. The United Nations Scientific Committee on the Effects of Atomic Radiation [33] referred to this as "probably the most consistent finding in the [experimental] work analysed" and "a finding that is not unexpected in view of the different developmental stages of the animals at irradiation".

Very few data exist to test the possibility that the cells that give rise to the characteristic solid cancers of childhood may continue to be susceptible to radiation carcinogenesis for a few weeks after birth. The most important are the observations on nearly 3000 infants who were given X-ray therapy for an enlarged thymus in Rochester, New York, between 1926 and 1957, about a third of whom were treated when less than a week old [34, 35]. High doses were localized to the upper half of the body. Seven cases of leukaemia, six of thyroid cancer, and five of other solid tumours occurred under 15 years of age against, respectively, 1.1, 0.0 and 4.0 expected from the experience of unirradiated siblings (RE Shore, personal communication, 1996).

The almost 15 000 children given radiotherapy for skin haemangiomas in Stockholm from 1920 to 1959 were first treated at a mean age of 6 months [36, 37], which was too late to be relevant. No material excess of childhood leukaemia was, in any case, observed in this population: 11 deaths against 9.8 expected (this estimate may be slightly too high, as it is based on the assumption that the incidence of childhood leukaemia in Sweden was

Table 3. Relative risk of different types of childhood cancer following irradiation *in utero*, OSCC data for deaths during 1953–1967 (after Bithell and Stewart [12])

Type of cancer	No. of deaths		Relative risk	95% confidence interval
	Total	Associated with irradiation *in utero*		
Lymphatic leukaemia	2007	290	1.54	(1.34, 1.78)
Myeloid leukaemia	866	120	1.47	(1.20, 1.81)
Other and undefined leukaemia	1179	159	1.43	(1.19, 1.71)
Lymphoma	719	92	1.35	(1.07, 1.69)
Wilm's tumour	590	87	1.59	(1.25, 2.01)
Central nervous system	1332	179	1.42	(1.20, 1.69)
Neuroblastoma	720	99	1.46	(1.17, 1.83)
Bone	244	26	1.11	(0.74, 1.66)
Other	856	129	1.63	(1.33, 1.98)
All leukaemias	4052	569	1.49	(1.33, 1.67)
All solid tumours	4461	612	1.45	(1.30, 1.62)
All cancers	8513	1181	1.47	(1.34, 1.62)

Monson and MacMahon [11], in the study carried out in the northeastern United States, found a relative risk of leukaemia of 1.52 (95% confidence interval 1.18–1.95) and of solid tumours of 1.27 (95% confidence interval 0.95–1.70).

constant before 1958 when reliable incidence data were first obtained, as it was in Denmark from 1943 [38], and that during this earlier period childhood leukaemia was invariably fatal. It is, however, unlikely to be much in excess as only 13% of the person years at risk were associated with infants treated before 1940 [37]). Too few infants received substantial doses of radiation from the atomic bomb explosions in Japan to provide any relevant data, only about 70 being estimated to have received doses of 0.5 Gy or more at any time within a year of birth [31]. These few data provide no justification for concluding that the OSCC findings are anomalous.

Risk observed in cohort studies

Perhaps the most serious reason for doubt is the lack of evidence of a correspondingly increased risk in the three most substantial cohort studies that have been reported, most notably in the cohort of 1263 Japanese children who could be followed completely from birth to their fifteenth birthday and were *in utero* at the time of the atomic bomb explosions [39, 40]. Only two of the 753 children who received a dose of at least 0.01 Gy developed cancer (a nephroblastoma and a hepatoma) under 15 years of age, and their doses were 0.56 and 1.39 Gy. The average dose received in the exposed group of children was 0.309 Gy, and the number of expected cancer cases can be calculated from Japanese national data to be at most 0.43 [40]. The excess absolute risk is therefore estimated to have been at least 0.7% per Gy, with 95% confidence limits of −0.1% and 2.6% per Gy. As no case of leukaemia was observed there was obviously no excess. Making the conservative assumption that half of the expected number of childhood cancers were leukaemias, the upper 95% confidence limit for the excess risk of leukaemia can be calculated and was 1.2% per Gy. Both these upper confidence limits are appreciably less than the excess risks estimated by the National Radiological Protection Board from the Oxford Survey (6.0% and 2.5% per Gy). The doses used in the Japanese study were uterine rather than fetal, and may be revised slightly upwards due to a suspected underestimate of the neutron dose in Hiroshima [41], but such changes should have little effect on the risk coefficients. A more important consideration is the probability of cell sterilization by the highest doses received *in utero*. Mole [6] argued that if this were taken into account the risk coefficients for moderate doses would have to be at least doubled. Twice nought (for leukaemia) is still nought; but on these grounds the upper 95% confidence limits would certainly be raised—unless, as can be responsibly argued, particularly for leukaemia, the risk coefficients derived for moderate doses need to be halved when extrapolating to low doses.

Another consideration is that mortality among the Japanese survivors has been systematically monitored only from 1950 and it is possible that some cases of childhood cancer which occurred before this date were unrecorded. This might be particularly so for childhood leukaemia, since infections are common in the early stages of the disease and in the difficult conditions which pertained during the years immediately following the bombings some leukaemia-related deaths from infectious illness may not have been recognized as leukaemic. An associated suggestion by Stewart and Kneale [42] is that the persistent effects of acute bone marrow damage caused by the high doses received *in utero* produced an elevated level of deaths from infectious diseases early in childhood. However, Yoshimoto et al [39] have noted that there is no evidence that deaths from infectious diseases were increased in Japanese infants exposed *in utero*, and a similar suggestion concerning those exposed postnatally [42] is thought unlikely to lead to large biases [43, 44].

The lack of commensurate excess risks in the Japanese data may, therefore, either be dismissed as an unusual effect of chance (with perhaps one or two cases of childhood leukaemia failing to be diagnosed during the first 5 years after the bombings) or taken as evidence against the inferences drawn from the case-control studies. In either case, the uncertainties associated with the risk coefficients derived both from the OSCC and the Japanese children must be borne in mind and conclusions tempered accordingly.

Continued observation of the Japanese cohort (a slightly different cohort including 1413 persons assigned the latest maternal dose estimates, who were alive in 1950) to the end of 1989 [31, 45] has resulted in the addition of 22 cancers arising at 15–44 years of age, 13 of which were in those exposed to 0.01 Gy or more *in utero*, including two cases of leukaemia, one in an 18-year-old woman and one in a 29-year-old man. A slight but statistically non-significant excess of cancer overall was found in those exposed compared with those unexposed (51 cases per 100 000 person-years compared with 42 per 100 000 person-years, for the period 1950–1989). This, however, might not have any direct bearing on the question at issue, as the types of cancer concerned are for the most part so different. Nonetheless, if an excess risk in adulthood were eventually to be demonstrated, this would raise the question of the magnitude of the lifetime risk of cancer associated with the low doses received during obstetric radiography, which has not yet been addressed directly in epidemiological studies. In this respect, it is of interest that among those receiving radiation therapy in infancy for

thymic enlargement or skin haemangioma, there is some evidence for an excess risk of cancer in adult life, notably breast cancer [34, 36].

The other two substantial cohort studies are of children of women in Baltimore, London and Edinburgh who were examined radiographically during pregnancy. In Baltimore [46], 13 cancers were observed in the 19 889 exposed children against 23 in the 35 753 unexposed controls, giving a relative risk of 1.02 (95% confidence interval 0.52–2.01). In London and Edinburgh [47], nine leukaemias were observed in the 39 166 exposed children against 10.5 expected from leukaemia rates for Britain, a relative risk of 0.86 (95% confidence interval 0.41–1.55). However, one of the authors (RD) became dissatisfied with the adequacy of the identification of the irradiated women, when he tried to extend the study some years later, and believes that the results are unreliable.

Some smaller cohort studies of children irradiated *in utero* have also been published. The results from five cohorts of more than 200 exposed children, for which the number of cancers expected could be calculated reliably [48–52], together with those of the Baltimore cohort [46], are presented in Table 4. Overall, 12 cancer deaths were found in the exposed children in the smaller cohorts compared with 6.7 expected from the unexposed groups. This expected number is very similar to that which can be calculated using British cancer mortality rates for the appropriate periods [54]. Addition of three very small cohorts of less than 200 exposed children [55–57], for which expected numbers of cancers could be calculated from British mortality rates, and in which no cancer deaths were observed, would add 0.3 to this expected number of deaths. A further cohort study carried out by Train [58] in Dumfries, which found three cancer deaths among 2869 exposed children, has not been included because an accurate estimate of the number of person-years at risk cannot be obtained from the published information. If the findings of the five small cohort studies are added to those of Diamond et al [46], as in Table 4, an overall relative risk of 1.2 is obtained with 95% confidence limits of 0.7 and 2.0 [59]. This relative risk of 1.2, while not significantly different from 1.0, is suggestive of a raised risk associated with irradiation *in utero*, and is statistically compatible with an excess relative risk of about 40% obtained from the case-control studies. If the results of Court Brown et al's cohort [47] are also included, despite the doubts about their reliability and an overlap with the cohort of Lewis [49], the relative risk is reduced to 1.1 (95% confidence interval 0.7–1.7).

Conclusion

We conclude that there is strong evidence that low dose irradiation of the fetus *in utero*, particularly in the last trimester, causes an increased risk of cancer in childhood. The proportional increase in risk associated with an obstetric X-ray examination has been small, characteristically about 40% in the past, but the finding is based on large numbers and is consistent in many different studies in several countries. It cannot plausibly be explained by recall bias in case-control studies, nor by confounding with obstetric conditions that led to radiographic examination. The idea that the raised risk directly reflects cause and effect is supported by the increase in relative risk with the increase in the number of X-ray films used during the examination, by the reduction in relative risk over time that has been associated with a reduction in fetal dose, and by the results of animal experiments that show the fetus to be susceptible to the induction of cancer by radiation.

Of the four reasons that have been cited for rejecting causality, one is probably invalid (the idea that the excess risk of childhood leukaemia

Table 4. Cancer mortality rates in cohorts of children irradiated *in utero*[a]

Study (years of birth)	Number of cancer deaths in exposed and unexposed groups of children		Excess number in exposed group	
	Exposed	Unexposed	(O-E)	Var(O-E)
Baltimore (1947–1959) [46]	13/19889	23/35753	0.1	8.3
Paris (1947–1952) [48]	2/491	0/468	1.0	0.5
London (1943–1958) [49][b]	1/11443	7/33752	−1.0	1.5
Lyon (1948–1956) [50]	1/5353	1/5353	0.0	0.5
Chicago (1947–1949) [51][c]	4/982	6/1759	0.4	2.3
Nashville (1945–1949) [52]	4/634	0/655	2.0	1.0
All			2.5	14.1

[a]All these cohorts involved exposure due to radiographic examination with the exception of the Nashville cohort [52] for which the exposure was from the administration of radioactive iron.
[b]Leukaemia only. Overlaps with the study of Court Brown et al [47].
[c]Oppenheim et al [53] studied slightly different groups and reported one leukaemia death in 857 exposed children against two leukaemia deaths in 1129 unexposed children.

associated with irradiation *in utero* is much greater than with irradiation in early childhood) and two may be invalid (that twins do not have a raised incidence of childhood cancer despite a tendency to have been irradiated *in utero* more often than singletons, and that the excess relative risk applies almost equally to leukaemia and nearly all other childhood cancers, while irradiation in childhood principally affects only leukaemia). Only one reason would appear to be serious: namely, the lack of any comparable excess in cohorts of children known to have been irradiated *in utero*, most notably in those exposed to radiation from the explosion of the atomic bombs in Japan. The absence of any appreciable excess among the Japanese children may be attributed partly to an unusual play of chance and possibly to incomplete follow-up in the first few years after the bombings. However, apart from the Japanese children, when those cohorts for which relative risks can be calculated reliably are combined, an increased risk is obtained which is consistent with the combined results of the case-control studies.

On the balance of evidence, we 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.

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