Parental Pre-Conception Diagnostic X-Ray Exposure and Risk of Childhood Leukemia

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Abstract

In utero X-ray exposure has been well established as a risk factor for childhood leukemia. Whether parental pre-conception exposure to radiation is associated with the risk of childhood leukemia, however, has been much debated. This report summaries the major findings from a serial of Chinese and U.S. studies addressing this issue.

In 1987, we reported from a case-control study conducted in Shanghai, China, that paternal pre-conceptional X-ray exposure may be related to the risk of childhood leukemia. Based on interviews of mothers of 309 childhood leukemia cases and 618 controls, we found that paternal exposure to more than 10 X-rays before conception was associated to a 3.9-fold excess risk of leukemia in offspring. We followed-up this finding in a subsequent study conducted in the same population involving direct interviews of fathers of 166 pairs of leukemia cases and controls. This study suggested the adverse effect of paternal X-ray exposure was mainly confined to children diagnosed with leukemia under the age of 2 years. Such an association was again demonstrated in a U.S. case-control study of leukemia among children diagnosed at 18 months or younger. In collaboration with the U.S. Children's Cancer Group (CCG), we recruited 302 infant leukemia cases and 558 matched controls. Paternal pre-conception X-ray exposures, particularly those received closer to the conception and in anatomic sites closer to the gonads, were related to a significantly elevated risk of acute lymphocytic leukemia (ALL). A positive dose response association was observed between ALL and number of paternal X-rays of the lower GI and lower abdomen (trend test, $P<0.01$), upper GI ($P=0.04$) and chest ($P=0.08$). The risk of acute myeloid leukemia (AML) was unrelated to paternal X-ray exposure, except for a marginally significant association (trend test $P=0.07$) for upper GI X-rays. A recently completed large-scale CCG study of ALL (1842 ALL and 1986 controls, aged 0 to 15 years) again found a suggestive association between paternal pre-conceptional X-ray exposure and ALL risk among young children, but not in older children. Another recent CCG study of AML (525 cases and 619 controls, aged 0 to 18 years), on the other hand, found no positive association in any age group. No association between maternal pre-conception X-ray exposure and childhood leukemia was found in any of the five studies described above.

These studies suggest that paternal exposure to diagnostic X-ray before conception may be associated with an increased risk of leukemia, mainly ALL, among very young children. The nature of this association, however, remains unknown. Future research on the relation between low-dose radiation and childhood leukemia should focus on obtaining actual dose of exposure, measure of biologic exposure markers and host susceptibility.

Introduction

Exposure to high dose radiation, such as atomic bomb and radiotherapy, is well known to be leukemogenic [1,2]. The interest in studying low-dose radiation exposure has been highlighted recently by the finding from a case-control study conducted in Seascale, United Kingdom, in which

the offspring of male workers exposed to 100 Millie Sieverts (mSv) or higher of ionizing radiation prior to conception demonstrated a six-fold elevation in risk of leukemia [3]. Considerable debate has been focused on whether such an association is just a chance finding. The absence of an increased risk of leukemia in offspring of Japanese atomic bomb survivors [4], and offspring of nuclear workers in other settings [5,6], the lack of statistical compatibility of the distribution of paternal preconceptional radiation exposure dose, and the clustering of childhood leukemia occurring in Seascale [7] have added to this debate. The association between paternal diagnostic X-ray exposure and the risk of childhood cancer has received little attention. [8,9] Over the last 10 years, we have conducted five case-control studies of childhood leukemia in China and the U.S., in which diagnostic X-ray was one of the major study hypotheses. This report summaries the findings of these studies regarding parental preconception X-ray exposure and the risk of childhood leukemia, with a focus on the association of leukemia risk among children during the first two years of life.

Subjects and Methods

The designs of the five studies are briefly summarized in Table 1. The cases of the two Chinese studies were identified from a population-based Shanghai tumor registry, and controls were randomly selected from the general population in Shanghai and individually matched to cases on sex and calendar year of birth. The first Shanghai study included 309 cases diagnosed with leukemia before the age of 15 years during January 1, 1974 and May 31, 1986 and 618 individually matchedcontrols [9]. The exposure information was obtained from in-person interviews with mothers of study participants. The second Shanghai study was designed to follow-up on the findings from the first study, particularly the associations with paternal exposures, and thus in the vast majority of cases (92%) and controls (94%), both parents were interviewed in person about their own exposures [10]. Exposure information was obtained from 642 pairs of childhood cancer cases and individually matched controls, including 166 acute leukemia cases who were under the age of 15 years with a newly diagnosed leukemia during June 1, 1986 and December 31, 1991 and their matched controls. The three U.S. studies (designated protocols CCG-E09, CCG-E14 and CCG-E15) were conducted by the Children's Cancer Group (CCG), a cooperative clinical trials group with approximately 100 members and affiliated institutions in the United States, Canada and Australia [11,12]. Cases were identified from the CCG registration files. Controls were randomly selected using a random digit dialing procedure and individually matched to cases on the year of birth (within a year of age of the case for the CCG-E09 study, within 25% at the age of diagnosis of the case for the CCG-E14 and CCG-E15 study), on geography (telephone area code and exchange), and ethnicity (black, non-black, for E14 and E15). The CCG-E09 study, including 302 leukemia cases and 558 controls, was designed to examine the association of parental exposures with leukemia in children diagnosed under the age of 18 months. The CCG-E14 study, including 558 cases and 619 matched controls, was conducted to examine parental and childhood exposures associated with acute myeloid leukemia (AML) in children under the age of 18 years. The CCG-E15 study included 1842 acute lymphocytic leukemia (ALL) cases and 1986 matched controls and was designed to examine the role of parental and childhood exposures in children with ALL diagnosed under the age of 15. Exposure information of all three U.S. studies were collected through a telephone

interview with mothers and fathers (if available) of the study subjects. The father's questionnaires were completed for 280 cases and 511 controls for CCG-E09 study, 490 cases and 566 controls for CCG-E14 study, and 1801 cases and 1813 controls for CCG-E15 study. Of these completed paternal questionnaires, direct interviews with fathers were obtained for 89% of cases and 71% of controls for CCG-E09 study, 82.4% cases and 64.0% of controls for CCG-E14 study and 83.4% of cases and 67.7% of controls for CCG-E15 study. The remaining interviews were completed by mothers as surrogates for the fathers.

Odds ratios (ORs), as approximations of relative risk, were used to measure the association between X-ray exposures and the risk of childhood leukemia. Conditional logistic regression was employed in data analyses to obtain ORs and 95% confidence intervals (CIs), adjusting for potential confounders. [13]

Results

Shanghai Childhood Leukemia Studies [9,10]

In the first Shanghai leukemia study, the number of paternal pre-conception diagnostic X-ray was significantly higher among leukemia cases than controls. The risk of both ALL and AML was positively correlated with the number of paternal pre-conception X-ray exposure but was unrelated to maternal pre-conception diagnostic X-ray exposure (Table 2). This study, however, was limited because father's exposure information was provided by the mother and thus might result in misclassification.

A new study was initiated to follow-up on the findings from the first study. In the second study, both mother and father of the study subjects were independently interviewed. Overall, paternal or maternal X-ray exposure was not related to an increased risk of childhood leukemia (Table 3). However, when analyses were restricted to leukemia cases diagnosed under the age of 2 years, a non-statistically significant association between paternal X-ray exposure and childhood leukemia was observed (OR=1.94, 95%CI=0.3-12.6). But neither the point estimates nor the trend test was statistically significant, perhaps due to a small sample size. Moreover, there were also too few study subjects under age of 2 to allow for a stratified analysis by leukemia types. Nevertheless, this study suggested that age at diagnosis of leukemia might be an important modifying factor in the association of paternal X-ray exposure with childhood leukemia.

CCG-E09 Infant Leukemia Study [11]

The CCG-E09 study was designed to study the pre-conception and pre-natal exposure as risk factors of childhood leukemia. Of the 302 cases included in this study, 203 were diagnosed with ALL and 88 with AML. The remaining 11 patients had other types of leukemia. The large series of young leukemia cases included in this study provided us an unique opportunity to evaluate in depth the effect of parental X-ray exposure in the development of childhood leukemia.

It was shown in this study that the risk of infant leukemia was significantly increased among those children whose fathers reported ever having pre-conception X-ray exposure of the chest (OR=1.44), limb (OR=1.46), upper GI tract (OR=1.87) or lower GI tract (OR=2.24). The elevated risk tended to be higher for exposures that occurred in the month or the year before conception than for those occurring earlier, although most point estimates were not statistically significant due to the small number of exposed subjects (Table 4). X-ray exposures of the head and neck (mainly dental X-rays) were not related to risk.

The relation of paternal pre-conception X-ray exposure to leukemia risk was further

evaluated according to the number of X-ray exposures at specific sites and by major histopathologic types of leukemia (Table 5). The risk of ALL increased with the number of X-rays the father received to the upper GI (trend test P=0.04), lower GI and lower abdomen (P<0.01), and chest (P=0.08). Risk of ALL was also substantially elevated (OR=2.48, 95%CI=0.85-7.29), although not statistically significantly, among children whose fathers had five or more X-rays of the back and spine. In contrast, risk of ALL was not associated with paternal X-ray exposure of the head and neck or limbs. The risk of AML was less consistently associated with paternal X-ray exposure, with an indication of a positive association for X-rays of the upper GI (trend test P=0.07) but not for other anatomic locations (Table 5).

Analyses restricted to subjects with direct father interview data revealed that the ORs of ALL related to lower GI and abdomen X-ray were increasingly higher (OR=3.9, 95%CI=1.77-8.58 and OR=5.64, 95%CI= 1.52-20.95 for one and two or more exposures, respectively). The ORs of ALL related to upper GI X-ray (OR=1.33, 95%CI=0.65-2.7, and OR=2.15, 95%CI= 0.67-6.96 for one and two or more exposures) and chest X-ray (OR=1.38, 95%CI=0.54-3.57 for 10 or more exposure), however, were attenuated. No significant association between paternal pre-conception X-ray exposure and risk of AML was observed (data not shown).

More fathers of cases than controls reported exposure to radioactive materials in an occupational setting (OR=1.7, 95%CI=1.07-2.71) or had worn a radiation badge at work (OR=2.25, 95%CI=1.16-4.37). The association between paternal diagnostic X-ray and the risk of infant leukemia remained after adjustment for occupational radiation exposure. The adjusted ORs for ALL were 4.02 (95% CI=1.55-10.44), 2.72 (95%CI=0.98-7.55) and 2.18 (95%CI= 0.98-4.48) for the highest exposure categories of lower GI/abdomen, upper GI, and chest X-ray, respectively.

Maternal diagnostic X-ray examination a month or more before conception of the index child was not related to the risk of infant leukemia, irrespective of timing or exposure site (Table 6). Maternal X-ray exposure in the month prior to conception of the index child, however, was related to an increased risk (OR=4.5, 95%CI=1.05-19.28). Although based on the small numbers of exposed subjects, elevated risks with X-ray exposure within a month prior to pregnancy were observed for most exposure sites (Table 6).

Leukemia risk was unrelated to the number of maternal pre-conception X-rays, even when examined within histopathologic types and exposure sites (Table 7). There was no appreciable confounding effect of paternal exposure on maternal exposure or vice versa, and no indication of interaction between paternal and maternal X-ray exposure.

Mothers of cases were more likely, although not statistically significantly, than control mothers to report ever having been exposed occupationally to radioactive materials (OR=1.82, 95%CI=0.93-3.56). No difference, however, was observed for cases and controls with respect to mothers' reported use of radiation badges on the job (OR=1.05, 95%CI=0.34-3.18).

CCG-E14 Childhood AML Study and CCG-E15 Childhood ALL Study

In these two recent completed case-control studies, we again found that paternal pre-conception X-ray exposure was related to a moderately elevated risk of ALL, with risk being slightly higher among young children, although the later was not statistically significant. No significant association was observed between paternal X-ray and risk of AML. Similarly, maternal pre-conception X-ray exposure was not associated

with the risk of childhood leukemia, regardless the leukemia type and age at diagnosis (Table 8).

Discussion

Although the studies evaluating the association of paternal pre-conception occupational exposure to radiation and risk of childhood leukemia in offspring were equivocal, a positive association of paternal pre-conception diagnostic X-ray exposure and the risk of childhood leukemia, particularly among young children, has been repeatedly demonstrated in several studies [8-11]. Early in the 1960's, Graham et al. reported that parents of childhood cancer cases are more like to be exposed to diagnostic X-ray prior to conception [8]. The five studies under review suggested that paternal exposure to radiation prior to conception is associated with an increased risk of leukemia among young children. The CCG studies, particularly the CCG-E09 also revealed that the elevated risks were mainly attributable to the excess risk of ALL and the positive association was more evident for exposures of high frequency, occurring at sites closer to the gonads or time periods closer to conception.

It is conceivable that if pre-conception radiation exposure is indeed related to the risk of leukemia in offspring, a stronger association would be observed among the youngest children (i.e., those diagnosed in the first two years of life) due to the prezygotic nature and minimum of confounding from post-natal exposures. It is noticeable that among the sub-group of cases who were resident in Seascale near Sellafield at diagnosis, all four acute lymphocytic leukemia cases with a higher paternal occupational radiation exposure (> 50 mSv) were diagnosed before age 6 (2 cases were age 2, one age 4, and one age 5 at diagnosis of leukemia), while only one of the four ALL cases with very low (0.1 to 49 mSv, 1 case) or no (3 cases) paternal radiation exposure were under age 6 at diagnosis (Table 9). [14] Another UK-based study found that paternal pre-conception occupational exposure to radiation, even at doses lower than the 5 mSv level, was associated with an increased risk of leukemia among children under the age of five. [15] These observations provided further support of our finding that age at diagnosis of leukemia may be the crucial factor in determining the effect of paternal radiation exposure and risk of leukemia in offspring.

The association between paternal pre-conception radiation exposure and risk of infant leukemia is intriguing. Alternative explanations, however, need to be considered before any etiologic connection can be made. Of major concern is the accuracy of exposure assessment, since only interview information was obtained for five studies. Although the short time period between conception and diagnosis of disease among young children substantially reduced the likelihood of recall bias, we can not exclude the possibility that parents of cases might recall exposures more readily than parents of controls and might telescope the time of exposures. However, the elevated risk associated with paternal pre-conception X-ray exposure being confined to specific leukemia type (ALL) and anatomic sites (e.g., GI, lower abdomen and chest), and no excess risk being linked to maternal exposure suggested that recall bias is unlikely the sole explanation.

Selective participation of subjects casts some concerns for the U.S. studies since 13-26% of eligible cases and 28-31% of eligible controls did not have paternal exposure information. For those with completed paternal questionnaire data, mother was the surrogate respondents for 11-18% of case fathers and 29-36% of control fathers. It is noted that non-participating parents were less educated compared to participating parents. To control for this potential selection bias, we adjusted for parental

education throughout our analyses. Residual bias, if any, resulting from selective participation according to educational level, would tend to lead to an under-estimation of the disease-radiation association, since high education was found to be related to more X-ray exposure. [16] Additional analyses restricted to subjects with\par direct father interview did not show an indication of major misclassification of exposure by including the surrogate interview data.

Another alternative explanation is that the underlying diseases that required X-ray examination or their related medications might cause mutation of the parental germ cells and, in turn, increase the risk of leukemia in their offspring. To address this concern, we reviewed the questionnaires of CCG-E09 study participants to evaluate if the excess lower GI and abdomen X-ray exposure among cases was attributed to an excess of certain diseases or medications. We did not observe any patterns of disease or medications that could account for the excess of X-rays among cases. Therefore, if an underlying disease or medication was the cause of infant leukemia, we would have to assume that many paternal diseases or medications were involved. Unfortunately, a detailed medical history of parents prior to conception of the index child was not obtained for the five studies, which precluded a thorough evaluation of the confounding effect of medical conditions on X-ray exposure. Nevertheless, the association between paternal occupational radiation exposure prior to conception and risk of infant leukemia observed in the CCG-E09 study would argue against paternal disease history and medication use as a sole explanation of the radiation/leukemia association that we observed.

Although germline mutation is believed to be a rare origin for childhood cancers, there are some biologic data available indicating a potential role for germline transmission of mutation or genomic instability in the development of cancers among experimental settings. For example, exposure of bone marrow stem cells to X-rays or α-particles has been shown to be related to about 2% and 40%, respectively, of chromosome abnormalities in the daughter cells.[17] A delayed chromosomal instability was found in cultured cells several generations after X-ray exposure. [18,19] Experiments on 15,000 mice demonstrated that X-ray exposure of parental gonads substantially increased the incidence rate of both lung cancer and leukemia in offspring. [20] The dose of radiation used in those experiments, however, was much higher than that used for human X-ray examinations.

It is well accepted that cancers are consequences of the combined effect of environmental exposures and host response. Therefore, to understand the etiologic role of paternal diagnostic X-ray exposure on childhood cancer, we need to consider both environmental exposures and host susceptibility factors. Working towards this, we have developed the following hypothesis (Figure). Radiation exposure to gonads may cause DNA damages in spermatogonia. If the radiation dose is high and DNA damage is severe, the germ cells will die. Low dose radiation, however, may result in minor damage in germ cells (detectable or yet not detectable), which are not fatal to germ cells. This damage may be repaired among subjects with normal DNA repair capacity but persist and accumulate among subjects with impaired DNA repair function. If one of these germ cells results in a pregnancy, it might result in miscarriage, stillbirth, or a susceptible offspring who would develop leukemia once he/she is exposed in utero or post-natally to a leukemogenic factor.

Direct evidence linking genetic markers of pre-conception exposure to diagnostic X-ray and parental DNA repair function to leukemia risk among young children are

crucial for testing this hypothesis and should be a priority for future studies.
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Table 1: Summary of Study Design

	Year	Age	Cases	Controls	Source of Information
Shanghai childhood leukemia study (1)	1974-86	<15 yrs	309	618	mother
Shanghai childhood cancer study (2)	1986-91	<15 yrs	166	166	both parents
CCG-E09 infant leukemia study	1983-88	≤18 mos	302	558	both parents
CCG-E14 AML study	1988-92	<18 yrs	525	619	both parents
CCG-E15 ALL study	1988-92	<15 yrs	1842	1986	both parents

Table 2: Childhood leukemia and parental pre-conception diagnostic X-ray exposure
Shanghai childhood leukemia study (1)

		Total leukemia			ALL			ANLL		
	Controls	Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Father										
None	41	11	1.0	---*	---	---	---	---		
1-5	419	166	1.4	0.7-2.7	100	1.0	---	55	1.0	---
6-10	112	77	2.4	1.5-5.0	46	1.9	1.2-2.8	18	1.3	0.7-2.4
≥11	45	53	3.9	1.7-8.6	26	2.6	1.5-4.6	20	3.7	2.0-7.0
Trend Test			P<0.01			P<0.01			P<0.01	
Mother**										
None	98	43	1.0	---	25	1.0	---	13	1.0	---
1-5	381	170	1.1	0.7-1.7	94	1.0	0.6-1.6	55	1.6	0.7-3.3
6-10	109	71	1.0	0.6-1.7	39	0.9	0.5-1.7	21	1.4	0.5-3.5
≥11	30	24	1.1	0.5-2.3	14	1.1	0.3-2.8	5	0.9	0.2-3.3
Trend Test			P=0.91			P=0.82			P=0.94	

Adjusted for age, sex, birth weight, birth order, born in rural area, prenatal x-ray exposure, chloramphenicol and syntomycin usage, mother's age at menarche, and maternal occupational exposures during pregnancy. Unknowns excluded from analysis.

* Reference group includes individuals with ≤ 5 reported exposures.

** Further adjusted for paternal x-ray exposure.

Table 3: Paternal Diagnostic X-Ray Exposure and Risk of Acute Leukemia
Shanghai childhood cancer study (2)

Exposure during 2 years before conception	All cases (n=166)		<2 yrs at diagnosis (n=15)	
	OR	95% CI	OR	95% CI
None	1.0		1.0	
1	0.7	0.4-1.3	1.69	0.37-7.82
≥2	0.9	0.5-1.7	1.94	0.30-12.59

Adjusted for maternal age, birth weight, paternal smoking prior to the birth of index child.

Table 8: Parental Pre-conception X-Ray Exposure and Risk of Childhood Leukemia
CCG-E14 and CCG-E15 studies

Exposure during 2 years before conception	**All case**		**Under age of 2 years**	
	OR	**95% CI**	**OR**	**95% CI**
Paternal Exposure				
ALL	Cases/controls = 1618/1722		Cases/controls = 173/182	
None	1.0		1.0	
1	1.21	0.93-1.60	1.35	0.58-3.12
≥2	1.34	1.10-1.64	1.51	0.81-2.79
AML	Cases/controls = 490/566		Cases/controls = 124/142	
None	1.0		1.0	
1	1.13	0.76-1.67	1.53	0.25-3.52
≥2	1.24	0.85-1.80	0.52	0.18-1.49
Maternal Exposure				
ALL	Cases/controls = 1842/1986		Cases/controls = 187/197	
None	1.0		1.0	
1	0.92	0.72-1.19	0.60	0.25-1.46
≥2	1.10	0.90-1.35	1.03	0.53-1.99
AML	Cases/controls = 525/619		Cases/controls = 129/147	
None	1.0		1.0	
1	1.06	0.74-1.51	1.32	0.55-3.15
≥2	1.02	0.54-1.91	2.03	0.60-6.89

Table 4: Risk of infant leukemia associated with paternal pre-conception X-ray exposure *CCG-E09 study*

Ever had:		Cases (%)[a] N=280	Controls (%)[a] N=511	OR[b]	95% CI
Total X-ray	Never	3.2	3.3	1.0	
	Ever (prior to pregnancy)	96.8	96.7	1.08	0.42-2.81
	More than a year	50.4	57.9	0.95	0,36-2.52
	Within a year	42.1	36.6	1.32	0.49-3.54
	Within a month	4.3	2.2	2.56	0.67-9.75
Head & neck X-ray	Never	8.5	5.3	1.0	
	Ever (prior to pregnancy)	91.5	94.7	0.75	0.39-1.45
	More than a year	54.0	60.6	0.69	0.35-1.34
	Within a year	35.3	32.9	0.89	0.45-1.78
	Within a month	2.2	1.2	1.16	0.31-4.36
Chest X-ray	Never	34.4	41.5	1.0	
	Ever (prior to pregnancy)	65.6	58.5	1.44	1.04-2.01
	More than a year	57.5	51.7	1.43	1.01-2.01
	Within a year	7.0	6.4	1.43	0.73-2.79
	Within a month	1.1	0.4	7.51	0.69-81.5
Limb X-ray	Never	38.0	45.2	1.0	
	Ever (prior to pregnancy)	62.0	54.8	1.46	1.05-2.03
	More than a year	55.6	49.9	1.44	1.03-2.01
	Within a year	5.7	4.3	1.60	0.75-3.39
	Within a month	0.7	0.6	2.79	0.37-21.15
Back or spine X-ray	Never	74.1	72.6	1.0	
	Ever (prior to pregnancy)	25.9	27.4	0.99	0.69-1.42
	More than a year	23.3	25.0	0.96	0.66-1.41
	Within a year	2.2	2.0	1.18	0.40-3.49
	Within a month	0.4	0.4	2.05	0.12-35.09
Upper GI X-ray	Never	79.9	88.2	1.0	
	Ever (prior to pregnancy)	20.1	11.8	1.87	1.20-2.90
	More than a year	17.9	11.6	1.76	1.13-2.75
	Within a year	1.8	0.2	6.48	0.71-58.92
	Within a month	0.4	0		
Lower GI or abdomen X-ray	Never	79.0	88.5	1.0	
	Ever (prior to pregnancy)	21.0	11.5	2.24	1.44-3.47
	More than a year	18.0	10.9	1.99	1.25-3.16
	Within a year	2.9	0.6	5.93	1.52-23.10
	Within a month	0	0		

a Frequencies were obtained for all cases and controls pooled, ignoring matching status. Subjects with missing values were excluded.

b ORs were derived from conditional logistic regression model and adjusted for paternal age, education and drinking.

Table 5: Risk of infant leukemia associated with the number of paternal pre-conception X-ray exposures *CCG-E09 study*

Number of X-rays by anatomic site		Total Leukemia (N=280) OR[1] (95% CI)	ALL (N=191) OR[1] (95% CI)	AML (N=79) OR[1] (95% CI)
Head & neck	None	1.0	1.0	1.0
	1-9	0.77 (0.38-1.53)	0.65 (0.27-1.59)	1.01 (0.29-3.60)
	10-19	0.66 (0.32-1.37)	0.50 (0.20-1.25)	1.29 (0.31-5.31)
	20+	0.97 (0.46-2.05)	0.67 (0.26-1.73)	1.82 (0.45-7.32)
	trend test:	*p=0.66*	*p=0.55*	*p=0.19*
Chest	None	1.0	1.0	1.0
	1-4	1.35 (0.95-1.93)	0.93 (0.61-1.44)	2.93 (1.42-6.04)
	5-9	1.46 (0.85-2.52)	1.31 (0.67-2.54)	2.35 (0.85-6.51)
	10+	1.97 (0.99-3.94)	2.21 (1.0-4.90)	1.08 (0.15-7.83)
	trend test:	*p=0.02*	*p=0.08*	*p=0.10*
Limb	None	1.0	1.0	1.0
	1-4	1.41 (0.99-2.02)	1.65 (1.08-2.54)	0.99 (0.47-2.06)
	5-9	1.78 (1.05-3.00)	1.74 (0.92-3.27)	1.83 (0.67-5.04)
	10+	1,21 (0.61-2.41)	1.41 (0.65-3.05)	0.77 (0.14-4.28)
	trend test:	*p=0.07*	*p=0.08*	*p=0.57*
Back & spine	None	1.0	1.0	1.0
	1-2	0.83 (0.54-1.26)	0.76 (0.45-1.28)	1.26 (0.57-2.80)
	3-4	1.11 (0.56-2.18)	1.20 (0.53-2.70)	1.15 (0.31-4.31)
	5+	2.32 (0.91-5.95)	2.48 (0.85-7.29)	1.02 (0.09-11.63)
	trend test:	*p=0.35*	*p=0.34*	*p=0.67*
Upper GI	None	1.0	1.0	1.0
	1	1.59 (0.97-2.60)	1.37 (0.73-2.55)	1.65 (0.69-3.94)
	2+	3.29 (1.34-8.08)	2.71 (0.99-7.44)	5.31 (0.53-53.40)
	trend test:	*p<0.01*	*p=0.04*	*p=0.07*
Lower GI & abdomen	None	1.0	1.0	1.0
	1	2.38 (1.41-4.02)	3.36 (1.69-6.70)	1.02 (0.38-2.77)
	2+	2.09 (1.01-4.32)	3.78 (1.49-9.64)	0.19 (0.02-1.72)
	trend test:	*p<0.01*	*p<0.01*	*p=0.25*

[1] ORs were derived from conditional logistic regression model and adjusted for paternal age, education, and drinking.

Table 6: Risk of infant leukemia associated with maternal pre-conception X-ray exposure *CCG-E09 study*

Ever had:		Cases (%)[a] N=302	Controls (%)[a] N=558	OR[b]	95% CI
Total X-ray	Never	2.0	1.6	1.0	
	Ever (prior to pregnancy)	98.0	98.4	0.87	0.29-2.68
	More than a year	51.3	56.1	0.84	0.27-2.61
	Within a year	41.1	40.9	1.02	0.32-3.21
	Within a month	5.6	1.4	4.50	1.05-19.28
Head & neck X-ray	Never	4.0	3.2	1.0	
	Ever (prior to pregnancy)	96.0	96.8	0.82	0.37-1.81
	More than a year	56.3	58.2	0.77	0.35-1.72
	Within a year	35.3	37.5	0.84	0.37-1.91
	Within a month	4.3	1.1	3.64	1.04-12.71
Chest X-ray	Never	44.4	43.7	1.0	
	Ever (prior to pregnancy)	55.6	56.3	1.04	0.77-1.40
	More than a year	49.2	50.8	1.01	0.74-1.38
	Within a year	5.8	5.3	1.06	0.55-2.06
	Within a month	0.7	0.2	4.42	0.39-50.60
Limb X-ray	Never	61.9	60.2	1.0	
	Ever (prior to pregnancy)	38.1	39.8	0.95	0.71-1.28
	More than a year	35.1	36.6	0.95	0.70-1.30
	Within a year	2.3	2.7	0.87	0.33-2.27
	Within a month	0.7	0.5	1.44	0.23-8.84
Back or spine X-ray	Never	81.9	78.8	1.0	
	Ever (prior to pregnancy)	18.1	21.2	0.87	0.60-1.25
	More than a year	15.7	19.6	0.83	0.56-1.21
	Within a year	1.7	1.3	1.27	0.38-4.25
	Within a month	0.7	0.4	1.97	0.27-14.63
Upper GI X-ray	Never	80.5	79.2	1.0	
	Ever (prior to pregnancy)	19.5	20.8	0.99	0.68-1.45
	More than a year	18.9	19.5	1.01	0.69-1.49
	Within a year	0.7	1.3	0.54	0.11-2.75
	Within a month	0	0		
Lower GI or abdomen X-ray	Never	78.0	76.6	1.0	
	Ever (prior to pregnancy)	22.0	23.4	1.00	0.70-1.42
	More than a year	20.3	22.3	0.99	0.69-1.41
	Within a year	1.7	1.1	1.27	0.35-4.58
	Within a month	0	0		

a Frequencies were obtained for all cases and controls pooled, ignoring matching status. Subjects with missing values were excluded.

b ORs were derived from conditional logistic regression model and adjusted for maternal age, education and drinking.

Table 7: Risk of infant leukemia associated with the number of maternal pre-conception X-ray exposures *CCG-E09 study*

Number of X-rays by anatomic site		Total Leukemia (N=302) OR[1] (95% CI)	ALL (N=203) OR[1] (95% CI)	AML (N=88) OR[1] (95% CI)
Head & neck	None	1.0	1.0	1.0
	1-9	0.84 (0.38-1.87)	0.66 (0.25-1.73)	1.27 (0.24-6.79)
	10-19	0.73 (0.73-1.67)	0.48 (0.18-1.32)	1.63 (0.29-9.23)
	20+	0.86 (0.37-2.00)	0.61 (0.22-1.69)	1.34 (0.24-7.55)
	trend test:	*p=0.88*	*p=0.40*	*p=0.75*
Chest	None	1.0	1.0	1.0
	1-4	1.01 (0.74-1.39)	1.00 (0.68-1.48)	1.09 (0.60-1.97)
	5-9	1.16 (0.62-2.18)	1.15 (0.53-2.47)	1.22 (0.39-3.89)
	10+	1.28 (0.58-2.83)	0.70 (0.19-2.51)	1.77 (0.57-5.56)
	trend test:	*p=0.53*	*p=0.92*	*p=0.35*
Limb	None	1.0	1.0	1.0
	1-4	0.93 (0.68-1.27)	0.89 (0.61-1.31)	0.92 (0.52-1.62)
	5-9	1.00 (0.47-2.13)	1.01 (0.42-2.40)	0.82 (0.15-4.61)
	10+	1.87 (0.71-4.90)	2.28 (0.66-7.85)	1.11 (0.22-5.71)
	trend test:	*p=0.64*	*p=0.68*	*p=0.87*
Back & spine	None	1.0	1.0	1.0
	1-2	0.86 (0.58-1.30)	0.78 (0.48-1.27)	0.93 (0.41-2.09)
	3-4	1.19 (0.52-2.73)	1.02 (0.36-2.88)	1.76 (0.41-7.66)
	5+	0.76 (0.25-2.30)	0.63 (0.18-22.5)	1.25 (0.11-14.48)
	trend test:	*p=0.63*	*p=0.34*	*p=0.65*
Upper GI	None	1.0	1.0	1.0
	1	0.97 (0.64-1.48)	0.82 (0.49-1.38)	1.38 (0.63-2.99)
	2+	1.05 (0.51-2.17)	1.17 (0.47-2.96)	0.18 (0.02-1.56)
	trend test:	*p<0.99*	*p=0.82*	*p=0.49*
Lower GI & abdomen	None	1.0	1.0	1.0
	1	0.93 (0.61-1.43)	0.88 (0.53-1.47)	1.05 (0.44-2.48)
	2+	1.13 (0.67-1.90)	1.04 (0.55-1.97)	1.26 (0.50-3.21)
	trend test:	*p=0.79*	*p=0.90*	*p=0.65*

[1] ORs were derived from conditional logistic regression model and adjusted for maternal age, education, and drinking.

Table 9: Description of leukemia cases who were resident at Seascale at diagnosis

Type of Leukemia	Age at Diagnosis	Paternal Radiation (mSv)
ALL	2	50-99
ALL	2	>100
ALL	3	0
ALL	4	>100
ALL	5	50-99
ALL	7	0
ALL	11	0.1-49
ALL	16	0
CLL	19	>100

Figure