Risk of Childhood Leukemia Associated with Diagnostic Irradiation and Polymorphisms in DNA Repair Genes

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The purpose of the study was to measure risk of childhood acute lymphoblastic leukemia associated with reported postnatal diagnostic X rays and to determine if it was modified in the presence of variants in genes involved in DNA repair. We conducted a population-based case–control study with 491 cases and 491 healthy controls among children 0–9 years of age at diagnosis. To evaluate gene–environment interaction, we used a subgroup of 129 cases. The adjusted odds ratio (OR) for one reported postnatal child X ray versus none was 1.04 [95% confidence interval (CI), 0.72–1.49], whereas the OR for two or more X rays was 1.61 (CI, 1.13–2.28). Among girls, the former ORs were 1.14 (CI, 0.66–1.96) and 2.26 (1.20–4.23), respectively. Among girls who carried the *hMSH3* [exon (ex) 23] variant, the ORs were 3.33 (CI, 0.75–14.82) for one X ray and 0.27 (CI, 0.05–1.57) for two or more X rays, whereas among those who carried the *XRCCI* (ex 6) variant, the ORs were 1.45 (0.11–19.08) and 6.66 (0.78–56.63), respectively. On the other hand, at low levels of exposure, boys seemed protected by the variant *hMLH1* (ex 8). The latter results must be interpreted with caution but suggest that the effect of diagnostic X rays could be modified by variants in repair genes according to sex. Few studies have evaluated the risk of postnatal diagnostic irradiation, which was moderately strong here; we are not aware of any studies that also considered the effect of polymorphisms in DNA repair genes. Based on the present results, both aspects deserve further study. *Key words*: childhood leukemia, diagnostic irradiation, DNA repair genes, gene–environment interaction, polymorphisms. *Environ Health Perspect* 108:495–498 (2000). [Online 12 April 2000]
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Prenatal diagnostic irradiation is a recognized risk factor for childhood cancer (*1*), but the risk associated with postnatal diagnostic irradiation is not well established. Excluding studies where children received radiation as a treatment, we found only a few studies that considered postnatal diagnostic X rays as a risk factor for childhood leukemia (*2–8*); however, their results are consistent in that reported exposure in cases was almost always more frequent than in controls.

Reduced DNA repair capacity may increase susceptibility to breast and lung cancers (*9,10*) as well as to hematologic malignancies. For instance, the development of leukemia and lymphoma in cases of Fanconi anemia or ataxia telangiectasia is associated with defective DNA repair (*11,12*). Therefore, DNA repair genes may play a key role in tumor development and in radiosensitivity. Recently, common variants were identified at the coding sequence of *XRCC1* (*13*), a gene involved in the base excision repair (*14*), as well as in the DNA mismatch repair genes *hMLH1* and *hMSH3* (*15*). Although the significance of these variants is not completely clear at this time (*16*), it is plausible that they would be associated with altered DNA repair capacity and with modified susceptibility to cancer. We can then hypothesize that postnatal irradiation in a child with certain forms of DNA repair genes would be at increased risk of cancer.

The objectives of this study were to measure the effect of reported postnatal diagnostic irradiation on childhood acute lymphoblastic leukemia (ALL) and to carry out a preliminary study to assess whether this effect seems modified by DNA repair gene variants.

Materials and Methods

Case ascertainment. The study methods have been described by Infante-Rivard et al. (*17*). Cases diagnosed between 1980 and 1993 in the province of Québec (Canada) and aged between 0 and 9 years were recruited from tertiary care centers designated by government policy to treat and hospitalize children in the province with cancer. Tracing cases from these hospitals is equivalent to a population-based ascertainment. For feasibility (cost) reasons, children living in the less populated and the most distant regions from urban centers were not included in the study. Based on population denominators, the regions not studied would include approximately 10% of the provincial population. For similar reasons, from 1991 to 1993, only cases from the Metropolitan Montréal region (approximately 60% of the provincial population) were included in the study. Because cancer care is covered under the universal health plan, we believe that a negligible number of children, if any, were treated outside the province.

A case [*International Classification of Diseases, 9th Revision* (World Health Organization, Geneva) coding 204.0] was determined to have ALL on the basis of clinical and biologic standard criteria by an oncologist or a hematologist in a tertiary care center. To identify cases, we used: *a*) hospitalization data from the provincial government's computerized discharge data files; *b*) hospitalization censuses from the respective hospitals (we checked all medical records with a relevant discharge diagnosis); *c*) lists maintained by hematology–oncology laboratories of histologic data for cases; and *d*) outpatient oncology records from the largest pediatric center in the province (Hôpital Saint-Justine, Montréal).

Control ascertainment. Population-based controls (one per case) were matched on age (within 24 months), sex, and region of residence at the time of diagnosis. These regions are based on administrative and geographic criteria determined by the government and they cover a wide territory. The

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population-based controls were chosen from family allowance files. The family allowance is a government stipend which, at the time of the study, was awarded to all legal resident families with children in Canada. According to the expected distribution of cases based on matching criteria, we randomly chose a list of 10 potential controls from the family allowance files.

Children who were adopted, lived in foster families, whose family spoke neither French nor English, or lived out of the country were considered ineligible. We also did not consider children whose mother was in prolonged psychiatric treatment, or whose parents were both unavailable. We identified 510 eligible cases and interviewed 491 parents (96.3%); 588 eligible controls were recruited and 493 (83.8%) parents participated. Among controls, 74 children were the second control on the list of eligibles, 9 were the third choice, and 1 was the fourth. The others were first choices on the list of eligibles. Reasons for nonparticipation were a confidential telephone number, refusal, or a nontraceable family. Two strata without cases were ultimately rejected, leaving 491 cases to be used in the analysis and 491 healthy population controls.

Data collection. Permission to access cases was granted by the institutional review board of each hospital; permission to access controls was granted by the provincial agency regulating access to public databases with nominal information. Soon after the anticipated reception of a letter introducing the general purpose of the study, trained interviewers contacted the parents to schedule an appointment for the interview, which was administered by telephone using a structured questionnaire. Questionnaires were reviewed as were completed and feedback was regularly provided to interviewers.

The questionnaire included information on possible confounding variables as well as on diagnostic irradiation. Mothers were asked about specific X rays during pregnancy, such as pelvimetry and abdominal X rays. The mothers also answered questions about the nature and number of X rays for the study child after birth. For instance, we asked, "has your child ever had a pulmonary X ray?"; if the answer was yes, we asked how many times he or she had such an exam, at what age, and if it was for diagnostic or routine purposes. Pelvimetries and children's X rays are described as the total number reported.

Data analysis. We used conditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CIs). In addition to the matching variables, the OR were adjusted for maternal age and level of schooling, pelvimetries, and abdominal X rays and diseases during pregnancy.

We evaluated the linear component of the trend for the number of the child's X rays by reparameterizing the categories for the number of X rays and introducing a single variable in the model. We assessed departure from linearity by comparing the log-likelihood of a model where the variable is entered as a single parameter with that of a model where the single parameter is present as well as the square of this parameter (a quadratic term) (*18*).

Case-only study. To circumvent the practical and ethical problems associated with taking blood from normal controls (children posing an added difficulty), several authors have proposed the use of case-only studies, where cases with the genotype at risk (defining carriers of specific mutations) are compared to cases without the given mutation with respect to exposure (*19–21*). This approach will not allow the direct estimation of the effect of the exposure nor of the genotype on risk but will allow the estimation of the interaction effect between exposure and the mutation. One of the advantages of this design is that it is more efficient than the traditional case–control approach to estimate the interaction parameter. The validity of this design to estimate the interaction OR depends on the assumption that among controls, genotype and exposure are independent, i.e., the fact of having the mutation will not influence the exposure.

Genotyping. A sample of 129 cases from the Hôpital Sainte-Justine and which were part of our case–control study had already been genotyped (*22*). All of the parents accepted our use of DNA material that was already provided for diagnostic and therapeutic purposes. We used a polymerase chain reaction (PCR)/allele-specific-oligonucleotide (ASO) hybridization assay to genotype four allelic variants in three DNA repair genes: exon 6 of *XRCC1* (Arg-to-Trp substitution at codon 194), exon 8 of *hMLH1* (Ile-to-Val substitution at codon 219), exon 21 of *hMSH3* (Arg-to-Glu change at codon 940), and exon 23 of *hMSH3* (Thr-to-Ala modification at codon 1036). With this method, ASOs complementary to each of the variants distinguishing between the mutant and the normal alleles are used as probes to hybridize dot-blots containing PCR products (*23*). We extracted genomic DNA from cells derived either from mouth epithelium, peripheral blood, or bone marrow in remission, as previously described (*24*).

Because we studied inherited polymorphisms rather than somatic mutations, the genetic integrity of the samples after treatments should not be of concern. We studied mutations that are unique and established in human populations, where they were presumably introduced as a result of a single mutation event. The probability that such an event may recur during cancer development and/or treatment is negligible.

Data analysis. For the case-only study, we used unconditional logistic regression to estimate the interaction ORs and their CIs, adjusting for age and sex of the child.

Results

Case–control study. The case and control groups each included 216 girls and 275 boys. Fifteen cases were younger than 1 year of age (3%); 64 cases were younger than 2 years of age (13%), and 249 cases were younger than 4 years of age (51%). In the majority of pairs (i.e., 465 of 491), the age difference between case and control was < 3 months; for other pairs, the difference ranged between 3 and 12 months or more. Other descriptive data for cases and controls are shown in Table 1; slightly more case than control mothers were in the higher age group and in the lower levels of schooling. More postnatal X rays were reported for cases than for controls.

Analyzing the relation between postnatal X rays and the incidence of ALL without controlling for additional variables than the matching factors, the results were as follows: one reported child X ray (versus none) was associated with an OR of 1.01 (CI, 0.71–1.45) and two or more X rays with an OR of 1.60 (CI, 1.13–2.24).

Results for child's X rays adjusted for prenatal X rays (pelvimetry and abdominal X rays), maternal age, and level of schooling were as follows: one X ray, OR = 1.04 (CI, 0.72–1.49) and two or more X rays, OR = 1.61 (CI, 1.13–2.28). The latter ORs did not materially change when also adjusting for maternal pregnancy diseases. When excluding

Table 1. Sociodemographic, pregnancy, and diagnostic X-ray variables for cases and controls.

Characteristics	Cases (*n*)	Controls (*n*)
Maternal age (years)		
< 20	21	30
20–33	418	423
≥ 34	52	38
Maternal level of schooling		
University	90	95
College or completed secondary	244	256
Some secondary, primary, none	157	139
Pelvimetry		
None	458	449
1	25	34
> 1	8	7
Abdominal X ray[a]		
No	487	488
Yes	4	2
Child's X rays[b]		
None	268	302
1	86	96
≥ 2	119	82

[a]During pregnancy. [b]Excluding dental.

the infants younger than 1 year of age, the ORs remained almost identical; i.e., 1.06 (CI, 0.74–1.52) and 1.62 (CI, 1.14–2.30) for one and two or more X rays, respectively.

There was no statistically significant departure from linearity in the relation between the number of the child's X rays and ALL; the change in OR for each increase in the level of child's X rays was 1.25 (CI, 1.06–1.49).

To account for latency, we excluded the X rays received 1 or 3 months before the date of diagnosis; 8 cases and 11 controls had an X ray in the month before the date of diagnosis, whereas 26 cases and 19 controls had one in the 3 months before the diagnosis. The adjusted OR for one X ray when removing those X rays received in the month before the diagnosis was 1.07 (CI, 0.74–1.56), whereas that for two or more X rays was 1.85 (CI, 1.28–2.69). Removal of the X rays in the 3 months before the diagnosis resulted in ORs of 1.08 (CI, 0.73–1.59) and 1.78 (CI, 1.21–2.63) for one and two or more X rays, respectively.

The nature of X rays was very similar in both groups, as most were bone X rays; almost all procedures in both groups were to establish a diagnosis.

Finally, we estimated the risk of ALL for child's X rays stratifying on sex (Table 2); fewer girls than boys had received X rays. In addition, there was a smaller percentage of girls who had received two or more X rays. The risk of ALL was somewhat more elevated for girls.

Case-only study. Results from the genotyped cases are shown in Table 3. A maximum of 129 cases was available for these analyses. Results show that when all of the genotyped group was considered together, the variant *hMLH1* [exon (ex) 8] conferred protection at low level of exposure, whereas the variant *hMSH3* (ex 23) was associated with an increased risk at the same level of exposure. The variants *hMLH1* (ex 8) and *hMSH3* (ex 21) modified the risk among boys at low level of exposure (the first variant was protective and the second increased risk); among girls, risk was increased with the variants *hMSH3* (ex 23) and *XRCC1* (ex 6) (at low level for the first variant and at high level for the second).

Table 2. Adjusted ORs[a] and CIs for the association of child's postnatal diagnostic X rays[b] and ALL by sex.

X rays (*n*)	Girls		Boys	
	No.	OR (CI)	No.	OR (CI)
None	275	1.00	295	1.00
1	73	1.14 (0.66–1.96)	109	0.94 (0.56–1.55)
≥ 2	68	2.26 (1.20–4.23)	133	1.39 (0.91–2.14)

[a]Adjusted for maternal age and maternal level of schooling. [b]Excludes dental X rays.

Discussion

The effect of receiving more than two postnatal X rays was associated with a significant and moderately elevated risk of ALL. Although consistent with the results of previous studies (*2–8*), the question of differential parental recall remains a concern in case–control studies. We carried out a validation substudy for prenatal X rays with the present data, comparing reported X rays (of any type except dental X rays) with those found in the maternal hospital medical record (*25*). We also reviewed studies on parental recall in case–control studies of adverse pregnancy outcomes and chronic childhood diseases. Our results show that both case and control mothers underreported prenatal X rays in a relatively similar manner (64% sensitivity in cases and 71% in controls). This conclusion is also applicable to the majority of studies reviewed. Thus, although underreporting seems a frequent problem, important differences in recall were rarely observed, and if so, they were mainly under the circumstances of possible clusters with publicized potential risk factors. Of course, these findings do not guarantee the absence of differential recall for child X rays in the present study, but the presence of such a bias cannot be automatically assumed.

Removing the X rays taken close to the time of diagnosis did not materially alter the results. However, the notion of latency in childhood leukemia is not defined and these time periods were arbitrarily chosen.

The data suggest that the effect of postnatal diagnostic irradiation may be more pronounced among girls. Explanations for the results by sex are not readily available. Studies of prenatal paternal irradiation in mice (mating with a nonirradiated female) show an increase in the incidence of leukemia in females (*26*). In addition, recent analyses from atomic bomb survivors exposed *in utero* and as children younger than 6 years of age suggest a similar observation: although there were only 10 cancer deaths among those exposed *in utero* (n = 807), 9 occurred in females (*27*). Finally, females irradiated for retinoblastoma also seem at greater risk of a second cancer (*28*). Although these risk situations are quite different from the situation in the present study, they may nevertheless indicate a form of susceptibility to ionizing radiation for female children.

Radiation doses to children from common X rays show substantial variations between hospitals within the same time period and geographic territory (*29–34*). Factors such as changes in technical staff within the same radiologic unit, whether the unit is in a specialized or a general center, the age of X-ray generators, the body size of the child, and other more technical aspects related to the procedure itself affect the dosage. Unfortunately we have no dose estimation for the X rays received by the children in this study. X rays were administered in centers all over the province, from specialized to general, over a period of > 20 years (from 1970 to 1993; cases entered the study between 0 and 9 years of age between 1980 and 1993). Dose variability information from the literature and the conditions of X-ray administration in this study indicate that doses were likely to be quite variable. These observations are unlikely to explain our results because it is probable that doses were the same for cases and controls. However, they are useful to draw attention to the fact that control of dosage does not seem fully achieved for pediatric diagnostic irradiation, leaving a potential for doses that are not optimal. Children may be receiving radiation at higher doses than previously believed at an age where they are more susceptible to radiation.

Overall, our preliminary results on gene–environment interaction suggested the following observations: risks may be increased or decreased by the variants; risks do not necessarily increase with higher level of exposure; and finally, some variants modify risks in girls and others in boys. Most results were estimated with large confidence intervals and must be interpreted with caution because chance could still be an explanation for the findings. Nevertheless, we believe that the present results are plausible, given previous

Table 3. Case-only interaction ORs and CIs between DNA repair gene polymorphisms and reported exposure to postnatal diagnostic X rays.

X rays (*n*), sex (*n*)	DNA repair gene variants			
	hMLH1 (ex 8) (*n* = 129)	*hMSH3* (ex 21) (*n* = 122)	*hMSH3* (ex 23) (*n* =125)	*XRCC1* (ex 6) (*n* = 110)
0[a]	1.00	1.00	1.00	1.00
1[a]	0.33 (0.13–0.84)	1.42 (0.52–3.83)	1.71 (0.68–4.26)	1.16 (0.30–4.38)
≥ 2[a]	0.97 (0.39–2.36)	0.97 (0.36–2.60)	0.71 (0.29–1.73)	1.06 (0.32–3.54)
1[b]				
Boys	0.26 (0.07–0.87); *n* = 79	2.95 (0.75–11.03); *n* = 75	1.07 (0.31–3.63); *n* = 71	1.05 (0.21–5.12); *n* = 66
Girls	0.49 (0.11–2.11); *n* = 50	0.42 (0.07–2.48); *n* = 47	3.33 (0.75–14.82); *n* = 54	1.45 (0.11–19.08); *n* = 44
≥ 2[b]				
Boys	0.76 (0.26–2.25); *n* = 79	1.79 (0.50–6.42); *n* = 75	0.99 (0.33–2.96); *n* = 71	0.44 (0.09–2.07); *n* = 66
Girls	1.58 (0.30–8.24); *n* = 50	0.42 (0.07–2.48); *n* = 47	0.27 (0.05–1.57); *n* = 54	6.66 (0.78–56.63); *n* = 44

[a]ORs adjusted for age and sex of the child. [b]Adjusted for age of the child.

observations from adult cancer studies, and should provide an incentive for further studies. Variants can protect against risk or increase risk (*35*). Also, some authors have suggested (*36,37*) that the role of variants could be more marked at low levels of exposure than at high levels because at high levels the metabolic pathways could already be overwhelmed regardless of the presence of variants. Finally, in one of the only studies carried out on the risk of ALL in relation to polymorphisms in genes encoding enzymes involved in the metabolism of xenobiotics (*22*), we observed that the risk associated with carrying at least one *CYP1A1*4* allele was significantly protective in girls (OR = 0.2; CI, 0.05–0.9), whereas it increased in boys (OR = 1.48). These observations underscore the complexity of interactions between personal and exposure characteristics and gene polymorphisms. For this reason, the present results should be interpreted as a first step in the description of some gene–environment interactions in childhood ALL.

The assumption required for the validity of the interaction OR in the case-only study (independence of exposure and genotype in the population) was not directly checked but it seems unlikely that it would be violated. Violation of the assumption could imply, for instance, that healthy children with variants would stay away from diagnostic X rays.

Genes involved in DNA repair are critical for maintaining the integrity of genetic material transmitted from one cell to another and for protection against mutations leading to cancer. Mammalian cells rely on DNA repair systems to maintain their genomic integrity. Genes involved in the repair of double-strand DNA breaks (such as *XRCC1*) (*38*) that can be induced by X rays and other ionizing radiation, are especially relevant to cancer risk. *XRCC1*-linked polymorphism was associated with cancer in radiosensitive patients (*39*). This observation is supported by the existence of rare human disease syndromes associated with pronounced cellular sensitivity to DNA-damaging agents that arise from deficiencies in DNA repairs. Such instability syndromes (e.g., xeroderma pigmentosum, ataxia telangiectasia, Bloom syndrome, and Fanconi anemia) show marked predisposition for hematologic malignancies. The expression of the *hMSH3* gene, a component of the mismatch repair machinery (*40*), is significantly decreased in patients with hematologic malignancies (*41*), suggesting a role in leukemogenesis. The role of *hMSH3* in radiosensitivity is still unclear; it could be through involvement in transcription-coupled repair of both ultraviolet- and ionizing-radiation-induced DNA damage. This mechanism requires genes involved in DNA mismatch repair (*42*).

Although prenatal X rays are considered a causal factor for ALL (*1*), the role of postnatal X rays is typically not considered a causal factor for ALL. A recent review of the effects of ionizing radiation on cancer risk from an epidemiologic perspective does not include results on postnatal diagnostic X rays (*43*). On the other hand, uncertainty toward dose control in pediatric X rays, greater susceptibility of children (*28*), and the results in this study may be sufficient to justify other studies.

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