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Prenatal X-Ray Exposure and Rhabdomyosarcoma in Children: A Report from the Children's Oncology Group (COG)

Seymour Grufferman, M.D., Dr. P.H.[1,2], **Frederick Ruymann, M.D.**[2,3], **Simona Ognjanovic, Ph.D.**[4], **Erik B. Erhardt, M.S.**[1], and **Harold M. Maurer, M.D.**[2,5]

[1] Division of Epidemiology and Biostatistics, Department of Internal Medicine, University of New Mexico

[2] The Intergroup Rhabdomyosarcoma Study, University of Minnesota

[3] Division of Hematology/Oncology/BMT, Nationwide Children's Hospital, University of Minnesota

[4] Department of Pediatrics, University of Minnesota

[5] University of Nebraska Medical Center

Abstract

The association between antenatal diagnostic x-ray exposure and risk of rhabdomyosarcoma (RMS) in children was assessed in a national case-control study of 319 RMS cases and 319 matched controls. Data were collected by telephone interviews of subjects' parents. Overall, an odds ratio (OR) of 1.9 (95% confidence interval = 1.1–3.4) was found for any x-ray examination of the mother during pregnancy. Risk was greatest for x-ray exposure during the first trimester OR = 5.7 (95% CI = 1.2–27.8) and was also increased for the third trimester (OR=2.0, 95% CI=0.9–4.6), while second trimester exposure was not associate with increased risk. A non-significant increase in risk was found for any x-rays of the abdomen, pelvis, chest or back. Increased risk was significantly associated with "other" x-ray exposures (RR = 2.9, 95% CI = 1.1–7.7), primarily composed of dental x-rays. The association was strongest between embryonal RMS and first trimester exposure (RR = 10.5, 95% CI = 1.5–458.4). This observation regarding embryonal RMS, and our previous report of an increased frequency of major malformations in RMS are compatible with findings from animal studies in which ptc heterozygous knockout mice exhibited an increased risk of radiation-induced development defects and of spontaneously occurring embryonal RMS.

Keywords

dental x-rays; rhabdomyosarcoma; pregnancy; radiation; ptc pathway; sonic hedgehog pathway

INTRODUCTION

Prenatal x-ray exposure is one of the few well-established environmental risk factors for childhood cancer. Following the initial report by Giles, et al., in 1956 (1), there have been numerous studies linking diagnostic radiation exposure in utero with an increased risk of childhood cancer (2–17). Most report an increased risk of childhood leukemia following in utero radiation exposure and the odds ratios have been on the order of 1.5. Many studies were limited by considering only children dying of cancer and only mothers' abdominal or pelvic

Address reprint requests to Dr. Grufferman at MSC 10 5550, University of New Mexico Albuquerque, NM 87131, U.S.A, sgrufferman@salud.unm.edu.

x-ray examinations. Less attention has been paid to the association between prenatal x-ray exposure and risk of cancers other than leukemia. In general, the increased risk of "solid" tumors (usually considered as all other non-leukemia childhood cancers) is significantly greater than unity, but lower than that for leukemia (11,18,19). There has been no study which specifically assessed the risk of rhabdomyosarcoma following prenatal x-ray exposure.

The conduct of a large national case-control study of childhood rhabdomyosarcoma (RMS) in the U.S. allowed us to evaluate in utero radiation exposure as a risk factor for the disease (20). This study has several advantages over many previous studies that assessed associations between prenatal x-ray exposure and childhood cancer. Extensive questionnaire data were collected directly from subjects' parents regarding the type and time of mothers' diagnostic x-ray examinations during pregnancy. Data were collected for both surviving and dying patients. Detailed obstetric histories permitted the consideration of possible indications for diagnostic radiographic examinations as potential confounders. Lastly, the RMS cases ranged in age at diagnosis from 0–20 years allowing for assessment of late childhood effects of prenatal radiation exposures.

MATERIALS AND METHODS

Study Population

Cases—Cases were patients with RMS in the previous Intergroup Rhabdomyosarcoma Study (IRS), which in the year 2000 became part of the Children's Oncology Group. A few our case-control study results have been reported previously (20,21). The IRS was a clinical trials group that coordinated treatment protocols for 80–85% of all childhood RMS cases in the U.S. (22, 23). Cases were aged 0–20 years at diagnosis and were consecutively entered into the IRS-III trial from April, 1982 through July, 1988. The diagnoses of all cases were confirmed by central expert pathology review.

There were 511 patients aged 0–20 years in IRS-III during the study period of whom 440 cases were eligible for this study and 351 had completed interviews. Ineligible cases (n=71) had no home telephone (n=29), were not US residents (n=9), their families did not speak English or Spanish (n=15) or their Institutions' Review Board (IRB) did not approve the study (n=18). In addition, 89 eligible cases did not participate due to parental (n=41) or physicians' (n=30) refusals, while 18 families could not be located (24). In summary, 73% (322) of eligible cases were interviewed and matched with controls.

Controls—Controls were selected by random-digit telephone dialing (22,25). Cases' telephone area code and first five digits of their number were used with two randomly selected terminal digits to search for controls by telephone calling. Controls were matched to cases on race, sex and age (within 1 year for cases aged 0–5 years at diagnosis and within 3 years for cases aged 5–20 years). Of homes with a matching child, 22% refused to participate. Controls could not be obtained for 8% of cases.

Data Collection—Data were collected by telephone interview of parents using a structured questionnaire. The mean duration of the interviews was 70 minutes for case and 68 minutes for control families. Interviews were conducted in English or Spanish (6 case and 2 control families). The interviews collected data on a variety of childhood environmental exposures, family history, past medical history, parents' occupational history and mothers' obstetric history. On average, parents were asked to recall perinatal exposures that occurred eight to nine years prior to the interview.

An obstetric history, which was focused on the subjects' gestation and delivery, was obtained from subjects' mothers. Mothers were specifically asked "Did you have any x-rays during the

pregnancy?", "What parts of your body were x-rayed?", and "During which trimesters?". Mothers were also asked about a variety of problems and illnesses that they might have had during the index pregnancy.

Data Analysis—Conditional logistic-regression models were used to obtain odds ratio (OR) estimates of the relative risk (RR) of RMS associated with factors such as mothers' history of x-ray studies during pregnancy (SAS version 6, Cary, NC) (26). Potentially confounding variables were considered in the multivariate models used to obtain adjusted OR. These are identified in the Table footnotes.

RESULTS

Characteristics of Study Subjects

Cases and controls were quite similar with regard to a number of characteristics such as mean age at time of diagnosis of the case child (7.6 versus 7.5 years). The mean ages of subjects' mothers and fathers were identical at the time of cases' diagnoses (33.8 years for mothers and 36.6 for fathers). Case families had significantly lower annual income levels (p=0.03) than did control families (24) (Table 1). No other differences in characteristics of cases and controls reached statistical significance (data not shown).

Table 2 compares cases and controls with regard to several obstetric factors. Cases and controls were quite comparable in birth order, type of delivery, numbers and outcomes of their mothers' prior pregnancies, mean number of prenatal medical visits, mean parents' ages at birth of the index child and mean birth weight. Cases were more likely to be premature at birth and controls were more likely to be overdue at delivery. Case mothers were also more likely to have had spotting/cramping/abnormal vaginal bleeding during pregnancy.

Possible Indications for Pregnancy X-rays

Possible indications for obtaining x-ray studies during pregnancy were assessed. Prematurity occurred significantly more frequently in cases than in controls (OR = 4.4, CI = 1.7–11.6) as did cramping, spotting or abnormal bleeding (OR = 1.9, 1.2–2.9). There were no other significant case-control differences in intrapartum illnesses that might possibly lead to x-ray examinations of the mothers. Consideration of prematurity and cramping/bleeding in multivariate analyses did not change the results very much from univariate analyses. We report the percentage of reported x-ray exams by cases and controls in Table 3 and the unadjusted and adjusted results in Table 4.

Diagnostic X-rays and RMS Risk

Table 4 presents the results of analyses of mothers' diagnostic x-rays during subjects' pregnancies. X-ray examinations were classified with regard to the trimester and site of exposure. The ORs presented have been adjusted for the matching factors (age, sex, race), the length of pregnancy, type of delivery and presence of spotting, cramping, or abnormal vaginal bleeding during pregnancy, given that these conditions could be indication for further evaluation by x-ray. Adjustment for socio-economic status did not change the ORs, therefore this adjustment was not included in the presented data. Likewise, the adjustment for matching factors did not significantly affect the ORs; both unadjusted and adjusted ORs (95% CIs) are shown in Table 4, while we are discussing only adjusted values in the text. Overall, the OR for the association between any diagnostic x-ray exposure during pregnancy and risk of RMS was 1.9 (95% confidence interval (CI) = 1.1–3.4). It appears that "any" x-ray exposure during the first trimester was associated with the strongest risk (OR = 5.7, 95% CI = 1.2–27.8), however, subgroup analyses should be interpreted with caution due to small numbers in some subgroups. Although most previously reported findings on in utero radiation exposure and childhood

cancer risk were focused on pelvic and abdominal x-rays, we found an increased, but not statistically significant OR (1.4, 0.7–2.9) for RMS and such exposures. When we grouped all truncal exposures, the OR was 1.5 (95% CI = 0.8–3.1), while the OR for all other exposures was 2.9 (1.1–7.7). This category included dental (12 case and 3 control mothers), lower extremity (4 case and 3 control mothers), and head and neck x-rays (2 case and 0 control mothers).

Although the questionnaire did not ask about use of lead shielding during x-ray procedures, four case mothers and no control mothers reported that shielding had been used during their examinations. Three of the four mothers reported the use of shielding during dental x-rays (one in the first and two in the second trimester of pregnancy) and one during a first trimester x-ray examination of her foot. If these cases are excluded from the analyses, the overall OR for any x-ray exposure becomes 1.8 (1.0–3.3) and for any first trimester x-rays the OR becomes 5.1 (1.0–34.1). Since no questions regarding lead shielding were asked and all of the subjects volunteering such information were case mothers, there is a reasonable likelihood of selective recall and reporting by case mothers. It is quite possible that some of the control mothers were also shielded but were not as apt as case mothers to recall and report it. Thus, the results using all reports of x-rays by subjects' mothers are probably less biased estimates than results which exclude volunteered reports of shielding.

Other Factors

Some earlier studies considered birth order of cases in their analyses, since first-born children might have greater exposure to in utero x-rays than might later born children (1,2,6,13). Our results show an OR of 1.8 (0.8–3.9) for first born children based on 18 cases and 11 controls being exposed. For second birth order children the OR was 8.0 (1.8–34.8) based on 17 cases and 3 controls exposed; for third birth rank or higher the OR was 0.9 (0.3–2.4) based on 7 cases and 8 controls exposed.

The association between radiation exposure during pregnancy and RMS risk was also stratified by age of cases at diagnosis. Cases were divided into four five-year age groups. The ORs for each of the four age groups is greater than unity although only the OR for the 0–4 year group is statistically significantly higher (OR = 3.2, 1.2–8.7).

Stratification by RMS subtype (Table 5) showed the highest risk for development of embryonal RMS after in utero x-ray exposure (OR=2.3, 1.2–4.4), while exposure during the first trimester of pregnancy led to the highest risk (OR=10.5, 1.5–458.4).

DISCUSSION

In utero exposure to x-rays has been identified as a risk factor for childhood leukemia (18). Our results suggest that childhood RMS could be added to the list of cancers associated with in utero diagnostic x-irradiation. The magnitude of risk of RMS associated with x-rays during pregnancy appears to be somewhat higher than that reported for leukemia and other solid tumors, however more studies are needed to confirm this.

In our study, all x-ray examinations of subjects' mothers during pregnancy were considered. This led to the observation that x-ray exposure other than those of the abdomen and pelvis might be associated with an increased risk of RMS. For example, eleven case mothers reported having had dental x-rays (three of which were done with lead shielding), but only three control mothers reported this. Six of the eleven case mothers reporting dental x-rays had the examinations done during their second or third trimester of pregnancy; all three of the exposed control mothers had their x-ray examinations done in the last two trimesters of pregnancy. This is somewhat surprising, since most dental x-rays are not done on an emergency basis and thus,

could be deferred until after pregnancy. Although dental x-ray beams are focused on the teeth and supporting bony structures, there is considerable opportunity for scatter of the rays, particularly when downward-angled beams are used or when old equipment is used or films are taken by inadequately trained personnel. The same opportunity for scatter of x-rays might exist also for the three other non-truncal x-rays reported by case mothers (two lower extremity and one sinus film) and the two reported by control mothers (two lower extremity films). In the absence of systematic data on shielding during these examinations we can only conjecture about these exposures.

Although the exact mechanism by which ionizing radiation exposure of the fetus produces childhood cancers is not known, radiation induces genome instability leading to accumulation of DNA damage and alteration in DNA and histone methylation (27,28). Rodents have been validated as good models for prediction of risk of perinatal x-ray-induced carcinogenesis in humans (29), despite marked differences in the physiology of gestation (30). A possible mechanism for the induction of RMS by radiation exposure is suggested by a report of RMS and radiation hypersensitivity in a mouse model of Gorlin (nevoid basal cell carcinoma) syndrome (31,32). Gorlin syndrome is characterized by a constellation of clinical problems including generalized overgrowth of the body, cysts, skeletal abnormalities and a predisposition to benign and malignant tumors. Hahn et al., studied the multiple-pass transmembrane receptor patched (ptc) in a mouse model. Ptc is thought to be a tumor suppressor gene and patients with Gorlin syndrome have germline mutations in ptc (33). They found that mice heterozygous for ptc inactivation develop features consistent with Gorlin syndrome and also have a high incidence of RMS of the embryonal type only. It has recently been proposed in Ptc1 deficient mice, which develop basal cell carcinoma, that deregulation of the Shh/Ptc1 pathway represents the initiating step, but that additional genetic damage by radiation in genes serving critical functions in the regulation of cell proliferation, apoptosis, response to DNA damage, such as p53, is required for tumor formation (34). The evidence that the Ptc pathway may play an important role in RMS development in humans in not limited to Gorlin syndrome patients who possess germline Ptc mutations. In addition, 30% of sporadic RMS show genomic loss of Ptc1 at locus 9q22 (35). Ptc is a receptor for sonic hedgehog (Shh) and Shh/Ptc pathways play a key role in hypaxial skeletal muscle development, and is required for normal differentiation of early developing muscle (36). Deregulation of this pathway is detected in a substantial percentage of sporadic RMS (37).

A previous paper from our case-control study of RMS, reported an increased frequency of neurofibromatosis and major malformations in RMS cases (20). Several case series of RMS patients have also found an increased frequency of malformations (20,38). RMS patients were found to have a particularly increased frequency of central nervous system anomalies (20, 38). The observations of an increased risk of RMS in children exposed to ionizing radiation in utero and of an increased occurrence of malformations in children with RMS raise the question of whether our findings may be related to the ptc receptor and the signaling pathway of muscle development in which it is involved.

In searching for additional indirect support for this question in our data, we examined the risks associated with x-ray exposure when stratified by histologic type of RMS. This was done to see if embryonal RMS, the histologic type observed to occur spontaneously in the mouse model, was more strongly associated with x-ray exposure in humans than were the other histologic types. Table 5 shows the results of this analysis. The highest odds ratio (12.1) was observed for first trimester x-ray exposure in embryonal RMS cases. This is based on 10 exposed cases versus 1 exposed control, hence the wide 95% confidence interval which nonetheless excludes the null value. Our observation of a very high OR for first trimester exposure is consistent with the suggestion of Zhan and Helman (1998)(39) that perhaps there is a critical window of time in which developing skeletal muscle is sensitive to ptc alterations

(39). Nevertheless, observations of an increased frequency of major malformations in RMS and of ionizing radiation induced RMS, particularly embryonal RMS, suggest that ptc alterations might play a role in the etiology of this malformation. Although the ORs are generally highest for embryonal RMS, the ORs appear to be elevated for other types of RMS, as well. Similar to our findings of the highest risk among the embryonal tumor subtype, a recent study of solid tumor occurrence after in utero x-ray exposure revealed that the increased risk of brain tumor development was confined to the embryonal subtype (PTEN) (40).

Despite these observations, there are several limitations to our study. Even though this represents one of the largest case-control studies ever conducted on this rare tumor, the infrequency of the exposure precluded detailed analyses. Only 13.5% of cases and 6.8% of controls reported any x-ray exposure during pregnancy. Further, there is concern of recall bias; mothers of case children may tend to over-report exposure compared to mothers of control children. In addition, differential recall bias among cases is possible. For example, case mothers might more accurately recall an x-ray exposure that would be more readily perceived as causal (abdominal/pelvic x-ray) than a more distant exposure (dental x-ray). On the other hand, it is also possible that they would be less likely to report an exposure they may consider causal. It is therefore impossible to address whether differential recall bias played a role in our study. However, it is reassuring that we found an association between x-ray exposure and risk of one (embryonal) but not both RMS subtypes. Namely, there is no reason to believe that a mother of a child with embryonal RMS would recall the exposure differently than a mother of a child with alveolar RMS. We also did not collect information regarding shielding. As we noted, there was an average of 8 years between exposure and interview. Despite these concerns, we found a strong positive association between maternal x-ray exposure and embryonal RMS (less so with other RMS), which is congruent with the animal data.

A recent large analysis (>1800 cases) of childhood acute lymphoblastic leukemia (ALL) found little evidence of an association with prenatal diagnostic x-ray exposure (41). The authors conclude that declining exposure levels through declines in radiation levels in x-rays and a medical practice decrease in x-rays provided to pregnant women may explain these null findings. Mothers in our study were pregnant with study subjects approximately during the 1970s and 1980s, thus covering a period of time when radiation dosages were higher and x-ray practices for women of childhood bearing age may have been less adhered to. For example, comparison of two UK dental surveys, one carried out in the late 1980s and the other in the late 1990s, showed that the mean patient entrance dose caused by dental x-rays has decreased by 40% (42)

Although Alice Stewart and colleagues reported on the dangers of in utero x-ray exposures fifty years ago, insufficient attention has been paid to the consideration that women of child-bearing age should be assumed to be pregnant when it comes to radiographic examinations. The use of lead apron shielding of uninvolved body areas during x-ray studies has grown widespread but lapses still occur. In addition, concerns remain that a routinely used leaded apron of 0.25 mm lead thickness may not provide sufficient protection (43,44). Prior to routine shielding of the neck, downward pointing beams from dental x-rays could reach the gravid uterus. While routine lead shielding of the neck (thyroid) has been added by most dentists, in the current age of digital x-rays the radiation exposure has been significantly decreased (45), which may reduce adherence to this practice.

In conclusion, our study supports the association between in utero x-ray exposure and the risk of RMS and supports the view that in addition to brain tumors, other solid tumors may occur after such exposure. This is the largest case-control study of RMS to date and the exposure levels were surprisingly high given the public awareness of possible carcinogenic effect of in

utero x-ray exposure. Therefore findings from our study reinforce prevention guidelines to avoid the potential hazards of diagnostic x-ray exposure to unborn children.

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References

1. Giles D, Hewitt D, Stewart A, Webb J. Malignant disease in childhood and diagnostic irradiation in utero. Lancet 1956;271:447. [PubMed: 13358242]
2. Bithell JF, Stewart AM. Pre-natal irradiation and childhood malignancy: a review of British data from the Oxford Survey. Br J Cancer 1975;31:271–87. [PubMed: 1156514]
3. Court Brown WM, Doll R, Hill RB. Incidence of leukaemia after exposure to diagnostic radiation in utero. Br Med J 1960;2:1539–45. [PubMed: 13695977]
4. Diamond EL, Schmerler H, Lilienfeld AM. The relationship of intra-uterine radiation to subsequent mortality and development of leukemia in children. A prospective study. Am J Epidemiol 1973;97:283–313. [PubMed: 4701674]
5. Graham S, Levin LM, Lilienfeld AM, et al. Preconceptual, intrauterine, and postnatal irradiation as related to leukemia. Natl Cancer Inst Monogr 1966;19:347–71. [PubMed: 5905674]
6. Harvey EB, Boice JD, Honeyman M, Flannery JT. Prenatal x-ray exposure and childhood cancer in twins. N Engl J Med 1985;312:541–5. [PubMed: 3969117]
7. Jablon S, Kato H. Childhood cancer in relation to prenatal exposure to atomic-bomb radiation. Lancet 1970;2:1000–3. [PubMed: 4098041]
8. Macmahon B. Prenatal x-ray exposure and childhood cancer. J Natl Cancer Inst 1962;28:1173–91. [PubMed: 14468031]
9. Mole RH. Antenatal irradiation and childhood cancer: causation or coincidence? Br J Cancer 1974;30:199–208. [PubMed: 4476218]
10. Mole RH. Childhood cancer after prenatal exposure to diagnostic X-ray examinations in Britain. Br J Cancer 1990;62:52–68.
11. Monson, RR.; MacMahon, B. Prenatal x-ray exposure and cancer in children. In: Boice, JD.; Fraumeni, JF., editors. Radiation Carcinogenesis: Epidemiology and Biological Significance. New York: Raven Press; 1984.
12. Murray R, Heckel P, Hempelmann LH. Leukemia in children exposed to ionizing radiation. N Engl J Med 1959;261:585–9. [PubMed: 14425443]
13. Polhemus DW, Koch R. Leukemia and medical radiation. Pediatrics 1959;23:453–61. [PubMed: 13633361]
14. Rodvall Y, Pershagen G, Hrubec Z, Ahlbom A, Pedersen NL, Boice JD. Prenatal X-ray exposure and childhood cancer in Swedish twins. Int J Cancer 1990;46:362–5. [PubMed: 2394502]
15. Stewart A, Webb J, Hewitt D. A survey of childhood malignancies. Br Med J 1958;1:1495–508. [PubMed: 13546604]
16. Stiller CA. Retinoblastoma and low level radiation. BMJ 1993;307:461–2. [PubMed: 8400926]
17. Totter JR, MacPherson HG. Do childhood cancers result from prenatal x-rays? Health Phys 1981;40:511–24. [PubMed: 7228702]
18. Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. Br J Radiol 1997;70:130–9. [PubMed: 9135438]
19. Wakeford R, Little MP. Risk coefficients for childhood cancer after intrauterine irradiation: a review. Int J Radiat Biol 2003;79:293–309. [PubMed: 12943238]
20. Yang P, Grufferman S, Khoury MJ, Schwartz AG, Kowalski J, Ruymann FB, Maurer HM. Association of childhood rhabdomyosarcoma with neurofibromatosis type I and birth defects. Genet Epidemiol 1995;12:467–74. [PubMed: 8557179]

21. Grufferman S, Schwartz AG, Ruymann FB, Maurer HM. Parents' use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children. Cancer Causes Control 1993;4:217–24. [PubMed: 8318638]
22. Grufferman S, Delzell E, Delong ER. An approach to conducting epidemiologic research within cooperative clinical trials groups. J Clin Oncol 1984;2:670–5. [PubMed: 6726305]
23. Ruymann, FB.; Grufferman, S. Introduction and epidemiology of soft tissue sarcomas. In: Ruymann, FB.; Maurer, HM.; Pochedly, CE., editors. Rhabdomyosarcomas and related tumors in Children and Adolescents. Boca Ranton: CRC Press; 1991. p. 3-18.
24. Grufferman S, Wang HH, DeLong ER, Kimm SY, Delzell ES, Falletta JM. Environmental factors in the etiology of rhabdomyosarcoma in childhood. J Natl Cancer Inst 1982;68:107–13. [PubMed: 6948120]
25. Grufferman S, Gula MJ, Olshan AF, et al. Experience with random digit telephone dialing for control selection in case-control study of children. Paediatr Perinat Epidemiol 1991;5:A17–8.
26. SAS Technical Report P-217 Version 6. Carry: SAS Institute Inc;
27. Pogribny I, Raiche J, Slovack M, Kovalchuk O. Dose-dependence, sex- and tissue-specificity, and persistence of radiation-induced genomic DNA methylation changes. Biochem Biophys Res Commun 2004;320:1253–61. [PubMed: 15249225]
28. Pogribny IP, James SJ, Jernigan S, Pogribna M. Genomic hypomethylation is specific for preneoplastic liver in folate/methyl deficient rats and does not occur in non-target tissues. Mutat Res 2004;548:53–9. [PubMed: 15063136]
29. Anderson LM. Predictive values of traditional animal bioassay studies for human perinatal carcinogenesis risk determination. Toxicol Appl Pharmacol 2004;199:162–74. [PubMed: 15313588]
30. Witorsch RJ. Low-dose in utero effects of xenoestrogens in mice and their relevance to humans: an analytical review of the literature. Food Chem Toxicol 2002;40:905–12. [PubMed: 12065211]
31. Hahn H, Wicking C, Zaphiropoulous PG, et al. Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. Cell 1996;85:841–51. [PubMed: 8681379]
32. Johnson RL, Rothman AL, Xie J, et al. Human homolog of patched, a candidate gene for the basal cell nevus syndrome. Science 1996;272:1668–71. [PubMed: 8658145]
33. Gorlin RJ. Nevoid basal-cell carcinoma syndrome. Medicine (Baltimore) 1987;66:98–113. [PubMed: 3547011]
34. Mancuso M, Pazzaglia S, Tanori M, et al. Basal cell carcinoma and its development: insights from radiation-induced tumors in Ptch1-deficient mice. Cancer Res 2004;64:934–41. [PubMed: 14871823]
35. Bridge JA, Liu J, Weibolt V, et al. Novel genomic imbalances in embryonal rhabdomyosarcoma revealed by comparative genomic hybridization and fluorescence in situ hybridization: an intergroup rhabdomyosarcoma study. Genes Chromosomes Cancer 2000;27:337–44. [PubMed: 10719362]
36. Li X, Blagden CS, Bildsoe H, Bonnin MA, Duprez D, Hughes SM. Hedgehog can drive terminal differentiation of amniote slow skeletal muscle. BMC Dev Biol 2004;4:9. [PubMed: 15238161]
37. Ragazzini P, Gamberi G, Pazzaglia L, et al. Amplification of CDK4, MDM2, SAS and GLI genes in leiomyosarcoma, alveolar and embryonal rhabdomyosarcoma. Histol Histopathol 2004;19:401–11. [PubMed: 15024701]
38. Ruymann FB, Maddux HR, Ragab A, et al. Congenital anomalies associated with rhabdomyosarcoma: an autopsy study of 115 cases. A report from the Intergroup Rhabdomyosarcoma Study Committee (representing the Children's Cancer Study Group, the Pediatric Oncology Group, the United Kingdom Children's Cancer Study Group, and the Pediatric Intergroup Statistical Center). Med Pediatr Oncol 1988;16:33–9. [PubMed: 3277029]
39. Zhan S, Helman LJ. Glimpsing the cause of rhabdomyosarcoma. Nat Med 1998;4:559–60. [PubMed: 9585226]
40. Stalberg K, Haglund B, Axelsson O, Cnattingius S, Pfeifer S, Kieler H. Prenatal X-ray exposure and childhood brain tumours: a population-based case-control study on tumour subtypes. Br J Cancer 2007;97:1583–7. [PubMed: 17971773]
41. Shu XO, Potter JD, Linet MS, et al. Diagnostic X-rays and ultrasound exposure and risk of childhood acute lymphoblastic leukemia by immunophenotype. Cancer Epidemiol Biomarkers Prev 2002;11:177–85. [PubMed: 11867505]

42. Napier ID. Reference doses for dental radiography. Br Dent J 1999;186:392–6. [PubMed: 10365461]
43. Nortje CJ, Harris AM, Lackovic KP, Wood RE. Does the lead apron and collar always reduce radiation dose? SADJ 2001;56:502–4. [PubMed: 11885424]
44. Wood RE, Harris AM, van der Merwe EJ, Nortje CJ. The leaded apron revisited: does it reduce gonadal radiation dose in dental radiology? Oral Surg Oral Med Oral Pathol 1991;71:642–6. [PubMed: 2047109]
45. Jones GA, Burton EL. E-Speed dental film, time to take a new look? J Tenn Dent Assoc 1992;72:32–4. [PubMed: 1625454]

Table 1

Characteristics of subjects and their families

Characteristics	Cases		Controls	
	N	(%)[a]	N	(%)[a]
Sex of child				
Male	214	(67.1%)	214	(67.1%)
Female	105	(32.9%)	105	(32.9%)
Race of child				
White	284	(89.0%)	288	(90.3%)
Black	20	(6.3%)	21	(6.6%)
Other	15	(4.7%)	10	(3.1%)
Mother's educational level				
less than high school	45	(14.1%)	38	(12.0%)
high school	132	(41.4%)	126	(39.7%)
more than high school	142	(44.5%)	153	(48.3%)
Father's educational level				
less than high school	54	(17.1%)	36	(11.6%)
high school	112	(35.3%)	111	(35.8%)
more than high school	151	(47.6%)	163	(52.6%)
Total annual family income				
$0–19,999	103	(32.8%)	75	(23.9%)
$20,000–39,999	129	(41.1%)	154	(49.0%)
$40,000+	82	(26.1%)	85	(27.1%)
Age at diagnosis of index child[b]				
Child	7.6	(5.3)	7.5	(5.5)
Maternal	33.8	(6.8)	33.8	(7.0)
Paternal	36.6	(7.5)	36.6	(8.0)

[a] percentage of respondents to each question (excluding unknowns)

[b] mean (standard deviation)

Table 2

Pregnancy characteristics of cases and controls

Characteristics	Cases		Controls	
	N	(%)[a]	N	(%)[a]
Birth rank of index child				
First	138	(43.4%)	139	(43.9%)
Second	102	(32.1%)	99	(31.2%)
Third+	78	(24.5%)	79	(24.9%)
Type of delivery				
Vaginal	259	(81.2%)	272	(86.3%)
Caesarean	60	(18.8%)	43	(13.7%)
Length of pregnancy				
Normal	257	(81.3%)	255	(81.2%)
Premature	25	(7.9%)	9	(2.9%)
Overdue	34	(10.8%)	50	(15.9%)
Spotting/cramping/abnormal vaginal bleeding during pregnancy	67	(21.1%)	37	(11.9%)
Number of pregnancies[b]	3.1	(1.6)	3.2	(1.6)
Previous pregnancies	0.4	(0.9)	0.4	(0.8)
Stillbirths/miscarriages/abortions				
Living infants	2.6	(1.3)	2.7	(1.3)
Number of prenatal visits[b]	13.3	(4.1)	13.5	(4.8)
Index child birth weight (lbs)[b]	7.4	(1.4)	7.5	(1.1)
Age at index child birth (years)[b]				
Paternal	29.0	(5.9)	29.0	(6.4)
Maternal	26.2	(5.2)	26.2	(5.2)

[a] percentage of respondents to each question (excluding unknowns)

[b] mean (standard deviation)

Table 3

Reported mothers' diagnostic x-ray examinations during pregnancy by exposure site

Site Category	Cases		Controls	
	N	(%)[a]	N	(%)[a]
Pelvis	15	(4.8%)	11	(3.5%)
Abdomen	9	(2.9%)	4	(1.3%)
Back	1	(0.3%)	0	(0.0%)
Chest	4	(1.3%)	2	(0.6%)
Dental	12	(3.8%)	3	(1.0%)
Sinus	1	(0.3%)	0	(0.0%)
Neck	1	(0.3%)	0	(0.0%)
Lower extremity	4	(1.3%)	3	(1.0%)

[a] percentage of respondents to each question (excluding unknown)

Table 4

Risk of RMS and mothers' diagnostic x-ray examinations during pregnancy by trimester and site of exposure

Trimester of X-ray	Site of X-ray examination[a] Cases (%)/Controls (%)[b] Unadjusted OR (95% CI)[c] Adjusted OR (95% CI)[d]				
	Abdomen/Pelvis[e]	Other Truncal[f]	All Truncal	Other[g]	Any
First	4(1.3)/2(0.6)	2(0.6)/0(0.0)	5(1.6)/2(0.6)	8(2.6)/0(0.0)	12(3.9)/2(0.6)
	2.0 (0.4 – 11.0)	na	2.5 (0.5 – 13.0)	na	6.2 (1.4 – 27.8)
	1.4 (0.2 – 8.7)	na	1.9 (0.3 – 10.7)	na	5.7 (1.2 – 27.8)
Second	4(1.3)/4(1.3)	1(0.3)/1(0.3)	5(1.6)/4(1.3)	6(1.9)/5(1.6)	9(2.9)/8(2.6)
	1.0 (0.2 – 4.0)	1.0 (0.1 – 16.0)	1.2 (0.3 – 4.7)	1.2 (0.4 – 4.0)	1.1 (0.4 – 2.9)
	0.8 (0.2 – 3.5)	na	0.8 (0.2 – 3.5)	0.8 (0.2 – 3.1)	0.9 (0.3 – 2.4)
Third	16(5.1)/9(2.9)	1(0.3)/1(0.3)	17(5.5)/10(3.2)	4(1.3)/1(0.3)	21(6.8)/11(3.5)
	1.8 (0.8 – 4.1)	1.0 (0.1 – 16.0)	1.7 (0.8 – 3.8)	4.0 (0.4 – 36.1)	2.0 (0.9 – 4.1)
	1.8 (0.7 – 4.6)	1.2 (0.1 – 20.4)	1.7 (0.7 – 4.2)	4.8 (0.5 – 45.6)	2.0 (0.9 – 4.6)
Any	24(7.7)/15(4.8)	5(1.6)/2(0.6)[h]	28(9.0)/16(5.2)	18(5.8)/6(1.9)	42(13.5)/21(6.8)
	1.6 (0.8 – 3.2)	2.5 (0.5 – 13.0)	1.8 (0.96 – 3.4)	3.1 (1.2 – 7.9)	2.1 (1.2 – 3.7)
	1.4 (0.7 – 2.9)	2.2 (0.4 – 12.4)	1.5 (0.8 – 3.1)	2.9 (1.1 – 7.7)	1.9 (1.1 – 3.4)

[a] includes multiple x-ray exposure

[b] percentage of respondents to each question (excluding unknowns)

[c] odds ratio (95% confidence limits) unadjusted

[d] odds ratio (95% confidence limits) adjusted for matching factors (age, sex and race) and the length of the pregnancy, the type of delivery and the presence of spotting, cramping or abnormal vaginal bleeding during pregnancy.

[e] includes sites: pelvis, pelvimetry, uterus, uterus nos, abdomen, stomach, stomach nos, upper GI, IVP

[f] includes sites: back, chest

[g] includes sites: dental, sinus, neck, lower extremity

[h] includes 1 case for whom the site of x-ray was chest, trimester unknown

Table 5

In utero radiation exposure and risk of RMS by trimester of exposure and histologic type of RMS

Histologic Type	Cases		Trimester of Exposure OR (95%CI)[a]			
	N	Exposed	First	Second	Third	Any
Embryonal[b]	212	29	10.5(1.5 –458.4)[d]	0.8(0.2 – 3.3)[d]	2.1(0.8 – 5.3)	2.3(1.2 – 4.4)
Other[c]	107	13	2.0(0.1 – 118.0)[d]	2.0(0.3 – 22.5)[d]	1.8(0.4 – 8.5)[d]	1.9(0.7 – 5.1)

[a] unmatched analyses

[b] includes 1 case for whom the trimester was unknown

[c] includes 66 alveolar cases

[d] exact OR (95% CI)