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Maternal Exposure To Medical Radiation And Wilms Tumor In The Offspring: A Report From The Children's Oncology Group

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Abstract

Objective—This study examined the association between pre-conception and in-utero maternal medical radiation exposure and Wilms tumor, using data from a large population-based case-control study.

Methods—Cases were identified from the National Wilms Tumor Study Group. Controls were identified by random digit dialing and frequency matched to child's age and geographic area of residence in the United States and Canada. Interview data from 512 cases and 509 controls were analyzed using multivariable logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) for Wilms tumor and exposure to: 1) maternal X-ray alone and; 2) all medical radiation types (X-ray, CT, RT, Nuclear scans, Fluoroscopy) combined, for the period from two years before conception until child birth were estimated after adjustment for age, geographic area, maternal education, and household income.

Results—We found no consistent association between the risk of Wilms tumor and either maternal X-ray exposure (OR 0.9, 95% CI 0.7–1.3) or all medical radiation types combined (OR 0.9, 95% CI 0.7–1.2). No meaningful associations were seen for analysis of gonadal or non-gonadal radiation exposure.

Conclusion—Our study did not find any consistent pattern of association between Wilms tumor and maternal radiation exposure during pre-pregnancy or pregnancy period. With these negative results combined with the lower radiation doses currently used, we think further studies on radiation exposure as a risk factor for Wilms tumor are not warranted.

Keywords

Wilms Tumor; Children's Oncology Group; Radiation; Maternal

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Introduction

Wilms tumor is the most common primary malignant renal tumor in the pediatric population. From the latest U.S. Surveillance Epidemiology and End Results (SEER) data for 2001–2004, the reported incidence rate of Wilms tumor was 7.1 per 1,000,000 children aged 0–14 years [1]

Over the past few decades there has been striking improvement in the treatment of Wilms tumor and it is now commonly recognized as a paradigm in the multimodality therapy of solid childhood cancers [2]. Although there have been many putative risk factors for Wilms tumor, none have been unequivocally established except for very rare genetic conditions and congenital anomalies including aniridia and genitourinary tract anomalies [3]. The relatively young age at diagnosis of Wilms tumor suggests that pre-conception and in utero exposures may contribute to its etiology [4]. A variety of parental environmental, lifestyle, and medical exposures have been examined in relation to Wilms tumor [5–9], but none have been established as risk factors.

Medical radiation has been examined as a risk factor for many cancers, including several childhood malignancies. A large 1956 case–control study of children who died of cancer, including Wilms tumor, was the first study to propose a possible association between prenatal radiographs and increased incidence of certain childhood cancers [10]. Subsequently, this relationship was examined in many studies; and although inconsistent in their conclusions, several studies reported elevated relative risk estimates ranging from over 1.1 to 2.2 [11–15]. Some associations have been reported in singleton as well as twin pregnancies [16]. Notably, the more recent studies have reported lower relative risks than earlier ones [17–21]. This decrease in risk has paralleled the consistent decline in doses of medical radiation over the past decades [22–24].

In a review of data from Oxford Survey of Childhood Cancers, Bithell and Stewart reported relative risks of different types of solid childhood cancers and leukemias following irradiation in-utero. A relative risk of 1.59 (95% confidence interval (95% CI) 1.25–2.01) for developing Wilms Tumor was reported with prenatal irradiation exposure. No published study has specifically evaluated the association between maternal exposure to medical radiation and Wilms tumor. We examined the association of pre-conception and in-utero maternal medical radiation exposure and Wilms tumor using data from a large North American case-control study.

Materials and Methods

Cases

Cases were newly diagnosed Wilms tumor patients less than 16 years of age, at one of the 128 participating hospitals in the United States and Canada between 1999 and 2002 [8]. Eligible cases included all patients at any stage of pathologically confirmed diagnosis of Wilms tumor and registered with the National Wilms Tumor Study (NWTS)-5 clinical and biology study protocols (CCG#4941, POG#9440). The NWTS was a North American collaborative clinical trial study of the treatment and biology of Wilms tumor. The National Wilms Tumor Study Group (NWTSG) included members of the two national pediatric collaborative clinical trials groups, namely the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG) (now merged into the Children's Oncology Group). COG was estimated to have included about 95% of all newly diagnosed Wilms tumor cases under the age of 15 years in the United States and Canada [25].

Patients diagnosed with clear cell sarcoma and rhabdoid tumor of the kidney were not eligible for inclusion in the study. Other inclusion criteria were an English or Spanish speaking biologic mother, and a telephone in the house to identify the controls using random digit dialing and to conduct an interview with the case and control mothers. All participating institutions obtained IRB approval for the study. Treating physicians provided consent to approach the parents of the patients for permission to participate in the study.

A total of 653 cases were determined to be potentially eligible. Of these, 512 case mothers were successfully interviewed (78.4% of those eligible). Reasons for non-inclusion were: Absence of data on primary exposure (n=11), lost-to-follow-up (n=58), refusal to participate (n=47), and other reasons (n=25).

Controls

Controls were identified through list-assisted random digit dialing (RDD) and were frequency matched to cases according to age at diagnosis using 3 age strata (< 2 years, 2–3 years, and 4 + years of age) and geographic region of residence using five strata (four U.S. Census regions including Midwest, Northeast, South and West plus Canada). A 51% response proportion for the RDD screening phase was obtained. Of 682 eligible control mothers identified, 509 (74.6%) completed the interviews.

Interviews

Structured computer-assisted telephone interviews were conducted with the mothers of both cases and controls. The case diagnosis date and the initial RDD screening date were chosen as the reference dates, for cases and controls, respectively. Information was collected on various potential risk factors for Wilms tumor including demographic factors, pregnancy history, birth characteristics, childhood exposures, parental occupational history, family medical history, and use of tobacco, alcohol, and medication.

One interview section focused entirely on maternal radiation exposure in the period ranging from 2 years before pregnancy through the child's birth. History of any form of medical radiation exposure including traditional X-rays, computerized tomography (CT) scans, nuclear medicine examinations, fluoroscopy and any radiation treatment (RT) by the specific time period was obtained. Participants were instructed to exclude dental X-rays from their responses. For this analysis, reports of ultrasound, mammography or magnetic resonance imaging have been excluded.

Statistical Analyses

Odds ratios (ORs) and 95% CIs for the association between radiation exposure and Wilms tumor were estimated using unconditional logistic regression. Radiation exposure was assessed in two ways: 1) traditional X-rays alone and 2) all medical radiation types (X-ray, CT, RT, NMR) combined

The two frequency matching variables which included 3 age strata for child’s age at reference date and 5 geographic region strata were adjusted for in all models. In addition, we evaluated the following potential confounders: child’s gender, maternal education, household income, race and maternal age. *A priori*, we decided to adjust for household income and maternal education to account for the selection bias potentially introduced due to the random digit dialing method and non-response in the study sample. **We** generated two statistical models in the analysis. Model 1 included the matching variables only; Model 2 included household income, maternal education, and the two matching variables. There was no appreciable difference in the effect estimates between Models 1 and 2. Further addition of child’s gender, race, maternal smoking and maternal age to the models did not materially alter the effect estimates and thus

we did not include any of them in our final model. Thus, our final model included the matching variables and the two *a priori* confounders, maternal education and annual household income. The referent category for all analyses included mothers without radiation exposure in the period from two years before conception until child birth.

For each model, we also assessed the association by site-specific X-ray exposure defined as gonadal or non-gonadal exposure. All radiation exposure including the lower gastrointestinal and reproductive tracts was classified as gonadal; non-gonadal regions included all other anatomical sites.

Data were also analyzed for five different exposure periods: between 2-1 year before conception, 1 **year** before conception through conception and the three trimesters during pregnancy. Additional analyses were conducted by case subgroups defined by the presence and type of nephrogenic rests, tumor site, stage, and multicentricity. Nephrogenic rests are foci of abnormally present nephrogenic renal blastemal cells. These are considered as precursors of Wilms tumor. Nephroblastomatosis is the diffuse presence of nephrogenic rests. Nephroblastomatosis may be perilobar; intralobar or panlobular. Usually the more primitive elements are situated intralobarly, thus the intralobar Nephroblastomatosis has been associated more frequently with the development of Wilms tumor than the perilobar blastemal rests.

Factors examined as potential effect measure modifiers included child's gender, maternal education, household income, and maternal age. Effect measure modification was based on the significance ($p < 0.10$) of the likelihood ratio test of the first order interaction term in the logistic regression model compared to the model without the term. None of these variables emerged as effect measure modifiers in our analyses.

All statistical analyses were conducted using SAS 9.1.3 [26].

Results

A total of 512 cases and 509 control mothers completed the interview including questions on the primary exposure of interest and were included in the final analysis. The age distribution of cases at diagnosis was: <2 years =146 (28.5%), 2–3 years = 161(31.5%), 4+ years= 205 (40%). The distribution of socio-demographic factors among cases and controls are presented in Table 1. These characteristics of cases and controls in the study population were generally similar. A notable exception was that there were higher odds of a female subject developing Wilms tumor as compared to males after adjusting for the matching variables child age at reference and geographic area. (OR 1.5, 95%CI 1.2 −1.9). This finding has also been reported in previous studies from Wilms tumor data set [8,9]. There were no material differences in cases and controls with respect to maternal age, maternal education, or household income.

A total of 94/512 (18.4%) case mothers and 103/509 (20.2%) control mothers reported having had at least one traditional X-ray in the period from 2 years before conception until the child's birth. Among these women, 82 (16%) case mothers and 89 (17.5%) control mothers had at least one X-ray before pregnancy. Thirteen (2.5%) case mothers and 18 (3.5%) control mothers had at least one exposure during pregnancy. (Table 2).

For all types of medical radiation exposure combined, a total of 100/512 (19.5%) of case mothers and 114 (22.4%) of control mothers reported at least one radiation exposure over the defined study period with all radiation types combined (data not shown).

Overall, we did not find any association between maternal traditional X-ray exposure and the risk of Wilms tumor (OR 0.9, 95% CI 0.7–1.3) (Table 2). A total of 17 subjects had no

traditional X-rays but had received any non-traditional X-rays, and were excluded from this analysis: n=6 cases and 11 controls.

No pattern of elevated odds ratios was found for any of the separate exposure periods (between 2-1 year before conception, 1 year before conception through conception and each of the three trimesters during pregnancy) (Table 2). Although, no consistent pattern was observed, we did find a weakly elevated, but imprecise, odds ratio for pre-pregnancy gonadal X-ray exposure. (Before pregnancy OR= 1.4 95% CI 0.5–3.8; during pregnancy OR=1.0, 95% CI 0.1–15.5). No such results were seen for non-gonadal exposures (before pregnancy OR= 0.9, 95% CI 0.6–1.3; during pregnancy OR=0.7, 95% CI 0.3–1.4).

A subgroup analysis by type of nephroblastomatosis, revealed no differences in the odds of developing Wilms tumor associated with a specific rest type based on maternal X-ray or any radiation exposure (Table 3). Further, analysis by case subgroups based on tumor site, stage, multicentricity and predominant histologic pattern also did not show any material differences for radiation exposure (data not shown). However, the odds ratios were imprecise, due to smaller sample sizes in the subgroups.

When we repeated each of the above analyses for all radiation exposure types combined the results were essentially the same (data not shown).

Discussion

This is the largest and most detailed study to evaluate the association between maternal radiation exposure in the pre-conception period and different trimesters of pregnancy and the risk of Wilms tumor in the offspring. Our results show no pattern of elevated risk for Wilms tumor with either traditional X-rays alone or with all forms of radiation types (X-ray, CT, Fluoroscopy, and RT) combined. When exposure was analyzed by anatomical site, we saw a slightly elevated, but imprecise risk of Wilms for gonadal exposures in the pre-pregnancy period (OR= 1.4, 95% CI 0.5–3.8). However, for this estimate and the one for gonadal exposure during pregnancy, the confidence intervals were very wide due to relatively few gonadal exposures in the study. Also, we did not find a pattern of increased risk by time period or Wilms tumor subgroup defined by biologic factors, although the latter analyses were limited by small numbers for some subgroups.

Our finding that in utero and pre-conception radiation exposure was not consistently associated with the development of Wilms tumor differs from early studies of childhood leukemias and solid cancers that reported weak to moderate increases in risk [10–12,18,21].

Based on the available literatures, there is no clear evidence to support any particular period of gestation when the fetus might be at greatest risk for Wilms tumor with radiation exposure. There is inconsistency in results with some studies suggesting higher risk of childhood cancer with X-ray exposure in the last trimester [22] while others have reported a higher risk in the first trimester and more so in the first eight weeks after conception when organogenesis occurs [27]. In our study, however, there was also no apparent variation in risk associated with exposure during different window periods comprising the 2 pre-pregnancy years and the three trimesters of pregnancy.

Our failure to demonstrate an association between maternal radiation exposure and Wilms tumor in offspring probably reflects the clinical use of exponentially less radiation in recent decades [23,28]. The Oxford Survey of Childhood Cancers also reported a significant decrease in the relative risk of cancers between the birth cohort years 1940–1976 which closely paralleled the decline in the radiation doses occurring over the same period. This temporal relationship between a decrease in radiation dose per film and an apparent decreased risk of

cancers accords with a causal hypothesis of radiation for cancer [22,28]. Many recent studies have specifically explored the relationship of prenatal X-ray exposure with other solid tumor types [29–31]. There is supporting evidence from these studies for our results as none of these studies have reported any significant associations.

Our analysis is based on the largest population-based case-control study of Wilms tumor to date. We also have data available on a range of possible confounders that were included as part of the interview. Although this is one of the largest epidemiologic studies of risk factors for Wilms tumor, our ability to detect a precise effect estimate with some radiation exposures was limited. Another limitation of our study is that the information on radiation exposure was self-reported and was not validated from medical records. With the mean age at diagnosis of cases and the reference date from controls of 4.4 and 3.3 years respectively, the recall period for the mothers for a medical examination like X-ray is long.

It is also possible that case mothers might have a tendency to over-report the results thus tending to bias the estimates away from the null. Also, the case mothers might report the radiation exposures more accurately relative to control mothers. The resulting differential misclassification would tend to bias the estimates either towards or away from the null. However a few studies have validated the results of the initial case-control studies of childhood cancer and radiation exposure finding that maternal statements could largely be confirmed from antenatal records, irrespective of having been from a case or a control mother. These studies found essentially similar associations were found whether maternal reports or clinical records were used in the analysis. Thus, these studies concluded that recall bias had relatively little effect.[32,33]

Although we have adjusted for maternal education and annual household income as a surrogate for potential selection bias due to response and the use of RDD controls, we cannot fully exclude the influence of selection bias. Finally, combining an analyses of all types of radiation exposure (e.g. X-ray, CT and radiation therapy) together may also be a source of exposure misclassification as some types of radiation involve much higher doses than others. We did not find it meaningful to analyze each radiation type separately because of the sparse numbers for many specific radiation types except traditional X-rays.

Previous studies including the Oxford Survey of Childhood Cancers supported an increased risk in childhood cancers with increasing doses of exposure. The Oxford survey for deaths between 1953–1972 reported a slope of 0.194 excess relative risk per X-ray film [28]. Although, some previous studies have done a dose response analysis using number of X-rays as a proxy of the radiation doses [34], dosimeter studies have reported up to 30-fold variation in radiation doses of same X-ray examination depending on the choice of film and technique of radiography [35,36]. The X-ray examinations included in our study have been performed over about 16 years in hundreds of hospitals in two different countries. With such a huge range of possible doses, it was not possible to do an accurate dose-response assessment.

We conclude from our study that there is no consistent evidence of any overall association between Wilms tumor in the offspring and maternal radiation exposure during pre-pregnancy or pregnancy period. In the light of these results from the largest study of Wilms tumor cases to date, we suggest that any further studies of medical radiation exposure as a risk factor for Wilms tumor are not warranted.

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Table 1

Demographic characteristic of cases and age/region-matched controls, United States and Canada, 1999–2002

Factor	Cases N=512		Controls N=509	
	n	%	n	%
Gender				
Male	218	42.6	270	53.1
Female	294	57.4	239	46.9
Child's age at reference date				
< 2 years	146	27.9	137	26.9
2–3years	161	31.5	141	27.7
4+ years	205	40.5	231	45.4
Geographic region				
Midwest	156	30.5	152	29.9
Northeast	69	13.5	59	11.6
South	174	34	180	35.4
West	57	11.1	62	12.2
Canada	56	10.9	56	11
Mother's race				
White	384	75	398	78.2
African American	68	13.3	57	11.2
Hispanic	42	8.2	33	6.5
Other	18	3.5	21	4.1
Mother's education[a]				
0–11 years	43	8.4	40	7.9
High school degree	134	26.2	114	22.4
> High school	335	65.4	354	69.7
Household income[b]				
<10k	46	9.0	37	7.9
10–20k	79	15.5	96	20.4
21–30k	63	12.4	67	14.2
31–40k	65	12.6	65	13.8
41–50k	64	12.2	63	13.4
51+k	156	30.2	143	30.3
Mother's age				
<20 years	39	7.6	37	7.3
20–24 years	110	21.5	103	20.2
25–30 years	178	34.8	162	31.8
31+	185	36.1	207	40.7

[a] There was 1 missing value for a control mother's education

[b] There were 77 missing values for household income (39 cases and 38 controls).

Table 2

Maternal X-ray exposure from 2 years before conception through child birth and the odds of developing Wilms tumor.

Exposure	Cases		Controls		Odds Ratio 1[a]	Lower 95% CI	Upper 95% CI	Odds Ratio 2[b]	Lower 95% CI	Upper 95% CI
	n	%	N	%						
Total X ray (Gonadal and Non-gonadal)										
None (Referent)[c]	412	81.4	395	79.3	1			1		
Any (2 years before pregnancy to childbirth)	94	18.6	103	20.7	0.9	0.7	1.2	0.9	0.7	1.3
Pre- pregnancy										
(1–2 years before pregnancy)	74	14.6	72	14.5	1.0	0.7	1.5	1.1	0.7	1.5
(1 year before pregnancy)	43	8.5	56	11.2	0.7	0.5	1.1	0.8	0.5	1.2
During pregnancy										
Ist Trimester	9	1.8	10	2.0	0.8	0.3	2.1	0.8	0.3	2.1
2nd Trimester	8	1.6	11	2.2	0.7	0.3	1.8	0.7	0.3	1.7
3rd Trimester	8	1.6	9	1.8	0.9	0.3	2.4	0.9	0.3	2.2
Gonadal X ray										
Pre-pregnancy	11	2.2	9	1.8	1.2	0.5	3.0	1.4	0.5	3.8
During pregnancy	1	0.2	1	0.2	1.1	0.1	17.0	1.0	0.1	15.5
Non-gonadal X ray										
Pre-pregnancy	82	16.2	89	17.9	0.9	0.7	1.3	0.9	0.7	1.3
During pregnancy	13	2.6	18	3.6	0.7	0.3	1.4	0.7	0.3	1.4

[a] Odds Ratio from Model 1 which includes the two frequency matched variables: child's age at diagnosis and geographic region of residence.

[b] Odds Ratio from Model 1 which includes household income, maternal education, and the 2 matching variables.

[c] A total of 17 subjects who had no traditional X-rays but had any received any non-traditional X-ray were excluded from this category: n=6 cases and 11 controls.

Table 3

Distribution Of Maternal X-Ray And Overall Radiation Exposure Indicated By Presence Of Nephrogenic Nests.

	(Nephroblastomatosis combination)			
	Negative	**PLNR+[a]**	**ILNR+[b]**	**Total**
No Maternal X-ray	193 (80.1)	55 (78.6)	91 (88.4)	339
Maternal X-ray+	48 (19.9)	15 (21.4)	12 (11.6)	75
Total	241	70	103	414
No Maternal Radiation	192 (79.7)	54 (77.1)	89 (86.4)	335
Maternal Radiation +	49 (20.3)	16 (22.9)	14 (13.6)	79
Total	241	70	103	414
Frequency Missing = 8				

[a] PLNR+ indicates Perilobar nephroblastomatosis present.

[b] ILNR+ indicates Intralobar nephroblastomatosis present.