Maternal Occupational Exposure to Ionizing Radiation and Major Structural Birth Defects

Hyeyeun Lim[1], A.J. Agopian[1], Lawrence W. Whitehead[1], Charles W. Beasley[2], Peter H. Langlois[3], Robert J. Emery[1], Dorothy Kim Waller*[1], and the National Birth Defects Prevention Study

Background: Ionizing radiation (IR) is known to be carcinogenic and mutagenic, but little is known about the association between maternal occupational exposure to IR and birth defects. **Methods:** We studied 38,009 mothers who participated in the National Birth Defects Prevention Study and delivered between 1997 and 2009. We assessed odds ratios [ORs] for the association between maternal occupations with potential exposure to IR and 39 birth defects. **Results:** We observed significant odds ratios (ORs) for isolated hydrocephaly (adjusted OR [AOR], 2.1; 95% confidence interval [CI], 1.1–4.2), isolated anotia/microtia (AOR, 2.0; 95% CI, 1.0–4.0), isolated colonic atresia (crude OR, 7.5; 95% CI, 2.5–22.3), isolated omphalocele (AOR, 2.3; 95% CI, 1.1–4.6) and isolated anencephaly (crude OR, 0.23; 95% CI, 0.06–0.94). We also observed a nonsignificant OR for birth defects in aggregate (AOR, 2.0; 95% CI, 0.9–4.6) among mothers with potential occupational exposure to fluoroscopy. **Conclusion:** We assessed 39 birth defects, observing that maternal occupations with potential exposure to IR were associated with a significantly increased risk for 4 birth defects and a significantly protected risk for 1 birth defect. These results should be interpreted cautiously because our measurement of exposure is qualitative, some of these associations may be due to occupational exposures that are correlated with IR and some may be due to chance. However, these findings serve as the first evaluation of these relationships in a large study and may be useful for generating hypotheses for future studies.

Birth Defects Research (Part A) 103:243–254, 2015.

Key words: ionizing radiation; occupational; fluoroscopy; birth defects; anotia; hydrocephalus; omphalocele; colon atresia; anencephaly

Introduction

Ionizing radiation (IR) is widely used for diagnostic and therapeutic medical procedures, and also for industrial and commercial purposes. At a sufficient level of exposure, it can be carcinogenic, mutagenic, and an organ system toxicant (Health Risks Exposure to Low Levels of Ionizing Radiation BEIR VII Phase 2, 2006; Schauer and Linton, 2009). Teratogenic effects of IR may occur either by means of damage to the DNA in the ovum before conception or by means of cell death or cell damage in the embryo during early pregnancy (Kirk and Lyon, 1984; Marchetti et al., 2001; Health Risks Exposure to Low Levels of Ionizing Radiation BEIR VII Phase 2, 2006; De Santis et al., 2007; Xu et al., 2008).

In the United States, the average dosage of IR from occupational sources has decreased substantially. Workers deemed likely to receive a whole body dose of >5 mSv per year are provided with a monitoring badge to measure any occupational doses that are received (Occupational Safety and Health Administration, 1970). If a person's dose is greater than the annual effective dose limit (50 mSv per year), further action must be taken including changes in job duties, work time and equipment. However, there are occupational groups such as pilots and flight crew who receive relatively high exposures to IR, but are not covered by the federal regulations (Bailey, 2000; Friedberg and Copeland, 2003).

If a woman voluntarily declares that she is pregnant and she is likely to be exposed to IR at her workplace, she must be monitored with the goal of not exceeding an exposure of 0.5 mSv per month during the entire pregnancy (The National Council on Radiation Protection and Measurements, 2009a). However, approximately 50% of women do not recognize their pregnancies until 4 weeks of gestation or later at which point the embryo may already have been exposed to IR during the critical period of organogenesis (Dott et al., 2010).

Existing studies of maternal occupational exposure to IR and birth defects are generally limited to one occupation, and include very small numbers of birth defects resulting in low statistical power (Doyle et al., 2000; Irgens et al., 2003; Shirangi et al., 2009). To date, there are two population-based studies of occupational exposure to IR and all birth defects. A cohort study conducted in Germany, included 3816 pregnancies and only assessed

Supported by Pilot Project Funding from Grant No.2T42OH008421 from the National Institute for Occupational Safety and Health (NIOSH)/Center for Disease Control and Prevention to the Southwest Center for Occupational and Environmental Health, a NIOSH Education and Research Center and a grant funded by NISOH (Grand No.: R03OH010315).
[1]University of Texas School of Public Health, UTHealth, Houston, Texas
[2]University of Texas School of Medicine, UTHealth, Houston, Texas
[3]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas

*Correspondence to: Dorothy Kim Waller, The University of Texas, UTHealth, School of Public Health, 1200 Pressler Street, E-619 Houston, TX 77030. E-mail: kim.waller@uth.tmc.edu

Published online 28 March 2015 in Wiley Online Library (wileyonlinelibrary.com). Doi: 10.1002/bdra.23340

birth defects in aggregate (Wiesel et al., 2011). The other study is the Baltimore-Washington Infant Study which assessed the association between maternal occupational exposure to IR and congenital cardiac defects including 4390 cases of congenital cardiac defects and 3572 controls (Ferencz et al., 1993, 1997).

Our objective in this study was to use data from the National Birth Defects Prevention Study (NBDPS) to investigate whether potential maternal exposure to occupational sources of IR during the periconceptional period increases the risk of having a fetus affected by any of 39 birth defects.

Methods

STUDY POPULATION

The NBDPS is a case-control study with 10 participating sites: Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. Infants or fetuses who were delivered between October 1, 1997, and December 31, 2009, were eligible for the current study. For the majority of participating sites, cases were live-born infants, fetal deaths of at least 20 weeks' gestation and elective pregnancy terminations of any gestational age. Controls were live-born infants without major birth defects, randomly selected from birth certificates or birth hospitals to represent the birth population from which the cases were drawn. This study was approved by the institutional review boards of each of the participating study sites and the Centers for Disease Control and Prevention. Detailed study methods have been published previously (Yoon et al., 2001; Rasmussen et al., 2003).

All cases were reviewed by clinicians affiliated with the NBDPS according to established guidelines and were classified as isolated, multiple, or complex birth defects (Schnitzer et al., 1995). Cases with isolated birth defects were defined as having either one major birth defect, two or more major birth defects affecting only one organ system, or one major birth defect with a sequence of related defects. Cases with multiple birth defects had two or more major unrelated defects in different organ systems.

Birth defects that were known or strongly suspected to have been caused by single-gene disorders or chromosomal abnormalities were excluded from the NBDPS. Utah was unable to contribute cases of orofacial clefts in 2003, California only began to contribute cases of pulmonary valve stenosis beginning on January 1, 2002, and cases of congenital cataracts were only contributed study-wide beginning January 1, 2000. For calculations involving these birth defects, we excluded information from control mothers for those locations and study periods during which cases were not available. As all cases of hypospadias were male, for analyses of hypospadias, controls were restricted to mothers of male infants.

EXPOSURE ASSESSMENT

Maternal interviews were conducted using a standardized, computer-assisted telephone interview in English or Spanish. Interviews were completed within an average of 11 months from the estimated date of delivery for cases, and 9 months for controls, which allowed for sufficient time for identification of cases and abstraction and review of medical records.

The occupational section of the NBDPS questionnaire asked mothers whether they were homemakers, students, unemployed, or in military service and recorded up to 6 different jobs during the periconceptional period. Mothers who listed the occupation of homemaker, student or unemployed were excluded to limit the possibility of bias due to the "healthy worker" effect. The questionnaire asked mothers "What were the names of the companies or organizations you worked for", "What was your job title there?", "What did your division make or do?", "What were your main activities or duties?", and "Describe any chemicals or substances you handled or machines that you used or worked in the same room with". Also, mothers were asked to give the month and year that they started each job.

The NBDPS coded all maternal occupations and industries using mother's responses to the questions described above and the 2000 Standard Occupational Classification code and the 2007 North American Industry Classification System. However, these occupational codes were too broad to capture occupations with exposure to IR. For that reason, we used a textual analysis to scan all the open-ended questions described above. In occupational epidemiology, a qualitative approach of this type is often used for exposure assessment when only questionnaire-based data are available for job title, workplace and job activities (Nieuwenhuijsen, 2004; Ignacio and Bullock, 2006).

Based on recent reports on occupational exposures to ionizing radiation in the US, similar reports for Canada and the data base of the occupational information network (O*NET) (Annual reports on occupational radiation exposure in Canada, 2008; National Council on Radiation Protection and Measurements, 2009a, 2009b; The Occupational Information Network) we developed a list of workplaces, industries, job titles, and job activities with potential exposure to IR. In addition, an extensive literature review was also done to identify any additional occupational or workplace exposures using the following main search terms; ionizing radiation, occupational, occupations, workplace, fluoroscopy, CT scan, x-ray, radioactive, isotope, health care, research, airline, construction, manufacturing, retail, administrative, postal worker, oil, gas and radiation safety. The completed list was reviewed by five of the authors of this manuscript (L.W.W., C.W.B., R.J.E., D.K.W., and H.L.). One of these authors is a hospital based health physicist with 20 years of experience (C.W.B.), one is a university health physicist (R.J.E.) with 20 years of experience, one is an industrial hygienist with 20 years of experience (L.W.W.), one has 20 years of experience as an epidemiologist with an additional 7 years of experience

working in a hospital as an RN (D.K.W.), and the lead author is a PhD candidate in environmental science (H.L.).

A SAS program (SAS Institute, Cary, NC) was used to scan all of the answers to the questions described above for strings of characters that would identify mothers who had workplaces, occupations or activities with potential exposure to IR. The strings of characters that were used were designed to account for typos, misspellings and abbreviations (Appendix 1) and reviewed by the five professionals listed above. When a maternal occupation was "scan positive", the text of their answer was read by three of the authors (L.W.W., D.K.W., and H.L.) to verify whether IR was present in their workplace and that their particular occupation or job activities involved the use of IR. If the mother had a job that typically involves the use of IR or if she gave one or more key words related to IR such as x-ray, CT scan, radioactive, cardiac catheter lab etc., she was coded as having potential exposure to IR. Otherwise, she was considered to be unexposed and assigned to the referent group. We also randomly selected 2000 mothers from the referent group and two authors read the text of their answers (D.K.W. and H.L.) to verify that their workplace, their particular occupation and job activities were not involved in use of IR. All reviewers were blinded to the case-control status when they reviewed the text of the mother's answer.

There were several health care workers who stated in their text response that they were exposed to IR because they were around radiographic exam machines at their workplace; however based on their occupations and job activities it was clear that they were not in the vicinity of the x-ray machines when they were operating. These individuals were coded as unexposed. Those mothers whose responses were ambiguous such that we could not tell whether they were exposed to IR or not, were coded as missing.

As the level of exposure to IR can vary greatly across different occupations and job activities, mothers with potential exposure to IR were further classified into nine subgroups according to their source of exposure to IR. Hospital workers were classified as exposed to: (1) fluoroscopy including c-arm, (2) nuclear medicine, (3) computed tomography (CT) including computed axial tomography (CAT), (4) other IR sources including planar x-ray, portable x-ray, dual-energy x-ray absorptiometry, mammogram, and any other sources of IR. Because we were unable to distinguish exposures to stationary x-rays and portable x-rays, we grouped all planar x-rays into one category. The other five subgroups were workers exposed to IR in (5) dental clinics, (6) animal clinics, (7) research institutions, (8) flight crew, and (9) other occupations. Among the hospital workers, some mothers reported more than one source of exposures to IR. In those cases, the mother was assigned to the exposure group that was likely to have the highest level of exposure based on the following hierarchy (fluoroscopy > nuclear medicine > CT scan > other IR sources) (Kim et al., 2008; National Council on Radiation Protection and Measurements, 2009a, 2009b).

Only potential exposures that occurred during the critical period (3 months before to 3 months after conception) were considered.

To assess exposures that mothers in this study had to radiographic exams as patients, we used interview questions that asked whether the mother had an x-ray, or scans that were unrelated to their pregnancy, the type of scan and when it was done.

STATISTICAL ANALYSIS

Logistic regression was used to examine odds ratios (ORs) for the association between potential maternal occupational exposure to IR during the critical period and 39 selected birth defects. Among the birth defect phenotypes included in the NBDPS, we assessed only those with $\geq$3 or more exposed cases, as those phenotypes with fewer cases would not have allowed estimation of sufficiently precise ORs.

We assessed the possibility of confounding from the following maternal characteristics: maternal age at delivery, race, level of education, pre-pregnancy body mass index (BMI) pre-existing diabetes, smoking, use of supplements containing folic acid, any consumption of alcohol, use of illicit drugs, household income, first live birth, and study location.

We ran backward logistic regression models separately for the each of 39 categories of birth defects. Variables that resulted in a change in the ORs of 10% or more for any birth defect were considered to be confounders and were retained in the final models for all birth defects. Thus, all adjusted odds ratios (AOR) were adjusted for maternal age, race, level of education, study location, household income, pre-pregnancy BMI and use of illicit drugs (Van Gelder et al., 2009). The format for the variables that were entered into the final models is shown in Table 1. When fewer than five exposed cases remained after adjusting, we reported crude odds ratios (COR), because when a cell has four observations or less adjustment by multiple factors is likely to be less accurate than the COR (Greenland, 2000).

To determine whether any of the associations we observed were affected by the presence of cases with multiple birth defects, we repeated analyses restricting the sample to isolated cases. We also reran our analyses excluding mothers who were exposed to diagnostic tests involving IR during the critical period.

In order to compare our findings with the previous German study of occupational exposures (Wiesel et al.,

TABLE 1. *Demographic Characteristics among Mothers Who Reported at Least One Occupation during the Periconceptional Period[a], National Birth Defects Prevention Study, 1997 to 2009*

	Case (*N* = 18,621)		Control (*N* = 6,820)		
	N	**%**	***N***	**%**	**Crude OR (95% CI[g])**
Maternal age at delivery (yrs)					
< 18	290	1.56	99	1.45	1.08 (0.86, 1.37)
18 - 24	5367	28.83	1919	28.14	1.03 (0.96, 1.11)
25 - 29	5242	28.16	1933	28.35	1.00
30 - 34	4767	25.61	1854	27.19	0.95 (0.88, 1.02)
35 - 39	2375	12.76	850	12.47	1.03 (0.94, 1.13)
≥ 40	576	3.09	164	2.41	1.30 (1.08, 1.55)
Maternal race/ethnicity					
Non-Hispanic white	11970	64.34	4377	64.22	1.00
Non-Hispanic black	1961	10.54	797	11.69	0.90 (0.82, 0.98)
Hispanic, born in US	1658	8.91	579	8.49	1.05 (0.95, 1.16)
Hispanic, born out of US	1768	9.50	608	8.92	1.06 (0.96, 1.17)
Other	1248	6.71	455	6.68	1.00 (0.90, 1.12)
Maternal education (yrs)					
0 - 8	578	3.11	183	2.69	1.06 (0.89, 1.26)
9 - 11	1480	7.96	493	7.24	1.01 (0.89, 1.13)
12	4663	25.07	1559	22.88	1.00
13 - 15	5657	30.41	2065	30.31	0.92 (0.85, 0.99)
≥ 16	6223	33.46	2513	36.89	0.83 (0.77, 0.89)
Pre-pregnancy BMI (kg/m^2)					
Underweight (< 18.5)	886	4.88	316	4.73	1.08 (0.95, 1.24)
Normal weight (18.5 - 24.9)	9410	51.79	3634	54.43	1.00
Overweight (25 - 30)	4238	23.32	1560	23.36	1.05 (0.98, 1.13)
Obese (≥ 30)	3637	20.02	1167	17.48	1.20 (1.12, 1.30)
Household income ($)					
< 10,000	2487	14.01	871	13.56	0.98 (0.90, 1.07)
10,000 < 50,000	8480	47.78	2918	45.42	1.00
≥ 50,000	6781	38.21	2635	41.02	0.89 (0.83, 0.94)
Preexisting diabetes					
Yes	377	2.03	40	0.59	3.50 (2.52, 4.85)
No	18219	97.97	6770	99.41	1.00
Any consumption of alcohol[b]					
Yes	7639	41.25	2878	42.40	0.95 (0.90, 1.01)
No	10878	58.75	3910	57.60	1.00
Any smoking[c]					
Yes	3925	21.10	1304	19.13	1.13 (1.05, 1.21)
No	14681	78.90	5514	80.87	1.00
Use of supplements containing folic acid[d]					
Daily use	8360	44.91	3016	44.23	1.00

TABLE 1. *Continued*

	Case ($N = 18,621$)		Control ($N = 6,820$)		
	N	**%**	***N***	**%**	**Crude OR (95% CI[g])**
Any use	5039	27.07	1816	26.63	1.01 (0.94, 1.07)
No use	5218	28.03	1987	29.14	0.95 (0.89, 1.01)
Illicit drug use[e]					
Yes	1084	5.83	356	5.22	1.12 (0.99, 1.27)
No	17523	94.17	6460	94.78	1.00
Parity					
First live birth	9025	48.50	3069	45.02	1.15 (1.09, 1.22)
≥Second or greater	9584	51.50	3748	54.98	1.00
Study site					
Arkansas	2533	13.61	886	12.99	1.00
California	1978	10.62	644	9.44	1.07 (0.96, 1.21)
Iowa	2044	10.98	899	13.18	0.80 (0.71, 0.89)
Massachusetts	2581	13.86	905	13.27	1.00 (0.90, 1.11)
New Jersey	1189	6.39	392	5.75	1.06 (0.93, 1.22)
New York	1373	7.37	615	9.02	0.78 (0.70, 0.88)
Texas	1680	9.02	632	9.27	0.85 (0.75, 0.96)
CDC/Atlanta	2181	11.72	752	11.03	1.01 (0.91, 1.14)
North Carolina	1323	7.11	547	8.02	0.93 (0.83, 1.05)
Utah	1735	9.32	547	8.02	1.11 (0.98, 1.25)
Mean number of words in all questions on occupations[f]	18.00		17.9		
Healthcare worker					
Yes	2453	13.17	938	13.75	0.95 (0.88, 1.03)
No	16168	86.83	5882	86.25	1.00
Potential occupational exposure to ionizing radiation					
Yes	442	2.37	186	2.73	0.87 (0.73, 1.03)
No	18179	97.63	6634	97.14	1.00

[a]Between 3 months prior to conception and the end of the 1st trimester of pregnancy

[b]Any consumption of alcohol between 1st month of pregnancy and 4th month of pregnancy

[c]Any smoking between 1 month prior to conception and the end of the 1st trimester of pregnancy

[d]Use of supplements containing folic acid between 1 month prior to conception and the end of the 1st month of pregnancy

[e]Use of illicit drugs between 3 month prior to conception and the date of delivery

[f]Questions on workplace, job title, duties, any chemicals or substances mother handled

[g]95% confidence interval

2011), we calculated ORs for the effect of any potential occupational exposure to IR and all study birth defects in aggregate. Then, we stratified the ORs for potential occupational exposure to IR and all birth defects in aggregate according to the nine different sources of exposure to IR described above.

All analyses were performed using the statistical software package SAS (release 9.3, SAS Institute, Cary, NC).

Results

After excluding 17 mothers with any lifetime history of radiotherapy or cancer, and 12,551 mothers who were unemployed, homemakers or students during periconceptional period, our study included 18,621 mothers of infants with birth defects and 6820 mothers of infants without birth defects who participated in the NBDPS between 1997 and 2009. Of those mothers, 84% held only

one job during the critical period, while 13% had two jobs, 2% had three jobs, and 1% had more than three jobs. Table 1 shows the frequency of selected characteristics of cases and controls. Compared with control mothers, cases mothers were more likely to be 40 years of age or older, smokers, obese, diabetic, or giving birth to their first child. Cases mothers were less likely to have household income of $50,000 or more. Overall, 2.3% of case mothers and 2.7% of control mothers were in occupations with potential exposure to IR and 13.1% of case mothers and 13.7% of control mothers were employed in the health care industry (Table 1).

Table 2 shows ORs for the associations between potential occupational exposure to IR during the critical period and 39 birth defects. Compared with mothers who were unlikely to be exposed to IR at their workplace, mothers who were in occupations with potential exposure to IR had significantly elevated ORs for hydrocephaly (AOR, 2.06; 95% CI, 1.14–3.71), anotia/microtia (AOR, 1.91; 95% confidence interval [95% CI], 1.08–3.39), and colonic atresia (COR, 6.79; 95% CI, 2.31–19.9). Mothers who were in occupations with potential exposure to IR had a lower risk of having a child with anencephaly (COR, 0.21; 95% CI, 0.05–0.84) and hypospadias (AOR, 0.62; 95% CI, 0.40–0.94).

When the analyses were restricted to isolated birth defects, significant ORs remained for anencephaly (COR, 0.23; 95% CI, 0.06–0.94), hydrocephaly (AOR, 2.18; 95% CI, 1.11–4.25), anotia/microtia (AOR, 2.03; 95% CI, 1.03–4.00), and colonic atresia (COR, 7.51; 95% CI, 2.53–22.3). The AOR for isolated hypospadias was no longer significantly protective (AOR, 0.66; 95% CI, 0.43–1.01). Also, isolated omphalocele was significantly elevated (AOR, 2.32; 95% CI, 1.15–4.69).

In Table 3, we collapsed all birth defects in the study into one group so that we could calculate AOR for all birth defects in aggregate. There was no association between mothers who had potential exposure to IR and all birth defects in aggregate (AOR, 0.88; 95% CI, 0.74–1.05).

We also calculated AORs for the association between each of the 9 subgroups for source of exposure to IR and all birth defects in aggregate (Table 3). Among mothers with potential exposure to IR, approximately 58% worked in a hospital, 27% worked in dental offices and remainder worked in animal clinics, research institutions, as flight crew or in other occupations potentially exposed to IR. Compared with mothers who were unlikely to be exposed to IR at their workplace, mothers who reported they were exposed to dental x-rays had a lower risk of having a child with one of the birth defects in NBDPS (AOR, 0.70; 95% CI, 0.51–0.97). For mothers who reported they were exposed to fluoroscopy and mothers who were exposed to all other occupations with potential IR, the ORs were elevated but were not significant (AOR, 2.06; 95% CI, 0.92–4.64) and (AOR, 2.54; 95% CI, 0.58–11.2), respectively. There were no associations between any of the other six subgroups and all birth defects in aggregate. When the analyses by different sources of IR were restricted to isolated birth defects, the ORs remained decreased for dental x-rays (AOR, 0.67; 95% CI, 0.48–0.94), and the ORs remained increased but not significant for fluoroscopy and IR from other occupations; (AOR, 2.12; 95% CI, 0.93–4.80), and (AOR, 2.79; 95% CI, 0.93–12.4), respectively (Table 3).

A total of 1817 mothers (7%) were exposed to IR as a result of diagnostic tests that they received as a patient during the critical period. Of these 1817 mothers, 64 also had potential exposure to IR from their occupation. When the 1817 mothers who had exposure to IR from diagnostic tests were excluded from our analyses, the ORs for anencephaly, hydrocephaly, and colonic atresia remained significant; (COR, 0.11; 95% CI, 0.02–0.81), (AOR, 1.94; 95% CI, 1.05–3.59), and (COR, 10.78; 95% CI, 3.24–35.84), respectively. However, after this restriction, the AORs for anotia/microtia and omphalocele were no longer significantly elevated (AOR, 1.46; 95% CI, 0.75–2.84) and (AOR, 1.58; 95% CI, 0.84–2.97) (data not shown).

Discussion

This study examined the relationship between potential maternal occupational exposures to IR and 39 major birth defects using data from the NBDPS, a large population-based study of birth defects. We calculated two ORs for each birth defect, one for all infants affected by a particular defect and one for infants that were affected only by that birth defect, that is, isolated birth defects. As none of the categories of isolated birth defects overlap, we used isolated ORs to interpret multiple statistical comparisons. Among the 39 ORs for isolated birth defects, we observed significant elevated ORs for four birth defects: hydrocephaly, anotia/microtia, colonic atresia, and omphalocele with *p*-values of 0.02, 0.04, 0.0001, and 0.01, respectively, and we observed a significant protective OR for anencephaly with a *p*-value of 0.008. Only, the association with colonic atresia remained significant when we used a Bonferroni adjustment to determine the cut-point for a significant *p*-value ($0.05/39 = 0.001$). However, as the association with colonic atresia is based on only 4 exposed cases, we cannot exclude the possibility that even this association may have occurred due to chance, residual confounding or exposure misclassification.

Use of dosimeters to directly measure the level of occupational exposure to IR is the most accurate way to estimate occupational exposures. However, conducting such a study would involve following an extremely large cohort of female workers of child bearing age, identifying those who wear monitoring badges and became pregnant and assessing birth defects that occur in their children. To identify the same number of cases of birth defects with

TABLE 2. *Adjusted Association between Maternal Occupational Exposure to Ionizing Radiation during the Periconceptional Period[a] and Birth Defects, National Birth Defects Prevention Study, 1997 to 2009*

	Birth defects[b]				Isolated birth defects			
	Unexposed	Exposed		AOR	Unexposed	Exposed		AOR
	(*N*)	(*N*)	(%)	(95% CI[c])	(*N*)	(*N*)	(%)	(95% CI[c])
Non-cardiac birth defects[d]								
Controls	6121	183	2.90		6121	183	2.90	
Anencephaly[e]	311	2	0.64	0.21 (0.05, 0.84)	276	2	0.72	0.23 (0.06, 0.94)
Spina bifida	638	17	2.60	0.99 (0.59, 1.65)	559	15	2.61	0.98 (0.57, 1.68)
Encephalocele[e]	117	3	2.50	0.84 (0.26, 2.65)	88	1	1.12	0.37 (0.05, 2.62)
Hydrocephaly[k]	251	13	4.92	2.06 (1.14, 3.71)	180	10	5.26	2.18 (1.11, 4.25)
Anophthalmos/microphthalmos[e]	106	3	2.75	0.90 (0.28, 2.85)	60	1	1.64	0.54 (0.08, 3.92)
Congenital cataracts[e, f]	185	3	1.60	0.54 (0.17, 1.69)	162	2	1.22	0.41 (0.10, 1.67)
Anotia/microtia[l]	299	14	4.47	1.91 (1.08, 3.39)	203	10	4.69	2.03 (1.03, 4.00)
Choanal atresia[e]	92	3	3.16	1.10 (0.35, 3.51)	46	1	2.13	0.74 (0.10, 5.41)
Cleft palate alone[g]	870	18	2.03	0.71 (0.44, 1.17)	710	15	2.07	0.71 (0.42, 1.22)
Cleft lip w/wo cleft palate[g]	1645	35	2.08	0.79 (0.55, 1.14)	1453	30	2.02	0.75 (0.51, 1.11)
Esophageal atresia	432	17	3.79	1.28 (0.76, 2.13)	189	7	3.57	1.08 (0.50, 2.36)
Intestinal atresia/stenosis[e]	257	4	1.53	0.65 (0.26, 1.58)	213	3	1.39	0.63 (0.23, 1.70)
Duodenal atresia/stenosis	120	5	4.00	1.46 (0.58, 3.66)	74	3	3.90	1.37 (0.43, 4.39)
Colonic atresia/stenosis[e,m]	21	4	16.0	6.79 (2.31, 19.9)	19	4	17.4	7.51 (2.53, 22.3)
Anorectal atresia/stenosis	553	11	1.95	0.72 (0.39, 1.34)	231	7	2.94	1.11 (0.51, 2.42)
Biliary atresia/stenosis[e]	119	3	2.46	0.87 (0.27, 2.76)	97	2	2.02	0.71 (0.17, 2.89)
Hypospadias[h]	1513	32	2.07	0.62 (0.40, 0.94)	1352	31	2.24	0.66 (0.43, 1.01)
Limb reduction deficiency	654	25	3.68	1.39 (0.90, 2.14)	478	17	3.43	1.26 (0.76, 2.10)
Craniosynostosis	850	24	2.75	0.81 (0.52, 1.25)	770	21	2.65	0.76 (0.48, 1.21)
Diaphragmatic hernia	437	15	3.32	1.19 (0.69, 2.04)	341	13	3.67	1.26 (0.70, 2.25)
Omphalocele[n]	253	11	4.17	1.72 (0.91, 3.23)	145	9	5.84	2.32 (1.15, 4.69)
Gastroschisis	695	8	1.14	0.75 (0.35, 1.58)	632	7	1.10	0.70 (0.32, 1.56)
Amniotic band syndrome	179	5	2.72	1.29 (0.52, 3.21)	157	5	3.09	1.43 (0.57, 3.59)
Sacral agenesis[e]	42	3	6.67	2.23 (0.69, 7.22)	5	1	16.7	5.94 (0.71, 49.6)
Cardiac birth defects[i]								
Control	6121	183	2.90		6121	183	2.90	
Heterotaxia with CHD[e]	168	5	2.89	1.16 (0.46, 2.89)	21	1	4.55	1.49 (0.20, 11.0)
Single ventricle/complex heart	175	6	3.31	1.23 (0.53, 2.85)	139	6	4.14	1.42 (0.61, 3.28)
Tetralogy of fallot	706	11	1.53	0.54 (0.29, 1.01)	571	10	1.72	0.61 (0.32, 1.17)
D-transposition of the great arteries	429	6	1.38	0.46 (0.20, 1.06)	393	6	1.50	0.50 (0.22, 1.13)
AVSD	217	6	2.69	0.93 (0.40, 2.13)	166	5	2.92	1.00 (0.40, 2.49)
TAPVR	147	6	3.92	1.63 (0.70, 3.79)	137	6	4.20	1.81 (0.78, 4.22)
Hypoplastic left heart syndrome	360	5	1.37	0.51 (0.21, 1.24)	330	5	1.49	0.54 (0.22, 1.33)
Coarctation of the aorta	613	12	1.92	0.62 (0.34, 1.12)	546	11	1.97	0.63 (0.34, 1.17)
Aortic stenosis	262	11	4.03	1.28 (0.68, 2.40)	249	10	3.86	1.22 (0.63, 2.36)

TABLE 2. *Continued*

	Birth defects[b]				Isolated birth defects			
	Unexposed (*N*)	Exposed (*N*)	Exposed (%)	AOR (95% CI[c])	Unexposed (*N*)	Exposed (*N*)	Exposed (%)	AOR (95% CI[c])
Pulmonary valve stenosis[j]	829	21	2.47	0.84 (0.53, 1.34)	761	20	2.56	0.88 (0.55, 1.41)
VSD perimembranous	998	34	3.29	1.27 (0.87, 1.86)	837	29	3.35	1.25 (0.83, 1.87)
ASD secundum	1274	29	2.23	0.83 (0.55, 1.25)	1035	21	1.99	0.72 (0.45, 1.15)
ASD NOS	367	6	1.61	0.62 (0.27, 1.42)	289	5	1.70	0.63 (0.25, 1.58)
Association: COA + VSD[e]	167	4	2.34	0.81 (0.30, 2.20)	142	4	2.74	0.96 (0.35, 2.61)
Association: VSD + ASD	444	6	1.33	0.50 (0.22, 1.14)	347	5	1.42	0.50 (0.20, 1.23)

[a]Exposures occurring between 3 month prior to conception and the end of the 1st trimester of pregnancy

[b]Includes isolated, multiple, or complex birth defects.

[c]95% Confidence Interval

[d]Adjusted for study site, maternal education level, age at delivery, ethnicity, household income, maternal BMI, and street drug use

[e]Crude odds ratios if number of exposed <5

[f]Compared with 5323 (5167 unexposed, and 156 exposed)

[g]Compared with 6214 (6035 unexposed, and 179 exposed)

[h]Compared with 3217 (3127 unexposed, and 90 exposed)

[i]Adjusted for study site, maternal education level, age at delivery, ethnicity, household income, maternal BMI, and street drug use

[j]Compared with 6084 (5904 unexposed, and 180 exposed)

[k]Sources of exposure were nuclear medicine (1), fluoroscopy (1), CT scan (1), standard x-rays at hospital (6), and dental x-ray (4)

[l]Sources of exposure were fluoroscopy (1), standard x-rays at hospital (5), dental x-ray (5), animal clinic (1), research institution (1), and other occupations (1)

[m]Sources of exposure were standard x-rays at hospital (2), and dental x-ray (2)

[n]Sources of exposure were x-rays at hospital (3), dental x-ray (7), and research institution (1)

maternal exposure to IR that are present in our study ($n = 442$) and assuming a prevalence rate for all major birth defects of 3.0%, it would be necessary to prospectively follow 14,733 pregnant women who were occupationally exposed to IR and a much larger number who were not exposed. Data from individuals monitored by dosimeters also have uncertainties due to the type of dosimeter, the policy of particular workplace and the degree to which workers comply with the policy or recommendation to wear it (Shapiro, 2002).

A population-based study of the association between occupational exposure to IR and birth defects was recently conducted in Germany (Wiesel et al., 2011). Based on a prospective follow-up of 3816 pregnancies, Wiesel et al. (2011) observed that mothers who reported wearing a dosimeter during early pregnancy were 3.2 times more likely to have an infant affected by any type of birth defect (AOR, 3.2; 95% CI, 1.2–8.7) compared with mothers without occupational exposures to IR. However, only 29 women in their study reported wearing a dosimeter and of these only 4 had an infant with a birth defect (ventricular septal defect, hydronephrosis, ectopic kidney, and microtia/auricular artesian). In contrast, we assessed maternal exposure based on mother's descriptions of their occupations, workplaces and job activities and included 442 case mothers and 186 control mothers with potential occupational exposure to IR. Thus, compared with Wiesel et al. (2011), our study has a much larger sample size and less precise measurements of exposure, and we observed no association between potential maternal occupational exposure to IR and all NBDPS birth defects in aggregate (AOR, 0.88; 95% CI, 0.74–1.05).

A US population-based case control study, The Baltimore-Washington infant study 1981 to 1989, assessed the association between potential maternal occupational exposure to IR during the periconceptional period and a range of categories of cardiac birth defects (Ferencz et al., 1993, 1997). This study also measured occupational exposure to IR by maternal interview. They assessed 4390 cases of cardiac birth defects and 3572 controls and observed a significant elevated OR for isolated outflow tract anomalies (AOR, 2.6; 95% CI, 1.1–6.0). However, this OR was based on only two exposed cases. In contrast, we observed no association between potential maternal occupational exposure to IR and any of the outflow tract anomalies in the NBDPS data (hypoplastic left heart syndrome, coarctation of the aorta, aortic stenosis, and pulmonary valve stenosis).

TABLE 3. *Adjusted Association between Maternal Occupations with Potential Exposure to Different Sources of Ionizing Radiation and Any NBDPS Birth Defects during the Periconceptional Period,[a] National Birth Defects Prevention Study, 1997 to 2009*

	Birth defects					Isolated birth defects				
	Case		Control			Case		Control		
Source of radiation	(*N*)	(%)	(*N*)	(%)	AOR[b] (95% CI[c])	(*N*)	(%)	(*N*)	(%)	AOR [b] (95% CI[c])
Unexposed	16948	97.6	6121	97.1		14428	97.6	6121	97.1	
Exposed	425	2.4	183	2.9	0.88 (0.74 – 1.05)	362	2.4	183	2.9	0.87 (0.73, 1.05)
Hospital/radiology suites										
Fluoroscopy[d]	37	0.21	7	0.11	2.06 (0.92, 4.64)	33	0.22	7	0.11	2.12 (0.93, 4.80)
X-ray CT scan[e]	8	0.05	5	0.08	0.61 (0.20, 1.86)	4	0.03	5	0.08	0.34 (0.09, 1.28)
Nuclear medicine	9	0.05	3	0.05	1.19 (0.32, 4.41)	7	0.05	3	0.05	1.03 (0.27, 4.02)
Standard X-ray[f]	197	1.13	87	1.38	0.89 (0.69, 1.15)	169	1.14	87	1.38	0.88 (0.68, 1.15)
Dental Clinic										
X-rays	109	0.63	56	0.89	0.70 (0.51, 0.97)	90	0.61	56	0.89	0.67 (0.48, 0.94)
Animal Clinic										
X-rays	17	0.10	12	0.19	0.53 (0.25, 1.12)	15	0.10	12	0.19	0.55 (0.26, 1.18)
Research institution	8	0.05	3	0.05	1.08 (0.28, 4.09)	6	0.04	3	0.05	0.97 (0.24, 3.90)
Flight crew	26	0.15	8	0.13	1.17 (0.53, 2.58)	25	0.17	8	0.13	1.30 (0.58, 2.89)
Other occupations	14	0.08	2	0.03	2.54 (0.58, 11.2)	13	0.09	2	0.03	2.79 (0.93, 12.4)

[a]The exposure period was between 3 month prior to conception and the end of the first month of pregnancy

[b]Adjusted for study site, maternal education level, age at delivery, race/ethnicity, household income, street drug use, and maternal BMI

[c]95% Confidence Interval

[d]37 exposed cases with the following defects; isolated cardiac septal defects (10), isolated cardiac left outflow tract obstruction (4), other heart defects (3), isolated oral clefts (5), isolated spina bifida (2), isolated craniosynostosis (2), isolated hypospadias (3), other isolated non-cardiac defects (6), multiple birth defects (2)

[e]Crude odds ratios if number of exposed less than 5 ($\leq$ 4)

[f]Including portable x-ray, DEXA, and mammogram

A study published in 1929 described 74 women who underwent radiation treatment for uterine cancer and were inadvertently exposed to IR during early pregnancy and reported high rates of infants with mental retardation, and anomalies of the eye (Murphy, 1929; Goldstein, 1929, 1930). Also, surviving children of women who were within 1000 meters of the atomic blasts at Nagasaki and Hiroshima during early pregnancy had elevated rates of mental retardation and microcephaly which may have been due to brain anomalies (Yamazaki et al., 1954; Neel, 1958). In contrast to these early studies of high levels of exposure to IR, we observed an elevated OR for only one of the three brain defects (hydrocephaly) in our study.

When we stratified mothers by source of potential exposure to IR, mothers who used fluoroscopy in their workplace had a borderline elevation in the frequency of all birth defects in aggregate. Even though there were insufficient numbers to evaluate individual phenotypes, it is worth noting that a variety of different types of birth defects occurred among infants born to the 37 case mothers who were exposed to fluoroscopy. These defects included one hydrocephaly case, and one anotia/microtia case, but did not include any cases of colonic atresia/stenosis or omphalocele. Thus, our findings for fluoroscopy are mostly independent of our findings for these four birth defects.

The administration of fluoroscopy involves the use of much higher levels of IR compared with planar x-rays and personnel who administer it must remain close to the patient during the procedure, whereas workers who administer planar x-rays and CT scans generally stay behind a shielded enclosure during x-ray (Vano et al., 2009; Fazel et al., 2009; Health Physics Society Specialists in Radiation Safety, 2010). Although workers are required to wear personal protective equipment during fluoroscopy; it has been shown that lead aprons do not eliminate all of the radiation dose over the apron (Vano et al., 2006). Therefore, those who work with fluoroscopy can still be exposed to IR. Moreover, a recent study demonstrated that health care workers who are occupationally exposed to

fluoroscopy have a fivefold increase in the development of cataracts compared with unexposed workers (Ciraj-Bjelac et al., 2010).

We know of no previous study of maternal exposure to fluoroscopy in the workplace and birth defects. Our study is the first to raise the possibility that pregnant women who work in hospital units where fluoroscopy is used may have an elevated risk of birth defects. However, it is important to note that the levels of exposure to personnel who use fluoroscopy vary depending on the type of fluoroscopy machine, procedure, and total fluoroscopy time-factors that we were not able to measure in this study. Workers in these units may also be exposed to additional factors which we were not able to control, that is, anesthetic gases and stressful working conditions (Figa-Talamanca, 2000; Shuhaiber et al., 2002; Duran et al., 2013).

We observed that mothers who reported that they used dental x-rays in their workplace had protective ORs for all NBDPS birth defects in aggregate. A previous study of 8157 women who worked in dental clinics between 1976 and 1986 also observed that they had no increase in the risk of all birth defects in aggregate (Ericson and Källén, 1989). Workers at dental clinics may also be exposed to additional factors which we were not able to control, that is, anesthetic gases, mercury, and amalgam (Rowland et al., 1994; Leggat et al., 2007).

Shuhaiber et al. (2002) conducted a prospective study of 95 women working in veterinarian practices (Shuhaiber et al., 2002). They observed four birth defects and concluded that there was no evidence for an increased rate of birth defects. Our finding of no association between 46 mothers with potential exposure to IR in animal clinics and all birth defects in aggregate is consistent with the results reported by Shuhaiber et al. (2002), although both estimates are based on small numbers of exposed mothers and qualitative measurements of exposure.

The lack of an association that we observed between working as a pilot or a member of a flight crew and birth defects was also consistent with a cohort study of pilots and cabin attendants conducted by Irgens et al. (2003) in Norway (Irgens et al., 2003). They observed no increase in the risk of birth defects in 3693 female cabin attendants. Our finding of no association between 34 mothers who worked as a pilot or cabin attendant and all types of birth defects is consistent with their results although very limited in sample size.

In our study, the average length of recall was 1.5 years; much shorter than the average recall period in a Canadian study by Brisson et al. (1991), in which women were asked to recall their occupational histories thinking back 1 to 11 years (Brisson et al., 1991). Brisson et al. (1991) observed that 84% of all women had exact agreement between what they recalled and union records. Thus, mothers in our study were very likely to have accurately recalled their occupations during early pregnancy. Also, on average, mothers of affected infants and mothers of control infants used the same number of words to answer the questions on occupations, suggesting that mothers of cases did not elaborate more in their responses compared with mothers of controls.

Conclusions

Our study has several strengths. The NBDPS is one of the largest studies of birth defects ever conducted and includes rare birth defects that have only rarely been studied. However, despite the very large overall sample size of this study, statistical power remains low for rare birth defects. Also, as the NBDPS database includes data on maternal exposures to many different potential risk factors for birth defects during the critical period, we were able to limit the possibility for confounding by a variety of factors, including maternal exposure to IR from diagnostic exams.

The use of a qualitative measurement of exposure is an important limitation of this study. In many workplaces, exposures to IR are well-controlled through engineering, administrative decisions and the use of personal protective equipment. Thus, the majority of the mothers in occupations with potential exposure to IR probably had low levels of exposure to IR (Occupational Safety and Health Administration, 1970; The National Council on Radiation Protection and Measurements, 2009a, 2009b). As we could not distinguish high dose exposures from low dose exposures, we may have missed associations with birth defects that were present only among highly exposed women.

Also, as the NBDPS database does not include birth defects that were known or strongly suspected to have been caused by single-gene disorders or chromosomal abnormalities, we were not able to assess the association between maternal exposure to IR and Down syndrome and other monogenetic or chromosomal disorders.

Future studies should attempt to measure additional factors such as exposure to anesthetic gases, workplace stress, and variability in levels of naturally occurring IR. They should also consider including, Down syndrome, other chromosomal abnormalities and single-gene disorders (Hemminki et al., 1985; Shuhaiber et al., 2002; Bhatti et al., 2010).

To our knowledge, this is the third population based study of maternal occupational exposure to IR and birth defects that has been conducted and the only study with sufficient statistical power to calculate separate risk estimates for different types of noncardiac birth defects. Overall, we observed no association between potential maternal occupational exposure to IR and all birth defects in aggregate. This is consistent with the fact that the levels of occupational exposure to IR in the US are not thought to be associated with harmful health effects to pregnant workers. Although, the frequency of several phenotypes of birth defects was increased among mothers with potential maternal exposure to IR in their workplace, these results

should be interpreted cautiously. The results of this study are likely to be useful for generating hypotheses for further studies of exposure to IR.

APPENDIX

CHARACTER STRINGS USED IN SCANNING PROGRAM

Acute, acute care, anest, anesth, anesthet, animal clinic, animal hosp, animal hospital, animal science, astronaut, beta emitter, bone density test, brine, burn pit, c arm, c14, carbon-14, cardia, cardiac, cardio, cardiology, c-arm, cat scan, CATH, catheterization, cave, CCU, chiro, chiropract, chiropractor, clean pipe, co60, coal, cobalt, copper, cosmic, critical care, critical patient, CRNA, CT, CT machine, CT scan, CT tech, CVICU, dental ass, dental hyg, dentist, derrick, dexa, DEXA, drill for oil, drilling, ED, electron, emergency department, emergency room, EMT, endodontist, ER, ER nurse, ER physic, ER staff, excavator, fish hatchery, flight, fluoro, flying, gamma, gas pipe, gas well, gastro, gastroenterology, geothermal, hyge, i-, i-131, ICN, ICU, imaging, intensive care, iodine, irradiation, isotope, ium, loadmaster, logger, logging, mammogram, mine, miner, mineral, neonatal, neurologist, NICU, nuclear, O.R, oil, oil field, oil industry, oil pipe, oil produce, oil produce, oil refinery, oil well, oncology, operating room, OR, OR nurse, OR tech, ortho, p32, period, phosphorus, physicist, physics, pilot, pipeline, pipeline tech, plutonium, podiat, power plant, premature, prenatal, produced water, propane pump, prosthodontist, radiate, radiation, radio, radio active, radio tech, radioactive, radiograph, radiographer, radioisotope, radiolog, radiologist, radiology, radiopharm, radiopharmacist, radon, RDH, registered nurse, respiratory thera, RN, sewage, sludge, speech path, speech thera, steward, surg, surgeon, surgical, tech, thoron, tomography, transport, trauma, tunnel, underground, uranium, urolog, vascular, vet, veterinary, waste disposal, waste water, water plant, well dig, well logger, wellhead, x ray, xray, x-ray

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