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Maternal Diet during Pregnancy and Unilateral Retinoblastoma

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Abstract

Purpose—Previous studies have suggested a role for parental diet in childhood cancer prevention, but there are few studies of retinoblastoma. The aim of this study was to examine the relation between maternal diet and unilateral retinoblastoma.

Methods—A case-control study of 163 unilateral RB cases and 136 controls ascertained information on maternal diet during pregnancy using a standardized food frequency questionnaire. Logistic regression was used to assess the relation between retinoblastoma and food groups and dietary patterns.

Results—We observed a negative association between retinoblastoma and intake of fruit [odds ratio (OR)=0.38, 95% confidence interval (CI) 0.14, 1.02]. Positive associations were seen with intake of cured meats (OR=5.07, 95%CI 1.63, 15.70) and fried foods (OR: 4.89, 95% CI: 1.72–13.89). A food pattern of high fruits and vegetables and low fried food and sweets was negatively associated with disease (OR=0.75, 95%CI 0.61, 0.92).

Conclusion—Our study provides preliminary evidence that mothers who consume diets higher in fruit and lower in fried foods and cured meats during pregnancy may reduce the risk of unilateral retinoblastoma in their offspring.

Keywords

Retinoblastoma; Risk factors; Childhood cancer epidemiology; Diet; Fruit; Fried food

INTRODUCTION

Retinoblastoma is a rare childhood tumor of the embryonal retina with a mean age-adjusted incidence rate of 11.8 cases per million children ages 0–4 years in the U.S (1). This tumor inspired Knudson's "two-hit" model of tumorigenesis, since it requires inactivation of both

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Conflicts of Interest

The authors also state that there is no conflict of interest with respect to the contents of this manuscript for any individual author.

alleles of the *RB1* tumor suppressor gene in a retinal cell (2). More recently additional genetic defects such as aneuploidy and genetic instability have been implicated in retinoblastoma tumorigenesis (3, 4). Bilateral disease, which accounts for 25% of cases, is considered familial when an *RB1* mutation is inherited from a parent and sporadic when a new germline mutation occurs in *RB1* gene of the child (1, 5). Either event will lead to the presence of one mutated *RB1* allele in every cell, and an additional mutation (‘second hit’) is needed to inactivate the normal *RB1* allele in a retinal cell to initiate tumorigenesis (6). Among children who inherit an *RB1* mutation, 85% go on to develop bilateral retinoblastoma, usually before age 5. Unilateral retinoblastoma, which accounts for 75% of retinoblastoma cases most often results from two somatic mutations to the *RB1* gene and incidence peaks at age 6–7 months (5). In spite of knowledge about genetic mechanisms responsible for retinoblastoma, risk factors for sporadic retinoblastoma are largely unknown. The five-year survival rate for retinoblastoma in the U.S. is estimated to be over 93%, but treatments may result in loss of vision (5). Identification of targets for prevention is important to reduce the burden of this disease in the U.S. and in many developing countries where mortality rates are much higher (7).

In unilateral retinoblastoma the mutations to the *RB1* gene occur mostly after conception, thus prenatal and early childhood exposures are thought to be important for its etiology. In a large population based case-control study of childhood cancer in California we conducted previously, we found elevated odds for unilateral retinoblastoma among children of U.S.-born Hispanic women and decreased odds among children of mothers born in Mexico (8). We also observed elevated odds in infants born to mothers exposed to higher levels of traffic related air pollution during pregnancy (9–11). Previously identified possible risk factors for unilateral disease include prenatal x-ray exposure and low maternal education level (12).

Mother’s prenatal diet and nutrients have been investigated as possible risk and protective factors for childhood cancer (13, 14). Food contains known mutagens such as heterocyclic amines and polycyclic aromatic hydrocarbons in red meat cooked at high temperatures and N-nitroso compounds in cured meats and probable carcinogens such as acrylamides in baked, grilled and fried foods (13, 15). Some dietary components such as antioxidants from fruits and vegetables can reduce the risk of somatic mutations potentially conferring some protective benefits (13, 15).

Few studies have examined parental diet and retinoblastoma. Bunin et al. assessed effects of mother’s and father’s preconception diets on sporadic bilateral retinoblastoma and reported possible protection due to father’s consumption of dairy and fruit in the year prior to conception and a harmful effect from cured meats and sweets (16). No associations were seen with maternal diet; this is consistent with the observation that 85% of germ line mutations for sporadic bilateral retinoblastoma originate in the father’s sperm (17, 18).

Only a single study thus far examined maternal diet and unilateral retinoblastoma. This hospital-based case-control study in Mexico found an increased risk with maternal consumption of less than 2 servings of vegetables per day during pregnancy (19). Risk was also increased among children with maternal pregnancy diets low in folate and lutein/zeaxanthin from fruits and vegetables (19). A U.S. case-control study also found multivitamin use during pregnancy to reduce unilateral disease risk (12). Here we investigate associations between maternal prenatal diet and unilateral retinoblastoma among children in the United States and Canada in a multi-institutional case-control study.

METHODS

Study population

The study had the primary aim of investigating the associations of sporadic bilateral retinoblastoma and unilateral retinoblastoma with parental exposures and polymorphisms in DNA repair and carcinogen metabolizing enzyme genes. Parental exposure information was obtained via structured telephone interviews conducted from 2008 to 2012 with both parents when available. The questionnaire collected information on basic demographics and preconception and prenatal parental exposures possibly related to retinoblastoma risk including occupational exposures, medical radiation, diet, supplement use, tobacco, alcohol, and residential pesticide use. For the present study we focused on unilateral cases without a germline mutation.

Cases were diagnosed with unilateral retinoblastoma at a US or Canadian institution that is a member of the Children's Oncology Group or Wills Eye Hospital (Philadelphia) between July 1, 2006 and June 30, 2012. Each participating COG institution, the Wills Eye Hospital, and the UCLA Office for Human Research Protection approved the study. Participants were eligible if they resided in North America, had at least one parent who spoke English or Spanish, and had at least one biological parent available to participate in the study.

Of the 242 unilateral case mothers originally identified for the study, 17 (7%) refused to participate or to be interviewed; 27 (11%) could not be interviewed before the study ended; 6 (2%) could not be located; 5 (2%) were not eligible for the study because genetic testing showed the disease was familial or mosaic; 1 (<1%) was not eligible because they were not from the US or Canada; and 1 (<1%) was not eligible because the case child had been adopted or was in foster care. In total, 185 case mothers were interviewed. Approximately 3% of maternal interviews were completed by a proxy (usually, the father).

Parents of cases were asked to nominate the child's friends or relatives under age 15 years to be contacted as possible controls. For unilateral retinoblastoma, mother's exposures were the focus, thus, the female adult relatives selected as controls were not allowed to be biologically related to the case's mother. The study aimed to match one cancer-free child in the same age group at time of interview (0–1, 2–3, 4–5, 6–7, 8–9, 10–11,12–13 and 14–15 years) to each case. If the parents nominated more than one control, we tried to recruit the child closest in age to the case. If the control was not successfully recruited, we attempted to recruit the next control until we obtained a control or until we contacted all potential controls. Hence, some controls were not matched by age group. Unfortunately, the study was not able to recruit controls for all cases, similar to our previous retinoblastoma study (20). Of the 218 potential controls that were originally nominated by case mothers (143 by unilateral cases and 75 by bilateral cases), 40 (18%) refused to participate or did not respond to interview requests; 21 (10%) could not be interviewed before the study ended; 2 (1%) were not eligible, and for 8 (4%) control children, only the father was interviewed. After excluding one control who did not complete the food frequency questionnaire (FFQ) and 27 subjects with missing values for important covariates, 163 unilateral RB cases and 136 controls were available for analysis in this study; of these, there were 85 matched case-control pairs. Written consent was provided for blood and saliva samples, and verbal consent was given for telephone interviews.

Dietary assessment

A 72-item modified Willett food frequency questionnaire was used to assess mother's diet during pregnancy (21). Frequency of consumption of specific foods during the second trimester of pregnancy was collected; this time period was chosen to examine the general pregnancy diet after the mother made any pregnancy-related dietary changes and after morning sickness had passed. Since portion size information was not collected, a standard portion size was used to calculate total calories per day, with caloric information taken from the USDA database (22). Food frequency was converted to servings per day as: (never or less than once per month"=0; "1 to 3 per month"=.08; "1 per week"=.14; "2 to 4 per week"=.43; "5 to 6 per week"=.8; "1 per day"=1.0; "2 to 3 per day"=2.5; "4 to 5 per day"=4.5; "6+ per day"=6 (23). Servings per day for individual food items were totaled within 13 food groups (number of items): fruit (6), citrus fruit (2), dairy (7), vegetables, excluding potatoes (14), meat and seafood (14), poultry (2), fresh red meat (4), cured meat (3), seafood (5), grains (8), sweets, including beverages (9), fried foods (4), alcohol (3) (Table S-1).

We investigated dietary patterns because in general they help mitigate the problem of confounding by correlated nutrients or foods, account for interactions between foods, and because the effects of overall diet are likely stronger than the effects of individual foods on health outcomes (24). To capture dietary patterns we created two a priori dietary scores: one capturing a diet high in fruits and vegetables and low in red and cured meats similar to Chuang *et al* and based on studies showing associations between red and cured meat consumption and cancer (13, 15, 25–27), and one capturing a diet high in fruits and vegetables and low in fried foods and sweets based on the probable carcinogenicity of acrylamide (13, 15). The scores were constructed based on food group tertiles, assigning a zero for fruits and vegetable intake in the lowest tertile, 1 for the middle tertile and 2 for the top tertile. The opposite coding was used for red meat, cured meat, fried food and sweets. Hence the score ranged from 0 to 8, with higher values indicating healthier diets.

Statistical analysis

Both conditional and unconditional logistic regression models were used to estimate odds ratios and 95% confidence intervals (CIs) for unilateral retinoblastoma as the dependent variable. Conditional regression preserves the matched design of the study, while unconditional regression allowed us to include all cases and controls after breaking the matches and adjusting for the matching variable age group at interview (0–<2 years, 2–<4 years, 4+ years). To improve statistical power and address potential overmatching we chose to additionally use the entire population in unconditional analyses. We created tertiles of servings per day for each food group based on the distribution in controls. For the dietary scores we employed continuous and categorical variables (0–2 points=low, 3–5 points =

medium, 6–8 points =high). We also calculated Pearson correlation coefficients between food groups and dietary scores. We adjusted for mother's race (white non-Hispanic, Hispanic, other) and education (<high school, high school graduate, some college/other training, college graduate or more), whether mothers smoked the month before or during pregnancy (yes/no), household income (<$35,000, $35000–$50000, $50000–$75000, > $75000), total calories per day (continuous), and prenatal vitamin use of 9–10 months during pregnancy (yes/no). Marital status was not included in our final adjusted models because it did not change estimates by 10% or more. We conducted all analyses using SAS version 9.3. Because food frequency questionnaires may be less accurate across ethnic groups, we conducted sensitivity analyses examining non-Hispanic White mothers only (76% of mothers in our population) (28, 29). To examine effects for other foods independent of fruit, vegetable, and fried food intakes, we conducted sensitivity analyses of our results with additional adjustment for fruit and vegetable consumption due to their possible protective effects and for fried foods due the possible harmful effect we observed.

RESULTS

Interviews took place with parents 0–13 years after pregnancy (median=2.8 years). Characteristics of the study population are shown in Table 1, and their distributions in food intake are shown in Table 2. Cases were younger than controls while control mothers were more likely to have a college or higher education (67% vs 53%), to be non-Hispanic white (76% vs 57%), and to be never smokers (70% vs 58%). Matched pairs were similar demographically.

Crude and adjusted odds ratios and 95% confidence intervals for tertiles of food groups (in servings per day) are shown in Table 3. In our interpretation of the results we considered the direction and magnitude of effect estimates, the width of confidence intervals, and the consistency of the results across conditional and unconditional models. For consumption in the top compared to the lowest tertile, negative associations were observed for fruit (OR: 0.38, 95% CI: 0.14–1.02), dairy (OR: 0.36, 95% CI: 0.12–1.09), and red meat (OR: 0.35, 95% CI: 0.11–1.13) in adjusted conditional logistic models. We observed increased adjusted odds in the top tertiles of consumption for poultry (OR: 2.33, 95% CI: 0.82–6.63), cured meat (OR: 5.07, 95% CI: 1.63–15.70), seafood (OR: 2.20, 95% CI: 0.92–5.26), sweets (OR: 2.21, 95% CI: 0.81–6.06), and fried foods (OR: 4.89, 95% CI: 1.72–13.89). Unconditional logistic regression based on all controls and ignoring the matching yielded effect estimates for these foods in the same direction that were somewhat lower in magnitude.

In sensitivity analyses restricted to non-Hispanic Whites, the effect sizes for the consumption of fried foods and unilateral retinoblastoma increased in conditional regression analyses (OR for the top tertile: 8.24, 95% CI 1.91–35.51). Effect estimates for seafood among non-Hispanic Whites were similar to those estimated in the entire study population. Additional adjustment for fruit, vegetable, and fried food consumption left effect estimates largely unchanged (results not shown).

Our two dietary scores showed negative associations with increasing scores (Table 4); i.e. the odds of unilateral retinoblastoma decreased by 25% with every 1 point increase in our 8 point scale capturing a maternal diet with high fruit and vegetable and low fried foods and sweets intake during the second trimester of pregnancy. For every 1 point increase in our score measuring high fruit and vegetable intake and low red and cured meat intake we observed a 16% decrease in the odds of unilateral retinoblastoma.

DISCUSSION

Our results suggest that higher consumption of fruit and lower consumption of cured meats and fried foods by mothers during pregnancy may reduce odds of unilateral retinoblastoma in their offspring. Also, a dietary pattern characterized by high fruit and vegetable consumption and low consumption of fried foods and sweets as well as a dietary pattern with high fruit and vegetable and low consumption of red and cured meats during pregnancy may reduce the odds of unilateral retinoblastoma in offspring. We additionally observed possible protective associations among children of mothers who consumed higher amounts of dairy and red meat, as well as possible harmful associations for highest maternal intake of poultry, seafood, and sweets although the confidence intervals were wide and results should be interpreted with caution.

Our results for the dietary scales showed diets higher in fruits and vegetables might be protective. Although the populations were quite different, this is in line with a previous hospital-based, case-control study of Mexico City children aged ≤6 years which found an increased risk of unilateral retinoblastoma in children of mothers who consumed less than 2 servings of vegetables per day during pregnancy adjusting for maternal education and socioeconomic status indicators (19). Although the Mexico City study did not observe an association with fruit consumption alone as we did, it reported increased risk with lower maternal consumption of folate, B6, α-carotene, and lutein/zeaxanthin from fruit and vegetables. The slight differences in results may reflect differences in dietary patterns between our predominantly non-Hispanic white population and this population of mothers in Mexico City, or differences in dietary assessment. The Mexico City study assessed diet by interview with three open-ended questions about the foods mothers typically consumed for breakfast, lunch and dinner and consumption frequency of each food per week. Vegetable consumption may have been particularly important in this population because only 43% of case mothers and 53% of control mothers took multivitamins at any time during pregnancy, and this study took place before the adoption of folic acid fortification of flour in Mexico (19, 30). Fruit and vegetable consumption has been associated with lower risk of several cancers in adults (13). Protective associations were also found for maternal fruit and vegetable consumption during pregnancy and acute lymphoblastic leukemia (ALL), childhood brain tumors and germ cell tumors (31–34). The protection has been attributed to dietary fibers, antioxidants, flavonoids, and salicylic acid contents (13). Although our results show a decreased risk with fruit consumption, we observed a positive association for citrus (which included citrus juice), but the results were not consistent between models (Table 3). The positive association is possibly an artifact and due to chance or caused by bias from losing participants when switching from the unconditional to the conditional model.

The effect sizes for the consumption of fried foods and unilateral retinoblastoma were strong in our study and increased further in sensitivity analyses when restricting to non-Hispanic

Whites (OR for the top tertile: 8.24, 95% CI 1.91–35.51). As we additionally observed possible elevated risks for consumption of sweets during pregnancy, these findings could be due to acrylamide, which has been classified as a probable carcinogen, and is found in baked goods and fried foods, especially fried potatoes (13, 15). Acrylamide acts as a mitotic spindle inhibitor in the nucleus and could interfere with chromosome segregation and DNA repair leading to DNA mutations and carcinogenesis (15).

Our results showing diets lower in cured meats as possibly protective are consistent with previous findings suggesting associations between cancer in adults and higher cured meat consumption (25). Cured meats contain nitrates which are transformed into N-nitroso compounds, known carcinogens, in the body (13, 15). The harmful association we found for cured meats is supported by several studies of childhood brain tumors showing associations with mothers' consumption of cured meats during pregnancy (27).

We had originally hypothesized that due to the heterocyclic aromatic amines (HAAs) and polycyclic aromatic hydrocarbons (PAHs) formed when meat cooks at high temperatures, intake of red meat would be related to higher risk (13, 15). Our findings of a possible protective association for red meat was thus surprising, and it also did not appear to be driven by any correlations with other foods (correlations between red meat intake and grain intake, r=0.25; fried foods r=0.24; vegetables r=0.24). Women who chose to consume high amounts of red meat in their pregnancies may have been previously diagnosed with anemia, which was inversely related to nonheritable retinoblastoma in an earlier study (12). In that study, the authors hypothesized that it was not anemia itself that was likely protective, but rather its treatment, e.g. intake of multivitamins or iron.

Although the confidence intervals were wide, we observed decreased risk with higher dairy consumption and increased risk with higher poultry consumption. Other studies have found both increased and decreased risk of cancers in adults with greater poultry and dairy consumption (13). Among controls in our study dairy consumption was moderately correlated with fruit and vegetable consumption (Pearson correlation coefficients = 0.44 and 0.39, respectively), however protective associations for dairy remained after adjustment for fruits and vegetables, as well as adjustment for our two healthy diet scales (results not shown). Diets high in fast food may also be lower in dairy, but we were not able to account for intake of fast food (35). Although the etiology of unilateral and bilateral retinoblastoma differ in terms of the timing of mutations, it is interesting to note that the findings for maternal diet in relation to unilateral retinoblastoma and those from our previous study for paternal diet in relation to bilateral retinoblastoma are remarkably similar. For sporadic bilateral retinoblastoma, reductions of risk were observed for higher paternal consumption of dairy and fruit during the year prior to conception, while higher intakes of cured meats and sweets were associated with increases in risk (16, 36). Maternal consumption of the same food groups during pregnancy had similar associations with unilateral retinoblastoma in the current study. In the bilateral retinoblastoma study, the associations were specific for paternal diet, i.e. the mothers' consumption of these food groups was not associated with risk. This indicates that the similarity of paternal/bilateral and maternal/unilateral findings is not explained by the correlation between the paternal and maternal diet in the bilateral retinoblastoma study. The similarity of dietary findings for unilateral and bilateral retinoblastoma could indicate the mechanisms for mutations of *RB1* are similar in both types of retinoblastoma or could be due to shared biases in both studies since the same dietary assessment tool and similar methods were used.

Thirty-five percent of our study participants reported no seafood consumption, and another 28% consumed seafood once a week or less. Servings per day of seafood were moderately correlated with fried foods (Pearson's correlation coefficient=0.44), which may account for some of the increased risk we observed. The findings for seafood may be chance findings. However, carcinogenic heterocyclic aromatic amines and PAHs found in meat cooked at high temperatures are also found in fish, and smoked fish contains carcinogenic N-nitroso compounds (13, 15). Additionally, seafood intake is associated with higher intake of mercury, which adversely affects neurodevelopment, as well as PCBs and dioxins, which are carcinogenic (37). We were not able to account for type of fish consumed or preparation methods, other than frying, in our study.

When using friend and relative controls in case-control studies overmatching on lifestyle-related factors is likely. Indeed, a simulation study conducted for a similar population suggested overmatching on demographic factors, but to a lesser degree on lifestyle factors such as parental smoking (20). Overmatching on diet would be expected to result in reduced statistical power to detect associations between diet and the outcome. The difficulties with control recruitment resulted in some differences between case and control characteristics; specifically, cases without a matched control were more likely to be non-White and of lower socioeconomic status, and thus were dropped in all analyses of matched pairs (20). This will further limit the exposure distribution of diet in the matched population, while analyses based on all cases and controls may be more affected by confounding due to SES, which we attempted but may not have succeeded in controlling for completely. Given these limitations, we provided results from both conditional and unconditional analyses for comparison.

We expected some dietary measurement error because food frequency questionnaires were administered to mothers 0–13 years after pregnancy with approximately 83% completing the questionnaire within 5 years after pregnancy. Differential recall bias may have occurred if case mothers recalled diet more or less accurately than control mothers. Associations for unhealthy foods could be biased downward if case mothers were more likely to underreport consumption of foods perceived to be unhealthy to minimize feelings of guilt regarding their child's cancer; however if that had occurred, we might have expected to have also seen inverse associations with vegetable consumption. A previous study found that quintile based agreement in diet reported during pregnancy with pregnancy diet reported 3–7 years after pregnancy was 60–69% for telephone interviews and 69–79% for self-administered questionnaires, which is similar to or slightly lower than recall for diet in adult life in general (38). However, that study did not examine differences between cases and controls. Given the young age of retinoblastoma onset (median=1.7 years) we do not expect the child's diet to be a source of confounding. Another limitation is that we did not collect information on portion size, but Willett has argued that the inclusion of portion sizes in food frequency questionnaires does not markedly improve measurement of intake (28). The food frequency questionnaire we used was previously validated, although not for pregnancy diet, and has been successfully used for other studies of childhood cancer (21, 36).

In spite of these limitations, this study is one of only a few on this topic for retinoblastoma. For a very rare cancer a relatively large number of cases were ascertained at major referral institutions in the U.S. and Canada. Detailed information on socioeconomic and other risk factors allowed us to control for many possible confounders.

CONCLUSION

Our study provides preliminary evidence that mothers who consume diets higher in fruit and lower in fried foods and cured meats during pregnancy may reduce the risk of unilateral retinoblastoma in their offspring. The association with fried foods is interesting and should be investigated further in relation to childhood cancer. Future studies should consider additional methods of dietary assessment. Given the low number of cases diagnosed in the U.S. each year, approximately 300 children with either unilateral or bilateral disease, and the difficulty of obtaining detailed dietary information, inclusion of biomarkers is unlikely and studies on this topic will continue to be challenging (5).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of unilateral retinoblastoma cases and controls

	All subjects				Matched pairs			
	Controls (n=144)		**Cases (n=183)**		**Controls (n=92)**		**Cases (n=92)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Child's age								
0–<2 years	42	29	68	37	22	24	32	35
2–<4 years	43	30	68	37	29	32	31	34
4+ years	59	41	47	26	41	45	29	32
Household income								
<$35,000	29	21	56	34	21	24	23	26
$35000–$50000	19	14	17	10	9	10	13	15
$50000–$75000	29	21	30	18	18	20	20	22
>$75000	59	43	61	37	40	45	33	37
Missing	8		19		4		3	
Mother's education								
<High School	6	4	15	8	3	3	5	5
High School graduate	15	10	31	17	14	15	13	14
Some college/other training	26	18	40	22	17	18	15	16
College graduate or more	97	67	97	53	58	63	59	64
Mother's race								
White non-Hispanic	109	76	104	57	71	77	62	67
Hispanic	18	13	45	25	11	12	19	21
Other	17	12	34	19	10	11	11	12
Mother smoked in the month before or during pregnancy								
Never smoker	101	70	107	58	66	72	55	60
Yes	17	12	41	22	10	11	15	16
No	26	18	35	19	16	17	22	24
Took prenatal vitamin 9+ mos of pregnancy								
Yes	89	62	98	54	56	61	57	62
No	55	38	84	46	36	39	35	38

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Table 2

Intake of foods (servings per day) among unilateral retinoblastoma cases and controls

	All subjects				Matched pairs			
	Controls (n=144)		Cases (n=183)		Controls (n=92)		Cases (n=92)	
	n	%	n	%	n	%	n	%
Fruit (servings per day)								
0 – 1.37	48	33	75	41	32	35	33	36
>1.37 – 2.43	49	34	65	36	30	33	38	41
>2.43 – 8	47	33	43	24	30	33	21	23
Citrus (servings per day)								
0 – 0.16	52	36	65	36	39	42	27	29
>0.16 – 0.86	50	35	79	43	32	35	44	48
>0.86 – 3.5	42	29	39	21	21	23	21	23
Dairy (servings per day)								
0 – 1.57	48	33	73	40	30	33	31	34
>1.57 – 2.73	48	33	57	31	31	34	34	37
>2.73 – 6.51	48	33	53	29	31	34	27	29
Vegetables (servings per day)								
0.44 – 1.66	48	33	56	31	31	34	20	22
>1.66 – 2.66	48	33	72	40	30	33	41	45
>2.66 – 6.94	48	33	54	30	31	34	30	33
Poultry (servings per day)								
0 – 0.16	48	33	59	32	31	34	26	28
>0.16 – 0.43	63	44	57	31	40	43	32	35
>0.43 – 1.08	33	23	67	37	21	23	34	37
Red meat (servings per day)								
0 – 0.30	50	35	75	41	26	28	37	40
>0.30 – 0.65	53	37	62	34	34	37	31	34
>0.65 – 2.22	41	28	46	25	32	35	24	26
Cured meat (servings per day)								
0 – 0.08	64	44	65	36	45	49	31	34

	All subjects				Matched pairs			
	Controls (n=144)		Cases (n=183)		Controls (n=92)		Cases (n=92)	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
>0.08 – 0.16	32	22	42	23	23	25	24	26
>0.16 – 1.31	48	33	76	42	24	26	37	40
Seafood (servings per day)								
0 – 0	57	40	58	32	38	41	30	33
>0 – 0.14	40	28	50	27	23	25	27	29
>0.14 – 2.22	47	33	75	41	31	34	35	38
Grains (servings per day)								
0.14 – 1.65	48	33	66	36	30	33	33	36
>1.65 – 2.37	50	35	59	32	31	34	28	30
>2.37 – 6	46	32	58	32	31	34	31	34
Sweets (servings per day)								
0 – 0.88	49	34	52	28	34	37	28	30
>0.88 – 1.75	47	33	67	37	31	34	35	38
>1.75 – 4.58	48	33	64	35	27	29	29	32
Fried foods (servings per day)								
0 – 0.08	59	41	48	26	44	48	23	25
>0.08 – 0.24	38	26	49	27	18	20	29	32
>0.24 – 1.51	47	33	86	47	30	33	40	43
Total energy (calories)								
467 – 1179	36	25	42	23	23	25	19	21
>1179 – 1560.5	36	25	50	27	23	25	26	28
>1560.5 – 1964.5	36	25	44	24	26	28	23	25
>1964.5 – 3938	36	25	47	26	20	22	24	26
High fruits/vegetables, low fried food/sweets								
Mean	144	4.08	182	3.54	92	4.21	91	3.78
0–2	30	21	50	27	20	22	21	23
3–5	81	56	103	57	47	51	52	57
6–8	33	23	29	16	25	27	18	20
High fruits/vegetables, low red/cured meat								

	All subjects				Matched pairs			
	Controls (n=144)		**Cases (n=183)**		**Controls (n=92)**		**Cases (n=92)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Mean	144	4.17	182	3.92	92	4.14	91	4.07
0–2	27	19	39	21	15	16	16	18
3–5	82	57	109	60	57	62	56	62
6–8	35	24	34	19	20	22	19	21

Table 3

Associations (OR (95%CI)) between tertiles of food groups (servings per day) during the 2nd trimester of pregnancy and unilateral retinoblastoma

		Conditional Logistic Model							Unconditional Logistic Model[a]					
		n=92 matched sets[b]			n=85 matched sets[c]				Cases: n=183, Controls: n=144			Cases: n=163, Controls: n=136		
Food group tertiles (servings per day)	Case N	Crude OR	95% C.I.		Adj OR[d]	95% C.I.		Case N	Crude OR	95% C.I.		Adj OR[d]	95% C.I.	
Fruit														
0 – 1.37	33	**ref**	~	~	**ref**	~	~	75	**ref**	~	~	**ref**	~	~
>1.37 – 2.43	38	**1.17**	0.60	2.26	**0.86**	0.38	1.94	65	**0.87**	0.51	1.47	**0.84**	0.46	1.54
>2.43 – 8	21	**0.70**	0.34	1.46	**0.38**	0.14	1.02	43	**0.60**	0.35	1.05	**0.56**	0.28	1.12
Citrus														
0 – 0.16	27	**ref**	~	~	**ref**	~	~	65	**ref**	~	~	**ref**	~	~
>0.16 – 0.86	44	**2.17**	1.04	4.51	**2.23**	0.94	5.29	79	**1.30**	0.78	2.18	**1.34**	0.75	2.39
>0.86 – 3.5	21	**1.58**	0.70	3.56	**1.98**	0.72	5.44	39	**0.78**	0.44	1.39	**0.76**	0.39	1.50
Dairy														
0 – 1.57	31	**ref**	~	~	**ref**	~	~	73	**ref**	~	~	**ref**	~	~
>1.57 – 2.73	34	**1.06**	0.52	2.15	**0.61**	0.25	1.52	57	**0.83**	0.49	1.42	**0.79**	0.43	1.48
>2.73 – 6.51	27	**0.83**	0.39	1.76	**0.36**	0.12	1.09	53	**0.78**	0.46	1.35	**0.62**	0.30	1.27
Vegetables														
0.44 – 1.66	20	**ref**	~	~	**ref**	~	~	56	**ref**	~	~	**ref**	~	~
>1.66 – 2.66	41	**2.03**	0.96	4.27	**2.39**	0.93	6.19	72	**1.26**	0.74	2.16	**1.68**	0.90	3.15
>2.66 – 6.94	30	**1.46**	0.70	3.03	**1.04**	0.39	2.74	54	**0.97**	0.56	1.69	**1.07**	0.54	2.12
Poultry														
0 – 0.16	26	**ref**	~	~	**ref**	~	~	59	**ref**	~	~	**ref**	~	~
>0.16 – 0.43	32	**0.91**	0.42	1.93	**0.92**	0.36	2.38	57	**0.72**	0.42	1.22	**0.82**	0.44	1.53
>0.43 – 1.08	34	**1.90**	0.88	4.10	**2.33**	0.82	6.63	67	**1.62**	0.91	2.87	**1.71**	0.86	3.40
Red meat														
0 – 0.30	37	**ref**	~	~	**ref**	~	~	75	**ref**	~	~	**ref**	~	~
>0.30 – 0.65	31	**0.58**	0.27	1.23	**0.53**	0.22	1.30	62	**0.80**	0.48	1.34	**0.80**	0.45	1.43
>0.65 – 2.22	24	**0.44**	0.19	1.03	**0.35**	0.11	1.13	46	**0.78**	0.45	1.37	**0.68**	0.35	1.33
Cured meat														

Food group tertiles (servings per day)	Conditional Logistic Model							Unconditional Logistic Model[a]						
	n=92 matched sets[b]				n=85 matched sets[c]			Cases: n=183, Controls: n=144				Cases: n=163, Controls: n=136		
	Case N	Crude OR	95% C.I.		Adj OR[d]	95% C.I.		Case N	Crude OR	95% C.I.		Adj OR[d]	95% C.I.	
0 – 0.08	31	**ref**	~	~	**ref**	~	~	65	**ref**	~	~	**ref**	~	~
>0.08 – 0.16	24	**1.77**	0.77	4.07	**2.90**	0.99	8.55	42	**1.27**	0.71	2.29	**1.41**	0.75	2.67
>0.16 – 1.31	37	**2.83**	1.24	6.44	**5.07**	1.63	15.70	76	**1.64**	0.99	2.73	**1.53**	0.85	2.77
Seafood														
0 – 0	30	**ref**	~	~	**ref**	~	~	58	**ref**	~	~	**ref**	~	~
>0 – 0.14	27	**1.48**	0.71	3.09	**1.44**	0.60	3.45	50	**1.21**	0.69	2.13	**1.45**	0.78	2.71
>0.14 – 2.22	35	**1.46**	0.71	2.99	**2.20**	0.92	5.26	75	**1.65**	0.97	2.79	**2.03**	1.12	3.69
Grains														
0.14 – 1.65	33	**ref**	~	~	**ref**	~	~	66	**ref**	~	~	**ref**	~	~
>1.65 – 2.37	28	**0.84**	0.43	1.64	**0.59**	0.25	1.38	59	**0.76**	0.44	1.31	**0.75**	0.40	1.43
>2.37 – 6	31	**0.92**	0.46	1.83	**0.59**	0.21	1.61	58	**0.88**	0.51	1.51	**0.79**	0.38	1.67
Sweets														
0 – 0.88	28	**ref**	~	~	**ref**	~	~	52	**ref**	~	~	**ref**	~	~
>0.88 – 1.75	35	**1.39**	0.68	2.83	**1.78**	0.75	4.23	67	**1.31**	0.76	2.26	**1.50**	0.81	2.78
>1.75 – 4.58	29	**1.31**	0.64	2.72	**2.21**	0.81	6.06	64	**1.25**	0.72	2.16	**1.24**	0.61	2.49
Fried foods														
0 – 0.08	23	**ref**	~	~	**ref**	~	~	48	**ref**	~	~	**ref**	~	~
>0.08 – 0.24	29	**2.86**	1.28	6.39	**6.34**	2.14	18.83	49	**1.66**	0.93	2.97	**1.81**	0.95	3.44
>0.24 – 1.51	40	**2.65**	1.21	5.82	**4.89**	1.72	13.89	86	**2.41**	1.42	4.11	**2.01**	1.08	3.76

[a] Adjusted for matching variable age group

[b] Unilateral retinoblastoma cases and cancer-free controls were matched on age group at time of interview (0–1, 2–3, 4–5, 6–7, 8–9, 10–11,12–13 and 14–15 years).

[c] Seven matched sets were dropped due to missing values for one of the adjustment variables.

[d] Adjusted for mother's race and education, mother smoked month before or during pregnancy, household income, prenatal vitamin use, and total calories per day.

Table 4

Associations (OR (95%CI)) between dietary patterns during the 2nd trimester of pregnancy and unilateral retinoblastoma

	Conditional Logistic Model						Unconditional Logistic Model[a]					
	n=91 matched sets[b]			n=84 matched sets[c]			Cases: n=182, Controls: n=144			Cases: n=162, Controls: n=136		
	Crude OR	**95% C.I.**		**Adj OR[d]**	**95% C.I.**		**Crude OR**	**95% C.I.**		**Adj OR[d]**	**95% C.I.**	
High fruit/veg, low fried food/sweets												
Continuous	**0.89**	0.76	1.04	**0.75**	0.61	0.92	**0.85**	0.75	0.96	**0.88**	0.77	1.01
0–2	**ref**	~	~	**ref**	~	~	**ref**	~	~	**ref**	~	~
3–5	**1.09**	0.52	2.31	**0.60**	0.24	1.54	**0.75**	0.44	1.30	**0.97**	0.52	1.81
6–8	**0.71**	0.30	1.65	**0.26**	0.08	0.81	**0.53**	0.27	1.05	**0.70**	0.33	1.49
High fruit/veg, low red/cured meat												
Continuous	**0.97**	0.81	1.15	**0.84**	0.67	1.04	**0.92**	0.81	1.04	**0.95**	0.83	1.09
0–2	**ref**	~	~	**ref**	~	~	**ref**	~	~	**ref**	~	~
3–5	**0.95**	0.46	1.97	**0.53**	0.22	1.29	**0.94**	0.53	1.67	**0.99**	0.52	1.90
6–8	**0.89**	0.35	2.29	**0.55**	0.17	1.73	**0.65**	0.32	1.29	**0.73**	0.34	1.58

[a] Adjusted for matching variable age group

[b] Unilateral retinoblastoma cases and cancer-free controls were matched on age group at time of interview (0–1, 2–3, 4–5, 6–7, 8–9, 10–11,12–13 and 14–15 years). One case missing vegetable intake was excluded.

[c] Seven matched sets were dropped due to missing values for one of the adjustment variables.

[d] Adjusted for mother's race and education, mother smoked month before or during pregnancy, household income, prenatal vitamin use, and total calories per day.