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Original Contribution

Maternal Dietary Patterns During Early Pregnancy and the Odds of Childhood Germ Cell Tumors: A Children's Oncology Group Study

Jessica R. B. Musselman, Anne M. Jurek, Kimberly J. Johnson, Amy M. Linabery, Leslie L. Robison, Xiao-Ou Shu, and Julie A. Ross*

* Correspondence to Dr. Julie A. Ross, Division of Epidemiology and Clinical Research, Department of Pediatrics, University of Minnesota, MMC 422, 420 Delaware Street Southeast, Minneapolis, MN 55455 (e-mail: rossx014@umn.edu).

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Maternal diet during pregnancy may be associated with cancer in offspring. Intake of individual foods, as well as dietary patterns, can be used when examining these relations. Here, the authors examined associations between maternal dietary intake patterns and pediatric germ cell tumors (GCTs) using principal components analysis and logistic regression. Mothers of 222 GCT cases aged less than 15 years who were diagnosed at a Children's Oncology Group institution between 1993 and 2001 and those of 336 frequency-matched controls completed a self-administered food frequency questionnaire of diet during early pregnancy. Four dietary patterns were identified: ''Western,'' ''fruits and vegetables,'' ''protein,'' and ''healthful.'' With adjustment for birth weight, parity, and vitamin use, the fruits and vegetables pattern was significantly associated with a lower odds for GCTs (odds ratio (OR) = 0.83, 95% confidence interval (CI): 0.69, 0.99; 2 sided). Upon stratification, the fruits and vegetables pattern was significantly associated with a lower odds in males (OR = 0.66, 95% CI: 0.47, 0.92) but not females (OR = 0.91, 95% CI: 0.72, 1.14). A quantitative assessment of assumed nondifferential reporting error indicated no notable deviations from unadjusted odds ratio estimates. Results of this exploratory analysis suggest that maternal prenatal dietary patterns could be considered in future studies of GCTs in offspring.

eating; factor analysis; mental recall; neoplasms, germ cell and embryonal; prenatal nutritional physiological phenomena

Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; GCT, germ cell tumor; OR, odds ratio.

Childhood germ cell tumors (GCTs) are a group of histologically and biologically heterogeneous neoplasms that are classified together because of their common cellular origin in the primordial germ cell (1). GCTs are extremely rare, with roughly 225 new cases reported annually in the United States (2), comprising roughly 3.5% of the cancers in persons under 15 years of age (1); however, evidence suggests that incidence rates may be increasing (1, 3, 4). The only consistent factor associated with an increased risk of childhood and adult GCTs is cryptoorchidism (1, 5–8).

The early age of onset of childhood GCTs suggests that in utero exposures may be important (9, 10). One such exposure that has yet to be studied in childhood GCTs is maternal diet during pregnancy. Maternal diet is known to be a key source of micro- and macronutrients during crucial stages of fetal development (11) that has been associated with health outcomes in the offspring (11–14), although its relation to GCTs has not been previously examined.

When analyzing dietary intake, researchers can consider individual foods as either independent entities or part of a larger pattern or diet (13, 15). Compared with analyses that assume each food is an independent entity, statistical analysis techniques such as factor analysis that account for dietary patterns when assessing associations between diet and disease might be more fully able to capture the consumption experience (15, 16) and can be useful when there is not a single food or type of foods hypothesized to be associated with a disease. Factor analysis is a common method to evaluate dietary patterns (13, 17). When factor analysis is applied to a food frequency questionnaire (FFQ),

a large number of individual foods are condensed to a set of identifiable dietary patterns (or components) that account for a large portion of variation in the data (16, 17). No prior study has examined maternal dietary intake patterns and their association with the risk of childhood GCTs, particularly using latent variable factor analysis methods to classify distinct dietary typologies. Therefore, we undertook an analysis of dietary patterns and childhood GCTs among participants in a case-control study.

MATERIALS AND METHODS

Subjects

This study has been described in detail elsewhere (9, 10). Briefly, children newly diagnosed with a GCT (germinoma, seminoma, dysgerminoma, embryonal carcinoma, yolk-sac tumor, choriocarcinoma, immature teratoma, and mixed germ-cell tumor) at any anatomic site (except for those found in the brain, because of its extreme rarity and the difficulty in accurate diagnosis) were ascertained from Children's Oncology Group institutions prior to the age of 15 years. To be eligible, cases must have been diagnosed between January 1, 1993, and December 31, 2001, and be registered with the Children's Oncology Group Statistics and Data Center (Arcadia, California). In addition, cases were required to have a biologic mother who could speak English and a telephone in the child's home. Approval from the institutional review board was obtained before participants were enrolled.

Mothers were asked to complete both a telephone interview and a self-administered questionnaire. The self-administered questionnaire contained questions regarding diet, smoking habits, alcohol consumption, and chemical exposures. The telephone interview contained questions regarding demographic and clinical information on the mother and the index child including race, education, and income of the parents, as well as detailed information on illnesses and medications that occurred during and immediately preceding the index pregnancy.

Of the 496 potentially eligible cases registered at a Children's Oncology Group institution, 344 (69%) met the eligibility criteria. Of those excluded ($n = 152$), 70 (56%) were ineligible because of incorrect pathology or age, 26 (17%) had a GCT located in the brain, 20 (13%) had a physician who refused, 32 (21%) did not have a biologic mother who spoke English, and 4 (3%) did not have a biologic mother available for interview. Telephone interviews were completed for 278 of 344 mothers (81%), of which 8 children were deceased at the time of the interview. Interviews could not be completed because of refusal ($n = 44$, 13%), nonworking phone numbers ($n = 20$, 6%), and inability to schedule an interview ($n = 2$, 1%). Self-administered questionnaires were returned by 333 (97%) case mothers.

Controls were identified by using random digit dialing and were frequency matched to cases on the basis of sex, year of birth (within 1 year), and geographic location at the time of diagnosis (at the state level). Matching frequencies were 1:2 for males and 1:1 for females in order to maximize study power, since germ-cell tumor incidence is lower in boys than girls. The methods used for identifying and enrolling controls are described previously (10, 18). Briefly, 634 households with an eligible child were identified. Of these, telephone interviews were completed for 423 potential controls (67%). Interviews could not be completed because of refusal ($n = 182$, 29%), change in phone number ($n = 28$, 4%), or other reasons ($n = 1$, 0.1%). Self-administered questionnaires were returned by 428 (69%) control mothers.

Data collection

Assessment of dietary intake. Case and control mothers completed a 21-item FFQ that was included in the self-administered questionnaire (refer to Table 2 for a list of FFQ items). The FFQ was brief because diet was not a main focus of the study given the lack of knowledge overall regarding the etiology of GCTs. The FFQ measured usual consumption of each food from the time period lasting from 1 month before pregnancy through the first month of pregnancy. Participants recorded food item frequency (times per day, week, or month); consumption of each item was then converted to average servings per day. Questionnaires were excluded from analysis if responses for any of the food items were missing. Information on serving size was not available and, thus, analyses were performed on frequency of consumption only.

Dietary patterns. Dietary patterns were derived from the 21 food items on the FFQ by using principal components analysis (15, 16). Factor pattern extraction was performed with an orthogonal varimax rotation with PROC FACTOR in SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina) with the METHOD = PRINCIPAL option. Criteria for selecting the number of factors to be retained were based on the scree test, percent variability explained, eigenvalue >1, and interpretability. A factor pattern score was calculated for each dietary pattern for each participant. A FFQ item was considered to be an important component to a given factor if it had a high loading (± 0.30 or more). Scores were calculated by finding the product of the consumption of each food item per day and the factor loading for that food and then by summing these products across all 21 food items. Although an increase in score is indicative of increased conformity to a particular pattern (i.e., high consumption of high loading items), conformity can be achieved in essentially 3 ways: a moderate increase in the consumption of several foods that load high on that factor, a large increase in consumption of a single food with high loadings, or a decrease in consumption of foods that load negatively on that factor.

Statistical analysis

Cases and controls were compared by using logistic regression for similarities in demographic and pregnancy characteristics including maternal age, maternal race, maternal education, maternal parity, vitamin supplementation use, household income, age of the index child, and sex of the index child.

Unconditional logistic regression models were used to estimate odds ratios and 95% confidence intervals for the

Table 1. Distribution of Data on Demographic Factors in a Case-Control Study of Childhood Germ Cell Tumors and Maternal Diet During Early Pregnancy, Children's Oncology Group, United States, 1993–2001[a]

Variable	Total						Males						Females					
	Cases (n = 222)		Controls (n = 336)		OR[b]	95% CI	Cases (n = 69)		Controls (n = 141)		OR[b]	95% CI	Cases (n = 153)		Controls (n = 194)		OR[b]	95% CI
	No.	%	No.	%			No.	%	No.	%			No.	%	No.	%		
Child's age, years																		
0	45	20.27	76	22.62	1.00	Referent	20	28.99	37	26.24	1.00	Referent	25	16.34	39	20.10	1.00	Referent
1–4	72	32.43	81	24.11	1.50	0.92, 2.44	32	46.38	34	24.11	1.74	0.84, 3.60	40	26.14	46	23.71	1.36	0.70, 2.62
5–10	39	17.57	84	25.00	0.78	0.46, 1.33	3	4.35	30	21.28	0.19	0.05, 0.68	36	23.53	54	27.84	1.04	0.54, 2.00
11–14	66	29.73	95	28.27	1.17	0.72, 1.90	14	20.29	40	28.37	0.65	0.29, 1.47	52	33.99	55	28.35	1.48	0.79, 2.77
Birth weight, g																		
≤3,000	56	25.23	74	22.02	1.33	0.89, 2.01	13	18.84	24	17.02	1.41	0.65, 3.06	43	28.10	49	25.26	1.24	0.76, 2.02
3,001–4,000	130	58.56	229	68.15	1.00	Referent	38	55.07	99	70.21	1.00	Referent	92	60.13	130	67.01	1.00	Referent
≥4,001	36	16.22	33	9.82	1.92	1.14, 3.23	18	26.09	18	12.77	2.61	1.23, 5.53	18	11.76	15	7.73	1.70	0.81, 3.54
Maternal age at index pregnancy, years																		
≤24	70	31.53	94	27.98	1.10	0.73, 1.68	20	28.99	30	21.28	1.90	0.89, 4.07	50	32.68	64	32.99	0.81	0.48, 1.35
25–29	81	36.49	120	35.71	1.00	Referent	20	28.99	57	40.43	1.00	Referent	61	39.87	63	32.47	1.00	Referent
30–34	46	20.72	90	26.79	0.76	0.48, 1.19	17	24.64	43	30.50	1.13	0.53, 2.41	29	18.95	46	23.71	0.65	0.36, 1.17
≥35	25	11.26	32	9.52	1.16	0.64, 2.10	12	17.39	11	7.80	3.11	1.19, 8.15	13	8.50	21	10.82	0.64	0.29, 1.39
Parity at index pregnancy																		
1	61	27.48	109	32.44	1.00	Referent	16	23.19	50	35.46	1.00	Referent	45	29.41	59	30.41	1.00	Referent
2	71	31.98	92	27.38	1.38	0.89, 2.14	24	34.78	39	27.66	1.92	0.90, 4.11	47	30.72	52	26.80	1.19	0.68, 2.06
3	45	20.27	79	23.51	1.02	0.63, 1.65	19	27.54	27	19.15	2.20	0.98, 4.96	26	16.99	52	26.80	0.66	0.36, 1.21
4 or more	45	20.27	56	16.67	1.44	0.87, 2.37	10	14.49	25	17.73	1.25	0.50, 3.15	35	22.88	31	15.98	1.48	0.80, 2.75
Maternal race																		
White	174	78.38	289	86.01	1.00	Referent	57	82.61	124	87.94	1.00	Referent	117	76.47	164	84.54	1.00	Referent
Nonwhite	48	21.62	47	13.99	1.70	1.09, 2.64	12	17.39	17	12.06	1.54	0.69, 3.43	36	23.53	30	15.46	1.68	0.98, 2.89
Maternal education																		
High school or less	87	39.19	98	29.17	1.00	Referent	24	34.78	31	21.99	1.00	Referent	63	41.18	67	34.54	1.00	Referent
Some post-high school	65	29.28	108	32.14	0.68	0.45, 1.03	21	30.43	48	34.04	0.57	0.27, 1.18	44	28.76	60	30.93	0.78	0.46, 1.31
College graduate	50	22.52	97	28.87	0.58	0.37, 0.91	22	31.88	44	31.21	0.65	0.31, 1.35	28	18.30	52	26.80	0.57	0.32, 1.02
Advanced degree	20	9.01	33	9.82	0.68	0.37, 1.28	2	2.90	18	12.77	0.14	0.03, 0.68	18	11.76	15	7.73	1.28	0.59, 2.75

Annual household income, $																			
<20,000	63	28.38	62	18.45	1.00	Referent	21	31.34	27	19.15	1.00	Referent	42	27.45	35	18.32	1.00	Referent
20,001–30,000	55	24.77	87	25.89	0.62	0.38, 1.01	14	20.90	34	24.11	0.53	0.23, 1.23	41	26.80	53	27.75	0.65	0.35, 1.18
30,001–50,000	53	23.87	102	30.36	0.51	0.32, 0.83	18	26.87	43	30.50	0.54	0.24, 1.19	35	22.88	58	30.37	0.50	0.27, 0.93
>50,000	49	22.07	82	24.40	0.59	0.36, 0.97	14	20.90	37	26.24	0.49	0.21, 1.13	35	22.88	45	23.56	0.65	0.35, 1.22
Vitamin use during pregnancy																		
Yes	190	85.59	309	92.24	1.00	Referent	62	89.86	134	95.04	1.00	Referent	128	83.66	174	90.16	1.00	Referent
No	32	14.41	26	7.76	0.50	0.29, 0.86	7	10.14	7	4.96	0.46	0.16, 1.38	25	16.34	19	9.84	0.56	0.30, 1.06

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Missing information on sex for 1 control.
[b] Odds ratio from logistic regression.

effect of each dietary factor pattern (continuous variables) on GCT odds. The models were adjusted for the index child's age and sex and for appropriate confounders. Relevant confounders were selected from a set of potential confounders by using stepwise selection methods (19) in which the confounder with the greatest effect (in percent change) on the parameter estimate was added to the model. This was repeated for the confounder with the next highest effect until adding another failed to alter the size of the parameter estimate by more than 5%. Potential confounders considered for model entry were maternal age, maternal race, maternal education, parity, vitamin use, household income, and index child's birth weight. Additional subgroup analyses were conducted by stratifying data on the basis of the index child's sex and age at diagnosis ($\leq$5 years vs. >5 years).

Finally, we performed a nonprobabilistic sensitivity analysis (20) to quantify the effect of misreporting dietary intake. We assumed 3 scenarios for the percentage of mothers misreporting dietary intake and 3 scenarios for the degree of misreporting. We examined nondifferential reporting error because we assumed that the mothers of children with and without GCTs would not recall dietary practices differently. The 3 scenarios for the percentage of mothers reporting error in dietary intake were as follows: 1) 25% of the mothers overreported and 75% underreported; 2) 50% of the mothers overreported and the other 50% underreported; and 3) 75% of the mothers overreported and 25% underreported. We represented the degree of misreporting by a moderate (0.5 standard deviation units) and severe (1.0 and 1.5 standard deviation units) change in standard deviation. Because factor pattern scores are a function of the loadings (which are fixed following dietary pattern identification) and consumption, the adjustment of the dietary pattern score corresponds to an adjustment of reported intake. Odds ratios adjusted for reporting error were compared with the original unadjusted odds ratios.

RESULTS

Of mothers who returned the self-administered questionnaire, 222 of 333 (67%) case mothers and 336 of 428 (79%) control mothers had no missing items on the FFQ. The histologic subtypes of the 222 cases included 99 yolk sac tumors (36 male, 63 female), 55 teratomas (malignant teratoma, immature teratoma; 12 male, 43 female), 36 seminomas (seminoma, dygerminoma, germinoma; 2 male, 34 female), 22 other nonseminoma (embryonal carcinoma, choriocarcinoma, polyembyoma; 15 male, 7 female), 8 other (mixed germ cell tumor components; 3 males, 5 females); and 2 not specified (1 of each sex).

Demographic characteristics overall and by sex are given in Table 1. Cases and controls differed on the index child's sex; 69% of cases were female compared with approximately 58% of control children, which was expected given the different frequency matching in the sampling of male and female controls. Slightly over 50% of cases were diagnosed under the age of years. Cases tended to have both higher (>4,000 g) and lower (<3,000 g) birth weights, with cases being significantly more likely than controls, especially

males, to have a high birth weight. Overall, case mothers and control mothers did not differ significantly in age or parity at the index pregnancy. However, male cases tended to have both younger (age, ≤24 years) and older (age, ≥35 years) mothers than male controls; an opposite pattern was observed among female cases. Case mothers tended to have lower levels of education and income than did control mothers and were more likely to be nonwhite. Case mothers were less likely to have used vitamin supplements during pregnancy.

In general, case mothers and control mothers were similar in their daily food consumption for each of the individual items on the FFQ (Table 2), although case mothers tended to consume higher quantities of chips and fried potatoes and fewer cruciferous vegetables. Of note, the means and standard deviations from the extracted dietary pattern scores indicated that cases and controls did not significantly differ in adherence on any factor score and that both cases and controls had factor scores that followed the expected standard normal distribution.

Four distinct dietary patterns were identified from the factor analysis: ''Western diet,'' ''fruits and vegetables,'' ''proteins,'' and ''healthful'' (Table 3). ''Western diet'' had high positive loadings for processed meats and packaged snack foods. The second pattern, ''fruits and vegetables,'' had high loadings for carrots, fruits, juices, green salads, and cruciferous vegetables. Eggs, bacon, pork, and fried chicken all loaded high on the third ''proteins'' factor. The fourth pattern, ''healthful,'' was composed of high loadings on foods such as skim/low-fat milk and other vegetables and high negative loadings on foods such as whole milk, processed foods, and fried chicken. The cheese product food item had moderate loadings on both the ''Western diet'' and the ''proteins'' patterns. Fruits loaded on both ''healthful'' and ''fruits and vegetables,'' although their loading was considerably higher for the latter pattern (0.61 compared with 0.30). Factor loadings for each pattern are shown in Table 3.

Among controls, consumption patterns differed by race, with nonwhites adhering more to all dietary patterns except ''proteins'' and vitamin nonusers adhering more to both the ''Western'' and ''fruits and vegetables'' patterns (results not shown). Higher household income and maternal education were associated with greater adherence to the ''proteins'' pattern.

In the initial unadjusted analysis, none of the 4 factor patterns reached statistical significance, although a 1-unit increase in score for the ''fruits and vegetables'' factor was modestly associated with a reduced risk (odds ratio (OR) = 0.86, 95% confidence interval (CI): 0.72, 1.02) (Table 4). After adjustment for matching variables and covariates (vitamin use, parity, and birth weight), the ''fruits and vegetables'' pattern was inversely associated (OR = 0.83, 95% CI: 0.69, 0.99), while all other factor patterns remained unassociated with GCTs. Results for stratification by age of diagnosis (before or after age 5 years) yielded estimates in a similar direction (Table 4), although none was significant. There were also no significant associations between dietary patterns and GCTs in the female subgroup. However, analysis of the males-only subgroup showed significant decreased risk associated with GCTs (OR = 0.66, 95% CI: 0.47, 0.92) with the ''fruits and vegetables'' factor pattern. Further, an interaction term examining this factor pattern between age of diagnosis and the index child's sex suggested evidence of effect modification ($P = 0.002$), with male cases diagnosed before age 5 years showing the strongest effect.

Nonprobabilistic sensitivity analyses on the effects of nondifferential reporting error are given in Table 5. Minor to severe degrees of nondifferential reporting error did not grossly alter the results, although overreporting seemed to exert a larger influence than assumed underreporting. Thus, our results were not sensitive to various degrees of assumed reporting error.

DISCUSSION

This study focused on maternal diet between 1 month before pregnancy through the first month of pregnancy and odds of childhood GCTs. Using factor analysis to extract dietary factor patterns, we performed a more comprehensive evaluation of maternal diet as an exposure than would be obtained by analyzing each food individually. We found that, in early pregnancy, higher adherence to a diet that is high in fruits and vegetables was associated with a decreased odds for childhood GCTs. In general, high or low adherence to diets high in proteins and diets high in snack or processed foods was not associated with risk of childhood GCTs.

Our findings are consistent with results from other studies indicating the role of diet and cancer—particularly the inverse association between fruits and vegetables and cancer. For example, fruit consumption during pregnancy was found to be protective against medulloblastoma in children (21), and several studies have reported evidence of an inverse association with maternal fruit and/or vegetable consumption and childhood leukemia (22–24). In studies of adult cancers, a protective effect of diets high in fruits and vegetables has been found for breast (25), colorectal (16), and cancers of the digestive tract (15). Many of these studies also reported positive associations between cancer and ''Western'' diets, and though our results failed to significantly replicate these findings, they were consistent in the direction of the estimated effect. Fruits and vegetables are naturally rich in micronutrients and antioxidants that may confer a health benefit to the developing fetus (11, 26), while chemical additives in processed Western foods or the lack of essential nutrients in a low fruit and vegetable diet may be detrimental to normal growth (11, 13). In addition, inverse associations have been reported for maternal vitamin supplementation and GCTs (8). Vitamin use was found to be a confounder in our analyses, and mothers who take vitamins could also be more likely to engage in healthy eating behaviors, such as high consumption of fruits and vegetables.

This study represents one of the largest epidemiologic studies conducted for childhood GCTs (9) and, as such, holds great potential for elucidating environmental risk factors associated with childhood GCTs. However, the study has several limitations. First, diet is extremely difficult to

Table 2. Mean Intakes Per Day of Items From a Food Frequency Questionnaire in a Case-Control Study of Childhood Germ Cell Tumors, Children's Oncology Group, United States, 1993–2001

Variable	Mean (SD)		*t* statistic (df = 556)	*P* Value[a]
	Cases (*n* = 222)	Controls (*n* = 336)		
FFQ item, servings per day				
Cookies, cake, pastry, or pie	0.48 (0.56)	0.43 (0.42)	−1.30	0.20
Snack foods such as chips and popcorn	0.42 (0.58)	0.35 (0.37)	−1.74	0.08
Butter/margarine	1.01 (0.75)	1.08 (0.70)	1.06	0.29
Potato chips, fried potatoes	0.41 (0.43)	0.33 (0.30)	−2.38	<0.05
Potatoes, not fried	0.35 (0.35)	0.36 (0.37)	0.31	0.76
Hot dogs, lunch meats	0.29 (0.30)	0.32 (0.30)	1.15	0.25
Hamburger/meatloaf	0.23 (0.23)	0.21 (0.15)	−1.07	0.29
Green salads	0.36 (0.31)	0.40 (0.31)	1.82	0.07
Fruit juices	0.74 (0.84)	0.75 (0.74)	0.09	0.93
Carrots	0.24 (0.28)	0.25 (0.27)	0.29	0.77
Fruit (not including juice)	0.90 (0.83)	0.97 (0.93)	0.97	0.33
Broccoli, cauliflower, radishes, turnips	0.24 (0.29)	0.31 (0.36)	2.22	<0.05
Eggs	0.31 (0.27)	0.33 (0.32)	0.84	0.40
Bacon or sausage	0.15 (0.20)	0.15 (0.23)	−0.12	0.90
Fried chicken	0.10 (0.13)	0.09 (0.15)	−0.56	0.57
Cheese products	0.47 (0.46)	0.50 (0.42)	0.59	0.56
Pork	0.12 (0.24)	0.10 (0.11)	−1.31	0.19
Beef, not including ground beef	0.25 (0.28)	0.23 (0.22)	−0.90	0.37
Other vegetables not already included	0.62 (0.56)	0.64 (0.52)	0.39	0.70
Skim or low-fat milk	0.96 (1.09)	1.09 (1.15)	1.37	0.17
Whole milk	0.47 (0.88)	0.40 (0.81)	−0.95	0.34
Dietary factor pattern, score[b]				
Western diet	0.05 (1.23)	−0.04 (0.81)	−1.04	0.30
Fruits and vegetables	−0.09 (0.99)	0.06 (1.01)	1.69	0.09
Proteins	0.002 (1.07)	−0.001 (0.95)	−0.04	0.97
Healthful	−0.08 (1.00)	0.06 (1.00)	1.60	0.11

Abbreviations: FFQ, food frequency questionnaire; SD, standard deviation.

[a] *P* value *t* test.

[b] Factor pattern scores were calculated for each pattern by summing the products of the consumption of each food item per day and the factor loading for that food. Means and standard deviations of these scores were then separately calculated for cases and controls to examine whether the case and control factor scores followed the assumed standard normal distribution.

measure accurately (27). The results of our analyses were based on the self-reported intake of diet during a pregnancy that could have taken place several years in the past (28). Although some studies have suggested that dietary recall during a past pregnancy is fairly good, it is not completely accurate (28–30). We attempted to formally account for recall bias by performing a sensitivity analysis to assess the impact of recall error. The results of our nonprobabilistic sensitivity analysis suggested that adjustment for assumed nondifferential reporting error did not change our odds ratio estimates.

The limitation of recall bias is compounded by the fact that the study FFQ assessed only 21 items and did not include any grains. Furthermore, the study FFQ did not assess portion size in any way, so there was no way to standardize consumption bulk in our analyses. In addition, the FFQ covered only the diet during the time 1 month prior to pregnancy through the first month. It is entirely possible that an

Table 3. Factor Loadings[a] of 4 Dietary Factor Patterns From Principal Components Analysis in a Case-Control Study of Childhood Germ Cell Tumors, Children's Oncology Group, United States, 1993–2001

FFQ Item	Dietary Pattern			
	Western Diet	Fruits and Vegetables	Proteins	Healthful
Cookies, cake, pastry, or pie	0.74[a]	0.01	−0.09	−0.09
Snack foods such as chips and popcorn	0.77[a]	−0.01	−0.08	−0.06
Butter/margarine	0.46[a]	0.24	0.03	0.11
Potato chips, fried potatoes	0.64[a]	−0.05	0.34	−0.22
Potatoes, not fried	0.51[a]	0.24	−0.06	−0.16
Hot dogs, lunch meats	0.54[a]	−0.19	0.20	0.04
Hamburger/meatloaf	0.39[a]	−0.16	0.25	−0.07
Green salads	−0.05	0.65[a]	−0.13	−0.09
Fruit juices	0.05	0.53[a]	0.26	−0.05
Carrots	0.04	0.63[a]	−0.27	0.04
Fruit, not including juice	0.01	0.61[a]	0.05	0.30
Broccoli, cauliflower, radishes, turnips	0.02	0.58[a]	0.18	−0.01
Eggs	0.04	0.21	0.56[a]	0.01
Bacon or sausage	0.11	−0.06	0.61[a]	−0.01
Fried chicken	0.07	−0.07	0.47[a]	−0.40
Cheese products	0.27[a]	0.14	0.27[a]	0.20
Pork	−0.03	0.01	0.42[a]	−0.07
Beef, not including ground beef	0.16	0.12	0.15	−0.24[a]
Other vegetables not already included	0.02	0.34	0.18	0.42[a]
Skim or low-fat milk	−0.02	0.19	−0.04	0.71[a]
Whole milk	0.14	0.22	0.17	−0.67[a]

Abbreviation: FFQ, food frequency questionnaire.
[a] Highest loading.

alternative window of exposure is more relevant to the development of GCTs, such as later in pregnancy when the fetus begins to undergo an accelerated rate of cell replication (31); however, this is not likely, as evidence suggests that dietary patterns including fruits and vegetable consumption are fairly stable including the period before, during, and after pregnancy (32, 33).

It should also be noted that dietary factor pattern scores did not significantly differ between cases and controls (Table 2). This could indicate either that case mothers and control mothers really do have similar dietary patterns or that our sample size and/or FFQ were not sufficient to detect potentially relevant differences. Further, our odds ratio estimates remained relatively unchanged upon adjustment for potential confounders. This could indicate either a robustness of our results or a failure to identify and accurately measure legitimate confounders that would have impacted our results had they been entered into the model. Because we carefully selected potential confounders for stepwise regression (19) based on current knowledge of the disease, we think it unlikely that we failed to identify important confounders; however, residual confounding could still exist because of inaccurate measurement of the confounders.

Selection bias is also a potential concern in this study, particularly because only 69% of the control mothers returned the FFQ (compared with 97% of case mothers), and of those, only 67% of case mothers and 79% of control mothers returned an FFQ that was complete enough for analysis. If the mothers who were included in the study differed from those who were not, this could introduce bias into the study. We cannot assess the differences between participants and nonparticipants, but among those who returned the FFQ, there were no statistically significant differences between those returning a partial versus a complete questionnaire in terms of maternal age, educational level, or income. However, mothers who did not return a complete FFQ were significantly more likely to be nonwhite than mothers who returned a complete FFQ ($P = 0.02$).

Finally, GCTs have many histologic subtypes (1), and each one may have its own etiology such that other significant case-control differences could not be detected. Moreover, there were sex-specific differences in subtype frequency.

Table 4. Odds Ratios and 95% Confidence Intervals for Subgroup Analyses of the Index Child's Sex and Age at Diagnosis Among Cases ($n = 222$) and Controls ($n = 336$) From the Children's Oncology Group, United States, 1993–2001

Subgroup	Western		Fruits and Vegetables		Proteins		Healthful	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Overall (both sexes, all ages)								
Crude	1.09	0.92, 1.30	0.86	0.72, 1.02	1.00	0.84, 1.19	0.87	0.73, 1.03
Model 1[a]	1.09	0.92, 1.31	0.87	0.73, 1.04	0.98	0.83, 1.17	0.95	0.80, 1.14
Model 2[b]	1.09	0.91, 1.30	0.83	0.69, 0.99	0.95	0.80, 1.14	0.91	0.76, 1.09
Sex[c]								
Boys ($n = 210$)	1.10	0.75, 1.62	0.66	0.47, 0.92	0.86	0.59, 1.26	0.99	0.70, 1.40
Girls ($n = 347$)	1.08	0.89, 1.32	0.91	0.72, 1.14	0.97	0.79, 1.19	0.90	0.73, 1.12
Age at diagnosis[d]								
$\leq$5 years ($n = 289$)	1.09	0.87, 1.37	0.92	0.71, 1.19	0.86	0.68, 1.08	0.95	0.73, 1.22
>5 years ($n = 269$)	1.10	0.81, 1.50	0.76	0.57, 1.00	1.10	0.82, 1.48	0.86	0.65, 1.13

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Model 1: adjusted for child's sex and age.
[b] Model 2: adjusted for child's birth weight, maternal vitamin supplementation, and parity.
[c] Adjusted for child's age, birth weight, maternal vitamin supplementation, and parity.
[d] Adjusted for child's sex, birth weight, maternal vitamin supplementation, and parity.

However, limited power due to small subtype-specific sample sizes prevented us from exploring dietary patterns by histologic subtype.

Despite these limitations, our findings are supported by the many positive aspects of the study design and the careful and systematic analyses that we performed. In addition to having a large sample size, the study represents cases and controls from a wide catchment area, and thus our results may be generalizable to the US population. The extremely high response rate among case mothers (97%) and the moderate response rate among controls (69%) are also a major asset. Furthermore, assessment of potential selection bias indicated that its influence on our findings is most likely fairly limited, with regard to both participants and nonparticipants and between those who submitted complete versus incomplete FFQs. Although the FFQ may have limitations, it is a cost-effective and efficient way to quickly and easily assess dietary consumption. Furthermore, the results of our sensitivity analyses suggest that our findings are robust to the types of reporting errors we assumed.

In summary, our findings suggest that, during early pregnancy, a maternal diet high in fruits and vegetables may

Table 5. Crude Odds Ratios Adjusted for Nondifferential Reporting Error by Dietary Factor Pattern in a Case-Control Study of Childhood Germ Cell Tumors, Children's Oncology Group, United States, 1993–2001

% Misreported		SD Units Corrected	Odds Ratio			
Over	Under		Western Diet	Fruits and Vegetables	Proteins	Healthful
0	0	0	1.09[a]	0.86[a]	1.00[a]	0.87[a]
25	75	0.5	1.10	0.86	1.01	0.87
		1.0	1.11	0.87	1.02	0.88
		1.5	1.13	0.88	1.03	0.89
50	50	0.5	1.10	0.86	1.00	0.86
		1.0	1.12	0.87	1.01	0.87
		1.5	1.13	0.87	1.02	0.88
75	25	0.5	1.11	0.87	1.02	0.88
		1.0	1.12	0.89	1.03	0.90
		1.5	1.14	0.90	1.04	0.90

Abbreviation: SD, standard deviation.
[a] Crude odds ratio without adjustment for reporting error.

decrease the odds of GCTs. Further research on maternal diet during early pregnancy is recommended.

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Author affiliations: Division of Pediatric Epidemiology and Clinical Research, University of Minnesota, Minneapolis, Minnesota (Jessica R. B. Musselman, Anne M. Jurek, Kimberly J. Johnson, Amy M. Linabery, Julie A. Ross); University of Minnesota Masonic Cancer Center, Minneapolis, Minnesota (Anne M. Jurek, Julie A. Ross); Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee (Leslie L. Robison); and Division of Epidemiology, Department of Medicine, Vanderbilt Ingram-Cancer Center and Center for Health Services Research, Vanderbilt University, Nashville, Tennessee (Xiao-Ou Shu).

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