

Maternal Smoking and Testicular Germ Cell Tumors

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Abstract

Testicular germ cell tumors (TGCT) are the most common cancer among men ages 15 to 35 years in the United States. The well-established TGCT risk factors cryptorchidism, prior diagnosis of TGCT, and family history of testicular cancer indicate that exposures in early life and/or in the familial setting may be critical to determining risk. Previous reports of familial clustering of lung cancer in mothers and testicular cancers in sons suggest that passive smoking in childhood may be such an exposure. To clarify the relationship of passive smoking exposure to TGCT risk, data from 754 cases and 928 controls enrolled in the Servicemen's Testicular Tumor Environmental and Endocrine Determinants study were analyzed. Data from 1,086 mothers of the cases and controls were also examined. Overall, there was no relationship between maternal [odds ratio (OR), 1.1; 95%

confidence interval (95% CI), 0.9-1.3] or paternal smoking (OR, 1.0; 95% CI, 0.8-1.3) and TGCT risk. Although living with a nonparent smoker was marginally related to risk (OR, 1.4; 95% CI, 1.0-2.1), there was no relationship with number of smokers, amount smoked, or duration of smoking. Responses from both case-control participants and mothers also revealed no relationship between either maternal smoking while pregnant or while breast-feeding. Results did not differ by TGCT histology (seminoma, nonseminoma). These results do not support the hypothesis that passive smoking, either *in utero* or in childhood, is related to risk of TGCT. Other early life exposures, however, may explain the familial clustering of lung cancer in mothers and TGCT in sons. (Cancer Epidemiol Biomarkers Prev 2006;15(10):1820-4)

Introduction

The incidence of testicular germ cell tumors (TGCT) has been increasing in the United States for several decades, particularly among men of European ancestry (1). The etiology, however, remains poorly understood, with the only well-documented risk factors being cryptorchidism, prior history of TGCT, and family history of TGCT (2). In addition to these factors, the similarity of testicular carcinoma *in situ* to primordial germ cells suggests that TGCT risk is determined very early in life, possibly even *in utero* (3, 4). Which factors could explain both familial clustering and *in utero* etiology are not certain, although suggestions have included maternal age, maternal weight, *in utero* hormone levels, nutrition, environmental endocrine modulators, and maternal smoking (5-8).

The maternal smoking hypothesis is based on ecologic studies of lung and testicular cancer rates (8, 9) and on familial cancer studies (10-13). Direct examinations of maternal smoking and TGCT have also been reported from case-control studies and have not, in general, supported the hypothesis (14-19). It has been suggested, however, that the data from the case-control studies may be inaccurate, as most previous studies have only included data collected from the mothers of the cases and controls (9). As mothers who smoked might be reluctant to report behavior harmful to their children and might be more likely to be deceased by the time their son developed TGCT, the studies could have resulted in biased estimates of risk. To overcome this possible obstacle, the current study queried case-control participants, as well as

mothers, about the mothers' smoking habits. In addition, the smoking habits of other household residents were ascertained to examine other possible sources of passive smoking.

Materials and Methods

Study Population. Details about the U.S. Servicemen's Testicular Tumor Environmental and Endocrine Determinants study have been previously reported.⁵ In brief, the study enrolled participants between 2002 and 2005. To be eligible, servicemen had to have at least one serum sample stored in the Department of Defense Serum Repository (Silver Spring, MD) and to be younger than age 46 years. Using a person-specific ID, the specimens in the Department of Defense Serum Repository computerized database were linked to the Defense Medical Surveillance System (20) and to other military medical databases to determine which military personnel had developed TGCT while on active duty between 1988 and 2003. Diagnoses of TGCT were limited to classic seminoma or nonseminoma (embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, teratomas, and mixed germ cell tumor), as spermatocytic seminoma occurs primarily among older men and is thought to have an etiology distinct from other TGCTs. Nine hundred sixty-one eligible case participants were initially identified. Of these men, 76 could not be traced, 27 had died, 3 were deployed to a combat zone, 2 were found to be ineligible, 22 did not complete study enrollment before the cutoff date, 77 refused to participate, and 754 were enrolled as cases.

Men with a sample in the Department of Defense Serum Repository who did not subsequently develop TGCT were eligible to participate as controls. Due to the transient nature of the military population, each case was initially matched to four

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possible controls on age (within 1 year), race (White, Black, other), and date of serum sample draw (within 30 days). Every attempt was made to enroll the first of the four possible controls. If the man could not be enrolled within 30 days, attempts began to enroll the next possible control. Among the controls, attempts were made to enroll 2,579 men. Three hundred eighty-five men could not be traced, 18 had died, 64 were deployed to a combat zone, 2 were found to be ineligible, 32 did not complete study enrollment before the cutoff date, 928 were lost because they did not respond to attempts to contact them within 30 days, 222 refused to participate, and 928 were successfully enrolled. Among the 754 cases and 928 controls, there were 720 matched case-control pairs.

To participate in the study, each man was asked to complete a study questionnaire, donate a buccal cell sample collected in mouthwash, grant permission to use his Department of Defense Serum Repository serum specimen, and sign an informed consent document. In addition, each participant was asked for permission to contact his mother to enroll her in the study. Of the 1,682 case-control participants, 1,247 (74.1%) granted permission for their mothers to be contacted. One thousand eighty-eight mothers agreed to participate, 72 refused to participate, 16 could not be traced, 41 were coded as ineligible, and 28 had not completed enrollment at the time the study concluded. Two mothers did not provide any information on their smoking habits and, so, were excluded from the current analysis.

Each case-control participant was administered a computer-assisted telephone interview composed of nine modules. Cases were asked questions in reference to a date 1 year before their TGCT diagnosis (referred to as the 'reference date'). Control participants were assigned the same reference date as their matched case. Each mother completed a computer-assisted telephone interview consisting of 11 modules.

The study was approved by Institutional Review Boards of the National Cancer Institute (Rockville, MD) and the Walter Reed Army Institute for Research (Forest Glen, MD).

Statistical Analysis. The data from the mothers and the sons were analyzed in a similar fashion. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to estimate the association of the variables of interest with risk of TGCT. Given the matched case-control design, risk estimates adjusting for confounders were first generated using conditional logistic regression, restricting the analysis to only the 720 matched sets. Modeling using unconditional logistic regression was subsequently done using the data from all participants. As this involved breaking the match, risk estimates derived from the unconditional logistic regression models were first minimally adjusted, taking into account only the three matching factors: age at reference date, race, and date of serum sample collection. Further adjustment (in the fully adjusted model) was then made for known TGCT risk factors: cryptorchidism and family history of testicular cancer. When applicable, tests for linear trend in risk according to the ordinal scale of a given variable were conducted to evaluate possible dose-response relationships. In addition, stratified analyses by tumor histology were done to assess whether risks of seminoma and nonseminoma differed. One case was excluded from these analyses because tumor histology was unknown. As results using conditional and unconditional logistic regression were similar, only those using the latter approach are presented. Statistical analyses were conducted using Statistical Analysis System release 8.2 (SAS Institute, Inc., Cary, NC). All tests were two sided, with $P < 0.05$ defined as statistically significant.

Results

The distributions of demographic variables in the study population are displayed in Table 1. As cases and controls

Table 1. Selected characteristics of cases and controls

	Cases (n = 754), n (%)	Controls (n = 928), n (%)	P*
Age (y)			
18-20	65 (8.6)	68 (7.3)	0.96
21-25	248 (32.9)	311 (33.5)	
26-30	212 (28.1)	265 (28.6)	
31-35	132 (17.5)	161 (17.3)	
36-40	75 (10.0)	97 (10.5)	
41-46	22 (2.9)	26 (2.8)	
Race			
White	635 (84.2)	788 (84.9)	0.42
Black	22 (2.9)	35 (3.8)	
Other	97 (12.9)	105 (11.3)	
Cryptorchism			
No	713 (94.6)	912 (98.3)	<0.0001
Yes	41 (5.4)	16 (1.7)	
Family history of testicular cancer [†]			
No	721 (95.6)	914 (98.5)	<0.001
Yes	33 (4.4)	14 (1.5)	
Mother participated in study			
Yes	515 (68.3)	561 (60.4)	<0.001
No	239 (31.7)	367 (39.6)	
Mother deceased			
No	646 (85.7)	797 (85.9)	0.63
Yes	82 (10.9)	109 (11.7)	
Missing data	26 (3.4)	22 (2.3)	

*P of χ^2 test.

[†]Family history in first- and second-degree relatives.

were matched on age and race, there were no differences in the overall distributions of these variables. Approximately 85% of the study population were White, 4% were Black, and 11% were members of other racial/ethnic groups. Cases were more likely than controls to have a history of cryptorchism ($P < 0.0001$) and to have a family history of testicular cancer ($P < 0.001$). Mothers of cases were significantly more likely to participate than were mothers of controls ($P < 0.0001$), but there was no difference in the proportion of mothers who had died in the two groups ($P = 0.63$; Table 1).

The relationship of passive smoking and TGCT risk, as reported by the cases and controls, is shown in Table 2. Overall, living in a household from birth to age 18 years with a person or persons who smoked was not related to risk (OR, 1.1; 95% CI, 0.9-1.3). Similarly, risk was not related to mother's smoking (OR, 1.1; 95% CI, 0.9-1.3), father's smoking (OR, 1.0; 95% CI, 0.8-1.3), or both parents' smoking (OR, 1.0; 95% CI, 0.8-1.3). Risk was marginally associated, however, with living in a household with a smoker or smokers other than parents (OR, 1.4; 95% CI, 1.0-2.1). Risk was also associated with living in a household where 'light' smoking was the norm on a typical day (OR, 1.2; 95% CI, 1.0-1.6). In contrast, risk was not associated with living in a household where smoking was typically either 'moderate' or 'heavy.' Risk was also not associated with the total number of smokers in the household. All relationships of passive smoking to TGCT risk were seen equally among the seminoma cases and nonseminoma cases. In regard to maternal smoking in pregnancy, there was no relationship overall nor was there any relationship separately among the seminomas and nonseminomas. In addition to analyzing the smoking exposures as a single variable, smoking was also analyzed as two separate variables based on the exposure from parents and the exposure from other household members. The results of the analysis did not differ from the previous analysis (data not shown).

The relationship of duration of passive smoking to TGCT risk is displayed in Table 3. TGCT risk was not associated with duration of mother's smoking (18 years versus none; OR, 1.0; 95% CI, 0.7-1.2) or father's smoking (18 years versus none; OR, 1.0; 95% CI, 0.8-1.3). Similarly, there was no association with duration of 'others' smoking (OR, 1.3; 95% CI, 0.6-2.9).

Table 2. Passive smoking exposure from birth to age 18 years and TGCT risk

	Overall		Seminoma		Nonseminoma	
	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)
Smokers in household						
No	264/341	1.0	109/341	1.0	154/341	1.0
Yes	486/583	1.1 (0.9-1.3)	210/583	1.1 (0.8-1.5)	276/583	1.1 (0.9-1.4)
Mother	316/390	1.1 (0.9-1.3)	140/390	1.1 (0.8-1.5)	176/390	1.1 (0.8-1.4)
Father	356/446	1.0 (0.8-1.3)	152/446	1.0 (0.8-1.4)	204/446	1.1 (0.8-1.4)
Both parents	212/272	1.0 (0.8-1.3)	92/272	1.0 (0.7-1.4)	120/272	1.1 (0.8-1.4)
Other people	67/63	1.4 (1.0-2.1)	33/63	1.8 (1.1-2.9)	34/63	1.2 (0.8-1.9)
No. smokers in household						
None	264/341	1.0	109/341	1.0	154/341	1.0
1	241/284	1.1 (0.9-1.4)	101/284	1.1 (0.8-1.6)	140/284	1.1 (0.8-1.5)
2	222/272	1.1 (0.8-1.4)	95/272	1.0 (0.7-1.5)	127/272	1.1 (0.8-1.5)
3+	22/27	1.0 (0.6-1.8)	13/27	1.4 (0.7-2.9)	9/27	0.8 (0.3-1.7)
Amount smoked						
None	264/341	1.0	109/341	1.0	154/341	1.0
Light	265/282	1.2 (1.0-1.6)	126/282	1.3 (1.0-1.8)	139/282	1.2 (0.9-1.6)
Moderate	160/234	0.9 (0.7-1.2)	62/234	0.9 (0.6-1.2)	98/234	1.0 (0.7-1.3)
Heavy	48/62	1.0 (0.7-1.5)	20/62	0.9 (0.5-1.6)	28/62	1.1 (0.7-1.8)
Mother smoked while pregnant						
No	264/318	1.0	106/318	1.0	158/318	1.0
Yes	86/116	0.9 (0.6-1.2)	37/116	0.9 (0.5-1.3)	49/116	0.9 (0.6-1.4)
Missing	404/494		177/494		226/494	

NOTE: Data taken from case-control questionnaire.

*Adjusted for age (continuous), race, cryptorchism, and family history of testicular cancer.

Cumulative passive smoking exposure was also unrelated to TGCT risk (OR, 1.0; 95% CI, 0.7-1.3). The results were similar for seminoma and nonseminoma cases.

An examination of maternal smoking, based on data from the mothers' questionnaire, is shown in Table 4. There were no differences between the case and control mothers in whether they had ever smoked (OR, 1.0; 95% CI, 0.8-1.3), whether they smoked while pregnant with the participant son (OR, 1.0; 95% CI, 0.8-1.4), or whether they smoked while breast-feeding the participant son (OR, 1.2; 95% CI, 0.7-2.0). Similarly, there were no differences in age at smoking initiation, the amount smoked daily, the duration of smoking, or in the duration of smoking after the son's birth. There were no differences between the seminoma and nonseminoma cases in the results.

Discussion

Age-period-cohort analyses of TGCT incidence data have consistently reported a significant effect on risk of birth

cohort (3, 7, 21). A birth cohort effect suggests that the increase is related to changing prevalence of one or more risk factors in the population (1). Despite the fact that the risk factors for TGCT are poorly understood, evidence suggests that the risk of TGCT may be determined very early in life, possibly even *in utero*. Some suggested early life risk factors include environmental endocrine modulators (6), maternal body size (22), childhood nutrition (5), and maternal smoking (8).

An examination of parallel trends in rates of testicular cancer and female lung and bladder cancers led Clemmesen (8) to hypothesize that maternal cigarette smoking was a risk factor for TGCT. Clemmesen also suggested that the maternal smoking hypothesis was consistent with the dip in TGCT risk among men born during World War II in Denmark (23). Using a similar ecologic design, Pettersson et al. (9) found a correlation between the prevalence of smoking among young women and testicular cancer incidence in Sweden, Norway, and Denmark, although not in Finland.

Table 3. Years of passive smoking exposure from birth to 18 years

	Overall		Seminoma		Nonseminoma	
	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)
None	264/341	1.0	109/341	1.0	154/341	1.0
Mother smoked (y)						
<12	75/71	1.4 (1.0-2.0)	31/71	1.4 (0.9-2.3)	44/71	1.4 (0.9-2.2)
12-17	52/65	1.0 (0.7-1.6)	23/65	1.0 (0.6-1.8)	29/65	1.1 (0.6-1.7)
18	184/252	1.0 (0.7-1.2)	84/252	1.0 (0.7-1.4)	100/252	0.9 (0.7-1.3)
Father smoked (y)						
<12	94/96	1.3 (0.9-1.8)	40/96	1.3 (0.8-2.0)	54/96	1.3 (0.9-1.9)
12-17	72/99	1.0 (0.7-1.4)	33/99	1.0 (0.6-1.6)	39/99	0.9 (0.6-1.4)
18	185/245	1.0 (0.8-1.3)	75/245	0.9 (0.6-1.3)	110/245	1.1 (0.8-1.4)
Cumulative smoking by others (y)						
<8	27/25	1.4 (0.8-2.5)	10/25	1.3 (0.6-2.9)	17/25	1.6 (0.8-3.1)
8-16	19/24	1.1 (0.6-2.0)	9/24	1.4 (0.6-3.2)	10/24	0.9 (0.4-1.8)
>16	14/14	1.3 (0.6-2.9)	11/14	2.3 (1.0-5.3)	3/14	0.5 (0.1-1.9)
Cumulative smoking by parents and others (y)						
<18	147/159	1.2 (0.9-1.6)	58/159	1.2 (0.8-1.8)	89/159	1.2 (0.9-1.7)
18-28	183/216	1.1 (0.9-1.4)	87/216	1.2 (0.8-1.7)	96/216	1.1 (0.8-1.5)
>28	148/203	1.0 (0.7-1.3)	62/203	0.9 (0.6-1.3)	86/203	1.0 (0.7-1.4)

NOTE: Data taken from case-control questionnaire.

*Adjusted for age (continuous), race, cryptorchism, and family history of testicular cancer.

Table 4. Maternal smoking and TGCT risk

	Overall		Seminoma		Nonseminoma	
	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)
Mother smoked						
No	227/249	1.0	82/249	1.0	145/249	1.0
Yes	287/311	1.0 (0.8-1.3)	124/311	1.2 (0.9-1.7)	163/311	0.9 (0.7-1.2)
While pregnant	151/165	1.0 (0.8-1.4)	64/165	1.1 (0.8-1.7)	87/165	0.9 (0.7-1.3)
While breast-feeding	34/32	1.2 (0.7-2.0)	12/32	1.0 (0.5-2.1)	22/32	1.3 (0.7-2.3)
Age started smoking (y)						
Never	227/249	1.0	82/249	1.0	145/249	1.0
<17	106/114	1.0 (0.8-1.4)	49/114	1.3 (0.9-2.1)	57/114	0.9 (0.6-1.3)
17-18	76/81	1.0 (0.7-1.5)	32/81	1.2 (0.7-1.9)	44/81	0.9 (0.6-1.4)
>18	104/115	1.0 (0.7-1.4)	42/115	1.0 (0.7-1.6)	62/115	0.9 (0.6-1.4)
Cigarettes/d						
Never	227/249	1.0	82/249	1.0	145/249	1.0
<10	70/97	0.8 (0.5-1.1)	30/97	0.9 (0.5-1.5)	40/97	0.7 (0.4-1.1)
10-17	83/77	1.2 (0.8-1.7)	33/77	1.2 (0.8-2.0)	50/77	1.1 (0.8-1.7)
>17	130/133	1.1 (0.8-1.5)	60/133	1.4 (0.9-2.1)	70/133	0.9 (0.6-1.3)
Duration of smoking (y)						
Never	227/249	1.0	82/249	1.0	145/249	1.0
<22	99/101	1.1 (0.8-1.5)	41/101	1.3 (0.8-2.1)	58/101	1.0 (0.6-1.4)
22-32	102/103	1.1 (0.8-1.5)	42/103	1.3 (0.8-2.0)	60/103	0.9 (0.6-1.4)
>32	84/104	0.9 (0.6-1.3)	39/104	1.0 (0.6-1.6)	45/104	0.8 (0.6-1.3)
Duration of smoking after son's birth (y)						
Never	227/249	1.0	82/249	1.0	145/249	1.0
<15	87/103	0.9 (0.7-1.3)	34/103	1.1 (0.7-1.7)	53/103	0.9 (0.6-1.3)
15-24	95/89	1.1 (0.8-1.6)	39/89	1.5 (0.9-2.4)	56/89	0.9 (0.6-1.4)
>24	104/117	1.0 (0.7-1.4)	50/117	1.1 (0.7-1.7)	54/117	0.9 (0.6-1.4)

NOTE: Data taken from mothers' questionnaire.

*Adjusted for son's age (continuous), race, cryptorchism, and family history of testicular cancer.

In contrast to the ecologic studies, the maternal smoking hypothesis has not been supported by prior retrospective studies or by the current study. At least six previous case-control studies (14-19) have examined the association, and none have reported a positive relationship. In fact, one study (19) reported a protective effect of heavier (i.e., ≥ 12 cigarettes daily) smoking (OR, 0.6; 95% CI, 0.4-0.9), although not of lighter smoking. Another of the studies also found that the risk of heavier smoking (i.e., >20 cigarettes daily) was less (OR, 0.8) than the risk of lighter smoking (OR, 1.5), although neither risk estimate was statistically significant (14). In five of the case-control studies (14-16, 18, 19), the smoking data were collected from the mothers, whereas in the sixth (17), the data were obtained from the case-control participants themselves. The source of the data has subsequently been suggested to be a concern for several reasons (9). These reasons include the possibility that mothers who smoked in pregnancy may be less likely to participate in studies because of higher morbidity and mortality rates or may be reluctant to admit to smoking while pregnant. These theoretical biases do not seem to have affected the current study, however. Firstly, there was no difference in the percentage of case and control mothers who were deceased at the time of the study (case mothers, 10.9%; control mothers 11.7%; $P = 0.63$). Secondly, case mothers did not seem to have higher morbidity rates as they participated at a significantly higher rate than did control mothers (case mothers, 69.8%; control mothers, 60.3%; $P < 0.0001$). Finally, in the current study, the data were obtained from both mothers and sons and the lack of an association was apparent using both sources of data. In addition, it is not clear that mothers who smoke in pregnancy are likely to deny it, as studies of the issue have reported inconsistent results (24-27).

Although case-control studies have not supported Clemmensen's hypothesis, a significant association between maternal lung cancer and testicular cancer in sons has been reported in several family studies. Record linkage studies of family data from Sweden and Norway have found significant clustering of parental lung cancer and testicular cancer in sons (10-13, 28), although studies from Denmark have not found similar

associations (29, 30). However, one of the Swedish studies noted that, although TGCT was significantly associated with parental lung cancer, the association was stronger for late-onset TGCT, which argued against a prenatal exposure (11). The record linkage studies have not been able to examine smoking per se, and although the majority of lung cancer is related to smoking, the extent to which the family clusters can be attributed to smoking is not clear. For example, a study from the United Kingdom reported a borderline significantly increased risk of lung cancer among mothers of testicular cancer patients (OR, 5.0; 95% CI, 0.9-29.6), but found no association between maternal smoking and risk of TGCT among the same individuals (17). Perhaps even more telling is the result of a recent study in the United States that examined cancer in the families of nonsmoking lung cancer probands. The study found that there was a significantly increased risk of testicular cancer among the relatives of the nonsmoking lung cancer cases (31). This result may suggest that the lung cancer-testicular cancer association is due to common genetic susceptibility rather than to smoking. If this is the case, it presents opportunities for identifying susceptibility genes that may not have been previously considered.

As TGCT has been suggested to be part of a testicular dysgenesis syndrome (32), it might be expected that, if maternal smoking were a risk factor for TGCT, it would also be a risk factor for the other testicular dysgenesis syndrome disorders. Cryptorchism is the testicular dysgenesis syndrome disorder most closely linked to TGCT, and the relationship between cryptorchism and maternal smoking has been examined in at least nine studies. Of these, three studies have reported a positive association (33-35), whereas six have reported no association (36-41). Among studies of hypospadias, either a protective association (42) or no association (33, 43-47) have been reported. The final testicular dysgenesis syndrome disorder, impaired spermatogenesis, has been studied less often with respect to maternal smoking, but a positive association has been reported in two studies (48, 49), whereas a null association has been reported in a third (50). Overall, the studies of testicular dysgenesis syndrome disorders do not strongly support maternal smoking as a risk factor.

Why the maternal smoking hypothesis is supported by ecologic studies but not by case-control studies is not clear, but is unlikely to be due to the reasons previously suggested (9). Although it is possible that other inherent biases in case-control studies mask the real association, the current study was well positioned to study the maternal smoking hypothesis. In the current study, cases and controls were drawn from the same well-defined population (military servicemen), and the participation rate was high. In addition, the male U.S. military population is not limited to a single geographic area or subset of the population, which makes it likely that the results from this study can be generalized to other populations. The study also included only pathologically confirmed TGCTs, suggesting that the results are somewhat more precise than studies that have enrolled participants without regard to histology or confirmation of diagnoses. Possible study limitations were that participants were asked to remember events that happened years in the past and that differential misclassification bias may have occurred as the respondents were cognizant of disease status. The reliance on memory of events in the past, however, is common to most case-control studies and is difficult to avoid when researching rare tumors.

In conclusion, the current study does not support the hypothesis that maternal smoking is related to the development of TGCT. The co-occurrence of lung and testicular cancer in some families, however, may be due to genetic susceptibility to some other early life exposure. Further study of these families may be helpful in identifying clues to risk of both familial and sporadic TGCT.

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