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Fertility among Testicular Cancer Survivors: A case-control study in the U.S.

Christopher Kim¹, Katherine A. McGlynn², Ruth McCorkle³, Tongzhang Zheng², Ralph L. Erickson⁵, David W. Niebuhr⁵, Shuangge Ma¹, Yaqun Zhang⁶, Yana Bai⁷, Li Dai⁸, Barry I. Graubard², Briseis Kilfoy², Kathryn Hughes Barry^{1,2}, and Yawei Zhang¹

¹ Yale School of Public Health, Yale University, New Haven, CT, USA

² Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD, USA

³ Yale School of Nursing, Yale University, New Haven, CT, USA

⁴ Chinese National Institute of Environment Health and Related Product Safety, China CDC, Beijing, China

⁵ Walter Reed Army Institute of Research, Forest Glen, MD

⁶ Gansu Provincial Design and Research Institute of Environmental Science, Lanzhou, Gansu, China

⁷ Department of Epidemiology and Biostatistics, Lanzhou University School of Public Health, Lanzhou, China

⁸ National Center for Birth Defect Monitoring, West China Second University Hospital, Sichuan University, Chengdu, China

Abstract

Introduction—Testicular germ cell tumors (TGCT) disproportionately affect men between the ages of 15 and 49 years, when reproduction is typical. Although TGCT treatment directly affects gonadal tissues, it remains unclear whether there are long-term effects on fertility.

Methods—To examine post-TGCT treatment fertility, study participants in a previously conducted case-control study were contacted. The men were initially enrolled in the US Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) study between 2002 and 2005. A total of 246 TGCT cases and 236 controls participated in the current study and completed a self-administered questionnaire in 2008-2009.

Results—TGCT cases were significantly more likely than controls to experience fertility distress (OR 5.23; 95% CI 1.99-13.76) and difficulty in fathering children (OR 6.41; 2.72-15.13). Cases were also more likely to be tested for infertility (OR 3.65; 95% CI 1.55-8.59). Cases, however, did not differ from controls in actually fathering children (OR 1.37; 95% CI 0.88-2.15). These findings were predominantly observed among nonseminoma cases and cases treated with surgery only or surgery-plus-chemotherapy.

Discussion—While expressing greater fertility distress, higher likelihood of fertility testing, and difficulty fathering children, these data suggest that TGCT survivors are no less likely to father children than are other men. It is possible that treatment for TGCT does not permanently affect

fertility or, alternatively, that TGCT survivors attempt to father children with greater persistence or at younger ages than do other men.

Introduction

Testicular cancer is one of the most treatable of all cancers. According to the American Cancer Society, the 5-year relative survival rate in the United States is over 96%, and more than 140,000 U.S. men are survivors of testicular cancer [1]. Because testicular cancer is the most common cancer among young men aged between 15-49 years [2], an age range where men commonly father children, affected men may be concerned with their ability to reproduce and remain fertile after treatment. Additionally, infertility treatments can be cost prohibitive.

The most common treatment for testicular cancer is a combination of orchiectomy, surgical removal of the affected testis, and either radiotherapy or chemotherapy. Both radiotherapy and chemotherapy may cause cytotoxicity [3], which can affect sperm production even beyond the effects resulting from orchiectomy.

Prior studies assessing fertility after testicular cancer treatment have reported some impairment [4-12]. These studies, however, vary in scope and quality as a large number have used a case-only study design [4-7,9-13] and included small sample sizes [4-5,7,9-12]. Additionally, most studies were conducted in European populations [5-11]. The impact of culture and treatment modalities specific to the US warrants an investigation of this topic in a US population.

In an attempt to overcome the shortcomings of previously published studies, we conducted a matched case-control study in U.S. military servicemen to examine whether testicular cancer survivors have impaired fertility compared to other men from the same population.

Methods

Study Population

The study population has been previously described [13]. In brief, all study participants were enrolled in the US Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) study between 2002 and 2005. At the time of enrollment, eligible servicemen were age 46 years or younger and had at least one serum sample stored in the Department of Defense Serum Repository (DoDSR, Silver Spring, MD). Using a person-specific ID, the specimens in the DoDSR computerized database were linked to the Defense Medical Surveillance System (DMSS) and to other military medical databases in order to determine which military personnel had developed TGCT after the date of serum donation while on active duty. Diagnoses of TGCT were limited to classic seminoma or nonseminoma (embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, teratomas, mixed germ cell tumor). A total of 961 eligible cases were identified and 754 were enrolled (78.5%). Men who had never had a diagnosis of TGCT and had a blood serum sample in DoDSR were eligible to be controls. Controls were pair-matched to cases based on age (within 1 year), race (white, black, other) and date of serum sample draw (within 30 days). Of 1,150 potential controls, 928 participated in the study (80.7%).

In May 2008, 1,571 STEED participants with available contact information were mailed a letter of invitation to participate in the current study. The men were also mailed a standardized and validated self-administrated questionnaire on sexual functioning, fertility and general quality of life. Participants were given the option of completing the questionnaire by phone, although few respondents elected to do so. By the end of April

2009, 559 of these mailings were returned due to undeliverable addresses. A total of 1012 letters were delivered and 575 responses were received to the questionnaire request (56.8%). From the 575 responses, 24 had died, 69 refused, and 482 completed the questionnaire for a total response rate of 47.6%.

The study was approved by Institutional Review Boards of Yale University, the National Cancer Institute and the Walter Reed Army Institute for Research.

Data Collection

Mailed questionnaires were completed by the study participants as a part of a quality of life study. The questionnaire contained six questions pertaining to fertility since TGCT treatment (for cases) or corresponding TGCT treatment matched date (for controls). Respondents were asked if they had fertility distress, had difficulty conceiving, had been tested for infertility, and had fathered children since time of diagnosis of cancer for cases and the corresponding matched date for each control.

Statistical Analysis

All sexual functioning data were collected as categorical variables. To account for the matched design of the study, each variable was analyzed per response level utilizing an unconditional logistic regression model controlling for age (continuous), body mass index (BMI) (<25, 25-30, >30), income (<\$50,000, \$50,000-\$70,000, >\$70,000), race (white, other), smoking (never, former, current), and low sperm count (yes, no) to estimate adjusted odds ratios. An association between banked sperm and fathering children could not be assessed due to small numbers. To obtain p-values for the categorical variables, each fertility function indicator (yes/no) was entered as a dichotomous variable in the logistic model. To obtain the p-value for trend, a given sexual function indicator was entered as an ordinal term in the logistic model for the person tested (man/woman/both/none) and number of children (0-7). All P statistics are Wald chi-squares. In all analyses, the no sexual dysfunction response served as the reference group; except for the person tested for fertility where none was the reference group. Univariate analyses were conducted to compare selected characteristics between cases and controls. All p-values were two-sided. All analyses were conducted using SAS statistical software (version 9.1.3; SAS Institute, Cary, NC, USA).

Results

A total of 482 individuals (246 cases and 236 controls) participated in the study (Table 1). There were no statistically significant differences between cases and controls in the distributions of age ($P=0.873$), income ($P=0.592$), education ($P=0.105$), BMI ($P=0.627$) or race ($P=0.084$). For cases, the median time between diagnosis and interview was 14 years (mean=13.70 years), and the median time between matched date and interview for controls was 14 years (mean=13.66 years). All cases were diagnosed at least five years prior to interview.

The distributions of the above mentioned variables in the original STEED population were similar to the distributions in the current study population. For example, the mean reference age was 27.8 years and 27.9 years for STEED cases and controls, respectively and 29.3 years and 29.1 years for the current participants, respectively. The percentages of overweight (BMI = 25-30) individuals in the STEED population were 43.2% (cases) and 47.5% (controls) while the percentages in the current study were 47.2% (cases) and 42.8% (controls). The distribution of total number of fathered children including prior to TGCT treatment or matched date for the STEED population (1 child: 20.4%, 2 children: 31.7%, 3

children: 12.5%, 4+ children: 5.1%) was similar to that for the current study (1 child: 18.7%, 2 children: 33.1%, 3 children: 13.7%, 4+ children: 4.8%).

Overall, cases from the study population expressed more concern about fertility than did control men (Table 2). Cases were significantly more likely to have fertility distress (OR 5.23; 95% CI 1.99-13.76) than were controls. Similarly, cases had significantly more difficulty in fathering children (OR 6.41; 95% CI 2.72-15.13). There was significantly more fertility testing overall (OR 3.65; 95% CI 1.55-8.59), which included both the cases and their spouses compared to the controls and their spouses (OR 3.40; 95% CI 1.28-9.02). Despite concerns over fertility, there was no significant difference in fathering children between the cases and controls (OR 1.37, 95% CI 0.88-2.15) although there was a significant trend ($P=0.023$). Six men in the case group, but no men in the control group, fathered children from cryogenically banked sperm. Results did not change significantly when men fathering children through banked sperm were excluded from analysis.

In comparison with controls, cases who received radiotherapy reported no significant difference in fertility distress (OR 1.39; 95% CI 0.32-5.98), difficulty in fathering children (OR 2.39; 95% CI 0.70-8.15), or actually fathering children (OR 0.84; 95% CI 0.41-1.71). However, cases who received radiotherapy were significantly more likely than controls to have had fertility testing (OR 3.65; 95% CI 1.07-12.42) (Table 3). One of 18 cases who received radiotherapy fathered a child through banked sperm. Results did not change significantly when men fathering children through banked sperm were excluded from analysis.

Compared to controls, cases who received chemotherapy were significantly more likely to experience fertility distress (OR 5.79; 95% CI 1.59-21.09) and difficulty in fathering children (OR 7.58; 95% CI 2.48-23.22) (Table 3). Similarly, cases who received chemotherapy reported significantly more fertility testing than did controls (OR 4.53; 95% CI 1.50-13.66), including testing for both partners (OR 5.31; 95% CI 1.60-17.61). Despite concerns about their ability to father children, cases treated with chemotherapy were more likely to have fathered children than controls (OR 2.24; 95% CI 1.14-4.41). Three of 29 cases who received chemotherapy fathered children via banked sperm. Results did not change significantly when men fathering children through banked sperm were excluded from analysis.

Cases treated only with surgery were significantly more likely than controls to have had fertility distress (OR 4.61; 95% CI 1.43-14.95) and difficulty in fathering children (OR 5.30; 95% CI 1.90-14.82). They were also more likely to have been tested for infertility (OR 4.53; 95% CI 1.67-12.27), as were their partners (OR 4.13; 95% CI 1.32-12.88) (Table 3). Two of 44 cases who were treated with surgery-only fathered children via banked sperm. Results did not change significantly when men fathering children through banked sperm were excluded from analysis.

Analyses stratified by histology found that nonseminoma cases experienced significantly more fertility distress (OR 6.77; 95% CI 2.38-19.23) and difficulty in fathering children (OR 6.55; 95% CI 2.61-16.41) than did controls. Nonseminoma cases were also significantly more likely to have been tested for infertility (OR 3.56; 95% CI 1.41-8.97), had testing for both partners (OR 4.40; 95% CI 1.59-12.16), and to have fathered children (OR 1.85; 95% CI 1.12-3.05) compared to controls (Table 4). Fewer differences were observed for seminoma cases, who experienced increased difficulty in fathering children (OR 4.49; 95% CI 1.57-12.87) and who were more likely to have been tested for infertility (OR 4.20; 95% CI 1.48-11.90) than were controls.

Discussion

In this study of fertility after treatment for TGCT, cases were more likely than controls to experience concern about fertility and to have more problems in fathering children, as measured by responses to questions about fertility distress, difficulty in fathering children, and infertility testing. Despite greater concern, however, cases were not less likely to have fathered children than controls. These findings were predominantly observed among nonseminoma cases and cases treated with surgery-only or with surgery-plus-chemotherapy. Men in these groups also were more likely to report fathering children since their diagnosis than were controls.

The results of this study are generally consistent with existing literature, suggesting that concern over fertility issues may result from treatment for testicular cancer [4-11]. Observations of increased fertility distress, difficulty in fathering children, and increased fertility testing among cases, compared to controls, are similar to other studies [6-7], but the current study noted no significant difference in actually fathering children. This study avoids the limitations of some earlier, case-only, studies by including a control group [4-7,9-12] that was matched on some socio-demographic variables. Additionally, to our knowledge, this is the first case-control study to systematically assess fertility in a non-clinical setting after treatment for testicular cancer conducted in a population of US-born men.

All cases in the current study were treated with surgery. In addition, some men also received radiotherapy or chemotherapy. Standard orchiectomy often includes retroperitoneal lymph node dissection (RPLND). RPLND is a procedure done in addition to orchiectomy which can cause interference with ejaculatory function and cause retrograde ejaculation [14], although there is a nerve-sparing procedure which has reasonable success at limiting interference with ejaculation which has been utilized since the 1990s [15]. Recently, an increasing number of men are put under surveillance instead of being treated with RPLND. A previous study noted that a large portion of men undergoing orchiectomy experienced fertility distress [16]. Before treatment, physicians will typically inform patients that infertility could result from surgery if RPLND is needed. Men are also generally made aware of the option for banking sperm prior to treatment [1]. Fertility distress could be a result of physicians suggesting the possibility of infertility and fear that the removal of testicular tissue could lead to inability to father children.

Distress could be a significant consequence of needing to be treated for TGCT and fertility testing. Fertility distress may not always be isolated to the partner with potential infertility [17], and stress may also affect the partners of the men [18]. Also, women may be tested concurrently with men to identify contraindications to using assisted reproductive options based on female fertility issues, which could explain the 3.5-fold increase in fertility testing for both the man and woman. Additionally, because of the young age of onset of TGCT and treatment, these men may seek assisted fertility options immediately or soon after treatment, leading to an increase in fertility testing. Interestingly, several men reported difficulty in fathering children, but did not report feeling fertility distress (n=16, 5% of men responding to both questions). Of the 56 men reporting difficulty fathering after TGCT treatment, 23 (2 controls/21 cases) men reported difficulty fathering prior to treatment, consistent with the hypothesis that impaired spermatogenesis and TGCT are co-members of a Testicular Dysgenesis Syndrome [19]. Also, men who did not report fertility distress were just as likely to father children (n=93, 34%) compared to those who experienced fertility distress (n=13, 34%). However, a greater proportion of men who experience fertility distress may be attempting to father children, when compared to men not experiencing distress. A difference in interest in fatherhood could have balanced the likelihood of fathering children between the two groups, even if fertility distress is truly associated with a decreased likelihood of

fathering children. This study, however, did not collect information on interest in fathering children. Additionally, in a study by Shover et al. [20], young cancer survivors often wished to have children, and cancer survivors lacking adequate information on options after cancer treatment-related infertility often felt anxiety and distress.

In several studies, 25% [6], 21% [11], and 20% [21] of the TGCT survivors attempting to father children were unsuccessful in achieving their long-term fathering wishes. In this current study, 33% had difficulty fathering children, but the number of men who were unable to successfully father children is unknown. Our finding of no adverse impact of treatment for testicular cancer on the ability to father children might, in part, be due to spermatogenesis and ejaculation returning post-treatment. Another study observed successful fatherhood of children post-treatment within the first two years after treatment [22]. However, this could not explain the increased likelihood of fathering children that we observed for some treatment and histologic subtypes. It is also conceivable; however, the observed effect could be due to confounding by interest in fatherhood or interest at younger ages, which could have overwhelmed a true adverse effect of testicular cancer treatment on the ability to father children. For example, it is possible that emphasis of patient-provider discussions on fertility and precautionary measures such as sperm banking could lead men diagnosed with testicular cancer to try for children at a younger age than control men. Given that our study population was relatively young, it is possible that we saw a suggestion of increased fatherhood among cases because not enough time had passed for a similar proportion of controls to achieve fatherhood. An additional possible reason for our findings is that the cases who successfully fathered children might have been more likely to respond to the questionnaire. Also, it is possible that cases might have better connections to the health care system than the controls as a result of having received treatment for testicular cancer and therefore might have received more medical assistance in fathering children.

The finding of increased fertility distress among cases treated with chemotherapy plus surgery when compared to controls could be due to concerns about cytotoxicity as previous studies have suggested systemic chemotherapy treatments can result in azoospermia [23]. A previous study of testicular cancer treatment suggested that long-term aspermia can be a problem for some individuals, but by 24 months post treatment, more than 75% percent of patients were no longer aspermic, but oligospermic (note: due to the age of this paper, aspermic and oligospermic are assumed to indicate azoospermia and oligozoospermia, respectively) [4], and another study identified 79% of their patient group as azoospermatic, but only 31% were unsuccessful in fathering children [23].

Nonseminoma survivors expressed greater overall fertility distress and difficulty in fathering children compared to controls, than did men with seminoma compared to controls. One explanation could be that nonseminoma occurs, on average, at a younger age than does seminoma [2] (27.4 years versus 33.1 years in this study). Additionally, nonseminoma cases are more likely to receive chemotherapy than are seminoma cases. Men with nonseminoma were more likely to father children (55 out of 130) than men with seminoma (23 out of 111). Men with nonseminoma were also more likely to father multiple children (27 out of 130) than men with seminoma (11 out of 111). These results suggest that the younger age at diagnosis of nonseminoma allows a greater window of opportunity to father children post-treatment. It is also plausible due to the older age of diagnosis of seminoma cases, these men may have already fathered children prior to diagnosis and treatment of TGCT and not attempted to father children after treatment.

Treatment for impaired fertility can carry a large financial burden. Depending on the type of treatment, assisted reproductive technology treatments can cost in excess of \$70,000 [24]. This cost is particularly burdensome as health insurance plans cover infertility treatment

poorly or not at all, and in particular, Tri-care (active military health coverage) offers diagnostic assistance and a few treatment options [24] and the Veterans Administration covers only “limited infertility” treatment for women [25]. Thus, it is important to know what realistic options are available to men who wish to have children.

The current study had several major strengths. All cases were histologically confirmed which minimized potential disease misclassification. This study also employed a control population as the referent group, an uncommon characteristic among many studies assessing fertility [4-7,9-12]. Because the study was conducted several years removed from the diagnosis of cancer, any temporary loss of fertility due to treatment should no longer have been present. Additionally, as was requested on the questionnaire, all the cases in this study correctly reported children fathered after treatment for TGCT.

Despite the strengths of the study, shortcomings in data collection were present. We had no information on the severity of concern or treatments utilized by individuals to help in the fathering process. Due to the subjective nature of fertility, many responses included “Don't Know,” and these responses are not included in analyses, which artificially reduced the sample size. The response rate was not optimal, but the sampled group appeared to be representative of the STEED group as the distribution of demographic and fertility variables share similarities between the STEED and current study which indicates limited selection bias. Stratification of some results resulted in small cell sizes which limits statistical power for detecting case-control differences and increases statistical variability of the effect estimates.

In summary, compared to controls, TGCT survivors were more likely to report fertility distress and being tested for infertility, but no less likely to father children. However, the proportions of case and control men whose fathering wishes were unfulfilled are unknown. This study provides little support for the hypothesis that fertility is adversely affected by treatment in long-term TGCT survivors.

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Table 1
Demographic characteristics of cases and controls

<i>Characteristic</i>	<i>Controls (n=236)</i>		<i>Cases (n=246)</i>	
	Number	Percentage (%)	Number	Percentage (%)
Age				
18 - 39	84	35.91	94	38.53
40 - 49	104	44.07	100	40.98
50+	47	19.92	50	20.49
P-value	0.873			
Education Completed				
High/Vocation School	75	31.78	76	31.15
College/University	84	35.59	101	41.39
Graduate/Professional	73	30.93	64	26.23
Missing	4	1.69	3	1.23
P-value	0.592			
Income				
<\$15,000 - \$49,999	44	17.94	49	20.01
\$50,000 - \$90,000	70	29.91	89	36.33
\$90,000+	115	49.15	95	38.78
Missing	7	2.99	12	4.90
P-value	0.105			
BMI				
<18.5 – 25	46	19.49	51	20.74
25 – 30	101	42.80	116	47.15
>30	89	37.71	79	32.11
P-value	0.627			
Race				
White	222	94.07	220	89.43
Other	14	5.92	26	10.59
P-value	0.084			

Table 2
Overall odds ratios regarding fertility

Whole Group	Cases	Controls	OR (95% CI)
Fertility Distress			
Yes	32	6	5.23 (1.99-13.76)
No	118	155	1.0
P-value	<0.001		
Difficulty in Fathering Children			
Yes	48	8	
No	98	136	6.41 (2.72-15.13)
P-value	<0.0001		
Tested for Infertility			
Yes	38	8	3.65 (1.55-8.59)
No	183	210	1.0
P-value	<0.0001		
Person Tested			
Man	12	4	1.46 (0.40-5.27)
Woman	1	3	0.34 (0.034-3.44)
Both	25	6	3.40 (1.28-9.02)
None	78	76	1.0
P-trend	0.002		
Fathered Children			
Yes	83	58	1.37 (0.88-2.15)
No	163	178	1.0
P-value	0.16		
# Children Fathered			
0	163	178	1.0
1	40	27	1.64 (0.91-2.95)
2	25	11	2.16 (0.96-4.90)
3+	13	7	2.06 (0.74-5.73)
P-trend	0.023		

All models adjusted by BMI, income, age, smoking status, race, and low sperm count

Table 3

Odds ratios regarding fertility by treatment type

	Radiation + Surgery			Chemotherapy + Surgery			Surgery Only		
	Controls	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Fertility Distress									
Yes	6	6	1.39 (0.32-5.98)	14	5.79 (1.59-21.09)	8	4.61 (1.43-14.95)		
No	155	47	1.0	28	1.0	39	1.0		
P-value			0.66		0.0077		0.011		
Difficulty in Fathering Children									
Yes	8	10	2.39 (0.70-8.15)	21	7.58 (2.48-23.22)	13	5.30 (1.90-14.82)		
No	136	37	1.0	24	1.0	34	1.0		
P-value			0.16		0.0004		0.0015		
Tested for Infertility									
Yes	8	8	3.65 (1.07-12.42)	15	4.53 (1.50-13.66)	12	4.53 (1.67-12.27)		
No	210	72	1.0	45	1.0	55	1.0		
P-value			0.038		0.0073		0.0030		
Person Tested									
Man	4	3	1.09 (0.15-7.75)	5	2.24 (0.42-12.07)	5	3.93 (0.94-16.55)		
Woman	3	0	0.001 (inf.)	0	0.001 (inf.)	1	0.97 (0.10-9.68)		
Both	6	6	2.86 (0.73-11.22)	11	5.31 (1.60-17.61)	8	4.13 (1.32-12.88)		
None	76	30	1.0	24	1.0	21	1.0		
P-trend			0.94		0.26		0.0098		
Fathered Children									
Yes	58	18	0.84 (0.41-1.71)	29	2.24 (1.14-4.41)	29	1.78 (0.99-3.20)		
No	178	70	1.0	36	1.0	44	1.0		
P-value			0.63		0.025		0.0306		
# Children Fathered									
0	178	70	1.0	36	1.0	44	1.0		
1	27	9	1.03 (0.40-2.66)	15	2.65 (1.13-6.22)	15	1.89 (0.88-4.06)		
2	11	6	1.47 (0.36-5.96)	10	3.93 (1.38-11.18)	8	2.42 (0.88-6.70)		
3+	7	3	2.34 (0.49-11.36)	4	2.11 (0.42-10.51)	6	3.05 (0.93-10.06)		

	<i>Radiation + Surgery</i>		<i>Chemotherapy + Surgery</i>		<i>Surgery Only</i>	
	Controls	Cases OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
P-trend		0.30		0.016		0.0098

All models adjusted by BMI, income, age, smoking status, race, and low sperm count

Table 4

Odds ratios regarding fertility by histological subtype

	Nonseminoma			Seminoma		
	Controls	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases
Fertility Distress						
Yes	6	22	6.77 (2.38-19.23)	10	1.61 (0.76-8.94)	
No	155	60	1.0	58	1.0	
P-value			0.0003			0.13
Difficulty in Fathering Children						
Yes	8	30	6.55 (2.61-16.41)	18	4.49 (1.57-12.87)	
No	136	56	1.0	42	1.0	
P-value			<0.0001			0.0051
Tested for Infertility						
Yes	8	23	3.56 (1.41-8.97)	15	4.20 (1.48-11.90)	
No	210	96	1.0	87	1.0	
P-value			0.0071			0.0070
Person Tested						
Man	4	7	2.21 (0.53-9.13)	8	2.83 (0.65-12.31)	
Woman	3	1	0.54 (0.054-5.32)	0	0.001 (inf.)	
Both	6	18	4.40 (1.59-12.16)	8	2.79 (0.80-9.71)	
None	76	44	1.0	34	1.0	
P-trend			0.074			0.27
Fathered Children						
Yes	45	55	1.85 (1.12-3.05)	23	0.80 (0.42-1.52)	
No	178	75	1.0	88	1.0	
P-value			0.016			0.51
# Children Fathered						
0	178	75	1.0	88	1.0	
1	27	28	1.98 (1.04-3.78)	12	1.01 (0.42-2.43)	
2	11	17	2.85 (1.22-6.68)	8	1.46 (0.43-4.96)	
3+	7	10	2.43 (0.81-7.24)	3	1.76 (0.37-8.33)	

	<i>Nonseminoma</i>		<i>Seminoma</i>	
	Controls	Cases OR (95% CI)	Cases	OR (95% CI)
P-trend		0.037		0.42

All models adjusted by BMI, income, age, smoking status, race, and low sperm count