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Sexual Functioning among Testicular Cancer Survivors: A Case-Control Study in the U.S.

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Abstract

Objective—Sexual function among testicular cancer survivors is a concern because affected men are of reproductive age when diagnosed. We conducted a case-control study among United States military men to examine whether testicular cancer survivors experienced impaired sexual function.

Methods—A total of 246 testicular cancer cases and 236 ethnicity and age matched controls were enrolled in the study in 2008-2009. The Brief Male Sexual Function Inventory (BMSFI) was used to assess sexual function.

Results—Compared to controls, cases scored significantly lower on sex drive (5.77 vs. 5.18), erection (9.40 vs. 8.63), ejaculation (10.83 vs. 9.90), and problem assessment (10.55 vs. 9.54). Cases were significantly more likely to have impaired erection (OR 1.72; 95% CI 1.11-2.64), ejaculation (OR 2.27; 95% CI 1.32-3.91), and problem assessment (OR 2.36; 95% CI 1.43-3.90). In histology and treatment analysis, nonseminoma, chemotherapy and radiation treated cases risk of erectile dysfunction, delayed ejaculation, and/or problem assessment were greater when compared to controls.

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Conclusion—This study provides evidence that testicular cancer survivors are more likely to have impaired sexual functioning compared to demographically matched controls. The observed impaired sexual functioning appeared to vary by treatment regimen and histologic subtype.

Keywords

Testicular cancer; sexual function; military men

Introduction

Testicular cancer was the most common cancer among young men aged between 15-49 years in the U.S.[1]. Between 1975 and 2004, the incidence rate of testicular cancer in young men rose from 2.9 per 100,000 men to 5.1 per 100,000 men[2]. Testicular cancer was one of the most treatable and curable of all cancers. The American Cancer Society reported that the 5-year relative survival rate for men was over 96%, and estimated that approximately 140,000 men currently living in the United States were survivors of testicular cancer. Testicular Germ Cell Tumors (TGCT) comprised the majority of all testicular cancers[3].

Sexual health and functioning were significant concerns as a majority of TGCT survivors were still of reproductive age. With a high survival rate and positive prognosis, a concern of individuals surviving testicular cancer was the development of various quality-of-life issues, including sexual functioning, reproductive ability, and psychological well-being[4]. Unilateral orchidectomy, a surgery common for treating testicular cancer, can result in decreased testosterone levels, but not necessarily in physical dysfunction[5]. Radiotherapy and chemotherapy for TGCT have been reported to be associated with decreased testosterone production, vascular damage and thereby decreasing semen counts and possibly causing erectile dysfunction[6, 7]. However, impaired spermatogenesis was a risk factor of TGCT[8], and impaired function may not be a result of TGCT treatment.

Sexual functioning was a product of both physiological and psychological ability[9, 10]. Body image influenced the psychological state of a man[11]. After testicular cancer, patients noted a significant change in their bodies, leading to poorer self-esteem, sexual dysfunction[12], and psychological distress[13]. The least invasive procedure (surveillance) led to the lowest amount of physiological dysfunction (erection, ejaculation)[14], although regardless of treatment, all procedures led to an increase in psychological-based dysfunction (i.e. decreased libido and desire)[4].

A number of studies have investigated sexual functioning among testicular cancer survivors[5, 6, 14-24]. Results from these studies, however, have been inconsistent. Multiple instruments were used to assess sexual functioning in different studies, which made comparison of the results a challenge. In addition, a majority of the early studies lacked comparison groups[5, 15, 17-19]. Many of the studies have been conducted in Europe or Asia[1-4, 8, 15, 17, 20] very few studies have been conducted in the US[14, 21] where treatment and the patients attitudes may have differed, particularly in the older studies.

Given the uncertainty of sexual functioning among testicular cancer survivors, the limitations of early studies, as well as the small number of the studies conducted among American men, we conducted a case-control study among US military servicemen to examine whether testicular cancer survivors experienced impaired sexual functioning compared to their age and ethnicity matched controls.

Methods

Study Population

The study population has been previously described[25]. 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 matched to cases based on age (within 1 year), ethnicity (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 (n=15) elected to do so. By the end of April 2009, 559 (35.5%) of these mailings were returned due to undeliverable addresses. A total of 1012 (64.4%) letters were delivered and 575 (56.8% of delivered) responses were received to the questionnaire request. From the 575 responses, 24 had died, 69 refused, and 482 completed the questionnaire. The participation rate was 48.8% (482 completed/988 delivered and living).

The study was approved by Institutional Review Boards of the Yale University, New Haven, CT, National Cancer Institute, Rockville, MD and the Walter Reed Army Institute for Research, Forest Glen, MD.

Data Collection

Sexual function was measured using the Brief Male Sexual Function Inventory (BMSFI), first utilized in 1995 by O'Leary et al.[26] at Harvard Medical School. This questionnaire consisted of 11 questions on sexual drive, erectile function, problem assessment (self-perception of problems), and overall sexual satisfaction which asked respondents to rate several areas of sexual functioning on a 0 (no function) to 4 (fully able) scale. All responses in each section were totaled for a summary score. The strengths of the survey were in its validity, reliability, and parsimony. Previous work suggested valid and reliable data from the BMSFI[27, 28].

Statistical Analysis

All sexual functioning data were collected as ordinal variables. Within each section (sex drive, erection, ejaculation, problem assessment, overall), all questions were summed for a section score. The summary score from each section was compared between cases and controls, and cases were further stratified by treatment modality and histologic subtype. To test difference of mean scores between control and case groups, a two-sided t-test at $\alpha = 0.05$ was conducted. Additionally, each section score was dichotomized into two categories, dysfunction/function, where dysfunction was classified as an average score of <3 per

question per section. An unconditional logistic regression model controlling for age (continuous), BMI (kg/m^2) (<25, 25-30, >30), income (<$50,000, $50,000-$70,000, > $70,000), low sperm count (yes, no), ethnicity (white, other), and smoking status (never, former, current) was utilized to estimate adjusted odds ratios of sexual dysfunction between TGCT cases and controls. To compare treatment modality and histologic subtype, the unconditional logistic model was stratified by treatment (control, surgery, radiation, chemotherapy) or histology (control, seminoma, nonseminoma). In all models, the no sexual dysfunction response (average score ≥3 per question per section) served as the reference group. Univariate analyses were conducted to compare selected characteristics between cases and controls. To obtain the p for trend, a given sexual function indicator was entered as an ordinal term in the logistic model. All p-values were two-sided. All analyses conducted with SAS (version 9.1.3; SAS Institute, Cary, NC, USA).

Results

Characteristics of the study population

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 by age (P=0.873), income (P=0.592), education (P=0.105), BMI (P=0.627) or ethnicity (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 (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).

Sexual Functioning Summary

Summary scores for each section (sex drive, erection, ejaculation, problem assessment, overall satisfaction) were presented for all controls and cases and also stratified by treatment group and histology subtype (Table 2).

Compared to controls, cases scored significantly lower on sex drive (5.77 vs. 5.18), erection (9.40 vs. 8.63), ejaculation (10.83 vs. 9.90), and problem assessment (10.55 vs. 9.54). Overall sexual satisfaction was not statistically different (P=0.22). With the exception of surgery-only treatment, the other treatment groups and histology subtypes scored significantly lower compared to controls in sex drive (not chemotherapy and nonseminoma), erection, ejaculation, and problem assessment.

Risk of sexual dysfunction

Cases were at greater risk of sexual dysfunction (Table 3). Compared to controls, cases were significantly more likely to have erectile dysfunction (OR 1.72; 95% CI 1.11-2.64), ejaculatory dysfunction (OR 2.27; 95% CI 1.32-3.91), and problem assessment (OR 2.36; 95% CI 1.43-3.90) in the prior 30 days. However, there was no significant difference in sex drive and overall sexual satisfaction between cases and controls.

Treatment modality

Compared to controls, chemotherapy and radiation treatment increased the risk of dysfunction(Table 4). Chemotherapy treated cases risk of delayed ejaculation (OR 4.81; 95% CI 2.25-10.29) and problem assessment (OR 3.20; 95% CI 1.55-6.59) were significantly elevated. Radiation treated cases risk of erectile dysfunction (OR 1.77; 95% CI 1.01-3.13) and problem assessment (OR 1.96; 95% CI 1.03-3.74) were also significantly elevated, although not to the same magnitude as chemotherapy cases. Surgery-only treated cases risk of sexual dysfunction was not significantly different than controls.

Histologic subtype

Risk of sexual dysfunction for nonseminoma histologic subtype cases was elevated compared to controls (Table 5). Risk of erectile dysfunction (OR 1.80; 95% CI 1.08-2.98), ejaculatory dysfunction (OR 3.06; 95% CI 1.63-5.75), and problem assessment (OR 3.00; 95% CI 1.68-5.34) were elevated. Seminoma histologic subtype cases risk of sexual dysfunction were not significantly different than controls.

Separate stratified analysis by age (<40 years of age, >40 years of age) yielded similar results to the overall analysis (data not shown). Stratified analysis by dividing sexual dysfunction outcomes into quartiles yielded small cells and unstable odds ratios.

Conclusion

In this case-control study of sexual functioning among US servicemen, TGCT survivors experienced greater impairment and/or dysfunction compared with controls. Sexual dysfunction varied by treatment modality. Combined chemotherapy and surgery treatment showed a greater risk of decreased libido or ejaculatory dysfunction, while a combination of radiation and surgery treatment was more closely associated with erectile dysfunction. Additionally, nonseminoma histologic subtype noted a greater risk of erectile dysfunction, ejaculatory dysfunction, and problem assessment.

The results from this study were generally consistent with the existing literature suggesting sexual dysfunction may be the result of TGCT and/or its treatment[4-7, 14, 17-19, 21-24, 29]. In a meta-analysis[14] and review of sexual functioning among cancer survivors[29], the prevalence of any sexual dysfunction ranged from 1%-51%[14, 29]. As pointed out by meta-analyses and reviews[14, 21, 29], early studies used inconsistent tools to measure dysfunction, leading to wide ranging estimates. In addition, few studies used valid comparison groups and/or were plagued by poor study design[14, 21].

This study suggested that combined chemotherapy and surgery treatment was more likely to result in sexual dysfunction, particularly with regard to libido and ejaculation, while combined radiation and surgery treatment was more likely to result in erectile dysfunction. Surgery-only treatment cases did not report sexual dysfunction that was significantly different from controls. In the Jonker-Pool meta-analysis, the highest prevalence of erectile dysfunction was found among men treated with a combination of radiation and surgery (25%)[14], which was consistent with this study. However, Jonker-Pool et al. showed that surgery-only was associated with the highest loss of ejaculatory function; however, those results were based on retroperitoneal lymph node dissection (RPLND) surgery-only results, assessed from six studies, and may have been biased by two studies that were of lower quality. Since nerve-sparing techniques, which preserve postoperative ejaculatory function after RPLND, were not common until the mid-1990s[30], it is possible that the patients enrolled in this study were more likely to be treated by nerve-sparing techniques compared to patients enrolled in early studies found in the meta-analysis.

Lowered testosterone production from orchiectomy probably does not account for sexual impairment as serum testosterone levels have not been associated with sexual dysfunction[23, 31]. Traditional retroperitoneal lymph node dissection has led to ejaculatory dysfunction[30], but not the loss of ability to have an erection[32]. However, erectile functioning can be affected by combined treatment with chemotherapy or radiation therapies causing physiological damage to the vascular tissue[15, 33]. Treatment alone did not appear to be a sufficient cause of sexual dysfunction, suggesting that decreased libido may have a substantial psychological basis in conjunction with a physiological component as suggested by Jacobsen et al.[8], Jonker-Pool et al.[14], and Incrocci[11].

Previous studies have shown radiation treatment has decreased Leydig cell testosterone production[6], and damaged blood vessels and nerves within the penile region[7], which resulted in reduction of sensitivity, blood flow, ability to have an erection, and the amount of semen ejaculated[11]. Chemotherapy can also damage vascular tissue[7] which may have led to difficulty ejaculating or having an erection. Chemotherapy, however, did not appear to be a significant cause of DNA damage within the testes and has not shown to affect the amount of testosterone produced over the long term[34]. Chemotherapy has altered sexual functioning from months to years after treatment[28, 35, 36], indicating chemotherapy-related sexual dysfunction could be a result of both vascular damage and psychological well-being.

One substantive issue that Jonker-Pool, et al. noted in their meta-analyses was the lack of standardization and consistent methodologies used in many studies[14]. A major strength of this study was the standardized and validated questionnaire utilized by researchers [18, 27, 28]. The BMFSI survey was quick for subjects to complete and was an accurate representation of overall sexual functioning and, as such, the results were consistent and comparable to other BMFSI studies. If a subject wished to be interviewed rather than fill out the questionnaire himself (very few completed telephone questionnaires n=15(3%)), interviewers were blinded to treatment status limiting interviewer bias. Additionally, all cases were histologically confirmed, reducing potential misclassification of disease status. The study used a cancer-free control population as the referent group, an uncommon characteristic among many studies assessing sexual functioning. Because the study was conducted several years removed from the diagnosis of cancer, any temporary loss of sexual function due to treatment should no longer be present. As there was no difference in the ages of the cases and controls, age-related differences in sexual functioning[37] were unlikely to have affected the results. Finally, because time since initial diagnosis and treatment of testicular cancer was at least five years, this study assessed long-term sexual functioning.

A weakness of the study was that we were unable to confirm whether sexual dysfunction was a result of the disease and/or its treatment or was a pre-existing condition. The long-term follow-up may have introduced a recall bias, although a previous study suggested differential recall bias of sexual dysfunction occurred primarily within the first 12 months post treatment[38], so differential recall bias between cases and controls in this study was unlikely. In addition, the sample size was limited when stratified by disease subtypes and treatment strategy. Another limitation of this study was a lower participation rate than the overall STEED study. However, when comparing key demographic variables from participants of the current study to the STEED study, there was little variation suggesting potential selection bias was unlikely.

In summary, this study supported the hypothesis that testicular cancer survivors experienced sexual dysfunction, particularly for nonseminoma testicular cancer survivors, and those who had chemotherapy and radiotherapy treatment. Future studies may benefit from larger sample sizes to improve statistical stability of odds ratio estimates and a clinical-based

assessment of sexual dysfunction for improved consistency and greater specificity of function assessment.

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Table 1

Demographic characteristics of cases and controls

Characteristic	*Controls (n=236)*		*Cases (n=246)*	
	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				
<$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				
<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

Summary scores of reported sexual functioning (BMFSI) among cases and controls during the past 30 days.

	Scores[a,b] *(standard deviation)*	*P-value*[*]
Sex Drive		
Controls	5.77 (1.79)	
Cases	**5.18 (2.25)**	**0.0015**
Radiation	**5.00 (2.29)**	**0.0015**
Chemotherapy	**5.17 (2.26)**	**0.022**
Surgery	5.55 (2.10)	0.37
Nonseminoma	**5.33 (2.18)**	**0.034**
Seminoma	**5.01 (2.32)**	**0.0008**
Erection		
Controls	9.40 (2.53)	
Cases	**8.63 (3.19)**	**0.0033**
Radiation	**8.09 (3.41)**	**0.0002**
Chemotherapy	8.89 (2.93)	0.16
Surgery	9.33 (2.83)	0.83
Nonseminoma	9.02 (2.89)	0.18
Seminoma	**8.16 (3.48)**	**0.0002**
Ejaculation		
Controls	10.83 (2.14)	
Cases	**9.90 (2.94)**	**0.0001**
Radiation	**9.74 (3.09)**	**0.0004**
Chemotherapy	**9.76 (2.79)**	**0.0015**
Surgery	10.43 (2.66)	0.19
Nonseminoma	**10.03 (2.73)**	**0.0024**
Seminoma	**9.75 (3.16)**	**0.0003**
Problem Assessment		
Controls	10.55 (2.59)	
Cases	**9.54 (3.47)**	**0.0004**
Radiation	**9.22 (3.68)**	**0.0003**
Chemotherapy	**9.31 (3.60)**	**0.0024**
Surgery	10.48 (2.55)	0.85
Nonseminoma	**9.75 (3.20)**	**0.011**
Seminoma	**9.28 (3.75)**	**0.0003**
Overall Sexual Satisfaction		
Controls	2.69 (1.14)	
Cases	2.55 (1.29)	0.22
Radiation	2.51 (1.39)	0.22
Chemotherapy	2.42 (1.25)	0.093
Surgery	2.84 (1.13)	0.33
Nonseminoma	2.60 (1.23)	0.48

	Scores [a,b] ***(standard deviation)***	***P-value*** [*]
Seminoma	2.50 (1.37)	0.17

[*] All P-values reported are cases/treatments/histologies compared to controls.

[a] Scores computed by summing answers per sexual functioning section. **Bold** indicates statistically significant at 0.05

Table 3

Estimated OR of Sexual Dysfunction in cases versus controls including by treatment group and histology

All groups	***Controls***	***Cases***	**OR[a] (95% CI)**
Sex Drive			
Functional	143	131	1.0 (ref)
Dysfunctional[b]	93	115	1.30 (0.87-1.93)
P-value	0.20		
Erection			
Functional	177	157	1.00 (ref)
Dysfunctional[b]	59	89	**1.72 (1.11-2.64)**
P-value	0.014		
Ejaculation			
Functional	208	188	1.00 (ref)
Dysfunctional[b]	28	58	**2.27 (1.32-3.91)**
P-value	0.0031		
Problem Assessment			
Functional	208	172	1.00 (ref)
Dysfunctional[b]	28	74	**2.36 (1.43-3.90)**
P-value	0.0007		
Overall Sexual Satisfaction			
Functional	208	139	1.00 (ref)
Dysfunctional[b]	28	107	1.05 (0.71-1.56)
P-value	0.81		

[a]Analysis adjusted for age, BMI, income, smoking status, low sperm count, and race. **Bold** indicates statistically significant at 0.05

[b]Dysfunction definition: Sex Drive: <6, Erection/Ejaculation/Problem Assessment: <9, Overall: <3

Table 4

Estimated OR of Sexual Dysfunction in cases versus controls by treatment group

Treatment	*Controls*	*Chemotherapy*	OR[a](95% CI)	*Radiation*	OR[a](95% CI)	*Surgery*	OR[a](95% CI)
Sex Drive							
Functional	143	131	1.00 (ref)	43	1.00 (ref)	45	1.00 (ref)
Dysfunctional[b]	93	115	1.30 (0.87-1.93)	46	1.31 (0.76-2.26)	31	1.15 (0.66-2.00)
P-Trend	0.64						
Erection							
Functional	143	157	1.00 (ref)	43	1.00 (ref)	45	1.00 (ref)
Dysfunctional[b]	93	89	**1.72 (1.11-2.64)**	46	1.31 (0.76-2.26)	31	1.15 (0.66-2.00)
P-Trend	0.13						
Ejaculation							
Functional	143	188	1.00 (ref)	43	1.00 (ref)	45	1.00 (ref)
Dysfunctional[b]	93	58	**2.27 (1.32-3.91)**	46	1.31 (0.76-2.26)	31	1.15 (0.66-2.00)
P-Trend	0.0009						
Problem Assessment							
Functional	143	172	1.00 (ref)	43	1.00 (ref)	45	1.00 (ref)
Dysfunctional[b]	93	74	**2.36 (1.43-3.90)**	46	1.31 (0.76-2.26)	31	1.15 (0.66-2.00)
P-Trend	0.010						
Overall Sexual Satisfaction							
Functional	143	139	1.00 (ref)	43	1.00 (ref)	45	1.00 (ref)
Dysfunctional[b]	93	107	1.05 (0.71-1.56)	46	1.31 (0.76-2.26)	31	1.15 (0.66-2.00)
P-Trend	0.54						

[a]Analysis adjusted for age, BMI, income, smoking status, low sperm count, and race. **Bold** indicates statistically significant at a=0.05

[b]Dysfunction definition: Sex Drive: <6, Erection/Ejaculation/Problem Assessment: <9, Overall: <3

Table 5

Estimated OR of Sexual Dysfunction in cases versus controls by histologic subtype

Histology	***Controls***	***Nonseminoma***	**OR[a](95% CI)**	***Seminoma***	**OR[a](95% CI)**
Sex Drive					
Functional	143	74	1.00 (ref)	57	1.00 (ref)
Dysfunctional[b]	93	60	1.38 (0.87-2.20)	55	1.20 (0.72-1.99)
P-value	0.39				
Erection					
Functional	177	89	1.00 (ref)	68	1.00 (ref)
Dysfunctional[b]	59	45	**1.80 (1.08-2.98)**	44	1.62 (0.95-2.77)
P-value	0.047				
Ejaculation					
Functional	208	101	1.00 (ref)	87	1.00 (ref)
Dysfunctional[b]	28	33	**3.06 (1.63-5.75)**	25	1.64 (0.85-3.20)
P-value	0.0024				
Problem Assessment					
Functional	203	93	1.00 (ref)	79	1.00 (ref)
Dysfunctional[b]	33	41	**3.00 (1.68-5.34)**	33	1.80 (0.98-3.32)
P-value	0.0009				
Overall Sexual Satisfaction					
Functional	141	76	1.00 (ref)	63	1.00 (ref)
Dysfunctional[b]	95	58	1.10 (0.70-1.75)	49	0.98 (0.60-1.63)
P-value	0.89				

[a]Analysis adjusted for age, BMI, income, smoking status, low sperm count, and race. **Bold** indicates statistically significant at a=0.05

[b]Dysfunction definition: Sex Drive: <6, Erection/Ejaculation/Problem Assessment: <9, Overall: <3