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ERECTILE DYSFUNCTION IN MALE SURVIVORS OF CHILDHOOD CANCER—A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY

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Abstract

INTRODUCTION—With survival rates of over 80%, the number of survivors from pediatric cancer continues to increase. Late effects resulting from cancer and cancer therapy are being characterized, but little information exists on sexual health for male survivors of childhood cancer.

AIM—To assess erectile dysfunction (ED) in adult male survivors of childhood and adolescent cancers and to identify potential risk factors for ED.

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METHODS—1622 male survivors and 271 eligible siblings in the Childhood Cancer Survivor Study (CCSS) cohort completed the Male Health Questionnaire (MHQ), which provided information regarding sexual practices and sexual function. Combined with demographic, cancer, and treatment information from medical record abstraction, the results of the MHQ were analyzed using multivariable modeling. The International Index of Erectile Function (IIEF) was used to identify ED in subjects.

MAIN OUTCOME MEASURE—International Index of Erectile Function (IIEF)

RESULTS—Survivors (mean age 37.2 years; Standard Deviation (SD) 7.3 years) reported significantly lower sexual activity in the year prior to the survey than siblings (mean age 38.8 years; SD 8.5 years) without cancer. ED was reported by 12.3% (95% Confidence Interval (CI) 10.4%–14.3%) of survivors and 4.2 % (95% CI 2.0%–7.9%) of siblings. Survivors demonstrated significantly higher relative risk (RR) for ED (RR 2.63; 95% CI 1.40–4.97). In addition to older age, survivors who were exposed to higher dose (≥ 10 Gy) testicular radiation (RR 3.55; 95% CI 1.53–8.24), had surgery on spinal cord/nerves (RR 2.87; 95% CI 1.36–6.05), prostate surgery (RR 6.56; 95% CI 3.84–11.20) or pelvic surgery (RR 2.28; 95% CI 1.04–4.98) were at higher risk for ED.

CONCLUSION—Male survivors of childhood cancer have a greater than 2.6-fold increased risk for ED and certain cancer-specific treatments are associated with increased risk. Attention to sexual health, with its physical and emotional implications, as well as opportunities for early detection and intervention in these individuals may be important.

Keywords

Cancer survivorship; sexual dysfunction; erectile dysfunction; pediatric cancer

INTRODUCTION

With advances in treatment for individuals diagnosed with cancer, survival rates for all ages continue to rise, and there is a growing focus on long-term health and quality of life in this population^{1,2}. Consequently, there are increasing numbers of survivors of childhood cancer who face challenges as they get older. Over 80% of those diagnosed with childhood cancer currently survive at least 5 years, and most recent estimates show that there were nearly 400,000 childhood cancer survivors in the United States at the start of 2012³. Despite the significant advancement in knowledge regarding the health status of this population as they age^{4,5}, relatively little information has been published regarding the sexual health of male survivors of childhood cancer as they move into adulthood.

In general, male survivors of childhood cancers remain at risk for the sexual issues that all aging men face. However, the effects of a cancer diagnosis and treatment may add other risks and concerns⁶. We sought to analyze self-reported data from a large cohort of childhood cancer survivors to better understand these issues. These data captured information related to sexual function and relationships, infertility, perceived risk from cancer and treatment, and overall health. In this particular report, we specifically address erectile dysfunction in this group, given the attention this subject has received in other

populations and its relative lack in childhood cancer survivors, recognizing that it is only one of the issues affecting patients.

The Childhood Cancer Survivor Study (CCSS) cohort, consisting of over 14,000 survivors who were diagnosed from 1970–1986⁷, was utilized to assess four specific aims: 1) to determine the frequency and type of sexual activities adult male survivors report compared to adult sibling controls, 2) to determine the prevalence of erectile dysfunction (ED), using the International Index of Erectile Function (IIEF), in survivors relative to siblings, 3) to determine the effects of treatment and other socio-demographic, health or cancer-related variables on erectile function, and 4) to identify the frequency and types of therapies used to treat ED in male survivors compared to siblings.

METHODS

The CCSS is a retrospective cohort of five-year survivors of childhood cancer from 26 participating institutions in the United States and Canada who were diagnosed between 1970–1986. Cancer diagnosis and treatment data were collected through medical record abstracts, and ongoing assessment of health and quality of life continues to be obtained through self-report in periodic surveys. Siblings of survivors were also included as a comparison group. Details of the study design and cohort have been previously published^{7,8}. The institutional review board at each institution approved the study; informed consent was obtained from all participants.

Primary diagnosis and detailed treatment data were collected using a structured medical record abstraction form. Cumulative alkylating agent exposure was calculated using cyclophosphamide equivalent dose⁹. The initial baseline questionnaire was administered beginning in 1994 with follow-up questionnaires through 2009.

On the CCSS long-term follow-up #4 questionnaire, male survivors and siblings 18 years and older (at time of questionnaire) were asked if they would consider participating in a study “to better understand fertility and sexual function in males.” A total of 2961 survivors and 723 siblings (of the eligible 4000 male survivors and 1097 male siblings who completed the follow-up #4 questionnaire) expressed interest in completing this additional questionnaire. The Male Health Questionnaire (MHQ) was subsequently mailed in 2008–09 to this group. The MHQ was created to obtain information about sexual experiences and practices as well as sexual function, infertility, testicular function, and perceptions of the impact of cancer diagnosis and treatment on sexual function among this cohort (questionnaires available at <https://ccss.stjude.org/documents/questionnaires/original-cohort-questionnaires.html>).

Embedded within the MHQ was the previously validated International Index of Erectile Function (IIEF)¹⁰. The 15-question IIEF is divided into five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Each domain can be scored separately. An IIEF Erectile Function domain (IIEF-EF) score of 25 was used as the definition of ED for this study¹¹. The IIEF-EF domain items are designed to assess erectile function in men who have been sexually active within the past four weeks.

IIEF-EF domain scores and the binary (yes/no) outcome were computed only for subjects who were sexually active during the four-week period prior to completing the questionnaire. All subjects were asked whether they had ever received treatment for ED. Subjects responding “yes” were asked to provide information about treatment type.

Other definitions were consistent with prior publications involving the CCSS cohort. Cardiac conditions followed the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 as recently reported among CCSS patients¹² with grade 3 conditions considered severe or disabling and grade 4 conditions considered life-threatening. For physical activity, subjects who reported engaging in at least 30 minutes of moderate intensity physical activity on 5 days per week or at least 20 minutes of vigorous intensity physical activity on 3 days per week were classified as meeting the CDC guidelines for physical activity that were in place at the time of the follow-up #4 questionnaire¹³. This is the same definition used in a previous report regarding physical activity in childhood cancer survivors¹⁴.

Data Analysis

Data collected were tabulated for descriptive statistics, and statistical models were created to compare results between groups. Estimates of the relative risk (RR) and corresponding 95% confidence intervals (CI) for ED and ED treatment were calculated using generalized linear modeling. A log-link model, rather than a logistic model, was chosen because ED was not rare in the study population and hence the log-link is more suitable for estimating relative risk. The model utilized a Poisson error distribution with robust variance estimation¹⁵. When evaluating associations between cancer treatment variables and the ED outcomes, the factors investigated were testicular radiation, alkylating agents, surgery on the spinal cord or sympathetic nerves, prostate surgery, pelvic surgery, orchiectomy, age at cancer diagnosis, age at MHQ, and race. Preliminary univariable models were estimated, and any factors with a univariable p-value less than 0.20 were considered candidates for further evaluation in a multivariable context. Alkylating agents, orchiectomy, age at cancer diagnosis, and race were not significant in the univariate model and were therefore not included in the final model. The final multivariable model selected for each outcome included factors that showed a multivariable p-value <0.05, plus any additional factors whose omission would alter another factor's relative risk estimate by more than 10%.

For the survivor versus sibling comparisons, the ED outcome frequencies were tabulated and presented along with the raw (univariable) RR estimate and an adjusted RR estimate that accounts for age at MHQ, general health status, physical activity level, and selected self-reported health conditions (cardiac condition grade 3 or higher, hypertension requiring medication, diabetes, depression, other major psychiatric illness, prostate disease, current use of exogenous testosterone). Analyses comparing survivors versus siblings accounted for potential within-family correlation by utilizing Generalized Estimating Equation methodology. P-values <0.05 were considered statistically significant. All statistical tests were two-sided.

RESULTS

A total of 1622 survivors and 274 siblings completed and returned the MHQ for analysis, and this represented approximately 40% and 25%, respectively, of CCSS males who completed the follow-up #4 questionnaire (Figure 1). Three siblings were excluded from analysis due to a cancer diagnosis reported on a previous CCSS questionnaire. Mean age of analyzed survivors and siblings at time of MHQ completion was 37.2 years (SD 7.3 years) and 38.8 years (SD 8.5 years), respectively. Demographic characteristics and treatment variables for MHQ respondents and nonrespondents have been previously described in detail ¹⁶. Briefly, survivors who completed the MHQ were slightly older than survivor nonrespondents (mean age at start of MHQ distribution: 37.2 years for respondents, 35.3 years for nonrespondents). The survivor respondent group had a higher proportion who were white race (93.4%) and married (75.9%), compared to nonrespondents (84.8% white, 60.5% married). Treatment characteristics were similar for MHQ respondents and nonrespondents. Demographic data for the study cohort are provided in Table 1 with comparison of MHQ participants and non-participants in a supplemental table (A).

Frequency of sexual activities

All siblings and 99.2% of survivors reported sexual activity in their lifetime ($p=0.23$, Table 1), with 92.9% of survivors and 97.4% of siblings self-reporting sexual activity alone or with a partner in the past year ($p<0.0001$). Survivors that reported a lifetime experience with the opposite gender were 94.9% (vs. 97.0% of siblings) and with the same gender were 4.2% (vs. 5.2%). Past year sexual experience of survivors with opposite gender was 80.5% (vs. 82.2%) and with same gender was 2.2% (vs. 3.3%).

Prevalence of erectile dysfunction

A total of 12.3% (95% CI 10.4%–14.3%) of survivors and 4.2% (95% CI 2.0%–7.9%) of siblings had IIEF-EF scores ≥ 25 (Table 2). Survivors were at greater risk for ED than siblings (RR 2.63; 95% CI 1.40–4.97) among subjects with recent (past four weeks) sexual activity (Table 3). Comparatively, when separately asked the single questions, “How frequently in the past month have you had the problems listed...,” 23.9% and 31.7% of survivors reported some degree of “difficulty getting an erection” or “losing an erection during sexual activity”, respectively. This compared to 19.8% ($p=0.15$) and 23.4% ($p<0.01$) of siblings, respectively. The mean scores for the remaining domains of the IIEF are listed in a supplemental table (B).

Risk factors related to sexual function in survivors

In addition to older age, testicular radiation dose ≥ 10 Gy (RR 3.55; 95% CI 1.53–8.24), history of surgery involving the spinal cord or sympathetic nerves (RR 2.87; 95% CI 1.36–6.05), and history of prostate surgery (RR 6.56; 95% CI 3.84–11.20) or pelvic surgery (RR 2.28; 95% CI 1.04–4.98) were all significantly associated with ED among the survivors (Table 4). Health status variables assessed at time of the MHQ (e.g. general health) were not included in the treatment factors model because they may themselves be downstream consequences of treatment factors.

Long-term follow-up characteristics of survivors with and without ED (Figure 2)

A significantly higher percentage of the survivors with IIEF-EF scores in the normal range reported good to excellent general health (94.5% vs. 80.4%), and a significantly lower percentage reported an advanced cardiac condition (5.6% vs. 10.5%), previous diagnosis of depression (10.5% vs. 25.9%), or history of smoking (14.4% vs. 21.0%) when compared to survivors with lower IIEF-EF scores ($p<0.05$).

Frequency of treatment for sexual dysfunction

A total of 5.9% of survivors and 2.3% of siblings reported ever having received treatment for ED (RR 2.73; 95% CI 1.26–5.94) (Table 3). With rare exception, reported ED treatment consisted of oral medication.

DISCUSSION

When cancer occurs early in life, the cancer experience may have an adverse effect on an individual's sexual functioning in the formative years that may potentially persist throughout his lifetime. In this study, we characterized erectile dysfunction in a large cohort of adult males treated for childhood cancers and a sibling comparison group based on responses collected about ED and other issues in the MHQ. The data suggest that survivors may be at higher risk for subsequent ED. Previous work from our group demonstrated that these survivors are also at higher risk for male infertility but that many go on to father children, although they may have fewer children than they originally desire¹⁶.

Male survivors who responded to the MHQ were less likely to have engaged in some type of sexual experience in the year prior to the survey than their siblings, although the vast majority of both groups were sexually active. There may be multiple reasons, including sexual dysfunction, for being less sexually active. Based on analysis of IIEF-EF scores, cancer survivors had significantly higher RR for ED than siblings. The relatively low percentage of total subjects reaching the definition of ED is most likely a reflection of the lower ages of the group compared to other well-known general health cohorts, such as the Massachusetts Male Aging Study, where more than half of men aged 40–70 years reported erectile dysfunction¹⁷. Less data exist on the prevalence of erectile dysfunction in younger, healthy men, and reports have varied widely. Study populations for this group are historically heterogeneous, and the incidence is often different based on the country of origin. The multinational Cross-National Survey on Male Health Issues (CNSMHI) reported the prevalence of ED in men <40 years of age at 4–6%, although the percentage varied slightly between individual countries in the study, with the U.S. showing values similar to the UK, Italy and Germany but higher than France and Spain in the 30–39 year-old patient subgroup, the range where the majority MHQ patients reside¹⁸. For CNSHMI, the categorization of ED was based on a single self-report question, but the percentage of subjects <40 years defined as having ED is comparable to our MHQ sibling control group.

ED can result from vascular, neurologic, psychogenic, and/or hormonal factors, and often the etiology in individual patients is multifactorial¹⁸. For the cancer patient, the physiologic alteration that can result from cancer treatment exposures, including chemotherapy, radiation

and surgery, is often compounded by the psychological impact of the diagnosis and treatment experience on intimacy and sexual function^{20–22}. In previous reports, adult survivors of childhood cancer have expressed concern regarding their sexual function^{6, 23–25}. In the current study, survivors with a history of higher dose testicular radiation, spinal cord/nerve surgery, prostate surgery, or pelvic surgery did have a higher risk of ED than survivors without these exposures. While erectile dysfunction has been associated with testosterone deficiency²⁶, high dose alkylators, which can cause Leydig cell damage and testosterone deficiency, were not associated with increased risk of ED in this study. Patients exposed to high-dose alkylators had no statistically higher use of testosterone replacement therapy that could help explain this result. Previous reports have also shown Leydig cell damage can occur at testicular radiation doses of 20 Gy²⁷, but there was suggestion of ED in patients who had received lower doses.

Based on experience in prostate cancer patients, we know that radiation treatment to the pelvis can induce ED, possibly through effects on the corpora cavernosa or penile bulb²⁸. The fact that significant differences in IIEF-EF scores were seen with exposures of 10 Gy to the testes may suggest vulnerability for permanent changes of the penile structures at a young age, although the specific dose threshold could not be unequivocally determined due to the smaller numbers of patients receiving the higher doses. Adults may be more resistant to radiation, as doses of around 50 Gy to the penile bulb were needed to show significant effects on erectile function²⁹. All CCSS survivors responding to the MHQ had less than this dose, and only 5% received > 10 Gy. Nerves controlling erectile function course along the posterior-lateral prostate, and surgery in that region likely has effects on these neurovascular bundles, which explains the higher risk of ED in patients who had prostate or pelvic surgery³⁰. None of the survivors who had prostate surgery also had higher dose radiation therapy. Importantly, the techniques of both radiation and surgical therapy for prostate cancer have continued to advance over the years, and these refinements may lessen the adverse effects for future patients. Although the numbers of subjects having pelvic or spinal surgery is small in this series, the association with ED was strongly significant in the multivariable model. While the connection between ED and pelvic surgery may not be surprising and likely true at any age, it is important to highlight that treatment to this area at a young age may have long-lasting ramifications for sexual function, even if the patient/family and treating provider are not considering that as a priority at the time.

Erectile function is often difficult to measure as it can change based on situational influences. Therefore, self-reported questionnaires are often used so that patients can report on collective experiences over a period of time rather than at single points in time. The self-report nature of the MHQ, like all self-report questionnaires, is potentially a limitation of the current study. Likewise, the IIEF was primarily first used to assess responses of men during drug development of phosphodiesterase-5 inhibitors and may have differing utility in other clinical scenarios³¹. Nonetheless, the IIEF represents one of the most widely used assessments for ED, so its inclusion as an outcome measure seems appropriate and understandable to the clinician. The nature of the study does not allow for collection of data through individual patient interviews, but clearly qualitative research methodology, like interviews, combined with structured questionnaire responses would augment the current interpretation of the data²².

Data collection is also limited by the subjects' ability and willingness to fully respond to MHQ questions. CCSS subjects complete a number of questionnaires during participation, and motivation to complete a particular set of questions, like the MHQ, may be different for individual subjects. Nonetheless, an extensive effort was made to collect and analyze data in a standardized fashion across all subjects to allow meaningful comparisons. Despite the relatively lower response rate to the questionnaire, the end study sample represents the largest known group to address these questions in this population. The demonstrated higher RR for receiving treatment for ED in the survivor group compared to the sibling group appears to corroborate the higher RR of ED, as measured by the IIEF-EF.

Finally, men place significant importance on sexual functioning, yet they often fail to discuss it with their physicians³². Additionally, physicians frequently do not ask about sexual concerns, resulting in many disorders going untreated³³. As cancer patients survive years beyond treatment of their life-threatening disease, quality of life issues become increasingly important. Understanding sexual concerns of male childhood cancer survivors will allow treating clinicians to better predict male health late effects for future generations, as well as provide treatment for those who experience difficulties. The evidence-based Long-Term Follow-Up Guidelines of the Children's Oncology Group (COG) recommend screening for low testosterone and infertility after high dose alkylator therapy/heavy metal exposure, testicular radiation, and orchiectomy; screening for psychosexual dysfunction after spinal cord surgery; and screening for sexual dysfunction after pelvic surgery³⁴. Screening tools, like the Sexual Health Inventory for Men (SHIM)³⁵, can assist both patients and providers in identifying items of concern, but further development of questionnaires for this population may be important. As knowledge and treatment options have expanded since the time of diagnosis for these men in this study, examination of adult survivors in the future will also be important.

CONCLUSIONS

As measured by the IIEF-EF, male survivors of childhood cancer demonstrate higher risk of ED than their siblings. Likewise, survivors were more likely than siblings to have received treatment for ED. Age greater than 40 years, testicular radiation ≥ 10 Gy, surgery on spinal cord/nerves and prostate or pelvic surgery were significantly associated with ED in survivors. Further studies on ED in this patient population and on early intervention to either prevent or mitigate ED should be performed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow chart for Male Health Questionnaire recruitment and participation

Figure 2.
Health and lifestyle characteristics of survivors by IIEF-EF score

Table 1Comparison of study participants by survivors and siblings[#]

Characteristic	Survivors [Total N=1622]		Siblings [Total N=271]		p-value
	Number	(%)	Number	(%)	
Race/ethnicity					
White (non-Hispanic)	1441	(93)	253	(97)	0.06
Black (non-Hispanic)	30	(2)	0	(0)	
Hispanic	44	(3)	5	(2)	
Other	27	(2)	3	(1)	
Age at MHQ completion					
20–29 years	270	(17)	43	(16)	0.03
30–39 years	705	(43)	107	(39)	
40–49 years	562	(35)	91	(34)	
50+ years	85	(5)	30	(11)	
Mean age in years (SD)	37.4y	(7.3)	38.8y	(8.5)	
Primary cancer diagnosis					
Leukemia	535	(33)	--		
CNS tumors	138	(9)	--		
Hodgkin lymphoma	259	(16)	--		
Non-Hodgkin lymphoma	179	(11)	--		
Kidney (Wilms tumor)	132	(8)	--		
Neuroblastoma	81	(5)	--		
Soft tissue sarcoma	145	(9)	--		
Bone cancer	153	(9)	--		
Age at cancer diagnosis					
0–4 years	553	(34)	--		
5–9 years	360	(22)	--		

Characteristic	Survivors [Total N=1622]		Siblings [Total N=271]		p-value
	Number	(%)	Number	(%)	
10–14 years	377	(23)	--	--	
15–21 years	332	(20)	--	--	
Testicular radiation dose (Gy)					
None	506	(34)	--	--	
<4.0	875	(59)	--	--	
4.0 to <10	43	(3)	--	--	
10 (mean 21; maximum 48)	71	(5)			
Cyclophosphamide Equivalent Dose (mg/m ²)					
None	678	(48)	--	--	
>0 to <8000	342	(24)	--	--	
8000 to <16,000	254	(18)			
16,000 (mean 22,449; maximum 50,357)	147	(10)	--	--	
Surgery on spinal cord/sympathetic nerves					
Yes	44	(3)	--	--	
No	1493	(97)	--	--	
Prostate surgery					
Yes	13	(1)	--	--	
No	1524	(99)	--	--	
Sexual activity in lifetime					
Yes	1567	(99)	270	(100)	0.23
-with opposite gender	1498	(95)	262	(97)	
-with same gender	67	(4)	14	(5)	
No	12	(1)	0	(0)	
Mean age of ejacularche in years (SD)	13.4y	(2.3)	13.0y	(1.7)	

Characteristic	Survivors [Total N=1622]		Siblings [Total N=271]		p-value
	Number	(%)	Number	(%)	
Sexual activity over past year					
Yes	1482	(93)	262	(97)	<0.0001
No	114	(7)	7	(3)	
General health (self-reported)					
Excellent	248	(15)	57	(21)	0.02
Very good	659	(41)	112	(41)	
Good	541	(34)	86	(32)	
Fair or Poor	160	(10)	16	(6)	
Marital status					
Married or living as married	1053	(65)	189	(70)	0.14
Not married and not living as married	561	(35)	82	(30)	
Met CDC recommendations for physical activity					
Yes	796	(50)	156	(58)	0.02
No	787	(50)	114	(42)	
Grade 3+ cardiac condition					
Yes	127	(8)	7	(3)	<0.0001
No	1495	(92)	264	(97)	
Hypertension requiring medication					
Yes	229	(14)	28	(10)	0.06
No	1393	(86)	243	(90)	
Diabetes					
Yes	55	(3)	5	(2)	0.18
No	1567	(97)	266	(98)	

Characteristic	Survivors [Total N=1622]		Siblings [Total N=271]		p-value
	Number	(%)	Number	(%)	
Currently taking testosterone					
Yes	105	(7)	6	(2)	0.005
No	1498	(93)	264	(98)	
Depression (self-reported)					
Yes	228	(14)	37	(14)	0.77
No	1352	(86)	232	(86)	
Other major psychiatric illness (self-reported)					
Yes	26	(2)	4	(2)	0.84
No	1518	(98)	259	(98)	
Pelvic surgery (self-reported)					
Yes	42	(3)	2	(1)	0.06
No	1520	(97)	265	(99)	
Prostate disease (self-reported)					
Yes	35	(2)	12	(5)	0.09
No	1507	(98)	252	(95)	

Due to information not provided for some study participants, total numbers for each group do not always sum to total number in cohort.

Table 2

Frequency of ED and treatment for ED

HIEF-EF 25				Ever received treatment for ED				
Survivors		Siblings		Survivors		Siblings		
Frequency	(% Yes)	Frequency	(% Yes)	Frequency	(% Yes)	Frequency	(% Yes)	
Overall #	143 / 1166	(12)	9 / 213	(4)	88 / 1474	(6)	6 / 260	(2)
Age at MHQ completion ^{†, ‡}								
20–29 years	13 / 176	(7)	2 / 30	(7)	4 / 242	(2)	1 / 38	(3)
30–39 years	54 / 519	(10)	0 / 87	(0)	31 / 641	(5)	2 / 105	(2)
40–49 years	65 / 419	(16)	2 / 76	(3)	38 / 520	(7)	1 / 89	(1)
50+ years	11 / 52	(21)	5 / 19	(26)	15 / 71	(21)	2 / 27	(7)
General health (self-reported) ^{†, ‡}								
Excellent	7 / 200	(4)	1 / 49	(2)	9 / 234	(4)	0 / 54	(0)
Very good	48 / 522	(9)	6 / 91	(7)	18 / 632	(3)	1 / 107	(1)
Good	60 / 358	(17)	2 / 62	(3)	40 / 476	(8)	3 / 83	(4)
Fair/poor	28 / 84	(33)	0 / 11	(0)	21 / 129	(16)	2 / 16	(13)
Met CDC recommendations for physical activity								
Yes	74 / 597	(12)	6 / 126	(5)	36 / 736	(5)	3 / 150	(2)
No	66 / 541	(12)	3 / 86	(3)	52 / 703	(7)	3 / 109	(3)
Grade 3+ cardiac condition [†]								
Yes	15 / 72	(21)	1 / 4	(25)	10 / 107	(9)	0 / 7	(0)
No	128 / 1094	(12)	8 / 209	(4)	78 / 1367	(6)	6 / 253	(2)
Hypertension requiring medication ^{†, ‡}								
Yes	26 / 156	(17)	3 / 21	(14)	19 / 198	(10)	1 / 27	(4)
No	117 / 1010	(12)	6 / 192	(3)	69 / 1276	(5)	5 / 233	(2)

	IIEF-EF 25				Ever received treatment for ED			
	Survivors	Frequency	(% Yes)	Siblings	Survivors	Frequency	(% Yes)	Siblings
Diabetes ^{†, ‡}								
Yes	7 / 29	(24)	(24)	2 / 3	8 / 48	(17)	(17)	1 / 5
No	136 / 1137	(12)	(12)	7 / 210	80 / 1426	(6)	(6)	5 / 255
Depression (self-reported) ^{†, ‡}								
Yes	36 / 142	(25)	(25)	2 / 28	29 / 200	(15)	(15)	2 / 33
No	103 / 1004	(10)	(10)	7 / 183	56 / 1245	(4)	(4)	4 / 225
Other major psychiatric illness (self-reported) ^{†, ‡}								
Yes	5 / 12	(42)	(42)	0 / 3	7 / 23	(30)	(30)	0 / 4
No	128 / 1111	(12)	(12)	9 / 203	74 / 1391	(5)	(5)	6 / 248
Prostate disease (self-reported) [†]								
Yes	7 / 21	(33)	(33)	0 / 11	10 / 31	(32)	(32)	1 / 12
No	126 / 1099	(11)	(11)	9 / 196	72 / 1382	(5)	(5)	5 / 241
Currently taking testosterone (self-reported) ^{†, ‡}								
Yes	19 / 68	(28)	(28)	0 / 5	14 / 84	(17)	(17)	2 / 6
No	124 / 1092	(11)	(11)	9 / 207	74 / 1383	(5)	(5)	4 / 253

[†] Indicates that this factor was significantly associated ($p < 0.05$) with IIEF-EF 25 overall among all participants. Where numbers permitted, interaction tests were performed to assess whether the association with IIEF-EF 25 differed for survivor and sibling groups; no statistically significant interactions were found.

[‡] Indicates that this factor was significantly associated ($p < 0.05$) with ever having received treatment for ED overall among all participants. Where numbers permitted, interaction tests were performed to assess whether the association with ED treatment differed for survivor and sibling groups; no statistically significant interactions were found.

[#] Rates calculated on total number of participants on whom information was available

[†] Psychiatric illness other than depression or obsessive-compulsive disorder

IIEF-EF = International Index of Erectile Function (Erectile Function Domain); ED = erectile dysfunction

Table 3
Multivariable comparison summary of survivors and siblings for ED and treatment of ED

Outcome measure	Frequency (% Yes)	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk [/] (95% CI)
ED			
Survivors	143/1166 (12%)	2.90 (1.50, 5.60)	2.63 (1.40, 4.97)
Siblings	9/213 (4%)	1.00 (referent)	1.00 (referent)
Self-reported receiving treatment for ED			
Survivors	88/1474 (6%)	2.59 (1.14, 5.86)	2.73 (1.26, 5.94)
Siblings	6/260 (2%)	1.00 (referent)	1.00 (referent)

[/] Adjusted for age at time of MHQ, general health level, physical activity, grade 3 or higher cardiac condition, hypertension requiring medication, diabetes, depression and other major psychiatric illness, prostate disease and current use of exogenous testosterone.

IIIEF-EF = International Index of Erectile Function (Erectile Function Domain); ED = erectile dysfunction

Table 4Demographic and treatment-related risk factors for ED in survivors^{#†}

	Frequency (%) of survivors with ED [†]	Relative risk for ED (95% CI)	p-value
Age at MHQ completion			
50+ years	8 / 35	(23)	3.47 (1.39–8.69)
40–49 years	53 / 358	(15)	2.12 (1.10–4.09)
30–39 years	42 / 448	(9)	1.42 (0.73–2.76)
20–29 years	11 / 161	(7)	1.00 (referent)
Testicular radiation dose			
10 Gy	5 / 17	(29)	3.55 (1.53–8.24)
4.0 Gy to <10 Gy	5 / 21	(24)	1.45 (0.56–3.78)
>0 Gy <4.0 Gy	72 / 559	(13)	1.32 (0.89–1.95)
None	29 / 340	(9)	1.00 (referent)
Surgery on spinal cord/sympathetic nerves (records/self-reported)			
Yes	6 / 20	(30)	2.87 (1.36–6.05)
No	105 / 937	(11)	1.00 (referent)
Prostate surgery (records/self-reported) ^A			
Yes	7 / 10	(70)	6.56 (3.84–11.20)
No	104 / 947	(11)	1.00 (referent)
Pelvic surgery (self-reported)			
Yes	7 / 21	(33)	2.28 (1.04–4.98)
No	103 / 956	(11)	1.00 (referent)

[#] Only cancer treatment factors and basic demographic characteristics were considered in this model. Health status variables assessed at time of the Men's Health Questionnaire (e.g. general health) were not included in the treatment factors model because they may themselves be downstream consequences of treatment factors.

[†] For analyses assessing the impact of treatments received for primary cancer, subjects who experienced a recurrence or second malignant neoplasm were excluded.

^A Biopsies or other diagnostic procedures not included