Adverse Health Outcomes in Relationship to Hypogonadism After Chemotherapy: A Multicenter Study of Testicular Cancer Survivors

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ABSTRACT

Background: This study examined the prevalence of hypogonadism, its clinical and genetic risk factors, and its relationship to adverse health outcomes (AHOs) in North American testicular cancer survivors (TCS) after modern platinum-based chemotherapy. **Patients and Methods:** Eligible TCS were <55 years of age at diagnosis and treated with first-line platinum-based chemotherapy. Participants underwent physical examinations and completed questionnaires regarding 15 AHOs and health behaviors. Hypogonadism was defined as serum testosterone levels ≤3.0 ng/mL or use of testosterone replacement therapy. We investigated the role of 2 single nucleotide polymorphisms (rs6258 and rs12150660) in the sex hormone–binding globulin (SHBG) locus implicated in increased hypogonadism risk in the general population. **Results:** Of 491 TCS (median age at assessment, 38.2 years; range, 18.7–68.4 years), 38.5% had hypogonadism. Multivariable binary logistic regression analysis identified hypogonadism risk factors, including age at clinical evaluation (odds ratio [OR], 1.42 per 10-year increase; P=.006) and body mass index of 25 to <30 kg/m² (OR, 2.08; P=.011) or ≥30 kg/m² (OR, 2.36; P=.005) compared with <25 kg/m². TCS with ≥2 risk alleles for the SHBG SNPs had a marginally significant increased hypogonadism risk (OR, 1.45; P=.09). Vigorous-intensity physical activity appeared protective (OR, 0.66; P=.07). Type of cisplatin-based chemotherapy regimen and socioeconomic factors did not correlate with hypogonadism. Compared with TCS without hypogonadism, those with hypogonadism were more likely to report ≥2 AHOs (65% vs 51%; P=.003), to take medications for hypercholesterolemia (20.1% vs 6.0%; P<.001) or hypertension (18.5% vs 10.6%; P=.013), and to report erectile dysfunction (19.6% vs 11.9%; P=.018) or peripheral neuropathy (30.7% vs 22.5%; P=.041). A marginally significant trend for increased use of prescription medications for either diabetes (5.8% vs 2.6%; P=.07) or anxiety/depression (14.8% vs 9.3%; P=.06) was observed. **Conclusions:** At a relatively young median age, more than one-third of TCS have hypogonadism, which is significantly associated with increased cardiovascular disease risk factors, and erectile dysfunction. Providers should screen TCS for hypogonadism and treat symptomatic patients.

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Background

Testicular cancer is the most common cancer among young men (age 18–39 years).[1] Currently, >95% of patients are cured of the disease.[2] Although some patients with stage I disease are cured with orchiectomy only, those with advanced or recurrent disease will typically require cisplatin-based chemotherapy. Although testicular cancer survivors (TCS) can now expect to live for >40 years after diagnosis,[3] they are at risk for short- and long-term complications related to cancer therapy, including hypogonadism.[4]

Hypogonadism and its health effects have been largely studied in the general population in older men, because testosterone levels decrease with aging.[5–8] Hypogonadism has been linked to obesity, high cholesterol levels, cardiovascular disease (CVD), and decreased bone mineral density.[9,10] Recent genetic investigations in the general population have identified 2 single nucleotide polymorphisms (SNPs) in the sex hormone–binding globulin gene (SHBG) through genome-wide association studies associated with increased risk for hypogonadism.[11] No study, however, has examined the prevalence of hypogonadism in North American TCS and its relationship to adverse health outcomes (AHOs).

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Most TCS have had one testicle (or both) surgically removed and have received chemotherapy that can damage the function of the remaining testicle, and thus are already at elevated risk for hypogonadism compared with the general population. In addition, an inherently increased risk may be due to testicular dysgenesis syndrome, a constellation of conditions proposed to also elevate risk of testicular cancer.[12–14]

This study examined the prevalence of AHOs in relationship to hypogonadism among TCS enrolled in the Platinum Study, a multicenter North American investigation of the long-term effects of cisplatin-based chemotherapy. The role of *SHBG* gene polymorphisms in hypogonadism risk among TCS are also investigated for the first time.

Patients and Methods

Participants

The Platinum Study protocol evaluated late consequences of platinum-based chemotherapy and was approved by the Institutional Review Boards at all participating institutions.[15] Each study participant provided written informed consent allowing access to their medical records since their cancer diagnosis. Eligibility criteria included confirmed diagnosis of germ cell tumor (GCT), age <55 years at diagnosis, treatment with first-line platinum-based chemotherapy, no salvage chemotherapy, no radiotherapy, and no antecedent chemotherapy for another primary cancer. All participants were disease-free at the time of clinical evaluation and were undergoing routine follow-up at the participating site. The first 491 consecutively enrolled TCS for whom funding was available to measure serum testosterone were included in this analysis. Participants in this analysis were similar to the first 1,214 survivors enrolled in the Platinum Study[16] in terms of age at testicular cancer diagnosis (*P*=.81), age at clinical evaluation for the Platinum Study (*P*=.30), and other clinical and sociodemographic characteristics (supplemental eTable 1, available with this article at JNCCN.org). Data on the prevalence of metabolic syndrome and its risk factors in this cohort have been previously described.[17]

Assessments

Patient-Reported Health Outcomes and Lifestyle Behaviors

TCS completed a questionnaire regarding health outcomes, lifestyle behaviors, and current prescription medications with indications (including antihypertensive, diabetic, and lipid-lowering medications). Each of the following conditions was considered an AHO (definitions provided in supplemental eTable 2): hypercholesterolemia and on prescription medication, hypertension and on prescription medication, erectile dysfunction (ED), diabetes and on prescription medication, psychotropic

prescription medications for anxiety and/or depression, CVD, peripheral vascular disease, thromboembolic disease, renal disease, peripheral neuropathy, Raynaud phenomenon, benign thyroid disease, tinnitus, hearing impairment, and problems with balance/vertigo/dizziness. Demographic information included age at cancer diagnosis and at clinical evaluation, race, education, employment, and marital status. Smoking status was categorized as current, former, or never-smoker. Physical activity was reported as the average time per week engaged in various forms of exercise, using validated questionnaires.[18] Moderate- and vigorous-intensity physical activity were defined as participating in at least 1 activity per week with a metabolic equivalent (MET) of 3 to <6 METs or ≥6 METs, respectively.[16,19,20]

Data Collection From Medical Records

Study staff abstracted data according to a standardized protocol.[15,16] Collected data included diagnosis date, histology, and site of GCT, and the name, dose, dates of administration, number of cycles, and cumulative dose for each cytotoxic drug. All data were entered into the eClinical system (www.eClinicalWorks.com), supported by the study coordinating center.

Clinical Evaluation

TCS underwent a brief physical examination, which included measurement of height and weight. Body mass index (BMI) was calculated as kg/m². Blood samples were drawn and time of collection was recorded, and the samples were then frozen and shipped to the central laboratory. Serum levels of testosterone were measured using commercial assays. Hypogonadism was defined using the FDA definition (serum testosterone level ≤3.0 ng/mL)[21] or use of testosterone replacement therapy.

DNA Genotyping and Imputation

DNA was extracted from blood samples collected at clinical evaluation. SNPs were genotyped on the HumanOmniExpressExome-8 BeadChip Kit (Illumina, Inc.) at the RIKEN Center for Integrative Medical Sciences. Because the SNPs of interest are not called on this chip, we performed genotype imputation following standard quality control measures as previously described.[22] Imputation was performed on the University of Michigan Imputation Server[23] with the following parameters: 1000 Genomes Phase 1 (version 3) SHAPEIT2 (no singletons) reference panel, SHAPEIT phasing, and the EUR (European) population. SNP calls were converted to risk allele dosage format.

Statistical Analyses

Data were summarized with median (ranges) for continuous variables and proportions for categorical variables in 2 TCS subgroups defined by the presence or absence of hypogonadism. Variables in the 2 groups were

compared using the Pearson chi-square and 2-sided Wilcoxon rank sum tests for categorical and continuous variables, respectively. To determine factors associated with hypogonadism in TCS, variables that were significantly different between the 2 groups with regard to clinical, sociodemographic, and other characteristics were included in the multivariable binary logistic regression analysis. Adjusted odds ratios (ORs), 95% CIs, and P values were reported. Cumulative number of risk alleles in *SHBG* was also included in the multivariable model due to evidence for its role in the determination of serum testosterone concentrations in the general male population.[11] All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc.). All tests were 2-sided, with $P<.05$ considered statistically significant.

Results

Population Characteristics of TCS
A total of 491 TCS were assessed, with a median age at clinical evaluation of 38.2 years (Table 1). In all, 189 TCS (38.5%) met criteria for hypogonadism. TCS with hypogonadism were significantly older at clinical evaluation than those without hypogonadism (median age, 42.6 vs 36.5 years; $P<.001$). Most TCS received bleomycin/etoposide/cisplatin (BEP; 55.4%) or etoposide/cisplatin (EP; 32.4%), but hypogonadism prevalence did not differ by treatment regimen ($P=.95$) or cumulative dose of cisplatin or bleomycin ($P=.99$ and .56, respectively). TCS with hypogonadism had a significantly higher prevalence of being overweight or obese (83.1% vs 69.2%; $P<.001$), and were less likely to participate in vigorous-intensity physical activity (56.1% vs 72.5%; $P<.001$) compared with those without hypogonadism.

Factors Associated With Hypogonadism in TCS
In multivariable binary logistic regression analysis, age at clinical evaluation (OR, 1.42 per 10-year increase in age; 95% CI, 1.10–1.83; $P=.006$) and being overweight (BMI, 25 to <30 kg/m²; OR, 2.08; 95% CI, 1.18–3.66; $P=.011$) or obese (BMI, ≥30 kg/m²; OR, 2.36; 95% CI, 1.29–4.31; $P=.005$) were significantly associated with increased risk for hypogonadism (Table 2). Although significant in bivariate analysis, vigorous-intensity physical activity was only marginally associated with reduced hypogonadism risk (OR, 0.66; 95% CI, 0.41–1.04; $P=.07$) after adjusting for other independent variables in the model. TCS with 2 or 3 risk alleles had a trend for increased risk of hypogonadism compared with TCS with no or 1 risk allele in multivariable analysis (OR, 1.45; 95% CI, 0.95–2.24; $P=.09$).

Association Between Hypogonadism and AHOs
Among all 15 AHOs included in the survey, 28% of TCS with hypogonadism reported ≥4 AHOs compared with

16% of those without hypogonadism (Figure 1), and TCS with hypogonadism were less likely to report no or only one AHO (35%) compared with those without (49%) ($P=.002$). Associations between specific AHOs and hypogonadism are shown in Table 3. Compared with TCS without hypogonadism, those with hypogonadism were significantly more likely to take medications for hypercholesterolemia (20.1% vs 6.0%; $P<.001$), hypertension (18.5% vs 10.6%; $P=.013$), and ED (19.6% vs 11.9%; $P=.018$), with a marginal trend toward increased use of prescription medications for either diabetes (5.8% vs 2.6%; $P=.07$) or anxiety/depression (14.8% vs 9.3%; $P=.06$). TCS with hypogonadism were also significantly more likely to report symptoms of moderate or severe peripheral neuropathy (30.7% vs 22.5%; $P=.041$) compared with those without hypogonadism. As expected, no associations were observed between hypogonadism and several of the AHOs, such as tinnitus and hearing loss.

Association of Genetic Variants in *SHBG* With Hypogonadism
We assessed the association of 2 SNPs (rs6258 and rs12150660) in the *SHBG* locus previously implicated in increased hypogonadism risk in the general population.[11] SNPs rs12150660 and rs6258 showed, respectively, high imputation quality (R^2, 0.99 and 0.87), high call rate (>99.7% and >99.8%), and perfect Hardy-Weinberg equilibrium ($P=.98$ and .97). Because rs6258 is a rare variant (minor allele frequency, 0.69%), there were no homozygous minor patients and only 7 heterozygous patients in the cohort. Both SNPs displayed effect sizes similar to those reported previously in the general population (rs6258: OR, 1.6; $P=.5$; rs12150660: OR, 0.79; $P=.28$). When the risk for hypogonadism was analyzed according to the cumulative number of risk alleles for rs12150660 (G) and rs6258 (T) (Figure 2), OR per each additional risk allele was 1.26 (95% CI, 0.91–1.76; P for trend $=.17$).

Discussion
To date, this is the largest investigation of the prevalence of hypogonadism and associated AHOs among North American TCS after treatment with modern cisplatin-based chemotherapy. It is also the first series to investigate the influence of genetic variants in the *SHBG* gene on hypogonadism risk in TCS. At a median age of only 38 years at clinical evaluation, >38% of TCS had low testosterone levels or were on testosterone replacement therapy. Significant risk factors included increasing age and BMI. Although vigorous-intensity physical activity appeared protective and genetic variants in *SHBG* may have influenced hypogonadism risk, results were of borderline significance.

Table 1. Patient Characteristics

Characteristic	All Patients n (%)	Hypogonadism Present, n (%)	Hypogonadism Absent, n (%)	P Value[a]
Total	491 (100)	189 (100)	302 (100)	
Median age at testicular cancer diagnosis (range), y	30.6 (15.4–49.9)	33.5 (15.9–49.9)	29.6 (15.4–49.7)	**<.001**
Clinical characteristics				
Age at clinical evaluation for Platinum Study				
Median (range), y	38.2 (18.7–68.4)	42.6 (20.2–68.4)	36.5 (18.7–68.1)	**<.001**
<30 y	101 (20.6)	29 (15.3)	72 (23.9)	
30–39 y	168 (34.2)	51 (27.0)	117 (38.7)	**<.001**
40–49 y	139 (28.3)	63 (33.3)	76 (25.2)	
≥50 y	82 (16.7)	46 (24.3)	36 (11.9)	
Missing	1 (0.2)	0	1 (0.3)	
Tumor histology				
Seminoma	130 (26.5)	63 (33.3)	67 (22.2)	.007
Nonseminoma/Mixed	361 (73.5)	126 (66.7)	235 (77.8)	
Tumor site				
Testis	438 (89.2)	172 (91.0)	266 (88.1)	.32
Extragonadal	53 (10.8)	17 (9.0)	36 (11.9)	
Tumor stage				
I	128 (26.1)	50 (26.5)	78 (25.8)	
II	189 (38.5)	74 (39.2)	115 (38.1)	.66
III	111 (22.6)	38 (20.1)	73 (24.2)	
Not stated	63 (12.8)	27 (14.3)	36 (11.9)	
Cumulative dose of cisplatin, mg/m²				
<300	28 (5.7)	10 (5.3)	18 (6.0)	
300	155 (31.6)	60 (31.7)	95 (31.5)	
301–399	17 (3.5)	7 (3.7)	10 (3.3)	.99
400	265 (54.0)	103 (54.5)	162 (53.6)	
>400	23 (4.7)	8 (4.2)	15 (5.0)	
Received carboplatin	3 (0.6)	1 (0.5)	2 (0.7)	
Cumulative dose of bleomycin, IU				
0	198 (40.3)	72 (38.1)	126 (41.7)	
>0–180,000	37 (7.5)	18 (9.5)	19 (6.3)	
181,000–270,000	183 (37.3)	69 (36.5)	114 (37.7)	.56
271,000–360,000	72 (14.7)	30 (15.9)	42 (13.9)	
>360,000	1 (0.2)	0 (0)	1 (0.3)	

Abbreviations: BEP, bleomycin/etoposide/cisplatin; EP, etoposide/cisplatin; METs, metabolic equivalents.
[a]P value from Wilcoxon test for continuous variables or chi-square for categorical variables. Missing values were not included in P value calculation. Statistically significant P values are in bold.
[b]Of survivors who received BEP, 170 and 92 were administered BEP x 3 and BEP x 4, respectively.
[c]All 159 survivors received EP x 4.
[d]This category includes 15 patients treated with ifosfamide/etoposide/cisplatin (VIP regimen), 3 patients treated with carboplatin, and 41 patients with other chemotherapy regimens.
[e]Nonwhite race includes: Asian, 19 (3.9%); black/African American, 6 (1.2%); American Indian, 1 (0.2%); more than one race, 9 (1.8%); and declined to answer/other/unknown, 40 (8.1%).
[f]Vigorous- and moderate-intensity physical activity groups are not mutually exclusive. Nine different activities were surveyed in the Platinum Study, some were moderate-intensity and some vigorous-intensity. If a subject reported that he spent 1 hour walking per week (ie, a moderate-intensity activity) and 30 minutes running per week (ie, a vigorous-intensity activity), he was included as a yes for both "any moderate" and "any vigorous" activity[19,20]; 3 survivors did not provide data on physical activity.
[g]One patient without hypogonadism was missing a body mass index value and was not included in the calculation of P value.
[h]Samples from these patients had not been processed in time to be included in the genotyping performed for this study and are not included in the calculation of P value.

Table 1. Patient Characteristics (cont.)

| Characteristic | All Patients n (%) | Hypogonadism | | P Value[a] |
		Present, n (%)	Absent, n (%)	
Platinum-based chemotherapy				
BEP[b]	272 (55.4)	106 (56.1)	166 (55.0)	
EP[c]	159 (32.4)	60 (31.7)	99 (32.8)	.95
Other[d]	59 (12.0)	22 (11.6)	37 (12.3)	
Not stated	1 (0.2)	1 (0.5)	0 (0)	
Time since last chemotherapy				
Median (range), y	4.7 (0.4–24.2)	4.9 (1.0–23.7)	4.4 (0.4–24.2)	.17
<2 y	80 (16.3)	30 (15.9)	50 (16.6)	
2–5 y	219 (44.6)	82 (43.4)	137 (45.4)	
6–9 y	75 (15.3)	28 (14.8)	47 (15.6)	.82
≥10 y	113 (23.0)	48 (25.4)	65 (21.5)	
Not stated	4 (0.8)	1 (0.5)	3 (1.0)	
Sociodemographic characteristics				
Race				
White	416 (84.7)	160 (84.7)	256 (84.8)	.97
Nonwhite[e]	75 (15.3)	29 (15.3)	46 (15.2)	
Marital status				
Married/Living as married	295 (60.1)	125 (66.1)	170 (56.3)	**.038**
Not married/prefer not to say	196 (39.9)	64 (33.9)	132 (43.7)	
Education				
Less than college graduate	60 (12.2)	20 (10.6)	40 (13.2)	
Some college, college graduate	318 (64.8)	125 (66.1)	193 (63.9)	.67
Postgraduate level	104 (21.2)	41 (21.7)	63 (20.9)	
Other/Prefer not to say	9 (1.8)	3 (1.6)	6 (2.0)	
Employment status				
Not employed/prefer not to say	58 (11.8)	25 (13.2)	33 (10.9)	.44
Employed	433 (88.2)	164 (86.8)	269 (89.1)	
Health behaviors				
Smoking status				
Never-smoker	276 (56.2)	103 (54.5)	173 (57.3)	
Former smoker	166 (33.8)	68 (36.0)	98 (32.5)	.75
Current smoker	47 (9.6)	18 (9.5)	29 (9.6)	
Not stated	2 (0.4)	0 (0)	2 (0.7)	

Abbreviations: BEP, bleomycin/etoposide/cisplatin; EP, etoposide/cisplatin; METs, metabolic equivalents.

[a]P value from Wilcoxon test for continuous variables or chi-square for categorical variables. Missing values were not included in P value calculation. Statistically significant P values are in bold.

[b]Of survivors who received BEP, 170 and 92 were administered BEP x 3 and BEP x 4, respectively.

[c]All 159 survivors received EP x 4.

[d]This category includes 15 patients treated with ifosfamide/etoposide/cisplatin (VIP regimen), 3 patients treated with carboplatin, and 41 patients with other chemotherapy regimens.

[e]Nonwhite race includes: Asian, 19 (3.9%); black/African American, 6 (1.2%); American Indian, 1 (0.2%); more than one race, 9 (1.8%); and declined to answer/other/unknown, 40 (8.1%).

[f]Vigorous- and moderate-intensity physical activity groups are not mutually exclusive. Nine different activities were surveyed in the Platinum Study, some were moderate-intensity and some vigorous-intensity. If a subject reported that he spent 1 hour walking per week (ie, a moderate-intensity activity) and 30 minutes running per week (ie, a vigorous-intensity activity), he was included as a yes for both "any moderate" and "any vigorous" activity[19,20]; 3 survivors did not provide data on physical activity.

[g]One patient without hypogonadism was missing a body mass index value and was not included in the calculation of P value.

[h]Samples from these patients had not been processed in time to be included in the genotyping performed for this study and are not included in the calculation of P value.

Table 1. Patient Characteristics (cont.)

Characteristic	All Patients n (%)	Hypogonadism Present, n (%)	Hypogonadism Absent, n (%)	P Value[a]
Average number of alcoholic drinks in past year				
Rarely or never	99 (20.2)	43 (22.8)	56 (18.5)	.15
≤4 per week	219 (44.6)	92 (48.7)	127 (42.1)	
5 per week to 1 daily	109 (22.2)	33 (17.5)	76 (25.2)	
≥2 daily	58 (11.8)	21 (11.1)	37 (12.3)	
Not stated	6 (1.2)	0 (0)	6 (2.0)	
Moderate-intensity physical activity (3–6 METs)[f]				
No	28 (5.7)	15 (7.9)	13 (4.3)	.09
Yes	460 (93.7)	173 (91.5)	287 (95.0)	
Not stated	3 (0.6)	1 (0.5)	2 (0.7)	
Vigorous-intensity physical activity (≥6 METs)[f]				
No	163 (33.2)	82 (43.4)	81 (26.8)	**<.001**
Yes	325 (66.2)	106 (56.1)	219 (72.5)	
Not stated	3 (0.6)	1 (0.5)	2 (0.7)	
Physical examination and genetic variants				
Body mass index[g]				
Median (range), kg/m²	27.7 (18.0–52.8)	28.7 (18.0–47.7)	27.1 (19.6–52.8)	**<.001**
<25 kg/m²	124 (25.3)	32 (16.9)	92 (30.5)	**<.001**
≥25 kg/m²	366 (74.5)	157 (83.1)	209 (69.2)	
Cumulative number of risk alleles in rs6258 and rs12150660 (SHBG)				
0 or 1	176 (35.8)	62 (32.8)	114 (37.7)	.22
2 or 3	228 (46.4)	94 (49.7)	134 (44.4)	
Not genotyped[h]	87 (17.7)	33 (17.5)	54 (17.9)	

Abbreviations: BEP, bleomycin/etoposide/cisplatin; EP, etoposide/cisplatin; METs, metabolic equivalents.

[a]P value from Wilcoxon test for continuous variables or chi-square for categorical variables. Missing values were not included in P value calculation. Statistically significant P values are in bold.
[b]Of survivors who received BEP, 170 and 92 were administered BEP x 3 and BEP x 4, respectively.
[c]All 159 survivors received EP x 4.
[d]This category includes 15 patients treated with ifosfamide/etoposide/cisplatin (VIP regimen), 3 patients treated with carboplatin, and 41 patients with other chemotherapy regimens.
[e]Nonwhite race includes: Asian, 19 (3.9%); black/African American, 6 (1.2%); American Indian, 1 (0.2%); more than one race, 9 (1.8%); and declined to answer/other/unknown, 40 (8.1%).
[f]Vigorous- and moderate-intensity physical activity groups are not mutually exclusive. Nine different activities were surveyed in the Platinum Study, some were moderate-intensity and some vigorous-intensity. If a subject reported that he spent 1 hour walking per week (ie, a moderate-intensity activity) and 30 minutes running per week (ie, a vigorous-intensity activity), he was included as a yes for both "any moderate" and "any vigorous" activity[19,20]; 3 survivors did not provide data on physical activity.
[g]One patient without hypogonadism was missing a body mass index value and was not included in the calculation of P value.
[h]Samples from these patients had not been processed in time to be included in the genotyping performed for this study and are not included in the calculation of P value.

Similar to findings in the general population[24–28] and in European studies of TCS,[29–34] TCS with hypogonadism in our study were more likely to report components of metabolic syndrome than TCS with normal testosterone levels. In particular, they were at least 3 times more likely to take medications for high cholesterol levels (P<.001) and almost twice as likely to take medications for high blood pressure (P=.013) and diabetes (P=.07). These observations may explain findings in previous studies that TCS treated with chemotherapy experience up to a 7-fold increased risk for CVD, with upswings in risk typically observed ≥10 years after therapy.[35–39] Because the median cohort follow-up time was <5 years, we have not yet observed an increase in cardiovascular events among TCS with hypogonadism, but long-term follow-up of all survivors is planned. The association between hypogonadism and peripheral neuropathy was unexpected and may represent a chance finding. However, we previously showed that peripheral sensory neuropathy among TCS is associated with weight gain adjusted for years since treatment (P=.004).[40] Thus, it is possible that TCS with significant neuropathy may not be able to

Table 2. Multivariable Binary Logistic Regression Analysis of Potential Risk Factors for Hypogonadism in TCS and Other Malignant GCTs

Variable	OR	95% CI	P Value[a]
Age at clinical evaluation, per 10 y	1.42	1.10–1.83	**.006**
Marital status			
Married/Living as married	—	—	Ref
Not married	0.79	0.50–1.25	.31
Tumor histology			
Seminoma	—	—	Ref
Nonseminoma/Mixed	0.79	0.48–1.31	.36
Body mass index			
<25 kg/m²	—	—	Ref
25 to <30 kg/m²	2.08	1.18–3.66	**.011**
≥30 kg/m²	2.36	1.29–4.31	**.005**
Vigorous-intensity physical activity (≥6 METs)			
No	—	—	Ref
Yes	0.66	0.41–1.04	.07
Cumulative number of risk alleles in rs6258 and rs12150660 (*SHBG*)			
0 or 1 risk alleles	—	—	Ref
2 or 3 risk alleles	1.45	0.95–2.24	.09

Abbreviations: GCT, germ cell tumor; METs, metabolic equivalents; OR, odds ratio; TCS, testicular cancer survivors.

[a]Bold indicates ORs with $P<.05$. For the multivariable binary logistic regression analyses, 88 survivors were excluded due to unavailable data for ≥1 variables.

Figure 1. Prevalence of total number of AHOs in TCS and other malignant germ cell tumors with or without hypogonadism. TCS with hypogonadism were more likely to report more AHOs compared with those without. Chi-square test, $P=.002$.
Abbreviations: AHO, adverse health outcome; TCS, testicular cancer survivors.

exercise adequately, and consequently develop obesity that increases hypogonadism risk, as it does among men in the general population.[7] The prevalence of metabolic syndrome in TCS and its risk factors have been reviewed in detail elsewhere.[17]

In our investigation, the cumulative dose of cisplatin did not correlate with the prevalence of hypogonadism. Other studies[41,42] have reported a higher prevalence of hypogonadism in TCS who received higher doses of cisplatin. Because most patients in the current series (89.1%) received a cumulative cisplatin dose between 300 and 400 mg/m², this may explain the lack of correlation observed.

Ohlsson et al[11] recently performed a meta-analysis of genome-wide association data in 14,429 men from 7 cohorts in the general population and identified 2 SNPs at the *SHBG* locus as independently associated with serum testosterone concentration. In our study, these SNPs also appeared to affect testosterone concentration but were of borderline statistical significance. In addition, although the magnitude of influence of these genetic variants on serum testosterone concentration (OR, 1.26 per additional risk allele) in TCS was somewhat less than reported in the general population (OR,
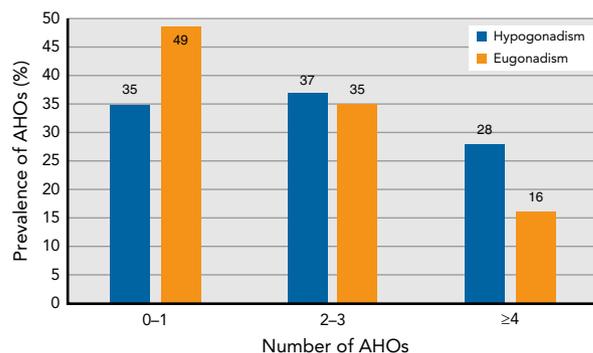
1.62 per additional risk allele), the 95% CIs overlapped substantially. In addition, it is possible that other genetic variants, possibly ones that predispose to testicular dysgenesis syndrome (eg, *INSL3* and *LGR8*),[43–45] may be of higher importance in TCS. As pointed out by Ohlsson et al,[11] the eventual clinical use of these genetic variants will require further investigation. A critical question is the extent to which these polymorphisms might also influence the eventual development of CVD, and not only mediate low testosterone levels. It is important to note that the prevalence of hypogonadism was substantially higher in our survivors (38.5%) compared with subjects included in the meta-analysis by Ohlsson et al[11] (13.5%) (Figure 2). This is despite the fact that the median age of our TCS was only 38 years at the time of clinical evaluation compared with a mean age of 61.7 years for those included in Ohlsson et al.[11] This places TCS at risk of the complications of hypogonadism for many more decades than men without a history of testicular cancer.

Studies of the effect of testosterone replacement therapy on metabolic abnormalities and CVD risk in TCS are sparse. Investigations in middle-aged and highly functioning older men with no cancer history showed favorable effects on lipid metabolism, bone mineral density, muscle mass, and fat-free body mass.[9,10] However, evidence regarding the effect of testosterone replacement on CVD risk has been conflicting,[46] with one clinical trial showing an unexpected increase in adverse CVD events in older men treated with testosterone,[47] but another series reporting no excess CVD events.[48] A recent report from the Testosterone Trials (TTrials) group[49] showed a significantly greater increase in coronary artery noncalcified plaque volume among older men with symptomatic hypogonadism treated with testosterone gel for 1 year compared with placebo.[49] However, none of these trials[47–49] was designed

Table 3. Associations Between AHOs and Hypogonadism[a]

AHO	Status	All Patients n (%)	Hypogonadism		P Value[b]
			Present, n %	Absent, n (%)	
Hypercholesterolemia and on prescription medication	Yes No	56 (11.4) 432 (88.0)	38 (20.1) 151 (79.9)	18 (6.0) 281 (93.0)	**<.001**
Hypertension and on prescription medication	Yes No	67 (13.6) 419 (85.3)	35 (18.5) 152 (80.4)	32 (10.6) 267 (88.4)	**.013**
Erectile dysfunction	Yes No	73 (14.9) 413 (84.1)	37 (19.6) 149 (78.8)	36 (11.9) 264 (87.4)	**.018**
Diabetes and on prescription medication	Yes No	19 (3.9) 458 (93.3)	11 (5.8) 170 (89.9)	8 (2.6) 288 (95.4)	.07
Psychotropic prescription medications for anxiety and/or depression	Yes No	56 (11.4) 435 (88.6)	28 (14.8) 161 (85.2)	28 (9.3) 274 (90.7)	.06
Cardiovascular disease	Yes No	5 (1.0) 466 (94.9)	3 (1.6) 178 (94.2)	2 (0.7) 288 (95.4)	.32
Peripheral vascular disease	Yes No	13 (2.6) 460 (93.7)	7 (3.7) 174 (92.1)	6 (2.0) 286 (94.7)	.24
Thromboembolic disease	Yes No	4 (0.8) 469 (95.5)	1 (0.5) 180 (95.2)	3 (1.0) 289 (95.7)	.58
Renal disease	Yes No	16 (3.3) 452 (92.1)	9 (4.8) 171 (90.5)	7 (2.3) 281 (93.0)	.14
Peripheral neuropathy	Yes No	126 (25.7) 358 (72.9)	58 (30.7) 128 (67.7)	68 (22.5) 230 (76.2)	**.041**
Raynaud phenomenon	Yes No	91 (18.5) 393 (80.0)	42 (22.2) 146 (77.2)	49 (16.2) 247 (81.8)	.11
Benign thyroid disease	Yes No	11 (2.2) 462 (94.1)	4 (2.1) 177 (93.7)	7 (2.3) 285 (94.4)	.90
Tinnitus	Yes No	170 (34.6) 317 (64.6)	66 (34.9) 122 (64.6)	104 (34.4) 195 (64.6)	.94
Hearing impairment	Yes No	156 (31.8) 311 (63.3)	62 (32.8) 119 (63.0)	94 (31.1) 192 (63.6)	.76
Problems with balance/vertigo/dizziness	Yes No	42 (8.6) 428 (87.2)	16 (8.5) 165 (87.3)	26 (8.6) 263 (87.1)	.95

Abbreviation: AHO, adverse health outcome.

[a]Definitions for AHOs are shown in eTable 2. For some AHOs, data were not always available. Overall, <5% of survivors elected not to state whether they had ≥1 of the AHOs; these data were excluded from P value calculations.

[b]Chi-square test was used for calculation of P value. Bold indicates P value <.05.

to prospectively assess adverse cardiovascular events, and moreover, these findings may not apply to considerably younger TCS. For young TCS with symptomatic hypogonadism, testosterone replacement should be considered, and future research is needed to stringently address both the benefits and risks of testosterone replacement therapy. Two studies that examine the effect of testosterone replacement versus placebo on CVD risk factors and various biomarkers have recently started recruiting TCS in Europe (ClinicalTrials.gov identifiers: NCT02991209 and NCT03339635). Although results of these trials may provide some insights, the duration of each is ≤12 months, and thus it is unlikely that they will be able to provide information on the risk of CVD outcomes.

Strengths and Limitations

Strengths of our study include the large number of patients, detailed medical chart abstraction, and evaluation of several risk factors for hypogonadism, including genetic variants. We also used a definition for hypogonadism that is clinically relevant and easily applicable to clinical practice. However, any cross-sectional design has potential limitations and does not allow us to infer causation either of evaluated risk factors to hypogonadism or of hypogonadism to associated AHOs. Although our investigation included many AHOs, by design it was largely focused on cisplatin-related toxicities. Issues such as sexual dysfunction and fertility will be investigated in additional longitudinal follow-up of this cohort. Because blood samples were collected at routine clinic visits, serum testosterone levels were measured only once per patient and did not always occur in the morning as per the recommendation for testosterone testing. Although the SNPs of interest were imputed and not genotyped, they were in perfect linkage disequilibrium with a nearby genotyped SNP.
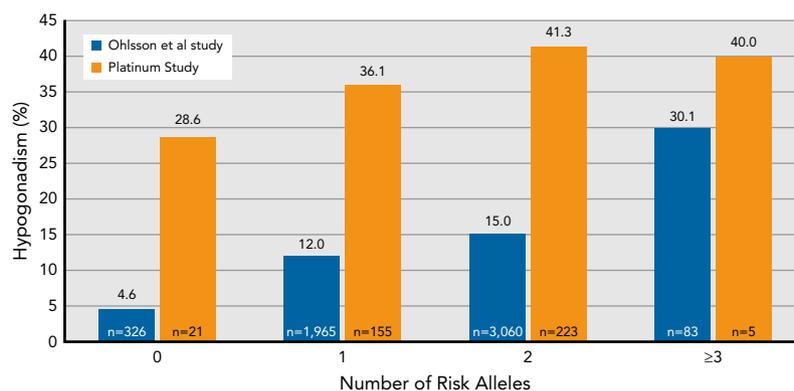
Figure 2. Prevalence of hypogonadism per cumulative number of risk alleles in *SHBG* in the Platinum Study versus Ohlsson et al.[11] Percentage of men with hypogonadism among 404 survivors of testicular cancer compared with 5,434 men in the general population included in a meta-analysis by Ohlsson et al,[11] according to the number of combined risk alleles for rs12150660 (G) and rs6258 (T) in *SHBG*. No survivor in the Platinum Study had 4 risk alleles and only 5 survivors had 3 risk alleles. Odds ratio (OR) per each additional risk allele was 1.26 (95% CI, 0.91–1.76; *P* for trend =.17). This compares with an OR of 1.62 per risk allele in the general population (95% CI, 1.41–1.86; *P* for trend $=6.5\times10^{-12}$).

Conclusions

At a relatively young age, there is a high prevalence of hypogonadism among North American TCS treated with modern cisplatin-based chemotherapy. Major risk factors include increasing age and obesity. Hypogonadism was strongly associated with risk factors for CVD. The clinical value of assessing possible genetic variants in the role of hypogonadism requires further study before these are recommended for use in the clinic. In the meantime, TCS should be encouraged to maintain a normal body weight and a healthy lifestyle. Although there are currently no evidence-based guidelines, Bhasin et al[50] recommend that healthcare providers screen for hypogonadism by surveying TCS for the classic symptoms of hypogonadism (decreased energy, depressed mood, decreased sexual desire and performance, and night sweats)[50] and prescribe testosterone replacement therapy to survivors who have low testosterone levels on 2 occasions and have symptoms related to low testosterone.

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