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ORIGINAL REPORT

Cumulative Burden of Morbidity Among Testicular Cancer Survivors After Standard Cisplatin-Based Chemotherapy: A Multi-Institutional Study

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ABSTRACT

Purpose

In this multicenter study, we evaluated the cumulative burden of morbidity (CBM) among > 1,200 testicular cancer survivors and applied factor analysis to determine the co-occurrence of adverse health outcomes (AHOs).

Patients and Methods

Participants were ≤ 55 years of age at diagnosis, finished first-line chemotherapy ≥ 1 year previously, completed a comprehensive questionnaire, and underwent physical examination. Treatment data were abstracted from medical records. A CBM score encompassed the number and severity of AHOs, with ordinal logistic regression used to assess associations with exposures. Nonlinear factor analysis and the nonparametric dimensionality evaluation to enumerate contributing traits procedure determined which AHOs co-occurred.

Results

Among 1,214 participants, approximately 20% had a high (15%) or very high/severe (4.1%) CBM score, whereas approximately 80% scored medium (30%) or low/very low (47%). Increased risks of higher scores were associated with four cycles of either ifosfamide, etoposide, and cisplatin (odds ratio [OR], 1.96; 95% CI, 1.04 to 3.71) or bleomycin, etoposide, and cisplatin (OR, 1.44; 95% CI, 1.04 to 1.98), older attained age (OR, 1.18; 95% CI, 1.10 to 1.26), current disability leave (OR, 3.53; 95% CI, 1.57 to 7.95), less than a college education (OR, 1.44; 95% CI, 1.11 to 1.87), and current or former smoking (OR, 1.28; 95% CI, 1.02 to 1.63). CBM score did not differ after either chemotherapy regimen ($P = .36$). Asian race (OR, 0.41; 95% CI, 0.23 to 0.72) and vigorous exercise (OR, 0.68; 95% CI, 0.52 to 0.89) were protective. Variable clustering analyses identified six significant AHO clusters (χ^2 $P < .001$): hearing loss/damage, tinnitus (OR, 16.3); hyperlipidemia, hypertension, diabetes (OR, 9.8); neuropathy, pain, Raynaud phenomenon (OR, 5.5); cardiovascular and related conditions (OR, 5.0); thyroid disease, erectile dysfunction (OR, 4.2); and depression/anxiety, hypogonadism (OR, 2.8).

Conclusion

Factors associated with higher CBM may identify testicular cancer survivors in need of closer monitoring. If confirmed, identified AHO clusters could guide the development of survivorship care strategies.

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INTRODUCTION

The number of cancer survivors has increased markedly in recent decades, with an estimated 18 million in the United States by 2022.[1] Given these increasing numbers, having an understanding and quantifying the late effects of cancer and its treatment to inform survivorship care strategies are important. An important population in which to assess adverse health outcomes (AHOs) are survivors of testicular cancer, the most common cancer in men ages 18 to 39 years.[2] Since effective cisplatin-based chemotherapy was introduced in the 1970s,[3] the overall age-adjusted 5-year relative survival rate is > 95%,[4] and survivors remain at risk for decades for the late effects of cancer and its treatment. Characterization of AHOs is

ASSOCIATED CONTENT

Appendix

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facilitated by the homogeneity of treatment regimens. For four decades, therapy for advanced testicular cancer typically has consisted of platinum-based chemotherapy. For good-risk disease, standard treatment comprises either three cycles of bleomycin, etoposide, and cisplatin (BEP × 3) or four cycles of etoposide plus cisplatin (EP × 4), whereas for intermediate- or poor-risk testicular cancer, four cycles of BEP (BEP × 4) or four cycles of etoposide, ifosfamide, and cisplatin (VIP × 4) are administered.[5,6] Although treatment of good-risk testicular cancer with BEP × 3 versus EP × 4 results in lower cisplatin exposure, it is accompanied by potential bleomycin adverse effects.[7] To our knowledge, no study has evaluated the cumulative burden of morbidity (CBM) after BEP × 4 versus VIP × 4 or after BEP × 3 versus EP × 4 and has taken into account both the number and the severity of AHOs. Such characterization is important to develop risk-stratified, evidence-based follow-up recommendations. Moreover, as noted previously,[8] a better understanding of AHOs may help to guide testicular cancer management, especially in the controversial area of whether good-risk patients should receive EP × 4 or BEP × 3.

To provide new information about CBM after contemporary cisplatin-based chemotherapy for testicular cancer, we examined both the number and the severity of AHOs among 1,214 testicular cancer survivors enrolled in the Platinum Study, a large, multicenter clinical investigation.[9] We evaluated the co-aggregation of AHOs to identify co-occurring clusters and identified clinical, sociodemographic, and behavioral factors associated with an elevated CBM.

PATIENTS AND METHODS

Study Population

The Platinum Study was approved by each participating institution's institutional review board, and all participants provided written informed consent. The cohort was described in detail previously.[2,10] Briefly, eligible testicular cancer survivors had a histologic/serologic diagnosis of germ cell tumor, were age ≤ 55 years at diagnosis, completed first-line cisplatin-based chemotherapy ≥ 1 year previously, and were undergoing routine follow-up at the participating site. All participants are referred to as testicular cancer survivors. At study enrollment, participants reported current prescription medication use with indication, underwent a brief physical examination, and completed comprehensive health questionnaires. Cancer diagnosis and treatment data were abstracted from medical records (Appendix, online only). Testicular cancer survivors indicated the average time per week of participating in various physical activities during the past year.[11,12] These activities were grouped into vigorous (≥ 6 metabolic equivalent tasks) and nonvigorous (< 6 metabolic equivalent tasks) activities (Appendix).[13]

Measurement of AHOs

Participant responses were mapped to individual AHOs and graded according to severity on a 0 to 4-point scale using a modified version of the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03)[14] as in prior studies.[15,16] A multidisciplinary panel of experts agreed on all grades (C.F., H.D.S., D.M.S., S.D.F., L.H.E., and L.B.T.). Appendix Table A1 (online only) lists individual AHOs and grading criteria.[15,16] If no response was provided (< 1%), the AHO was conservatively treated as no symptom/diagnosis. CBM score was calculated on the basis of the number and severity of AHOs by following methods adapted from Geenen et al[15] (Appendix Table A2, online only). A secondary CBM score, CBM_{Pt}, was calculated using AHOs previously related to cisplatin exposure (ie, peripheral sensory neuropathy, autonomic neuropathy, hearing damage, tinnitus, kidney disease).[17,18]

Statistical Analysis

Discrete and continuous data were described using numbers (percentages) and medians (ranges), respectively. Sociodemographic, health behavior, and treatment variables were individually tested for association with CBM score using t (continuous variables) or Pearson's χ^2 (categorical variables) test. Variables then were combined in a multivariable ordinal logistic regression model, with CBM score as the dependent variable. Unless otherwise noted, variables with Wald χ^2 P value ≥ .1 in the full model were removed from the final model. In the latter, the very high and severe CBM categories were collapsed given sparse data. Multivariable models that investigated the effect of cumulative cisplatin dose on CBM_{Pt} score included the same covariates as the main model, except that chemotherapy regimen was omitted given its strong correlation with cumulative cisplatin dose.

Ordinal logistic regression examined the relationship between CBM score and self-reported health (the dependent variable). For all ordinal logistic regression models, the assumption of proportionality of odds across response categories was confirmed by comparing the Bayesian information criterion for the proportional odds model to that from a partial proportional odds model. Stata 14.1 software (StataCorp; College Station, TX) was used for all descriptive statistics and regression analyses.

Cluster analysis of variables was performed with nonlinear factor analysis and the nonparametric conditional item-pair covariance method of the cross-validated dimensionality evaluation to enumerate contributing traits procedure (Appendix). Each AHO was dichotomized: grades 0 and 1 were combined, and grades 2, 3, and 4 were combined. Because of sparse numbers, transient ischemic attack and stroke were collapsed into a single AHO; hypertriglyceridemia and hypercholesterolemia were combined into hyperlipidemia. Average item-pair odds ratios (ORs) were calculated by averaging the log OR across AHO pairs and then by exponentiating the average value.

RESULTS

Median age at evaluation for 1,214 testicular cancer survivors was 37 years (range, 18 to 74 years), and median time since chemotherapy completion was 4.2 years (range, 1 to 30 years; Table 1). Of all participants, 1,157 (95.3%) were seen in the clinic during routine follow-up care, and approximately 90% completed chemotherapy within 15 years of enrollment. Most participants (1,035 [85.3%]) received BEP × 3 (460 [37.9%]), BEP × 4 (222 [18.3%]), or EP × 4 (353 [29.1%]); 44 received VIP, typically four cycles (n = 32). Median cumulative cisplatin dose was 400 mg/m^2, with approximately one third receiving 300 mg/m^2 (447 [36.8%]). Retroperitoneal lymph node dissection was performed in 46.3% of participants. Most survivors were white (85.3%), married/living as married (61.0%), employed (88.7%), and educated beyond high school (88.3%).

The most prevalent AHOs of any severity were obesity (41.7% grade 2, 26.0% grade 3, 3.9% grade 4), sensory neuropathy (28.3% grade 1, 14.5% grade 2, 13.4% grade 3), tinnitus (25.0% grade 1, 7.1% grade 2, 7.5% grade 3), and hearing damage (24.5% grade 1, 13.5% grade 2, 1.2% grade 3; Table 2). Raynaud phenomenon occurred in approximately 33% of participants (15.6% grade 1, 8.7% grade 2, 9.1% grade 3) and pain in approximately 25% (13.6% grade 1, 9.8% grade 2, 1.5% grade 3). Hypogonadism (10.2% grade 2) and erectile dysfunction (15.9% grade 1, 12.5% grade 2) also were observed.

Table 1. Clinical, Sociodemographic, and Health Behavior Characteristics of 1,214 Survivors of Cisplatin-Treated Germ Cell Tumors

Clinical Characteristic	No. (%)
Age at diagnosis, years[a]	
Median (range)	30 (15-60)
< 20	89 (7.3)
20-29	482 (39.7)
30-39	403 (33.2)
≥ 40	232 (19.2)
Age at evaluation, years	
Median (range)	37 (18-74)
< 20	9 (0.7)
20-29	265 (21.8)
30-39	436 (35.9)
40-49	314 (25.9)
50-59	164 (13.5)
60-69	26 (2.1)
Calendar year of diagnosis[b]	
Before 2000	146 (12.0)
2000-2004	145 (11.9)
2005-2009	317 (26.1)
2010-2016	598 (49.3)
Histologic type	
Seminoma	310 (25.5)
Nonseminoma	885 (72.9)
Not otherwise specified	19 (1.6)
Tumor site[c]	
Testis	1,069 (88.1)
Extragonadal	135 (11.1)
Type of cisplatin-based chemotherapy[d]	
BEP, cycles	710 (58.5)
≤ 2	21
3	460
4	222
≥ 5	7
EP, cycles	388 (32.0)
≤ 3	23
4	353
≥ 5	12
VIP, cycles	44 (3.6)
3	4
4	32
≥ 5	8
Other[e], cycles	69 (5.7)
≤ 2	11
3	8
4	41
≥ 5	9
Cumulative dose of cisplatin, mg/m^2[f]	
Median (range)	400 (100-828)
< 300	61 (4.9)
300	447 (36.8)
301-399	44 (3.2)
400	589 (48.5)
> 400	55 (4.4)
Retroperitoneal lymph node dissection[g]	
Yes	562 (46.3)
No	639 (52.6)
Time since completion of chemotherapy, years[h]	
Median (range)	4.2 (1-30)
< 2	329 (27.1)
2-5	423 (34.8)
6-9	186 (15.3)
≥ 10	261 (21.5)
Sociodemographic characteristic	
Race[i]	
White	1,036 (85.3)
African American	16 (1.3)
Asian	59 (4.9)
Other	68 (5.6)
Marital status[j]	
Single or never married	389 (32.0)
Married/living as married	740 (61.0)
Widowed, divorced, separated	70 (5.8)
Education[k]	
High school or less	139 (11.5)
After high school but not college graduate	289 (23.8)
College or university graduate	508 (41.9)
Postgraduate	275 (22.7)
Employment status[l]	
Unemployed	74 (6.1)
Employed	1,077 (88.7)
Retired	15 (1.2)
On disability leave	30 (2.5)
Health behavior	
Smoking status[m]	
Never	714 (58.8)
Former	392 (32.3)
Current	107 (8.8)
Average No. of alcoholic drinks in past year[n]	
Rarely or never	239 (19.7)
1-3/mo	180 (14.8)
1-6/wk	569 (46.9)
≥ 1/d	218 (18.0)
Engage in vigorous physical activity (≥ 6 METs)[o]	
Yes	835 (68.8)
No	378 (31.1)

(continued in next column)

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; MET, metabolic equivalent task; VIP, etoposide, ifosfamide, and cisplatin.

[a]Age at diagnosis was not available for eight participants.

[b]Year of diagnosis was not available for eight participants.

[c]Tumor site was not available for 10 participants.

[d]Of the 52 participants treated with VIP × 4, 44% had mediastinal disease, whereas 47% had disease confined to the testis; in the remainder (9%), other extragonadal sites were involved. This contrasts with the smaller percentage of participants with mediastinal disease (ie, ≤ 7.2%) in the other treatment groups.

[e]Other chemotherapy regimens were cisplatin and ifosfamide (n = 25); cisplatin, vinblastine, and bleomycin (n = 6); ifosfamide, bleomycin, cisplatin, and etoposide (n = 6); and other cisplatin-based regimens (n = 32). The number of cycles was not available for four participants who received a chemotherapy regimen designated as other.

[f]Cumulative dose of cisplatin was not available for 18 participants.

[g]Retroperitoneal lymph node dissection status was not available for 13 participants.

[h]Time since completion of chemotherapy was not available for 15 participants.

[i]Race was not stated for 19 participants.

[j]Marital status was not stated for 15 participants.

[k]Education status was not stated for three participants.

[l]Employment status was not stated for 18 participants.

[m]Smoking status was not stated for one participant.

[n]Alcohol consumption was not stated for eight participants.

[o]Exercise was assessed in this study with a validated questionnaire[11,12] that asks participants to report their average time per week (over the past year) spent at each of nine recreational activities: walking or hiking (including walking to work); jogging (> 10 min/mile); running (≤ 10 min/mile); bicycling (including stationary bike); aerobic exercise/dance or exercise machines; lower-intensity exercise, yoga, stretching, or toning; tennis, squash, or racquetball; lap swimming; and weight lifting or strength training. Each physical activity was assigned a MET value, which is a commonly used metric for describing the relative energy expenditure of a specific type of physical activity (1 MET = 1 kcal/kg/h or the energy cost of sitting quietly). The MET values for each activity were then used to calculate MET-h/wk for each participant, and these were grouped into categories of vigorous or nonvigorous physical activity according to standard definitions.[13] Physical activity was not stated for one participant.

Table 2. Prevalence of Adverse Health Outcomes By Severity Grade

Adverse Health Outcome	Severity Grade, No. (%)				
	All	1	2	3	4
Peripheral sensory neuropathy*	683 (56.3)	344 (28.3)	176 (14.5)	163 (13.4)	NA†
Autonomic neuropathy‡§	323 (26.6)	234 (19.3)	68 (5.6)	21 (1.7)	NA
Hearing damage‡	476 (39.2)	297 (24.5)	164 (13.5)	15 (1.2)	0
Tinnitus‡	481 (39.6)	304 (25.0)	86 (7.1)	91 (7.5)	NA
Raynaud phenomenon‡	405 (33.4)	189 (15.6)	105 (8.7)	111 (9.1)	NA
Pain*	302 (24.9)	165 (13.6)	119 (9.8)	18 (1.5)	NA
Kidney disease*	30 (2.5)	27 (2.2)	3 (0.3)	NA	NA
Hypercholesterolemia*	96 (7.9)	NA	96 (7.9)	NA	NA
Hypertriglyceridemia*	6 (0.5)	NA	6 (0.5)	NA	NA
Hypertension*	114 (9.4)	NA	114 (9.4)	NA	NA
Diabetes*	37 (3.0)	NA	20 (1.7)	17 (1.4)	NA
Coronary artery disease*	20 (1.6)	4 (0.3)	7 (0.6)	9 (0.7)	NA
Transient ischemic attack‡	8 (0.7)	8 (0.7)	NA	NA	NA
Stroke‡	6 (0.5)	NA	6 (0.5)	NA	0
Peripheral artery disease*	56 (4.6)	27 (2.2)	14 (1.2)	15 (1.2)	NA
Thromboembolic event*	88 (7.2)	NA	44 (3.6)	44 (3.6)	NA
Obesity‖	868 (71.5)	NA¶	506 (41.7)	315 (26.0)	47 (3.9)
Thyroid disease*	39 (3.2)	20 (1.7)	19 (1.6)	NA	NA
Anxiety and/or depression#	75 (6.2)	NA	75 (6.2)	NA	NA
Erectile dysfunction*	345 (28.4)	193 (15.9)	152 (12.5)	NA	NA
Hypogonadism#	124 (10.2)	NA	124 (10.2)	NA	NA

Abbreviation: NA, not applicable.
*On the basis of patient-reported outcomes and prescription medication use.
†NA because data needed to assign these toxicities according to the Common Terminology Criteria for Adverse Events (version 4.03) definitions were not captured in the current study.
‡On the basis of patient-reported outcomes.
§Among participants with grade 0, 1, 2, and 3 autonomic neuropathy, 22, seven, two, and one, respectively, reported that they take a β-blocker.
‖Calculated using weight and height assessments from the physical examination conducted at clinical evaluation.
¶Common Terminology Criteria for Adverse Events (version 4.03) does not include a grade 1 for obesity.
#On the basis of prescription medication use.

Figure 1 shows the CBM scores. Approximately 20% of participants had a high (180 [14.8%]), very high (46 [3.8%]), or severe (one [0.1%]) score, whereas 76% had a very low (104 [8.6%]), low (458 [37.7%]), or medium (360 [29.7%]) score. Only 5.4% of participants had no AHOs. All 47 with a very high or severe CBM score had grade 4 obesity.

Bivariable associations of clinical, sociodemographic, and health behavior factors with CBM score are shown in Appendix Table A3 (online only). In a multivariable model (Table 3) that controlled for time since chemotherapy and enrollment center, the following were significantly associated with higher CBM score: older attained age (OR, 1.18 per 5 years), BEP × 4 (OR, 1.44 *v* BEP × 3), VIP × 4 (OR, 1.96 *v* BEP × 3), less than a college-level education (OR, 1.44), current disability leave (OR, 3.53), and former or current smoking status (OR, 1.28). Although the OR for VIP × 4 was slightly higher than that for BEP × 4, the difference was not significant ($P = .36$). Disease stage was not associated with CBM score ($P = .48$), which suggests that increased scores after BEP × 4 or VIP × 4 were not explained by more-advanced tumor status. CBM scores after EP × 4 and BEP × 3 were similar ($P = .65$). No significant differences were observed for individual AHOs except Raynaud phenomenon ($P < .001$), for which prevalence and severity after BEP × 3 (183 [39.8%]: 18.5% grade 1, 10.4% grade 2, 10.9% grade 3) exceeded EP × 4 (84 [23.8%]: 12.2% grade 1, 16.8% grade 2, 4.8% grade 3).

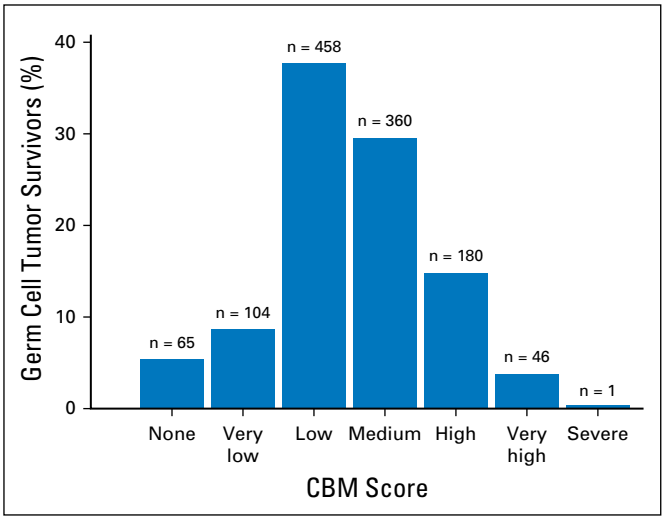

Fig 1. Distribution of cumulative burden of morbidity (CBM) score among 1,214 participants in the Platinum Study.

Asian race (OR, 0.41) and vigorous exercise (OR, 0.68) were inversely associated with higher CBM score. Lower risk in Asian testicular cancer survivors reflects that fewer participants had higher severity grades for 15 of 22 AHOs versus white survivors (eg, peripheral sensory neuropathy: 8.5% *v* 13.5% grade 3; hearing loss: 8.5% *v* 14.1% grade 2, 0% *v* 1.2% grade 3). Similar trends were observed for autonomic neuropathy, tinnitus, Raynaud phenomenon, pain, kidney disease, hypertension, coronary artery disease, peripheral artery disease, obesity, thyroid disease, depression/anxiety, erectile dysfunction, and hypogonadism.

The relationship between cumulative cisplatin dose and overall CBM score was of borderline significance (OR per 100 mg/m^2,

Table 3. Multivariable Ordinal Logistic Regression of Factors Associated With Cumulative Burden of Morbidity Score

Variable	OR (95% CI)	*P*
Age at evaluation (per 5 years)*	1.18 (1.10 to 1.26)	**< .001**
Time since chemotherapy completion, years		
< 2	Ref.	—
2-5	0.91 (0.68 to 1.23)	.540
6-9	0.61 (0.42 to 0.89)	**.010**
≥ 10	0.55 (0.38 to 0.85)	**.002**
Race		
White	Ref.	—
Black/African-American	1.56 (0.49 to 5.03)	.450
Asian	0.41 (0.23 to 0.72)	**.002**
Other	1.05 (0.63 to 1.76)	.840
Education		
College or postcollege graduate	Ref.	—
Less than college education	1.44 (1.11 to 1.87)	**.006**
Current employment status		
Employed	Ref.	—
Unemployed	0.90 (0.55 to 1.47)	.660
Retired	1.10 (0.36 to 3.39)	.870
Disability leave	3.53 (1.57 to 7.95)	**.002**
Smoking status		
Never	Ref.	—
Current or former	1.28 (1.02 to 1.63)	**.037**
Vigorous physical activity (≥ 6 METs)†		
No	Ref.	—
Yes	0.68 (0.52 to 0.89)	**.004**
Retroperitoneal lymph node dissection‡		
No	Ref.	—
Yes	0.88 (0.69 to 1.12)	.310
Type of chemotherapy§, × No. of cycles		
BEP × 3	Ref.	—
EP × 4	1.09 (0.75 to 1.60)	.650
BEP × 4	1.44 (1.04 to 1.98)	**.028**
VIP × 4	1.96 (1.04 to 3.71)	**.039**

NOTE. ORs and *P* values are from an adjusted model that includes all other variables listed in the table as well as enrollment center, with cumulative burden of morbidity score as the outcome (dependent) variable. The very high and severe categories were collapsed because of sparse data. Analysis includes 1,013 (83.4%) testicular cancer survivors with nonmissing data for all variables in the model. Boldface indicates significance at $P < .05$.

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; EP, etoposide plus cisplatin; MET, metabolic equivalent task; OR, odds ratio; Ref., reference; VIP, etoposide, ifosfamide, and cisplatin.

*Age at diagnosis was not included in the model given the strong correlation with age at evaluation ($r = 0.81$), which was included.

†See Table 1 footnote o and the Appendix for details on the assessment of physical activity.

‡Retroperitoneal lymph node dissection was retained in the multivariable model to control for potential residual confounding given its correlation with chemotherapy regimen ($P < .001$); approximately 34%, 55%, 66%, and 44% of testicular cancer survivors treated with BEP × 3, EP × 4, BEP × 4, and VIP × 4, respectively, had a retroperitoneal lymph node dissection.

§Disease stage was not significantly associated with cumulative burden of morbidity score ($P = .48$), which suggests that increased scores after BEP × 4 or VIP × 4 were not explained by a more-advanced tumor status.

1.16; 95% CI, 0.99 to 1.37; $P = .064$) in the multivariable model. However, when limited to conditions previously attributed to cisplatin,[14,15] each 100 mg/m^2 increase in cumulative dose was associated with significantly worse CBM_{Pt} (OR per 100 mg/m^2, 1.34; 95% CI, 1.14 to 1.58; $P < .001$).

Increasing CBM score was significantly associated with worse self-reported health. Compared with testicular cancer survivors with a score of 0, the risk of worse self-reported health among those scored as very low, low, medium, high, or very high/severe was 1.94 (95% CI, 1.08 to 3.48), 2.82 (95% CI, 1.72 to 4.62), 5.91 (95% CI, 3.56 to 9.81), 10.90 (95% CI, 6.28 to 18.93), and 34.17 (95% CI, 16.54 to 70.62), respectively.

Results from both variable clustering methods converged in the analysis of AHOs to yield six major groups of signs/symptoms (χ^2 for model fit, $P < .001$), with pairwise ORs for given clusters as follows: hearing loss/damage, tinnitus (OR, 16.3); metabolic disorders (diabetes, hypertension, hyperlipidemia; OR, 9.8); neuropathy and related conditions (sensory neuropathy, autonomic neuropathy, pain, Raynaud phenomenon; OR, 5.5); cardiovascular disease (CVD) and related conditions (coronary artery disease, stroke, kidney disease, peripheral artery disease, thromboembolism, obesity; OR, 5.0); erectile dysfunction, thyroid disease (OR, 4.2); and hypogonadism, depression/anxiety (OR, 2.8). Clusters hearing loss/damage, tinnitus and neuropathy and related conditions, although distinct, were strongly correlated ($r = 0.658$; $P < .001$), as were clusters erectile dysfunction, thyroid disease and hypogonadism, depression/anxiety ($r = 0.914$; $P < .001$).

DISCUSSION

To our knowledge, the results are based on the largest study to date in testicular cancer survivors administered contemporary cisplatin-based chemotherapy. We characterize the CBM by showing that even at a young age, approximately one in five patients has a score of high to severe, with only 5% reporting no AHOs. Although CBM was higher in participants treated with BEP × 4 or VIP × 4 (*v* BEP × 3), scores did not differ significantly between the two regimens ($P = .36$). CBM score also did not differ between BEP × 3 and EP × 4, the standard approaches for good-risk disease. The higher prevalence and severity of Raynaud phenomenon after BEP × 3 is consistent with the known relationship with bleomycin,[7] although Raynaud phenomenon also may be related to cisplatin.[19] Increasing cumulative cisplatin dose significantly increased risk for a higher CBM score for AHOs related to neuropathy, ototoxicity, and kidney disease. The strong association between higher CBM score and worse self-reported health indicates that the score reflects a health status perceptible to patients. These and other new findings are discussed next.

Previous US investigations of testicular cancer survivors[2,20-24] have been limited in scope, generally by either not addressing AHOs[21,23,24] or evaluating fewer than five conditions[22] (Appendix Table A4, online only). Although three studies obtained treatment information from medical records, only Oh et al[22] (143 patients) examined AHOs (n = 4) by therapy. Hashibe et al[20] evaluated AHOs through linkage with International Classification of Diseases, Ninth Revision, codes, but results were not presented by treatment, and only 168 patients received chemotherapy (type unspecified). In contrast, we evaluated a wide spectrum of AHOs by type and severity among > 1,200 testicular cancer survivors with detailed treatment information. The resultant CBM score comprises a range of AHOs likely related to testicular cancer and its treatment and to long-term platinum retention. After chemotherapy completion, circulating serum platinum remains measurable at levels up to 1,000 times above normal for 20 years.[25] Ongoing endothelial cell and vascular damage[26] occur for many years, and long-term serum platinum levels have been significantly related to neuropathy,[27] hypertension,[28] and hypercholesterolemia.[28]

Because testicular cancer occurs largely in white males,[29] data on Asian patients are sparse. Decreased risks of a higher CBM score in Asian versus white testicular cancer survivors largely reflect the lower occurrence of high-severity grades in Asians for most AHOs. These include known treatment-related toxicities, which possibly reflects differences in drug absorption, distribution, metabolism, and excretion, among others. Although we adjusted for sociodemographic and health behavior factors, other unmeasured influences may have accounted for this finding, which remain to be confirmed.

Although the CBM score was slightly higher after VIP × 4 than after BEP × 4, the difference was not significant ($P = .36$). Both are standard chemotherapy regimens for intermediate- and poor-risk disease[5,6] and show equivalent survival. Although an early, randomized trial showed that VIP × 4 is associated with greater acute toxicity than BEP × 4,[30] no study has subsequently addressed long-term AHOs as we have done. Additional follow-up, as planned for this cohort, is required to quantify further the CBM associated with each regimen. CBM also was similar for BEP × 3 versus EP × 4, the two commonly applied regimens for good-risk disease. In a curable disease such as testicular cancer with a long life expectancy and equivalent therapy options, the availability of AHO data becomes increasingly important to inform treatment decisions.[8]

The striking association between CBM score and self-reported health indicates that the score captures outcomes that affect patients' self-perception of health. The risk of worse self-reported health among patients with very high/severe CBM scores rose to > 30-fold compared with those with a score of 0. These results also underscore the need to assess outcomes that affect self-perceived health because these can guide the development of survivorship care strategies that patients value.

To our knowledge, we have performed the first variable-based factor analysis of AHOs in long-term cancer survivors. Prior analyses have largely been conducted in patients either during cancer treatment,[31,32] shortly after therapy completion,[33,34] or during palliative/hospice care.[35] Only Kim et al[36] evaluated patients who were either 2 to 5 years (n = 66) or > 5 years (n = 56) postcancer diagnosis, although some were still undergoing treatment. Factor analysis provides insights into groups of conditions that may co-occur and perhaps share etiology. For example, hearing loss and tinnitus reflect known cisplatin-associated damage to the auditory system.[10,37] Associations between neuropathy and Raynaud phenomenon have been reported in individuals with no chemotherapy exposure,[38,39] although the biologic basis is incompletely understood, and co-occurrence could reflect symptom cross-reporting. Pain is frequently associated with chemotherapy-induced peripheral neuropathy, with no agents currently available for prevention or treatment.[40]

The cluster of hyperlipidemia, hypertension, and diabetes present at the time of clinical evaluation represents components of the metabolic syndrome,[41] consistent with studies that report increased metabolic syndrome risk among European testicular cancer survivors.[42-45] The co-occurrence of AHOs related to CVD supports European investigations who showed a 1.4-fold to sevenfold higher CVD risk among cisplatin-treated testicular cancer survivors versus either the general population or patients managed with surgery alone.[26,46-49] Presentation with one or more of these AHOs suggests closer screening for other cluster-related conditions that could signal an elevated risk for CVD morbidity and mortality.[7] Hypogonadism and depression, respectively, represent a biologic consequence of testicular cancer treatment[50,51] and possibly associated psychological outcomes. A potential relationship between hypogonadism and depression in the general population has been recognized, with other symptoms including muscle weakness and loss of energy.[52-56]

An association of erectile dysfunction and thyroid disease has not been previously shown in testicular cancer survivors as it has in noncancer populations.[57-63] Of 39 testicular cancer survivors with thyroid disease, 33 and six reported hypothyroidism and hyperthyroidism, respectively. Although associations of hypothyroidism[57,62,63] and hyperthyroidism[57,61-63] with erectile dysfunction were observed in several studies in noncancer populations, a relationship with hypothyroidism was not confirmed in the largest investigation to date,[61] possibly because of the low prevalence, and requires additional investigation.

The strong association between vigorous physical activity and lower CBM score as well as with a reduced absolute number of AHOs in prior analyses[2] can inform future intervention strategies. Studies of childhood cancer survivors have shown that exercise reduces the risk of late effects, such as CVD,[64] and the same likely applies to testicular cancer survivors. The apparent inverse relation between increased risk of a high CBM score and follow-up time is due to the disproportionate contribution of early-onset toxicities (eg, neuropathy, tinnitus), which are more prevalent than later-onset toxicities (eg, hypercholesterolemia, hypertension), which reflects the relatively short median follow-up time and young cohort age.

A major strength of this study is the estimation of both the number and the severity of AHOs in a large testicular cancer survivorship cohort treated primarily with EP × 4, BEP × 3, BEP × 4, or VIP × 4 chemotherapy regimens. Other strengths include the high participation rate (93%), detailed medical chart abstraction, and estimation of risk without the confounding effect of radiotherapy. An inherent limitation to all cross-sectional studies is the inability to assess causality between clinical, sociodemographic, and health behavior characteristics and CBM score. AHOs largely were self-reported without baseline data, similar to previous testicular cancer survivorship studies.[21,23,65] As in Geenen et al,[15] a limitation is that we could not compare the CBM score with that of a normative population given the unavailability of data. Equivalent weight was assigned to all AHOs, whereas testicular cancer survivorship may weigh these differently; some AHOs capture symptoms that can markedly affect survivors (eg, neuropathy), whereas others encompass conditions treated by medications that may be less bothersome (eg, hypertension). Additional studies are needed to investigate the effect of specific AHOs on health-related quality of life in this understudied population.

In conclusion, at a median follow-up of only 4.2 years, approximately one in five testicular cancer survivors have a CBM score of high, very high, or severe. Of note, no difference in CBM score was observed among survivors who received BEP × 4 versus VIP × 4 chemotherapy or among those given EP × 4 versus BEP × 3, although the long-term monitoring of patients is important. The value of variable clustering analysis in revealing the co-occurrence of AHOs is underscored by our findings and should be considered for other groups of long-term cancer survivors to highlight potential areas of research into the mechanistic bases of toxicities. Ongoing genetic research in the current cohort has already begun to characterize biologic pathways that underlie cisplatin-related

toxicities[66,67] and that can identify new research opportunities aimed at developing agents to prevent, mitigate, and treat adverse sequelae not only among testicular cancer survivors but also among other survivors after cisplatin-based chemotherapy. In the interim, if confirmed, the current results could inform survivorship care strategies and assist health care providers in identifying conditions, or groups of conditions, for which to screen, counsel, and treat testicular cancer survivors.

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Cumulative Burden of Morbidity Among Testicular Cancer Survivors After Standard Cisplatin-Based Chemotherapy: A Multi-Institutional Study

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Appendix

Methods

Study Population

All participants received first-line cisplatin-based chemotherapy for either initial germ cell tumor or recurrence after active surveillance. Participants could not have received subsequent salvage chemotherapy, radiotherapy, or antecedent chemotherapy for another primary cancer. All participants were disease free at the time of clinical assessment.

Data Collection From Medical Records and Clinical Evaluation

Study personnel were trained in person to abstract data using a standard protocol and forms modified from previous investigations[11] (Travis LB, et al: J Natl Cancer Inst 86:1450-1457, 1994; Travis LB, et al: J Natl Cancer Inst 87:524-530, 1995; Travis LB, et al: N Engl J Med 340:351-357, 1999; Travis LB, et al: J Natl Cancer Inst 94:182-192, 2002). Detailed data on cancer diagnosis and treatment, including names and doses of all cytotoxic drugs were abstracted directly from medical records.

Sociodemographic Characteristics, Patient-Reported Health Outcomes, and Lifestyle Behaviors

Patient-reported outcomes and lifestyle behaviors were assessed through self-reporting using validated questionnaires.[11,12,68-71] To minimize recall bias, we applied strict definitions to assessment times. Validated questionnaires that queried symptoms over the past 4 weeks were selected, and for those adverse health outcomes (AHOs) for which Common Terminology Criteria for Adverse Events (version 4.03) grading took into account prescription medication use (ie, peripheral sensory neuropathy, pain, kidney disease, hypercholesterolemia, hypertriglyceridemia, hypertension, diabetes, peripheral artery disease, thromboembolic event, thyroid disease, anxiety/depression, erectile dysfunction, hypogonadism), we only took into account current prescription medication use (with usage for $>$ 1 month), with data provided by the patient at the time of clinical assessment. For sociodemographic characteristics, we assessed current marital and employment status. Self-reported race and education level were determined at the time of enrollment. For health behaviors, we used standardized questions drawn from validated survey tools to assess current or former smoking status, alcohol consumption, and physical activity over the past year.

For health behaviors, we used validated questionnaires to assess current or former smoking status, alcohol consumption, and physical activity over the past year. Exercise was assessed with a validated questionnaire[11,12] that asked participants to report their average time per week (over the past year) spent in each of nine recreational activities: walking or hiking (including walking to work); jogging ($>$ 10 min/mile); running ($\leq$ 10 min/mile); bicycling (including stationary bike); aerobic exercise/dance or exercise machines; lower-intensity exercise, yoga, stretching, or toning; tennis, squash, or racquetball; lap swimming; and weight lifting or strength training. Each physical activity was assigned a metabolic equivalent task (MET) value, which is a commonly used metric for describing the relative energy expenditure of a specific type of physical activity (1 MET = 1 kcal/kg/h or the energy cost of sitting quietly).[11] The MET values for each activity were then used to calculate MET-hours per week for each participant, and these were grouped into categories of vigorous or nonvigorous physical activity according to standard definitions (Ainsworth, et al: Med Sci Sports Exerc 43:1575-1581, 2011).

Measurement of AHOs

Symptoms related to a single underlying condition were grouped to avoid overcounting (eg, coronary artery disease was defined as a single AHO by combining coronary artery disease, angina, heart attack or myocardial infarction, and related procedures). For 12 AHOs in which current prescription medication use determined grade, medications were only considered if participants started use during or after cancer treatment.

Statistical Analysis

Nonlinear factor analysis used the probit link and WLSMV (weighted least squares means and variance) estimation with Mplus software (Muthén, et al: 2017) and the nonparametric conditional item-pair covariance method of the cross-validated dimensionality evaluation to enumerate contributing traits procedure (Monahan, et al: Appl Psychol Meas 31:483-503, 2007; Zhang, et al: Psychometrika 64:213-249, 1999) using the expl.detect function from the sirt (supplementary item response theory) R package (https://CRAN.R-project.org/package=sirt) and its default N.est option of a 50-50 split in training and validation data sets for replications.

Table A1. AHOs That Comprise the Cumulative Burden of Morbidity Score

AHO and Platinum Study Items Used to Assign Severity Grade	Grade			
	1	2	3	4
Peripheral sensory neuropathy	A little	Quite a bit	Very much	NA
Tingling fingers/hands or toes/feet*				
Numbness in fingers/hands or toes/feet*				
Shooting or burning pain in fingers/hands or toes/feet*				
Difficulty with distinguishing between hot and cold water*				
Problems with standing/walking because of difficulty feeling ground under feet*				
Pain and tingling in fingers/hands or toes/feet†				
Prescription medication use‡				
Autonomic neuropathy	A little	Quite a bit	Very much	NA
Dizzy when standing up from a sitting or lying position*				
Hearing loss/damage	A little (difficulty hearing or reduced hearing) or yes (persistent dizziness or vertigo)	Quite a bit or very much (difficulty hearing or reduced hearing)	Hearing loss that requires a hearing aid in one or both ears or complete deafness in one ear	Complete deafness in both ears
Difficulty hearing*				
Reduced hearing†				
Hearing loss that requires a hearing aid§				
Complete deafness§				
Persistent dizziness or vertigo§				
Tinnitus	A little	Quite a bit	Very much	NA
Ringing in ears†				
Raynaud phenomenon	A little	Quite a bit	Very much	NA
White, cold fingers/hands or toes/feet when it is cold†				
Pain	A little bit	Moderately or quite a bit or medication use	Extremely	NA
How much pain interferes in normal work (including work outside the home, inside the house, in the yard)‖				
Prescription medication use‡				
Kidney disease	Have condition	Have condition and medication use	NA	NA
Told by physician of condition				
Prescription medication use‡				
Hypercholesterolemia	NA	Have condition and medication use	NA	NA
Told by physician of condition				
Prescription medication use for high total cholesterol or low HDL cholesterol‡				
Hypertriglyceridemia	NA	Medication use for condition	NA	NA
Prescription medication use‡				
Hypertension	NA	Have condition and medication use	NA	NA
Told by physician of condition				
Prescription medication use‡				
Diabetes	NA	Have condition and taking tablets or pills	Have condition and taking insulin	NA
Told by physician of condition				
Prescription medication use‡				

(continued on following page)

Table A1. AHOs That Comprise the Cumulative Burden of Morbidity Score (continued)

AHO and Platinum Study Items Used to Assign Severity Grade	Grade 1	Grade 2	Grade 3	Grade 4
Coronary artery disease Told by physician of condition, angina Told by physician of condition, coronary artery disease Heart attack or myocardial infarction Had relevant procedure	Have angina or coronary artery disease	Have angina or coronary artery disease and either medication use, angioplasty, or stent placement	Had heart attack or myocardial infarction or have had coronary bypass surgery	NA
Transient ischemic attack Told by physician of condition	Have condition	NA	NA	NA
Stroke Told by physician of condition Surgical procedure	NA	Have condition	NA	Have condition and had carotid artery surgery
Peripheral artery disease Pain in calf when walking (intermittent claudication) Had relevant procedure Prescription medication use‡	Have condition	Have condition and medication use	Have condition and had peripheral artery surgery	NA
Thromboembolic event Blood clot in leg (deep vein thrombosis) Blood clot in lung (pulmonary embolism) Prescription medication use‡	NA	Have deep vein thrombosis	Have pulmonary embolism or medication use	NA
Obesity, BMI,¶ kg/m^2	NA	25-29	30-39	≥ 40
Thyroid disease Overactive thyroid Underactive thyroid Prescription medication use‡	Have condition	Have condition and medication use	NA	NA
Anxiety/depression Prescription medication use‡	NA	Medication use for condition	NA	NA
Erectile dysfunction Difficulty with getting or maintaining an erection* Prescription medication use‡	A little	Quite a bit or very much or medication use	NA	NA
Hypogonadism Prescription medication use‡	NA	Medication use for condition	NA	NA

NOTE. For conditions that are based on more than one question, the severity grade was assigned according to the response that reported the greatest or most severe symptom.

Abbreviations: AHO, adverse health outcome; BMI, body mass index; HDL, high-density lipoprotein; NA, not applicable (data needed to assign grade were not captured).

*Assessed with the European Organisation for Research and Treatment of Cancer Chemotherapy-Induced Peripheral Neuropathy 20-item quality-of-life questionnaire on the basis of symptoms experienced over the past 4 weeks.[68] For each item, participants were asked whether the symptom started before, during, or after chemotherapy. If participants responded that the symptoms started before chemotherapy, those responses were not considered when assigning severity grade.

†Assessed with the Scale for Chemotherapy-Induced Long-Term Neurotoxicity questionnaire on the basis of symptoms experienced over the past 4 weeks.[69] For each item, participants were asked whether the symptom started before, during, or after chemotherapy. If participants responded that the symptom started before chemotherapy, those responses were not considered when assigning severity grade.

‡Prescription medications taken for at least the past 4 weeks were only used to assign grade if the participant reported that the indication was for the given AHO and that the medication was started during or after chemotherapy.

§Item is from the Hearing Handicap Inventory by Ventry and Weinstein[70] and assessed symptoms at the time of clinical evaluation. For each item, participants were asked to report the age (in years) at first occurrence. If onset of symptoms was before their age of germ cell tumor diagnosis, those responses were not considered when assigning severity grade.

‖Item is from the 36-Item Short Form Survey and assessed symptoms experienced over the past 4 weeks.[71]

¶BMI is based on physical examination performed at time of clinical assessment.

Table A2. Definition of the Cumulative Burden of Morbidity Score on the Basis of Number and Severity of Individual Adverse Health Outcomes

Grade	None	Very Low	Low	Medium	High	Very High	Severe
1	0	≥ 1	Any number	Any number	Any number	Any number	Any number
2	0	0	≥ 1	Any number	Any number	Any number	Any number
3	0	0	0	≥ 1	≥ 2	≤ 1	≥ 2
4	0	0	0	0	0	1	1

NOTE. Methods adapted from Geenen et al.[15] Modifications include division of the low category into very low and low and division of the high category into high and very high to reflect the granularity of data collected in the current study.

Table A3. Association Among Clinical, Sociodemographic, and Health Behavior Factors and Cumulative Burden of Morbidity Score

Variable	Cumulative Burden of Morbidity Score, No. (%)						*P*
	None	Very Low	Low	Medium	High	Very High/ Severe[a]	
No. of participants	65	104	458	360	180	47	
Mean age at evaluation, years (SD)	32 (8.5)	36 (9.6)	38 (10.0)	39 (10.2)	42 (10.2)	39 (11.3)	< .001
Mean age at diagnosis, years (SD)	27 (7.3)	30 (8.4)	31 (8.2)	31 (8.8)	34 (9.4)	33 (8.4)	< .001
Mean years since treatment (SD)[b]	4.5 (4.2)	5.7 (5.1)	6.5 (5.6)	6.5 (6.1)	6.4 (6.2)	4.7 (4.8)	.020
Race[c]							.002
White	49 (4.7)	82 (7.9)	397 (38.3)	309 (29.8)	161 (15.5)	38 (3.7)	
African American	0	3 (18.8)	3 (18.8)	4 (25.0)	3 (18.8)	3 (18.8)	
Asian	7 (11.9)	11 (18.6)	22 (37.3)	14 (23.7)	5 (8.5)	0	
Other	6 (8.8)	6 (8.8)	22 (32.4)	22 (32.4)	8 (11.8)	4 (5.9)	
Education[d]							< .001
High school education or less	4 (2.9)	6 (4.3)	42 (30.2)	46 (33.1)	31 (22.3)	10 (7.2)	
Post–high school training or some college	12 (4.2)	25 (8.7)	88 (30.5)	88 (30.5)	62 (21.5)	14 (4.8)	
College or postcollege graduate	49 (6.3)	73 (9.3)	328 (41.9)	224 (28.6)	86 (11.0)	23 (2.9)	
Marital status[e]							.016
Single/never married	26 (6.7)	38 (9.8)	148 (38.1)	107 (27.5)	48 (12.3)	22 (5.7)	
Married/living as married	37 (5.0)	63 (8.5)	275 (37.2)	232 (31.4)	111 (15.0)	22 (3.0)	
Divorced/separated	1 (1.4)	2 (2.8)	30 (42.3)	16 (22.5)	18 (25.7)	3 (4.3)	
Current employment status[f]							< .001
Employed	57 (5.3)	87 (8.1)	426 (39.6)	328 (30.5)	143 (13.3)	36 (3.3)	
Unemployed	5 (6.7)	11 (14.9)	22 (29.7)	18 (24.3)	12 (16.2)	6 (8.1)	
Retired	0	3 (20.0)	3 (20.0)	3 (20.0)	6 (40.0)	0	
Disability	0	1 (3.3)	3 (10.0)	7 (23.3)	16 (53.3)	3 (10.0)	
Smoking status[g]							.036
Never	48 (6.9)	72 (10.1)	267 (37.4)	202 (28.3)	92 (12.9)	33 (4.6)	
Former	14 (3.6)	26 (6.6)	151 (38.5)	122 (31.1)	68 (17.4)	11 (2.8)	
Current	3 (2.8)	6 (5.6)	39 (36.5)	36 (33.6)	20 (18.7)	3 (2.8)	
No. of alcoholic drinks in past year[h]							.001
Rarely/never	11 (4.6)	18 (7.5)	81 (33.9)	67 (28.0)	46 (19.3)	16 (6.7)	
1-3/mo	13 (7.2)	12 (6.7)	63 (35.0)	52 (28.9)	27 (15.0)	13 (7.2)	
1-6/wk	33 (5.8)	62 (10.9)	219 (38.5)	169 (29.7)	72 (12.7)	14 (2.5)	
≥ 1/d	7 (3.2)	11 (5.1)	92 (42.2)	70 (32.1)	35 (16.1)	3 (1.4)	
Engage in vigorous physical activity[i]							< .001
No	14 (3.7)	20 (5.3)	123 (32.5)	116 (30.7)	76 (20.1)	29 (7.7)	
Yes	51 (6.1)	84 (10.1)	334 (40.0)	244 (29.2)	104 (12.5)	18 (2.2)	
Retroperitoneal lymph node dissection[j]							.110
No	39 (6.1)	50 (7.8)	227 (35.4)	199 (31.0)	95 (14.9)	32 (5.0)	
Yes	26 (4.6)	53 (9.4)	228 (40.4)	159 (28.2)	83 (14.7)	15 (2.7)	
Bleomycin							.580
No	25 (5.2)	42 (8.7)	195 (40.5)	134 (27.8)	71 (14.7)	15 (3.1)	
Yes	40 (5.5)	62 (8.5)	263 (35.9)	226 (30.9)	109 (14.9)	32 (4.4)	

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Table A3. Association Among Clinical, Sociodemographic, and Health Behavior Factors and Cumulative Burden of Morbidity Score (continued)

Variable	Cumulative Burden of Morbidity Score, No. (%)						*P*
	None	Very Low	Low	Medium	High	Very High/ Severe[a]	
Type of chemotherapy[k] × No. cycles							.190
EP × 4	15 (4.3)	35 (9.9)	146 (41.4)	99 (28.1)	48 (13.6)	10 (2.8)	
BEP × 3	31 (6.7)	40 (8.7)	169 (36.7)	138 (30.0)	59 (12.8)	23 (5.0)	
BEP × 4	9 (4.1)	16 (7.2)	88 (36.0)	66 (29.7)	43 (19.4)	8 (3.6)	
VIP × 4	2 (6.5)	0	9 (29.0)	13 (40.6)	7 (21.9)	1 (3.1)	

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; EP, etoposide plus cisplatin; SD, standard deviation; VIP, etoposide, ifosfamide, and cisplatin.
[a]Categories were collapsed because of sparse data. Among the 47 participants, 46 had a cumulative burden of morbidity score of very high and one had a score of severe.
[b]*P* value derives from analysis of log-transformed values as a result of unequal variance between groups. Means and SDs are from untransformed values.
[c]Data on race were not available for 35 participants.
[d]Data on education level were not available for three participants.
[e]Data on marital status were not available for 15 participants.
[f]Data on employment status were not available for 19 participants.
[g]Data on smoking status were not available for 19 participants.
[h]Data on alcohol consumption were not available for nine participants.
[i]Data on physical activity were not available for one participant.
[j]Data on retroperitoneal lymph node dissection were not available for 13 participants.
[k]Other chemotherapy regimens not included in the comparisons are EP other than four cycles (n = 28), BEP other than three or four cycles (n = 28), VIP other than four cycles (n = 12), and other platinum-based regimens (n = 72).

Table A4. Summary of US Studies of Testicular Cancer Survivors

Characteristic	First Author and Population								
	Fung[2]	Reilley[23a]	Kim[21]		Oh[22]		Shinn[24a]	Hashibe[20b]	
	Testicular Cancer	Testicular Cancer	Testicular Cancer	Men Without Cancer	Testicular Cancer, Treated With Platinum	Testicular Cancer, Not Treated With Platinum	Testicular Cancer	Testicular Cancer	Men Without Cancer[c]
No. of patients	952[d]	189	246	236	118	25	162	785	3,323
Cohort source	Eight cancer centers in United States and Canada	Pennsylvania Cancer Registry	STEED study[e]	STEED study	MD Anderson genitourinary cancer clinic	MD Anderson genitourinary cancer clinic	MD Anderson genitourinary cancer clinic	Utah population database	Utah population database
Calendar years of testicular cancer diagnosis	1979-2015	1990-2005	1988-2002	—	NA	NA	NA	1991-2007	—
Age at testicular cancer diagnosis, years	Median, 31; range, 15-53	NA	29.3[f,g]	29.1[h,i]	NA	NA	Mean, 32.1; SD, 8.6	Median, 31; range, 15-58	—
Ethnicity, %									
White	86	95	90	94.1	NA	NA	87	99	94
Other	14	5	10	5.9	NA	NA	13	1	2.6
Unknown	0	0	0	0	NA	NA	0	0	3.5
Type of therapy,[i] %									
Chemotherapy	100[j]	33	18	—	NA[k]	NA[k]	61[l]	21.4[l]	—
Radiation	0	85	24	—	NA[m]	NA[m]	29[n]	38.5[n]	—
Surgery	100	69	58	—	NA[o]	NA[o]	1[p]	37.1[p]	—
Other treatment	0	0	0	—	NA	NA	8[q]	3.1[r]	—
Source of therapy data	Medical record	Self-report	Self-report	—	Medical record	Medical record	Medical record	Medical record	—
Duration of follow-up, years	Median, 4.3; range, 1-29.9[s]	Mean, 6.78; SD, 3.8[t]	13.7[f,g,t]	NA	8.6[f,g,t]	7.3[f,g,t]	Mean, 4.5; SD, 1.6[s]	Median, 10[t]; range, 5-21	Median, 11.8; range, 5-21
Age at evaluation, years	Median, 37; range, 19-68	Mean, 43.6; SD, 9.9	NA[u]	NA[v]	Median, 40.4[f]; range, 17-72	Median, 44.6[f]; range, 20-74	Mean, 37.2; SD 9.0	Median, NA; range, 22-69[w]	Median, NA; range, 22-69[x]
BMI $\geq$ 25 kg/m^2	73.3[y]	83.5	79.3[z]	80.51[aa]	NA	NA	NA	62.3[bb]	63.8[cc]
Waist circumference, cm	Median, 94; range, 57-190	NA	NA	NA	NA	NA	NA	NA	NA
Prevalence of health behaviors, %[dd]									
Current smoker	8.3	25	NA	NA	NA	NA	19	NA	NA
Physical activity									
Moderate level	95.8[ee]	NA[ff]	NA	NA	NA	NA	NA	NA	NA
Vigorous level	69.0[ee]	NA[ff]	NA	NA	NA	NA	15.9[gg]	NA	NA
Heavy drinking[hh]	11.4	34.9	NA	NA	NA	NA	46	NA	NA
Prevalence of AHOs, %[dd,ii,jj,kk]									
Cardiovascular and related disorders									
Hypertension	11.6	NA	NA	NA	33[ll]	47.6[ll]	NA	11.7/1,000 PY	11.1/1,000 PY
Hyperlipidemia	10.5	NA	NA	NA	14.6	28	NA	6.3/1,000 PY[mm]	3.9/1,000 PY[mm]
Coronary artery disease	0.7	NA	NA	NA	5.4	0	NA	1.2/1,000 PY	1.3/1000 PY
Cerebrovascular disease	1.0	NA	NA	NA	0	0	NA	0.6/1,000 PY	0.9/1,000 PY
Peripheral vascular disease	3.0	NA	NA	NA	NA	NA	NA	NA	NA

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Table A4. Summary of US Studies of Testicular Cancer Survivors (continued)

Characteristic	First Author and Population								
	Fung[2]	Reilley[23a]	Kim[21]		Oh[22]		Shinn[24a]	Hashibe[20b]	
	Testicular Cancer	Testicular Cancer	Testicular Cancer	Men Without Cancer	Testicular Cancer, Treated With Platinum	Testicular Cancer, Not Treated With Platinum	Testicular Cancer	Testicular Cancer	Men Without Cancer[c]
Thromboembolic disease	0.5	NA	NA	NA	NA	NA	NA	1.2/1,000 PY[nn]	1.0/1,000 PY[nn]
Raynaud phenomenon	18.7	NA	NA	NA	NA[oo]	NA[oo]	NA	NA	NA
Neurotoxicity									
Hearing issues and/or tinnitus	47.9	NA	NA	NA	NA	NA	NA	0.6/1,000 PY	0.2/1,000 PY
CIPN	27.0	NA	NA	NA	NA	NA	NA	4.4/1,000 PY	3.0/1,000 PY
Other									
Renal disease	2.6	NA	NA	NA	5.8	0	NA	1.4/1000 PY	1.6/1,000 PY
Diabetes on medication	3.1	NA	NA	NA	NA	NA	NA	3.3/1,000 PY	4.0/1,000 PY
Thyroid disease	2.4	NA	NA	NA	NA	NA	NA	NA	NA
Hypogonadism on medication	9.9	NA	NA	NA	NA	NA	NA	NA	NA
Erectile dysfunction	12.1	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: BMI, body mass index; CIPN, chemotherapy-induced peripheral neuropathy; NA, not available; PY, person-year; SD, standard deviation; STEED, Servicemen's Testicular Tumor Environmental and Endocrine Determinants.

[a]No control group was included.

[b]Statistically significant hazards ratios (HRs) that compared results in patients with testicular cancer versus men without cancer were observed for hyperlipidemia (HR, 1.70; 95% CI, 1.19 to 2.41). Nonsignificant HRs were observed for coronary artery disease (0.93), cerebrovascular disease (0.67), diabetes (0.63), hypertension (0.99), hypertriglyceridemia (1.0), obesity (0.93), peripheral neuropathy (1.29), hearing loss (1.79), thromboembolic disease (pulmonary embolism [1.3]), renal failure (0.79), and dyslipidemia (1.14).

[c]Men without cancer were randomly selected from patients in the Utah Population Database for whom medical records were available at the University of Utah Health Sciences Center data warehouse or the Intermountain system. Each patient with testicular cancer was matched to four to five men without cancer on birth year, birth region, and date of last residence in Utah.

[d]Of 952 patients, 842 (88.5%) had testicular germ cell tumors (GCTs), whereas 109 (11.4%) had GCTs at other sites. For one (0.1%) patient, GCT site was unknown. All patients in Fung et al[2] also are included in the current study.

[e]The STEED study had a response rate of 47.6%. Men who never had a diagnosis of testicular GCT and had a blood serum sample in the Department of Defense Serum Repository were eligible for participation in the control group.

[f]Mean value.

[g]SD was not available.

[h]Mean age at reference date.

[i]Because treatment groups in Reilley et al,[23] Kim et al,[21] Oh et al,[22] Shinn et al,[24] and Hashibe et al[20] did not consist of mutually exclusive categories, patients may have had more than one type of treatment. Patients with testicular GCTs in Fung et al[2] received platinum-based chemotherapy after surgical management.

[j]All testicular cancer survivors received cisplatin-based chemotherapy.

[k]Among testicular cancer survivors administered chemotherapy, 82.5% received platinum-based regimens, although the number who received cisplatin- versus carboplatin-based chemotherapy was not provided. The remaining patients (17.5%) received non–platinum-based chemotherapy.

[l]Surgery and chemotherapy.

[m]Among all 143 survivors, 30 (21%) had received radiation.

[n]Surgery and radiotherapy.

[o]Among all 143 survivors, 138 (96.5%) had had orchiectomy.

[p]Surgery only.

[q]These patients received other treatments, including surgery, radiation, and chemotherapy.

[r]Patients received other treatments, including radiotherapy only; chemotherapy only; or radiation, chemotherapy, and orchiectomy, or their treatments were unknown.

[s]Duration of follow-up since completion of testicular cancer therapy.

[t]Duration of follow-up since testicular cancer diagnosis.

[u]Mean or median age at evaluation was not provided, but the study reported the percentage of testicular cancer survivors in the following age ranges: 18 to 29 years, 3%; 30 to 39 years, 36%; 40 to 49 years, 41%; and ≥ 50 years, 20.5%.

[v]Mean or median age at evaluation was not provided, but the study reported the percentage of control group participants in the following age ranges: 18 to 29 years, 3.4%; 30 to 39 years, 32.5%; 40 to 49 years, 44.1%; and ≥ 50 years, 19.9%.

[w]Mean or median age at the end of follow-up was not provided, but the study reported the percentage of patients in the following age ranges: 22 to 35 years, 18.2%; 35 to 44 years, 33.8%; 45 to 54 years, 31.7%; and 55 to 69 years, 16.3%.

[x]Mean or median age was not provided, but the study reported the percentage of control group participants in the following age ranges: 22 to 35 years, 16%; 35 to 44 years, 35.1%; 45 to 54 years, 31.7%; and 55 to 69 years, 17.2%.
[y]Among 952 testicular cancer survivors, 42.4% were overweight (BMI, 25 to < 30 kg/m^2), and 30.9% were obese (BMI, ≥ 30 kg/m^2).
[z]Among 246 testicular cancer survivors, 47.2% were overweight (BMI, 25 to 29.9 kg/m^2), and 32.1% were obese (BMI, > 30 kg/m^2).
[aa]Among 236 control group participants, 42.8% were overweight (BMI, 25 to 29.9 kg/m^2), and 37.71% were obese (BMI, > 30 kg/m^2).
[bb]BMI at baseline. Among 785 testicular cancer survivors, 44.3% were overweight (BMI, 25 to 29.9 kg/m^2), and 18% were obese (BMI, > 30 kg/m^2).
[cc]BMI at baseline. Among 3,323 men without cancer, 43.5% were overweight (BMI, 25 to 29.9 kg/m^2), and 20.3% were obese (BMI, > 30 kg/m^2).
[dd]For four studies[21,23,24] that included testicular cancer survivors from multiple treatment groups, health behaviors and outcomes were not stratified by type of therapy.
[ee]Vigorous activity was defined as ≥ 6 metabolic equivalent tasks and moderate activity as 3 to < 6 metabolic equivalent tasks.
[ff]Reported that 50.3% of survivors had adequate aerobic exercise and 28% had adequate strength and flexibility. The authors used the Rapid Assessment of Physical Activity, which assesses aerobic activity and strength and flexibility in adults.
[gg]Definition of vigorous activity not provided.
[hh]Heavy drinking was defined as two or more alcoholic drinks daily. Reilly et al[23] and Shinn et al[24] defined heavy drinking as five or more drinks at one time in past month.
[ii]Refer to the Methods section and Appendix Table A1 in Fung et al[2] for definitions of adverse health outcomes, which also were stratified by type of chemotherapy. Adverse health outcomes are based on patient report. Diagnoses of hypertension, hypercholesterolemia, and diabetes required that patients have been told by a physician that they had the condition and that they currently were taking prescription medications for the condition.
[jj]Definitions provided by Oh[22] are as follows: hypertension, prior diagnosis or use of antihypertensive medication; hyperlipidemia, prior diagnosis or use of cholesterol-lowering agents; coronary artery disease, prior diagnosis of angina or myocardial infarction; and renal insufficiency, prior diagnosis or creatinine level > 1.5 mg/dL. No diagnostic criteria were provided for Raynaud phenomenon.
[kk]To determine adverse health outcomes, Hashibe et al[20] used International Classification of Diseases, Ninth Revision, and Current Procedural Terminology codes.
[ll]Hypertension diagnosis was based on history plus measured blood pressure.
[mm]Percentages are shown for hypercholesterolemia. Hypertriglyceridemia also was assessed (incidence rate, 0.7 and 0.6/1,000 PY for the case and control groups, respectively; HR, 1.0; 95% CI, 0.37 to 2.70). The incidence rate of dyslipidemia (defined as high triglycerides, high cholesterol, and low high-density lipoprotein) was 9.7 and 8.7/1,000 PY for the case and control groups, respectively (HR, 1.14; 95% CI, 0.86 to 1.49). No definitions were provided for hypercholesterolemia, hypertriglyceridemia, or dyslipidemia.
[nn]Pulmonary embolism.
[oo]Among all 143 survivors, 16 (11.2%) reported Raynaud phenomenon.