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ORIGINAL REPORT

Multi-Institutional Assessment of Adverse Health Outcomes Among North American Testicular Cancer Survivors After Modern Cisplatin-Based Chemotherapy

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ABSTRACT

Purpose
To provide new information on adverse health outcomes (AHOs) in testicular cancer survivors (TCSs) after four cycles of etoposide and cisplatin (EPX4) or three or four cycles of bleomycin, etoposide, cisplatin (BEPX3/BEPX4).

Methods
Nine hundred fifty-two TCSs > 1 year postchemotherapy underwent physical examination and completed a questionnaire. Multinomial logistic regression estimated AHOs odds ratios (ORs) in relation to age, cumulative cisplatin and/or bleomycin dose, time since chemotherapy, socio-demographic factors, and health behaviors.

Results
Median age at evaluation was 37 years; median time since chemotherapy was 4.3 years. Chemotherapy consisted largely of BEPX3 (38.2%), EPX4 (30.9%), and BEPX4 (17.9%). None, one to two, three to four, or five or more AHOs were reported by 20.4%, 42.0%, 25.1%, and 12.5% of TCSs, respectively. Median number after EPX4 or BEPX3 was two (range, zero to nine and zero to 11, respectively; $P > .05$) and two (range, zero to 10) after BEPX4. When comparing individual AHOs for EPX4 versus BEPX3, Raynaud phenomenon (11.6% *v* 21.4%; $P < .01$), peripheral neuropathy (29.2% *v* 21.4%; $P = .02$), and obesity (25.5% *v* 33.0%; $P = .04$) differed. Larger cumulative bleomycin doses (OR, 1.44 per 90,000 IU) were significantly associated with five or more AHOs. Increasing age was a significant risk factor for one to two, three to four, or five or more AHOs versus zero AHOs (OR, 1.22, 1.50, and 1.87 per 5 years, respectively; $P < .01$); vigorous physical activity was protective (OR, 0.62, 0.51, and 0.41, respectively; $P < .05$). Significant risk factors for three to four and five or more AHOs included current (OR, 3.05 and 3.73) or former (OR, 1.61 and 1.76) smoking ($P < .05$). Self-reported health was excellent/very good in 59.9% of TCSs but decreased as AHOs increased ($P < .001$).

Conclusion
Numbers of AHOs after EPX4 or BEPX3 appear similar, with median follow-up of 4.3 years. A healthy lifestyle was associated with reduced number of AHOs.

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INTRODUCTION

Testicular cancer (TC) is the most common cancer among men age 18 to 39 years, with an age-adjusted 5-year relative survival of 95%.[1] This remarkable success is explained in large part by the introduction of platinum-based chemotherapy in the 1970s.[2] Today, the majority of patients with metastatic TC receive standard cisplatin-based chemotherapy, on the basis of international guidelines[3-5] related to prognostic groups.[6] For two decades, this standard chemotherapy has consisted of three cycles of bleomycin, etoposide, and cisplatin (BEPX3) or four cycles of etoposide and cisplatin (EPX4) for good-risk TC or four cycles of BEP (BEPX4) for intermediate- or poor-risk TC.[7,8] Given the curative potential of these commonly used regimens, it has become increasingly important to understand the occurrence of long-term

ASSOCIATED CONTENT

Appendix
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adverse health outcomes (AHOs). As recently pointed out by Oldenburg and Gietema,[9] better characterization of AHOs may also help guide TC treatment, especially in the controversial area of whether patients with good-risk TC should receive EPX4 or BEPX3. However, no series to date has quantified the type and prevalence of long-term AHOs in large numbers of patients treated with EPX4, BEPX3, or BEPX4. Although several European studies reported toxicities in TC survivors (TCSs),[10-14] many of these investigations included older therapeutic regimens, and no study included more than 10 patients treated with EPX4.

Characterization of long-term AHOs associated with modern curative regimens is also important to develop risk-stratified, evidence-based follow-up recommendations for TCSs, who now comprise > 4% of all cancer survivors.[15] Current follow-up guidelines by national and international organizations[3-5] for the prevention and treatment of long-term toxicities are limited, without broad consensus. The formulation of such guidelines, including the development of interventions to prevent or mitigate long-term effects, requires an assessment of AHOs, along with characterization of potential risk factors.[14,16,17] We aimed to provide new information on the type and prevalence of AHOs in large numbers of TCSs cured with either EP or BEP by initiating the Platinum Study, a large multicenter cohort of US and Canadian TCSs.[17]

METHODS

Participants

The Platinum Study was approved by Institutional Review Boards at all participating institutions. Each participant provided written informed consent allowing access to medical records since cancer diagnosis.

Eligibility criteria included: histologic/serological diagnosis of germ cell tumor (GCT), age < 55 years at diagnosis and > 18 years at enrollment, treatment with first-line cisplatin-based chemotherapy for either initial GCT or recurrence after active surveillance, no subsequent salvage chemotherapy, no radiotherapy, no antecedent chemotherapy for another primary cancer, and routine follow-up at the participating site. All participants were disease-free at the time of clinical evaluation and are referred to as TCSs.

Clinical Evaluation

TCSs underwent a brief physical examination and extensive audiometric testing, with the latter results published separately.[18] Body mass index (kg/m^2) was defined as normal, overweight, obese, or morbidly obese (< 25, 25 to < 30, 30 to 39, and ≥ 40 kg/m^2, respectively), with ≥ 30 kg/m^2 considered an AHO.[19] Waist circumference > 102 cm defined abdominal obesity.[20]

Patient-Reported Health Outcomes and Lifestyle Behaviors

TCSs completed a questionnaire regarding selected health outcomes that were targeted largely to those associated with cisplatin-based chemotherapy or with a TC diagnosis; in addition, lifestyle behaviors and current prescription medications were queried. Each of the following conditions was considered an AHO (definitions are listed in Appendix Table A1, online only): tinnitus, hearing impairment, peripheral neuropathy, problem with balance/vertigo/dizziness, renal disease, coronary artery disease (CAD), heart failure, cerebrovascular disease, hypertension and on prescription medication, Raynaud phenomenon, hypercholesterolemia and on prescription medication, peripheral vascular disease, thromboembolic disease, diabetes and on prescription medication, and hypogonadism with testosterone replacement. Obesity, use of psychotropic prescription medications, erectile dysfunction, and benign thyroid disease were each counted as an AHO. Chemotherapy-induced peripheral neuropathy was assessed through the European Organization for Research and Treatment of Cancer Chemotherapy-Induced Peripheral Neuropathy 20 scale[23] and the Scale for Chemotherapy-Induced Long-Term Neurotoxicity.[21] Peripheral neuropathy was diagnosed if participants reported "quite a bit" or "very much" to relevant questions.[21,23] TCS also self-rated health as excellent, very good, good, fair, or poor.

TCSs reported the average time per week engaged in various physical activities during the past year.[24] Total kilocalories per week were estimated by summing metabolic equivalent (MET) –hours for each physical activity and multiplying by the participant's weight (kilograms). Kilocalories per week were calculated for vigorous (≥ 6 METs) and moderate (3 to < 6 METs) physical activities.[25]

Data Collection From Medical Records

Study staff were trained in person to abstract data according to a standard protocol using forms adapted from prior studies.[26-31] Data included GCT diagnosis, and for each cytotoxic drug: name, dose, date(s) of administration, number of cycles, and cumulative dose. All data were entered into the eClinical system.[32]

Comparison Cohort

Matched controls for selected comparisons were chosen from the National Health and Nutrition Examination Survey (NHANES) using two consecutive data sets (2009 to 2012), following methods applied by the St Jude's Lifetime Cohort.[33] Controls (restricted to men without cancer) were matched 1:1 on race, age (within 5 years), educational level, and fasting status at blood collection.

Statistical Analysis

Data were summarized with medians (ranges) for continuous variables and proportions for categorical variables. To evaluate associations of clinical, demographic, and behavioral risk factors with AHO number, multinomial logistic regression, including all clinically relevant variables known to affect health outcomes, estimated the adjusted (multivariable) odds ratios (ORs), 95% CIs, and *P* values. For comparisons with NHANES controls, multinomial or binary logistic regression estimated the relative odds of TCSs having one of the following: elevated body mass index; waist circumference ≥ 102 cm; self-reported hypertension; elevated fasting total cholesterol (≥ 240 mg/dL), LDL ≥ 160 mg/dL, or triglyceride concentration ≥ 150 mg/dL; decreased fasting HDL (< 40 mg/dL); smoking status (ever, current); alcohol consumption > 2 d/wk; and self-reported health. Comparisons with lipid values were restricted to participants who fasted for at least 8 hours before venipuncture (N = 131 TCSs, N = 131 controls). All tests were two-tailed ($\alpha = 0.05$). The Mantel 1df χ^2 test for trend was used to determine the association between AHO number and self-rating of health. Data were analyzed with SAS statistical software program (SAS Institute Inc, Cary, NC).

RESULTS

Study Subjects

Of 1,024 eligible subjects, 952 (93.0%) consented to participate. Reasons for nonparticipation included lack of interest (n = 27), time commitment (n = 17), travel (n = 14), and miscellaneous concerns (n = 14). Participants and nonparticipants were similar in terms of age at TC diagnosis ($P = .52$), age at assessment ($P = .40$), and race ($P = .25$). Of all patients, 950 were seen in clinic as part of a scheduled follow-up visit and two were seen because of concern regarding recurrence. No patients were seen for treatment-related adverse effects.

Table 1. Clinical and Sociodemographic Characteristics of 952 Survivors of Cisplatin-Treated Germ Cell Tumors by Treatment Regimen

Characteristic	All Patients	Treatment Regimen		
		EPX4	BEPX3	BEPX4
Total	952[a] (100)	294 (100)	364 (100)	170 (100)
Clinical characteristic				
Age at diagnosis, years				
Median (range)	31 (15-53)	32 (17-53)	30 (15-50)	29 (16-49)
Age at clinical evaluation, years				
Median (range)	37 (19-68)	39 (20-68)	37 (19-66)	36 (30-61)
< 20	5 (0.5)	0	5 (1.4)	0
20-29	196 (20.6)	51 (17.3)	81 (22.2)	36 (21.2)
30-39	357 (37.5)	105 (35.7)	137 (37.6)	72 (42.4)
40-49	252 (26.5)	72 (24.5)	99 (27.2)	49 (28.8)
≥ 50[b]	142 (14.9)	66 (22.4)	42 (11.6)	13 (7.6)
Histologic type				
Seminoma	253 (26.6)	106 (36.1)	92 (25.3)	30 (17.6)
Nonseminoma[c]	699 (73.4)	188 (63.9)	272 (74.7)	140 (82.4)
Site				
Testis[d]	842 (88.5)	276 (93.9)	338 (92.9)	140 (82.4)
Extragonadal[e]	110 (11.5)	18 (6.1)	26 (7.1)	30 (17.6)
Cisplatin-based chemotherapy[f]				
BEP[g]	557 (58.5)	—	364 (100)	170 (100)
EP[h]	302 (31.7)	294 (100)	—	—
Other[i]	93 (9.8)	—	—	—
Cumulative dose of cisplatin, mg/m^2				
< 300	43 (4.5)	0	19 (5.2)	1 (0.6)
300	340 (35.7)	0	335 (92.0)	0
301-399	34 (3.6)	0	10 (2.7)	15 (8.8)
400	495 (52.0)	290 (98.6)	0	141 (82.9)
> 400	40 (4.2)	4 (1.4)	0	13 (7.6)
Cumulative dose of bleomycin, IU				
0	368 (38.7)	294 (100)	0	0
> 0-180,000	57 (6.0)	0	10 (2.7)	17 (10.0)
181,000-270,000	385 (40.4)	0	353 (97.0)	26 (15.3)
271,000-360,000	136 (14.3)	0	1 (0.3)	126 (74.1)
> 360,000	6 (0.6)	0	0	1 (0.6)
Calendar year of chemotherapy completion				
Before 2000[j]	95 (10.0)	23 (7.8)	33 (9.1)	19 (11.2)
2000-2009	368 (38.6)	123 (41.8)	126 (34.6)	70 (41.2)
2010-2015	489 (51.4)	148 (50.3)	205 (56.3)	81 (47.6)
Retroperitoneal lymph node dissection				
Yes	455 (47.8)	161 (54.8)	122 (33.5)	113 (66.5)
No[k]	497 (52.2)	133 (45.2)	242 (66.5)	57 (33.5)
Time from chemotherapy completion to clinical evaluation, years				
Median (range)	4.3 (1.0-29.9)	4.3 (1-23.9)	3.8 (1-25.3)	5.1 (1-23.7)
< 2	225 (23.6)	70 (23.8)	99 (27.2)	30 (17.7)
2-5	355 (37.3)	106 (36.1)	139 (38.2)	65 (38.2)
6-9	168 (17.7)	52 (17.7)	61 (16.7)	33 (19.4)
≥ 10	204 (21.4)	66 (22.4)	65 (17.9)	42 (24.7)
Sociodemographic characteristic				
Race				
White	817 (85.8)	246 (83.7)	330 (90.7)	141 (82.9)
Nonwhite[l]	135 (14.2)	48 (16.3)	34 (9.3)	29 (16.1)
Marital status				
Not married[m]	366 (38.5)	109 (37.1)	130 (35.7)	73 (42.9)
Married/living as married	586 (61.5)	185 (62.9)	234 (64.3)	97 (57.1)
Education				
High school or less	109 (11.4)	17 (5.8)	42 (11.5)	32 (18.8)
Some college/college graduate	627 (65.9)	201 (68.4)	243 (66.8)	108 (63.5)
Postgraduate level	203 (21.3)	75 (25.5)	74 (20.3)	26 (15.3)
Other or unknown	13 (1.4)	1 (0.3)	5 (1.4)	4 (2.4)

(continued on following page)

Table 1. Clinical and Sociodemographic Characteristics of 952 Survivors of Cisplatin-Treated Germ Cell Tumors by Treatment Regimen (continued)

Characteristic	All Patients	Treatment Regimen		
		EPX4	BEPX3	BEPX4
Employment status				
Not employed[n]	103 (10.8)	32 (10.9)	33 (9.1)	20 (11.8)
Employed	849 (89.2)	262 (89.1)	331 (90.9)	150 (88.2)

NOTE. Data presented as No. (%) unless otherwise noted. Of 1,024 eligible subjects, 952 (93%) consented to participate. Reasons for nonparticipation included lack of interest (n = 27), time commitment (n = 17), travel (n = 14), and other concerns: inconvenience (n = 4), concern with study procedures (n = 3), confidentiality issues (n = 2), health issues (n = 2), lack of insurance (n = 1), and unspecified reasons (n = 2). Of the 952 patients, 950 were seen in clinic as part of a scheduled follow-up visit and two were seen because of concern regarding recurrence. Clinical and sociodemographic characteristics were comparable for EPX4 and BEPX3 ($P > .05$), except for race and educational level ($P < .01$ each).

Abbreviations: BEPX3, three cycles of bleomycin, etoposide, cisplatin; BEPX4, four cycles of bleomycin, etoposide, cisplatin; EPX4, four cycles of etoposide, cisplatin; PVB, cisplatin, vinblastine, bleomycin; RPLND, retroperitoneal lymph node dissection; TCS, testicular cancer survivor; VeIP, vinblastine, ifosfamide, cisplatin; VIP, etoposide, ifosfamide, cisplatin.

[a]Of 952 patients in the study, most received EPX4 (n = 294), BEPX3 (n = 364), and BEPX4 (n = 170). The remainder received BEP other than three or four cycles (n = 23), EP other than four cycles (n = 8), and other regimens (n = 93). The other regimens consisted of other cisplatin-based regimens (n = 70), VIP (n = 22), and VeIP (n = 1).

[b]Fourteen participants were between 60 to 69 years of age at clinical evaluation.

[c]Includes eight participants with not-otherwise-specified germ cell tumor, with one participant with unknown histology.

[d]Five participants had bilateral testicular cancer.

[e]Fifty-nine, 36, and 14 participants had extragonadal germ cell tumors of the mediastinum, retroperitoneum, and other sites, respectively. This category also includes one participant with primary site not stated.

[f]Eighteen (1.9%), 374 (39.3%), 535 (56.2%), and 25 (2.6%) participants received two or fewer, three, four, and five or more cycles of cisplatin-based chemotherapy, respectively.

[g]Includes 130 (23.3%) participants with modification of dosing and schedules of BEP. The remaining 427 participants (76.7%) received the standard dosing and standard BEP schedule: each chemotherapy cycle consists of bleomycin, 30,000 IU days 1, 8, and 15; etoposide 100 mg/m^2 days 1 through 5; and cisplatin 20 mg/m^2 days 1 through 5. In addition, 364 (65.4%) and 170 (30.5%) participants received three and four cycles of BEP, respectively. The median cumulative cisplatin doses for the BEP group were 300 mg/m^2 (range, 198 to 653 mg/m^2).

[h]Includes 112 (37.1%) participants with modification of dosing and schedules of EP. The remaining 190 participants (62.9%) received the standard dosing and standard EP schedule: each chemotherapy cycle consists of etoposide 100 mg/m^2 days 1 through 5 and cisplatin 20 mg/m^2 days 1 through 5. The median cumulative cisplatin doses for the EP group were 400 mg/m^2 (range, 200 to 600 mg/m^2).

[i]Includes 70 participants with other cisplatin-based regimens, 22 participants with VIP and one participant with VeIP, but none with PVB. Each standard VIP chemotherapy cycle consists of etoposide 75 mg/m^2 days 1 through 5, cisplatin 100 mg/m^2 days 1 through 5, and ifosfamide 1,200 mg/m^2 days 1 through 5.

[j]Two participants completed chemotherapy before 1990. Among the 95 participants who completed chemotherapy before 2000, none reported that the indication for the clinic visit was concern about late effects; in 94 it was for routine follow-up, and one patient indicated "other reason, not specified."

[k]Includes three participants with retroperitoneal lymph node dissection status not stated. The lower number of TCSs having retroperitoneal lymph node dissection in BEPX3 (33.5%) compared with EPX4 (47.8%) likely reflects the different clinical practices for management of advanced testicular cancer at our study institutions, including types of chemotherapy used (BEPX3 *v* EPX4), and if RPLND was performed among patients with disseminated testicular cancer having a radiographic complete response after chemotherapy. Retrograde ejaculation is the most common long-term complication after nerve-sparing postchemotherapy RPLND and can affect 11% to 29% of TCSs.[34]

[l]The nonwhite population consisted of 11 (1.2%) black/African American, 44 (4.6%) Asian, one (0.1%) American Indian, 12 (1.3%) who identified more than one race, 61 (6.4%) other race, and six (0.6%) whose race was not stated.

[m]Includes 12 participants with marital status not stated.

[n]Includes 15 participants with employment status not stated.

Population Characteristics

Chemotherapy consisted largely of BEPX3 (38.2%), EPX4 (30.9%), and BEPX4 (17.9%; Table 1). Median age at clinical evaluation was 37 years (range, 19 to 68 years), and median time since chemotherapy completion was 4.3 years (range, 1.0 to 29.9 years). Most (85.8%) TCSs were white,[35] married or cohabitating (61.5%), and had at least a college education (64.0%). Clinical and sociodemographic characteristics were comparable for EPX4 and BEPX3 ($P > .05$), except for race and educational status (each $P < .01$).

More than 70% of TCSs were overweight (42.4%) or obese (30.9%; Table 2). Only 8.3% of participants currently smoked; 11.4% consumed two or more alcoholic drinks daily, and 69.0% engaged in weekly vigorous-intensity physical activity. Physical examination findings and health behaviors were similar for EPX4 and BEPX3 ($P > .05$), except for smoking status ($P < .01$).

AHOs

Overall, 79.6% TCSs reported at least one AHO, and 20.1%, 15.0%, 10.1%, and 12.5% reported two, three, four, or five or more AHOs, respectively (Table 3). Median number of AHOs after EPX4 or BEPX3 was two, with 34.3% and 35.1% of TCSs reporting three or more AHOs, respectively. The type and prevalence of individual AHOs after EPX4 and BEPX3 were similar ($P > .05$), except Raynaud phenomenon (11.6% *v* 21.4%; $P < .01$), peripheral neuropathy (29.2% *v* 21.4%; $P = .02$), and obesity (25.5% *v* 33.0%; $P = .04$). Among all TCSs, the most common AHOs were tinnitus (37.1%), self-reported hearing impairment (31.5%), obesity (30.9%), and peripheral neuropathy (27.0%). Both peripheral neuropathy and tinnitus and/or hearing impairment were reported by one in six (16.4%) TCSs. Current prescription medication use for hypertension, hypercholesterolemia, and diabetes was noted by 11.6%, 10.5%, and 3.1% of TCSs, respectively. After BEPX4, the type and prevalence of AHOs were similar to EPX4 and BEPX3, with the exception of erectile dysfunction (20.0%).

Number of AHOs was inversely associated with self-rating of health (Fig 1), with the latter declining as AHO numbers increased ($P < .001$). Among 194 TCSs with no AHOs, 80.4%, 18.6%, and 1.0% self-reported health as excellent/very good, good, or fair/poor. In contrast, among 119 TCSs with five or more AHOs, the comparable percentages were 26.9%, 56.3%, and 16.8%, respectively.

Increasing age at clinical evaluation was associated with significantly increased risks of one to two, three to four, or five or

Table 2. Physical Examination Findings and Health Behaviors for 952 Survivors of Cisplatin-Treated Germ-Cell Tumors by Treatment Regimen

Characteristic	All Patients*	Treatment Regimen		
		EPX4	BEPX3	BEPX4
Total	952 (100)	294 (100)	364 (100)	170 (100)
Physical examination results				
Body mass index, kg/m^2				
Median (range)	28 (18-67)	27 (18-49)	28 (18-67)	28 (18-66)
< 25 (normal)	241 (25.3)	77 (26.2)	91 (25.0)	38 (22.4)
25-29 (overweight)	404 (42.4)	137 (46.6)	150 (41.2)	71 (41.8)
30-39 (obese)	259 (27.2)	66 (22.4)	103 (28.3)	55 (32.4)
≥ 40 (morbidly obese)	35 (3.7)	9 (3.1)	17 (4.7)	3 (1.7)
Not available	13 (1.4)	5 (1.7)	3 (0.8)	3 (1.7)
Waist circumference, cm				
Median (range)	94 (57-190)	93 (62-145)	94 (57-180)	95 (73-190)
< 102	673 (70.7)	218 (74.1)	256 (70.3)	109 (64.1)
≥ 102	264 (27.7)	74 (25.2)	101 (27.7)	58 (34.1)
Not available	15 (1.6)	2 (0.7)	7 (1.9)	3 (1.8)
Weight gain since chemotherapy, pounds†				
None	9 (1.0)	7 (2.4)	1 (0.3)	0
< 10	405 (42.5)	147 (50.0)	160 (44.0)	55 (32.4)
11-20	102 (10.7)	30 (10.2)	31 (8.5)	24 (14.1)
> 20	41 (4.3)	5 (1.7)	9 (2.5)	14 (8.2)
Lost weight	246 (25.8)	85 (28.9)	94 (25.8)	38 (22.4)
Not available	149 (15.7)	20 (6.8)	69 (18.9)	39 (22.9)
Health behavior				
Smoking status				
Never smoker	552 (58.0)	155 (52.7)	233 (64.0)	91 (53.5)
Former smoker	321 (33.7)	124 (42.2)	102 (28.0)	58 (34.1)
Current smoker	79 (8.3)	15 (5.1)	29 (8.0)	21 (12.4)
Average No. of alcoholic drinks in past year				
Rarely or never	182 (19.1)	46 (15.6)	72 (19.8)	43 (25.3)
≤ 4 per week	436 (45.8)	153 (52.0)	153 (42.0)	66 (38.8)
5 per week to 1 per day	221 (23.2)	65 (22.1)	96 (26.4)	37 (21.8)
≥ 2 per day	108 (11.4)	28 (9.5)	42 (11.5)	22 (12.9)
Not stated	5 (0.5)	2 (0.7)	1 (0.3)	2 (1.2)
Moderate-intensity physical activity (3 to < 6 METs)‡§				
Any moderate-intensity activity	912 (95.8)	285 (97.0)	351 (96.4)	162 (95.3)
Vigorous-intensity physical activity (≥ 6 METs)‡§				
Any vigorous-intensity activity	657 (69.0)	207 (70.4)	261 (71.7)	108 (63.5)

NOTE. Data presented as No. (%) unless otherwise noted.
Abbreviations: BEPX3, three cycles of bleomycin, etoposide, cisplatin; BEPX4, four cycles of bleomycin, etoposide, cisplatin; EPX4, four cycles of etoposide, cisplatin; METs, metabolic equivalents.
*Please refer to Table 1 footnotes for a description of chemotherapy regimens. Physical examination findings and health behaviors were similar for EPX4 and BEPX3 ($P > .05$), except for smoking status ($P < .01$).
†Objective weight gain since chemotherapy was calculated by subtracting the weight recorded at the time of chemotherapy from the weight recorded at the time of clinical evaluation.
‡Among all participants, the median total kilocalories expended per week (interquartile range) was 991 (207 to 2,342). Each physical activity was assigned a MET value (1 MET = 1 kcal/kg/h, or the energy cost of sitting quietly) from which MET-hours per week were calculated. Total kilocalories per week were calculated by summing the product of the time per week engaged in specific physical activities and MET value equivalents for this activity and then multiplying this value by the subject's weight (in kilograms).[25,36]
§The moderate-intensity and vigorous-intensity physical activity groups are not mutually exclusive. Nine different activities were surveyed, some of which are moderate-intensity activities and some of which are vigorous-intensity activities. If a participant 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.[25,36]

more AHOs, compared with no AHOs (OR, 1.22, 1.50, and 1.87, respectively), whereas vigorous physical activity was associated with significantly decreased AHOs (OR, 0.62, 0.51, and 0.41, respectively; Table 4). Cumulative bleomycin dose was significantly associated with five or more AHOs (OR, 1.44 [95% CI, 1.20 to 1.71] per 90,000 IU), with nonsignificant risks of the same magnitude (OR, 1.40 [95% CI, 0.95 to 2.05] per 100 mg/m^2) for cumulative cisplatin dose. When AHOs were limited to those previously linked to cisplatin (peripheral neuropathy, hearing loss, tinnitus), ORs (per 100 mg/m^2) for one (n = 288), two (n = 185), and three (n = 84) AHOs compared with no AHOs were 1.14 (95% CI, 0.87 to 1.49; $P = .34$), 1.48 (95% CI, 1.11 to 1.97; $P = .01$), and 1.46 (95% CI, 1.002 to 2.13; $P = .05$), respectively (footnote, Table 4). For Raynaud syndrome, the OR (per 100 mg/m^2 of cisplatin) was 1.0 (95% CI, 0.77 to 1.29), and for bleomycin, the OR (per 90,000 IU) was 1.31 (95% CI, 1.16 to 1.47).

Statistically significant risk factors for three to four AHOs also included noncollege graduate (OR, 1.88), nonmarried status (OR, 1.85), and current (OR, 3.05) or former smoking (OR, 1.61). These characteristics were also associated with significantly increased risks of five or more AHOs (OR, 2.57, 1.89, 3.73, and 1.76, respectively).

Compared with matched NHANES controls, TCS had significantly higher risks of elevated concentrations of fasting total

Table 3. Numbers and Types of Self-Reported AHOs Among 952 Cisplatin-Treated Germ Cell Tumor Survivors

AHO	Total Patients (N = 952)	Treatment Regimen		
		EPX4 (n = 294)	BEPX3 (n = 364)	BEPX4 (n = 170)
Total No. of AHO				
Median (range)	2 (0-11)	2 (0-9)	2 (0-11)	2 (0-10)
0	194 (20.4)	64 (21.8)	83 (22.8)	25 (14.7)
1	209 (21.9)	68 (23.1)	71 (19.5)	42 (24.7)
2	191 (20.1)	61 (20.8)	82 (22.5)	27 (15.9)
3	143 (15.0)	48 (16.3)	48 (13.2)	25 (14.7)
4	96 (10.1)	28 (9.5)	38 (10.4)	18 (10.6)
≥ 5	119 (12.5)	25 (8.5)	42 (11.5)	33 (19.4)
No. of AHOs by time since chemotherapy completion, years				
< 2	2 (0-11)	2 (0-7)	1 (0-11)	2 (0-6)
2-5	2 (0-10)	2 (0-8)	2 (0-7)	2 (0-8)
6-9	2 (0-9)	1 (0-7)	2 (0-7)	1 (0-6)
≥ 10	3 (0-10)	3 (0-9)	3 (0-7)	2 (0-10)
Number of AHOs by age at clinical evaluation, years				
≤ 29	1 (0-7)	1 (0-6)	1 (0-6)	2 (0-6)
30-39	2 (0-10)	1 (0-7)	2 (0-6)	2 (0-10)
40-49	2 (0-11)	2 (0-7)	2 (0-11)	3 (0-8)
≥ 50	3 (0-10)	3 (0-9)	3 (0-7)	5 (0-10)
Type of AHO[a]				
Tinnitus				
Yes	353 (37.1)	104 (35.4)	130 (35.7)	65 (38.2)
No[b]	599 (62.9)	190 (64.6)	234 (64.3)	105 (61.8)
Hearing impairment[c]				
Yes	300 (31.5)	95 (32.3)	109 (30.0)	56 (33.0)
No	652 (68.5)	199 (67.7)	255 (70.0)	114 (67.0)
Peripheral neuropathy[d]				
Yes	257 (27.0)	86 (29.2)	78 (21.4)	54 (31.8)
No	695 (73.0)	208 (70.8)	286 (78.6)	116 (68.2)
Peripheral neuropathy plus tinnitus and/or hearing issue				
Yes	156 (16.4)	49 (16.7)	48 (13.2)	31 (18.2)
No	796 (83.6)	245 (83.3)	316 (86.8)	139 (81.8)
Hypertension and on prescription medication				
Yes	110 (11.6)	35 (11.9)	45 (12.4)	15 (8.8)
No[e]	842 (88.4)	259 (88.1)	319 (87.6)	155 (91.2)
Hypercholesterolemia and on prescription medication				
Yes	100 (10.5)	32 (10.9)	31 (8.5)	20 (11.8)
No[f]	852 (89.5)	262 (89.1)	333 (91.5)	150 (88.2)
Cardiovascular disease[g]				
Yes	14 (1.5)	4 (1.4)	4 (1.1)	2 (1.2)
No[h]	938 (98.5)	290 (98.6)	360 (98.9)	168 (98.8)
Raynaud phenomenon				
Yes	178 (18.7)	34 (11.6)	78 (21.4)	49 (28.8)
No[i]	774 (81.3)	260 (88.4)	286 (78.6)	121 (71.2)
Peripheral vascular disease				
Yes	29 (3.0)	5 (1.7)	8 (2.2)	10 (5.9)
No[j]	923 (97.0)	289 (98.3)	356 (97.8)	160 (94.1)
Thromboembolic disease[k]				
Yes	5 (0.5)	0	0	4 (2.4)
No	947 (99.5)	294 (100)	364 (100)	166 (97.6)
Renal disease				
Yes	25 (2.6)	7 (2.4)	6 (1.6)	7 (4.1)
No[l]	927 (97.4)	287 (97.6)	358 (98.4)	163 (95.9)
Diabetes and on prescription medication[m]				
Yes	30 (3.1)	9 (3.1)	10 (2.7)	3 (1.8)
No	922 (96.9)	285 (96.9)	354 (97.3)	167 (98.2)
Benign thyroid disease				
Yes	23 (2.4)	6 (2.0)	9 (2.5)	5 (2.9)
No[n]	929 (97.6)	288 (98.0)	355 (97.5)	165 (97.1)
Problems with balance/vertigo/dizziness[o]				
Yes	89 (9.3)	26 (8.8)	37 (10.2)	16 (9.4)
No	863 (90.7)	268 (91.2)	327 (89.8)	154 (90.6)
Hypogonadism with testosterone therapy[p]				
Yes	93 (9.9)	25 (8.6)	37 (10.3)	16 (9.5)
No	851 (90.1)	267 (91.4)	323 (89.7)	152 (90.5)

(continued on following page)

Table 3. Numbers and Types of Self-Reported AHOs Among 952 Cisplatin-Treated Germ Cell Tumor Survivors (continued)

AHO	Total Patients (N = 952)	Treatment Regimen		
		EPX4 (n = 294)	BEPX3 (n = 364)	BEPX4 (n = 170)
Erectile dysfunction				
Yes	115 (12.1)	28 (9.5)	39 (10.7)	34 (20.0)
No[q]	837 (87.9)	266 (90.5)	325 (89.3)	136 (80.0)
Psychotropic prescription medication for anxiety and/or depression[r]				
Yes	99 (10.4)	34 (11.6)	27 (7.4)	20 (11.8)
No	853 (89.6)	260 (88.4)	337 (92.6)	150 (88.2)

NOTE. Data presented as No. (%) or median (range). Refer to Appendix Table A1 for definitions of each AHO.

Abbreviations: AHO, adverse health outcome; BEPX3, three cycles of bleomycin, etoposide, cisplatin; BEPX4, four cycles of bleomycin, etoposide, cisplatin; CAD, coronary artery disease; DVT, deep vein thrombosis; EORTC-CIPN20, European Organization for Research and Treatment of Cancer Chemotherapy-Induced Peripheral Neuropathy 20 Scale; EPX4, four cycles of etoposide, cisplatin; SCIN, Scale for Chemotherapy-Induced Long-Term Neurotoxicity; TCS, testicular cancer survivor.

[a] P values derived from the χ^2 test comparing the proportions of AHOs reported by TCSs in the EPX4 and BEPX3 treatment groups. Except for Raynaud phenomenon ($P < .01$) and peripheral neuropathy ($P = .02$), the P values for all other AHOs were $> .05$.

[b] Category includes three participants for whom this outcome was not stated.

[c] Among all 952 participants, 270 (28.4%) reported problems hearing words, sounds, or language in crowds, 13 (1.4%) required hearing aid, and two (0.2%) had complete deafness (questions derived from the hearing handicap inventory by Ventry and Weinstein[22]); 109 (11.4%) had "quite a bit" or "very much" difficulty hearing, and 75 (7.9%) had "quite a bit" or "very much" reduced hearing (EORTC-CIPN20 and SCIN).[21,23] Category includes 48 participants for whom this outcome was not stated.

[d] Among all 952 participants, the number of patients reporting "quite a bit" or "very much" to the following questions are as follows: 123 (12.9%) tingling fingers or hands, 167 (17.5%) tingling toes or feet, 121 (12.7%) numbness in fingers or hands, 161 (16.9%) numbness in toes or feet, 34 (3.6%) shooting/burning pain in fingers or hands, 70 (7.4%) shooting/burning pain in toes or feet (EORTC-CIPN20)[23]; 134 (14.1%) pain and tingling in toes or feet, and 86 (9.0%) pain and tingling in hands or fingers (SCIN).[21] Category includes 16 participants for whom this outcome was not stated.

[e] Category includes 11 participants for whom this outcome was not stated.

[f] Category includes three participants for whom this outcome was not stated.

[g] Includes CAD, heart failure, and cerebrovascular disease (categories not mutually exclusive and each category was counted as one AHO). Among all participants, seven (0.7%) reported coronary artery disease (three occurrences for coronary artery disease, five occurrences of angioplasty or stent, and five occurrences of heart attack or myocardial infarction), one patient reported heart failure, and 10 (1.0%) reported cerebrovascular disease (six occurrences of transient ischemic attacks, four occurrences of stroke, and one occurrence of carotid artery surgery).

[h] Category includes 21 participants for whom this outcome was not stated.

[i] Category includes 12 participants for whom this outcome was not stated.

[j] Category includes 19 participants for whom this outcome was not stated.

[k] DVT and pulmonary embolism developed simultaneously in three participants and was counted as one thromboembolic event for each. The remaining two participants reported DVT only. Category includes 19 participants for whom this outcome was not stated.

[l] Category includes 26 participants for whom this outcome was not stated.

[m] Among all participants, 13 (1.4%) and 22 (2.3%) reported use of insulin and oral antiglycemic agents, respectively (categories not mutually exclusive). Category includes 15 participants for whom this outcome was not stated.

[n] Category includes 19 participants for whom this outcome was not stated.

[o] Of the 89 patients, 47 reported persistent dizziness or vertigo and 63 reported symptoms of dizziness when standing up (categories not mutually exclusive). Category includes 40 participants for whom this outcome was not stated.

[p] Eight participants who underwent bilateral orchiectomy were excluded from this category.

[q] Category includes seven participants for whom this outcome was not stated.

[r] Participants could report more than one psychotropic medication. Psychotropic medications used by the 99 participants include aripiprazole (n = 2), alprazolam (n = 5), amphetamine-dextroamphetamine (n = 9), bupropion (n = 10), buspirone (n = 1), citalopram (n = 6), clonazepam (n = 8), desvenlafaxine (n = 1), diazepam (n = 1), duloxetine (n = 7), escitalopram (n = 16), fluvoxamine (n = 1), fluoxetine (n = 4), hydroxyzine (n = 1), lisdexamfetamine (n = 4), lorazepam (n = 6), methylphenidate (n = 5), nortriptyline (n = 2), olanzapine (n = 2), paroxetine (n = 7), trazodone (n = 5), sertraline (n = 11), and venlafaxine (n = 7).

cholesterol (OR, 4.76) and LDL cholesterol (OR = 2.42) but lower risks of increased fasting HDL cholesterol (OR, 0.38; $P = .001$; Table 5). TCSs had significantly higher self-reported health and were less likely to be current (OR, 0.22; $P < .001$) or ever smokers (OR, 0.64; $P < .001$).

DISCUSSION

The Platinum Study represents the largest cohort to date of TCSs treated with EPX4, BEPX3, and BEPX4 with an assessment of the prevalence and type of AHOs. A new finding includes that more than one third of TCSs at a median age of 37 years reported three or more AHOs, with similar prevalence and type after EPX4 and BEPX3, except for peripheral neuropathy, Raynaud phenomenon, and obesity. Factors consistently associated with increased numbers of AHOs included age at clinical evaluation, current smoking, lower educational attainment, and nonmarried status. Weekly vigorous physical activity was noteworthy for its uniformly inverse association with AHOs. Self-reported health was excellent/very good in 59.9% of TCSs, but decreased as AHOs increased ($P < .001$). These and other new findings are discussed below.

AHOs: Quantification and Type by Treatment Regimen

Prior studies of BEP included a median of 126 patients (range, 25 to 287), and EPX4 could not be separately evaluated because fewer than 10 patients received the latter regimen.[10,11,37-39] Of four small US-based investigations,[40-43] a limited number of AHOs was addressed in one series (143 patients)[41] but also included treatments with carboplatin-based and other non–cisplatin-based regimens and excluded established cisplatin complications (eg, neuropathy).

Both ototoxicity and cisplatin-induced peripheral neuropathy were reported by one in six TCSs, a combination of symptoms that to our knowledge have not yet been jointly evaluated. This finding is particularly noteworthy, because preliminary genetic analyses

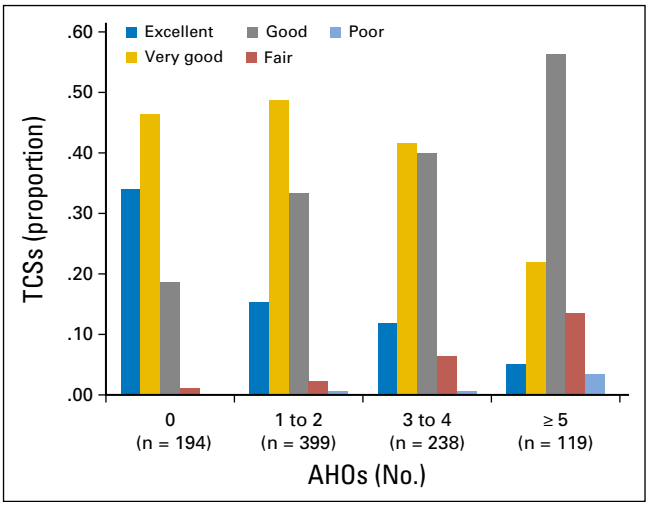

Fig 1. Proportion of testicular cancer survivors (TCSs) with excellent, very good, good, fair, and poor self-reported health by number of adverse health outcomes (AHOs). *P* value for association of number of AHOs with self-reported health was < .01 (Mantel 1df χ^2 test of trend). Self-reported health was not indicated by one participant with one to two AHOs and one participant with three to four AHOs.

among our patients show that peripheral neuropathy–associated genes demonstrate a striking enrichment for significant gene-level associations with ototoxicity ($P < 2.2 \times 10^{-16}$).[44] Understanding the extent to which various cisplatin-related adverse effects may share underlying genetic architecture provides an inroad into delineating the underlying pathophysiology of symptom constellations and the eventual development of preventive strategies.[45]

The highly significant association between increasing age at clinical evaluation and number of AHOs reflects in part comorbidities acquired with advancing age, apart from cisplatin-related toxicities (Appendix Table A2, online only). Although no independent effect of time since chemotherapy was observed, this likely reflects the relatively short follow-up duration and commensurate weighting of results by acute-onset toxicities. Among survivors of childhood cancer with substantially longer follow-up,[46] the number of AHOs indeed increases with time. In addition, an important question not only for TCS but also for other patients receiving cisplatin-based chemotherapy with long-term survival is the extent to which the severity of selected acute-onset toxicities, such as hearing loss, may be accelerated during the aging process.[18]

The significant association between cumulative cisplatin dose and the number of cisplatin-related AHOs extends existing evidence that cisplatin contributes to the development of peripheral neuropathy[38,39] and ototoxicity,[18,37,38] with dose-dependent relationships noted previously for each individually.[18,37,38] However, for other AHOs, such as hypogonadism, orchiectomy likely partly contributes, although evidence suggests that this outcome may be accentuated in patients administered cisplatin-based chemotherapy.[47] Raynaud phenomenon is a known toxicity of bleomycin[39] and may be associated with cisplatin.[38] Although we found no association with cumulative cisplatin dose and Raynaud phenomenon, risk was significantly elevated by 1.3-fold per 90,000-IU increase in bleomycin dose, a finding consistent in part with Glendenning et al,[39] who evaluated risk in 180,000-IU increments (OR, 2.9 per 180,000-IU increase; $P < .001$).

AHOs and Self-Reported Health

The extent to which increasing numbers of AHOs significantly and negatively affect self-reported health is noteworthy and underscores the importance of patient-reported outcomes in survivorship research. Norwegian TCSs had lowered Short Form-36 Physical Component summary scores[48] and increased risks of anxiety disorders, which were associated with peripheral neuropathy, compared with age-adjusted normative data.[49] Dahl et al[14] reported that neurotoxic adverse effects, anxiety/depression, and musculoskeletal issues were associated with poor quality of life. Fleer et al[50] found that chronic disease was also a quality-of-life correlate, although an association with number of conditions was not evaluated.

Cardiovascular Disease

Two European investigations[10,11] evaluated cardiovascular disease incidence and risk factors in at least 300 cisplatin-treated TCSs (Appendix Table A3, online only). Among 390 TCSs treated with BEP (n = 168), carboplatin-based regimens (n = 138), or cisplatin, vinblastine, bleomycin (n = 19), a 6.7% incidence of cardiovascular events was reported (median follow-up, 9.7 years),[11] although results were not stratified by treatment. Haugnes et al[10] reported a CAD prevalence of 6.2% among 364 TCSs receiving BEP (n = 160; median follow-up, 19 years). The substantially lower CAD prevalence here likely reflects the shorter follow-up, younger attained age, and differences in underlying risk factors (eg, diet, activity) between US and European populations.[51]

Compared with NHANES controls, TCSs were 2.4- to 4.8-fold more likely to demonstrate significantly elevated fasting LDL and total cholesterol. Use of lipid-lowering medications (10.5%) was only slightly lower than in TCSs (14.0%) evaluated by Haugnes et al[10] (median age, 49 years). Although antihypertensive medication use in the Norwegian study was 26.0%,[10] use in our patients (11.6%) is comparable to the British cohort (13.3%; median follow-up age, 41 years).[11]

AHOs and Health-Related Behaviors and Sociodemographic Factors

To our knowledge, the association of physical activity on the subsequent development of AHOs in TCSs has not been assessed in US[40-42] or European[10-13] studies. Two US studies[42,43] reported that 19% to 25% of TCSs continued to smoke after diagnosis, but associations with AHOs were not evaluated. The low prevalence of smoking here may reflect in part TCS management at large cancer centers, many of which have smoking cessation programs.

TCSs with lower educational levels and those who were unmarried experienced greater numbers of AHOs, associations that to our knowledge have not been previously examined in other US[40-43] and European[10-13] TCS studies. In the Childhood Cancer Survivor Study,[52] lower educational attainment was significantly associated (OR, 2.0) with at least one adverse health status domain. In contrast, for adult-onset cancer survivors, to our knowledge there are no data addressing the effect of sociodemographic parameters on AHOs, although these characteristics have been evaluated in terms of influence on cancer diagnosis, treatment, and survival. For example, lower socioeconomic level and single status are associated with cancer diagnoses at more advanced stages, receipt of less-aggressive treatment, and increased cancer-specific and all-cause mortality.[53-55]

Table 4. Multinomial Logistic Regression Analyses of AHOs in 915 Survivors of Cisplatin-Treated Germ Cell Tumors

Characteristic	No. of AHOs					
	1-2 *v* 0		3-4 *v* 0		≥ 5 *v* 0	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Clinical						
Age at clinical evaluation, per 5 years	1.22 (1.07 to 1.39)	**.003**	1.50 (1.30 to 1.73)	**< .001**	1.87 (1.56 to 2.23)	**< .001**
Cumulative dose of cisplatin,* per 100 mg/m^2	1.13 (0.83 to 1.54)	.437	1.18 (0.84 to 1.67)	.342	1.40 (0.95 to 2.05)	.091
Cumulative dose of bleomycin, per 90,000 IU	1.05 (0.93 to 1.20)	.430	1.07 (0.93 to 1.24)	.370	1.44 (1.20 to 1.71)	**< .001**
Time since chemotherapy completion, per year	0.98 (0.94 to 1.02)	.308	0.98 (0.93 to 1.02)	.286	0.97 (0.92 to 1.02)	.269
Sociodemographic						
Race						
Nonwhite	0.85 (0.52 to 1.42)	.540	0.61 (0.33 to 1.13)	.117	0.42 (0.17 to 1.04)	.061
White	—	Ref	—	Ref	—	Ref
Education						
Not college graduate	1.35 (0.88 to 2.06)	.165	1.88 (1.18 to 2.99)	**.008**	2.57 (1.46 to 4.53)	**.001**
College or post graduate	—	Ref	—	Ref	—	Ref
Marital status						
Not married	1.48 (0.97 to 2.25)	.067	1.85 (1.15 to 2.97)	**.011**	1.89 (1.04 to 3.44)	**.036**
Married/living as married	—	Ref	—	Ref	—	Ref
Health behavior						
Smoking status						
Current smoker	2.46 (0.98 to 6.20)	.056	3.05 (1.13 to 8.22)	**.028**	3.73 (1.21 to 11.46)	**.022**
Former smoker	1.05 (0.71 to 1.56)	.806	1.61 (1.04 to 2.50)	**.034**	1.76 (1.01 to 3.06)	**.045**
Never smoker	—	Ref	—	Ref	—	Ref
Average No. of alcoholic drinks in past year						
≤ 4 per week	0.78 (0.46 to 1.32)	.361	0.62 (0.35 to 1.10)	.102	0.73 (0.36 to 1.46)	.370
5 per week to 1 per day	0.93 (0.51 to 1.68)	.804	0.70 (0.36 to 1.35)	.283	0.52 (0.22 to 1.23)	.137
≥ 2 per day	1.41 (0.64 to 3.07)	.393	1.16 (0.50 to 2.70)	.739	1.27 (0.48 to 3.39)	.627
Rarely or never	—	Ref	—	Ref	—	Ref
Physical activity intensity†						
Moderate (3 to < 6 METs)						
Yes	1.83 (0.61 to 5.50)	.283	1.95 (0.60 to 6.40)	.269	1.42 (0.41 to 4.97)	.584
No	—	Ref	—	Ref	—	Ref
Vigorous (≥ 6 METs)						
Yes	0.62 (0.39 to 0.98)	**.041**	0.51 (0.31 to 0.84)	**.008**	0.41 (0.23 to 0.73)	**.003**
No	—	Ref	—	Ref	—	Ref

NOTE. Bold indicates ORs with $P < .05$. For the multinomial logistic regression analyses, 37 participants were excluded because of unavailable data for one or more variables.

Abbreviations: AHO, adverse health outcome; METs, metabolic equivalents; OR, odds ratios; Ref, reference.

*When AHOs were limited to those previously linked to cisplatin (peripheral neuropathy, hearing loss, tinnitus), the OR (per 100 mg/m^2) for one (n = 288), two (n = 185), and three (n = 84) AHOs compared with no AHOs were 1.14 (95% CI, 0.87 to 1.49), $P = .34$; 1.48 (95% CI, 1.11 to 1.97), $P = .01$; and 1.46 (95% CI, 1.002 to 2.13), $P = .05$.

†Refer to footnote § in Table 2 for definition of vigorous and moderate intensity physical activity.

Strengths and Limitations

A major strength of our study is that our estimate of the type and prevalence of AHOs is based on the largest number of TCSs to date treated with EPX4, BEPX3, and BEPX4, with results stratified by regimen. Other strengths include the high participation rate (93%), physical examinations, medical chart abstraction, assessment of AHOs and health behaviors, and estimation of risk without the confounding effect of radiotherapy. Although our investigation included many AHOs, it was largely focused on cisplatin-related toxicities and thus did not include psychosocial/mental health outcomes or pulmonary toxicity. Because bleomycin is avoided in patients at high risk for lung toxicity, we do not expect the low prevalence of clinically significant pulmonary toxicity to materially affect our overall conclusions.[56] Nonetheless, our results should be considered a minimal estimate of AHO number, without an assessment of severity and with a relatively short median follow-up time. Furthermore, some toxicities may be underestimated; for example, in our prior report,[18] self-reported hearing loss was 31.5% compared with 80% hearing deficits detected by objective audiometric evaluation. As in previous studies of TCSs[14,40,42] and adult survivors of childhood cancer,[57,58] AHOs were largely self-reported, without baseline data before treatment. Any cross-sectional design has potential inherent limitations and does not allow us to infer causation of evaluated risk factors to AHOs and determine the exact prevalence, although prospective data collection is planned. Moreover, our AHO estimates represent the long-term effects of EPX4, BEPX3, and BEPX4 as administered at major cancer centers; thus, our results may not be generalizable to community-based settings.

In conclusion, at a median follow-up of 4.3 years, the prevalence and type of AHOs among TCSs receiving EPX4, BEPX3, or BEPX4 appear largely similar, although a strong influence of increasing age is apparent. Because alterations in the successful TC regimens are unlikely, our results underscore the importance of continued follow-up of TCSs to determine the extent to which AHOs might increase as the cohort matures.[9] Similarly, ongoing genetic research to broaden our understanding of the biologic basis and causal pathways of cisplatin-associated AHOs[44,45,59] is needed to form the foundation for the development of preventive and interventional strategies. Although increasing numbers of AHOs were associated with a significant decline in self-reported health,

Table 5. Comparison of Physical Examination Findings, Lipid Profiles, and Health Behaviors in 952 Survivors of Cisplatin-Treated Germ Cell Tumors with a Matched Normative Population

Variable	Platinum Study, No. (%)	NHANES, No. (%)	OR (95% CI)[a]	P[b]
Total No. of participants	952 (100)	952 (100)	—	—
Physical examination finding				
Body mass index, kg/m^2[c]				
Median (range)	27.5 (18.0-67.0)	27.8 (16.5-66.2)	—	.446
≥ 30 (obese)	294 (31.3)	321 (35.4)	0.94 (0.74-1.20)	.037
25 to < 30 (overweight)	404 (43.0)	338 (37.3)	1.23 (0.97-1.55)	—
< 25 (normal)	241 (25.7)	248 (27.3)	1.0 (Reference)	—
Waist circumference, cm[d]				
Median (range)	94.0 (57.0-190.0)	98.5 (68.0-172.2)	—	**< .001**
≥ 102	264 (28.2)	355 (40.9)	0.58 (0.47-0.69)	**< .001**
< 102	673 (71.8)	514 (59.2)	1.0 (Reference)	—
Lipid profile				
Total cholesterol, mg/dL[e]				
Median (range)	202 (119-387)	187 (108-272)	—	**< .001**
≥ 240	37 (28.2)	10 (7.36)	4.76 (2.25-10.07)	**< .001**
< 240	94 (71.8)	121 (92.4)	1.0 (Reference)	—
HDL cholesterol, mg/dL[e]				
Median (range)	55 (15-104)	44 (21-90)	—	**< .001**
< 40	20 (15.3)	42 (32.1)	0.38 (0.21-0.70)	**.001**
≥ 40	111 (84.7)	89 (67.9)	1.0 (Reference)	—
LDL cholesterol, mg/dL[e]				
Median (range)	124 (16-257)	117 (29-206)	—	**.033**
≥ 160	28 (21.4)	13 (9.9)	2.42 (1.08-5.42)	.076
130-159	31 (23.7)	32 (24.4)	1.09 (0.55-2.15)	—
100-129	39 (29.8)	49 (37.4)	0.89 (0.48-1.68)	—
< 100	33 (25.2)	37 (28.2)	1.0 (Reference)	—
Triglycerides, mg/dL[e]				
Median (range)	116 (38-936)	125 (39-376)	—	.604
≥ 150	39 (29.8)	41 (31.3)	0.88 (0.49-1.57)	.877
100-149	42 (32.1)	44 (33.6)	0.87 (0.48-1.59)	—
< 100	50 (38.2)	46 (35.1)	1.0 (Reference)	—
Cardiovascular health outcome				
Self-reported high blood pressure[f]				
Yes	155 (16.8)	185 (19.4)	0.83 (0.66-1.06)	.141
No	766 (83.2)	766 (80.6)	1.0 (Reference)	—
Health behavior				
Smoking status[g]				
Ever	398 (41.8)	503 (52.8)	0.64 (0.54-0.77)	**< .001**
Never	552 (58.2)	449 (47.2)	1.0 (Reference)	—
Current: yes	79 (8.5)	286 (30.0)	0.22 (0.17-0.28)	**< .001**
Current: no	848 (91.5)	666 (70.0)	1.0 (Reference)	—
No. days per week of alcohol consumption[h]				
> 2 days	324 (34.1)	186 (23.9)	1.64 (1.33-2.03)	**< .001**
≤ 2 days	627 (65.9)	591 (76.1)	1.0 (Reference)	—
Self-rating of health[i]				
Excellent	161 (17.0)	103 (12.6)	4.18 (2.77-6.30)	**< .001**
Very good	409 (43.1)	285 (34.8)	3.84 (2.67-5.51)	—
Good	331 (34.9)	299 (36.6)	2.96 (2.06-4.26)	—
Fair or poor	49 (5.2)	131 (16.0)	1.0 (Reference)	—

NOTE. Bold indicates ORs with $P < .05$. Comparison group was drawn from the 2009-2012 cycle of the NHANES (n = 5,206 men). Controls were matched (1:1) on age, race, educational level, and fasting status at time of venipuncture (at least 8 hours fasting) to the Platinum Study participant.

Abbreviations: NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

[a]Binary logistic regression was used for dichotomous outcomes, and multinomial logistic regression was used for outcomes with more than one level. OR and 95% CI represent odds of a particular health outcome for participants in the Platinum Study compared with the NHANES normative population.

[b]Bivariate P values derived from the Wilcoxon rank sum test compared median values of outcomes between Platinum Study and NHANES participants. Bivariate P values derived from χ^2 tests compared Platinum Study and NHANES participants across all levels of an outcome.

[c]There were a total of 58 missing values for body mass index: 13 in the Platinum Study and 45 in NHANES. In addition, four participants in the Platinum Study and five NHANES participants were underweight.

[d]There were a total of 98 missing values for waist circumference: 15 in the Platinum Study and 83 in NHANES.

[e]For the first 500 participants in the Platinum Study, we measured total serum cholesterol, including HDL and LDL, and triglyceride concentrations with standard assays; 131 (26.2%) participants fasted for at least 8 hours before venipuncture. The reported cholesterol values were restricted to patients who had fasted for at least 8 hours before venipuncture: 131 participants each in the Platinum Study and in NHANES.

[f]Blood pressures were self-reported and did not require the use of prescription medications for hypertension. There were a total of 32 missing values: 31 in the Platinum Study and one in NHANES.

[g]There were a total of 25 unknown values for current smoking status: 25 in the Platinum Study and 0 in NHANES.

[h]There were a total of 176 unknown values for alcohol consumption: one in the Platinum Study and 175 in NHANES.

[i]There were a total of 136 unknown values for self-reported health: two in the Platinum Study and 134 in NHANES.

more TCSs rated their health as excellent, very good, or good compared with NHANES controls.

In view of our observed associations, health care providers should promote a healthy lifestyle among TCSs, including tobacco cessation, physical activity, and weight control. Future prospective studies should aim to identify high-risk groups who develop life-threatening conditions that can be reduced by follow-up management.

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Appendix

Table A1. Definitions of Adverse Health Outcomes in the Platinum Study

Definition
Tinnitus: Answered "yes" to any of the following questions: (1) "quite a bit" or "very much" ringing in ears* or (2) ringing or buzzing in ears.†
Hearing impairment: Answered "yes" to any of the following questions: (1) "quite a bit" or "very much" for difficulty hearing‡; (2) "quite a bit" or "very much" reduced hearing*; (3) problems hearing words, sounds, or language in crowds†; (4) require hearing aid†; (5) complete deafness.†
Peripheral neuropathy: Answered "quite a bit" or "very much" to any of the following questions: (1) tingling in fingers or hands‡; (2) tingling in toes or feet‡; (3) numbness in fingers or hands‡; (4) numbness in toes or feet‡; (5) shooting/burning pain in fingers or hand‡; (6) shooting/burning pain in toes or feet‡; (7) pain and tingling in toes or feet*; or (8) pain and tingling in hands or fingers.*
Hypertension and on prescription medication: Answered "Yes" to (1) have you ever been diagnosed with high blood pressure and "Yes, current" to (2) have you ever taken prescription medications for high blood pressure (including current use).
Hypercholesterolemia and on prescription medication: Answered "yes, current" to the following question: have you ever taken prescription medications for high cholesterol.
Coronary artery disease: Answered "yes" to any of the following questions: (1) coronary artery disease; (2) angioplasty or stent placement; (3) coronary bypass surgery; or (4) heart attack or myocardial infarction.
Heart failure: Answered "yes" to heart failure.
Cerebrovascular disease: Answered "yes" to any of the following questions: (1) mini-stroke (transient ischemic attack); (2) stroke; or (3) carotid artery surgery.
Raynaud phenomenon: Answered "quite a bit" or "very much" to any of the following questions: (1) white/cold hands/fingers when it is cold* or (2) white/cold feet/toes when it is cold.*
Peripheral vascular disease: Answered "yes" to either of the following questions: (1) pain in calf (lower leg) when walking (intermittent claudication) or (2) surgery in the artery in your pelvis or legs (peripheral artery surgery).
Thromboembolic disease: Answered "yes" to either of the following questions: (1) blood clot(s) in leg (deep venous thrombosis) and taking an anticoagulant; or (2) blood clot(s) in lung (pulmonary embolism) and taking an anticoagulant.
Renal disease: Answered "yes" to kidney disease (renal disease).
Diabetes and on prescription medication: Answered "yes" to either of the following questions: (1) diabetes requiring insulin or (2) diabetes requiring tablets or pills.
Benign thyroid disease: Answered "yes" to either of the following questions: (1) overactive thyroid (hyperthyroidism) or (2) underactive thyroid (hypothyroidism).
Problems with balance/vertigo/dizziness: Answered "yes" to any of the following questions: (1) "quite a bit" or "very much" dizzy when standing up‡ or (2) persistent dizziness or vertigo.
Hypogonadism with testosterone replacement: Reported using testosterone replacement therapy. Excludes participants who had undergone bilateral orchiectomy.
Erectile dysfunction: Answered "quite a bit" or "very much" to the following question: getting or maintaining an erection.‡
Psychotropic prescription medications for anxiety and/or depression: Reported using anxiolytic, antidepressant, or stimulants.
Obesity: Body mass index $\geq$ 30 kg/m^2 on clinical evaluation.

*Questionnaire item is from the Scale for Chemotherapy-Induced Long-Term Neurotoxicity (SCIN).[21]
†Questionnaire item is derived from the hearing handicap inventory by Ventry and Weinstein.[22]
‡Questionnaire item is from the European Organization for Research and Treatment of Cancer Chemotherapy-Induced Peripheral Neuropathy 20.[23]

Table A2. Number of Adverse Health Outcomes in 952 Cisplatin-Treated Germ-Cell Tumor Survivors According to Clinical and Sociodemographic Characteristics and Health Behaviors

Characteristic	No. of Adverse Health Outcomes				
	0	1-2	3-4	≥ 5	Total Patients
No. of patients	194 (20.4)	400 (42.0)	239 (25.1)	119 (12.5)	952 (100)
Clinical characteristic					
Age at clinical evaluation, years					
< 30	55 (27.4)	97 (48.3)	36 (17.9)	13 (6.5)	201 (100)
30-39	93 (26.1)	158 (44.2)	81 (22.7)	25 (7.0)	357 (100)
40-49	34 (13.5)	100 (39.7)	79 (31.3)	39 (15.5)	252 (100)
≥ 50	12 (8.5)	45 (31.7)	43 (30.3)	42 (29.6)	142 (100)
Cumulative dose of cisplatin, mg/m^2					
Median (range)	400 (200-800)	400 (200-600)	400 (198-700)	400 (200-800)	400 (198-800)
≤ 399	91 (21.8)	172 (41.2)	101 (24.2)	53 (12.7)	417 (100)
≥ 400	103 (19.3)	228 (42.6)	138 (25.8)	66 (12.3)	535 (100)
Cumulative dose of bleomycin, IU					
Median (range)	270,000 (90,000-360,000)	270,000 (90,000-540,000)	270,000 (60,000-675,000)	270,000 (84,000-540,000)	270,000 (60,000-675,000)
0	76 (20.6)	160 (43.5)	99 (26.9)	33 (9.0)	368 (100)
> 0-180,000	8 (14.0)	21 (36.9)	18 (31.6)	10 (17.5)	57 (100)
181,000-270,000	86 (22.3)	163 (42.3)	92 (23.9)	44 (11.4)	385 (100)
271,000-360,000	24 (17.6)	53 (39.0)	28 (20.6)	31 (22.8)	136 (100)
> 360,000	0	3 (50.0)	2 (33.3)	1 (16.7)	6 (100)
Retroperitoneal lymph node dissection					
Yes	93 (20.4)	194 (42.6)	113 (24.8)	55 (12.1)	455 (100)
No*	100 (20.2)	206 (41.7)	124 (25.1)	64 (13.0)	494 (100)
Time from chemotherapy completion, years					
< 2	56 (24.9)	102 (45.3)	46 (20.4)	21 (9.3)	225 (100)
2-3	47 (20.9)	93 (41.3)	64 (28.4)	21 (9.3)	225 (100)
4-9	59 (19.8)	138 (46.3)	64 (21.5)	37 (12.4)	298 (100)
≥ 10	32 (15.7)	67 (32.8)	65 (31.9)	40 (19.6)	204 (100)
Sociodemographic characteristic					
Race†					
White	161 (19.7)	336 (41.1)	211 (25.8)	109 (13.3)	817 (100)
Nonwhite	32 (24.8)	62 (48.1)	26 (20.2)	9 (7.0)	129 (100)
Education‡					
Not college graduate	48 (14.5)	127 (38.5)	96 (29.1)	59 (17.9)	330 (100)
College or postgraduate	145 (23.8)	267 (43.8)	139 (22.8)	58 (9.5)	609 (100)
Marital status§					
Not married	71 (20.1)	159 (44.9)	88 (24.8)	36 (10.2)	354 (100)
Married/living as married	121 (20.6)	236 (40.3)	147 (25.1)	82 (14.0)	586 (100)
Health behavior					
Smoking status					
Never smoker	128 (23.2)	243 (44.0)	122 (22.1)	59 (10.7)	552 (100)
Former smoker	60 (18.7)	120 (37.4)	94 (29.3)	47 (14.6)	321 (100)
Current smoker	6 (7.6)	37 (46.8)	23 (29.1)	13 (16.5)	79 (100)
Average number of alcoholic drinks in past year‖					
Rarely or never	27 (14.8)	70 (38.5)	55 (30.2)	30 (16.5)	182 (100)
≤ 4 per week	100 (22.9)	179 (41.1)	104 (23.9)	53 (12.2)	436 (100)
5 per week to 1 per day	50 (22.6)	103 (46.6)	51 (23.1)	17 (7.7)	221 (100)
≥ 2 per day	15 (13.9)	46 (42.6)	29 (26.9)	18 (16.7)	108 (100)
PA intensity¶					
No moderate-intensity PA	7 (17.9)	12 (30.8)	10 (25.6)	10 (25.6)	39 (100)
Any moderate-intensity PA (3 to < 6 METs)	187 (20.5)	388 (42.5)	229 (25.1)	109 (11.9)	913 (100)

(continued on following page)

Table A2. Number of Adverse Health Outcomes in 952 Cisplatin-Treated Germ-Cell Tumor Survivors According to Clinical and Sociodemographic Characteristics and Health Behaviors (continued)

Characteristic	No. of Adverse Health Outcomes				
	0	1-2	3-4	≥ 5	Total Patients
No vigorous-intensity PA	36 (12.2)	112 (38.0)	87 (29.5)	60 (20.3)	295 (100)
Any vigorous-intensity PA (≥ 6 METs)	158 (24.0)	288 (43.8)	152 (23.1)	59 (9.0)	654 (100)

NOTE. Data presented as No. (%) unless otherwise noted.
Abbreviations: MET, metabolic equivalent; PA, physical activity.
*Includes three participants for whom retroperitoneal lymph node dissection was not stated.
†Six participants did not provide their race.
‡Thirteen participants had other educational status or did not report.
§Twelve participants did not state their marital status.
‖Five participants did not state their alcohol consumption status.
¶Refer to footnote § in Table 2 for definition of vigorous and moderate intensity physical activity.

Table A3. Prevalence of CVD Risk Factors in Testicular Cancer Survivors Managed with Chemotherapy or Surgery in Selected Clinical Studies

Variable	First Author			
	Huddart[11]		Haugnes[10]	
Total No. of patients	632		570	
Calendar years of diagnosis	1982-1992		1980-1994	
Time period evaluated after diagnosis	Entire time period taken together		> 2 years	
Type(s) of chemotherapy*	BEP, PVB, carboplatin-based regimens, and others		BEP, PVB	
Treatment group	Chemotherapy	Surgery	Chemotherapy	Surgery
No. of patients	390	242	364	206
Median age at follow-up, years (range)	41 (23-72)	45 (27-76)	49 (31-69)	49 (32-68)
Median follow-up, years (range)	9.7 (0-19.8)	11.4 (0-19.9)	19 (13-28)	19 (13-28)
Prevalence of CVD risk factors,† %				
Obesity				
Mean BMI (kg/m^2)	26.3	26.5	26.7 (± SD 4.0)	27.7 (± SD 3.9)
BMI 25-30 (overweight)	NA	NA	NA	NA
BMI > 30 (obese)	NA	NA	17	19
Hypertension	13.3	8.9	26	12
Lipid-lowering medication	0.7	1.7	14	14
Diabetes	NA	NA	5.4	4.0
Metabolic syndrome	NA	NA	34	32
Tobacco use: current smoker	24	24	24	19

NOTE. Studies are limited to populations that included at least 300 cisplatin-treated testicular cancer survivors and provided data on CVD risk factors through clinical evaluation.
Abbreviations: BEP, bleomycin, cisplatin and etoposide; BMI, body mass index; CVD, cardiovascular disease; NA, not available; PVB, cisplatin, vinblastine, bleomycin; SD, standard deviation.
*Types of chemotherapy regimens are as follows: Huddart et al[11]: largely BEP (n = 168), PVB (n = 19), and carboplatin-based regimens (n = 138), although number of cycles of chemotherapy was not reported. Haugnes et al[10]: largely BEP (n = 160) or PVB (n = 110), although number of cycle of chemotherapy was not reported.
†Definitions for risk factors are as follows: Huddart et al[11]: Hypertension: clinical history of hypertension. Lipid-lowering medication: current use of lipid-lowering medication. Haugnes et al[10]: Hypertension: use of antihypertensive medication. Lipid-lowering medication: self-reported use of lipid-lowering medication. Diabetes: prevalent self-reported diabetes and/or fasting serum glucose ≥ 198 mg/dL. Metabolic syndrome was defined according to Grundy SM, et al: Circulation 109:433-438, 2004. To define metabolic syndrome, blood samples to measure plasma levels of glucose and lipids were drawn at each general practitioner's office, generally after an overnight fast.