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## Predicting Cardiovascular Disease Among Testicular Cancer Survivors After Modern Cisplatin-based Chemotherapy: Application of the Framingham Risk Score

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### Abstract

Testicular cancer survivors are at increased risk of cardiovascular disease after cisplatin-based chemotherapy. Among 787 testicular cancer survivors, the Framingham Risk Score for cardiovascular disease was elevated among less educated and less vigorously active patients, but did not differ by chemotherapy regimen (4 cycles of EP [etoposide and cisplatin] or 3–4 cycles of BEP [bleomycin, etoposide, and cisplatin]). Follow-up and counseling in high-risk subgroups is recommended.

**Background**—Testicular cancer survivors (TCSs) are at increased risk of cardiovascular disease (CVD) after cisplatin-based chemotherapy (CBCT). Identifying at-risk survivors would allow

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early intervention, but risk prediction tools such as the Framingham Risk Score (FRS) have not been applied to TCSs given modern chemotherapy.

**Methods**—TCSs > 1 year post-CBCT were evaluated. Associations between FRS and clinical, socioeconomic, and lifestyle measures and treatment regimen (4 cycles, etoposide and cisplatin [EP × 4]); 3 or 4 cycles, bleomycin plus EP (BEP × 3, BEP × 4) were analyzed with general linear multivariable models. Controls from the National Health and Nutrition Examination Survey were matched 1:1 to TCSs by age, race, and education with differences in mean FRS evaluated with 2-sided *t* tests.

**Results**—Of 787 TCSs (median age, 37.3 years; median follow-up, 4.2 years), 284, 342, and 161 received EP × 4, BEP × 3, or BEP × 4, respectively. TCSs had higher median systolic blood pressure (126 vs. 119 mm Hg; *P* < .001), but fewer were smokers (8.4% vs. 28.2%; *P* < .001) than controls. In multivariable analysis, no significant differences in FRS between EP × 4, BEP × 3, and BEP × 4 were observed, but less than college education (*P* < .001) and lack of vigorous exercise (*P* = .006) were associated with higher FRS. Mean FRS did not differ between TCSs and controls (6.8% vs. 7.3%; *P* = .67).

**Conclusion**—This is the first study to apply the office-based FRS to TCSs. Chemotherapy regimen (BEP × 3 vs. EP × 4) was not associated with FRS, but less educated and less vigorously active patients had higher FRS, and present a high-risk subgroup for intense follow-up and counseling.

## Keywords

Cytotoxic drugs; Germ cell tumor; Late effects; NHANES controls; Risk model

## Introduction

Testicular cancer is the most common malignancy in men 18 to 40 years old, with a relative 5-year survival of 95%.<sup>1</sup> Even among men with metastatic disease, nearly 80% achieve long-term survival.<sup>2,3</sup> Current standard therapy for advanced testicular cancer consists of cisplatin-based chemotherapy (CBCT), with either 3 or 4 cycles of bleomycin, etoposide, and cisplatin (BEP × 3 or BEP × 4) or 4 cycles of etoposide and cisplatin (EP × 4), depending on prognostic group and suspected individual risk of side effects.

Given the long life expectancy of testicular cancer survivors (TCSs), clinical research during the past 20 years has focused on identifying, preventing, and managing treatment-related long-term adverse health outcomes in order to maximize survival and long-term quality of life.<sup>4,5</sup> Cardiovascular disease (CVD) is a life-threatening adverse health outcome among TCSs.<sup>6</sup> European studies have reported a 1.4- to 7-fold higher CVD risk among cisplatin-treated TCSs than in either the general population or in TCSs managed with surgery alone.<sup>7–10</sup> Therefore, identifying high-risk patients and preventing CVD are major goals during follow-up. Although several models predicting the likelihood of future CVD events have been validated in the general United States (US) population, to our knowledge, none of these risk tools have been tested among North American TCSs or a large cohort of patients treated with contemporary CBCT.

In the general population of patients without a history of prior CVD, the Framingham Risk Score (FRS) is one of the most widely used prediction models for estimating an individual's probability (from 0% to 100%) of experiencing a cardiac (coronary heart disease, myocardial infarction, angina pectoris, heart failure, coronary death) or vascular disease event (stroke, transient ischemic attack, peripheral arterial disease) within the next 10 years. The 2008 version<sup>11</sup> of the FRS initially included fasting concentrations of lipids, which are not always available for patients seen in general practice. Therefore, an "office-based" FRS that eliminated laboratory values was developed, which performed as well as the original risk score.<sup>11,12</sup> The office-based risk score relies on age at evaluation, systolic blood pressure (SBP), hypertension treatment, body mass index (BMI), current smoking, and history of diabetes. For example, for a 30-year-old without a history of smoking or diabetes and with a BMI of 23, and a SBP of 120 mm Hg on no anti-hypertensive medication, the office-based FRS would predict a 1.67% probability of experiencing a cardiovascular event within 10 years. In contrast, for a 50-year-old male smoker with diabetes, a BMI of 32, and a SBP of 140 mm Hg while on anti-hypertensive medication, the office-based FRS would predict a 10-year risk of 50.7%.

The primary aims of the current investigation were to estimate the 10-year risk of the first occurrence of CVD with the office-based FRS among North American TCSs given contemporary CBCT, consisting of either EP  $\times$  4, BEP  $\times$  3, or BEP  $\times$  4. We also investigated the extent to which medical, sociodemographic, and lifestyle behaviors influenced FRS in TCSs and compared FRS among TCSs with those of age-matched controls in the general population.<sup>11</sup>

## Patients and Methods

### The Platinum Study

The Platinum Study was designed to identify long-term morbidities in TCSs who received CBCT. The study was approved by Institutional Review Boards at 8 US and Canadian cancer centers.<sup>13</sup> Each participant provided written informed consent allowing access to data in all medical records since cancer diagnosis. Eligibility criteria included a histologic or serologic diagnosis of testicular or extragonadal germ cell tumor (GCT), age less than 55 years at diagnosis and at least 18 years at enrollment, treatment with first-line CBCT for advanced GCT completed at least 1 year before enrollment, no subsequent salvage chemotherapy, no radiotherapy, no antecedent chemotherapy for another primary cancer, and follow-up at the participating site. All participants, including those with extragonadal GCT, are referred to as TCSs.

### Eligibility Criteria for Current Analysis

Current analyses were limited to Platinum Study participants who received BEP or EP. Other major reasons for exclusion (Figure 1) were CVD history at study enrollment ( $n = 42$ ) as required by the Framingham Risk Model<sup>11</sup> or missing data for 1 or more FRS components ( $n = 62$ ).

## Data Collection

Height and weight were recorded to calculate BMI ( $\text{kg}/\text{m}^2$ ). The mean of 2 SBP values obtained in the seated position from the same arm at least 5 minutes apart was used to derive the FRS calculation.

TCSs completed a 36-item questionnaire regarding sociodemographic variables, adverse health outcomes, lifestyle behaviors, and current prescription medication use. For the present analysis, race was coded as white versus nonwhite, marital status as married or cohabitating versus single, and education level of at least a college graduate versus less. Answers to questions about prescription medication use for hypertension, a diagnosis of diabetes, and current tobacco use were categorized as yes versus no. Participants also reported the average time per week they engaged in vigorous physical activity during the past year.<sup>14</sup> Vigorous activity was defined as participating in at least 1 activity per week with a metabolic equivalent (MET) of 6 or more.

## Control Group

Controls were selected from the 2011 to 2012 and 2013 to 2014 National Health and Nutrition Examination Surveys (NHANES). Controls were restricted to men with neither a history of cancer nor CVD (per FRS specifications)<sup>11</sup> for whom data on all FRS variables were available as done in prior studies.<sup>15</sup> Controls were matched 1:1 to TCSs by race, age (within 5 years), and educational level as defined above.<sup>15</sup>

## FRS Calculation

The office-based FRS is derived from a Cox proportional hazards regression model equation<sup>11</sup> that estimates the probability of an individual with no prior history of CVD experiencing a CVD event (coronary heart disease, myocardial infarction, angina pectoris, heart failure, coronary death, stroke, transient ischemic attack, or peripheral arterial disease) in the next 10 years. A risk score was calculated for each participant and control. Each individual's score was allocated to 1 of 5 risk categories: very low, < 5%; low, 5 to < 10%; intermediate, 10 to < 20%; high, 20 to < 30%; very high, 30%.<sup>16</sup>

## Statistical Methods

Distributions of continuous variables, including age, SBP, BMI, and FRS were assessed for normality using the Kolmogorov-Smirnov test. Non-normally distributed continuous variables were positively skewed and therefore log-transformed. Individual components of the FRS were compared between TCSs and controls with *t* tests and  $\chi^2$  tests.

Initially, univariate associations between FRS in TCSs and demographic characteristics, lifestyle factors, and chemotherapy treatments were assessed with general linear regression models (with risk score as the dependent variable) for each independent variable alone (crude models), and then with cancer center and log-transformed age at clinical evaluation as a continuous variable (center- and age-adjusted models). Owing to sparse numbers, patients with non-white race were grouped together. Subsequently, a multivariable analysis was performed in which the center- and age-adjusted model included all variables that were significant ( $P < .05$ ) on either univariate or center- and age-adjusted univariate analysis.

For all general linear regression models, the crude means and adjusted Least Square Means (LSMEANS) of the log transformed FRS were exponentiated back to the original scale for presentation. To compare the FRS between categories of variables with more than 2 groups (eg, chemotherapy regimen), the Tukey-Kramer post-hoc adjustment was used to control family wise alpha at 0.05 for multiple pairwise comparisons.

All tests were conducted at a 0.05 significance level, and all tests were 2-sided. Data were analyzed with the SAS statistical software program (version 9.4, 2014).

## Results

### Study Subjects

Median ages of the 787 eligible TCSs at diagnosis and clinical evaluation were 30.8 and 37.3 years, respectively (Table 1). Most survivors had a testicular primary tumor (92%) and nonseminoma histology (72.9%). TCSs were predominantly white, married or cohabitating, and had at least a college education. The median time since completion of chemotherapy was 4.2 years (range, 1–29.9 years) and 284, 342, and 161 were treated with EP, BEP × 3, and BEP × 4, respectively. Median age at evaluation for TCSs who had received EP was approximately 2 years older (38.4 vs. 36.5 years) than that of BEP-treated patients ( $P < .001$ ). Overall, 503 (64%) of 787 TCSs received bleomycin.

### Comparison With Controls

The median SBP of TCSs exceeded that of controls (126 vs. 119 mm Hg;  $P < .001$ ), whereas controls were more than 3 times as likely to be current smokers as TCSs (28.2% vs. 8.4%;  $P < .001$ ) (Table 2). In contrast, there were no significant differences in BMI or the proportion of men treated for hypertension or diabetes between TCSs and controls. The overall mean FRS was similar for TCSs and controls (6.75 and 7.27;  $P = .67$ ) and increased with age in both groups (Table 3). More than 1 in 5 (21.2%) TCSs had a 10-year risk of a cardiovascular event of 10% or greater (Table 4). Overall, the proportion of TCSs and controls in each of the 5 FRS risk categories did not differ significantly ( $P = .45$ ;  $\chi^2$  test for proportions).

### Univariate Analyses of the Effect of Selected Variables on Framingham Risk Scores

Among TCSs, mean FRS differed by race, marital status, and vigorous exercise in crude analyses (Table 5). After adjusting for cancer center and age, significant associations were no longer observed for race and marital status, but mean FRS was significantly higher for TCSs without a college education than for college graduates/postgraduates (5.07 and 4.39, respectively;  $P < .001$ ), and for those who were less physically active than for those who participated in vigorous exercise (4.92 and 4.45, respectively;  $P < .001$ ). Even if the alpha of 0.05 was adjusted for a family of 6 comparisons in Table 5 using the conservative Bonferroni method (ie, family-wise adjusted alpha of 0.0083), the education and vigorous physical activity variables ( $P < .0001$ ) would remain statistically significant. Importantly, in crude models and in models adjusted for cancer center and age, significant differences in risk scores were not observed between EP, BEP × 3 cycles, and BEP × 4 cycles (4.67, 4.54, and 4.70, respectively). Because the distribution of chemotherapy regimens and race differed

by cancer center, it was necessary to adjust for center in age-adjusted univariate analyses and in multivariate analyses described below.

### Multivariate Analyses of the Effect of Selected Variables on FRS

Variables that were significant ( $P < .05$ ) in the crude or center-and age-adjusted univariate analyses in Table 5 were entered into a multivariable linear regression model to determine which variables were associated with FRS among TCSs (Table 6). After adjusting for center and age, less than a college education ( $P < .001$ ) and lack of vigorous exercise ( $P = .006$ ) were associated with higher FRS. Race and marital status were again not significantly associated with risk scores. Collinearity diagnostics showed no evidence of multicollinearity, which, along with small standard errors, indicate that the multivariable model was precise in estimating the independent effects of each risk factor and covariate when adjusted for each other.

### Discussion

To our knowledge, this is the first study to either evaluate the predicted 10-year risk of CVD among a large number of TCSs given contemporary CBCT or to consider North American patients. Importantly, we found no difference in FRS between EP  $\times$  4, BEP  $\times$  3, or BEP  $\times$  4, and demonstrate for the first time that TCS who engaged in vigorous exercise, a modifiable risk factor, had a significantly lower FRS than those who did not. Lower education status was associated with a significantly elevated FRS. Although TCS were 3 times less likely to be current smokers compared with matched controls, it is noteworthy that their overall FRS was similar to that of a normative population. These and other new findings are discussed below.

Few US studies have evaluated any type of adverse health outcome among TCSs.<sup>17–21</sup> Most investigations to date have been restricted in both size (143–246 patients) and scope, focusing on only health behaviors<sup>18,19</sup> or quality of life,<sup>20</sup> with limited treatment exposure data.<sup>21</sup> Only 1 small study ( $n = 143$  TCSs) by Oh et al<sup>21</sup> presented data on CVD and was limited to estimates of the prevalence of hypertension, hyperlipidemia, and coronary artery disease, without stratification by treatment. No US study has quantified future CVD risk in TCSs.

To our knowledge, the current investigation also represents the first evaluation of predicted CVD risk among TCSs by type of modern chemotherapy (ie, EP  $\times$  4, BEP  $\times$  3, and BEP  $\times$  4). Importantly, we identified no significant difference in FRS between patients who received EP  $\times$  4 as compared to those given BEP  $\times$  3, the 2 regimens typically used for good-risk advanced TC.<sup>22,23</sup> The rarity of data with regard to any type of adverse health outcome after EP  $\times$  4 (other than the Platinum Study)<sup>17</sup> is noteworthy, with only 9 patients included in the largest series to date.<sup>24</sup> Our study is also unique through its inclusion of only a few patients given more than 4 cycles of CBCT as well as elimination of older chemotherapy regimens, resulting in a more homogeneous cohort. Our findings are thus applicable to contemporary patients treated in a standard fashion.

Although risk scores did not differ by chemotherapy regimen, number of cycles, or inclusion of bleomycin, we confirmed the favorable association between lower projected CVD risk and more active lifestyles and higher educational status reported in the general population.<sup>25–27</sup> These findings are reassuring and provide data to support physician recommendations to cisplatin-treated TCSs to exercise regularly and adopt other practices consistent with a healthy lifestyle. Less educated patients may require more intensive counseling.

Two previous studies found conflicting results regarding predicted CVD risk in European TCSs compared with the general population. A small study<sup>28</sup> of 176 Dutch CBCT-treated TCSs (median follow-up, 8.8 years), which compared the original laboratory-based FRS with that of the general population, found no difference in predicted 10-year CVD risk. In contrast, another European investigation evaluating a risk model predicting fatal CVD events within 10 years found higher scores among TCSs.<sup>29</sup> Although the laboratory-based FRS has not been applied to other cohorts of TCSs, results for this prediction tool have been mixed for other groups of cancer survivors<sup>30–32</sup> and underscore the importance of caution when applying risk models developed in the general population to cancer survivors. In fact, risk models for cancer survivors may need to include different or additional component factors beyond those relevant to the general population, in particular, type and amount of cytotoxic exposures. As the FRS does not take into account treatment-associated risk factors for CVD in TCS, such as CBCT, our projections likely represent underestimates of 10-year risk. Further, although the FRS is based on classic CVD risk factors (ie, age, smoking status, diabetes, hypertension, and obesity) that may be increased by cisplatin exposure, it does not take into account the effect of direct cisplatin-related damage to the vascular endothelium, which can lead to endothelial dysfunction and atherosclerosis.<sup>6</sup>

The incidence of CVD is known to be significantly increased among TCSs treated with CBCT compared with either the general population or TCSs managed with surgery alone.<sup>7,8,10,33</sup> Importantly, TCS may live for upwards of 40 years following curative therapy, and thus remain at CVD risk for decades. Thus, the development of new models predicting lifetime (as opposed to 10-year) CVD risk should be considered in this population.<sup>34</sup> Salz et al<sup>35</sup> recently pointed to the absence of published, clinically relevant risk prediction models for cancer survivors, despite the presence of several late effects appropriate for model development. These investigators also called for increased efforts to develop tools for predicting the risk of important, potentially modifiable late effects in cancer survivors, such as CVD.<sup>35</sup>

Only 2 small US studies<sup>18,19</sup> of TCSs have addressed the prevalence of tobacco use. The percentage of current smokers reported by Shinn et al<sup>18</sup> (n = 162 TCSs) and Reilley et al<sup>19</sup> (n = 189 TCSs) were 19% and 25%, respectively, both higher than we observed (8.4%), but comparable with NHANES controls (28.2%). A larger proportion of CBCT-treated Norwegian<sup>7</sup> and Dutch<sup>9</sup> survivors were also current smokers (24% and 31%, respectively). Only the study by Shinn et al<sup>18</sup> addressed physical activity in US TCSs, with 16% reporting vigorous activity, considerably smaller than the 70% noted here. In a population-based Norwegian study of CBCT-treated TCSs,<sup>7</sup> 54% patients reported vigorous physical activity. Thus, our TCSs may represent a “favorably selected” population by virtue of being treated and followed at major cancer centers.

Our findings emphasize the importance of primordial prevention; that is, preempting the development of antecedent CVD risk factors, especially in young populations of cancer survivors, including TCSs. Predictive models that include both clinical and genetic risk factors for predecessors of overt CVD would be even more informative in knowing which patients should be targeted for more intensive follow-up and the early application of preventive and interventional strategies.

### Strengths and Limitations

Strengths of our study include the large sample size compared with previous series, the restriction to only patients treated with contemporary chemotherapy regimens, the focus on North American patients, and the in-depth data on patient demographics and treatment characteristics. In addition, the large number of TCSs treated with EP  $\times$  4 is a unique aspect of our study that allowed comparison of EP  $\times$  4 to BEP  $\times$  3 that was not possible in prior series. Limitations include the use of a cross-sectional rather than longitudinal design, the relatively short median follow-up time of 4.2 years after chemotherapy, and the lack of information on pre-chemotherapy TCSs characteristics, consistent with the limitations of prior studies.<sup>32,33</sup> Further, our TCSs were enrolled at tertiary centers of excellence for TC management and may not represent the broader population of TCSs throughout North America.

### Conclusions

In the first study to apply a CVD risk prediction model to North American TCSs, no difference in FRS between the contemporary regimens of EP  $\times$  4, BEP  $\times$  3, or BEP  $\times$  4 was observed. Lack of vigorous exercise and less education were associated with significantly greater 10-year office-based FRS. Despite being 3 times less likely to smoke cigarettes and quite physically active, mean FRS was similar between TCSs and age-matched controls. Nevertheless, our data demonstrate that among TCS, these habits are associated with lower CVD risk. Our results illustrate the potential limitations of applying risk prediction models, valid in the general population, to cancer survivors without also taking into account cancer-specific and treatment-specific risk factors. Future studies, preferably based on longitudinal investigations spanning several decades, should focus on developing and testing novel prediction models for lifetime CVD risks in TCSs after CBCT tailored to this population. In the interim, less educated TCSs and those who do not participate in vigorous exercise may represent high-risk subgroups to target for closer follow-up and counseling.

### Clinical Practice Points

- After CBCT, TCSs are at increased risk of developing CVD. Identifying at-risk TCSs would allow early intervention. In the general population, 10-year risk for CVD is quantifiable by the office-based FRS, which requires only 6 variables: patient age, current smoking status, BMI, SBP, use of anti-hypertensive medication, and history of diabetes.
- We applied the office-based FRS for the first time to 787 North American TCSs who were treated with the 3 common modern CBCT regimens. After a median observation time of 4.2 years (range, 1–30 years), FRS was significantly elevated



among less educated and less vigorously active patients, but did not differ by chemotherapy regimen (EP  $\times$  4; or 3–4 cycles of BEP). However, mean values of blood pressure in TCSs were significantly greater than those of matched men in the general population. FRS may also underestimate the CVD risk in this population because it does not take into account the effect of direct cisplatin-related endothelial toxicity that can result in endothelial dysfunction and promote atherosclerosis.

- Clinicians should repeatedly inform TCSs about the beneficial impact of vigorous physical activity on the risk of CVD. Less educated patients may require more intense counseling and follow-up. In addition, the role of clinical, laboratory-based, and TC-cancer specific risk factors on the development of CVD should be evaluated after longer follow-up.

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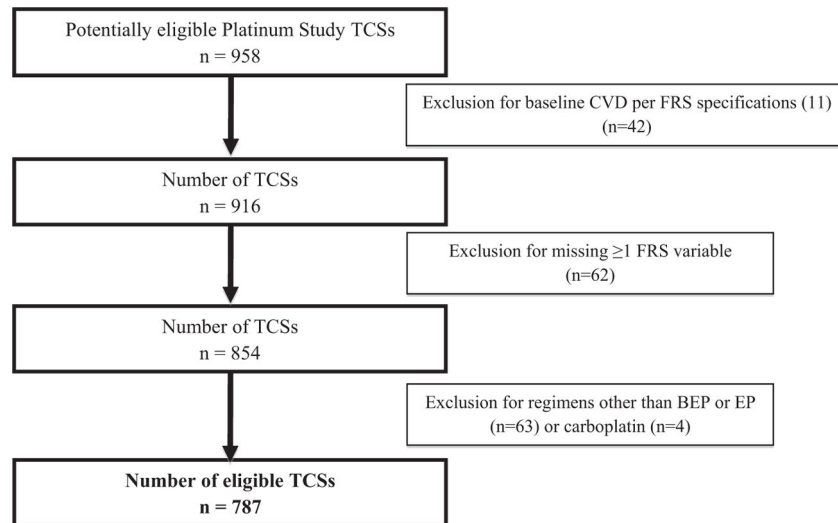
The Platinum Study Group consists of Howard D. Sesso (Brigham and Women's Hospital); Clair J. Beard and Stephanie Curreli (Dana-Farber Cancer Institute); Lois B. Travis, Lawrence H. Einhorn, Mary Jacqueline Brames, and Kelli Norton (Indiana University); Darren R. Feldman, Kevin C. Oeffinger, Erin Jacobsen, and Deborah Silber (Memorial Sloan Kettering Cancer Center); Rob Hamilton and Lynn Anson-Cartwright (Princess Margaret Hospital); Nancy J. Cox and M. Eileen Dolan (University of Chicago); David J. Vaughn, Linda Jacobs, Sarah Lena Panzer, and Donna Pucci (University of Pennsylvania); Debbie Baker, Cindy Casaceli, Chunkit Fung, Eileen Johnson, and Deepak Sahasrabudhe (University of Rochester); and Robert D. Frisina (University of South Florida). The Platinum Study Group Advisory Committee consists of George Bosl (Memorial Sloan-Kettering Cancer Center); Sophie D. Fossa (Norwegian Radium Hospital); Mary Gospodarowicz (Princess Margaret Hospital); Leslie L. Robison (St. Jude Children's Research Hospital); and Steven E. Lipshultz (Wayne State University).

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**Figure 1.** Patient Selection in a Study of Cardiovascular Risk Among Survivors of Testicular Cancer  
Abbreviations: BEP = bleomycin, etoposide, and cisplatin; CVD = cardiovascular disease; EP = etoposide and cisplatin; FRS = Framingham Risk Score; TCSs = testicular cancer survivors.

**Table 1**

Clinical Characteristics of 787 Cisplatin-treated Germ Cell Tumor Survivors According to Chemotherapy Regimen

Characteristic	All Patients N = 787	Chemotherapy Regimen		
		EP <sup>a</sup> n = 284 (%)	BEP × 3 <sup>b</sup> n = 342 (%)	BEP × 4 <sup>c</sup> n = 161 (%)
Median age at diagnosis, y (range)	30.8 (15.2–52.5)	32.3 (17.2–52.5)	29.9 (15.2–49.7)	28.8 (16.0–48.1)
Median age at clinical evaluation, y (range)	37.3 (18.7–68.4)	38.4 (20.0–68.4)	36.9 (18.7–65.6)	36.3 (20.0–59.1)
Histology				
Seminoma	209 (26.6)	99 (34.9)	80 (23.4)	30 (18.6)
Nonseminoma	574 (72.9)	184 (64.8)	261 (76.3)	129 (80.1)
Germ cell tumor NOS <sup>d</sup>	4 (0.5)	1 (0.4)	1 (0.3)	2 (1.2)
Primary site				
Testis	724 (92.0)	267 (94.0)	319 (93.3)	138 (85.7)
Extragenital	63 (8.0)	17 (6.0)	23 (6.7)	23 (14.3)
Race				
White	684 (86.9)	241 (84.9)	311 (90.9)	132 (82.0)
Non-white <sup>e</sup>	103 (13.1)	43 (15.1)	31 (9.1)	29 (18.0)
Marital status				
Not married <sup>f</sup>	295 (37.5)	107 (37.7)	121 (35.4)	67 (41.6)
Married/living as married	492 (62.5)	177 (62.3)	221 (64.6)	94 (58.4)
Education				
Less than college graduate <sup>g</sup>	254 (32.3)	73 (25.7)	112 (32.7)	69 (42.9)
College graduate or postgraduate <sup>h</sup>	523 (66.5)	210 (73.9)	225 (65.8)	88 (54.7)
Other or unknown	10 (1.3)	1 (0.4)	5 (1.5)	4 (2.5)
Mean cumulative cisplatin dose, mg/m <sup>2</sup> (SD)				
<300	35 (4.5)	1 (0.4)	32 (9.4)	2 (1.2)
300	301 (38.3)	2 (0.7)	299 (87.4)	0
301–399	24 (3.1)	0	10 (2.9)	14 (8.7)
400	400 (50.8)	273 (96.1)	1 (0.3)	126 (78.3)
>400	27 (3.4)	8 (2.8)	0	19 (11.8)
Cumulative bleomycin dose, IU				
0	284 (36.1)	284 (100)	0	0
>0–180,000	43 (5.5)	0	24 (7.0)	19 (11.8)
181,000–270,000	342 (43.5)	0	316 (92.4)	26 (16.2)
271,000–360,000	114 (14.5)	0	2 (0.6)	112 (69.6)
>360,000	4 (0.5)	0	0	4 (2.5)
Time since completion of chemotherapy				
Median, y (range)	4.2 (1.0–29.9)	4.1 (1.0–23.9)	4.0 (1.0–25.2)	5.1 (1.0–29.9)

Characteristic	All Patients N = 787	Chemotherapy Regimen		
		EP <sup>a</sup> n = 284 (%)	BEP × 3 <sup>b</sup> n = 342 (%)	BEP × 4 <sup>c</sup> n = 161 (%)
<2	196 (24.9)	72 (25.4)	95 (27.8)	29 (18.0)
2–5	292 (37.1)	104 (36.6)	125 (36.6)	63 (39.1)
6–9	138 (17.5)	49 (17.3)	58 (17.0)	31 (19.3)
10	161 (20.5)	59 (20.8)	64 (18.7)	38 (23.6)

Abbreviations: BEP = bleomycin, etoposide, and cisplatin; EP = etoposide and cisplatin; IU = International Units; NOS = not otherwise specified.

<sup>a</sup>Of 284 patients who received EP, 2 received 3 cycles, 275 had 4 cycles, and 7 had 5 cycles.

<sup>b</sup>Of 342 patients, 14 had 2 cycles of BEP, and 328 had 3 cycles of BEP.

<sup>c</sup>Of 161 patients, 154 had 4 cycles of BEP, and 7 had 5 cycles of BEP.

<sup>d</sup>Germ cell tumor, NOS includes 1 participant with unknown histology.

<sup>e</sup>Non-white participants consisted of 7 Black/African American; 34 Asian; 1 American Indian; 1 Native Hawaiian Pacific Islander; 10 who designated more than one race; 30 other race; 15 who declined to answer (or unknown); and 5 for whom race was not stated.

<sup>f</sup>Among 295 patients, 241 were single or never married, 45 were widowed or divorced or separated, and 9 patients did not report marital status.

<sup>g</sup>Includes 79 patients with high school or less and 175 patients with training after high school or some college.

<sup>h</sup>Includes 351 patients who were college graduates and 172 patients with postgraduate level.

Distribution of Office-based Framingham Risk Score Components Among 787 Testicular Cancer Survivors and Matched Controls<sup>a</sup> by Cancer Treatment

Table 2

Characteristic	Testicular Cancer Survivors			Controls	
	Total, N = 787	EP, n = 284	BEP Cycles 3, n = 342	BEP Cycles 4, n = 161	N = 787
Median age, y	37.3	38.4	36.8	36.3	37.0
Range, y	18.7–68.4	20–68.4	18.7–65.6	20–59.1	20.0–70.0
Median BMI, kg/m <sup>2</sup>	27.4	26.9	28.0	27.3	27.6
Range, kg/m <sup>2</sup> <sup>b</sup>	18.0–66.0	18.1–48.6	18.1–60.2	18.0–66.0	17.0–66.2
Median SBP, mm Hg	126	123	127	126	119
Range, mm Hg <sup>c</sup>	96–190	98–168	96–190	99–171	89–196
BP treatment, n (%)					
No	701 (89.1)	254 (89.4)	300 (87.7)	147 (91.3)	704 (89.5)
Yes	86 (10.9)	30 (10.6)	42 (12.3)	14 (8.7)	83 (10.5)
Current smoker, n (%) <sup>d</sup>					
No	721 (91.6)	270 (95.1)	313 (91.5)	138 (85.7)	565 (71.8)
Yes	66 (8.4)	14 (4.9)	29 (8.5)	23 (14.3)	222 (28.2)
Diabetes, n (%)					
No	768 (97.6)	276 (97.2)	332 (97.1)	160 (99.4)	757 (96.2)
Yes	19 (2.4)	8 (2.8)	10 (2.9)	1 (0.6)	30 (3.8)

Abbreviations: BEP = bleomycin, etoposide, and cisplatin; BMI = body mass index; BP = blood pressure; EP = etoposide and cisplatin; SBP = systolic blood pressure.

<sup>a</sup>Controls were derived from the National Health and Nutrition Examination Survey (NHANES) and matched 1:1 to Platinum Study patients by age, race, and education (refer to Methods).

<sup>b</sup>All BMI values were confirmed as accurate.

<sup>c</sup>The *P*-value (*t* test between mean of log-transformed SBP between all Platinum Study patients vs. NHANES controls) is significant (*P* < .001).

<sup>d</sup>The *P*-value ( $\chi^2$  between all Platinum Study patients vs. NHANES controls) is significant (*P* < .001).

Table 3  
 Mean 10-Year Office-based Framingham Risk Scores for 787 Testicular Cancer Survivors and Matched Controls<sup>a</sup> by Age Category

Age Category	Testicular Cancer Survivors		Controls		<i>P</i> <sup>b</sup>
	Patients, n (%)	Risk Score, Mean (SD)	Controls, n (%)	Risk Score, Mean (SD)	
All ages, y	787 (100)	6.75 (6.8)	787 (100)	7.27 (8.3)	0.67
<30	167 (21.2)	1.63 (1.0)	153 (19.5)	1.51 (0.9)	0.19
30–39	304 (38.6)	3.89 (2.0)	312 (39.6)	4.05 (3.0)	0.99
40–49	209 (26.6)	9.64 (5.0)	201 (25.5)	9.38 (5.0)	0.39
50	107 (13.6)	17.23 (9.4)	121 (15.4)	19.34 (12.5)	0.28

<sup>a</sup>Controls were derived from the National Health and Nutrition Examination Survey (NHANES) and matched 1:1 to Platinum Study patients by age, race, and education (refer to Methods).

<sup>b</sup>*P*-values are calculated using *t* test between mean of log-transformed Framingham Risk Score between Platinum Study patients and NHANES controls.



**Table 4**

Ten-Year Office-based FRSs for Cardiovascular Events Among Testicular Cancer Survivors and Matched Controls<sup>a</sup> by Risk Category

FRS Categories <sup>b</sup>	Testicular Cancer Survivors, <sup>b</sup> n (%)	Controls, <sup>b</sup> n (%)
All categories	787 (100)	787 (100)
Very low (<5%)	435 (55.3)	431 (54.8)
Low (5%–9.9%)	185 (23.5)	175 (22.3)
Intermediate (10%–19.9%)	126 (16.0)	130 (16.5)
High (20%–29.9%)	31 (3.9)	31 (3.9)
Very high (≥30%)	10 (1.3)	20 (2.5)

Abbreviation: FRS = Framingham Risk Score.

<sup>a</sup>Controls were derived from the National Health and Nutrition Examination Survey (NHANES) and matched 1:1 to Platinum Study patients by age, race, and education (refer to Methods).

<sup>b</sup>Comparison between FRS categories in the Platinum Study and NHANES groups was not significant ( $P = .45$ ;  $\chi^2$  test for proportions).

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**Table 5**

Univariate Predictors of 10-year FRS in Testicular Cancer Survivors

Sociodemographic Characteristic	Patients, n	Crude Model <sup>d</sup>		Adjusted Model <sup>a</sup>	
		Mean FRS <sup>b</sup>	P <sup>c</sup>	Adjusted LSMEANS of FRS <sup>b</sup>	P <sup>c</sup>
Race <sup>d</sup>					
White	684	4.79		4.63	
Nonwhite <sup>e</sup>	98	2.96	<.001	4.46	.34
Education <sup>f</sup>					
Less than college graduate <sup>g</sup>	254	4.83		5.07	
College graduate or postgraduate <sup>h</sup>	523	4.36	.15	4.39	<.001
Marital status <sup>i</sup>					
Single/divorced/separated	286	2.78		4.64	
Married/living as married	492	5.94	<.001	4.57	.63
Vigorous physical activity ( ≥ 6 METs) <sup>j</sup>					
No	232	6.54		4.92	
Yes	552	3.83	<.001	4.45	<.001
Chemotherapy regimen					
EP	284	4.85		4.64	
BEP	503	4.31	.09	4.59	.81
Chemotherapy regimen, no. cycles					
EP	284	4.85	Ref <sup>k</sup>	4.67	Ref <sup>k</sup>
BEP 3 cycles	342	4.32	.26	4.54	.81
BEP 4 cycles	161	4.30	.38	4.70	.98

Abbreviations: BEP = bleomycin, etoposide, and cisplatin; EP = etoposide and cisplatin; FRS = Framingham Risk Score; IU = International Units; LSMEANS = Least Square Means (adjusted means); MET = metabolic equivalent of task; Ref = reference.

<sup>a</sup>Crude results are from univariate analysis; adjusted models are adjusted for cancer center and log-transformed age (continuous variable) using LSMEANS.

<sup>b</sup>Both crude means and LSMEANS are calculated for log-transformed FRS and then exponentiated to original scale.

<sup>c</sup>P-values are calculated from the General Linear Model.

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<sup>p</sup>Five patients did not state their race.

<sup>c</sup>The 98 nonwhite participants include 7 Black/African American, 34 Asian, 1 Native Hawaiian Pacific Islander, 1 American Indian, 30 other, 15 who declined to answer (or unknown race), and 10 who designated more than one race.

<sup>f</sup>Ten patients had other educational status or did not report it.

<sup>g</sup>Includes 79 patients with high school or less and 175 patients with training after high school or some college.

<sup>h</sup>Includes 351 patients who were college graduates and 172 patients who completed postgraduate training.

<sup>i</sup>Nine patients did not report marital status.

<sup>j</sup>Three patients had missing data on physical activity.

<sup>k</sup>All pairwise differences were tested using the Tukey-Kramer post-hoc adjustment method. *P*-values reported in the table are for pairwise comparisons between each category and a specified reference category.

**Table 6**

Multivariate Age-adjusted Analysis for the Association Between 10-year FRS and Race, Marital Status, Education, and Vigorous Physical Activity

Characteristic	Multivariate Analysis <sup>a,b</sup>	
	Adjusted LSMEANS of FRS <sup>c</sup>	<i>P</i> <sup>d</sup>
Race		
White	4.83	
Nonwhite	4.51	.11
Marital status		
Single/divorced/separated	4.69	
Married/living as married	4.65	.79
Education		
Less than college graduate	4.98	
College graduate or postgraduate	4.37	<.001
Vigorous physical activity		
No	4.86	
Yes	4.48	.006

Abbreviations: FRS = Office-based Framingham Risk Score; LSMEANS = Least Square Means (adjusted means).

<sup>a</sup>The multivariate model included all variables that were significant ( $P < .05$ ) on either univariate or center- and age-adjusted univariate analysis (see Table 5).

<sup>b</sup>The multivariate model is adjusted for cancer center and log-transformed age and variables shown in the table (race, marital status, education, and vigorous physical activity).

<sup>c</sup>The LSMEANS are calculated for log-transformed FRS and then exponentiated to the original scale (refer to Methods).

<sup>d</sup>*P*-values are calculated from the General Linear Model (refer to Methods).