Original Study

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 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.

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Introduction

Testicular cancer is the most common malignancy in men 18 to 40 years old, with a relative 5-year survival of 95%.[1] Even among men with metastatic disease, nearly 80% achieve long-term survival.[2,3] 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.[4,5] Cardiovascular disease (CVD) is a life-threatening adverse health outcome among TCSs.[6] 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.[7-10] 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[11] 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.[11,12] 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 × 4, BEP × 3, or BEP × 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.[11]

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.[13] 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[11] or missing data for 1 or more FRS components (n = 62).

Data Collection

Height and weight were recorded to calculate BMI (kg/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.[14] 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)[11] for whom data on all FRS variables were available as done in prior studies.[15] Controls were matched 1:1 to TCSs by race, age (within 5 years), and educational level as defined above.[15]

FRS Calculation

The office-based FRS is derived from a Cox proportional hazards regression model equation[11] 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%.[16]

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