Clinical and Genetic Risk Factors for Adverse Metabolic Outcomes in North American Testicular Cancer Survivors

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Running title: Metabolic outcomes after testis cancer

This is the author's manuscript of the article published in final edited form as:
Abu Zaid, M., Gathirua-Mwangi, W. G., Fung, C., Monahan, P. O., El-Charif, O., Williams, A. M., … Group, for the P. S. (2018). Clinical and Genetic Risk Factors for Adverse Metabolic Outcomes in North American Testicular Cancer Survivors. Journal of the National Comprehensive Cancer Network, 16(3), 257–265.
https://doi.org/10.6004/jnccn.2017.7046

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Prior Publication: Presented in part as an Oral Presentation at the 2017 Cancer Survivorship Symposium: Advancing Care and Research, San Diego, CA (Abstract included in the submission). Research was also featured in a video interview in the ASCO Post Newsreels and in an article with editorial in the ASCO Post (3/10/2017).

Funding:

Primary Funding Source: This study was funded by the National Cancer Institute (R01 CA157823 (to LBT)). WGM is supported by 3R01CA196243-02S1 and K05CA175048. The National Cancer Institute had no role in the design of the study; the collection, analysis, or interpretation of data; the writing of the manuscript; or the decision to submit the manuscript for publication.

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Financial support: Lois B. Travis

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ABSTRACT:

Background: Testicular cancer survivors (TCS) are at significantly increased risk for cardiovascular disease (CVD), with metabolic syndrome (MetS) an established risk factor. No study has addressed clinical and genetic MetS risk factors in North American TCS.

Patients and Methods: TCS were <55 years at diagnosis and received first-line chemotherapy. Patients underwent physical examination, and had lipid panels, testosterone, and soluble cell adhesion molecule-1 (sICAM-1) evaluated. A SNP in rs523349 (5-α-reductase gene, *SRD5A2*), recently implicated in MetS risk, was genotyped. Using standard criteria, MetS was defined as ≥3 of the following: hypertension, abdominal obesity, hypertriglyceridemia, decreased high-density lipoprotein (HDL), and diabetes. Matched controls derived from the National Health and Nutrition Examination Survey.

Results: We evaluated 486 TCS (median age: 38.1 years). TCS had a higher prevalence of hypertension versus controls (43.2% vs. 30.7%, P<.001), but were less likely to have decreased HDL (23.7% vs. 34.8%, P<.001) or abdominal obesity (28.2% vs. 40.1%, P<.001). Overall MetS frequency was similar (21.0% and 22.4%, P=.59), did not differ by treatment (P=.20), and was not related to rs523349 (P=.61). For other CVD risk factors, TCS were significantly more likely to have elevated low-density lipoprotein (LDL) (17.7% vs. 9.3%, P<.001), total cholesterol (26.3% vs 11.1%, P<.001), and body mass index ≥25 kg/m^2 (75.1% vs. 69.1%, *P*=.04). In multivariate analysis, age at evaluation (*P*<.001), testosterone ≤3.0 ng/mL (OR=2.06, *P*=.005), and elevated sICAM-1 ($OR_{\text{highest vs. lowest quartile}}$=3.58, *P*=.001) were significantly associated with MetS.

Discussion: Metabolic abnormalities in TCS are characterized by hypertension, increased LDL and total cholesterol, but lower rates of decreased HDL and abdominal obesity signifying possible shifts in fat distribution and fat metabolism. These changes are accompanied by hypogonadism and inflammation.

Conclusion: TCS have high prevalence of CVD risk factors that may not be entirely captured by standard MetS criteria. Cancer treatment-associated MetS requires further characterization.

1. INTRODUCTION

Testicular cancer (TC) is the most common cancer among men aged 18 to 39 years, with increasing incidence over the past 20 years.[1] With cisplatin-based chemotherapy, patients with metastatic disease have achieved unprecedented survival rates,[2] with cure expected in 80%.[3] Overall, the 5-year relative survival rate for all TC patients is 95%.[4] As a result, 1 in 600 men in the U.S. is now a TC survivor (TCS), [5] with a gain of upwards of 40 years of life.[6] Thus, TCS comprise a unique population in which to study the long-term adverse effects of cancer treatment in adult-onset cancer survivors.[7] In particular, TCS given chemotherapy experience up to 7-fold increased long-term risks for cardiovascular disease (CVD) compared to controls.[8-13]

In the general population, metabolic syndrome (MetS) is a major risk factor for CVD.[14] MetS is a constellation of interrelated CVD risk factors, including insulin-resistance, hypertension, elevated triglyceride levels, decreased high-density lipoprotein (HDL) levels, and obesity.[14] Using various definitions, European studies of TCS have reported a wide variation in the prevalence of MetS, ranging from 13%-39%.[15-19] Some investigations have demonstrated MetS risk to be higher among TCS compared to controls,[15-18] but others have not.[19] Boer et al.[20] reported MetS to be more prevalent in TCS carrying the minor allele of a single nucleotide polymorphism (SNP), rs523349 (V89L), compared to wild type (33% vs. 19%, P=.032). This SNP is a nonsynonymous coding variant in the gene *SRD5A2,* encoding steroid 5-α-reductase type II. The prevalence of MetS was particularly high (66.7%) in TCS who had low testosterone levels (<4.3 ng/mL) and carried a minor allele (homozygous or heterozygous) genotype.

Given the conflicting data on MetS prevalence in European studies of TCS and the lack of information in North American patients, we evaluated for the first time MetS and associated risk factors among a large cohort of North American TCS.[21] We also examined the reported association of the rs523349 SNP with MetS in our patients.

2. PATIENTS AND METHODS

2.1 Participants

The Platinum Study evaluates the late consequences of platinum-based chemotherapy and was approved by Institutional Review Boards at all participating institutions.[21,22] Each participant provided written informed consent allowing access to medical records since cancer diagnosis. Eligibility criteria included: diagnosis of germ cell tumor (GCT) at age <55 years; treatment with first-line platinum-based chemotherapy, no salvage chemotherapy, no radiotherapy, and no antecedent chemotherapy for another primary cancer. All participants were disease-free at the time of clinical evaluation. We included in this analysis all TCS for whom blood samples had been analyzed and who had complete data on all MetS components.

2.2 Assessments

2.2.1 Socio-demographic, lifestyle, and behavioral factors. TCS completed a questionnaire regarding health outcomes, lifestyle behaviors and current prescription medications (including antihypertensive, diabetic and lipid-lowering medications). Demographic information included age at cancer diagnosis and clinical evaluation, race, education, employment and marital status. Smoking status was categorized as current, former, or never smoker. Physical activity was reported as the average time per week engaged in various forms of exercise.[23] Moderate- and vigorous-intensity physical activity were defined as participating in at least one activity per week with a metabolic equivalent (MET) of 3 to <6 METs or ≥6 METs, respectively.[24,25]

2.2.2 Data collection from medical records. Study staff abstracted data according to a uniform protocol, using forms adapted from a prior study.[22] Data included date of GCT diagnosis, histology and site of GCT, 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,[26] supported by the study coordinating center.

2.2.3 Clinical evaluation. TCS underwent a physical examination measuring height, weight, and waist circumference. Body mass index (BMI) was calculated as kg/m^2. Blood pressure was measured twice after resting for 5 minutes and averaged. Blood samples were drawn and time of last meal was recorded. Blood samples were frozen and shipped to the central laboratory. Serum levels of testosterone, luteinizing hormone (LH), lipids, creatinine; and soluble cell adhesion molecule-1 (sICAM-1), a known CVD biomarker,[27-29] were measured using commercial assays. Hypogonadism was defined using the U.S. Food and Drug Administration definition (total serum testosterone ≤3.0 ng/mL),[30] which is commonly used in clinical practice.

2.2.4 DNA genotyping and imputation. DNA was extracted from blood samples collected at clinical evaluation. SNPs were genotyped on the Illumina HumanOmniExpressExome chip (Illumina, San Diego) at the RIKEN Center for Integrative Medical Science (Yokohama, Japan). Because the SNP of interest is not called on this chip, we performed genotype imputation following standard quality control measures as previously described.[31] Imputation was performed on the University of Michigan Imputation Server[32] with the following parameters: 1000G Phase 1 v3 Shapet2 (no singletons) reference panel, SHAPEIT phasing, and the EUR (European) population. Linkage Disequilibrium (LD) structures around the variant of interest were determined using NIH's LDLink[33] using the CEU (European) population.

2.3 Definition of MetS

MetS was defined using a modification of the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) Guidelines[14] as the presence of ≥3 of the following (Table 1): 1) systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or use of antihypertensive medication; 2) abdominal obesity (waist circumference ≥102 cm); 3) self-reported diabetes and medication use; 4) HDL cholesterol <40 mg/dL or lipid-lowering medication; and 5) serum triglyceride level ≥150 mg/dL (fasting) or ≥175 mg/dL (non-fasting). These MetS critera were developed by several major organizations to represent one harmonized definition.[14] Criteria for HDL and triglyceride cut-points were adapted from recent guidelines.[34]

2.4 Control group

Matched controls for selected comparisons were chosen from the National Health and Nutrition Examination Survey (NHANES) using two consecutive data sets (2011-2012 and 2013-2014), following methods applied by the St. Jude's Lifetime Cohort.[35] Controls (restricted to men without cancer) were matched 1:1 on race, age (within 5-years), and educational level.

2.5 Statistical analyses

Data were summarized with median (ranges) for continuous variables and proportions for categorical variables in two TCS subgroups defined by the presence or absence of MetS. The two groups were compared using the Pearson chi-square and two-sided Wilcoxon Rank Sum tests on categorical and continuous variables, respectively. TCS were compared to controls using the Pearson chi-square test with regard to the prevalence of various MetS components, as well as other CVD risk factors not included in the NCEP ATP III criteria. A composite score was calculated based on the cut-points for the individual MetS components, with a range of 0-5; zero indicated no abnormal components. Based on MetS diagnostic criteria,[14] participants with a composite score of 3-5 were classified with MetS.

To determine factors associated with MetS in TCS, a two-step approach was used. First, logistic regression models were used to estimate the odds ratios (OR), 95% confidence intervals (CI) and *P*-values for all clinical, demographic, behavioral, and laboratory measures. Second, factors that were significantly associated with MetS in univariate analyses were included in the multivariable model. All statistical analyses were conducted using SAS version 9.4. All tests were two-sided, with *P*-values <.05 considered statistically significant.

3. RESULTS

3.1 TCS characteristics. Median time from chemotherapy completion to study enrollment was 4.7 years (range=0.4-23.9) (Table 2). TCS with MetS (n=102) were significantly older at clinical evaluation compared to those without MetS (n=384) (median 44.4 vs. 36.6 years, *P*<.001). TCS received either bleomycin, etoposide and cisplatin (BEP) (54.7%) or etoposide and cisplatin (EP) (33.1%), but MetS prevalence did not differ by treatment regimen nor by cumulative dose of cisplatin or bleomycin. TCS with MetS had a significantly higher prevalence of obesity (60.8% vs. 22.7%, *P*<.001), hypogonadism (46.1% vs. 26.8%, *P*<.001), and elevated sICAM levels compared to those without MetS (Table 3).

3.2 Comparison with matched controls. TCS were more likely to have hypertension (43.2% vs. 30.7%, *P*<.001), but less likely to have low HDL (23.7% vs. 34.8%, *P*<.001) and abdominal obesity (28.2% vs. 40.1%, *P*<.001) compared to controls (Table 4). Although overall MetS prevalence in TCS and controls was comparable (21.0% vs. 22.4%, *P*=.59), there were significant differences in other CVD risk factors not included in the NCEP ATP III definition. TCS were more likely to have elevated LDL ≥160 mg/dL (17.7% vs. 9.3%, *P*<.001), total cholesterol ≥240 mg/dL (26.3% vs. 11.1%, *P*<.001), and BMI ≥25 kg/m^2 (75.1% vs. 69.1%, *P*=.04). Also, a larger proportion of TCS than controls reported participating in moderate- (93.8% vs 42.4%, *P*<.001) or vigorous-intensity physical activity (66.7% vs. 33.5%, *P*<.001), and were less likely to be current smokers (9.3% vs. 25.9%, *P*<.001).

3.3. Factors associated with MetS in TCS. Results of univariate analysis of factors potentially associated with MetS are shown in Table 5. Factors statistically significant on univariate analysis were incorporated into a multivariate model, in which age, low serum testosterone and sICAM remained significantly associated with MetS (Table 6). For every 10-year increase in age at clinical evaluation, MetS risk increased by 1.7-fold (95% CI=1.33-2.30, *P*<.001). Testosterone level ≤3.0 ng/mL was associated with a significant two-fold increased risk of MetS compared with higher levels (*P*=.005). MetS risk increased monotonically with increasing sICAM level (OR=3.58 comparing highest vs. lowest quartile, *P*=.001). Educational level, marital status, alcohol intake and vigorous-intensity physical activity were not associated with MetS risk in the multivariate model.

3.4 Genetic Association of MetS with *SRD5A2*. The SNP rs523349 showed high imputation quality (R^2=1), call rate (>0.99) and perfect Hardy-Weinberg equilibrium (*P*=1.0). This imputed SNP was in perfect LD with a nearby genotyped SNP, rs12467911. LDLink revealed that the expected LD R^2 in a European population is 0.975. Genotype frequencies by MetS status are presented in Table 7. The variant genotype did not correlate with MetS (*P*=.61).

4. DISCUSSION

Our investigation represents the largest to date to address the prevalence of metabolic abnormalities in TCS treated with contemporary platinum-based regimens and is the only investigation of North American patients. At a median age of only 38 years, three in four TCS were overweight or obese, 43% had hypertension, and a significantly higher proportion had elevated LDL or total cholesterol than did matched controls. Overall, one in five TCS had MetS according to the NCEP ATP III definition.[14] There was no difference in the prevalence of MetS by treatment regimen (BEP vs. EP) nor by cumulative dose of cisplatin or bleomycin. Significant risk factors for MetS included hypogonadism, increasing age and increasing level of sICAM. No association with MetS was observed with the variant genotype for rs523349.

Westerink et al. recently pointed out that the etiology of cancer treatment-induced metabolic syndrome (CTI-MetS) differs from MetS in the general population,[36] where sedentary lifestyle, along with excess caloric intake, are the primary causes.[14] In contrast, CTI-MetS is multifactorial and differs by cancer diagnosis, treatment and patient characteristics. Surgery,[37,38] radiotherapy,[39] chemotherapy[18,19,40] and hormonal therapy[41-45] have each been shown to induce CTI-MetS. In TCS, hypogonadism and chemotherapy rather than sedentary behavior are likely the main causes for metabolic abnormalities. Our TCS were at least twice more likely than controls to engage in moderate or vigorous-intensity physical activity. Despite this, we did not find a significant difference in the prevalence of MetS between TCS and NHANES controls, likely because MetS criteria originally developed for the general population[14] do not reflect the full spectrum of metabolic abnormalities seen in TCS.

The relationships between hypogonadism with MetS and CVD in the general population[46-51] and TCS[13,16-19] are well-established. In our study, about one third of survivors were hypogonadal, which is higher than reported in the general population,[52] but not unexpected since our participants had undergone orchiectomy. In our cohort, TCS with hypogonadism were twice as likely to have MetS in multivariate analysis. Hypogonadism also correlated with obesity, hypertension, high LDL and total cholesterol in univariate analysis (data not shown). Hypogonadism may also explain the lower prevalence of low HDL in TCS compared to controls as androgens can have a suppressive effect on HDL.[53] In addition, the smaller waist circumference in TCS compared to controls while having a higher BMI may be explained by increased femoral adipose tissue deposition observed in hypogonadal compared with eugonadal patients.[54]

Studies of the effect of testosterone replacement on MetS and CVD risk in TCS are sparse. While such investigations in older men in the general population showed favorable effects on lipid metabolism, bone mineral density, muscle mass, and fat-free body mass,[55,56] the effects of testosterone replacement on CVD risk have been conflicting.[57] One clinical trial showed an excess of CVD adverse events in older men treated with testosterone compared with placebo,[58] but another trial in a similar population did not.[59] However, these findings may not apply to young and physically active TCS. For young TCS with symptomatic hypogonadism, testosterone replacement should be considered, and future research is needed to address both the benefits and risks of testosterone replacement therapy.

Inflammation is considered a critical pathogenic component of atherosclerosis.[60] de Haas et al. provided a comprehensive assessment of pro-inflammatory markers in chemotherapy-treated TCS, finding significantly elevated levels of several markers in patients with MetS vs. those without MetS.[17] Herein, we found that sICAM levels increased with increasing MetS risk even after adjustment for age and additional risk factors in multivariate analysis. sICAM is an adhesion molecule that serves a critical role in the adhesion and transmigration of leucocytes across the endothelial wall, an early step in the formation of the atherosclerotic plaque.[61] Epidemiological studies have shown strong, positive associations between sICAM levels and future CVD events in apparently healthy men and women.[27-29] Vaughn et al. reported sICAM levels to be higher in TCS treated with chemotherapy than surgery only, suggesting a direct mechanism for CVD through chemotherapy-induced endothelial dysfunction.[62] In vitro studies further support this hypothesis.[63-65]

There has been increasing interest in personalizing care for cancer survivors. One approach is to identify genetic variants that can predispose survivors to selected adverse health outcomes.[7] In this study, we evaluated a SNP (rs523349) in the steroid 5-α-reductase type II gene recently associated with MetS in TCS.[20] This SNP decreases enzyme activity and thus the conversion of testosterone to the more active metabolite dihydrotestosterone.[66] The frequencies of the wild type and variant rs523349 in our cohort were comparable to those in Boer et al[20] (Table 7); however, in our cohort with more than twice the sample size, we found no association with MetS. An approach that accounts for multiple genes involved in relevant pathways may better identify clinically actionable results that could inform risk-adapted management approaches.

The prevalence of MetS in our patients is within the range (17%–41%) reported in European studies of platinum-treated TCS (summarized in Table 8).[13,15-19] Although each European series used slightly different criteria for MetS than applied here, it is still possible to compare the prevalence of individual MetS components. The most pronounced component of MetS among our TCS was hypertension (43%). Haugnes et al[19] found significantly increased risks of hypertension in cisplatin-treated patients compared with surgically treated patients (≥45% vs. 34%) as did Willemse et al[18] (31% vs. 14%). The association between cisplatin-based chemotherapy, hypertension, and CVD in TCS is well-established, and has been reviewed elsewhere.[7,65]

Strengths and limitations:

Strengths of our study include the large number of patients, detailed medical chart abstraction, and use of contemporary and homogeneous platinum-based chemotherapy regimens. We used a definition for hypogonadism that is clinically-relevant and easily applicable to clinical practice.

However, any cross-sectional design has potential limitations and does not allow us to infer causation of evaluated risk factors to MetS, although prospective data collection is planned for this cohort. Also, the SNP of interest was imputed and not genotyped, although it was in perfect LD with a nearby genotyped SNP. Our participants also represent for the most part well-educated TCS followed at major academic institutions and the prevalence of MetS may be higher in community-based settings.

Moreover, participants in the population-based NHANES cohort may not be comparable to our TCS in terms of all relevant sociodemographic and lifestyle variables.

Conclusion and recommendations:

There is a high prevalence of metabolic abnormalities in TCS treated with chemotherapy at a relatively young age and shortly after completion of cancer treatment. The etiology of MetS in cancer survivors likely differs from the general population,[36] thus, applying criteria developed for the general population to cancer survivors may underestimate CVD risk. Importantly, longitudinal cohort studies of survivors are needed to develop more accurate risk prediction models for CVD. Meanwhile, it is reasonable to assume that management strategies for components of MetS may have similar positive effects on CVD prevention. Providers are encouraged to screen and adequately treat TCS for hypertension, dyslipidemia and hypogonadism. Further, all TCS should be encouraged to adopt practices consistent with a healthy lifestyle, including maintenance of ideal body weight, avoidance of tobacco use and engagement in regular exercise.

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Table 1: Criteria Used to Define Metabolic Syndrome (MetS)

Measure	**AHA/NHLBI modified NCEP ATPIII criteria for MetS[14]**	**Definition used for current study**
Elevated blood pressure	$BP_{systolic}$ ≥130 mmHg and/or $BP_{diastolic}$ ≥85 mmHg or Drug treatment for hypertension	$BP_{systolic}$ ≥130 mmHg and/or $BP_{diastolic}$ ≥85 mmHg or Drug treatment for hypertension*
Elevated waist circumference	Population- and country-specific definitions: U.S. ≥102 cm in men	≥102 cm
Elevated fasting glucose	≥100 mg/dL	Self-reported diabetes and Taking drug treatment for diabetes†
Reduced HDL	<40 mg/dL in males; or Drug treatment for reduced HDL	<40 mg/dL or Drug treatment for reduced HDL (including statins, fibrates and nicotinic acid)‡
Elevated triglycerides	≥150 mg/dL or Drug treatment for elevated triglycerides	≥150 mg/dL (fasting) or ≥175 mg/dL (non-fasting)‡ or Drug treatment for elevated triglycerides§
Metabolic syndrome	≥3 criteria	≥3 criteria

Abbreviations: AHA/NHLBI = American Heart Association/National Heart Lung Blood Institute BP = blood pressure; HDL = High density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Program's Adult Treatment Panel III

* Study participants were asked "Have you ever taken prescription medications for high blood pressure?" This criteria was considered met if participants answered "yes, current use"
† Study participants were asked "Has a doctor or other health care provider ever told you that you had one of the following conditions, or have you ever had one of the following procedures: 1) Diabetes requiring insulin? 2) Diabetes requiring tablets or pills?" This criteria was considered met if the participant answered "Yes" to either question. Haugnes et al[19] used a similar definition, but substituted "or" for "and". Neither Haugnes et al[19] nor the current study measured fasting glucose.
‡ Cutoff for non-fasting measurements based on joint consensus statement of European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine.[39]
§ Study participants were asked "Have you ever taken prescription medications for high cholesterol?". This criteria was considered met if participants answered "yes, current use". This may have included statins, fibrates and/or nicotinic acid.

Table 2: Clinical and Sociodemographic Characteristics of 486 Survivors of Testicular Cancer and Other Malignant Germ Cell Tumors at Clinical Evaluation

Characteristic	All patients N (%)	Metabolic Syndrome		*P*-value*
		Present N (%)	Absent N (%)	
Total	486 (100%)	102 (100%)	384 (100%)	
Clinical Characteristics				
Age at diagnosis, years				
Median [range]	30.3 [15.4-49.9]	35.2 [15.7-49.7]	29.7 [15.4-49.9]	**<.001**
<30	229 (47.1)	32 (31.4)	197 (51.3)	
30-39	159 (32.7)	39 (20.6)	120 (31.3)	
40-49	98 (20.2)	31 (30.4%)	67 (17.4)	
Age at clinical evaluation, years				
Median [range]	38.1 [18.7-68.4]	44.4 [20.8-68.4]	36.6 [18.7-68.1]	**<.001**
<30	101 (20.8)	9 (8.8)	92 (24.0)	
30-39	168 (34.6)	24 (23.5)	144 (37.5)	
40-49	138 (28.4)	40 (39.2)	98 (25.5)	
≥50	79 (16.3)	29 (28.4)	50 (13.0)	
Histologic type				
Seminoma	128 (26.3)	34 (33.3)	94 (24.5)	.07
Nonseminoma†	358 (73.7)	68 (66.7)	290 (75.5)	
Site				
Testis‡	433 (89.1)	89 (87.3)	344 (89.6)	.48
Extragonadal	53 (10.9)	13 (12.7)	40 (10.4)	
Platinum-based chemotherapy				
BEP	266 (54.7)	62 (60.8)	204 (53.1)	.20
EP	161 (33.1)	26 (25.5)	135 (35.2)	
Other§	59 (12.1)	14 (13.7)	45 (11.7)	
Cumulative dose of cisplatin, mg/m^2				
Median [range]	400 [198-800]	400 [200-600]	400 [198-800]	.16
<300	28 (5.8)	10 (9.8)	18 (4.7)	.33
300	152 (31.3)	34 (33.3)	118 (30.7)	
301-399	17 (3.5)	3 (2.9)	14 (3.6)	
400	264 (54.3)	50 (49.0)	214 (55.7)	
>400	22 (4.5)	5 (4.9)	17 (4.4)	
Other‖	3 (0.6)	0	3 (0.8)	
Cumulative dose of bleomycin, IU				
0	200 (41.2)	34 (33.3)	166 (43.2)	.17
>0-180,000	36 (7.4)	12 (11.8)	24 (6.3)	
181,000-270,000	178 (36.6)	38 (37.3)	140 (36.5)	
271,000-360,000	71 (14.6)	18 (17.6)	53 (13.8)	
>360,000	1 (0.2)	0	1 (0.3)	
Sociodemographic Characteristic				
Race				
White	414 (85.2)	94 (92.2)	320 (83.3)	.05
Non-white¶	72 (14.8)	8 (7.8)	64 (16.7)	
Marital status				
Not married#	195 (40.1)	31 (30.4)	164 (42.7)	**.022**
Married/Living as married	291 (59.9)	71 (69.6)	220 (57.3)	
Education				
Less than college graduate	169 (34.8)	47 (46.1)	122 (31.8)	**.006**

College graduate or more	309 (63.6)	53 (52.0)	256 (66.7)	
Other/unknown/prefer not to say	8 (1.6)	2 (2.0)	6 (1.6)	
Employment status				
Not employed	54 (11.1)	15 (14.7)	39 (10.2)	.19
Employed	432 (88.9)	87 (85.3)	345 (89.8)	

Abbreviations: BEP = bleomycin, etoposide, cisplatin; EP = etoposide, cisplatin; IU = international units; METs = metabolic equivalents; MetS = metabolic syndrome

* *P*-value from Wilcoxon Test for continuous variables or Chi-square for categorical variables. Missing values were not included in *P*-value calculation. Statistically significant *P*-values are bolded.
† Includes 5 patients with germ cell tumor, NOS or unidentified histology (4 without MetS and 1 had MetS)
‡ Includes one survivor with unknown primary tumor site who had MetS.
§ This category includes 14 survivors (11 without MetS and 3 with MetS) treated with ifosfamide/etoposide/cisplatin (VIP regimen), 3 survivors treated with carboplatin (all three with no MetS), and 41 survivors with other chemotherapy regimens (31 with no MetS and 10 with MetS). Chemotherapy regimen data was not available for one survivor who is diagnosed with MetS.
‖ Three survivors were treated with carboplatin instead of cisplatin.
¶ The non-white population consisted of 5 (1.0%) Black/African American; 18 (3.7%) Asian; 1 (0.2%) American Indian; 9 (1.9%) who identified more than one race; 24 (4.9%) other race; and 9 (1.9%) whose race was not stated.
# Not married includes 157 (32.3%) TCS who were single, 30 (6.2%) survivors who were widowed/divorced/separated, and 8 (1.6%) who preferred not to disclose marital status.

Table 3: Physical Examination and Laboratory Findings of 486 Survivors of Testicular Cancer and Other Malignant Germ Cell Tumors at Clinical Evaluation

Characteristic	All patients N (%)	Metabolic Syndrome		*P*-value*
		Present N (%)	Absent N (%)	
Total	486 (100%)	102 (100%)	384 (100%)	
Body mass index (kg/m²)				
Median [range]	27.7 [18.0-52.8]	31.2 [23.7-46.3]	26.9 [18.0-52.8]	**<.001**
<25 (normal)	121 (24.9)	5 (4.9)	116 (30.2)	
25-29 (overweight)	216 (44.4)	35 (34.3)	181 (47.1)	
30-39 (obese)	128 (26.3)	51 (50.0)	77 (20.1)	
≥40 (morbidly obese)	21 (4.3)	11 (10.8)	10 (2.6)	
Testosterone (ng/mL)				
Median [range]	3.7 [0.1- 4.6]	3.4 [0.1-4.6]	3.8 [0.2-3.9]	**<.001**
Low (≤3.0)	150 (30.9)	47 (46.1)	103 (26.8)	**<.001**
Normal (>3.0)	332 (68.3)	54 (52.9)	278 (72.4)	
Not available	4 (0.8)	1 (1.0)	3 (0.8)	
Luteinizing hormone (mIU/mL)				
Median [range]	7.9 [0.1-48.7]	7.8 [0.1-46.5]	8.0 [0.1-48.7]	0.32
Normal (<9.3)	279 (57.4)	58 (56.9)	221 (57.6)	.73
Above normal range (≥9.3)	200 (41.2)	39 (38.2)	161 (41.9)	
Not available	7 (1.4)	5 (4.9)	2 (0.5)	
Creatinine (mg/dL)				
Normal (<1.3)	401 (82.5)	87 (85.3)	314 (81.8)	.41
High (≥1.3)	85 (17.5)	15 (14.7)	70 (18.2)	
sICAM-1 (ng/mL)				
Median (range)	151 [40-882]	165 [95-633]	146 [40-882]	**<.001**
Lowest quartile (<124)	121 (24.9)	12 (11.8)	109 (28.4)	
2nd quartile (124-151)	122 (25.1)	25 (24.5)	97 (25.3)	
3rd quartile (152-193)	122 (25.1)	32 (31.4)	90 (23.4)	
Highest quartile (>193)	121 (24.9)	33 (32.4)	88 (22.9)	
***SRD5A2* rs523349 genotype, N (%)**				
Wild type (VV)	196 (40.3)	40 (39.2)	156 (40.6)	.61
Variant (VL/LL)†	209 (43.0)	47 (46.1)	162 (42.2)	
Not genotyped‡	81 (16.7)	15 (14.7)	66 (17.2)	

Abbreviations: sICAM-1 = serum soluble cell adhesion molecule-1

**P*-value from Wilcoxon Test for continuous variables or Chi-square for categorical variables. Missing values were not included in *P*-value calculation

† Includes 177 TCS who are heterozygous (VL) genotype and 32 with homozygous (LL) genotype.

‡ Samples from these patients had not been processed in time to be included in the genotyping performed for this study.

Table 4: Comparison of Metabolic Syndrome*, its Components and Selected Cardiovascular Disease Risk Factors among 486 Survivors of Testicular Cancer and Other Malignant Germ Cell Tumors with a Matched Normative Population*

	Platinum Study N (%)	NHANES N (%)	*P*-value†
Total	486 (100%)	486 (100%)	
Components of Metabolic Syndrome*			
Blood pressure			
Elevated or on BP medication	210 (43.2)	149 (30.7)	**<.001**
Normal (systolic <130 mmHg, diastolic <85 mmHg, and not on BP medication)	276 (56.8)	337 (69.3)	
Waist circumference			
≥102 cm	137 (28.2)	195 (40.1)	**<.001**
<102 cm	349 (71.8)	291 (59.9)	
Diagnosis of diabetes and use of medication			
Yes	19 (3.9)	21 (4.3)	.75
No	467 (96.1)	465 (95.7)	
High density lipoprotein cholesterol			
Low (<40 mg/dL) or on cholesterol medication‡	115 (23.7)	169 (34.8)	**<.001**
Normal (≥40 mg/dL and not on cholesterol medication)	371 (76.3)	317 (65.2)	
Triglycerides§			
Elevated or on cholesterol medication‡	195 (40.1)	174 (35.8)	.17
Normal	291 (59.9)	312 (64.2)	
Metabolic Syndrome*			
Yes (≥3 components)	102 (21.0)	109 (22.4)	.59
No (<3 components)	384 (79.0)	377 (77.6)	
Number of abnormal metabolic syndrome components			
0	151 (31.1)	154 (31.7)	.58
1	142 (29.2)	120 (24.7)	
2	91 (18.7)	103 (21.2)	
3	64 (13.2)	62 (12.8)	
4	30 (6.2)	39 (8.0)	
5	8 (1.7)	8 (1.6)	
CVD risk factors not included in the MetS definition			
Body mass index, kg/m²			
≥25 (overweight or obese)	365 (75.1)	336 (69.1)	**.04**
<25 (normal)	121 (24.9)	150 (30.9)	
Total cholesterol, mg/dL			
≥240	128 (26.3)	54 (11.1)	**<.001**
<240	358 (73.7)	432 (88.9)	
LDL cholesterol, mg/dL			
≥160	86 (17.7)	43 (9.3)	**<.001**
<160	400 (82.3)	418 (90.7)	
Smoking Status			
Never smoker	273 (56.2)	248 (51.0)	**<.001**
Former smoker	167 (34.4)	112 (23.1)	
Current smoker	45 (9.3)	126 (25.9)	
Not stated	1 (0.2)	0 (0.0)	
Moderate-intensity physical activity (3 to <6 METs)¶			
No	27 (5.6)	280 (57.6)	**<.001**
Yes	456 (93.8)	206 (42.4)	
Not stated	3 (0.6)	0 (0.0)	

Vigorous-intensity physical activity (≥6 METs)¶			
No	159 (32.7)	323 (66.5)	**<.001**
Yes	324 (66.7)	163 (33.5)	
Not stated	3 (0.6)	0 (0.0)	

Abbreviations: BP = blood pressure; CVD = cardiovascular disease; LDL = low-density lipoprotein; MetS = metabolic syndrome; NHANES = National Health and Nutrition Examination Survey

* Please refer to Methods for definition of MetS. Controls were 1:1 age-, race- and educational level-matched males from the National Health and Nutrition Examination Survey (NHANES).
† *P*-values obtained from Pearson chi-square test.
‡ Patients were asked if they had ever taken prescription medications for high cholesterol. These may have included statins, fibrates and/or nicotinic acid.
§ Cut-off points for elevated triglycerides are 150 mg/dL for those who had fasted for 8 hours or more and 175 mg/dL for those who had less than 8 hours of fasting prior to blood sample collection.[39]
‖ 25 participants in the NHANES cohort had missing data on LDL cholesterol.
¶ The vigorous-intensity and moderate-intensity physical activity groups are not mutually exclusive. There are a total of 9 different activities surveyed in the Platinum Study, some of which are moderate-intensity activities and some of which are vigorous-intensity activities. If a subject reported that he spent one hour walking a week (i.e. a moderate-intensity activity) and 30 minutes running per week (i.e. a vigorous-intensity activity), he was included as a yes for both “any moderate” and “any vigorous” activity.[23,24] Three survivors did not provide data on physical activity.

Table 5: Univariate Analyses of Potential Risk Factors for Metabolic Syndrome in Survivors of Testicular Cancer and Other Malignant Germ Cell Tumors

Variable	Metabolic Syndrome (Present vs. Absent) OR (95% CI)	*P*-value
Clinical Characteristic		
Age at diagnosis, per 10 years	**1.66 (1.28, 2.15)**	**<.001**
Age at clinical evaluation, per 10 years	**1.99 (1.57, 2.53)**	**<.001**
Cumulative dose of cisplatin, per 100 mg/m^2	0.78 (0.56, 1.09)	.15
Cumulative dose of bleomycin, per 90,000 IU	0.99 (0.95, 1.03)	.62
Sociodemographic Characteristic		
Race		
White	2.13 (0.98, 4.62)	.06
Non-white	Ref	
Marital status		
Married/living as married	**1.98 (1.17, 3.34)**	**.011***
Widowed/divorced/separated	1.87 (0.72, 4.87)	.20
Single*	Ref	
Education		
Less than college graduate	**1.86 (1.19, 2.91)**	**.007**
At least college graduate	Ref	
Employment		
Employed	0.64 (0.32, 1.27)	.20
Not employed	Ref	
Laboratory Finding		
Testosterone (ng/mL)		
Low (≤3.0)	**2.35 (1.5, 3.69)**	**<.001**
Normal (>3.0)	Ref	
LH		
Above normal range (≥9.3)	0.92 (0.59, 1.45)	.73
Normal (<9.3)	Ref	
Creatinine		
High (≥1.3)	0.77 (0.42, 1.42)	.41
Normal (<1.3)	Ref	
sICAM-1 Quartile (ng/mL)		
Lowest quartile (<123.53)	Ref	
2nd quartile (123.53-150.74)	**2.34 (1.12, 4.91)**	**.024**
3rd quartile (151.64-192.77)	**3.23 (1.57, 6.63)**	**.001**
Highest quartile (>192.77)	**3.41 (1.66, 6.98)**	**.001**
Health Behavior		
Smoking Status		
Former smoker	1.13 (0.71, 1.80)	.62
Current smoker	1.13 (0.53, 2.43)	.75
Never smoker	Ref	
Alcohol Use		
≤4 per week	0.77 (0.44, 1.32)	.34
5 per week to 1 daily	**0.36 (0.17, 0.74)**	**.006**
≥2 daily	0.76 (0.36, 1.62)	.48
Rarely or never	Ref	

Physical activity intensity		
Moderate (3 to <6 METs)		
Yes	1.17 (0.43, 3.18)	.75
No	Ref	
Vigorous (≥6 METs)		
Yes	**0.45 (0.29, 0.71)**	**.001**
No	Ref	

Abbreviations: CI = confidence interval; LH = luteinizing hormone; METs = metabolic equivalents; sICAM-1 = serum soluble cell adhesion molecule-1

* The apparent protective effect of single status is likely due to these participants being younger. The correlation is not significant when marital status is adjusted for age at clinical evaluation.

Table 6: Multinomial Logistic Regression Analyses of Potential Correlates with Metabolic Syndrome in Survivors of Testicular Cancer and Other Malignant Germ Cell Tumors*

Clinical Factor	OR	95% CI	*P*-value
Clinical and Sociodemographic Characteristics			
Age at clinical evaluation, per 10 years	**1.75**	1.33-2.30	**<.001**
Education			
Not college graduate	1.51	0.91-2.51	.11
College or post graduate	-	-	Ref
Marital status			
Not married	0.88	0.51-1.49	.62
Married/living as married	-	-	Ref
Laboratory Findings			
Serum testosterone (ng/mL)			
Low (≤3.0)	**2.06**	1.25-3.39	**.005**
Normal (>3.0)	-	-	Ref
sICAM-1 (ng/mL)			
Lowest quartile (<124)	-	-	Ref
2nd quartile (124-151)	**2.73**	1.24-6.06	**.01**
3rd quartile (152-193)	**3.21**	1.48-6.95	**.003**
Highest quartile (>193)	**3.58**	1.66-7.75	**.001**
Health Behaviors			
Average number of alcoholic drinks in past year			
≤4 per week	0.85	0.46-1.56	.60
5 per week to 1 daily	0.47	0.21-1.05	.07
≥2 daily	0.73	0.31-1.69	.46
Rarely or never	-	-	Ref
Vigorous intensity physical activity (≥ 6 METs)			
Yes	0.84	0.49-1.44	.53
No	-	-	Ref

Abbreviations: CI = confidence interval; METs = metabolic equivalents; OR = odds ratios; Ref = reference; sICAM-1 = serum soluble cell adhesion molecule-1; Bold indicates ORs with *P*<.05

* For the multinomial logistic regression analyses, 18 survivors were excluded due to unavailable data for one or more variables.

Table 7: Comparison of Prevalence of Metabolic Syndrome (MetS) in Genotype Groups for SNP rs523349 (V89L) in *SRD5A2* Gene between TCS in Boer et al[20] and in the Platinum Study

	Boer *et al* (n= 173)			**Platinum Study (n= 405)**		
	Wild type (VV) (n= 91, 52.6%)	**Variant (VL/LL)** (n= 82, 47.4%)*	***P*-value**	**Wild type (VV)** (n= 196, 48.4%)	**Variant (VL/LL)** (n= 209, 51.6%)†	***P*-value**
MetS‡ (%): all survivors	19%	33%	**.03**	20%	22%	.61
MetS (%): testosterone <4.3 ng/mL	33%	67%	Not reported	26%	25%	.98
MetS (%): testosterone ≥4.3 ng/mL	17%	20%	Not reported	16%	19%	.60

Abbreviations: MetS = metabolic syndrome; SNP = single nucleotide polymorphism; TCS = testicular cancer survivors

* 64 TCS with heterozygous (VL) genotype and 18 with homozygous (LL) genotype.
† 177 TCS with heterozygous (VL) genotype and 32 with homozygous (LL) genotype.
‡ For assessment of the metabolic syndrome, Boer et al. used the American Heart Association/National Heart Lung Blood Institute (AHA/NHLBI) classification[67] with the metabolic syndrome diagnosed if three or more of the following criteria were present: central obesity (waist circumference ≥102 cm), high triglycerides (≥1.7 mmol/L [≥150 mg/dL] or on medication), low high-density lipoprotein (HDL) cholesterol (<1.03 mmol/L [<40 mg/dL] or on medication), high blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg or on medication), and high glucose (≥5.6 mmol/L [100 mg/dL] or on medication).

Table 8: Prevalence of Metabolic Syndrome (MetS), Component Criteria, and Related Variables in Studies of Testicular Cancer Survivors (TCS)

	Haugnes et al (2007)[19] Norway				Wethal et al (2007)[16] Norway		de Haas et al (2012)[17] Netherlands (Groningen)	Willemse et al (2013)[18] Netherlands (Leiden)		
	Chemotherapy (BEP, PVB, other)[*]		Surgery only[†]	Healthy controls[‡]	Chemotherapy (BEP, PVB)[§]	Surgery only[‖]	Chemotherapy (BEP, EP, other)[¶]	Chemotherapy (BEP, other)[#]	Surgery only[**]	Healthy controls[††]
	Cis ≤850 mg	Cis >850 mg								
Number of patients	376	88	225	1150	218	140	173	176	58	360
Clinical and demographic characteristics										
Median age at TC diagnosis, years (range)	29 (15-52)	26 (15-48)	29 (16-53)	--	28 (23-34)	29 (24-35)	28 (16-25)[‡‡]	31.2 (14.2-54.2)	30.4 (20.0-61.9)	--
Median age at follow-up, years (range)	42 (23-60)	36 (25-59)	41 (24-60)	48 (30-60)	41 (34-46)	40 (36-47)	37 (19-59)	38.7 (18.2-63.4)	36.6 (20.1-69.5)	43.1 (18-70)
Median follow-up, years (range)	11.8 (5-22)	9.4 (5-20)	11.8 (5-21)	n/a	12 (8-15)	11 (7-15)	5 (3-20)	8.8 (0.6-30.2)	6.2 (0.1-2)	n/a
Calendar years of therapy	1980-1994			n/a	1980-1994		1977-2004	n/a	n/a	n/a
Smoking status (%)										
Never smoker	144 (41)	48 (58)	89 (42)	370 (33)	n/a	n/a	72 (42)	n/a[§§]	n/a[§§]	n/a[§§]
Ever smoker	207 (55)	35 (40)	123 (55)	734 (64)	n/a	n/a	100 (58)	n/a[§§]	n/a[§§]	n/a[§§]
Current non-smoker	n/a	n/a	n/a	n/a	122 (61.3)	71 (62.8)	107 (62)	n/a[§§]	n/a[§§]	n/a[§§]
Current smoker	n/a	n/a	n/a	n/a	77 (38.7)[‖‖]	42 (37.2)[‖‖]	65 (38)	n/a[§§]	n/a[§§]	n/a[§§]
Prevalence of MetS, components included in definition, and related variables, N(%)[¶¶]										
Metabolic syndrome[##]	149 (40)	42 (48)[***]	72 (33)	584 (51)	–[†††] (17.6)	–[†††] (6.3)	44 (25)	29 (16.7)[‡‡‡]	5 (8.8)[‡‡‡]	29 (8.1)
Hypertension	166 (45)[***]	42 (48)[***]	77 (34)	568 (50)	n/a	n/a	100 (59)	53 (31.0)[***]	8 (14.0)	81 (22.5)
Obesity[§§§]	60 (16)[‖‖‖]	23 (26)[***]	28 (13)	237 (21)	n/a	n/a	29 (17)	51 (29.3)	10 (17.5)	70 (19.4)
Hypercholesterolemia	246 (67)	63 (73)	151 (67)	963 (84)	n/a	n/a	n/a	n/a	n/a	n/a
Dyslipidemia (Low HDL or statin usage)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	35 (20.1)	7 (12.3)	36 (10.0)
Elevated triglycerides	n/a	n/a	n/a	n/a	n/a	n/a	50 (29)	61 (35.1)	13 (22.8)	84 (23.3)
Insulin resistance	n/a	n/a	n/a	n/a	n/a	n/a	n/a	11 (6.3)	2 (3.5)	16 (4.4)
Diabetes[¶¶¶]	11 (2.9)	2 (2.3)	4 (1.8)	33 (2.9)	5 (2.5)	2 (1.6%)	n/a	n/a	n/a	n/a
Age-adjusted OR (95% CI) for MetS										
Survivors vs. healthy controls	1.0[###] (0.8-1.2)			1.0	n/a	n/a	2.2[****] (1.5-3.3)	1.9[††††] (1.1-3.2)	n/a	1.0
Chemotherapy vs. surgery only	1.5[###,‡‡‡‡]	2.8[###] (1.6-4.7)	1.0	n/a	3.7 (1.5-9.1)	1.0	n/a	2.1 (0.8-5.7)	1.0	n/a
Chemotherapy vs. healthy controls	n/a	2.1[###] (1.3-3.4)	n/a	1.0	n/a	n/a	n/a	2.3[††††] (1.3-4.0)	n/a	1.0
Markers of gonadal function										
	Mean (SD)				**Median (IQR)**		**Median (range)**	**Median (range)**		
Testosterone (nmol/L)	15.6 (5.8)	14.8 (5.8)	16.2 (4.9)	14.4 (5.5)	15.3 (12.0-18.7)	16.2 (13.1-20.6)	15.0[§§§§] (9-31); MetS 18.0 (4-37); No MetS	14.1[§§§§,‖‖‖‖] (6.4-32.1)	16.8 (7.6-33.9)[§§§§]	n/a

Luteinizing hormone (IU/L)	n/a	n/a	n/a	n/a	5.2[ǁǁǁǁǁ] (3.6-7.8)	4.4 (3.2-6.7)	6.4 (2.5-18.7); MetS 5.5 (1.6-33.1); No MetS	6.8 (0.4-48.1)	5.9 (0.1-36.4)	n/a
Pro-inflammatory markers[¶¶¶¶]										
Leptin (ng/mL)	n/a	n/a	n/a	n/a	5.3 (3.0-9.5)	4.8 (2.3-9.7)	12.8[#####] (2.4-43.3); MetS 3.7 (0.2-66.1); No MetS	n/a	n/a	n/a
hsCRP (mg/L)	n/a	n/a	n/a	n/a	1.2 (0.7-2.4)	1.2 (0.6-2.0)	1.6 (0.2-13.4); MetS 1.1 (0.2-31.8); No MetS	<3 (<3-30)	<3 (<3-18)	n/a
Biochemical markers										
HDL (mmol/L)	n/a	n/a	n/a	n/a	1.1[ǁǁǁǁǁ] (1.0-1.3)	1.0 (1.1-1.4)	n/a	1.4 (0.6-4.1)	1.3 (0.7-2.7)	1.3 (0.6-2.9)
Triglycerides (mmol/L)	n/a	n/a	n/a	n/a	1.6[ǁǁǁǁǁ] (1.0-2.4)	1.2 (0.9-2.0	n/a	1.3[ǁǁǁǁǁ] (0.3-7.4)	1.0 (0.4-4.3)	1.2 (0.4-4.3)
Apolipoprotein A1 (g/L)	n/a	n/a	n/a	n/a	1.4 (1.3-1.5)	1.4 (1.3-1.6)	n/a	n/a	n/a	n/a
Clinical variables										
Systolic blood pressure (mm Hg)	n/a	n/a	n/a	n/a	125[ǁǁǁǁǁ] (120-140)	120 (115-130)	n/a	126 (90-200)	122 (95-185)	130 (110-200)
Body mass index (kg/m^2)	n/a	n/a	n/a	n/a	25.7 (23.8-27.9)	26.2 (24.3-28.6)	n/a	25.6 (18.4-36.4)	24.2 (16.8-38.5)	25.8 (19.5-42.6)
Risk factors for MetS[*****], Odds Ratio (95% CI; p value)										
Low serum testosterone[†††††]	0.96 (0.93-0.98; *P*=0.001)				0.93 (0.87-0.99; *P*=0.015)		4.1 (1.8-9.3; *P*=0.001)	1.7[‡‡‡‡‡] (0.8-3.6)		
Smoking status[§§§§§]	1.48 (1.00-2.18; *P*=0.273)				n/a		n/a	2.0[‡‡‡‡‡] (1.0-4.0)		
Cisplatin dose[ǁǁǁǁǁǁ]	3.05 (1.72-5.40; *P*=0.002)				n/a		n/a	n/a		
Luteinizing hormone	n/a				0.89 (0.81-0.98; *P*=0.021)		n/a	n/a		
Apolipoprotein A1	n/a				0.003 (0-0.019; *P*<0.001)		n/a	n/a		

Abbreviations: BEP = bleomycin, etoposide, cisplatin; BOP/VIP = bleomycin, vincristine, cisplatin/etoposide, ifosfamide, and cisplatin; CEB = carboplatin, etoposide, and bleomycin; CI = confidence interval; Cis = cisplatin; EP, etoposide, cisplatin; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; IQR = interquartile range; LH = luteinizing hormone; MetS = metabolic syndrome; n/a = not available; OR = odds ratio; PVB = cisplatin, vinblastine, bleomycin; PVB/BEP = alternating courses of PVB and BEP; SD = standard deviation; TC = testicular cancer; TCS = testicular cancer survivors

[*] Most patients received cisplatin-based chemotherapy (n=442, 95%), primarily in combination with etoposide and bleomycin or vinblastine and bleomycin. The number of patients or number of chemotherapy cycles in each treatment group was not provided. A subgroup (n=22, 5%) received carboplatin instead of cisplatin and were included in the Cis ≤850mg group, as MetS risk did not differ from those who received cisplatin-based chemotherapy. Additionally, 66% (n=304) of all chemotherapy-treated patients underwent retroperitoneal surgery and 10% (n=47) received additional radiotherapy (primarily infradiaphragmatic).

[†] Patients either underwent retroperitoneal surgery (n=124) or had been included in a surveillance program after orchiectomy without subsequent relapse. No patient received radiotherapy or chemotherapy.

[‡] Haugnes et al selected healthy controls from the Tromsø Study,[68] a population-based study conducted during the same time period as the TCS follow-up study, but excluded individuals 60 years or older or treated with testosterone substitution.

§ Treatment included cisplatin in combination with bleomycin, vinblastine (before 1985) or etoposide (post 1985), with or without surgery. Numbers of patients in each treatment category were not provided.
‖ Patients either underwent retroperitoneal lymph node dissection or were under surveillance after orchiectomy.
¶ Most patients received BEP or EP (n=159, 92%). The number of cycles of chemotherapy in each treatment group was not provided; neither were the number of patients. One patient (1%) received alternating BEP and PVB, while 13 patients (7%) received 'other' regimens that included CEB (carboplatin, etoposide and bleomycin) or BOP/VIP (bleomycin, vincristine, cisplatin/etoposide, ifosfamide, and cisplatin).
# All patients were diagnosed with disseminated TC and treated with orchiectomy and combination chemotherapy, primarily consisting of BEP (99%), with a median cisplatin dose of 604 (0-1750) mg. The number of treatment cycles was not provided. Two patients received carboplatin instead of cisplatin.
** Patients were diagnosed with Stage I disease and treated with orchiectomy alone.
†† Healthy controls consisted of men from the general population, living in the same geographical area, who had participated in a 2009 cardiovascular disease screening program; data were obtained from general practitioners' health screening records.
‡‡ Age at treatment
§§ Authors indicated that smoking behavior was comparable in all groups of patients and controls (smoker prevalence ~40%), but did not present numbers or percentages for each smoking status category, or clarify whether "smoker" was defined as "current smoker" or "ever smoker".
‖‖ Smoking data missing for 27 patients in the surgery group and 19 patients in the chemotherapy group.
¶¶ Haugnes and Wethal collected data on prevalence of diabetes. Haugnes reported Type 2 diabetes in 33 (2.9%) healthy controls, 4 (1.8%) TCS treated with surgery only, 11 (2.9%) TCS treated with Cis ≤850mg, and 2 (2.3%) TCS treated with Cis >850mg. Wethal reported Type 1 or Type 2 diabetes in 2 (1.6%) TCS treated with surgery only and 5 (2.5%) TCS treated with chemotherapy.
Studies used different criteria to define MetS. 1) Haugnes et al modified the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III)[69] definition so that MetS was present when a patient met ≥2 of the following criteria: hypertension (BP ≥140/90 mmHg or medication), obesity (BMI ≥30 kg/m^2), diabetes (self-reported diabetes or use of diabetes medication), or hypercholesterolemia (serum total cholesterol ≥5.2 mmol/l (≥200 mg/dL) or medication). 2) Wethal et al modified the NCEP-ATP III[70] definition so that MetS was present when a patient met ≥3 of the following criteria: hypertension (systolic BP ≥130 mm Hg or diastolic BP ≥85 mmHg, or medication), hypertriglyceridemia (serum triglycerides ≥1.70 mmol/L), dyslipidemia (HDL<1.04 mmol/L), or obesity (BMI ≥30 kg/m^2). Wethal excluded use of serum glucose measurements because subjects were non-fasting and also excluded a history of diabetes (n=15). 3) de Haas et al used the American Heart Association/National Heart, Lung, and Blood Institute classification,[67] which defines MetS as meeting ≥3 of the following criteria: central obesity (waist circumference ≥102 cm), hypertriglyceridemia (≥1.7 mmol/L or medication), dyslipidemia (HDL <1.03 mmol/L or medication), hypertension (systolic ≥130 mmHg or diastolic ≥85 mmHg or medication), or hyperglycemia (≥5.6 mmol/L or medication). 4) Willemse et al classified MetS by using two different guidelines. For consistency among studies presented in this table, we selected results derived from their application of the NCEP-ATPIII definition,[69] i.e., MetS is present when ≥3 of the following criteria are met: hypertension (systolic BP ≥135 mmHg and diastolic BP ≥85 mmHg), obesity (waist circumference ≥102 cm), insulin resistance (fasting glucose ≥6.1 mmol/L (110 mg/dL), dyslipidemia (HDL-cholesterol <1.03 mmol/L (40 mg/dL) or statin usage), or hypertriglyceridemia (serum triglycerides ≥1.7 mmol/L (150 mg/dL)).
*** *P*<0.05 between compared to surgery group
††† Number of patients not provided.
‡‡‡ Three TCS were diagnosed with diabetes mellitus before orchiectomy (n=1) or combination CT (n=2) and were excluded from these analyses, thus, prevalence estimates are based on a total of 57 surgery patients and 174 chemotherapy patients.
§§§ Obesity was defined as BMI ≥30 kg/m^2 (Haugnes et al) or waist circumference ≥102 cm (de Haas et al; Willemse et al).
‖‖‖ *P*<0.05 between compared to cisplatin >850 mg group.
¶¶¶ Haugnes et al included subjects with Type 2 diabetes. Wethal et al included subjects with Type 1 and Type 2 diabetes. Willemse et al indicated that five subjects developed diabetes during follow-up period, but did not specify their treatment group(s).
Adjustment for total testosterone did not significantly change any of the results.

**** Healthy controls consisted of 1,085 men (1,020 from the Retention of Renal and Vascular End-stage Disease (PREVEND) study[71,72] and 65 from the sibling controls participating in a childhood cancer survivor study (CCS)[73]) with data on waist circumference, blood pressure, fasting lipid and glucose levels, and medication use. Median age was 44 years (range 18-55).
†††† Smoking-adjusted risk of MetS for all TCS was 1.8 (95% CI, 1.1-3.1) compared to healthy controls, and for TCS treated with chemotherapy the risk was 1.5 (95% CI, 1.1-2.0) compared to healthy controls.
‡‡‡‡ OR was obtained from a figure where no numerical values were provided for the corresponding 95% CI or *P*-value.
§§§§ 34 TCS (1 surgery and 33 combination-CT) had serum testosterone levels <104 µmol/L.
‖‖‖‖ *P*<0.05 between surgery and chemotherapy groups
¶¶¶¶ Wethal et al also measured von Willebrand factor (%) in TCS who received chemotherapy (14.7; 11.9-18.9) or surgery alone (15.0; 10.7-18.8); *P*=0.63. de Haas et al also measured the following serum proinflammatory markers in TCS who received chemotherapy (median; range): 1) von Willebrand factor (%) in patients with MetS (98; 28-220) vs. those without MetS (96; 37-296); *P*=0.516. 2) adiponectin (µg/mL) in patients with MetS (5.00; 2.04-11.19) vs. those without MetS (7.23; 2.76-17.40); *P*<0.0001. 3) Fibrinogen (g/L) in patients with MetS (3.2; 1.5-5.0) vs. those without MetS (2.8; 1.2-6.3); p=0.038. 4) Tissue plasminogen activator (ng/mL) in patients with MetS (11.0; 3.7-21.0) vs. those without MetS (6.5; 1.5-21.0); *P*<0.0001. 5) Plasminogen activator inhibitor-1 (ng/mL) in patients with MetS (57.0; 7.8-312.0) vs. those without MetS (19.0; 3.0-62.0); *P*<0.0001. 6) Ratio of plasminogen activator inhibitor-1 to tissue plasminogen activator in patients with MetS (5.4; 1.5-31.6) vs. those without MetS (3.2; 0.5-7.1); *P*<0.0001.
P<0.0001 between chemotherapy patients categorized with MetS versus those without MetS.
***** All results derive from logistic regression models that used data only from TCS and designated MetS as the dependent variable. The Haugnes et al model adjusted for treatment group (referent: surgery), total testosterone (continuous), pack-years (referent: never smoker), physical activity (referent: no activity), educational level (referent: low), family status (referent: living alone), and age (continuous). The Wethal et al model adjusted for treatment group (referent: surgery), testosterone (continuous), LH (continuous), Apo-A1 (continuous), and age (continuous). The de Haas et al model only included adjustment for age. Willemse et al did not specify whether, if any, other variables were included in the model.
††††† Haugnes et al and Wethal et al treated testosterone as a continuous variable and found increased risk for MetS in TCS with low testosterone. de Haas et al and Willemse et al treated total testosterone as a categorical variable. Willemse et al found an increased risk of MetS in TCS with serum testosterone in the lowest quartile (<12.0 nmol/L), as compared with the upper 3 quartiles. de Haas et al found an increased risk for MetS in TCS with total testosterone <15 nmol/l, as compared with ≥15 nmol/L.
‡‡‡‡‡ *P*-value not provided.
§§§§§ Haugnes et al found an increased risk of MetS in TCS who smoked ≥20 pack-years, as compared with never smokers. Willemse et al found an increased risk of MetS in TCS who smoked, as compared with non-smokers. Willemse et al also found an increased risk of MetS in healthy controls who smoked, as compared with non-smokers: OR 1.6 (95% CI 0.7-3.4).
‖‖‖‖‖ Risk for MetS in TCS receiving a cisplatin dose >850 mg, as compared with TCS in the surgery group.

Acknowledgments:

The Platinum Study Group consists of Howard D. Sesso (Brigham and Women's Hospital); Clair J. Beard and Stephanie Curreri (Dana-Farber Cancer Institute); Lois B. Travis, Lawrence H. Einhorn, Mary Jacqueline Brames, and Kelli Norton (Indiana University); Darren R. Feldman, Erin Jacobsen, and Deborah Silber (Memorial Sloan-Kettering Cancer Centre); Rob Hamilton and Lynn Anson-Cartwright (Princess Margaret Cancer Center); Nancy J. Cox and Eric Gamazon (Vanderbilt University); M. Eileen Dolan and Omar El-Charif (University of Chicago); David J. Vaughn, Linda Jacobs, and Donna Pucci (University of Pennsylvania); Debbie Baker, Cindy Casaceli, Chunkit Fung, and Eileen Johnson (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).