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Prevalence and Consequences of Androgen Deficiency in Young Male Cancer Survivors in a Controlled Cross-Sectional Study

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Background: Testosterone replacement in hypogonadal males improves body composition, sexual function, and health-related quality of life. Male cancer survivors are at risk of androgen deficiency; however, when and in whom testosterone should be replaced remain unanswered questions.

Objective: The aim of our study was to define the prevalence of androgen deficiency in this patient group through assessment of testosterone levels and related measures.

Design: This was a cross-sectional, observational study of cases and controls. We recruited 176 cancer survivors and 213 controls, aged 25–45 yr.

Results: Of cancer survivors, 97% had received chemotherapy and 40% radiotherapy. Cancer survivors had lower total testosterone (tT) levels than controls (mean difference 2.67 nmol/liter; 95% confidence interval 1.58–3.76; $P = 0.003$), and 24 of 176 (13.6%; 95% confidence interval 9.3–19.5) had a tT less than 10 nmol/liter, which was less than 2.5% centile for controls. Cancer survivors had a greater fat mass, higher fasting insulin and glucose levels, increased fatigue, and reduced sexual function and health-related quality of life. In both cohorts, the tT correlated negatively with insulin levels and negatively with body fat mass; however, the difference in tT between them was independent of fat mass. We measured tT and SHBG and calculated bioavailable testosterone. The changes in calculated bioavailable testosterone were similar to tT.

Conclusions: A significant proportion of young male cancer survivors had a frankly low tT associated with an increased fat mass and insulin level compared with controls. These factors would be predicted to improve in response to testosterone replacement therapy and provide a powerful argument for an interventional study of testosterone therapy in young male cancer survivors. **(*J Clin Endocrinol Metab* 92: 3476–3482, 2007)**

TESTICULAR DAMAGE IS common in men treated with chemotherapy and radiotherapy (1, 2). Because the germinal epithelium of the testes is more susceptible to damage than the Leydig cell, infertility is a relatively frequent consequence, but testosterone deficiency is less common (3, 4). Testosterone replacement in the severely hypogonadal patient, regardless of cause, increases bone density and muscle mass, reduces body fat, and improves energy and sexual function (5). However, the diagnosis of testosterone deficiency is complex, and recent clinical guidelines recommend: "only making a diagnosis of androgen deficiency in men with consistent symptoms and signs and an unequivocally low testosterone level" (6). This provides a challenge for the physician when confronted by the young male cancer survivor who frequently has symptoms of fatigue and sexual dysfunction, and borderline testosterone levels.

In clinical practice the biochemical diagnosis of androgen deficiency is largely based on the measurement of total testosterone (tT). However, many laboratories only provide a single reference range for tT derived from samples taken at different times of the day. The timing of tT measurement is important because there is a distinct circadian rhythm with higher levels in the morning (7), and it is well recognized that tT levels decrease with age (8–10). In the largest longitudinal study of 890 men, there was an age-invariant decline in tT of 0.124 nmol/liter·yr (9). The lack of aged-matched data for young men presents a problem for the physician attempting to make a diagnosis of androgen deficiency in this age group. For these reasons we have specifically focused our study on young men aged 25–45 yr with matched controls, and been careful to take all measurements between 0800 and 1000 h. In this patient group, the majority of patients received chemotherapy, and only a small proportion had radiotherapy alone.

Howell *et al.* (2) investigated a group of cancer survivors who had received high-dose chemotherapy for a variety of malignancies. They identified a cohort of 36 men with bio-

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Abbreviations: ALP, Alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CV, coefficient of variation; β-CTX, C-terminal telopeptide; DXA, dual energy x-ray absorptiometry; E_2, estradiol; GHQ-12, General Health Questionnaire-12; HRQOL, health-related quality of life; RSE, Rosenberg Self-Esteem Questionnaire; SF-36, Short Form-36; TB, total body; TBI, TB irradiation; TFM, truncal fat mass; tT, total testosterone.

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chemical evidence of mild Leydig cell insufficiency, as defined by an increased LH level and a tT in the lower half of the normal range. These patients, aged 27–52 yr, had reduced bone mineral density (BMD), sexual activity, and alteration in mood (11, 12). Based on these observations, they completed a placebo-controlled study of testosterone replacement in a similar group of 35 cancer survivors (13). During the 12-month study period, there was no change in body composition, sexual function, or energy levels on testosterone treatment. The failure of an improvement on testosterone treatment may relate to small patient numbers, resistance to testosterone, or the fact that patients with a testosterone level in the normal range were selected.

The aims of our study were to investigate the prevalence of frankly low testosterone levels in a large cohort of younger male cancer survivors aged 25–45 yr compared with healthy controls, and to determine whether those with frank hypogonadism differed from survivors and controls without androgen deficiency with respect to body composition, sexual function, and health-related quality of life (HRQOL).

Patients and Methods

Ethics

The study was approved by the local ethics committee, and all subjects gave written informed consent.

Subjects

Cancer survivors. A total of 176 male cancer survivors were recruited from outpatient clinics. At consent, subjects were aged 25–45 yr, and had been treated for nonhormone-dependent cancers with cytotoxic chemotherapy and/or radiotherapy, including cranial irradiation or radiotherapy fields involving the testes. Survivors were defined as off active treatment and in remission for at least 2 yr before enrolling for the study. Patients were excluded if their original tumor was hormone dependent (*e.g.* prostate, breast) or they were currently receiving testosterone replacement therapy.

Controls. A total of 213 men aged 25–45 yr with no history of malignant disease or testosterone therapy were recruited both by advertisement in the community and from general practitioner surgeries by selecting consecutive names from the register of patients who fitted the age and gender criteria.

We chose to select both subject and controls that were able to sign informed consent and had no history of receiving testosterone replacement therapy. As such, we included men in both groups with preexisting health conditions such as diabetes, so that the sample was representative of the wider population. At the time of study, three cancer survivors and two controls were known to have diabetes.

Study design

This was a cross-sectional, observational study. All subjects underwent assessments of BMD, body composition, and quality of life. Information was collected regarding age and previous medical history. In addition, blood was taken for hormone assays.

Assessment of BMD and body composition

A single BMD measurement of the total body (TB) was measured by dual energy x-ray absorptiometry (DXA) using a Lunar Expert (software version 1.91) in 103 cases (73 cancer survivors and 30 controls) and Lunar Prodigy (software version 8.10.027) in 284 cases (100 cancer survivors and 184 controls) (GE Lunar Corp., Madison, WI). For both machines, manufacturer's precision of measurement for TB is 1%. The BMD was measured in gram per square centimeters and was weight adjusted. Body composition measurements of lean and fat mass were made from the TB DXA scans. The manufacturer (GE Lunar Corp.) was unable to supply cross-calibration information regarding TB and body composition measurements between the two machines. For quality assurance purposes, a spine phantom was measured during the period of the study and showed a 5% difference between the two devices. To address the issue of using two DXA machines, we performed three sets of analyses: 1) unadjusted results derived from both DXA devices, 2) with a correction factor to adjust in differences between the two devices, and 3) data from the Lunar Prodigy alone. The BMD and body composition results presented in Table 4 are the raw unadjusted values derived from both DXA devices. Furthermore, in our statistical analysis, we tested for an effect of machine type by including a machine type term in the linear model and observed no significant effect (of machine type) on the linear model predicting testosterone ($P = 0.344$).

Hormone assays

Blood was drawn in all subjects between 0800 and 1000 h after an overnight fast. tT, estradiol (E_2), LH, FSH, insulin, and C-terminal telopeptide (β-CTX) were all measured using electrochemiluminescence immunoassays (Roche Diagnostics, Indianapolis, IN). Interassay coefficients of variation (CVs) were less than 1.1, 5.7, 1.2, 1.8, 1.9, and 1.8%, respectively, for tT, E_2, LH, FSH, insulin, and β-CTX. SHBG was measured by an immunometric assay (Immulite 2000; Diagnostic Products Corp., Los Angeles, CA; SHBG: interassay CV 2.5%). Glucose was measured by Vitros GLU Slides (Ortho-Clinical Diagnostics, Inc., New York, NY; interassay CV 1.9%). Bone-specific alkaline phosphatase (ALP) and ferritin were both measured using chemiluminescent immunoassays (Beckman Coulter Ireland, Inc., Galway, Ireland; interassay CV 1.7% and 2.6, respectively). IGF-I was measured by immunoradiometric assay (Nichols Institute Diagnostics, San Clemente, CA; interassay CV 10.3%). All precision information was taken from the manufacturer's serum data. Lower detection limits were: tT 0.069 nmol/liter; E_2 18.4 pmol/liter; LH 0.10 mIU/ml; FSH 0.10 mIU/ml; insulin 0.2 μU/ml; β-CTX 0.01 ng/ml; SHBG 0.02 nmol/liter; glucose 1.11 mmol/liter; bone-specific ALP 0.1 μg/liter; ferritin 0.2 ng/ml; and IGF-I 6 ng/ml. Free testosterone levels were calculated from the tT and SHBG measurements using the formula given by Vermeulen *et al.* (14). Free Estrogen Index was calculated by: (tE_2/SHBG * 100).

Quality of life assessment

General well-being, self-esteem, fatigue, and sexual function were assessed on a touch-screen computer using several validated questionnaires. HRQOL was assessed using the Short Form-36 United Kingdom version 2 (SF-36) (QualityMetric Inc., Lincoln, RI) and General Health Questionnaire-12 (GHQ-12) (NFERNelson Publishing Co. Ltd., Swindon, Wiltshire, UK). Self-esteem was assessed using the Rosenberg Self-Esteem Questionnaire (RSE) (NFERNelson Publishing Co. Ltd). Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy Fatigue Scale Version 4 (Elmhurst Northwestern Healthcare, Evanston, IL). Sexual function was assessed using the Derogatis Interview for Sexual Functioning-SR II (male version) (15).

Statistical analyses

All statistical analyses were done using SPSS for Windows (SPSS, Inc., Chicago, IL). All medical, biochemical, bone density, and body composition data were plotted and tested for normality. Means, SE values, and confidence intervals (CI) were estimated and reference intervals defined. Subjects (survivors and controls) were split into categories by half-decade of age. The two independent samples Student's *t* test was used for comparisons of continuous outcome data between controls and survivors and within groups at different thresholds of testosterone. χ^2 Tests were used for comparisons of dichotomous variables between the groups. To allow for multiple comparisons, we have reported Bonferroni corrected *P* values and 95% confidence limits. The Pearson correlation coefficient (r) was calculated and interpreted such that an r value greater than ± 0.4 implies a weak correlation, ± 0.6 a moderate correlation, and ± 0.8 a strong correlation.

Results

Control and patient details (Table 1)

A total of 176 male cancer survivors and 213 controls aged between 25 and 45 yr were studied. The mean age of survivors (37.3 yr) was similar to that of the controls (36.4 yr; $P = 0.11$). The mean age of diagnosis was 28.6 yr (SD 8.3, range 1.2–41.9). Of patients, 97% had received chemotherapy, and 40% had received radiotherapy. There were 11 men who received a mean dose of 3355 cGy in a mean of 18 fractions, either directly or indirectly to the testes. Of these, one man also received total body irradiation (TBI), including the testes, of 1200 cGy in six fractions. A further four men had TBI with a mean dose of 1330 cGy in eight fractions. There were 15 men who received radiation to the brain with a mean dose of 3144 cGy in 18 fractions. Three of these men later received further radiation to the brain with a mean extra dose of 1647 cGy in nine fractions.

Testosterone levels (Fig. 1)

There was a significant ($P = 0.012$) age-dependent decrease in tT levels with tT levels declining by 0.2 nmol/liter (95% CI 0.1–0.3) for every 1-yr increase in age. There was no statistical evidence that this relationship, between age and tT, was different in survivors and controls ($P = 0.240$). Overall, tT levels were significantly lower in cancer survivors compared with controls (mean difference 2.7 nmol/liter; 95% CI 1.6–3.8; $P = 0.003$). After allowing for age, on average tT levels were 2.5 nmol/liter lower (95% CI 1.4–3.6; $P = 0.012$) in cancer survivors compared with controls. In the cancer survivors, the correlation between tT and age at diagnosis ($r = -0.28$; $P = 0.002$) was stronger than that with age at study ($r = -0.16$, 0.240), *i.e.* the older the patient at diagnosis, the lower the testosterone level. In cancer survivors there was no difference in tT between survivors who received radiotherapy and those who did not (mean difference 0.8; $P = 0.240$), and there was no difference according to diagnosis or radiation field. Of 176 survivors, 24 (13.6%) (95% CI 9.3–19.5) had a tT less than 10 nmol/liter, which was less than 2.5% centile for controls.

For the calculated bioavailable testosterone, the age-related changes between controls and survivors were similar to those seen with tT, but less marked.

TABLE 1. Primary diagnosis for 176 male cancer survivors, frequency of chemotherapy and of radiotherapy fields in 71 survivors who received radiotherapy

	n (%)
Cancer diagnosis	
Lymphoma	72 (40.9)
Germ cell (testicular)	68 (38.6)
Leukemia	11 (6.3)
Gastrointestinal	7 (4.0)
Brain	6 (3.4)
Sarcoma	5 (2.8)
Skin	1 (0.6)
Other	6 (3.4)
Received chemotherapy	170 (96.5)
BEP	45 (26.2)
ChlVPP/PABIOE	17 (9.9)
CHOP	16 (9.3)
POMB/ACE	10 (5.8)
Carboplatin	10 (5.8)
5FU (QUASAR)	8 (4.7)
Other	64 (38.3)
Received radiotherapy	71 (40.3)
Local (involved) field	29
Locoregional (thorax)	20
Locoregional (abdomen)	7
Wide field (thorax)	8
Wide field (abdomen)	2
Extended field (thorax/abdomen)	1
TBI	4

BEP, Bleomycin, etoposide, cisplatin; ChlVPP/PABIOE, chlorambucil, vinblastine, procarbazine, prednisolone/prednisolone, doxorubicin, bleomycin, vincristine, etoposide; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; 5FU, fluorouracil; POMB/ACE, bleomycin, vincristine, cisplatin, etoposide, actinomycin D, cyclophosphamide, methotrexate.

Correlations with tT (Table 2)

The strongest correlation for tT was with SHBG, and almost identical results were seen for controls and cancer survivors. tT was negatively related to insulin, TB fat mass, and total trunk fat mass, and a very similar relationship was seen in controls and cancer survivors, although the correlations were stronger in the cancer survivors. Of importance, no relationship with a correlation ± 0.4 was seen among measures of quality of life, fatigue, sexual function, and tT.

Relationship between tT and truncal fat mass (TFM) (Fig. 2)

There was a negative correlation of −0.43 ($P = 0.012$) between tT and TFM. Linear regression modeling found that there was no statistical evidence that this relationship, between tT and TFM, was different in survivors and controls ($P = 0.240$). The linear regression model suggested a decline in tT of 0.33 nmol/liter tT (95% CI 0.25–0.41; $P = 0.012$) per kg increase in TFM. However, as can be seen by the two parallel regression lines, there was a 1.9 nmol/liter (95% CI 0.8–2.9; $P = 0.012$) difference in tT between the controls and cancer survivors, which was consistent for all levels of fat mass observed in the sample, *i.e.* after allowing for a patient's fat mass, there is still a difference in tT levels between the healthy controls and cancer survivors.

Relationship between tT and TFM and age

Multiple linear regression models suggested that there was no interaction between age and TFM when trying to predict tT ($P = 0.240$). Therefore, age and TFM can be regarded as independent predictors of tT. Table 3 shows the relationship among tT and three explanatory variables of age, TFM, and group simultaneously. In this model, TFM and group (cancer survivor or control) are statistically significant predictors of tT, but age is not ($P = 0.06$).

Comparison of variables between controls and survivors (Table 4)

There was no difference in height between controls and cancer survivors, but the cancer survivors had a greater fat mass than controls. LH levels were significantly higher in the survivors as were FSH levels, but no differences were seen according to diagnosis or radiotherapy field. Fasting blood

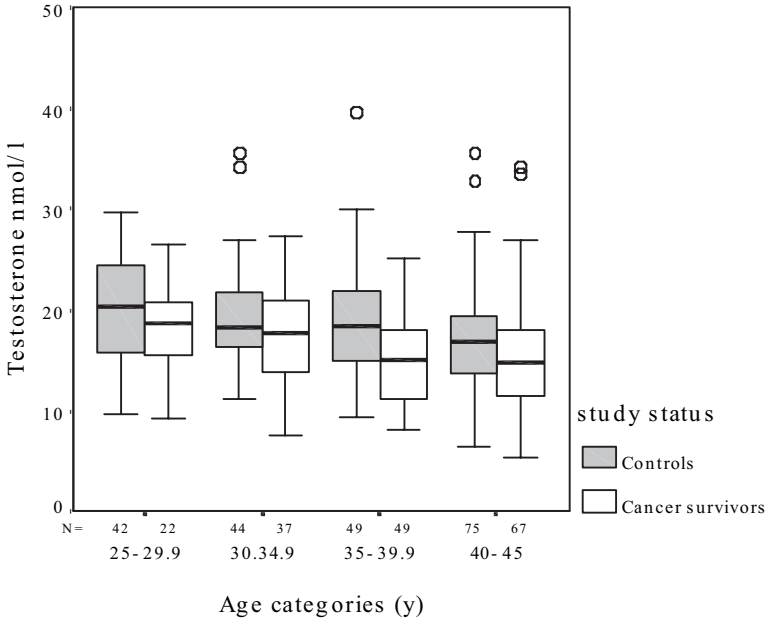

FIG. 1. Box and whisker plot of tT (nmol/liter) in survivors and controls on the y-axis by half-decades of age on the x-axis. The numbers (N) in each subcategory are given on the x-axis.

glucose levels were significantly higher in the cancer survivors, as were the insulin levels. Insulin and body mass index (BMI) were correlated r = 0.54, however, the difference in insulin levels between the groups remains after allowing for BMI, *i.e.* insulin is 2.04 μU/ml higher in survivors compared with controls (95% CI 0.62–3.47). Ferritin levels were significantly higher in cancer survivors than controls, and within the survivor cohort, ferritin levels were significantly higher in patients treated for leukemia. Quality of life scores showed significantly impaired quality of life in the survivors compared with the healthy controls using the SF-36, but not the GHQ-12. There was no difference in self-esteem between the two groups as measured by the RSE. Fatigue and sexual function were significantly impaired in the cancer survivors compared with the healthy controls.

TABLE 2. Correlations with tT in which the r value was either more than 0.4 or less than −0.4 in either the controls or survivors

Variable	Controls	Survivors
Total fat mass		
r value	−0.349	−0.473
P value[a]	0.0009	0.0009
n	209	172
TB fat mass		
r value	−0.318	−0.487
P value[a]	0.0009	0.0009
n	209	172
E_2		
r value	0.442	0.277
P value[a]	0.0009	0.018
n	210	175
SHBG		
r value	0.588	0.584
P value[a]	0.0009	0.0009
n	210	175
Insulin		
r value	−0.425	−0.426
P value[a]	0.0009	0.0009
n	209	174

[a] Statistical significance.

Analysis of variables by percentile of tT

We performed a within-group comparison of variables between those who had a tT level below a specific threshold (percentile) and those with a tT level above this percentile. The threshold tT values were derived from the control population. For both the cancer survivors and controls, subjects with a tT level less than the 50th centile still had a significantly greater BMI, TFM, and insulin level compared with subjects who had a tT greater than the 50th centile. Quality of life was also impaired at most thresholds below the 50th centile for tT in survivors, but there was no difference seen in controls. We dichotomized the testosterone levels in the cancer survivors into two groups: low (tT $<$ 10 nmol/liter, less than the 2.5% percentile for the testosterone levels in the health controls) and normal (tT $\geq$ 10 nmol/liter) and used multiple logistic regression with this binary outcome to see what factors were associated with a "low" testosterone level in cancer survivors. Multiple logistic regression suggested that SHBG, FSH, insulin, and SF-36 score were significantly associated ($P < 0.05$) with a low testosterone level in cancer survivors.

LH levels were not significantly higher in the patients with a tT less than 10 nmol/liter compared with those with a tT more than 10 nmol/liter: mean LH 8.06 *vs.* 7.07 mIU/ml, respectively ($P = 0.3$). In the controls the 2.5–97.5% range for LH was 1.98–8.79 (mean = 4.8), so we used 8.8 mIU/ml as upper limit for normal. In the cancer survivors, 42 of 176 (23.9%) had an LH more than 8.8 mIU/ml. Of the 24 survivors with a tT less than 10 nmol/liter, only eight had an increased LH, although 19 had an increased FSH. In the five of 24 survivors with low tT but normal LH and FSH, none had received cranial irradiation. In the 42 cancer survivors with an increased LH, only eight had a low tT less than 10 nmol/liter, and in the 97 patients with an increased FSH, only 19 had a low tT less than 10 nmol/liter. E_2 did not differ between survivors with a low or increased LH.

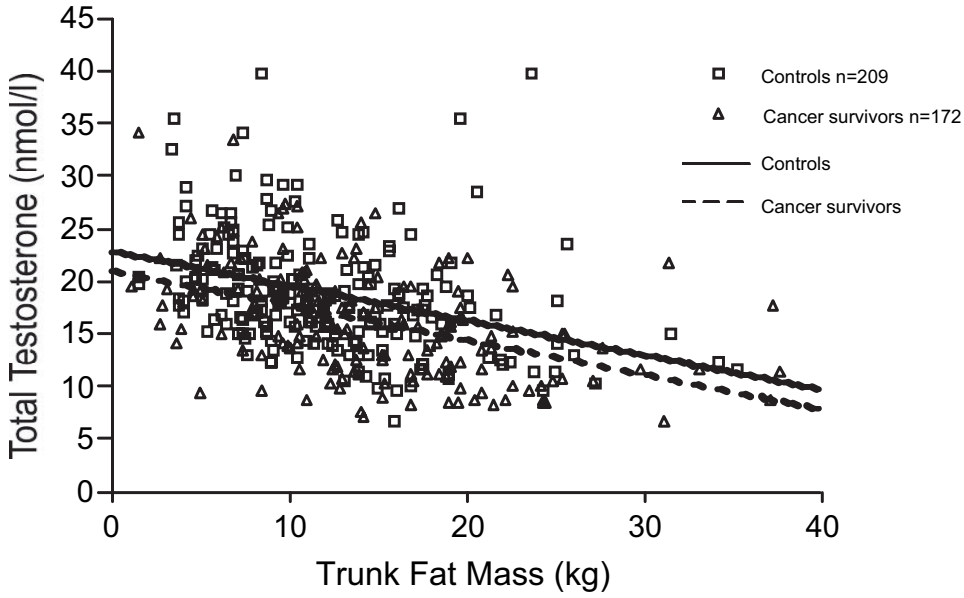

FIG. 2. The relationship between TFM (kg) and tT (nmol/liter) in controls and survivors. The relationship is linear, and the difference between the intercepts in the regression lines is significant ($P = 0.00036$). However, the slopes of the regression lines were not significantly different ($P = 0.56$). The equations for the regression lines are given as: tT = 22.75 − 0.33 TFM − 1.86 group [SE (0.58) (0.04) (0.52) R^2 (0.21)].

BMD and body composition data (Table 4)

To verify the robustness of the data, given the change in DXA machine during the study, analysis was repeated using a correction factor as described in the *Patients and Methods*, and also data derived from a single machine were analyzed. The only significant difference among the three analyses was that lean body mass was significantly different between the groups after the correction factor was applied, and data derived from the Lunar Prodigy alone showed a more marked difference for TB and regional fat. In summary, all three analyses showed no difference in BMD between the survivors and controls, but the analyses did show that survivors had a greater TB and TFM.

Discussion

We found that a significant proportion (13.6%) of young male cancer survivors have a frankly low tT (<10 nmol/liter) compared with matched healthy controls. Patients with low tT had an increased fat mass, fasting glucose and insulin levels, and reduced HRQOL compared with patients with normal testosterone levels. In both patients and controls, the tT showed a negative correlation with fat mass, however, the reduced tT levels seen in cancer survivors could not be explained by this difference in fat mass.

Appropriate biochemical measures for defining androgen deficiency have been much debated over the last decade (16).

TABLE 3. Regression coefficients for multiple linear regression model to predict testosterone

	Coefficients		*t*	Significance	95% CI for B	
	B	SE			Lower bound	Upper bound
Model 1						
Intercept	25.63	1.61	15.88	0.00001	22.46	28.81
Age	−0.08	0.04	−1.89	0.060	−0.017	0.00
TFM (kg)	−0.31	0.04	−8.24	0.00001	−0.38	−0.23
Group	−1.86	0.52	−3.60	0.004	−2.87	−0.84

Dependent variable: testosterone (nmol/liter).

We measured tT and SHBG, and calculated bioavailable testosterone using a well-established formula (7). The changes in calculated bioavailable testosterone were similar to tT, both for age-related changes and comparisons between patients and controls; thus, bioavailable testosterone appeared to provide no extra information.

We believe the strengths of our study rest with its focus on young men. We observed an age-related decline in tT levels in our control cohort, and this is consistent with previous reports that included older men (9, 10). In cancer survivors the men aged 40–45 yr had significantly lower tT levels than those aged 25–30 yr. In our controls the lower 2.5% centile for tT was 10 nmol/liter, and this is consistent with the published literature for the lower limit of the normal range in healthy young men. In recent clinical guidelines, the lower limit for tT was quoted as 10.4 nmol/liter (300 ng/dl) (6).

It is believed that Leydig cell function is more susceptible to radiation damage in prepubertal life (17); thus, one might have expected that the younger the patient and the further out from treatment, the lower the tT would have been. However, the opposite was true: the older the patients at treatment, the lower the tT, and there was no relationship between length of time from diagnosis and tT.

The measurement of LH and FSH levels is used to distinguish between primary (testicular) and secondary (pituitary) hypogonadism. In cancer survivors exposed to chemotherapy, it would be expected that most patients would have primary hypogonadism, and in those exposed to cranial irradiation alone, secondary hypogonadism. Almost all our patients had received chemotherapy, and as expected, we found that cancer survivors had significantly higher LH levels compared with controls. However, there was no difference in LH levels according to diagnosis, whether the patient received radiotherapy or by radiotherapy field. LH levels did not correlate with tT in either cancer survivors or controls, and even more importantly, LH levels did not differ within patient groups between those with a frankly low tT and those with a normal tT. These results are surprising and not what

TABLE 4. Comparison of variables between controls and cancer survivors

Variable	Controls, mean (n, SD)	Survivors, mean (n, SD)	Difference (CI)	*P* value[a]
Demographics				
Age (SD)	36.4 yr (213, 6.0)	37.3 yr (176, 5.76)	−0.96 yr (−2.14–0.21)	0.560
Pack yr smoked	3.44 (213, 7.6)	5.03 (176, 9.5)	−1.58 (−3.32–0.16)	0.560
Units alcohol per wk	16.8 (213, 14.0)	15.6 (176, 15.1)	1.21 (−1.73–4.14)	0.560
Height (m)	1.79 (213, 0.07)	1.79 (176, 0.07)	0.004 (−0.010–0.017)	0.560
Weight (kg)	85.5 (213, 14.3)	88.9 (176, 17.2)	−3.43 (−6.57 to −0.28)	0.560
Biochemical measures				
tT (nmol/liter)	18.75 (210, 5.55)	16.07 (175, 5.26)	2.67 (1.58–3.76)	**0.003**
FAI-V	0.44 (210, 0.12)	0.37 (175, 0.11)	0.06 (0.04–0.09)	**0.003**
E_2 (pmol/liter)	104.9 (210, 24.4)	106.8 (175, 27.5)	−1.88 (175–27.5)	0.560
FEI	422.9 (210, 199.2)	446.3 (175, 27.5)	−23.3 (−65.2–18.6)	0.560
SHBG (nmol/liter)	28.76 (211, 11.2)	27.7 (17.5, 11.2)	1.05 (−1.20–3.30)	0.560
LH (mIU/ml)	4.79 (210, 1.77)	7.20 (174, 4.05)	−2.41 (−3.06 to −1.76)	**0.003**
FSH (mIU/ml)	3.94 (210, 2.06)	12.85 (174, 9.56)	−8.90 (−10.36 to −7.45)	**0.003**
IGF-I (ng/ml)	161.5 (209, 47.5)	156.9 (171, 47.6)	4.63 (−5.02–14.29)	0.560
β-CTX (ng/ml)	0.45 (210, 0.16)	0.42 (174, 0.39)	0.03 (−0.02–0.09)	0.560
Bone-specific ALP (μg/liter)	12.63 (210, 3.64)	13.09 (175, 4.89)	−0.459 (−1.33 to 0.42)	0.560
Ferritin (ng/ml)	86.6 (210, 62.4)	164.4 (174, 191.6)	−77.8 (−107.6 to −47.9)	**0.003**
Glucose (mmol/liter)	5.3 (211, 0.5)	5.6 (175, 0.8)	−0.21 (−0.35 to −0.07)	**0.006**
Insulin (μU/ml)	8.4 (209, 4.91)	11.61 (174, 11.04)	−3.20 (−4.98 to −1.42)	**0.011**
BMD and body composition (unadjusted)				
TB BMD (g/cm^2)	1.271 (213, 0.94)	1.293 (173, 0.95)	−0.021 (−0.041 to −0.002)	0.560
BMI (kg/m^2)	26.5 (213, 4.0)	27.6 (176, 5.1)	−1.16 (−2.07 to −0.26)	0.392
TB fat mass (kg)	21.1 (212, 10.1)	24.9 (173, 11.2)	−3.8 (−5.9 to −1.7)	**0.028**
TB lean mass (kg)	59.1 (212, 6.5)	58.0 (173, 7.6)	0.7 (−0.3 – 2.6)	0.560
TFM (kg)	12.3 (212, 6.3)	14.5 (173, 7.1)	−2.2 (−3.6 to −0.9)	**0.028**
Truncal lean mass (kg)	28.5 (212, 3.9)	28.7 (173, 5.8)	−0.1 (−1.1–0.8)	0.560
Psychometric measures				
SF-36	82.6 (213, 11.7)	72.4 (171, 18.5)	10.1 (6.9 to 13.3)	**0.003**
RSE	17.8 (213, 4.8)	18.6 (171, 5.5)	−0.85 (−1.9–0.2)	0.560
GHQ-12	10.7 (213, 4.6)	11.12 (171, 5.5)	−0.45 (−1.5–0.591)	0.560
FACIT fatigue	45.0 (213, 7.1)	39.6 (171, 10.8)	5.4 (3.52–7.3)	**0.003**
DISF-SR II	103.3 (213, 20.8)	92.0 (171, 32.1)	11.26 (5.8–16.9)	**0.005**

FACIT, Functional Assessment of Chronic Illness Therapy; FAI-V, free testosterone level; FEI, Free Estrogen Index.
[a] *P* values for comparison between subjects and controls (*bold*, $P < 0.05$).

would be predicted, and we do not have a ready explanation. We wondered whether cranial irradiation could explain the results, but in the 24 cancer survivors with a tT less than 10 nmol/liter, only eight had an increased LH, and in those without an increased LH, none had received cranial irradiation. In contrast, 19 of the 24 had an increased FSH; however, in the 97 patients with an increased FSH, only 19 had a low tT. Thus, the presence of an increased LH or FSH did not predict low tT levels, and this did not appear to be confined to any specific patient group according to diagnosis or treatment. LH levels maybe influenced by E_2 levels. E_2 levels did not differ between cancer survivors and controls. In the controls, E_2 levels were significantly lower in the patients with the lower tT levels, but not in the cancer survivors. However, there was a significant positive correlation between E_2 and tT, and, thus, E_2 was lower with lower tT, and this was greater for controls than cancer survivors. On balance, our results suggest that in cancer survivors, the measurement of LH cannot be used to define androgen deficiency.

We found no difference in BMD or markers of bone turnover between survivors and controls. It is recognized that some patient groups do have an increased fracture rate after cancer treatment for prostate (18) and breast (19), but this is likely to be a consequence of hormone deficiency rather than the cancer treatment *per se*. The change in DXA machine from a Lunar Prodigy to a Lunar Expert during the study was an unavoidable limitation; however, there was no evidence of effect of machine type on the results, and analysis from Prodigy machine alone found similar results.

We observed a significant relationship among fat mass, TFM, and tT levels in both patients and controls. tT decreased by 0.33 nmol/liter (95% CI 0.25–0.41) for every additional kilogram of fat mass. The relationship between tT and fat mass has been reported in men of all ages (20, 21). We also found that insulin and blood glucose levels were increased in both patients and controls with lower testosterone levels. There is increasing evidence for a relationship among tT, fat mass, and insulin sensitivity, and low tT levels have been related to mortality (22), although an intriguing historical study of male castrati did not show an increase in mortality (23). In the cancer survivors, tT levels were on average 2.67 nmol/liter lower than the controls, and this difference was independent of the difference in fat mass. This suggests that cancer treatment results in a decrease in tT and that this decline is not just a consequence of increased adiposity. Previous studies have shown conflicting effects of testosterone on insulin sensitivity (6). In normal men testosterone did not increase insulin sensitivity (24), but it did in middle-aged obese men (25) and in diabetic patients (26). We can speculate that cancer survivors may be at an increased risk for mortality related to their low tT level, which could potentially be reversed by testosterone replacement.

We observed that ferritin levels were significantly higher in cancer survivors than controls, specifically in the patients

who had a diagnosis of leukemia. It is recognized that a late effect of leukemia treatment is iron overload (27, 28). However, it is also possible the increased ferritin levels could reflect liver damage. If so, one might anticipate a relationship with SHBG, a liver-derived binding protein, and/or that SHBG would differ between patients and controls, but this was not the case. Iron overload states are a cause of hypogonadism, and one could speculate that if certain subsets of cancer survivors have a mild iron overload, this could contribute to the reduced tT levels.

Cancer survivors had significantly impaired HRQOL, fatigue, and sexual function compared with controls, but no difference in self-esteem. However, none of the questionnaires showed an overall correlation with tT levels, and in the controls, results did not differ between subjects with a low or high tT level. These results suggest that the impaired HRQOL in cancer survivors is not solely related to androgen deficiency, but the observation that patients with lower tT have greater impairment does suggest that replacement therapy may improve these symptoms.

In conclusion, our study provides an important starting point from which to develop a large randomized placebo-controlled trial of testosterone replacement in selected cancer survivors with androgen deficiency. Such a prospective study could address the issue of which cancer survivors would benefit from testosterone replacement.

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