Imaging, Diagnosis, Prognosis

Serum Sex Steroids Depict a Nonlinear U-Shaped Association with High-Risk Prostate Cancer at Radical Prostatectomy
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Abstract

**Purpose:** To assess the association between preoperative serum total testosterone (tT), 17β-estradiol (E₂), sex hormone–binding globulin (SHBG), and tT–E₂ ratio values with high-risk prostate cancer (as defined by the National Comprehensive Cancer Network practice guidelines) at radical prostatectomy.

**Experimental Design:** Serum E₂, tT, and SHBG were dosed the day before surgery (7:00–11:00 am) in a cohort of 724 candidates to radical prostatectomy. Restricted cubic spline functions tested the association between predictors (i.e., model 1: age, body mass index, and serum tT, E₂, and SHBG levels; model 2: tT–E₂ values instead of tT and E₂ levels) and high-risk prostate cancer.

**Results:** Low-, intermediate-, or high-risk prostate cancer was found in 251 (34.7%), 318 (43.9%), and 155 (21.4%) patients, respectively. Patients in the high-risk class showed the lowest tT, E₂, and tT–E₂ ratio values (all \( P < 0.02 \)). At univariate analysis, only age, tT, E₂, and tT–E₂ ratio values were significantly associated with high-risk prostate cancer (all \( P < 0.006 \)). At multivariate analyses considering model 1 variables, age (\( P = 0.03 \)), serum tT (all \( P < 0.001 \)), and E₂ (all \( P < 0.01 \)) were associated with high-risk prostate cancer; only tT–E₂ ratios achieved independent predictor status for high-risk prostate cancer (all \( P < 0.001 \)) when considering model 2. Both the lowest and the highest tT, E₂, and tT–E₂ values depicted a nonlinear U-shaped significant association with high-risk prostate cancer.

**Conclusions:** These data showed that preoperative serum sex steroids are independent predictors of high-risk prostate cancer, depicting a nonlinear U-shaped association.

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Introduction

Data from several population-based studies failed to show a significant association between circulating levels of androgens [including total testosterone (tT)] and increased risk of prostate cancer (1). In this context, despite long-held axiomatic convictions about T-centric and T-dependent prostate carcinogenesis (i.e., the higher the level of circulating T, the greater the risk of developing prostate cancer), low serum tT levels, rather than high levels, were associated with an increased risk of prostate cancer in both animal and human studies (2–4).

Similarly, data on radical prostatectomy populations have shown no unambiguous evidence reporting that preoperative circulating tT levels were associated with poor prognosis, including increased stage at presentation (5, 6), advanced pathologic stages (5–9), higher rate of positive surgical margins (5, 6), increased risk of biochemical failure (9–12), and worse survival (9, 13). Likewise, controversies still exist about the relationship between serum tT levels and Gleason score; indeed, numerous studies (2, 3, 14–17), but not all (18), have reported low serum tT levels, rather than high levels, in association with advanced or high-grade prostate cancer at surgery. A comprehensive serum hormonal milieu has scarcely been investigated in terms of prediction of pathologic outcomes in patients undergoing radical prostatectomy, with significant controversial findings (19–24).

Virtually, all previous reports assumed a linear relationship between the hormonal milieu and the examined endpoints (5–17). On the basis of this concept of linearity, especially in the relationship between T and prostate cancer, androgen deprivation therapy (ADT) has always been confirmed as a standard treatment for metastatic prostate cancer (25), with the specific purpose of completely breaking down circulating T levels and preventing any interaction with the various androgen receptors. However, previous reports suggested that high tT values, as well as low tT values, may be associated with adverse outcomes. This suggestion indicates a rather nonlinear relationship, with both extremes (high and low) predicting worse outcomes.
Sex Steroids Are Nonlinearly Associated with High-Risk Prostate Cancer

Translational Relevance
Although a comprehensive serum hormonal milieu has scarcely been investigated in terms of prediction of pathologic outcomes in patients undergoing radical prostatectomy, virtually all previous reports assumed a linear relationship between the circulating hormonal milieu and the examined endpoints. On the basis of this concept of linearity, especially in the relationship between testosterone and prostate cancer, androgen deprivation therapy has always been confirmed as a standard treatment for metastatic prostate cancer, with the specific purpose of completely breaking down circulating testosterone levels and preventing any interaction with the various androgen receptors. The findings of this exploratory analysis show, for the first time, that preoperative serum total testosterone and estradiol levels and the total testosterone–estradiol ratio are independent predictors of high-risk prostate cancer, as defined according to the National Comprehensive Cancer Network (NCCN) guidelines, but they depict a nonlinear U-shaped correlation (i.e., both the lowest and the highest circulating levels of sex steroids are significantly associated with high-risk prostate cancer). This innovative finding could support the concept that the use of androgen deprivation therapy, as either a standard treatment for metastatic prostate cancer or as an adjuvant systemic therapy for high-risk men, could be even differently tailored according to the endocrine network at the root of the prostate cancer behavior, thus potentially supporting the newly developed and evolving hormonal therapy which is aimed at reducing androgen signaling and controlling prostate cancer growth even in the presence of very low circulating androgen levels. Likewise, current findings may also contribute to supporting the use of androgen replacement therapy, which is undertaken commonly but cautiously in aging men with testosterone deficiency syndrome, as testosterone substitution might be titrated to a “safe” level.

To test this hypothesis, (i) we analyzed the association between preoperative serum tT and high-risk prostate cancer, as defined according to the National Comprehensive Cancer Network (NCCN) practice guidelines stratification (26), in a large cohort of nonscreened white European patients with prostate cancer undergoing radical prostatectomy at a single institution and (ii) we evaluated the association of 17β-estradiol (E₂), sex hormone-binding globulin (SHBG), and tT–E₂ ratio values with high-risk prostate cancer in the same cohort of men.

Materials and Methods

Patient population
The analyses were based on a cohort of 838 nonscreened Caucasian-European patients with prostate cancer who underwent radical prostatectomy at a single academic referral center between June 2007 and May 2011. For the specific purpose of this analysis, none of the patients had uncontrolled diabetes, thyroid disease, hyperprolactinemia, hypoalbuminemia, or liver disease. Moreover, none of the patients had taken any hormonal neoadjuvant treatment or other hormonal preparations during the previous 12 months. Symptoms of late-onset hypogonadism were not specifically collected for this cohort of men.

All patients were comprehensively assessed with a detailed preoperative evaluation, including age; measured body mass index (BMI), defined as weight in kilograms by height in square meters; total serum prostate-specific antigen (PSA; Abbott Axym PSA assay; Abbott Laboratories); biopsy Gleason sum; and clinical stage determined by a senior attending urologist, according to the 2002 American Joint Committee on Cancer staging system (27). Hypogonadism was defined as tT <3 ng/ml. (28).

For the specific purpose of this analysis, candidates for radical prostatectomy were stratified for their risk of biochemical recurrence after definitive therapy according to the NCCN guidelines v.4.2011 (26) into low-risk (tumors stage, T1 or T2a; Gleason score, ≤6; and serum PSA level, <10 ng/ml), intermediate-risk (tumors stage, T2b or T2c; Gleason score, 7; and serum PSA level, 10–20 ng/ml), and high- or very high-risk (tumors stage, ≥T3a; Gleason score, 8–10; and serum PSA level, >20 ng/ml) of recurrence.

A total of 114 men were excluded because they lacked one or more of the entry criteria: preoperative PSA was missing (n = 12; 1.4%), clinical stage was missing or imprecise (n = 46; 5.5%), biopsy Gleason was imprecise (n = 22; 2.6%), or measured preoperative BMI was missing (n = 34; 4.1%). A sample of 724 patients (86.4%) was included in the analysis.

The study was approved by the local ethics committee; likewise, the assay of this protocol was approved by the local institutional review board. Informed consent was obtained from each patient before enrollment after full explanation of the purpose and nature of all procedures used.

Hormone measurements
To reflect the common practice of a clinical biochemistry laboratory, we elected to measure circulating hormones using commercially available analytic methods. In this context, a single preoperative venous blood sample was drawn from each participant at least 4 weeks after transrectal ultrasound–guided prostate needle biopsy. Samples were drawn between 7:00 and 11:00 am on the day before surgery (29) and were kept at 4°C until serum was separated by centrifugation at 4°C. Serum aliquots were then stored at −80°C until assay. In all cases, tT levels were measured via a direct chemiluminescence immunoassay (ADVIA Centaur; Siemens Medical Solutions Diagnostics); E₂ was measured by a heterogeneous competitive magnetic separation assay (Bayer Immuno 1 System, Bayer Corp.); and SHBG levels were measured via a solid-phase, chemiluminescent immunometric assay on Immulite 2000 (Medical Systems SpA). The same laboratory was used for all patients. The intra- and

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interassay coefficients of variation (CV) were <6% and <8%, respectively, for both tT and E2. The intra- and interassay CVs for SHBG were <5% and <6%, respectively.

**Main outcome measures**

The primary endpoint of this analysis was to assess whether serum tT levels were differently distributed across NCCN Guidelines risk classes in a nonscreened homogeneous cohort of Caucasian-European patients undergoing radical prostatectomy. The secondary endpoint was to assess the behavior of both circulating E2 and SHBG and tT–E2 ratio values in the same cohort of men according to NCCN Guidelines stratification.

**Statistical analyses**

Data are presented as mean (median; range). The statistical significance of differences in means and proportions was tested with the one-way ANOVA and the \( \chi^2 \) trend test, respectively. Exploratory analyses were initially applied to all variables in a preliminary analysis, and variables were then kept where appropriate as significant to the results. Logistic regression models tested the association between predictors (e.g., age; BMI; continuously coded tT, E2, SHBG levels; and tT–E2 values) and NCCN Guidelines risk classes. Two models were developed: model 1 included age, BMI, and continuously coded tT, E2, and SHBG levels; model 2 included age, BMI, and tT–E2 ratio values. Restricted cubic spline functions with 3 knots tested the potential nonlinear association between predictors and high-risk prostate cancer and were used to display the data graphically (30, 31).

All statistical analyses were conducted using the R statistical package (R Foundation for Statistical Computing). All tests were 2-sided, with a significance level set at 0.05.

**Results**

Table 1 lists the characteristics and descriptive statistics of the entire cohort of patients. Table 2 reports the characteristics and descriptive statistics examined according to NCCN Guidelines risk-class segregation. Patients in the high-risk class showed the lowest serum tT and E2 levels as well as the lowest mean tT–E2 ratio (all \( P \leq 0.02 \)). In contrast, patients did not differ in terms of age, BMI, and serum SHBG values (all \( P \geq 0.05 \)) across the classes of risk. Hypogonadism was found in 177 (24.4%) of the whole cohort of patients. Hypogonadal patients were significantly more frequent across classes of increased risk (\( P \leq 0.001 \); Table 2).

Figure 1A–C depicts the relationship between predictors (e.g., serum tT, E2, and tT–E2 values) and high-risk prostate cancer. In this context, high-risk prostate cancer was significantly more frequent both for the lowest and the highest circulating levels of serum tT and E2, depicting a nonlinear U-shaped risk relationship (Fig. 1A and B). A similar finding was observed for the relationship between tT–E2 values and high-risk prostate cancer (Fig. 1C). In contrast, the relationship of serum SHBG, age, and BMI with high-risk prostate cancer did not show similar behavior (Figs. 1D, 2, and 3).

According to univariate analysis, age at surgery, serum tT, E2, and tT–E2 ratio were significantly associated with high-risk prostate cancer (all \( P \leq 0.006 \)), whereas BMI and circulating SHBG values were not (Table 3). At multivariate analyses, considering model 1 variables, patient age and circulating levels of both tT and E2 achieved independent predictor status for high-risk prostate cancer (all \( P \leq 0.03 \)) whereas BMI and SHBG levels did not. Conversely,
considering multivariate analyses for model 2 variables, only tT–E2 ratio values achieved independent predictor status for high-risk prostate cancer \((P < 0.001; \text{Table 3})\).

Both univariate and multivariate analyses confirmed the nonlinear U-shaped relationship between the examined hormones and high-risk prostate cancer, where the lowest (10th percentile) and highest (90th percentile) values predisposed to a higher risk of more aggressive prostate cancer (Table 3).

According to univariate analysis, age at surgery, serum tT, E2, and tT–E2 ratio were significantly associated with low-risk prostate cancer (all \(P < 0.02\)) whereas BMI and circulating SHBG values were not (Table 3). At multivariate analyses, considering model 1 variables, only circulating levels of E2 showed a trend toward significance for intermediate-risk prostate cancer (all \(P = 0.05\)) whereas all other variables did not. Conversely, considering multivariate analyses for model 2 variables, only tT–E2 ratio values achieved independent predictor status for intermediate-risk prostate cancer (all \(P < 0.04\); Table 3) both univariate and multivariate analyses confirmed the nonlinear inverse U-shaped relationship between the examined hormones and intermediate-risk prostate cancer whereas the lowest (<10th percentile) and highest (>90th percentile) values predisposed to a lower probability of intermediate-risk prostate cancer (Table 3).

### Discussion

We tested whether preoperative circulating tT, E2, and SHBG levels and tT–E2 ratio values were associated with high-risk prostate cancer, defined according to the NCCN practice guidelines stratification, in a large, homogeneous cohort of nonscreened Caucasian-European men undergoing radical prostatectomy at a single academic institute. Our interest was fueled by the existing controversies about the role of circulating sex steroids as established predictors of pathologic outcomes at radical prostatectomy, usually stemming from the T-centric and T-dependent premise that...
there is a sort of linear relationship between the hormonal milieu and the specific prostate cancer outcome.

To the best of our knowledge, the findings of this exploratory analysis show, for the first time, that preoperative serum tT and E2 levels and the tT–E2 ratio are independent predictors of high-risk prostate cancer, defined using the NCCN guidelines, but they depict a nonlinear U-shaped correlation (i.e., both the lowest and the highest circulating levels of sex steroids are significantly associated with high-risk prostate cancer). Conversely, these data showed that both BMI and SHBG levels are not multivariate predictors of high-risk prostate cancer.

One strength is that the current study was a single-institute survey with a large cohort of nonscreened, homogeneous, same-race patients for which all laboratory assessments, surgical procedures, and specimen evaluations were conducted using a consistent method. A second strength is that the patients included in this study presented a wide variety of low- and high-risk tumors, possibly allowing for adequate variability in the baseline serum sex steroids to

Figure 1. A–C, the relationship between serum tT levels (ng/mL), E2 levels (pg/mL), and tT–E2 values and high-risk prostate cancer at radical prostatectomy, respectively. The y-axis represents the risk (logarithmic scale) of high-risk prostate cancer at radical prostatectomy. In this context, high-risk prostate cancer was significantly more frequent both for the lowest and the highest circulating levels of serum tT and E2 (all P < 0.03), depicting a nonlinear U-shaped risk behavior (A and B). Similar behavior was observed for the relationship between tT–E2 values and high-risk prostate cancer (all P < 0.001; C). D, the relationship between serum SHBG levels (nmol/L) and high-risk prostate cancer at radical prostatectomy. The y-axis represents the risk (logarithmic scale) of high-risk prostate cancer at radical prostatectomy.
provide robust analysis. Third, all blood samples were correctly drawn after an overnight fast between 7:00 and 11:00 [level 2a, grade A (ref. 29)], thus avoiding a potential methodologic flaw due to different collection times and diurnal variation of the steroid hormones. A further strength is that we rigorously excluded men with uncontrolled diabetes, thyroid disease, hyperprolactinemia, hypoalbuminemia, or liver diseases as well as those patients who had taken any form of hormonal preparation during the previous 12 months (32). Similarly, the prevalence of hypogonadism was 24.4% within our cohort of patients and is comparable with prevalence estimates from other studies (33). The latter observation certainly corroborates the validity of our cohort of men as a representative sample of patients with prostate cancer, although the results of our exploratory analysis may be optimal for this cohort of nonscreened patients. These results should be validated externally with men from different countries or ethnic backgrounds.

Although contradictory findings have been reported, androgens are still believed to be critical determinants in normal and neoplastic growth and development of the prostate (16). Likewise, many data on radical prostatectomy populations have made it clear that there is a close correlation between circulating androgens—including the value of T as well as the condition of hypogonadism—and pathologic outcomes, although a unique direction that supports incontrovertible biology has not yet been identified (5–18). Moreover, although androgens and estrogens both play significant roles in the prostate, their specific balance seems to be even more critical in maintaining prostate health and tissue homeostasis in adulthood. Collectively, animal data have revealed that elevated T in the absence of estrogens may lead to the development of hypertrophy and hyperplasia of the prostate gland but not to malignancy (34). In contrast, high estrogen levels and low T have been shown to lead to the development of inflammation with aging and in premalignant lesions (34). Interestingly, T is the major precursor of E2 in men via a conversion mediated by the P450 aromatase enzyme (34, 35). Aromatase is active in adipose tissue, adrenal glands, the testicles, and the prostate (22), meaning that it acts as a potential key regulator of the ratio of androgens to estrogens within the prostate (22, 35). The local intraprostatic conversion of androgens to both reduced androgens and estrogens (35) is certainly of major importance according to the presence and function of local steroid metabolizing enzymes. Combined evidence supports the concept that aromatase expression and activity in the prostate may be upregulated at the tumor site, eventually resulting in an altered T-to-estrogen ratio. The almost complete lack of any observation of the potential significance of the T-to-estrogen ratio as a predictor of high-risk prostate cancer could further stigmatize the value of our findings.

Patient age emerged as an independent predictor of high-risk prostate cancer at both univariate and multivariate analysis considering model 1 variables; restricted cubic spline functions depicted a trend toward a linear increase throughout years of age (Fig. 2). This result is coupled with the available controversial data about the impact of age on prostate cancer; indeed, it is often suggested that older men are more likely to be diagnosed with high-risk prostate cancer and subsequently have lower overall survival (36). Interestingly, Pierorazio and colleagues (9) recently showed that higher levels of serum free T are associated with an increased risk of aggressive prostate cancer among older men. In contrast, some data support even less aggressive prostate cancer in older men (37).
### Table 3. Univariate and multivariate logistic regression analyses with restricted cubic spline functions with 3 knots predicting low-, intermediate-, and high-risk class prostate cancer [OR; P (95% CI)] among the whole cohort of patients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Low-risk</th>
<th>Intermediate-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UVA model</td>
<td>MVA models</td>
<td>UVA model</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.98; 0.02</td>
<td>0.98; 0.08</td>
<td>0.98; 0.11</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>1.00; 1.00</td>
<td>1.01; 0.84</td>
<td>1.01; 0.69</td>
</tr>
<tr>
<td>tT</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E₂</td>
<td>1.05; 0.02</td>
<td>1.01; 0.59</td>
<td>1.05; 0.02</td>
</tr>
<tr>
<td>SHBG</td>
<td>0.93; 0.001</td>
<td>0.98; 0.43</td>
<td>0.96; 0.02</td>
</tr>
<tr>
<td>tT/E₂ ratio</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E₂</td>
<td>1.00; 0.001</td>
<td>1.27; 0.003</td>
<td>1.15; 0.07</td>
</tr>
<tr>
<td>SHBG</td>
<td>0.96; 0.05</td>
<td>0.98; 0.41</td>
<td>0.91; 0.24</td>
</tr>
</tbody>
</table>

NOTE: Restricted cubic spline functions with 3 knots tested the potential nonlinear association between predictors and NCCN Guidelines prostate cancer risk classes. Two models were developed: model 1 included age, BMI, and continuously coded tT, E₂, and SHBG levels; model 2 included age, BMI, and tT–E₂ ratio values.

Abbreviations: MVA, multivariate; UVA, univariate.
Our analysis found that preoperative BMI did not achieve independent predictor status for high-risk prostate cancer, although restricted cubic spline functions depicted a sort of U-shaped correlation (Fig. 3). Our findings contrast with several previous studies showing that obesity is associated with an increased risk of aggressive disease (38–40). We are aware of the number of biases potentially contributing to these discrepancies, primarily including the multiple biologic links that certainly exist between obesity, with its dramatic impact on the metabolism in general and on the metabolism of steroids specifically, and prostate cancer.

Our study is not devoid of limitations. The study reports the results of a sophisticated exploratory analysis that may be optimal for this cohort of nonscreened, same-race patients but that would deserve external validation with an independent sample and, possibly, with men from different countries or ethnic backgrounds. A second limitation is that our study did not use gas chromatography-mass spectrometry (41), which is considered the gold standard for measuring circulating T levels; in contrast, to reflect common practice of a clinical biochemistry laboratory, we elected to measure circulating T using commercially available analytic methods. A further major limitation comes from the idea that endocrine biology of prostate tissue is dependent on the exposure time at a given concentration of sex steroid, which, in turn, depends on serum fluctuations during the lifespan of the individual. In this context, one may speculate that a single serum assessment might not adequately represent the prostate’s hormonal environment throughout the lifespan of each subject or at least for the duration of the malignant transformation and progression toward higher aggressiveness. However, we consider it almost clinically impossible to follow the circulating hormonal milieu of a sufficient number of men across their entire lives to assess the role of sex steroids as independent predictors of the eventual biology of prostate cancer. Our analyses did not even consider the correlation between androgen concentrations in the circulation and actual concentrations in the prostate (42). Although the lack of that assessment might be considered a methodologic flaw, it eventually exceeds the clinical applicability of biochemical parameters that may be of interest as routinely available predictors of pathologic outcomes at radical prostatectomy.

As a final point, it is certainly of importance to emphasize that the study lacks a measurement of either circulating or intraprostatic dihydrotestosterone (DHT), the 5α-reduced T product which binds androgen receptors with high affinity both at the normal and the prostate tumor tissue level (43, 44), eventually acting as a more active androgen than T (45). Overall, 5α-reductase inhibitors (5ARI) reduce serum DHT and dutasteride is shown to cut circulating DHT values by at least 90% in men with localized prostate cancer (46, 47). Translationally, the 2 largest trials that investigated the use of 5ARI showed an overall relative reduction of 23% to 25% in prostate cancer diagnoses, with an absolute increase in the incidence of high-grade prostate cancer in the chemoprevention group in both trials (48, 49). More recently, dutasteride has shown to significantly delay prostate cancer progression as compared with placebo (50), and these findings have supported the idea that using a 5ARI may become of benefit to reduce the need for aggressive treatment in men undergoing active surveillance for low-risk prostate cancer (50). The absence of any DHT measurement makes it impossible to obtain a correct and refined assessment of what might objectively be the role of the U-shaped association described between circulating sex steroids and high-risk prostate cancer in justifying how a variation of the serum levels of these extremely active androgens may affect the prostatic cell biology and the pathophysiologic history of the prostate tissue itself. However, although further studies are certainly needed, we could speculate that for the lowest T and T–E2 ratio values, DHT hydrophobicity may strengthen human androgen receptor intermolecular interactions, slow the dissociation rate of bound androgen, and stabilize the ligand-bound androgen receptor (45); moreover, at the lowest androgen levels, DHT formation could be also secured and maintained by increased levels of 5α-reductase isofoms present at higher levels in prostate cancer but less expressed in normal human physiology (45). Conversely, it emerges paradoxically more difficult to explain the correlation between the highest levels of sex steroids (mainly T) and high-risk prostate cancer as debating such a relationship by stressing that for high values of those circulating hormones there is a greater substrate for 5α-reductases, a greater possibility of activation of the intraprostatic androgen receptor, and subsequently a greater likelihood of high-risk prostate cancer would certainly be too simplistic.

Conclusions

Our data suggest that preoperative circulating T and E2 levels and the T–E2 ratio were associated with high-risk prostate cancer, stratified according to the NCCN Practice Guidelines, in a large, homogeneous cohort of nonscreened, same-race men undergoing radical prostatectomy. The association between the serum sex steroids and prostate cancer aggressiveness depicted a nonlinear U-shaped behavior (i.e., both the lowest and the highest circulating levels of sex steroids resulted significantly associated with high-risk prostate cancer). Patient age shows an overall trend toward significance. Conversely, these data showed that both BMI and SHBG levels are not multivariate predictors of high-risk prostate cancer. Further studies are needed to more comprehensively understand the complex biology of the endocrine network in promoting different facets of prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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