Relationships of Serum Androgens and Estrogens to Prostate Cancer Risk: Results from a Prospective Study in Finland

Joanne F. Dorgan,1 Demetrius Albanes, Jarmo Virtamo, Olli P. Heinonen, D. Walt Chandler, Mirta Galmarini, Lisa M. McShane, Michael J. Barrett, Joseph Tangrea, and Philip R. Taylor

Divisions of Cancer Epidemiology and Genetics [J. F. D.], Clinical Sciences [D. A., J. T., P. R. T.], and Cancer Treatment and Diagnosis [L. M. M.], National Cancer Institute, Bethesda, Maryland 20892; National Public Health Institute, Helsinki, Finland SF-00300 [J. V., O. P. H.]; Endocrine Sciences, Inc., Calabasas Hills, California 91301 [D. W. C.]; Quest Diagnostics, Inc., San Juan Capistrano, California 92690 [M. G.]; and Information Management Services, Inc., Silver Spring, Maryland [M. J. B.]

Abstract

Several lines of evidence suggest that sex hormones may be involved in the etiology of prostate cancer. We conducted a prospective nested case-control study to evaluate the relationships of serum androgens and estrogens to prostate cancer using serum collected at baseline for the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. The 29,133 male smokers who participated in the trial were 50–69 years old at baseline. During 5–8 years of follow-up, 246 men were diagnosed with prostate cancer, and 116 of these were randomly selected for inclusion in the current study. For each case, two controls matched on age, date of blood collection, intervention group, and study center were selected. Hormones were measured in serum by RIA using standard procedures. None of the individual androgens or estrogens was significantly related to prostate cancer. These findings were unaltered by simultaneous evaluation of serum androgen and estrogen concentrations in multivariate models. These results do not support a strong relationship of serum androgens and estrogens with prostate cancer in smokers. Within-person variation in concentrations of some hormones may have contributed to the lack of significant associations.

Introduction

Prostate cancer is the most common cancer among men in the United States (1) and the second most common in the European Community (2). The causes of prostate cancer, however, remain largely unknown, with age, race, and family history of disease being the only established risk factors (3). Testosterone and its more potent metabolite DHT are necessary for normal growth and development of the prostate (4), and several lines of evidence suggest a role for sex hormones in the etiology of prostate cancer. In rats, prostate tumors can be induced by prolonged administration of testosterone, and estrogens enhance this effect (5). In men, surgical castration prevents prostate cancer (6), and suppression of androgen production by orchectomy or use of pharmacological agents is effective in the palliative treatment of prostate cancer (7). However, epidemiological studies that evaluated the relationships of serum hormones to prostate cancer risk have yielded inconsistent results (8–24).

In an effort to clarify the relationships of serum androgens and estrogens to prostate cancer risk, we conducted a prospective nested case-control study using serum collected at baseline in the ATBC Study from 116 men subsequently diagnosed with prostate cancer and matched controls.

Materials and Methods

The ATBC Study was a randomized controlled clinical trial conducted jointly by the National Public Health Institute of Finland and the United States National Cancer Institute between 1985 and 1993 to evaluate the effects of α-tocopherol and β-carotene supplementation on lung cancer incidence. A secondary objective was to evaluate the effects of supplementation with these micronutrients on the incidence of cancer at other sites, including the prostate. The study design and methods have been described in detail previously (25). In this section, we provide an overview of the entire study and details relevant to the current analysis.

Men were recruited for the ATBC Study from the 290,406 men who were 50–69 years old and living in southwestern Finland in 1985–1988. Because lung cancer was the primary outcome of interest in the ATBC Study, participants were restricted to smokers of five or more cigarettes per day. Participants were also restricted to men with no pre-existing malignancies (other than nonmelanoma skin cancer and carcinoma in situ) or other serious illnesses or conditions that might...
interfere with participation in the study for 6 years and to men not taking supplemental vitamin E (>20 mg/day), vitamin A (>20,000 IU/day), or β-carotene (>6 mg/day).

Baseline characteristics of the 29,133 eligible men who participated in the study were ascertained prior to randomization. Information on sociodemographic characteristics, medical history, occupation, physical activity, and diet was collected by questionnaire while heights and weights were measured. The men were asked to fast for 12 h prior to blood sampling. Serum was separated, divided into 1 ml aliquots, and stored in glass vials at −70°C for future analysis. Ninety-nine percent of baseline blood samples were collected in the morning, and 95% were collected before 10:00 am.

Men were randomly assigned to one of four intervention groups: (a) 50 mg/day α-tocopherol; (b) 20 mg/day β-carotene; (c) 50 mg/day α-tocopherol and 20 mg/day β-carotene; or (d) placebo. Active intervention continued for 5–8 years (median, 6.1 years) through April 30, 1993. As reported previously (26), men who received α-tocopherol supplements as participants in the α-tocopherol or α-tocopherol plus β-carotene arms of the study had a significantly lower incidence of prostate cancer than did men who did not receive α-tocopherol.

A total of 246 prostate cancers were diagnosed during the active intervention phase of the ATBC Study (through April 30, 1993). Cancers were identified primarily through the Finnish Cancer Registry and the Register of Causes of Death. Participants were also asked about prostate cancer diagnoses at visits to study centers that were scheduled three times per year. The study protocol did not include screening for prostate cancer by clinical examination or by prostate-specific antigen measurement.

Central review of medical records of cases was performed independently by two oncologists for diagnostic confirmation and staging according to the criteria of the American Joint Committee on Cancer (27). A random sample of 84 prostate cancer cases was re-reviewed by a urologist who confirmed all diagnoses. Histological or cytological specimens were available for central review from 98% of prostate cancers. Two independent pathologists reviewed specimens for malignancy, histological type, and histological/cytological grade. Ninety-eight percent of the 195 cases with histology specimens were classified as adenocarcinomas.

For the study of serum hormones and prostate cancer, 116 prostate cancer cases were randomly selected. This number was chosen because it was believed that it would provide adequate power to detect meaningful associations and not unnecessarily use valuable baseline serum from the ATBC Study. For each case, two matched controls who were alive and were the same age (±1 year) as the case on his date of diagnosis and who were free of any cancer other than nonmelanoma skin cancer for the duration of follow-up were randomly selected using incidence density sampling. To conserve serum from cancer cases, we excluded men with cancer at sites other than the prostate from potential controls. This exclusion is unlikely to bias hormone estimates in controls because it decreased the pool of eligible men by only 7.5% and because serum hormones are not believed to be of major etiological importance for the most common cancers in men other than prostate. Controls were matched to cases on date (±28 days) of baseline blood collection, intervention group, and local study center. For nine cases, two controls fulfilling the matching criteria were not available, and for each case, controls were selected using expanded matching criteria for age (±2 years) and date (±45 days) of blood collection. Matching on date of blood collection and age at the date of the cases’ diagnosis resulted in an indirect match on age at blood collection. The control’s age was within 2 years of the case’s age at blood collection 99% of the time, and the remaining 1% were within 3 years.

Androgens and SHBG in baseline serum samples were measured by Endocrine Sciences, Inc. (Calabasas Hills, CA), and estrogens were measured by Quest Diagnostics, Inc. (San Juan Capistrano, CA) using standard procedures. Testosterone and DHT were measured by RIA after extraction with hexane and ethyl acetate and separation by aluminum oxide chromatography. SHBG was measured by an immunoradiometric assay, and the proportion of testosterone that was non-SHBG-bound (free plus albumin-bound) was determined by ammonium sulfate precipitation. The amount of testosterone that was non-SHBG-bound was then calculated as the product of the total testosterone concentration and the proportion that was non-SHBG-bound. Androstenedione was measured by RIA after extraction with hexane and ethyl acetate and separation from the aqueous phase by centrifugation. Dehydroepiandrosterone sulfate was subjected to enzyme hydrolysis, and the released dehydroepiandrosterone was measured directly by RIA. Androstanediol glucuronide also was subjected to enzymolysis after extraction with a polar solvent. The released androstanediol was then extracted with hexane ethyl acetate and purified using high-pressure liquid chromatography prior to RIA. Estradiol in serum was measured by RIA following extraction with an organic solvent and celtate/ethylcar- boxylyl glycyllycyl glycyl chromatography. Estrone was extracted with an organic solvent and separated by celtate chromatography and double antibody/polyethylene glycol precipitation prior to quantification by RIA.

Serum samples were organized into assay batches as triplets of matched case-control sets to eliminate between batch variability as a source of variance in case-control comparisons. Within-batch coefficients of variation calculated from masked replicate quality control samples included in all batches were as follows: testosterone, 5.5%; non-SHBG-bound testosterone, 5.4%; DHT, 8.9%; androstanediol, 7.0%; dehydroepiandrosterone sulfate, 11.3%; androstanediol glucuronide, 12.3%; estradiol, 13.7%; estrone, 14.1%; and SHBG, 4.2%.

Relationships of serum hormones to prostate cancer risk for the matched sets were evaluated using conditional logistic regression (28). Exposure hazard ratios were calculated as an estimate of RR. Men were stratified into quartiles based on their hormone levels relative to the distribution in controls, and a set of categorical (dummy) variables was included in models. Models also were fit using continuous data to test for linear trends in relationships between serum hormones and prostate cancer. Spearman correlations were used to evaluate the relationships of serum hormone concentrations to men’s characteristics, including BMI [= weight (kg)/height (m²)], education, physical activity, energy, fiber and alcohol ingestion, number of cigarettes smoked/day, and time since last ate and time of day of blood collection. The model for each hormone was refit with a-tocopherol or a-tocopherol plus β-carotene arms of the study included in models. Exploratory principal components analysis was used in an attempt to identify linear combinations of hormones related to prostate cancer risk (29). Analyses were performed using SAS Statistical Software (30).
Results

The characteristics of cases and controls at baseline are summarized in Table 1. Because of the demographics of Finland, all study participants were white. The mean age of participants was 60.8 (± 5.1) years. Only smokers were eligible to participate in the study, and the mean number of cigarettes smoked per day for both cases and controls was 17 (± 8.3). A positive history of BPH was reported by 7.8% of cases, compared to 4.3% of controls, but the difference was not statistically significant. Heights and weights of cases and controls were comparable, as were distributions of other characteristics investigated. Cases and controls had similar intakes of energy, dietary fiber, alcohol, and percentage of calories from fat. The physical activity levels of cases and controls included in this analysis were also similar.

At the time of diagnosis, men with prostate cancer had a mean age of 64.7 (± 5.4) years. The median time from blood collection to diagnosis was 4.1 years, with a range of <1-7.2 years. Distributions of times from blood collection to diagnosis and of tumor stages and grades are shown in Table 2. Adjusted for age at blood collection, serum concentrations of hormones and SHBG were not correlated significantly with tumor stage, grade, or time from blood collection to diagnosis.

The distributions of serum hormone concentrations did not differ between cases and controls (Table 3), and none of the individual hormones was significantly related to prostate cancer risk (Table 4). The T:DHT ratio, an inverse indicator of 5α-reductase activity, was also not statistically significantly related to prostate cancer risk, although a gradient of increasing risk across progressively higher quartiles of this ratio was apparent. The ratio of testosterone to androstenediol glucuronide, another indicator of 5α-reductase activity, was not related to risk. Adjustment for potential confounders, including BMI and BPH, at baseline did not materially change results.

Hormones measured for this study are metabolites of one another. As expected, serum concentrations of many of the hormones were significantly correlated. However, adjustment of each hormone for other hormones analyzed did not materially alter unadjusted results presented in Table 4. The Spearman correlation between testosterone and estradiol was 0.43 (P < 0.001). When included in a model with estradiol and SHBG, RRs for increasing quartiles of testosterone were 1.0, 1.3 (95% CI = 0.6–2.7), 0.8 (95% CI = 0.3–1.9), and 0.8 (95% CI = 0.3–2.0). Comparable RRs for estradiol from the same model were 1.0, 1.4 (95% CI, 0.7–2.8), 1.2 (95% CI = 0.6–2.5), and 1.5 (95% CI = 0.7–3.2). The addition of DHT and androstenediol glucuronide to this model did not alter findings. There was no evidence for interaction between hormones in relation to prostate cancer risk when they were evaluated on the continuous scale. Exploratory principal components analysis also did not reveal any linear combinations of hormones related to prostate cancer risk.

Tests for interaction did not suggest that relationships of serum hormones to prostate cancer risk varied by age at blood collection. Hormone-prostate cancer relationships also did not differ for preclinical and clinical disease. Furthermore, associations were not altered by time from blood collection to diagnosis when evaluated by tests for interaction or restriction of analysis to men diagnosed at least 2 years after blood collection. Intervention group, however, significantly (P = 0.047) modified the association of serum androstenedione concentration with prostate cancer risk. Men who received α-tocopherol in the trial (α-tocopherol and α-tocopherol plus β-carotene arms) were at a significantly reduced risk of prostate cancer. When we restricted analysis to the 68 case-control sets who did not receive α-tocopherol, men with higher serum levels of androstenedione were at a nonsignificant (P_trend = 0.14) increased risk of prostate cancer. The RRs for men in the lowest to highest tertiles for androstenedione were 1.0, 1.1 (95% CI, 0.5–2.4), and 2.1 (95% CI, 0.9–4.8). Conversely, a nonsignif-

### Table 1: Characteristics of cases and controls at baseline

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 116)</th>
<th>Controls (n = 231)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>A. Continuous variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60.82 ± 5.44</td>
<td>60.76 ± 5.08</td>
<td>0.57</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.12 ± 7.74</td>
<td>173.64 ± 7.77</td>
<td>0.39</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.57 ± 12.67</td>
<td>77.48 ± 12.49</td>
<td>0.43</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.23 ± 3.62</td>
<td>25.69 ± 3.63</td>
<td>0.17</td>
</tr>
<tr>
<td>Cigarettes (no./day)</td>
<td>16.96 ± 8.33</td>
<td>17.10 ± 8.25</td>
<td>0.92</td>
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<tr>
<td>B. Categorical variables</td>
<td></td>
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<tr>
<td>Treatment group</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Placebo</td>
<td>33</td>
<td>28.4</td>
<td>66</td>
</tr>
<tr>
<td>β-Carotene only</td>
<td>35</td>
<td>30.2</td>
<td>69</td>
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<tr>
<td>α-Tocopherol only</td>
<td>22</td>
<td>19.0</td>
<td>44</td>
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<tr>
<td>β-Carotene and α-tocopherol</td>
<td>26</td>
<td>22.4</td>
<td>52</td>
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<tr>
<td>Education</td>
<td>0.68</td>
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<td></td>
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<tr>
<td>Common school</td>
<td>84</td>
<td>72.4</td>
<td>177</td>
</tr>
<tr>
<td>Some high school</td>
<td>21</td>
<td>18.1</td>
<td>36</td>
</tr>
<tr>
<td>High school graduate</td>
<td>11</td>
<td>9.5</td>
<td>18</td>
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<tr>
<td>Martial status</td>
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<tr>
<td>Married</td>
<td>90</td>
<td>77.6</td>
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<tr>
<td>Single</td>
<td>6</td>
<td>5.2</td>
<td>8</td>
</tr>
<tr>
<td>Divorced</td>
<td>13</td>
<td>11.2</td>
<td>16</td>
</tr>
<tr>
<td>Widowed</td>
<td>7</td>
<td>6.0</td>
<td>17</td>
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<tr>
<td>Positive BPH history</td>
<td>9</td>
<td>7.8</td>
<td>10</td>
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</tbody>
</table>

Notes:
- * Geometric mean.
- SD of the geometric mean.
- From conditional logistic regression.
Table 3  Mean serum hormone concentrations

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Cases (n = 116)</th>
<th>Controls (n = 231)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean± SD</td>
<td>Mean± SD</td>
<td></td>
</tr>
<tr>
<td>Testosterone (nm)</td>
<td>20.10± 6.91</td>
<td>20.46± 6.59</td>
<td>0.62</td>
</tr>
<tr>
<td>Non-SHBG-bound testosterone (nm)</td>
<td>5.11± 1.86</td>
<td>4.98± 1.62</td>
<td>0.50</td>
</tr>
<tr>
<td>Dihydrotestosterone (nm)</td>
<td>1.77± 0.67</td>
<td>1.85± 0.65</td>
<td>0.27</td>
</tr>
<tr>
<td>Androstenedione (nm)</td>
<td>4.66± 1.40</td>
<td>4.69± 1.32</td>
<td>0.93</td>
</tr>
<tr>
<td>DHEAS± (µM)</td>
<td>6.08± 3.61</td>
<td>5.72± 3.34</td>
<td>0.47</td>
</tr>
<tr>
<td>Androstenediol glucuronide (nm)</td>
<td>3.13± 1.81</td>
<td>3.06± 1.69</td>
<td>0.70</td>
</tr>
<tr>
<td>Estradiol (nm)</td>
<td>0.10± 0.03</td>
<td>0.10± 0.03</td>
<td>0.88</td>
</tr>
<tr>
<td>SHBG (nM)</td>
<td>0.15± 0.05</td>
<td>0.15± 0.04</td>
<td>0.88</td>
</tr>
<tr>
<td>Non-SHBG-bound testosterone (nm)</td>
<td>82.57± 27.57</td>
<td>85.21± 29.24</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*a Geometric mean.
*b SD of the geometric mean.
*c P from conditional logistic regression.
*d DHEAS, dehydroepiandrosterone sulfate.

Discussion

Results of this prospective nested case-control study in Finnish men do not support a relationship between prediagnostic serum hormone levels and prostate cancer in smokers. None of the androgens or estrogens measured were significantly related to prostate cancer risk in univariate or multivariate models that included two or more hormones.

Our findings are in agreement with the majority of prior prospective studies that have evaluated the relationship between serum sex hormones and prostate cancer (16–23). In general, prospective studies have yielded null results. However, similar to our results, three earlier studies (16, 18, 21) reported a positive relationship between prostate cancer and the T:DHT ratio, but only in the recent analysis from the Physicians’ Health Study by Gann et al. (21) was the association statistically significant. In the Physicians’ Health Study, a significant positive association of serum testosterone and an inverse association of estradiol and prostate cancer were also observed in a multivariate model including several hormones. However, when we fit a model that included both testosterone and estradiol, neither hormone was related to risk. When we fit the same model as Gann et al. (21), results for testosterone and estradiol were unchanged. Associations were stronger for older men in the Physicians’ Health Study, and the younger age of ATBC Study participants may have contributed to discrepancies in findings.

All participants in the ATBC Study were smokers at baseline, and smokers have been reported to have higher serum androgen and estrogen concentrations compared to nonsmokers (31, 32), as well as larger decreases in testosterone levels with age (33). Because our study did not include any nonsmokers, we cannot directly evaluate whether smoking modified serum hormone-prostate cancer associations. However, the only hormone concentration significantly correlated with number of cigarettes smoked per day in ATBC Study controls was estrone (age adjusted Spearman r = −0.15, P = 0.04), and adjustment for number of cigarettes smoked per day did not materially change risk estimates for prostate cancer associated with serum concentrations of estrone or other hormones.

The wide CIs we observed for RR estimates indicate low power in our study. Although we designed the study to detect a 10% difference in mean testosterone levels between cases and controls with 80% power, our observed difference was <1%, with controls' values slightly higher than cases. We thought that our sample size estimates were conservative, because they
were calculated for unmatched comparisons, and matching tends to increase efficiency by reducing the variance of case-control differences. However, matching on age may have drawn cases’ and controls’ hormone values closer together than expected for an unmatched comparison.

Within-person variation in hormone levels due to biological fluctuations in men’s serum hormone levels may have also reduced our chances of observing associations with prostate cancer. We recently conducted a small study to examine the variability of testosterone and DHT measured in a group of men the same age as men in the ATBC Study. Similar to the ATBC Study, serum was collected between 8:00 a.m. and 10:00 a.m. Our preliminary analyses estimate that within-person variation may account for a quarter to a third of total variation in serum levels of these hormones, which could substantially attenuate RR estimates and reduce power.

All hormone concentrations in the current study were within the adult male normal ranges for the laboratories that performed the assays. SHBG concentrations, however, were generally above the normal range reported by the laboratory. This difference was later found to be due partially to an error in standard value assignment by the laboratory, which increased all SHBG concentrations by a constant multiple. SHBG concentrations were not used in estimating non-SHBG-bound testosterone concentrations, and therefore, problems with the SHBG assay do not affect non-SHBG-bound testosterone results. The percentage of testosterone that was non-SHBG-bound (median = 25%) was slightly lower than expected, which suggests that some of the elevation in participants’ SHBG was real and possibly related to their ages or other behavioral or constitutional factors. Although our absolute values for SHBG were high, relative concentrations of SHBG should be correct and analysis of the relationship of SHBG with prostate cancer should be valid. This is supported by the strong inverse correlation of SHBG and BMI that we observed in controls (Spearman \( r = -0.47; P = 0.0001 \)), which is a well-established relationship (34).

Treatment group in the ATBC Study significantly modified the relationship of serum androstenedione and prostate cancer. Higher levels of androstenedione were associated with a nonsignificant increased risk of prostate cancer only among men who did not receive \( \alpha \)-tocopherol supplements. Given the number of statistical tests performed, the significant interaction between treatment group and androstenedione concentration in relation to prostate cancer risk may have been a chance occurrence. However, Barrett-Connor et al. (17) previously reported a significant positive association of androstenedione with prostate cancer. Animal studies suggest that \( \alpha \)-tocopherol may be involved in steroidogenesis (35–37), and in men, supplemental \( \alpha \)-tocopherol has been reported to increase serum testosterone concentration (35). Although serum testosterone was not associated with prostate cancer risk in our data, \( \alpha \)-tocopherol supplementation could have caused other hormonal changes that modified androstenedione-prostate cancer associations. Given the lower incidence of prostate cancer among men who received \( \alpha \)-tocopherol supplements in the ATBC Study and the probable involvement of sex hormones in prostate cancer etiology, further exploration of the effects of \( \alpha \)-tocopherol on sex hormone metabolism in men seems warranted.

The men in our study were 50–69 years of age at blood collection. Although few men reported a history of clinically apparent BPH, subclinical BPH is extremely common in men of this age, with a prevalence rate of 68% reported in one study (38). Men with BPH have been reported to have higher serum levels of testosterone and DHT and lower levels of estradiol compared to normal controls (8, 12, 14). To determine whether the high prevalence of BPH among men at the age of our study participants may have limited our ability to identify hormonal risk factors for prostate cancer, we reanalyzed hormone-prostate cancer associations after eliminating from controls any man who had BPH at baseline or during follow-up before the age of his matched case’s prostate cancer diagnosis. Elimination of these 27 controls did not materially change results from those reported for all men. Therefore, the lack of significant associations between sex hormones and prostate cancer in our data cannot be attributed to a high prevalence of BPH in the controls.

Subclinical prostate cancer has been estimated to affect 15–30% of men over 50 years of age (39). A high prevalence of subclinical disease at baseline, if present, could have biased results.

Considerable clinical evidence supports a role for sex hormones in the epidemiology of prostate cancer. It remains unclear, however, whether serum hormone concentrations are important. Testosterone, the main circulating androgen in men, is metabolized to the more potent androgen, DHT, by 5a-reductase (40). Two isozymes of this enzyme have been identified. Although both are expressed in liver, in adults, type II predominates in the prostate and other male accessory sex glands, whereas type I is expressed in skin (40). Serum levels of DHT, therefore, may not reflect concentrations of this hormone in the prostate. Furthermore, the serum T:DHT ratio may relate to total 5a-reductase activity but may not be a good indicator of type II activity, which is probably more important for prostate cancer.

In conclusion, results of this prospective study do not support strong relationships of serum androgens and estrogens with prostate cancer risk in smokers. Within-person variation in concentrations of some hormones may have contributed to the lack of significant associations.

References


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