Serum Testosterone and Sex Hormone-Binding Globulin Concentrations and the Risk of Prostate Carcinoma

A Longitudinal Study

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BACKGROUND. It has been hypothesized that high androgen levels are determinants of prostate carcinoma.

METHODS. Serum concentrations of testosterone, sex hormone-binding globulin (SHBG), and androstenedione were analyzed to determine their role as predictors of prostate carcinoma in a longitudinal, population-based, nested case–control study. The serum concentrations of testosterone, SHBG, and androstenedione were determined from serum samples collected by the Finnish Mobile Clinic Health Examination Survey between 1968–1972 and stored at -20 °C. During a follow-up period of 24 years, a total of 166 prostate carcinoma cases occurred among men who originally were cancer free. Two controls (matched for age and municipality) were chosen.

RESULTS. There was no association between serum testosterone, SHBG, or androstenedione concentrations and the occurrence of subsequent prostate carcinoma in the total study population or in subgroups determined based on age or body mass index. The association was not strengthened by simultaneous adjustment for the hormonal variables.

CONCLUSIONS. The results of the current study do not appear to corroborate the hypothesis that serum testosterone, SHBG, or androstenedione are determinants of the subsequent occurrence of prostate carcinoma. ***Cancer*** **1999;86:312–5.**

KEYWORDS: epidemiologic, hormone, nested case–control study, prostate carcinoma, serum sample.

Androgens are necessary for the growth, maintenance, and functional activity of the prostate gland. Accordingly, it appears likely that these hormones also play some role in the development of prostate carcinoma. However, this does not necessarily mean that variation in hormone levels within the normal endogenous range would be reflected in prostate carcinoma risk, although this is a reasonable possibility.

Studies comparing circulating male sex hormone levels in subjects with and without prostate carcinoma have produced widely varying results.[1,2] Indeed, hormone levels in prostate carcinoma cases have been found to be elevated, decreased, and similar to those found in controls. Some of these inconsistencies may be explained by the effects of clinical prostate carcinoma and its treatment on hormone levels and by the difficulty in obtaining representative controls.

To our knowledge to date five studies have measured hormone

levels in serum or plasma obtained before prostate carcinoma cases were diagnosed.[3–7] According to Barrett-Connor et al.,[4] plasma androstenedione showed a positive dose-response gradient. None of the studies revealed a clear association between unadjusted testosterone levels and the risk of prostate carcinoma. However, Gann et al.[7] analyzed the data one step further. They found a marked correlation between the levels of testosterone and sex hormone-binding globulin (SHBG). A significant trend toward an increase in prostate carcinoma risk was observed with increasing levels of plasma testosterone when adjusted for the SHBG levels.

The current study was designed to examine the predictive value of serum concentrations of testosterone, SHBG, and androstenedione on the subsequent occurrence of prostate carcinoma.

METHODS

Between 1966–1972 the Mobile Clinic Health Examination Survey performed multiphasic health examinations in certain rural, semiurban, and industrial municipalities from different parts of Finland.[8] A total of 62,440 adult whites age ≥ 15 years were invited to take part in the study. The participation rate was 82.5%. All participants completed a premailed questionnaire that was checked at the baseline examination. The questionnaire yielded information regarding smoking status. Body height and weight were measured and the body mass index was calculated. Serum samples were drawn and were stored at −20 °C.

The study design is described in more detail elsewhere.[8] Briefly, screening for prostate carcinoma is not the norm in Finland and information concerning subsequent incidence rates of prostate carcinoma was available through the nationwide Finnish Cancer Registry.[9] Frozen serum samples existed for a subpopulation and after the exclusion of persons who were found to have cancer during the baseline examination the population at risk was comprised of 16,481 men. During a maximum follow-up period of 24 years (to the end of 1991), 166 prostate carcinoma cases (according to code 177 of the 7th edition of the International Classification of Diseases, published in 1955 by the World Health Organization) were diagnosed.

A case–control study design, nested within the cohort, was chosen. Two controls were selected for each prostate carcinoma case by individual matching for age and municipality (including time for serum sample storage). The controls were drawn from the same municipality as the cases, and age was matched as closely as possible. A total of 300 controls were selected. None of the men were receiving exogenous testosterone.

TABLE 1
Mean Levels of Baseline Variables among Prostate Carcinoma Cases and Controls

Variable	Mean (SD) Cases (N = 166)	Mean (SD) Controls (N = 300)	*P* value for difference
Age (yrs)	58.6 (10.4)	58.3 (10.1)	0.68
Body mass index (kg/m^2)	25.7 (3.06)	26.0 (2.82)	0.45
Current smoker (%)	31.3	37.3	0.17
Testosterone (nmol/L)	25.4 (9.9)	25.0 (7.9)	0.69
SHBG (nmol/L)	56.1 (24.4)	55.6 (20.0)	0.84
Testosterone/SHBG	0.484 (0.164)	0.511 (0.317)	0.34
Androstenedione (nmol/L)	8.05 (8.8)	8.75 (8.0)	0.48

SD: standard deviation; SHBG: sex hormone-binding globulin.

Hormone concentrations in the serum samples for each case and its matched control were analyzed independently of case–control status (of which the laboratory personnel were unaware). Serum testosterone and androstenedione concentrations were quantified by commercial radioimmunoassay kits from Diagnostic Products Corporation (Los Angeles, CA) and SHBG concentrations were quantified by commercial time-resolved fluoroimmunoassay kits (Wallace Ltd., Turku, Finland). The interassay coefficients of variation for high, median, and low level controls ranged from 4.5–7.2% for testosterone, 6.6–8.7% for SHBG, and 9.5–11.7% for androstenedione.

The relative risk of prostate carcinoma between quintiles of serum hormone concentrations was estimated by the conditional logistic model.[10] Adjustment for confounding factors and estimation of effect modification were performed by including the variables in the model. Tests for significance were performed by the likelihood ratio test based on the model.

RESULTS

The mean age of prostate carcinoma cases at the time of baseline examination was 59 years (range, 18–78 years) (Table 1). The mean levels of serum testosterone, SHBG, or androstenedione did not differ significantly between prostate carcinoma cases and controls. There was a strong association between serum testosterone and SHBG concentrations; the age-adjusted correlation coefficients among prostate carcinoma cases and corresponding controls were 0.65 and 0.62, respectively.

None of the hormonal variables were predictive of subsequent prostate carcinoma incidence rates during the entire follow-up period. The relative risk of the disease between the highest and lowest quintiles of serum testosterone was 1.27 (95% confidence interval

TABLE 2
Relative Risk of Prostate Carcinoma between Quintiles of Serum Hormones

Serum hormone	Quintile	Relative risk (95% confidence interval)			
		Unadjusted	Total follow-up[1]	Include first 8 years[1]	Exclude first 8 years[1]
Testosterone	1 (lowest)	1	1	1	1
	2	1.32 (0.71–2.45)	1.33 (0.69–2.55)	2.41 (0.49–11.86)	0.90 (0.40–1.99)
	3	1.30 (0.70–2.39)	1.23 (0.62–2.42)	1.47 (0.22–9.68)	1.31 (0.60–2.86)
	4	1.14 (0.59–2.19)	1.07 (0.50–2.29)	0.34 (0.05–2.37)	1.76 (0.71–4.37)
	5 (highest)	1.27 (0.67–2.37)	1.23 (0.55–2.76)	0.68 (0.09–5.17)	2.01 (0.76–5.29)
	P value for trend	0.68	0.78	0.10	0.06
SHBG	1 (lowest)	1	1	1	1
	2	1.45 (0.80–2.62)	1.39 (0.74–2.61)	3.98 (0.75–21.20)	1.04 (0.50–2.16)
	3	1.17 (0.62–2.20)	0.98 (0.48–1.99)	4.36 (0.72–26.28)	0.63 (0.27–1.49)
	4	1.23 (0.65–2.34)	1.10 (0.50–2.42)	2.74 (0.37–20.22)	0.70 (0.28–1.79)
	5 (highest)	1.19 (0.60–2.38)	1.12 (0.44–2.88)	3.03 (0.27–34.41)	0.91 (0.30–2.82)
	P value for trend	0.80	0.96	0.31	0.83
Androstenedione	1 (lowest)	1	1	1	1
	2	0.72 (0.39–1.34)	0.70 (0.37–1.33)	0.74 (0.13–4.07)	0.70 (0.33–1.50)
	3	1.21 (0.67–2.21)	1.20 (0.65–2.22)	2.79 (0.67–11.54)	0.97 (0.46–2.03)
	4	0.93 (0.49–1.79)	0.91 (0.45–1.82)	1.80 (0.36–8.87)	0.67 (0.30–1.56)
	5 (highest)	0.91 (0.50–1.66)	0.92 (0.49–1.72)	1.49 (0.36–6.08)	0.75 (0.35–1.60)
	P value for trend	0.51	0.62	0.54	0.59

SHBG: sex hormone-binding globulin.
[a] Serum testosterone sex hormone-binding globulin and androstenedione, smoking status, and body mass index were included in the model.

[95% CI], 0.67–2.37) and the corresponding values for serum SHBG and serum androstenedione were 1.19 (95% CI, 0.60–2.38), and 0.91 (95% CI, 0.50–1.66), respectively (Table 2). Simultaneous study of the three hormonal variables and further adjustment for smoking and body mass index did not appear to alter the results significantly (Table 2). Testosterone was not associated significantly with prostate carcinoma incidence rates during the first 8 years of follow-up but there was an association, although not a significant one, after exclusion of the first 8 years of follow-up (Table 2).

There was no interaction between serum testosterone and SHBG or serum testosterone and androstenedione and prostate carcinoma, whereas there was a suggestive interaction between SHBG and androstenedione (Table 3). No clear evidence of interaction between serum hormone concentration and age or body mass index was observed (data not shown).

TABLE 3
Relative Risk of Prostate Carcinoma at Testosterone, SHBG, and Androstenedione Levels below and above the Median

	Relative risk (95% confidence interval)		*P* value for interaction
	SHBG		
Testosterone	< 52.1	≥ 52.1	
< 23.5	1	1.30 (0.71–2.38)	
≥ 23.5	1.44 (0.77–2.67)	1.20 (0.74–1.92)	0.30
	Androstenedione		
Testosterone	< 5.0	≥ 5.0	
< 23.5	1	1.03 (0.59–1.81)	
≥ 23.5	1.23 (0.68–2.21)	1.14 (0.66–1.98)	0.80
	Androstenedione		
SHBG	< 5	≥ 5.0	
< 52.1	1	0.64 (0.36–1.15)	
≥ 52.1	0.73 (0.41–1.33)	1.09 (0.64–1.85)	0.05

SHBG: sex hormone-binding globulin.

DISCUSSION

In accordance with Gann et al.[7] we did not observe any difference in the mean levels of testosterone and SHBG between cases and controls. We found a correlation between levels of testosterone and SHBG that was even stronger than that observed by Gann et al.[7] When these levels were adjusted simultaneously, Gann et al.[7] found a statistically significant increasing risk of prostate carcinoma with increasing levels of testosterone and an inverse trend in prostate carcinoma risk with increasing levels of SHBG. No corresponding interaction was noted in the current series; the adjustment did not alter the crude figures.

However, we did note a nonsignificant association between testosterone level and incidence rate of prostate carcinoma when the time period from the time of baseline examination to the diagnosis of prostate car-

cinoma was taken into account. When the period was long (> 8 years), a high testosterone level was associated with an increased risk; conversely, when the period was short (< 8 years), a high testosterone level was associated with a low risk of prostate carcinoma. This may indicate that testosterone plays some role in the initiation of carcinoma whereas subclinical carcinoma suppresses testosterone production. However, these findings should be interpreted with caution because manifest prostate carcinoma typically is not associated with low testosterone levels.

Different studies have shown a wide variation in sex hormone levels. Variation in laboratory methods obviously accounts for the majority of this difference, yet some differences have been shown to exist between populations.[11] Likewise, racial differences exist in the activity of 5-α reductase.[12] This enzyme metabolizes testosterone into dihydrotestosterone, which is a more potent androgen than testosterone and is the principal factor driving cell proliferation in the prostate. There is a greater than tenfold variation between populations in the incidence rate of and mortality from prostate carcinoma.[1] It is possible that diet and other environmental factors, genes, and hormones all play a role in this context. Accordingly, there remains the possibility that a high hormone level is a predictor of prostate carcinoma in one population but not in another. Our study series represented the Finnish male population as a whole, whereas that of Gann et al.[7] was drawn from physicians in the U.S.

Androstenedione is an androgen, less potent than testosterone, that is secreted by the testis, adrenal cortex, and ovary. Approximately 50% of the androgen activity in females is from androstenedione; in the male the role of this hormone is much less significant. When analyzed by tertiles, Barrett-Connor et al.[4] found in their prospective study a statistically significant association between plasma androstenedione levels and prostate carcinoma. No differences emerged in other sex hormones included in the study. This finding regarding androstenedione was not confirmed in a large series by Nomura et al.[6] Other prospective studies[3,5,7] did not include androstenedione in the battery of tests. Because androstenedione only plays a minor role as an androgen in males, it is our belief that there are no valid a priori reasons to presume that this hormone in particular would be involved in the pathogenesis of prostate carcinoma. In the current study, there was no difference in the mean androstenedione level between cases and controls. Likewise, analysis by quintiles did not reveal any trend.

Currently, the role of physiologic variations in the androgen levels remains undetermined. The most crucial limitation of the current study and previous studies was that only single prediagnostic serum samples were available. Because the long term persistence of testosterone, SHBG, and androstenedione concentrations is unknown, inference regarding the results is more problematic the longer the follow-up of prostate carcinoma incidence rates lasts. In particular, attempts to invalidate the current hypothesis require more support from future methodologic research to develop measurements of androgen status that can be ascertained as reproducible in the long term.

The current study did not lend support to the contention that high androgen levels predict the incidence rate of prostate carcinoma. Further longitudinal epidemiologic studies with repeated serum determinations and in different ethnic groups are warranted to elucidate the association between serum androgen levels and the occurrence of prostate carcinoma.

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