Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies

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Summary This paper presents a quantitative review of the data from eight prospective epidemiological studies, comparing mean serum concentrations of sex hormones in men who subsequently developed prostate cancer with those in men who remained cancer free. The hormones reviewed have been postulated to be involved in the aetiology of prostate cancer: androgens and their metabolites testosterone (T), non-SHBG-bound testosterone (non-SHBG-bound T), di-hydrotestosterone (DHT), androstenediol glucuronide (A-diol-g), androstenedione (A-dione), dehydroepiandrosterone sulphate (DHEAS), sex hormone binding globulin (SHBG), the oestrogens, oestrone (E), oestradiol (E2), oestriol (E3), oestriol dihydrodiol (E3 diol), androstanediol glucuronide (A-diol-g), and luteinizing hormone (LH) and prolactin. The ratio of the mean hormone concentration in prostate cancer cases to that of controls (and its 95% confidence interval (CI)) was calculated for each study, and the results summarized by calculating the weighted average of the log ratios. No differences in the average concentrations of the hormones were found between prostate cancer cases and controls, with the possible exception of A-diol-g which exhibited a 5% higher mean serum concentration among cases relative to controls (ratio 1.05, 95% CI 1.00–1.11), based on 644 cases and 1048 controls. These data suggest that there are no large differences in circulating hormones between men who subsequently go on to develop prostate cancer and those who remain free of the disease. Further research is needed to substantiate the small difference found in A-diol-g concentrations between prostate cancer cases and controls.

Keywords: prostate cancer; steroid hormones; androstenediol glucuronide; prospective studies; review

The incidence of prostate cancer varies widely, with Western countries having rates 30–50 times higher than those in Far-Eastern countries (Parkin et al, 1992) and it is now the commonest incident cancer and the second most common cause of cancer mortality in North American men (Parker et al, 1996). The reasons for the wide differences in prostate cancer incidence between populations are not yet established, but the fact that an increase in prostate cancer has been seen among Asian migrants to the USA (Shimizu et al, 1991) suggests that environmental or lifestyle factors are important. However, other than race, age and a family history of prostate cancer (Nomura and Kolonel, 1991), aetiological risk factors remain largely unknown, although it has been suggested that the adoption of Western dietary habits with a high fat and/or low plant food consumption may be associated with prostate cancer risk (Adlercreutz, 1990). Furthermore, it has been postulated that dietary factors may exert their effects by altering sex hormone metabolism, and that this may play a significant role in the progression of latent lesions into clinically relevant cancer (Montie and Pienta, 1994).

Many epidemiological studies have been conducted over the last 20 years in an attempt to identify differences in sex hormone metabolism between prostate cancer patients and controls, and in individuals from high- and low-risk populations, by measuring differences in serum hormone levels. The evidence from case-control studies that circulating hormone levels are related to prostate cancer is inconsistent (Flanders, 1986), and these studies suffer from the problem that disease status may well alter serum concentrations of androgens. As such, it is impossible to interpret any differences present in serum levels between cases and controls in relation to the aetiology of the disease. Prospective studies reduce the possibility that changes in hormone levels are due to disease status as blood samples are taken some years prior to diagnosis. This paper presents a quantitative review (meta-analysis) of the published data from prospective studies which compared serum concentrations of sex hormones in men who subsequently developed prostate cancer with those in men who remained cancer free.

MATERIALS AND METHODS

Papers were identified by searching the Medline database, 1966–1998, using combinations of the following keywords: hormones; androgens; prostate cancer; prospective; serum. The reference lists of the relevant papers were also examined. Ten papers reporting results from eight prospective studies were identified for inclusion in this meta-analysis, of which seven were nested case-control studies where controls were chosen according to specific matching criteria (Nomura et al, 1988, 1996; Comstock et al, 1993; Hsing and Comstock, 1993; Carter et al, 1995; Gann et al, 1996; Guess et al, 1997; Vatten et al, 1997; Dorgan et al, 1998) and one was a cohort study in which the controls were all participants with no diagnosis of prostate cancer (Barrett-Connor et al, 1990). Two papers (Nomura et al, 1988; Comstock et al, 1993) include cases that are a subset of the prostate cancer cases described in other papers (Nomura et al, 1996; Hsing and Comstock, 1993), but are included in this review as they have analysed different hormones.

Table 1 shows the characteristics of the study populations. All studies, except Barrett-Connor et al (1990), included matching for...
Table 1 Characteristics of the study populations and follow-up times for the seven nested case-control studies and one prospective cohort study

| Reference            | Study population                                           | Study period (recruitment to end of follow-up) | Age at recruitment (years) | Mean years to diagnosis (range) | No. cases | No. controls | Matching criteria                      |
|----------------------|------------------------------------------------------------|-----------------------------------------------|----------------------------|---------------------------------|-----------|-------------|---------------------------------------|
| Nomura et al (1988, 1996) | 6860 participants of the Honolulu Heart Program, Oahu, Hawaii | 1971–1996a | 45–68 | 7 (< 1–14)b | 141c | 141c | Age<br>Ethnicity (Japanese-American)<br>Date of venipuncture<br>Time of day of venipuncture<br>No prior history of prostatic surgery |
| Barrett-Connor et al (1990) | 1008 participants of the Rancho Bernardo Study, CA, USA | 1972–1986 | 40–79 | 8 (1–14) | 57 | 951 | Age<br>Time of day of venipuncture<br>Age Ethnicity (Caucasian) |
| Hsing & Comstock (1993) and Comstock et al (1993) | 25 620 residents of Washington County, MD, USA | 1974–1987 | 35–94 | Not given (1–12) | 98d | 98d | Age<br>Time of day of venipuncture<br>Age Ethnicity (Caucasian) |
| Carter et al (1995) | 1459 participants of the Baltimore Longitudinal Study of Aging, Baltimore, MD, USA | 1958–1990 | 55–90 | Not given (7–25) | 16 | 16 | Age<br>Date of venipuncture |
| Gann et al (1996) | 22 071 participants of the Physicians’ Health Study, USA | 1982–1992 | 40–84 | 6 (range not given) | 222 | 390 | Age<br>No prior history of prostatic surgery<br>Smoking<br>Ethnicity (Caucasian)<br>Date of venipuncture<br>Clinic location |
| Guess et al (1997) | 128 992 participants of the Kaiser Permanente Medical Care Program (KPMCP), US | 1964–1987 | Not given | 14 (5–23) | 106 | 106 | Age<br>Ethnicity (Caucasian)<br>Date of venipuncture<br>Clinic location<br>Age<br>Time of day of venipuncture<br>Age Ethnicity (Caucasian)<br>Date of venipuncture<br>Clinic location |
| Vatten et al (1997) | 28 000 blood donors, Oslo, Norway | 1973–1994 | 42–66 | 10 (1–19) | 59 | 180 | Age<br>Smoking (all smokers)<br>Time of day of venipuncture<br>Age Ethnicity (Caucasian)<br>Date of venipuncture<br>Clinic location<br>Smoking (all smokers) |
| Dorgan et al (1998) | 29 133 participants of the Alpha-Tocopherol, Beta-Carotene Study (ATBC), Finland | 1985–1993 | 50–69 | 4 (< 1–7) | 116 | 231 | Age<br>Smoking (all smokers)<br>Time of day of venipuncture<br>Clinic location<br>Age Ethnicity (Caucasian)<br>Date of venipuncture<br>Clinic location<br>Smoking (all smokers) |

*aNomura et al (1988) follow-up period: 1971–1984. *bNot given in Nomura et al (1988) paper. *cNomura et al (1988) included 98 matched case-control pairs which are a subset of Nomura et al (1996) study population. *dComstock et al (1993) included 81 matched case-control pairs which are a subset of Hsing et al (1993) study population. *eMedian given.

Age. Most populations were predominantly Caucasian, although in one study the participants were all Japanese-American (Nomura et al, 1988, 1996), and in another the ethnic composition was not stated (Carter et al, 1990). Six studies had matched for years since blood sample was taken (Nomura et al, 1988, 1996; Carter et al, 1995; Gann et al, 1996; Guess et al, 1997; Vatten et al, 1997; Dorgan et al, 1998); three for time of day of venipuncture (Nomura et al, 1988, 1996; Barrett-Connor et al, 1990; Dorgan et al, 1998); two for previous history of prostatic surgery (Nomura et al, 1988, 1996; Gann et al, 1996), and two for smoking (Gann et al, 1996; Dorgan et al, 1998).

To present the results in a consistent format, the mean concentration of each hormone for cases and controls was extracted from the published data, and the ratio of the mean among cases to that of controls was calculated. Either serum or plasma concentrations were used, but considering their similarity, they shall be referred to as serum values. For each individual study, the standard errors of the means were used to calculate an approximate standard error of the log ratio. This was then used to obtain a 95% confidence interval (CI) for the log ratio which was exponentiated to give a corresponding CI for the ratio. Median values rather than means were published in three studies, and additional information was sought from the authors in order to obtain the means and standard errors for cases and controls.

In order to summarize the results, weighted averages of the study-specific log ratios were calculated, with weights determined by the inverse of the variance of each log ratio. The degree of heterogeneity in the log ratios between individual studies was assessed by $\chi^2$ tests.

The results are displayed separately for each hormone in figures 1 to 11 where each study-specific estimate of the ratio of the mean concentration in cases to controls is plotted as a square and its CI is denoted by the horizontal line crossing through it. The area of each square is inversely proportional to the variance of the log ratio and reflects the amount of statistical information available for that particular estimate. Where the CI extends beyond the scale of the plot it is indicated by an arrow. The summary estimate (the weighted average of the log ratios) is plotted as an open diamond, the horizontal tips of which represent the 95% CI.
1 Testosterone

First author  Year  Cases/controls  ratio  95% CI  Ratio and 95% CI
Barrett-Connor 1990 59/945 0.95 (0.85–1.06)
Hsing 1993 98/98 1.02 (0.89–1.17)
Carter 1995 16/16 0.83 (0.62–1.11)
Gann 1996 222/390 1.02 (0.94–1.10)
Nomura 1996 141/141 1.00 (0.91–1.10)
Guess 1997 106/106 0.99 (0.90–1.09)
Vatten 1997 59/180 0.97 (0.88–1.07)
Dorgan 1998 116/231 0.98 (0.91–1.06)

All studies 817/2107 0.99 (0.95–1.02)

Test for heterogeneity $\chi^2 = 3.3; P < 0.1, NS$

2 Non-SHBG bound testosterone

First author  Year  Cases/controls  ratio  95% CI  Ratio and 95% CI
Nomura 1996 105/105 1.04 (0.90–1.19)
Guess 1997 104/106 1.01 (0.99–1.14)
Dorgan 1998 116/231 1.03 (0.95–1.11)

All studies 325/442 1.02 (0.96–1.09)

Test for heterogeneity $\chi^2 = 0.1; P > 0.1, NS$

3 Dihydrotestosterone

First author  Year  Cases/controls  ratio  95% CI  Ratio and 95% CI
Hsing 1993 98/98 1.00 (0.89–1.12)
Gann 1996 222/390 0.97 (0.88–1.07)
Nomura 1996 141/141 1.03 (0.94–1.14)
Vatten 1997 59/180 0.98 (0.88–1.10)
Dorgan 1998 116/231 0.96 (0.88–1.04)

All studies 636/1040 0.98 (0.94–1.03)

Test for heterogeneity $\chi^2 = 1.6; P > 0.1, NS$

RESULTS

Figures 1–11 summarize the results of eight prospective studies which reported the serum concentration of testosterone (T), non-SHBG bound T, dihydrotestosterone (DHT), androstenediol glucuronide (A-diol-g), androstenedione (A-dione), dehydroepiandrosterone sulphate (DHEAS), sex hormone binding globulin (SHBG), oestrone, oestradiol, luteinizing hormone (LH) and/or prolactin in men who subsequently developed prostate cancer in comparison to men who remained free of the disease. Most information was available for T with 817 cases. There was no evidence that the serum concentration of T was different between cases and controls, with a pooled ratio of 0.99 (95% CI 0.95–1.02) and there was no evidence of heterogeneity between the studies. The pooled estimates for the other hormones included data from between 114 and 644 cases and no significant differences in mean concentrations between prostate cases and controls were found. However, all five studies that measured A-diol-g reported a higher mean concentration among cases relative to controls which was reflected in the pooled ratio of 1.05 (95% CI 1.00–1.11). Thus, cases had, on average, a 5% higher mean serum concentration of A-diol-g than controls, based on 644 cases and 1048 controls.

4 Androstanediol glucuronide

First author  Year  Cases/controls  ratio  95% CI  Ratio and 95% CI
Gann 1996 222/390 1.06 (0.98–1.14)
Nomura 1996 141/141 1.09 (0.97–1.23)
Guess 1997 106/106 1.02 (0.91–1.16)
Vatten 1997 59/180 1.02 (0.90–1.17)
Dorgan 1998 116/231 1.06 (0.93–1.21)

All studies 644/1048 1.05 (1.00–1.11)

Test for heterogeneity $\chi^2 = 0.8; P > 0.1, NS$

5 Androstenedione

First author  Year  Cases/controls  ratio  95% CI  Ratio and 95% CI
Barrett-Connor 1990 59/948 0.96 (0.87–1.10)
Nomura 1996 141/141 1.05 (0.97–1.13)
Dorgan 1998 116/231 0.99 (0.93–1.06)

All studies 316/1320 1.01 (0.97–1.06)

Test for heterogeneity $\chi^2 = 1.4; P > 0.1, NS$

6 Dehydroepiandrosterone sulphate

First author  Year  Cases/controls  ratio  95% CI  Ratio and 95% CI
Comstock 1993 81/81 0.88 (0.72–1.09)
Dorgan 1998 116/231 1.02 (0.90–1.16)

All studies 197/312 0.98 (0.88–1.10)

Test for heterogeneity $\chi^2 = 1.3; P > 0.1, NS$

DISCUSSION

This quantitative review reveals no convincing evidence that serum levels of endogenous sex hormones, their precursor compounds and metabolites and related binding protein, differ between men who subsequently go on to develop prostate cancer and those who do not. The pooled estimate for A-diol-g does, however, suggest that prostate cancer cases had a 5% higher serum concentration relative to controls.

Differences in oestradiol levels of approximately 15% have been found to influence the risk of hormone-sensitive cancers, as found for breast cancer risk in post-menopausal women (Thomas et al., 1997). The finding that circulating serum levels of A-diol-g are 5% higher in prostate cancer cases than controls is consistent with the hypothesis that elevated hormonal activity is important in the progression of hormone-sensitive cancers. Circulating androgen levels are likely to be only weakly correlated with the hormonal environment within the prostate gland, therefore small differences in circulating serum levels of A-diol-g may reflect larger differences in androgen activity within the prostate gland that are of biological relevance. Elevated A-diol-g concentrations may reflect an increased transformation from T to DHT within the prostate gland, which reported the serum concentration of testosterone (T), non-SHBG bound T, dihydrotestosterone (DHT), androstenediol glucuronide (A-diol-g), androstenedione (A-dione), dehydroepiandrosterone sulphate (DHEAS), sex hormone binding globulin (SHBG), oestrone, oestradiol, luteinizing hormone (LH) and/or prolactin in men who subsequently developed prostate cancer in comparison to men who remained free of the disease. Most information was available for T with 817 cases. There was no evidence that the serum concentration of T was different between cases and controls, with a pooled ratio of 0.99 (95% CI 0.95–1.02) and there was no evidence of heterogeneity between the studies. The pooled estimates for the other hormones included data from between 114 and 644 cases and no significant differences in mean concentrations between prostate cases and controls were found. However, all five studies that measured A-diol-g reported a higher mean concentration among cases relative to controls which was reflected in the pooled ratio of 1.05 (95% CI 1.00–1.11). Thus, cases had, on average, a 5% higher mean serum concentration of A-diol-g than controls, based on 644 cases and 1048 controls.
Test for heterogeneity $\chi^2 = 3.7; \, P > 0.1, \text{NS}$

### 8 Oestrone

| First author     | Year | Cases/controls ratio | 95% CI | Ratio and 95% CI |
|------------------|------|----------------------|--------|------------------|
| Nomura           | 1988 | 98/98                | 0.94   | (0.86–1.03)      |
| Barrett-Connor   | 1990 | 59/94                | 0.99   | (0.91–1.07)      |
| Hsing            | 1993 | 98/98                | 1.05   | (0.95–1.16)      |
| Dorgan           | 1998 | 116/231              | 1.00   | (0.94–1.07)      |
| All studies      |      | 371/1374             | 0.99   | (0.95–1.03)      |

Test for heterogeneity $\chi^2 = 1.7; \, P > 0.1, \text{NS}$

### 9 Oestradiol

| First author     | Year | Cases/controls ratio | 95% CI | Ratio and 95% CI |
|------------------|------|----------------------|--------|------------------|
| Nomura           | 1988 | 98/98                | 0.96   | (0.88–1.04)      |
| Barrett-Connor   | 1990 | 59/94                | 0.99   | (0.91–1.07)      |
| Hsing            | 1993 | 98/98                | 1.05   | (0.95–1.16)      |
| Dorgan           | 1998 | 116/231              | 1.00   | (0.94–1.07)      |
| All studies      |      | 592/1765             | 0.99   | (0.96–1.02)      |

Test for heterogeneity $\chi^2 = 2.2; \, P > 0.1, \text{NS}$

### 10 Luteinising hormone

| First author     | Year | Cases/controls ratio | 95% CI | Ratio and 95% CI |
|------------------|------|----------------------|--------|------------------|
| Hsing            | 1993 | 98/98                | 1.03   | (0.84–1.27)      |
| Carter           | 1995 | 16/16                | 0.75   | (0.55–1.03)      |
| All studies      |      | 114/114              | 0.94   | (0.79–1.11)      |

Test for heterogeneity $\chi^2 = 2.7; \, P > 0.1, \text{NS}$

### 11 Prolactin

| First author     | Year | Cases/controls ratio | 95% CI | Ratio and 95% CI |
|------------------|------|----------------------|--------|------------------|
| Hsing            | 1993 | 98/98                | 1.00   | (0.87–1.14)      |
| Gann             | 1996 | 222/390              | 1.02   | (0.88–1.19)      |
| All studies      |      | 320/488              | 1.01   | (0.91–1.12)      |

Test for heterogeneity $\chi^2 = 0.0; \, P > 0.1, \text{NS}$

**Figures 7–11** Ratio of mean hormone levels between cases and controls for sex hormone binding globulin, oestrone, oestradiol, luteinising hormone and prolactin
al, 1988), may be markedly different between high- and low-risk populations, and it may be that differences in circulating hormone levels at these critical times of development are more relevant to subsequent prostate cancer risk. It may therefore be more appropriate to collect several specimens from an individual over many years to achieve the necessary sensitivity to detect small differences in hormone levels.

This quantitative review suggests that there are no large differences between prostate cancer cases and controls in serum hormone concentrations measured in samples taken some years prior to diagnosis. Serum concentrations of A-diol-g were consistently slightly higher in men who subsequently went on to develop prostate cancer, and may reflect higher androgenic activity in these men.

ACKNOWLEDGEMENTS

We would like to thank Dr Barrett-Connor, Ricki Bettencourt, Dr Guess and Dr Gann for providing data additional to those which had been published. This project was funded by the Imperial Cancer Research Fund.

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