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Postmenopausal levels of sex hormones and risk of breast carcinoma *in situ:* Results of a prospective study

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We report on a prospective study to assess the association of postmenopausal serum levels of sex hormones with subsequent risk of breast carcinoma *in situ.* We conducted a case-control study nested within the cohort of the New York University Women's Health Study, a large prospective study documenting a positive association of circulating levels of estrogens and androgens with invasive breast cancer. The study included 69 cases of incident *in situ* carcinoma and 134 individually matched controls. No statistically significant trend of increasing risk with increasing level of any of the hormones was observed. Odds ratios (95% CIs) for the highest tertile relative to the lowest were 1.10 (0.51–2.39) for estradiol, 0.95 (0.41–2.19) for estrone, 1.63 (0.69–3.88) for testosterone, 0.99 (0.44–2.24) for androstenedione, 0.99 (0.45–2.20) for dehydroepiandrosterone sulfate and 0.81 (0.38–1.74) for sex hormone–binding globulin. Adjusting for potential confounders did not materially affect the results, nor did limiting the analysis to the 59 cases of ductal carcinoma *in situ,* the lesion thought to be the direct precursor of most invasive breast cancers. Our results are at variance with the positive associations observed in this same cohort with risk of invasive breast cancer. Possible explanations for our results include lack of power, an effect of sex hormones limited to the progression from *in situ* to invasive tumors, overrepresentation of indolent tumors or an effect of sex hormones on the induction of only a subset of *in situ* tumors, those that would develop into invasive tumors.

Key words: estrogen; androgen; estradiol; estrone; testosterone; dehydroepiandrosterone sulfate; sex hormone–binding globulin; breast carcinoma in *situ*; ductal carcinoma *in situ*; prospective study

There is a large amount of evidence on the role of both exogenous[1–3] and endogenous[4] sex hormones in the development of invasive breast cancer. However, little is known regarding the role of these hormones in breast carcinoma *in situ,* although with the increasing use of mammographic screening, these noninvasive tumors represent approximately 20% of all breast cancers diagnosed every year in the United States.[5] DCIS is usually considered the true precursor of invasive ductal carcinoma because of its frequent coexistence with invasive lesions, the high rate of recurrence as an invasive tumor at its original site and the presence of shared chromosomal changes in both DCIS and synchronous, adjacent invasive cancer, demonstrating their clonal, evolutionary relationship.[6] Whether LCIS, which is often an incidental biopsy finding because of its lack of mammographic or ultrasound features, is a precursor of invasive lobular carcinoma or a marker of increased breast cancer risk remains unclear because about half of the cases of invasive breast cancer following a diagnosis of LCIS are in the contralateral breast and some are of ductal type.[7]

We examined the association of postmenopausal serum levels of sex hormones with subsequent risk of breast carcinoma *in situ* in a case-control study nested within the cohort of the NYU Women's Health Study, a large prospective study documenting a positive association of circulating levels of estrogens and androgens with invasive breast cancer risk.[8]

Material and methods

Study cohort

Between 1985 and 1991, the NYU Women's Health Study enrolled 14,275 healthy women aged 34–65 at the Guttman Breast Diagnostic Institute, a breast cancer screening center in New York City.[9] Women who had been pregnant or had taken hormone medications in the 6 months preceding their visit were not eligible. At the time of enrollment, women were classified as postmenopausal if they reported no menstrual cycles in the previous 6 months, a total bilateral oophorectomy or a hysterectomy without total oophorectomy prior to natural menopause and their age was 52 years or older. A total of 7,054 participants (49.4%) were postmenopausal.

After written informed consent was obtained, demographic, medical, anthropometric, reproductive and dietary data were collected through self-administered questionnaires. Nonfasting peripheral venous blood (30 ml) was drawn prior to breast examination. After centrifugation, serum samples were divided into 1 ml aliquots and immediately stored at –80°C for subsequent biochemical analysis. Up to 1991, women who returned for annual breast cancer screening were invited to contribute additional blood donations.

Nested case-control study of breast cancer

Breast cancer cases were identified through active follow-up of the cohort by mailed questionnaires approximately every 2–4 years and telephone interviews for nonrespondents as well as record linkage with the US National Death Index and state cancer registries in New York, New Jersey and Florida. Medical and pathology reports were requested to confirm the diagnosis. For each case, 2 controls were selected at random from the appropriate risk sets. The risk set for a case consisted of all women who were postmenopausal at enrollment, were alive and free of cancer at the time of diagnosis of the case and matched the case on age at enrollment (±6 months), date of enrollment (±3 months) and number (1, 2, 3+) and dates (±3 months) of subsequent blood donations, if any. Menopausal status was confirmed by measuring FSH in all women for whom the lag time between last menstrual

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma *in situ;* DHEAS, dehydroepiandrosterone sulfate; DSL, Diagnostic System Laboratories; FSH, follicle-stimulating hormone; IARC, International Agency for Research on Cancer; LCIS, lobular carcinoma *in situ;* NYU, New York University; OR, odds ratio; SHBG, sex hormone–binding globulin.

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period and blood donation was <2 years, who were <60 years old at entry and who reported having had a hysterectomy without complete bilateral oophorectomy.

Laboratory analyses

All assays were performed in the Hormones and Cancer Group laboratory at the IARC in Lyon, France. Cases were always included in the same laboratory batch as their matched controls, and laboratory personnel were blinded as to case/control status. Assays were selected based on the results of a validity study.[10] Estradiol, estrone and androstenedione were measured by direct double-antibody radioimmunoassay (DSL, Webster, TX); testosterone and DHEAS were measured by direct radioimmunoassay (Immunotech, Marseille, France); SHBG was measured by a direct sandwich immunoradiometric assay (Cis-Bio, Gif-sur-Yvette, France); and FSH was measured by an immunoradiometric assay (DSL). Mean intra- and inter-batch coefficients of variation were, respectively, 5.3% and 14.6% for estradiol (at a concentration of 95 pmol/l), 6.7% and 14.4% for estrone (at 74 pmol/l), 7.8% and 13.5% for androstenedione (at 1.4 nmol/l), 8.7% and 15.8% for testosterone (at 1.4 nmol/l), 5.4% and 14.7% for DHEAS (at 1.62 μmol/l) and 5.6% and 13.5% for SHBG (at 40 nmol/l).

Statistical methods

The distributions of known breast cancer risk factors in cases and controls were compared using the conditional logistic regression model, to take into account the matching.[11] To test for differences in hormone (and SHBG) levels between case and control subjects, we used a mixed-effects regression model, taking into account the matched design: after natural logarithmic transformation to reduce departures from the normal distribution, hormone (or SHBG) levels were modeled as a function of a random stratum effect (matched set) and a fixed effect for case/control status.[12]

To compute ORs, serum measurements were categorized into tertiles, using the frequency distribution of the cases and the controls combined. Matched set data were analyzed using conditional logistic regression.[11] ORs were computed relative to the lowest tertile. Reported trend test p values correspond to hormone variables treated as ordered categorical variables. Analyses were also performed on log-transformed continuous variables. All p values are 2-sided.

Results

By March 1, 1998, the date of the latest complete round of follow-up, 69 women postmenopausal at enrollment had been first diagnosed with breast carcinoma *in situ* 1 year or more after entry into the study. Pathology reports were obtained for 46 cases (66.7%), and the remaining 23 cases (33.3%) were confirmed by the tumor registries. Histology was intraductal for 59 cases, lobular for 7 cases and unknown for 3 cases. Among the 138 controls initially selected, 4 were excluded because, subsequent to the time their matched case was diagnosed with breast carcinoma *in situ,* they themselves developed some type of cancer; and their serum samples were reserved for studies of these other cancers.

Table I presents selected characteristics of the study participants. Median age at enrollment was 58 years (10th–90th percentiles, 52–64) and at diagnosis, 65 years (10th–90th percentiles, 60–71). Compared to controls, cases were characterized by a later age at first full-time pregnancy (25 *vs.* 24 years, $p < 0.05$). For the 78% of subjects for whom education information was available, cases had a higher frequency of education beyond college (51% *vs.* 41%, $p < 0.05$).

There was no statistically significant difference between cases and controls in any of the hormones (Table II). Similarly, no trend in risk was observed with increasing tertiles of hormone concentrations (Table III). Adjusting for potential confounders one at a time did not materially affect the results. We do not present analyses controlling for all potential confounders simultaneously because, due to the relatively small size of our study, such analyses led to unstable OR estimates. There were no statistically significant trends in analyses of hormones on the continuous scale.

Table IV presents an analysis limited to the 59 cases of DCIS. Similar to our overall results, we did not observe an association of risk with sex hormones or SHBG in this subgroup.

Discussion

At variance with the results for invasive breast cancer,[4] including our own observations in this same cohort,[8,13] we did not find an association between postmenopausal circulating levels of sex hormones or SHBG and risk of breast carcinoma *in situ.* Similar results were observed in analyses limited to DCIS. What are possible explanations for these results, which appear contradictory in light of the now accepted facts that *in situ* carcinoma is one of the stages of breast carcinogenesis and that nearly all invasive ductal breast cancers arise from DCIS?[6] One hypothesis consistent with our results is that sex hormones influence the progression of carcinoma *in situ* to invasive breast cancer, rather than the earlier stages leading to carcinoma *in situ.* Estrogens, however, are thought to affect carcinogenesis through increased cell proliferation and associated increased probability of genetic errors during DNA replication, as well as possibly through direct oxidative DNA damage.[14] Under these mechanisms, it is not clear why estrogens would impact the acquisition of invasiveness, one of the latest stages of tumorigenesis, but not affect the transition from normal tissue to DCIS, the phase during which many of the hallmark cellular events of breast tumorigenesis occur, such as accumulation of genetic changes, oncogene expression and loss of normal cell-cycle regulation.[6]

The specific features of *in situ,* as opposed to invasive, tumors suggest alternative explanations. First, our failure to detect a

TABLE I – STUDY PARTICIPANT CHARACTERISTICS

	Cases (n = 69)	Controls (n = 134)
Age (years) at enrollment, median (10th–90th percentiles)	58 (52–64)	58 (52–63)
Age (years) at diagnosis, median (10th–90th percentiles)	65 (60–71)	
Age (years) at menarche, median (10th–90th percentiles)	13 (10–14)	13 (11–15)
Nulliparous (%)	18 (26.1%)	35 (26.1%)
Age (years) at first full-term pregnancy, median (10th–90th percentiles)*	25 (21–34)	24 (19–30)
Age (years) at menopause, median (10th–90th percentiles)	50 (38–55)	51 (42–55)
Prior bilateral oophorectomy (%)	8 (11.6%)	19 (14.2%)
First-degree family history of breast cancer (%)	15 (21.7%)	26 (19.4%)
Prior breast biopsy (%)	12 (17.4%)	27 (20.2%)
Height (cm), median (10th–90th percentiles)	163 (152–168)	163 (155–170)
Weight (kg), median (10th–90th percentiles)	66 (56–82)	64 (56–82)
Body mass index (kg/cm^2), median (10th–90th percentiles)	25.2 (20.6–31.2)	24.2 (20.8–30.4)
Education higher than college (%)[1]*	35/52 (50.7%)	55/107 (41.0%)

[1]Unknown for 25% of cases and 20% of controls. *$p < 0.05$.

TABLE II – MEDIAN (10TH–90TH PERCENTILES) OF SERUM LEVELS OF HORMONES AND SHBG IN CASES AND CONTROLS

Hormone, unit	Cases (n = 69)	Controls (n = 134)	p[1]
Estradiol, pmol/l	92.6 (58.6–153)	90.8 (55.2–148)	0.77
Estrone, pmol/l	78.3 (49.9–137)	73.2 (47.1–127)	0.21
Testosterone, nmol/l	0.56 (0.19–1.54)	0.52 (0.18–1.30)	0.41
Androstenedione, nmol/l	2.37 (1.16–4.37)	2.46 (1.30–5.27)	0.25
DHEAS, μmol/l	1.92 (0.70–4.90)	1.91 (0.81–4.66)	0.83
SHBG, nmol/l	42.2 (18.1–103)	45.3 (19.0–78.0)	0.72

[1]p values are from a mixed-effects model on log-transformed variables, controlling for matching factors.

TABLE III – ORS FOR BREAST CARCINOMA *IN SITU* BY TERTILES OF SERUM SEX HORMONES AND SHBG LEVELS AMONG POSTMENOPAUSAL WOMEN IN THE NYU WOMEN'S HEALTH STUDY

Hormone	Cases, n (%)	Controls, n (%)	OR[1] (95% CI)
Estradiol			
1	20 (29.9)	46 (34.8)	1.0
2	25 (37.3)	41 (31.1)	1.39 (0.66–2.94)
3	22 (32.8)	45 (34.1)	1.10 (0.51–2.39)
p for trend			0.77
Estrone			
1	20 (29.4)	46 (35.1)	1.0
2	28 (41.2)	38 (29.0)	1.77 (0.81–3.87)
3	20 (29.4)	47 (35.9)	0.95 (0.41–2.19)
p for trend			0.84
Testosterone			
1	19 (29.2)	44 (35.5)	1.0
2	22 (33.8)	41 (33.1)	1.34 (0.60–2.97)
3	24 (36.9)	39 (31.5)	1.63 (0.69–3.88)
p for trend			0.26
Androstenedione			
1	19 (27.9)	47 (35.6)	1.0
2	30 (44.1)	37 (28.0)	1.97 (0.94–4.11)
3	19 (27.9)	48 (36.4)	0.99 (0.44–2.24)
p for trend			0.95
DHEAS			
1	23 (35.4)	42 (31.8)	1.0
2	19 (29.2)	47 (35.6)	0.77 (0.36–1.66)
3	23 (35.4)	43 (32.6)	0.99 (0.45–2.20)
p for trend			0.99
SHBG			
1	25 (36.2)	43 (32.1)	1.0
2	22 (31.9)	46 (34.3)	0.79 (0.39–1.58)
3	22 (31.9)	45 (33.6)	0.81 (0.38–1.74)
p for trend			0.90

[1]Controlling for matching factors.

TABLE IV – ORS FOR DCIS BY TERTILES OF SERUM SEX HORMONES AND SHBG LEVELS AMONG POSTMENOPAUSAL WOMEN IN THE NYU WOMEN'S HEALTH STUDY

Hormone	Cases, n (%)	Controls, n (%)	OR[1] (95% CI)
Estradiol			
1	18 (31.5)	38 (33.6)	1.0
2	21 (36.8)	36 (31.9)	1.17 (0.53–2.57)
3	18 (31.6)	39 (34.5)	0.94 (0.40–2.23)
p for trend			0.91
Estrone			
1	17 (29.3)	40 (35.4)	1.0
2	24 (41.4)	33 (29.2)	1.83 (0.79–4.23)
3	17 (29.3)	40 (35.4)	1.02 (0.42–2.48)
p for trend			0.99
Testosterone			
1	18 (32.7)	35 (33.3)	1.0
2	18 (32.7)	36 (34.3)	1.01 (0.43–2.38)
3	19 (34.6)	34 (32.4)	1.14 (0.44–2.94)
p for trend			0.78
Androstenedione			
1	17 (29.3)	40 (35.4)	1.0
2	25 (43.1)	32 (28.3)	1.79 (0.80–3.99)
3	16 (27.6)	41 (36.3)	0.94 (0.41–2.14)
p for trend			0.89
DHEAS			
1	20 (36.4)	36 (31.9)	1.0
2	17 (30.9)	39 (34.5)	0.80 (0.34–1.87)
3	18 (32.7)	38 (33.6)	0.84 (0.35–2.03)
p for trend			0.71
SHBG			
1	20 (33.9)	38 (33.3)	1.0
2	19 (32.2)	40 (34.2)	0.89 (0.41–1.91)
3	20 (33.9)	38 (32.5)	1.01 (0.45–2.30)
p for trend			0.97

[1]Controlling for matching factors.

positive association between estrogen levels and DCIS could be due to a sampling artifact. The vast majority of *in situ* tumors are detected through screening, and screen-detected tumors tend to include an overrepresentation of slow-growing tumors.[15] This phenomenon, referred to as "length bias" in the screening literature,[16] results from the fact that slow-growing tumors spend more time in the various transition stages from normal tissue to invasive cancer, including the *in situ* stage. As a result, they are more likely to be diagnosed at the *in situ* stage than fast-growing tumors, which are more likely to be diagnosed at the invasive stage. In studies of screen-detected tumors, the association with disease of a factor which accelerates the multistep process of tumor development, and is therefore a true risk factor, will be weakened because the case group will have been depleted of the tumors that were most influenced by this factor, *i.e.,* the fastest-growing tumors. Estrogens, by increased cell proliferation and accumulated genetic changes, would be expected to accelerate the tumor-development process. If so, they will be associated mainly with fast-growing tumors, which are only briefly in the *in situ* phase, so the bulk of the *in situ* tumors detected through screening will be indolent ones that are little affected by estrogens; as a result, the association of estrogens with *in situ* tumors will be weak or null. Length bias could therefore explain why we did not observe the positive association between estrogen levels and *in situ* tumors that we previously observed with invasive breast cancer.

A lack of association between sex hormones and risk of DCIS could also be observed if sex hormones impact the development of only a subset of these tumors. Although the natural history of DCIS is not fully known because current standard practice is to remove these tumors, it appears that a subset of DCIS may remain indolent through a woman's lifetime.[17,18] If sex hormones are associated with the formation of DCIS that will eventually progress into invasive tumors but not with the formation of DCIS that will evolve no further, the hormone–disease associations observed in the overall group of *in situ* tumors will be attenuated by the inclusion of nonevolving tumors. The differences in genetic alterations observed in DCIS tumors with low and high nuclear grade, one of the main factors predictive of local recurrence, support the hypothesis that DCIS is a heterogeneous disease with potentially independent tumor-development pathways.[19]

It is possible that some controls harbored breast carcinoma *in situ* for the following reasons: *(i)* reporting by our study participants may have been incomplete because our questionnaire inquired about breast cancer without further specification and some women may not have considered *in situ* carcinoma as breast

cancer, *(ii)* reporting of *in situ* tumors to tumor registries may be less complete than reporting of invasive tumors and *(iii)* some controls may not have been screened recently for breast cancer and may have had undetected *in situ* carcinoma. Such misclassification, which would be expected to be nondifferential with respect to endogenous hormonal levels and therefore to bias results toward the null, could have contributed to the lack of association that we observed. However, we believe that inclusion of controls carrying breast carcinoma *in situ,* although possible, was a rare event in our study and had little impact on our results because, firstly, the proportion of all breast cancers that were *in situ* was 18.4% in our study, a result close to what has been observed in several screened populations.[20–24] Secondly, controls were matched to cases on number (1, 2, 3+) and approximate dates of blood donations, which were solicited when women returned to the mammography clinic for screening during the accrual period of the study (1985–1991). In this way, controls were matched to cases with respect to screening behavior, at least during the accrual period of the study. Indeed, 72% of controls had exactly the same number of screening visits with blood donations as their matching cases. Thirdly, the similar proportions of cases and controls with a family history of breast cancer and with prior breast biopsy provide indirect evidence that screening was not more common among cases than controls.

An advantage of our study is its prospective design, which permits analysis of prediagnostic hormone levels and reduces the risk of selection bias. A limitation is its small sample size and consequent limited power. No trend in risk was observed, though, in analyses based on continuous hormone levels, which have greater power than analyses based on tertiles. Our study had 80% power to detect fairly small differences in geometric means, *e.g.,* 10% for estradiol and 11.5% for estrone (observed differences were $<2\%$). However, the limited power of our study remains a concern, in particular if, as discussed above, the hypothesis that endogenous sex hormones affect the development of only a subset of *in situ* tumors is verified.

In our prospective study, we assessed the role of endogenous sex hormones in the development of breast carcinoma *in situ.* Several studies have examined the association of exogenous estrogens, *i.e.,* oral contraceptives and hormone replacement therapy, with carcinoma *in situ;* but, as reviewed recently,[25] no consistent relationships have emerged. It is of interest that the well-documented positive association of body mass index with postmenopausal invasive breast cancer has not been observed with *in situ* carcinoma in older women.[25] In our study, although the median body mass index was slightly larger in cases than in controls, the difference was not statistically significant and there was no evidence of a trend of increasing risk with increasing body mass index. The association of body mass index with postmenopausal invasive breast cancer is usually attributed to the higher levels of circulating estrogens in these women[26] because the main source of endogenous estrogens after menopause is the conversion of androgens to estrogens in adipose tissue. The lack of association of body mass index with *in situ* carcinoma risk in postmenopausal women is therefore consistent with the lack of association of endogenous estrogens that we observed. In light of the increasing frequency of these tumors, additional studies to clarify the role of hormones in the development of breast carcinoma *in situ* are warranted.

In conclusion, we did not find an association of postmenopausal levels of estrogens and androgens with risk of breast carcinoma *in situ.* Similar results were observed in analyses limited to ductal carcinoma *in situ,* the lesion thought to be the direct precursor of invasive breast cancers. These results are in contrast with the positive associations observed in this same cohort with risk of invasive breast cancer. Possible explanations for our results include lack of power, an effect of sex hormones primarily on the progression from *in situ* to invasive tumors, overrepresentation of indolent (non-estrogen-responsive) tumors among cases or an effect of sex hormones on the induction of only a subset of *in situ* tumors, those that would develop into invasive tumors.

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