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A Pilot Study of Urinary Estrogen Metabolites (16alpha-OHE_1 and 2-OHE_1) in Postmenopausal Women with and without Breast Cancer

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Abstract

The two main pathways for metabolizing estrogen are via 16α-hydroxylation and 2-hydroxylation. The 16α-hydroxy metabolites are biologically active; the 2-hydroxy metabolites are not. It is suggested that women who metabolize a larger proportion of their endogenous estrogen via the 16α-hydroxy pathway may be at significantly elevated risk of breast cancer compared with women who metabolize proportionally more estrogen via the 2-hydroxy pathway. In particular, it is suggested that the ratio of urinary 2-hydroxyestrone (2-OHE_1) to 16α-hydroxyestrone (16α-OHE_1) is an index of reduced breast cancer risk. This pilot study compared this ratio in postmenopausal women diagnosed with breast cancer to those of healthy controls. Urinary concentrations of estrone (E_1), 17ß-estradiol (E_2) and estriol (E_3) were also quantified. White women who were subjects in a previous breast cancer case-control study at our institution were eligible for inclusion. All participants provided a sample of their first morning urine. The results from the first 25 cases and 23 controls are presented here. The ratio of 2-OHE_1 to 16α-OHE_1 was 12% lower in the cases (p=0.58). However, urinary E_1 was 30% higher (p=0.10), E_2 was 58% higher (p=0.07), E_3 was 15% higher (p=0.48), and the sum of E_1, E_2, and E_3 was 22% higher (p=0.16) in the cases. These preliminary results do not support the hypothesis that the ratio of the two hydroxylation metabolites (2-OHE_1/16α-OHE_1) is an important risk factor for breast cancer or that it is a better predictor of breast cancer risk than levels of E_1, E_2 and E_3 measured in urine. -- *Environ Health*

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Abbreviations used: E_1, estrone; E_2, 17ß-estradiol; E_3, estriol; EIA, enzyme immunoassay; HPLC, high-performance liquid chromatography; 2-OHE_1, 2-hydroxyestrone; 16α-OHE_1, 16α-hydroxyestrone; RIA, radioimmunoassay.

Introduction

Overwhelming evidence supports a role of ovarian hormones in the etiology of breast cancer (1). At menopause circulating estrogens decline sharply, explaining in large part, and possibly completely, the decreased breast cancer risk associated with early menopause (2). In postmenopausal women, the major source of estrogen arises from the peripheral conversion of androstenedione in adipose tissue (3). This, together with decreased sex hormone-binding globulin levels, is the most probable explanation for the higher breast cancer risk in obese postmenopausal women (4). Both elevated serum estrogen levels (5-16) and increased urinary excretion rates of estrone (E_1), 17ß-estradiol (E_2) and estriol (E_3) have been found in breast cancer cases as compared with controls (17-24).

The two main pathways for metabolizing estrogen are via 16α-hydroxylation and 2-hydroxylation, and the major estrogen metabolites excreted in urine are 2-hydroxy products [2-hydroxyestrone (2-OHE_1), 2-hydroxyestradiol (2-OH-E_2), 2-methoxyestrone (2-MeO-E_1)], nonmetabolized E_1, 16α-hydroxy products [E_3, αhydroxyestrone (16α-OHE_1)]and E2 (25). The 16α-metabolites are biologically active (26,27); the 2-hydroxy metabolites are not (28).

The extent to which estrogen is metabolized via the 16α-hydroxylation pathway may be associated with breast cancer risk (29-31). Increased 16α-hydroxylation activity, but not 2-hydroxylation activity, has been observed in mice strains with high spontaneous mammary tumor formation (29). In humans, the extent of biotransformation of ^3H-E_2 via the 16α-hydroxylation pathway was 4.6-fold higher in terminal duct lobular units in breast tissue from breast cancer cases than in breast tissue from reduction mammoplasty controls (32). Two other epidemiologic studies

suggested that the extent of 16α-hydroxylation was higher in women with breast cancer (33) and in women with high familial risk of breast cancer (34) than in controls. However, a third study found no elevation of 16α-hydroxylation in breast cancer cases compared with controls (25).

We selected women interviewed in a previous population-based epidemiologic study to determine whether postmenopausal women with breast cancer have a lower ratio of urinary 2-OHE_1 to 16α-OHE_1 than controls. We report here the data from the first 25 cases and 23 controls.

Methods

This study was approved by the local Institutional Review Board. Written informed consent was obtained from each participant.

Eligible cases were identified from women between 55 and 64 years of age diagnosed with histologically confirmed breast cancer, identified through the Los Angeles County Cancer Surveillance Program (a National Cancer Institute Surveillance, Epidemiology, and End Results Program Registry), who had participated in a previous breast cancer case-control study conducted at our institution (35). The dates of diagnosis were 1 March 1987 through 31 December 1989. Only women diagnosed with incident cancer at stage II or less [tumor size ≤ T_2, nodes ≤ N_1, and no distant metastasis (M_0), or T_3, N_0, M_0] were included (36). Eligible controls were participants in the same case-control study who had not been diagnosed with breast cancer. Subjects had to be English-speaking whites (including Hispanics), and residents of Los Angeles County.

Cases and controls were contacted; the most recent interviewees were contacted first. Eligibility was determined based on a phone interview. Subjects who had used medications during the previous 6 months that may have interfered with estrogen metabolism (specifically, cimetidine, thyroxine, estrogen, progesterone, tamoxifen, or ω3 fatty acid supplements) (37-40) were eliminated from the study. Subjects who had general anesthesia in the previous 3 months or weighed more than 200 lb (90 kg) were also excluded.

A box containing a 100-ml urine vial with a 100-mg ascorbate tablet, a small cooler with an ice pack, an informed consent form, and a questionnaire on recent intake of medication, alcohol, and specific foods was shipped to each eligible woman who agreed to participate. First morning urine samples were collected, aliquoted, and frozen at -70°C within 6 hr after specimens were produced.

Urine samples were sent to two different laboratories. Batches of 30 samples (15 from cases, 15 from controls, including 10% duplicates) were coded and shipped on dry ice. The only identifiers on the samples were code numbers ensuring that the laboratories were blinded as to case or control status of the individual samples and to the identity of duplicates.

Enzyme Immunoassay of 16α-OHE_1 and 2-OHE_1

Measurements of urinary 16α-OHE_1 and 2-OHE_1 were carried out using commercially available competitive enzyme immunoassay (EIA) kits (Estramet, Immuna Care Corporation, Bethlehem, PA) to measure 2-OHE_1 and 16α-OHE_1 directly in urine. The two metabolites were measured simultaneously to avoid interassay variation. This method has been described in detail by Klug et al. (41). In brief, monoclonal antibodies to the estrogen metabolites were immobilized directly to the solid phase, and the metabolite standards were conjugated to alkaline phosphatase

enzyme. Each urine sample was acidified and subjected to ß-glucuronidase/aryl sulfatase hydrolysis before assay.

The 16α-OHE_1 and 2-OHE_1 EIA kits were validated by comparing values obtained with these kits to values obtained by gas chromatography-mass spectroscopy (41). The inter- and intraassay coefficients of variation for 2-OHE_1 and 16 α-OHE_1 were between 7 and 13% (41). Creatinine values above 0.20 mg/ml are considered necessary to obtain adequate reproducibility of the 2-OHE_1 and 16α-OHE_1 assays (HL Bradlow, personal communication).

Radioimmunoassay of Urinary E_1, E_2, and E_3

Measurements of urinary E_1, E_2, and E_3 were carried out using high-performance liquid chromatography-radioimmunoassay (HPLC-RIA). Each urine sample was acidified and subjected to ß-glucuronidase/aryl sulfatase hydrolysis before assay.

Following the addition of approximately 1000 dpm of ^{3}H-E_1, ^{3}H-E_2, and ^{3}H-E_3, which served as internal standards to follow procedural losses, solid phase extraction was performed. Ethyl acetate was used to extract the estrogens, the organic solvent was evaporated and the extract was subjected to HPLC. A reverse-phase HPLC column (C_{18}; 5μ) was used to elute E_3, E_2, and E_1 in a gradient of acetonitrile:water:acetic acid (40:60:0.1) at a flow rate of 1 ml/min. The retention times for E_3, E_2, and E_1 were 4, 13, and 16 min, respectively.

The E_1, E_2, and E_3 fractions were quantified by RIA, using methods previously described by Katagiri et al. (42), Stanczyk et al. (43), and Cassidenti et al. (44). Appropriate quality controls were used with each set of samples that was assayed to monitor assay reliability.

Statistical Analysis

All directly measured hormone variables were lognormally distributed, and the statistical significance of the difference in these variables between cases and controls was evaluated using t tests of the natural logs of these values. The statistical significance of the differences in 2-OHE_1/16α-OHE_1 between cases and controls was evaluated using Wilcoxon's nonparametric rank sum test. Statistical analyses were conducted using SAS (SAS Institute, Cary, NC).

Results

The full study will include almost 100 cases and 100 controls. We reported here results from the first subset of the women enrolled in the study.

Table 1. Mean levels of estrogen metabolites in postmenopausal breast cancer cases and controls.

Urinary metabolite[a]	Cases, $n = 25$ Mean	SE	Controls, $n = 23$ Mean	SE	Difference,[b] %	p value
2-OHE_1	7.09	0.99	7.98	0.77	−8.9	0.99
16α-OHE_1	5.27	0.47	4.88	0.37	8.0	0.61
2-OHE_1/16α-OHE_1	1.39	0.10	1.58	0.20	−12	0.58
E_1	3.14	0.34	2.42	0.34	30	0.10
E_2	0.97	0.14	0.55	0.06	58	0.07
E_3	5.53	0.66	4.90	0.49	15	0.48
$E_1 + E_2 + E_3$	9.64	0.94	7.97	0.91	22	0.16

[a] ng/(mg creatinine). [b] [1−(cases mean value)/(controls mean value)] × 100.

The results for the first two batches of urine samples were available for the analyses reported here. These represented 27 cases, 27 controls, and 6 duplicate samples. We excluded six samples with low creatinine values. Among the remaining 25 cases and 23 controls, the mean 16α-OHE_1 was 8.0% higher and the mean 2-OHE_1 was 3.9% lower in cases than in controls (Table 1). The ratio of 2-OHE_1 to 16α-OHE_1 was 12.0% lower in cases. None of these differences were statistically significant. The individual values of 2-OHE_1/16α-OHE_1 are plotted in Figure 1.

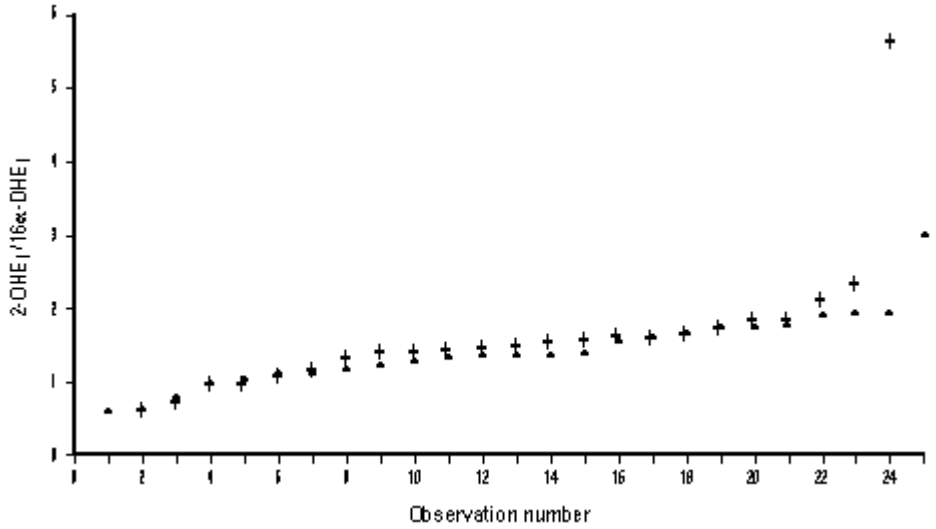

Figure 1. Urinary 2-OHE_1/αOHE$_1$ in 25 postmenopausal breast cancer cases (●) and 23 controls (+).

Ratios of 2-OHE_1/16α-OHE_1 below 2.0 have been suggested as an index of high risk of breast cancer (HL Bradlow, personal communication). However, in this study, nearly all cases and controls had at least this low ratio; 20 of 23 controls and 24 of 25 cases had ratios less than 2.0.

E_1 was 30% higher (p=0.10) and E_2 was 58% higher (p=0.07) in cases than in controls. E_3 was 15% higher and the sum of E_1, E_2, and E_3 was 22% higher in cases; neither result was statistically significant.

The coefficients of variation for the six blind duplicates were 13% for 2-OHE_1, 20% for 16α-OHE_1, 13% for E_1,

14% for E_2, and 24% for E_3.

Discussion

Our results confirm previous studies that E_1 and E_2 are higher in urine of postmenopausal breast cancer cases than controls (17-24). However, we found only small differences between cases and controls in urinary levels of 16α-OHE_1, 2-OHE_1, and the ratio of the two.

The epidemiologic data addressing the 2-OHE_1/16α-OHE_1 hypothesis are sparse. Schneider and co-workers used a radiometric method to determine the extent of 2- and 16α-hydroxylation (33). They injected 33 peri- and postmenopausal breast cancer patients and 10 postmenopausal controls with E_2 tracers labeled with ^3H in the 17α, C-2, and 16α position. They drew serial blood samples before and after isotope administration and determined the rate and extent of the oxidative metabolism at positions 17α, C-2, and 16α. Cases had 60% higher extent of 16α-hydroxylation than controls; this difference was statistically significant. However, the two groups did not differ significantly in the extent of 2-hydroxylation, which was only 5% higher among cases. The ratio of the average level of 16α-hydroxylation to the average level of 2-hydroxylation was 52% greater in the breast cancer cases than in the controls. No data on total estrogen values were provided.

The only other published study of 16α-/2-hydroxylation in breast cancer patients was performed by Adlercreutz et al. (25). They examined estrogen metabolites in young Finnish premenopausal breast cancer cases (*n*=10) and control women on an omnivorous normal Finnish diet (*n*=12) or on a lacto-vegetarian diet (*n*=11). There was no statistically significant difference in 2-OHE_1, 16α-OHE_1, or total urinary estrogens (E_1, E_2, E_3, 2-OHE_1, 16α-OHE_1, and eight other estrogen metabolites) between breast cancer patients and omnivores or breast cancer patients and lacto-vegetarians.

Both of the above-mentioned studies measured metabolites after breast cancer diagnosis. In an attempt to determine whether an elevated ratio of α- to 2-hydroxylation precedes diagnosis, Osborne and co-workers used radiometric methods to study estrogen metabolism in premenopausal women presumed to be at high or low risk of breast cancer (34). They found that women at high risk of breast cancer (family history of breast cancer or epithelial atypia in a previous biopsy) had a significantly higher (22%) extent of 16α-hydroxylation than women without high-risk lesions or a family history (low-risk controls). High-risk women had a similarly elevated extent of 16α-hydroxylation of E_2 as the breast cancer patients in the study by Schneider et al. (33). Translated to relative risks, the data of Osborne et al. (34) suggest that one standard deviation increase in the extent of 16α-hydroxylation from the level of low-risk controls may result in a 3-fold elevation of breast cancer risk. No data on total estrogen values were provided.

Several factors could also have affected our results. We studied a select group of women with few extraneous factors that might influence estrogen metabolism. With this approach we excluded a large number of women. Based on the first 300 women identified, we excluded 55 to 60% for a variety of reasons: 10% were above 200 lb, 15% were smokers, 25% of controls were taking estrogen replacement therapy, 10% were on other medications, and at least 20% of the cases were on tamoxifen. However, none of these exclusions appear likely to introduce any biases in any direction because they were applied equally to cases and controls.

The intraassay coefficients of variation for the assays used in this study were 13 and 20%, respectively. These values are somewhat higher than the published values of approximately 10% (41). It is, however, unclear whether the

original reproducibility tests were conducted in pre- or postmenopausal women. Ziegler (45) addresses reproducibility problems elsewhere in this volume. She found that the reproducibility of this assay was low when testing urines with low estrogen concentrations. As a result of these findings, both the 2-OHE_1 and 16α-OHE_1 tests are being adjusted to improve reproducibility at low concentrations (HL Bradlow, personal communication).

The evidence is rather clear that certain diets influence the extent of 16α- and 2-hydroxylation (46-49). Recent dietary changes in cases-controls could obscure or accentuate the differences between these groups. We addressed this issue by asking participants whether they have changed their diet in the past 10 years, and we will include a complete analysis of these data in a subsequent report on the completed study.

It is not known whether the onset of cancer may affect 2- and 16α-hydroxylation. We are therefore conducting another study examining the association between the extent of 2- and 16α-hydroxylation and familial risk of breast cancer in healthy young women.

In conclusion, our preliminary results from this case-control study of breast cancer in postmenopausal women do not support the hypothesis that the ratio of urinary 2-OHE_1 to 16α-OHE_1 is a better predictor of breast cancer risk than urinary E_1, E_2, and E_3.

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