Short communication

Assessing individual risk for breast cancer: role of oestrogens and androgens

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Introduction

With a focus on early diagnosis and improved treatment strategies, investigative studies and clinical trials over the past two decades have improved the recurrence-free and overall survival rates in breast cancer patients. However, women and their physicians have increasingly recognized the substantial cost and emotional burden resulting from breast cancer diagnosis and treatment. Prevention of the disease avoids these problems but requires an ability to predict risk. Selection of women at higher risk enhances the benefit/risk ratio of preventative agents [1]. Several valid methods are currently available for risk assessment, but their ability to identify women at moderate risk is limited [2]. Several factors, not included in the currently available models, could potentially enhance the predictive power of risk prediction methods. These factors include measurement of plasma androgens and oestrogens, as well as mammographic density, bone density and body mass index (BMI). A history of weight gain, age of menopause, fracture, alcohol use, magnitude of exercise and duration of breast feeding could also contribute.

Plasma hormone levels and breast cancer risk

Data from a large collaborative European study reported by Kaaks and coworkers [3] provide strong prospective evidence for the independent roles played by androgens and oestrogens in predicting breast cancer risk. In a similar study, Key and colleagues [4] pooled data from nine studies of similar type and drew comparable conclusions. A summary of the details of these studies is beyond the scope of this short communication but can be found in the report by Santen and coworkers [1], with specific details provided elsewhere [3,4]. __The methodology involved the collection of a single blood sample from each postmenopausal woman and subsequent follow-up over a period of 2 to 12 years. Women developing breast cancer and those who did not were grouped according to hormone levels into those in the first, second, third, fourth and fifth quintiles. The relative risk for breast cancer in quintiles two to four were compared with those in the first quintile.

Based upon these collaborative studies, the relative risks (RRs; and 95% confidence intervals [CIs]) for developing breast cancer in women in the top quintile of each hormone level compared with the bottom quintile are summarized in rank order in Table 1 [3,4].

Total plasma oestradiol (E_2) correlated (correlation coefficient or R value) substantially with the other hormones measured. Correlation coefficients were as follows: 0.96 for free E_2, 0.87 for non-sex hormone binding globulin E_2, 0.59 for oestrone, and 0.60 for oestrone sulphate (E_1S). Correlations of E_2 with androgens were significant but weaker: 0.37 for testosterone, 0.35 for androstenedione, 0.29 for dehydroepiandrosterone (DHEA) sulphate, and 0.2 for DHEA. Levels of androgens and oestrogens appeared to provide independent information, according to the available statistical analyses. For example, when E_2 was not adjusted for androgens, the RR associated with a doubling of hormone concentration was 1.31 (95% CI 1.17 to 1.48), and 1.18 (95% CI 1.04 to 1.34) when E_2 was adjusted for testosterone. When testosterone was unadjusted, the RR associated with a doubling of hormone concentration was 1.42 (95% CI 1.25 to 1.61) and 1.32 (95% CI 1.15 to 1.51) when adjusted for E_2. When corrected for the level of BMI, the predictive nature of the oestrogen levels was considerably reduced because BMI correlates well with free plasma E_2 level [5]. The measurement of these hormones was then examined in women who were otherwise at high risk for breast cancer based on other epidemiological factors. Even in the highest category of risk, measurements of androgens and oestrogens provided a statistically significant assessment of risk [6].

BMI = body mass index; CI = confidence interval; DHEA = dehydroepiandrosterone; E_1S = oestrone sulphate; E_2 = oestradiol; GC/MS/MS = gas chromatography/tandem mass spectrometry; RIA = radioimmunoassay; RR = relative risk.

Table 1

Relative risks for breast cancer associated with hormone levels: top versus bottom quintile

Hormone	RR (95% CI)
Free E_2	2.58 (1.76 to 3.78)
Non-SHBG-E_2	2.39 (1.62 to 3.54)
Testosterone	2.22 (1.59 to 3.10)
Estrone	2.19 (1.48 to 3.22)
Androstenedione	2.15 (1.44 to 3.21)
DHEA	2.04 (1.21 to 3.45)
Total estradiol	2.00 (1.47 to 2.71)
Estrone sulfate	2.00 (1.26 to 3.16)
DHEAS	1.75 (1.26 to 2.43)
SHBG	0.66 (0.43 to 1.00)

Data from Kaaks [3] and Key [4], and their coworkers. DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; E_2, oestradiol; SHBG, sex hormone binding globulin.

It is not surprising that the oestrogens correlated one with another. Prior studies in cell culture models demonstrated that titrated E_1S is converted into E_2 and that the oestrogen found in the nucleus under these conditions is E_2. E_1S can stimulate growth of MCF-7 breast cancer cells in proportion to its conversion to E_2 and appearance in the nucleus as E_2 [7]. Why would androgens correlate with breast cancer risk independently of oestrogens? One hypothesis suggests that plasma oestrogens reflect the extraglandular production of oestrogens in fat tissue and androgens provide the substrate for aromatase in the breast itself. Both are regulated differently and thus could provide independent information.

Careful analysis of the prospective studies of hormones and breast cancer risk uncovers problems with currently available E_2 radioimmunoassays (RIAs). There was a nearly fivefold difference in mean levels of E_2 among the nine different studies identified by Key and coworkers [4], presumably as a result of lack of sensitivity and precision of the RIAs used to measure these steroids in postmenopausal women. For this reason, we have reported data comparing E_2 levels by gas chromatography/tandem mass spectrometry (GC/MS/MS) and RIA in three groups of postmenopausal women [8]. Although the overall correlation of oestrogen levels is excellent ($r = 0.83$, $P < 0.001$), the correlation breaks down when correlations are made in the lowest tertile of values ($r = 0.29$, not significant). Accumulating data suggest that the RIAs are measuring cross-reacting material, which elevates the oestrogen levels above those detected by RIA [9]. For example, the yeast recombinant DNA and HeLa cell bioassays, as well as the GC/MS/MS methods, all measure substantially lower oestrogen levels than RIA. We conclude that the correlative studies must be repeated using more valid GC/MS/MS assays. With such assays, it should be possible to identify a group of women at much lower risk for breast cancer, whose E_2 levels could be accurately measured using the more sophisticated methodology [2].

Competing interests

The author declares that they have no competing interests.

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References

1. Santen RJ, Boyd NF, Chlebowski RT, Cummings S, Cuzick J, Dowsett M, Easton D, Forbes JF, Key T, Hankinson SE, Howell A, Ingle J, Breast Cancer Prevention Collaborative Group: **Critical assessment of new risk factors for breast cancer: considerations for development of an improved risk prediction model.** *Endocr Relat Cancer* 2007, **14:**169-187.
2. Tyrer J, Duffy SW, Cuzick J: **A breast cancer prediction model incorporating familial and personal risk factors.** *Stat Med* 2004, **23:**1111-1130 [erratum appears in *Stat Med* 2005, **24:** 156].
3. Kaaks R, Rinaldi S, Key TJ, Berrino F, Peeters PH, Biessy C, Dossus L, Lukanova A, Bingham S, Khaw KT, Allen NE, Bueno-de-Mesquita HB, van Gils CH, Grobbee D, Boeing H, Lahmann PH, Nagel G, Chang-Claude J, Clavel-Chapelon F, Fournier A, Thiebaut A, Gonzalez CA, Quiros JR, Tormo MJ, Ardanaz E, Amiano P, Krogh V, Palli D, Panico S, Tumino R, *et al.*: **Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition.** *Endocr Relat Cancer* 2005, **12:**1071-1082.
4. Key T, Appleby P, Barnes I, Reeves G, Endogenous Hormones and Breast Cancer Collaborative Group: **Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies.** *J Natl Cancer Inst* 2002, **94:**606-616.
5. Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, Stanczyk FZ, Stephenson HE Jr, Falk RT, Miller R, Schatzkin A, Allen DS, Fentiman IS, Key TJ, Wang DY, Dowsett M, Thomas HV, Hankinson SE, Toniolo P, Akhmedkhanov A, Koenig K, Shore RE, Zeleniuch-Jacquotte A, Berrino F, Muti P, Micheli A, Krogh V, Sieri S, Pala V, Venturelli E, *et al.*: **Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women.** *J Natl Cancer Inst* 2003, **95:**1218-1226.
6. Eliassen AH, Missmer SA, Tworoger SS,Hankinson SE: **Endogenous steroid hormone concentrations and risk of breast cancer: does the association vary by a woman's predicted breast cancer risk?** *J Clin Oncol* 2006, **24:**1823-1830.
7. Santner SJ, Ohlsson-Wilhelm B, Santen RJ: **Estrone sulfate promotes human breast cancer cell replication and nuclear uptake of estradiol in MCF-7 cell cultures.** *Intl J Cancer* 1993, **54:**119-124.
8. Santen RJ, Demers L, Ohorodnik S, Settlage J, Langecker P, Blanchett D, Goss PE, Wang S: **Superiority of gas chromatography/tandem mass spectrometry assay (GC/MS/MS) for estradiol for monitoring of aromatase inhibitor therapy.** *Steroids* 2007, **72:**666-671.
9. Stanczyk FZ, Lee JS, Santen RJ: **Standardization of steroid hormone assays: why, how, and when?** *Cancer Epidemiol Biomarkers Prev* 2007, **16:**1713-1719.