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Review

Relationships of sex steroid hormone levels in benign and cancerous breast tissue and blood: A critical appraisal of current science

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ABSTRACT

A systematic review of the literature on sex steroid measurement in breast tissue identified only 19 articles meeting the following criteria: menopausal status given; steroids measured in tissue homogenates by conventional RIA with a purification step or by mass spectrometry; and values reported per g tissue or per g protein. Twelve articles were analyzed in detail for: ratios of sex steroid hormone levels in cancerous or benign tissues to blood levels, stratified by menopausal status; ratios between the different hormone levels within tissues or within blood; and difference in these ratios between tissue and blood compartments. Estrogen and androgen concentrations varied greatly in benign and cancerous tissues and in blood between individuals. Postmenopausal, but not premenopausal, estradiol concentrations were significantly higher in cancerous compared to benign breast tissue. The estradiol/estrone ratio was lowest in premenopausal benign tissue, and substantially higher in premenopausal cancerous tissue and postmenopausal benign and cancerous tissues. Estradiol and estrone levels were considerably higher in tissue than in plasma in both premenopausal and postmenopausal women. Androgen levels were generally higher in the benign than the cancerous tissue, and tissue androgen levels were higher than in plasma, suggesting *in situ* aromatization of androgens to estrogens in breast cancer tissue. Limited available data on levels of hydroxylated estrogens in breast tissue compared to corresponding levels in plasma or urine were reviewed, but due to the paucity of studies no conclusions can presently be drawn regarding the relationship of the 2-hydroxyestrone:16α-hydroxyestrone ratio to breast cancer risk and genotoxic effects of 4-hydroxylated estrogens. Finally, data on hormone levels in breast adipose tissue were analyzed; high levels of androstenedione and testosterone and significant estrone and estradiol levels in breast adipocytes from postmenopausal breast cancer patients are consistent with an obesity–inflammation–aromatase axis occurring locally in breast tissue. The controversies regarding the source of intratumoral estrogens in the breast are summarized.

Contents

Abbreviations: IDC, invasive ductal carcinoma; DCIS, ductal carcinoma *in situ*; TDLU, terminal ductal lobular unit.

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1. Introduction

Sex steroid hormones, prolactin, and other hormonal and non-hormonal factors shape the microanatomy of the normal breast, control its physiological function over the life course, and influence breast cancer risk [1]. The significance of hormones in the pathogenesis of estrogen receptor positive (ER+) tumors is firmly established; however, our understanding of the mechanisms behind these effects remains incomplete, and knowledge about the possible contributions of hormones in the development of estrogen receptor negative (ER−) cancers is limited [2,3]. Furthermore, although the levels and actions of hormones in breast tissue undoubtedly play a critical role in breast physiology and carcinogenesis, the relationships of circulating and tissue levels remain incompletely studied. We argue that critical gaps in our knowledge about the actions of hormones in breast carcinogenesis have impeded efforts to develop improved methods of risk stratification and prevention that substantially lower breast cancer mortality.

We hypothesize that improving our knowledge of sex steroid hormone concentrations in normal and cancerous breast tissues, defining the determinants of the local concentrations of these hormones, and understanding their effects on benign, pre-neoplastic and cancerous breast epithelium and its microenvironment are important for improving risk prediction, prevention and treatment. Accordingly, we have critically assessed the literature on sex steroid hormone measurements in breast tissues and propose that future studies are needed to assess effects of hormones on the "molecular histology" and molecular pathology of the breast. We propose that integration of these two fields, i.e., sex steroid hormone measurements in breast tissue in conjunction with molecular tissue studies, can advance our understanding of early carcinogenesis and facilitate translational goals.

2. Experimental

We performed a systematic review of English and non-English articles retrieved via PubMed to obtain data on estrogen and androgen concentrations in benign and cancerous breast tissue and, where available, in corresponding serum or plasma samples in premenopausal and postmenopausal women. Additional studies were identified by scanning the reference lists of relevant articles. Search terms included estrogen, androgen, breast, cancer, tissue, and concentration. Since most of the data comprised hormone level analyses in individuals with existing breast cancer, only limited causal inferences could be drawn because of possible effects of the disease itself on hormone distribution in both the affected and non-affected breast tissue and in the circulation. The article selection process is summarized in Fig. 1. A total of 88 articles were identified on our preliminary search, with another 22 articles identified through supplemental search. Articles were initially screened by title, assessing relevance to breast tissue and circulating concentrations of estradiol (E_2), estrone (E_1), androstenedione, and testosterone. Thirty-eight pertinent articles were identified and assessed for eligibility; of these articles, 19 were excluded for varying reasons. We chose to review only those articles that met the following criteria: (a) menopausal status of study participants was given, including phase of menstrual cycle in premenopausal women; (b) concentrations of estrogens and androgens were measured in tissue homogenates; (c) hormones were measured by conventional RIA (with at least one purification step) or by a mass spectrometry assay; (d) steroid hormone values were reported per gram of tissue or protein. Two authors (FZS and BWM) individually evaluated whether the articles fulfilled the inclusion criteria. A total of 12 articles were qualified for inclusion in our systematic review.

In a different analysis, we searched PubMed and found only a relatively small number of studies on hydroxylated estrogen concentrations in breast tissue and urine, and we used data from our own studies to describe sex steroid hormone concentrations in breast adipose tissue. Finally, we addressed the controversy regarding the source of intratumoral estrogen in the breast.

The estrogen and androgen data are shown as reported in the cited publications, with the following exceptions: SI units were converted to gravimetric units and standard error (SE) values were converted to standard deviations (SDs) for consistency.

For comparison of tissue concentrations (ng/g tissue) of the steroids with corresponding plasma levels, we equated 1 mL of plasma with 1 g of tissue, although we recognize that this is a rough approximation. The main comparisons of interest included: (a) ratios of cancerous or benign tissue hormone concentrations to blood levels, stratified by menopausal status; (b) ratios between levels of different hormones within tissues or within blood, and the differences in these ratios between the tissue and blood compartments.

3. Results

3.1. Systematic review of studies of sex steroid hormones in normal and diseased breast tissue

3.1.1. Measurement of sex steroid hormones in benign and cancerous breast tissue specimens; studies where data are expressed in ng/g tissue.

Bonney and coworkers [4] compared the interconversion of E_2 and E_1 in benign and cancerous tissues from the same breast and related the estrogen concentrations in these tissues to corresponding plasma levels. Primary breast cancers were removed at mastectomy from 17 women aged 35–79 years (3 premenopausal, 3 perimenopausal, 11 postmenopausal) and fibroadenomas were removed from 3 postmenopausal women. Cancerous tissue was dissected free from non-tumor tissue. In the majority of cases, histologically benign tissue was obtained from the same breast. The status of tissue (benign vs. cancerous) was verified by histologic examination, but receptor status of the carcinomas was not reported. E_2 and E_1 concentrations were measured in cancerous tissue homogenates and plasma from postmenopausal women (average age 62 years), using RIAs with preceding diethyl ether extraction. Mean E_2 and E_1 concentrations (ng/g tissue) were 2–3 times higher in cancerous tissue than in benign tissue ($P < 0.02$ and $P < 0.05$, respectively) (Table 1). Mean E_2 concentrations were