The Role of Endogenous Hormones in the Etiology and Prevention of Breast Cancer: The Epidemiological Evidence

Paola Muti

Department of Social and Preventive Medicine, University at Buffalo, State University of New York, 270 Farber Hall, 3435 Main Street, Buffalo, NY 14214, USA
muti@buffalo.edu

1 Introduction .................................... 246
2 Sex Hormones and Breast Cancer in Postmenopausal Women ........ 246
3 Sex Hormones and Breast Cancer in Premenopausal Women .......... 248
4 Hyperinsulinemic Insulin Resistance, Insulin-Growth Factor Bioavailability, Glucose Metabolism, and Breast Cancer Risk .................. 250
5 Conclusions .................................... 252

References ......................................... 253

Abstract Breast cancer is the most common cause of cancer death in women worldwide. Rates vary about fivefold around the world, but they are increasing in regions that until recently had low rates of disease. Despite the numerous uncertainties surrounding the etiology of breast cancer, intensive epidemiological, clinical, and genetic studies have identified a number of biological and social traits as risk factors associated with breast cancer. Principal among them is the evidence of BRCA1 and BRCA2 susceptibility genes, familial history of breast cancer, age, higher socioeconomic status, ionizing radiation, tallness in adult life, alcohol consumption, and a variety of hormone and metabolic factors. Among the hormonal influences, a relevant etiological function has been ascribed to unopposed exposure to elevated levels of estrogens and androgens. In addition, new epidemiologic evidence has indicated that among the metabolic factors, glucose metabolism, hyperinsulinemic insulin resistance, and insulin-like growth factor bioavailability may also play a role in breast cancer. These endocrine and metabolic factors may represent future targets for breast cancer prevention.

Breast cancer is the most common cause of cancer death in women worldwide. Rates vary about fivefold around the world, but they are increasing in regions that until recently had low rates of disease [1–3]. Despite the numerous uncertainties surrounding the etiology of breast cancer, intensive epidemiological, clinical, and genetic studies have identified a number of biological and social traits as risk factors associated with breast cancer. Principal among them is the evidence of BRCA1 and BRCA2 susceptibility genes,
familial history of breast cancer, age, higher socioeconomic status, ionizing radiation, tallness in adult life, alcohol consumption, and a variety of hormone and metabolic factors [4, 5]. Among the hormonal influences, a relevant etiological function has been ascribed to unopposed exposure to elevated levels of estrogens and androgens [4–7]. In addition, new epidemiological evidence has indicated that among the metabolic factors, glucose metabolism, hyperinsulinemic insulin resistance, and insulin-like growth factor bioavailability may also play a role in breast cancer. These endocrine and metabolic factors may represent future targets for breast cancer prevention.

1 Introduction

In 1896, Beatson was the first to hypothesize the influence of ovarian activity on formation and progression of breast cancer [8]. At that time, these hormones were not known to be a unique class of substances. The first experimental proof of their presence in follicular liquids of a premenopausal ovary and their cancer promotion potential was shown more than 30 years later by Lacassagne [9]. In vitro and in vivo studies using natural, synthetic, or both kinds of sex steroid hormones demonstrated their potential in the formation and progression of benign and malignant tumors [10–11].

Epidemiological evidence of an association between sex steroid hormones and breast cancer risk based on retrospective study design, such as case-control studies, has been generally inconsistent. When the results were consistent across a few independent studies and supportive of the association of hormones and breast cancer, the findings were still compatible with the non-causal hypothesis that high hormone levels in breast cancer cases were due entirely or in part by the presence of the tumors or as consequence of the disease. Because of the disease-status effect on the endocrine or metabolic profile, this report describes only evidence from prospective cohort studies.

2 Sex Hormones and Breast Cancer in Postmenopausal Women

The hypothesis that cumulative exposure of breast tissue to ovarian hormones is one of the major determinants of breast cancer has existed for at least 30 years. Epidemiological evidence has been well corroborated the existence of the association in postmenopausal women. During the last 10 years, nine research groups have published results from prospective studies of endogenous hormones and breast cancer: Columbia, MO, USA [13, 14]; Guernsey, UK [15]; Nurses’ Health Study, USA [16]; New York University Women’s Health Study (NYU WHS), USA [17, 18]; Study of Hormones and Diet in the
Etiology of Breast Tumors (ORDET), Italy [19]; Rancho Bernardo, USA [20, 21]; Radiation Effects Research Foundation (RERF), Japan [22]; Study of Osteoporotic Fractures (SOF), USA [23]; and Washington County, USA [24, 25]. These studies, based on recruitment of thousands of healthy women and on their epidemiological surveillance, have indicated that high levels of estrogens and androgens precede the occurrence of breast cancer risk in postmenopausal women.

A recent pooled analysis of these nine large prospective cohort studies has then further supported the role of endogenous hormones in the etiology of breast cancer [26].

![Fig. 1. Relative risk (RR) of breast cancer by fifth of hormone concentration. CI confidence interval; DHEA dehydroepiandrosterone; DHEAS dehydroepiandrosterone sulfate; SHBG sex hormone binding globulin. (From [26])](image-url)
As reported in Fig. 1, in the pooled analysis of the prospective studies examining risk by quintiles of hormone serum concentration, both estrogens and androgens were significantly associated with an increase in breast cancer risk, with evidence of a dose-response relationship. The relative risk for breast cancer for women in the highest quintile for estradiol compared with women in the lowest quintile was 2.00 (95% confidence interval 1.47–2.71). The relative risks in the highest quintile compared with the lowest quintile for the other estrogens and the androgens were all approximately 2, and the highest relative risks were in the highest quintiles for free estradiol [relative risk 2.58 (1.76–3.78)] and non-sex hormone binding globulin (non-SHBG)-bound estradiol [relative risk 2.39 (1.62–3.54)]. For SHBG there was a significant inverse association with breast cancer risk [relative risk in top fifth 0.66 (0.43–1.00)].

Although the postmenopausal ovaries secrete a very small amount of estrogens, circulating estrogens in women after menopause are still produced through peripheral aromatization of the androgens, primarily androstenedione and testosterone. Thus, part of the etiological relation linking serum androgens to breast cancer could be explained by their aromatization into estrogens. In the pooled analysis, we separated by adjustment and stratification the effect of androgens on breast cancer risk from the effect of estrogens. We observed that the association between androgens and breast cancer held after adjustment for estrogens, indicating an independent effect of androgens on breast cancer risk.

Thus, results of this pooled analysis of the worldwide data from prospective studies has established not only that serum concentrations of endogenous sex hormones are precursors of breast cancer in postmenopausal women, but also that both estrogens and androgens are independently associated with the development of the disease through two possible independent pathways. While circulating estrogens may act directly on the breast tissue and breast cancer cells, the action of serum androgens may be mediated through their aromatization into estrogens within breast tissue and in breast cancer cells [27].

3 Sex Hormones and Breast Cancer in Premenopausal Women

The normal human ovaries produce all three classes of sex steroids: estrogens, progesterone, and androgens and all three have been considered in analytical studies on breast cancer etiology in premenopausal women.

Among the hormonal influences, a major role has been attributed to the unopposed exposure to elevated levels of estrogens. Various analytical studies on estrogens and breast cancer risk led to contradictory results irrespective of the type of estrogens they were analyzing [28]. Estradiol is by far the
most potent and the highest concentrated naturally occurring estrogen in premenopausal women. Thus, epidemiological studies conducted in premenopausal women have usually focused on estradiol in their analysis. Prospective studies with information from premenopausal women reported higher follicular but lower luteal estradiol in premenopausal women who subsequently developed breast cancer than in a sample of cohort members of the Washington County prospective study chosen as controls [25]. The opposite was previously found by Wysowski et al. [29], in the same cohort study. Rosenberg et al. [30] reported, in a case-control study nested in the New York University Women’s Health Study, similar estradiol levels in cases and controls (although further adjustments for stage of menstrual cycle at blood drawing suggested that estradiol was on average non-significantly higher in cases). Kabuto et al. [22] found in the prospective cohort study conducted in Japan higher levels of bioavailable estradiol in breast cancer cases than in controls. Results from the prospective study conducted in the island of Guernsey (UK) by Key and colleagues showed that premenopausal breast cancer cases excreted less estrogen than controls when estrogens were determined in urine [31] and that estrogen levels were higher in cases than in controls when the hormones were determined in blood, although the difference was small and not statistically significant [32]. The number of breast cancer cases in those studies ranged between 22 [25] and 79 [30]. Several of those studies tried to control the ovarian phase variability using time interval between the date at specimen collection and the date at the subsequent menstrual period either as a matching variable or variable to adjust for in the analysis [30–32]. On the contrary, Wysowski et al. [29] and Helzlsouer et al. [25] used the time interval between date at the menstrual period preceding the blood collection and the date at blood drawing, while Kabuto et al. [22] did not control for menstrual phase. Only Helzlsouer et al. [25] controlled for hormone circadian rhythm, matching the set of cases and controls on time-of-the-day at blood drawing, although no specification on this matching criterion was given. All determinations performed in blood used radioimmunoassay methods, although none specified whether the determinations were done using direct or indirect methods and single or duplicate assays. This information may have influenced the technical variability of the hormone determination and thus the precision of the observed risk estimates.

Almost all prospective studies analyzing the relation of breast cancer with endogenous androgens in premenopausal women showed a positive association of testosterone levels with risk, with the only exception of Wysowski et al.[29] who did not find a difference in testosterone levels between breast cancer cases and controls in his nested case-control study. However, all observed risks were of low magnitude and not statistically significant [22, 25, 32].
During the menstrual cycle, progesterone, in conjunction with estrogens, regulates the functions of the sex organs. This hormone is important in preparing the uterus for implantation of the blastocyst and in maintaining pregnancy. In nonpregnant women, progesterone is secreted mainly during the luteal phase of the ovarian cycle by the corpus luteum, a yellow glandular mass in the ovary formed by an ovarian follicle following the discharge of its ovum.

Only a few prospective cohort studies have reported the association of luteal phase progesterone levels with subsequent breast cancer, but the number of cases was very small. Thomas et al. [32] reported a 9% lower mean serum concentration of progesterone, measured in early luteal phase, in cases than in controls (the study was based on 12 breast cancer cases). Wysowski et al. [29] found a 29% lower mean concentration of progesterone in cases than in control subjects after matching on time since last menstrual period (based on 17 breast cancer cases). Helzlsouer et al. [25], contrarily, reported a higher concentration of luteal phase progesterone in cases, but the study was based on nine breast cancer cases only. None of these differences was statistically significant.

In summary, evidence derived from prospective cohort studies is consistent to some extent, at least for the association of androgens with breast cancer. However, the small number of breast cancer cases in these studies and the difficulty in controlling hormone variability over the ovarian cycle may have weakened the strength of the observed association.

4 Hyperinsulinemic Insulin Resistance, Insulin-Growth Factor Bioavailability, Glucose Metabolism, and Breast Cancer Risk

In addition to the sex steroid hormones, there is some reason to believe that insulin and insulin-like growth hormone (IGF)-I and glucose metabolism may also play a role in breast cancer etiology.

Insulin is a powerful mitogenic agent [35], inducing a dose-dependent growth response in breast cancer cell lines acting via insulin receptor [36]. Moreover, insulin may also play a role in tumor promotion by up-regulation of ovarian steroid secretion [37]. Overall, insulin stimulates androgen production in ovarian tissue samples in in vitro studies [38–40].

IGF-I is a small peptide (about 7,500 Da) with a significant structural homology with proinsulin and insulin [41], which is highly regulated by growth hormone (GH) [42]. Despite their distinct immunological difference, IGFs and insulin share not only important similarities in their structure, their receptors, and their signaling pathways which determine their biological actions, but they also have a common ancestor, possibly an old serine protease [43]. The ancestor molecule may have stimulated cell and tissue
growth after food intake, and this function probably included some “insu-
lin-like activity.” The latter seems to have been refined by the emergence of
proinsulin, whereas growth-promoting activity has been preserved mostly
in the IGFs. Thus, despite the divergence of their biological functions and
their refinement and adaptation to specific purposes, both insulin and IGFs
share some common functions: IGFs respond to hyperglycemic stimulus
and exert acute effects on metabolism, and insulin is able to stimulate
growth [44, 45]. IGF-I stimulates multiple cellular responses that are related
to growth, including synthesis of DNA, RNA, and cellular proteins [46]. IGF-
I has well-documented effects on cell proliferation, and similarly to insulin,
IGF-I has been shown to inhibit programmed cell death (apoptosis) [42–49].
Furthermore, in breast cancer cell lines, concentrations of insulin and IGF-I
receptors are increased [50, 51]. The biological activity of IGF-I within tis-
suies, including breast epithelium, is regulated by a family of major plasmatic
binding proteins (IGFBPs), and partially also by the local production of
IGF-I and IGFBPs within tissues [42, 52–53]. At least seven different IGFBPs
have been identified so far, but only three of these (IGFBP-1, -2, and -3)
are found at significant levels in blood. Over 90% of IGF-I is bound with
IGFBP-3 plus another glycoprotein, called acid-labile subunit (ALS). Most of
the remaining fraction is bound to the smaller binding proteins IGFBP-1
and IGFBP-2. A decrease in plasma IGFBP-3, with a transfer of IGF-I to
IGFBP-1 or IGFBP-2, may result in greater IGF-I availability to its tissue re-
ceptors, since the large IGF-I/IGFBP-3/ALS complex cannot pass through
the capillary barrier to target tissues, while the smaller complexes of IGF-I
with IGFBP-1 or IGFBP-2 can [42, 53].

There is increasing evidence that IGF-I is also a direct modulator of the
formation and biological availability of ovarian steroid hormones. IGF-I has
been shown to share with insulin the function to up-regulate the secretion of
sex steroid hormones and increase their bioactivity through the inhibition
of sex hormone-binding globulin secretion in the liver [54–56].

There is consistent prospective epidemiological evidence of a close asso-
ciation between IGF-I and breast cancer risk, however more often in pre-
menopausal women [57–60]. To date, three prospective studies have been
conducted on serum insulin or C-peptide and breast cancer risk [58, 59, 61].
No evidence for a positive association between C-peptide and breast cancer
was found by Jernström et al. in older postmenopausal women [61]; howev-
er, the study was limited by the small sample of breast cancer cases included
in the analysis (45 breast cancer cases). Toniolo et al. [58] reported a posi-
tive association of C-peptide with premenopausal and postmenopausal
breast cancer risk that was not statistically significant. Nonfasting condition
at blood collection for these studies may, at least in part, explain the weak-
ness of the observed association. In our recently published analysis [59], us-
ing a nested case-control study in the ORDET cohort prospective cohort, we
observed a 70% relative risk increase for breast cancer in the two highest
quartiles of fasting insulin levels; however, all the confidence intervals included unity.

Glucose may play a direct role in the development of breast cancer by favoring the “selection” of malignant cell clones [62]. Neoplastic cells have been shown to extensively utilize glucose for proliferation [62]. Increased metabolism of glucose toward the pentose phosphate pathways is one of the central metabolic characteristics of malignant tissues [62].

In our above-mentioned study [59], we also analyzed the hypothesis that serum fasting glucose is associated with breast cancer. In premenopausal women, glucose was strongly and significantly associated with breast cancer risk: the age, body mass index (BMI), and reproductive variable adjusted relative risk for the highest quartile of serum glucose versus the lowest was 2.8 [95% confidence interval 1.2–6.5], \( p = 0.02 \).

5 Conclusions

Breast cancer incidence rates are higher in Western countries than in Africa or Asia. Although both genetic and environmental factors may explain the large geographic variation in incidence rates, studies on migrants who moved from countries characterized by low incidence (i.e., Japan) to countries with higher incidence (i.e., the United States and Italy) showed a significant increase in breast cancer incidence in individuals that migrate in comparison with their peers in the countries of origin. This evidence suggests that environmental factors play a significant role in breast cancer development. In countries with high breast cancer incidence rates, lifestyle is characterized by an energy-dense diet rich in total and saturated fat and refined carbohydrates, and by low physical activity. A sedentary life and a high-fat, low-complex-carbohydrate diet have been associated with impaired glucose metabolism, hyperinsulinemic insulin resistance, and elevated serum levels of androgens and estrogens, the metabolic and endocrine patterns previously described to be associated to breast cancer risk. Hormones and metabolic factors therefore, might represent a possible etiological linkage between lifestyle characteristics and breast cancer.

Recent studies have observed the efficacy of changes in diet and in lifestyle in improving insulin sensitivity and reducing the availability of sex hormones [63–73]. These studies may indicate possible strategies for future breast cancer prevention.
References


