

Sex Steroids and Breast Cancer: An Overview*

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ABSTRACT

Sex steroids, also known as sex hormones are synthesized naturally by the gonads (ovaries or testes). The two main classes of sex steroids, androgens and estrogens, are crucial hormones for the proper development and function of the body; they regulate sexual differentiation, the secondary sex characteristics, and sexual habits. They are also well known to influence many common cancers, especially hormonally driven cancers such as breast and prostate cancer. In this report, we review the association of sex steroids with cancer and the potential use of endocrine manipulation in cancer therapy as well as the limitations and challenges faced in this field.

Keywords: Sex Steroids; Hormones; Breast; Cancer

1. Introduction

Sex steroids, also known as sex hormones are synthesized naturally by the gonads (ovaries or testes) [1], and are released into the blood to reach target tissues and exert their endocrine action, or by conversion from other sex steroids in other tissue such as liver or fat. The two main classes of sex steroids are androgens and estrogens, of which the most important human derivatives are testosterone and estradiol, respectively. Androgens also include androstenedione, dehydroepiandrosterone, and dihydrotestosterone. Estrogens include estriol and estrone [2]. Progesterone is a third class of sex steroids, distinct from androgens and estrogens. Progesterone is the most important and only naturally occurring human progestogen. In general, androgens are considered “male sex hormones” since they have masculinizing effects, while estrogens and progestogens are considered “female sex hormones” although all types are present in each sex, albeit at different levels (**Figures 1** and **2**). In this report, we review the association of sex steroids with cancer and the potential use of endocrine manipulation in cancer therapy as well as the limitations and challenges faced in this field.

2. Sex Steroids and Risk for Cancer

Sex steroids are crucial hormones for the proper development and function of the body; they regulate sexual differentiation, the secondary sex characteristics, and sexual habits. They are also well known to influence many common cancers [3], most notably the 2 hormonally related cancers: breast [4,5] and prostate cancer [6] due to interplay between a variety of hormonally related and genetic risk factors. As an example, high levels of circulating testosterone and low levels of sex hormone-binding globulin (SHBG) are associated with increased risks of prostate cancer. Low levels of circulating estradiol may represent an additional risk factor [6]. Breast cancer risk for postmenopausal women is positively associated with the circulating concentrations of estrogens and androgens [7-9]. Also, it has been suggested that the increase in risk of postmenopausal breast cancer associated with obesity may be largely explained by the relatively high circulating concentrations of free estradiol in obese postmenopausal women [10,11].

3. Issues with Understanding the Role of Sex Steroids in Cancer

Despite the relatively extensive research and epidemiological studies examining the correlation of sex steroids and the risk of breast cancer, several potential limitations

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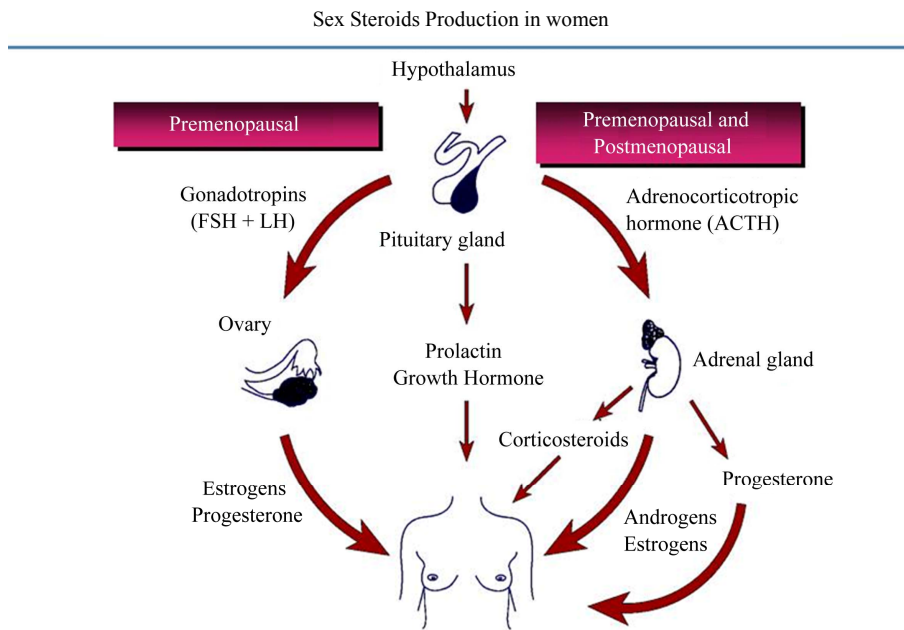


Figure 1. Sex hormones production in women.

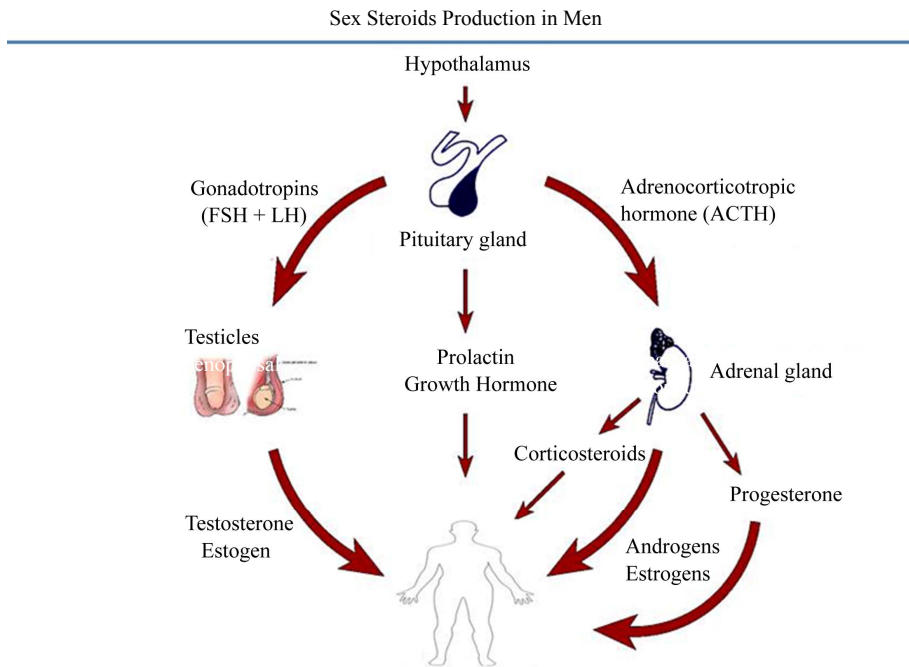


Figure 2. Sex hormones production in men.

have lead to failing in fully understanding the role of endogenous hormones in cancer etiology. These can be summarized as follows: 1) difficulties in reliably measuring sex hormones, which are complex in both their metabolic pathways and interactions with other biological markers [12-14]. This is especially true for premenopausal women, whereby the wide variation in hormonal levels over the duration of the menstrual cycle requires careful attention to the timing of sample collections.

Similarly, serum testosterone and androstenedione levels are the most commonly measured androgens, but they also demonstrate substantial daily variability, while most epidemiological data are based on a single blood sample collected at nonstandard times [14]; 2) the lack of reliability of serum steroid levels measured by radioimmunoassay. The appropriate methods to reliably measure sex hormones remain unclear. Radioimmunoassays have been most commonly used to measure estrogens, how-

ever, other sensitive methods are being evaluated, including a liquid chromatography—mass spectrometry technique that simultaneously measures 15 estrogen metabolites [15]. Future studies are needed to better understand interrelationships of endogenous hormones with other circulating markers associated with breast cancer risk, including androgens, as well as isoforms relevant to breast cancer. A recent novel approach for measuring estrogens was reported using urinary estrone glucuronide (E1G) in premenopausal women [16]. The method accounts for cyclic variation in hormone levels during the periovulatory and luteal phases of the menstrual cycle. Using that approach, Johnson *et al.* [17] observed that lower urinary E1G levels were associated with a single-nucleotide polymorphism (SNP) in the cytochrome P450 3A gene (CYP3A). Furthermore, using data from targeted genotyping and genome-wide association study (GWAS) datasets comprising more than 10,000 breast cancers and 17,000 control subjects, a proxy SNP that tags the CYP3A SNP was found to be associated with a weak reduction in the risk of breast cancer, notably in women younger than 50 years. This finding could reflect an enhanced ability to detect gene—hormone interactions among women with higher estrogen levels. The appropriate methods to reliably measure hormones in premenopausal women and the key biochemical isoforms relevant to breast cancer risk remain, however, unclear. Although the E1G measurement used in the study is novel, it is not without interpretative difficulties due to issues in measurement reproducibility and its unknown relationship(s) with hormone markers used in other studies; 3) a third potential limitation in understanding the role of sex steroids in cancer is related to using serum hormonal levels frequently to gauge the hormonal levels at the tissue level. This is especially problematic when using serum testosterone levels to study androgenic effects because the circulating testosterone is tightly bound to SHBG, while only the free hormone is bioactive [14]. SHBG and thus, total testosterone levels, vary widely based on genetic, metabolic, and endocrine influences. It is now suggested that measurement of free or bioavailable testosterone might predict androgenic effects more accurately than total testosterone levels [14]

4. Sex Steroids and Breast Cancer Treatment

In the first half of the twenty century, endocrine (also known as hormonal) therapy which involves reducing the amount of estrogen in the body or blocking the effect of estrogen became recognized as a viable treatment for breast cancer. This process depends on the presence of the hormone receptors: the estrogen and progesterone receptors (ER and PR). All breast tumors can be simplistically divided into hormone-receptor-positive (HR+) and

hormone-receptor-negative (HR–) cases. Hormonal therapy is considered the main systemic treatment for HR+ breast cancers and is not effective against HR– breast cancer. About 70% - 80% of breast cancers are ER+. Almost 65% of ER+ breast cancers are also PR+. Nearly 13% cases are ER+ and PR– [18]. There are currently four main different modalities of hormonal therapies [18, 19]: 1) ovarian suppression or ablation using irreversible oophorectomy, irradiation, or more commonly the utilization of luteinizing hormone-releasing hormone (LHRH) analogs, which effects a temporary loss of ovarian function; 2) selective estrogen receptor modulators (SERM) (e.g., tamoxifen, toremifene); 3) aromatase inhibitors (anastrozole, exemestane, letrozole); and 4) estrogen receptors downregulators (fulvestrant). The first three modalities are used to the treatment of early stages of breast cancer while all four modalities can be used for the treatment for advanced metastatic breast cancer. The currently available aromatase inhibitors are anastrozole, exemestane, and letrozole.

Tamoxifen is the oldest and most-prescribed SERM, which binds to and inhibits estrogen receptor signaling in the breast. As a receptor antagonist, it is effective in both premenopausal and postmenopausal women. It has ER-stimulating effects in other tissues, including bone (resulting in preservation of bone density) and endometrium (leading to a 2- to 4-fold increased risk of endometrial cancer) [20,21]. Tamoxifen has been approved for breast cancer treatment since the early 1980s. It has been shown in multiple studies to decrease breast cancer associated mortality and recurrence versus placebo in the adjuvant treatment of breast cancer; 5 years of tamoxifen therapy resulting in about 50% reduction in recurrence and 25% reduction in mortality [22]. The common side effects associated with tamoxifen use include hot flashes (up to 80%), vaginal bleeding (2% - 25%) or discharge (10% - 55%), urinary frequency or urgency (10%), mood changes (15% - 20%) or depression (2% - 12%), and thromboembolic events. For premenopausal women diagnosed with HR+ breast cancer, tamoxifen remains the standard hormonal treatment [23]. Most recently, the result of the ATLAS (Adjuvant Tamoxifen Longer Against Shorter) trial was reported [24]. It showed that, among women with ER-positive disease, 10 years of tamoxifen (versus 5 years) reduced the risk of breast cancer recurrence (617 recurrences in 3428 women allocated to continuous tamoxifen versus 711 in 3418 controls, $p = 0.002$), reduced breast cancer mortality (331 deaths versus 397 deaths, $p = 0.01$), and reduced overall mortality (639 deaths versus 722 deaths, $p = 0.01$). The reductions in adverse breast cancer outcomes appeared to be less extreme before than after year 10 (recurrence rate ratio [RR] 0.90 [95% CI 0.79 - 1.02], during years 5 - 9, and 0.75 [0.62 - 0.90] in later years); breast cancer mortality

0.97 [0.79 - 1.18] during years 5 - 9 and 0.71 [0.58 - 0.88] in later years. The cumulative risk of recurrence during years 5 - 14 was 21.4% for women allocated to continuous tamoxifen versus 25.1% for controls; breast cancer mortality during years 5 - 14 was 12.2% for women allocated to continuous tamoxifen versus 15.0% for controls (absolute mortality reduction 2.8%). This study has a major, immediate impact on premenopausal women with HR+ early breast cancer. Ongoing studies are attempting to clarify whether ovarian suppression is also necessary in premenopausal women diagnosed with HR+ breast cancer as estrogens are mostly produced in ovaries [25]. This can be achieved using medication such as luteinizing-hormone-releasing hormone (LHRH) antagonist, e.g. goserelin, and leuprolide (temporary) or by surgically removing the ovaries (permanent suppression). For postmenopausal women, a number of studies have compared aromatase inhibitors with tamoxifen [26]. Aromatase is the enzyme (found in body fat, adrenal glands, and breast tissue as well as tumor cells) responsible for converting other steroid hormones into estrogen [26]. Aromatase is the sole source of estrogen in postmenopausal women. As the aromatase inhibitors have no effect on ovarian estrogen production, they are effective in postmenopausal women. Considering the overall results, it appears that an aromatase inhibitor is slightly superior in improving disease free survival in postmenopausal women with early stage HR+ breast cancer with fewer serious side effects but with no improvement in overall survival compared to tamoxifen. Common side effects of AIs include hot flashes (10% - 35%), arthralgia/arthritis (20%), headache (10% - 15%), vaginal dryness (2%), and mood changes (20%) [27,28]. Aromatase inhibitors are approved for the upfront adjuvant treatment of postmenopausal women with HR+ breast cancer. Other acceptable options include switching to an aromatase inhibitor after taking tamoxifen for 2 or 3 years (for a total of 5 years of hormonal therapy) as it has been shown to offer more benefits than 5 years of tamoxifen [30,31]. The optimal duration and sequence for the use of aromatase inhibitors has not been clearly defined, but their benefits for breast cancer recurrence and survival clearly support their use in all postmenopausal women [19]. Ongoing trials are evaluating outcomes in patients receiving longer durations of AI therapy. The MA.17R trial is evaluating letrozole versus placebo for 5 years in postmenopausal women with primary breast cancer who have completed about 5 years of AI therapy [32]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-42 trial is evaluating 5 years of letrozole versus placebo in post-menopausal women with hormone receptor-positive breast cancer who have completed 5 years of hormonal therapy (either 5 years of an AI or 5 years of a combination of up to 3 years of tamoxifen followed by

an AI) [33]. Both trials are evaluating Disease Free Survival (DFS), overall survival, distant recurrence, and long-term safety. Androgens have a predominantly inhibitory effect on the growth of breast cancer cells, both *in vitro* and *in vivo* [34-37], potentially through induction of apoptosis [37]. Historically, androgens have been used successfully as hormonal therapy for advanced ER positive breast cancer [38]. However androgen therapy (e.g., fluoxymesterone or testosterone) has not gained popularity due to a high incidence of undesirable, virilizing side effects (Table 1).

5. Conclusion

Sex steroids are crucial hormones for the proper development and function of the body. They also play an important role in many common cancers, including breast cancer. This led to adopting endocrine manipulation as an effective methodology to treat many hormonally related cancers. Future studies are needed to better refine the optimal methods for measuring sex hormones and to better understand interrelationships of endogenous hormones with other circulating markers associated with cancer. In HR+ positive breast cancer, hormonal therapy is the mainstay of treatment. Hormonal treatments function stimulates existing micro-metastases or dormant cancer cells by decreasing estrogen's ability. The most commonly used types of hormonal therapy medicines include: 1) aromatase inhibitors (anastrozole, exemestane, letrozole), for postmenopausal women with early or advanced breast cancer; 2) the selective estrogen receptor modulators (SERM) tamoxifen, used in pre- or postmenopausal women with early or advanced breast cancer; and 3) the estrogen receptors downregulator fulvestrant,

Table 1. Evolution of therapeutic hormonal therapy methods in breast cancer treatment.

Class/Hormonal method	Side effects	Years
		1950-1970s
Progesterone	Thromboembolism	
Estrogen	Uterine cancer, cardiovascular disease	
Prednisone	Hyperglycemia	
Aminoglutethimide	Hepatotoxicity, hypothyroidism	
Ovarian irradiation		
Adnexectomy	Hirsutism, acne	
Testosterone		1980s
Tamoxifen	Hot flashes, mood changes, thromboembolic events, endometrial cancer	1990s
Aromatase inhibitors	Arthralgias, bone demineralization, hypercholesterolemia	

used in postmenopausal women with advanced breast cancer. To date, there are no robust clinically available tools that can be used to reliably identify patients that are likely to be selectively responsive to one hormonal therapy versus another. Ongoing trials are attempting to identify the optimal duration of AI therapy. Tamoxifen given for 10 years appear to reduce recurrences and mortality in early stage breast cancer, based on findings from the ATLAS trial which might soon have an impact on the current standard of care for women taking tamoxifen.

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