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Mini-review

Estrogen metabolism and breast cancer

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ABSTRACT

There is currently accumulating evidence that endogenous estrogens play a critical role in the development of breast cancer. Estrogens and their metabolites have been studied in both pre- and postmenopausal women with more consistent results shown in the latter population, in part because of large hormonal variations during the menstrual cycle and far fewer studies having been performed in premenopausal women. In this review we describe in detail estrogen metabolism and associated genetic variations, and provide a critical review of the current literature regarding the role of estrogens and their metabolites in breast cancer risk.

Introduction

Breast cancer remains an overwhelming health burden, with an estimated 232,670 new breast cancer cases and 40,000 deaths among women living in the U.S. in 2014 [1]. Age is the strongest risk factor for breast cancer. Unlike many cancers that increase beginning at the end of the fifth decade of life, breast cancer begins to rise in the third decade of life, most likely due to the effects of ovarian hormones on breast tissue [2–4]. More than 2/3 of all new cases occur after the age of 55 and women older than 65 have a relative risk greater than 4.0 when compared with those younger than 65.

To date, many additional risk factors for breast cancer have been identified. Some risk factors are non-modifiable, such as age, BRCA1 and BRCA2 gene mutations, family history, reproductive history, and high-dose radiation to the chest. Others are potentially modifiable, such as high endogenous estrogens, hormone therapy, obesity (for postmenopausal breast cancer) and alcohol consumption [2,3]. There is some controversy regarding whether or not the risk factor of high mammographic density is modifiable [5–9].

Since a number of these known risk factors are related to endogenous estrogen levels, the effect of estrogens on breast carcinogenesis has drawn a great deal of attention in the last two decades, with evidence suggesting that estrogens play a causal role in the etiology of breast cancer [10]. In this review, we will discuss the metabolism of estrogens and will present a detailed analysis of published data evaluating the role of circulating and urinary estrogens and their metabolites in human breast cancer.

Estrogen metabolism

All steroid hormones originate from C27 cholesterol (Fig. 1). The main source of cholesterol required for the synthesis of steroid hormones (steroidogenesis) is LDL-cholesterol [11]. Cholesterol is metabolized down a number of enzymatic pathways and is converted to the 21-, 19-, and 18-carbon steroid hormones, respectively.

The first step in ovarian steroidogenesis is the movement of cholesterol into the mitochondrion. This step is regulated by the steroidogenic acute regulatory protein (*StAR*) encoded by the *STAR* gene [12]. The next step involves the conversion of cholesterol to preg nenolone, catalyzed by the mitochondrial side-chain cleavage enzyme complex. Preg nenolone acts as a precursor for all steroid hormones. It is metabolized by different enzymes, and under the action of 17-hyroxylase/17, 20-lyase enzyme, a product of the CYP17A1 gene is converted to progesterone or androstendione. Androstendione, in turn, is further metabolized to other androgens or estrogens.

Estrogens are among very few aromatic molecules in humans. They are all C18 steroids and consist of one benzene ring, a phenolic hydroxyl group at C3, and a hydroxyl group (17β-estradiol) or a

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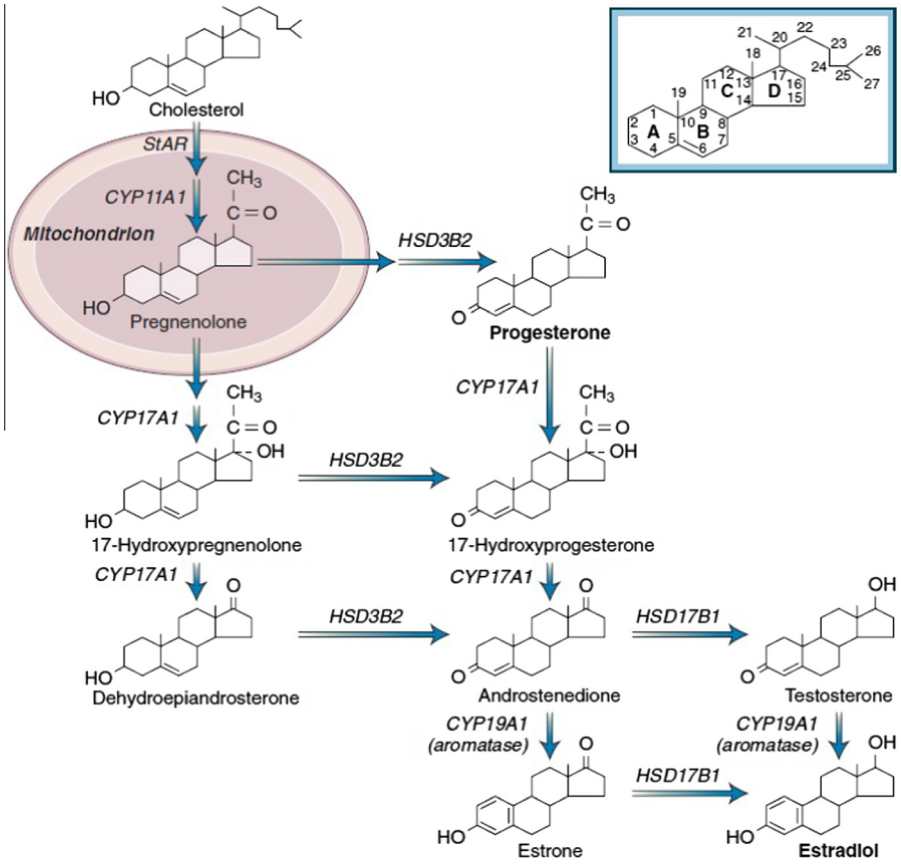

Fig. 1. Pathways of steroid hormone synthesis in humans. *Abbreviations:* StAR, steroidogenic acute regulatory protein; CYP11A1, side-chain cleavage of P450; CYP17A1, 17-hydroxylase/17,20- lyase; HSD3B2, 3β-hydroxysteroid dehydrogenase-Δ5,4 isomerase type 2; CYP19A1, aromatase; HSD17B1, 17β-hydroxysteroid dehydrogenase type 1 [13].

ketone group (estrone) at C17 (Fig. 1). The main estrogens circulating in the human body are estradiol and estrone, as well as 16-hydroxyestradiol (estriol). Although estriol is usually the major estrogen in pregnant women [13], and is the most abundant estrogen in the urine of all women, estradiol is the most biologically active estrogen, primarily secreted by ovarian granulosa cells located next to theca cells and regulated by follicle-stimulating hormone (FSH). Estrone is reversibly converted to estradiol through the action of 17β-hydroxysteroid dehydrogenase enzyme [14]. Androstenedione, the most important product of the theca cells during the follicular phase of the menstrual cycle, is not biologically active; however, it acts as a precursor for both estrone and testosterone in the ovaries and peripheral tissues [15]. Testosterone, in turn, is converted to estradiol by the action of aromatase enzyme in the peripheral tissues (Fig. 1).

In premenopausal women, estradiol synthesized in the ovaries is the most important estrogen, while in postmenopausal women, estrone synthesized in peripheral tissues is predominant. Aromatase (CYP19), encoded by the *CYP19A1* gene, is the rate-limiting enzyme in catalyzing the conversion of androgens to estrogens [16,17]. Given the importance of this enzyme, blocking aromatase activity is an important pharmacological tool used for the treatment of estrogen-dependent diseases such as breast cancer, endometriosis, and endometrial cancer.

Estradiol and estrone are metabolized by three competitive pathways involving irreversible hydroxylations catalyzed by the NADPH-dependent cytochrome P450 (CYP) enzymes including CYP1A1, CYP1B1, and CYP1A2 (Fig. 2). Estrone and estradiol are hydroxylated at positions C2, C4 and C16 and are converted to catechol estrogens (2-hydroxyestrone, 4-hydroxyestrone, 2-hydroxyestradiol, and 4-hydroxyestradiol), and 16α-hydroxyestrone. Estriol is produced by the hydroxylation of estradiol or 16α-hydroxyestrone. Catechol estrogens are further metabolized (methylated) to methoxyestrogens (2-methoxyestrone, 4-methoxyestrone, 2-methoxyestradiol and 4-methoxyestradiol) by the catechol-O-methyltransferase (COMT) enzyme (Figs. 2 and 3).

In addition to methylation, parent estrogens and catechol estrogens are also conjugated with glucuronic acid and sulfate by hepatic phase II enzymes including UDP-glucuronosyltransferases and sulfotransferases, respectively. Conjugation is considered a detoxification reaction by which hormones either become water soluble and are excreted in the urine or feces, or turn into a more lipophilic moiety with elevated half-lives (Fig. 2) [18–20].

2-Hydroxylation pathway

Quantitatively, the 2-hydroxylation pathway is the major metabolic pathway compared to the 4- and 16-hydroxylation pathways. The cytochrome P-450 enzymes, including CYP1A1 and CYP1B1, are major phase I enzymes mainly expressed in breast and liver tissues [21]. These enzymes, along with CYP1A2, catalyze the C2 hydroxylation of parent estrogens to their respective catechol estrogens [22]. Two-hydroxylated estrogens possess low binding affinity for the estrogen receptor (ER) [23,24]. These metabolites demonstrate reduced hormonal potency when compared with estradiol, and both non-estrogenic and anti-estrogenic activities have been attributed to them. There is some evidence from cell culture studies in ER+ human MCF-7 breast cancer cells suggesting that 2-hydroxyestrone and 2-hydroxyestradiol inhibit cell growth and proliferation [25,26]. In addition, 2-hydroxy metabolites have been associated with normal cell differentiation and apoptosis [27,28]. Taken together, these findings have led

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