Introduction

Estrogens are essential for development of the reproductive system in women, in whom they exert beneficial effects in a large number of tissues, including breast, bone, brain, and cardiovascular system. In contrast, the proliferation and genetic instability induced by estrogens in breast and uterus have been considered to increase further the likelihood that normal cells will transform into a malignant type. Over the past 30 years a large number of case-control and cohort studies have been conducted that examined circulating levels of estrogens and/or their urinary excretion to detect any differences in estrogen concentrations that may contribute to cancer. Based on their findings it has been suggested that increased estrogen exposure for lengthy periods of time may induce breast cancer [1–3].

Several observations have also associated in situ production of hydroxylated estrogen metabolites, namely catecholestrogens, with the development of estrogen-sensitive cancers. Oxidative reactions are also important because 2- and 4-hydroxylated metabolites possess distinctive biologic properties as compared with estradiol (E_2), the 4-hydroxylated metabolites being particularly important to the carcinogenic effects of estrogen [4–6]. It is also important to emphasize that these metabolic reactions not only take place in the liver but also in estrogen target tissues such as breast, ovary and uterus,
and thus they play a critical role in the local homeostasis of E₂ and its metabolites.

In addition to the hydroxylation of estrogen, it has been known for many years that estrogen can be conjugated in breast tissue. Conjugative estrogen metabolism includes sulfonation [7,8], glucuronidation [9,10] and O-methylation [11], which are catalyzed by sulfotransferases, UDP-glucuronosyltransferases (UGTs) and catechol-O-methyltransferase (COMT), respectively. Sulfates and glucuronides are the most abundant circulating estrogen conjugates [12]. Several recent observations support a role for UGT enzymes in relation to estrogen metabolism and cancer risk in estrogen target tissues [13–19]. This review addresses the most recent findings regarding the identification of UGT enzymes responsible for the glucuronidation of E₂ and its metabolites, and their potential role in breast cancer susceptibility.

**Site of production and secretion of estrogens in women during aging**

In comparison with men, who exhibit relatively constant blood levels of androgen after puberty, circulating levels of sex steroid hormones in women vary tremendously throughout life. During ovarian cycles the follicles and the corpus luteum are important sources of E₂ and estrone (E₁), the serum concentrations of which range from 50 to 300 pg/ml and from 30 to 250 pg/ml, respectively [20–23]. E₁ sulfate (E₁S) is also found in the circulation (concentration approximately 1 ng/ml), but it is probably formed by estrogen sulfotransferase, which is present in several tissues (Fig. 1). In adult women the term ‘circulating estrogen’ is generally used to refer to E₂ and E₁, as well as their derivatives 2/4-OHCE and 2/4-methoxy-catecholestrogen (MeOCE). The resulting estrogen glucuronides are devoid of biologic activities. AR, androgen receptor; 3β-HSD, 3β-hydroxysteroid dehydrogenase; CYP19, aromatase; ∆5-diol, androstenediol; DHT, dihydrotestosterone; ER, estrogen receptor; MeO, methoxy; OH, hydroxy; testo, testosterone.

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**Figure 1**

Estrogen biosynthesis and metabolism in breast tissue. In breast tissue, estrogens come directly from ovaries or they are synthesized from androgens secreted by the adrenals. (1) The first metabolic pathway of estrogen involves the transformation of estradiol (E₂) to estrone (E₁) by 17β-hydroxysteroid dehydrogenase (17β-HSD) and its subsequent conjugation to estrone sulfate (E₁S) by estrogen sulfotransferase. (2) Both E₂ and E₁ can be oxidized by the action of different cytochrome P450 enzymes to generate 2- and 4-hydroxy-catecholestrogen (OHCE). (3) These metabolites can be further methoxylated by catechol-O-methyltransferase (COMT). (4) UDP-glucuronosyltransferases (UGTs) are able to conjugate parent estrogens E₂ and E₁, as well as their derivatives 2/4-OHCE and 2/4-methoxy-catecholestrogen (MeOCE). The resulting estrogen glucuronides are devoid of biologic activities. AR, androgen receptor; 3β-HSD, 3β-hydroxysteroid dehydrogenase; CYP19, aromatase; ∆5-diol, androstenediol; DHT, dihydrotestosterone; ER, estrogen receptor; MeO, methoxy; OH, hydroxy; testo, testosterone.
enhance further the half-life of E2 because these enzymes sulfotransferase, respectively. This pathway is considered to are substrates of UGT-inactivating enzymes. and those responsible for the back transformation of E1S to E2 are present in several tissues of the body, including the breast [34]. In contrast, the other three pathways, which are active within target cells, generate estrogen metabolites with distinctive biologic properties as compared with E2, with only one metabolic process leading to complete inactivation of estrogen (i.e. glucuronidation catalyzed by UGT enzymes; Fig. 1).

The second pathway employs several cytochrome P450 (CYP) enzymes that use E2 and E1 as substrates for extensive oxidative metabolism at various positions in the estrogen molecule [35]. Recently, the specificity of 15 human CYPs to estrogen was thoroughly characterized by Lee and coworkers [36], and they concluded that the major oxidative products formed from E2 by CYPs are the 2-hydroxy-catecholestrogens (OHECs) and 4-OHECs (Fig. 1). As indicated above, these catecholestrogens possess distinct biologic properties as compared with E2. For instance, several groups have postulated that the depurinating adducts formed from 4-OHECs may generate mutations that initiate cancer, whereas 2-OHCE metabolites may protect against cancer [4,6,35,37–40].

The formation of 2-OHCEs and 4-OHCEs in breast tissue was recently studied by Rogan and coworkers [41]. Those investigators quantified the total pool of conjugated and nonconjugated E1, E2, their hydroxylated metabolites at positions 2 and 4, and methylated derivatives of catecholestrogens in breast tissue samples, after treatment of tissue homogenates with glucuronidase/sulfatase to release the corresponding unconjugated steroids. In tissues obtained from healthy women, they found that levels of the 2- and 4-hydroxy and/or methoxy metabolites were within the same ranges as the parent estrogens E1 and E2 (about 1–2 ng/g tissue). In tumor tissues a significant increase in 4-OHCE concentrations was noted, which is in agreement with several previous reports that indicated changes in estrogen metabolism in cancer tissue that favour the 4-hydroxy pathway and formation of the genotoxic catecholestrogen quinones [4,42]. As a subsequent step to production of 2-OHCEs and 4-OHCEs in mammary tissue, COMT adds a methyl group to 2-OHCEs and, to a lesser degree, 4-OHCEs (Fig. 1) [35,43,44]. O-methylation of 2-OHCE into 2-methoxy-catecholestrogen results in the formation of a protective metabolite with very potent inhibitory action on cell proliferation, tubulin activity, and angiogenesis [45–47].

Overall, these data are in agreement with the concept that E1 and E2 are converted by CYP and COMT in estrogen sensitive tissues before their release into the circulation; this would account for the difficulties in relating serum E2 concentrations to exposure to estrogen in target tissues, particularly in postmenopausal women. It is also clear that the hydroxylated estrogens are subsequently conjugated locally by UGT enzymes, as suggested by previous observations [9,41]. In the following section we address the extensive knowledge on UGT enzymes and recent findings that support a role for these enzymes in estrogen inactivation in the breast tissue.

The glucuronidation process leads to biologically inactive estrogens

Conjugation by glucuronidation, which is catalyzed by UGT enzymes, is a pathway found in all vertebrates and has primarily been studied because of its role in the detoxification of exogenous compounds, mostly drugs [48–51]. UGTs are membrane-bound enzymes that are
present in the endoplasmic reticulum, which mediate transfer of the ubiquitous co-substrate glucuronic acid group of uridine diphospho-glucuronic acid to the functional group (e.g. hydroxyl, carboxyl, amino, sulfur) of a specific substrate. This biochemical reaction increases the polarity of the target compound, and the resulting glucuronide product is generally water soluble, less toxic, and more easily excreted from the body than is the parent compound. The glucuronide is subsequently recognized by the biliary and renal organic anion transport systems, which enable secretion into urine and bile. Because addition of glucuronic acid to compounds changes their structure, glucuronidation modifies the biological activity of the parent molecule and therefore prevents it binding to receptors. As a result, it is believed that most glucuronides, including estrogen glucuronides, correspond to inactive end-products of the parent estrogen and are devoid of biologic activity.

**Human UDP-glucuronosyltransferase enzymes**

Based on homology of primary structures, the UGT proteins have been categorized into two families, UGT1 and UGT2, in which the latter is further subdivided into two subfamilies, UGT2A and UGT2B. In humans, there are 16 functional UGT proteins, of which nine are of the UGT1 family (UGT1A1, A3–A10) and seven are of the UGT2 family (UGT2B4, B7, B10, B11, B15, B17 and B28) [48–50,52].

In contrast to the UGT2B subfamily, which comprises several independent genes that are located on chromosome 4q13 [53–55], members of the UGT1 family are derived from a single gene locus (UGT1) that spans about 210 kilobases on chromosome 2 (2q37) and is composed of 17 exons [52,56,57]. To synthesize the final enzyme, only one of 13 different exon-1 sequences on the locus is associated with four downstream exons, which are common to all UGT1 isoforms. Of the 13 exon-1 sequences, nine encode functional proteins (UGT1A1, UGT1A3–A10) and four correspond to pseudogenes (p; UGT1A2p, UGT1A11p, UGT1A12p and UGT1A13p) [52,56,57]. The regulatory sequences flanking each of the exon 1 regions are thought to dictate the individual expression profile of the UGT1 isoforms [52,58].

Two members of the UGT2A subfamily localized to chromosome 4q13 have also been characterized and share approximately 70% identity with the UGT2Bs. The biologic function of UGT2As was proposed to be the termination of odorant signals, although it is not limited to this function because their transcripts have been detected in the liver and several extrahepatic tissues [49,59,60].

UGT1 and UGT2 proteins are composed of 527–530 amino acid residues, for a molecular weight of 50–57 kDa. The exon-1 sequence of UGTs encodes the substrate-binding domain (amino-terminal half of the protein), whereas the four common exons of the UGT1 gene and exons 2–6 of the UGT2B genes encode the co-substrate-binding domain (carboxyl-terminal half of the protein). The presence of different possible substrate-binding domains confers the great substrate specificity and selectivity of UGT proteins, together with their broad tissue expression profiles. UGTs are localized in the liver and in all ports of entry of chemicals, including the epithelial surfaces of the nasal mucosa, the gut, skin, white blood cells and lung [58], and they probably play a pivotal role in eliminating synthetic substances and pollutants.

Although it was believed for many years that glucuronidation is a process limited to elimination of exogenous compounds and synthetic drugs, recent data indicate that these enzymes represent key elements in the homeostasis of a number of endobiotics, including steroid and thyroid hormones, bilirubin, fatty acids, and biliary acids [10,61–64]. For instance, in a steroid target tissue such as the prostate, high concentrations of glucuronides from dihydrotestosterone metabolites have been measured, and expression of highly specific androgen-conjugating UGT enzymes UGT2B15 and UGT2B17 has been detected [65]. It is believed that these polar metabolites represent the final step of androgen metabolism in this tissue.

**Glucuronidation of estrogens by UDP-glucuronosyltransferases expressed in the breast tissue**

Knowledge on the substrate specificity of human UGT enzymes for estrogens has progressed significantly in recent years. Data indicate that members of the UGT1 family have preferential recognition for estrogens, whereas only one member of the UGT2B subfamily, namely UGT2B7, has been found to be active on these molecules [66–71]. The bilirubin-conjugating enzyme UGT1A1 was initially reported to possess very high specificity for E2 and to be responsible for formation of E2-3-glucuronide (E2-3G) in human liver [71,72]. Until recently little information was available regarding the conjugation of catecholestrogens and their methoxylated metabolites.

Glucuronidation of catecholestrogens may occur at three sites of hydroxylation, namely 3, 17, and 2 or 4 (Fig. 2), and localization of the glucuronide group on the steroid molecule was only possible using high performance liquid chromatography mass spectrometry comparison with authentic standards [66]. Six UGTs – 1A1, 1A3, 1A8, 1A9, 1A10, and 2B7 – were found to conjugate E2 and E1, their hydroxyls and their methoxy derivatives. The regioselectivity of the glucuronidation reaction has been demonstrated for E2, which is conjugated at positions 3 and 17 by at least two different UGTs, namely UGT1A1...
and UGT2B7, respectively [67,73,74]. In the case of catecholestrogens, glucuronidation occurs predominantly at the 3-hydroxyl position of 2-OHCEs and the 4-hydroxyl position of 4-OHCEs and is performed by a limited number of UGT enzymes (Fig. 2) [66]. These reactions are mostly mediated by UGT1A1 and UGT1A8, which have a preference for 2-hydroxy E1 and 2-hydroxy E2, whereas UGT2B7 has greater specificity for 4-hydroxy E1 and 4-hydroxy E2 (Fig. 2) [13,68,75,76].

These data were obtained using UGT proteins that are over-expressed in eukaryotic cells, but little is known regarding the actual level of their formation in breast tissue. On the other hand, the presence of high levels of estrogen glucuronides in breast cyst fluid strongly suggests that estrogen glucuronides are formed in situ. This observation was recently confirmed in studies that demonstrated expression of several UGTs in estrogen-sensitive tissues, including breast tissue [13,14,16,66,77]. In addition, the capacity of breast tissue to form estrogen glucuronides in vitro was demonstrated by enzymatic assays [13]. Accordingly, given the substrate specificity of UGTs for E2 and its various metabolites, and their presence in the breast, it is believed that this pathway may contribute to in situ metabolic transformation of estrogen and participate in the maintenance of their homeostasis [13–16,78].

Recent data on the potential role played by UDP-glucuronosyltransferases in breast cancer risk

UGT enzymes that metabolize estrogen to inactive compounds are highly polymorphic in humans (for review [50]). The presence of genetic variations associated with altered enzymatic activity or expression of this metabolic pathway may result in significant changes in breast estrogen levels and subsequent modification of cancer risk. To date, few investigations have tested this hypothesis. Studies of the associations between genetic polymorphisms, hormone circulating levels, and breast cancer risk may yield important insights into the physiologic roles played by these enzymes.

Four population-based studies of breast cancer patients have assessed the association between genetic variability in the E2 conjugating UGT1A1 enzyme and risk for breast cancer [14,15,17,19]. UGT1A1 is expressed in human breast parenchyma and is involved in the formation of the major glucuronide of E2, E2-3G [14,73]. UGT1A1 status is genetically determined by the presence of a common polymorphism in its promoter region. This polymorphism is characterized by a variation in the number of TA repeats in the TATA box region of the gene. Six TA repeats characterizes the common allele (UGT1A1*1) whereas the most common variant allele consists of seven TA repeats in the A(TA)nTAA motif (UGT1A1*28). Two less frequent alleles, A(TA)5TAA and A(TA)8TAA, are referred to as UGT1A1*36 and UGT1A1*37 [79]. In in vitro investigations it has been demonstrated that the presence of seven and eight repeats leads to a decrease in UGT1A1 gene expression [14,80,81]. Based on these findings, the four UGT1A1 promoter alleles were divided into two phenotypic classes [15,80–83]. The first category of alleles are alleles with high transcriptional activity (UGT1A1*1 and *36), and their presence results in high levels of UGT1A1 protein. The second group of alleles – the low transcriptional activity alleles (UGT1A1*28 and *37) – lead to lower levels of expressed UGT1A1 protein.

In epidemiologic studies it was hypothesized that the presence of lower levels of UGT1A1 protein (individuals with UGT1A1*28 and *37) would result in decreased production of estrogen glucuronides and consequently potential higher exposure to E2 as compared with patients who carry the UGT1A1*1 and/or *36 alleles. This hypothesis was first tested in an analysis of 200 African-American women with invasive breast cancer and 200
matched control individuals [14], which revealed that the low activity alleles (UGT1A1*28 [A(TA)7TAA] and UGT1A1*37 [A(TA)8TAA]) were slightly positively associated with breast cancer (odds ratio [OR] 1.8, 95% confidence interval [CI] 1.0–3.1; \( P = 0.06 \)). Among premenopausal women the association was stronger for estrogen receptor (ER)-negative breast cancer (OR 2.1, 95% CI 1.0–4.2; \( P = 0.04 \)) than for ER-positive breast cancer (OR 1.3, 95% CI 0.6–3.0; \( P = 0.5 \)). A second study [19] suggested that the risk for ER-negative tumors is increased in the presence of polymorphism in the UGT1A1 gene. The second, recent study conducted in 163 (mostly postmenopausal) women, diagnosed with stage I breast cancer and enrolled in the HEAL (Health, Eating, Activity and Lifestyle) study [19]. Contrary to the reported association of UGT1A1 genotype with an elevated risk for breast cancer in premenopausal African-American women, this second study found a reduced risk for ER-negative breast tumor (OR 0.0, 95% CI 0.0–0.5; \( P \) for trend = 0.03) in breast cancer women with the UGT1A1 variant *28/*28 genotype as compared with UGT1A1*1/*1.

The mechanism by which estrogen leads to the development of ER-negative tumors is not well understood, but it is clear that hormones are essential to the genesis of both hormone dependent and independent mammary tumors [84–86]. Hormones can trigger the development of ER-negative tumors via hormone-induced stimulation and secretion of growth factors produced by hormone responsive ER-positive cells or other mammary cell types. Furthermore, ER-negative tumors may arise following prolonged exposure and inadequate elimination of catecholestrogen reactive metabolites formed locally in the mammary gland.

The relationship between UGT1A1 variant alleles and risk for breast cancer was not observed in a larger study of 455 Caucasian women with breast cancer and 603 women without breast cancer within the Nurses’ Health Study [15]. A fourth study investigated 1047 breast cancer cases and 1083 community-based control individuals as part of the Shanghai Breast Cancer Study [17] – a population-based case–control study. Consistent with the increased risk observed among premenopausal African-American women [14], a higher risk for breast cancer was evident only in those Chinese women who were younger than 40 years (OR 1.7, 95% CI 1.0–2.7), and not among women who were 40 years old or older (OR 0.8, 95% CI 0.7–1.1) [17].

Analysis of the relationship of this UGT1A1 polymorphism and levels of circulating estrogens revealed that healthy postmenopausal women who were not using hormone replacement therapy tended to have higher \( E_2 \) and \( E_1 \) levels associated with the low activity allele [15]. Consistent with these findings, Sparks and coworkers [19] recently showed that breast cancer patients with the UGT1A1*28 homozygous variant genotype tended to have increased concentrations of \( E_2 \) as compared with cancer patients with the UGT1A1*1/*1 genotype. However, in that study of breast cancer patients, the majority of women were overweight and on tamoxifen therapy, which may alter estrogen levels independent of UGT1A1 genotype.

These findings support a role of the glucuronidation pathway in estrogen metabolism and its potential contribution to the regulation of the estrogenic environment in target cells. Additional studies are needed to assess clearly the relationship between UGT genotypes and hormonal status in healthy women and women with breast cancer. In support of the potential role of UGTs in modulating exposure of breast cells to hormones, a recent report suggested that inter-individual differences in estrogen glucuronidation influence breast density. Compared with women with the UGT1A1*1/*1 genotype, premenopausal women with the UGT1A1*28 allele had a lower breast density (−43.1% difference; \( P = 0.04 \)) whereas postmenopausal women presented with greater breast density (+32.0% difference; \( P = 0.05 \)) [78]. However, the effect of aging on the relationship between UGT1A1 genotype and breast density remains unclear. Based on the direction of the changes in breast density observed among women with different UGT1A1 genotypes, we would expect premenopausal women with the UGT1A1*28 allele to have decreased risk for breast cancer, and postmenopausal women with the UGT1A1*28 allele to have increased risk. However, as stated above, the UGT1A1 genotype did not alter risk for breast cancer in the large, nested, case–control study from the Nurses’ Health Study [15], in which the Caucasian women studied in relation to breast density were a subset. It seems that the effect on breast density may be insufficient to modify breast cancer risk via the UGT1A1-mediated pathway.

These preliminary findings raise a number of questions. It is not known whether this polymorphism in the UGT1A1 gene has a direct effect on altering estrogen glucuronidation, and indeed whether it would affect solely \( E_2 \) glucuronidation or the conjugation of its hydroxylated and methoxylated metabolites, as predicted by the \textit{in vitro} metabolic profile for estrogens [66]. It is likely that polymorphisms in other UGTs that are active toward various estrogens may also play a role. In addition, inter-individual differences in estrogen glucuronidation due to other environmental and dietary factors may also influence breast density or breast cancer risk. In fact, it is still largely unknown how breast tissues metabolize via the glucuronidation pathway under physiologic and pathologic conditions. The available data concerning the difference in
expression of UGT in normal versus cancer cells suggest that this metabolic pathway is downregulated during breast carcinogenesis, and as a consequence this would allow greater exposure to estrogen. More specifically, expression of UGT2B7, a 4-OHCE metabolizing UGT [68,69], was shown to be decreased in cancerous mammary gland tissue as compared with normal tissue, and was over-expressed in in situ lesions [13]. Furthermore, the presence of the UGT2B7 protein was shown to be highly variable between individuals in the epithelium lining the mammary gland ductal system. A previous study reported that glucuronidation activity was lower in breast cancer specimens as compared with normal tissues [88]. Because UGT2B7 is highly reactive UGT for 4-OHCEs, it was suggested that UGT2B7 would protect the mammary gland from genotoxic 4-OHCEs (bearing in mind that mammary gland is a tissue that also expresses CYP1B1, which is involved in the local formation of 4-OHCE) [89,90]. In support of this hypothesis, Gestl and coworkers [13] measured glucuronidation rates of 4-hydroxy E1, and activities were significantly lower in neoplastic tissues than in normal tissues, which is consistent with the hypothesis of a locally protective role of the UGT2B7 enzyme. To date, no expression data are available for other UGTs in cancer versus normal breast tissues, and it remains to be clearly demonstrated whether alterations in glucuronidation rates or expression levels result in increased estrogen bioavailability within target cells and consequent impact on cancer risk. Analytical methods for the analysis of estrogen glucuronides would need to be developed to address these issues carefully.

To conclude, recent findings support possible influences of the UGT1A1 genotype and UGT2B7 expression on metabolism and excretion of estrogen, which might affect the hormonal status of the breast and therefore modulate the risk for developing cancer. However, conflicting findings raised questions, particularly regarding the role played by UGT1A1 genotypes. Overall, the findings have revealed differences in associations of UGT1A1 genotypes with ER-negative breast cancer and breast density by menopausal status, and this needs additional corroboration. Racial differences in susceptibility to breast cancer associated with genetic factors such as polymorphisms in the UGT1A1 promoter were also evident. Larger studies are needed to uncover its exact role as well as the involvement of other estrogen-metabolizing UGTs.

Conclusion

Little is known on the biologic role of UGTs in estrogen target cells, but recent data support a key inactivation role of this biochemical pathway in breast tissue. This function is distinctive of those of other phase I and II metabolizing enzymes such as CYPs and COMT, which lead respectively to the generation of reactive metabolites, some with carcinogenic effects, and estrogen methoxy metabolites that possess protective properties. It is now clear that UGTs confer polarity to a wide range of estrogens and that this reaction not only takes place in the liver but also in estrogen target tissues, producing glucuronides of estrogens that are readily excreted from the tissues and released into the circulation. Nevertheless, the UGT-mediated metabolic pathway remains a largely unexplored area in the field of estrogen metabolism, but recent data point toward the concept that this pathway may participate in the homeostasis of tissue concentrations of E1, E2, catechol estrogens, and methoxy derivatives, in coordination with P450-mediated hydroxylations and COMT-mediated methylation.

Competing interests

The author(s) declare that they have no competing interests.

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