Review

Estrogen Pathway Polymorphisms and Mammographic Density

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Abstract. *Elevated mammographic density (MD) is strongly associated with breast cancer risk and the estrogen pathway has been proposed as a potential mechanism for this association. It has been repeatedly observed that several established estrogen-related factors associated with breast cancer risk, such as parity and hormone replacement therapy, are also associated with MD. However, the association of circulating estrogen levels (known to be strongly positively associated with breast cancer risk) with MD has so far been inconsistent. Since MD is highly heritable, single nucleotide polymorphisms (SNPs) in genes involved in the estrogen pathway and their relation with MD could provide information that would help understand the link between MD and breast cancer risk. This review of 18 studies describes the relation of SNPs located in genes of the estrogen pathway (genes coding for hydroxysteroid dehydrogenases (HSD3B1, HSD17B1), cytochrome P450 (CYP1A1, CYP1A2, CYP17A1, CYP19A1 and CYP1B1), catechol-O-methyltransferase (COMT), uridine diphospho-glucuronosyltransferase (UGT1A1), sulfotransferases (SULT1A1, SULT1E1) and for estrogen receptors alpha and beta (ESR1, ESR2)) with MD. Most of the SNPs evaluated showed no association with MD when analyses were performed on overall study population. However, when this relation was assessed within strata based on estrogen-related factors, a few SNPs (HSD17B1 (rs2010750, rs598126 and rs676387), COMT (rs4680), UGT1A1 (rs8175347) and ESR1 (rs9340799)) seemed to be related to MD in the same direction of their associations with breast cancer risk. Since such data are very limited, additional research including stratified analyses by factors related to estrogen are needed to validate these findings.*

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There is substantial evidence that steroid hormones, such as estrogens, play an important role in the etiology of breast cancer. In fact there is an established strong positive association between circulating levels of estrogens and the risk of breast cancer (1), and several mechanisms have been postulated to be responsible for the carcinogenic effect of estrogens. Their binding to estrogen receptors (ER) stimulates breast cell proliferation through direct and indirect actions on the enhanced production of growth factors (2). Estrogen metabolites, generated by the action of the cytochrome P450 enzyme, may also elicit direct genotoxic effects by increasing mutation rates (3). Moreover, estrogens are believed to induce aneuploidy (4). Therefore, several enzymes and receptors involved in the estrogen pathway have been suggested to play a role in the development of breast cancer (3, 5). Specific single nucleotide polymorphisms (SNPs) located in genes of this pathway could directly or indirectly lead to variations in activities which may have an effect on breast cancer risk. In addition, estrogens are known to regulate the activity of several enzymes and receptors in the estrogen pathway (6-10), therefore the relation between SNPs of such genes and breast cancer risk could be different among strata of women based on their level of estrogen. For instance, certain SNPs located in genes coding for hydroxysteroid dehydrogenase (*HSD17B1*), cytochrome P450 (*CYP1A1, CYP1A2, CYP17A1, CYP19A1* and *CYP1B1*), catechol-*O*-methyltransferase (*COMT*), uridine diphospho-glucuronosyltransferase (*UGT1A1*), sulfotransfe-rases (*SULT1A1, SULT1E1*) and estrogen receptors alpha and beta (*ESR1, ESR2*) have been associated with breast cancer risk

among premenopausal or postmenopausal women (11-23), or in some strata of other hormone-related factors such as parity, hormone replacement therapy (HRT) use, age at menarche or body mass index (BMI) (11, 24-29). These factors are associated with various steroid hormones, but all with estrogen, and will be referred to as estrogen-related factors for clarity. Premenopausal or nulliparous women, hormone-users, those who had an early menarche or an elevated BMI (particularly amongst postmenopausal women) have higher circulating levels of estrogen compared to their respective counterparts (30-35).

Mammographic density (MD) refers to the proportion of the breast that appears light on mammography. An elevated MD represents a higher proportion of fibroglandular tissue and has been shown to be positively associated with the proliferative activity of cells within this tissue (36, 37). It is now known that MD is a strong and independent risk factor for breast cancer as it has been repeatedly found that women with 75% or more MD have a four-to six-fold greater risk of breast cancer compared to women with no measurable dense breast tissue (38, 39). A potential mechanism by which MD is associated with breast cancer risk could be *via* the estrogen pathway. For instance, in addition to the proliferative effect on fibroglandular cells of the breast by endogenous or exogenous estrogens (3, 40), several breast cancer risk factors related to estrogens such as parity, menopausal status and HRT use, are also associated with MD (41). But so far, studies have failed to reveal a consistent association between circulating levels of estrogens and MD. Since MD is highly heritable (42), evaluating the relation of SNPs located in estrogen-related genes and MD could be a pertinent approach to a better understanding of the role that estrogens may have on MD. This could also bring new light on the link between MD and breast cancer risk. This review of 18 studies (Table I) presents the relation of SNPs located in genes involved in the estrogen pathway (*HSD3B1, CYP17A1, CYP19A1, HSD17B1, CYP1A1, CYP1A2, CYP1B1, COMT, UGT1A1, SULT1A1, SULT1E1, ESR1* and *ESR2*) with MD.

Mammographic Density, Breast Cancer Risk and Estrogens

In 1976, Wolfe described a method to classify variations in the appearance of the breast on a mammography. Based on a visual observation of the morphology of the breast, and of its proportion occupied by fibroglandular tissue, he created a qualitative four-category scale. From the first to the fourth category, he found a stepwise progression in the incidence of developing carcinoma of the breast (43). Since then, several methods have been proposed to classify MD. Among qualitative measuring methods, there is the Breast Imaging Reporting and Data System (BI-RADS), which is a four-category visual classification of MD. There is also a five-category method based on anatomic-mammographic correlations called the Tabar classification. There are also three quantitative approaches which measure MD as the percentage of the breast occupied by fibroglandular tissue that appears light on a mammogram. Mostly used in recent studies, is the computer-assisted thresholding method which generates an estimation of MD on a digitalized mammogram. MD can also be manually measured with a planimeter as an outlining tool, or visually estimated by an expert reader. Regardless of the type of assessment, MD has consistently been positively associated with breast cancer risk (38). A meta-analysis including 42 studies concluded that MD is one of the strongest risk factors for breast cancer (38). Moreover, one group recently showed that women who experienced a reduction in MD of at least one BI-RADS category over a period of six years had a 28% lower breast cancer risk compared to women whose MD was unchanged (44).

Many risk factors associated with breast cancer are associated with MD in a similar way. Several of these factors are related to estrogens. Factors such as nulliparity, low number of births, late age at first full-term pregnancy, late age at menopause, and HRT use are all associated with an increase in MD (45, 46) and breast cancer risk (39, 41). These observations, combined with the fact that estrogens have proliferative properties and that extensive MD reflects greater proliferation of fibroglandular cells (2, 36, 37), suggest that estrogens could possibly explain the link between MD and breast cancer risk. Supporting this idea, it was shown that the use of tamoxifen, a selective estrogen receptor modulator (SERM), was associated with a decrease in breast cancer risk (47) and also with a decrease in MD (48, 49).

Taking into account the proliferative effect of estrogens and that MD reflects the extent of fibroglandular breast cell proliferation, it would be reasonable to speculate that increased endogenous estrogens would be associated with an elevated MD, but results from studies are inconsistent (50-58). Cross-sectional studies conducted among premenopausal women showed no association (56, 58) as did five of the eight studies conducted among postmenopausal women (50-53, 55). The remaining three studies showed contradictive results, as MD was either positively (54) or negatively (56, 57) associated with estrogen levels. This underscores the fact that MD may better reflect lifetime exposure to endogenous estrogens than a single measurement of circulating levels. Since the allelic distribution of SNPs is constant over time for each individual and that inherited factors are thought to explain 60-70% of the variance in MD (46), the evaluation of the association between SNPs in genes involved in the estrogen pathway and MD may lead to a better understanding of the link between MD and breast cancer risk.

The Estrogen Pathway

Enzymes in estrogen biosynthesis. Several enzymes are involved in estrogen biosynthesis (Figure 1). First and foremost, progestogens which derive from cholesterol, are metabolized by

Table I. *Main characteristics of studies included in the review.*

First author, year, country	(Ref)	Participants	Density assessment	Gene: polymorphisms studied	Analyses within strata based on estrogenic activity
Chambo, 2009, Brazil	(95)	123, Postmenopausal; Caucasian	% MD Computer assisted BI-RADS	*CYP17A1*: rs743572/T27C	NA
Crandall, 2009, USA	(105)	451, Premenopausal (26%), early perimenopausal (74%); White (49%), Chinese (24%), Japanese (22%), African-American (6%)	% MD Planimeter	*CYP1A1*: rs2606345, rs4646903/T3801C, rs1531163, rs1048943/Ile462Val *CYP1B1*: rs1056836/Val432Leu, rs1800440/Asn453Ser, rs162555 *CYP19A1*: rs700519/Arg264Cys, rs2414096, rs1008805, rs2446405, rs2445759, rs936306, rs749292, hCV8234946 *HSD17B1*: rs615942/Ser55Tyr, rs592389, rs2830 *ESR1*: rs2234693/*Pvu*II, rs9340799/*Xba*I, rs728524, rs3798577 *ESR2*: rs1256030, rs1256049, rs1255998	NA
De Moura Ramos, 2009, Brazil	(170)	120, Postmenopausal; Caucasian	% MD Computer assisted BI-RADS	*ESR1*: rs9340799/*Xba*I, *Hae*III, *Msp*I	NA
Dumas, 2010, Canada	(113)	741, Premenopausal; Caucasian	% MD, DA (cm^2) Computer assisted	*COMT*: rs4680/Val158Met *CYP1B1*: rs1056836/Val432Leu *ESR1*: rs2234693/*Pvu*II, rs9340799/*Xba*I, rs2077647, rs2228480 *ESR2*: rs3829768, rs1256049 *HSD17B1*: rs676387, rs598126, rs2010750	Parity Hormonal derivatives used Age at menarche Body mass index
Haiman, 2002, USA	(82)	396, Premenopausal (44%), postmenopausal (43%); Caucasian (62%), African-American (38%); Breast cancer patients	% MD Computer assisted	*COMT*: rs4680/Val158Met *CYP17A1*: rs743572/T27C *HSD17B1*: rs605059/Ser312Gly HSD3B1: rs1047303/ Asn367Thr	Premenopausal only HRT use among postmenopausal women
Haiman, 2003, USA	(93)	538, Premenopausal (17%), postmenopausal (73%); Caucasian	% MD Computer assisted	*COMT*: rs4680/Val158Met *CYP1A1*: rs1048943/Ile462Val, rs4646930/T3801C *CYP1B1*: rs1056836 /Val432Leu *CYP17A1*: rs743572/T27C *CYP19A1*: (TTTA)n/ n=7-13, rs10046 *UGT1A1*: rs8175347 /[A(TA)n TAA] repeat/n=6 or n=7 (UGT1A1*28)	Menopausal status HRT use among postmenopausal women
Hong, 2003, Canada	(153)	352, Premenopausal (51%), postmenopausal (49%); Caucasian (84%), Jewish (5%), East Asian (4%), other (7%)	% MD Computer assisted	*COMT*: rs4680/Val158Met	Menopausal status

Table I. *continued*

Table I. *Continued*

First author, year, country	(Ref)	Participants	Density assessment	Gene: polymorphisms studied	Analyses within strata based on estrogenic activity
Hong, 2004, Canada	(96)	354, Premenopausal (51%), postmenopausal (49%); Caucasian (84%), East Asian (4%), Jewish (5%), other (7%)	% MD Computer assisted	*CYP17A1*: rs743572/T27C	Menopausal status
Li, 2010, Sweeden	(84)	1731, Postmenopausal; Caucasian; Breast cancer patients (52%), controls (48%)	% MD Computer assisted	*COMT*: rs12484658, rs174675, rs5993883, rs3810595, rs4646315, rs165774, rs174696, rs9306235, rs2073747, rs1990277 *CYP1A1*: rs6495121, rs1799814, rs2470893, rs2472297, rs1350194 *CYP1B1*: rs163076, rs2256327, rs163086, rs1056836/Val432Leu, rs2551188 *CYP17A1*: rs17115100, rs1004467, rs3781286, rs2486758, rs7089422 *CYP19A1*: rs9972359, rs934632, rs7167936, rs4646, rs959564, rs12595627, rs12050767, rs17523880, rs8031463, rs3751592, rs2470150, rs1902585, hCV8234885, hCV3060064 *HSD3B1*: rs6428822, rs4659175, rs1341013, rs6672903, rs2298029, rs911245, rs10923844 *HSD17B1*: rs2830, rs2854977, rs650558, rs1474040, rs878291, rs9903251 *SULT1A1*: rs17639997, rs12445705, rs11074907, rs11074904, rs6839, rs2411453 *SULT1E1*: rs1529039, rs1220725, rs3775779, rs4149534, rs1220716 rs4149525, rs1154741 *UGT1A1*: rs2741019, rs1377460, rs7587916, rs4663327, rs7597496, rs10929302, rs6742078, rs1042640, rs11563250, rs6719561, rs10169532, hCV256966	NA
Lord, 2005, USA	(148)	232, Postmenopausal; White non-latina (46%), Black non-latina (15%), Latina (27%), Asian or Pacific Islander (12%)	% MD Computer assisted	*COMT*: rs4680/Val158Met *CYP1B1*: rs1056836 /Val432Leu *UGT1A1*: [A(TA)n TAA] <7/≥7 TA repeats	NA
Maskarinec, 2004, USA	(94)	328, Premenopausal (82%), postmenopausal (18%); Asian (41%), Caucasian (36%), Mixed/other (23%)	% MD Computer assisted	*COMT*: rs4680/Val158Met *CYP1A1*: rs1048943/Ile462Val *CYP1A2*: rs762551/A164C *CYP1B1*: rs1056836/ Val432Leu CYP17A1: rs743572/T27C	Menopausal status

Table I. *continued*

Table I. *Continued*.

First author, year, country	(Ref)	Participants	Density assessment	Gene: polymorphisms studied	Analyses within strata based on estrogenic activity
Olson, 2007, USA	(104)	550, Premenopausal (27%), postmenopausal (73%); Caucasian (93%), other (7%)	% MD Computer assisted	*CYP19A1*: rs7176005, rs6493497, rs4774585, rs936308, rs7181866, rs2008691, rs1062033, rs10459592, rs4775936, rs3759811, rs2289105, rs10046, rs4646, rs11575899, $(TTTA)_{8,10,12}$, intron 5 (602), exon 2.a (-429), exon 1f (-725)	NA
Stone, 2007, Australia	(83)	457, Postmenopausal (67%); European (95%), Pacific Island (5%); Twin sisters (63%), singleton sisters (37%)	% MD, DA (cm^2), NDA (cm^2) Computer assisted	*COMT*: rs4680/Val158Met *HSD3B1*: rs1047303/Asn367Thr	NA
Takata, 2007, USA	(132)	575, Postmenopausal (67%); Japanese (47%), Caucasian (32%), Native Hawaiian (21%); Breast cancer patients (57%), controls (43%)	% MD, DA (cm^2) Computer assisted	*COMT*: rs4680/Val158Met *CYP1A2*: rs762551/A164C	Menopausal status HRT use among postmenopausal women Body mass index
Van Duijnhoven, 2005, Netherlands	(168)	620, Premenopausal (29%), postmenopausal (71%); Caucasian; Never HRT users	% MD, DA (cm^2) Computer assisted	*ESR1*: rs2234693/*Pvu*II, rs9340799/*Xba*I	NA
Van Duijnhoven, 2006, Netherlands and UK	(169)	1576, Premenopausal (28%), Postmenopausal (72%); Caucasian	% MD, DA (cm^2) Computer assisted	*ESR1*: rs2234693/*Pvu*II, rs9340799/*Xba*I	NA
Warren, 2006, UK	(51)	1413, Postmenopausal; Caucasian	% MD Visually assessed Boyd six-categories	*COMT*: rs4680/Val158Met, rs6269, rs4633, rs4818 *CYP1B1*: rs1056836/Val432Leu, rs10012, rs1056827 *CYP17A1*: rs743572/T27C, rs6163, rs6162 *CYP19A*: rs10046, IVS4 [TCT]+/- *ESR1*: rs2234693/ *Pvu*II	NA
Yong, 2010, USA	(156)	175, Premenopausal; Non Hispanic/Latino (97%), Hispanic/Latino (3%)	% MD Computer assisted	*UGT1A1*: rs8175347/[A(TA)n TAA] repeat/ n=6 or 7 SULT1A1: rs9282861 *SULT1E1*: rs3775768 and rs4149530 (in haplotype)	NA

All studies are cross-sectional except Lord *et al*. (148) and Van Duijnhoven *et al*. (169) which are a clinical trial and a longitudinal study, respectively. % MD, Percentage mammographic density. NA, Not applicable. BI-RADS, Breast Imaging Reporting and Data System. DA, Dense area. HRT, Hormonal replacement therapy. NDA, Non-dense area.

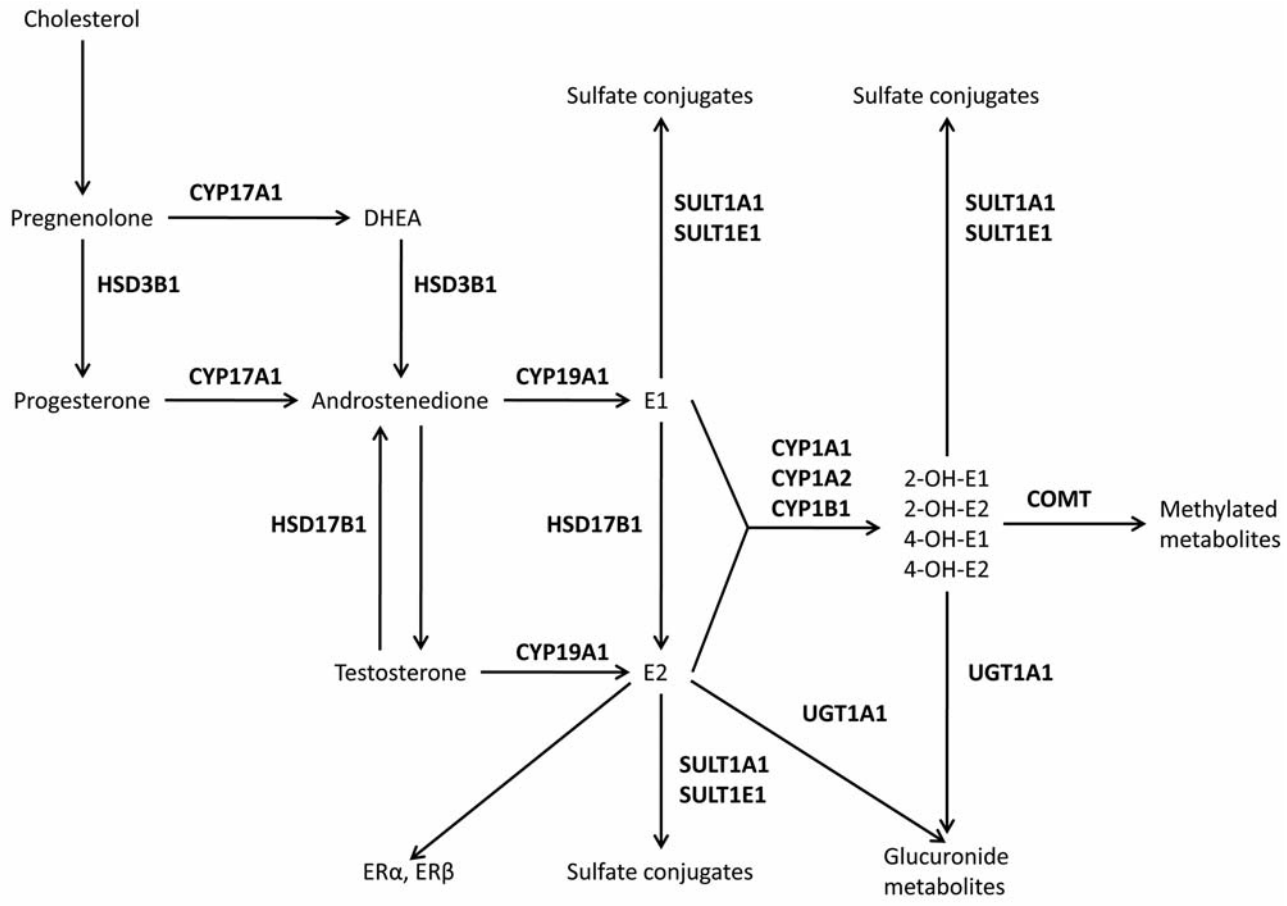

Figure 1. *The estrogen pathway. Hydroxysteroid dehydrogenases (HSD3B1, HSD17B1), cytochrome P450 (CYP1A1, CYP1A2, CYP17A1, CYP19A1 and CYP1B1), catechol-O-methyltransferase (COMT), uridine diphospho-glucuronosyltransferase (UGT1A1), sulfotransferases (SULT1A1, SULT1E1) and estrogen receptors (ER) alpha and beta.*

the cytochrome P450 17A1 (CYP17A1) enzyme to become androgens (pregnenolone to dehydroe-piandrosterone (DHEA) and progesterone to androstenedione) (59). Upstream from their conversion to estrogens, androgens undergo transformation with the help of the enzymes hydroxysteroid dehydrogenase 3B1 (HSD3B1) (DHEA to androstenedione) and hydroxysteroid dehydrogenase 17B1 (HSD17B1) (androstenedione to testosterone) (5). Subsequently, androstenedione and testosterone are respectively converted to estrone (E_1) and 17β-estradiol (E_2) by the cytochrome P450 19A1 (CYP19A1) enzyme (5). Finally, HSD17B1 promotes the transformation of E_1 to E_2 (5) which is the most biologically active estrogen in breast tissue (4). Hormones in estrogen biosynthesis are believed to influence breast cell proliferation either directly as they bind to ER, or indirectly by their further conversion to estrogens (4, 60, 61).

Enzymes in estrogen catabolism. Other enzymes participate in estrogen catabolism (Figure 1). E_1 and E_2 undergo 2-hydroxylation by CYP1A1 and CYP1A2 and become catechol estrogens (CEs) 2-OH-E_1 and 2-OH-E_2 (5, 7). They also undergo 4-hydroxylation by CYP1B1 and become CEs 4-OH-E_1 and 4-OH-E_2 (5). These 4-OH may provide excessive mitogenic stimulation because their binding to ER is of longer duration than that of E_2 (62) and they are believed to generate reactive estrogen intermediates that may damage DNA and induce tumorigenesis (63-65). Conversely 2-OH bind to ER with less affinity compared to E_2, making them less potent mitogenic agents (62). These CEs are methylated by COMT, rendering them water-soluble and thus excreted in urine (66). They also follow the glucuronidation and sulfation pathways *via* UGT1A1, SULT1A1 and SULT1E1, which catalyze their conversion, as well as the conversion of E_1 and E_2 to inactivated metabolites (67-71).

Estrogen receptors. There are two known ERs, ERα and ERβ. They are nuclear receptors that mediate estrogen action by regulating gene transcription (Figure 1). The activated ER complex triggers the synthesis of mRNA and consequently the production of a number of proteins that produce the physiological effects of the hormone (72). They are both

expressed in normal as well as in malignant breast tissue (73, 74). ERα expression seems to be linked to breast cell proliferation. A study by Russo *et al*. suggested that the content of ERα in normal mammary tissue varies depending on the degree of lobular development, in parallel with cell proliferation (2). Conversely, ERβ seems to have antiproliferative functions (75). In all breast cancer cell lines studied *in vivo*, the proliferative effect of estradiol is believed to be mediated by ERα (75). Moreover, during tumorigenesis, an increase in the expression of ERα and a decrease of ERβ expression are observed (76).

Estrogen Pathway Polymorphisms and Mammographic Density

SNPs in genes involved in estrogen biosynthesis. HSD3B1: The gene coding for the enzyme HSD3B1 is located on chromosome 1p13.1. Even though activity of HSD3B1 has been detected in normal (77) and malignant breast cells (78), Weibe and Lewis found no difference in the activity of this enzyme in tumorigenic (MCF-7, MDA-MB-231 and T-47D) compared to nontumorigenic (MCF-10A) breast cancer cells (79). To our knowledge, SNP (rs1047303) Asn367Thr in exon 4 of *HSD3B1* gene has not been specifically studied in relation to breast cancer risk, however, its association with MD has been assessed. Little is known about the function of the variant allele, but the change from amino acid Asn to Thr creates a new protein kinase C (PKC) phosphorylation site. Because PKC isoenzymes are involved in cell proliferation, the Thr allele may be related to increased cell proliferation (80, 81). Studies showed that the variant Thr was associated with an increase in MD among African-American breast cancer patients (82), but with a decrease in MD among populations predominantly composed of Caucasian women (82, 83). The genotype distribution appears to differ between these two ethnicities, with very few African-American being homozygotes for the variant allele compared to Caucasians (82). Stratified analysis by menopausal status or by HRT use did not reveal a significant relation between this SNP and MD (82). Furthermore, Li *et al*. evaluated seven other SNPs in *HSD3B1* gene and concluded that none of them seemed to influence postmenopausal MD among Caucasian women (84).

CYP17A1: The gene coding for CYP17A1 is located on chromosome 10, locus q24.3. One of the SNPs related to this gene, T27C (rs743572), is of particular interest because the change from allele T to allele C creates an additional promoter site believed to enhance transcription of the *CYP17A1* gene (85) and thus increase this enzyme's activity (86). Moreover, the serum estrogen level has been shown to be higher in premenopausal and postmenopausal women carrying the variant (C) allele (87, 88). Therefore, carriers of allele C are expected to be at higher risk of developing breast cancer. This assumption was corroborated in some studies (17, 89), but not all (90-92). A similar association between the variant allele and MD would also be expected, but none of the studies showed a significant association (51, 82, 93-96). When analyses were stratified by race (82, 94), menopausal status (82, 93, 94, 96) or HRT use (82, 93), there was still no association within strata. However, Hong *et al*. found that plasma insulin, alcohol and dietary fat intake, separately, may interact with the variant allele to affect MD (96). Besides T27C, several other *CYP17A1* SNPs have been investigated among postmenopausal Caucasian women, but none showed a significant relation with MD (51, 84).

CYP19A1: Chromosome 15q.21.1 harbors the gene coding for CYP19A1. This enzyme participates in the conversion of androgens to E_1 and E_2 and is referred to as aromatase. An elevated level of aromatase expression has been observed in breast tumors relative to normal breast tissue (97). Moreover, aromatase activity has been shown to stimulate breast cancer cell growth (98) and has been proven to be the main source of E_2 in breast tumors and surrounding tissues among postmenopausal women (99, 100). The variant alleles of both SNPs rs10046 (T) and rs936306 (T) are suggested to be 'high activity alleles' since they have been associated with higher levels of postmenopausal circulating E_2 and E_1 respectively (101, 102). Although a recent analysis showed null results between each of these SNPs and breast cancer risk (92), the variant allele of rs10046 (T) has been related to an increase in breast cancer risk and to a higher level of aromatase mRNA in breast tumors (103). Based on these observations, it is possible to expect that each of these variants would be related to an increase in MD. However, some authors found no association between rs10046 SNP and MD before (51, 93, 104) or after stratification by menopausal status or HRT use (93) among Caucasian women, while others observed an inverse association of rs936306 SNP with MD among a population composed of premenopausal women of mixed ethnicity, and this association seemed to be stronger when assessed among white women only (105). The frequency of this latter variant allele appears to be lower among white women than among those of other ethnicities (105). Several other SNPs, including alleles $(TTTA)_8$, $(TTTA)_{10}$ and $(TTTA)_{12}$ which have been associated with an increased breast cancer risk (106, 107), were evaluated and showed no correlation with MD (51, 84, 104, 105).

HSD17B1: The enzyme HSD17B1 is coded by a gene located on chromosome 17 at region q11-21. This enzyme has been shown to be overexpressed in malignant breast tissue of postmenopausal women, and this could lead to a higher concentration of E_2 in the tumor (108). Miyoshi *et al*. showed that the increase in E_2/E_1 ratio and in HSD17B1 expression in tumoral breast tissue seemed more pronounced among postmenopausal than among premenopausal women (109). To

date, the function of variant alleles of four SNPs in strong linkage disequilibrium (rs2010750 (A), rs598126 (T), rs605059 (G) and rs676387 (C)) remains unclear. However, Fiegelson *et al*. showed that each of these variant alleles was associated with an increased risk of ER-negative breast tumors among Caucasian women (110). It has been shown that ER-negative tumors have lower levels of E_2 as compared to ER-positive tumors and they also have lower levels of E_2 than those of normal breast tissue (111). Conversely, circulating E_2 levels have been positively associated with the risk of developing ER^+ and progesterone receptor $(PR)^+$ breast tumors (112), and E_2 levels in ER^+ tumors are higher than those in normal breast tissue (111). Based on results from Feigelson *et al*. we could speculate that variant alleles of each of these SNPs could possibly be associated with an increased MD among women with lower levels of estrogen. When assessed in a population of parous or nulliparous premenopausal women, or of postmenopausal women using or not HRT, no relations were found between the above SNPs and MD (82, 113). However, among premenopausal Caucasian women who never used hormonal derivatives, MD increased with each additional copy of the variant allele of SNPs rs2010750 (A), rs598126 (T) and rs676387 (C), while an association in the opposite direction was observed among women with higher levels of estrogen, such as those who never used hormones, had an elevated BMI (>24.4 kg/m^2) or an early menarche (≤12 years) (113). Although the former observations are consistent with the earlier mentioned hypothesis, the former and latter results suggest that the relation between the variant allele of these SNPs and MD varies according to the level of estrogen. Some other SNPs have been evaluated and did not appear to influence MD in the overall study population (84, 105).

SNPs in genes involved in estrogen catabolism. CYP1A1: The gene for CYP1A1 is located on chromosome 15 locus q24.1. Regarding the activity of this enzyme, the CYP1A1 protein level was shown to be lower in malignant breast tissue than in normal breast tissue (114). Research focused on several SNPs related to this gene and two of them (believed to be in linkage disequilibrium) have been suggested to have a variant allele that increased the activity of this enzyme, rs4646903 (T3801C, a substitution in the 3' non-coding region) and rs1048943 (Ile462Val in exon 7) SNPs (115-117). Since CYP1A1 catalyzes the conversion of E_1 and E_2 to CEs 2-OH-E_1 and 2-OH-E_2 which have a reduced estrogenic activity (7, 62), these variants (alleles C or Val) should be associated with a decrease in breast cancer risk and they have been in some (118, 119) but not all (120-122) studies. Recent meta-analyses showed that the variant allele of rs1048943 (Val) was associated with a lower breast cancer risk among East-Asian women, and among a worldwide population of premenopausal women, but with an increased breast cancer risk among Caucasian women (15, 123). An observed decrease in MD is therefore possible in conjunction with each of these variants, but studies have not shown significant associations in their overall population or within strata based on ethnicity (Asian or Caucasian), menopausal status or HRT use (93, 94, 105). Other SNPs were evaluated and they also showed no significant influence on MD (84, 105).

CYP1A2: The CYP1A2 enzyme is encoded by a gene located on chromosome 15 at region q24.1. An experimental study showed that of all the CYP enzymes tested, CYP1A2 has the highest 2-hydroxylation activity on E_1 (124). The variant allele (C or *CYP1A2**1F) of SNP rs762551 or A164C, is thought to be associated with a reduced activity of the enzyme (125, 126), therefore we should expect it to be related to a decrease in the conversion of E_2 to 2-OH-E_2 which has reduced estrogenic activity. Most authors speculate that the variant allele should be correlated to an increase in breast cancer risk (94, 127, 128) since a higher E_2/2-OH-E_2 ratio is expected. However, premenopausal women carrying the CC genotype were shown to have less circulating E_2 than women that were homozygous for the common allele (AA) (127). Furthermore, the activity of the CYP1A2 enzyme appears to be up-regulated by estrogen (7). Based on these observations, the variant allele should be related to a decrease rather than an increase in breast cancer risk among women with high levels of estrogen such as premenopausal women compared to postmenopausal women. However, results from studies on the association between this SNP and breast cancer risk are inconclusive (16, 129-131). Nevertheless, the limited number of studies evaluating the relation between this SNP and MD show that among multiethnic populations, the variant allele (C) is associated with a decrease in MD for women with high levels of estrogen such as premenopausal women (94), and with an increase in MD for women with lower levels of estrogen, such as lean women or postmenopausal not using HRT (132). As for *HSD17B1* SNPs, results suggest that the relation between the rs762551 SNP and MD may be different according to the level of estrogen.

CYP1B1: The gene coding for the CYP1B1 enzyme is located on chromosome 2 locus p21. This enzyme's 4-hydroxylase action generates 4-OH-E_2 which is thought to provide excessive mitogenic stimulation of breast cells because its binding to ER is of longer duration than that of E_2 (62). The activity of this enzyme is known to be up-regulated by estrogen (6). The most studied SNP in relation to breast cancer risk is rs1056836, also designated by Val432Leu, in exon 3 of the *CYP1B1* gene. The expected effect of the Leu (C) variant on breast cancer risk is unclear since it has been associated with both increased and reduced breast cell proliferation (133-135), although the Leu allele is known to be related to a decrease in 4-hydroxylase activity compared to the Val allele (133). Research on the possible influence of this SNP on breast cancer risk showed inconclusive results, whether assessed among the overall population (12, 16, 29, 130, 136-143), by race (16, 143-145), or within strata based on

estrogen-related factors (12, 29, 139, 140, 146, 147). Seven studies evaluated the relation of rs1056836 SNP with MD and none of them found any association among premenopausal women (93, 94, 105, 113), postmenopausal women (51, 84, 93, 148), both menopausal status (93, 94), or by ethnicity (94, 105). However, one group found that the Leu allele was related to higher premenopausal MD among nulliparous women and those who ever used hormones (113), and a clinical trial showed that the increase in MD related to HRT use was greater among postmenopausal women carrying the Leu allele (148). These observations suggest that this allele appears to influence MD among women with higher levels of estrogen such as nulliparous women and past or current hormonal users. Nonetheless, no significant association was observed between the Leu allele and premenopausal MD within strata of BMI or age at menarche (113). Some other SNPs have been investigated as to their relation with MD but no associations were found (51, 84, 105).

COMT: The *COMT* gene is located on chromosome 22q11.21. CEs 2-OH and 4-OH are methylated by the COMT enzyme to become methylethers, water-soluble compounds which have little or no binding affinity for ER (149) and are mostly excreted (66). In fact, the most active CE conjugative pathway is methylation by COMT (66). The SNP (rs4680) Val158Met in exon 4 is the most studied SNP for its relation to breast cancer risk. The Met allele is associated with a two to three-fold decrease in the activity of this enzyme (150, 151). Several authors have therefore hypothesized that this variant allele would increase breast cancer risk because of less inactivation of CE 4-OH, but results have been conflicting (11, 14, 91, 92, 152). Heterogeneity in the levels of estrogen in women across studies may explain these conflicting results since the activity of COMT is down-regulated by estrogen (8) and thus the effect of the Met allele in reducing the enzyme's activity may be apparent only among women with high levels of estrogen. Two groups suggest that carrying the Met allele increased the risk of breast cancer among women with high levels of estrogen such as premenopausal women, postmenopausal women with an elevated BMI, prolonged HRT users or women with a young age at menarche, while they observed associations in the opposite direction in some counterpart strata of women with lower levels of estrogen such as postmenopausal women or lean postmenopausal women (11, 14). To date, lack of association has been observed between this SNP and MD among the overall population of premenopausal and/or postmenopausal women (51, 82, 83, 93, 94, 113, 132, 148, 153), with one exception of a negative association observed among premenopausal women of mixed ethnicities (94). Although no association has been observed between rs4680 SNP and MD by menopausal status (82, 93, 132, 153), parity or BMI (113, 132) within studies, some associations were found within other strata of women based on their levels of estrogen. Some found that among Caucasian women, the Met allele was associated with a decrease in MD within subgroups of lower levels of estrogen such as women with a late menarche, and never or past hormonal derivative users (93, 113), while one study observed an increase in MD among breast cancer patients who were current HRT users (higher levels of estrogen) (82). Moreover, a clinical trial showed that the increase in MD related to HRT use was greater among mostly postmenopausal Caucasian women carrying the Met allele (148). These observations indicate that the relation between the Met allele and MD may vary according to the level of estrogen but this remains to be validated as few data are available. Other SNPs have been evaluated for their relation to postmenopausal MD and null results were observed (51, 84).

UGT1A1: The gene coding for this enzyme is located on chromosome 2 at region q37. By glucuronidation, the UGT1A1 enzyme inactivates E_2 and CEs metabolites (70). Individuals deficient for this enzyme exhibit a 70% reduction in the glucuronidation of E_2 (68). A common genotype variation of *UGT1A1* is the TA-repeat [$A(TA)_nTAA$] in the promoter region (154). The SNP rs8175347 or TA6/TA7 *UGT1A1,* is the most studied for its relation to breast cancer risk. *In vitro* studies showed that the variant TA7-repeat (*UGT1A1**28) allele is associated to a 30% reduction in *UGT1A1* gene transcription and to a decrease in *UGT1A1* gene expression (154, 155). Therefore we should expect it to be associated with an increase in breast cancer risk because of less inactivation of E_2 and 4-OH, which have proliferative properties. This hypothesis was assessed in several studies and a recent meta-analysis concluded that there was no association overall, but when the analysis was restricted to Caucasian women, which their majority were postmenopausal, *UGT1A1**28 was associated with an increase in breast cancer risk (19). A similar association was observed among Chinese women with a shorter period of estrogenic stimulation or lower levels of estrogen (25) (such as those who have fewer than 22 menstrual years or those under 40 years old who had a late age at menarche (≥14 years) (33)). The relation between this variant allele and MD seems to behave in a comparable way as it was positively associated with MD among postmenopausal Caucasian women, but negatively associated with MD among premenopausal Caucasian women (93). When assessed among the study's overall population, another group observed no significant association between this variant and premenopausal MD (156), as did two other groups who evaluated other SNPs among postmenopausal women (84, 148).

SULT1A1: The *SULT1A1* gene is located on chromosome 16p12.1-p11.2. The enzyme related to this gene inactivates by sulfation active forms of various estrogens such as E_1, E_2 and catecholestrogens (70, 71). SULT1A1 appears to be the sulfotransferase isoform primarily responsible for estrogen sulfation in breast tumors. A common genotype variation of

SULT1A1 is the change from Arg to His at codon 213 (rs9282861). Functional assays in human platelets and liver showed that the variant allele His was associated with significantly reduced sulfotransferase activity compared to the common allele (157, 158). Meta-analyses concluded that there was no association between this SNP and the risk of breast cancer (159, 160). However, when populations were stratified by ethnicity, the His allele seemed to be associated with an increased risk among Asian women (159). The relation between this SNP and MD has been assessed in one study and the variant allele appeared to be associated with a decrease in MD among a population of premenopausal women, white in their majority (156). The frequency of this variant allele appears to be higher among Caucasian women than among Asian women (159). Six other SNPs in the *SULT1A1* gene have been evaluated as to their relation to postmenopausal MD by one group, who found null results (84).

SULT1E1: Chromosome 4q13 harbors the gene coding for SULT1E1. As for SULT1A1, this enzyme participates in the metabolism of estrogens E_1, E_2 and catecholestrogens, forming inactive sulfate conjugates (70, 71). SULT1E1 exhibits the highest affinity for estrogens among all sulfotransferases (71). Unlike *SULT1A1*, which is primarily responsible for estrogen sulfation in breast tumors, the *SULT1E1* gene appears to be mostly expressed in normal breast epithelial cells (161). Data on the functionality of variant alleles of most of the SNPs of this gene are not available and to our knowledge, none of the SNPs studied in relation to MD has been evaluated regarding their possible association with breast cancer risk. The relation of individual and/or combined SNPs with premenopausal MD (156) or postmenopausal MD (84) showed null results.

SNPs in estrogen receptor genes. ESR1: ERα is encoded by a gene located on chromosome 6 locus q25.1. Since one of the mechanisms by which estrogen promotes the proliferation of both normal and neoplasic breast epithelial cells is through its binding to ERα, and that the content of ERα in breast tissue is associated with increased breast cell proliferation (2, 4), a modification in the expression of this gene could influence MD or breast cancer risk. Indeed, a statistically significant increased protein expression of ERα in normal epithelium of women with high breast density as compared to those with low density was observed in a study conducted among postmenopausal women (162). *In vitro* studies showed that the expression of ERα in breast cancer cells seems to be down-regulated by estradiol (9, 10). Research mostly focused on SNPs rs2234693 (*Pvu*II) or rs9340799 (*Xba*I), which are in strong linkage disequilibrium. Possible explanations as to how these intronic SNPs may influence the level of ERα expression are that some introns contain regulatory sequences that affect transcriptional regulation (163), or that the SNP may be in linkage disequilibrium with an exon alteration, which affects ERα protein function (164). To date, the impact of the variant alleles (*Pvu*II (C) or *Xba*I (G)) on *ESR1* transcription has not been well established. A recent meta-analysis including 11 studies found reduced breast cancer risk of borderline significance for homozygous carriers of the variant allele of SNP rs2234693 (C), while no association was observed for SNP rs9340799 (G) (165). Others have shown that each of these variants seemed to be associated with a reduced breast cancer risk among women with lower levels of estrogen (13, 166, 167), and these associations seem to follow the same direction as those emerging from some of the studies on MD. The variant allele of rs9340799 (G) was significantly associated with a decrease in MD among a population composed mostly of postmenopausal women who were all never HRT users, and a similar association of borderline significance was found for rs2234693 (C) (168). Conversely, premenopausal homozygote Caucasian carriers of the variant allele (CC) of rs2234693 have been shown to present higher MD than carriers of at least one common allele (TT or TC), and a similar association of borderline significance was also observed for rs9340799 (GG *versus* GA or AA) (105). It is therefore plausible that the level of estrogen may influence the relation between these SNPs and MD. However, no association has been observed within strata of estrogen-related factors among premenopausal women (113), nor in overall population of premenopausal and/or postmenopausal women (51, 113, 169). Other SNPs evaluated (rs2228480, rs728524, rs3798577 and rs2077647) showed no association with MD in premenopausal and/or postmenopausal populations (105, 113, 170).

ESR2: The gene coding for ERβ is located on chromosome 14q23.2. As for ERα, ERβ stimulates transcription of ER-responsive genes in an E_2-dependent manner (171). However, ERβ is believed to have antiproliferative properties in cells in which both receptors are expressed (172). ERβ, in many ways, antagonizes the functions of ERα in malignant breast cells and in these cells, ERβ is expressed at lower levels than in normal breast cells (75). We could speculate that the expression of this receptor would be inversely associated with MD, but this relation has been evaluated in one study, which found a borderline significantly positive association (173). *In vitro* studies suggest that ERβ variants may influence the development of breast cancer (174, 175). However, SNP rs1256049 in exon 6 of the *ESR2* gene, which is the most studied SNP, showed no significant differences in its allelic distribution when 5647 patients with invasive breast cancer were compared to 7555 controls (176). A meta-analysis including eight studies and a recent analysis evaluated this relation and both came to the same conclusion (21, 92). Furthermore, this SNP has not been shown to influence MD among premenopausal Caucasian women (105, 113), premenopausal women of mixed origin (105), nor among

subgroups based on estrogen-related factors (parity, hormonal derivatives used, BMI and age at menarche) (113). Three other SNPs related to *ESR2* (rs1256030, rs1255998 and rs3829768) have also been evaluated and none of them have been shown to exert influence on MD among premenopausal women (105, 113). Since breast cancer risk has been suggested as being influenced by SNP rs1256049 when assessed in combination with several other *ESR2* SNPs in haplotype analysis (176, 177), further investigation as to whether this SNP affects MD should perhaps include haplotype analysis.

Conclusion

This review of the relation between MD and SNPs located in *HSD3B1, CYP17A1, CYP19A1, HSD17B1, CYP1A1, CYP1A2, CYP1B1, COMT, UGT1A1, SULT1A1, SULT1E1, ESR1* and *ESR2* genes shows that the majority of these SNPs are not associated with MD when this relation is assessed among overall study populations. These observations suggest that genetic variants in the estrogen pathway might not explain the link between MD and breast cancer risk. The lack of association could perhaps emanate from heterogeneity of study populations as women's estrogen levels probably differ significantly from one population to the next because of their dissimilarities in factors influencing estrogen levels, such as menopausal status or ethnicity, to name a few. Since several genes discussed in this review are known to be regulated by estrogen, this disparity in study populations could make the revealing of a consistent association hard to achieve.

However, it is interesting to observe that within strata of women based on their levels of estrogen, allelic distribution of some SNPs in *HSD17B1* (rs2010750, rs598126 and rs676387), *COMT* (rs4680), *UGT1A1* (rs8175347) and *ESR1* (rs9340799) genes seems to be associated with MD and breast cancer risk in a similar direction. Furthermore, for seven SNPs located in four genes (*HSD17B1* (rs2010750, rs598126 and rs676387), *CYP1A2* (rs762551), *UGT1A1* (rs8175347) and *ESR1* (rs2234693 and rs9340799)), the association between the variant allele and MD is in opposite directions when assessed among strata of women with high or low levels of estrogen. Moreover, each of these SNPs seems to be related to MD in the anticipated direction which was based either on biological fact concerning the effect of the variant allele, or on the influence that these SNPs appeared to exert on breast cancer risk. However, some inconsistencies were observed between studies and this could be due to the fact that few assessed the association between these SNPs and MD according to various estrogen-related factors among one source population. Comparing findings within an estrogen-related stratum between two studies with two distinct populations could be problematic as results could be influenced by heterogeneity between the study populations and methodologies. Furthermore, stratification was performed in a way that the factor in question was divided roughly into two categories, leaving subcategories not accounted for. For example, the type of HRT used was not considered, as strata were defined as never and past users *versus* current users; strata regarding parity were defined as having had no full-term pregnancy *versus* having one or more, regardless of the age of first birth; and strata of BMI were defined as underweight or normal *versus* overweight or obese. Moreover analyses conducted among premenopausal women did not consider the phase of the menstrual cycle during which the mammography was performed. Ideally, this matter should be considered in the study design or accounted for in the analysis even if variations in MD related to the menstrual cycle are believed to be small (178). Some of the studied SNPs are known to be in strong linkage disequilibrium with others located near them on the gene so that associations observed could be attributable to other functional SNPs. However, this event would lead to nondifferential misclassification bias and the actual effect of the functional variant on MD could possibly be of greater extent (179). There is also the possibility of residual confounding by unmeasured factors, although most of the analyses discussed in this review were adjusted for multiple potentially confounding factors. Some limitations regarding this type of study are that genotype alone does not measure the complete phenotypic effect because enzyme activities might, for example, be induced or inhibited by environmental factors. Moreover, most of the cited studies conducted their analyses among Caucasian women, therefore findings might not be applied generally to other ethnic populations.

Regarding strata based on estrogen-related factors defined here as high or low estrogen levels, it is presumed that circulating estrogen or E_2 levels are similar or positively correlated to those of breast tissue. This assumption still needs to be verified, as very little is known about the level of estrogens in breast tissue, especially among healthy women, and their association with breast cancer estrogen-related risk factors. Some (180), although not all (181, 182), found a positive correlation between the level of E_2 in plasma and in breast tissue. It is not known if fluctuations in circulating estrogens related to the menstrual cycle result in similar fluctuations in breast tissue of premenopausal women. In addition, menopausal status might not be a factor that alone determines the estrogen levels of women as being high or low because some found that E_2 levels in normal breast tissue were similar in premenopausal and postmenopausal women, while their circulating E_2 levels were clearly different (183). This might explain why some of the associations found among strata of postmenopausal women with high estrogen levels were not also found among premenopausal women. However, the level of E_2 in breast tissue was positively correlated to BMI among postmenopausal women and to parity among premenopausal women (182, 184). These correlations are similar to those of BMI and parity with circulating E_2 (31, 53, 185).

Nevertheless, the hypothesis that the levels of estrogen would modify the relation of SNPs located in genes involved in the estrogen pathway and MD has to be verified through more research since very few of the existing studies were designed to test such modifying effects. Information from these studies can be used as important preliminary data for determining approaches for future larger scale epidemiologic studies. Further investigation should include stratified analysis based on diverse estrogen-related factors as previous studies have mostly been conducted among predominantly postmenopausal populations and other stratified analysis, based on HRT use is limited. Moreover, analyses conducted in a large population of premenopausal and postmenopausal women where fine stratification could be made based on endogenous and exogenous estrogen-related factors would provide pertinent data, as group comparison deriving from the same population could accentuate the validity of the results. Since level of estrogens vary during the menstrual cycle, it is important to consider the phase of the menstrual cycle of premenopausal women during which the mammography and blood sampling are performed in order to provide reliable estimates of the association of estrogen pathway polymorphisms with MD according to circulating levels of estrogen.

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