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Review

Genetic Polymorphisms and Cancer Susceptibility of Breast Cancer in Korean Women

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Breast cancer is the most prevalent cancer among women in Western countries, and its prevalence is also increasing in Asia. The major risk factor for breast cancer can be traced to reproductive events that influence the lifetime levels of hormones. However, a large percentage of breast cancer cases cannot, be explained by these risk factors. The identification of susceptibility factors that predispose individuals to breast cancer (for instance, if they are exposed to particular environmental agents) could possibly give further insight into the etiology of this malignancy and provide targets for the future development of therapeutics. The most interesting candidate genes include those that mediate a range of functions. These include carcinogen metabolism, DNA repair, steroid hormone metabolism, signal transduction, and cell cycle control. We conducted a hospital-based case-control study in South Korea to evaluate the potential modifying role of the genetic polymorphisms of selected low penetrance genes that are involved in carcinogen metabolisms (i.e., *CYP1A1, CYP2E1, GSTM1/T1/P1, NAT1/2,* etc.), estrogen synthesis and metabolism (i.e., *CYP19, CYP17, CYP1B1, COMT, ER-*α, etc.), DNA repair (i.e., *XRCC1/3, ERCC2/4, ATM, AGT,* etc.), and signal transduction as well as others (i.e., *TGF-*β, *IGF-1, TNF-*β, *IL-1B, IL-1RN*, etc.). We also took into account the potential interaction between these and the known risk factors of breast cancer. The results of selected genes will be presented in this mini-review.

Keywords: Breast cancer, Case-control study, Genetic polymorphisms, Low penetrance genes

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Introduction

Breast cancer is the most prevalent cancer among women in Western countries, and its prevalence is also increasing in Asia (Parkin *et al*., 1997; Yoo *et al.*, 2002). In 1994, the incidence rate of female breast cancer in Korean (adjusted for the world population) was 10.9 per 100,000, which was far lower than that of Western countries, and even lower than any other Asian country. The major risk factor for breast cancer can be traced to reproductive events that influence the lifetime levels of hormones (Feigelson and Henderson, 1996; Zhu and Conney, 1998).

A large percentage of breast cancer cases cannot, however, be explained by these risk factors. The identification of susceptibility factors that predispose individuals to breast cancer (for example, if they are exposed to particular environmental agents) could possibly give further insight into the etiology of this malignancy. Inherited differences in the capacity to metabolize environmental carcinogens have recently been suggested to modify individual susceptibility to breast cancer. Therefore, the identification of new breast cancer susceptibility genes would yield new insight into breast tumorigenesis, and could provide targets for the future development of therapeutics.

In this respect, the most interesting candidate genes include those that mediate a range of functions. This includes carcinogen metabolism, DNA repair, steroid hormone metabolism, signal transduction, and cell cycle control. Although the relative risks of these low penetrance susceptibility genes to the development of breast cancer are generally lower than those from high penetrance susceptibility genes (e.g., *BRCA1*, *BRCA2*, etc.), the population attributable risk of low penetrance genes are much higher than those of the high penetrance gene since the frequency of variant alleles of low penetrance genes are higher in the general population. Therefore, higher public health significance rests on these low penetrance genes with the hope of obtaining more mechanistic insights into human breast carcinogenesis, as well as the targeted-preventive approaches to the individuals with at risk

Table 1. List of Genes and SNPs analyzed in Korean breast cancer cases and controls

Group	Gene	SNP	Cases	Controls
Xenobiotics metabolism	*GSTM1*	deletion	167	176
	GSTT1	deletion	168	184
	GSTP1	Ile105Val	167	179
	NAT1	11 variants	277	310
	NAT2	24 variants	277	310
	CYP2E1	G-1019C 5'UTR	329	337
	NQO1	C609T	265	295
	EPHX	Tyr113His	149	175
	ALDH2	G1543A	510	388
DNA repair	*hOGG1*	Ser326Cys	269	283
	XRCC1	Arg194Trp	268	285
		Arg339Gln	269	284
	XRCC3	Thr241Met	440	276
	ERCC4	T2505C	376	335
	ERCC2	Asp312Asn	476	337
	ATM	C2119T	467	332
	AGT	Gly160Arg	417	330
	HER2	Ile655Val	505	389
Cytokine & growth factor	*TGFB1*	Leu10Pro	511	392
	TNFB	A252G	506	387
	IGF1	G2502 3'UTR	512	389
	IL-1B	C-31T	512	394
	IL1RN	86bp VNTR	512	391
Estrogen metabolism	*ER-α*	*PuvII*	201	195
		XbaI	201	195
	CYP1A1	T6235C	355	210
		A4889G	461	339
	CYP1B1	Val432Leu	268	301
	CYP17	T-1931C 5'UTR	420	322
	CYP19	Arg264Cys	379	343
	COMT			
Others	*BAR2*	Gln27Glu	508	389
	MTHFR	C667T	273	266

genotypes.

We conducted a hospital-based case-control study in South Korea to further evaluate the potential modifying role of the genetic polymorphisms of selected genes that are involved in carcinogen metabolisms, estrogen metabolism, signal transduction, and DNA repair. We also took into account the potential interaction between these and the known risk factors of breast cancer (Table 1). The results of the selected genes will be presented in this mini-review.

GSTM1 and T1

The inherited metabolic capacity of glutathione *S*-transferases (GSTs) have been related to the individual breast cancer risk (Helzlsouer *et al.*, 1998). GSTs are a superfamily of enzymes that are involved in conjugation with reactive intermediates to soluble glutathione, and therefore, play an important role in the detoxification of endogenous and exogenous toxicants. GSTM1 can detoxify carcinogenic polycyclic aromatic hydrocarbons (PAHs), such as benzo[a]pyrene (BaP) and mycotoxin aflatoxin, while GSTT1 can detoxify smaller reactive hydrocarbons, such as ethylene oxide and diepoxybutane. It can also metabolize solvents. GSTs may also have a role in the metabolism of lipid and DNA products of oxidative stress (Zhu and Conney, 1998). About half of the Asian population lacks GSTM1 and GSTT1 enzyme activities, due to homozygous deletions of the respective genes.

In our study (Park *et al.*, 2000), for the *GSTM1* null

Table 2. Frequency of *GSTM1* and *GSTT1* genotypes in the study populations

	All women			Premenopausal women			Postmenopausal women		
	Cases N (%)	Controls N (%)	OR* (95% CI)	Cases N (%)	Controls N (%)	OR* (95% CI)	Cases N (%)	Controls N (%)	OR* (95% CI)
GSTM1									
Present	78 (41.5)	86(47.5)	1.0 (ref.)	43(37.7)	49(50.5)	1.0 (ref.)	35(47.3)	34(42.5)	1.0 (ref.)
Null	110(58.5)	95(52.5)	1.3 (0.84-2.06)	71(62.3)	48(49.5)	2.0 (1.05-3.69)	39(52.7)	46(57.5)	0.9 (0.45-1.93)
GSTT1									
Present	94(50.0)	105(58.0)	1.0 (ref.)	57(50.0)	55(56.7)	1.0 (ref.)	37(50.0)	48(60.0)	1.0 (ref.)
Null	94(50.0)	76(42.0)	1.6 (0.98-2.54)	57(50.0)	42(43.3)	1.7 (0.94-3.24)	37(50.0)	32(40.0)	1.3 (0.64-2.80)

*OR: odds ratio, 95% CI : 95% confidence interval of odds ratio. The ORs were adjusted for age, education, body mass index, age at menarche, age at first pregnancy, age at menopause, smoking, alcohol consumption, duration of breast feeding, family history of breast cancer, and menopausal status at baseline.

Table 3. Association between combined of *GST* genotypes and breast cancer risk

	Cases N (%)	Controls N (%)	OR (95% CI)
Combination of *GSTM1* and *GSTT1**			
No null	32 (17.0)	48 (26.5)	1.0 (ref.)
One null	108 (57.5)	95 (52.5)	1.7 (0.98-3.08)
Both null	48 (25.5)	38 (21.0)	2.2 (1.13-4.45)

*Risk of combination of *GST* genotypes significantly increased by likelihood ratio test to assess linear increase in risk of breast cancer as the number of null genotype increased (P for trend = 0.02). The ORs were adjusted for education, body mass index, age at menarche, age at first pregnancy, age at menopause, duration of breast feeding, and family history of breast cancer.

genotype, a statistically significant effect was observed among the premenopausal women (OR = 2.0, 95% CI = 1.1-3.7); whereas, the significant effect of *GSTT1* null genotype (OR = 1.6, 95% CI = 1.0-2.5) in all of the study subjects was mainly attributable to the premenopausal women group (OR = 1.7, 95% CI = 0.9-3.2) (Table 2). When the potential combined effect of the *GSTM1* and *GSTT1* genotypes was examined, then the concurrent lack of both of the genes posed more than a two-fold risk of breast cancer (OR = 2.2, 95% CI = 1.1-4.5) (Table 3). The most remarkable risk was seen after stratification by the menopausal status at the time of diagnosis; among alcohol-consuming premenopausal women, the concurrent lack of both the *GSTM1* and *GSTT1* genes resulted in more than a five-fold risk of breast cancer (OR = 5.3, 95% CI = 1.0-27.8) (Table 4).

COMT

Catechol *O*-methyltransferase (COMT) is one of the key enzymes that are involved in the metabolism of catecholamine in humans. The presumed mechanisms of catechol estrogen in breast carcinogenesis were recently reviewed by Zhu and Conney (1998). Catechol estrogen causes DNA damage either directly, or through its quinone metabolites (Yager and Liehr, 1996). In our study (Yim *et al.*, 2001), the subjects with at least one *COMT-L* allele had an almost two-fold risk of breast cancer when compared with the *COMT-HH* genotype individuals (OR = 1.7, 95% CI = 1.04-2.78) (Table 5).

ER-α

The estrogen receptor α (*ER-α*) is an important mediator of the hormonal response in estrogen-sensitive tissues, such as the breast and bones. Therefore, it is conceivable that a variation in the *ERα* function could affect the proliferation of these tissues. In agreement with this, functional-potentially important polymorphisms in the *ERα* gene have, although inconsistently, been associated with bone density and breast cancer, as well as endometrial cancer risks. In our recent unpublished study, the *Pvu*II genotype distribution showed no difference between the cases and controls, but the *Xba*I xx genotype posed more than a two-fold risk of breast cancer (OR = 2.38, 95% CI = 1.58-3.59) when compared with the X allele that contained genotypes. This increase was mainly attributable to the postmenopausal breast cancer risk (OR = 3.79, 95% CI = 1.89-7.62). Combined with *XbaI* and *PvuII*, ORs were 2.32 (95% CI = 1.42-3.81) for xxPP or xxPp genotype and 2.44 (95% CI = 1.49-3.99) for xxpp genotype when compared with the genotype that contained the X allele; their increased risks were statistically significant (P for trend

Table 4. Interaction between the combined of *GST* genotypes and alcohol consumption

GST genotypes	Never drinker			Ever drinker		
	Cases N (%)	Controls N (%)	OR (95% CI)	Cases N (%)	Controls N (%)	OR (95% CI)
All women[§]						
No null	23 (16.9)	38 (25.5)	1.0 (ref.)	9 (17.3)	10 (31.3)	1.0 (ref.)
One null	80 (58.8)	77 (51.7)	1.7 (0.94-3.14)	28 (53.8)	18 (56.2)	1.7 (0.59-5.08)
Two nulls	33 (24.3)	34 (22.8)	1.6 (0.79-3.25)	15 (28.9)	4 (12.5)	4.2 (1.01-17.31)
Premenopausal women[§]						
No null	11 (14.5)	15 (21.1)	1.0 (ref.)	6 (15.8)	8 (30.8)	1.0 (ref.)
One null	46 (60.5)	43 (60.6)	1.5 (0.60-3.52)	20 (52.6)	15 (57.7)	1.8 (0.51-6.22)
Two nulls	19 (25.0)	13 (18.3)	2.0 (0.70-5.70)	12 (31.6)	3 (11.5)	5.3 (1.03-27.76)
Postmenopausal women						
No null	12 (20.0)	21 (28.4)	1.0 (ref.)	3 (21.4)	2 (33.3)	1.0 (ref.)
One null	34 (56.7)	33 (44.6)	1.8 (0.77-4.24)	8 (57.2)	3 (50.0)	1.8 (0.19-16.49)
Two nulls	14 (23.3)	20 (27.0)	1.2 (0.46-3.28)	3(21.4)	1 (16.7)	2.0 (0.11-35.81)

[§]P for trend in ever-drinker < 0.05

P-value for interaction; P = 0.02 for premenopausal women, P = 0.08 for postmenopausal women. These P-values for interaction are not changed after adjustment for body mass index.

Table 5. Association between *COMT* genotypes and development of breast cancer by menopausal status

Genotype	Cases N (%)	Controls N (%)	OR (95% CI)*
All women (cases=163, controls=163)			
HH	81 (50)	101 (62)	1.0 (ref.)
HL	79 (48)	46 (28)	2.3 (1.35-3.85)
LL	3 (2)	16 (10)	0.2 (0.07-0.92)
HH	81 (50)	101 (62)	1.0 (ref.)
HL+LL	82 (50)	62 (38)	1.7 (1.04-2.78)
Postmenopausal women (cases=72, controls=72)			
HH	34 (47)	42 (58)	1.0 (ref.)
HL	37 (52)	23 (32)	2.0 (1.00-3.96)
LL	1 (1)	7 (10)	0.2 (0.02-1.50)
HH	34 (47)	42 (58)	1.0 (ref.)
HL+LL	38 (53)	30 (42)	1.6 (0.82-3.02)
Premenopausal women (cases=91, controls=91)			
HH	47 (52)	59 (65)	1.0 (ref.)
HL	42 (46)	23 (25)	2.3 (1.21-4.33)
LL	2 (2)	9 (10)	0.3 (0.06-1.35)
HH	47 (52)	59 (65)	1.0 (ref.)
HL+LL	44 (48)	32 (35)	1.7 (0.95-3.13)

*OR; odds ratio, 95% CI; 95% confidence interval of odds ratio. The ORs were adjusted for education, age at menarche, age at first pregnancy, number of live birth baby, duration of breast feeding, smoking, drinking, body mass index and family history of breast cancer.

<0.001) (Table 7). When the selected tumor phenotypes were considered, then the C/G heterozygote posed a 3.5-fold probability (95% CI = 1.02-11.88) and the G/G homozygote a 4.7-fold probability (95% CI = 1.11-19.83) of the positive PR expression when compared with the C/C homozygote (Table 7) (Kang *et al*., 2002).

XRCC1

XRCC1 is thought to play a role in the multistep base excision repair pathway. There the "non-bulky" base adducts are removed that are produced by methylation, oxidation, reduction, or fragmentation of bases by ionizing radiation or

Table 6. Frequency of *ERα XbaI* and *PvuII* genotypes in the study populations

	All women			Premenopausal women			Postmenopausal women		
Genotype	Cases (%) (n=201)	Controls (%) (n=195)	Adjusted OR (95% CI)*	Cases (%) (n=122)	Controls (%) (n=109)	Adjusted OR (95% CI)*	Cases (%) (n=79)	Controls (%) (n=81)	Adjusted OR (95% CI)*
XbaI									
XX	11(5.5)	7(3.6)	1.0 (ref.)	6(4.9)	3(2.8)	1.0 (ref.)	5(6.3)	3(3.7)	1.0 (ref.)
Xx	60(29.8)	102(52.3)	0.4(0.2-1.1)	39(32.0)	54(49.5)	0.4(0.1-1.7)	21(26.6)	46(56.8)	0.2(0.1-0.9)
Xx	130(64.7)	86(44.1)	1.1(0.4-2.9)	77(63.1)	52(47.7)	0.8(0.2-3.4)	53(67.1)	32(39.5)	0.9(0.2-4.3)
XX or Xx	71(35.3)	109(55.9)	1.0 (ref.)	45(36.9)	57(52.3)	1.0 (ref.)	26(32.9)	49(60.5)	1.0 (ref.)
Xx	130(64.7)	86(44.1)	2.4(1.6-3.6)	77(63.1)	52(47.7)	1.9(1.1-3.2)	53(67.1)	32(39.5)	3.9(1.9-7.8)
PvuII									
PP	35(17.4)	26(13.3)	1.0 (ref.)	21(17.2)	18(16.5)	1.0 (ref.)	14(17.7)	8(9.9)	1.0 (ref.)
Pp	91(45.3)	105(53.9)	0.6(0.4-1.2)	56(45.9)	58(53.2)	0.9(0.4-1.8)	35(44.3)	45(55.5)	0.4(0.2-1.2)
Pp	75(37.3)	64(32.8)	0.9(0.5-1.7)	45(36.9)	33(30.3)	1.2(0.6-2.7)	30(38.0)	28(34.6)	0.7(0.2-1.9)
PP or Pp	126(62.7)	131(67.2)	1.0 (ref.)	77(63.1)	76(69.7)	1.0 (ref.)	49(62.0)	53(65.4)	1.0 (ref.)
Pp	75(37.3)	64(32.8)	1.3(0.8-1.9)	45(36.9)	33(30.3)	1.4(0.8-2.4)	30(38.0)	28(34.6)	1.3(0.7-2.6)
Combined genotypes									
X allele genotypes **	71(35.4)	109(55.8)	1.0 (ref.)	45(36.9)	57(52.2)	1.0 (ref.)	26(32.9)	49(60.4)	1.0 (ref.)
xxPP/xxPp	64(31.8)	43(22.1)	2.4(1.4-3.9)	37(30.3)	26(23.9)	1.8(0.9-3.5)	27(34.2)	16(19.8)	3.8(1.7-8.8)
Xxpp	66(32.8)	43(22.1)	2.5(1.5-4.0)	40(32.8)	26(23.9)	1.9(1.0-3.6)	26(32.9)	16(19.8)	3.9(1.7-9.1)
P for trend			<0.001			<0.05			<0.001

*: Odds ratio were adjusted for age, education level and family history of breast cancer. **: XXPP, XXPp, XXpp, XxPP, XxPx, and Xxpp

Table 7. The association between ERα C975G polymorphism and tumor markers

Genotypes	Tumor marker number (%)			OR (95% CI)	*P* for trend
		Negative	Positive		
C/C	ER	10 (53)	9 (47)	1.0 (ref.)	
C/G	(n=89)	21 (40)	31 (60)	1.6 (0.57-4.72)	0.06
G/G		4 (22)	14 (78)	3.9 (0.93-16.26)	
		Negative	Positive		
C/C	PR	15 (79)	4 (21)	1.0 (ref.)	
C/G	(n=89)	27 (52)	25 (48)	3.5 (1.02-11.88)	0.04
G/G		8 (44)	10 (56)	4.7 (1.11-19.83)	
		Negative	Positive		
C/C	p53	8 (42)	11 (58)	1.0 (ref.)	
C/G	(n=88)	23 (45)	28 (55)	0.9 (0.31-2.57)	0.02
G/G		15 (83)	3 (17)	0.1 (0.03-0.68)	
		Negative	Positive		
C/C	c-erbB2	10 (53)	9 (47)	1.0 (ref.)	
C/G	(n=88)	20 (39)	31 (61)	1.7 (0.60-4.80)	0.60
G/G		8 (44)	10 (56)	1.4 (0.38-0.68)	
		Negative	Positive		
C/C	bcl-2	7 (37)	12 (63)	1.0 (ref.)	
C/G	(n=88)	13 (25)	38 (75)	1.7 (0.55-5.25)	0.16
G/G		3 (17)	15 (83)	2.9 (0.62-13.76)	

Table 8. Association between the *XRCC1* genotypes and breast cancer risk

	All women			Premenopausal women			Postmenopausal women		
	Cases N (%)	Controls N (%)	OR (95% CI)	Cases N (%)	Controls N (%)	OR (95% CI)	Cases N (%)	Controls N (%)	OR (95% CI)
XRCC1 codon 194									
Arg/Arg	88 (42.9)	92 (44.9)	1.0 (ref.)	54 (43.6)	57 (49.6)	1.0 (ref.)	34 (42.0)	32 (37.6)	1.0 (ref.)
Arg/Trp	94 (45.9)	86 (41.9)	1.1 (0.76-1.73)	54 (43.6)	45 (39.1)	1.3 (0.74-2.18)	40 (49.4)	39 (45.9)	1.0 (0.50-1.86)
Trp/Trp	23 (11.2)	27 (13.2)	0.9 (0.48-1.67)	16 (12.8)	13 (11.3)	1.3 (0.57-2.95)	7 (8.6)	14 (16.5)	0.5 (0.17-1.32)
			P for trend=1.0			P for trend=0.4			P for trend=0.2
XRCC1 codon 399									
Arg/Arg	92 (44.9)	90 (43.9)	1.0 (ref.)	52 (41.9)	60 (52.2)	1.0 (ref.)	40 (49.4)	28 (33.0)	1.0 (ref.)
Arg/Gln	79 (38.5)	101 (49.3)	0.8 (0.51-1.16)	52 (41.9)	49 (42.6)	1.2 (0.72-2.10)	27 (33.3)	50 (58.8)	0.4 (0.19-0.74)
Gln/Gln	34 (16.6)	14 (6.8)	2.4 (1.20-4.72)	20 (16.2)	6 (5.2)	3.8 (1.44-10.30)	14 (17.3)	7 (8.2)	1.4 (0.50-3.91)
			P for trend=0.2			P for trend=0.02			P for trend=0.5

The ORs were adjusted for age, education, body mass index, age at menarche, age at first pregnancy, age at menopause, smoking, alcohol consumption, duration of breast feeding, family history of breast cancer, and menopausal status at baseline.

oxidative damage (Yu *et al.*, 1999). Three polymorphisms in the *XRCC1* gene have been described, which resulted in Arg194Trp, Arg280His, and Arg399Gln amino acid changes in the XRCC1 protein (Shen *et al.*, 1998). The codon 194 and codon 280 polymorphic sites are located in a linker region that separates the DNA polymerase β-interacting domain from the PARP-interacting domain. The codon 399 polymorphic site is located in the COOH-terminal side of the PARP-interacting domain, within the BRCT domain, which is homologous to the COOH-terminal region of the breast cancer susceptibility gene *BRCA1*. Recently, the *XRCC1* codon 399 polymorphism has been associated with significant alterations in the DNA repair capacity; whereas, no such data exists for the codon 194 and 280 polymorphisms.

In our recent study (Kim *et al*., 2002), the *XRCC1* codon 194 polymorphism did not influence the breast cancer risk; whereas, homozygosity for the codon 399 Gln allele placed women at a 2.4-fold risk (95% CI = 1.20-4.72) for this malignancy; the risk increased to 3.8-fold (95% CI = 1.44-10.30) in the premenopausal women. The risk of breast cancer increased with the number of Gln alleles (P for trend = 0.02) (Table 8).

Conclusions

Breast cancer is the second most frequent cancer in Korean women, and the incidence is increasing in both Western countries and Korea. Although a substantial proportion of breast cancer cases are explained by well-established risk factors (*i.e.*, later age at first pregnancy, nulliparity, and first-degree family history of breast cancer), the reason for the observed worldwide increase in breast cancer incidences is still largely unknown. The molecular epidemiological approaches using the genetic information in a population-based observational study will provide better mechanistic insights of breast cancer etiology, as well as efficient preventive measures to genetically susceptible population in the future.

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