Genetic Susceptibility of Breast Cancer in Korea

-Molecular Epidemiological Approaches-

Departments of Preventive Medicine and [1]Surgery, Seoul National University College of Medicine

Dae Hee Kang, M.D. and Dong-Young Noh, M.D.[1]

INTRODUCTION

Breast cancer is the most prevalent cancer among women in Western countries and its prevalence is also increasing in Asia. (*1,2*) In 1994, the incidence rate of female breast cancer in Korea, adjusted for the world population, was 10.9 per 100,000, which was far lower than those of Western countries and even lower than those of other Asian countries. The major risk factors relating to breast cancer can be traced to reproductive events influencing lifetime levels of hormones.(*3,4*)

A large proportion of breast cancer cases cannot, however, be explained by the above risk factors. The identification of susceptibility factors predisposing an individual to breast cancer, if 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 susceptibilities to breast cancer. Therefore, the identification of new breast cancer susceptibility genes might yield new insight into breast tumorigenesis, and could provide targets for future therapeutic developments.

In this respect the most interesting candidate genes include those mediating a range of functions, such as 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 attributable risk of low penetrance genes are much higher than those of the high penetrance genes, since the frequency of their variant alleles are higher in the general population. Thus, higher public health significance lays with these low penetrance genes, With their use it may be possible to obtain greater mechanistic insights into human breast carcinogenesis as well as targeted preventive approaches to the individuals with 'at risk' genotypes (Table 1).

We have conducted a hospital based case-control study in South Korea to further evaluate the potential modifying role of the genetic polymorphisms of selected genes involved in the metabolism of carcinogens, estrogen metabolism, signal transduction, and DNA repair, also taking into account the potential interaction between these and known risk factors of breast cancer (Table 2). The results from selected genes will be presented in this mini-review.

GSTM1/T1

The inherited metabolic capacity of glutathione *S*-transferases (GSTs), have been related with the individual risk of breast cancer.(*5*) GSTs are a superfamily of enzymes involved in the conjugation of 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 the mycotoxin, aflatoxin, while GSTT1 can detoxify smaller reactive hydrocarbons, such as

Table 1. Types of susceptibility genes

Factors	Single	Susceptibility
Gene frequency	Rare	Common (>1%)
Penetrance	High	Low
AR/RR	High	Low
PopulationAR	Low	High
Study setting	Family	Population
Study type	Linkage	Association

Correspondence: Daehee Kang, Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea. (E-mail) dhkang@snu.ac.kr

Table 2. List of genes and SNPs analyzed in Korean breast cancer and controls

Group	Gene	SNP	Case	Control
Xenobiotics Metabolism	*GSTM1*	Deletion	167	176
	GSTT1	Deletion	168	184
	GSTP1	Ile105Val	167	179
	NAT1		277	310
	NAT2		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	Ile665Val	505	389
Cytokine & growth factor	*TGFB1*	Leu10Pro	511	392
	TGFB	A252G	506	387
	IGF1	G2502 3'UTR	512	389
	IL-1B	C-31T	512	394
	IL1RN	86bp VNTR	512	391
Estrogen metabolism	*ER*	PuvII	138	129
		XbaI	138	129
	CYP1A1	T6235C	290	133
		A4889G	461	339
	CYP1B1	Bal432Leu	268	301
	CYP17	T-1931C 5'UTR	420	322
	CYP19	Arg264Cys	379	343
	COMT			
Others	*BAR2*	Gln27Glu	508	389
	MTHFR	C667T	273	266

ethylene oxide and diepoxybutane, and can also metabolize solvents. GSTs may also have a role in the metabolism of lipid and DNA oxidative stress products.(*3*) Both GSTM1 and GSTT1 enzyme activities are absent from about half the Asian population due to homozygous deletions of the respective genes.

In our earlier study,(*6*) for the *GSTM1* null genotype, a statistically significant effect was observed among 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 study subjects was mainly attributable to the premenopausal women group (OR=1.7, 95% CI=0.9～3.2) (Table 3). When the potential combined effect of the *GSTM1* and *GSTT1* genotypes was examined, a concurrent lack of both genes posed a more than two-fold risk of breast cancer (OR=2.2, 95% CI=1.1～4.5) (Table 4). The most remarkable risk was seen after stratification due to menopausal status at the time of diagnosis; among alcohol-consuming premenopausal women a concurrent lack of both genes resulted in a

Table 3. 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 4. 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.

Table 5. 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 adjustmenent for BMI.

Table 6. Association between COMT genotypes and development of breast cancer by menopausal status

Genotype	Cases (%)	Controls (%)	OR (95% CI)*
All women (cases=163, controls=163)			
HH	81 (50)	101 (62)	1.0 (reference)
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 (reference)
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 (reference)
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 (reference)
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 (reference)
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 (reference)
HL+LL	44 (48)	32 (35)	1.7 (0.95～3.13)

*OR = odds ratio; 95% CI = 95% confidence interval of odds ratio. OR was adjusted for education, age at menarche, age at first pregnancy, number of live birth baby, duration of breast feeding, smoking, drinking, BMI and family history of breast cancer.

more than five-fold risk of breast cancer (OR=5.3, 95% CI= 1.0～27.8) (Table 5).

COMT

Catechol *O*-methyltransferase (COMT) is one of the key enzymes involved in the metabolism of catecholamine in humans. The presumed mechanisms of catechol estrogen in breast carcinogenesis were recently reviewed by Zhu and Conney.(*3*) Catechol estrogen causes DNA damage, either directly or, through its quinone metabolites(*8*) In our earlier study,(*7*) subjects with at least one *COMT-L* allele had an almost two-fold risk of breast cancer compared with the *COMT-HH* genotype individuals (OR=1.7; 95% CI=1.04～ 2.78) (Table 6).

ER

The estrogen receptor α (*ERα*) is an important mediator of the hormonal response in estrogen-sensitive tissues, such as breast and bone. It is therefore conceivable that variation in the *ERα* function could affect proliferation of these tissues. This is supported by, the potentially functionally important polymorphisms in the *ERα* gene having, although inconsistently, been associated with bone density, breast cancer and endometrial cancer risks. In our recent unpublished study, the *Pvu*II genotype distribution showed no differences between cases and the controls, but the *Xba*I xx genotype posed a more than two-fold risk of breast cancer (OR: 2.38, 95% CI: 1.58～3.59) compared with the X allele containing genotypes. This increase was mainly attributable to the risk of postmenopausal breast cancer (OR: 3.79, 95% CI: 1.89～7.62). Combining *XbaI* and *PvuII* with other genotypes, the ORs were 2.32 (95% CI: 1.42～3.81) for the xxPP or xxPp genotypes and 2.44 (95% CI: 1.49～3.99) for xxpp genotype compared with the genotypes containing the X allele, and their increased risks were statistically significant (P for trend＜0.001) (Table 7). When the selected tumor phenotypes were considered, 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 positive PR expression, compared with the C/C homozygote (Table 8).(*9*)

Table 7. Frequency of ERα XbaI and *PvuII* genotypes in the study populations

Genotype	All women			Premenopausal women			Postmenopausal women		
	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	6 (4.9)	3 (2.8)	1.0	5 (6.3)	3 (3.7)	1.0
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	45 (36.9)	57 (52.3)	1.0	26 (32.9)	49 (60.5)	1.0
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	21 (17.2)	18 (16.5)	1.0	14 (17.7)	8 (9.9)	1.0
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	77 (63.1)	76 (69.7)	1.0	49 (62.0)	53 (65.4)	1.0
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	45 (36.9)	57 (52.2)	1.0	26 (32.9)	49 (60.4)	1.0
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.

XRCC1

XRCC1 is thought to play a role in the multistep base excision repair pathway, where “non-bulky” base adducts produced by the methylation, oxidation, reduction, or fragmentation of bases by ionizing radiation, or oxidative damage, are removed.(*10*) Three polymorphisms in the *XRCC1* gene have been described, and result in the $Arg^{194}Trp$, $Arg^{280}His$, and $Arg^{399}Gln$ amino acid changes in the XRCC1 protein.(*11*) The codons 194 and 280 polymorphic sites are located in a linker region that separates the DNA polymerase (interacting domain from the PARP-interacting domain. The codon 399 polymorphic site is located on 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 polymorphisms of codons 194 and 280.

In our recent study,(*12*) the *XRCC1* codon 194 polymorphism had no influence toon the risk of breast cancer, whereas homozygosity for the codon 399 Gln allele placed women at a 2.4-fold increased risk (95% CI=1.20～4.72) of this malignancy; the risk increased to 3.8-fold (95% CI=1.44～10.30) in premenopausal women. The risk of breast cancer was found to increased with the number of Gln alleles (P for trend=0.02) (Table 9).

CONCLUSIONS

Breast cancer is second only to stomach cancer as the most frequent cancer in Korean women and incidences are 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 birth, nulliparity,

Table 8. The association between ERα $C^{975}G$ polymorphism and tumor markers

Genotypes	Tumor marker number (%)			OR (95% CI)	P for trend
		Negative	Positive		
C/C	ER (n=89)	10 (53)	9 (47)	1.0 (reference)	
C/G		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 (n=89)	15 (79)	4 (21)	1.0 (reference)	
C/G		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 (n=88)	8 (42)	11 (58)	1.0 (reference)	
C/G		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 (n=88)	10 (53)	9 (47)	1.0 (reference)	
C/G		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 (n=88)	7 (37)	12 (63)	1.0 (reference)	
C/G		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 9. 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 (reference)	54 (43.6)	57 (49.6)	1.0 (reference)	34 (42.0)	32 (37.6)	1.0 (reference)
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 (reference)	52 (41.9)	60 (52.2)	1.0 (reference)	40 (49.4)	28 (33.0)	1.0 (reference)
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.

and a first-degree family history of breast cancer, the reason for the observed worldwide increase in breast cancer incidence is still largely unknown (might I suggest this is possibly due to the improvements in education and screening for the condition). Molecular epidemiological approaches, using genetic information in population-based observational studies,

could provide better mechanistic insights of breast cancer etiology and efficient preventive measures to genetically susceptible populations.

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