

TABLE A
Distribution of demographic and risk factors among cases and controls in the entire sample set.

	Overall Discovery Set			Southern CA			Central FL			Kansas City, KS/MO			Oklahoma City, OK			Seattle, WA			South Carolina			
	Cases	Controls	p-value	Cases	Controls	p-value	Cases	Controls	p-value	Cases	Controls	p-value	Cases	Controls	p-value	Cases	Controls	p-value	Cases	Controls	p-value	
Age ⁺	49.8(± 9.3)	49.8(± 9.3)	-	50.3(±8.7)	47.6(±8.7)	-	48.6(±9.5)	46.9(±9.3)	-	48.9(±9.2)	49.5(±9.6)	-	50.3(±9.5)	50.8(±9.2)	-	49.1(±9.1)	49.6(±8.9)	-	47.6(±8.6)	48.9(±9.6)	-	
Age Menarche ⁺	12.4(± 2.1)	12.6(± 2.3)	-	12.5(±1.3)	12.8(±1.5)	-	12.5(±1.6)	12.9(±1.8)	-	12.5(±1.4)	12.6(±1.5)	-	12.7(±1.5)	12.7(±1.5)	-	12.7(±1.7)	12.9(±1.5)	-	12.6(±1.4)	13.5(±8.8)	-	
Age First Live Birth ⁺	24.1(± 5.1)	24.1(± 5.3)	-	24.9(±5.6)	25.2(±5.2)	-	25.4(±5.7)	25.5(±5.9)	-	24.1(±4.4)	23.9(±4.9)	-	23.1(±4.7)	22.9(±4.8)	-	26.2(±5.8)	26.8(±5.5)	-	25.2(±5.8)	25.6(±5.3)	-	
Affected First Degree Relatives*	0	1299 (78.0)	2549 (76.5)	173 (74)	308 (75)		177 (79)	432 (80)		285 (80)	474 (84)		815 (78)	1551 (73)		183 (77)	434 (78)		74 (75)	136 (72)		
	1	329 (19.7)	706 (21.2)	52 (22)	97 (23)		46 (20)	103 (19)		66 (19)	83 (15)		208 (20)	509 (24)		46 (19)	104 (19)		21 (21)	50 (26)		
	≥ 2	39 (2.3)	78 (2.3)	-	8 (4)	7 (2)	-	2 (1)	5 (1)	-	5 (1)	6 (1)	-	20 (2)	67 (3)	0.003	9 (4)	20 (3)	-	4 (4)	4 (2)	-
HRT Usage*	≤50	213 (23)	345 (18)	11 (11)	17 (14)		18 (23)	24 (15)		41 (24)	51 (22)		118 (27)	219 (19)		20 (20)	24 (12)		5 (15)	10 (15)	-	
	>50	700 (77)	1561 (81)	0.001	89 (89)	102 (86)	-	60 (77)	131 (85)	-	125 (76)	183 (78)	-	317 (73)	916 (81)	<0.001	81 (80)	173 (88)	-	28 (85)	56 (85)	-
No HRT Usage*	≤50	534 (62)	553 (53)		40 (63)	56 (52)		50 (62)	77 (54)		101 (74)	42 (35)		250 (57)	272 (61)		75 (68)	73 (45)		18 (72)	33 (56)	-
	>50	326 (38)	482 (47)	<0.001	24 (37)	51 (48)	-	31 (38)	65 (46)	-	36 (26)	78 (65)	<0.001	192 (43)	174 (39)	-	36 (32)	88 (55)	<0.001	7 (28)	26 (44)	-

⁺ Mean (SD)
^{*} n (%)
 - = p>0.05

The characteristics of cases and controls that comprised the discovery and validation sets are shown. The t-test was used to test for difference of means and the χ^2 -test was used for frequency analyses. Overall, the case and control populations are similar except for use of hormone replacement therapy (HRT). Although the frequency of controls reporting a family history of breast cancer is higher than generally reported in the literature, another case-control study has reported similar levels of enrollment of controls with a first degree relative with breast cancer (Zhu Y, et al. Breast Cancer Res. 2005;7:R745-52. The increased family history reported by controls was consistent at the different collection sites except in Oklahoma City where the controls had a higher frequency of family history. This most likely reflects the fact that the control population most likely to undergo screening mammography is also willing to participate in research studies. The potential impact of these controls on the results of this study would likely be an underestimation of the magnitude and significance of any association of a genotype of a common polymorphism with breast cancer risk. The genotypes of these controls were in Hardy-Weinberg Equilibrium suggesting that they are representative of a general population at steady state. Because of the differences in the frequency of cases and controls reporting HRT use, analyses adjusting for HRT use were performed to confirm age-specific genetic associations.

TABLE B
18 SNPs in 12 SH Pathway Genes

Gene	Name	Chromosome Location	Gene Function	dbSNP ID	Polymorphism	Effect of SNP on Function	References	
							Functional	Epidemiological
<i>COMT</i>	Catechol-O-methyltransferase	22q11.2	Inactivates catechol estrogens by methylation.	rs4680	G→A Val158Met	↓ methylation activity	1	2, 3, 4, 5
<i>CYP1A1</i>	Cytochrome P450 Family 1A, polypeptide 1	15q22-q24	Oxidation of estradiol and estrone through 2- and 4-hydroxylation.	rs4646903	T(m1)→C(m2) 3'UTR	↑ enzyme activity	6, 7	8, 9
				rs1048943	A→G Ile462Val	↑ catalytic activity	10	9, 11, 12
<i>CYP11B2</i>	Cytochrome P450 Family XIB, polypeptide 2	12p13	Synthesis of aldosterone in renin-angiotensin system.	rs1799998	C→T Promoter -344	↑ aldosterone secretion	13, 14	15
<i>CYP1B1</i>	Cytochrome P450, family 1, subfamily B, polypeptide 1	2p21-p22	Metabolizes estrogens and other xenobiotics via hydroxylation.	rs10012	C→G Arg48Gly	↑ enzyme activity	16, 17	18
				rs1056836	G→C Val432Leu	↑ enzyme activity		19, 20, 21
<i>CYP 17</i>	Cytochrome P450, family 17, subfamily A, polypeptide 1	10q24.3	Synthesis of sex steroids via 17-alpha hydroxylation and 17,20-lyase activity.	rs743572	T→C 5'UTR	↑ mRNA abundance	22, 23	24, 25
<i>CYP19</i>	Cytochrome P450 , family 19, Subfamily A, polypeptide 1 - aka Aromatase	15q21.1	Terminal enzyme in estrogen synthesis that catalyzes formation of C18 estrogens from C19 androgens.	rs10046	C→T 3'UTR	↑ activity phenotype	26	26
				rs700519	C→T Arg264Cys	unknown	NA	27
<i>EPHX1</i>	Epoxide hydrolase (microsomal)	1q42.1	Activation and detoxification of exogenous chemicals such as polycyclic hydrocarbons.	rs1051740	T→C Tyr113His	↓ enzyme activity	28	29

ERA	Estrogen receptor alpha	6q25.1	Ligand-activated transcription factor that mediates growth and differentiation of normal mammary tissue through binding of estrogen.	rs2077647	T→C Ser10Ser	neutral polymorphism	30	31, 32
PGR	Progesterone Receptor	11q22	Mediates the effects of progesterone during normal breast development. PGR is produced as two isoforms: PR-A (opposes the effects of PR-B) and PR-B (promotes breast cell proliferation).	rs1042838	G→T Val660Leu	↑ half life of PR mRNA	33	34, 35, 36
				rs10895068	G→A Promoter + 331	↑ transcription of the PR-B isoform	37	38, 39
SHBG	Sex Hormone Binding Protein	17p13-p12	Modulates bioavailability of sex hormones in target tissues. Involved in sex steroid signaling.	rs6529	A→G Asp356Asn	↑ levels of SHBG	40, 41, 42, 43, 44	45, 46
				rs1799941	A→G 5'UTR	↑ levels of SHBG		
SOD2	Manganese superoxide dismutase	6p25.3	Intra-mitochondrial, manganese-dependent, free radical scavenger that metabolizes reactive oxygen species to hydrogen peroxide.	rs1799725	C→T Val16Ala	may affect protein transport	47	48, 49, 50
UGT1A7	UDP glycosyltransferase 1, family, polypeptide A7	2q37	Detoxification of lipophilic xenobiotics, hormones and drugs by glucuronidation.	rs17868324	AA→CG Lys131Arg	↑ enzyme activity	51, 52	53, 54, 55
				rs11692021	T→C Trp208Arg	↓ enzyme activity		

Characteristics of the Polymorphisms

Eleven polymorphisms are non-synonymous SNPs leading to amino acid changes in proteins while one (*ERA*) is a synonymous SNP that does not change the amino acid but has been associated with increased BC risk. Six SNPs are regulatory and occur in promoter or 3'UTR regions. Most of the SNPs have been directly associated with enzymatic or other physiological alterations, although they could still be markers for other causative polymorphisms via linkage disequilibrium. All have been examined in at least one epidemiological study for association with risk of breast and/or other cancers.

Complete Reference List for Table B

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TABLE C
Overall associations with BC risk in the discovery set

SNP	Genotype	Case n (%)	Control n (%)	OR (95%CI)^a	HWE p-value^b
COMT	A/A	405(25)	900(27)	1.0(ref) ^c	0.8
	G/A	825(51)	1631(50)	1.1(0.9-1.3)*	
	G/G	396(24)	755(23)	1.2(0.9-1.4)*	
CYP1A1 (3'UTR)	m1/m1	1324(81)	2604(79)	1.0	0.6
	m1/m2	292(18)	657(20)	0.8(0.8-1.0)*	
	m2/m2	16(1)	38(1)	0.8(0.5-1.5)	
CYP1A1 (I462V)	A/A	1516(93)	3024(92)	1.0	0.1
	G/A	110(6)	260(7)	0.8(0.7-1.1)*	
	G/G	1(1)	1(1)	1.9(0.5-1.5)	
CYP11B2	T/T	486(29)	1044(32)	1.0	0.5
	C/T	842(51)	1613(48)	1.1(0.9-1.3)*	
	C/C	323(20)	651(20)	1.1(0.9-1.3)	
CYP1B1 (R48G)	C/C	837(51)	1711(52)	1.0	0.2
	C/G	659(40)	1305(40)	1.0(0.9-1.2)	
	G/G	144(9)	280(8)	1.1(0.8-1.3)	
CYP1B1 (V432L)	C/C	512(31)	1013(31)	1.0	0.2
	C/G	798(49)	1664(50)	0.9(0.8-1.1)	
	G/G	336(20)	629(19)	1.1(0.9-1.3)	
CYP17	T/T	611(37)	1280(39)	1.0	0.4
	C/T	784(47)	1541(46)	1.1(0.9-1.2)	
	C/C	256(16)	493(15)	1.1(0.9-1.3)	
CYP19 (3'UTR)	T/T	461(28)	883(27)	1	0.6
	C/T	830(51)	1650(50)	0.9(0.8-1.1)	
	C/C	349(21)	758(23)	0.9(0.7-1.0)*	
CYP19 (R264C)	C/C	1534(93)	3075(93)	1.0	0.3
	C/T	111(6)	221(6)	0.1(0.8-1.3)	
	T/T	3(<1)	2(<1)	1.2(0.5-18.0)	
EPHX1	T/T	800(49)	1615(49)	1.0	0.4
	C/T	686(41)	1375(41)	1.0(0.9-1.1)	
	C/C	162(10)	315(10)	1.0(0.8-1.3)	
ERA	T/T	458(28)	917(28)	1.0	0.7
	C/T	826(50)	1633(49)	1.0(0.9-1.2)	
	C/C	360(22)	749(23)	0.9(0.8-1.1)	
PGR (V660L)	G/G	1140(69)	2344(71)	1.0	0.3
	T/G	454(28)	879(27)	1.1(0.9-1.2)	
	T/T	47(3)	71(2)	1.4(0.9-1.9)	

PGR (nt331)	G/G	1472(89)	2944(89)	1.0	0.1
	G/A	117(10)	361(10)	0.9(0.8-1.2)	
	A/A	9(1)	16(1)	1.1(0.5-2.6)	
SHBP (5'UTR)	G/G	925(56)	1848(56)	1.0	0.4
	G/A	602(37)	1246(38)	0.9(0.8-1.1)	
	A/A	118(7)	210(6)	1.1(0.8-1.4)	
SHBP (D356N)	G/G	1294(79)	2591(78)	1.0	0.3
	G/A	329(20)	665(20)	0.9(0.8-1.1)	
	A/A	22(1)	51(2)	0.9(0.5-1.4)	
SOD2	T/T	392(24)	861(26)	1.0	0.7
	C/T	816(49)	1667(50)	1.1(0.9-1.2)	
	C/C	440(27)	786(24)	1.2(1.0-1.5)**	
UGT1A7 (K131R)	AA/AA	645(41)	1335(42)	1.0	0.2
	AA/CG	727(46)	1446(45)	1.0(0.9-1.2)	
	CG/CG	211(13)	430(13)	1.0(0.8-1.2)	
UGT1A7 (W208R)	T/T	609(38)	1219(38)	1.0	0.3
	C/T	745 (47)	1503(46)	0.9(0.9-1.1)	
	C/C	231(15)	503(16)	0.9(0.8-1.1)	

^a OR, relative risk; CI, confidence interval

^b HWE, Hardy-Weinberg equilibrium

^c (ref), reference; **, $p \leq 0.05$ also shown in bold; *, $0.05 < p < 0.1$

TABLE D
ASGAs with BC risk in the discovery set

SNP	Genotype	OR (95%CI) ^a			OR (95%CI)			OR (95%CI)		
		Case	Control	OR (95%CI) ^a	Case	Control	OR (95%CI)	Case	Control	OR (95%CI)
		Young (30-44)			Middle (45-54)			Old (50-69)		
		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
COMT	A/A	106(21)	282(27)	1.0(ref) ^b	160(27)	339(28)	1.0	130(28)	253(27)	1.0
	G/A	272(53)	512(50)	1.4(1.1-1.8)**	289(49)	593(50)	1.0(0.8-1.3)	236(50)	473(50)	0.9(0.7-1.3)
	G/G	131(26)	238(23)	1.5(1.1-2.0)**	145(24)	261(22)	1.2(0.9-1.6)	104(22)	226(23)	0.9(0.6-1.2)
CYP1A1 (3'UTR)	m1/m1	416(81)	801(78)	1.0	478(70)	944(79)	1.0	384(82)	769(80)	1.0
	m1/m2	92(18)	219(21)	0.8(0.6-1.1)	112(19)	239(20)	0.9(0.7-1.2)	82(17)	179(19)	0.9(0.7-1.2)
	m2/m2	3(1)	10(1)	0.6(0.2-2.1)	8(1)	16(1)	0.9(0.4-2.3)	4(1)	12(1)	0.7(0.2-2.1)
CYP1A1 (I462V)	A/A	469(93)	946(92)	1.0	552(92)	1092(91)	1	447(95)	886(93)	1
	G/A	37(7)	82(8)	0.9(0.7-1.3)	42(7)	99(8)	0.8(0.6-1.2)	26(5)	71(7)	0.7(0.4-1.1)
	G/G	0(0)	0(0)	NS ^c	1(<1)	1(<1)	NS	0(0)	0(0)	NS
CYP11B2	T/T	163(32)	306(30)	1.0	183(30)	372(31)	1.0	124(26)	332(35)	1.0
	C/T	272(53)	499(48)	1.0(0.8-1.3)	293(49)	599(50)	0.9(0.8-1.2)	251(52)	460(48)	1.5(1.1-1.9)**
	C/C	79(15)	228(22)	0.6(0.5-0.9)**	125(21)	232(19)	1.1(0.8-1.5)	106(22)	170(17)	1.7(1.2-2.3)**
CYP1B1 (R48G)	C/C	254(50)	498(48)	1.0	328(55)	658(55)	1.0	227(48)	486(51)	1.0
	C/G	206(40)	442(43)	0.9(0.7-1.1)	232(38)	436(36)	1.1(0.8-1.3)	200(42)	390(41)	1.1(0.9-1.4)
	G/G	50(10)	89(9)	1.1(0.8-1.6)	39(7)	109(9)	0.7(0.5-1.0)*	50(10)	78(8)	1.4(0.9-2.0)
CYP1B1 (V432L)	C/C	164(32)	308(30)	1.0	168(28)	360(30)	1.0	163(34)	311(32)	1.0
	C/G	244(48)	548(53)	0.8(0.6-1.1)	304(51)	601(50)	1.1(0.9-1.4)	223(46)	461(48)	0.9(0.7-1.2)
	G/G	104(20)	177(17)	1.1(0.8-1.5)	127(21)	242(20)	1.1(0.8-1.5)	94(20)	188(20)	0.9(0.7-1.3)
CYP17	T/T	203(39)	380(37)	1.0	212(35)	467(39)	1.0	178(37)	384(40)	1.0
	C/T	235(46)	499(48)	0.9(0.7-1.1)	298(50)	545(45)	1.2(0.9-1.5)*	226(47)	449(47)	1.1(0.8-1.4)
	C/C	77(15)	160(15)	0.9(0.6-1.2)	90(15)	190(16)	1.0(0.8-1.4)	77(16)	130(13)	1.3(0.9-1.8)
CYP19 (3'UTR)	T/T	142(28)	267(26)	1.0	181(30)	303(25)	1.0	127(26)	286(30)	1.0
	C/T	254(50)	538(53)	0.9(0.7-1.1)	297(50)	614(52)	0.8(0.6-1.0)*	251(53)	444(46)	1.3(0.9-1.6)*
	C/C	114(22)	220(21)	0.9(0.7-1.3)	119(20)	279(23)	0.7(0.5-0.9)**	101(21)	230(24)	1.0(0.7-1.4)
CYP19 (R264C)	C/C	472(92)	966(93)	1.0	569(94)	1122(93)	1.0	445(93)	888(92)	1.0
	C/T	39(7)	61(6)	1.3(0.9-2.0)	31(5)	79(7)	0.8(0.5-1.2)	35(7)	70(7)	1.0(0.6-1.5)
	T/T	1(<1)	1(<1)	NS	2(<1)	0(0)	NS	0(0)	1(1)	NS

EPHX1	T/T	248(48)	503(49)	1.0	289(48)	596(49)	1.0	234(49)	464(48)	1.0
	C/T	204(40)	437(42)	0.1(0.7-1.2)	250(42)	478(40)	1.1(0.9-1.3)	213(44)	415(44)	1.0(0.8-1.3)
	C/C	62(12)	90(9)	1.4(1.0-2.0)*	62(10)	131(11)	0.9(0.7-1.4)	33(7)	81(8)	0.8(0.5-1.2)
ERA	T/T	150(29)	301(30)	1.0	163(27)	335(28)	1.0	135(28)	256(27)	1.0
	C/T	257(51)	477(46)	1.1(0.8-1.4)	303(51)	596(50)	1.0(0.8-1.3)	235(49)	504(52)	0.9(0.7-1.1)
	C/C	104(20)	252(24)	0.8(0.6-1.1)	135(22)	268(22)	1.0(0.8-1.4)	108(23)	200(21)	1.0(0.7-1.4)
PGR (V660L)	G/G	368(71)	724(71)	1.0	419(70)	870(73)	1.0	319(67)	669(70)	1.0
	T/G	134(26)	275(27)	1.0(0.7-1.2)	159(27)	309(26)	1.1(0.8-1.3)	144(30)	267(28)	1.1(0.9-1.4)
	T/T	13(3)	26(2)	1.0(0.5-1.9)	19(3)	20(1)	2.0(1.0-3.7)**	13(3)	25(2)	1.1(0.5-2.2)
PGR (nt331)	G/G	459(89)	932(89)	1.0	523(86)	1070(88)	1.0	437(90)	844(87)	1.0
	G/A	56(10)	104(10)	1.1(0.8-1.5)	77(13)	129(11)	1.2(0.9-1.6)	42(9)	117(12)	0.7(0.5-1.0)*
	A/A	2(1)	3(1)	1.4(0.2-8.1)	4(1)	8(1)	1.0(0.3-3.4)	3(1)	4(<1)	1.4(0.3-6.5)
SHBP (5UTR)	G/G	292(57)	564(55)	1.0	336(56)	691(58)	1.0	266(56)	538(56)	1.0
	G/A	186(36)	394(38)	0.9(0.7-1.1)	220(37)	446(37)	1.0(0.8-1.2)	179(37)	360(37)	1.0(0.8-1.3)
	A/A	38(7)	71(7)	1.0(0.7-1.6)	41(7)	65(5)	1.3(0.8-1.9)	34(7)	65(7)	1.0(0.7-1.6)
SHBP (D356N)	G/G	407(79)	801(78)	1.0	471(79)	945(79)	1.0	373(78)	754(79)	1.0
	G/A	98(19)	217(21)	0.9(0.7-1.2)	122(20)	235(19)	1.0(0.8-1.3)	99(21)	196(20)	1.0(0.8-1.3)
	A/A	10(2)	13(1)	1.5(0.7-3.5)	5(1)	23(2)	0.4(0.2-1.1)*	6(1)	13(1)	0.9(0.3-2.5)
SOD2	C/C	140(27)	252(24)	1.0	154(26)	320(27)	1.0	113(23)	258(27)	1.0
	C/T	257(50)	517(50)	0.9(0.7-1.1)	285(47)	601(50)	1.0(0.8-1.3)	244(51)	482(50)	1.2(0.9-1.5)
	T/T	116(23)	267(26)	0.8(0.6-1.0)	161(27)	283(23)	1.1(0.9-1.5)	123(26)	224(23)	1.3(0.9-1.7)
UGT1A7 (K131R)	AA/AA	188(38)	439(44)	1.0	226(39)	488(42)	1.0	207(46)	366(39)	1.0
	AA/CG	229(46)	447(44)	1.2(0.9-1.5)	289(49)	524(45)	1.2(0.9-1.5)	188(42)	425(46)	0.8(0.6-1.0)**
	CG/CG	77(16)	122(12)	1.5(1.0-2.0)**	71(12)	155(13)	0.9(0.7-1.4)	56(12)	139(15)	0.7(0.5-1.0)*
UGT1A7 (W208R)	T/T	183(37)	371(37)	1.0	237(41)	435(37)	1.0	167(37)	375(40)	1.0
	C/T	240(48)	467(46)	1.0(0.8-1.3)	266(45)	554(47)	0.9(0.7-1.1)	217(48)	431(46)	1.1(0.9-1.4)
	C/C	75(15)	174(17)	0.9(0.6-1.2)	80(14)	182(16)	0.8(0.6-1.1)	68(15)	130(14)	1.2(0.8-1.7)

a OR, relative risk; CI, confidence interval

b (ref), reference; **, p≤0.05 also shown in bold; *, 0.05<p<0.1

c NS, not sufficient number of samples to analyze this genotype