Review

A Systematic Review Of Genetic Polymorphisms and Breast Cancer Risk[1]

Alison M. Dunning,[2] Catherine S. Healey,[2] Paul D. P. Pharoah,[2,3] M. Dawn Teare,[2] Bruce A. J. Ponder, and Douglas F. Easton

Cancer Research Campaign Human Cancer Genetics Group, University Department of Oncology [A. M. D., C. S. H., P. D. P. P., B. A. J. P.], and Cancer Research Campaign Genetic Epidemiology Group, University Department of Community Medicine [M. D. T., D. F. E.], Strangeways Research Laboratories, Worts Causeway, Cambridge CB1 8RN, United Kingdom

Abstract

Studies investigating the relationship between common genetic variants and cancer risk are being reported with rapidly increasing frequency. We have identified 46 published case-control studies that have examined the effect of common alleles of 18 different genes on breast cancer risk. Of these, 12 report statistically significant associations, none of which were reported by more than one study. However, many of the studies were small: 10 of the 46 had 80% power or greater to detect a rare allele homozygote relative risk <2.5. We therefore combined the results of individual studies to obtain more precise estimates of risk. Statistically significant differences in genotype frequencies were found in three case-control comparisons of unselected cases. These were for *CYP19* $(TTTA)_n$ polymorphism [$(TTTA)_{10}$ carrier odds ratio (OR) = 2.33; $P = 0.002$], the *GSTP1* Ile105Val polymorphism (Val carrier OR = 1.60; $P = 0.02$), and the *TP53* Arg72Pro polymorphism (Pro carrier OR = 1.27; $P = 0.03$). In addition, the *GSTM1* gene deletion was found to be significantly associated with postmenopausal breast cancer (null homozygote OR = 1.33; $P = 0.04$). There was also some evidence that homozygotes for the *PR* PROGINS allele are protected against breast cancer, although this result was of borderline statistical significance. For polymorphisms in *BRCA1, COMT, CYP17, CYP1A1, NAT1,* and *NAT2,* the best estimate of risk either from the individual studies or the meta-analyses was sufficiently precise to exclude a relative risk of 1.5 or greater. For the polymorphisms in *EDH17B2, ER, CYP2D6, CYP2E1, GSTT1, HSP70,* and *TNFα,* the risk estimates, although nonsignificant, were insufficiently precise to exclude a moderate risk (>1.5). Precise estimation of the risks associated with these and other as yet untested genes, as well as investigation of more complex risks arising from gene-gene and gene-environment interactions, will require much larger studies.

Introduction

Breast cancer is a common disease in Western societies, with a lifetime prevalence of 1 in 12 in the United Kingdom (1) and 1 in 8 in the USA (2). Although 10–15% of breast cancer cases have some family history of the disease, only 5% can be explained by rare, highly penetrant mutations in genes such as *BRCA1* and *BRCA2* (3) First-degree relatives of breast cancer patients have a 2-fold increase in risk over the general population (4), most of which cannot be accounted for by *BRCA1/2* (5). Although some of the familial risk may be due to shared environment, there may be other common, low-penetrance genetic variants which alter predisposition to breast cancer.

A frequently used experimental design for identifying common low-penetrance alleles is the association study (6). In this design, polymorphic genotype frequencies are compared between groups with different phenotypes. The aim is to study polymorphisms that may either be causally related to disease risk or are in strong linkage disequilibrium with disease-causing variants. Phenotypes investigated can be either continuously variable, such as serum lipid levels, or discrete, such as disease cases *versus* matched controls, in which instance the study design is a classic case-control study. The simplest polymorphisms to use are biallelic, which most commonly arise from a SNP,[4] and give rise to three different genotype classes: the common allele homozygote, the heterozygote, and the rare allele homozygote. Multiallelic, repeat length polymorphisms (microsatellites), such as the $(TTTA)_n$ polymorphism in *CYP19*, can also be used, but these usually give rise to many genotypes. Genotypes often are grouped to simplify analysis, but this is valid only if a rational grouping strategy can be applied. Furthermore, the higher mutation rate in microsatellites is likely to lead to weaker associations unless the polymorphism itself is functional (*e.g.*, the androgen receptor polyglutamine tract and prostate cancer risk). Genetic association studies using populations are more powerful than linkage studies within pedigrees for identifying low-penetrance alleles, which by definition may not be expressed in multiple members of a single family (7). However, at present, association studies can be carried out only on candidate genes.

There are a variety of ways of presenting gene polymorphism data in relation to breast cancer risk, depending on the nature of the polymorphism. In the case of simple biallelic polymorphisms, allele frequencies in cases and controls can be

Received 12/3/98; revised 6/22/99; accepted 7/12/99.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] This work was supported by the Cancer Research Campaign (CRC). B. A. J. P. is a Gibb Fellow of the Cancer Research Campaign.
[2] These authors contributed equally to this study.
[3] To whom requests for reprints should be addressed, at CRC Human Cancer Genetics Group, University Department of Oncology, Strangeways Research Laboratories, Worts Causeway, Cambridge CB1 8RN, UK.

[4] The abbreviations used are: SNP, single nucleotide polymorphism; OR, odds ratio; COMT, catechol-*O*-methyltransferase; GST, glutathione-*S*-transferase; NAT, *N*-acetyl transferase; UTR, untranslated region.

Table 1 Genetic polymorphisms investigated in relation to breast cancer risk

Gene	Base change	Amino acid change	Detection method	Functional effect
Steroid hormone metabolism genes				
COMT	Exon 4 G → A	Val158Met	Creates *Hsp*92II and *Nla*III sites	Reduced activity
CYP17	Promoter T → C (T1931C)	None	Creates *Msp*AI site	Creates a fifth *Sp1* site and might increase transcription
CYP19	Intron 4 $(TTTA)_u$ microsatellite	None	PCR fragment size	Unlikely
	Intron 4 TCT insertion/deletion	None	PCR fragment size	Unlikely
CYP2D6	2367delA (*A* allele)	Frameshift	Creates *Bsi*WI site	Nonfunctioning enzyme
	Intron 3 G → A (G1934A) (*B* allele)	Premature stop at residue 544	Destroys *Bst*NI site	Nonfunctioning enzyme
	Del Lys281 (*C* allele)		Allele-specific amplification	Catalytically normal enzyme, but wrong cellular compartment
	17.5-kb deletion (*D* allele)		Southern blot	No enzyme
EDH17B2	Exon 6 A → G	Ser312Gly	Creates *Bsp*UI site	Unlikely
ER	CCC325CCG	Pro325Pro	Allele-specific oligohybridization	None
	Intron 1/exon 2 *Xba*I site		Southern blot	Unlikely
PR	Alu repeat insertion in intron G	None	PCR fragment size or creates *Taq*I site	Unlikely
Carcinogen metabolism genes				
CYP1A1	Exon 7 A → G (A4889G)	Ile462Val	Creates *Nco*I site	Uncertain, possible increase in enzyme activity
	3′ UTR T → C (T6235C)	None	Creates *Msp*I site	None
	Exon 7 C → A (C4887A)	Thr461Asp	Creates *Bsa*I site	Unknown
	3′ UTR T → C (T5639C)	None	Creates *Msp*I site	None
CYP2E1	Intron 6 unspecified	None	Creates *Dra*I site	Unlikely
GSTM1	Gene deletion		Allele-specific PCR	Null individuals have no enzyme
GSTP1	A313G	Ile105Val	Creates *Alu*26I site	Reduced enzyme activity
GSTT1	Gene deletion		Allele-specific PCR	Null individuals have no enzyme activity
NAT1	A1088T	None		Possible increase in enzyme activity
NAT2	G191A		Creates *Msp*I site	Low activity allele
	C481T		Destroys *Kpn*I site	Low activity allele
	G590A		Destroys *Taq*I site	Low activity allele
	G857A		Destroys *Bam*H1 site	Low activity allele
Other genes				
BRCA1	C2731T	Pro871Leu	Allele-specific oligohybridization	Unknown
BRCA1	G1186A	Gln356Arg	Creates *Rsa*I site	Unknown
HSP70-2	1267	Silent	Creates *Pst*I site	Unknown
HSP70-hom	2437	Met493Thr	Creates *Nco*I site	Unknown
TNF-α	-308 G → A	None	Allele-specific PCR	Increased constitutive and inducible levels TNF-α
TP53	Exon 3 G → C	Arg72Pro	Allele-specific PCR	Unknown
	16-bp insertion in intron 3	None		Unlikely
	Intron 6 G → A	None	Creates *Msp*I site	Unlikely

compared using the χ^2 test to ascertain statistical significance. However, this method does not produce an easily interpretable measure of the magnitude of breast cancer risk and also lacks statistical power compared with some alternatives. A more appropriate method is to compare genotype frequencies of the three possible genotypes among cases and controls. The relative risk of breast cancer for each genotype is then estimated by the OR. The baseline group is usually the common allele homozygote, which by definition has an OR (and relative risk) of 1. Depending on the allele frequencies, the number of rare allele homozygotes may be very small, particularly in small studies, and the associated OR will have a wide confidence interval. Under these circumstances, it is common to combine the heterozygotes and rare-allele homozygotes and calculate the rare allele carrier OR. However, this risk estimate is valid only if the genetic model is dominant, an assumption that should not be made without appropriate evidence. For multiallelic polymorphisms, it is common to group alleles together and analyze the data in the same way as for a biallelic polymorphism.

The first low-penetrance breast cancer susceptibility locus identified by the association approach was the *HRAS1* minisatellite (8). This has more than 30 alleles, of which 4 are common, whereas the rest, which have a combined frequency of ~0.06, are classified as "rare." These rare alleles have been found to be associated with a 1.9-fold increased relative risk of breast cancer (and increased risk of other cancers) and are estimated to account for 9% of all breast cancer incidence. However, the molecular mechanism underlying this association remains unclear. The *HRAS1* locus has been reviewed extensively (8, 9) and so will not be considered further here.

Association studies have also been performed on other genes with putative involvement in breast cancer susceptibility. The candidate genes studies thus far can be divided into three main groups: genes for proteins with roles in steroid hormone metabolism; genes coding for carcinogen metabolism enzymes; and common alleles of genes that have been identified through family studies such as *TP53* and *BRCA1*. The candidate gene polymorphisms reviewed here are listed in Table 1.

Steroid Hormone Metabolism Genes. Several factors alter exposure to endogenous hormones, and many of these, such as age at menarche, age at first pregnancy, number of pregnancies, and age at menopause, alter breast cancer risk (10). Hence, genes involved in the metabolism of sex hormones are strong

candidates for breast cancer susceptibility genes. Those in the sex hormone biosynthesis pathway may affect production of, and thus exposure to, the most active estrogen; estradiol. Genes in this pathway include *CYP17*, *CYP19*, and the gene for 17β-hydroxysteroid dehydrogenase type 2.

The bioavailability of hormones is partially controlled by catabolism, and catechol estrogens (2 hydroxy-estrogens) are the major breakdown products of estrogens. COMT is a phase II enzyme that methylates catechol-estrogens during their conjugation and inactivation. It has two forms: one membrane-bound and the other cytosolic; both are expressed in breast tissue and share a polymorphism associated with differences in methylation activity.

The sex hormones control the activation of responsive genes by first binding to specific receptors and forming complexes that can in turn bind to sequences in the promoters of downstream, hormone-responsive genes. Thus, steroid hormone receptor genes, such as *ER*, *PR*, and *AR*, are candidates for breast cancer susceptibility genes.

Carcinogen Metabolism Genes. Several enzymes have evolved for the detoxification of xenobiotic compounds, and their gene expression is induced in response to the presence of the compound (*e.g.,* polycyclic aromatic hydrocarbons found in tobacco smoke). The actions of phase I and phase II enzymes render susceptible compounds more soluble and more readily excreted and ought to reduce cancer risk. However, the more soluble products of some compounds are even more potent carcinogens than the less soluble form. Hence, a genetic change that increases the expression of the gene or the activity of the protein produced may increase the amount of reactive carcinogen formed and, thus, increase the risk of cancer.

Two phase I enzymes, CYP1A1 and CYP2D6, are induced by, and act on, carcinogens found in tobacco smoke. Both have polymorphic differences in either inducibility or activity. CYP2E1, an enzyme that metabolizes ethanol, is also a candidate because epidemiological studies suggest that breast cancer risk is increased with alcohol consumption (11).

The GST family are phase II enzymes that detoxify carcinogens and their reactive intermediates, such as those produced by *CYP1A1*, by facilitating their conjugation to glutathione and subsequent excretion. For both *GSTM1* and *GSTT1* [reviewed by Rebbeck (12)], a high percentage of the Caucasian population are homozygous for null alleles (up to 60 and 20%, respectively) and have no detoxifying GST activity. Levels of DNA adducts, sister-chromatid-exchange, and somatic genetic mutations may be increased in carriers of *GSTM1* and *GSTT1* null genotypes (12).

The *N*-acetyl transferases, NAT1 and NAT2, are also phase II enzymes, and they participate in the detoxification of the arylamines, some of the main carcinogenic components of tobacco smoke, and also the amines produced during the cooking of meat (13, 14). However, the action of NATs on these carcinogens can produce electrophilic ions that may induce point mutations in DNA. Polymorphism in both genes results in two phenotypes: slow acetylators who are homozygous for low-activity alleles, and fast acetylators who carry one or more high-activity alleles.

Common Alleles of High-Penetrance Genes. Mutations in the *TP53* and *BRCA1* genes are associated with a high lifetime risk of breast and other cancers (15, 16). *TP53* is a tumor suppressor gene whose protein is produced in response to DNA damage through radiation or genotoxic agents, resulting in cell cycle arrest in G_1 and induction of pathways leading to DNA repair or apoptosis. Mutation in the *TP53* gene results in decreased p53 activity, which may lead to failure of cells with DNA damage to arrest and thus to continue to replicate with damaged DNA. In the case of *BRCA1*, where the protein function is still uncertain, the majority of confirmed mutations generate truncated proteins that are likely to have severely reduced activity. It has been hypothesized that amino acid substitutions outside the major functional domains may confer more moderate breast cancer risks. The majority of these substitutions are rare (17), and putative functional effects remain unconfirmed. However, it has been possible to test empirically the risks associated with the common polymorphisms.

Some of the genes discussed above have been assessed in multiple studies, whereas attempts to replicate the findings of other studies have yet to be reported. Here we have attempted to identify all of the published reports. Because most of these are based on small sample sizes, we have combined the results where possible in meta-analyses to obtain more precise estimates of risk. We discuss the implications of these findings and highlight areas where further work could be carried out profitably.

Materials and Methods

Literature Search. Published studies were identified using the Medline (National Library of Medicine, Washington DC) and BIDS databases for 1983–July 1998, using the search terms "breast-neoplasms" and "polymorphism(s)." We also searched for studies on each specific candidate gene: for example, for *CYP17* the terms "CYP17" and "breast neoplasm" were used. In addition, the bibliographies of studies identified by the electronic searches were hand searched. Eligible studies were those that compared genotypic or allele frequencies of candidate genes in a series of breast cancer cases with a series of non-breast cancer controls using genomic DNA. Studies in which tumor DNA was used from cases with genomic DNA from controls were excluded. Studies of *HRAS* alleles and breast cancer risk were also excluded because these have been reviewed extensively by other authors (8, 9).

Meta-analysis. Whenever possible, raw data from comparable studies were analyzed jointly, using likelihood methods. Analyses were based on logistic regression and were carried out using the program S Plus. Each study was treated as a separate stratum, and the (control) allele or carrier frequencies in each study were permitted to be distinct, enabling studies with very different population frequencies to be considered jointly. For those metabolic polymorphisms associated with a specific phenotype, the principal analyses combined genotypes by phenotype classes (for example, poor metabolizer, slow acetylator). For all other polymorphisms, ORs were compared for each genotype. Genotype-specific ORs were estimated assuming that the genotype frequencies in controls were consistent with Hardy-Weinberg equilibrium (18). Likelihood ratio tests (with degrees of freedom equal to number of genotypes $-$ 1) were then used to test whether the ORs differed significantly from 1. If significant evidence of an association was found, a test for heterogeneity was performed. Ninety-five percent confidence intervals were calculated by direct examination of the likelihood surface. Joint analysis by subgroup (*e.g.,* menopausal status) could only be performed if studies reported results for each subgroup. Specific analysis considering confounding factors such as age was not possible because raw data were not available.

Table 2 Description of association studies of genetic polymorphisms and breast cancer risk

Authors	Country	Cases			Controls			Ethnic group	Comments	Genes studied
		n	Source	Age (years)	*n*	Source	Age (years)			
Agundez *et al.* 1995 (19)	Spain	160	NS[a]	26–87	132	NS	19–81	White Spanish		*NAT2*
Ambrosone *et al.* 1995 (20)	USA	177	P	Post-men	233	P	Post-men			*CYP1A1*
Ambrosone *et al.* 1996 (21)	USA	119	H	Pre-men	114	P	Pre-men	NS		*NAT2*
		185	H	Post-men	213	P	Post-men			
Andersen *et al.* 1994 (22)	Norway	191	H	27–94	204	P	NS	NS	Various sources of male and female controls used	*ER*
Bailey *et al.* 1998 (23)	USA	164	H	NS	162	NS	NS	Caucasian	Controls matched on age	*CYP1A1, GSTM1*
		59	H	NS	59	NS	NS	African-American		*GSTT1*
Buchert *et al.* 1993 (24)	USA	167	H	29–80	114	H	25–61	Caucasian		*CYP2D6*
Campbell *et al.* 1996 (25)	UK	208	NS	NS	113	NS	NS	NS		*P53*
Charrier *et al.* 1999 (26)	France	361	P	26–80	437	P	18–101	Caucasian		*GSTM1*
Chouchane *et al.* 1997 (27)	Tunisia	40	H	Mean = 43	106	P	Mean = 39		Controls were healthy blood donors	*TNF-α, HSp-70*
Dunning *et al.* 1997 (28)	UK	212	H	<70	277	P	45–70	Caucasian	East-Anglian case-control series	*BRCA1*
		268	P	<36					UK case-control study	
		321	P	36–45	353	P	36–45		UK case-control study	
Dunning *et al.* 1998 (29)	UK	835	P	<55	591	P	45–75	>90% Caucasian		*CYP17*
Feigelson *et al.* 1997 (30)	USA	174	P	45–75	285	P	45–75	Asian, Latino, African American	Nested case-control study	*CYP17*
Garrett *et al.* 1995 (31)	Ireland	187	NS	NS	90	NS	NS	NS		*PR*
Haiman *et al.* 1999 (32)	USA	464	P	NS	619	P	NS	Caucasian	Nested case-control study within the Nurses' Health Study	*CYP19*
Harries *et al.* 1997 (33)	Scotland	62	H	37–82	155	H	NS	Caucasian		*GSTP1*
Helzlsouer *et al.* 1998 (34)	USA	110	P	Mean = 60	113	P	Mean = 60	NS	Nested case-control study, controls matched for age, race, and menopausal status	*GSTM1, GSTP1, GSTT1*
Helzlsouer *et al.* 1998 (35)										*COMT*
Lavigne *et al.* 1997 (39)										*CYP17*
Hunter *et al.* 1997 (40)	USA	466	P	Mean = 61	466	P	Mean = 61	NS	Nested case-control study using incident cases from the Nurses' Health Study. Controls matched on age, menopausal status, and postmenopausal hormone use	*NAT2, CYP1A1*
Ishibe *et al.* 1998 (41)										
Huober *et al.* 1991 (36)	Germany	108	H	20–80	123	H	20–80	NS	Phenotype study. Controls were patients with benign breast disease	*CYP2D6*
Iwase *et al.* 1996 (42)	UK	70	H	NS	30	NS	NS	NS		*ER*
Kawajiri *et al.* 1993 (43)	Japan	93	H	NS	347	NS	NS	Japanese		*p53*
Kelsey *et al.* 1997 (44)	USA	245	P	NS	245	P	NS	>95% Caucasian	Prevalent cases	*GSTM1*
		240	P		240	P			Incident cases	
									Nested case-control study within Nurses' Health Study. Controls matched on age and menopausal status	
Kristensen *et al.* 1998 (37)	Norway/ Sweden	366	H	27–93	252	PH	1–85	NS	172 controls from Norwegian population register; 80 Swedish controls from genetic counseling clinic	*CYP19*
Ladero *et al.* 1991 (45)	Spain	98	H	Mean = 59	446	NS	Mean = 25	NS	Phenotype study	*CYP2D6*
Ladona *et al.* 1996 (46)	Spain	187	H	26–87	151	NS	18–83	White Spanish		*CYP2D6*
Lancaster *et al.* 1998 (38)	USA	68	H	NS	101	H	NS	NS		*PR*

Table 2 Continued

Authors	Country	Cases			Controls			Ethnic group	Comments	Genes studied
		n	Source	Age (years)	*n*	Source	Age (years)			
Mannermaa *et al.* 1994 (47)	Finland	149	H	NS	161	NS	NS	Caucasian	Sporadic breast cancer	*EDH17B2*
	UK	41			29	NS	NS	Caucasian	Familial breast cancer (3 case families)	
Manolitsas *et al.* 1997 (48)	UK	292	NS	NS	220	NS	NS	NS		*PR*
Mavridou *et al.* 1998 (49)	UK	224	NS	NS	254	NS	NS	NS		*TP53*
Millikan *et al.* 1998 (51)	USA	654	P	20–70+	642	P	20–70+	Caucasian, African-American		*COMT*
Millikan *et al.* 1998 (50)	USA	498	P	20–70+	473	P	20–70+	Caucasian, African-American		*NAT1, NAT2*
Peller *et al.* 1995 (52)	Israel	20	H	NS	38	NS	NS	NS		*TP53*
Pontin *et al.* 1998 (53)	UK	129	H	Mean = 56	79	H	Mean = 42	NS	Phenotype study	*CYP2D6*
Siegelmann-Danieli *et al.* 1999 (55)	USA	348	H	27–79	145	H	27–79	Caucasian		*CYP19*
Shields *et al.* 1996 (54)	USA	106	P	Pre-men	113	P	Pre-men	Caucasian		*CYP2E1*
		166	P	Post-men	221	P	Post-men			
Sjalander *et al.* 1996 (56)	Sweden	212	HP	NS	689	P	NS	White Swedish	Nested case-control study with additional 35 cases from hospital series	*TP53*
Smith *et al.* 1992 (57)	UK	437	NS	NS	720	Various	NS	Caucasian		*CYP2D6*
Southey *et al.* 1998 (58)	Australia	388	P	<40	294	P	<40	NS	Age-matched controls	*ER*
Taioli *et al.* 1995 (59)	USA	51	H	20–69	269	P	29–70	Caucasian, African-American	Cases identified from a cohort of women attending screening clinic	*CYP1A1*
Thompson *et al.* 1998 (60)	USA	141	P	Pre-men	134	P	Pre-men	NS		*COMT*
		140		Post-men	155		Post-men			
Wang-Gohrke *et al.* 1998 (61)	Germany	107	H	Mean = 55	305	H	Mean = 36			*TP53*
Weston *et al.* 1998 (62)	USA	123	H	NS	240	H	NS	Caucasian, Hispanic, African-American		*CYP17*
Zheng *et al.* 1999 (63)	USA	154	P	55–69	330	P	55–69	Caucasian	Nested case-control study in Iowa Womens Health Study	*NAT1*
Zhong *et al.* 1993 (64)	UK	197	H	NS	225	PH	NS	NS		*GSTM1*

[a] NS, not stated; P, population; Post-men, postmenopausal; H, hospital; Pre-men, premenopausal; PH, population and hospital.

Results

We identified 46 eligible studies (19–64), which are listed in Table 2. Although the basic study designs were all the same, a wide variety of sources of both cases and controls were used. Most reported studies were quite small: the median number of cases and controls combined was 391 (range, 58–1431).

The results of the individual studies are given in Table 3, which shows the relative risk of breast cancer associated with the different polymorphisms as estimated by the OR and 95% confidence interval. To present these data in a coherent and easily comparable manner, we have given the genotypic risks. If these were not reported by individual studies, wherever possible, we have estimated the appropriate ORs and confidence intervals from the published raw data.

Although 18 genes have been studied, few investigators have reported significant risks, and where significant results have been reported, these have often not been confirmed by other studies of the same polymorphism. The associations that have been reported as significant by at least one study are discussed below.

Steroid Hormone Metabolism Genes. The *COMT* Val158 Met polymorphism has been investigated in three studies. Thompson *et al.* (60), found a significantly increased risk of premenopausal breast cancer in $COMT^{\text{Met carrier}}$ women, with a nonsignificantly reduced risk of postmenopausal cancer. However, an earlier study had reported the opposite (although nonsignificant) effects for the same genotype, *i.e.*, a reduced risk of premenopausal cancer and an increased risk of postmenopausal breast cancer (39), and a third study found no effect in unselected cases (51). Conflicting results have also been reported in four studies of the 1931T→C polymorphism in the *CYP17* promoter. Fiegelson *et al.* (30) found an increased risk of breast cancer for the $CYP17^{C}$ carrier in a subgroup analysis of 40 advanced cases, a finding not confirmed in three other studies (29, 35, 62). A possible role for *CYP19* in breast cancer has been suggested by Haiman *et al.* (32) and Kristensen *et al.* (37) reported an increased risk for carriers of the $(TTTA)_{12}$ alleles; however, another group reported a statistically significant inverse association for this allele (55), and our own unpublished data have failed to confirm a significant risk (65). Haiman *et al.* also found a significantly increased risk for carriers of the rare $(TTTA)_{10}$ allele (32), but again this finding has not been confirmed by others (55, 65). Of two studies of the estrogen receptor gene polymorphism, CCC325CCG, one found a significantly elevated risk for the G carrier (42), but a subsequent, larger study failed to confirm this result (58).

Carcinogen Metabolism Genes. One or more of four different polymorphisms in *CYP1A1* have been assessed in four different studies, two of which have investigated the role of these polymorphisms in Caucasians and African Americans separately. The only significant result reported was in the study of Taioli

Table 3 Genetic risks of breast cancer by gene and study

Gene/polymorphism	Case details	"Rare" allele frequency in controls[a]	Risk group	OR	95% CI[b]	Comments
Steroid hormone metabolism genes						
COMT Val158Met						
Lavigne *et al.* 1997 (39)	All cases	0.52	*Val/Met* het	1.30	0.69–3.07	ORs adjusted for age
			Met/Met hom	1.45	0.66–2.58	
	Pre-men cases		*Val/Met* het	0.57	0.14–2.40	
			Met/Met hom	0.24	0.04–1.51	
	Post-men cases		*Val/Met* het	1.70	0.77–3.75	
			Met/Met hom	2.18	0.93–5.1	
Thompson *et al.* 1998 (60)	Pre-men cases	0.43	*Val/Met* het	**2.5**	**1.4–4.6**[c]	ORs adjusted for age and education
			Met/Met hom	1.7	0.8–3.4	
			Met carrier	**2.2**	**1.3–3.7**	
	Post-men cases	0.54	*Val/Met* het	0.7	0.4–1.2	
			Met/Met hom	**0.4**	**0.2–0.8**	
			Met carrier	0.6	0.3–1.0	
Millikan *et al.* 1998 (51)	All cases	0.35	*Val/Met* het	0.8	0.5–1.2	ORs adjusted for age and reproductive factors
			Met/Met hom	0.8	0.4–1.5	
CYP17 promoter T → C						
Feigelson *et al.* 1997 (30)	All cases	0.41	*C* carrier	1.32	0.87–2.00	
	Advanced cases		*C* carrier	**2.52**	**1.07–5.94**	
Dunning *et al.* 1998 (29)	All cases	0.38	*CC* hom	1.17	0.92–1.49	
			C carrier	1.10	0.89–1.37	
	Advanced cases		*C* carrier	0.88	0.38–2.01	
Helzlsouer *et al.* 1998 (35)	All cases	0.42	*CC* hom	0.89	0.41–1.95	
			C carrier	0.81	0.45–1.46	
	Advanced cases		*CC* hom	1.39	0.26–7.28	
			C carrier	1.06	0.32–3.58	
Weston *et al.* 1998 (62)	All cases	0.38	*CC* hom	1.16	0.58–2.32	
			C carrier	1.08	0.69–1.69	
	Aggressive disease		*C* carrier	0.9	0.4–2.0	
CYP19 $(TTTA)_n$						
Healey *et al.* 1999 (65)		0.021	$(TTTA)_{12}$ carrier	1.19	0.68–2.08	
Kristensen *et al.* 1998 (37)		0.016	$(TTTA)_{12}$ carrier	**2.42**	**1.03–5.90**	
Siegelmann-Danieli *et al.* 1999 (55)		0.016	$(TTTA)_{12}$ carrier	0.29	0.12–0.69	
Haiman *et al.* 1999 (32)		0.020	$(TTTA)_{12}$ carrier	1.76	0.99–3.14	Carrier frequency estimated from published allele frequency
Healey *et al.* 1999 (65)		0.008	$(TTTA)_{10}$ carrier	1.56	0.59–4.57	
Siegelmann-Danieli *et al.* 1999 (55)		0.018	$(TTTA)_{10}$ carrier	1.07	0.35–3.91	
Haiman *et al.* 1999 (32)		0.005	$(TTTA)_{10}$ carrier	**4.84**	**1.87–14.8**	Carrier frequency estimated from published allele frequency
EDH17B2 Ser312Gly						
Mannermaa *et al.* 1994 (47)	Sporadic cases	0.47	*Ser/Gly*	0.62	0.36–1.07	
			Gly/Gly	0.85	0.43–1.70	
			Gly carrier	0.68	0.40–1.14	
	Familial cases		*Ser/Gly*	0.44	0.11–1.62	
			Gly/Gly	1.02	0.19–5.49	
			Gly carrier	0.56	0.15–1.91	
*ER Xba*I RFLP						
Andersen *et al.* 1994 (22)		0.68	Hom	2.02	0.96–4.31	
			Het	2.00	0.92–4.37	
			*Xba*I carrier	2.01	0.98–4.17	
ER CCC325CCG						
Iwase *et al.* 1996 (42)		0.133	*G* allele carriers	**2.91**	**1.05–8.28**	No G homozygotes in controls
Southey *et al.* 1998 (58)		0.209	*CG* het	1.09	0.79–1.50	
			GG hom	1.59	0.70–3.63	
			G allele carrier	1.13	0.77–1.50	
PR PROGINS						
Garrett *et al.* 1995 (31)		0.18	*T1/T2*	1.55	0.86–2.82	
			T2/T2	0.40	0.06–2.49	
			T2 carrier	1.39	0.79–2.45	
Manolitsas *et al.* 1997 (48)		0.14	*T2* carrier OR	0.77	0.50–1.18	
Lancaster *et al.* 1998 (38)		0.13	*T2* carrier OR	0.90	0.38–2.09	
Carcinogen metabolism genes						
CYP1A1 Ile462Val						
Ambrosone *et al.* 1995 (20)	Post-men cases	0.077	*Ile/Val* het	1.53	0.88–2.66	
			Val/Val hom	2.85	0.49–16.56	

Table 3 Continued

Gene/polymorphism	Case details	"Rare" allele frequency in controls[a]	Risk group	OR	95% CI[b]	Comments
Taioli *et al.* 1995 (59)	All cases	0.091	*Ile/Val* het	1.1	0.3–4.0	No *Val/Val* homozygous cases
Ishibe *et al.* 1998 (41)	All cases	NS	*Val* carrier	0.88	0.58–1.33	Multivariate-adjusted OR
Bailey *et al.* 1998 (23)	All Caucasian	0.037	*Ile/Val* het	1.26	0.57–2.78	No *Val/Val* homozygotes
CYP1A1 3′ UTR T6235C						
Taioli *et al.* 1995 (59)	Caucasian	0.115	*TC* het	1.7	0.6–4.9	
	African-American	0.218	*TC* het	2.4	0.7–7.7	
			CC hom	**9.7**	**2.0–47.9**	
Ishibe *et al.* 1998 (41)	All cases	NS	*C* carrier	1.05	0.74–1.50	Multivariate-adjusted OR
Bailey *et al.* 1998 (23)	Caucasian	0.096	*TC* het	1.49	0.81–2.74	
			CC hom	0.84	0.22–3.19	
	African-American	0.247	*TC* het	0.51	0.23–1.13	
			CC hom	0.52	0.08–3.32	
CYP1A1 3′ UTR T5639C						
Taioli *et al.* 1995 (59)	African American	0.081	*TC* het	1.2	0.3–5.3	No *CC* homozygotes
Bailey *et al.* 1998 (23)	African-American	0.119	*TC* het	0.75	0.31–1.83	No *CC* homozygotes
CYP1A1 Thr461Asp						
Bailey *et al.* 1998 (23)	Caucasian	0.043	*Thr/Asp* het	0.81	0.34–1.94	
			Asp/Asp hom	0.97	0.06–15.71	
CYP2D6 poor metabolizer						
Buchert *et al.* 1993 (24)	All cases	0.061	Poor metabolizer	1.18	0.42–3.45	Tested for *A*, *B*, and *D* alleles
	Pre-men	0.12		1.54	0.35–7.66	Poor metabolizer = low-activity allele
	Post-men			0.61	0.12–4.11	homozygote or compound heterozygote
Smith *et al.* 1992 (57)	All cases	0.043	Poor metabolizer	0.90	0.47–1.71	Tested for *A*, *B*, and *D* alleles
Huober *et al.* 1991 (36)	All cases	0.073[d]	Poor metabolizer	1.73	0.66–4.63	Phenotype study
Ladona *et al.* 1996 (46)	All cases	0.040[d]	Poor metabolizer	0.66	0.16–2.69	Tested for *A*, *B*, and *C* alleles
Pontin *et al.* 1998 (53)	All cases	0.062[d]	Poor metabolizer	1.70	0.63–4.67	Phenotype study
Ladero *et al.* 1991 (45)	All cases	0.052[d]	Poor metabolizer	2.09	0.97–4.48	Phenotype study
CYP2E1						
Shields *et al.* 1996 (54)	Pre-men	0.09	*C* carrier	1.04	0.48–2.24	
	Post-men	0.07	*C* carrier	1.01	0.55–1.84	
GSTM1 deletion						
Zhong *et al.* 1993 (64)	All cases	0.418[e]	Null	1.27	0.87–1.87	
Ambrosone *et al.* 1995 (20)	Post-men cases	0.502[e]	Null	1.10	0.73–1.64	Adjusted for age, age at menarche/first pregnancy/menopause, BMI, and family history
Kelsey *et al.* 1997 (44)	Prevalent cases	0.51	Null	1.30	0.91–1.86	Null cases associated with improved
	Incident cases	0.48	Null	1.08	0.74–1.57	survival
Bailey *et al.* 1998 (23)	Caucasian	0.383[e]	Null	0.77	0.50–1.20	
	African-American	0.407[e]		0.75	0.35–1.58	
Helzlsouer *et al.* 1998 (34)	All cases	0.464[e]	Null	**2.10**	**1.22–3.64**	Adjusted for age and menopausal status
	Pre-men cases			1.0	0.28–3.45	
	Post-men cases			**2.50**	**1.34–4.65**	
Charrier *et al.* 1999 (26)	All cases	0.51	Null	1.19	0.90–1.59	
	<50 years			0.97	0.69–1.35	
	≥50 years			**1.99**	**1.19–3.32**	
GSTT1 deletion						
Helzlsouer *et al.* 1998 (34)	All	0.214[e]	Null	1.50	0.76–2.95	Adjusted for age and menopausal status
	Pre-men			1.50	0.42–5.32	
	Post-men			1.50	0.67–3.34	
Bailey *et al.* 1998 (23)	Caucasian	0.272[e]	Null	1.08	0.66–1.75	
	African-American	0.288[e]		0.63	0.27–1.47	
GSTP1 Ile105Val						
Helzlsouer *et al.* 1998 (34)	All	0.29	*Ile/Val* het	1.48	0.81–2.73	Adjusted for age and menopausal status
	Pre-men			1.98	0.44–8.81	
	Post-men			1.33	0.68–2.61	
	All		*Val/Val* hom	1.97	0.77–5.02	
	Pre-men			0.54	0.04–6.67	
	Post-men			2.71	0.91–8.03	
Harries *et al.* 1997 (33)	All	0.28	*Ile/Val* het	1.53	0.83–2.84	
			Val/Val hom	1.58	0.49–5.06	
NAT1 A1088T						
Millikan *et al.* 1998 (50)	Pre-men cases	0.47	*T* carrier	1.2	0.8–1.8	
	Post-men cases	0.46	*T* carrier	1.0	0.7–1.5	
Zheng *et al.* 1999 (63)		0.17	*T* carrier	1.18	0.77–1.81	

Table 3 Continued

Gene/polymorphism	Case details	"Rare" allele frequency in controls[a]	Risk group	OR	95% CI[b]	Comments
NAT2						
Agundez *et al.* 1995 (19)		0.51[f]	Rapid acetylator	2.23	0.96–5.16	Baseline group = very rapid acetylator (wt/wt)
			Slow acetylator	2.08	0.92–4.69	Rapid acetylator (wt/variant)
						Slow acetylator (variant/variant)
Ambrosone *et al.* 1996 (21)	Pre-men cases	0.57[f]	Slow acetylator	0.9	0.7–2.0	Baseline group = rapid acetylator
	Post-men cases	0.53[f]	Slow acetylator	1.3	0.8–1.9	
Hunter *et al.* 1997 (40)	All cases	0.62[f]	Slow acetylator	0.9	0.7–1.2	Multivariate OR, baseline group = rapid acetylator
Millikan *et al.* 1998 (50)	Pre-men cases	0.51[f]	Slow acetylator	1.1	0.7–1.6	Baseline group = rapid acetylator
Other genes	Post-men cases	0.52[f]	Slow acetylator	0.7	0.5–1.0	
BRCA1 Pro871Leu						
Dunning *et al.* 1997 (28)		0.316	*Pro/Leu*	1.15	0.92–1.44	
			Leu/Leu	1.24	0.85–1.79	
BRCA1 Gln356Arg						
Dunning *et al.* 1997 (28)		0.070	*Glu/Arg*	0.88	0.63–1.23	No *Arg/Arg* cases
TP53 intron 3 16-bp insertion						
Campbell *et al.* 1996 (25)	All cases	0.16	*A1/A2* het	0.80	0.45–1.43	*A2* allele defined as presence of duplication
			A2/A2 hom	0.51	0.07–3.90	
Sjalander *et al.* 1996 (56)	All cases	0.132	*A1/A2* het	1.07	0.73–1.58	*A2* allele defined as presence of duplication
			A2/A2 hom	0.54	0.10–1.90	
Wang-Gohrke *et al.* 1998 (61)		0.12	*A1/A2* het	1.38	0.81–2.34	*A2* allele defined as presence of duplication
			A2/A2 hom	2.08	0.24–15.6	
TP53 intron 6 G → A						
Peller *et al.* 1995 (52)		0.558	*GA* het	2.17	0.62–7.66	
Sjalander *et al.* 1996 (56)		0.129	*GA* het	1.06	0.71–1.57	
			AA hom	0.73	0.18–2.25	
Mavridou *et al.* 1998 (49)		0.098	*GA* het	1.05	0.63–1.74	
			AA hom	0.28	0.01–2.90	
Wang-Gohrke *et al.* 1998 (61)		0.11	*GA* het	1.67	0.97–2.85	
			AA hom	1.08	0.02–13.6	
TP53 Arg72Pro						
Kawajiri *et al.* 1993 (43)		0.35	*Arg/Pro*	1.20	0.73–2.00	
			Pro/Pro	0.51	0.15–1.44	
			Pro carrier	1.07	0.66–1.76	
Sjalander *et al.* 1996 (56)		0.272	*Arg/Pro*	**1.45**	**1.03–2.04**	
			Pro/Pro	1.55	0.92–2.62	
			Pro carrier	**1.47**	**1.08–2.00**	
Wang-Gohrke *et al.* 1998 (61)		0.26	*Arg/Pro*	1.17	0.72–1.90	
			Pro/Pro	0.71	0.20–2.06	
			Pro carrier	1.10	0.69–1.75	
HSP70-hom						
Chouchane *et al.* 1997 (27)		0.41	*N1/N2*	**3.56**	**1.13–11.3**	No *N2/N2* controls
HSP70-2						
Chouchane *et al.* 1997 (27)		0.04	*P1/P2*	1.74	0.52–7.57	
			P2/P2	**27.5**	**3.47–308**	
			P2 carrier	2.36	0.72–10.0	
TNF-α 308T → A						
Chouchane *et al.* 1997 (27)	BrCa	0.17	*TA* het	**3.49**	**1.52–8.80**	
			AA hom	4.80	0.06–382	
			A carrier	**3.53**	**1.55–8.11**	

[a] For genes, frequency of each allele is close to 0.5, frequency of putative risk allele is given.
[b] CI, confidence interval; het, heterozygote; hom, homozygote; Pre-men, premenopausal; Post-men, postmenopausal; NS, not stated; BMI, body mass index.
[c] ORs in bold indicate statistically significant results.
[d] Low-activity allele carrier/poor metabolizer phenotype frequency.
[e] Null genotype frequency.
[f] Slow acetylator phenotype frequency.

et al. (59), who found an increased breast cancer risk for African-American women who were CC homozygote for the 3′UTR T→C (T6235C). In contrast, the other study of African-American women found a nonsignificantly reduced breast cancer risk associated with this genotype (23). Of five studies of the *GSTM1* gene deletion, only one found that null individuals were at significantly increased risk (34), and in subgroup analysis, this effect was restricted to postmenopausal breast cancer. Charrier *et al.* (26) also found a significantly increased risk of breast cancer in the subgroup of patients diagnosed over the age of 50.

Other Genes. A significant effect of the Arg72Pro polymorphism in *TP53* has been reported by Sjalander *et al.* (56), who found that $TP53^{Arg/Pro}$ heterozygotes were at increased risk, as

Table 4 Results of joint analysis

Gene/polymorphism	Cases	Studies combined	Risk group	H_1 vs H_0		OR	95% CI[a]	
				χ^2 (*df*)	*P*			
COMT Val158Met	All cases	(39, 51, 60)	*Val/Met*	2.14 (2)	0.34	0.88	0.75–1.05	
			Met/Met			0.86	0.67–1.09	
COMT Val158Met	Pre-men	(39, 60)	*Val/Met*	0.25 (2)	0.88	0.96	0.76–1.23	
			Met/Met			0.91	0.63–1.31	
COMT Val158Met	Post-men	(39, 60)	*Val/Met*	2.69 (2)	0.26	0.83	0.66–1.04	
			Val/Val			0.82	0.59–1.13	
CYP17 promoter T → C	All cases	(29, 30, 35, 62)	*C* carrier	1.28 (1)	0.26	1.10	0.93–1.30	
CYP17 promoter T → C	Advanced cases	(29, 30, 35, 62)	*C* carrier	1.48 (1)	0.22	1.28	0.86–1.91	
CYP19 $(TTTA)_n$	All cases	(32, 37, 55, 65)	$(TTTA)_{12}$ carrier	1.98 (1)	0.16	1.26	0.91–1.74	
CYP19 $(TTTA)_n$	All cases	(32, 55, 65)	$(TTTA)_{10}$ carrier	9.62 (1)	0.002	2.33	1.36–4.17	Evidence for heterogeneity (χ^2 = 5.34; *P* = 0.069)
ER CCC325CCG	All cases	(42, 58)	*CG*	4.74 (2)	0.09	1.34	1.02–1.76	
			GG			1.25	0.68–2.23	
			G carriers	2.29 (1)		1.25	0.94–1.68	
PR PROGINS	All cases	(31, 38, 48)	*T1/T2*	4.97 (2)	0.08	0.97	0.73–1.28	
			T2/T2			0.41	0.15–0.95	
CYP1A1 Ile462Val	All cases	(23, 41, 59)	*Val* carrier	0.14 (1)	0.71	0.94	0.68–1.30	*Val/Val* homozygotes rare
CYP1A1 3′ UTR T6235C	All Caucasian	(23, 41, 59)	*C* carrier	1.71 (1)	0.19	1.20	0.91–1.58	*CC* homozygotes rare
CYP1A1 3′ UTR T6235C	All African-American	(23, 59)	*TC* het	1.30 (2)	0.52	0.97	0.54–1.73	
			CC hom			1.72	0.56–4.69	
CYP2D6	All cases	(24, 36, 45, 46, 53, 57)	Poor metabolizer		0.08	1.36	0.96–1.91	
GSTM1 deletion	All cases	(23, 34, 44, 64)	Null	2.66 (1)	0.10	1.14	0.97–1.35	
GSTM1 deletion	Pre-men	(26, 34)	Null	0.05 (1)	0.83	0.96	0.70–1.34	
GSTM1 deletion	Post-men	(20, 26, 34)	Null	4.11 (1)	0.04	1.33	1.01–1.76	Evidence for heterogeneity (χ^2 = 6.21, 2 *df*; *P* = 0.045)
GST1 deletion	All Caucasian	(23, 34)	Null	0.75 (1)	0.39	1.18	0.81–1.73	
GSTP1 Ile105Val	All cases	(33, 34)	*Ile/Val*	6.52 (2)	0.04	1.61	1.10–2.34	No evidence for heterogeneity
			Val/Val			1.83	0.95–4.48	(χ^2 = 0.16; *P* = 0.69)
			Val carrier	5.42 (1)	0.02	1.60	1.08–2.39	No evidence for heterogeneity (χ^2 = 0.03; *P* = 0.86)
NAT1	All cases	(50, 63)	*T* carrier	0.24 (1)	0.63	1.07	0.82–1.39	
NAT2	All cases	(19, 21, 40, 50)	Slow acetylator	0.15 (1)	0.70	0.97	0.84–1.13	
NAT2	Pre-men case	(21, 50)	Slow acetylator	0.085 (1)	0.77	1.05	0.78–1.40	
NAT2	Post-men cases	(21, 50)	Slow acetylator	0.61 (1)	0.44	0.90	0.69–1.17	
TP53 Arg72Pro	All cases	(43, 56, 61)	*Arg/Pro*	4.64 (2)	0.10	1.23	1.02–1.58	
			Pro/Pro			1.12	0.74–1.65	
			Pro carrier	4.52 (1)	0.03	1.27	1.02–1.59	
TP53 intron 6 A → G		(49, 52, 56, 61)	*AG*	1.95 (2)	0.38	1.16	0.91–1.47	
			AA			0.84	0.32–1.79	
TP53 intron 16-bp insertion		(43, 56, 61)	*A1/A2*	0.16 (2)	0.92	1.02	0.79–1.31	
			A2/A2			0.89	0.39–1.79	

[a] CI, confidence interval; Pre-men, premenopausal; Post-men, postmenopausal; het, heterozygote; hom, homozygote.

were $TP53^{Pro}$ carriers. Pro homozygotes were also at increased risk, although the confidence intervals were wide and the effect was not statistically significant. Two other studies of the same polymorphism had found no significant effect (43, 61). The genes *HSP-70* and *TNF-α* have been investigated by one group, which found significantly increased risk for rare allele carriers of both genes (see Table 3). However, this study was small, and their results have not been confirmed or refuted by other groups.

Meta-analysis. Comparable data from more than one study that could be combined were available for 25 different combinations of polymorphism and patient subgroups. The results of these analyses are given in Table 4. Statistically significant differences in genotype frequencies were found in three case-control comparisons of unselected cases. These were for *CYP19* $(TTTA)_n$ polymorphism [$(TTTA)_{10}$ carrier OR = 2.33; *P* = 0.002], the *GSTP1* Ile105Val polymorphism (Val carrier OR = 1.60; *P* = 0.02), and the *TP53* Arg72Pro (Pro carrier OR = 1.27; *P* = 0.03). In addition, the *GSTM1* gene deletion was found to be significant in postmenopausal breast cancer (null homozygote OR = 1.33; *P* = 0.04). There was also some evidence that homozygotes for the *PR* PROGINS allele are protected against breast cancer, although this result was of borderline statistical significance.

Gene-Environment Interaction. Although there is little epidemiological evidence that cigarette smoking is associated with breast cancer, studies have assessed the possible interaction between polymorphisms in the genes that encode carcinogen-metabolizing enzymes, *CYP1A1*, *NAT2*, *CYP2E1*, and *GSTM1*, with smoking (20, 21, 40, 41, 44, 50, 54). None of these studies found an overall increase in breast cancer risk with the variant genotypes, but some reported interactions with smoking. Ambrosone *et al.* (20) found an increase in risk in "light" smokers who carried the Val462 allele. In contrast, Ishibe *et al.* (41) found no interaction with the Ile462Val polymorphism but did find an increased risk in current smokers who were C carriers of the T6235C polymorphism. For NAT2, Ambrosone *et al.*

(21) found an association between smoking >15 cigarettes per day and risk that was limited to slow acetylators, but two subsequent larger studies found that cigarette smoking was not appreciably associated with breast cancer among either fast or slow acetylators (40, 50). *CYP2E1* genotype and smoking has been investigated in one study (54), which found a risk of premenopausal breast cancer in smokers who were also carriers of the *Dra*I cutting site in intron 6. However, this result was only statistically significant after adjustment for other risk factors, and the confidence intervals were wide. A lack of interaction between *GSTM1* genotype and cigarette smoking has been reported by Kelsey *et al.* (44).

Lavigne *et al.* (39) looked for interactions between the Val158 Met polymorphism in the *COMT* gene and several factors including family history, menopausal status, smoking, alcohol, oral contraceptive use, and hormone replacement therapy. Helzlsouer *et al.* (34) also explored the possibility of interactions between *GSTM1*, *GSTP1*, and *GSTT1* genotypes with family history, hormone replacement therapy, cigarette smoking, alcohol consumption, and body mass index. Although no overall effect was found in either study, both reported interactions with menopausal status and body mass index, and Helzlsouer *et al.* (34) additionally noted an interaction between *GSTT1* and alcohol consumption. However, no studies attempting to confirm these quite complex interactions have yet been published.

Gene-Gene Interaction. The possibility of gene-gene interactions have rarely been explored. One small study carried out genotyping in three genes: *CYP1A1*, *GSTM1*, and *GSTT1* (23). No interaction between these genes was found. The studies of Helzlsouer *et al.* (34) on the GST genes and Lavigne *et al.* (39) on *COMT* were carried out on the same populations. The increased relative risk of postmenopausal breast cancer for $GSTM1^{Null}$ and $GSTP1^{Ile/Val}$/$GSTP1^{Val/Val}$ women of around 2 was found to be increased to a 3–4-fold increased risk if they were also $COMT^{Met/Met}$. Again, no confirmatory studies have yet been published.

Discussion

We have found a substantial number of reports of studies that have investigated candidate genes for low-penetrance breast cancer susceptibility alleles. Despite this research effort, there is no clear evidence that any of these polymorphisms are strongly associated with breast cancer risk. Of the individual studies, few of the reported associations have been statistically significant, and no significant association has been reported by more than one study. In some cases, this might be due to a lack of statistical power in individual studies. Even among the significant associations, the magnitude of the effect found is rarely greater than 2.5-fold increased risk. If the rare allele frequency is 0.2, 315 cases and 315 controls would be required to detect this magnitude of risk for a rare allele homozygote with 90% power at the 5% significance level: 10 of the 46 studies reported were larger than this.

We have attempted to reduce this lack of power by combining results in meta-analyses, but even the results of these need to be interpreted with some caution. Of the 25 associations tested in at least two studies, 4 were significant at the 5% level. One of these was significant only in a subgroup of cases (postmenopausal) and was not significant overall. Such subgroup-specific associations must always be treated with caution given that there is no clear *a priori* reason to suspect a subgroup effect. Moreover, only one of the associations has a significance levels of <1%. Given the number of polymorphisms being tested, a significance level of 10^{-4} or smaller would be required to provide strong evidence.

In any systematic review, a major cause for concern is the potential for publication bias. The most common scenario is the nonpublication of negative studies (*i.e.,* those finding no significant association), resulting in bias of any meta-analysis away from the null. We cannot exclude this possibility for the three polymorphisms with significant results in the meta-analyses. For the polymorphisms for which we have found no evidence for an association between genotype and breast cancer risk, it is possible, but unlikely, that bias toward the null has occurred. There is an urgent need for databases into which the results of all association studies (positive and negative) with candidate genes can be entered to minimize the effects of publication bias.

Consistency of reporting added further complications to the meta-analysis; many studies do not describe the ethnicity of their study populations; therefore, we have combined samples on the assumption that any variant studied will have the same effect in all populations. This assumption may only be valid if the variant studied is truly functional with respect to breast cancer risk. If the variant is simply a neutral marker for some other functional variant, the assumption may be invalid because linkage disequilibrium relationships often differ between populations. In addition, there is no consensus nomenclature for SNPs: early reports often described the restriction enzyme site involved, but there are instances of multiple polymorphisms detected by the same restriction enzyme within a single gene (*e.g.,* there are two polymorphisms creating *Msp*I sites in *CYP1A1*). More recent studies usually identify the base substitution, but in introns and UTRs of genes, this can also be arbitrary. In Table 1, we presented the SNP and its general position (*e.g.,* exon 3, intron 6, 3′UTR) for clarity, but workers will need to refer to the original articles for sufficient detail to replicate the DNA assays. The requirement for public databases of SNPs has recently been recognized (66), and it is hoped these will then provide a standardized description. Furthermore, methodological difficulties have been caused by genes having several different polymorphisms in linkage disequilibrium with one another. For example, *CYP1A1* has two SNPs in strong linkage disequilibrium with one another; these are the exon 7 Ile462Val and the 3′UTR T→C (T6253C) SNPs. Both have been shown to be significantly associated with risk of some neoplasms (although not breast cancer), but combining them in a meta-analysis would require a somewhat more complicated analytical approach.

Several studies have reported on putative gene-gene and gene-environment interactions. The results of these analyses should, however, be treated with caution. The problem of *post hoc* subgroup analyses and multiple hypothesis testing renders the interpretation of positive results difficult. Negative results also should be treated with caution because few studies will have had sufficient power to detect moderate interaction effects. For example, 1500 cases and 1500 controls would be required to detect an interaction between two genotypes each with a frequency of 0.1 and a relative risk of 1.1 but with a relative risk of 2.5 when combined. These analyses should, therefore, be treated as hypothesis generating rather than hypothesis testing.

Despite these concerns, we believe some firm conclusions can be drawn. For several polymorphisms, the best estimate of risk either from the individual studies or the combined meta-analyses is sufficiently precise to exclude a relative risk of 1.5. These include the polymorphisms in *BRCA1*, *COMT*, *CYP17*, *CYP1A1*, *NAT1*, and *NAT2*. This does not necessarily imply

that a negligible fraction of breast cancer incidence is attributable to such genes. For example, the upper confidence interval for the *CYP17* effect (1.39) would still correspond to a population-attributable fraction of ~20%. We have, however, concluded that these polymorphisms contribute little to the familial aggregation of breast cancer: the same effect would correspond to a relative risk to siblings of cases of ~1.01 [for details of calculation, see Easton (67)], whereas epidemiological studies have found the relative risk to be ~2-fold.

For other polymorphisms, the risk estimates, although nonsignificant, are insufficiently precise to exclude a moderate risk (>1.5), and larger studies are needed to obtain more precise risk estimates. These include polymorphisms in *EDH17B2*, *ER*, *CYP2D6*, *CYP2E1*, *GSTT1*, *HSP70*, *PR*, and *TNFα*. Finally, the polymorphisms in *CYP19*, *GSTM1*, *GSTP1*, and *TP53* appear to be stronger candidates for low-penetrance breast cancer susceptibility genes, although they too need to be confirmed in larger studies. It is more likely, however, that the majority in variation in susceptibility to breast cancer is due to genes that have yet to be identified or tested. Candidate genes include those involved in DNA repair and micro- and macronutrient metabolism. In addition, gene-gene and gene-environment interactions may be important determinants of breast cancer risk. Such interactions would produce substantially increased risks in individuals with the right combination of factors, but large studies would be required to elucidate these effects. Further work is clearly needed to address these issues, but these studies will need to be substantially larger than the association studies published to date.

Acknowledgments

We thank Katie Blyth (Department of Pathology, University of Cambridge) for help in obtaining references.

References

1. Pharoah, P. D. P., and Mackay, J. Absolute risk of breast cancer in women at increased risk: a more useful clinical measure than relative risk? Breast, *7:* 255–259, 1998.

2. National Cancer Institute. SEER Cancer Statistics Review, 1973–1995. Bethesda, MD: National Cancer Institute, 1999.

3. Newman, B., Austin, M. A., and Lee, M. Inheritance of human breast cancer: evidence for autosomal dominant transmission in high risk families. Proc. Natl. Acad. Sci. USA, *85:* 3044–3048, 1988.

4. Pharoah, P. D. P., Day, N. E., Duffy, S., Easton, D. F., and Ponder, B. A. J. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int. J. Cancer, *71:* 800–809, 1997.

5. Peto, J., Easton, D. F., Matthews, F. E., Ford, D., and Swerdlow, A. J. Cancer mortality in relatives of women with breast cancer: the OPCS study. Int. J. Cancer, *65:* 273–283, 1996.

6. Khoury, M. J. Genetic epidemiology. *In:* K. Rothman and S. Greenland (eds.), Modern Epidemiology, pp. 609–622. New York: Lippincott-Raven, 1997.

7. Risch, N., and Merikangas, K. The future of genetic studies of complex diseases. Science (Washington DC) *273:* 1516–1517, 1996.

8. Krontiris, T. G., Devlin, B., Karp, D. D., Robert, N. J., and Risch, N. An association between the risk of cancer and mutations in the *HRAS1* minisatellite locus. N. Engl. J. Med., *329:* 517–523, 1993.

9. Weston, A., and Godbold, J. H. Polymorphisms of H-*ras*-1 and *p53* in breast cancer and lung cancer: a meta-analysis. Environ. Health Perspect., *105* (Suppl 4)*:* 919–926, 1997.

10. Kelsey, J. L., Gammon, M. D., and John, E. M. Reproductive factors and breast cancer. Epidemiol. Rev., *15:* 36–47, 1993.

11. Hunter, D. J., and Willett, W. C. Nutrition and breast cancer. Cancer Causes & Control, *7:* 56–68, 1996.

12. Rebbeck, T. R. Molecular epidemiology of the human glutathione *S*-transferase genotypes *GSTM1* and *GSTT1* in cancer susceptibility. Cancer. Epidemiol., Biomarkers & Prev., *6:* 733–743, 1997.

13. Hein, D. W., Doll, M. A., Rustan, T. D., Gray, K., Feng, Y., Ferguson, R. J., and Grant, D. M. Metabolic activation and deactivation of arylamine carcinogens by recombinant human NAT1 and polymorphic NAT2 acetyltransferases. Carcinogenesis (Lond.), *14:* 1633–1638, 1993.

14. Badawi, A. F., Hirvonen, A., Bell, D. A., Lang, N. P., and Kadlubar, F. F. Role of aromatic amine acetyltransferases, NAT1 and NAT2, in carcinogen-DNA adduct formation in the human urinary bladder. Cancer Res., *55:* 5230–5237, 1995.

15. Shattuck-Eidens, D., McClure, M., Simard, J., Labrie, F., Narod, S., Couch, F., Hoskins, K., Weber, B., Castilla, L., and Erdos, M. A collaborative survey of 80 mutations in the *BRCA1* breast and ovarian cancer susceptibility gene. Implications for presymptomatic testing and screening. JAMA, *273:* 535–541, 1995.

16. Børresen, A. L., Andersen, T. I., Garber, J., Barbier-Piraux, N., Thorlacius, S., Eyfjörd, J., Ottestad, L., Smith-Sørensen, B., Hovig, E., Malkin, D., and Freind, S. H. Screening for germ line *TP53* mutations in breast cancer patients. Cancer Res., *52:* 3234–3236, 1992.

17. Friend, S., Børresen, A. L., Brody, L., Casey, G., Devilee, P., Gayther, S., Goldgar, D., Murphy, P., Weber, B. L., and Wiseman, R. Breast cancer information on the web. Nat. Genet., *11:* 238–239, 1995.

18. Lathrop, G. Estimating genotype relative risks. Tissue Antigens, *22:* 160–166, 1983.

19. Agundez, J. A. G., Ladero, J. M., Olivera, M., Roman, J. M., and Benitez, J. Genetic analysis of the arylamine *N*-acetyl transferase polymorphism in breast cancer patients. Oncology, *52:* 7–11, 1995.

20. Ambrosone, C. B., Freudenheim, J. L., Graham, S., Marshall, J. R., Vena, J. E., Brasure, J. R., Laughlin, R., Nemoto, T., Michalek, A. M., Harrington, A., Ford, T. D., and Shields, P. G. Cytochrome P4501A1 and glutathione *S*-transferase (*M1*) polymorphisms and postmenopausal breast cancer risk. Cancer Res., *55:* 3483–3485, 1995.

21. Ambrosone, C. B., Freudenheim, J. L., Graham, S., Marshall, J. R., Vena, J. E., Brasure, J. R., Michalek, A. M., Laughlin, R., Nemoto, T., Gillenwater, K. A., and Shields, P. G. Cigarette smoking, *N*-acetyltransferase 2 genetic polymorphisms, and breast cancer risk. JAMA, *276:* 1494–1501, 1996.

22. Andersen, T. I., Heimdal, K. R., Skrede, M., Tveit, K., Berg, K., and Børresen, A. L. Oestrogen receptor (*ESR*) polymorphisms and breast cancer susceptibility. Hum. Genet., *94:* 665–670, 1994.

23. Bailey, L. R., Roodi, N., Verrier, C. S., Yee, C. J., Dupont, W. D., and Parl, F. F. Breast cancer and *CYPIA1*, *GSTM1*, and *GSTT1* polymorphisms: evidence of a lack of association in Caucasians and African Americans. Cancer Res., *58:* 65–70, 1998.

24. Buchert, E. T., Woosley, R. L., Swain, S. M., Oliver, S. J., Coughlin, S. S., Pickle, L., Trock, B., and Riegel, A. T. Relationship of *CYP2D6* (debrisoquine hydroxylase) genotype to breast cancer susceptibility. Pharmacogenetics, *3:* 322–327, 1993.

25. Campbell, I. G., Eccles, D. M., Dunn, B., Davis, M., and Leake, V. p53 polymorphism in ovarian and breast cancer. Lancet, *347:* 393–394, 1996.

26. Charrier, J., Maugard, C. M., Le Mevel, B., and Bignon, Y. J. Allelotype influence at glutathione *S*-transferase *M1* locus on breast cancer susceptibility. Br. J. Cancer, *79:* 346–353, 1999.

27. Chouchane, L., Ahmed, S. B., Baccouche, S., and Remadi, S. Polymorphism in the tumor necrosis factor-α promotor region and in the heat shock protein 70 genes associated with malignant tumors. Cancer (Phila.), *80:* 1489–1496, 1997.

28. Dunning, A. M., Chiano, M., Smith, N. R., Dearden, J., Gore, M., Oakes, S., Wilson, C., Stratton, M., Peto, J., Easton, D., Clayton, D., and Ponder, B. A. Common *BRCA1* variants and susceptibility to breast and ovarian cancer in the general population. Hum. Mol. Genet., *6:* 285–289, 1997.

29. Dunning, A. M., Healey, C. S., Pharoah, P. D. P., Foster, N., Easton, D. F., Day, N. E., and Ponder, B. A. J. Polymorphism in the steroid metabolism gene *CYP17* and risk of breast cancer. Br. J. Cancer, *77:* 2045–2047, 1998.

30. Feigelson, H. S., Coetzee, G. A., Kolonel, L. N., Ross, R. K., and Henderson, B. E. A polymorphism in the *CYP17* gene increases the risk of breast cancer. Cancer Res., *57:* 1063–1065, 1997.

31. Garrett, E., Rowe, S. M., Coughlan, S. J., Horan, R., McLinden, J., Carney, D. N., Fanning, M., Kieback, D. G., and Headon, D. R. Mendelian inheritance of a *Taq*I restriction fragment length polymorphism due to an insertion in the human progesterone receptor gene and its allelic imbalance in breast cancer. Cancer Res. Ther. Control, *4:* 217–222, 1995.

32. Haiman, C. A., Hankinson, S. E., Speizer, F. E., and Hunter, D. J. A tetranucleotide repeat polymorphism in *CYP19* and breast cancer risk. Proc. Am. Assoc. Cancer Res., *40:* 194, 1999.

33. Harries, L. W., Stubbins, M. J., Forman, D., Howard, G. C. W., and Wolf, C. R. Identification of genetic polymorphisms at the glutathione *S*-transferase *Pi* locus and association with susceptibility to bladder, testicular and prostate cancer. Carcinogenesis (Lond.), *18:* 641–644, 1997.

34. Helzlsouer, K. J., Selmin, O., Huang, H-Y., Strickland, P. T., Hoffman, S., Alberg, A. J., Watson, M., Comstock, G. W., and Bell, D. Association between glutathione *S*-transferase *M1*, *P1*, and *T1* genetic polymorphisms and development of breast cancer. J. Natl. Cancer Inst., *90:* 512–518, 1998.

35. Helzlsouer, K. J., Huang, H-Y., Strickland, P. T., Hoffman, S., Alberg, A. J., Comstock, G. W., and Bell, D. A. Association between *CYP17* polymorphism and the development of breast cancer. Cancer Epidemiol., Biomarkers & Prev., *7:* 945–949, 1998.

36. Huober, J., Bertram, B., Petru, E., Kaufmann, M., and Schmahl, D. Metabolism of debrisoquine and susceptibility to breast cancer. Breast Cancer Res. Treat., *18:* 43–48, 1991.

37. Kristensen, V. N., Andersen, T. I., Lindblom, A., Erikstein, B., Magnus, P., and Børresen-Dale, A. L. A rare *CYP19* (aromatase) variant may increase the risk of breast cancer. Pharmacogenetics, *8:* 43–48, 1998.

38. Lancaster, J. M., Berchuck, A., Carney, M. E., Wiseman, R., and Taylor, J. A. Re: "Progesterone receptor gene polymorphism and risk for breast and ovarian cancer." Br. J. Cancer, *78:* 277, 1998.

39. Lavigne, J. A., Helzlsouer, K. J., Huang, H-Y., Strickland, P. T., Bell, D. A., Selmin, O., Watson, M. A., Hoffman, S., Comstock, G. W., and Yager, J. D. An association between the allele coding for a low activity variant of catechol-*O*-methyltransferase and the risk for breast cancer. Cancer Res., *57:* 5493–5497, 1997.

40. Hunter, D. J., Hankinson, S. E., Hough, H., Gertig, D. M., Garcia Closas, M., Spiegelman, D., Manson, J. E., Colditz, G. A., Willett, W. C., Speizer, F. E., and Kelsey, K. A prospective study of *NAT2* acetylation genotype, cigarette smoking, and risk of breast cancer. Carcinogenesis (Lond.), *18:* 2127–2132, 1997.

41. Ishibe, N., Hankinson, S. E., Colditz, G. A., Spiegelman, D., Willett, W. C., Speizer, F. E., Kelsey, K. T., and Hunter, D. J. Cigarette smoking, cytochrome P450 1A1 polymorphisms, and breast cancer risk in the Nurses' Health Study. Cancer Res., *58:* 667–671, 1998.

42. Iwase, H., Greenman, J. M., Barnes, D. M., Hodgson, S., Bobrow, L., and Mathew, C. G. Sequence variants of the estrogen receptor (*ER*) gene found in breast cancer patients with ER negative and progesterone receptor positive tumors. Cancer Lett., *108:* 179–184, 1996.

43. Kawajiri, K., Nakachi, K., Imai, K., Watanabe, J., and Hayashi, S. Germ line polymorphisms of *p53* and *CYP1A1* genes involved in human lung cancer. Carcinogenesis (Lond.), *14:* 1085–1089, 1993.

44. Kelsey, K. T., Hankinson, S. E., Colditz, G. A., Springer, K., Garcia-Closas, M., Spiegelman, D., Manson, J. E., Garland, M., Stampfer, M. J., Willett, W. C., Speizer, F. E., and Hunter, D. J. Glutathione *S*-transferase class μ deletion polymorphism and breast cancer: results from prevalent versus incident cases. Cancer Epidemiol., Biomarkers & Prev., *6:* 511–515, 1997.

45. Ladero, J. M., Benitez, J., Jara, C., Llerena, A., Valdivielso, M. J., Munoz, J. J., and Vargas, E. Polymorphic oxidation of debrisoquine in women with breast cancer. Oncology, *48:* 107–110, 1991.

46. Ladona, M. G., Abildua, R. E., Ladero, J. M., Roman, J. M., Plaza, M. A., Agundez, J. A., Munoz, J. J., and Benitez, J. *CYP2D6* genotypes in Spanish women with breast cancer. Cancer Lett., *99:* 23–28, 1996.

47. Mannermaa, A., Peltoketo, H., Winqvist, R., Ponder, B. A. J., Kiviniemi, H., Easton, D. F., Poutanen, M., Isomaa, V., and Vihko, R. Human familial and sporadic breast cancer: analysis of the coding regions of the 17β-hydroxysteroid dehydrogenase 2 gene (*EDH17B2*) using a single-strand conformation polymorphism assay. Hum. Genet., *93:* 319–324, 1994.

48. Manolitsas, T. P., Englefield, P., Eccles, D. M., and Campbell, I. G. Re: "No association of a 306-bp insertion polymorphism in the progesterone receptor gene with ovarian and breast cancer." Br. J. Cancer, *75:* 1398–1399, 1997.

49. Mavridou, D., Gornall, R., Campbell, I. G., and Eccles, D. M. *TP53* intron 6 polymorphism and the risk of ovarian and breast cancer. Br. J. Cancer, *77:* 676–677, 1998.

50. Millikan, R. C., Pittman, G. S., Newman, B., Tse, C. K., Selmin, O., Rockhill, B., Savitz, D., Moorman, P. G., and Bell, D. A. Cigarette smoking, *N*-acetyltransferases 1 and 2, and breast cancer risk. Cancer Epidemiol., Biomarkers & Prev., *7:* 371–378, 1998.

51. Millikan, R. C., Pittman, G. S., Tse, C. K., Duell, E., Newman, B., Savitz, D., Moorman, P. G., Boissy, R. J., and Bell, D. A. Catechol-*O*-methyltransferase and breast cancer risk. Carcinogenesis (Lond.), *19:* 1943–1947, 1998.

52. Peller, S., Kopilova, Y., Slutzki, S., Halevy, A., Kvitko, K., and Rotter, V. A novel polymorphism in intron 6 of the human *p53* gene: a possible association with cancer predisposition and susceptibility. DNA Cell Biol., *14:* 983–990, 1995.

53. Pontin, J. E., Hamed, H., Fentiman, I. S., and Idle, J. R. Cytochrome p450dbl phenotypes in malignant and benign breast disease. Eur. J. Cancer, *26:* 790–792, 1998.

54. Shields, P. G., Ambrosone, C. B., Graham, S., Bowman, E. D., Harrington, A. M., Gillenwater, K. A., Marshall, J. R., Vena, J. E., Laughlin, R., Nemoto, T., and Freudenheim, J. L. A cytochrome P4502E1 genetic polymorphism and tobacco smoking in breast cancer. Mol. Carcinog., *17:* 144–150, 1996.

55. Siegelmann-Danieli, N., and Buetow, K. H. Constitutional genetic variation at the human aromatase gene (*Cyp19*) and breast cancer risk. Br. J. Cancer, *79:* 456–463, 1999.

56. Sjalander, A., Birgander, R., Hallmans, G., Cajander, S., Lenner, P., Athlin, L., Beckman, G., and Beckman, L. *p53* polymorphisms and haplotypes in breast cancer. Carcinogenesis (Lond.), *17:* 1313–1316, 1996.

57. Smith, C. A., Moss, J. E., Gough, A. C., Spurr, N. K., and Wolf, C. R. Molecular genetic analysis of the cytochrome P450-debrisoquine hydroxylase locus and association with cancer susceptibility. Environ. Health Perspect., *98:* 107–112, 1992.

58. Southey, M. C., Batten, L. E., McCredie, M. R. E., Giles, G. C., Dite, G., Hopper, J. L., and Venter, D. J. Estrogen receptor polymorphism at codon 325 and risk of breast cancer in women before age forty. J. Natl. Cancer Inst., *90:* 533–536, 1998.

59. Taioli, E., Trachman, J., Chen, X., Toniolo, P., and Garte, S. J. A *CYP1A1* restriction fragment length polymorphism is associated with breast cancer in African-American women. Cancer Res., *55:* 3757–3758, 1995.

60. Thompson, P. A., Shields, P. G., Fruedenheim, J. L., Stone, A., Vena, J. E., Marshall, J. R., Graham, S., Laughlin, R., Nemoto, T., Kadlubar, F. F., and Ambrosone, C. B. Genetic polymorphisms in catechol-*O*-methyltransferase, menopausal status and breast cancer risk. Cancer Res., *58:* 2107–2110, 1998.

61. Wang-Gohrke, S., Rebbeck, T. R., Besenfelder, W., Kreienberg, R., and Runnebaum, I. B. *p53* germline polymorphisms are associated with an increased risk for breast cancer in German women. Anticancer Res., *18:* 2095–2099, 1998.

62. Weston, A., Pan, C-F., Bleiweiss, I. J., Ksieski, H. B., Roy, N., Maloney, N., and Wolff, M. S. *CYP17* genotype and breast cancer risk. Cancer Epidemiol., Biomarkers & Prev., *7:* 941–944, 1998.

63. Zheng, W., Deitz, A. C., Campbell, D. R., Wen, W. Q., Cerhan, J. R., Sellers, T. A., Folsom, A. R., and Hein, D. W. *N*-acetyltransferase 1 genetic polymorphism, cigarette smoking, well-done meat intake, and breast cancer risk. Cancer Epidemiol., Biomarkers & Prev., *8:* 233–239, 1999.

64. Zhong, S., Wyllie, A. H., Barnes, D., Wolf, C. R., and Spurr, N. K. Relationship between the *GSTM1* genetic polymorphism and susceptibility to bladder, breast and colon cancer. Carcinogenesis (Lond.), *14:* 1821–1824, 1993.

65. Healey, C. S., Dunning, A. M., Durocher, F., Teare, D., Easton, D. F., and Ponder, B. A. J. Polymorphisms in the human aromatase cytochrome P450 gene (*CYP19*) and breast cancer risk. Carcinogenesis (Lond.), in press, 1999.

66. Collins, F. S., Guyer, M. S., and Charkravarti, A. Variations on a theme: cataloging human DNA sequence variation. Science (Washington DC), *278:* 1580–1581, 1997.

67. Easton, D. F. Cancer risks in A-T heterozygotes. Int. J. Radiat. Biol., *66:* S177–S182, 1994.

A Systematic Review Of Genetic Polymorphisms and Breast Cancer Risk

Alison M. Dunning, Catherine S. Healey, Paul D. P. Pharoah, et al.

Cancer Epidemiol Biomarkers Prev 1999;8:843-854.