

REVIEW ARTICLE

Genes other than *BRCA1* and *BRCA2* involved in breast cancer susceptibility

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This review focuses on genes other than the high penetrance genes *BRCA1* and *BRCA2* that are involved in breast cancer susceptibility. The goal of this review is the discovery of polymorphisms that are either associated with breast cancer or that are in strong linkage disequilibrium with breast cancer causing variants. An association with breast cancer at a 5% significance level was found for 13 polymorphisms in 10 genes described in more than one breast cancer study. Our data will help focus on the further analysis of genetic polymorphisms in populations of appropriate size, and especially on the combinations of such polymorphisms. This will facilitate determination of population attributable risks, understanding of gene-gene interactions, and improving estimates of genetic cancer risks.

(odds ratio (OR) 1-1.5) to moderate (OR 1.5-2) increase in the lifetime breast cancer risk. Because mutations in these so-called low penetrance genes are expected to be present in a large number of people, the population attributable risk (PAR) for breast cancer explained by these genes (in combination with environmental exposures) may be substantial¹³ and (potentially) considerably higher than the PAR caused by rare mutations of high penetrance genes such as *BRCA1* and *BRCA2*.¹⁴⁻¹⁵ The published polymorphisms (a locus where two or more alleles are each present at a frequency $\geq 1\%$ in the population) were, in general, studied because of their biological plausibility.¹⁶⁻²¹ Some polymorphisms may partly account for the difference in the sensitivity of women to environmental factors, such as the use of replacement oestrogens.²⁰ In subjects carrying low penetrance gene mutations, environmental factors might especially affect the risk of developing breast cancer. One subject may be 10-200 times more sensitive than another²² and may therefore develop cancer, while others at the same level of exposure will not. With the identification of important low penetrance gene mutations along with their interaction with environmental factors, specific prevention may become possible. Research on low penetrance genes involved in breast cancer is still in its infancy. Whole genome screens for determining low penetrance genes are currently not yet financially feasible.

This review focuses on genes other than *BRCA1* and *BRCA2* that may be involved in breast cancer susceptibility. Although mutations or polymorphisms in many of the genes described can also play a role in other types of common cancer, such as colorectal, ovarian, or prostate cancer, this review addresses only breast cancer. The aim of the pooled analysis was to find polymorphisms that may either have a causative relation to breast cancer or that are in strong linkage disequilibrium (LD) with breast cancer causing variants (for example, situations where certain haplotype combinations of alleles at different loci occur more frequently than would be expected from random association). We studied only the relation of the polymorphisms to breast cancer risk, since we assumed that environmental factors will play

Breast cancer is the most common cancer in women in the western world.¹ In breast cancer development, genetic and environmental factors play a role with family history being the most important factor for determining breast cancer risk. This risk is a function of the number of relatives affected with breast and ovarian cancer, the degree of relationship to these relatives, and their age at diagnosis of the disease.²⁻³

Hereditary breast cancer accounts for 5-9% of all breast cancers.⁴ It was estimated that the combination of *BRCA1* and *BRCA2* gene mutations was responsible for approximately 80% of the families with hereditary breast cancer.⁵⁻⁶ These estimates, however, may be too high owing to the way patients are selected, namely on the basis of a pronounced family history of the disease. More recent estimates put this risk at about 30%.⁷ Mutations of the *BRCA1* and *BRCA2* genes do not explain the occurrence of breast cancer in every breast cancer prone family.⁸ At least one other major breast cancer susceptibility gene is proposed to exist.⁹⁻¹⁰ In addition, a number of rare genetic syndromes are associated with high breast cancer risk. Together, these rare syndromes account for less than 1% of all hereditary breast cancers.¹¹

Apart from these well defined, high penetrance genes, there may be other genes that also increase the susceptibility to breast cancer. Candidates are proto-oncogenes and genes involved in metabolic, oestrogen, and immunomodulatory pathways.¹² Each of these genes probably confers only a small

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Abbreviations: OR, odds ratio; CI, confidence interval; PAR, population attributable risk; LD linkage disequilibrium; LOH, loss of heterozygosity; RR, relative risk

Table 1 Breast cancer susceptibility genes with their localisation and presumed function

Gene	Location and function
<i>BRCA1</i>	17q21, DNA RP*, guardian of genome integrity ^{292 293}
<i>BRCA2</i>	13q12-13, DNA RP, guardian of genome integrity ^{294 295}
<i>TP53</i>	17p13.1, DNA RP, protection against replication of damaged DNA ²⁹⁶⁻²⁹⁸
<i>ATM</i>	11q22-23, DNA RP, sensor in cellular response to DNA double strand breaks ^{299 300}
<i>PTEN</i>	10q23.3, TSG†, suppresses cell cycle progression and induction of apoptosis ³⁰¹
<i>LKB1</i>	19p13.3, serine/threonine kinase, otherwise unknown function
<i>HRAS1</i>	11p15, proto-oncogene, control of cell growth and differentiation ³⁰²
<i>NAT1</i>	8p22, MP‡, detoxification of arylamines ^{17 139 303 304}
<i>NAT2</i>	8p22, MP, detoxification of arylamines ^{17 139 303 304}
<i>GSTM1</i>	1p13.3, MP, detoxification of a wide range of xenobiotics, including environmental carcinogens, chemotherapeutic agents, and reactive oxygen species ³⁰⁵⁻³⁰⁷
<i>GSTP1</i>	11q13, MP, detoxification of numerous chemicals including chemotherapy agents and catechol oestrogens ^{170 179 308}
<i>GSTT1</i>	11q, MP, detoxification of a wide range of xenobiotics, including environmental carcinogens, chemotherapeutic agents, and reactive oxygen species ^{17 305 307}
<i>CYP1A1</i>	15q, MP, EP§, metabolism of oestrogens and PAHs ^{17 185 309}
<i>CYP1B1</i>	2p21, MP, metabolism of PAHs ^{194 310}
<i>CYP2D6</i>	22q11-ter, MP, metabolism of many commonly prescribed drugs, including debrisoquine and codeine ^{17 311}
<i>CYP17</i>	10q24.3, EP, balance of oestrogens, progesterones, and androgens ^{114 212}
<i>CYP19</i>	11q21.1, EP, catalysing the conversion of androgens into oestrogens, determines the local oestrogen level ³¹²⁻³¹⁴
<i>ER</i>	6q25.1, EP, binding and transfer of oestrogens to the nuclei, ER modulates transcription of a number of growth factors (IGF-1, TGF α) ³¹⁵⁻³¹⁷
<i>PR</i>	11q22-23, EP ³¹⁸
<i>AR</i>	Xq11-12, EP
<i>COMT</i>	22q11.2, EP, conjugation and inactivation of catechol oestrogens ³¹⁹⁻³²²
<i>UGT1A1</i>	2q37, MP, EP, phase II drugs metabolism and maintain intracellular steady state levels of oestrogen ³²³⁻³²⁵
<i>TNFα</i>	6p21, IP¶, central mediator in the inflammatory response and immunological activities to tumour cells ²⁶⁵⁻²⁶⁷
<i>HSP70</i>	6p21, molecular chaperones, regulation of structure, subcellular localisation, and turnover of cell proteins ^{271 326}
<i>HFE</i>	6p21, IMP**
<i>TFR</i>	3q, IMP ³²⁷
<i>VDR</i>	12q, cell differentiation ³²⁸⁻³³⁰
<i>APC</i>	5q22, inhibits the progression of cells from G1 to S phase, apoptosis, cell-cell interactions ³³¹
<i>APOE</i>	19q13.2, lipid metabolism ³³²
<i>CYP2E1</i>	10q24.3-ter, MP, metabolism of acetone, ethyl glycol, and ethanol ^{17 333}
<i>EDH17B2</i>	17q12.21, EP, catalyses the reaction between oestrone and oestradiol ^{334 335}
<i>HER2</i>	17q21, proto-oncogene, control of cell growth and proliferation ^{336 337}
<i>TBR1</i>	9q33-34, cell growth ³³⁸

*DNA RP: DNA repair pathway. †TSG: tumour suppressor gene. ‡MP: metabolic pathway. §EP: oestrogen pathway. ¶IP: immuno pathway. **IMP: iron metabolism pathway.

an equal role in all studies. The external variables taken into account were, where possible, menopausal state and ethnicity. Pooled analyses were performed on all polymorphisms. In addition, the sample size required to detect an association with breast cancer susceptibility with sufficient power was addressed.

METHODS

Search of published studies

Published studies were identified using the PubMed databases from 1980 to 2000, using the search terms “breast”, “cancer”, “risk”, and “polymorphism(s)”. For each specific candidate gene, a separate search was performed. For example, the terms “*HRAS1*”, “breast”, “cancer”, and “risk” were used for *HRAS1*. In addition, the references of studies identified by the electronic searches were also evaluated. Studies eligible for our pooled analysis were those that compared genotype or allele frequencies of candidate genes in breast cancer cases with non-breast cancer controls using genomic DNA. The polymorphisms reported in breast cancer patients and controls in more than one study are described separately. When more than one polymorphism in one gene (for example, *CYP1A1*) or polymorphisms in different genes in the same region (for example, the HLA region) were examined in only one single study, they are also included. The different genes along with their localisation and presumed function are presented in table 1.

Lay out per gene

For the known genetic syndromes associated with increased breast cancer susceptibility, the possible germline mutations in familial and sporadic breast cancer patients were addressed, followed by somatic mutations, loss of heterozygosity (LOH),

the loss of one of the two alleles at a given locus in a tumour), and hypermethylation. According to Knudson’s “two hit theory”,²³ the two hits required for tumour development are generally thought of as an intragenic mutation (germline or somatic) and LOH. Recently, it has been shown that hypermethylation of the promoter region of a gene can also be one of the hits required in cancer development^{24 25} because this can silence the gene.²⁶

Pooled analysis

For a better insight into the possible effects of the various genes on breast cancer susceptibility, a pooled analysis for each polymorphism was performed. The results of this analysis are shown in table 2. The raw numbers of cases and controls from comparable studies were analysed together. The genotype specific ORs and the 95% confidence intervals (CIs) were calculated for all studies combined, without adjustment for external variables. This can result in values that differ from those in the original article. Whenever possible, a distinction was made between women heterozygous and homozygous for the variant allele. Where metabolic polymorphisms are assumed to be associated with a specific phenotype, a distinction was made between phenotype and genotype based studies (for example, *CYP2D6*, *NAT2*). For the genotype studies, the genotypes were combined according to phenotypic classes. Also, where possible, separate analyses were performed for the three major ethnic subgroups, white, African-American, and Asian.

The ORs and the 95% CIs of the studies used in the pooled analysis of polymorphisms in three genes are shown in figs 1 (the *HRAS1* polymorphism), 2 (the PROGENS polymorphism of the *PR* gene), and 3 (the polymorphisms in the vitamin D receptor (*VDR*) gene).

Table 2 Genetic polymorphisms and their allele frequencies, total number of cases and controls published, risk genotypes with their ORs and 95% confidence intervals, PAR, and sample size required to detect an association

Polymorphisms	Allele frequency	Cases*	Controls*	Risk G†	OR	95% CI	PAR	Sample size‡
<i>Tp53</i>								
Intron 3	0.17	667	1981	W§/V¶	0.97	0.79-1.18		2900
				V/V	0.46	0.25-0.84		
Exon 4	0.36	552	2219	W/V	1.08	0.88-1.13		2200
				V/V	0.70	0.51-0.95		
Intron 6	0.17	733	2160	W/V	0.92	0.75-1.11		1500
				V/V	0.30	0.15-0.57		
<i>HRAS1</i>	0.08	2029	3252	V carriers	2.04	1.73-2.41	14%	430
<i>L-myc</i>	0.50	593	214	W/V	1.12	0.77-1.63		4000
				V/V	1.29	0.82-2.02		
<i>NAT1</i>	0.24	646	796	V carriers	1.13	0.91-1.39	5%	9100
<i>NAT2</i>								
Phenotype	0.62	476	785	V/V	0.87	0.70-1.10		7400
Genotype	0.61	1665	1809	V/V	0.99	0.87-1.13		1 410 000
<i>GSTM1</i>	0.72	2776	2710	V/V	1.13	1.02-1.26	6%	8900
<i>GSTP1</i>	0.32	538	397	W/V	1.19	0.91-1.56	17%	610
				V/V	2.15	1.30-3.56		
<i>GSTT1</i>	0.49	1324	1076	V/V	1.04	0.86-1.25		117 000
<i>CYP1A1</i>								
m1	0.15	1371	1241	W/V	0.99	0.83-1.19		41 000
				V/V	1.20	0.78-1.86		
m2	0.11	791	1468	W/V	1.18	0.94-1.48		8000
				V/V	0.93	0.51-1.69		
m3	0.09	85	178	V carriers	1.04	0.54-2.03		150 000
m4	0.03	223	221	V carriers	0.99	0.43-2.24		5 940 000
<i>CYP1B1</i>								
Codon 119	0.14	339	361	W/V	1.62	1.15-2.29		870
				V/V	0.60	0.11-3.31		
Codon 432	0.66	745	747	W/V	0.84	0.61-1.17		2700
				V/V	1.09	0.79-1.50		
Codon 453	0.14	223	223	W/V	0.96	0.62-1.49		31 000
				V/V	1.24	0.33-4.71		
<i>CYP2D6</i>								
Phenotype	0.26	335	777	V/V	2.22	1.39-3.55	8%	610
Genotype	0.18	831	1165	W/V	1.19	0.97-1.45	6%	4600
				V/V	1.26	0.81-1.96		
<i>CYP17</i>	0.40	2725	2531	W/V	0.99	0.88-1.11		82 000
				V/V	1.05	0.89-1.23		
<i>CYP19</i>								
TTTA repeat								
*10 allele	0.01	3934	3514	V carriers	1.59	1.01-2.48	1%	6800
*12 allele	0.02	3934	3514	V carriers	1.11	0.83-1.49		77 000
TCT intron 4	0.35	599	433	W/V	0.79	0.61-1.03		4500
				V/V	1.03	0.69-1.56		
Intron 6	0.48	223	164	W/V	1.15	0.72-1.85		3300
				V/V	1.33	0.77-2.29		
Codon 264	0.30	160	125	W/V	0.83	0.50-1.35		4600
				V/V	0.91	0.38-2.14		
<i>ER</i>								
PvuII	0.54	704	53	W/V	0.84	0.40-1.78		10 000
				V/V	0.93	0.41-2.13		
XbaI	0.29	191	204	W/V	0.99	0.65-1.51		1200
				V/V	0.50	0.25-0.99		
Codon 325	0.21	646	324	W/V	1.04	0.79-1.38		27 000
				V/V	1.19	0.54-2.65		
<i>PR</i>	0.14	1106	965	W/V	0.95	0.78-1.16		2400
				V/V	0.32	0.16-0.65		
<i>COMT</i>	0.44	1166	1167	W/V	0.92	0.76-1.10		18 000
				V/V	0.89	0.71-1.12		
<i>UGT1A1</i>	0.34	655	808	W/V	0.99	0.80-1.24		110 000
				V/V	1.05	0.75-1.47		
<i>HLA</i>								
TNF-alpha	0.21	40	106	W/V	3.49	1.62-7.51	50%	79
				V/V	4.80	0.28-81.1		
<i>HSP70-2</i>	0.45	40	106	W/V	1.74	0.55-5.52	85%	11
				V/V	27.5	4.30-176		
<i>HSP70-hom</i>	0.23	40	106	V carriers	3.56	1.26-10.01	23%	84
<i>VDR</i>								
ApaI	0.47	135	110	W/V	1.54	0.85-2.80	38%	290
				V/V	2.54	1.20-5.39		
BmsI	0.35	231	467	W/V	1.16	0.83-1.62	12%	1900
				V/V	1.51	0.87-2.64		
FokI	0.41	278	410	W/V	1.03	0.73-2.64	3%	41 000
				V/V	1.09	0.69-1.73		
TaqI	0.57	1197	867	W/V	0.95	0.74-1.20		61 000
				V/V	0.93	0.72-1.20		
Poly-A	0.27	143	300	W/V	1.59	1.04-2.42	42%	310
				V/V	2.76	1.35-85		
<i>APOE</i>	0.07	260	332	E2 allele	0.99	0.62-1.59		2 800 000
	0.13			E4 allele	0.89	0.62-1.26		14 000
<i>EDH17B2</i>	0.54	190	190	W/V	0.59	0.37-0.94		1500
				V/V	0.90	0.50-1.60		
<i>HER2</i>	0.13	339	359	W/V	1.26	0.88-1.79	20%	110
				V/V	12.76	1.62-98.9		
<i>TBR-1</i>	0.06	152	735	W/V	1.58	0.96-2.59	6%	1400
<i>TFR</i>	0.40	165	294	W/V	1.01	0.66-1.55	4%	7500
				V/V	1.20	0.70-2.05		

*Cases and controls: all studies combined. †Risk G: risk genotype. ‡Sample size: the number of patients and controls required to detect an association, with power of 90% and a significance level of 0.0026 (correction for multiple testing). §W: wild type. ¶V: variant allele.

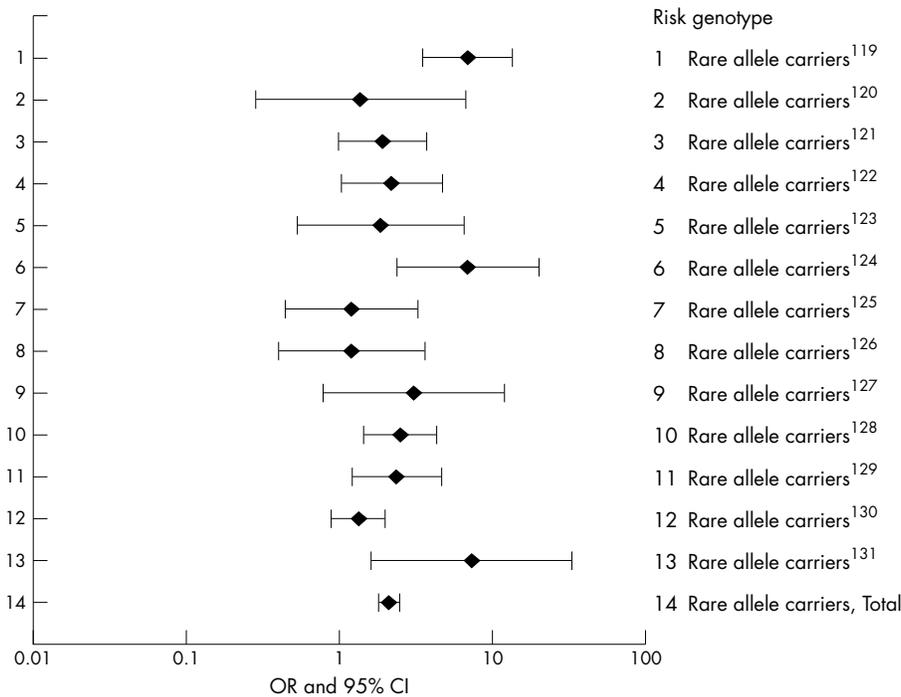


Figure 1 The *HRAS1* polymorphism and breast cancer risk. The results of 12 studies (OR and 95% CI) are depicted as well as the result of the pooled analysis comprising 2029 cases and 3252 controls.

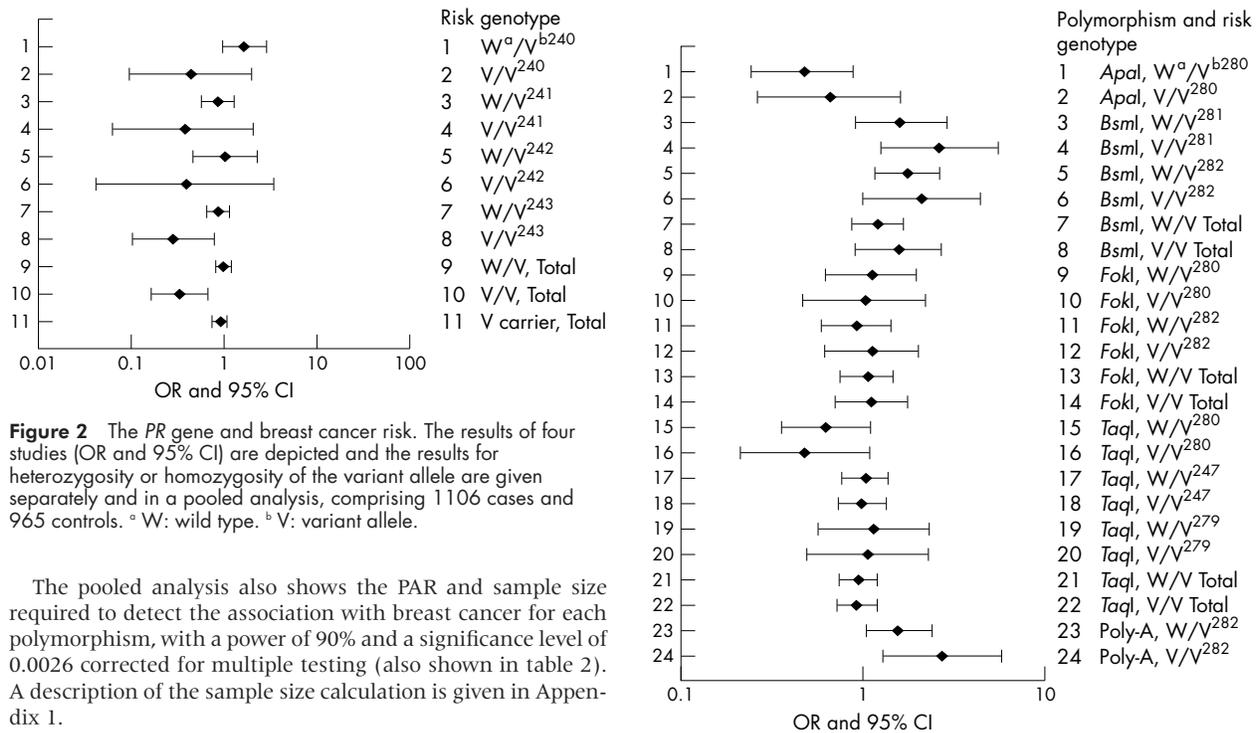


Figure 2 The *PR* gene and breast cancer risk. The results of four studies (OR and 95% CI) are depicted and the results for heterozygosity or homozygosity of the variant allele are given separately and in a pooled analysis, comprising 1106 cases and 965 controls. ^a W: wild type. ^b V: variant allele.

The pooled analysis also shows the PAR and sample size required to detect the association with breast cancer for each polymorphism, with a power of 90% and a significance level of 0.0026 corrected for multiple testing (also shown in table 2). A description of the sample size calculation is given in Appendix 1.

RESULTS

The unknown “BRCA3” gene

Based on several studies, a region on chromosome 8p11-21 is considered to be involved in hereditary and sporadic breast cancer. Linkage analysis in eight French breast cancer families showed a multipoint lod of 2.51 (a lod score >3.0 is the accepted statistical significance level for linkage of a genetic locus with a disease) with two markers on chromosome 8p.²⁷ Linkage analysis in two large German breast cancer families, with negative lod scores for the *BRCA1* and *BRCA2* locus,

Figure 3 The vitamin D receptor gene and breast cancer risk. The results of five studies (OR and 95% CI) are depicted in the graph and the data for five polymorphisms are given separately, with the distinction between heterozygosity and homozygosity for the variant allele. For *BsmI* the total is 231 cases and 467 controls, for *FokI* 278 cases and 410 controls, and for *TaqI* 1197 cases and 867 controls. ^a W: wild type. ^b V: variant allele.

showed a multipoint lod score of 3.30 at two other markers, localised between the two markers in the French study, on chromosome 8p.²⁸ In studies focusing on chromosome 8p, LOH

was observed in 46-74% of unselected human breast tumours,²⁷⁻²⁹⁻³⁶ in 86% of the familial tumours,³² in 78% of tumours in women with a specific *BRCA2* mutations (that is, the 999del5 mutation),³⁶ and in 83% of male breast tumours.³⁷ In ductal breast carcinoma in situ, LOH on 8p is observed in 0-37% of cases,³⁰⁻³⁸⁻³⁹ suggesting LOH on 8p is associated with invasive behaviour of the tumour. Based on these LOH studies, there are at least two different regions of minimal overlap of LOH on chromosome 8p. The region on 8p discussed earlier²⁷⁻²⁸ is localised in one of these regions. Mapped genes in this region include *hEXTIL*,³⁴ *WRN*,⁴⁰ and *LHRH*.⁴¹⁻⁴² No somatic or germline mutations have, as yet, been detected in these genes in breast cancer cases.

Rare genetic syndromes with increased breast cancer risk

The *Tp53* gene and Li-Fraumeni syndrome

Inactivating mutations in the *Tp53* gene have been found in many tumour types⁴³⁻⁴⁴ including breast cancer.⁴⁵ Li-Fraumeni syndrome is an autosomal dominant disorder, caused by germline mutations in the *Tp53* gene. This syndrome is characterised by an increased risk of soft tissue and osteosarcomas, leukaemias, brain tumours, adrenocortical carcinomas, and breast cancers.⁴⁶ The risk of developing breast cancer before the age of 45 is 18-fold higher for affected females as compared to the general population.⁴⁶ The excess is greatest before the age of 20 and declines with increasing age (relative risk (RR) for breast cancer after the age of 45 = 1.8).⁴⁶ Germline mutations in the *Tp53* gene have been estimated to account for less than 1% of breast cancer cases.⁴⁷⁻⁵¹ However, somatic mutations in the *Tp53* gene are reported in 19-57% of human breast cancers⁵²⁻⁵⁷ and LOH is found in 30-42%.⁵²⁻⁵⁴ There is no association between somatic *Tp53* mutations and LOH at the *Tp53* locus,⁵²⁻⁵⁵ suggesting that one inactivated allele may be sufficient for breast cancer development.⁵⁴ Hypermethylation of the promoter region of the *Tp53* gene does not play a role in breast cancers.⁵⁸

Three different *Tp53* polymorphisms (in intron 3, exon 4, and intron 6) have been studied in breast cancer patients. All three polymorphisms exhibit strong linkage disequilibrium with each other.⁵⁹ In five studies examining the intron 3 polymorphism, none found an association with increased breast cancer risk.⁶⁰⁻⁶⁴ Surprisingly, the breast cancer risk for homozygous carriers of the variant allele was decreased. When all studies were combined, the OR for heterozygous carriers of the variant allele was 0.97 (95% CI 0.79-1.18) and was 0.46 (95% CI 0.25-0.84) for homozygous carriers. The exon 4⁶¹⁻⁶⁵ and the intron 6⁶¹⁻⁶⁴⁻⁶⁶⁻⁶⁷ polymorphisms showed similar results. Thus, a decreased breast cancer risk for homozygous variant allele carriers was found for all three polymorphisms in the *Tp53* gene. These homozygous variant allele carriers comprise 3% (intron 3), 13% (exon 4), and 3% (intron 6) of all the women and, thus, up to 13% of women have decreased breast cancer risks.

Four studies⁶¹⁻⁶⁴ examined all three polymorphisms in the *Tp53* gene in relation to breast cancer risk. In one of the two studies examining haplotypes, an association was observed between the haplotype composed of the three variant alleles and the risk of breast cancer among white populations (OR=2.18, 95% CI 1.17-4.07).⁶² This association was not found in Hispanic (OR=0.24, 95% CI 0.05-1.11) or African-American patients (OR=1.13, 95% CI 0.46-2.81)⁶² nor in patients from Pakistan (OR=0.77, 95% CI 0.38-1.56).⁶⁴ The two other studies⁶¹⁻⁶³ did not construct haplotypes, but compared genotype combinations. The first study found a marginally significant association between breast cancer and the genotype combination that is heterozygous for all three polymorphisms (OR=1.68, 95% CI 0.99-2.86).⁶³ This genotype combination did not exclude the haplotype composed of three variant alleles from being at risk. The second study found

associations between breast cancer and two genotype combinations.⁶¹ With the first genotype combination (OR=2.94, 95% CI 1.37-6.27), heterozygous for the intron 3 and 6 polymorphisms and homozygous for the exon 4 variant allele, the haplotype of three variant alleles is still supported. With the second genotype combination (OR=1.61, 95% CI 1.13-2.30), homozygous for the intron 3 and 6 wild type allele and heterozygous for the exon 4 polymorphism, the variant allele haplotype is not possible. The fact that the four studies used different methods to examine the polymorphisms hampers the comparison of results. However, the analysis showed that the haplotype composed of the three variant alleles is associated with an increased breast cancer risk, particularly in white breast cancer patients.

The *ATM* gene and ataxia telangiectasia

Most A-T patients do not survive to an age at which breast cancer generally occurs.⁶⁸ A-T carriers (heterozygous for *ATM* mutations) are sensitive to late onset apoptosis after x ray irradiation owing to accumulation of cell cycle checkpoint abnormalities.⁶⁹ In several studies, A-T carriers appear to have an increased breast cancer risk (OR 3.3-8⁷⁰⁻⁷⁶ and PAR 3.8-8.5%⁶⁸⁻⁷³⁻⁷⁵). However, in all studies the OR was determined with the observed/expected method and all groups were small. One study found no increased breast cancer risk among A-T carriers.⁷⁷ The risk of A-T carriers to develop breast cancer is estimated to be 11% by the age of 50 and 30% by the age of 70.⁷⁸

Germline mutations in the *ATM* gene are rare in breast cancer families without features of A-T.⁷⁹⁻⁸⁰ In sporadic breast cancers, germline and somatic mutations in the *ATM* gene are also rare,⁸¹⁻⁸² even in young patients⁸³⁻⁸⁴ and patients with bilateral breast cancer.⁸⁵ In 88 breast cancer patients with a family history of breast cancer and leukaemia or lymphoma, three germline mutations in the *ATM* gene have been found.⁷⁹ Chen *et al*⁸⁰ examined these three mutations and none appeared to be causal. In 82 Dutch breast cancer patients (diagnosed before the age of 45, >5 years survival) including 33 bilateral cases, seven germline mutations were found, one out of frame splice site mutation (detected three times), three truncating mutations, and one in frame deletion.⁸⁶ It was hypothesised that the existence of two distinct classes of A-T mutations (truncating and missense) might explain some of the seemingly contradictory data on cancer risk associated with the *ATM* gene.⁸⁷⁻⁸⁸ The truncating mutations act as null mutations because they produce low cellular levels of an unstable ATM protein. Because truncating mutation carriers have 50% of wild type ATM activity, they will have an almost normal phenotype. Some missense mutations encode stable, but functionally abnormal proteins that are present at normal intracellular levels. These proteins could compete in complex formation with the normal ATM protein, resulting in a dominant negative cellular phenotype. The functional loss in *ATM* missense mutation carriers might be more severe than in *ATM* truncating mutation carriers and, thus, only *ATM* missense mutations might be associated with an increased cancer risk.⁸⁸ In most studies, A-T carrier detection in breast cancer cases was based on the protein truncation test and could only detect truncating mutations. Support for the existence of two functionally distinct classes of mutations can be derived from a study describing an increased breast cancer risk in two A-T families with a specific *ATM* missense mutation (T7271G) in both homozygotes and heterozygotes, with an age specific incidence rate based OR of 12.7 (95% CI=3.53-45.9).⁸⁹ This mutation results in an aberrant full length ATM protein level comparable with unaffected subjects.⁸⁹ Another explanation for the seemingly contradictory data on breast cancer risk is that the carrier frequency of A-T mutations could be much lower than the described 1% of the general population causing a low PAR. If this is the case, the OR for breast cancer in A-T

carriers can be high (as found in the A-T families), while mutations in the *ATM* gene are rarely detected in sporadic breast cancer patients.

A recent study of 138 Austrian hereditary breast and ovarian cancer (HBOC) patients without *BRCA1* and *BRCA2* mutations⁹⁰ showed functionally significant *ATM* germline mutations in at least 8.7% of the HBOC patients. The penetrance for one of the mutations (L1420F) was estimated to be 85% at age 60.

In conclusion, although the exact association remains unclear, a role for the *ATM* gene in breast cancer susceptibility is plausible.

The *PTEN* gene and Cowden syndrome

Cowden syndrome is an autosomal dominant disorder, characterised by the development of hamartomas and benign tumours. Mutations in the *PTEN* gene are present in 80% of Cowden syndrome families.⁹¹⁻⁹² Truncating *PTEN* mutations in Cowden syndrome families are associated with cancer⁹³ and cause a 25-50% lifetime breast cancer risk in women.⁹²⁻⁹⁴⁻⁹⁵ No mutations in the *PTEN* gene have been detected in breast cancer families and families with breast and brain cancer without features of Cowden syndrome.⁹⁶⁻⁹⁹ In sporadic breast cancer patients, germline and somatic mutations in the *PTEN* gene are rare¹⁰⁰⁻¹⁰⁴ even in young patients.⁹⁶⁻¹⁰⁵ LOH at the *PTEN* locus is found in 11-41% of sporadic breast cancers,¹⁰²⁻¹⁰⁴⁻¹⁰⁶ but no somatic mutations have been observed in the remaining allele.¹⁰³⁻¹⁰⁴⁻¹⁰⁶ It is, however, still possible that an epigenetic phenomenon such as hypermethylation of the promoter region inactivates the remaining allele.¹⁰⁷ In one study (in 177 breast cancer patients with a positive family history for breast cancer and without *BRCA1* and *BRCA2* mutations), an association was found between a polymorphism in intron 4 of the *PTEN* gene and a lower age of diagnosis of breast cancer (42.7 versus 48.1 years).⁹⁸ No comparison, however, was made with healthy controls. In conclusion, the *PTEN* gene is not likely to play a role in classical hereditary breast cancer. In sporadic breast cancers, LOH at the *PTEN* locus is detected, but since no alterations have been found in the remaining allele, it is not currently known whether *PTEN* plays a role in sporadic breast cancer susceptibility.

The *LKB1* gene and Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is an autosomal dominant disorder characterised by hamartomatous polyps in the small bowel and pigmented macules of the buccal mucosa, lips, fingers, and toes.¹⁰⁸ This syndrome is caused by truncating germline mutations in the *LKB1* gene.¹⁰⁹⁻¹¹⁰ Patients with Peutz-Jeghers syndrome have an increased breast cancer risk.¹⁰⁸⁻¹¹¹ No germline mutations were detected in 22 patients from 14 breast cancer families with LOH on chromosome 19p.¹¹² In 62 primary breast cancers in women without Peutz-Jeghers syndrome, no somatic mutations were found in the *LKB1* gene and LOH was observed in only 8%.¹¹³ In conclusion, the *LKB1* gene seems to play a role in breast cancer susceptibility, but only in patients with Peutz-Jeghers syndrome.

Low penetrant breast cancer susceptibility genes

There are several classes of potential low penetrance breast cancer susceptibility genes, such as proto-oncogenes, metabolic pathway genes, oestrogen pathway genes, and immunomodulatory pathway genes.

Proto-oncogenes

Proto-oncogenes are involved in the regulation of normal cell growth and differentiation. Mutations in proto-oncogenes lead to disturbances in the cell cycle and can result in abnormal growth or proliferation.¹¹⁴ Well known proto-oncogenes are the *RAS* genes, the *HER2* gene, and the *myc* genes.

HRAS1

The *HRAS1* gene encompasses four exons flanked by a variable tandem region repeat at the 3' end.¹¹⁵⁻¹¹⁶ This minisatellite locus is composed of four common alleles (94% of the white population¹¹⁷) and dozens of variants, the so-called intermediate and rare alleles. Each variant allele is derived from the common allele nearest in size to it.¹¹⁸ The *HRAS1* polymorphism was examined in 13 studies.¹¹⁹⁻¹³¹ Positive ORs were detected in all studies (fig 1), five of which reached significance¹¹⁹⁻¹²⁴⁻¹²⁸⁻¹²⁹⁻¹³¹ with ORs of 2-7. Combining the studies showed an association between rare *HRAS1* alleles and breast cancer (OR=2.03, 95% CI 1.72-2.40), with a PAR of 14%. There are, however, several methodological problems in performing this pooled analysis, since the choice of the cut off point between rare, intermediate, and common alleles is difficult to make and the distribution of the alleles in subgroups of the population varies between studies.¹³² The choice of rare alleles (frequency <4%) is not the same for all studies and does not correspond to any previous biological interpretation.¹³² In most studies there are four common alleles and the rest of the alleles are listed as rare. With this as the criterion, our pooled analysis indicated that the rare *HRAS1* alleles are associated with a moderately increased risk of breast cancer.

L-myc

Three studies focused on *L-myc* and breast cancer risk.¹³³⁻¹³⁵ In one study, no controls were examined.¹³⁴ Another study found an association with breast cancer¹³⁵ for women heterozygous (OR=2.25, 95% CI 1.12-4.51) and homozygous (OR=2.63, 95% CI 1.22-5.68) for the variant allele. When all three studies were combined for our pooled analysis, no association with breast cancer was found.

Metabolic pathway genes

Enzymes involved in metabolic pathways are of interest because of their possible role in (de)toxication of chemical compounds.¹³⁶ A number of metabolic pathway genes, including the *cytochrome p450* family, the *GST* family, and the *NAT1* and *NAT2* genes, are thought to have evolved as an adaptive response to environmental exposure to toxins, including some carcinogens. The prediction is therefore that any alteration in the activity of these enzymes would result in an altered susceptibility to potentially toxic (mutagenic) compounds. This may determine the rate at which somatic mutations occur in genes in response to environmental exposures, resulting in an altered cancer susceptibility. The cytochrome p450 family proteins are known as phase I enzymes. In general, these enzymes metabolically activate carcinogens.¹³⁷ A genotype associated with an increased phase I enzyme activity might therefore increase breast cancer risk.¹³⁸ The *NAT* and *GST* family proteins are known as phase II enzymes. These enzymes metabolically inactivate carcinogens. The substrates for phase II enzymes include carcinogenic compounds activated by the phase I enzymes. A genotype associated with decreased phase II activity might therefore increase breast cancer risk.¹³⁸

N-acetyl transferase (NAT)

Both *NAT1* and *NAT2* are polymorphic with so-called fast and slow phenotypes. Slow acetylators produce proteins that are either poorly expressed, are unstable, or have partially reduced catalytic activities.¹³⁹ In theory, having the slow acetylator phenotype could mean that aromatic amines are metabolised more slowly and that slow acetylators might, therefore, be at increased breast cancer risk.¹¹⁴

NAT1

The *NAT1**10 allele is associated with the rapid acetylation phenotype; all other alleles represent slow alleles.¹³⁹⁻¹⁴¹ This allele is present in 30% of populations of European

ancestry.¹⁴² Two studies found no association with breast cancer risk either separately or combined.^{143 144} The *NAT1* polymorphism does not appear to play a major role in breast cancer susceptibility, although a small increase in breast cancer risk cannot be excluded.

NAT2

The acetylation capacity in *NAT2**4 homozygotes in vivo is higher than in *NAT2**4 heterozygotes and all variant alleles have lower acetylation capacities.¹⁴⁵ The population frequency of the fast acetylator genotype of the *NAT2* gene is 22-78%.¹⁴⁵⁻¹⁴⁷ None of seven studies found an increased breast cancer risk for the slow acetylator *NAT2* phenotype,¹⁴⁸⁻¹⁵⁴ while two studies found a decreased breast cancer risk.^{148 155} No association with breast cancer risk was found when all studies were combined. The results for the *NAT2* genotype were similar. No effect on breast cancer risk was found when the studies were combined in our pooled analysis.^{143 155-159} In conclusion, the *NAT2* polymorphism does not play a role in breast cancer susceptibility.

Combination of *NAT1* and *NAT2*

One study examined both polymorphisms.¹⁴³ No association between these polymorphisms and breast cancer was observed for either the *NAT1* or *NAT2* genes separately or combined.

Glutathione S-transferase (GST) family

Deletion variants that are associated with a lack of enzyme function exist at *GSTM1* and *GSTT1*.¹⁶⁰ Homozygotes for null deletions in the *GSTM1* and/or *GSTT1* genes may have an impaired ability to eliminate carcinogens metabolically and may therefore be at increased cancer risk.

GSTM1

GSTM1 is polymorphically expressed as *GSTM1*-0 or null (homozygous deletion) and *GSTM1a* and *GSTM1b*.¹⁶⁰ Between 20 and 60% of the general population are homozygous null for the *GSTM1* gene.¹⁶¹⁻¹⁶⁴ The *GSTM1* null variant has been well examined in breast cancer studies with varying results.¹⁶⁵⁻¹⁷⁸ Our pooled analysis showed an association between this polymorphism and breast cancer risk, although this increase is very small and only marginally significant (OR=1.13, 95% CI 1.00-1.26). The combined sample size is large enough to exclude a moderate increase in breast cancer risk for *GSTM1* null homozygous carriers.

GSTP1

In 31% (24/77) of the breast cancer cases, hypermethylation of the *GSTP1* promoter region was detected.¹⁷⁹ A polymorphism, the isoleucine to valine substitution at codon 105, has been associated with reduced conjugating activity of the gene.¹⁸⁰ This polymorphism has been examined in three studies.^{170 176 181} Our pooled analysis showed a moderately increased breast cancer risk for women homozygous for the Val allele (OR=1.86, 95% CI 1.05-3.3) with a PAR of 14%. Thus, the *GSTP1* polymorphism appears to play a role in breast cancer susceptibility, although the total number of cases (n=301) and controls (n=397) was small.

GSTT1

The *GSTT1* gene has two functionally different genotypes, *GSTT1*-0 or null (homozygous deletion) and *GSTT1*+ (one or two undeleted alleles).¹⁶⁰ The *GSTT1* null genotype has been linked to increased DNA damage from experimental carcinogens.¹⁸² In different populations, 9-64% are homozygous null for the *GSTT1* gene.^{164 182-184} Six studies examining this polymorphism showed no association with breast cancer.^{169 170 172 175-177} The results were similar for premenopausal and postmenopausal women. Based on the combined sample

size, a moderate increase in breast cancer risk can be excluded for women homozygous null for the *GSTT1* polymorphism.

Combination of *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms

Six studies^{169 170 172 175-177} examined both *GSTM1* and *GSTT1* polymorphisms and breast cancer risk and four of them^{170 172 176 177} also analysed the *GSTP1* polymorphism. In one study, no controls were examined and it was therefore not included in our pooled analysis.

Of the five studies that examined the combination of two of the *GST* genes, one found an association between the two risk genotype and breast cancer for all three combinations of *GST* genes.¹⁷⁰ Another detected an association between the two risk genotype for the *GSTM1* and *GSTT1* gene and breast cancer.¹⁷⁷ Pooled analysis showed an increased breast cancer risk for the one and the two risk genotype of all three gene combinations, although only the two risk genotype of the *GSTM1* and *GSTP1* combination reached significance (OR=1.65, 95% CI 1.00-2.71).

For the two studies where all three polymorphisms were examined, the results were similar.^{170 176} The study that observed associations with the two risk genotypes also showed an association between the three high risk alleles and breast cancer.¹⁷⁰ When both studies were combined, increased breast cancer risks were observed for carriers of the one, two, or three risk genotype, although only the two risk genotype reached significance (OR=1.90, 95% CI 1.13-3.22).

Cytochrome p450 family

Certain substrates, including almost all carcinogens, are metabolically activated by cytochrome p450 metabolism, which results in the formation of mutagenic, chemically reactive electrophiles. Most prescribed drugs are substrates for one or more cytochrome p450 isoenzymes.¹⁷ Individual cytochrome p450 isoenzymes have a unique substrate specificity, although a certain overlap between the enzymes is observed.¹⁷

CYP1A1

This gene codes for aryl hydrocarbon hydroxylase (AHH).¹¹⁴ AHH is strongly inducible; differences in xenobiotic metabolic activity between subjects even within a family can be over 200-fold.¹⁸⁵ Changes in AHH activity, resulting in different oestrogen levels, could affect breast cancer risk.^{16 114} Four polymorphisms have been described in the *CYP1A1* gene, namely the m1 polymorphism, the m2 polymorphism (associated with increased enzyme activity in vitro, both for homozygotes and heterozygotes for the variant allele^{186 187}), the m3 polymorphism (only present in African-Americans), and the m4 polymorphism. The m1 and m2 polymorphisms are in linkage disequilibrium,¹⁷ whereas the African-American specific polymorphism (m3) does not cosegregate.¹⁷ Five studies examined the m1 polymorphism with varying results.^{169 188-191} Combining all studies of white populations^{169 188 189 191} showed an association between heterozygous carriers of the variant allele and an increased breast cancer risk (OR=1.33, 95% CI 1.06-1.66). Two of the studies also examined African-Americans.^{169 191} No association with breast cancer was observed, but the total number of cases (n=84) and controls (n=177) was small and a (moderately) increased risk cannot be excluded. No overall association was detected in a Chinese study.¹⁹⁰ An increased breast cancer risk was found for postmenopausal women homozygous for the m1 variant allele (OR=2.97, 95% CI 1.14-7.76), but the number of subjects was small (78 cases and 81 controls). When all studies, regardless of ethnicity, were combined, no association was found between breast cancer and the m1 polymorphism.

No association with breast cancer risk was found in eight studies examining the m2 polymorphism^{16 167 169 189-192} regardless of whether they were analysed separately or were

combined. However, by combining the two studies which analysed postmenopausal women only,¹⁶⁷⁻¹⁹⁰ an association with breast cancer was found for both heterozygous carriers of the m2 variant allele (OR=1.59, 95% CI 1.07-2.37) and women homozygous for the variant allele, although the latter association is not significant (OR=2.53, 95% CI 0.92-6.96). This is probably because of lack of power. The African-American specific m3 variant allele does not seem to play a role in breast cancer susceptibility.¹⁶⁹⁻¹⁹¹ No association with breast cancer was observed in the one study¹⁶⁹ that examined the m4 polymorphism.

In conclusion, a small increased breast cancer risk was found in the white population for the m1 polymorphism and a moderately increased breast cancer risk in postmenopausal women was detected for the m2 polymorphism. A moderate increase in breast cancer risk for variant allele carriers cannot be excluded for all four polymorphisms owing to lack of power. Additional data are required to define the precise association between this gene and breast cancer, particularly in the white population and in postmenopausal women.

CYP1B1

The CYP1B1 enzyme exceeds other p450 enzymes in both oestrogen hydroxylation activity and expression in breast tissue.¹⁹³ Four polymorphisms have been described in this gene and all variants have higher hydroxylation activity.¹⁹³ These variant alleles may be associated with changes in oestrogen metabolism and therefore breast cancer risk. Three of these polymorphisms were examined in breast cancer patients and controls. The codon 432 polymorphism was examined in three studies.¹⁹⁴⁻¹⁹⁶ Large differences in variant allele frequencies were found between different populations with the variant allele frequency ranging from 0.15 to 0.68, with even large differences between two Asian studies.¹⁹⁵⁻¹⁹⁶ When all studies were combined, our pooled analysis found no association between the codon 432 polymorphism and breast cancer. The study examining the codon 119 polymorphism detected an association with an increased breast cancer risk in women heterozygous for the variant allele (OR=1.62, 95% CI 1.15-2.29).¹⁹⁵ However, in women homozygous for the variant allele, a non-significant decrease in risk was found (OR=0.6, 95% CI 0.11-3.31). No association with breast cancer was observed for the codon 453 polymorphism.¹⁹⁴

One study examined both the codon 119 and codon 432 polymorphisms.¹⁹⁵ The two polymorphisms were genetically independent and no association with an increased breast cancer risk was found for any combination of them.

CYP2D6

The CYP2D6 variant allele is the result of a deletion of a 17.5 kb region including the entire CYP2D6 gene.¹⁹⁷ In white populations, 5% are homozygous for this polymorphism.¹⁷⁻¹⁹⁸ These poor metabolisers are unable to metabolise agents such as debrisoquine and codeine.¹⁷ Seven studies, with varying results, examined this polymorphism, three phenotypically¹³⁶⁻¹⁹⁹⁻²⁰⁰ and four genotypically.¹⁹⁷⁻²⁰¹⁻²⁰³ When the phenotype studies were combined, a moderately increased breast cancer risk was found for poor metabolisers (OR=2.22, 95% CI 1.39-3.55) with a PAR of 8%. When the genotype studies were combined, an association was detected for carriers (homozygous and heterozygous combined) of the variant allele (OR=1.49, 95% CI 1.26-1.77), with a PAR of 6%. In conclusion, this polymorphism may play a role in increased breast cancer susceptibility.

Oestrogen pathway genes

Experimental, clinical, and epidemiological studies show that oestrogen and progesterone play a major role in growth and differentiation of normal breast tissue.¹¹⁴⁻²⁰⁴ A prolonged or increased exposure to oestrogen is associated with increased

breast cancer risk.²⁰⁵⁻²⁰⁶ Endogenous and exogenous hormones stimulate cell proliferation, and thus enhance the chance of accumulating random genetic errors. The most widely accepted risk factors for breast cancer such as age at menarche, age at first pregnancy, number of pregnancies, breast feeding, age at menopause, and obesity,¹⁻¹²⁻²⁰⁷ can be considered measures of the cumulative dose of oestrogen that breast epithelium is exposed to over time.²⁰⁵⁻²⁰⁸ Several oestrogen metabolites can directly or indirectly cause oxidative DNA damage.²⁰⁹⁻²¹⁰ In conclusion, genes involved in the metabolism of sex hormones (that is, oestrogens) are interesting candidates for breast cancer susceptibility genes.²⁰⁷⁻²¹¹

Cytochrome p450 family CYP17

A polymorphism in the CYP17 gene was detected in the 5' untranslated region. The variant allele of this polymorphism has an additional SpI type promoter site. Since it is thought that the number of 5' promoter elements correlates with promoter activity,¹¹⁴ women with this allele might have higher oestradiol levels.²¹² An association between the presence of at least one variant allele and an increased serum oestrogen and progesterone level at day 11 and day 22 of the menstrual cycle is found in young, nulliparous women.²¹³ One male breast cancer study (64 cases and 58 controls) observed an increased risk for variant allele carriers (OR=2.10, 95% CI 1.04-4.27).²¹⁴ Ten studies on female breast cancer examined this.¹⁸⁻²¹⁴⁻²²¹ One found an association (OR= 1.99, 1.15-3.45) between variant allele carriers (homozygous and heterozygous) and breast cancer in young women (<37 years of age),²²² but the number of cases (n=109) and controls (n=117) were small. Six other studies in premenopausal women²¹⁴⁻²¹⁶⁻²¹⁸⁻²¹⁹⁻²²¹⁻²²³ showed no association between this polymorphism and breast cancer. When all studies were combined in our pooled analysis, no association with breast cancer was found. In conclusion, based on the combined sample size, even a small increase in breast cancer risk overall can be excluded. However, because the studies did not further discriminate for age, an increased risk for breast cancer in young women carrying the variant allele cannot be excluded.

CYP19

Several polymorphisms have been described in the CYP19 gene. A tetranucleotide repeat polymorphism, (TTTA)_n, is located in intron 4, about 80 nucleotides downstream from exon 4.²²⁴ Our pooled analysis of the five studies examining the (TTTA)₁₀ allele polymorphism²²⁵⁻²²⁹ showed an OR of 1.59 (95% CI 1.01-2.48), with a PAR of 1%. There is, however, a problem in performing a pooled analysis on this polymorphism, because the studies use different methods to detect the alleles. Two studies found eight different alleles while the three others found seven, six, and five respectively. Two other polymorphisms in intron 4 and 6 described in one study were in strong linkage disequilibrium with the tetranucleotide polymorphism.²²⁹ No association with breast cancer was detected for either polymorphism. Another polymorphism (codon 264) also showed no association with breast cancer.²³⁰ In conclusion, this gene might play a (minor) role in breast cancer susceptibility.

Oestrogen receptor (ER) gene

ER is a critical determinant of cellular responsiveness to oestrogen and is thought to play an important role in breast cancer promotion.¹¹⁴ Germline and somatic mutations in the ER gene in breast cancer cases are rare.²³¹ Five somatic mutations in the ER gene have been found in only four out of 300 human breast tumours.²³²⁻²³⁴ Methylation of the promoter region of the ER gene was detected in 25% of ER negative breast cancers, while no methylation was found in ER positive tumours and normal breast specimens.²³⁵ Several polymorphisms in the ER

gene have been described. The *PvuII* polymorphism in intron 1 was examined in three studies,^{233 236 237} one of which did not use controls.²³³ The two other studies found no association with breast cancer, although the genotypes of cases (and not of controls) were only given in one.²³⁷ When the three studies were combined, with control genotypes from one study,²³⁶ no association was found. The total number of controls (n=53), however, is very small. The *XbaI* polymorphism²³⁷ showed a decreased breast cancer risk (OR=0.50, 95% CI 0.25-0.99) for homozygous carriers of the variant allele (10.5 kb allele). In this study, both the number of cases (n=191) and controls (n=204) was small. A third polymorphism, in codon 325, is located in the hormone binding domain and might therefore be correlated with the ER function.²³⁴ This was examined in three studies,^{233 234 238} including one study without controls.²³³ No association with breast cancer was found when the three studies were combined.

Surprisingly, only five relatively small studies examined polymorphisms in the *ER* gene. Owing to the small sample sizes, an association with breast cancer risk can neither be confirmed nor excluded.

Progesterone receptor (*PR*) gene

Methylation of the CpG islands in the 5' region of the *PR* gene was found in 40% of PR negative breast cancers cases (6/15) and not found in 15 PR positive tumours or normal breast specimens.²³⁵ A polymorphism in intron 7 of the *PR* gene has been described. The variant PROGINS allele consists of a 306 bp insertion of the Alu subfamily.²³⁹ Four studies studied this polymorphism in relation to breast cancer risk.²⁴⁰⁻²⁴³ Although the studies observed different ORs for heterozygous carriers, the ORs for women homozygous for the PROGINS allele were similar, ranging from 0.27-0.63 (fig 2). Pooled analysis of these studies showed that the OR for women homozygous for the variant allele was 0.32 (95% CI 0.16-0.65). Thus, instead of an increased risk, four studies separately and combined found a decreased breast cancer risk for homozygous carriers of the PROGINS allele.

Androgen receptor (*AR*) gene

A mutation in the *AR* gene was detected in three male breast cancer patients with (partial) androgen resistance, two brothers²⁴⁴ and one sporadic patient.²⁴⁵ An increased risk of breast cancer was found in women with *BRCA1* mutations (165 women with breast cancer, 139 without) if they inherited at least one *AR* allele with >27 CAG repeats.²⁴⁶ Two other studies in sporadic breast cancer patients found no association between the number of CAG repeats and breast cancer risk (in total, 876 cases and 810 controls).^{247 248} This polymorphism therefore does not appear to play a major role in breast cancer susceptibility.

Catechol-O-methyltransferase (*COMT*)

A polymorphism was identified in the *COMT* gene at codon 158²⁴⁹; the normal allele was designated *COMT-H* and the variant allele *COMT-L*. The variant allele encodes a thermolabile form of the enzyme with reduced activity. Four studies examined this polymorphism.^{19 219 250 251} No increased breast cancer risk (overall, for premenopausal or for postmenopausal women) was found when all studies were combined.

Uridine diphospho-glucuronosyltransferase 1A1 (*UGT1A1*) gene

A TA repeat polymorphism has been reported in the promoter region of the *UGT1A1* gene. Increasing the number of repeats in this polymorphism leads to a decrease in enzyme activity.^{252 253} The wild type allele (*UGT1A1*1*) contains six TA repeats and the most common variant allele (*UGT1A1*28*) seven. Two other variant alleles (*UGT1A1*33*, five repeats and *UGT1A1*34*, eight repeats) have been found almost exclusively in the African-American population.^{252 254} Among premenopausal women, an association was found in an African-

American population.²⁵³ An increased breast cancer risk (OR=1.8, 95% CI 1.0-3.1) was detected for heterozygous and homozygous carriers of the variant alleles with a decreased enzyme activity (*UGT1A1*28* and *UGT1A1*34*). In a white population in another study, no association was found.²⁵⁴ No association between breast cancer risk and the *UGT1A1*28* allele was detected when the studies were combined.

HLA region

The principal function of the highly polymorphic HLA antigens is to bind peptide fragments, so that they can be optimally presented to cytotoxic T lymphocytes and natural killer cells.²⁵⁵ The HLA antigens play a major role in immunity, self-recognition, and cell and tissue differentiation. Several studies observed no association with breast cancer.²⁵⁶⁻²⁵⁹ Other studies have indicated that different HLA antigens may either be risk factors for or protective against breast cancer.²⁶⁰⁻²⁶³ No strong associations with specific alleles were found and (some of) the results were contradictory. In one study, a family was examined in which more than 40% of the members of two generations had cancer (mostly breast, endometrial, and gastrointestinal).²⁶⁴ Positive lod scores to markers within or near the HLA region were found. None of the lod scores, however, reached significance.²⁶⁴ In conclusion, several reports have indicated that different HLA alleles may be risk factors for or protective factors against cancer. No clear associations with specific alleles have been detected.

Tumour necrosis factor α (*TNF α*) gene

The *TNF α* gene is a central mediator in the inflammatory response and immunological activities towards tumour cells.²⁶⁵⁻²⁶⁷ One polymorphism in the *TNF α* gene occurs in a series of repeating conserved motifs and is not randomly distributed. It therefore most likely has some functional and selective effect.²⁶⁸ The rare *TNF2* allele of this polymorphism lies on the extended haplotype A1-B8-DR3-DQ2,²⁶⁶ which is associated with autoimmunity and high *TNF α* production.^{269 270} A comparison of the data²⁶⁸ suggests that there may be a small effect of the -308 polymorphism, with the *TNF2* allele being associated with slightly higher levels of *TNF α* production. An association between *TNF2* allele carriers (heterozygous and homozygous) and breast cancer risk was shown in one study which included 40 breast cancer patients and 106 controls (OR=3.53, 95% CI 1.65-7.54).²⁶⁷

Heat shock protein 70 (*HSP70*) gene

In the HLA region, three intronless genes encoding members of *HSP70* are located centromerically to the *TNF* genes. The genes have been identified as *HSP70-1*, *HSP70-2*, and *HSP70-hom*.²⁷¹ *HSP70* is a determining factor in immunological mechanisms against tumour cells²⁶⁷ and HSPs can serve as a target for anti-tumour immune recognition by antibodies and T cells.^{272 273} Conversely, *HSP70* expression on tumour cells is correlated with the inhibition of monocytotoxic activity, which can protect tumour cells against host immunological reactions.²⁶⁷ Whether *HSP70* acts as an anti-tumour immune response enhancer or as a tumour promoter may depend on *HSP70* genotypes.²⁶⁷ One study showed that the variant allele carriership of the *HSP70-hom* gene was associated with breast cancer (OR=3.56, 95% CI 1.26-10.01), whereas carriership of the *HSP70-2* gene was not (OR=2.36, 95% CI 0.75-7.33).²⁶⁷

Iron metabolism

Experimental, clinical, and epidemiological investigations have shown that iron can influence carcinogenesis.²⁷⁴ Increased body iron stores have been associated with cancer risk. A number of genes are involved in iron metabolism, including the haemochromatosis gene (*HFE*) and the transferrin receptor (*TFR*) gene.

The HFE gene and hereditary haemochromatosis (HH)

So far, two point mutations (Cys282Tyr and His63Asp) have been detected in the *HFE* gene of HH patients. Over 80% of haemochromatosis patients are homozygous for the Cys282Tyr mutation.²⁷⁵ Heterozygous carriers, comprising 15% of the American population, have, on average, increased iron stores as compared to non-carriers.^{276, 277} In a study of 1950 HH heterozygotes and 1656 controls, no increased breast cancer risk was detected (OR=0.98, 95% CI 0.81-1.19).²⁷⁷ In another study with 165 cases and 294 controls, no association was found between breast cancer and the *HFE* and *TFR* genotypes when the genotypes were tested both separately and together.²⁷⁸ In conclusion, the *HFE* and *TFR* genes do not play a major role in breast cancer susceptibility.

Other genes

Vitamin D receptor (*VDR*) gene

Five polymorphisms of the *VDR* gene have been studied in breast cancer patients and controls. Four of these, the *TaqI*, *ApaI*, *BsmI*, and the poly-A polymorphism, are located in the 3' region of the gene and are in linkage disequilibrium with each other. One polymorphism, *FokI*, is located in the 5' region of the gene and is not in linkage disequilibrium with the other polymorphisms. The *TaqI* polymorphism, associated with increased serum vitamin D3 levels,²⁷⁹ was examined in three studies.^{247, 279, 280} No association with breast cancer was found in our pooled analysis (fig 3). The *BsmI* polymorphism was investigated in two studies and, when they were combined, again no association with breast cancer was found (fig 3).^{281, 282} The two other polymorphisms in the 3' region of the gene, the *ApaI* and the poly-A polymorphism, were each addressed in one small study. For both polymorphisms, an increased breast cancer risk was found for carriers (heterozygous and homozygous) of the variant allele (*ApaI*, OR=1.56, 95% CI 1.09-2.24²⁸⁰; poly-A, OR=1.73, 95% CI 1.16-2.59²⁸²; fig 3). Pooled analysis of the two studies on the *FokI* polymorphism^{280, 282} detected no association with breast cancer (fig 3). In one study, haplotypes of the *ApaI* (variant allele a) and the *TaqI* (variant allele T) polymorphisms were tested. Women with the genotype aaTT (homozygous for the haplotype of both variant alleles) had an increased breast cancer risk (OR=2.5, 95% CI 1.02-6.5) as compared to women with the genotype AaTt.²⁸⁰ The results of the different polymorphisms in this gene are contradictory, and it remains unclear whether the *VDR* gene plays a role in breast cancer susceptibility.

The APC gene

Breast tumours (n=227) were screened for truncating mutations in exon 15 of the *APC* gene (77% of the coding sequence) and only one somatic mutation was found.²⁸³ Somatic mutations in the *APC* gene were detected in 13 of 70 breast cancer cases in another study.²⁸⁴ Most of these mutations were outside the mutation cluster region that has been noted for colorectal cancer.²⁸⁴ One of the polymorphisms in the *APC* gene, the I1307K polymorphism, is specific to Ashkenazi Jews. In Ashkenazi Jewish women with breast cancer without a *BRCA1* or *BRCA2* mutation, no association between breast cancer and the I1307K polymorphism was detected.^{285, 286} In another study, the presence of the I1307K allele among *BRCA1/2* carriers was not associated with a further increase of cancer risk.²⁸⁷ This polymorphism probably does not play a role in breast cancer susceptibility.

Combinations of polymorphisms in different genes

One study examined the four polymorphisms in the *CYP1A1* gene and the *GSTM1* and *GSTT1* polymorphisms.¹⁶⁹ None of these polymorphisms, either separately or combined, was associated with increased breast cancer risks. Others analysed a combination of the m2 polymorphism in the *CYP1A1* gene

and the *GSTM1* polymorphism and again no associations were found.¹⁶⁷ One study²¹⁹ examined the m1 polymorphisms in the *CYP1A1* gene and the polymorphisms in the *CYP17* and *COMT* genes. The presence of at least two putative high risk genotypes was associated with an increased risk of breast cancer (OR=3.47, 95% CI 1.21-9.99).

In conclusion, in a few studies with small sample sizes, combinations of polymorphisms were examined.

DISCUSSION

This review, which examined 34 polymorphisms in 18 different genes, described in more than one breast cancer study, whenever possible with pooled analysis, showed an association with breast cancer for 13 polymorphisms in 10 genes. Increased breast cancer risks were found for the polymorphisms in *HRAS1*, *GSTM1*, *GSTP1*, *CYP1B1* (codon 119), *CYP2D6*, *CYP19*, and *VDR* (*ApaI* and poly-A), with PARs ranging from 1-41%. Interestingly, decreased breast cancer risks were found for women homozygous for the variant allele for the intron 3, exon 4, and intron 6 polymorphisms in the *Tp53* gene, the *XbaI* polymorphism in the *ER* gene, and the *PROGINS* polymorphism in the *PR* gene. Women with these genotypes may represent a subpopulation where prevention strategies can be less intensive than in the general population. The pooled analysis was performed on large (>2000 cases) sample sizes for the *HRAS1*, *GSTM1*, and *CYP19* polymorphisms. There is, therefore, strong evidence for increased breast cancer risks associated with these polymorphisms, although the increase in breast cancer risk for the *GSTM1* polymorphism is very small. More research on these three genes will probably only narrow the confidence intervals and not change either the ORs or the allele frequencies. The sample sizes studied for other polymorphisms, such as *Tp53* (intron 3, exon 4, and intron 6), *GSTP1*, *CYP1B1* (codon 119), *ER* (*XbaI*), and *VDR* (*ApaI* and poly-A), were quite small (<1000 cases). Because of this, the association with increased breast cancer risk is not confirmed. The sample sizes for the polymorphisms of *CYP2D6* and *PR* were intermediate (between 1000 and 2000 cases). Our pooled analysis indicated that there is an association with breast cancer, although more research (larger sample size) could slightly change both the ORs and the allele frequencies. The pooled analysis for 12 other polymorphisms in nine genes, namely *L-myc*, *NAT1*, *NAT2*, *GSTT1*, *CYP1A1*, *CYP17*, *AR*, *COMT*, and *UGT1A1*, showed no association with breast cancer. For *NAT2*, *GSTT1*, and *CYP17*, the polymorphisms with large sample sizes, an association with breast cancer can be excluded. For polymorphisms with small (*L-myc*, *NAT1*, *CYP1A1* (m2, m3 and m4), *AR*, and *UGT1A1*) or intermediate (*CYP1A1* (m1) and *COMT*) sample sizes, an association with breast cancer cannot be excluded.

Somewhat different rules are applicable for polymorphisms described in only one study. To conclude from a negative result that the original effect is likely to be an artefact, a sample size of roughly four times the initial study is needed when replicating these studies (see Appendix 1). Eight polymorphisms (*TNF- α* ,²⁶⁷ *HSP70-2*,²⁶⁷ *HSP70-hom*,²⁶⁷ *APOE*,²⁸⁸ *EDH17B2*,²⁸⁹ *HER2*,²⁹⁰ *TBR-1*,²⁹¹ and *TFR*²⁷⁸) are each described in only one study, all of which have (very) small sample sizes. A weak association with breast cancer was found for five of these (*TNF- α* , *HSP70-2*, *HSP70-hom*, *EDH17B2*, and *HER2*). Replication of this is needed either to confirm or reject the tentative findings.

Strikingly little research has been performed on combinations of polymorphisms which are addressed in only a few studies in breast cancer patients. An association with increased breast cancer risk was found for combinations of polymorphisms in the different *GST* genes, although the total number of cases (n=238) and controls (n=240) was small and the association was only marginally significant. No

evidence was observed for other associations with breast cancer for certain combinations, but this was mainly because of small sample sizes. For polymorphisms not associated with breast cancer when studied separately, an association is still possible in combination with other polymorphisms. Since the products of several genes interact (almost half of the reviewed genes play a role in oestrogen metabolism), interactions between the genes are likely.

When the variant itself is non-functional, but in linkage disequilibrium with some other functional variant, the overall risks may not be applicable to all populations, as linkage disequilibrium for certain variants often differ between populations.²¹

Finally, it is not unlikely that other genes exist that give rise to variation in breast cancer susceptibility, but have not yet been identified and/or tested. A whole genome screen would be the ideal method to detect new breast cancer susceptibility genes. This method, however, is still too expensive to carry out in large study populations. Until this is (economically) feasible, it would be useful to collect data on an appropriately sized, well described study population. Analysis of several (or all) of the polymorphisms already known to be associated with breast cancer in the same population will increase our understanding of the aetiology of breast cancer. More specific risk assessments will become available for women individually,¹⁶ with targeted breast cancer prevention strategies.¹³

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Appendix 1 Sample size calculation

More than one study. The statistical power for actual investigations into disease genes can be tackled by postulating a simple biallelic genetic model and assuming that the disease gene itself (or a 100% linked and associated marker) is observed. Relative risks of the disease can then be specified for homozygotes for the wild type allele (aa), heterozygotes (aA), and homozygotes for the variant allele (AA). This allows for variations in penetrance and dominant, additive, or recessive models. Other input parameters that the model needs are the disease frequency, the frequency of the variant allele, the required power, and the significance level. The basis of the calculation is the determination of the a posteriori genotype distribution of the frequencies of alleles transmitted from unaffected parents to their affected child. The genotypes constructed by the alleles that are not transmitted serve then as (pseudo) controls as in the transmission/disequilibrium test. Power calculations for the difference in the frequencies of binomial entities are performed using a normal approximation. Sample sizes required are then calculated for detecting differences between cases and controls in allele frequencies, in variant allele carriers and in homozygotes for the variant allele.

Although the assumption of 100% linked and associated markers is not entirely realistic, it does indicate an order of magnitude for the power of an actual investigation. This will probably be lower as a function of genetic distance and allelic frequency match between marker and disease alleles. The actual calculations are done on a Microsoft Excel® spreadsheet, available from the first author on request.

Only one study. When only one association study is available on a polymorphism, it is likely to be a positive one. It is therefore unlikely that a reliable disease model can be obtained from it. Because of this, the sample size cannot be computed with the formula presented in the previous section. A second study will need a sample size at least four times as large as the original one in order either to replicate or refute the association. The reason for the factor 4 is as follows. Assume that the power for the first study to find a significant difference between cases and controls is equal to 0.50. For example, for a disease model with a variant allele frequency of 0.20, a disease frequency of 10%, and genotypic relative risks for aA and AA both equal to 1.5, the power to detect a difference between cases and controls at a significance level of 5% is 0.502 in a study with 164 trios. To detect the same difference with a power of 0.95, 656 trios are required, which is exactly a factor of 4 larger. Even for a weak genetic disease model with a variant allele frequency of 0.50, a disease frequency of 10% and genotypic relative risks both equal to 1.1, this factor is 3.9996 (5001 trios in first study versus 20 002 in the replication study). In order to replicate the first study with a power of 90% (instead of 95%), the required increase in sample size is a factor of 3.165.

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ECHO

Another risk factor for MI?



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Platelet receptor gene $Ib\alpha$ -5T/C Kozak polymorphism may influence the risk of MI, concludes a preliminary UK study. In the prelude to MI platelets attach, through a glycoprotein complex GPIb/IX/V, to von Willebrand factor on plaques in the arterial walls. Four subunits (GPIb α , GPIb β , GPIX, GPV) comprise the receptor complex, each specified by a single gene; the GPIb α subunit has the binding site for von Willebrand factor. Douglas *et al* speculated that the GPIb α -5T/C sequence Kozak polymorphism—affecting GPIb/IX/V expression—and GPIb α variable number tandem repeats (VNTRs)—affecting its structure and lengthening the receptor—might alter the risk of MI. GPIb α Kozak polymorphism is a thymine (T) or cytosine (C) at position -5 around the ATG initiator codon; GPIb α VNTR has four variants (A-D) in descending molecular size.

Douglas *et al* analysed how common these genotypes were in patients aged 33–80 years (180 white, 76 Indian Asian), recruited at cardiac catheterisation, for those with confirmed MI (one group) and without (another group) but otherwise matched for known risk factors.

GPIb α Kozak homozygous TT genotype was strongly linked with MI (infarct group TT 85.2%, TC 12.5%, CC 2.3%; non-infarct group TT 67.3%, TC 32.7%, CC 32.7%; $p=0.001$) as was TT versus TC and CC genotypes. GPIb α VNTR genotypes showed no link, except marginally, between CC and all other genotypes. Neither polymorphism was linked with severity of arterial disease.

TT Kozak genotype may be important in MI, the authors conclude, but confirmation awaits a larger prospective study.

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