REVIEW ARTICLE

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

M M de Jong, I M Nolte, G J te Meerman, W T A van der Graaf, J C Oosterwijk, J H Kleibeuker, M Schaapveld, E G E de Vries

J Med Genet 2002;**39**:225–242

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

See end of article for authors' affiliations

Correspondence to:
Dr E G E de Vries,
Department of Medical
Oncology, University
Hospital Groningen,
Hanzeplein 1, PO Box
30.001 RB, Groningen,
The Netherlands;
E.G.E.de.Vries@int.azg.nl

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, TGFα) 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 oestradio ^{334 335}
<i>HER2</i>	17q21, proto-oncogene, control of cell growth and proliferation ^{336 337}
<i>TβRI</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>								
Apal	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 was 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 below 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 6^{61-64,66-67} 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 studies^{61,63} 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 patients^{83,84} 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.¹⁴⁴

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.^{148 153} 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.

Progesteron 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

ACKNOWLEDGEMENTS

This work was supported by grant RUG-98-1665 of the Dutch Cancer Society and by the Comprehensive Cancer Centre Northern Netherlands.

Authors' affiliations

M M de Jong, W T A van der Graaf, E G E de Vries, Department of Medical Oncology, University Hospital, Groningen, The Netherlands

M M de Jong, I M Nolte, G J te Meerman, J C Oosterwijk, Department of Medical Genetics, University Hospital, Groningen, The Netherlands

M M de Jong, J H Kleibeuker, Department of Gastroenterology, University Hospital, Groningen, The Netherlands

M Schaapveld, Comprehensive Cancer Centre Northern Netherlands, Groningen, The Netherlands

REFERENCES

- Parkin DM**. Epidemiology of cancer: global patterns and trends. *Toxicol Lett* 1998;**102-103**:227-34.
- Claus EB**, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer* 1994;**73**:643-51.
- Claus EB**. The genetic epidemiology of cancer. *Cancer Surv* 1995;**25**:13-26.
- Ford D**, Easton DF. The genetics of breast and ovarian cancer. *Br J Cancer* 1995;**72**:805-12.
- Rebbeck TR**, Couch FJ, Kant J, Calzone K, DeShano M, Peng Y, Chen K, Garber JE, Weber BL. Genetic heterogeneity in hereditary breast cancer: role of BRCA1 and BRCA2. *Am J Hum Genet* 1996;**59**:547-53.
- Greene MH**. Genetics of breast cancer. *Mayo Clin Proc* 1997;**72**:54-65.
- Ligtenberg MJ**, Hogervorst FB, Willems HW, Arts PJ, Brink G, Hageman S, Bosgoed EA, van der Looij E, Rookus MA, Devilee P, Vos EM, Wigbout G, Struycken PM, Menko FH, Rutgers EJ, Hoefsloot EH, Mariman EC, Brunner HG, van't Veer LJ. Characteristics of small breast and/or ovarian cancer families with germline mutations in BRCA1 and BRCA2. *Br J Cancer* 1999;**79**:1475-8.
- Easton D**. Breast cancer genes - what are the real risks? *Nat Genet* 1997;**16**:210-11.
- Phelan CM**, Lancaster JM, Tonin P, Gumbs C, Cochran C, Carter R, Ghadirian P, Perret C, Moslehi R, Dion F, Faucher MC, Dole K, Karimi S, Foulkes W, Lounis H, Warner E, Goss P, Anderson D, Larsson C, Narod SA, Futreal PA. Mutation analysis of the BRCA2 gene in 49 site-specific breast cancer families. *Nat Genet* 1996;**13**:120-2.
- Serova OM**, Mazoyer S, Puget N, Dubois V, Tonin P, Shugart YY, Goldgar D, Narod SA, Lynch HT, Lenoir GM. Mutations in BRCA1 and BRCA2 in breast cancer families: are there more breast cancer-susceptibility genes? *Am J Hum Genet* 1997;**60**:486-95.
- Hoskins KF**, Stopfer JE, Calzone KA, Merajver SD, Rebbeck TR, Garber JE, Weber BL. Assessment and counseling for women with a family history of breast cancer. A guide for clinicians. *JAMA* 1995;**273**:577-85.
- Martin AM**, Weber BL. Genetic and hormonal risk factors in breast cancer. *J Natl Cancer Inst* 2000;**92**:1126-35.
- Rebbeck TR**. Inherited genetic predisposition in breast cancer. A population-based perspective. *Cancer* 1999;**86**(suppl 11):2493-501.
- Andersen TI**. Genetic heterogeneity in breast cancer susceptibility. *Acta Oncol* 1996;**35**:407-10.
- te Meerman GJ**, de Vries EGE. Relevance of high and low penetrance. *Lancet* 2001;**358**:331.

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.

- 16 **Rebbbeck TR**, Rosvold EA, Duggan DJ, Zhang J, Buetow KH. Genetics of CYP1A1: coamplification of specific alleles by polymerase chain reaction and association with breast cancer. *Cancer Epidemiol Biomarkers Prev* 1994;**3**:511-14.
- 17 **Smith G**, Stanley LA, Sim E, Strange RC, Wolf CR. Metabolic polymorphisms and cancer susceptibility. *Cancer Surv* 1995;**25**:27-65.
- 18 **Feigelson HS**, Coetzee GA, Kolonel LN, Ross RK, Henderson BE. A polymorphism in the CYP17 gene increases the risk of breast cancer. *Cancer Res* 1997;**57**:1063-5.
- 19 **Lavigne JA**, Helzlsouer KJ, Huang HY, Strickland PT, Bell DA, Selmin O, Watson MA, Hoffman S, Comstock GW, Yager JD. An association between the allele coding for a low activity variant of catechol-O-methyltransferase and the risk for breast cancer. *Cancer Res* 1997;**57**:5493-7.
- 20 **Coughlin SS**, Piper M. Genetic polymorphisms and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 1999;**8**:1023-32.
- 21 **Dunning AM**, Healey CS, Pharoah PD, Teare MD, Ponder BA, Easton DF. A systematic review of genetic polymorphisms and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1999;**8**:843-54.
- 22 **Venitt S**. Mechanisms of carcinogenesis and individual susceptibility to cancer. *Clin Chem* 1994;**40**:1421-5.
- 23 **Knudson AG Jr**, Hethcote HW, Brown BW. Mutation and childhood cancer: a probabilistic model for the incidence of retinoblastoma. *Proc Natl Acad Sci USA* 1975;**72**:5116-20.
- 24 **Baylin SB**, Herman JG, Graff JR, Vertino PM, Issa JP. Alterations in DNA methylation: a fundamental aspect of neoplasia. *Adv Cancer Res* 1998;**72**:141-96.
- 25 **Jones PA**, Laird PW. Cancer epigenetics comes of age. *Nat Genet* 1999;**21**:163-7.
- 26 **Bianco T**, Chenevix TG, Walsh DC, Cooper JE, Dobrovic A. Tumour-specific distribution of BRCA1 promoter region methylation supports a pathogenetic role in breast and ovarian cancer. *Carcinogenesis* 2000;**21**:147-51.
- 27 **Kerangueven F**, Essioux L, Dib A, Noguchi T, Allione F, Geneix J, Longy M, Lidereau R, Eisinger F, Pebusque MJ, Jacquemier J, Bonaiti-Pellie C, Sobol H, Birnbaum D. Loss of heterozygosity and linkage analysis in breast carcinoma: indication for a putative third susceptibility gene on the short arm of chromosome 8. *Oncogene* 1995;**10**:1023-6.
- 28 **Seitz S**, Rohde K, Bender E, Nothnagel A, Kolbe K, Schlag PM, Scherneck S. Strong indication for a breast cancer susceptibility gene on chromosome 8p12-p22: linkage analysis in German breast cancer families. *Oncogene* 1997;**14**:741-3.
- 29 **Yaremko ML**, Recant WM, Westbrook CA. Loss of heterozygosity from the short arm of chromosome 8 is an early event in breast cancers. *Genes Chromosomes Cancer* 1995;**13**:186-91.
- 30 **Yaremko ML**, Kutza C, Lyzak J, Mick R, Recant WM, Westbrook CA. Loss of heterozygosity from the short arm of chromosome 8 is associated with invasive behavior in breast cancer. *Genes Chromosomes Cancer* 1996;**16**:189-95.
- 31 **Kerangueven F**, Noguchi T, Coulter F, Allione F, Wargniew V, Simony L, Longy M, Jacquemier J, Sobol H, Eisinger F, Birnbaum D. Genome-wide search for loss of heterozygosity shows extensive genetic diversity of human breast carcinomas. *Cancer Res* 1997;**57**:5469-74.
- 32 **Seitz S**, Rohde K, Bender E, Nothnagel A, Pidde H, Ullrich OM, El-Zehairy A, Haensch W, Jandrig B, Kolbe K, Schlag PM, Scherneck S. Deletion mapping and linkage analysis provide strong indication for the involvement of the human chromosome region 8p12-p22 in breast carcinogenesis. *Br J Cancer* 1997;**76**:983-91.
- 33 **Adelaide J**, Chaffanet M, Imbert A, Allione F, Geneix J, Popovici C, van Alewijk D, Trapman J, Zeillinger R, Borresen DA, Lidereau R, Birnbaum D, Pebusque MJ. Chromosome region 8p11-p21: refined mapping and molecular alterations in breast cancer. *Genes Chrom Cancer* 1998;**22**:186-99.
- 34 **Suzuki A**, Shao X, Song XQ, Hanaoka T, Irie S, Kashiwada M, Samara G, Close LG, Aoki T, Fujimori M, Ishikawa Y, Hatori M, Hosaka M, Sakurada A, Sato M, Ohuchi N, Satomi S, Fukushima S, Horii A, Sato T. Identification of a 5-cM region of common allelic loss on 8p12-p21 in human breast cancer and genomic analysis of the hEXT1L/EXT1/EXTL3 gene in this locus. *Int J Oncol* 1999;**15**:443-51.
- 35 **Yokota T**, Yoshimoto M, Akiyama F, Sakamoto G, Kasumi F, Nakamura Y, Emi M. Localization of a tumor suppressor gene associated with the progression of human breast carcinoma within a 1-cM interval of 8p22-p23.1. *Cancer* 1999;**85**:447-52.
- 36 **Sigbjørnsdóttir BI**, Ragnarsson G, Agnarsson BA, Huipung C, Barkardóttir RB, Egilsson V, Ingvarsson S. Chromosome 8p alterations in sporadic and BRCA2 999del5 linked breast cancer. *J Med Genet* 2000;**37**:342-7.
- 37 **Chuaqui RF**, Sanz-Ortega J, Vocke C, Linehan WM, Sanz-Espionera J, Zhuang Z, Emmert-Buck MR, Merino MJ. Loss of heterozygosity on the short arm of chromosome 8 in male breast carcinomas. *Cancer Res* 1995;**55**:4995-8.
- 38 **Anbazhagan R**, Fujii H, Gabrielson E. Allelic loss of chromosomal arm 8p in breast cancer progression. *Am J Pathol* 1998;**152**:815-19.
- 39 **Wang JC**, Radford DM, Holt MS, Helms C, Goate A, Brandt W, Parik M, Phillips NJ, DeSchryver K, Schuh ME, Fair KL, Ritter JH, Marshall P, Donis-Keller H. Sequence-ready contig for the 1.4-cM ductal carcinoma in situ loss of heterozygosity region on chromosome 8p22-p23. *Genomics* 1999;**60**:1-11.
- 40 **Yu CE**, Oshima J, Fu YH, Wijsman EM, Hisama F, Alisch R, Matthews S, Nakura J, Miki T, Ouais S, Martin GM, Mulligan J, Schellenberg GD. Positional cloning of the Werner's syndrome gene. *Science* 1996;**272**:258-62.
- 41 **Gerbault-Seureau M**, Vielh P, Dutrillaux B. Recurrent HSR in the centromeric region of chromosome 8 in breast cancer. *Ann Genet* 1987;**30**:146-51.
- 42 **Bruskiewicz R**, Schertzer M, Wood S. A 2.8 megabase YAC contig spanning D8S339, which is tightly linked to the Werner syndrome locus. *Genome* 1997;**40**:77-83.
- 43 **Levine AJ**, Momand J, Finlay CA. The p53 tumour suppressor gene. *Nature* 1991;**351**:453-6.
- 44 **Malkin D**. Germline p53 mutations and heritable cancer. *Annu Rev Genet* 1994;**28**:443-65.
- 45 **Harris CC**, Hollstein M. Clinical implications of the p53 tumor-suppressor gene. *N Engl J Med* 1993;**329**:1318-27.
- 46 **Garber JE**, Goldstein AM, Kantor AF, Dreyfus MG, Fraumeni JF, Jr., Li FP. Follow-up study of twenty-four families with Li-Fraumeni syndrome. *Cancer Res* 1991;**51**:6094-7.
- 47 **Prosser J**, Elder PA, Condie A, MacFadyen I, Steel CM, Evans HJ. Mutations in p53 do not account for heritable breast cancer: a study in five affected families. *Br J Cancer* 1991;**63**:181-4.
- 48 **Borresen AL**, Andersen TI, Garber J, Barbier PN, Thorlacius S, Eyfjord J, Ottestad L, Smith SB, Hovig E, Malkin D, Friend SH. Screening for germ line TP53 mutations in breast cancer patients. *Cancer Res* 1992;**52**:3234-6.
- 49 **Prosser J**, Porter D, Coles C, Condie A, Thompson AM, Chetty U, Steel CM, Evans HJ. Constitutional p53 mutation in a non-Li-Fraumeni cancer family. *Br J Cancer* 1992;**65**:527-8.
- 50 **Sidransky D**, Tokino T, Helzlsouer K, Zehnbauser B, Rausch G, Shelton B, Prestigiacomo L, Vogelstein B, Davidson N. Inherited p53 gene mutations in breast cancer. *Cancer Res* 1992;**52**:2984-6.
- 51 **Patel UA**, Perry M, Crane RC. Screening for germline mutations of the p53 gene in familial breast cancer patients. *Eur J Clin Invest* 1995;**25**:132-7.
- 52 **Osborne RJ**, Merlo GR, Mitsudomi T, Venesio T, Liscia DS, Cappa AP, Chiba I, Takahashi T, Nau MM, Callahan R, Minna JD. Mutations in the p53 gene in primary human breast cancers. *Cancer Res* 1991;**51**:6194-8.
- 53 **Coles C**, Condie A, Chetty U, Steel CM, Evans HJ, Prosser J. p53 mutations in breast cancer. *Cancer Res* 1992;**52**:5291-8.
- 54 **Thompson AM**, Anderson TJ, Condie A, Prosser J, Chetty U, Carter DC, Evans HJ, Steel CM. p53 allele losses, mutations and expression in breast cancer and their relationship to clinicopathological parameters. *Int J Cancer* 1992;**50**:528-32.
- 55 **Deng G**, Chen LC, Schott DR, Thor A, Bhargava V, Ljung BM, Chew K, Smith HS. Loss of heterozygosity and p53 gene mutations in breast cancer. *Cancer Res* 1994;**54**:499-505.
- 56 **Greenblatt MS**, Bennett WP, Hollstein M, Harris CC. Mutations in the p53 tumor suppressor gene: clues to cancer etiology and molecular pathogenesis. *Cancer Res* 1994;**54**:4855-78.
- 57 **Shiao YH**, Chen VW, Scheer WD, Wu XC, Correa P. Racial disparity in the association of p53 gene alterations with breast cancer survival. *Cancer Res* 1995;**55**:1485-90.
- 58 **Nayak BK**, Das BR. Mutation and methylation status of p53 gene promoter in human breast tumours. *Tumour Biol* 1999;**20**:341-6.
- 59 **Själander A**, Birgander R, Kivela A, Beckman G. p53 polymorphisms and haplotypes in different ethnic groups. *Hum Hered* 1995;**45**:144-9.
- 60 **Campbell IG**, Eccles DM, Dunn B, Davis M, Leake V. p53 polymorphism in ovarian and breast cancer. *Lancet* 1996;**347**:393-4.
- 61 **Själander A**, Birgander R, Hallmans G, Cajander S, Lenner P, Athlin L, Beckman G, Beckman L. p53 polymorphisms and haplotypes in breast cancer. *Carcinogenesis* 1996;**17**:1313-16.
- 62 **Weston A**, Pan CF, Ksieski HB, Wallenstein S, Berkowitz GS, Tartter PI, Bleiweiss U, Brower ST, Senie RT, Wolff MS. p53 haplotype determination in breast cancer. *Cancer Epidemiol Biomarkers Prev* 1997;**6**:105-12.
- 63 **Wang GS**, Rebbbeck TR, Besenfelder W, Kreienberg R, Runnebaum IB. p53 germline polymorphisms are associated with an increased risk for breast cancer in German women. *Anticancer Res* 1998;**18**:2095-9.
- 64 **Khalil S**, Hameed A, Khalil T, Ayub Q, Qamar R, Mohyuddin A, Mazhar K, Qasim MS. P53 mutations, polymorphisms, and haplotypes in Pakistani ethnic groups and breast cancer patients. *Genet Test* 2000;**4**:23-9.
- 65 **Kawajiri K**, Nakachi K, Imai K, Watanabe J, Hayashi S. Germ line polymorphisms of p53 and CYP1A1 genes involved in human lung cancer. *Carcinogenesis* 1993;**14**:1085-9.
- 66 **Peller S**, Kopilova Y, Slutski S, Halevy A, Kvitek K, Rotter V. A novel polymorphism in intron 6 of the human p53 gene: a possible association with cancer predisposition and susceptibility. *DNA Cell Biol* 1995;**14**:983-90.
- 67 **Mavridou D**, Gornall R, Campbell IG, Eccles DM. TP53 intron 6 polymorphism and the risk of ovarian and breast cancer. *Br J Cancer* 1998;**77**:676-7.
- 68 **Swift M**, Reitnauer PJ, Morrell D, Chase CL. Breast and other cancers in families with ataxia-telangiectasia. *N Engl J Med* 1987;**316**:1289-94.
- 69 **Shigeta T**, Takagi M, Delia D, Chessa L, Iwata S, Kanke Y, Asada M, Eguchi M, Mizutani S. Defective control of apoptosis and mitotic spindle checkpoint in heterozygous carriers of ATM mutations. *Cancer Res* 1999;**59**:2602-7.
- 70 **Pippard EC**, Hall AJ, Barker DJ, Bridges BA. Cancer in homozygotes and heterozygotes of ataxia-telangiectasia and xeroderma pigmentosum in Britain. *Cancer Res* 1988;**48**:2929-32.
- 71 **Borresen AL**, Andersen TI, Trelli S, Heiberg A, Moller P. Breast cancer and other cancers in Norwegian families with ataxia-telangiectasia. *Genes Chrom Cancer* 1990;**2**:339-40.

- 72 **Morrell D**, Chase CL, Swift M. Cancers in 44 families with ataxia-telangiectasia. *Cancer Genet Cytogenet* 1990;**50**:119-23.
- 73 **Swift M**, Morrell D, Massey RB, Chase CL. Incidence of cancer in 161 families affected by ataxia-telangiectasia. *N Engl J Med* 1991;**325**:1831-6.
- 74 **Easton DF**. Cancer risks in A-T heterozygotes. *Int J Radiat Biol* 1994;**66**(suppl 6):S177-82.
- 75 **Athma P**, Rappaport R, Swift M. Molecular genotyping shows that ataxia-telangiectasia heterozygotes are predisposed to breast cancer. *Cancer Genet Cytogenet* 1996;**92**:130-4.
- 76 **Janin N**, Andrieu N, Ossian K, Laugel A, Croquette MF, Griscelli C, Debre M, Bressac-de-Paillerets B, Aurias A, Stoppa-Lyonnet D. Breast cancer risk in ataxia telangiectasia (AT) heterozygotes: haplotype study in French AT families. *Br J Cancer* 1999;**80**:1042-5.
- 77 **Cortessis V**, Ingles S, Millikan R, Diep A, Gatti RA, Richardson L, Thompson WD, Paganini HA, Sparkes RS, Haile RW. Linkage analysis of DRD2, a marker linked to the ataxia-telangiectasia gene, in 64 families with premenopausal bilateral breast cancer. *Cancer Res* 1993;**53**:5083-6.
- 78 **Easton DF**. The inherited component of cancer. *Br Med Bull* 1994;**50**:527-35.
- 79 **Vorechovsky I**, Luo L, Lindblom A, Negri M, Webster AD, Croce CM, Hammarstrom L. ATM mutations in cancer families. *Cancer Res* 1996;**56**:4130-3.
- 80 **Chen J**, Birkholz GG, Lindblom P, Rubio C, Lindblom A. The role of ataxia-telangiectasia heterozygotes in familial breast cancer. *Cancer Res* 1998;**58**:1376-9.
- 81 **Vorechovsky I**, Rasio D, Luo L, Monaco C, Hammarstrom L, Webster AD, Zaloudik J, Barbanti BG, James M, Russo G, Croce CM, Negri M. The ATM gene and susceptibility to breast cancer: analysis of 38 breast tumors reveals no evidence for mutation. *Cancer Res* 1996;**56**:2726-32.
- 82 **Bebb DG**, Yu Z, Chen J, Telatar M, Gelmon K, Phillips N, Gatti RA, Glickman BW. Absence of mutations in the ATM gene in forty-seven cases of sporadic breast cancer. *Br J Cancer* 1999;**80**:1979-81.
- 83 **FitzGerald MG**, Bean JM, Hegde SR, Unsul H, MacDonald DJ, Harkin DP, Finkelstein DM, Isselbacher KJ, Haber DA. Heterozygous ATM mutations do not contribute to early onset of breast cancer. *Nat Genet* 1997;**15**:307-10.
- 84 **Izatt L**, Greenman J, Hodgson S, Ellis D, Watts S, Scott G, Jacobs C, Liebmann R, Zvelebil MJ, Mathew C, Solomon E. Identification of germline missense mutations and rare allelic variants in the ATM gene in early-onset breast cancer. *Genes Chrom Cancer* 1999;**26**:286-94.
- 85 **Shafman TD**, Levitz S, Nixon AJ, Gibbons LA, Nichols KE, Bell DW, Ishioka C, Isselbacher KJ, Gelman R, Garber J, Harris JR, Haber DA. Prevalence of germline truncating mutations in ATM in women with a second breast cancer after radiation therapy for a contralateral tumor. *Genes Chrom Cancer* 2000;**27**:124-9.
- 86 **Broeks A**, Urbanus JH, Floore AN, Dahler EC, Klijn JG, Rutgers EJ, Devilee P, Russell NS, van Leeuwen FE, van't Veer U. ATM-heterozygous germline mutations contribute to breast cancer-susceptibility. *Am J Hum Genet* 2000;**66**:494-500.
- 87 **Gatti RA**, Tward A, Concannon P. Cancer risk in ATM heterozygotes: a model of phenotypic and mechanistic differences between missense and truncating mutations. *Mol Genet Metab* 1999;**68**:419-23.
- 88 **Meyn MS**. Ataxia-telangiectasia, cancer and the pathobiology of the ATM gene. *Clin Genet* 1999;**55**:289-304.
- 89 **Stankovic T**, Kidd AM, Sutcliffe A, McGuire GM, Robinson P, Weber P, Bedenham T, Bradwell AR, Easton DF, Lennox GG, Hailes N, Byrd PJ, Taylor AM. ATM mutations and phenotypes in ataxia-telangiectasia families in the British Isles: expression of mutant ATM and the risk of leukemia, lymphoma, and breast cancer. *Am J Hum Genet* 1998;**62**:334-45.
- 90 **Thorstenon YR**, Roxas A, Kroiss R, Wagner T, Oefner PJ. Germline carriers of ATM mutations are prevalent among Austrian hereditary breast and ovarian cancer (HBOC) patients. *Am J Hum Genet Suppl* 2001;**69**:205(148).
- 91 **Liaw D**, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, Bose S, Call KM, Tsou HC, Peacocke M, Eng C, Parsons R. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nat Genet* 1997;**16**:64-7.
- 92 **Marsh DJ**, Coulon V, Lunetta KL, Rocca-Serra P, Dahia PL, Zheng Z, Liaw D, Caron S, Duboue B, Lin AY, Richardson AL, Bonnetblanc JM, Bressieux JM, Cabarro-Moreau A, Chompret A, Demange L, Eeles RA, Yahanda AM, Fearon ER, Fricker JP, Gorlin RJ, Hodgson SV, Huson S, Lacombe D, LePrat F, Odent S, Toulouse C, Olopade OI, Sobol H, Tishler S, Woods CG, Robinson BG, Weber HC, Parsons R, Peacocke M, Longy M, Eng C. Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. *Hum Mol Genet* 1998;**7**:507-15.
- 93 **Marsh DJ**, Kum JB, Lunetta KL, Bennett MJ, Gorlin RJ, Ahmed SF, Bodurtha J, Crowe C, Curtis MA, Dasouki M, Dunn T, Feit H, Geraghty MT, Graham JM, Jr., Hodgson SV, Hunter A, Korf BR, Manchester D, Miesfeldt S, Murday VA, Nathanson KL, Parisi M, Pober B, Romano C, Eng C. PTEN mutation spectrum and genotype-phenotype correlations in Bannayan-Riley-Ruvalcaba syndrome suggest a single entity with Cowden syndrome. *Hum Mol Genet* 1999;**8**:1461-72.
- 94 **Starink TM**, van der Veen JP, Arwert F, de Waal LP, de Lange GG, Gille JJ, Eriksson AW. The Cowden syndrome: a clinical and genetic study in 21 patients. *Clin Genet* 1986;**29**:222-33.
- 95 **Eng C**. Genetics of Cowden syndrome: through the looking glass of oncology. *Int J Oncol* 1998;**12**:701-10.
- 96 **Tsou HC**, Teng DH, Ping XL, Brancolini V, Davis T, Hu R, Xie XX, Gruener AC, Schragar CA, Christiano AM, Eng C, Steck P, Ott J, Tavtigian SV, Peacocke M. The role of MMAC1 mutations in early-onset breast cancer: causative in association with Cowden syndrome and excluded in BRCA1-negative cases. *Am J Hum Genet* 1997;**61**:1036-43.
- 97 **Chen J**, Lindblom P, Lindblom A. A study of the PTEN/MMAC1 gene in 136 breast cancer families. *Hum Genet* 1998;**102**:124-5.
- 98 **Carroll BT**, Couch FJ, Rebbeck TR, Weber BL. Polymorphisms in PTEN in breast cancer families. *J Med Genet* 1999;**36**:94-6.
- 99 **Laugel A**, Lefebvre C, Laurent-Puig P, Caux V, Gad S, Eng C, Longy M, Stoppa-Lyonnet D. No evidence for germline PTEN mutations in families with breast and brain tumours. *Int J Cancer* 1999;**84**:216-19.
- 100 **Rhei E**, Kang L, Bogomolny F, Federici MG, Borgen PI, Boyd J. Mutation analysis of the putative tumor suppressor gene PTEN/MMAC1 in primary breast carcinomas. *Cancer Res* 1997;**57**:3657-9.
- 101 **Ueda K**, Nishijima M, Inui H, Watanabe M, Yayoi E, Okamura J, Yasutomi M, Nakamura Y, Miyoshi Y. Infrequent mutations in the PTEN/MMAC1 gene among primary breast cancers. *Jpn J Cancer Res* 1998;**89**:17-21.
- 102 **Freihoff D**, Kempe A, Beste B, Wappenschmidt B, Kreyer E, Hayashi Y, Meindl A, Krebs D, Wiestler OD, von Deimling A, Schmutzler RK. Exclusion of a major role for the PTEN tumour-suppressor gene in breast carcinomas. *Br J Cancer* 1999;**79**:754-8.
- 103 **Feilottor HE**, Coulon V, McVeigh JL, Boag AH, Dorion BF, Duboue B, Latham WC, Eng C, Mulligan LM, Longy M. Analysis of the 10q23 chromosomal region and the PTEN gene in human sporadic breast carcinoma. *Br J Cancer* 1999;**79**:718-23.
- 104 **Perren A**, Weng LP, Boag AH, Ziebold U, Thakore K, Dahia PL, Komminoth P, Lees JA, Mulligan LM, Mutter GL, Eng C. Immunohistochemical evidence of loss of PTEN expression in primary ductal adenocarcinomas of the breast. *Am J Pathol* 1999;**155**:1253-60.
- 105 **FitzGerald MG**, Marsh DJ, Wahner D, Bell D, Caron S, Shannon KE, Ishioka C, Isselbacher KJ, Garber JE, Eng C, Haber DA. Germline mutations in PTEN are an infrequent cause of genetic predisposition to breast cancer. *Oncogene* 1998;**17**:727-31.
- 106 **Singh B**, Ittmann MM, Krolewski JJ. Sporadic breast cancers exhibit loss of heterozygosity on chromosome segment 10q23 close to the Cowden disease locus. *Genes Chrom Cancer* 1998;**21**:166-71.
- 107 **Whang YE**, Wu X, Suzuki H, Reiter RE, Tran C, Vessella RL, Said JW, Isaacs WB, Sawyers CL. Inactivation of the tumor suppressor PTEN/MMAC1 in advanced human prostate cancer through loss of expression. *Proc Natl Acad Sci USA* 1998;**95**:5246-50.
- 108 **Giardiello FM**, Welsh SB, Hamilton SR, Offerhaus GJ, Gittelsohn AM, Booker SV, Krush AJ, Yardley JH, Luk GD. Increased risk of cancer in the Peutz-Jeghers syndrome. *N Engl J Med* 1987;**316**:1511-14.
- 109 **Hemminki A**, Markie D, Tomlinson I, Avizienyte E, Roth S, Loukola A, Bignell G, Warren W, Aminoff M, Hoglund P, Jarvinen H, Kristo P, Pelin K, Ridanpaa M, Salovaara R, Toro T, Bodmer W, Olschwang S, Olsen AS, Stratton MR, de la Chapelle A, Aaltonen LA. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature* 1998;**391**:184-7.
- 110 **Jenne DE**, Reimann H, Nezu J, Friedel W, Loff S, Jeschke R, Muller O, Back W, Zimmer M. Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. *Nat Genet* 1998;**18**:38-43.
- 111 **Bardman LA**, Thibodeau SN, Schaid DJ, Lindor NM, McDonnell SK, Burgart LJ, Ahlquist DA, Podratz KC, Pittelkow M, Hartmann LC. Increased risk for cancer in patients with the Peutz-Jeghers syndrome. *Ann Intern Med* 1998;**128**:896-9.
- 112 **Chen J**, Lindblom A. Germline mutation screening of the STK11/LKB1 gene in familial breast cancer with LOH on 19p. *Clin Genet* 2000;**57**:394-7.
- 113 **Bignell GR**, Barfoot R, Seal S, Collins N, Warren W, Stratton MR. Low frequency of somatic mutations in the LKB1/Peutz-Jeghers syndrome gene in sporadic breast cancer. *Cancer Res* 1998;**58**:1384-6.
- 114 **Weber BL**, Nathanson KL. Low penetrance genes associated with increased risk for breast cancer. *Eur J Cancer* 2000;**36**:1193-9.
- 115 **Goldfarb M**, Shimizu K, Perucho M, Wigler M. Isolation and preliminary characterization of a human transforming gene from T24 bladder carcinoma cells. *Nature* 1982;**296**:404-9.
- 116 **Capon DJ**, Chen EY, Levinson AD, Seeburg PH, Goeddel DV. Complete nucleotide sequences of the T24 human bladder carcinoma oncogene and its normal homologue. *Nature* 1983;**302**:33-7.
- 117 **Krontiris TG**. Detection of cancer predisposition by hypervariable region analysis. *Birth Defects* 1990;**26**:129-40.
- 118 **Kasperczyk A**, DiMartino NA, Krontiris TG. Minisatellite allele diversification: the origin of rare alleles at the HRAS1 locus. *Am J Hum Genet* 1990;**47**:854-9.
- 119 **Lidreau R**, Escot C, Theillet C, Champeme MH, Brunet M, Gest J, Callahan R. High frequency of rare alleles of the human c-Ha-ras-1 proto-oncogene in breast cancer patients. *J Natl Cancer Inst* 1986;**77**:697-701.
- 120 **Maestri I**, Castagnoli A, Bertusi M, Zandi G, Vettorello G, del Senno L. RFLPs of the Ha-ras 1 protooncogene in subjects with colon-rectal carcinomas. *Boll Soc Ital Biol Sper* 1987;**63**:305-10.
- 121 **Corell B**, Zoll B. Comparison between the allelic frequency distribution of the Ha-ras 1 locus in normal individuals and patients with lymphoma, breast, and ovarian cancer. *Hum Genet* 1988;**79**:255-9.
- 122 **Honda K**, Ishizaki K, Ikenaga M, Toguchida J, Inamoto T, Tanaka K, Ozawa K. Increased frequency of specific alleles of the c-Ha-ras gene in Japanese cancer patients. *Hum Genet* 1988;**79**:297-300.
- 123 **Mackay J**, Elder PA, Porteous DJ, Steel CM, Hawkins RA, Going JJ, Chetty U. Partial deletion of chromosome 11p in breast cancer correlates

- with size of primary tumour and oestrogen receptor level. *Br J Cancer* 1988;**58**:710-14.
- 124 **Saglio G**, Camaschella C, Giai M, Serra A, Guersio A, Peirone B, Gasparini P, Mazza U, Ceppellini R, Biglia N, Cortese P, Sisonodi P. Distribution of Ha-RAS-1 proto-oncogene alleles in breast cancer patients and in a control population. *Breast Cancer Res Treat* 1988;**11**:147-53.
 - 125 **Sheng ZM**, Guerin M, Gabillet M, Spielmann M, Riou G. c-Ha-ras-1 polymorphism in human breast carcinomas: evidence for a normal distribution of alleles. *Oncogene Res* 1988;**2**:245-50.
 - 126 **Barkardottir RB**, Johannsson OT, Arason A, Gudnason V, Egilsson V. Polymorphism of the c-Ha-ras-1 proto-oncogene in sporadic and familial breast cancer. *Int J Cancer* 1989;**44**:251-5.
 - 127 **Hall JM**, Huey B, Morrow J, Newman B, Lee M, Jones E, Carter C, Buehring GC, King MC. Rare HRAS alleles and susceptibility to human breast cancer. *Genomics* 1990;**6**:188-91.
 - 128 **Garrett PA**, Hulka BS, Kim YL, Farber RA. HRAS protooncogene polymorphism and breast cancer. *Cancer Epidemiol Biomarkers Prev* 1993;**2**:131-8.
 - 129 **Krontiris TG**, Devlin B, Karp DD, Robert NJ, Risch N. An association between the risk of cancer and mutations in the HRAS1 minisatellite locus. *N Engl J Med* 1993;**329**:517-23.
 - 130 **Firgaia FA**, Seshadri R, McEvoy CR, Dite GS, Giles GG, McCredie MR, Southey MC, Venter DJ, Hopper JL. HRAS1 rare minisatellite alleles and breast cancer in Australian women under age forty years. *J Natl Cancer Inst* 1999;**91**:2107-11.
 - 131 **Gosse-Brun S**, Sauvaigo S, Dayer A, Page M, Lortholary A, Larra F, Bignon YJ, Bernard-Gallon D. Specific H-Ras minisatellite alleles in breast cancer susceptibility. *Anticancer Res* 1999;**19**:5191-6.
 - 132 **Vineis P**, Caporaso N. The analysis of restriction fragment length polymorphism in human cancer: a review from an epidemiological perspective. *Int J Cancer* 1991;**47**:26-30.
 - 133 **Ishizaki K**, Kato M, Ikenaga M, Honda K, Ozawa K, Toguchida J. Correlation of L-myc genotypes to metastasis of gastric cancer and breast cancer. *J Natl Cancer Inst* 1990;**82**:238-9.
 - 134 **Champeme MH**, Bieche I, Latil A, Hacene K, Lidereau R. Association between restriction fragment length polymorphism of the L-myc gene and lung metastasis in human breast cancer. *Int J Cancer* 1992;**50**:6-9.
 - 135 **Togo AV**, Suspitsin EN, Grigoriev MY, Ilyushik ES, Karpova MB, Hanson KP, Imyanitov EN. L-myc polymorphism in cancer patients, healthy blood donors and elderly, tumor-free individuals in Russia. *Int J Cancer* 2000;**85**:747-50.
 - 136 **Huober J**, Bertram B, Petru E, Kaufmann M, Schmah D. Metabolism of debrisoquine and susceptibility to breast cancer. *Breast Cancer Res Treat* 1991;**18**:43-8.
 - 137 **Kiss I**, Sander J, Pajkos G, Bogner B, Hegedus G, Ember I. Colorectal cancer risk in relation to genetic polymorphism of cytochrome P450 1A1, 2E1, and glutathione-S-transferase M1 enzymes. *Anticancer Res* 2000;**20**:519-22.
 - 138 **Rebbeck TR**, Walker AH, Phelan CM, Godwin AK, Buetow KH, Garber JE, Narod SA, Weber BL. Defining etiologic heterogeneity in breast cancer using genetic biomarkers. *Prog Clin Biol Res* 1997;**396**:53-61.
 - 139 **Badawi AF**, Hirvonen A, Bell DA, Lang NP, Kadlubar FF. Role of aromatic amine acetyltransferases, NAT1 and NAT2, in carcinogen-DNA adduct formation in the human urinary bladder. *Cancer Res* 1995;**55**:5230-7.
 - 140 **Bell DA**, Badawi AF, Lang NP, Ilett KF, Kadlubar FF, Hirvonen A. Polymorphism in the N-acetyltransferase 1 (NAT1) polyadenylation signal: association of NAT1*10 allele with higher N-acetylation activity in bladder and colon tissue. *Cancer Res* 1995;**55**:5226-9.
 - 141 **Hughes NC**, Janezic SA, McQueen KL, Jewett MA, Castranio T, Bell DA, Grant DM. Identification and characterization of variant alleles of human acetyltransferase NAT1 with defective function using p-aminosalicylate as an in-vivo and in-vitro probe. *Pharmacogenetics* 1998;**8**:55-66.
 - 142 **Bell DA**, Stephens EA, Castranio T, Umbach DM, Watson M, Deakin M, Elder J, Hendrickse C, Duncan H, Strange RC. Polyadenylation polymorphism in the acetyltransferase 1 gene (NAT1) increases risk of colorectal cancer. *Cancer Res* 1995;**55**:3537-42.
 - 143 **Millikan RC**, Pittman GS, Newman B, Tse CK, Selmin O, Rockhill B, Savitz D, Moorman PG, Bell DA. Cigarette smoking, N-acetyltransferases 1 and 2, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1998;**7**:371-8.
 - 144 **Zheng W**, Deitz AC, Campbell DR, Wen WQ, Cerhan JR, Sellers TA, Folsom AR, Hein DW. N-acetyltransferase 1 genetic polymorphism, cigarette smoking, well-done meat intake, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1999;**8**:233-9.
 - 145 **Cascorbi I**, Drakoulis N, Brockmoller J, Maurer A, Sperling K, Roots I. Arylamine N-acetyltransferase (NAT2) mutations and their allelic linkage in unrelated Caucasian individuals: correlation with phenotypic activity. *Am J Hum Genet* 1995;**57**:581-92.
 - 146 **Bell DA**, Taylor JA, Butler MA, Stephens EA, Wiest J, Brubaker LH, Kadlubar FF, Lucier GW. Genotype/phenotype discordance for human arylamine N-acetyltransferase (NAT2) reveals a new slow-acetylator allele common in African-Americans. *Carcinogenesis* 1993;**14**:1689-92.
 - 147 **Lin HJ**, Han CY, Lin BK, Hardy S. Slow acetylator mutations in the human polymorphic N-acetyltransferase gene in 786 Asians, blacks, Hispanics, and whites: application to metabolic epidemiology. *Am J Hum Genet* 1993;**52**:827-34.
 - 148 **Bulovskaya LN**, Krupkin RG, Bochina TA, Shipkova AA, Pavlova MV. Acetylator phenotype in patients with breast cancer. *Oncology* 1978;**35**:185-8.
 - 149 **Ladero JM**, Fernandez MJ, Palmeiro R, Munoz JJ, Jara C, Lazaro C, Perez MG. Hepatic acetylator polymorphism in breast cancer patients. *Oncology* 1987;**44**:341-4.
 - 150 **Philip PA**, Rogers HJ, Millis RR, Rubens RD, Cartwright RA. Acetylator status and its relationship to breast cancer and other diseases of the breast. *Eur J Cancer Clin Oncol* 1987;**23**:1701-6.
 - 151 **Webster DJ**, Flook D, Jenkins J, Hutchings A, Routledge PA. Drug acetylation in breast cancer. *Br J Cancer* 1989;**60**:236-7.
 - 152 **Ilett KF**, Detchon P, Ingram DM, Castleden WM. Acetylation phenotype is not associated with breast cancer. *Cancer Res* 1990;**50**:6649-51.
 - 153 **Sardas S**, Cok I, Sardas OS, Ilhan O, Karakaya AE. Polymorphic N-acetylation capacity in breast cancer patients. *Int J Cancer* 1990;**46**:1138-9.
 - 154 **Agundez JA**, Ladero JM, Olivera M, Abildua R, Roman JM, Benitez J. Genetic analysis of the arylamine N-acetyltransferase polymorphism in breast cancer patients. *Oncology* 1995;**52**:7-11.
 - 155 **Ambrosone CB**, Freudenheim JL, Graham S, Marshall JR, Vena JE, Brasure JR, Michalek AM, Laughlin R, Nemoto T, Gillenwater KA, Shields PG. Cigarette smoking, N-acetyltransferase 2 genetic polymorphisms, and breast cancer risk. *JAMA* 1996;**276**:1494-501.
 - 156 **Hunter DJ**, Hankinson SE, Hough H, Gertig DM, Garcia CM, Spiegelman D, Manson JE, Colditz GA, Willett WC, Speizer FE, Kelsey K. A prospective study of NAT2 acetylation genotype, cigarette smoking, and risk of breast cancer. *Carcinogenesis* 1997;**18**:2127-32.
 - 157 **Huang CS**, Chern HD, Shen CY, Hsu SM, Chang KJ. Association between N-acetyltransferase 2 (NAT2) genetic polymorphism and development of breast cancer in post-menopausal Chinese women in Taiwan, an area of great increase in breast cancer incidence. *Int J Cancer* 1999;**82**:175-9.
 - 158 **Deitz AC**, Zheng W, Leff MA, Gross M, Wen WQ, Doll MA, Xiao GH, Folsom AR, Hein DW. N-Acetyltransferase-2 genetic polymorphism, well-done meat intake, and breast cancer risk among postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2000;**9**:905-10.
 - 159 **Delfino RJ**, Sinha R, Smith C, West J, White E, Lin HJ, Liao SY, Gim JS, Ma HL, Butler J, Anton CH. Breast cancer, heterocyclic aromatic amines from meat and N-acetyltransferase 2 genotype. *Carcinogenesis* 2000;**21**:607-15.
 - 160 **Rebbeck TR**. Molecular epidemiology of the human glutathione S-transferase genotypes GSTM1 and GSTT1 in cancer susceptibility. *Cancer Epidemiol Biomarkers Prev* 1997;**6**:733-43.
 - 161 **Seidegard J**, Pero RW, Markowitz MM, Roush G, Miller DG, Beattie EJ. Isoenzyme(s) of glutathione transferase (class Mu) as a marker for the susceptibility to lung cancer: a follow up study. *Carcinogenesis* 1990;**11**:33-6.
 - 162 **Alexandrie AK**, Sundberg MI, Seidegard J, Tornling G, Rannug A. Genetic susceptibility to lung cancer with special emphasis on CYP1A1 and GSTM1: a study on host factors in relation to age at onset, gender and histological cancer types. *Carcinogenesis* 1994;**15**:1785-90.
 - 163 **Lin HJ**, Han CY, Bernstein DA, Hsiao W, Lin BK, Hardy S. Ethnic distribution of the glutathione transferase Mu 1-1 (GSTM1) null genotype in 1473 individuals and application to bladder cancer susceptibility. *Carcinogenesis* 1994;**15**:1077-81.
 - 164 **Arruda VR**, Grignolli CE, Goncalves MS, Soares MC, Menezes R, Saad ST, Costa FF. Prevalence of homozygosity for the deleted alleles of glutathione S-transferase mu (GSTM1) and theta (GSTT1) among distinct ethnic groups from Brazil: relevance to environmental carcinogenesis? *Clin Genet* 1998;**54**:210-14.
 - 165 **Zhong S**, Wyllie AH, Barnes D, Wolf CR, Spurr NK. Relationship between the GSTM1 genetic polymorphism and susceptibility to bladder, breast and colon cancer. *Carcinogenesis* 1993;**14**:1821-4.
 - 166 **Paradiso A**, Vetrugno MG, Capuano G, Longo S, Sibiano L, Schittulli F, Corrales M, Barletta A, Pelagio G, De Lena M. Expression of GST-mu transferase in breast cancer patients and healthy controls. *Int J Biol Markers* 1994;**9**:219-23.
 - 167 **Ambrosone CB**, Freudenheim JL, Graham S, Marshall JR, Vena JE, Brasure JR, Laughlin R, Nemoto T, Michalek AM, Harrington A, Ford TD, Shields PG. Cytochrome P4501A1 and glutathione S-transferase (M1) genetic polymorphisms and postmenopausal breast cancer risk. *Cancer Res* 1995;**55**:3483-5.
 - 168 **Kelsey KT**, Hankinson SE, Colditz GA, Springer K, Garcia CM, Spiegelman D, Manson JE, Garland M, Stampfer MJ, Willett WC, Speizer FE, Hunter DJ. Glutathione S-transferase class mu deletion polymorphism and breast cancer: results from prevalent versus incident cases. *Cancer Epidemiol Biomarkers Prev* 1997;**6**:511-15.
 - 169 **Bailey LR**, Roodi N, Verrier CS, Yee CJ, Dupont WD, Parl FF. Breast cancer and CYP1A1, GSTM1, and GSTT1 polymorphisms: evidence of a lack of association in Caucasians and African Americans. *Cancer Res* 1998;**58**:65-70.
 - 170 **Helzlsouer KJ**, Selmin O, Huang HY, Strickland PT, Hoffman S, Alberg AJ, Watson M, Comstock GW, Bell D. Association between glutathione S-transferase M1, P1, and T1 genetic polymorphisms and development of breast cancer. *J Natl Cancer Inst* 1998;**90**:512-18.
 - 171 **Maugard CM**, Charrier J, Bignon YJ. Allelic deletion at glutathione S-transferase M1 locus and its association with breast cancer susceptibility. *Chem Biol Interact* 1998;**111-112**:365-75.
 - 172 **Nedelcheva Kristensen V**, Andersen TI, Erikstein B, Geitvik G, Skovlund E, Nesland JM, Borresen-Dale AL. Single tube multiplex polymerase chain reaction genotype analysis of GSTM1, GSTT1 and GSTP1: relation of genotypes to TP53 tumor status and clinicopathological variables in breast cancer patients. *Pharmacogenetics* 1998;**8**:441-7.
 - 173 **Ambrosone CB**, Coles BF, Freudenheim JL, Shields PG. Glutathione-S-transferase (GSTM1) genetic polymorphisms do not affect human breast cancer risk, regardless of dietary antioxidants. *J Nutr* 1999;**129**(suppl 2):565-8.

- 174 **Charrier J**, Maugard CM, Le Mevel B, Bignon YJ. Allelotype influence at glutathione S-transferase M1 locus on breast cancer susceptibility. *Br J Cancer* 1999;**79**:346-53.
- 175 **Garcia CM**, Kelsey KT, Hankinson SE, Spiegelman D, Springer K, Willett WC, Speizer FE, Hunter DJ. Glutathione S-transferase mu and theta polymorphisms and breast cancer susceptibility. *J Natl Cancer Inst* 1999;**91**:1960-4.
- 176 **Curran JE**, Weinstein SR, Griffiths LR. Polymorphisms of glutathione S-transferase genes (GSTM1, GSTP1 and GSTT1) and breast cancer susceptibility. *Cancer Lett* 2000;**153**:113-20.
- 177 **Park SK**, Yoo KY, Lee SJ, Kim SU, Ahn SH, Noh DY, Choe KJ, Strickland PT, Hirvonen A, Kang D. Alcohol consumption, glutathione S-transferase M1 and T1 genetic polymorphisms and breast cancer risk. *Pharmacogenetics* 2000;**10**:301-9.
- 178 **Rundle A**, Tang D, Zhou J, Cho S, Perera F. The association between glutathione S-transferase M1 genotype and polycyclic aromatic hydrocarbon-DNA adducts in breast tissue. *Cancer Epidemiol Biomarkers Prev* 2000;**9**:1079-85.
- 179 **Esteller M**, Corn PG, Urena JM, Gabrielson E, Baylin SB, Herman JG. Inactivation of glutathione S-transferase P1 gene by promoter hypermethylation in human neoplasia. *Cancer Res* 1998;**58**:4515-18.
- 180 **Zimniak P**, Nanduri B, Pikula S, Bendorowicz PJ, Singhal SS, Srivastava SK, Awasthi S, Awasthi YC. Naturally occurring human glutathione S-transferase GSTP1-1 isoforms with isoleucine and valine in position 104 differ in enzymic properties. *Eur J Biochem* 1994;**224**:893-9.
- 181 **Harries LW**, Stubbs MJ, Forman D, Howard GC, Wolf CR. Identification of genetic polymorphisms at the glutathione S-transferase P1 locus and association with susceptibility to bladder, testicular and prostate cancer. *Carcinogenesis* 1997;**18**:641-4.
- 182 **Wiencke JK**, Pemble S, Ketterer B, Kelsey KT. Gene deletion of glutathione S-transferase theta: correlation with induced genetic damage and potential role in endogenous mutagenesis. *Cancer Epidemiol Biomarkers Prev* 1995;**4**:253-9.
- 183 **Pemble S**, Schroeder KR, Spencer SR, Meyer DJ, Hallier E, Bolt HM, Ketterer B, Taylor JB. Human glutathione S-transferase theta (GSTT1): cDNA cloning and the characterization of a genetic polymorphism. *Biochem J* 1994;**300**:271-6.
- 184 **Nelson HH**, Wiencke JK, Christiani DC, Cheng TJ, Zuo ZF, Schwartz BS, Lee BK, Spitz MR, Wang M, Xu X. Ethnic differences in the prevalence of the homozygous deleted genotype of glutathione S-transferase theta. *Carcinogenesis* 1995;**16**:1243-5.
- 185 **Nebert DW**. Role of genetics and drug metabolism in human cancer risk. *Mutat Res* 1991;**247**:267-81.
- 186 **Hayashi S**, Watanabe J, Nakachi K, Kawajiri K. Genetic linkage of lung cancer-associated MspI polymorphisms with amino acid replacement in the heme binding region of the human cytochrome P450IA1 gene. *J Biochem (Tokyo)* 1991;**110**:407-11.
- 187 **Kawajiri K**, Nakachi K, Imai K, Watanabe J, Hayashi S. The CYP1A1 gene and cancer susceptibility. *Crit Rev Oncol Hematol* 1993;**14**:77-87.
- 188 **Fontana X**, Peyrottes I, Rossi C, Leblanc TP, Ettore F, Namer M, Bussiere F. Study of the frequencies of CYP1A1 gene polymorphisms and glutathione S-transferase mu1 gene in primary breast cancers: an update with an additional 114 cases. *Mutat Res* 1998;**403**:45-53.
- 189 **Ishibe N**, Hankinson SE, Colditz GA, Spiegelman D, Willett WC, Speizer FE, Kelsey KT, Hunter DJ. Cigarette smoking, cytochrome P450 1A1 polymorphisms, and breast cancer risk in the Nurses' Health Study. *Cancer Res* 1998;**58**:667-71.
- 190 **Huang CS**, Shen CY, Chang KJ, Hsu SM, Chern HD. Cytochrome P4501A1 polymorphism as a susceptibility factor for breast cancer in postmenopausal Chinese women in Taiwan. *Br J Cancer* 1999;**80**:1838-43.
- 191 **Taioli E**, Bradlow HL, Garbers SV, Sepkovic DW, Osborne MP, Trachman J, Ganguly S, Garte SJ. Role of estradiol metabolism and CYP1A1 polymorphisms in breast cancer risk. *Cancer Detect Prev* 1999;**23**:232-7.
- 192 **Moysich KB**, Shields PG, Freudenheim JL, Schisterman EF, Vena JE, Kostyniak P, Greizerstein H, Marshall JR, Graham S, Ambrosone CB. Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1999;**8**:41-4.
- 193 **Hanna IH**, Dawling S, Roodi N, Guengerich FP, Parl FF. Cytochrome P450 1B1 (CYP1B1) pharmacogenetics: association of polymorphisms with functional differences in estrogen hydroxylation activity. *Cancer Res* 2000;**60**:3440-4.
- 194 **Bailey LR**, Roodi N, Dupont WD, Parl FF. Association of cytochrome P450 1B1 (CYP1B1) polymorphism with steroid receptor status in breast cancer. *Cancer Res* 1998;**58**:5038-41.
- 195 **Watanabe J**, Shimada T, Gillam EM, Ikuta T, Suemasu K, Higashi Y, Gotoh O, Kawajiri K. Association of CYP1B1 genetic polymorphism with incidence to breast and lung cancer. *Pharmacogenetics* 2000;**10**:25-33.
- 196 **Zheng W**, Xie DW, Jin F, Cheng JR, Dai Q, Wen WQ, Shu XO, Gao YT. Genetic polymorphism of cytochrome P450-1B1 and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2000;**9**:147-50.
- 197 **Buchert ET**, Woosley RL, Swain SM, Oliver SJ, Coughlin SS, Pickle L, Trock B, Riegel AT. Relationship of CYP2D6 (debrisoquine hydroxylase) genotype to breast cancer susceptibility. *Pharmacogenetics* 1993;**3**:322-7.
- 198 **Wundrack I**, Sasiadek M, Blin N. Debrisoquine hydroxylase gene polymorphism in neurofibromatosis type 1. *Anticancer Res* 1997;**17**:4515-17.
- 199 **Pontin JE**, Hamed H, Fentiman IS, Idle JR. Cytochrome P450db1 phenotypes in malignant and benign breast disease. *Eur J Cancer* 1990;**26**:790-2.
- 200 **Ladero JM**, Benitez J, Jara C, Ilerena A, Valdivielso MJ, Munoz JJ, Vargas E. Polymorphic oxidation of debrisoquine in women with breast cancer. *Oncology* 1991;**48**:107-10.
- 201 **Smith CA**, Moss JE, Gough AC, Spurr NK, Wolf CR. Molecular genetic analysis of the cytochrome P450-debrisoquine hydroxylase locus and association with cancer susceptibility. *Environ Health Perspect* 1992;**98**:107-12.
- 202 **Ladona MG**, Abildua RE, Ladero JM, Roman JM, Plaza MA, Agundez JA, Munoz JJ, Benitez J. CYP2D6 genotypes in Spanish women with breast cancer. *Cancer Lett* 1996;**99**:23-8.
- 203 **Topic E**, Stefanovic M, Ivanisevic AM, Petrunic R, Curcic I. The cytochrome P450 2D6 (CYP2D6) gene polymorphism among breast and head and neck cancer patients. *Clin Chim Acta* 2000;**296**:101-9.
- 204 **Bernstein L**, Press MF. Does estrogen receptor expression in normal breast tissue predict breast cancer risk? *J Natl Cancer Inst* 1998;**90**:5-7.
- 205 **Begg L**, Kuller LH, Gutai JP, Caggliola AG, Wolmark N, Watson CG. Endogenous sex hormone levels and breast cancer risk. *Genet Epidemiol* 1987;**4**:233-47.
- 206 **Hulka BS**. Epidemiologic analysis of breast and gynecologic cancers. *Prog Clin Biol Res* 1997;**396**:17-29.
- 207 **Kelsey JL**, Gammon MD, John EM. Reproductive factors and breast cancer. *Epidemiol Rev* 1993;**15**:36-47.
- 208 **Henderson BE**, Feigelson HS. Hormonal carcinogenesis. *Carcinogenesis* 2000;**21**:427-33.
- 209 **Liehr JG**, Roy D. Free radical generation by redox cycling of estrogens. *Free Radic Biol Med* 1990;**8**:415-23.
- 210 **Zhu BT**, Conney AH. Is 2-methoxyestradiol an endogenous estrogen metabolite that inhibits mammary carcinogenesis? *Cancer Res* 1998;**58**:2269-77.
- 211 **Feigelson HS**, Henderson BE. Estrogens and breast cancer. *Carcinogenesis* 1996;**17**:2279-84.
- 212 **Carey AH**, Waterworth D, Patel K, White D, Little J, Novelli P, Franks S, Williamson R. Polycystic ovaries and premature male pattern baldness are associated with one allele of the steroid metabolism gene CYP17. *Hum Mol Genet* 1994;**3**:1873-6.
- 213 **Feigelson HS**, Shames LS, Pike MC, Coetzee GA, Stanczyk FZ, Henderson BE. Cytochrome P450c17alpha gene (CYP17) polymorphism is associated with serum estrogen and progesterone concentrations. *Cancer Res* 1998;**58**:585-7.
- 214 **Young IE**, Kurian KM, Annink C, Kunkler IH, Anderson VA, Cohen BB, Hooper ML, Wyllie AH, Steel CM. A polymorphism in the CYP17 gene is associated with male breast cancer. *Br J Cancer* 1999;**81**:141-3.
- 215 **Dunning AM**, Healey CS, Pharoah PD, Foster NA, Lipscombe JM, Redman KL, Easton DF, Day NE, Ponder BA. No association between a polymorphism in the steroid metabolism gene CYP17 and risk of breast cancer. *Br J Cancer* 1998;**77**:2045-7.
- 216 **Helzlsouer KJ**, Huang HY, Strickland PT, Hoffman S, Alberg AJ, Comstock GW, Bell DA. Association between CYP17 polymorphisms and the development of breast cancer. *Cancer Epidemiol Biomarkers Prev* 1998;**7**:945-9.
- 217 **Weston A**, Pan CF, Bleiweiss JJ, Ksieski HB, Roy N, Maloney N, Wolff MS. CYP17 genotype and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1998;**7**:941-4.
- 218 **Haiman CA**, Hankinson SE, Spiegelman D, Colditz GA, Willett WC, Speizer FE, Kelsey KT, Hunter DJ. The relationship between a polymorphism in CYP17 with plasma hormone levels and breast cancer. *Cancer Res* 1999;**59**:1015-20.
- 219 **Huang CS**, Chern HD, Chang KJ, Cheng CW, Hsu SM, Shen CY. Breast cancer risk associated with genotype polymorphism of the estrogen-metabolizing genes CYP17, CYP1A1, and COMT: a multigenic study on cancer susceptibility. *Cancer Res* 1999;**59**:4870-5.
- 220 **Nedelcheva Kristensen V**, Haraldsen EK, Anderson KB, Lønning PE, Erikstein B, Karesen R, Gabrielsen OS, Borresen-Dale AL. CYP17 and breast cancer risk: the polymorphism in the 5' flanking area of the gene does not influence binding to Sp-1. *Cancer Res* 1999;**59**:2825-8.
- 221 **Kuligina ES**, Togo AV, Susptitsin EN, Grigoriev MY, Pozharisskiy KM, Chagunava OL, Berstein LM, Theillet C, Hanson KP, Imanitov EN. CYP17 polymorphism in the groups of distinct breast cancer susceptibility: comparison of patients with the bilateral disease vs. monolateral breast cancer patients vs. middle-aged female controls vs. elderly tumor-free women. *Cancer Lett* 2000;**156**:45-50.
- 222 **Bergman JM**, Gentile M, Lundin AC, Wingren S. Association between CYP17 gene polymorphism and risk of breast cancer in young women. *Int J Cancer* 1999;**84**:350-3.
- 223 **Mitrunen K**, Jourenkova N, Kataja V, Eskelinen M, Kosma VM, Benhamou S, Vainio H, Uusitupa M, Hirvonen A. Steroid metabolism gene CYP17 polymorphism and the development of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2000;**9**:1343-8.
- 224 **Polymeropoulos MH**, Xiao H, Rath DS, Merrill CR. Tetranucleotide repeat polymorphism at the human aromatase cytochrome P-450 gene (CYP19). *Nucleic Acids Res* 1991;**19**:195.
- 225 **Kristensen VN**, Andersen TI, Lindblom A, Erikstein B, Magnus P, Borresen DA. A rare CYP19 (aromatase) variant may increase the risk of breast cancer. *Pharmacogenetics* 1998;**8**:43-8.
- 226 **Probst-Hensch NM**, Ingles SA, Diep AT, Haile RW, Stanczyk FZ, Kolonel LN, Henderson BE. Aromatase and breast cancer susceptibility. *Endocr Relat Cancer* 1999;**6**:165-73.
- 227 **Sieglmann-Danieli N**, Buetow KH. Constitutional genetic variation at the human aromatase gene (Cyp19) and breast cancer risk. *Br J Cancer* 1999;**79**:456-63.
- 228 **Haiman CA**, Hankinson SE, Spiegelman D, De Vivo I, Colditz GA, Willett WC, Speizer FE, Hunter DJ. A tetranucleotide repeat

- polymorphism in CYP19 and breast cancer risk. *Int J Cancer* 2000;**87**:204-10.
- 229 **Healey CS**, Dunning AM, Durocher F, Teare D, Pharoah PD, Luben RN, Easton DF, Ponder BA. Polymorphisms in the human aromatase cytochrome P450 gene (CYP19) and breast cancer risk. *Carcinogenesis* 2000;**21**:189-93.
 - 230 **Watanabe J**, Harada N, Suemasu K, Higashi Y, Gotoh O, Kawajiri K. Arginine-cysteine polymorphism at codon 264 of the human CYP19 gene does not affect aromatase activity. *Pharmacogenetics* 1997;**7**:419-24.
 - 231 **McGuire WL**, Chamness GC, Fuqua SA. Estrogen receptor variants in clinical breast cancer. *Mol Endocrinol* 1991;**5**:1571-7.
 - 232 **Karnik PS**, Kulkarni S, Liu XP, Budd GT, Bukowski RM. Estrogen receptor mutations in tamoxifen-resistant breast cancer. *Cancer Res* 1994;**54**:349-53.
 - 233 **Roodi N**, Bailey LR, Kao WY, Verrier CS, Yee CJ, Dupont WD, Parl FF. Estrogen receptor gene analysis in estrogen receptor-positive and receptor-negative primary breast cancer. *J Natl Cancer Inst* 1995;**87**:446-51.
 - 234 **Iwase H**, Greenman JM, Barnes DM, Hodgson S, Bobrow L, Mathew CG. Sequence variants of the estrogen receptor (ER) gene found in breast cancer patients with ER negative and progesterone receptor positive tumors. *Cancer Lett* 1996;**108**:179-84.
 - 235 **Lapidus RG**, Ferguson AT, Ottaviano YL, Parl FF, Smith HS, Weitzman SA, Baylin SB, Issa JPJ, Davidson NE. Methylation of estrogen and progesterone receptor gene 5' CpG islands correlates with lack of estrogen and progesterone receptor gene expression in breast tumors. *Clin Cancer Res* 1996;**2**:805-10.
 - 236 **Hill SM**, Fuqua SA, Chamness GC, Greene GL, McGuire WL. Estrogen receptor expression in human breast cancer associated with an estrogen receptor gene restriction fragment length polymorphism. *Cancer Res* 1989;**49**:145-8.
 - 237 **Andersen TI**, Heimdal KR, Skrede M, Tveit K, Berg K, Borresen AL. Oestrogen receptor (ESR) polymorphisms and breast cancer susceptibility. *Hum Genet* 1994;**94**:665-70.
 - 238 **Southey MC**, Batten LE, McCredie MR, Giles GG, Dite G, Hopper JL, Venter DJ. Estrogen receptor polymorphism at codon 325 and risk of breast cancer in women before age forty. *J Natl Cancer Inst* 1998;**90**:532-6.
 - 239 **Rowe SM**, Coughlan SJ, McKenna NJ, Garrett E, Kieback DG, Carney DN, Healdon DR. Ovarian carcinoma-associated TaqI restriction fragment length polymorphism in intron G of the progesterone receptor gene is due to an Alu sequence insertion. *Cancer Res* 1995;**55**:2743-5.
 - 240 **Garrett E**, Rowe SM, Coughlan SJ, Horan R, McLinden J, Carney DN, Fanning M, Kieback DG, Healdon DR. Mendelian inheritance of a TaqI restriction fragment length polymorphism due to an insertion in the human progesterone receptor gene and its allelic imbalance in breast cancer. *Cancer Res Ther Controls* 1995;**4**:217-22.
 - 241 **Manolitis TP**, Englefield P, Eccles DM, Campbell IG. No association of a 306-bp insertion polymorphism in the progesterone receptor gene with ovarian and breast cancer. *Br J Cancer* 1997;**75**:1398-9.
 - 242 **Lancaster JM**, Berchuck A, Carney ME, Wiseman R, Taylor JA. Progesterone receptor gene polymorphism and risk for breast and ovarian cancer. *Br J Cancer* 1998;**78**:277.
 - 243 **Wang-Gohrke S**, Chang-Claude J, Becher H, Kieback DG, Runnebaum IB. Progesterone receptor gene polymorphism is associated with decreased risk for breast cancer by age 50. *Cancer Res* 2000;**60**:2348-50.
 - 244 **Wooster R**, Mangan J, Eeles R, Smith S, Dowsett M, Averill D, Barrett-Lee P, Easton DF, Ponder BA, Stratton MR. A germline mutation in the androgen receptor gene in two brothers with breast cancer and Reifenstein syndrome. *Nat Genet* 1992;**2**:132-4.
 - 245 **Lobaccaro JM**, Lombroso S, Belon C, Galtier-Dereure F, Bringer J, Lesimple T, Heron JF, Pujol H, Sultan C. Male breast cancer and the androgen receptor gene. *Nat Genet* 1993;**5**:109-10.
 - 246 **Rebbbeck TR**, Kantoff PW, Krithivas K, Neuhausen S, Blackwood MA, Godwin AK, Daly MB, Narod SA, Garber JE, Lynch HT, Weber BL, Brown M. Modification of BRCA1-associated breast cancer risk by the polymorphic androgen-receptor CAG repeat. *Am J Hum Genet* 1999;**64**:1371-7.
 - 247 **Dunning AM**, McBride S, Gregory J, Durocher F, Foster NA, Healey CS, Smith N, Pharoah PD, Luben RN, Easton DF, Ponder BA. No association between androgen or vitamin D receptor gene polymorphisms and risk of breast cancer. *Carcinogenesis* 1999;**20**:2131-5.
 - 248 **Spurdle AB**, Dite GS, Chen X, Mayne CJ, Southey MC, Batten LE, Chy H, Trute L, McCredie MR, Giles GG, Armes J, Venter DJ, Hopper JL, Chenevix TG. Androgen receptor exon 1 CAG repeat length and breast cancer in women before age forty years. *J Natl Cancer Inst* 1999;**91**:961-6.
 - 249 **Lachman HM**, Papoulos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics* 1996;**6**:243-50.
 - 250 **Millikan RC**, Pittman GS, Tse CK, Duell E, Newman B, Savitz D, Moorman PG, Boissy RJ, Bell DA. Catechol-O-methyltransferase and breast cancer risk. *Carcinogenesis* 1998;**19**:1943-7.
 - 251 **Thompson PA**, Shields PG, Freudenheim JL, Stone A, Vena JE, Marshall JR, Graham S, Laughlin R, Nemoto T, Kadlubar FF, Ambrosone CB. Genetic polymorphisms in catechol-O-methyltransferase, menopausal status, and breast cancer risk. *Cancer Res* 1998;**58**:2107-10.
 - 252 **Beutler E**, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? *Proc Natl Acad Sci USA* 1998;**95**:8170-4.
 - 253 **Guillemette C**, Millikan RC, Newman B, Housman DE. Genetic polymorphisms in uridine diphospho-glucuronosyltransferase 1A1 and association with breast cancer among African Americans. *Cancer Res* 2000;**60**:950-6.
 - 254 **Guillemette C**, De Vivo I, Hankinson SE, Haiman CA, Spiegelman D, Housman DE, Hunter DJ. Association of genetic polymorphisms in UGT1A1 with breast cancer and plasma hormone levels. *Cancer Epidemiol Biomarkers Prev* 2001;**10**:711-14.
 - 255 **Pistillo MP**, Nicolo G, Salvi S, Capanni P, Perdelli L, Pasciucco G, Ferrara GB. Biochemical analysis of HLA class I subunits expression in breast cancer tissues. *Hum Immunol* 2000;**61**:397-407.
 - 256 **Cordon AL**, James DC. HLA and carcinoma of the breast. *Lancet* 1973;**2**:565.
 - 257 **Martz E**, Benacerraf B. Lack of association between carcinoma of the breast and HLA specificities. *Tissue Antigens* 1973;**3**:30-8.
 - 258 **Jong-Bakker M**, Cleton FJ, D'Amato J, Keuning JJ, Van Rood JJ. HLA antigens and breast cancer. *Eur J Cancer* 1974;**10**:555-8.
 - 259 **Perdue ST**, Terasaki PI, Mickey MR. HLA frequencies in cancer: a third study. *IARC Sci Publ* 1978;**20**:263-9.
 - 260 **Takasugi M**, Terasaki PI, Henderson B, Mickey MR, Menck H, Thompson RW. HLA antigens in solid tumors. *Cancer Res* 1973;**33**:648-50.
 - 261 **Bouillenne C**, Deneufbourg JM. Positive correlation between breast cancer incidence and HLA antigens. *Oncology* 1979;**36**:156-9.
 - 262 **Subira ML**, Crisci CD, Zornoza G, Sanz ML, Voltas J, Hernandez JL, Oehling A. Breast cancer and histocompatibility antigens. *Allergol Immunopathol (Madr)* 1979;**7**:411-16.
 - 263 **Biswal BM**, Kumar R, Julka PK, Sharma U, Vaidya MC. Human leucocytic antigens (HLA) in breast cancer. *Indian J Med Sci* 1998;**52**:177-83.
 - 264 **Gatti RA**, Sparkes RS, Field LL, Spence MA, Harris NS, Freidin M. Genetic linkage analysis in a high-risk cancer family: HLA and 24 other markers. *Cancer Genet Cytogenet* 1983;**8**:9-18.
 - 265 **Beutler B**, Cerami A. The biology of cachectin/TNF - a primary mediator of the host response. *Annu Rev Immunol* 1989;**7**:625-55.
 - 266 **Wilson AG**, de Vries N, Pociot F, di Giovine FS, van der Putte LB, Duff GW. An allelic polymorphism within the human tumor necrosis factor alpha promoter region is strongly associated with HLA A1, B8, and DR3 alleles. *J Exp Med* 1993;**177**:557-60.
 - 267 **Chouchane L**, Ahmed SB, Baccouche S, Remadi S. Polymorphism in the tumor necrosis factor-alpha promoter region and in the heat shock protein 70 genes associated with malignant tumors. *Cancer* 1997;**80**:1489-96.
 - 268 **Allen RD**. Polymorphism of the human TNF-alpha promoter - random variation or functional diversity? *Mol Immunol* 1999;**36**:1017-27.
 - 269 **Garcia-Merino A**, Alper CA, Usuku K, Marcus-Bagley D, Lincoln R, Awdeh Z, Yunis EJ, Eisenbarth GS, Brink SJ, Hauser SL. Tumor necrosis factor (TNF) microsatellite haplotypes in relation to extended haplotypes, susceptibility to diseases associated with the major histocompatibility complex and TNF secretion. *Hum Immunol* 1996;**50**:11-21.
 - 270 **Wilson AG**, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proc Natl Acad Sci USA* 1997;**94**:3195-9.
 - 271 **Sargent CA**, Dunham I, Trowsdale J, Campbell RD. Human major histocompatibility complex contains genes for the major heat shock protein HSP70. *Proc Natl Acad Sci USA* 1989;**86**:1968-72.
 - 272 **Young RA**. Stress proteins and immunology. *Annu Rev Immunol* 1990;**8**:401-20.
 - 273 **Suto R**, Srivastava PK. A mechanism for the specific immunogenicity of heat shock protein-chaperoned peptides. *Science* 1995;**269**:1585-8.
 - 274 **Weinberg ED**. The role of iron in cancer. *Eur J Cancer Prev* 1996;**5**:19-36.
 - 275 **Feder JN**, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, Dormishian F, Domingo R Jr, Ellis MC, Fullan A, Hinton IM, Jones NL, Kimmel BE, Kronmal GS, Lauer P, Lee VK, Loeb DB, Mapa FA, McClelland E, Meyer NC, Mintier G, Moeller N, Moore T, Morikang E, Wolff RK. A novel MHC class II-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996;**13**:399-408.
 - 276 **Adams PC**. Prevalence of abnormal iron studies in heterozygotes for hereditary hemochromatosis: an analysis of 255 heterozygotes. *Am J Hematol* 1994;**45**:146-9.
 - 277 **Nelson RL**, Davis FG, Persky V, Becker E. Risk of neoplastic and other diseases among people with heterozygosity for hereditary hemochromatosis. *Cancer* 1995;**76**:875-9.
 - 278 **Beckman LE**, Van Landeghem GF, Sikstrom C, Wahlin A, Markevarn B, Hallmans G, Lenner P, Athlin L, Stenling R, Beckman L. Interaction between haemochromatosis and transferrin receptor genes in different neoplastic disorders. *Carcinogenesis* 1999;**20**:1231-3.
 - 279 **Lundin AC**, Soderkvist P, Eriksson B, Bergman JM, Wingren S. Association of breast cancer progression with a vitamin D receptor gene polymorphism. South-East Sweden Breast Cancer Group. *Cancer Res* 1999;**59**:2332-4.
 - 280 **Curran JE**, Vaughan T, Lea RA, Weinstein SR, Morrison NA, Griffiths LR. Association of A vitamin D receptor polymorphism with sporadic breast cancer development. *Int J Cancer* 1999;**83**:723-6.
 - 281 **Ruggiero M**, Pacini S, Aterini S, Fallai C, Ruggiero C, Pacini P. Vitamin D receptor gene polymorphism is associated with metastatic breast cancer. *Oncol Res* 1998;**10**:43-6.
 - 282 **Ingles SA**, Garcia DG, Wang W, Nieters A, Henderson BE, Kolonel LN, Haile RW, Coetzee GA. Vitamin D receptor genotype and breast cancer in Latinas (United States). *Cancer Causes Control* 2000;**11**:25-30.

- 283 **Sorlie T**, Bukholm I, Borresen-Dale AL. Truncating somatic mutation in exon 15 of the APC gene is a rare event in human breast carcinomas. *Mutations in brief* no 179. Online. *Hum Mutat* 1998;**12**:215.
- 284 **Furuuchi K**, Tada M, Yamada H, Kataoka A, Furuuchi N, Hamada J, Takahashi M, Todo S, Moriuchi T. Somatic mutations of the APC gene in primary breast cancers. *Am J Pathol* 2000;**156**:1997-2005.
- 285 **Redston M**, Nathanson KL, Yuan ZQ, Neuhausen SL, Satagopan J, Wong N, Yang D, Nafa D, Abrahamson J, Ozelik H, Antin OD, Andrulis I, Daly M, Pinsky L, Schrag D, Gallinger S, Kaback M, King MC, Woodage T, Brody LC, Godwin A, Warner E, Weber B, Foulkes W, Offit K. The APC1307K allele and breast cancer risk. *Nat Genet* 1998;**20**:13-14.
- 286 **Woodage T**, King SM, Wacholder S, Hartge P, Struwing JP, McAdams M, Laken SJ, Tucker MA, Brody LC. The APC1307K allele and cancer risk in a community-based study of Ashkenazi Jews. *Nat Genet* 1998;**20**:62-5.
- 287 **Gershoni BR**, Patael Y, Dagan, Figer A, Kasinetz L, Kadouri E, Bruchim-Bar SR, Friedman E. Association of the I1307K APC mutation with hereditary and sporadic breast/ovarian cancer: more questions than answers. *Br J Cancer* 2000;**83**:153-5.
- 288 **Moysich KB**, Freudenheim JL, Baker JA, Ambrosone CB, Bowman ED, Schisterman EF, Vena JE, Shields PG. Apolipoprotein E genetic polymorphism, serum lipoproteins, and breast cancer risk. *Mol Carcinog* 2000;**27**:2-9.
- 289 **Mannermaa A**, Peltoketo H, Winqvist R, Ponder BA, Kiviniemi H, Easton DF, Poutanen M, Isomaa V, Viikko R. Human familial and sporadic breast cancer: analysis of the coding regions of the 17 beta-hydroxysteroid dehydrogenase 2 gene (EDH1B2) using a single-strand conformation polymorphism assay. *Hum Genet* 1994;**93**:319-24.
- 290 **Xie D**, Shu XO, Deng Z, Wen WQ, Creek KE, Dai Q, Gao YT, Jin F, Zheng W. Population-based, case-control study of HER2 genetic polymorphism and breast cancer risk. *J Natl Cancer Inst* 2000;**92**:412-17.
- 291 **Pasche B**, Kolachana P, Nafa K, Satagopan J, Chen YG, Lo RS, Brenner D, Yang D, Kirstein L, Oddoux C, Ostrer H, Vineis P, Varesco L, Jhanwar S, Luzzatto L, Massague J, Offit K. TbetaR-II(6A) is a candidate tumor susceptibility allele. *Cancer Res* 1999;**59**:5678-82.
- 292 **Hall JM**, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, King MC. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 1990;**250**:1684-9.
- 293 **Miki Y**, Swensen J, Shattuck ED, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, Bell R, Rosenthal J, Hussey C, Tran T, McClure M, Frye C, Hattier T, Phelps R, Haugen-Strano A, Katcher H, Yakumo K, Gholami Z, Shaffer D, Stone F, Bayer B, Wray C, Bogden B, Dayananth P, Ward J, Tonin P, Narod S, Bristow PK, Norris FH, Helvering L, Morrison P, Rostek P, Lai M, Barrett JC, Lewis C, Neuhausen S, Cannon-Albright LA, Goldgar D, Wiseman R, Kamb A, Skolnick MH. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 1994;**266**:66-71.
- 294 **Wooster R**, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, Nguyen K, Seal S, Tran T, Averil D, Fields P, Marshall G, Narod S, Lenoir GM, Lynch H, Feunteun J, Devilee P, Cornelisse C, Menko FH, Daly PA, Ormiston W, McManus R, Pye C, Lewis CM, Cannon-Albright LA, Peto J, Ponder BAJ, Skolnick MH, Easton DF, Goldgar DE, Stratton MR. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science* 1994;**265**:2088-90.
- 295 **Grimmond SM**, Palmer JM, Walters MK, Scott C, Nancarrow DJ, The BT, Elmes C, Pyke C, Khoo SK, Bennett I, Wetzig N, Hayward NK. Confirmation of susceptibility locus on chromosome 13 in Australian breast cancer families. *Hum Genet* 1996;**98**:80-5.
- 296 **McBride OW**, Merry D, Givol D. The gene for human p53 cellular tumor antigen is located on chromosome 17 short arm (17p13). *Proc Natl Acad Sci USA* 1986;**83**:130-4.
- 297 **Yonish RE**, Resnitzky D, Lotem J, Sachs L, Kimchi A, Oren M. Wild-type p53 induces apoptosis of myeloid leukaemic cells that is inhibited by interleukin-6. *Nature* 1991;**352**:345-7.
- 298 **Clarke AR**, Purdie CA, Harrison DJ, Morris RG, Bird CC, Hooper ML, Wyllie AH. Thymocyte apoptosis induced by p53-dependent and independent pathways. *Nature* 1993;**362**:849-52.
- 299 **Savitsky K**, Bar SA, Gilad S, Rotman G, Ziv Y, Vanagaite L, Tagle DA, Smith S, Uziel T, Sfez S, Ashkenazi M, Pecker I, Frydman M, Harnik R, Patanjali SR, Simmons A, Clines GA, Sartiell A, Gatti RA, Chessa L, Sand O, Lavin MF, Jaspers NGJ, Taylor AMR, Alfelt CF, Miki T, Weissmann SM, Lovett M, Collins FS, Shiloh Y. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. *Science* 1995;**268**:1749-53.
- 300 **Lavin MF**, Concannon P, Gatti RA. Eighth International Workshop on Ataxia-Telangiectasia (ATW8). *Cancer Res* 1999;**59**:3845-9.
- 301 **Li J**, Yen C, Liaw D, Podsypanina K, Bose S, Wang SI, Puc J, Milaresis C, Rodgers L, McCombie R, Bigner SH, Giovannella BC, Littmann M, Tycko B, Hibshoosh H, Wigler MH, Parsons R. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. *Science* 1997;**275**:1943-7.
- 302 **Heim S**, Mitelman F. Nineteen of 26 cellular oncogenes precisely localized in the human genome map to one of the 83 bands involved in primary cancer-specific rearrangements. *Hum Genet* 1987;**75**:70-2.
- 303 **Franke S**, Klawitz I, Schnakenberg E, Rommel B, van de Ven W, Bullerdiek J, Schlof W. Isolation and mapping of a cosmid clone containing the human NAT2 gene. *Biochem Biophys Res Commun* 1994;**199**:52-5.
- 304 **Hein DW**, Doll MA, Rustan TD, Ferguson RJ. Metabolic activation of N-hydroxyarylamines and N-hydroxyarylamides by 16 recombinant human NAT2 alleles: effects of 7 specific NAT2 nucleic acid substitutions. *Cancer Res* 1995;**55**:3531-6.
- 305 **Ketterer B**. Protective role of glutathione and glutathione transferases in mutagenesis and carcinogenesis. *Mutat Res* 1988;**202**:343-61.
- 306 **Pearson WR**, Vorachek WR, Xu SJ, Berger R, Hart I, Vannais D, Patterson D. Identification of class-mu glutathione transferase genes GSTM1-GSTM5 on human chromosome 1p13. *Am J Hum Genet* 1993;**53**:220-33.
- 307 **Hayes JD**, Pulford DJ. The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. *Crit Rev Biochem Mol Biol* 1995;**30**:445-600.
- 308 **Smith CM**, Ma NS, Nowak NJ, Shows TB, Gerhard DS. A 3-Mb contig from D11S987 to MLK3, a gene-rich region in 11q13. *Genome Res* 1997;**7**:835-42.
- 309 **Jaiswal AK**, Gonzalez FJ, Nebert DW. Human dioxin-inducible cytochrome P1-450: complementary DNA and amino acid sequence. *Science* 1985;**228**:80-3.
- 310 **Larsen MC**, Angus WG, Brake PB, Eltom SE, Sukow KA, Jefcoate CR. Characterization of CYP1B1 and CYP1A1 expression in human mammary epithelial cells: role of the aryl hydrocarbon receptor in polycyclic aromatic hydrocarbon metabolism. *Cancer Res* 1998;**58**:2366-74.
- 311 **Emanuel BS**, Seizinger BR. Report of the committee on the genetic constitution of chromosome 22. *Cytogenet Cell Genet* 1990;**55**:245-53.
- 312 **Tan L**, Muto N. Purification and reconstitution properties of human placental aromatase. A cytochrome P-450-type monooxygenase. *Eur J Biochem* 1986;**156**:243-50.
- 313 **Chen SA**, Besman MJ, Sparkes RS, Zollman S, Klisak I, Mohandas T, Hall PF, Shively JE. Human aromatase: cDNA cloning, Southern blot analysis, and assignment of the gene to chromosome 15. *DNA* 1988;**7**:27-38.
- 314 **Kristensen VN**, Borresen-Dale AL. Molecular epidemiology of breast cancer: genetic variation in steroid hormone metabolism. *Mutat Res* 2000;**462**:323-33.
- 315 **Kasid A**, Lippman ME. Estrogen and oncogene mediated growth regulation of human breast cancer cells. *J Steroid Biochem* 1987;**27**:465-70.
- 316 **Zuppan P**, Hall JM, Lee MK, Ponglikitmongkol M, King MC. Possible linkage of the estrogen receptor gene to breast cancer in a family with late-onset disease. *Am J Hum Genet* 1991;**48**:1065-8.
- 317 **Menasce LP**, White GR, Harrison CJ, Boyle JM. Localization of the estrogen receptor locus (ESR) to chromosome 6q25.1 by FISH and a simple post-FISH banding technique. *Genomics* 1993;**17**:263-5.
- 318 **Rousseau-Merck MF**, Misrahi M, Loosfelt H, Milgrom E, Berger R. Localization of the human progesterone receptor gene to chromosome 11q22-q23. *Hum Genet* 1987;**77**:280-2.
- 319 **Gulberg HC**, Marsden CA. Catechol-O-methyl transferase: pharmacological aspects and physiological role. *Pharmacol Rev* 1975;**27**:135-206.
- 320 **Grossman MH**, Emanuel BS, Budarf ML. Chromosomal mapping of the human catechol-O-methyltransferase gene to 22q11.1-q11.2. *Genomics* 1992;**12**:822-5.
- 321 **Winqvist R**, Lundstrom K, Salminen M, Laatikainen M, Ulmanen I. The human catechol-O-methyltransferase (COMT) gene maps to band q11.2 of chromosome 22 and shows a frequent RFLP with BglI. *Cytogenet Cell Genet* 1992;**59**:253-7.
- 322 **Weisz J**, Fritz WG, Gestl S, Clawson GA, Creveling CR, Liehr JG, Dabbs D. Nuclear localization of catechol-O-methyltransferase in neoplastic and nonneoplastic mammary epithelial cells. *Am J Pathol* 2000;**156**:1841-8.
- 323 **van Es HH**, Bout A, Liu J, Anderson L, Duncan AM, Bosma P, Oude ER, Jansen PL, Chowdhury JR, Schurr E. Assignment of the human UDP glucuronosyltransferase gene (UGT1A1) to chromosome region 2q37. *Cytogenet Cell Genet* 1993;**63**:114-16.
- 324 **Mackenzie PI**, Owens IS, Burchell B, Bock KW, Bairoch A, Belanger A, Fournel-Gigleux S, Green M, Hum DW, Iyanagi T, Lancet D, Louisot P, Magdalou J, Chowdhury JR, Ritter JK, Schachter H, Tephly TR, Tipton KF, Nebert DW. The UDP glucosyltransferase gene superfamily: recommended nomenclature update based on evolutionary divergence. *Pharmacogenetics* 1997;**7**:255-69.
- 325 **Belanger A**, Hum DW, Beaulieu M, Levesque E, Guillemette C, Tchernof A, Belanger G, Turgeon D, Dubois S. Characterization and regulation of UDP-glucuronosyltransferases in steroid target tissues. *J Steroid Biochem Mol Biol* 1998;**65**:301-10.
- 326 **Bakkenist CJ**, Koreth J, Williams CS, Hunt NC, McGee JO. Heat shock cognate 70 mutations in sporadic breast carcinoma. *Cancer Res* 1999;**59**:4219-21.
- 327 **Huerre C**, Uzan G, Grzeschik KH, Weil D, Levin M, Hors-Cayla MC, Boue J, Kahn A, Junien C. The structural gene for transferrin (TF) maps to 3q21-3qter. *Ann Genet* 1984;**27**:5-10.
- 328 **Smith EL**, Walworth NC, Holick MF. Effect of 1 alpha,25-dihydroxyvitamin D3 on the morphologic and biochemical differentiation of cultured human epidermal keratinocytes grown in serum-free conditions. *J Invest Dermatol* 1986;**86**:709-14.
- 329 **Taymans SE**, Pack S, Pak E, Orban Z, Barsony J, Zhuang Z, Stratakis CA. The human vitamin D receptor gene (VDR) is localized to region 12cen-q12 by fluorescent in situ hybridization and radiation hybrid mapping: genetic and physical VDR map. *J Bone Miner Res* 1999;**14**:1163-6.
- 330 **Lazzaro G**, Agadir A, Qing W, Poria M, Mehta RR, Moriarty RM, Das-Gupta TK, Zhang XK, Mehta RG. Induction of differentiation by 1alpha-hydroxyvitamin D(5) in T47D human breast cancer cells and its interaction with vitamin D receptors. *Eur J Cancer* 2000;**36**:780-6.

- 331 **Ho KY**, Kalle WH, Lo TH, Lam WY, Tang CM. Reduced expression of APC and DCC gene protein in breast cancer. *Histopathology* 1999;**35**:249-56.
- 332 **Olaisen B**, Teisberg P, Gedde-Dahl T. The locus for apolipoprotein E (apoE) is linked to the complement component C3 (C3) locus on chromosome 19 in man. *Hum Genet* 1982;**62**:233-6.
- 333 **Seidegard J**, Vorachek WR, Pero RW, Pearson WR. Hereditary differences in the expression of the human glutathione transferase active on trans-stilbene oxide are due to a gene deletion. *Proc Natl Acad Sci USA* 1988;**85**:7293-7.
- 334 **Winqvist R**, Peltoketo H, Isomaa V, Grzeschik KH, Mannervaa A, Vihko R. The gene for 17 beta-hydroxysteroid dehydrogenase maps to human chromosome 17, bands q12-q21, and shows an RFLP with Scal. *Hum Genet* 1990;**85**:473-6.
- 335 **Peltoketo H**, Piao Y, Mannervaa A, Ponder BA, Isomaa V, Poutanen M, Winqvist R, Vihko R. A point mutation in the putative TATA box, detected in nondiseased individuals and patients with hereditary breast cancer, decreases promoter activity of the 17 beta-hydroxysteroid dehydrogenase type 1 gene 2 (EDH17B2) in vitro. *Genomics* 1994;**23**:250-2.
- 336 **Schechter AL**, Stern DF, Vaidyanathan L, Decker SJ, Drebin JA, Greene MI, Weinberg RA. The neu oncogene: an erb-B-related gene encoding a 185,000-Mr tumour antigen. *Nature* 1984;**312**:513-16.
- 337 **Coussens L**, Yang-Feng TL, Liao YC, Chen E, Gray A, McGrath J, Seeburg PH, Libermann TA, Schlessinger J, Francke U. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. *Science* 1985;**230**:1132-9.
- 338 **Johnson DW**, Qumsiyeh M, Benkhalifa M, Marchuk DA. Assignment of human transforming growth factor-beta type I and type III receptor genes (TGFBRI and TGFBRI3) to 9q33-q34 and 1p32-p33, respectively. *Genomics* 1995;**28**:356-7.

ECHO

Another risk factor for MI?

Please visit the
Journal of
Medical
Genetics website
[www.jmedgenet.com]
for link to
this full article.

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 GPIIb/IX/V, to von Willebrand factor on plaques in the arterial walls. Four subunits (GPIIb, GPIIb, GPIX, GPV) comprise the receptor complex, each specified by a single gene; the GPIIb subunit has the binding site for von Willebrand factor. Douglas *et al* speculated that the GPIIb-5T/C sequence Kozak polymorphism—affecting GPIIb/IX/V expression—and GPIIb variable number tandem repeats (VNTRs)—affecting its structure and lengthening the receptor—might alter the risk of MI. GPIIb Kozak polymorphism is a thymine (T) or cytosine (C) at position -5 around the ATG initiator codon; GPIIb 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.

GPIIb 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. GPIIb 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.

▲ *Heart* 2002;**87**:70–74.