Pergamon

European Journal of Cancer Vol. 30A, No. 13, pp. 1957–1961, 1994

0959–8049/94 $7.00+0.00

0959-8049(94)00386-6

The Genetics of Breast Cancer

D.M. Black

INTRODUCTION

THE GENETIC basis of breast cancer has received a great deal of attention in the last 10 years. In that time, much progress has been made in characterising the alterations found in breast tumours in a few specific genes and in determining the locations of additional genes involved in this disease. It is believed that in the near future further breakthroughs in characterising the molecular genetic events leading to breast cancer will be achieved. These should offer new hope to women who have the disease, and to women from families in which there is a genetic susceptibility to breast cancer.

Neoplastic transformation of the breast has been shown to involve the accumulation of mutations in both genes which become oncogenic through the acquisition of a dominant function (the proto-oncogenes), and those which need to be inactivated for the initiation and progression of malignancy (recessive oncogenes or tumour suppressors). Tumour suppressor genes were first identified as the target of inactivating mutations in inherited cancer, while mutation of the dominantly acting oncogenes have been associated with somatic alteration in the developing tumour. However, the recent identification of the germline mutation of proto-oncogenes and of site-specific mutations in presumed tumour suppressor genes in familial cancers blurs this distinction.

PREDISPOSING GENES

Chromosomal abnormalities

The 'two-hit' hypothesis for inactivation of tumour suppressor genes was first suggested by Knudson [1], and confirmed in retinoblastoma (RB) for the case of rare RB patients who carry germline interstitial deletions of chromosome 13q14 [2]. A second conclusion could also be drawn from the observation of these deletions in RB patients. A specific chromosomal abnormality associated with a disease may indicate that there is a potential candidate region in which a gene or genes affected by the predisposing lesion is located. Since mutations of the same genes are believed to be involved in the development of both inherited and sporadic tumours, this holds true for both rare constitutional chromosomal abnormalities and for the more frequently observed tumour-specific chromosomal aberrations.

Cytogenetic and molecular analysis of breast cancer cell lines and breast tumour tissue have shown high frequencies of loss of heterozyosity (LOH) on chromosomes 1q, 3p, 6q, 7q, 9q, 11q, 15q, 16q, 17p, 17q, 18q and X [3]. The chromosome 18q losses are probably directed at the *DCC* gene and the 17p losses at the *TP53* gene, although losses on 17p which are distal to *TP53* have also been documented. The targets of the losses seen on other chromosome arms are currently under investigation.

Oncogenes

In breast tumours the sites of oncogenes are marked by regions of DNA amplification and gene overexpression. The three best characterised sites are found at chromosome 8q24, chromosome 11q13 and chromosome 17q12. The target genes are the *MYC* gene on chromosome 8, the *PRAD1*/CyclinD1 locus on chromosome 11 and the *ERBB2* locus on chromosome 17. *MYC* and cyclinD1 are amplified in approximately 15% of breast tumours, and *ERBB2* is amplified in 20% of breast tumours [4]. Overexpression of these oncogenes is also seen in breast tumours which do not show any DNA amplification. However, to date, no inherited alterations in any of these loci have been shown to be responsible for a familial susceptibility to breast cancer.

Genetic linkage

The collection of informative pedigrees segregating for breast cancer is the first step in determining to which chromosomal region the predisposing gene maps. The inheritance of a susceptibility to the cancer can be followed through a family and linkage to other markers can be assessed. Linkage to protein polymorphisms or to the expression of genetically controlled phenotypes has been completely superseded by the use of polymorphisms in DNA restriction fragment lengths, DNA minisatellites and DNA microsatellites. The combination of linkage analysis with the knowledge of disease-associated cytogenetic abnormalities and with LOH can result in a reasonably restricted region for analysis. The task of searching the whole human genome for genetic linkage has been very labour intensive. However, the development of a high density genetic map based on microsatellites, and the intensive genotyping methods which have been used to develop the map, should make it more feasible to carry out genomic searches for linked markers [5].

Genetics

Breast cancer is the most common cancer in women in the Europe, currently affecting one in twelve. Each year there are approximately 30 000 new cases in the U.K. Approximately 40% of women diagnosed with breast cancer die from the disease. The incidence of breast cancer is increasing, and this trend is likely to continue for some time, as no major environmental cause of breast cancer has yet been identified. This means that there is no known way of substantially reducing the risk [6].

Several risk factors have been identified for breast cancer. Some of these appear to be specific for either the premenopausal or postmenopausal disease. In both cases, a slightly increased (less than 2-fold) risk seems to be conferred by the following factors: an early age of menarche, a relatively small number of

Correspondence to D.M. Black at the Beatson Institute for Cancer Research, Garscube Estate, Switchback Road, Bearsden, Glasgow G61 1BD, U.K.

days between menstrual periods, cigarette smoking, birth in either the United States or northern Europe, a late age at the first full-term pregnancy and possibly alcohol consumption [4, 7–9]. A reduction of risk is seen in women who have undergone oophorectomy at an early age.

A slight reduction in the risk of premenopausal breast cancer is seen in women who have lactated. However, lactation appears to have no effect on the risk of postmenopausal breast cancer [10].

Long-term use of oestrogen replacement therapy (HRT) seems to confer an increased risk of postmenopausal breast cancer, and long term use of the oral contraceptive pill confers an increased risk of premenopausal breast cancer [11]. The latter risk seems to be dependent on the duration of exposure to oral contraceptives, with a greater than 8 year course giving a relative risk of about 1.5. It should be noted, however, that this risk is based on cases where women have been exposed to the older high-dose pills. It is likely that the modern 'lower-dose' pills are less harmful.

By far the greatest risk factor for breast cancer is a family history of the disease. A women who has two or more first degree relatives who have had breast cancer has almost a 50% risk of getting the disease [12, 13]. This indicates that there are familial breast cancer genes.

Although most breast cancer cases are not due to inherited factors, approximately 6% of cases result from an inherited susceptibility. This means that breast cancer is caused in approximately one in 200 women by an inherited mutation in a susceptibility gene. There are, therefore, approximately 150 000 women in the U.K. who carry a breast cancer susceptibility mutation. Women carrying this mutation have a greater than 80% lifetime risk of developing breast cancer, whereas non-carriers have a less than 10% chance of getting the disease [8, 14].

Ovarian cancer is approximately a fifth as common as breast cancer, with over 5000 new cases each year. Currently, approximately three quarters of the women diagnosed as having ovarian cancer die from this disease, and an estimated 5% of ovarian cancer cases are also thought to be due to an inherited susceptibility [15]. Interestingly, the risk of ovarian cancer is increased in relatives of women with breast cancer and *vice versa*. This suggests the existence of one or more genes which predispose to both breast and ovarian cancer.

The proportion of breast cancer cases, and probably also ovarian cancer cases, which are due to an inherited susceptibility varies with age. More than one-third of cases diagnosed before the age of thirty are estimated to be due to familial breast cancer. This proportion falls to about 1% for cases diagnosed after the age of eighty [12, 14]. However, it should be noted that in all age groups, the majority of breast cancer cases are due to sporadic disease. This fact is extremely important in trying to genetically map the breast cancer susceptibility genes, and in the management of families which carry these genes. Notably, in any large pedigree, there are likely to be sporadic breast cancer cases (phenocopies), so that even in families where it is possible to determine who has inherited the susceptibility gene, genetic counselling is going to be difficult as the women who have not inherited the susceptibility gene will still have a nearly one in ten risk of breast cancer.

Known susceptibility genes

The *TP53* gene is commonly mutated in sporadic forms of breast and ovarian cancer. Additionally, germline *TP53* mutations predispose women to many tumour types, including breast cancer [16, 17]. It is estimated that approximately 1% of breast cancer susceptibility is due to germline mutation in the *TP53* gene.

Additionally, breast cancers are often seen in women from hereditary non-polyposis colon cancer (HNPCC) families [18]. Some HNPCC families have recently been shown to be due to germline mutations in the human DNA mismatch repair genes *hMSH2*, on chromosome 2p and *hMLH1* on chromosome 3p. The overall contribution of germline mutations in mismatch repair genes to site-specific breast cancer susceptibility is currently unknown, although one would expect it to be slight.

Finally, the gene encoding the 16 kD (p16) inhibitor of cyclin-dependent kinase 4 (CDK4) has recently been shown to be frequently deleted in breast cancer cell lines. This gene, called *MTS1*, maps to chromosome 9p. It would, therefore, not be surprising if germline mutations in this gene also contributed to familial breast cancer susceptibility.

Mapped susceptibility genes

The gene which may be responsible for the majority of hereditary breast cancer cases is called *BRCA1* (breast cancer 1) and maps to the long arm of human chromosome 17 [19–21]. An international collaboration, involving over 200 families, has shown that the *BRCA1* gene is responsible for almost all families with a susceptibility to breast and ovarian cancer [22]. Approximately half of the families with only a susceptibility to breast cancer are believed to be due to *BRCA1* [22]. However, the actual contribution that *BRCA1* makes to breast cancer susceptibility, and the involvement of this gene in the sporadic disease cannot be fully determined until the *BRCA1* gene has actually been identified (see Note added in proof p. 1960). It is, nevertheless, probable that over 25 000 women in the U.K. carry germline *BRCA1* mutations. Studies of the 200 families mentioned above indicate that the women in these families have a risk of developing either breast or ovarian cancer of approximately 60% by the age of 50 years, rising to over 80% by the age of 70 years [22].

A detailed epidemiological investigation of a large *BRCA1*-linked family from Utah has been useful in describing the effect on women of carrying one particular *BRCA1* mutant allele [7]. In this family, the risk of breast or ovarian cancer in female carriers was only 40% by the age of 50 years, but it increased to 90% by the age of 70, suggesting that certain *BRCA1* alleles may also be important in late onset breast cancer families. It has also been suggested that female carriers of a *BRCA1* mutation are more likely to get breast cancer if they were born after 1930 [23]. A study carried out on a *BRCA1*-linked French-Canadian family showed that female carriers of the mutant *BRCA1* allele had a mean age of onset of 51 years if they were born before 1930. This mean age of onset went down to 40 years for female carriers born after 1930. The study also showed that less than 30% of the *BRCA1* carriers born before 1930 had developed breast cancer by the age of 45, whereas 65% of those born after 1930 had the disease by age 45. This difference was not seen for ovarian cancer in the same family, which suggests that there must be some interaction between the susceptibility to breast cancer conferred by the *BRCA1* mutation and an unidentified environmental risk factor of increasing frequency.

BRCA1 has been mapped by genetic linkage studies to the region of chromosome 17 between the markers D17S702 [24] and D17S78 [25] (see Figure 1 and Note added in proof p. 1960). This is a region of approximately one million base pairs, which

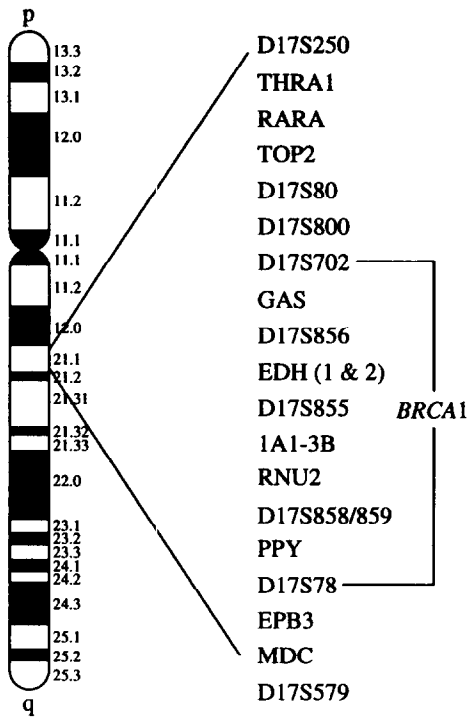

Figure 1. Chromosome 17 showing markers in the *BRCA1* region. The *BRCA1* gene has been mapped to a one million base pair interval at 17q21.1, flanked by the DNA markers D17S702 and D17S78.

harbours approximately 30 genes. It should be noted that all genetic mapping studies involving such a common disease are complicated by the very frequent occurrence of phenocopies which can implicate the wrong region of the chromosome if a critical recombinant is in fact a sporadic breast cancer case. As mentioned earlier, simply by chance, any large pedigree is likely to have one or more sporadic breast cancer cases, especially if the family has been selected on the basis of having multiple breast cancers. It is, therefore, important to treat all recombinants with caution, and novel recombinants have to be critically scrutinised. Ideally in terms of genetic linkage studies, an affected women with a recombinant chromosome will have had the disease at an early age (when sporadic breast cancer is relatively uncommon), and have passed on the chromosome to an affected daughter or granddaughter. Unfortunately, such informative recombinants are extremely rare. It is, therefore unlikely that it will be possible to substantially reduce the size of the *BRCA1* region by genetic mapping [6].

As can be seen from the figure, the *BRCA1* region contains previously described genes. Some of these would appear to be excellent candidates for *BRCA1*. The two oestradiol dehydrogenase genes (*EDH1* and *2*) encode the enzyme 17β-oestradiol dehydrogenase. This enzyme catalyses the conversion of inactive oestrone to the active form, 17β-oestradiol. As breast tumours are often 17β-oestrodiol-responsive, this gene made an excellent *BRCA1* candidate. However, exhaustive sequencing of the *EDH1* and *2* genes in the DNA from *BRCA1* carriers did not show any disease-causing mutations [25, 26].

A novel gene has recently been described which also seemed to be a good candidate for *BRCA1* [27]. This gene, which has been called 1A1-3B, was isolated by screening a cDNA expression library with an antibody against the ovarian cancer specific serum marker CA125. CA125 is a tumour antigen which is widely used in the diagnosis and management of ovarian cancer. As the *CA125* gene had not been genetically mapped, it seemed to be quite a coincidence that the *CA125* candidate gene (*1A1-3B*) mapped into the *BRCA1* region, bearing in mind that the *BRCA1* region is one million base pairs and the human haploid genome is three thousand million base pairs. However, no mutations in the coding exons of the *1A1-3B* gene have been found in either DNA from *BRCA1*-linked families or in DNA from sporadic premenopausal breast and ovarian tumours. It therefore seems unlikely that the *1A1-3B* gene is *BRCA1*, although the possibility of mutations in non-coding and promoter regions of the gene cannot be excluded. A metalloproteinase/disintegrin-like gene (*MDC*) was also put forward as a *BRCA1* candidate gene [28], the announcement being accompanied by a blaze of publicity. Excitement was generated as the *MDC* gene was also shown to be occasionally disrupted in sporadic breast tumours. However, as can be seen from the figure, the *MDC* gene maps distal (telomeric) to the marker D17S78, and so is outside the BRCA1 region. This means that it cannot, therefore, be considered as a plausible candidate for *BRCA1*.

LOH studies have shown that chromosome 17 markers are lost at significant frequencies in both sporadic breast and ovarian cancer [6]. LOH is seen in over 80% of late stage ovarian adenocarcinomas [29] and in 30–40% of breast carcinomas [30].

Analysis of breast and ovarian tumours from families in which the disease is linked to *BRCA1* also show LOH with chromosome 17 markers. As would be predicted from Knudson's 'two-hit' hypothesis, the alleles that are linked to the disease in these families are retained in the tumours and the wild-type alleles are lost [26, 31]. This results in the tumours being homozygous (two copies) or hemizygous (one copy) for the *BRCA1* mutation. This observation has been interpreted to mean that *BRCA1* is a tumour suppressor gene which acts recessively at the cellular level, even though a *BRCA1* mutation gives a dominant susceptibility to breast or ovarian cancer. However, it is possible that the observed loss is not directed at *BRCA1*, as there are many other putative tumour suppressor genes on chromosome 17, such as *TP53*. Interestingly, when chromosome 17 LOH is observed in ovarian tumours, the entire chromosome is almost always lost. Additionally, there does not seem to be any peak of allele loss in the *BRCA1* region, It is, therefore, unclear if *BRCA1* actually is a tumour suppressor gene. If *BRCA1* is a recessively acting tumour suppressor gene, it should be possible to find breast tumours and/or breast cancer cell lines with deletions in the gene. Occasional constitutional deletions would also be expected in the *BRCA1* region in linked families. To date, no such deletions have been reported which indicate that either they are extremely rare or that *BRCA1* is not in fact a tumour suppressor gene.

Ataxia-telangiectasia (A-T) is a rare progressive disorder in which there is variable immune dysfunction, an excess sensitivity to ionising radiation and two distinct patterns of susceptibility to malignancy [32, 33]. A-T is genetically transmitted and shows an autosomal recessive pattern of inheritance with a mutant gene frequency of between one in 100 and one in 200. There is evidence of genetic heterogeneity in A-T, however, the vast majority of A-T families are linked to a locus (the A-T gene) which has been mapped to a >5 cM interval on chromosome 11q22-q23. In the homozygous state, the A-T gene predisposes individuals to 70–250-fold increased risk of leukaemia and lymphoma. Additionally, carriers of one mutant copy of the gene (heterozygotes) have a significantly increased susceptibility

to many solid tumours including bladder, ovarian, pancreatic, prostate and stomach cancer. Most notably, A-T heterozygotes have been found to have a 6.8-fold increase in breast cancer in women [34]. Based on the estimations of the A-T gene frequency and incidence of breast cancer, it has been calculated that as many as 9% of women in the United States with breast cancer may be A-T heterozygotes [32, 33].

Not surprisingly, people have looked for linkage to the A-T gene in breast cancer families which do not appear to be linked to *BRCA1*. To date, no breast cancer families have been found which are linked to the A-T locus on chromosome 11q [35].

One late-onset breast cancer family has been described which showed slight evidence of linkage to the oestrogen receptor gene on human chromosome 12 [36]. However, this putative linkage has not yet been confirmed.

Unmapped susceptibility genes

There are most certainly additional unmapped genes which give women an inherited susceptibility to breast cancer. These genes can be divided into two types: those responsible for only susceptibility to breast cancer and those responsible for an increased risk of breast cancer and cancer at one or more other site. It appears that about half of the families which show susceptibility to only female breast cancer are not linked to the *BRCA1* locus on chromosome 17 [22]. These families are currently being used in linkage studies in the hope of mapping new susceptibility loci. It has recently been shown that families with both male and female breast cancer cases are not linked to *BRCA1* either, although they do show an autosomal dominant pattern of inheritance. Interestingly, women in these families also have susceptibility to ovarian cancer. Once the nature of the *BRCA1* gene product has been determined, it should be possible to seek out good candidate genes for *BRCA2,3*, etc.; in much the same way that the identification of *hMSH2* mutations in some HNPCC families suggested the role of the *hMLH1* gene, which was subsequently shown to be mutated in a second subset of HNPCC families.

Additionally, some breast cancer susceptibility will be due to unmapped genes which increase the risk to cancers at many sites. Such genes may encode products which are involved in either DNA repair, or cell cycle control, or alternatively they may be involved in hormonal responses. The fact such genes are known to exist makes their identification of crucial importance in trying to understand and combat breast cancer.

Male breast cancer

Although breast cancer in men is extremely rare, compared to breast cancer in women, it accounts for approximately 1% of all cancers in men and about 0.1% of cancer deaths. Like female breast cancer, a family history of both male and female breast cancer is a risk factor for male breast cancer. At least two familial male breast cancer genes exist. One of these is the androgen receptor (*AR*) gene on the X chromosome. Two families have been described which have an *AR* missense mutation; affecting adjacent amino acid residues, and segregating with the disease [37, 38]. However, the majority of male breast cancer susceptibility is not X-linked and so must be due to an as yet unmapped autosomal gene or genes. Families with a susceptibility for both male and female breast cancer exist (see above), and it is likely that families with an autosomal susceptibility to male breast cancer only will be identified.

CONCLUSIONS

The spectrum of genes which are involved in familial susceptibility to breast cancer is likely to be broad. A number of loci that predispose to breast cancer are expected to be identified within the next few years. Once these genes have been found it will be possible to identify individuals who carry high-risk alleles. Such individuals could then be put forward for intensive screening using both conventional medical and molecular strategies. They would also have the option of prophylactic removal of any nonessential target tissue for the disease, by mastectomy and/or oophorectomy in the case of breast/ovarian cancer. However, carrier detection is not the goal of the scientists who are trying to find the genes which cause a familial susceptibility to breast cancer. It is hoped that new opportunities for diagnosing and treating sporadic, as well as familial breast cancers, will be facilitated by knowledge of the molecular lesions responsible for the susceptibility to cancer in families. Molecular diagnosis will also become available for specific families and hopefully for sporadic disease by either detecting the mutant genes or their products in circulating blood, smears, or microscopic quantities of biopsied material. It may also be possible to detect alterations at very early stages of breast tumour development, once the genetic lesions involved have been determined. In the longer term, gene therapy approaches could be used either to treat somatic disease, or to replace mutant cancer susceptibility alleles with the wild-type copy of the gene.

Note added in proof—Subsequent to writing this review, three particularly important papers in the field of familial breast cancer have been published. Firstly, the long awaited *BRCA1* gene has been identified (Miki, Y *et al. Science* 1994, **266**, 66–71). The *BRCA1* gene spans over 100 kb, and is between the *EDH* and *1A1-3B* genes. The marker D17S855 is in an intron of the *BRCA1* gene (see Figure 1). So far, loss of function mutations have been found in *BRCA1* linked families, indicating that *BRCA1* is a tumour suppressor gene. Surprisingly, somatic mutations are not found in the *BRCA1* gene, in sporadic breast and ovarian tumours (Futreal A *et al. Science* 1994, **266**, 120–122). All the alterations reported to date are also present in the constitutional DNA from the patient, indicating they are germline mutations.

The other major breakthrough in this field is the mapping of *BRCA2*, a second high penetrance breast cancer susceptibility gene, to chromosome 13q12-q13 (Wooster R *et al. Science* 1994, **265**, 2088–2090). Unlike *BRCA1*, *BRCA2* also confers a greatly increased risk to breast cancer in men.

1. Knudson AG. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci USA* 1971, **68**, 820–823.
2. Yunis E, Zuniga R, Ramirez E. Retinoblastoma, gross internal malformations, and deletion at 13q14-q31. *Human Genet* 1981, **56**, 283–286.
3. Sato T, Tanigami A, Yamakawa K, *et al.* Allelotype of breast cancer: cumulative allele losses promote tumor progression in primary breast cancer. *Cancer Res* 1990, **50**, 7184–7189.
4. van de Vijver MJ. Molecular genetic changes in breast cancer, In Weinberg RA, ed: *Oncogenes and the Molecular Origins of Cancer*. New York, Cold Spring Harbor Press, 1993, 25–56.
5. Weber JL, May PE. Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. *Am J Human Genet* 1989, **44**, 388–396.
6. Black DM, Solomon E. The search for the familial breast-ovarian cancer gene. *TIGS* 1993, **9**, 22–26.
7. Goldgar DE, Fields P, Lewis CM, *et al.* A large kindred with 17q-linked breast and ovarian cancer: genetic, phenotypic and genealogical analysis. *JNCI* 1994, **86**, 200–209.
8. Bishop DT, Easton DF. Preface to the breast cancer linkage consortium papers. *Am J Human Genet* 1993, **52**, 677.
9. Bishop DT, Cannon-Albright L, McLellan T, Gardner EJ, Skolnick

MH. Segregation and linkage analysis of nine Utah breast cancer pedigrees. *Genet Epidemol* 1988, 5, 151–169.
10. Kelsey JL, John EM. Lactation and the risk of breast cancer. *New Engl J Med* 1994, **330**, 136–137.
11. Chilvers CED, Smith SJ. The effect of pattern of oral contraceptive use on breast cancer risk in young women: *BJC* 1994, **67**, 922–923.
12. Newman B, Austin MA, Lee M, King M-C Inheritance of human breast cancer: evidence for autosomal dominant transmission in high-risk families. *Proc Natl Acad Sci USA* 1988, **85**, 3044–3048.
13. Skolnick MH, Cannon-Albright LA, Goldgar DE, *et al.* Inheritance of proliferative breast disease in breast cancer families. *Science* 1990, **250**, 1715–1720.
14. Claus EB, Risch NJ, Thompson DW. Age at onset as an indicator of familial risk of breast cancer. *Am J Epidemiol* 1990, **131**, 961–972.
15. Schildkraut JM, Risch N, Thompson WD. Evaluating genetic association among ovarian, breast and endometrial cancer: evidence for a breast-ovarian relationship. *Am J Human Genet* 1989, **45**, 521–529.
16. Malkin D, Li FP, Strong LC, *et al.* Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* 1990, **250**, 1233–1238.
17. Srivastava S, Zou Z, Pirollo K, Blattner W, Chang EH. Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li–Fraumeni syndrome. *Nature* 1990; **348**, 747–749.
18. Lynch HT, Kimberling W, Albano WA, *et al.* Hereditary nonpolyposis colorectal cancer (Lynch syndromes I and II) 1. Clinical description of resource. *Cancer* 1985, **56**, 934–938.
19. Hall JM, Lee MK, Newman B, Morrow JE, Erson LA, Huey B, King M.-C. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 1990, **250**, 1684–1689.
20. Hall JM, Friedman L, Guenther C, *et al.* Closing in on a breast-cancer gene on chromosome-17q. *Am J Human Genet* 1992, **50**, 1235–1242.
21. Narod SA, Feunteun J, Lynch HT, *et al.* Familial breast-ovarian cancer locus on chromosome 17q12-23. *Lancet* 1991, **338**, 82–83.
22. Easton DF, Bishop DT, Ford D, Cockford GP, Consortium, a.t.B.C.L. Genetic linkage analysis in familial breast and ovarian cancer-Results from 214 families. *Am J Human Genet* 1993, **52**, 678–701.
23. Narod S, Lynch H, Conway T, Watson P, Feunteun J, Lenoir G. Increasing incidence of breast cancer in family with BRCA1 mutation: *lancet* 1993, **341**, 1101–1102.
24. Smith SA, DiCioccio RA, Struewing JP, *et al.* Localisation of the breast-ovarian cancer susceptibility gene (BRCA1) on 17q12-21 to an interval of ≤1cM. *Genes Chroms Cancer* 1994, **10**, 71–76.
25. Simard J, Feunteun J, Lenoir G, *et al.* Genetic mapping of the breast-ovarian cancer syndrome to a small interval on chromosome 17q12-21: exclusion of candidate genes EDH17B2 and RARA. *Human Mol Genet* 1993, **2**, 1193–1199.
26. Kelsell DP, Black DM, Bishop DT, Spurr NK. Genetic analysis of the BRCA1 region in a large breast/ovarian family: refinement of the minimal region containing BRCA1. *Human Mol Genet* 1993, **2**, 1823–1828.
27. Campbell IG, Nicolai HM, Foulkes WD, *et al.* A novel gene encoding a B-box protein within the BRCA1 region at 17q21.1. *Human Mol Genet* 1994, **3**, 589–594.
28. Emi M, Katagiri T, Harada Y, *et al.* A novel metalloprotease/disintegrin-like gene at 17q21.3 is somatically rearranged in two primary breast cancers. *Nat Genet* 1993, **5**, 151–157.
29. Foulkes WD, Black DM, Stamp GWH, Solomon E, Trowsdale J. Very frequent loss of heterozygosity throughout chromosome 17 in sporadic ovarian carcinoma. *Int J Cancer* 1993 **54**, 220–225.
30. Sato T, Tanigami A, Yamakawa K, Akiyama F, Kasumi F, Sakamoto G, Nakamura Y. Allelotype of breast cancer: cumulative allele losses promote tumor progression in primary breast cancer. *Cancer Res* 1990, **50**, 7184–7189.
31. Smith SA, Easton DF, Evans DGR, Ponder BAJ. Chromosome 17 allele loss in familial ovarian cancer. *Nat Genet* 1992, **2**, 128–131.
32. Peterson RDA, Funkhouser JD, Tuck-Muller CM, Gatti, RA. Cancer susceptibility in ataxia-telangiectasia. *Leukemia* 1992, **6**, 8–13.
33. Taylor A.M.R. Atxia telangiectasia genes and predisposition to leukaemia, lymphoma and breast cancer. *BJC* 1992, **66**, 5–9.
34. Swift M, Reitnauer PJ, Morrell D, Chase CL. Breast and other cancers in families with ataxia telangiectasia. *New Engl J Med* 1987, **316**, 1289–1294.
35. Wooster R, Ford D, Mangion J, Ponder BAJ, Easton DF, Stratton MR. Absence of linkage to the ataxia telangiectasia locus in familial breast cancer. *Human Genet* 1993, **92**, 91–94.
36. Zuppan P, Hall JM, Lee MK, Ponglikitmongkol M, King M.-C. Possible linkage of the estrogen receptor gene to breast cancer in a family with late-onset disease. *Am J Human Genet* 1991, **48**, 1065–1068.
37. Wooster R, Mangion J, Eeles R, *et al.* A germline mutation in the androgen receptor gene in two brothers with breast cancer and Reifenstein syndrome. *Nat Genet* 1992, **2**, 132–134.
38. Lobaccaro J-M, Lumbroso S, Belon C. Male breast cancer and the androgen receptor gene. *Nat Genet* 1993, 5, 109–110.

Pergamon

European Journal of Cancer Vol. 30A, No. 13, pp. 1961–1968, 1994

0959–8049/94 $7.00+0.00

0959-8049(94)00387-4

Multiple Endocrine Neoplasia Type 1 (MEN1)

J.T. Pang and R.V. Thakker

INTRODUCTION

MULTIPLE ENDOCRINE neoplasia type 1 (MEN1), which has also been referred to as Wermer's syndrome [1, 2], is characterised by the combined occurrence of tumours of the parathyroid glands, the pancreatic islet cells and the anterior pituitary gland [3–5]. In addition to these tumours which constitute the major components of MEN1, adrenal cortical, carcinoid and lipomatous tumours have also been described [3–10]. These MEN1 tumours may either be inherited in an autosomal dominant manner or they may occur sporadically, i.e. without a family history. However, this distinction between sporadic and familial cases may sometimes be difficult; in some sporadic cases, the family history may be absent because the parent with the disease may have died before developing symptoms. In addition, the combinations of the affected glands and their pathological features, e.g. hyperplasia or single or multiple adenomas of the parathyroid glands, have been reported to differ in members of

Correspondence to R.V. Thakker.
The authors are at the MRC Molecular Medicine Group, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, U.K.