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ROLE OF GENETIC FACTORS IN BREAST CANCER SUSCEPTIBILITY

ANNE-LISE BØRRESEN

Hereditary breast cancer is common and accounts for approximately 10–14% of all breast cancers. Knowledge of a family history of breast cancer may significantly influence diagnosis and therapy. Genetic heterogeneity has been demonstrated in familial breast cancer. Recently inherited mutations in the tumor suppressor gene p53, have been shown to be the underlying defect in the Li-Fraumeni syndrome. We have shown that defects in this gene also play a role in the predisposition to other familial breast cancers. The gene responsible for early onset familial breast and ovary cancer has recently been mapped to chromosome 17q21. For most of the sporadic breast cancers a multifactorial model, including variable genetic and environmental factors, has been considered. Two genetic risk factors which may predispose for a considerable portion of breast cancers are the gene causing ataxia telangiectasia (AT) and the gene that gives rise to proliferative breast disease (PBD). Identification of distinct genes enhancing the risk of breast cancer will give us the opportunity to identify high risk individuals. Such individuals may benefit from periodic examination affording the possibility of early diagnosis and treatment.

Key words: Breast cancer, hereditary factors, gene p53, ataxia telangiectasia, proliferative breast disease.

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Familial breast cancer was first recognized in the Roman medical literature of 100 AD (1), and familial clustering has been verified repeatedly in formal studies during the first half of this century. For most cases of breast cancer (probably more than 85%) a multifactorial model, which includes variable genetic and environmental factors, has been proposed to explain its etiology. Population-based studies have shown that a woman's risk of developing breast cancer is increased 1.5- to 3-fold if one first-degree relative (mother, daughter, or sister) had breast cancer and 5- to 10-fold if the relative had bilateral cancer, or if more than one first-degree relative had breast cancer (2). At least 9% of the familial cases seem to fulfil the criteria of dominant inherited disease (3). The hypothesis of a rare breast cancer susceptibility allele that is dominantly inherited has been supported by several groups (4–7). These studies have produced estimates of the gene frequency of a dominant susceptibility allele of 0.0006–0.008 in the population, and a life-time probability of breast cancer of up to 92% in genetically susceptible predisposed individuals.

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Correspondence to: Dr Anne-Lise Børresen, Dept. of Genetics, Inst. for Cancer Research, The Norwegian Radium Hospital, Montebello, N-0310 Oslo 3, Norway.

Hereditary breast cancer syndromes

A family is diagnosed as an hereditary breast cancer family (HBC) when breast cancer, sometimes in conjunction with other cancer types occurs frequently among family members and when these cancer diagnoses are distributed in the pedigree in a pattern consistent with mendelian transmission. HBC is characterized by an earlier age of onset, increased bilateral occurrence, heterogenous tumor association, and improved survival when compared to its sporadic counterpart. The penetrance is incomplete, and HBC is considered to be an inherited cancer susceptibility disorder which may require certain environmental

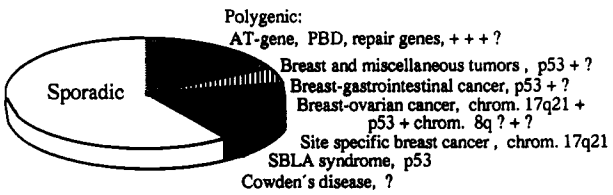

Fig. 1. Schematic illustration of the relative frequency of hereditary breast cancer syndromes and sporadic breast cancer. Genes and chromosomal regions identified to be involved in the cancer predisposition are indicated.

exposures for actual cancer development (3). The nature of the environmental influences in HBC is at present unknown, but their influence may account for the very variable expressivity and incomplete penetrance of the cancer phenotype.

Heterogeneity of HBC is clearly demonstrated, and a schematic illustration of this heterogeneity is shown in Fig. 1. Thus, we find families where breast cancer appears to be the single most dominant lesion, and families with propensity to breast and ovarian carcinoma, families with a complex syndrome characterized by proclivity to sarcoma, breast, brain, lung and laryngeal cancer, leukemia, and adrenocortical carcinoma, the so-called Li-Fraumeni syndrome or SBLA (8–11). Breast cancer has also been associated with gastrointestinal tract cancer (12–14). Colon cancer was the most frequent tumor followed by carcinoma of the stomac and pancreas. The autosomal dominant inherited disorder, Cowden's disease, is a disease which is characterized by multiple trichilemmomas, characteristically appearing on the face, oral fibromas and papillomas. In women with Cowden's disease the incidence of breast cancer is at least 50% and with a high frequency of bilateral disease (15).

Linkage analyses

Mapping of the genes responsible for the predisposition in hereditary breast cancer has been complicated by the heterogeneity of the disease (Fig. 1) and by unavoidable epidemiologic realities. The disease is common, but only a small portion of cases in the general population is attributable to inherited susceptibility. Thus, families may have multiple cases of breast cancer without inherited susceptibility, and 'sporadic' cases may occur even in families with inherited disease. In addition, the disease is not completely penetrant among susceptible persons with expression depending on gender, age, and non-genetic risk factors. Several linkage studies using random markers as blood types and serum enzymes, and candidate genes like oncogenes and tumor suppressor genes, have been performed over the last years. The results of some of these linkage analyses are shown in the Table. In the case of several oncogenes and a number of blood types and serum

Table

Linkage analyses in breast cancer families

Candidate gene	Candidate chromosome region	Linkage results		Reference
		Tentative	Confirmed	
Oncogenes				
Ha-ras	11p15.5	–		16
K-ras	12p12.1	–		16
N-ras	1p22	–		16
Myc	8p24	–		16
Myb	6q22-q23	–		16
ErbA-2	3pter-p21	–		16
Int-2	11p-13	–		16
Raf-1	3p25	–		16
Supressor genes				
Rb	13q14	–		17
p53	17p13	–/+	+	18, 19 and unpublished study by Børresen et al.
Serum enzymes/serum types				
GPT	8q24-qter	+	?	6, 20–22
ACP1	2p25	+	?	6, 21, 22
Rh	1p36.2-p34	+	?	6, 22
Regions frequently lost in breast tumors				
?	17q21	+	+	26

enzyme types linkage to HBC has been exlcuded. However, it is not yet clear whether the positive lod scores observed between HBC and the GPT and the ACP1 enzyme markers and the Rhesus blood group are significant. Of the two tumor suppressor genes investigated, the retinoblastoma gene could be excluded as the primary lesions for human breast cancer (17), while the p53 tumor suppressor gene seems to be associated with a high rate of breast and other cancers in families with the Li-Fraumeni syndrome (see below).

In view of Knudson's two hit hypothesis that the genes responsible for hereditary cancers are also frequently involved in sporadic cases, chromosomal regions frequently lost in breast tumors would be candidate regions for linkage analyses in hereditary breast cancers. Regions frequently lost in human breast tumors are located on chromosomes 3p, 11p, 13q, 16q, 17p, and 17q (23–25). Linkage analyses of markers mapping to chromosome 17q21 from Mary Clair King's group (26) have recently concluded that an as yet unidentified gene located in this region is responsible for the inherited susceptibility to early onset breast cancer. Their results have been strengthened by the group of Lenoir that obtained similar results in a study of five families with breast and ovarian cancer (27). There are several interesting candidate genes on chromosome 17q21, as shown in Fig. 2. Possible candidate genes could be the estradiol-17β-dehydrogenase (EDHB 17), the homeobox 2 gen (HOX2) which is involved in tissue differentiation and organogenesis, the NM23 tumor antimetastatic gene, the gene for the retinoic acid receptor α, (RAR α) the INT 4 gene, the human homologue of one of the mammary tumor virus integration sites in mouse, and the NGFR, the gene for the nerve growth factor receptor. However, the 17q21 region is large enough to accomodate several hundred genes, and other genes might therefore very well be candidates.

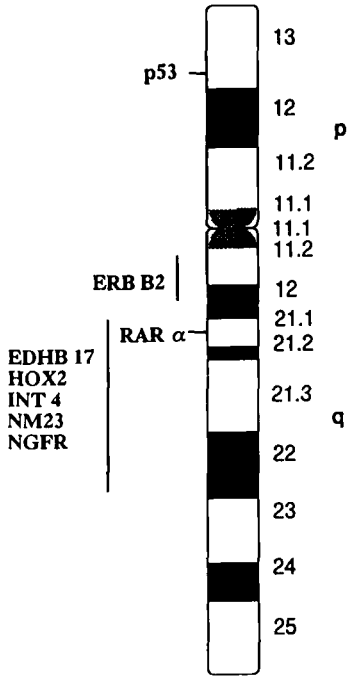

Fig. 2. Ideogram of chromosome 17 with major bands and position of genes that may be implicated in breast carcinomas.

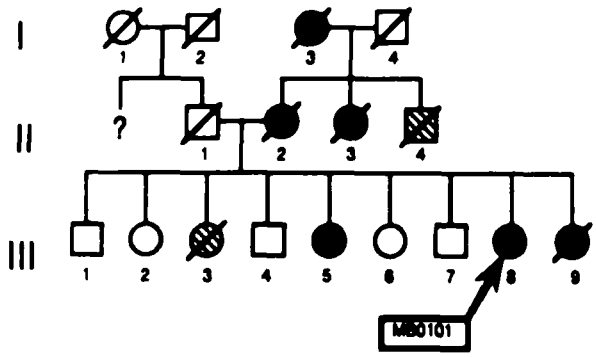

Fig. 3. Pedigree of family with germline p53 mutation
● breast cancer; ⊘ other cancers

Mutation analyses

Mutations in one copy of the p53 tumor suppressor gene and/or deletion of the normal gene are common events in many human cancers including those of the breast. The product of the normal p53 gene, which maps to the short arm of chromosome 17, apparently functions as a regulator of cell proliferation—a tumor suppressor—but there is evidence that point mutations can convert it into an oncogene. Inherited mutations of the p53 gene have recently been found to be the defect in the Li-Fraumeni syndrome (17–18). In a study by Prosser et al. (28), no p53 mutations were found among five site-specific breast cancer families. We have developed a rapid screening technique for detecting germ line p53 mutations (29), and have found that germ line p53 mutations also exist in breast cancer families outside the classical Li-Fraumeni syndrome ((30) and unpublished study by Børresen et al.) (Fig. 3). The frequency of such constitutional p53 mutations in hereditary breast cancer syndromes is at present unknown.

Predisposing genes in familial breast cancer

Familial aggregation of breast cancer, without hereditary criteria exist in 15–20% of the cases. In these polygenic traits (see Fig. 1) more than one gene is probably responsible for the cancer predisposition. Linkage analysis can therefore not be performed to identify these predisposing genes. Other strategies like twin studies, association studies and risk estimates in different defined genetic groups are more useful for this purpose. One of the genes which have been associated with an increased breast cancer

risk, is the gene for ataxia telangiectasia (AT). AT is an inherited autosomal recessive disorder assigned to chromosome 11q23 (31). Patients who are homozygous for AT have a progressive neurological disorder, varied immune dysfunction, an excess sensitivity to ionizing radiation, and exceptional high incidence of cancer. AT heterozygotes have an increased risk of cancer at all sites of 2.3-fold for men and 3.1-fold for women, compared to non carriers. The heterozygous mothers are at an 8-fold increased risk of breast cancer (32–34). With an estimated gene frequency of 1–3%, as much as 20% of the women with breast cancer might be AT carriers. A reliable procedure for identifying AT heterozogets would therefore be of considerable value. As a group, AT heterozygotes are also known to be more radiosensitive than non-AT carriers. A possible important implication for radiotherapy of the identification of AT heterozygotes has been considered (35). Five percent or more of breast cancer patients are unusually radiosensitive. If these patients could be singled out prior to treatment, the remaining patients could be given higher radiation doses, thus improving therapeutic effi-ciency. The radiosensitive breast cancer patients might be AT heterozygous, so that the detection of heterozygotes could improve therapy not only for them but also for cancer patients in general (35).

Proliferative breast disease (PBD) has been used to describe several benign breast lesions characterized by an excessive, but non-malignant proliferation of breast epithelial cells, located in the terminal portions of the ducts of the breast (36, 37). It has been suggested that PBD represents a premalignant state. Several cohort studies have demonstrated that women with PBD have a 2–5-fold increased risk of developing breast cancer, compared to women with non-proliferative breast lesions (38–40). Recently Skolnick et al. (41) examined the frequency of PBD in families that were ascertained by having two first-degree relatives with breast cancer, and tested the hypothesis that PBD and breast cancer are inherited lesions in these families. Cytological analysis of breast aspirates revealed PBD in 35% of clinically normal female first-degree relatives of breast cancer cases and in 13% of controls. Genetic analysis suggested that genetic predisposition causes both PBD and breast cancer in these kindreds. The study of Skolnick et al. (41) supports the hypothesis that this susceptibility is responsible for a considerable portion of breast cancers, including unilateral and postmenopausal breast cancer.

Conclusion

In conclusion, one must emphasize that the tip of the iceberg has barely been grazed with respect to the role of genetic factors in breast cancer susceptibility. At the present time, however, using molecular genetic tools, we are several steps closer to understanding the breast cancer genetics. Identification of germ line p53 mutations, the subsequent identification of the gene on 17q, and the gene responsible for PBD and the AT gene may ultimately lead to better understanding and early diagnosis of a great proportion of breast cancers. Identification of women at high risk of breast cancer on the basis of family history, examination of histology and growth of normal tissues, and subsequently by molecular analyses of the genes, should be of high priority. If we are to see real advances in early diagnosis and prevention, research efforts should be concentrated on these groups of women which may benefit from periodic examination giving the possibility of early diagnosis and treatment.

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