Hereditary Breast Cancer

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Information on genetics is in process of exponential growth, with a corresponding recognition that most medical information, screening and diagnostic tests, and disease processes have a genetic component. Hereditary breast cancer is a good example, showing the complexity of cancer genetics in a clinical context. The contribution of family history to the risk of developing breast cancer has been appreciated for some time. Breast cancer was believed to be a result of multiple genetic and environmental factors. Today it is known that single genes are also responsible for breast cancer and some of these genes (BRCA1 and BRCA2) can be identified by genetic testing. Genetic information on breast cancer is, however, still limited and although the tests that are now available can be beneficial, they also carry some risks and limitations.

FAMILIAR BREAST CANCER

Epidemiological studies show that a positive family history is a risk factor for breast cancer. Familiar breast cancer can be defined as the aggregation of two or more cases of breast tumour within a family. Early onset of tumours in probands and bilaterality of the disease are particular susceptibilities in breast cancer. The aggregation may be due to chance or can be related to common environmental factors shared by members of a given family, but it is likely that in many of these cases primary genetic factors are of some relevance. Among various types of genetic transmission, the multifactorial model seems to be the most appropriate for explaining the aggregation of cancers in these families. The interaction between many environmental factors and genetic background lends further support to this interpretation (1).

An explanation of the pathogenesis of breast cancer has been sought through many hypotheses. It is generally accepted that a cancer results from the accumulation of the genetic changes in a target cell. The mutation of several genes eventually leads to the onset of a cancerous phenotype. The inheritance of these mutated genes in the germline will cause cancer susceptibility in the next generation. Alfred Knudsen suggested that cancer results from the occurrence of a second mutation in a somatic target cell, so that the only difference between hereditary and non-hereditary tumours is the timing of the first mutation. The second mutation can affect either the remaining normal allele of the same gene (recessive trait) or one copy of a different gene (dominant trait) (2). The latter is the two-hit hypothesis, suggesting that as genetic susceptibility to breast and ovarian cancer results from inactivation of one allele in the germline followed by the loss of the other allele in somatic breast tissue, the mutations are recessive at the cellular level, although inheritance of breast and ovarian cancers in high-risk families follows an autosomal dominant pattern (3). Recently, a hypothesis on gatekeeper genes and caretaker genes has been suggested by Kinzler & Vogelstein (4). The inactivation of a caretaker gene indirectly promotes cancer by causing genomic instability, which in turn results in accelerated mutation of other genes, such as the gatekeeper genes. Apart from these, many other mechanisms have been presented.

When the isolation of a single gene responsible for the development of breast cancer was carried out in 1990 by King and colleagues using genetic linkage analysis to identify chromosome 17q12-21 at the location of this gene, now termed BRCA1, convincing evidence was available showing that a single gene can be responsible for some breast cancers.

HEREDITARY BREAST CANCER

Hereditary breast cancer is a heterogeneous entity and several clinical variants have been described. Site-specific breast cancer is the most common inherited type and is characterized by the predominance of breast cancer in these families. In hereditary breast/ovarian cancer, neoplasms of these two organs develop in susceptible individuals with a distribution in families that is consistent with dominant inheritance. However, a clear distinction between the two syndromes is not supported by molecular genetic studies, because the main susceptibility genes,

BRCA1 and BRCA2, are predisposed to both breast and ovarian cancers (5). Li-Fraumeni-syndrome (p53 mutation on chromosome 17p13) is characterized by early neoplasms, including soft tissue sarcoma, osteosarcoma, brain tumours, leukaemia, lung, laryngeal and adrenocortical cancer (6). Cowden disease is a rare type of inherited bilateral breast cancer; besides breast tumours and cysts, hamartomous lesions of the skin, oral fibromas, and benign and malignant thyroid tumours are common (7). Breast cancer is also described to be associated with tumours of the digestive organs. It has been estimated that 5–10% of breast cancers have a major inherited component (8). Mutations in the gene BRCA1 on chromosome 17q12-21 and gene BRCA2 on chromosome 13q12-13 may account for as much as two-thirds of inherited breast cancer and a diverse group of other genes comprise the remainder (9) (see Table 1). Specific mutations have been found recently in particular ethnic groups. Women diagnosed at a young age, those with bilateral breast cancer and those with a strong family history of breast and ovarian cancers are more likely to carry predisposing mutations in breast cancer-susceptibility genes than other women with disease (10). It has been estimated that penetrance of breast and ovarian cancer among BRCA1 carriers in high-risk families is 85% and 45% by age 70 years, but recent studies show that the age range could be much lower. In a community-based sample of Ashkenazi Jewish families, breast and ovarian cancer penetrance is only 50% and 15%, respectively (11). The most recent results of a population-based study from Iceland show that the mean risk of breast cancer in carriers of mutations in BRCA2 is lower (37.2% at age 70) than previously suggested (12).

GENETIC TESTING FOR BREAST CANCER

Genetic testing for the breast cancer risk genes BRCA1 and BRCA2 is now available. The extensive media coverage of findings in cancer genetics has created a situation in which public interest and demand have begun to outstrip relevant medical services and expertise. Unlike other medical tests, genetic tests provide information not only about the individual tested but also about that individual's parents, siblings and children. Genetic testing therefore has immediate implications for the entire family, implications that must be discussed and anticipated prior to testing. Genetic testing is not diagnostic—it does not alter someone's physical status from well to ill. It just gives knowledge. This knowledge has both advantages and disadvantages. Genetic testing can identify individuals at risk for hereditary breast and ovarian cancer and identify non-carriers in families with a known mutation but it does not detect all mutations.

Table 1

Causes of hereditary susceptibility to breast cancer

Gene	Proportion of hereditary breast cancer (%)
BRCA1	20–40
BRCA2	10–30
TP53	<1
PTEN	<1
Undiscovered genes	30–70

Table 2

Benefits and disadvantages of BRCA testing

Benefits	Disadvantages
*Identifies high risk	*Does not detect all mutations
*Identifies non-carriers in families with a known mutation	*Does not change the risk of sporadic cancer
*Provides early detection and prevention managements	*Efficacy of interventions is unproven
*May relieve anxiety	*May result in psychological or economic harm

A positive test result can end uncertainty and so decisions about preventive measures become more straightforward. The disadvantages of a positive test result include greater anxiety for the tested herself and her children and other relatives, and further health fears. A positive test can also cause some discrimination in getting life insurance or employment, or at least many people think this is so (13). A negative test result may lessen anxiety, and extra screening and preventive measures are not needed. The benefits and limitations of BRCA testing are presented in Table 2.

GENETIC COUNSELING

Counseling is a communication process that deals with the psychological, medical and genetic issues associated with the occurrence or risk of occurrence of a genetic disorder within a family and therefore plays a very important part in the field of hereditary breast cancer. Genetic counseling is not just the provision of the risk information, although giving information is an important part of it. Nor is counseling merely genetics education. The concept of risk really incorporates all of an individual, i.e. personal, emotional, social, and cultural values, beliefs and attitudes.

The recent publicity surrounding breast cancer in general, screening for cancer, and prevention trials has raised awareness in women who have a family history of breast cancer. This has led to demands for advice about risks and what to do about them. Access to cancer family history clinics are needed in primary healthcare. In Finland, the Finnish Cancer Society is coordinating the primary advice services. After assessing the risks, those who have a strong family history of cancer are sent to the genetic clinics of university hospitals.

Counseling is needed before and after testing and should be given by experts. The team of medical geneticists and oncologists in specialized clinics is the best option (14, 15).

Table 3

Recommended surveillance for breast cancer in BRCA-mutation carriers

Breast self-examination monthly (begin at age 18)
Annual or semi-annual breast examinations
Annual mammography, complemented by ultrasound (begin at age 25–35)

Counseling is also needed for those women participating in scientific trials.

THE CLINICAL MANAGEMENT OPTIONS

The efficacy of surveillance for mutation carriers is missing. Based on experts' opinions, the option of early detection of cancer is recommended. Breast self-examination is recommended monthly beginning early in adult life (e.g. by age 18–21 years). Clinical breast examination annually or half yearly is recommended to begin at age 25 to 35 years. Annual mammography is suggested, beginning at age 25 to 35 years. Individuals should be counseled that the risks and benefits of mammography before age 50 years have not been verified and that benefits for women aged 50 years and older are based on studies of average-risk women. Ultrasound has also been recommended at least for younger women (Table 3) (16). It is recommended that screening for ovarian cancer should be carried out annually or semi-annually using transvaginal ultrasound and serum Ca-125 levels, beginning at age 25–35 years, for BRCA1 mutation carriers (17).

Prophylactic mastectomy is not generally recommended but it is possible. However, the efficacy of prophylactic mastectomy in preventing invasive cancer in individuals with increased risk because of a cancer-predisposition gene is unknown (18). Prophylactic removal of the ovaries does appear to reduce the risk of ovarian cancer in women with a genetic predisposition to ovarian cancer. The exact magnitude of this reduction is not certain, but it is about a fourfold reduction in risk in small series (19). However, ovarian cancer can still occur in cells lining the abdominal cavity, even if the ovaries that were removed are normal. Clinical management of the BRCA mutation-positive patient is presented in Fig. 1.

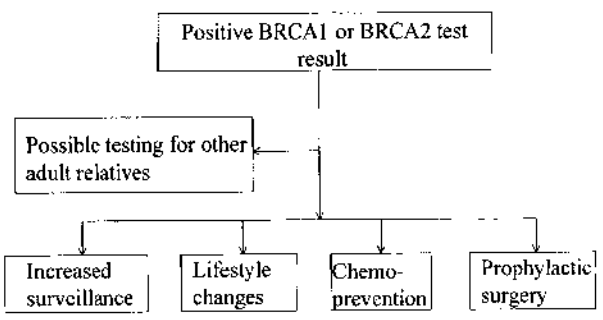

Fig. 1. Clinical management of BRCA mutation-positive women.

CHEMOPREVENTION

At present, chemoprevention is experimental. The option available at present is tamoxifen for breast cancer prevention. Tamoxifen is known to reduce the incidence of a new primary breast cancer in those with previous breast cancer by up to 40–50%. The early results of the NSABP prevention trial for high-risk women also show a reduction of 50% in breast cancer incidence in a short follow-up time (20). However, so far, there are no data showing that mutation carriers benefit from chemoprevention.

BREAST CANCER IN CARRIERS OF BRCA1 OR BRCA2 MUTATIONS

The histological characteristics of breast cancers caused by BRCA1 and, to a lesser extent, BRCA2 mutations differ from those of sporadic breast cancers. High-grade tumours tend to occur more often among BRCA1 mutation carriers than among controls. Furthermore, BRCA1 mutation carriers showed more pleomorphism, a higher mitotic count, and less tubule formation than controls (21).

The biology of BRCA1 included tumours also differs from those of sporadic tumours. BRCA1-induced tumours seem to be more often steroid receptor negative, DNA-aneuploid and they have a higher S-phase fraction than controls (22, 23).

CONCLUSION

Identification of the main susceptibility genes for breast cancer has created new clinical challenges and intensive research. Testing for mutated BRCA1 and BRCA2 is the basis for disease risk prediction in women with a family history of breast cancer. The dilemma is, however, that mutation carriers cannot turn to reliable preventive measures upon being informed of their risk. However, increased knowledge and understanding of the genetic and biologic mechanisms of tumorigenesis in those at risk will help to promote the development of chemopreventive agents and strategies for breast cancer.

REFERENCES

1. Anderson DE, Bedzioch MD. Familiar breast cancer risk. Cancer 1993; 72: 114–9.
2. Knudson AG. Mutation and cancer: statistical study of retinoblastoma. Proc. Natl. Acad. Sci. USA 1997; 68: 820–3.
3. Knudson AG. Hereditary cancer: two hits revisited. J. Cancer Res. Clin. Oncol. 1996; 122: 135–40.
4. Kinzler WK, Vogelstein B. Gatekeepers and caretakers. Science 1997; 386: 761–3.
5. Narod SA. Hereditary breast carcinoma syndromes. Cancer 1997; 80: 537–56.
6. Li FP, Garber JE, Fried FH, et al. Recommendation of predictive testing for germ line p53 mutations among cancer-prone individuals. J. Natl. Cancer Inst. 1992; 84: 1156–60.
7. Starink TM, van der Veen JPW, Arwent F, et al. The Cowden syndrome: a clinical and genetic study in 21 patients. Clin. Genet. 1986; 29: 222–33.

8. Claus EB, Schildkraut JM, Thompson WD, Risch NJ. The genetic attributable risk of breast and ovarian cancer. Cancer 1996; 77: 2318–24.
9. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar UK. Breast cancer linkage consortium. Risks of cancer in BRCA-1 mutation carriers. Lancet 1994; 343: 692–5.
10. Courch FJ, DeShano ML, Blackwook MA, et al. BRCA 1 mutations in women attending clinics that evaluate the risk of breast cancer. N. Engl. J. Med. 1997; 336: 1409–15.
11. Kaufman DJ, Tucker MA, Struewing JP. Breast and ovarian cancer penetrance in a historical cohort of BRCA1 carriers. Abstract. 21st Annual San Antonio Breast Cancer Symposium 1998.
12. Thorlacius S, Struewing JP, Hartge P, et al. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. Lancet 1998; 352: 1337–9.
13. Lapham EV, Kozma C, Weiss JO. Genetic discrimination: perspectives of consumers. Science 1996; 274: 621.
14. Croyle RT, Achilles JS, Lerman C. Psychologic aspects of cancer genetic testing. Cancer 1997; 80: 569–74.
15. Peters JA, Biesecker BB. Genetic counseling and hereditary cancer. Cancer 1997; 80:576
16. Lalloo F, Boggis CRM, Evans DGR, Shenton A, Threlfall AG, Howell A. Screening by mammography, women with a family history of breast cancer. Eur. J. Cancer 1998; 34: 937–40.
17. Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. JAMA 1997; 277: 997–1003.
18. Eeles JWR, Cole T, Taylor R, Lunt P, Baum M. Prophylactic mastectomy for genetic predisposition to breast cancer: The proband's story. Clin. Oncol. 1996; 8: 222–5.
19. Struewing JP, Watson P, Easton DF, Ponder BA, Lynch HT, Tucker MA. Effectiveness of prophylactic oophorectomy in inherited breast/ovarian cancer families, Am J Hum Genet 1995; 55: A70 no 384.
20. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: Report of the national surgical adjuvant breast and bowel project P-1 study. J. Natl. Cancer. Inst. 1998; 90: 1371–88.
21. Breast Cancer Lineage Consortium. Pathology of familiar breast cancer: differences between breast cancers in carriers of $BRCA_1$ or $BRCA_2$ mutations and sporadic cases. Lancet 1997; 349: 1505–10.
22. Johansson OT, Idvall I, Anderson C, et al. Tumour biological features of $BRCA_1$-induced breast and ovarian cancer. Eur. J. Cancer 1997; 33: 362–71.
23. Johansson OT, Ranstam J, Borg Å, Olsson H. Survival of $BRCA_1$ breast and ovarian cancer patients: a population-based study from southern Sweden. J. Clin. Oncol. 1998; 16: 397–404.