BRCA1 AND BRCA2 GENES - NEW RISK FACTORS IN HEREDITARY FORMS OF BREAST CANCER AND OVARIAN CARCINOMA

D. GODLEWSKI, M. KAPUŚCIŃSKA

Cancer Epidemiology and Prevention Union, Greatpoland Cancer Centre, 61-866 Poznań, Garbary 15, Poland

Cancer is one of the most serious problems in contemporary medicine. According to statistics, breast cancer is the most frequently diagnosed type of cancer among women in many countries. Despite widely spread breast cancer prevention programs, the number of diagnosed cases is continuously increasing at a rate of 1% per year [Beardsley, 1994; Special Raport, 1993]. The pathogenesis of this disease is still unknown. Considering the complex etiology of breast cancers, two basic groups of risk factors have been distinguished on the basis of social and genetic criteria [Davis and Bradlow, 1995; Special Raport, 1993]. The first group includes the impact of sex hormones and certain chemical compounds (the so called social xenoestrogens), the reproductive model, geographical factors, diet, socioeconomic factor, alcohol consumption and smoking. The other group encompasses risk factors of a hereditary nature which have been under intense investigation in the last few years. This resulted in the discovery of genes whose defects and the resulting expression disorders have an impact on the development of breast cancer. This achievement is undoubtedly the effect of an enormous development in genetic engineering and molecular biology.

The results of epidemiological research which has been carried out for several years in more than 200 American families with multiple history of breast or/and ovarian cancer (often in young people) suggested that the susceptibility to this disease was of hereditary nature [Collins, 1996]. The conjectures of the epidemiologists have been confirmed by genetic research performed during the last two years.

After four years of investigations, the first of the two known genes predisposing to breast and ovarian cancer was finally identified in October 1994 by M.H. Skolniyk et al. from University of Utah and labeled BCRA1 (BReast Cancer1) [Miki et al, 1994].

Fifteen months later the second gene related to the hereditary forms of breast and ovarian cancers was identified simultaneously by two independent teams from Great Britain and America and it was labeled BRCA2 (BReast Cancer2) [Marx, 1996; Miki et al, 1994].

Altogether, the defects in these genes are responsible for 80-90% of hereditary breast cancer cases [Szabo and King, 1995]. The remaining genetically conditioned cases can be attributed to genes such as p53, AT (ataxia telangiectasia), androgen receptor gene and the still undiscovered BRCA3 and BRCA4. Although research on these genes is at an infant stage, biologists, genetic engineers and doctors are already raising questions on how women carrying the defective genes can benefit from these discoveries.

The highest morbidity and mortality rates are observed among white women in highly developed countries. The cumulative risk of developing cancer by the age of 85 is estimated at 12,6% which means that in terms of statistics one in every 8 women will be affected. Hereditary cancer constitutes 5-10% of all diagnosed cases. Conjugate analysis, carried out in families with a family history of breast cancer, revealed that 45% of breast cancer cases were related to the mutation of BRCA1 in families with multiple cases of breast cancer. In families where breast cancer as well as ovarian cancer were observed, the rate was 75%. Carriers of mutations in any of the genes are at a higher risk of developing cancer at some point in their lives. Among women with BRCA1 mutations the cumulative risk of breast cancer rises to 85% and cumulative risk of ovarian cancer reaches 50%. Among male carriers of the mutation, the risk of acquiring prostate cancer rises threefold while the risk of colon cancer rises four times in men as well as in women. The other gene, BRCA2 is related to the existence of hereditary forms of breast cancer in men, among whom the disease occurs 100 times less often. The risk of developing breast cancer in male carriers of BCRA1 mutations by the age of 70 is estimated at 6%. Mutations in the gene have been found in 15% of all diagnosed cases of breast cancer among men. Defects in BCRA2 are also related to greater susceptibility to prostate and larynx cancer [Szabo and King, 1995].

According to early data on the frequency of BRCA 1 mutations in the general population, 1 in 200 women on average is a carrier of a

defected gene [Nowak, 1994]. In the light of the latest research data published in January 1996, it seems, that in some cases this value has been overestimated and in other cases it was underestimated. Research conducted among Jewish families showed that a mutation known as 185delAG (dinucleotide deletion in position 185 in the 2 exon) is frequently found among this population [Friedman et al, 1995]. It occurs in 1% of Jewish women that is at a rate of 1 in every 107 women. A corresponding rate for women excluding the Jewish ethnic group was estimated as 1:833 [Collins, 1996]. According to available data, the frequency of mutations in the BRCA1 gene is conditioned ethnically, the fact which must be taken into account when defining the frequency of mutations in a given population. We must also remember that not all the mutations in this gene have already been identified. The number of mutations will probably grow as was the case with other previously investigated genes such as p53. This fact will significantly influence the real value of the mutation prevalence rate.

The discovery of genes predisposing to breast cancer, the progress in screening techniques and the development of breast cancer prevention have all contributed to the early detection of cancer when the chances for cure are still high. It is understandable thus, that more and more women seek information on their individual breast cancer risk. This is especially important for women with a family history of breast cancer [Hoskins et al, 1995].

Recently, a few models for predicting breast cancer risk have been developed [Claus et al]. Risk evaluation guidelines, proposed by E.B.Claus et al, consider the number and configuration of affected family members and their age at onset, based on the assumption that the gene is transmitted as an autosomal dominant trait. The guidelines have been prepared on the basis of data coming from 4,730 patients with histologically confirmed breast cancer in the age group from 20 to 54 and 4,688 people in the control group. The data include information on cases of breast cancer in mothers and sisters of the affected women and the controls. The evaluation of risk on the basis of E.B.Claus's model pertains only to women belonging to the high risk group, that is those with at least one first-degree female relative suffering from breast cancer. Predictions based on E.B. Claus's model help to define breast cancer risk depending on the age of a woman with one or two relatives with breast cancer according to the relative's age at disease onset. Other models of breast cancer risk evaluation have also been developed; in addition to family history and age at diagnosis these models involve other factors such as age at primiparity, the number of undergone breast biopsies and age at menopause.

Any attempt to evaluate breast cancer risk is bound to be erroneous. This is due to the fact that because of the high morbidity rate in general population, a large number of women have at least one relative suffering from breast cancer which is not conjugated with the mutation in BRCA1 and BRCA2 genes. Nevertheless, the basis for evaluation of breast cancer risk in a particular patient is a properly gathered and well documented family history, according to which the pedigree analysis can be performed.

Investigations aiming at the localization and identification of BRCA1 and BRCA2 genes and identification of their mutations were based on families in which numerous cases of breast and ovarian cancer had been well documented for at least three generations. In such families the evaluation of risk is relatively easy. It must be remembered, however, that because in most cases we deal with families in which a detailed interviews (the base of risk evaluation) could not be performed, false positive or false negative results can be obtained. Furthermore, not all carriers of mutations in BRCA1 and BRCA2 genes present a family history of breast cancer and that is why not all of them are included in the high risk group [Hoskins et al, 1995; Langston et al, 1996].

Both of the discovered genes are very big - BRCA1 is almost ten times longer than the average human gene. The identified mutations (over 100 in the case of BRCA1 and 11 in the case of BRCA2) are dispersed, that means they occur along the entire sequence of the gene. Only 30% of the known mutations in BRCA1 were found in at least two examined families and only two, 185delAG and 5382insC, in over 25 analyzed families [Collins, 1996]. It is also hard to relate a particular mutation to a phenotype effect it causes. According to current estimates, a woman with a mutation in BRCA1 has a lifetime risk of developing breast cancer equal to 85%. In reality the probability of developing cancer depends on the type of mutation carried by the patient. For the time being, the discovery of defective BRCA1 or BRCA2 genes allows us only to inform the patient, that she exhibits a higher susceptibility to breast cancer and/or ovarian cancer. However, we cannot say when the disease will occur and whether it will occur at all. At the same time, the woman who is aware of the high risk of breast cancer has no other possibilities of preventing the development of the disease apart from frequent diagnostic examinations which lead to early diagnosis.

Research related to the identification of mutations uses techniques based on DNA analysis. Unfortunately none of the current techniques has a 100% sensitivity. Taking into

account the size of the gene as well as the dispersed nature of the mutation, it is understandable that the preparation of a reliable and relatively simple test encounters technical and financial problems. In the United States attempts to devise a test for detecting BRCA1 defects were undertaken by the Myriad Genetics Company. The Marag Genetics holds the license for BRCA1 gene and its utilization in medical diagnostics and are currently trying to obtain the license for BRCA2 gene [Leutwayler, 1995; Marx, 1996]. In the light of the facts mentioned above, a large group of oncologists and molecular biologists claim that, at present, research on the defects in the BRCA1 and BRCA2 genes should not be used as a diagnostic test for detecting asymptomatic susceptibility to breast or ovarian cancer.

The discovery of BRCA1 and BRCA2 gives hope for a better understanding of the molecular nature of hereditary breast cancer and for the introduction of a test to detect defects in these genes. Concurrently, there occurred questions and problems of not only medical or biological nature but also legal and ethical aspects. Advocates of tests claim that patients have the right to know whether they are at a high risk of breast cancer and it is unethical to withhold the information from them. Opponents claim that it is too early to introduce the tests, which can only be treated as scientific instruments, especially that, at the present state of knowledge, the interpretation of results is inconclusive.

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