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IT HAS been known for many years that a family history of breast carcinoma is, along with increasing age, the most important risk factor for the development of breast cancer. The elevated incidence of breast carcinoma and its genetic heterogeneity have limited, until recently, the understanding of its mechanisms of inheritance. Approximately 30% of patients with breast cancer have some degree of family history of breast carcinoma. Twelve per cent have two affected relatives, and 6% have three or more relatives.

Recently, the contribution of some genes to the predisposition of developing breast carcinoma has been demonstrated, the most important of which seem to be the genes *BRCA1* and *BRCA2*. *BRCA1* is a gene located in chromosome 17, that is linked to approximately 45% of hereditary, early-onset breast cancers and approximately 85% of cases of the hereditary breast and ovarian cancer syndrome. It has recently been estimated that the frequency of *BRCA1* mutation in the general population is 0.0006, and that the proportion of breast cancers due to *BRCA1* is 5% below 40 years of age. This relationship diminishes with age and *BRCA1* is associated with 2% of breast cancers between 40 and 49 years and 1% between 50 and 70 years. The cumulative risk of developing contralateral breast cancer in breast cancer patients who are *BRCA1* carriers seems to be very high: 87% by the age of 70 years (with 95% confidence limits from 72% to 95%). Specific mutations for particular population groups have been described, such as Ashkenazi or Sephardic Jews or Icelanders. It is remarkable that *BRCA1*-related breast cancers have a more favourable clinical course than other hereditary breast carcinomas. The *BRCA2* gene is localised in chromosome 13. Its contribution to hereditary breast carcinoma may be as high as 40%, although genetic testing is not as developed as in the case of *BRCA1*. Other genes with marginal contributions to hereditary breast cancer are *p53* and the ataxia-telangiectasia gene.

Several questions arise in relation to genetic testing in patients with breast cancer and their relatives.

Is the appropriate test available now or should we wait for new diagnostic developments? It is clear that the difficulties of detecting mutations in *BRCA1* are quite important, since *BRCA1* is a large gene with non-clustered mutations, which makes the available DNA testing very time-consuming and expensive. Perhaps the development of a biochemical (functional) test that detects the enzymatic activity of the *BRCA1* protein will allow a more precise and certainly less expensive massive testing.

Who should be tested? The number of relatives with breast cancer is a known marker for developing breast cancer. Many centres now accept genetic testing for only those families with three or more affected members. Age is also used as a selector for testing. Since the genes *BRCA1* and *BRCA2* are linked especially to early-onset breast cancer, usually only members of less than 40 years of age are tested to assess their risk.

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What should oncologists do when a high-risk individual is detected by genetic testing? This is certainly a complicated and unresolved question. There are physicians advocating for aggressive prophylactic therapies, including bilateral mastectomy and perhaps oophorectomy (see Dr Klijn's article). Other specialists favour a more conservative approach and recommend only a strict follow-up of such individuals (see Dr Janin's article). In the first case, we may be overtreating an otherwise young, healthy woman. In the second case, we may wait too long and, in the meanwhile, create a short or long period of anxiety for these young women who are told to undergo frequent tests and examinations.

Using an informal voting system of raised hands in our yearly meeting of ESMO, I had the responsibility of asking in a plenary session all participants their opinion regarding this topic. Around two-thirds of the audience disagreed with prophylactic removal of breast or ovaries compared with nearly all the audience at the start of the session. It can be concluded that this topic is just at the beginning of its development.

The question of whether to remove or not remove a woman's breasts and ovaries because she has an elevated risk of developing breast and ovarian carcinomas is difficult to answer since there are clear arguments for either of the two recommendations, as exemplified by Drs Klijn and Janin.

The development of new diagnostic tests for genetic diseases has placed medical oncologists in front of a new and unresolved problem. The works of Drs Klijn and Janin will undoubtedly stimulate many researchers to propose new approaches to this issue.