Presymptomatic diagnosis of hereditary breast cancer

ALERT | EARLY ASSESSMENT OF NEW HEALTH TECHNOLGIES | WWW.SBU.SE

This is a translation of version 1, published on February 2, 2000.
The latest version of this report is not available in English.

Published Oct 5, 2000
Version 1

Findings by SBU Alert

The discovery that mutations in two specific genes increase the risk for breast cancer and ovarian cancer has opened new opportunities to prevent hereditary cancer. Special programs to identify, investigate, follow up, and treat individuals with hereditary breast cancer are being developed in Sweden.

There is good* evidence that certain genes are associated with the risk for cancer. There is moderate* evidence regarding the effects of preventive interventions in women at high risk for cancer. However, no studies address the effects of morbidity, mortality, and cost-effectiveness of entire programs.

There is little opportunity to assess programs for genetic screening in randomized clinical trials. However, it is essential to analyze the overall effects of mortality and the economic impact of various strategies and programs using retrospective data and model analyses.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see “Grading of evidence”.

Alert is a joint effort by the Swedish Council on Technology Assessment in Health Care (SBU), the Medical Products Agency, the National Board of Health and Welfare, and the Federation of Swedish County Councils.

Technology

A strong genetic predisposition for breast cancer has been associated with two genes, ***BRCA1*** and ***BRCA2***. Mutations in ***BRCA1*** have also been found to carry a higher risk for ovarian cancer. Women at high risk for developing cancer can primarily be assigned to preventive investigations, but preventive surgical removal of the breasts (mastectomy) and ovaries (oophorectomy) may be considered in some cases. Mutation analysis may be offered to families with many cases of breast cancer. If diagnostic investigation reveals a mutation in a family member, other healthy family members may be informed about the implications of the findings for their own cancer risk and their opportunities for diagnostic examination.

Studying the family and charting a family tree (pedigree analysis) can identify families with autosomal dominant transmission (ie, similar for both genders) of genes for breast cancer. The risk of a particular family member can then be estimated, and individuals at high risk can be identified. Genetic epidemiological studies may also be used to assess risk [1–3].

Criteria used to identify individuals at high risk for breast cancer or ovarian cancer can arbitrarily be recognized. In Sweden the following delineation of high risk families is usually used:

- Three or more cases of parents, siblings, children (first-degree relatives) in at least two generations where at least one person was affected prior to 50 years of age (60 years of age for ovarian cancer).
- Two cases of first-degree family members where at least one was affected prior to age 40 (age 50 for ovarian cancer).
- Males with breast cancer.
- Mutation in a breast-cancer-associated gene in the family.

The indications are further enhanced when bilateral breast disease or multiple primary tumors are present in the same breast.

In addition to family studies, individuals who meet the criteria listed above may be offered molecular genetic tests of the ***BRCA1*** and ***BRCA2*** genes to determine whether a mutation in either of these genes can explain the accumulation of breast and ovarian cancer cases in the family. DNA from a blood sample is isolated and analyzed for mutations in the two genes. The method can identify approximately 80 per cent of the mutations. If a mutation is confirmed in a family, the same type of analysis may be offered to other family members to determine whether or not they carry the mutation.

Mutation carriers and women in families where mutations have not been confirmed, but where familial analysis (pedigree analysis) indicates a high risk for cancer, are referred to control programs or eventually prophylactic surgery. This intervention involves removal of both breasts followed by reconstructive surgery. Removal of the ovaries may also be necessary.

Target group

The prevalence of the ***BRCA1*** and ***BRCA2*** mutations in the Swedish population is unknown, and cannot be calculated with certainty unless the public is screened to determine the prevalence of inherited predisposition.

Approximately 4000 cases of breast cancer are detected annually in Sweden. An estimated 200 to 400 of these cases can be attributed to genetic factors with high penetration. If a mutation exists in half of these women, and we assume that each has a sibling and two children, then 300 to 600 first-grade relatives may be candidates for molecular genetic diagnosis and preventive measures. A wider demand for investigations may also be expected from second-degree and third-degree relatives, which could possibly double the need for genetic counseling and further investigation. The size of the primary target group can be expected to increase in the future with new diagnostic methods and increasing knowledge about the association between cancer and hereditary factors.

Future discoveries of other breast-cancer-associated genes will probably lead toward a need for reexaminations of previously investigated BRCA1/2 families.

Relation to other technology

Programs to prevent hereditary breast cancer focus on reducing morbidity and mortality from the disease. Mammography screening is one approach toward reducing breast cancer mortality. Such screening programs have been made widely available in much of Sweden, and are targeted at women aged 40 through 74 years. Women in the target group for presymptomatic diagnosis of hereditary breast cancer are often younger. Mammography screening has not been assessed in the younger age groups who need to be monitored for hereditary cancer.

Currently, no methods other than familial studies and genetic epidemiology are available to identify and assess individuals at risk for hereditary breast cancer.

Patient benefits

There are no assessments of patient benefits from overall programs to identify and prevent hereditary breast cancer. Indirect outcomes from followup of historical data show a large reduction in risk for both breast cancer and ovarian cancer following prophylactic surgery. These studies include assessments of prophylactic interventions in women found to be at high genetic risk.

A retrospective study conducted in North America between 1960 and 1993, included 639 women who had both breasts removed (bilateral mastectomy) for prophylactic reasons. On average, the women were aged 42 years when the surgery was performed, and the average followup time was 14 years. Based on the occurrence of breast cancer in the family, 214 of the women were found to belong to a high-risk group for developing breast cancer. The incidence of breast cancer in this high-risk group was compared with the incidence in their sisters who had not undergone bilateral mastectomy. The results showed that 1.8 per cent of the women who received prophylactic surgery, and 38.7 per cent of their sisters who did not receive prophylactic surgery, developed breast cancer. The results suggest a 90 per cent risk reduction in this high-risk group of women [6].

A decision analysis model [8] was used to study the effects of prophylactic mastectomy and oophorectomy on life expectancy among women who carry mutations in the ***BCRA1*** or ***BCRA2*** gene. In 30-year-old women, survival increased between 2.9 and 5.3 years following prophylactic mastectomy, depending on the cumulative risk of cancer, and between 0.3 and 1.7 years following surgical removal of the ovaries (oophorectomy). The gain in survival decreased with age but provided a substantial increase in the remaining life expectancy in younger women. The model assumes that prophylactic mastectomy yields an 85 per cent reduction in the risk for breast cancer, and oophorectomy yields a 50 per cent reduction in the risk for ovarian cancer.

One study developed a Markov model to investigate survival, quality of life, and cost-effectiveness in a Jewish population [4]. The results show that women who carried mutations in BRCA genes, which was common in this population, and who had undergone prophylactic surgery at a young age had substantially better survival, although the quality of life was not influenced.

Complications and side effects

Women with hereditary cancer are offered preventive treatment or regular mammography check-ups, which increases their exposure to radiation. Given the high basic risk for cancer in this population, the added risk of radiation should not substantially affect the total lifetime risk for breast cancer. However, mammography is insufficiently tested as a followup instrument in younger age groups. Consequently, there is a risk that equally favorable results as those achieved in screening older women are not possible due to physiological differences in the young breast compared to the older breast. An alternative being discussed is the regular use of MRI in check-ups.

Surgical intervention involving prophylactic removal of breast tissue does not fully eliminate the risk for breast cancer, but it reduces that risk. The operation is carried out in several stages and can be a difficult procedure for patients. Furthermore, there is a risk that cosmetic results do not meet patient expectations.

Since the findings from genetic studies affect more people than the patients themselves, the absence of genetic counseling for family members may result in psychosocial problems. Hence, relatives of patients should also have access to genetic information and diagnostic studies at specialty clinics.

Costs and cost-effectiveness

The costs of diagnostic testing in an individual with suspected hereditary breast cancer depend on the results of the investigation. Normally, the direct costs range from 5 000 SEK to 15 000 SEK per person, including psychosocial followup at specialty clinics. For the initial molecular genetic study of **BRCA1** and **BRCA2** genes in the first person in the family, costs range between 15 000 and 20 000 SEK. If a mutation is identified, the additional cost for a molecular genetic study is approximately 5 000 SEK per person. However, this cost can be expected to decline. Furthermore, there are the costs for check-ups and prophylactic surgery.

Cost and outcome data for total programs in Sweden are lacking, but health economic studies in other countries address prophylactic interventions in individuals identified as being at risk. A dissertation from Manchester has shown that it is less expensive for health services to offer genetic studies and prophylaxis for cancer than to treat cases of cancer that would have occurred without the interventions [7]. However, it is uncertain whether the results would apply to Swedish conditions.

In the model analysis from the United States referenced earlier, the authors estimated the effects on the length of life and quality of life in a Jewish population [4]. If both operations (mastectomy and oophorectomy) were performed, a woman aged 30 years could be expected to gain 1.9 quality-adjusted life years (QALY). Even considering the cost, the conclusion can be drawn that prophylactic treatment of women at high risk is cost-effective in relation to other medical interventions. In a later study, the same research group developed a model to assess genetic screening for three specific mutations in the same population, but selection was not based on family history [5]. Assuming that all women with a positive test result choose to undergo prophylactic mastectomy or oophorectomy, the authors estimate an average gain in survival of 33 days for each woman in the program. The cost per life year gained is estimated to be 168 000 SEK. The authors draw the conclusion that the method is cost-effective in comparison to, eg, mammography screening, but the model analysis must be confirmed by prospective observational studies and clinical trials.

Structure and organization of health services

Until further notice, the identification and genetic investigation of individuals suspected at higher risk for hereditary breast cancer should take place at specialty clinics having genetic, oncological, and psychosocial expertise. Such clinics exist, or are being developed, at all university hospitals in Sweden. Medical and psychosocial services should be provided within the county health services by physicians and other staff with expertise about the special circumstances associated with hereditary breast cancer. Networks for continuing education of staff should be linked to the specialty clinics. A "working group on genetic cancer clinics" has been active since 1994. This is a network of the oncogenetic clinics in Sweden that receives economic support from the Swedish Cancer Foundation (Cancerfonden). Under the leadership of The National Board of Health and Welfare, the working group will publish a state-of-the-art document addressing the diagnosis, followup, and care of individuals suspected to be at higher risk for hereditary cancer. In addition to breast cancer, the group is also addressing hereditary colon cancer, prostate cancer, endometrial cancer, ovarian cancer, malignant melanoma cancer, and basiloma [10].

Ethical aspects

Programs to identify and prevent hereditary breast cancer have ethical consequences and involve several types of complex decisions [12]. Genetic studies, directly or indirectly, include close relatives of the individual being examined, and the studies can impose upon their privacy. In particular, the right of family members to be informed about diagnostic results must be considered, as well as their right to refuse information. The principles for disseminating information within a family have been studied by the National Council on Medical Ethics (Statens medicinetiska råd) in Sweden [9]. This area has also been addressed by the National Board of Health and Welfare, which will develop guidelines for ethical considerations in genetic studies within the health services [11].

As with screening programs, programs aimed at preventing hereditary cancer subject some people without symptoms to interventions. These individuals may experience anxiety and are at risk of being harmed without knowing for certain whether they will benefit from their participation. Hence, at every stage – not only in connection with the genetic study itself – it is important to inform women about the state of knowledge and potential positive and negative consequences.

Diffusion in Sweden

Units for genetics and oncology at university hospitals in Sweden have special clinics for diagnosing suspected hereditary cancer. Molecular genetic laboratories for mutation analysis are available at the Oncology Department at Lund University Hospital, the Clinical Genetics Department at Sahlgrenska University Hospital, and at the Karolinska Hospital. Each of the clinics each have 350 to 400 new visits per year resulting from patients who suspect they are at high risk for familial breast cancer. The number of people who receive genetic information is probably substantially greater since relatives often accompany the patient to the physician.

Current evaluation research

The oncology and the genetic units in Lund and Stockholm have research groups involved in molecular genetic and psychosocial projects related to hereditary breast cancer.

In this context it should be noted that both of the genes analyzed for suspected hereditary breast cancer, **BRCA1** and **BRCA2**, are patented by a U.S. corporation, Myriad Genetics, which claims that the company will exercise its patent rights within the European Union.

Expert

Assoc Prof Ulf Kristoffersson, MD PhD, Lund University Hospital

Reviewer

Prof Håkan Olsson, MD PhD, Lund University Hospital

References

1. Burke W, Daly M, Garber J, Botkin J, Kahn MJ, Lynch P, McTiernan A, Offit K, Perlman J, Petersen G, Thomson E, Varricco C, for the Cancer Genetics Studies Consortium. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. JAMA 1997;277:997-1003.
2. Claus EB, Risch N, Thompson WD. Genetic analysis of breast cancer in the cancer and steroid hormone study. Am J Med Genet 1991;48:232-242.
3. Dörum A, Kristensen VM, Tropé CG, Möller P. Early detection of familial ovarian cancer. Eur J Cancer 1996;32A:1645-51.
4. Grann VR, Panageas KS, Whang W, Antman KH, Neugut AI. Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients. J Clin Oncol 1998;16:979-985.
5. Grann VR, Whang W, Jacobson JS, Heitjan DF, Antman KH, Neugut AI. Benefits and costs of screening Ashkenazi Jewish women for BRCA1 and BRCA2. J Clin Oncol 1999;17:494-500.
6. Hartman LC, Schad DJ, Woobs JE, Crotty TP, Myers JL, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 1999;340;77-84.
7. Lalloo FI. An evaluation of clinical and laboratory services for women at high risk of breast cancer. Thesis. Medical faculty, University of Manchester, UK. 1997.
8. Schrag D, Kuntz KM, Garber JE, Weeks JC. Decision analysis-effects of prophylactic mastectomy and oophorectomy on life expectance among women with BRCA1 or BRCA2 mutations. New Engl J Med 1997;336:1465-71.
9. Socialdepartementet. Synpunkter från Statens medicin-etiska råd. Uppsökande genetisk verksamhet. Dnr12/98. 1999.
10. Socialstyrelsen/medicinsk faktadatabas MARS. Utredning, uppföljning och omhändertagande av personer med misstänkt ärftligt ökad risk för tumörsjukdom. 1999 Under remissbehandling.
11. Socialstyrelsen Allmänna råd. Genetik inom hälso-och sjukvården. 1999. Under remissbehandling.
12. Vasen HF, Haites NE, Evans DG, Steel CM, Möller P, et al. The European Family Cancer Clinics. Current policies for surveillance and management in women at risk of breast-and ovarian cancer: a survey among 16 European family cancer clinics. Eur J Cancer 1998;34:1922-26.