

BREAST CANCER AND THE "DISCOVERY" OF BRCA GENES

Breast cancer is the most common form of cancer and the second major cause of death among American women today. In the general population, the risk of developing breast cancer increases with age (80% of cases occur in women older than 50), medical history and hormonal influences (excess estrogen plays a role in stimulating breast cell growth), among other variables. Three to five percent of the cases of invasive breast cancer diagnosed in 2001 were associated with mutations within BRCA1 or BRCA2, two breast cancer susceptibility genes identified in 1994. Studies on a related protein in yeast revealed that the BRCA genes participate in repairing radiation induced breaks in DNA. Mutations in these genes might disable this mechanism, leading to more errors in DNA replication and eventually to cancerous growth. In a way, this would make us age faster in terms of DNA replication capacity and thus render us more prone to developing breast cancer earlier than normal. Therefore, individuals who carry certain mutations in either BRCA gene are at an increased risk of being diagnosed with the disease. These mutations are thought to account for 80% of hereditary breast cancers. Despite certain gene testing capacity the best means to reduce mortality at a national rate is still through early detection and traditional preventive mechanisms, since screening an entire population for BRCA cancer predisposing mutations is not yet recommended. However, with recent developments and the planning of future research, we already face tough decisions regarding the field of cancer and genomics.

What We Know... And What We Don't Know

PREVALENCE & INHERITANCE OF MUTATION

The prevalence of BRCA1 cancer predisposing mutations in the general population is between 1/500 and 1/1000. According to the University of Rochester Medical Center Division of Genetics, 1/700 women carry either of the BRCA genes. Often these women come from cancer prone families in which the disease may have occurred at a young age. Certain mutations may be as much as ten times more common in Ashkenazi Jews and Icelanders. The BRCA mutations are inherited in an autosomal dominant manner: at least one of the proband's parents should carry the mutation, and the

proband's offspring have a 50% chance of inheriting it as well. Relatives of a positive tested individual should be informed of their own risks and options, but it is necessary to identify the proband's specific cancer disposing mutation before molecular genetic testing of either gene can be used in genetic counseling and testing of at risk family members. Most importantly, we must note that the risk of being diagnosed for breast cancer once a mutation has been identified depends on variables such as age, gender and mutation penetrance.

RISK OF CANCER DEVELOPMENT ONCE A MUTATION IS IDENTIFIED

The identification of a BRCA cancer predisposing mutation provides information about the risk of cancer development, but cannot say whether the cancer will develop or not, or what the response to medical treatment would be should cancer be diagnosed. The probability of cancer when the mutation is present (penetrance) is uncertain and seems to vary within families. Some women carrying a certain mutation may survive to an elderly age without developing cancer, some may have multiple primary cancers before the age of 50, and others may not develop cancer until after age 70. Penetrance estimates have been derived from a 1997 volunteer survey, a 1998 clinical series and a 1998 population based study.

The strongest evidence for variable risk comes from studies of multiple families with the same mutation within defined ethnic populations. For example, a study of Ashkenazi Jewish families found that individuals with certain mutations had a 56% risk of breast cancer (without a differentiation between BRCA1 and BRCA2 causation), and a study of Icelandic individuals presented that women with the 999del5 mutation in BRCA2 had a 37% risk of breast cancer by the age of 70. According to information provided by the National Cancer Institute, "According to lifetime risk estimates for women in the general population, about 12% will develop breast cancer, compared with 50 to 85% of women with an altered BRCA1 or BRCA2 gene." Another source, the University of Rochester Medical Center Division of Genetics, holds that women with inherited susceptibility genes may have a 37-87% risk of developing breast cancer. According to the Stanford Program in Genomics, Ethics and Society, early studies estimated that 51-73% of women with BRCA1 mutations will develop cancer by age 50 and 82-87% by age 70, and

that the risk for BRCA2 carriers may be as high as 87% by age 80 in high risk families. However, these figures represent broad ranges that may change as new research data comes about. Since most research has been conducted with cancer prone families, the estimates cited may overestimate penetrance values.

SURVIVAL AFTER BREAST CANCER DIAGNOSIS: PROGNOSIS

At a general level, prognosis for breast cancer survival depends upon the stage at which breast cancer is diagnosed and may not vary among individuals with BRCA mutations. Nevertheless, certain distinct pathological features of BRCA1 related tumors and other data suggest that breast cancer in individuals with either mutation have a pathogenic basis, which could lead to differences in prognosis. BRCA1 related tumors show an excess of medullar histopathology, are of higher histological grade, and are more likely to be estrogen and progesterone receptor negative. These and other features at the molecular level represent both favorable and adverse prognostic factors. Information regarding BRCA2-related tumors is limited, but they do not seem to have a characteristic histopathology. Most studies on prognosis have not found a significant difference in survival between individuals with BRCA mutations: while some reports suggest better (Marcus et al 1996, Porter et al 1994) some suggest worse (Foulkes et al 1997, Ansquer et al 1998) scenarios of prognosis when carrying the mutation. Given that most available data are based on small numbers, accurate estimates of prognosis would require prospective longitudinal studies with large numbers of women.

Testing

AVAILABLE TESTING

Cancer predisposing mutations are identified in the BRCA1 gene (chromosomal locus 17q21) or in BRCA2 gene (chromosomal locus 13q12.3) using DNA based molecular genetic testing. The tests available include ASO (allele specific oligonucleotide) testing, PRR (protein truncation testing), CSGE (confirmation sensitive gel electrophoresis, SSCP (single stranded conformational polymorphism), complete sequencing, Southern blot analysis, or a combination of techniques. However, no available technique can guarantee the identification of all cancer disposing mutations in the BRCA

genes. Testing costs can range from several hundred to several thousand dollars. Although some insurance policies may cover testing costs, given the problems that may arise from their knowledge of test results, individuals may prefer not to use their insurance to pay for testing. The availability of test results can take from weeks or months, depending on the test taken and certain circumstances present.

Testing is offered on a clinical basis primarily for individuals who are identified to be at high risk for carrying the relevant mutations, and for high-risk relatives of an individual with such identified mutations. Given the concerns for testing minors for adult onset conditions (such as issues of lack of proven prevention strategies and discrimination problems) testing for children under 18 is typically unaccepted. Prenatal testing is possible by extracting DNA from fetal cells obtained by amniocentesis at 16-18 weeks gestation or chronic villus sampling at 10-12 weeks gestation, but is usually only available for fetuses at 50% risk and requires genetic counseling.

COUNSELING STRATEGY

The website geneclinics.org provides a concise definition of genetic counseling as " A process, involving an individual or family, comprising: evaluation to confirm, diagnose, or exclude a genetic condition, malformation syndrome, or isolated birth defect; discussion of natural history and the role of heredity; identification of medical management issues; calculation and communication of genetic risks; provision of or referral for psychosocial support." Genetic counseling allows patients to make informed medical and personal decisions and should be offered to individuals considering, undergoing, and dealing with the results of genetic testing. Certain at risk individuals may want to test themselves to make better lifestyle and medical decisions, as well as to reduce their anxiety of not knowing whether they carry BRCA mutations. Testing is suggested for women with family histories of breast cancer or ovarian cancer consistent with autosomal dominant inheritance. Only after an affected family member has been identified with a BRCA mutation is mutational analysis more informative to unaffected family members and should genetic testing be done on at risk relatives. The type of issues that should be confronted with individuals before testing include perception of penetrance probabilities, optimal timing for testing, the

inability of genetic testing to detect presence or absence of cancer, support systems and psychological support, personally privacy/autonomy, possible effects of test results on cancer risk, screening protocols, implications for family members, emotional status, and the potential effects on personal relationships.

Responding to Test Results

NEGATIVE RESULTS & MUTATIONS OF UNCERTAIN SIGNIFICANCE

No conclusions can be reached from genetic tests that result in a negative diagnosis for BRCA mutations: they are uninformative. The negative test result may be false, or may not reflect certain other inherited cancer predisposing mutations in either the BRCA genes, or any in other genes. In any case, a negative result does not reduce cancer risk below that of the general population.

Mutations of uncertain clinical significance are sometimes identified through gene sequencing. To determine their significance, physicians follow methods such as carrying out family studies to determine whether the mutation segregates with cancer in family members. However, some methods are difficult to implement and usually not feasible as part of a clinical study. Therefore the patient must realize that the significance of these mutations may remain unclear.

BRCA-MUTATION -POSITIVE RESULT: AVAILABLE OPTIONS

Different organizations that assess the ethical, legal, and social implications of genetic testing have offered guidelines for individuals who carry BRCA mutations to follow. Given that no studies have revealed concrete evidence of the effect of most of the preventive measures offered, these recommendations are based primarily on expert opinion on presumed benefit, which changes as knowledge in the field increases.

Most data indicates that elevated breast cancer risk begins in the late twenties or early thirties. If cancer develops, it is important to detect it as soon as possible by carefully monitoring symptoms through the practice of breast self-examinations, clinical breast exams, and mammographies. The extent of surveillance depends on the individual's particular risk assessment.

General risk avoidance, involving the reduction of risk inducing behavior such as alcohol consumption and lack of regular exercise is always recommended despite their unknown effect on BRCA mutation carriers in particular. Although certain data suggests that oral contraceptives and hormone replacement therapy have an effect on breast cancer risk, there is not enough data to make recommendations concerning them regarding women with BRCA mutations.

Prophylactic surgery, which entails the removal of as much of the at risk tissue as possible in order to remove the chances of developing cancer, or preventive mastectomy (removal of healthy breasts) is an option that women must be informed of. According to expert panels there is insufficient evidence to recommend for or against these measures, given that they don't fully guarantee against cancer development. A study of all women receiving prophylactic mastectomy over a 30-year period at the Mayo Clinic in Minnesota estimated a 90% reduction in breast cancer risk from the procedure. However, this entails significant distress from a relatively drastic surgery, and most women choose against it even if they carry BRCA mutations and belong to high-risk families.

Chemoprevention, or the usage of medications such as tamoxifen and micronutrients such as dietary retinoids, vitamin E and selenium, is a method used to prevent a recurrence of cancer in women who have already been diagnosed with the disease. In these women, tamoxifen may also prevent new cancers from developing in the other breast. Still, it has not been determined whether high-risk women in the general population can benefit from taking tamoxifen as a preventive mechanism. A trial of treatment with tamoxifen in women identified with an increased breast cancer risk reported a 49% reduction in breast cancer with the treatment (Fisher et al 1998). However, tamoxifen reduced the incidence of estrogen-receptor-positive cancers, and not estrogen-receptor-negative ones, which are the ones most likely to occur in women with BRCA1 mutations. It is difficult to determine the benefit of tamoxifen without specifically testing women with BRCA mutations. Furthermore, significant adverse side effects of the drug must be taken into account.

The Aftermath: Looking Back

GOING THROUGH THE TESTING EXPERIENCE

Naturally, the testing experience and the knowledge of the test results (whatever they may imply) have a psychological effect that varies between individuals. In one study conducted by Matloff et al. more than half of the women who had a 50% increased chance of carrying BRCA mutations claimed they would choose to be tested for them.

This study measures the psychological distress associated with testing participants who received negative, uninformative, or positive test results. The 186 eligible women involved, aged eighteen years or older, were self-referred to the program, participated from 1995 to 1999, had a personal history of breast or ovarian cancer and a family history of these cancers. In general, they had a roughly 10% or higher probability of carrying a mutation in either of their BRCA genes. Most participants were white, aged 45 and older, married, employed, college-educated, and had annual family incomes above \$75,000. Twenty three percent of the women tested positive and seventy seven percent of them tested negative for BRCA mutations. Among the 93 eligible relatives tested, 38% tested positive and 62% tested negative.

There was no significant affect of any test result among women who had already been diagnosed with cancer ("affected" women). Among unaffected relatives, participants who tested negative exhibited significant reductions in perceived risk and distress compared with participants who tested positive, who did not exhibit any increased distress or perceived risk. The study suggests that clinic based testing can lead to psychological benefits for women who receive negative test results. And six months after disclosing the results, women who receive positive or uninformative test results did not exhibit increased distress or perceived risk.

Therefore, the study does not provide evidence for adverse psychological effects among women participating in BRCA testing. However, it must be noted that the participants received pre-test and post-test counseling. Moreover, the study was not representative of a diverse sampling of a city's population. According to the Stanford Program in Genomics, Ethics and Society, some people may risk "unforeseen psychological disruptances, family disruption, and adverse social consequences," furthermore, "Most

people and many healthcare providers, will not necessarily know or appreciate those kinds of risks when considering genetic testing for breast cancer susceptibility."

PROTECTING OUR PRIVACY

Revealing information about the results of genetic testing may affect an applicant's ability to access insurance, decrease an applicant's medical coverage, or raise their premium payments. Individuals must realize that when test results are placed in their medical records, these might not be kept private. If insurance companies or employers ask individuals for such information, failure to provide truthful information is considered fraud and may result in loss of insurance coverage or employment. Some protection from discrimination by employers is offered through the Americans with Disabilities Act. Recently, the Equal Employment Opportunity Commission expanded the definition of disabled to include individuals who carry genes that increase their risk of genetic disorders. However, the extent of this protection has not yet been tested in the courts, and degree of protection can vary from state to state. There arises the issue of whether insurance companies should cover the costs of genetic testing for women with high probabilities of carrying a gene, or the costs of increased surveillance or prophylactic surgery for women found to carry BRCA mutations. At the same time, there rises the issue of protecting a patient's privacy and safeguarding a patient against employment and insurance discrimination.

ON A WIDER SCALE...

Even though their prevalence is rare in the overall population, testing for BRCA mutations may be one of the first cases of widespread use of presymptomatic genetic testing in general medical practice. Therefore the policies that evolve around its management will set a precedent for future predisposition genetic testing. Decision making capacity that comes hand in hand with lack of knowledge is dangerous, but informed decision making and further research can lead to miraculous results in the improvement, individualization and precision of cancer treatment, as well as in more effective prevention.

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