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Cancer Prevention for Individuals with Inherited Mutations

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Long-term follow-up studies evaluating both the length and the quality of life of women who make different choices must be a priority in order to provide BRCA1/2 carriers with access to better information.

The discovery of the BRCA1 and BRCA2 genes in 1994 has stimulated clinical genetic testing for inherited susceptibility to breast-ovarian cancer. While the discovery of these genes may enable the prevention of potentially lethal disease, it also poses enormous challenges for patients and physicians. Testing may enable women who have multiple close relatives with breast and/or ovarian cancer to better define their own risks of developing cancer. Because of the enormous fear these cancers inspire and because of the widespread media attention the BRCA1 and BRCA2 genes have received, many women wonder whether they should consider genetic testing and what, if any, actions they might take if a mutation were to be discovered. Although there are strategies to decrease cancer risks, there is no perfect means of cancer prevention for those women who learn that they carry a mutation in one of these genes. This issue of RISK IN PERSEPCTIVE reviews the magnitude of cancer risks associated with BRCA1 and BRCA2 mutations and focuses on an undeniably extreme measure considered by some women: prophylactic surgical removal of the breasts and ovaries as a means of cancer prevention.

FREQUENCY OF BRCA1 AND BRCA2 MUTATIONS AND ASSOCIATED CANCER RISKS

In the US population, it is estimated that one to two in a thousand women are born with a mutation in BRCA1 or BRCA2. However, these mutations are more frequent in specific populations; for example, they are seen in 2.5% of individuals with Eastern European Jewish ethnic origin. Approximately 7 percent of breast cancers and 10 percent of ovarian cancers in the US are thought to be due to the presence of mutations in these genes. Cancers that develop at early ages or in women with many affected relatives are especially likely to be due to BRCA1/2 mutations.

Ascertaining the precise cancer risks associated with an inherited BRCA1 or BRCA2 mutation has been challenging. Since testing has been available for less than four years, it is not known just how many mutation carriers will ultimately develop cancer. Early estimates predicted that women with an inherited BRCA1 mutation faced an 87% probability of developing breast cancer by age 70 and a 63% probability of developing ovarian cancer by age 70. The breast cancer risks associated with BRCA2 are similar to BRCA1; the ovarian cancer risk is somewhat lower.

These early estimates were derived from studies of families with the most dramatic cancer histories; subsequent population-based studies have shown that the cancer risks for BRCA1/2 mutation carriers may not always be so extreme. A study by Struewing et. al in a large cohort of Ashkenazi Jewish women found that by age 70, 56% of mutations carriers had developed a breast cancer and 16% an ovarian cancer. In contrast, average American women with undefined genetic status have a lifetime breast cancer risk of 11%, and an ovarian cancer risk of 1.5%.

Although uncertainty persists as to the level of risk associated with having an inherited BRCA1 or BRCA2 mutation, it is very clear that not all mutation carriers are destined to develop cancer. Investigation of the modifying effects of other genetic and environmental factors are actively underway but have provided little insight thus far as to why some individuals with abnormal BRCA1/2 genes remain cancer-free.

CANCER PREVENTION STRATEGIES

Most women who learn they carry a BRCA1 or BRCA2 mutation have opted for close surveillance: semi-annual breast examinations and annual mammograms for early breast cancer detection and semi-annual pelvic examinations and pelvic ultrasounds for early ovarian cancer detection. The primary alternative to this approach is preventive surgery to remove the breasts (prophylactic mastectomy) and ovaries (prophylactic oophorectomy). To date, the vast minority of women have chosen to undergo prophylactic mastectomy whereas a moderate proportion of gene-carriers, particularly those who have reached menopause or completed childbearing, have elected prophylactic oophorectomy. The potentially profound effects of these surgeries on quality of life help explain why they are not elected more often.

Enormous excitement greeted the March 1998 announcement by the National Cancer Institute that results of a randomized placebo-controlled trial involving over 13,000 U.S. women show that the hormonal agent tamoxifen reduced the incidence of new breast cancers among women at increased risk by 45%. No data are yet available about how effective tamoxifen is for women whose increased breast cancer risk is due to a BRCA1/2 mutation, since genetic testing was not an original component of this trial. As these analyses are performed over the coming months, the anticipated clinical impact of tamoxifen for mutation carriers can be better assessed.

PROPHYLACTIC SURGERY

Intensified surveillance may detect breast and or ovarian cancers at a favorable early stage but does not prevent cancer. For this reason, women who carry BRCA1 or BRCA2 mutations may consider prophylactic mastectomy and/or oophorectomy despite a scant literature on the long-term outcomes of these procedures. It is clear that neither approach provides complete protection against developing cancer. Prospective data about the effectiveness of

prophylactic surgery from women who have undergone BRCA1/2 testing are being collected but will take years to accrue.

In the meantime, the available estimates are derived from retrospective studies of women who had prophylactic surgery prior to the availability of BRCA1/2 testing. Hartmann and her colleagues at the Mayo Clinic have recently reported data from a cohort of 1039 women comparing the observed incidence of breast cancers to the number expected if prophylactic mastectomy had not been performed. They estimated a 91% reduction in breast cancer incidence associated with this surgery. Similarly, prophylactic oophorectomy does not guarantee immunity from ovarian cancer as tumors that behave like ovarian cancers may still arise from cells lining the abdominal cavity that cannot be removed. Conservative estimates suggest that at least 50% of ovarian cancers might be prevented by prophylactic oophorectomy.

DECISION ANALYSIS: ESTIMATING THEIMPACT OF PROPHYLACTIC SURGERY ON LIFE EXPECTANCY

Decision analysis can help provide estimates of the impact of a treatment by simulating survival for hypothetical cohorts of patients who make different treatment decisions. Investigators affiliated with the Dana-Farber Cancer Institute and the Harvard Center for Risk Analysis constructed a decision-analytic model evaluating the impact of prophylactic mastectomy and/or oophorectomy on life expectancy for BRCA1 and BRCA2 carriers. Its purpose was to provide estimates of the effect of these procedures on survival for women who carry BRCA1 or BRCA2 mutations in order to facilitate informed decision making. Preferences concerning the tradeoffs between maximizing length and quality of life will influence the significance of these estimates for an individual woman.

Synthesizing available data about procedure efficacy, gene-associated cancer risks and cancer prognosis, the life expectancy gains from particular prophylactic surgical interventions compared to no prophylactic surgery were calculated. The life expectancy gains from various combinations of immediate and delayed prophylactic surgical strategies for women of different ages and at different levels of cancer risk were modeled using a Markov cohort simulation. Delayed surgery was considered because postponing surgery until after completion of childbearing and lactation may be important for some women.

The analysis made conservative assumptions about the degree of protection afforded by prophylactic surgeries and considered that prophylactic mastectomy reduced breast cancer risk by 85% and prophylactic oophorectomy reduced ovarian cancer risk by 50%. The impact of these surgeries on life expectancy of women with low risk mutations (40% cumulative breast cancer risk and 5% cumulative ovarian cancer risk), moderate risk mutations (60% cumulative breast cancer risk and 20% ovarian cancer risk), and high risk mutations (85% cumulative breast and 40% cumulative ovarian cancer risks) were each evaluated.

The study showed that 30 year-old women who elect both surgeries can anticipate from 3.2 to 7.6 years of life expectancy gain depending on whether they carry a mutation conferring low or high cancer risk. For prophylactic mastectomy alone, the gain ranges from 2.9 to 5.3 years. To place these gains in context, they greatly exceed the survival impact of widely accepted medical preventive measures such as smoking cessation, blood pressure control and screening mammography. The survival benefit of prophylactic mastectomy is 2 to 4 times that of chemotherapy for early stage breast cancer.

FURTHER READING:
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TABLE 1.
Age-specific life expectancy gains resulting from prophylactic surgery compared to cancer surveillance in women carrying a moderate risk mutation in BRCA1 or BRCA2.

CLINICAL STRATEGY	AGE 30	AGE 50
Life expectancy without prophylactic surgery (years)	42.3	29.6
Gain in life expectancy with prophylactic surgery (years)		
Mastectomy and oophorectomy	5.3	2.0
Mastectomy and delayed (10 years) oophorectomy	5.1	1.7
Mastectomy	4.1	1.6
Delayed (10 years) mastectomy	2.4	0.2
Oophorectomy	1.0	0.4

The anticipated impact of prophylactic oophorectomy is less substantial, both because ovarian cancer is less common and because the procedure appears less effective. Nonetheless, prophylactic oophorectomy results in an additional 0.2-1.7 years of life expectancy for 30-year old women. Delaying prophylactic oophorectomy until age 40 results in little compromise of this benefit. Life expectancy gains decline with age at the time of surgery and are minimal for 60-year old women. Table I shows the results of the analysis for women with "moderate" risk mutations conferring 60% breast cancer and 20% ovarian cancer risk by age 70.

NEED FOR ONGOING RESEARCH

Although this analysis shows that prophylactic surgery may result in increased life expectancy for BRCA1/2 mutation carriers, many will elect not to have these procedures because of their potentially profound effects on self-image and sexual and reproductive function. Women who opt for testing and as a result face difficult decisions about how to manage their cancer risks must have access to current data, clinical expertise and supportive counseling. Long-term follow-up studies evaluating both the length and the quality of life of women who make different choices must be a priority in order to provide BRCA1/2 carriers with access to better information. In order to accomplish this goal, clinical cancer geneticists encourage women contemplating testing to participate in research studies so that future estimates of the cancer risks and the effectiveness of cancer prevention strategies can be refined.