Prophylactic Mastectomy and Genetic Testing: An Update

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Purpose/Objectives: To examine and discuss the possible benefits and difficulties with recommending prophylactic mastectomy to BRCA1- and BRCA2-positive women.

Data Sources: Published research articles, professional review articles, textbooks.

Data Synthesis: Women with BRCA1 and BRCA2 mutations face a much higher risk of developing breast cancer than the general population, with limited options available for prevention. Prophylactic mastectomy has been shown to have a survival advantage in young women who carry BRCA1 and BRCA2 mutations. Challenges exist, however, in the use of prophylactic mastectomy and genetic testing.

Conclusions: Methods of preventing breast cancer in BRCA1- and BRCA2-positive women currently are limited to watch-and-wait surveillance, prophylactic mastectomy, and, perhaps, chemoprevention. Genetic testing and prophylactic mastectomy each present unique challenges while offering certain benefits as well. Recent studies have shown survival advantages to BRCA1- and BRCA2-positive women who undergo prophylactic mastectomy.

Implications for Nursing Practice: Nurses need to be aware of the complex issues surrounding testing for BRCA1 and BRCA2 mutations and prophylactic mastectomy to be able to provide current information to patients and assist in decision making.

Objectives for CE Enrollees

On completion of this CE, the participant will be able to

1. Discuss the indications for prophylactic mastectomy.
2. Discuss the challenge of interpreting genetic test results.
3. Discuss the ethical issues associated with genetic testing.

Key Points . . .

- Women who inherit BRCA1 or BRCA2 gene mutations face a much higher risk of developing breast cancer and other cancers than the general public, despite accounting for less than 10% of all breast cancers.
- Methods for the prevention of breast cancer in carriers of BRCA1 and BRCA2 mutations have not been proven conclusively.
- Many controversies, ethical dilemmas, and psychological implications surround genetic testing for breast cancer susceptibility genes and prophylactic mastectomy.
- Recent studies have demonstrated a survival advantage for a subgroup of BRCA-positive women who have undergone prophylactic mastectomy.

Examination of the issues surrounding the role of prophylactic mastectomy in the prevention of breast cancer is not new. Some consider the surgery a radical and disfiguring modality; others consider it the only preventive treatment for breast cancer presently

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available. With the discovery of inherited BRCA1 and BRCA2 gene mutations, however, a unique situation arises in which a patient may be receiving tertiary treatment while family members seek primary prevention. Oncology nurses are well-positioned to provide information surrounding the issues of inherited susceptibility and options available for prevention. Nurses must check and correct patients' perceptions to assist and support those who are facing difficult decisions surrounding prophylactic surgery, as well as to identify the need for support from genetic counselors, surgeons, psychologists, social workers, oncologists, and other healthcare professionals. With information on prophylactic mastectomy and genetic testing rapidly evolving, oncology nurses play a fundamental role in disseminating accurate and current information. This article reviews and discusses the role of prophylactic mastectomy for BRCA1- and BRCA2-positive women, risk assessment, and benefits and difficulties related to genetic testing. It makes further recommendations for oncology nurses in both clinical practice and research.

Prophylactic Mastectomy

Snyderman (1984) examined the pros and cons of prophylactic mastectomy within the context of prophylactic contralateral mastectomy as well as prophylactic surgery. More recently, Wapnir, Rabinowitz, and Greco (1990) reexamined this issue and concluded that prophylactic mastectomy has yet to be proven superior to surveillance. Researchers have looked at the selection of high-risk women for prophylactic mastectomy (Ariyan, 1985) and the experimental efficacy of prophylactic mastectomy in mice and rats (Nelson et al., 1989; Wong et al., 1986). Studies also have looked at the survival, quality of life, efficacy, and cost-effectiveness of prophylactic surgery for BRCA1- and BRCA2-positive patients (Burke et al., 1997; Grann, Panageas, Whang, Antman, & Neugut, 1998).

Indications for prophylactic mastectomy in the past have been diverse, and difficulties have resulted from variability in the definition of a precancerous lesion and the characteristics of high-risk patients (Snyderman, 1984). Ariyan (1985) included lobular and ductal carcinoma in situ, immediate family history of breast cancer or fibrocystic disease with multiple lesions, or multiple previous biopsies with persistent breast cysts as indications for prophylactic mastectomy. Snyderman submitted that patients with a remarkable family history, as well as those having a number of atypical biopsies or continuous new breast masses, may be considered for prophylactic mastectomy. Patients' extreme fear of cancer and physicians' anxiety regarding the efficacy of surveillance also have been included as indications (Wapnir et al., 1990). Haskell, Parker, and Love (1995) contend that prophylactic mastectomy appeals to women who are overwhelmed by their risk for breast cancer. For such patients, the intended benefit is not only removal of at-risk tissue but also a reduction in anxiety. Warmuth, Sutton, and Winer (1997) stated that patients at high risk of developing breast cancer or those who experience extreme anxiety related to their risk may be considered for prophylactic mastectomy. The factors that place a patient at high risk for breast cancer include increasing age, premenopausal bilateral breast cancer in a first-degree relative, a history of contralateral breast cancer, and certain precancerous or high-risk lesions (Schechter, 1985).

Lopez and Porter (1996) recognized that a better understanding of the epidemiology and pathology of breast cancer has led to a more selective approach of defining indications for prophylactic mastectomy. They specified that breast tissue with epithelial proliferative changes and cellular atypia is at increased risk of developing into cancer, but most breast biopsies reveal benign breast tissue rather than atypical hyperplasia. Prophylactic mastectomy of a contralateral breast following a diagnosis of breast cancer should be deliberated with consideration to the stage of the breast cancer, multifocality, the presence of carcinoma in situ, atypical hyperplasia in the remaining breast, and family history. Some authors have reported that the only time such radical surgery is warranted is for biopsy-proven, high-risk individuals (Wapnir et al., 1990). Though the indications for prophylactic mastectomy are few, the procedure should not be abandoned until a better understanding is available of the genetics of breast cancer and the ability to prevent it (Winchester, 1995).

Types of Prophylactic Mastectomy

Two procedures for prophylactic mastectomy are available: a subcutaneous mastectomy and a total (simple) mastectomy. In the past, subcutaneous mastectomies often were recommended in high-risk patients with breast cancer (Eldar, Meguid, & Beatty, 1984). Some patients preferred subcutaneous mastectomy because of superior cosmetic results (Wong et al., 1986). According to Snyderman (1984), subcutaneous mastectomy is not an acceptable alternative for prophylaxis because it leaves behind some breast tissue. The procedure preserves the nipple-areola complex and some underlying ductal tissue in the axillary tail and skin flaps, removing only 75%–95% of the breast tissue (Lopez & Porter, 1996; Morrow, Jordan, Takei, Grodishar, & Pierce, 1999; Temple, Lindsay, Magi, & Urbanski, 1991). Breast cancer following subcutaneous mastectomy has been reported, with figures ranging from 0.5%–1%, (Eldar et al.; Nelson et al., 1989; Temple et al.).

The preferred procedure is a total mastectomy (Baron & Borgen, 1997; Jordan, 1996; MacKay & Bostwick, 1996). This procedure removes the total breast, tail of Spence, areola, and nipple (Vogel, 1996), but Ariyan (1985) noted that it can be difficult to ascertain where breast tissue begins and ends. As a result, neither procedure for mastectomy can guarantee removal of all breast tissue.

Complications of Surgery

In 10%–59% of patients, complications such as hematoma, infection, and necrosis of the skin or nipple have been reported following a subcutaneous or total mastectomy. In addition to operative complications, aesthetic and psychological problems also may occur. These problems include irregular contour, wrinkling of the skin after delayed reconstruction, decrease or loss of sensitivity of the nipple, pain, asymmetry, unnatural contour while lying down, or an inability to sleep in a prone position (Holzgreve & Beller, 1987; Wapnir et al., 1990). Psychological evaluation prior to surgery may be prudent. Dissatisfaction with cosmetic results (e.g., feeling that breasts are too small or in the wrong position) may contribute to psycho-

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logical distress and have marked negative changes on patients' sex lives (Haskell et al., 1995; MacKay & Bostwick, 1996; Vogel, 1996).

Genetic Testing for Breast Cancer Risk

Breast cancer is the most common malignancy in North American women (American Cancer Society, 2000; National Cancer Institute of Canada, 2000) and is most treatable when detected in its early stages (Dollinger, Rosenbaum, & Cable, 1995). A subset known as inherited or hereditary breast cancer exists. A number of genes have been found to play a role in inherited breast cancer, including BRCA1 (Miki et al., 1994), BRCA2 (Tavtigan et al., 1996), and p53 (Li & Fraumeni, 1982; Sidransky et al., 1992). Mutations result in alterations in the ability of genes to produce a functioning protein. Fortunately, mutations in such genes as BRCA1 and BRCA2 are relatively rare, but they can create significant familial clusters of breast cancer (Greene, 1997). However, a striking family history cannot be counted on to identify all possible BRCA1 and BRCA2 mutation carriers (Collins, 1996).

The discovery of the BRCA1 gene in 1990 (Hall et al., 1990) and its subsequent cloning in 1994 (Miki et al., 1994), as well as the mapping of the BRCA2 gene in 1994 (Wooster et al., 1994) and its cloning in 1995 (Wooster et al., 1995), added another dimension to the controversy of prophylactic mastectomy. Both are large genes. BRCA1 is located on chromosome 17q21, with hundreds of different mutations discovered throughout the gene (Lindor, Greene, & the Mayo Familial Cancer Program, 1998). BRCA2 is located on chromosome 13q12-13 and, like BRCA1, multiple distinct mutations have been identified (Peto et al., 1999).

BRCA1 and BRCA2 appear to be highly penetrant tumor suppressor genes, each having a somewhat different function. BRCA1 has been associated with a family history of breast and ovarian cancer, whereas BRCA2 has been associated with male and female breast cancer and a lower incidence of ovarian cancer than is seen with BRCA1 (Brody & Biesecker, 1997; Greene, 1997). Penetrance, which refers to the probability that a woman with a BRCA mutation will develop breast cancer, was found to be the same irrespective of whether the mutation was inherited from the mother or father (Narod et al., 1995). No correlation has been found between genotype and phenotype of BRCA1 to explain the differences in penetrance or expressivity (the degree to which a heritable cancer is manifested in an individual carrying the gene mutation) between families (Weitzel, 1996). Brody and Biesecker believed that a germline mutation carrier has one normal allele and one mutated allele at birth, with subsequent deletion of the normal allele leaving only the mutated allele. Precisely how the BRCA1 and BRCA2 mutations lead to the development of breast cancer is not yet understood (Greene).

Rate of Occurrence

Inherited breast cancers resulting from highly penetrant genetic mutations comprise only 5%–10% of all breast cancers (Brody & Biesecker, 1997; Mark & McGowan, 1996). The BRCA1 and BRCA2 gene mutations may explain up to 90% of hereditary breast cancers, with the lifetime risk of developing breast cancer associated with BRCA1 apparently equal to that of BRCA2 (Brody & Biesecker). Among members of families with hereditary breast cancer who do not have BRCA1 mutations, an estimated 70% probably have BRCA2 mutations. In the general population, BRCA1 mutations occur as frequently as 1 in 300 (Weitzel, 1996).

Testing Methods and Interpretation

Testing for BRCA1 and BRCA2 is most reliable within members of families in which a mutation has been identified (Biesecker, 1997). Several methods are available to detect BRCA1 and BRCA2 mutations, the most common of which are direct DNA sequencing and single-strand conformation polymorphism assays. Despite being labor-intensive and expensive, direct DNA sequencing is the test of choice because mutations rarely are missed. Single-strand conformation polymorphism assays are easier to perform and less costly but do not detect all mutations (Warmuth et al., 1997). Ascertaining how sensitive and specific the testing is can be difficult because studies report using different methods of detection (Warmuth et al.). Loescher (1999) thoroughly reviewed methods of DNA testing.

The detection of mutations is extremely challenging given the size and complexity of the coding sequence. At least 80% of the genetic defects detected are frameshift or nonsense, often resulting in a nonfunctional protein (Brody & Biesecker, 1997; Greene, 1997; Weitzel, 1996). Establishing the risk of cancer development associated with different mutations is difficult (Brody & Biesecker). Rare mutations may or may not increase the risk of developing cancer (Langston, Malone, Thompson, Daling, & Ostrander, 1996). Because current tests are unable to detect all mutations or abnormalities, failure to find a mutation in a cancer-free individual at high risk is useful only if a specific mutation previously was identified in a first-degree relative (Greene; Warmuth et al., 1997).

Interpretation of test results can be formidable. False-positives, such as missense variations that do not cause disease, will exist (Collins, 1996). False negatives will occur because not all mutations will be detected. Part of the gene may have been unexamined, the defect may have been in an unexpressed code, or a gene that is as yet undiscovered may be responsible (Brody & Biesecker, 1997). The challenge then is to distinguish these from true negatives. In patients with a family history of breast cancer, a negative test may reflect that (a) the mutation was missed (i.e., false negative), (b) a different highly penetrant gene such as p53 or another unidentified gene is responsible, (c) multiple genes of lower penetrance are responsible, (d) the cluster of cancer is a chance event, or (e) the patient is a sporadic case even though it is a hereditary breast cancer family (Greene, 1997). Even a true negative result does not reduce the risk of developing breast cancer to zero; the risk still is equal to that of the general population of approximately 11% (Biesecker, 1997).

Risk Assessment

Reference frequently is made to "high-risk" patients when evaluating the risk of developing breast cancer. Accurate risk assessment is critical because individuals who

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are thought to be at a substantially higher risk than the general population may consider prophylactic surgery or follow more rigorous screening (Lynch et al., 1993; Thompson, 1994). Individuals perceive their risks within the context of past experience and may overestimate them based on unfounded factors. Unfortunately, current algorithms do not estimate risk accurately (Brody & Biesecker, 1997). The majority of women who develop breast cancer, in fact, have no known risk factors (Lerman & Croyle, 1994). But, what constitutes high risk? Part of the challenge in identifying high-risk patients is the lack of a consistent definition of high risk. Nevertheless, factors such as age, parity, and family history have been recognized as contributing to risk. Identification of BRCA gene mutations confers an extremely high risk for developing breast cancer.

Studies have shown that between 6% and 19% of patients with breast cancer have a family history (Colditz et al., 1993; Slattery & Kerber, 1993). A family history that includes premenopausal bilateral disease occurring frequently over multiple generations within a single lineage implies increased risk (Baron & Borgen, 1997; Brody & Biesecker 1997). The general characteristics used to determine high risk include number of affected first- and second-degree relatives, presence of ovarian cancer within the family, age at diagnosis of relatives with breast cancer, and relationships between affected individuals. A thorough family history must include three generations, incorporating affected and unaffected relatives as well as bilaterality of disease. In addition to genetic risk factors, some endocrine risk factors also may contribute to increased risk of developing breast cancer. These factors include menarche prior to age 12, menopause after age 55, nulliparity, and first pregnancy after age 30 (Sclafani, 1991).

Patients may question whether any risk factors can be modified to reduce the risk of developing breast cancer in high-risk individuals. Two strong factors associated with inherited susceptibility of breast cancer are early age at diagnosis and family history (Collins, 1996; Lerman & Croyle, 1994); these factors are not amenable to modification. Warmuth et al. (1997) examined the role of oral contraceptives, estrogen-replacement therapy, alcohol, and exercise. They summarized that modification of many of the risk factors associated with hereditary breast cancer was unlikely to affect the incidence of breast cancer in such individuals. Further, the interactions of various risk factors in women with a BRCA mutation may differ from the general population. A study by Narod et al. (1995) also looked at risk modification in BRCA1 carriers and found that increasing parity was associated with a reduced risk of breast cancer, but early age at first birth did not provide additional protection. They felt that reproductive factors seemed insufficient to explain the variance in gene expressivity and penetrance.

Genetic testing may be appropriate for women meeting certain criteria (see Figure 1). However, Langston et al. (1996) found that BRCA1 mutations were not only found in women with a strong family history of breast or ovarian cancer, demonstrating the difficulty in predicting such mutations on the basis of family history alone.

- A woman diagnosed with breast cancer prior to age 30
- A woman diagnosed with breast or ovarian cancer prior to age 50 whose mother, sister, or daughter also was diagnosed with breast or ovarian cancer before age 50
- A woman with breast cancer from a family with two or more cases of breast cancer and one or more cases of ovarian cancer
- An unaffected relative of an individual with a BRCA1 or BRCA2 mutation
- An Ashkenazi Jewish woman with a diagnosis of breast cancer before age 40 or ovarian cancer at any age

Figure 1. Appropriate Candidates for Genetic Testing

Note. Based on information from Greene, 1997.

Risk Estimates

The risk of developing cancer is expressed in different ways. Commonly, the risk is expressed as an absolute risk in which the rate of occurrence in the general population is specified as number of cases per a specified denominator (e.g., 25 per 100,000). Risk also may be expressed as a relative risk, in which the incidence of deaths from breast cancer within a group having a specific risk factor is compared to those without the risk factor (Love, 1989). A positive family history confers a relative risk of 2.0–3.0 (Greene, 1997). Lifetime risks also are used in which the chance that a woman will develop cancer is given as a percentage based on the assumption that she lives to be 90 (Olivotto, Gelman, & Kuusk, 1996). Thompson (1994) believed that lifetime risks are not the best way of calculating risk determination; rather, using 10-year period projections may be better. For example, the annual risk of developing breast cancer for a 50-year-old woman without a BRCA mutation is 1 in 550 per year. Her risk of developing breast cancer by age 50 is 1 in 63. The lifetime risk is the popularly quoted "one in nine" risk, which is specific to women who live to be 90 (Olivotto et al.).

The autosomal dominant mode of transmission of BRCA1 confers a 50% risk of inheriting the gene to each child of a carrier (Hoskins et al., 1995). For women who inherit the mutated gene, the lifetime risk of developing breast cancer is approximately 85% compared to the general population risk of 12%; the cumulative risk of a woman with a BRCA1 mutation developing breast cancer is approximately 3% by age 30, 19% by age 40, 51% by age 50, 54% by age 60, and 85% by age 70 (Easton, Ford, Bishop, & the Breast Cancer Linkage Consortium, 1995). For BRCA1-positive women with a primary breast cancer, the chances of developing a contralateral breast cancer are 48% by age 50 and 64% by age 70 (Burke et al., 1997; Greene, 1997).

Patients can be overwhelmed by these statistical risks. To add to the confusion, it has been recognized that research selection criteria probably has overestimated the link between early onset breast cancer and BRCA1 and BRCA2 mutations because such studies focused on families with remarkable histories of breast cancer (Burke et al., 1997). The obvious challenge is to keep the numerous statistics and probabilities relevant and accurate to the individual and her specific situation.

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Benefits of Genetic Testing

The ability to identify BRCA1 and BRCA2 carriers before symptomatic disease occurs opens a window of opportunity for prevention or early detection. Figure 2 lists red flags that may indicate a family has a predisposition to hereditary breast cancer. Genetic testing offers the potential for identifying individuals and families at high risk and targets those who might benefit from intense screening and perhaps preventive measures (Mahon, 1997). Although negative results are harder to interpret than positive results, genetic testing may prevent unnecessary surgery for BRCA1- and BRCA2-negative individuals, particularly in cases where a family member already might be contemplating a prophylactic mastectomy based on a misunderstanding of familial risk (Mark & McGowan, 1996).

Because women tend to overestimate or underestimate their risk of developing breast cancer (Baron & Borgen, 1997), knowledge of their BRCA status could provide a better means of risk estimation. Ideally, realizing one's BRCA status would motivate patients and physicians to establish an appropriate surveillance regimen and discuss preventive alternatives, including prophylactic mastectomy (Mark & McGowan, 1996). A prospective study by Lerman et al. (1996) found that individuals from hereditary breast cancer families felt that the benefits of genetic testing outweighed the risks and limitations. This study also found that BRCA1 carriers exhibited no increase in depression or functional impairment one month following test disclosure.

Women who learn that they carry the mutated BRCA1 or BRCA2 gene may feel better prepared to make decisions regarding exogenous hormone use, marriage, and childbearing (Greene, 1997). Some women reportedly felt better able to plan for prevention after knowing they were gene-positive (Lynch et al., 1993).

Limitations of Genetic Testing

Problems with genetic testing generally can be categorized into three groups: technical, ethical, and psychological. Technical difficulties relate to issues of sensitivity, specificity, and quality control of BRCA1 and BRCA2 testing (Greene, 1997). A positive gene test for BRCA1 and BRCA2 indicates a susceptibility to cancer development, not a certainty (Garber & Smith, 1996). It does not specify precisely when a cancer will develop or the pathology of the impending cancer (Biesecker, 1997). A risk exists that test results will be misinterpreted because interpretation seldom is straightforward (Biesecker). Distinguishing a true negative from a false negative is difficult. Even the most sophisticated tests currently available seem unable to detect all important abnormalities in the BRCA1 gene (Greene). Some of the rare sequence variants identified may be associated with higher likelihood of cancer but cannot be considered definitive mutations based on sequence formations alone (Langston et al., 1996). The difficulty then becomes differentiating true negatives from false negatives, in which missense mutations are found that are not disease-conferring. At present, correlating specific mutations with specific cancer risks is impossible (Greene). Test interpretation is uncertain outside the context of hereditary breast cancer, and, because most studies have been performed within stringently controlled criteria, the degree to which results can be generalized also is questionable (Baron & Borgen, 1997; Biesecker).

Genetic testing presents a number of ethical dilemmas. Most obvious, perhaps, is the question of the benefit of such testing in the presence of limited options for management or modifiable risks. Questions surround who should be responsible for the expense of the test and related services (e.g., counseling) (Baron & Borgen, 1997). Confidentiality is a serious consideration given that individuals may be subject to employment and insurance discrimination (Biesecker, 1997). Implications exist for all family members because learning one's BRCA1 and BRCA2 status could occur vicariously, as in the case of a mother who does not want to know whether she carries the mutated gene whose offspring is confirmed as BRCA1 positive. Implications also exist for paternity and adoption (Biesecker). Eugenics is another serious consideration (Engelking, 1995).

The psychological implications of genetic testing are far-reaching. What may be paralyzing to one individual may be motivational to another. Feelings of hopelessness, despair, anxiety, depression, fear, and negative self-concept may exist, or there may be feelings of relief, control, and improved quality of life (Engelking, 1995). Raffel (1998) reported that affected individuals may suffer from low self-esteem, feelings of being "defective," and guilt at having passed the gene on to children, whereas unaffected individuals may suffer from survivor guilt and fears about their own risks. Concerns exist that a negative test result will provide a false sense of security, especially for those who equate a negative result to zero risk (Brody & Biesecker, 1997). The remaining question is how to determine who will benefit from genetic testing in terms of psychological outcomes (Biesecker, 1997).

- Breast cancer at an early age (40 or younger)
- Several close family members with breast or ovarian cancer
- Bilateral development of breast (or ovarian) cancer
- A relative with more than one primary cancer
- Occurrence of breast and other cancers across several generations
- Rare or unusual cancers (e.g., male breast cancer)
- Breast (or ovarian) cancer in a family of Ashkenazi Jewish descent

Figure 2. Clues to the Inherited Predisposition to Breast Cancer

Counseling

The emotional aspect of breast cancer makes genetic counseling an integral part of the genetic testing process, which should involve a multidisciplinary team that includes physicians, nurses, genetic counselors, and social workers (Raffel, 1998). Counseling is a process that should include a precounseling assessment and education, informed consent, disclosure of results, and follow-up counseling. Precounseling and education should involve information on the sensitivity, specificity, and accuracy of

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BRCA1 and BRCA2 testing, options for examining risk without genetic testing, risk of passing the gene on to future generations, implications of positive and negative results and the possibility that test results will be uninformative, fees of testing and counseling, the risk of psychological distress, the risk of employment or insurance discrimination, the need for confidentiality, and the options and limitations of medical treatment after testing (Greene, 1997). Informed consent must include discussion of possible emotional reactions of guilt, grief, apprehension, and responsibility as well as feelings of alterations in self-esteem or body image and how to discuss results with family members (Raffel; Weitzel, 1996). Some individuals may benefit from explanations of how carrying a mutated gene increases the probability that other cells will go on to acquire additional mutations to produce cancer but that not all individuals with an inherited susceptibility will develop breast cancer. Expressing these probabilities in percentages and ratios may be helpful. Revealing test results in person is important because predicting how one will react is impossible (Raffel). Healthcare professionals involved in genetic testing also should be aware that some, but not all, members of hereditary breast cancer families will want to know their BRCA1 or BRCA2 status (Lerman et al., 1996).

Support for Prophylactic Mastectomy

Prophylactic mastectomy is a controversial operation that may be performed for women at high risk of developing breast cancer (MacKay & Bostwick, 1996). The goal is to reduce the risk of disease development by removing the tissue at risk (Jordan, 1996). In addition, the possibility exists of removal of occult carcinomas as well as improvement of psychological stressors related to extreme fears of developing cancer (Vogel, 1996). Because prophylactic mastectomy may be the only preventive option available for breast cancer (Mann & Borgen, 1998), healthcare workers must accurately estimate the patient's risk only after gathering a complete family history and involving the patient in discussions to evaluate her perceived risks and assist her in making an informed choice. The strongest argument in favor of prophylactic mastectomy stems from the significantly higher probability of developing breast cancer in BRCA1 and BRCA2 carriers—51% by age 50 and 85% by age 70 for BRCA1 carriers and an estimated 80% by age 70 for BRCA2 carriers (Lindor et al., 1998).

The efficacy of prophylactic mastectomy has been highly debated. As high as 97% reduction in risk of developing cancer following prophylactic mastectomy has been reported, although the same indications or surgical procedures were not consistently used (Schrag, Kuntz, Garber, & Weeks, 1997). Recently, two studies have evaluated the effects of prophylactic mastectomy on life expectancy of women with BRCA1 and BRCA2 mutations. Grann et al. (1998) found that survival was improved by 3.3 years in low-risk women and by 6 years in high-risk women following prophylactic mastectomy and oophorectomy. With adjustments for quality of life factored in, the benefits of prophylactic mastectomy combined with oophorectomy were reduced to 1.9 years in high-risk patients, although the benefits still were higher than for surveillance alone. Time trade-off techniques revealed that for those concerned with life expectancy, prophylactic surgery might be reasonable. Similarly, Schrag et al. concluded that substantial improvements in life expectancy could be achieved as a result of prophylactic surgery in younger women who are BRCA1 or BRCA2 positive, even using conservative estimates of efficacy. Both studies reach conclusions based on assumptions that the efficacy of prophylactic mastectomy is between 85% and 90%. In each study, prophylactic mastectomy improved survival to a greater degree than prophylactic oophorectomy. Hartmann et al. (1999) performed a retrospective study of women with a family history of breast cancer who had undergone a prophylactic mastectomy. Most of the women had a subcutaneous mastectomy as opposed to a total mastectomy. They found that the incidence of breast cancer and deaths from breast cancer were reduced by at least 90% in women with moderate and high risk. A limitation of this study was that not all of the criteria for high risk are strongly associated with BRCA mutations.

Temple et al. (1991) evaluated the technical adequacy of a total mastectomy as prophylaxis for breast cancer. Within the five-year follow-up period, none of the patients developed cancer. Notably, the sample size in this study was extremely small.

The pervasive argument in favor of prophylactic mastectomy concerns options for management of women considered at high risk for developing breast cancer. Current recommendations for such women vary somewhat in terms of suggested time frames. Burke et al. (1997) recommended a monthly breast examination starting at age 18–21, annual or semiannual clinical exam from age 25–35, and an annual mammogram starting at age 25–35. They rationalized that because mammography is less sensitive in young women, breast self-exams have more potential to benefit BRCA1- or BRCA2-positive women. They advised having annual mammograms at a consistent location with previous films available for comparison but caution that the benefits of this regimen to women younger than 50 need to be established and an increased risk of developing cancer may result by starting mammography at an early age. In comparison, Warmuth et al. (1997) recommended monthly breast self-examinations starting at age 20, clinical breast examinations every three years from age 20–40 (then yearly), and mammography every one to two years from age 50–69. Data on the efficacy of surveillance has been limited (Hoskins et al., 1995), but, according to Narod et al. (1995), intensive surveillance has not improved survival. As such, intense screening is of questionable efficacy.

The options outside of intensive screening are limited. Chemoprevention is promising but is in relatively early stages of investigation. Insufficient evidence exists for risk-factor modification concerning hormone replacement therapy, oral contraceptives, and lifestyle factors such as diet and exercise or possible interactions between these factors (Burke et al., 1997; Hoskins et al., 1995). Prophylactic mastectomy may be considered to decrease rather than eliminate risk entirely (Mark & McGowan, 1996). When a decision in favor of prophylactic mastectomy has

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been made, clearly a total mastectomy is preferred to a subcutaneous mastectomy (Baron & Borgen, 1997). Immediate reconstructive surgery following prophylactic mastectomy may make the decision to have such surgery more palatable to women.

Arguments Against Prophylactic Mastectomy

Accurate identification of the population at risk of developing breast cancer is problematic. The lack of a uniform system to determine risk makes assessment of efficacy difficult (Jordan, 1996). Concerns exist that current risk estimates of developing breast cancer in genetically predisposed women are overestimates based on striking family histories (Collins, 1996). Outside such remarkable family histories, the risk is unknown (Weitzel, 1996). Further, BRCA1 and BRCA2 mutations are not limited to women with strong family histories of breast cancer, therefore making it difficult to predict the presence of these mutations based on family history alone (Langston et al., 1996). Determining whether cancer is the result of an inherited gene is not always easy. If all offspring are male or the family size is small, the trait can be missed (Raffel, 1998; Weitzel).

Some of the statistical models used to predict risk may not be accurate. One well-known model by Gail et al. (1989) includes age at menarche, age at first live birth, number of first-degree relatives with breast cancer, the number of previous breast biopsies, and current age. But, this model has been found to be more accurate in women who undergo annual mammography. Also, the Gail model tends to underestimate the BRCA1 and BRCA2 risk because second-degree relatives are not considered, thereby excluding paternal family members. The Claus model (Claus, Risch, & Thompson, 1994) considers family history of breast cancer as the only risk factor and includes paternal and second-degree relatives to calculate cumulative breast cancer risk by age. The Couch model (Couch et al., 1997) predicts the probability of a BRCA1 mutation in a family based on the history of breast and ovarian cancers in the family. The Frank model (Frank et al., 1998) predicts the probability of a BRCA1 or BRCA2 mutation in a woman with breast cancer younger than 50 years of age by incorporating family history of breast and ovarian cancers. In addition, many of the currently used models are based on white females and therefore cannot be generalized to all populations. Risk models derived from minority populations have not yet been developed.

Despite the existence of algorithms and guidelines, the indications for a prophylactic mastectomy remain variable. Cancerphobia often has been cited as a reason for prophylactic mastectomy (Wapnir et al., 1990). Whether this is an appropriate indication is questionable. "High-risk" patients often are included in this group, but defining factors of such a patient is inconsistent.

Concerns have been raised about the ability of prophylactic mastectomy to remove risk. Identifying breast tissue to ensure that it all has been removed in surgery is considered anatomically difficult (King, Powell, & Love, 1993). Even a total mastectomy reportedly leaves some breast tissue (Haskell et al., 1995; Nelson et al., 1989), making it impossible to guarantee that a prophylactic mastectomy will prevent breast cancer 100%. Estimates are that 90%–95% of breast tissue is removed. Even with a radical mastectomy, where the pectoralis muscle and chest skin is resected (often requiring skin grafting), at best 98%–99% of breast tissue is removed (Ariyan, 1985). Secondarily, the risk of developing cancer does not decrease proportionate to the amount of breast tissue removed. Experimental data on animals suggest that the risk of carcinogenesis may be increased when the volume of target breast tissue has been reduced but not eradicated; however, whether this applies to humans is uncertain (Nelson et al.; Wong et al., 1986). An important theoretical question is whether remaining breast tissue is at 100% risk.

The finding of an occult carcinoma is insufficient justification for prophylactic mastectomy (Wapnir et al., 1990). In 1985, Schechter indicated that a decision to undergo prophylactic mastectomy must be predicated on more accurate methods of risk estimation and the efficacy of conservative breast surgery. According to Wapnir et al., prophylactic mastectomy must prove superior to surveillance in terms of overall survival. It is interesting that in 2000 these very issues continue to be debated, heightened by the addition of genetic testing to the arsenal.

Issues and Alternatives

Issues in patient selection for prophylactic mastectomy arise from disparity in the factors significant in determining high-risk patients. As well, the identification of those who should be tested for BRCA1 and BRCA2 mutations is a concern. Establishing and promoting the use of clearly defined, specific guidelines is necessary in determining high-risk patients for whom genetic testing or prophylactic mastectomy should be considered. This could best be accomplished by a collaborative effort that includes physicians, nurses, and genetic counselors. It also may be helpful to recall that for nearly all women, aside from those who are BRCA1 or BRCA2 positive, their chances of not having breast cancer exceeds their chance of developing it (Engelking, Kalinowski, & Howell, 1995).

Genetic testing presents different issues. The question exists of how the identification of a BRCA1 and BRCA2 mutation will affect the interventions offered and their effectiveness (Collins, 1996). Remembering that BRCA1 and BRCA2 mutations account for no more than 10% of all breast cancer cases is important. Mahon (1997) asked whether performing genetic testing is appropriate when no means of prevention is available. Others may question whether an individual can be denied the right to genetic testing based on the fact that prevention may not be possible.

Genetic testing has many far-reaching implications. The possibility exists of breach of confidentiality, which could lead to discrimination in health or life insurance (Collins, 1996; Mahon, 1997), employment risks, and social stigmatization (Lerman & Croyle, 1994). Studies also have shown a significant psychological impact on patients regardless of receiving positive or negative test results. Implications exist for the family as well as the individual (Lerman & Croyle). Medicolegal issues (e.g., charging physicians with failure to recommend screening for relatives

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of patients with breast cancer) may arise (Warmuth et al., 1997). Sociopolitical issues may create a clash between individual rights of privacy, choice, and ownership versus the role of the government (e.g., population screening, antidiscrimination legislation, quality control standards) (Engelking, 1995).

Genetic testing may provide a false sense of security for those who truly are BRCA1 negative because they still have a risk equal to that of the general population (Baron & Borgen, 1997), demonstrating the importance of counseling patients on the risks, benefits, and possible limitations of genetic counseling. A need also exists for appropriate surveillance, which also should be explained in genetic counseling. Those who are BRCA1 positive may be motivated to comply with screening or take preventive actions. However, knowledge of one's BRCA status also may decrease compliance for those who would rather not find a lump—early or otherwise (Lerman & Croyle, 1994).

A great many questions concerning genetic testing remain unanswered. At what stage of life should it be done (Mahon, 1997)? Who will pay for the tests and associated services such as counseling (Baron & Borgen, 1997)? Can the revelation of family secrets be avoided (Engelking, 1995)? Without answers to these and many other questions, the issues surrounding genetic testing cannot possibly be straightforward. There remains much to be learned before predisposition testing for cancer can be considered a panacea.

Prophylactic mastectomy contributes its own set of issues. Baron and Borgen (1997) refer to it as an unproven modality without documented, large-scale studies to support its safety, efficacy, or acceptance, yet it remains the only standard primary prevention modality. Jordan (1996) speculated that it is unlikely that a randomized trial ever will compare the efficacy of prophylactic mastectomy to intense surveillance or chemoprevention because of the subjective and highly emotional nature of the issue.

The effect of prophylactic mastectomy on anxiety is another question. According to Vogel (1996), it may increase anxiety rather than relieve it and also may cause other negative psychological concerns. The effectiveness of prophylactic surgery on anxiety reduction, however, has received less attention in the literature than actual efficacy of the surgical procedure (Jordan, 1996). A considerable amount of literature is dedicated to evaluating the occurrence of cancer following prophylactic mastectomy (particularly subcutaneous mastectomy) and the possibility that neither a total nor subcutaneous mastectomy guarantees 100% protection against developing cancer (Jordan; Wapnir et al., 1990). The issue in this case is the risk-benefit analysis, considering the risk a BRCA1- or BRCA2-positive woman faces in developing cancer by age 50. Conversely, Wapnir et al. feel that recommendations for prophylactic mastectomy will have to prove superior to surveillance in terms of overall survival and psychological impact.

Alternatives to prophylactic mastectomy presently are limited to a "wait and watch" regimen, with careful screening or clinical trials for chemoprevention. Table 1 outlines some of the options based on genetic test results. No data are available as yet to support that routine mammograms in younger, high-risk patients supplemented by breast self-examination will decrease the number of deaths from metastatic breast cancer in patients with BRCA1 or BRCA2 mutations. Indeed, speculation is that protocols should be different when treating women with these mutations, but insufficient data exist to support this at present (Collins, 1996). Results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) prospective Breast Cancer Prevention Trial (P1) comparing tamoxifen versus placebo found that the incidence of breast cancer was reduced by nearly 50% in women older than 60 and younger women who are at high risk (Fisher et al., 1998). However, whether these results will apply to BRCA1- or BRCA2-

Table 1. Treatment Options/Considerations Based on Possible Genetic Test Outcomes in Patients With a Strong Family History of Breast Cancer

Genetic Testing Results	BRCA1/2 Positive	BRCA1/2 Negative (no family mutation documented)	BRCA1/2 Negative (family mutation documented)	Inconclusive Results
Risk estimate	Up to 85% lifetime risk	Difficult to ascertain (range may be from 12%–85%)	Approximately 12% lifetime risk	Unclear
Options	Surveillance Prophylactic mastectomy Chemoprevention	Surveillance Prophylactic mastectomy Chemoprevention	Surveillance	Uncertain
Issues related to prophylactic mastectomy	Improved survival benefits Reduction in patient anxiety Quality-of-life issues	Possibility of false-negative test If strong family history, may be treated as gene positive Even if a true negative, patient remains at population risk Risk never equals zero	Risk equivalent to population risk	May face increased risk Impossible to give recommendations May increase patient anxiety

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positive women is not yet certain. Another NSABP trial study, the Study of Tamoxifen and Raloxifene, will compare the effectiveness of these two agents in preventing the development of breast cancer in women older than 60 or young women who are at increased risk.

Recommendations

Oncology nurses can do a great deal to address the issues surrounding prophylactic mastectomy for BRCA1- and BRCA2-positive women. First, nurses must become aware of the issues to be able to better inform and support patients facing such decisions. Oncology nurses need to recognize psychosocial issues of genetic testing and prophylactic mastectomy. Because no clearly defined answers that are right for every patient are available, this knowledge will assist nurses and patients in analyzing the risk-benefit ratio of each option to make a decision that is right for that patient.

Undoubtedly, the largest area for recommendations covers future research studies. Nurses have the opportunity to be involved in nursing research directly as nurse researchers or indirectly by facilitating research within their practice environment. Opportunities also exist for collaborative research among physicians, genetic counselors, nurses, and other healthcare professionals. Some of the areas to be studied include ethical questions raised by genetic testing, ways of predicting who may benefit from predictive testing, behavioral research into responses to test information, and psychological studies looking at psychological status, marital and family functioning, quality of life, health behavior, reproductive intentions, healthcare use (Biesecker, 1997; Langston et al., 1996), and chemoprevention for BRCA-positive women. Opportunity for debate of ethical issues within special interest groups and professional nursing associations that could lead to the development of position statements on specific issues also exists. Researchers must address the psychological effects of knowing BRCA1 or BRCA2 status for individuals and families, as well as the effect this knowledge has on compliance with early detection and screening measures.

Conclusion

Should prophylactic mastectomy be recommended based on BRCA1 or BRCA2 status? Although statistics reveal that carriers of these mutations constitute the minority of breast cancer cases, apparently these individuals face a risk much greater than the general population. Recognizing that deficiencies and strengths concerning genetic testing for the BRCA1 and BRCA2 mutations and prophylactic mastectomy exist, the lack of available options also is obvious. Genetic counseling is essential to ensure that carriers of these mutations are aware of the benefits, risks, and limitations of genetic testing. In the past, prophylactic mastectomy has been an unpopular option that was considered radical and inappropriate for all but a very select few. Recent preliminary studies have demonstrated that prophylactic mastectomy can improve survival outcomes for young women, but much work remains before specific recommendations can be made.

Much remains to be studied in terms of efficacy, outcomes, and ethics, and nurses are in an excellent position to initiate and contribute to such research. Standardized patient selection criteria for prophylactic mastectomy candidates and BRCA1 and BRCA2 screening needs to be developed through well-researched protocols in a manner that can be generalized to the population at large. Until more answers are available, oncology nurses must be knowledgeable about the arguments for and against prophylactic mastectomy, providing such information to patients in a supportive, unbiased manner that acknowledges individual circumstance.

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