BREAST CANCER AND THE ROLE OF
TAMOXIFEN IN PREVENTION

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Breast cancer is the leading cause of morbidity and mortality among U.S. women. It is the leading cause of cancer deaths in premenopausal women. Discoveries regarding breast cancer are proceeding rapidly and yet we have limited knowledge as to what causes breast cancer. The discovery of the BRCA genes was a major breakthrough in cancer research, but just what role genetics plays in the development of breast cancer and what the implications are for treatment and prevention remain somewhat elusive.

Lifetime exposure to estrogen also confers risk for developing breast cancer. Are these two factors interrelated? A recently published study claims that the drug Tamoxifen can reduce the incidence of breast cancer by 50%. This paper examines some of the research regarding the latest breast cancer discoveries with the end aim of allowing a critical examination of the role of Tamoxifen as a preventative measure.
Breast Cancer and the Role of Tamoxifen in Prevention

Breast cancer accounts for 32% of all cancers in American women, making it the most common cancer in American women (Rosenthal & Puck, 1999). It is the leading cause of morbidity and mortality among women in this country (Sellers, 1997). It is the leading cause of cancer deaths in premenopausal women (Rosenthal & Puck, 1999). Estimates range from 10-15% of all breast cancers that are thought to be familial. Since 180,000 women will be diagnosed with breast cancer this year (Marx, 1997), that means that 18,000 to 27,000 of these will have an inherited form of breast cancer. More significantly, 153,000 - 162,000 women will have sporadic cases of breast cancer. That is, they have no genetically inherited predisposition to developing breast cancer.

It is probably a safe assumption that most American women are not reading JAMA or the Journal of the National Cancer Institute for their information regarding breast cancer. According to Black, Nease and Tosteson (1995) most women report that they rely on their physicians for information. However, studies by Black et al. (1995) and Dolan, Lee and McDermott (1997) demonstrate that women greatly overestimate their risk and the risk reduction conferred by mammogram, while their physicians more realistically view mammographic screening. While popular media has been very successful in increasing women's awareness and use of screening, the information disseminated is necessarily incomplete simply by virtue of the rapidity of new discoveries and lack of time to fully explain them all. Health care providers face the same difficulty in keeping up with the pace of discovery. A brief literature search reveals literally hundreds of articles in the last 2 years alone dealing with the genetics of breast cancer. Before we have had time to begin to understand the implications and limitations of that knowledge, breaking news informs us that now we can prevent breast cancer 50% of the time by giving our
patients tamoxifen. The purpose of this paper is to attempt to put some of facts surrounding breast cancer into perspective in view of critically evaluating the place of tamoxifen in practice as a preventative measure against developing breast cancer.

Review of the Literature

Breast cancer risk

In the early 1990’s, the American Cancer society engaged in a massive public education campaign to increase use of mammography and breast self exam (BSE) to diagnose breast cancer early. It was hugely successful. However, according to Phillips, Glendon and Knight (1999), it also resulted in exaggerated fears in the general population about the risk of developing breast cancer. In two studies by Black et al. (1995) and Dolan et al. (1997) women tend to greatly overestimate their risk of developing and dying from breast cancer and to overestimate the screening benefits of mammography. In fact, Black et al. (1995) found that women perceived their risk of dying in the next ten years to be close to 10%, a figure very close to the ‘1 in 9’ statistic widely disseminated in breast cancer information literature. In both studies women also overestimated the reduction of risk from mammographic screening, with younger women attributing greater risk reduction than older women (Black et al., 1995, Dolan et al., 1997).

While lifetime risk of breast cancer is 1 in 9, a woman’s risk of developing breast cancer in any given decade of life is only 1 in 34 (Phillips, et al., 1999). The one woman in 9 who does develop breast cancer has a 50% chance of diagnosis after the age of 65 and has a 60% chance of surviving it and dying of some other cause (Phillips et al., 1999). One of the most important risk factors for developing breast cancer is age. Additionally, incidence of breast cancer, after rising for the past 10 years, has leveled off while death from breast cancer has declined, due to early
detection and use of adjuvant therapy for early stage disease (Phillips, et al., 1999). All of the statistics put forth by the American Cancer Society have been based on data that included all women, including those who have higher risk due to genetic or other biological factors (Phillips, et al., 1999).

Risk for developing breast cancer is increased by several factors. These are broadly lumped into three major groups: (a) genetic predisposition as represented by heritable mutations on BRCA1/2 and other genes not fully elucidated at this time, (b) all those things that increase a woman’s lifetime exposure to estrogen, i.e. early menarche, late menopause, first live birth after age 30, age greater than 50, and (c) environmental factors, including diet and exercise.

Predicting likelihood of developing breast cancer

In 1989, Gail and associates using data from the Breast Cancer Detection Demonstration Project (BCDDP) developed a model for predicting a woman’s risk for developing breast cancer over a specified interval of years. Using a case control model, they analyzed incidence rates of both carcinoma in situ (CIS) and invasive tumors in 1,354 white women with cancer who were being followed annually with mammogram and clinical exam as part of a larger breast cancer detection study and compared them to matched controls who received no recommendation for biopsy during the same screening period (Gail et al., 1989). The Gail et al. (1989) study chose 4 variables that they determined were the major predictors of breast cancer, namely family history in a first degree relative, late age at first childbirth, early menarche, and multiple previous benign breast biopsies. The authors state that these variables were validated by a previous, unreported analysis that they did of the data from the Cancer and Steroid Hormone Study (CASH) (Gail et al., 1989). Using logistic regression analysis, they determined the weight of each risk factor and converted it into a numerical expression of relative risk that can be calculated by multiplication...
of all of the factors. When the authors compared their predicted rates of breast cancer to the Surveillance, Epidemiology, and End Results Program (SEER), eight population based cancer registries throughout the United States, they found that their model overestimated incidences of breast cancer by 10-20% in the age group 30-64 years (Gail et al., 1989). The rates for patients over 65 years were roughly equal (Gail et al., 1989). This can probably be explained by the fact that increasing age is a risk factor that was not accounted for in the Gail model but is reflected in the SEER population. Another problem that the authors identified in their own study was the lack of pathology information on the benign breast biopsies (Gail et al., 1989). With the recognition that a benign biopsy with atypical hyperplasia (AT) confers higher risk than mere cystic benign lesions, the authors, in the discussion section of their article, added a correction factor to be used in calculating risk in women who have had AT biopsies (Gail et al., 1989). In their introduction, the authors state that many decisions, including whether or not to undergo prophylactic mastectomy, are dependent upon, among other things, the estimate of the probability that a woman will develop breast cancer in a defined period (Gail et al., 1989). Since this model over-estimates the risk of cancer by 10-20% by the authors’ calculation, using it to assist in deciding on mastectomy seems very risky.

In 1994, Spiegelman, Colditz, Hunter and Hertzmark undertook to evaluate and validate the Gail model of breast cancer prediction. They applied the Gail model to an independent population of women from the Nurses’ Health Study to test its performance in a population other than the one from which it was derived (Spiegelman et al., 1994). These authors found that the Gail model over predicted breast cancer 33% of the time overall and 30% in each subcategory individually (Spiegelman et al., 1994). They conclude that this model is less than satisfactory (Spiegelman et al., 1994).
Family History as risk factor

Family history of breast cancer as a risk factor has been observed as far back as 1860 when French surgeon, Paul Broca, documented his wife's history of 4 generations with breast cancer (as cited in Marcus, Page, et al., 1997). Slattery and Kerber (1993) utilized the information in the Utah Population Database for a case-control study to evaluate the impact of family history on risk for breast cancer. Because of the depth and completeness of the information in the database, they were able to analyze up to 7 generations of history. Overall, they found that 17-19% of breast cancer is familiarly linked (Slattery & Kerber, 1993). By weighting risk based upon degree of relative with breast cancer and then calculating cumulative risk, they were able to determine that the women with the highest risk scores, i.e. those with the most affected relatives, were three times more likely to develop breast cancer as the group with the lowest score (Slattery & Kerber, 1993). Of course, a weakness of this study is that the population under investigation was almost entirely white and so can only be said to represent white patterns of disease (Slattery & Kerber, 1993).

Colditz et al. (1993) examined data from the Nurses' Health Study and found that overall 2.5% of that population had breast cancers attributable to family history. Within a cohort of 2389 women with breast cancer, they compared women without a maternal history of breast cancer to women with such history and discovered that having a mother with breast cancer diagnosed before age 40 conferred a twofold increased risk of developing breast cancer (Colditz et al., 1993).

Genetics

Breast cancer genes. In the late 1980's when the BRCA1 region of chromosome 17q was identified as being associated with breast cancer, family history took on even more significance
(Miki et al., 1994). Then in 1994, Wooster et al. (1995) described the BRCA 2 gene on chromosome 13. Since their discovery the BRCA genes have generated a great deal of interest in the medical community and the public at large.

Multiple issues have been raised regarding the implications and applications of this discovery. The BRCA1 and BRCA2 genes were the first to be associated with an increased breast cancer. BRCA1 is a gene located on chromosome 17q, region 12-q23 (Narod et al., 1991) and BRCA2 is located on chromosome 13q12-q13 (Wooster, et al., 1995). Mutations on TP53 and on a gene responsible for Cowden's disease on chromosome 10q22-23 are also known to raise the risk of breast cancer but these are very rare (Lakhani, Easton & Stratton, 1997 and Lakhani, Jacquemier, et al., 1998) and will not be included in this review. The BRCA1 region encodes for a protein of 1863 amino acids (Miki, et al., 1994) and BRCA2 for a protein of 3418 amino acids (Wooster et al., 1994). The BRCA1 region has been strongly linked to breast cancer-ovarian syndrome (Miki et al., 1994, Narod et al., 1991). Roughly 10-15% of all breast cancers are genetically linked and of those, 80% are believed to be due to BRCA 1 and 2.

The majority of data about chromosomal sequencing of the BRCA genes and mutation prevalence comes from studies of high risk families, those with 4 or more first degree relatives with breast and/or ovarian cancer, some with as many as 10 members affected (Malone et al., 1998; Newman et al., 1998). These groups also contain an inordinately high number of members diagnosed at an early age, an unavoidable inclusion consequence as researchers attempted to look at generational patterns and thus selected for these rare families (Newman et al., 1998).

Investigating penetrance. In a relatively early genetic linkage study, Ford, Easton and Bishop et al. (1994) stated that in a 1992 study by Easton and others, BRCA1 carriers had a cumulative risk of 87% chance of developing breast cancer by age 70. Thirty three families
registered in the Breast Cancer Linkage Consortium (BCLC), a collection of cooperating research groups in the U.S. and Western Europe, were studied for estimating risk of breast or ovarian cancer in BRCA1 carriers (Ford, Easton, Bishop, et. al., 1994). Ford, Easton, Bishop and colleagues (1994) concluded that lifetime risk of breast or ovarian cancer for mutation carriers approaches 100%. Citing unpublished data, the authors state that they have determined that 2 alleles of BRCA1 confer a breast cancer risk of 91% and 70% by age 70 (Ford, Easton, Bishop et al., 1994). All families in the study had 4 or more members with ovarian or breast cancer diagnosed before age 60, which by methods outlined in their unpublished study established a 90% probability of being a BRCA1 carrier (Ford, Easton, Bishop et al., 1994). The problems with this report are obviously the lack of supporting data available due to being 'unpublished.' However, it is a very good example of the initial thinking regarding the genetic link to breast cancer practically being a foregone conclusion that a woman would develop breast cancer.

In 1997, Struweing et al. published their findings of a study of breast cancer in Ashkenazi Jewish women. This genetically distinct population has been shown to have characteristic mutations in BRCA1 and 2 and incidence of mutation occurrence of 1-2% (Struweing et al., 1997). In a case control study of 5318 women, the authors sought to demonstrate risk of developing cancer from the 2 BRCA genes (Struweing et al., 1997). The results of their study indicated that by age 70, a woman had a 56% chance of developing breast cancer and a 16% chance of developing ovarian cancer (Struweing et al., 1997). These figures are well below the estimates of 80-90% chance by previous estimates using kindred comparisons (Struweing et al., 1997). A problem with this study is that in this population essentially all of the cancers were
accounted for by only 4 mutations; over 130 mutations in BRCA1 alone have been identified so far (Couch & Weber, 1996).

In 1997, Couch, DeShano, Blackwood and Calzone obtained study participants from clinics that evaluate breast cancer risk in order to analyze DNA and evaluate the effectiveness of genetic linkage studies to predict BRCA1 carrier status. In this study, 263 women with breast cancer were tested by blood sample for DNA analysis of BRCA1 carrier status and this was then correlated to age at diagnosis, presence of ovarian cancer, combination of breast and ovarian cancer, and ethnic grouping (Couch, DeShano et al., 1997). Their findings show that only 16% of these women had a BRCA1 mutation (Couch, DeShano et al., 1997). When ovarian cancer was excluded from analysis, only 7% showed BRCA1 mutation (Couch, DeShano et al., 1997). Based on these findings, they estimated that only 40-50% of hereditary cancers can be linked to BRCA1/2, not 90% as had been postulated in early analyses (Couch, DeShano et al., 1997).

A major breakthrough study was published by Ford, Easton, and Stratton et al., in 1998. In this study 237 families culled from the Breast Cancer Linkage Consortium (BCLC), representing 21 investigating groups and 9 countries, were analyzed. All had been typed for linkage to either BRCA1 or BRCA2 and contained 4 or more members (male or female) with breast cancer, diagnosed before age 60 (Ford, Easton, Stratton et al., 1998). Ford, Easton, Stratton et al. (1998) state that this is the largest group of breast cancer patients in the world with known linkage to BRCA1/2 ever studied. Their goal was to estimate what proportions of families had disease due to BRCA1, BRCA2, or unidentified genes and to estimate penetrance of BRCA2 in a large data set. Data were analyzed by 2 statistical models, one from the CASH study in which susceptibility is conferred by autosomal dominance transmission, and the second in which BRCA1 is assumed to have a higher penetrance than in the CASH model (Ford, Easton,
Stratton et al., 1998). The authors found the differences between the two to be insignificant statistically. Incorporating mutation data that were available for 64 families with BRCA1 mutations demonstrated that the proportions of families estimated to be linked to BRCA1 by linkage data alone were almost identical to the estimates incorporating mutation data (Ford, Easton, Stratton et al., 1998). Table 1 summarizes the results of their study.

The most interesting finding of this study is the large shift in linkage when families of only 4 or 5 breast cancer and no ovarian cancer cases are evaluated (Ford, Easton, Stratton et al., 1998). From their data, Ford, Easton, Stratton et al. (1998) conclude that there are other breast cancer susceptibility genes responsible for a large portion of familial breast cancers and that these probably confer lower risk, but are more common in the population at large. Table 2 summarizes the risks of developing cancer due to BRCA genes based on the analyses in this report.

In 1998, Claus, Schildkraut, Iversen, Berry and Parmigiani enrolled a case-control cohort of women from the CASH study dataset of approx. 9,400 women. Of these, 4,730 were case subjects, diagnosed with breast cancer and 4,688 control women without breast cancer. BRCA1/2 carrier probability status was calculated for each subject and in-home interviews were conducted to assess family history (Claus et al., 1998). Their goal was to determine if BRCA carrier probability could be predicted on history alone. They then correlated the questionnaire responses with genetic typing from the SEER database (Claus et al., 1998). Case subjects were twice as likely to report a first degree relative with breast cancer than controls. An unexpected finding was that among predicted non-carriers of a BRCA mutation, family history was still a risk factor for developing breast cancer (Claus et al., 1998). Twenty-five percent of predicted non-carriers reported a first degree relative with breast cancer (Claus et al., 1998). Predicted
non-carriers who reported a first degree relative with breast cancer usually were diagnosed at a later age than predicted carriers and the relative was also diagnosed older than the relative of predicted carriers (Clause et al., 1998). The significance of this study is that even a modest family history imparts a degree of increased risk of breast cancer.

To test for the likelihood of BRCA linked breast cancer in newly diagnosed patients unselected for family history, Newman et al. (1998) did a case-control study in North Carolina in which newly diagnosed cancer patients and randomly selected age/race-matched controls were screened for genetic mutation at BRCA1 (Newman et al., 1998). Prevalence of inherited disease attributable to BRCA1 was 3.3% in white cases, 0% in black cases and 2.6% for the population as a whole (Newman et al., 1998). Among white women with any relative with breast cancer, 6.6% of disease was attributable to BRCA mutation, with the rate going up to 13.4% in the high risk families (Newman et al., 1998). Though they did not give specific incidences, the authors state that while no BRCA associated disease was found in the black women of this study, BRCA mutations have been identified in black women from high risk families (Newman et al., 1998).

In a similar study, Malone et al. (1998) evaluated women diagnosed with breast cancer before the age of 35 and before age 45 with first degree family history against controls to determine the incidence of BRCA gene caused disease in a general population. DNA sequencing was done from peripheral blood sampling. In women less than 35 years of age at diagnosis, 6.2% had germline BRCA1 mutations (Malone et al., 1998). In cases less than 45 years old with a first degree relative, 7.2% had a germline mutation in BRCA1 (Malone et al., 1998). As in all previous studies, women with multiple relatives with breast cancer or relatives with ovarian cancer demonstrated higher incidence of BRCA1 mutation (Malone et al., 1998, Newman et al., 1998).
The interesting conclusion that can be drawn from this data is that family history confers a wide range of risk for developing breast cancer. A great deal of research has dealt with determining the differences between the cancers caused by the BRCA genes, and the hormone receptor status, attempting to ascertain the natural history of the heritable forms of the disease and to determine effective treatment.

**Differences between BRCA cancers and sporadic cases**

**Histopathology.** In essentially one ongoing study, Marcus, Watson et al. in 1996 and Marcus, Page et al. in 1997 reported different histopathology for BRCA1, other heritable breast cancer and sporadic cancers. In 1996, Marcus, Watson et al. obtained 175 pathology specimens from women with breast cancer, blinded the slides and had them evaluated by pathologists. Their findings indicated that BRCA1 was associated with more medullary and atypical medullary tumors and tumors of no specific type (NST), higher aneuploidy, and an increased S-phase of mitosis (Marcus, Watson et al., 1996). In the group labeled other heritable cancers, an excess of tubular-lobular group (TLG) cancers was noted but questioned as to statistical significance because of the identification of only 2 known non-BRCA1 mutation carriers (Marcus, Watson et al., 1996)

In 1997, using the same sample but improved methods of evaluation, Marcus, Page et al. continued their comparison of tumor histopathology. In this study, they were able to isolated enough cancer specimens linked to BRCA2 to adequately compare morphologies. Their findings again indicated that BRCA1 was associated with more medullary and atypical medullary tumors, had higher aneuploidy, and was of higher grade by TNM staging, but that ductal carcinoma in situ (DCIS) incidence was significantly lower (Marcus, Page et al., 1997). There was also a
slightly lower rate of lobular carcinoma in situ (LCIS) though not statistically significant, and a lower rate of tubular-lobular group (TLG) cancers (Marcus, Page et al., 1997). BRCA2 seemed to be associated with higher rates of LCIS, higher rates of TLG, more no special type (NST) tumors with TLG features and with less tubule formation (Marcus, Page et al., 1997). They postulated that the BRCA2 phenotype may be more dependent on where on the gene the mutation occurs than the BRCA1 phenotype (Marcus, Page et al., 1997). They also report that BRCA1 phenotypes have better 5 year survival rates than BRCA2 phenotypes, but about the same survival rates as sporadic cases, which is consistent with Verhoog et al.'s (1998) findings.

Lakhani, Easton, Stratton and the Breast Cancer Linkage Consortium (1997) studied the histological features of breast cancer specimens of 440 patients with familial linked breast cancer, including 118 known to be linked to BRCA1 and 78 to BRCA2, and compared them to 547 specimens unselected for family history to determine if breast cancer due to BRCA1/2 has a different natural history from sporadic cancers. BRCA1 cancers were found to have a higher mitotic count, were of higher grade, and had significant pleomorphism (Lakhani, Easton et al., 1997). BRCA2 cancers showed significantly reduced tubule formation (Lakhani, Easton et al., 1997). The authors suggest that these findings may suggest the normal function of these genes is control of proliferation and genome stability in BRCA1 and maintenance of tissue architecture by BRCA2 (Lakhani, Easton et al., 1997). Both BRCA 1 and 2 demonstrated lower rates of tubular cancers than controls. Medullary and atypical medullary cancers occurred more frequently in the BRCA1 patients, but invasive lobar cancers were less frequent than controls (Lakhani, Easton et al., 1997). Also, as higher grade is usually indicative of poorer prognosis, the authors propose that BRCA1 breast cancers carry a graver outlook than other cancers.
(Lakhani, Easton et al., 1997). However, Verhoog et al. (1998) discovered that women with BRCA1 cancers actually have nearly equal 2 year and 5 year survival as sporadic cancers.

In 1998, Lakhani, Jacquemier et al. revisited the study above and engaged in a more detailed study of the cytological features of the tissue specimens previously obtained. By multifactorial analysis of the findings of both studies, they sought to identify the features that are independently associated with BRCA1/2 tumors (Lakhani, Jacquemier et al., 1998). The first study was carried out by 5 pathologists who were unaware of whether the slides being examined were case or control; this second study was carried out by 7 pathologists (Lakhani, Jacquemier et al., 1998). The cases were essentially the same as the first published report, but controls were different. Results of this analysis confirmed previous findings of high mitotic count in BRCA1 and high lymphocyte infiltration in the region of the tumor (Lakhani, Jacquemier et al., 1998). They noted that a previously unreported feature became significant in this analysis: both BRCA1 and BRCA2 showed continuous pushing margins, which indicates less likelihood of stromal infiltration with cancer cells (Lakhani, Jacquemier et al., 1998). The higher incidence of what was identified as medullary and atypical medullary (AM) carcinomas in BRCA1 patients can be explained by the findings of high mitotic count, lymphocyte infiltration and continuous pushing margins, the last two of which are some of the criteria for defining a medullary or AM tumor (Lakhani, Jacquemier et al., 1998). The authors report that, strictly speaking, the three features of the BRCA1 tumors listed above fall out as statistically significant for being independent tumor features, but since medullary carcinomas are dependent on more than just those features for definition, BRCA1 tumors cannot be said to be medullary per se (Lakhani, Jacquemier et al., 1998). LCIS and DCIS were noted to occur more infrequently in BRCA1/2 cancers than controls, though the rates of difference were only marginally statistically
significant. The authors believe that tumor histological differences may become important predictors of genetic status in patients who lack knowledge of family history. Since contralateral breast cancer occurs 5 times more often in BRCA1 carriers (Verhoog et al., 1998), this may indeed be of prognostic value.

Histopathology and hormone receptor status. In a study by Johannsson et al., published in 1996, tissue samples of breast cancer tumors from 57 families, 14 with BRCA1 associated disease were compared with non-hereditary cancer tissue samples to evaluate if there are differences in tumor types in genetically linked disease. Using the World Health Organization (WHO) tumor classification criteria, these authors found that the BRCA1 tumors were most often ductal type, showed high lymphocyte infiltration and higher grade (Johannsson et al., 1996). Comparison of tumor DNA revealed that BRCA1 tumor cells had higher S-phase fraction and higher rates of non-diploid DNA (Johannsson et al., 1996). Further, the authors found that BRCA1 associated cancers had significantly higher rates of estrogen and progesterone receptor negativity and c-erB-2 negativity (Johannsson et al., 1996). In their discussion of their findings, the authors compare their findings to those of the 1996 Marcus, Watson et al. study, cited above. They point out that the pathological features observed and used to classify tumor specimens in this study were very similar to those found by Marcus et al. (1996), but that since they are using the WHO criteria, they had to call the tumors by another name, i.e. ductal type rather than medullary/atypical medullary or NST (no special type) with medullary features (Johannsson et al., 1996). Of particular interest from this study is the finding that BRCA1 cancers are primarily hormone receptor negative. A question that they raised in regard to this finding is whether or not hormone receptor status is a function of the BRCA1 gene or a reflection of the tumor grade, as the BRCA1 tumors were all of higher grade than controls (Johannsson et al., 1996). If, in fact,
hormone receptor status can be found to be related to BRCA status, it would have implications for treatment and prevention. As the authors point out, it would have implications for using drugs such as tamoxifen for prevention in high risk families (Johannsson et al., 1996).

**Tumor size, node status and hormone receptor status.** Verhoog et al. (1998) set out to study another grouping of differences between women with heritable breast cancer and those with cancers not selected for family history. In a case-control comparison of Dutch women with breast cancer, these researchers looked at differences in tumor size, axillary node status, hormone receptor positivity or negativity, and survival rates (Verhoog et al., 1998). They found a trend toward medullary type tumors, in agreement with Marcus, Page et al. (1997), and a trend toward more node negative cancers in BRCA1 mutation carriers, but these differences were not statistically significant (Verhoog et al., 1998). Distribution of tumor size between the cases and controls were equal, though BRCA associated tumors were of higher grade (Verhoog et al., 1998). Two year and five year survival was fairly equal between BRCA1 carriers and controls, though there was a slight non-statistically significant tendency toward poorer survival in BRCA1 cancers (see table 3) (Verhoog et al., 1998). As BRCA1 tumors were found to be undifferentiated, have higher proliferation rates and a younger age at onset, these survival figures (see table 3) are somewhat surprising, but corroborate earlier findings by Porter, et al. (1994). Recurrence rates for contralateral cancer was significantly higher in BRCA1 patients, nearly 4 times higher, which may be of clinical value in deciding on prophylactic mastectomy of the unaffected breast (Verhoog et al., 1998). BRCA1 tumors were found to be estrogen receptor negative 67% of the time compared to sporadic cases which were ER negative only 34.7% of the time and progesterone receptor negative 70% and 33.8% respectively, correlating with the findings of Johannsson et al. (1996).
**Estrogen receptor status.** In light of the fact that at least 1/3 of breast cancers are estrogen receptor (ER) negative and of those that are positive, 40% are resistant to endocrine therapy, Roodi et al. (1995) set out to map the ER gene to determine if a mutation in the ER gene was the origin of these findings. They found only 2 mutations in 188 tumors examined, for an occurrence rate of less than 2%. Thus they conclude that ER gene mutations do not account for the estrogen receptor phenotype of breast cancers (Roodi et al., 1995). They did find that a polymorphism at codon 325 showed a strong association with a positive family history of breast cancer, but were unable to establish a link with breast cancer risk or occurrence (Roodi et al., 1995).

Khan, Rogers, Khurana, Meguid and Numann in 1998 investigated whether ER expression in normal breast tissue was predictive of breast cancer: specifically is enhanced estrogen responsiveness of breast epithelium responsible for breast cancer susceptibility? Estrogen exposure is a known risk factor for developing breast cancer, but the mechanism is poorly understood. Speculation includes estrogen induced proliferation providing more opportunity for mutation occurrence, cytotoxic estrogen by-products and high levels of estradiol in breast tissue (Khan et al., 1998). These investigators obtained specimens of normal breast epithelium from women with breast cancer undergoing breast surgery and from controls undergoing biopsy who were later confirmed to not have breast cancer. The incidence of ER positivity and negativity was compared between groups and then analyzed in reference to known endocrine risk factors such as early menarche or late age at first childbirth (Khan et al., 1998). In both pre- and post-menopausal women, those with breast cancer had significantly higher rates of ER positive expression in normal (i.e. non cancerous) breast epithelium (see table 4) (Khan et al.,
1998). However, they did find that post-menopausal women using HRT dramatically increased the rate of ER positivity in controls, making their rates equal to cases. The authors state that this finding needs to be pursued in larger studies as it may indicate that HRT increases breast cancer risk in post-menopausal women (Khan et al., 1998). The authors found no correlation between ER positive status and endocrine risk factors for breast cancer (Khan et al., 1998). They found that in case subjects there was a paradoxical increase in ER positivity toward the end of the menstrual cycle; normally this decreases (Khan et al., 1998). The authors pose the question that perhaps ER dysregulation or loss of normal regulatory mechanisms of the ER expression may confer increased risk of development of breast cancer (Khan et al., 1998).

In brief, while much has been discovered about breast cancer, there is much left to learn. Exact mechanisms of transmission in hereditary cases are unknown and there is evidence of many more genes involved in the development of breast cancer than just BRCA1/2. The natural histories of various types of breast cancer are different, which may have implications for treatment, screening and prevention. Introduced into the glut of information available is the approval of tamoxifen to prevent breast cancer by the FDA. What is the place of tamoxifen in therapy?

**Tamoxifen**

In 1992, the National Surgical Adjuvant Breast and Bowel Project (NSABP) began study P-1 to evaluate tamoxifen as a preventative measure against breast cancer. Because of dramatic results, the study was unblinded, halted and tamoxifen was approved as an agent to prevent primary breast cancer. Two European studies failed to validate the findings of the NSABP.

**American study.** Beginning in 1992, the NSABP began recruiting subjects to evaluate tamoxifen, a drug proven effective in treating breast cancer and reducing tumor recurrence
From 1992 to 1994, 11,000 women were recruited to the study; recruitment was interrupted for one year and then resumed to a total of 13,388 women recruited, consented and medically eligible (Fisher et al., 1998). Randomization was completed only in 1997. Women were eligible if they did not have cancer but did have risk factors for developing cancer and/or a predicted risk of doing so in the next 5 years (Fisher et al., 1998). Predicted risk of developing breast cancer was based upon a modified version of the Gail model, discussed above, using SEER rates of cancer occurrence instead of BCDDP rates and more current mortality rates (Fisher et al., 1998). Modifications to account for race were also incorporated into the model. The risk factors selected for inclusion in the study were primarily those not strongly linked to predicted BRCA carrier status, but to estrogen exposure over the lifetime, i.e. early menarche, late age at first childbirth, and multiple benign breast biopsies (by the Gail model), age greater than 60, or history of LCIS (shown by previously cited studies to be lower in BRCA carriers). After a weighted double-blind randomization process, the researchers had two groups of roughly 6500 women taking Tamoxifen 20mg per day or placebo, to be taken for 5 years (Fisher et al., 1998).

The authors report a 49% reduction in overall cancer occurrence (Fisher et al., 1998). The most dramatic results were seen in those cases that had a history of LCIS or atypical hyperplasia on biopsy (Fisher et al., 1998). In the atypical hyperplasia subgroup there were 8 cancer events in the placebo group to one event in the tamoxifen group (Fisher et al., 1998). Tumor size comparisons revealed twice as many of any give size tumor in the placebo group as the tamoxifen group, which would be expected if in fact 50% of cancers were prevented in the first place in the tamoxifen group. The placebo group had more node negative cancers than the tamoxifen group. Occurrence of estrogen receptor (ER) positive tumors was 69% lower in the
tamoxifen group (Fisher et al., 1998), again, not surprising given tamoxifen’s mechanism of action being competitive binding to estrogen receptors (Anonymous, 1999).

Though the population of minorities in the study was small, it is interesting to note that in black subjects there were 7 cases of breast cancer, 2 in the placebo arm and 5 in the tamoxifen group (Fisher et al., 1998). The occurrence of side effects in the placebo vs. tamoxifen group were: endometrial cancer (18 vs. 37), MI (28 vs. 31), DVT (22 vs. 35), pulmonary embolus (6 vs. 18), and stroke (24 vs. 38) (Fisher et al, 1998). The authors also report on the secondary aims of the study, to evaluate fracture prevention and cardiac effects, but those will not be addressed here.

The results of this study, if valid are a major breakthrough in women’s health. However, there are some problems with the study. At the time of the publication of the study, only 37% of participants had 60 months, i.e. 5 years, of follow-up (Fisher et al., 1998). That means that the vast majority of participants did not complete a 5 year course of therapy. By mere subtraction, one can determine that even those who were able to complete 5 years of drug therapy could only be followed for 1 year prior to publication of results. The Gail model for predicting breast cancer has been found to be significantly flawed by independent investigators (Spiegelman et al., 1994). Fisher et al. (1998) report that they adapted the Gail model but do not report if they did a trial of their model to establish its validity. Tamoxifen is a potent drug with significant side effects. What are the consequences of having taken it for 5 years, 5 years down the road? Is there a rebound cancer effect of tumors that are now tamoxifen resistant? Are women with risk factors expected to take it indefinitely? This study was a good start, but many critical questions remain unanswered.

Italian study. In a similarly structured, smaller Italian study, Veronesi et al. (1998) studied women at normal to low risk of developing breast cancer and found no difference
between tamoxifen and placebo. They did find a moderately protective effect of tamoxifen in women taking HRT (Veronesi et al., 1998), which, if confirmed by further study, may establish a method of treatment by which women who need the cardioprotective effects of estrogen can concurrently reduce their risk of breast cancer. By admission of the authors of this study, it is low power (Veronesi et al., 1998).

British study. Powles et al. (1998) over 10 years from 1986-1996 accrued patients with increased risk for breast cancer due to positive family history. Participants were randomized to placebo and tamoxifen groups in a double blind manner. Course of study was to include at least 5 years of drug therapy (a small number received drug for 8 years) and 5 years of follow-up, as in the NSABP P-1 study. Compliance with therapy was monitored by random blood tests. At the time of publication of this study, over 40% of participants had completed drug therapy and were into the 5 year post drug monitoring phase (Powles et al., 1998). This report is an interim analysis of data accrued so far and the study is ongoing.

Powles et al. (1998) have not observed to date any significant difference in tamoxifen vs. placebo groups for occurrence of breast cancer. Frequency rates of side effects, such as endometrial cancer and DVT, are comparable to the NSABP P-1 study. Women in the Italian study had all been hysterectomised and so had no endometrial cancer. HRT was not an exclusion criteria in this study as it was in the NSABP study but the authors state that they found no interaction between the effects of HRT and the occurrence of breast cancer (Powles et al., 1998). Powles et al. (1998) also collected blood from each participant that will be used to screen for breast cancer genes at some future unspecified date and study.

Comparison. A criticism leveled at the Powles study is that it is much smaller than the NSABP study. A critique by Pritchard (1998) states that the Powles study has 90% power to
detect a 50% reduction in breast cancer occurrence and so size of the study does not account for the different findings. Several factors could account for the discrepancy of findings, among them the populations studied. Powles et al. (1998) looked at women at risk because of family history. The NSABP study included those women whose risk was elevated primarily due to estrogenic factors. Since most BRCA tumors are ER negative, this may partially account for the differences in the studies (ref. Johannsson et al., 1996, Lakhani, Easton et al., 1997, Marcus, Page et al., 1996, Marcus, Watson et al., 1997, and Verhoog et al., 1998). Additionally, the women in the Powles study were younger on average than the NSABP group (62% age less than 50 compared to 40% in the NSABP trial) (Pritchard, 1998). Another possibility that has been suggested by Powles et al. (1998) and by Pritchard (1998) is that the reduction in cancer in the short follow-up in the NSABP trial is actually a treatment effect of occult cancers and is an effect that will average out over a longer follow-up period. As Pritchard (1998) points out, none of these studies have provided any good data about mortality.

Conclusion

While tamoxifen may indeed be the penicillin of the 21st century, it is premature to recommend it as a treatment option outside the clinical trial milieu. None of the studies on tamoxifen have addressed how long women are expected to take it as a cancer preventative. There are also medical ethics questions to be considered: is it ethical to expose healthy women to the potentially devastating side effects of tamoxifen when we do not know its long term effects on breast cancer prevention outcomes or how long they need to take it? Perhaps it needs to be studied in women with one or two risk factors with a known pathogenesis to more fully elucidate the cause and effect relationship between the drug and outcomes. The Powles et al.
(1998) study is still ongoing and it will be interesting to see the final analysis of their data. A new study involving raloxifene was recently approved and another European study is currently recruiting subjects for further tamoxifen studies. These studies should shed additional light on the topic and provide a more comprehensive scientific basis for tamoxifen’s place in therapy.
References


Table 1- Disease linked to BRCA genes vs. other (Ford, Easton, Stratton et al., 1998).

<table>
<thead>
<tr>
<th></th>
<th>Disease linked to:</th>
<th>BRCA2</th>
<th>other genes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRCA1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall (all families)</td>
<td>52%</td>
<td>35%</td>
<td>13%</td>
</tr>
<tr>
<td>Breast and ovarian cancer (no males)</td>
<td>88%</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>male breast cancer</td>
<td>19%</td>
<td>77%</td>
<td>4%</td>
</tr>
<tr>
<td>families with 4 or 5 breast cancers only</td>
<td>28%</td>
<td>5%</td>
<td>67%</td>
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</table>
Table 2 - Cancer risk of BRCA carriers (Ford, Easton, Stratton et al., 1998).

<table>
<thead>
<tr>
<th></th>
<th>breast or ovarian cancer by age 50</th>
<th>breast or ovarian cancer by age 70</th>
<th>breast cancer by age &lt;40</th>
<th>breast cancer by age &lt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>57%</td>
<td>83%</td>
<td>50%</td>
<td>80%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>29%</td>
<td>88%</td>
<td>30%</td>
<td>73%</td>
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</table>
Table 3 - Survival rates for BRCA vs. sporadic cancers (Verhoog et al., 1998).

<table>
<thead>
<tr>
<th></th>
<th>Disease free survival, 2 years</th>
<th>Disease free survival, 5 years</th>
<th>Overall survival at 2 years</th>
<th>Overall survival at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA patients</td>
<td>68%</td>
<td>49%</td>
<td>78%</td>
<td>63%</td>
</tr>
<tr>
<td>sporadic cases</td>
<td>73%</td>
<td>51%</td>
<td>88%</td>
<td>69%</td>
</tr>
</tbody>
</table>
Table 4 - Estrogen receptor status of normal breast epithelium (Khan et al., 1998).

<table>
<thead>
<tr>
<th></th>
<th>% Cases (women with breast cancer) with ER positive normal epithelium</th>
<th>% Controls with ER positive normal breast epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-menopausal</td>
<td>81.4</td>
<td>63.8</td>
</tr>
<tr>
<td>post-menopausal</td>
<td>88.5</td>
<td>69.8</td>
</tr>
</tbody>
</table>