Effective preventive treatments for hereditary breast cancer

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Effective preventive treatments for hereditary breast cancer

Kimberlie Anne Liebert
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2008
Dedication

I would like to dedicate this paper to my grandmother Helen Kind. She was a wonderful woman who lost her life to breast cancer. In addition, the dedication is extended to all persons affected by breast cancer, either personally or via a loved one.
Acknowledgements

A special thanks to Professor Lorraine Kenter, PA-C and Dr. Iman Mohamed for all of their hard work and assistance with this project.
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Introduction

Breast cancer is the second most common type of cancer among women in the United States, next to skin cancer (American Cancer Society, 2007). An American woman has a 12% chance of developing an invasive form of breast cancer during her lifetime. Developing breast cancer is a common fear among many women residing in the United States due to the fact that North American women have the highest rates of breast cancer in the world. Breast cancer is the second most frequent cause of death due to cancer in women. Thus, females at greatest risks for developing hereditary breast cancer may elect to undergo genetic testing to discover if they carry the mutated genes, BRCA1 or BRCA2. If a woman has either gene mutation, then she may attempt to prevent or delay the onset of breast cancer with a form of prophylactic treatment.

Genetic testing can now identify if a woman exhibits a mutated breast cancer gene. Mutations on either BRCA1 or BRCA2 are linked to breast cancer in 5% to 10% of the total cases (Agnantis, Paraskevaidis, & Roukos, 2004). If a woman is positive for the BRCA1 or BRCA2 gene mutation, her lifetime risk of developing breast cancer increases exponentially from 40% to 85%. Many factors play a role in determining the exact risk percentage; these include family history as well as genetic and environmental factors. Women who possess a mutated gene must plan accordingly to reduce her chance of acquiring breast cancer. The patient must be educated on all proactive options available which include increased surveillance, preventive medications and prophylactic surgery.

Women may choose to increase their frequency of screenings via clinical and self breast exams, mammography or MRI to reduce the risk of developing breast cancer. Drug therapy is another option in which chemopreventive agents, hormone replacement therapy and oral contraceptive pills all regulate the level of estrogen reaching the targeted breast and ovarian
tissue. Prophylactic surgery involves removal of the targeted organs, breasts and/or ovaries, thus hoping to alleviate the risk of developing cancer (Agnantis et al., 2004). The options include bilateral mastectomy (BM), bilateral salpingo-oophorectomy (BSO) or both procedures.

Practitioners continue to disagree over which surgical procedure is best for their patients. The breasts and ovaries are targeted by the BRCA mutated gene, although the genes are found in every cell in the body (Agnantis et al., 2004). Breast tissue is targeted the most by the BRCA mutated genes with ovaries and fallopian tubes being targeted to a lesser degree.

A study of 483 women with either the BRCA1 or BRCA2 mutation was performed. The follow up after 6.4 years concluded that women who underwent prophylactic mastectomy reduced their risk of developing breast cancer by 90% (Rebbeck et al., 2004). Meijers-Hejboer et al. reported none of the 76 women who underwent prophylactic mastectomy developed breast cancer after 3 years, whereas eight out of 63 patients who chose surveillance developed breast cancer (2001).

**Problem Statement**

Forty to eighty-five percent of patients with BRCA gene mutations will develop breast cancer (Agnantis et al., 2004). Therefore, providers are concerned about which prophylactic methods are most effective in the prevention of hereditary breast cancer.

**Purpose**

The purpose of this review is to evaluate the best methods of preventing breast cancer and associated cancers or complications in women with BRCA gene mutations as identified in peer-reviewed literature from 1999 to present date.
Research Questions

1) Are prophylactic mastectomies and bilateral salpingo-oophorectomies appropriate strategies for the prevention of hereditary breast cancer?

2) What is the recommended rate of increased surveillance (physical exams, MRI of breasts, etc) in this high risk population?

3) Is there a change in patient’s choice of preventive procedures with time, especially with the approval of tamoxifen or other chemopreventive agents?

Methods

This project is a literature review that summarizes peer reviewed journal articles, randomized controlled trials, literature review and clinical review articles found using Medline, PubMed and University of Toledo Electronic Journals. The search criterion comprises articles from 1999 to the present. Keywords used for the search include: prophylactic mastectomy, hereditary breast cancer, BRCA1 and BRCA2 mutated genes, preventive treatment for breast cancer, surveillance and BRCA, surveillance and high risk population and breast cancer, mammogram and BRCA.

Women of any age or race, as opposed to men, are the primary focus. Hereditary breast cancer linked to BRCA1 and BRCA2 mutated genes only are included in this clinical review. Research regarding diagnostic tools such as genetic testing and the outcomes of the preventive measures are summarized. Studies concerning the process of screening, genetic testing, counseling process, various methods to prevent breast cancer, results of the preventive strategies and other related cancers are reviewed. The project specifically includes preventive treatment methods such as increased surveillance, prophylactic mastectomy, bilateral salpingo-
oophorectomy and medications including tamoxifen, raloxifene, aromatase inhibitors, oral contraceptives and hormone replacement therapy.

**Background**

**Breast cancer**

Breast cancer is a malignant tumor that originates from cells in the breast tissue. Therefore, this type of tumor has the potential of invading satellite tissues and organs. Breast cancer affects mostly women and occasionally men (ACS, 2007). There are two sites within the breast tissue that breast cancer can originate. Ductal carcinomas begin in cells lining the ducts that carry milk from the lobule to the nipple; lobular carcinomas stem from cells that line the lobules or milk-producing glands. The cancer cells have the ability to enter the lymphatic vessels and then begin to proliferate within the axillary, internal mammary, supraclavicular or infraclavicular lymph nodes. Thus, the breast cancer can metastasize to distant areas in the body via the blood stream. It is important to note that not all breast cancer cases that have invaded the lymph node will develop metastases and alternately, metastases may occur in the absence of lymph node involvement.

Ductal carcinoma in situ (DCIS) is the most common type of non-invasive breast cancer and it is confined to the duct cells of the breast tissue (ACS, 2007). According to the American Cancer Society, “nearly all women diagnosed at this early stage of breast cancer can be cured.” Mammography is used most frequently to detect cancer in the DCIS stage. The breast nodule is biopsied and the pathologist examines the biopsy for cell necrosis. The tumor is staged higher if necrosis is seen. DCIS with necrosis is termed comedocarcinoma. Lobular Carcinoma in situ (LCIS) is not considered a true form of cancer, but often is categorized as a non-invasive type of cancer.
**Risk factors**

Non-modifiable risk factors for breast cancer include female gender, age, genes, family history, personal history, race, abnormal breast biopsy results, menstrual periods, previous chest radiation and diethylstilbestrol (DES) exposure (ACS, 2007). Other modifiable risk factors that may reduce the likelihood of a woman developing breast cancer include pregnancy prior to the age of 30, multiple pregnancies, breast feeding, exercise and healthy weight. Many other factors may be listed as causative agents towards a woman’s breast cancer risk, but are not proven at this time. High-fat diets, antiperspirants, bras, induced abortion, breast implants, environmental pollution, tobacco smoke and night work are all believed to play a role.

**BRCA1 and BRCA2**

BRCA gene mutations lead to an increased risk for breast cancer. These genes present as two different mutated forms, BRCA1 and BRCA2. The non-mutated forms of the genes function to suppress tumor growth by producing proteins that keep cell growth in check (ACS, 2007). The cytogenetic location for BRCA1 is 17q21; whereas the location for BRCA2 is 13q12.3.

Women with a BRCA1 mutation have a high lifetime risk of both breast cancer, 65% to 82% and ovarian cancer, 39% to 54% (Figure 1) (Agnantis et al., 2004) In comparison, BRCA2 carriers tend to exhibit lower levels of breast cancer, 45% to 82% and ovarian cancer, 11% to 23%. However, these risks are much higher than women in the general population.

Mary-Claire King et al. were part of the New York Breast Cancer Study Group looking at the breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2 (2003). As shown in Figure 2, the likelihood of inheriting the breast cancer gene from a relative is 20% by age 40, 55% by age 60 and greater than 80% by age 80. One half of the patients in this study received the inherited mutations from their fathers. Additionally, the study concluded two
reasons why some patients with the BRCA1 or BRCA2 mutations did not develop cancer. First, the family may have a low penetrance of either the BRCA1 or BRCA2 gene mutation and secondly, the family may be small, consisting of few women with the gene mutations, an abundant number of males, or normal alleles randomly separating the female relatives.

Some environmental factors may also be protective against breast cancer and thus lead to a later onset of cancer in those with BRCA1 or BRCA2 mutations (King et al., 2003). Early pregnancy, physical exercise as an adolescent, healthy weight at menarche and early adulthood are all nongenetic factors which have all shown to influence the penetrance in high-penetrance mutations. Given that fat tissue is a source of estrogen, healthy weight is an important protective factor against breast cancer (ACS, 2007).

**Genetic testing**

Genetic testing techniques can help identify the individuals who possess the BRCA gene mutation. The common method used is the multiplex ligation-dependent probe amplification; a DNA and RNA-based method to detect germline mutations in all classes and genomic rearrangements in BRCA gene mutation carriers (Gulati & Domchek, 2008). In result, gene-expression profiles are formulated based on the gene-array analyses (Agnantis et al., 2004). However, genetic testing is only 90% effective due to the fact that 10% of gene mutations are missed with current limitations (Gulati & Domchek). With the probe amplification technique, a majority of the missed genetic mutations are large genomic rearrangements. Fortunately, Myriad Genetics added a new form of testing called BRACAnalysis Rearrangement Test (BART) in August of 2006. BART is used to detect the large genomic arrangements which are commonly missed, but it is only offered to high-risk individuals.
The so-called “red flags” are a list of criteria used to determine which women are considered to be high-risk and advised to undergo genetic testing. The list includes two first-degree relatives diagnosed with breast cancer under fifty years of age, ovarian cancer in first- or second-degree relatives at any age, male breast cancer, a first-degree relative diagnosed with cancer in the breasts bilaterally, or at least three cases of breast cancer in first- or second-degree relatives (ACS, 2007). Ashkenazi Jewish women are advised to be tested if they have one first-degree relative with breast or ovarian cancer or two second-degree relatives with breast or ovarian cancer on the same side of the family. Furthermore, the American Cancer Society recommends all patients participate in genetic counseling prior to the testing process.

**Preventive treatments**

According to Agnantis et al., “Penetrance and impact of prevention strategies on cancer risk, survival and quality of life are the criteria considered for making a good decision” (2004). Short-term, nonsurgical methods provide a better quality of life, but long-term, patients will have a higher risk of developing breast cancer. Alternately, surgical procedures are correlated with high levels of protection against cancer, but are invasive and lead to adverse effects.

**Increased surveillance**

Increase in surveillance includes the addition of magnetic resonance imaging (MRI) screening to the annual mammogram and clinical breast exam. MRI screening can increase the rate of early breast cancer detection (Agnantis et al., 2004). Increasing the frequency of screenings to every six months can also aid in early diagnosis. However, use of MRI is not specific for detecting breast cancer and it may lead to unnecessary biopsies. Therefore, MRI is only used in high risk women as it does improve the sensitivity for detecting malignancies in BRCA1 or BRCA2 carriers at an earlier stage than mammography (Gulati & Domchek, 2008).
MRI has 79.5% sensitivity and 89.8% specificity for detecting invasive breast cancer as opposed to mammography at 33.3% sensitivity and 95% specificity (Figure 3). Both annual MRI and mammography screenings are recommended in high-risk women.

Self breast exams (SBE) are performed by the patient or partner and clinical breast exams (CBE) are performed by a health care provider. CBE have a 99.3% specificity rate in detecting breast cancer and should be done every six months even if one does not feel a lump with monthly SBE (Gulati & Domchek, 2008). If a patient or clinical provider finds a lump, it should be investigated appropriately.

A prospective study of 170 BRCA mutation carriers reported a significant increase in breast cancer and ovarian cancer occurrences following two years of surveillance as opposed to having BSO (Kauff et al., 2002). Figure 4 illustrates a similar trend between the BSO and surveillance groups; a larger percentage of BSO participants were cancer free at a five year follow-up. The surveillance method is linked to a higher rate of breast cancer and ovarian cancer diagnoses as well as increased mortality (Agnantis et al., 2004). Most often, ovarian cancer in BRCA carriers cannot be detected early via screening because of the lack of symptoms.

**Tamoxifen, raloxifene, aromatase inhibitors, oral contraceptives, HRT**

Specific drugs may be used to decrease the risk of developing cancer. Tamoxifen citrate (tamoxifen), for example, is a chemopreventive drug that blocks the effects of estrogen in the breast tissue (ACS, 2007). Therefore, tamoxifen is effective in women who currently have estrogen receptor (ER) positive tumors and tamoxifen lowers the chance of high risk patients developing breast cancer. Raloxifene is another medication used to block the effects of estrogen at the breast and uterus (Slanetz, Grandpre, Yeh, Kopans, & Mendel, 2004); therefore, works similar to tamoxifen. Anastrozole, letrozole and exemestane are aromatase inhibitors that are
currently being studied in post-menopausal women for their effectiveness as chemopreventive agents (ACS). The mechanism of action of Aromatase inhibitors (AIs) differs from tamoxifen and raloxifene; AIs block estrogen production. Therefore, the AI drugs are currently prescribed to decrease the risk of recurrent breast cancer cases.

Tamoxifen is a selective estrogen receptor modulator (SERM) that can be given to women as an adjuvant treatment for breast cancer, prophylaxis for women at risk for subsequent breast cancers and women at average risk for developing breast cancer (Slanetz et al., 2004). The drug is an antagonist in the breast tissue, competing with estrogen and binding to the ER. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention (P-1) trial has proven a decrease in the incidence of noninvasive and invasive cancers by approximately 50% when tamoxifen was given to both pre- and post-menopausal women for five years. However, the decreased incidence rate only affected the ER-positive tumors, decreasing by 69% and not affecting ER-negative tumors. According to Grann, breast cancers are often estrogen receptor-negative in mutation carriers, however most cancers in BRCA2 carriers are found to be estrogen receptor-positive (2000). This is due to the fact that the percentage of estrogen-receptor positive breast cancers increases with age and most women with BRCA1 or BRCA2 gene mutations develop breast cancer at a younger age.

Also, the use of tamoxifen for five years has shown to decrease mammographic breast tissue density (Slanetz et al., 2004). Nearly half of the women in the NSABP P-1 taking tamoxifen exhibited a decrease in tissue density, thus resulting in easier detection of mammographic abnormalities. In a study by Atkinson et al, 94 of 188 postmenopausal women reported a significant decrease in breast tissue density and it was concluded that this led to a reduced breast cancer risk. Women who do not show a decrease in breast tissue density while
taking tamoxifen for five years may be at a higher risk for recurrence or new primary tumors. The change in breast tissue density due to tamoxifen may signify which “SERM candidates will benefit most from prolonged treatment.”

Raloxifene is a SERM originally used to prevent osteoporosis and is now proven to prevent breast cancer in postmenopausal women (Grann et al., 2000). Raloxifene was tested in the Multiple Outcome of Raloxifene Evaluation (MORE) trial, which showed a 72% reduction in developing breast cancer (Slanetz et al., 2004); while Grann et al. found a 63% risk reduction in breast cancer development with raloxifene use. Additionally, patients undergoing chemoprevention reported having greater quality-adjusted life-years even when starting treatment at 40-50 years of age in comparison to women having prophylactic surgery. However, adjuvant chemotherapy increases survival by about eleven months in women with node-negative breast cancer and four months in women with node-positive breast cancer. Both prophylactic surgery and chemoprevention were less expensive than surveillance alone in terms of costs per year of life saved.

Aromatase is an essential enzyme involved in converting the adrenal androgens to estrogen (Ragaz, 1999). Therefore, Aromatase Inhibitors (AIs) cause estrogen levels to decrease and are an alternative to SERMs. Many research labs have proven that breast cancer tissue contains an increase in aromatase activity. New AIs are more selective and do not suppress aldosterone and glucocorticoid pathways. Tamoxifen is less effective and more harmful than AIs in the treatment breast cancer (Fatouros, Baltoyiannis, & Roukos, 2008). However, aromatase inhibitors are the better option in neoadjuvant chemotherapy in post-menopausal women. According to the ATAC (anastrozole, tamoxifen alone and combined) trial; anastrozole, an AI, is better at preventing contralateral breast cancer when compared to tamoxifen (Schiff, Chamness,
& Brown, 2003). One concerning side effect of AIs is a decrease in bone density (Fatouros et al.). Consequently, AIs must only be used in postmenopausal women receiving a continuous estrogen supply. In pre-menopausal women, the amount of estrogen produced is regulated by the pituitary and gonadotropin feedback loop. Therefore, AIs are not beneficial for pre-menopausal women.

Oral contraceptives were found to reduce the risk of women developing ovarian cancer by 54% while increasing the risk of breast cancer by 20% (Figure 5) (Grann et al., 2000). Additionally, hormone replacement therapy (HRT) has not been proven to demonstrate adverse effects in BRCA carriers as it can in the general population (Agnantis et al., 2004). The adverse effects include increased risk of breast cancer, coronary disease and thromboembolism. Also, since HRT displays an estrogen agonist effect in the breast, an increase in breast tissue density has been visualized on mammography in about 30% of women taking HRT (Slanetz et al., 2004). Such increase in density makes reading mammograms more difficult, thus reducing the sensitivity for screening.

**Prophylactic mastectomy, bilateral salpingo-oophorectomy, both**

Prophylactic surgery is superior to surveillance in preventing breast cancer in the clinical setting (Agnantis et al., 2004). Both BRCA carriers and oncologists have accepted the increased use of prophylactic surgery due to the high, 90%, protective effect. Table 1 compares the effects of surgical and surveillance prophylactic treatments for women with BRCA1 or BRCA2 mutations.

The question still remains as to which surgical procedure is superior. Removal of both breasts, ovaries and fallopian tubes results in the highest level of protection against breast cancer; however, this method is little to be desired by most women due to the high level of invasiveness
and complications (Agnantis et al., 2004). More commonly, women decide to have either a bilateral mastectomy (BM) or BSO, not both.

Prophylactic mastectomy is a preventive surgery performed in high risk women to reduce the likelihood of developing breast cancer and it is done prior to the diagnosis of breast cancer (ACS, 2007). Reasons to execute this procedure include BRCA1 or BRCA2 gene mutations, previous diagnosis of cancer, strong family history and lobular carcinoma in situ (LCIS) shown on biopsy. Nearly all of the breast tissue is removed, thus leading to a 90% breast cancer risk reduction (Gulati & Domchek, 2008). However, in a rare occurrence, a woman may develop cancer in the small amount of remaining breast tissue (ACS).

Bilateral salpingo-oophorectomy (BSO), another preventive surgery, involves the removal of both ovaries and fallopian tubes. Most breast tumors are caused by estrogen. BSO reduces the overall amount of estrogen in the body leading to a 53% decreased risk in developing breast cancer and 96% decrease in ovarian cancer (Agnantis et al., 2004). This decrease is due to the loss of the main estrogen supply, the ovaries (ACS, 2007). According to Eisen et al., breast cancer risk reduction seen with oophorectomy appears greatest when performed prior to age forty (Eisen et al., 2005). The risk reduction in breast cancer has been proven in patients with BRCA1 gene mutation even though most breast cancers due to BRCA1 are ER-negative (Gulati & Domchek, 2008). This is an important finding as BRCA1 patients do not respond to medications such as tamoxifen as effectively as BRCA2 patients due to the nature of the tumor receptors.

The low morbidity rate of BSO, 4% (Kauff et al., 2002), the ease of laparoscopic BSO along with the lack of reliable ovarian-cancer screening seems to persuade many women towards this procedure as opposed to BM (Agnantis et al., 2004). Bilateral salpingo-oophorectomy does
not eliminate the risk of breast and ovarian cancer completely as papillary serous carcinoma of the peritoneum (PSCP) can still occur (Domchek, Stopfer, & Rebbeck, 2006). PSCP is the presence of cancer on the peritoneal surface of the abdominal cavity. The mesothelial cells of the peritoneal tumor are identical to the cells in a papillary serous carcinoma of the ovary as both are from the same origin, yet an ovarian neoplasm is not present. Two to four percent of BRCA gene mutation patients develop PSCP after a prophylactic BSO.

Another point to note is that a remnant of the fallopian tube is left in the uterine wall when a BSO is performed (Domchek, Stopfer et al., 2006). Given that BRCA1 or BRCA2 mutation carriers are at an increased risk for fallopian tube cancer in comparison to the general population, one might consider a total abdominal hysterectomy at the time of the BSO.

Breast conserving surgery and mastectomy are commonly performed on non-hereditary forms of breast cancer (Agnantis et al., 2004). However, this is not the usual treatment in BRCA carriers as the remaining breast tissue including the contralateral breast are often sought after by the mutated BRCA genes.

**Other related cancers**

The lifetime risk factor for ovarian cancer is as high as 40% for women with BRCA1 mutation and up to 20% in BRCA2 mutation carriers (Gulati & Domchek, 2008). Screening for ovarian cancer is often ineffective. Transvaginal ultrasound and CA-125 cancer antigen levels detect ovarian cancer at a late stage. As mentioned previously, OCPs can decrease the risk of ovarian cancer by 50%, but a small increase in breast cancer results. Therefore, prophylactic oophorectomy is the most effective intervention for women with BRCA1 or BRCA2 gene mutations; thus, reducing the risk of developing ovarian cancer by 85% to 95% and breast cancer by at least 50%.
Timing is an important factor in performing an oophorectomy. Pre-menopausal women must be sure they are through bearing children before they elect to have this procedure performed. However, Prophylactic bilateral salpingo-oophorectomies (PBSOs) performed prior to the age 40 in women with a BRCA gene mutation are shown to have a larger risk-reduction compared to women with the same mutation after the age of 40 (Fatouros et al., 2008). Another factor for some women contemplating the procedure is that menopause is induced surgically. Gulati & Domchek referenced a study by Rebbeck et al. proving that short-term use of HRT, for 2-3 years, will not increase a woman’s risk of developing breast cancer if she has no prior history of breast cancer (2008). Annual endometrial screening is recommended to check for endometrial cancer in women taking short-term estrogen (Fatouros et al.).

**Findings**

1) *Breast cancer after prophylactic mastectomy in women with a BRCA1 or BRCA2 mutation*

The Meijers-Heijboer prospective study in 2001 examined the efficacy of the prophylactic bilateral mastectomy (BM) in BRCA carriers. There were a total of 139 participants, 76 underwent BM while the remaining 63 elected surveillance. The mastectomy group was modeled as a time-dependent covariate. After 2.9 ± 1.4 years, the treatment group revealed zero cases of breast cancer, while the surveillance group demonstrated eight cases of breast cancer after 3.0 ± 1.5 years had passed. The actual five year incidence rate among the surveillance group was 17 ± 7%. Therefore, when women with BRCA1 or BRCA2 gene mutations receive a prophylactic bilateral mastectomy, they will have a lower risk of developing breast cancer after three years (Meijers-Heijboer et al., 2001).

2) *Efficacy of Bilateral prophylactic mastectomy in women with a family history of breast cancer*
A retrospective study was conducted on women with a family history of breast cancer who underwent prophylactic bilateral mastectomy. This study was based on 639 patients at the Mayo clinic between 1960 and 1993. According to the women’s family history, two groups were formed, 214 at high risk and 425 at moderate risk. A control study comprised of the sisters of high risk patients and the Gail risk model, a formula used to identify breast cancer risk in patients, was also utilized to predict the amount of breast cancer cases if members in either group did not undergo surgery. After approximately 14 years, the Gail model projected 37.4 cases of breast cancer to be in the moderate risk group with four confirmed cases. Thus the risk declined by 89.5%. In the sisters of the high risk group members, 38.7% developed breast cancer; compared to 1.4% of the high risk women who underwent prophylactic mastectomy. This study shows that prophylactic mastectomy reduces the relative risk of developing breast cancer by 90% (Hartmann et al., 1999).

3) Surveillance behavior and prophylactic surgery after predictive testing for hereditary breast/ovarian cancer

The research performed by Claes et al. in 2005 included 34 carriers and 34 noncarriers of a BRCA1 or BRCA2 gene mutation. The participants’ chose between breast and ovarian cancer surveillance or prophylactic surgery and they were followed for one year after the genetic testing was performed. Nine percent of the carriers chose prophylactic mastectomy while the majority chose to continue surveillance. Following the test results, carriers increased adherence rates to mammography and clinical breast examination suggestions when compared to pre-test adherence rates. Carriers followed the recommendations more so than non-carriers (Figure 6) (Claes et al., 2005).
Discussion

Genetic testing is 90% effective when used appropriately in a population of high-risk women with a positive family history of breast cancer (Gulati & Domchek, 2008). Unfortunately, the common method used, multiplex ligation-dependent probe amplification, results in missing large genomic rearrangements in 1 of 10 women that undergo genetic testing. Thus, a woman may have a BRCA genetic mutation that has not been identified and must keep in mind that she may still be at an increased risk for breast cancer. However, the newer form of genetic testing, BRACAnalysis Rearrangement Test (BART), is utilized to detect the missed mutations (Gulati & Domchek). As a result, BART should become the standard for all high-risk individuals undergoing genetic testing for the BRCA1 and BRCA2 gene mutations.

Tamoxifen and raloxifene are both chemotherapeutic drugs with similar efficacies in preventing breast cancer; however their mechanisms of action differ. Raloxifene does not specifically target ER positive tumors, where tamoxifen does. In addition, aromatase inhibitors are only useful in postmenopausal women while they receive a continuous exogenous estrogen supply. Due to the fact that BRCA1 carriers fail to react to chemopreventive treatments and tamoxifen (Agnantis et al., 2004) surgical prevention is advisable. Whereas most BRCA2 patients have tumors that are receptive to estrogen, ER positive (Agnantis et al.) and therefore would respond to treatment with tamoxifen.

The study performed by Kauff et al. comparing the incidence of breast cancer in BRCA gene mutation carriers among those who chose increased surveillance compared to salpingo-oophorectomy has several flaws. The sample consisted of 170 women from only the New York area. The sample should include several geographic locations. In addition, the study only included women over the age of 35. Patients chose their own screening and preventive
interventions based on what was advised by physicians and staff. This could cause large variance in the results. The projected numbers of women who will not be diagnosed with breast cancer within five years are 69% in the surveillance group and 94% of the salpingo-oophorectomy group (Kauff et al., 2002). Despite the flaws in this study, the conclusions infer that surgical procedures offer greater protection against breast cancer than heightened surveillance.

A prospective study performed by Meijers-Heijboer et al. included 139 women ≥ to 25 years old with BRCA gene mutations who chose prophylactic bilateral mastectomy (PBM) or increased surveillance (2001). At a three year follow-up, eight of the 63 women in the surveillance group developed breast cancer; while all of the 76 participants in the PBM group remained cancer free. Again this study was limited to a specific population in the Netherlands. However, an important standardization and strong point of the study is that one practitioner performed all of the surgeries. Also, the individuals in the surveillance group all underwent the same regimen, monthly SBE, CBE every 6 months, yearly mammogram and MRI.

Prophylactic mastectomies do not eliminate future risks of breast cancer because the remaining breast tissue and other estrogen-receptor tissues are targeted by the mutated BRCA genes (Agnantis et al., 2004). Conversely, PBSO reduces the risk of both ovarian and breast cancer. PBSO is also associated with a better side-effect profile than prophylactic bilateral mastectomies (PBM) (Fatouros et al., 2008). On the other hand, the PBSO reduces breast cancer risk by 50% as compared to PBM reduction of 90% (Domchek, Stopfer et al., 2006). The studies show that the most effective treatments for hereditary breast cancer are PBSO in combination with the increase surveillance strategies listed above to detect breast cancer. Chemopreventive
agents may be used appropriately in conjunction with PBSO, but the medication should be chosen on a case-by-case basis as each has its limitations.

**Conclusion**

High-risk women should be encouraged to undergo genetic counseling and testing because the result may impact a woman’s decision regarding clinical management. Notification of the BRCA1 or BRCA2 mutation after genetic testing, causes a “significant impact on surgical decision-making among newly diagnosed breast cancer patients” (Schwartz et al., 2004) with emphasis placed on reducing the risk of developing an additional primary cancer (Gulati & Domchek, 2008).

With increased surveillance, high-risk women should have an annual MRI, annual mammography screenings, CBE every six months and SBE monthly (Gulati & Domchek, 2008). However, women with a BRCA gene mutation are more likely to undergo bilateral mastectomy than women who test negative or forgo testing (Schwartz et al., 2004). However, Domchek, Friebel et al. proved that PBSO is superior to PBM given that it reduces the risk of both breast and ovarian cancer and data reveals that PBSO decreases the overall death rate and cancer-specific mortality in women who have inherited mutations BRCA1 or BRCA2 (2006). In addition, PBM is correlated to higher morbidity and more side effects versus PBSO (Fatouros et al., 2008). Due to the fact that ovarian cancer is often diagnosed at such a late stage, experts recommend PBSO as the surgery of choice in preventing hereditary breast and ovarian cancer.

There is a current need for randomized trials directly evaluating surgical and nonsurgical prevention methods (Fatouros et al., 2008). For example, little data is available regarding primary prevention in the BRCA mutation carriers (Gulati & Domchek, 2008). Specifically, more research is required to determine the use of tamoxifen for chemoprevention of hereditary
breast cancer in women with BRCA1 or BRCA2 genes (Gulati & Domchek) and once this data is available, it should be compiled with the results from the NSABP-P1 trial. Additionally, there are no current statistics regarding the usefulness of raloxifene on those with BRCA1 or BRCA2 gene mutations (Gulati & Domchek). Trials regarding the use of aromatase inhibitors as primary prevention are being performed at the present time; (Gulati & Domchek) since the outcome is uncertain, there is a possibility of future research needed in this area as well.

Prevention strategy should ideally combine the best methods for cancer protection, survival and quality of life (Agnantis et al., 2004). Currently, published research suggests that surgical methods are superior as surgery offers greater than 90% risk reduction in comparison to increased surveillance (Fatouros et al., 2008). Prophylactic surgery does not treat the cause of the hereditary breast cancer, the mutated genes, but with removal of the targeted organs, it does lead to a lower risk of developing associated cancers and increased longevity (Agnantis et al.). In clinical practice however, the treatment is based on each patient’s personal preference.
References


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<td></td>
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<td></td>
<td>BRCA 2: ~50%</td>
</tr>
<tr>
<td>Reduction in ovarian and overall cancer risk</td>
<td>80-90%</td>
<td>0%</td>
<td>Screening: failure (late diagnosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary prevention: NA</td>
</tr>
<tr>
<td>Reduction in overall mortality</td>
<td>Hazard ratio .28 (95% confidence interval .10-.74)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Risk of late diagnosis</td>
<td>Breast: moderate</td>
<td>Breast: minimal</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Ovaries: minimal</td>
<td>Ovaries: very high</td>
<td></td>
</tr>
<tr>
<td>Morbidity (%)</td>
<td>Low (&lt;4%)</td>
<td>Moderate (10-30%)</td>
<td>No</td>
</tr>
<tr>
<td>Medication</td>
<td>Yes (HRT)</td>
<td>No</td>
<td>Yes (chemoprevention)</td>
</tr>
<tr>
<td>Adverse-effects profile on quality of life</td>
<td>Moderate (laparoscopic approach)</td>
<td>High</td>
<td>Minimal</td>
</tr>
</tbody>
</table>

Figure 1: Percentages of Breast Cancer and Ovarian Cancer in BRCA1 and BRCA2 mutation carriers

![Bar chart showing percentages of Breast Cancer and Ovarian Cancer in BRCA1 and BRCA2 mutation carriers.]

Figure 2: Likelihood of inheriting the breast cancer gene from a relative

![Line graph showing the likelihood of inheriting the breast cancer gene from a relative.]

Figure 3: Detection of Breast Cancer using MRI vs. Mammography

Figure 4: Kaplan-Meier Projections of Participants Cancer Free at 5 year Follow-up
Figure 5: Oral Contraceptives effect on the Risk of Ovarian Cancer and Breast Cancer

Figure 6: Compliance of Carriers vs. Non-carriers of BRCA gene mutation following current recommendations
Appendix A: Definitions

Bilateral Salpingo-oophorectomy – surgery to remove both ovaries and fallopian tubes

BRCA1, 2 genes - BRCA1, which stands for breast cancer gene one, early onset. The cytogenetic location is 17q21. BRCA2 stands for breast cancer gene two, early onset. The cytogenetic location is 13q12.3. The function of these genes is to keep breast cells growing normally and to prevent any cancer cell growth. But when these genes contain mutations, they are associated with an increased breast cancer risk.

Breast cancer - Breast cancer is a malignant tumor that originated from cells in the breast. This type of tumor has the potential of producing metastatic cancer in distant tissues and organs.

First degree relative - A family member who is one meiosis away from an individual (example: parent, sibling, offspring)

Gene mutation - mutation due to fundamental intramolecular reorganization of a gene

Hereditary breast cancer – cancer associated with genetic changes that occur only in breast cancer cells (somatic mutations). The way the breast cancer risk is inherited depends on the gene involved. Mutations in the BRCA1 and BRCA2 genes are inherited in an autosomal dominant pattern. The inheritance of breast cancer risk is unclear in other cases. People inherit an increased risk of cancer, not the disease itself. Not all people who inherit mutations in these genes will develop cancer.

Mastectomy - Surgical removal of a breast, sometimes including excision of the underlying pectoral muscles and regional lymph nodes. Also called mammectomy.

Second degree relative - A family member who is two meioses away from an individual or a relative who shares one-fourth of his/her genes with an individual (example: grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling)

Tamoxifen - An anti-estrogen drug that may be given to women with tumors that are positive for estrogen receptors. Thus, tamoxifen blocks estrogen from entering the breast tissues
Appendix B: Letter of Permission

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Abstract

OBJECTIVE: Given that 40% to 85% of patients with BRCA gene mutations will develop breast cancer, providers are concerned about which prophylactic methods are most effective to prevent the incidence of hereditary breast cancer. The purpose of this review was to evaluate the best preventive treatment methods for breast cancer and associated cancers in women with BRCA gene mutations according to peer-reviewed literature.

METHODS: A compilation of 15 peer reviewed journal articles, randomized controlled trials, literature review and clinical review articles between 1999 and 2008 were identified using Medline, PubMed and University of Toledo Electronic Journals.

CONCLUSION: Review of the literature revealed evidence indicating surgical interventions are superior to increased surveillance and preventive medications. Surgery offers more than 90% risk reduction in comparison to increased surveillance. Future research in this field is needed to conduct a direct comparison of surgical and nonsurgical prevention methods using randomized trials.