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Prophylactic mastectomy for the prevention of breast cancer

[Review]

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Abstract

Background: Breast cancer is the most common cancer and the second most common cause of cancer-related death among North American and Western European women. Recent progress in understanding the genetic basis of breast cancer, along with rising incidence rates, have resulted in increased interest in prophylactic mastectomy as a method of preventing breast cancer, particularly in those with familial susceptibility.

Objectives: The primary objective was to determine whether prophylactic mastectomy reduces death from any cause in women who have never had breast cancer and in women who have a history of breast cancer in one breast. The secondary objective was to examine the effect of prophylactic mastectomy on other endpoints including breast cancer incidence, breast cancer mortality, disease-free survival, physical morbidity, and psychosocial outcomes.

Search strategy: Electronic searches were performed in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Cancerlit, and the Science Citation Index.

Selection criteria: Inclusion criteria were studies in English of any design type including randomized or nonrandomized controlled trials, cohort studies, case-control studies, and case series with at least ten participants. Participants included women at risk for breast cancer in at least one breast. Interventions included all types of mastectomy performed for the purpose of preventing breast cancer, including subcutaneous mastectomy, total or simple mastectomy, modified radical mastectomy, and radical mastectomy.

Data collection and analysis: Information on patients, interventions, methods, and results were extracted by at least two independent reviewers. Methodological quality was assessed based on how well each study minimized potential selection bias, performance bias, detection bias, and attrition bias. Data for each study were summarized descriptively; quantitative meta-analysis was not feasible due to heterogeneity of study designs and insufficient reporting. Data were analyzed separately for bilateral prophylactic mastectomy (BPM) and contralateral prophylactic mastectomy (CPM).

Main results: Twenty-three studies, including more than 4,000 patients, met inclusion criteria. No randomized or nonrandomized controlled trials were found. Most studies were either case series or cohort studies. All studies had methodological limitations, with the most

common source of potential bias being systematic differences between the intervention and comparison groups that could potentially be associated with a particular outcome. Thirteen studies assessed the effectiveness of BPM. No study assessed all-cause mortality after BPM. All studies reporting on incidence of breast cancer and disease-specific mortality reported reductions after BPM. Nine studies assessed psychosocial measures; most reported high levels of satisfaction with the decision to have prophylactic mastectomy (PM) but more variable satisfaction with cosmetic results. Only one study assessed satisfaction with the psychological support provided by healthcare personnel during risk counseling and showed that more women were dissatisfied than satisfied with the support they received in the healthcare setting. Worry over breast cancer was significantly reduced after BPM when compared both to baseline worry levels and to the groups who opted for surveillance rather than BPM. Three studies reported body image/feelings of femininity outcomes, and all reported that a substantial minority (about 20%) reported BPM had adverse effects on those domains. Six studies assessed contralateral prophylactic mastectomy. Studies consistently reported reductions in contralateral incidence of breast cancer but were inconsistent about improvements in disease-specific survival. Only one study attempted to control for multiple differences between intervention groups, and this study showed no overall survival advantage for CPM at 15 years. Two case series were exclusively focused on adverse events from prophylactic mastectomy with reconstruction, and both reported rates of unanticipated re-operations from 30% to 49%.

Conclusions: While published observational studies demonstrated that BPM was effective in reducing both the incidence of, and death from, breast cancer, more rigorous prospective studies (ideally randomized trials) are needed. The studies need to be of sufficient duration and make better attempts to control for selection biases to arrive at better estimates of risk reduction. The state of the science is far from exact in predicting who will get or who will die from breast cancer. By one estimate, most of the women deemed high risk by family history (but not necessarily BRCA 1 or 2 mutation carriers) who underwent these procedures would not have died from breast cancer, even without prophylactic surgery. Therefore, women need to understand that this procedure should be considered only among those at very high risk of the disease.

For women who had already been diagnosed with a primary tumor, the data were particularly lacking for indications for contralateral prophylactic mastectomy. While it appeared that contralateral mastectomy may reduce the incidence of cancer in the contralateral breast, there was insufficient evidence about whether, and for whom, CPM actually improved survival.

Physical morbidity is not uncommon following PM, and many women underwent unanticipated re-operations (usually due to problems with reconstruction); however, these data need to be updated to reflect changes in surgical procedures and reconstruction.

Regarding psychosocial outcomes, women generally reported satisfaction with their decisions to have PM but reported satisfaction less consistently for cosmetic outcomes, with diminished satisfaction often due to surgical complications. Therefore, physical morbidity and post-operative surgical complications were areas that should be considered when deciding about PM. With regard to emotional well-being, most women recovered well postoperatively, reporting reduced cancer worry and showing reduced psychological morbidity from their baseline measures; exceptions also have been noted. Of the psychosocial outcomes measured, body image and feelings of femininity were the most adversely affected.

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Background

Breast cancer is the most common malignancy and second only to lung cancer as the major cause of cancer-related deaths among women in North America and Western Europe (Greenlee 2001). Moreover, the incidence of breast cancer is increasing (Greenlee 2001). About 15 million women in the United States alone seek medical attention every year because of concern about breast cancer.

Recent progress in understanding the genetic basis of certain breast cancers has led to increased interest in predicting cancer development and identifying women at high risk through the use of molecular methods. Women at high risk are particularly interested in preventing or reducing the risk of the subsequent development of breast cancer. Prophylactic mastectomy (PM) is among the alternatives usually offered for this purpose.

High-risk women who have no previous personal history of breast cancer may consider bilateral prophylactic mastectomy (BPM) as a means of primary prevention of the disease. Likewise, women who were previously diagnosed with a breast cancer in one breast and thus are at higher risk of developing a primary cancer in the other, or contralateral breast, may consider prophylactic mastectomy of that breast (contralateral prophylactic mastectomy or CPM) as an option to prevent the occurrence of a second breast cancer.

In the past, prophylactic mastectomy has been performed on women with any family history of breast cancer, painful breasts, cancer phobia, and history of breast biopsies (with or without proliferative disease). Recently, consideration for the procedure has tended to focus on women at high risk as determined by the identified presence of genetic mutations of the BRCA1 or BRCA2 genes, both of which are associated with increased risk of breast cancer, or by statistical models of risk such as the Gail model (Gail 1994) or other methods of estimating susceptibility. Most of the data used in this review did not allow subset identification by genetic testing.

As a preventive measure, prophylactic mastectomy remains controversial. Potential benefits include a reduction of risk of breast cancer and psychological peace of mind.

Potential disadvantages include the invasiveness of the procedure, and consequent morbidity. Previously, many PM surgeries were subcutaneous mastectomies, preserving the nipple-areola complex. Currently, the norm is to perform total mastectomies, removing all the tissue, the nipple, and the areola. A paradox now exists in which the surgical management of invasive breast cancer has become less radical, with the majority of women opting for breast conservation, while amputation of the breast is used for breast cancer prevention. Furthermore, no mastectomy can remove all breast tissue and, therefore, cannot eliminate all risk of breast cancer, even if this surgery is shown to be effective in reducing one's risk. In addition, prophylactic mastectomy may cause significant physical morbidity and/or affect women's quality of life. Further, because no test is available that can determine which 'high risk' women will actually develop breast cancer in the absence of the procedure, it is likely that many individuals will undergo PM needlessly. Likewise, prophylactic mastectomy is not the only alternative for women at high risk of breast cancer. Other possible options, of variable demonstrated efficacy, include chemoprevention with drugs such as tamoxifen (Fisher 1998), frequent surveillance with frequent clinical examinations and imaging studies, and/or oophorectomy.

Given the drastic and irreversible nature of prophylactic mastectomy, it is essential that women considering this procedure be able to make informed decisions based upon the best available evidence, consider both the benefits and limitations of the procedure, and weigh the risks and benefits of other alternatives.

This review evaluates the existing research literature on the effectiveness of prophylactic mastectomy in terms of overall mortality, breast cancer mortality, breast cancer incidence, disease-free survival, physical morbidity, and quality of life among both disease-free women and women with disease in one breast who have elective PM in the other non-diseased breast. There are some other reviews of the scientific literature concerning prophylactic mastectomy (Anderson 2001; Eisen 2000; Simmons 1997; Stefanek 2001). However, these reviews either have lacked a systematic search strategy, an assessment of methodological quality of the included studies, or a comprehensive scope including both physical and psychosocial outcomes.

Objectives

Primary objective:
to determine whether prophylactic mastectomy reduces death from any cause
* in women who have never had breast cancer
* in women who have a history of breast cancer in one breast.

Secondary objectives:

* to determine whether prophylactic mastectomy reduces breast cancer incidence and mortality
* to determine whether prophylactic mastectomy increases disease-free survival
* to examine the physical morbidity associated with prophylactic mastectomy
* to examine the quality of life, satisfaction, or other assessments of emotional or social function of women who undergo prophylactic mastectomy.

Criteria for considering studies for this review

Types of participants

Participants comprised women at risk from breast cancer. This included women with a positive family history of breast cancer, previous cancer in one breast, previous multiple breast biopsies, and previous diagnosis of lobular carcinoma in situ, atypical hyperplasia, or proliferative breast disease. A positive family history was defined by the authors of each reported study, and is the definitions are provided in the Table of 'Characteristics of included studies'.

Types of intervention

All types of prophylactic mastectomy were included, including subcutaneous mastectomy, total or simple mastectomy, modified radical mastectomy, and radical mastectomy.

Types of outcome measures

The primary outcome of this review is all-cause mortality.

Secondary outcomes are:
a) breast cancer mortality
b) breast cancer incidence
c) physical morbidity
d) quality of life (including satisfaction with the decision to have PM, satisfaction with cosmetic outcome, satisfaction with the medical process, psychological well-being, impact on body image, and impact on primary relationships and sexuality).

We did not pre-specify exclusion criteria related to duration of followup, but this information is available for each study in the summary table.

Types of studies

We searched for randomized trials as they provide the highest level of evidence. Because we knew it was unlikely that any would be found, we expanded our criteria to include studies of any design type including cohort, case control studies, and case series that had at least ten participants. Studies conducted during any time period and in any country were included but, because of limitations in our ability to read other languages, we only included studies reported in English.

Search strategy for identification of studies

The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2002) was searched for relevant studies on keywords "breast cancer prevention", "mastectomy", "prophylactic surgery", and "prophylactic mastectomy". Searches were performed of the electronic bibliographic databases MEDLINE and CancerLit (1966 to September 2002) (Table 01), and EMBASE (1974 to September 2002) (Table 02). In both search strategy tables the columns were combined using "and"; the rows were combined using "or". After the included studies were ascertained, these studies were entered into the Science Citation Index (SCI) to identify other studies that had cited those studies. The SCI lists were reviewed for additional relevant studies. Information about additional studies was obtained by reviewing reference lists of articles. A trained medical librarian developed and performed the searches.

Methods of the review

Two reviewers determined the eligibility of each study. Methodological quality was assessed for each eligible study. Statistical pooling was not performed due to lack of data and heterogeneity of study outcomes.

Description of the studies

Study Selection
The citation lists produced by the searches were divided into sublistings of a manageable size, and each was examined independently by at least two group members to determine

whether articles appeared to meet our inclusion criteria. Those two individuals resolved any differences by discussion. Copies of the articles that appeared to meet the inclusion criteria were obtained for closer examination, and two members of the group examined each. Two members of the group also examined information obtained about additional studies. The entire group reviewed all potentially eligible articles and made a final decision as to which should be included in the review.

Data collection and analysis

The entire group agreed upon uniform criteria for data abstraction before the process began. At least two group members independently examined and abstracted data from each article included in the review. The two members of the group resolved any differences by discussion. The entire group made final decisions as to presentation of the data in the review and the table of 'Characteristics of included studies'.

Because of the diversity of the included studies, it was not appropriate to statistically pool the data. Information is reported on study design, study population, interventions used, outcomes reported, and methodological study quality or possible biases. Women who have had breast cancer in one breast arguably were different from women who were at high risk but had never had breast cancer. Information, therefore, was presented separately on these groups. The type of mastectomy may be a predictor of the success of the procedure. Information, therefore, was also presented by type of mastectomy.

Methodological qualities of included studies

Methodological quality was assessed by three reviewers assessing whether or not the methods sufficiently minimized selection bias, performance bias, detection bias, and attrition bias (Clarke 2002). Selection bias was defined as systematic differences between comparison groups in prognosis or responsiveness to treatment. Typically, randomization is the method used to reduce selection bias. However, in observational studies, controlling for variables that may influence the results is the major way to reduce selection bias. Performance bias was defined as systematic differences in care provided apart from the intervention being evaluated. Detection bias was defined as systematic differences between comparison groups in how outcomes were ascertained, diagnosed or verified. Attrition bias was defined as systematic differences between comparison groups in withdrawals or exclusions of participants from the results of a study.

For studies with a comparison group (cohort studies or case series with a statistically modelled comparison group), we used the following questions to operationalize the above definitions:

(1) Selection bias: Were key risk/protective factors (confounders/co-interventions) adjusted for to ensure comparability between groups? Key risk/protective factors were identified from review articles on the topic. For breast cancer incidence, the following have been proposed to be important factors (Lise 1997): age, number of biopsies and histological status of previous biopsies, family history, use of other preventive options such as tamoxifen or oophorectomy, BRCA (breast cancer gene mutation) status, LCIS (lobular carcinoma in situ) status. For mortality, the following have been proposed as important prognostic variables (Chang 2003): age, stage at diagnosis, treatment, ER (estrogen receptor) status, HER2 status, and number of positive nodes. For incidence in contralateral studies, which is substantially affected by the features of the previous cancer, the following were considered important variables (Eisen 2000; Lopez 1996): stage of the previous carcinoma and the presence of multifocality in the ipsilateral breast, carcinoma in situ, atypical ductal or lobular hyperplasia in the remaining breast, strong family history of breast cancer, and BRCA mutation status, if known. For psychosocial studies, in which there are fewer known factors associated with both prophylactic mastectomy and outcome, the pre-existence of

psychological morbidity was deemed the major variable.

(2) Performance bias: Was the intervention (prophylactic mastectomy) confirmed in an objective way (i.e., medical or surgical records) and not determined exclusively by self-report?

(3) Detection bias: Was the outcome assessed in a valid way (e.g., validated pre/post instruments for psychosocial measures, medical records for incidence, medical/death records for vital status) and in the same way for both groups? Was the outcomes assessor masked to the treatment each patient received?

(4) Attrition bias: Was there a low dropout rate and/or were dropouts/withdrawals sufficiently accounted for so that the reviewer was convinced that differential reasons for dropping out did not occur?

For studies without a comparison group (convenience samples or case series without statistically modelled comparison groups), assessment questions for items 2 to 4 remained the same. However, selection bias (item 1) is a term that specifically pertains to assessing comparability between groups. Because there were no comparison groups in these studies we used the term 'preferential selection' for item 1 so as not to confuse the terminology with 'selection bias' used in studies with a comparison group. Item 1, preferential selection, asked the following question: was there evidence of a consecutive sample, or a clearly defined patient population (e.g., patients at a particular clinic at a particular time period) or some other method to minimize the chance that clinicians preferentially selected patients with favorable outcomes or that patients with better outcomes volunteered (healthy volunteer bias)?

From these checklists representing the four possible sources of bias, at least two reviewers rated all studies on all items. Results were compared and differences resolved by discussion to arrive at consensus (Table 03).

Classification of study designs
Various study designs were included and defined as follows:
(1) Case series: a report on a consecutive collection of patients treated in a similar manner without a concurrent control group (Haynes 1990).

(2) Convenience sample: individuals or groups selected at the convenience of the investigator or primarily because they were available at a convenient time or place (Haynes 1990).

(3) Prospective cohort study: a group of exposed and nonexposed individuals that have been followed over time to compare incidence (or rate of death from disease) between the groups (Gordis 1996). In prospective cohort studies, the recruitment, exposure/intervention, and outcomes must all have occurred after setting up the study.

(4) Retrospective cohort study: a group of exposed and nonexposed individuals that have been followed over time to compare incidence (or rate of death from disease) between the groups (Gordis 1996). In retrospective cohort studies, outcomes can have occurred prior to setting up the study or be collected afterwards, or both.

Results

Description of studies (table of 'Characteristics of included studies')
The search strategies identified 1,109 citations overall. Titles and abstracts of each study were reviewed by teams of two people. The majority of citations were excluded because the

citation did not appear relevant. Copies of 193 articles were retrieved and reviewed as possibly relevant. Of those, 22 articles involving 23 studies met the inclusion criteria and were included in this review. The remaining 171 articles are listed in the table 'Characteristics of excluded studies' with the reason for exclusion.

None of the studies involved controlled clinical trials, either randomized or nonrandomized. Of the 22 studies included, three studies (Hatcher 2001; Meijers 2001; Stefanek 1995) were prospective cohort studies. Five studies (Babiera 1997; Hartmann 1999; Lee 1995; Mulvihill 1982; Peralta 2000) were retrospective cohort designs. Twelve of the studies (Horton 1978; Hartmann 2001; McDonnell 2001; Pennisi 1987; Frost 2000; Gabriel 1997; Josephson 2000; Hopwood 2000; Zion 2000; Hartmann 1999; Evans 1999; Leis 1981) were quantitative case series studies. One study (Lloyd 2000) was a qualitative case series study using an in-depth interviewing technique. Two studies (Borgen 1998; Montgomery 1999) were a convenience sample. Additional features of each study (risk definitions, follow-up times, and attrition rates) are found in Table 04

Description of participants
Thirteen of the studies (Borgen 1998; Frost 2000; Hartmann 1999;[two studies in the same paper] Hartmann 2001; Hatcher 2001; Hopwood 2000; Josephson 2000; Lloyd 2000; Meijers 2001; Mulvihill 1982; Stefanek 1995; Zion 2000) involved women with no previous diagnosis of breast cancer who underwent bilateral prophylactic mastectomy to reduce their risk of getting breast cancer. Six of the studies (Babiera 1997; Lee 1995; Leis 1981; McDonnell 2001; Montgomery 1999; Peralta 2000) were of women with a previous diagnosis of breast cancer in one breast who underwent a prophylactic mastectomy of the contralateral breast to reduce the risk of getting a primary breast cancer in the other breast. Three studies (Evans 1999; Horton 1978; Pennisi 1987) included participants who had bilateral prophylactic mastectomies as well as some who had contralateral prophylactic mastectomies. One additional study (Gabriel 1997) did not specify whether the study participants had bilateral or contralateral prophylactic mastectomies.

Collectively, these studies presented data for 4,377 women who had prophylactic mastectomies. Participants in the studies of Frost 2000; Gabriel 1997; Hartmann 2001; McDonnell 2001; Zion 2000 were subsets of the participants in the Hartmann 1999 study. Care was taken not to count a participant more than once.

Of the 4,377 women, data were presented for 2,856 participants who had bilateral prophylactic mastectomies. The number of women involved in studies involving bilateral mastectomy and assessing physical outcomes was 2,310 (Hartmann 1999; Hartmann 2001; Horton 1978; Meijers 2001; Pennisi 1987; Zion 2000; Evans 1999); 1,058 women participated in studies looking at quality of life or other psychological or social outcomes (Frost 2000; Hatcher 2001; Hopwood 2000; Josephson 2000; Lloyd 2000; Montgomery 1999); and finally, 393 participants were involved in studies that presented information concerning both physical and psychological outcomes (Borgen 1998; Mulvihill 1982; Stefanek 1995).

The number of women participating in studies of contralateral mastectomy was 1,521 (Babiera 1997; Evans 1999; Horton 1978; Lee 1995; Leis 1981; McDonnell 2001; Montgomery 1999; Pennisi 1987; Peralta 2000). In one study involving 92 women, the type of mastectomy could not be determined (Gabriel 1997).

Description of outcomes
Only limited data were reported for all-cause mortality, the primary outcome for this review (Pennisi 1987; Peralta 2000). Instead, most available data were for secondary outcomes. Seven studies provided data for breast cancer mortality (Babiera 1997; Hartmann 1999 [2 studies in the same paper]; Lee 1995; Meijers 2001; Pennisi 1987; Peralta 2000). About half of the studies reported data concerning incidence of breast cancer (Babiera 1997; Borgen 1998; Evans 1999; Hartmann 1999; Hartmann 2001; Horton 1978; McDonnell 2001; Meijers 2001; Mulvihill 1982; Pennisi 1987; Peralta 2000).

Four studies included data for disease-free survival (Babiera 1997; Lee 1995; Leis 1981; Peralta 2000) and five reported data concerning physical morbidity (Gabriel 1997; Mulvihill 1982; Pennisi 1987; Stefanek 1995; Zion 2000). Nine studies reported data concerning quality of life, psychological morbidity, or other assessments of emotional or social function (Borgen 1998; Frost 2000; Hatcher 2001; Hopwood 2000; Josephson 2000; Lloyd 2000; Montgomery 1999; Mulvihill 1982; Stefanek 1995). One caveat: some papers on psychosocial outcomes may have been missed because PsychINFO was not searched.

Methodological quality of included studies (Table 03)

The methodological quality varied among studies. The most common source of potential bias was selection bias because most studies either did not adjust for potential confounding factors or failed to adjust for all of the major variables associated with a particular outcome. The results of these studies, therefore, were potentially confounded by other risk/protective factors. Performance bias (assessment of the prophylactic mastectomy) was generally not problematic as most studies were based on surgical reports and did not rely on self reports. The potential for detection bias varied among studies. Common sources of potential detection bias were recall bias in quality of life assessment (in which patients were asked, after PM, to rate their psychological status both before and after PM) and assessment of disease-free survival (in which regular intervals of follow up to detect recurrence of disease were not typically specified in CPM studies). Furthermore, studies generally did not report blinding/masking the study outcomes assessor or medical records extractor when determining cause of death from the medical record, another potential source of detection bias. Attrition bias was of concern in only a few studies as most studies accounted for all the participants in the initial sample they specified. However, in many cases there was no way to tell whether the number reported for the original cohort was correct.

Overall results

Participants who choose to undergo bilateral prophylactic mastectomy (BPM), to reduce the risk of having an initial breast cancer diagnosed, are almost certainly different in characteristics from those who already had an initial diagnosis of cancer in one breast and then choose contralateral prophylactic mastectomy (CPM) to reduce the risk of a primary breast cancer in the other breast. In light of this, we have reported the data for outcomes for BPM and CPM separately where possible.

A. Bilateral prophylactic mastectomy

As indicated above, 13 studies involved only participants who had bilateral prophylactic mastectomy.

1. All-cause mortality

None of the 13 studies reported all-cause mortality data.

2. Breast cancer (disease-specific) mortality (Table 04)

Three studies (Hartmann 1999 [2 studies in the same paper]; Meijers 2001) reported data concerning the effect of bilateral mastectomy on breast cancer mortality.

BRCA1 and BRCA2 mutations

In a prospective cohort design, Meijers 2001 reported that there was no death due to breast cancer among the 76 women who underwent BPM at three-years' follow-up, but there was one death among 63 women who chose surveillance.

High risk (Strong family history, but not necessarily BRCA 1 or 2 mutation carriers)

Hartmann 1999 followed 639 women at "high and moderate" risk of getting breast cancer. The median length of follow-up was 14 years. Of the 214 participants at "high risk" (as defined in Table 05) of breast cancer, two subsequently contracted and died of the disease, compared to 90 deaths in the control group (participants' sisters). Depending on the model used, the study reported an 81 to 94 % reduction in risk of dying from breast cancer following bilateral mastectomy.

Moderate risk

There were no deaths reported for the 425 participants in the "moderate risk" group (Hartmann 1999) compared to an expected 10.4 deaths using the Gail model. The reduction in risk for the "moderate risk" group, therefore, was 100 %.

3. Breast cancer incidence (Table 05)

Seven studies include data concerning the effects of bilateral prophylactic mastectomy on the incidence of breast cancer (Borgen 1998; Evans 1999; Hartmann 1999 [2 studies in the same paper]; Hartmann 2001; Meijers 2001; Mulvihill 1982). Two dealt with women who had BRCA 1 or 2 mutations, one dealt with high-risk women, one dealt with moderate-risk women, and the risk was unknown in three.

BRCA 1 and BRCA 2 mutations

Genetic testing for BRCA1 or BRCA2 mutations has been able to identify women who are considered at high risk for developing breast cancer for several years. The participants in two studies (Hartmann 2001; Meijers 2001) were women with BRCA1 or BRCA2 mutations. Hartmann 2001 reported no incidence of breast cancer (0 of 26) following BPM versus an expected incidence of 6 to 9 cancers in 26 women with BRCA1 or BRCA2 mutations. Various statistical models were used to estimate expected number of breast cancers and relative risk reduction, which ranged from 85% (95% CI 15.6% to 99.6%) to 100% (95% CI 54.1% to 100.0%). The follow-up time ranged from 5.8 to 28.5 years, with a median follow-up of 13.4 years.

Meijers 2001 conducted a prospective cohort study comparing BRCA1 or BRCA2 positive women choosing BPM with those choosing surveillance. There was a significant difference (0 of 76 versus 8 of 63, P=0.003) in incidence of breast cancer in the BPM group. Thus, the study reported a 100 % reduction in estimated risk of breast cancer incidence at three years of follow-up.

High risk. (Strong family history, but not necessarily BRCA 1 or 2 mutation carriers)

Hartmann 1999 used a retrospective cohort design to determine risk among the "high risk" group, with sisters acting as controls. High risk was defined as having a strong family history of breast cancer and did not exclude women with BRCA1 or 2 mutations. (See Table 04 for 'high-risk' criteria.) This study reported that 3 participants developed breast cancer after surgery compared to an expected incidence of 30 to 52.9 cancers. Thus, there was a 90 to 94% reduction in incidence for this group.

Moderate risk

In the same paper, Hartmann 1999 compared incidence from a case series to expected incidence using the Gail model for moderate-risk women, and this approach indicated significantly reduced incidence of breast cancer following surgery. Among the "moderate risk" group, 4 participants later developed breast cancer, compared to an estimate of 37.4 based on the Gail model, a reduction of 89.5 %. The median follow-up for all participants was 14 years, with 99% followed for at least 2 years.

The three remaining studies did not provide detail on risk assessment. Evans 1999 used a case series and compared actual incidence to expected incidence based on the Claus model, but this follow-up time was short, only 2.2 years. Mulvihill 1982 reported no incidence of breast cancer among the 9 subjects who had bilateral prophylactic surgery and 4 who had counseling only. This case series study made no approximation of risk reduction using a statistical model and included some women who would not be considered at risk today. The follow-up period for this study ranged from 1 to 12 years. Borgen 1998, in a convenience sample, reported that 3 of 370 women having prophylactic bilateral mastectomy, or less than 1%, subsequently were diagnosed with breast cancer. Follow-up ranged from 0.2 to 51.5 years with a mean of 14.8 years.

4. Disease-free survival

None of the studies reported data concerning disease-free survival following bilateral prophylactic mastectomy.

5. Physical morbidity (Table 06)

Two studies (Gabriel 1997; Zion 2000) focused on physical morbidity following BPM or CPM with breast reconstruction. Zion 2000 provided data on physical morbidity, defined as

unanticipated re-operations done for immediate postoperative complications following bilateral mastectomy with reconstruction; 290 of the 591 participants, or 49%, had unanticipated operations following the initial surgery. Reasons for the subsequent surgeries included the following: immediate postoperative complications (22%), implant-related issues (46%), and aesthetic concerns (32%). Further, 432 of 1182 (37%) original implants were removed with 90% being replaced.

Gabriel 1997 defined physical morbidity as "complications leading to unanticipated surgical interventions following breast implant." At five years, 34% (95% CI 27.2 to 41.3%) of cancer patients had complications compared to 30.4% (95% CI 23.1 to 38.4%) of women having prophylactic surgery and 12.0% (95% CI 9.1 to 15.2%) of women having implants for cosmetic reasons.

Two small case series (Mulvihill 1982; Stefanek 1995) also reported on physical morbidity. Stefanek 1995 found that 3 of 11 women who had reconstruction following BPM reported that the cosmetic results were "worse than expected." All three of them had silicone implants prior to the publicity about side effects of silicone. Two of these women had their implants removed due to rejection and subsequent infection. Mulvihill 1982 reported that all five women choosing BPM were enthusiastic about the operative results despite two having complications. One had two additional procedures due to infection and the other had severe contracture.

6. Psychosocial outcomes (Table 07)
Eight studies (Borgen 1998; Frost 2000; Hatcher 2001; Hopwood 2000; Josephson 2000; Lloyd 2000; Mulvihill 1982; Stefanek 1995) presented data concerning psychosocial outcomes (satisfaction with decision, satisfaction with cosmetic result, satisfaction with the medical process, or other assessments of emotional or social function). Data are derived from different sources ranging from subject-generated written responses to questionnaires to transcribed oral responses from in-depth personal interviews. The results of these studies varied.
a. Satisfaction with decision
None of these studies compared satisfaction with decision between women who chose surveillance and those who chose PM. Overwhelmingly, studies have found that women who have had BPM report satisfaction with their decision. Most of the women, when asked, said they would recommend the surgery to other women with the same risk (Stefanek 1995), would chose BPM again (Borgen 1998; Frost 2000), or had no regrets about their decision (Borgen 1998; Josephson 2000). Only a small minority of women reported dissatisfaction. Borgen 1998 found that 5% (21 of 370) of women in the study regretted their decision to have BPM. Regrets were more common among women reporting that the discussion of BPM had been initiated by the physician. Frost 2000 similarly found a correlation between dissatisfaction and listing physician's advice as the primary reason for BPM.
b. Satisfaction with cosmetic outcome
Cosmetic satisfaction generally pertained to satisfaction with breast reconstruction, and these results were less consistently favorable than satisfaction with the decision. Stefanek 1995 reported that, of the 11 of 14 who opted for breast reconstruction with BPM, 7/11 (64%) reported they were "quite a bit" or "very much" satisfied with the cosmetic results, 1 of 11 (9%) was "somewhat satisfied," and 3 of 11 (27.2%) were "dissatisfied," reporting their results were "worse than expected".

Frost 2000 reported similar findings to Stefanek's with 70% (393 of 562) either "satisfied" or "very satisfied" with BPM, 11% (69 of 562) neutral, and 19% (107 of 562) "dissatisfied" or "very dissatisfied." Although "satisfaction" in this study was a general question that could be interpreted by the respondent in any domain of satisfaction, the highest correlates to satisfaction were cosmetic results. For example, increased satisfaction with physical appearance and fewer problems with implants were highly significantly associated with BPM

satisfaction.

In a small Swedish case series, 13 of the 15 (87%) participants reported that the cosmetic results of their surgeries were better than expected (Josephson 2000). However, 53% (8 of 15) responded that they did not feel that their new breasts were part of their own body. Hopwood 2000 reported that 16% (7 of 45) required further psychiatric help following BPM, and the psychiatric distress was associated with surgical morbidity. Borgen 1998 reported 16% (52 of 331) found the cosmetic results of their BPM unacceptable.

Another important aspect of cosmetic satisfaction is the level of satisfaction among those women who opted for BPM without reconstruction. While the majority of women chose BPM with reconstruction, the minority who did not choose reconstruction appeared to be highly satisfied with their cosmetic decision. Stefanek 1995 found high satisfaction in the 3 of 14 women who did not undergo reconstruction. Similarly, Frost 2000 showed that choosing not to have reconstruction was highly correlated with satisfaction (P = 0.001).

c. Satisfaction with the medical process

Only one study (Josephson 2000) asked about patient satisfaction regarding the medical process of providing information and support. The aim of the study was to assess the degree to which the counseling procedure prepared women for BPM with immediate breast reconstruction. While satisfaction was high for most items, 10 of 15 (66%) reported being dissatisfied with the support they received during information sessions. The women found it difficult to translate the genetic information transmitted to them, reporting that they felt "blocked" from receiving the information.

d. Psychological well-being/ cancer-related anxiety

Hatcher 2001 reported that psychological morbidity for accepters (those who had BPM) decreased significantly (P = 0.04) postoperatively and less for decliners (those who decided not have BPM) in the same time period. Frost 2000 reported a diminished level of emotional concern about developing breast cancer in 74% (423 of 572) of those having BPM and neutral or favorable effects on emotional stability in 91% (520 of 572). In this same study, 86% (492 of 572) indicated no change or favorable effects on stress. Lloyd 2000 used qualitative interviews with 10 participants in order to identify the significant stages of the process of prophylactic mastectomy. These stages ranged from the initial decision to have the surgery, to "moving on" with one's life following the surgery, and all stages were superseded by an overarching theme of loss and suffering.

e. Body image/sexuality

Issues about sexuality and body image/femininity were addressed in many studies. Responses about sexuality ranged from no one reporting change in sexual activity or pleasure following BPM (Mulvihill 1982; Hatcher 2001), to 23% (132 of 572) reporting adverse effect on sexual relationships (Frost 2000), and 55.1% (27 of 49) reporting feeling less sexually attractive (Hopwood 2000). Furthermore, 23% (132 of 572) participants in the Frost 2000 study reported adverse effects in feelings of femininity, and 12% (6 of 49) of those in the Hopwood 2000 study reported moderate or much negative change in body image.

f. Impact on interpersonal relationship

Only one study (Josephson 2000) reported on impact on interpersonal relationships. In that small case series, 5 of 13 (38%) patients with partners indicated that their relationships with partners changed following surgery but did not specify how.

B. Contralateral prophylactic mastectomy

Five studies involved only participants with a previous diagnosis of breast cancer in one breast who chose to undergo a contralateral prophylactic mastectomy (CPM) in the other breast.

1. All-cause mortality (Table 08)

One study (Peralta 2000) reported data on 246 patients for overall survival at 15 years. Overall survival for participants having contralateral mastectomy was 64% (41 of 64) versus 48% (87

of 182) for those in the comparison group after controlling for multiple prognostic factors. This difference was not significant (P=0.26).

2. Breast cancer (disease-specific) mortality (Table 08)

Three studies (Peralta 2000; Lee 1995; Babiera 1997) provided data on breast cancer mortality, and the results were inconsistent among studies. All three studies were retrospective cohort studies comparing women who had chosen CPM to a group of women at the same clinical site who had elected not to undergo CPM. Only Peralta 2000 attempted to balance the two groups by adjustments in the analysis for multiple confounders. At 15 years of follow-up, there was a tendency toward improved disease-specific survival (P=0.06) only among the subgroup of patients with initial diagnoses of stage 0, 1 or 2 breast cancer: 71% (95% confidence interval 52% to 84%) versus 53 % (95% confidence interval 42% to 62%). Babiera 1997 found no disease-specific survival advantage at 5 years for patients with invasive lobular carcinoma. Lee 1995 reported a significant survival advantage for those who had CPM or biopsy in the contralateral breast at 15-year followup.

3. Incidence of breast cancer (Table 09)

Two studies (Peralta 2000; McDonnell 2001) reported data for contralateral breast cancer incidence after CPM, with both showing significantly lower breast cancer incidence in those who had CPM. Peralta 2000 reported that 0 of 64 participants who had prophylactic surgery subsequently developed contralateral breast cancer compared to 36 of 182 control patients (19.8%). This difference in incidence was significant (P=0.005).

McDonnell 2001 reported on a case series of 745 women (388 premenopausal, 357 postmenopausal) who underwent contralateral prophylactic surgery and were retrospectively followed for a median of 10 years. Eight of these women later developed breast cancer in the contralateral breast; 6 of the 8 were premenopausal. The expected contralateral incidence in premenopausal women, adjusted for treatment with tamoxifen and adjuvant therapy, was 106.2/388. Thus, the adjusted reduction in breast cancer incidence among premenopausal women was reported as 94.4%. Two of 357 postmenopausal women developed contralateral breast cancer following CPM. The expected incidence, adjusted for treatment with tamoxifen and adjuvant therapy, was 50.3 of 357, an adjusted reduction in breast cancer incidence of 96%. Unadjusted estimates of reductions in breast cancer risk were virtually the same. These estimated differences were all statistically significant (P<0.05).

4. Disease-free survival/ recurrence (Table 10)

Three studies (Babiera 1997; Leis 1981; Peralta 2000) reported varying results on data for disease-free survival. Follow-up intervals were not standardized in any of these studies for the groups. Therefore, no disease-free survival estimate has attempted to minimize the potential detection bias of the more frequently one looks, the more chances of finding something. Conversely, if one does not look, it can appear that the person has not relapsed (Johnson 2003).

Babiera 1997 showed that the five-year disease-free survival was 89% for participants receiving contralateral prophylactic mastectomy versus 90% for the control group. This difference was not statistically significant (P=0.98). Peralta 2000 reported that at 15 years, disease-free survival for the group receiving contralateral prophylactic surgery was 55% (95% CI=38% to 69%) compared to 28 % for the control group (95% CI 19% to 36%). The difference was statistically significant (P=0.01). Leis 1981 reported in a case series that, among 58 patients who were followed for 10 or more years, disease-free survival was 93.1% (54 of 58). Data were not reported for the 68 patients who received contralateral prophylactic mastectomy but were not followed for at least 10 years.

5. Physical morbidity

None of the studies reported data for physical morbidity.

6. Quality of life/psychological morbidity (Table 07)

One study (Montgomery 1999) presented data concerning quality of life, satisfaction with the

mastectomy, or other assessments of emotional or social function.

a. Satisfaction with decision

Montgomery 1999 reported the majority of women in the study were satisfied with their decision; only 6% (18 of 296) regretted their decision, with the cosmetic results being the number one reason cited. Regrets were less common in women with whom the discussion to have CPM was initiated by the physician than in women who initiated the discussion themselves. The study did not compare satisfaction with decision between women who chose surveillance and those who chose PM.

b. Satisfaction with cosmetic outcome

Montgomery 1999 reported that 16% (18 of 111) of those who had reconstruction found the cosmetic results of their reconstruction following CPM unsatisfactory.

As with BPM, there seemed to be correlation between satisfaction and reconstruction. Montgomery 1999 also found a correlation between having reconstruction and having regrets. The 185 women who opted not to have reconstruction after CPM had significantly less regret than the 111 who opted for reconstruction (p=0.01).

C. Combined bilateral and contralateral prophylactic mastectomy

Three studies (Horton 1978; Evans 1999; Pennisi 1987) included participants receiving BPM as well as participants receiving CPM. Collectively, the studies involved 1,782 participants; 1,595 of them` (89.5%) received bilateral prophylactic surgery, while 187 (10.5%) received contralateral mastectomy.

1. All-cause mortality

One study (Pennisi 1987) found that of the 70% of 1500 patients who were followed for 9 years, 0.3% died of "other causes." These are the only data provided concerning mortality from causes other than breast cancer. There are no data for all-cause mortality.

2. Breast cancer (disease-specific) mortality

One study (Pennisi 1987) reported simply that 3 of the 1,500 patients receiving prophylactic surgery subsequently died of breast cancer. Thirty percent of participants were lost to follow-up, however.

3. Incidence of breast cancer

All three studies reported data on breast cancer incidence, and all three reported few cases following prophylactic surgery. Horton et al. (1982) followed 104 women: 93 received bilateral mastectomy and 11 received contralateral mastectomy. No breast cancer developed in any participant following prophylactic surgery. Pennisi 1987 followed 1,500 participants: 1,361 received bilateral surgery and 139 received contralateral surgery. Six of the 1,500 participants (0.4%) developed breast disease following surgery. However, 30% of the participants were lost to follow-up. Evans reported data on 178 participants: 141 received bilateral surgery and 37 received contralateral surgery. No breast cancers developed after surgery in the participants who had prophylactic mastectomy, although the authors estimated that 4 cases would have been expected. Follow-up was less than five years.

4. Disease-free survival

None of the studies provided data concerning disease-free survival.

5. Physical morbidity

One study (Pennisi 1987) reported that 5% of patients receiving prophylactic surgery developed skin necrosis.

6. Quality of life/psychological morbidity

None of the studies presented data concerning quality of life, satisfaction with the mastectomy, or other assessments of emotional or social function.

Discussion

Bilateral prophylactic mastectomy incidence and mortality

The identification of gene mutations associated with breast cancer has resulted in renewed interest in BPM as a preventive therapy. Most of the data used in this review did not allow subset identification by genetic testing. As expected, our systematic review on BPM did not

identify any randomized controlled trials, nor is it likely that there will be any in the future. Although not optimal in terms of the reliability and validity of the information collected, a number of nonrandomized studies were available to assist women in the assessment of the effectiveness of the procedure. Consideration of other possible options of variable demonstrated efficacy, e.g., tamoxifen, oophorectomies, or simply surveillance, may also play a role in decision making.

The findings of the studies involving women with no previous history of breast cancer who underwent BPM were consistent in showing a reduced incidence of breast cancer and/or reduced breast cancer mortality, particularly in women at high risk for the disease. However, these findings should be taken in the context of the methodological limitations of the studies. The older studies included women who would no longer be considered high risk (Pennisi 1987; Mulvihill 1982; Horton 1978). Another study (Borgen 1998) recruited participants from ads in the public press and, therefore, posed the risk of healthy volunteer bias. Another study (Pennisi 1987) had a 30% attrition rate, posing the possibility of attrition bias. For other studies, follow-up times were of durations of less than five years (Meijers 2001; Evans 1999).

Furthermore, most studies lacked a comparison group. Three of the studies (Evans 1999; Hartmann 1999; Hartmann 2001) employed statistical modeling to simulate a comparison group, and this approach allowed the researchers to estimate the risk reduction attributable to BPM. These all found risk reductions in the PM group for both incidence and mortality.

Human data from breast reduction surgery adds biological plausibility to the theory that reducing the amount of breast tissue reduces the risk of breast cancer. Baasch 1996 reported on 1,240 women who had breast reduction surgery between 1943 and 1971 and who were followed until 1990. Using the number of breast cancers expected among Danish women, the study showed a risk reduction of 61% (95% CI 42% to 86%). The study also found that the reduction was greatest in women who had 600g or more of breast tissue removed. Similar results were obtained by Brinton 2001, who reported that women who had 800 grams or more of tissue removed per breast in breast reduction surgery had a 0.24 odds ratio (95% CI 0.1 to 0.05) of developing breast cancer. PM performed on rats has not shown any survival advantage from the procedure, but the relevance of the rodent model has been called into question (Eisen 2000; Winchester 1995).

In spite of these positive findings, there are some issues of which women considering this procedure should be aware. Women need to understand their true risk of developing breast cancer and dying from breast cancer. Among the 214 high-risk women (determined by family history but not necessarily BRCA1 or 2 mutation carriers) who underwent BPM in the Hartmann 1999 study, it has been estimated that most of the women would not have died from breast cancer in any case (Ernster 1999). Based on this, BPM is not a procedure that should be routinely considered by most women; rather, it is a radical surgical procedure to be considered only by those women at very high risk.

Contralateral prophylactic mastectomy incidence and mortality
Studies of CPM were also subject to methodological limitations leading to selection, detection, or attrition bias. Some studies (Leis 1981; Pennisi 1987; Montgomery 1999) had high dropout rates and lacked a comparison group. Lee 1995 combined in the study group women who had CPM with women who had a biopsy of the contralateral breast and thus, the risk exclusively for CPM women could not be ascertained. Efforts to control for important confounding factors varied among the studies. For example, McDonnell 2001 and Peralta 2000 used multivariate analyses to adjust for chemotherapy and tamoxifen therapy while only Peralta 2000 adjusted for stage of primary tumor.

Both of the studies assessing incidence of cancer in the contralateral breast while

controlling for chemotherapy and tamoxifen use (Peralta 2000; McDonnell 2001) reported markedly reduced incidences of breast cancer in the contralateral breast following CPM. This is consistent with the BPM findings and breast reduction surgery findings that reducing breast tissue can reduce risk of breast cancer incidence.

However, the most significant question about CPM is whether it improves survival for women who already have a diagnosis of breast cancer. Only one study (Peralta 2000) controlled for prognostic factors (e.g., features of the primary tumor) when assessing whether CPM improves survival. That study found no overall survival benefit at 15 years. When that same study assessed breast cancer (disease-specific) survival, there was a significant benefit only for the subgroup of patients with early stages of disease (stages 0, 1, 2). Thus, two of the three studies failed to control for most prognostic factors in spite of the fact that differences in baseline prognostic factors were noted between CPM and non-CPM patients.

Therefore, it is important to note that in women who have already been diagnosed with breast cancer, contralateral incidence reduction does not necessarily translate into survival advantage. This is because the risk of mortality from contralateral disease must always be weighed against risk of mortality from primary tumor metastases. "Patients at high risk for systemic spread of breast cancer may be inclined to request bilateral mastectomy to enhance their chance for survival. It is difficult, but necessary, to counsel patients that the risk of systemic disease far exceeds the risk of new ipsilateral or contralateral breast cancer" (Winchester 1995). Further caution is offered by Lise 1997 who recommend, "For women with previous breast cancer, their prognosis should be evaluated and if the risk of death from distant metastases exceeds that of a contralateral cancer, prophylactic mastectomy should not be considered."

Psychological and physical morbidity

The decision to have PM involves issues other than the surgical procedure. One of our objectives was to examine quality of life (QoL) issues postoperatively. For this group of studies, the most common methodological limitation was failure to address recall bias. About half of the studies (Borgen 1998; Frost 2000; Hopwood 2000; and Josephson 2000) collected only retrospective data, often asking patients to remember what their psychological state or body image was prior to surgery and comparing it with after surgery.

Another common limitation was that no study that assessed patient satisfaction reported having used a validated patient satisfaction instrument, and unvalidated patient satisfaction instruments have been known to overestimate the level of satisfaction (Ware 1988; Rubin 1991). No study assessing decision satisfaction had a control group of those who opted not to have PM. It is surprising that decision satisfaction was so high, especially since the authors of the largest study of 425 women at "moderate risk" have stated that many of the women in their moderate risk group would "not now be considered to have a markedly elevated risk of breast cancer" (Hartmann 1999a), and Stefanek 2001 has noted that it is not uncommon for a person to wonder if the surgery has been "wasted" (Newman 2001). While the high decision satisfaction may be real, it may also be due to positive response bias from cognitive dissonance, a phenomenon documented in unvalidated patient satisfaction measurements (Carr-Hill 1992) and an issue particularly relevant to surgical decision satisfaction (Homer 2000).

Within the methodological limitations mentioned above, some general trends can be observed. Generally, women reported satisfaction with their decisions to have BPM but were less consistent in satisfaction with cosmetic outcome; diminished satisfaction often was due to surgical complications. Therefore, physical morbidity and postoperative surgical complications should not be overlooked when making a decision about PM. Dissatisfaction with the decision to have BPM was correlated in two studies with either the discussion being initiated by the physician or the physician's advice to have BPM being the primary deciding

factor for the woman. Again, because decision satisfaction data were only collected postsurgically, we do not know the extent to which recall bias or cognitive dissonance influenced dissatisfied patients' recollections of the physician's role in decisionmaking. This correlation between regret and physician's role was not found to be true in the one CPM study that looked at regrets. Clearly, the primary motivation for having the procedure must come from the patient with the physician's role being to provide information on all available options without exercising undue pressure.

With regards to emotional well-being, most women recover well post-operatively, reporting reduced cancer worry and showing reduced psychological morbidity from their baseline measures (Hatcher 2001), but exceptions have been also noted.

In the end, this is a highly personal decision. Some women considering PM choose to live with a known risk of developing breast cancer. The comparison groups in many studies were women judged to be at high risk (using varying definitions of high risk) who were offered or considered undergoing BPM but opted not to have the surgery. The alternative of close surveillance was offered in most studies. Risk assessment and counseling were normally part of the decision-making process.

Summary

Overall, while a number of case series and retrospective cohort studies indicate that BPM is effective in reducing both incidence and death from breast cancer, various biases make it impossible to consider these findings reliable. The state of the science is far from exact in predicting who will get or die from breast cancer. By one estimate, most high-risk women, determined by strong family history but not necessarily BRCA 1/2 mutation carriers, who got BPM would not have died from breast cancer even without the surgery. Therefore, this procedure should be considered only for those at very high risk of the disease, e.g., women with BRCA1 and BRCA2 gene mutations.

The women who selected BPM tended to be more anxious and more likely to believe it was inevitable that they would develop breast cancer. The surgery tended to reduce anxiety in these women. However, given the number of the women who may be overtreated with BPM, it is critical that women and clinicians understand the true risk for each individual woman before considering surgery. Understanding their true risk, in and of itself, may reduce the anxiety and perception of inevitability of some of these women.

For women who have already been diagnosed with a primary tumor, the data were particularly lacking regarding indications for contralateral prophylactic mastectomy. While it appeared that contralateral mastectomy may reduce the incidence of cancer in the contralateral breast, there is insufficient evidence about whether, and for whom, CPM may actually improve survival.

Physical morbidity was not uncommon following PM and many women underwent unanticipated re-operations, usually due to problems with reconstruction. These data should be updated to reflect changes in surgical procedures and reconstruction.

Regarding psychosocial outcomes, women generally reported satisfaction with their decision to have PM, but were less consistently favorable regarding the cosmetic outcome. Often, diminished cosmetic satisfaction was associated with surgical complications and/or reconstruction. Therefore, physical morbidity and postoperative surgical complications are an area that should not be overlooked when making a decision about PM. Patient satisfaction was the least favorable regarding level of support provided by healthcare practitioners when providing risk assessment information. Further research needs to focus on how to make this information more understandable and how to minimize patients' stress when receiving it.

With regards to emotional well-being, most women recover well postoperatively, reporting reduced cancer worry and showing reduced psychological morbidity from their baseline measures, but exceptions were also noted. Of the psychosocial outcomes measured, body image and feelings of femininity were the most often adversely affected.

Conclusions

Implications for practice

Even if evidence from randomized trials existed to support a large benefit, prophylactic mastectomy is such an extreme intervention that a single recommendation for practice is probably not appropriate. Given the available evidence, if PM is considered at all, it should only be considered by women at the very highest risk (e.g., BRCA mutation carriers with high-penetrance mutations). The most important practice implications of these findings are that providers (1) should provide understandable and complete information for patients who are making their decision about whether to have PM, and (2) should ensure psychosocial support of the patient throughout the process.

Informational decision making

Stefanek 1995 reported that women have anecdotally said that the decision-making phase was the most difficult. Studies show that many women considering PM can highly overestimate their risk of disease (Stefanek 1995; Metcalf 2002). Women considering BPM should not only understand the risk of breast cancer, but also understand that, by one estimate, most of women having BPM would not have died from breast cancer even without having the surgery. Women considering contralateral PM after a primary diagnosis of breast cancer should understand that there are no good long-term data to indicate CPM will improve survival.

There is often confusion about what 'risk' means. It is important, therefore, to make sure that 'risk' is translated into understandable terminology. There is, for example, often confusion between absolute risk and relative risk. Absolute risk is the chance of developing breast cancer during a specified time. It is often expressed as the cumulative risk, i.e., the sum of the annual risks to a specific point in time. Relative risk expresses the comparison of the rate of disease in the population with the exposure under investigation against the rate in an unexposed but otherwise similar group" (Sakorafas 2002). As an illustration, if a woman who has an absolute risk of 2% for getting breast cancer over the next five years has her risk cut in half, the relative risk reduction would be 50%, while the absolute risk reduction would go from 2% to 1%.

Also, because both subcutaneous and total mastectomies result in incomplete removal of all breast tissue, it is important that women know breast cancer can still occur after PM (Eisen 2000). Therefore, what has been referred to as prophylactic mastectomy is more accurately termed 'risk reducing surgery' and should be discussed in the context of other options. Finally, women need to know that morbidity resulting in unanticipated re-operations is not uncommon (Zion 2000).

Psycho-social support

Beyond the informational needs, there is an emotional dimension to PM, and Lloyd 2000 suggest psychological support should be part of the entire process from decision making to resuming life after surgery. These views are supported by findings that there are some differences between women who select BPM (accepters) and those that consider it but do not choose to have a BPM (decliners). Those selecting BPM exhibit more anxiety -relieving behavior including doing more frequent breast self-examinations (Stefanek 1995), undergoing genetic testing more often (Hatcher 2001), and deciding to undergo prophylactic oophorectomy more often (Meijers 2001). Some studies (Mulvihill 1982; Stefanek 1995; Hatcher 2001) reported that

women selecting BPM were more anxious and were more likely to feel it was inevitable that they would get breast cancer than decliners.

During the decision-making phase, it may be important to emphasize that this is not an urgent decision, not a medical emergency, and that women can take their time in assimilating information and talking it over with others (Stefanek 1995). Having psychological counseling and ongoing support groups available throughout the decision-making and postoperative adjustment periods is also commonly recommended. Clearly women need information and psychosocial support during decision making as well as after surgery.

Implications for research

The benefits of BPM relative to chemoprevention are unclear because there are no prospective, randomized trials comparing the two. RCTs are needed (Palmieri 1999); however, some believe it is unlikely that a randomized controlled trial will ever be done given the radical nature of the procedure.

In the absence of RCTs, research can be improved by the use of population-based, prospective data that are collected on all women such as in the Scandinavian prospective cohort study (Meijers 2001). Such studies should adequately adjust for other variables that may influence the outcome, include morbidity data, and have sufficient follow-up time. As a short-term goal, authors of the included studies are encouraged to update their findings and control for major confounders in the analyses, a major limitation of the published studies thus far.

Establishing a PM registry, which includes all cases of prophylactic mastectomy and certain details about those undergoing the procedure, has been proposed by some as a way to glean important PM information in the absence of an RCT (Borgen 1998; Fentiman 1998; Weber 1995; Palmieri 1999). We do not recommend such a registry at this time given the absence of adequate legal protections governing privacy and confidentiality. Without adequate legal protections, inclusion in such a registry could have adverse consequences for participants and possibly their families with respect to insurance and employment discrimination. Similar legal issues could exist for the establishment, in conjunction with a registry, of a tissue bank that would shed light on whether certain mutations are most likely to manifest in breast cancer in spite of PM.

In the psychosocial research domain, there needs to be more understanding of the emotional impact on women of having the surgery in order to better support those women who choose it. "Emotionally, the operation invoked an extreme sense of loss in terms of sexuality and femininity. This sense of loss was linked to the lack of sensation in my breasts" (Eeles 1996). Future research could also focus on developing a screening tool that can predict those who are at risk for high emotional distress and, hence, may need additional supportive services.

Little is reported about the psychosocial impact of BPM and CPM on the people who have primary relationships with women undergoing the surgery. While a high-risk woman may accept and adjust to the cosmetic and sexuality side effects of PM for the peace of mind it offers, how her partner adjusts is unknown. Future studies should include interviews with those in primary relationships with women undergoing PM. Finally, the study finding by Josephson 2000 that most women were dissatisfied with the psychological support provided by healthcare personnel during risk counseling demonstrated that little is known about what creates an optimal counseling and decision-making environment.

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Potential conflict of interest

None.

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Contribution of Reviewer(s)

L Lostumbo reviewed articles for inclusion, extracted data from articles, created the tables, contributed conceptually to the formation of the paper, assessed the methodological quality of included studies, wrote and edited sections of the manuscript, and oversaw the administrative aspects of the paper.

N Carbine reviewed articles for inclusion, contributed conceptually to the formation of the paper, edited the paper, and participated in all key discussions regarding the paper.

J Wallace reviewed articles for inclusion, contributed conceptually to the formation of the paper, assessed the methodological quality of included studies, and participated in all key discussion regarding the paper.

J Ezzo reviewed articles for inclusion, contributed conceptually to the formation of the paper, assessed the methodological quality of included studies, wrote and edited pieces of the manuscript, and participated in all key discussions.

Synopsis

Women should be aware of their true risk of developing breast cancer and the limitations of current evidence when considering prophylactic mastectomy

Surgically removing both breasts to prevent breast cancer (bilateral prophylactic mastectomy or BPM) may reduce the incidence of breast cancer and improve survival in women with high breast cancer risk, but the studies have methodological limitations. After BPM, most are satisfied with their decision, but less satisfied with cosmetic results and body image. Many required additional surgeries. Most experience reduced cancer worry, but because women may overestimate their breast cancer risk, they need to understand their true risk if considering BPM. In women who have had cancer in one breast (and thus are at higher risk of developing a primary cancer in the other) removing the other breast may reduce the incidence of cancer in that other breast, but there is insufficient evidence that this improves survival.

Characteristics of included studies

Study: Babiera 1997

Methods: Retrospective cohort study

Participants: Family history/Risk - not reported

Interventions: CPM (modified radical mastectomy for primary ILC) =18

Comparison group: surveillance of the contralateral breast=115

Outcomes: Breast cancer incidence

Disease-specific survival

Notes:

Allocation concealment: D

Study: Borgen 1998

Methods: Convenience Sample

Participants: Family history/Risk - 220 (69%) reported having at least one 1st degree relative with breast cancer

Interventions: BPM=370

Outcomes: Quality of life

Breast cancer incidence

Notes:

Allocation concealment: D

Study: Evans 1999

Methods: Case series

Participants: Family history/Risk - women with a lifetime risk of breast cancer ranging from 25-80% using the Claus data

Interventions: BPM =141

CPM=37

Comparison group: Statistically modeled group based on the Claus model presuming no PM.

Outcomes: Breast cancer incidence

Notes:

Allocation concealment: D

Study: Frost 2000

Methods: Case series

Participants: Family history/Risk - all had a family history of breast cancer.

35% high risk - had a pedigree consistent with a single-gene autosomal dominant predisposition to breast cancer

65% - moderate risk

Interventions: BPM=609

Outcomes: Quality of life

Notes:

Allocation concealment: D

Study: Gabriel 1997

Methods: Case series

Participants: Patients having breast implant surgery. Family history/Risk - not reported

Interventions: Breast implant surgery

from PM=92

from cancer=125

for cosmesis=532

Outcomes: Physical morbidity

Notes:

Allocation concealment: D

Study: Hartmann 1999

Methods: Case Series and Retrospective cohort study

[1 paper, 2 studies]

Participants: Family history/Risk - all with a family history of breast cancer were included.

Interventions: BPM (subcutaneous or total)=639

High risk=214

Comparison group: Sisters without BPM=403

Moderate risk=425

Comparison group: Statistically modeled group based on Gail model presuming no BPM

Outcomes: Breast cancer incidence

Breast cancer mortality

Notes:

Allocation concealment: D

Study: Hartmann 2001

Methods: Case series

Participants: Patients who tested positive for BRCA1 or BRCA2 mutations.

Interventions: Treatment: BPM =26

Comparison group: Statistically modeled group using Struewing and Easton models presuming no BPM.

Outcomes: Breast cancer incidence

Notes:

Allocation concealment: D

Study: Hatcher 2001

Methods: Prospective cohort study

Participants: Family history/Risk - all had a family history of breast cancer or other high risk factors (undefined)

Interventions: BPM= 79

Comparison group: Surveillance=64

Outcomes: Quality of life

Notes:

Allocation concealment: D

Study: Hopwood 2000

Methods: Case series

Participants: Family history/Risk - women who had a > 1:4 lifetime risk of breast cancer

Interventions: BPM (subcutaneous with nipples preserved)=49

Outcomes: Quality of life

Notes:

Allocation concealment: D

Study: Horton 1978

Methods: Case series

Participants: Family history/Risk - not reported

Interventions: BPM=93

CPM=11

Outcomes: Breast cancer incidence

Notes:

Allocation concealment: D

Study: Josephson 2000

Methods: Case series

Participants: BPM and immediate reconstruction between 4/93 and 3/97.Family history/Risk - all with >20% risk of developing breast or ovarian cancer

Interventions: BPM with genetic counseling=17

Outcomes: Quality of life

Decision making process

Notes:

Allocation concealment: D

Study: Lee 1995

Methods: Retrospective cohort study

Participants: Family history/Risk:

CPM: 14/84 (13%) had a family history of breast cancer (undefined)

Comparison group: 28/299 (9%) had a family history of breast cancer (undefined)

Interventions: CPM =84

Undirected contralateral biopsies=21

Comparison group: Surveillance with no CPM=299

Outcomes: Breast cancer survival

Notes:

Allocation concealment: D

Study: Leis 1981

Methods: Case series

Participants: Family history/Risk - all high risk (undefined)

Interventions: CPM=127

Outcomes: Disease-free survival

Notes:

Allocation concealment: D

Study: Lloyd 2000

Methods: Case series

Participants: Family history/Risk- risk due to familial breast cancer. Women who had no previous diagnosis of breast cancer, DCIS or LCIS, and who were between 6 weeks and 3 years post-op.

Interventions: BPM=10

Outcomes: Quality of life

Notes:

Allocation concealment: D

Study: McDonnell 2001

Methods: Case series

Participants: Family history/Risk - all with a first breast cancer, who had a family history of breast or ovarian cancer.

Patients underwent CPM between 1960 and 1993.

388 = pre-menopausal

357 = post-menopausal

Interventions: CPM (41% subcutaneous, 59% total)=745

Comparison group: Simulated from age-adjusted life tables presuming no CPM.

Outcomes: Breast cancer incidence

Notes:

Allocation concealment: D

Study: Meijers 2001

Methods: Prospective cohort study

Participants: 139 women who had BRCA 1 or 2 mutations

Interventions: BPM (simple total)=76

Comparison group: Close observation = 63

Close observation= monthly breast self-examination, clinical breast examination every 6 months, and yearly mammography

Outcomes: Breast cancer incidence

Breast cancer mortality

Notes:

Allocation concealment: D

Study: Montgomery 1999

Methods: Convenience sample

Participants: Family history/Risk - 30% reported having at least one 1st degree relative with breast cancer

Interventions: CPM =296

Outcomes: Quality of life

Notes:

Allocation concealment: D

Study: Mulvihill 1982

Methods: Retrospective cohort study

Participants: Family history/Risk - all members of high-risk families with apparent excess

of breast cancer

Interventions: BPM=9

Comparison group: Counseling/surveillance=4

Outcomes: Quality of life

Breast cancer incidence

Notes:

Allocation concealment: D

Study: Pennisi 1987

Methods: Case series

Participants: Family history/Risk - not reported

Interventions: BPM (subcutaneous)=1361

CPM=139

Outcomes: Breast cancer incidence

Breast cancer mortality

Notes:

Allocation concealment: D

Study: Peralta 2000

Methods: Retrospective cohort study

Participants: Family history/Risk - CPM

- 23 (36%) had at least one 1st degree relative with breast cancer

19 (29%) had at least one 2nd degree relative with breast cancer

Comparison group:

- 35 (19.5%) had at least one 1st degree relative with breast cancer

-47 (26.1%) had at least one 2nd degree relative with breast cancer

Interventions: CPM=64 with primary breast cancer

Comparison group: primary breast cancer and no CPM= 82

Outcomes: Breast cancer incidence Disease-free survival

Breast cancer survival

All-cause survival

Notes:

Allocation concealment: D

Study: Stefanek 1995

Methods: Case series

Participants: Family history/Risk - all had at least one 1st degree relative with breast cancer

Interventions: BPM=14

Interested but decided against BPM=92

Not interest ed in BPM=58

Outcomes: Quality of life

Physical morbidity

Notes:

Allocation concealment: D

Study: Zion 2000

Methods: Case series

Participants: Family history/Risk - had a family history of breast cancer (undefined)

Interventions: BPM and breast reconstruction=591

Outcomes: Physical morbidity

Notes:

Allocation concealment: D

Key to abbreviations:

BPM - bilateral prophylactic mastectomy

CPM - contralateral prophylactic mastectomy

DCIS - ductal carcinoma in situ

ILC - invasive lobular cancer

LCIS - lobular carcinoma in situ

PM - prophylactic mastectomy

Characteristics of excluded studies

Study: Amaaki 1979

Reason for exclusion: Surgical technique article

Study: Anderson 2001b

Reason for exclusion: No original patient data

Study: Anonymous 1983

Reason for exclusion: No original patient data

Study: Anonymous 1991

Reason for exclusion: No original patient data

Study: Anonymous 1995

Reason for exclusion: No original patient data

Study: Ariyan 1985

Reason for exclusion: No original patient data

Study: Baasch 1996b

Reason for exclusion: On breast reduction surgery

Study: Beller 1986

Reason for exclusion: On the incidence of contralateral occult breast cancer

Study: Bergeson 1993

Reason for exclusion: Hypothetical case study

Study: Bilmoria 1995

Reason for exclusion: No original patient data

Study: Bilmoria 2002

Reason for exclusion: No original patient data

Study: Birkmeyer 1997

Reason for exclusion: No original patient data

Study: Bland 1996

Reason for exclusion: Surgical technique article

Study: Bohmert 1988

Reason for exclusion: On bilateral breast cancer

Study: Bostwick 1980

Reason for exclusion: Surgical technique article

Study: Bowers 1969

Reason for exclusion: Case study of 2

Study: Brinton 2001b

Reason for exclusion: Breast reduction surgery

Study: Bucholtz 2001

Reason for exclusion: No original patient data

Study: Buehler 1983

Reason for exclusion: About assessing risk

Study: Burke 1997

Reason for exclusion: Consensus statement

Study: Carenza 1980

Reason for exclusion: No original patient data

Study: Cheung 1997

Reason for exclusion: Surgical technique article

Study: Dawson 1998b

Reason for exclusion: Incidence of contralateral occult breast cancer

Study: Decker 1993

Reason for exclusion: No original patient data

Study: Dinner 1988

Reason for exclusion: No original patient data

Study: Dinner 1989

Reason for exclusion: Surgical technique article

Study: Dowden 1988

Reason for exclusion: Surgical technique

Study: Eeles 1996b

Reason for exclusion: Case report of 1

Study: Eisen 1999

Reason for exclusion: No original patient data

Study: Eisen 2000b

Reason for exclusion: No original patient data

Study: Ettelson 1993

Reason for exclusion: No original patient data

Study: Feldman 2001

Reason for exclusion: Case report

Study: Fentiman 1998b

Reason for exclusion: No original patient data

Study: Fisher 1988

Reason for exclusion: On breast cancer pathology

Study: Foster 1988

Reason for exclusion: About assessing risk

Study: Fredericks 1969

Reason for exclusion: Surgical technique article

Study: Fredericks 1975

Reason for exclusion: Surgical technique article

Study: Goin 1982

Reason for exclusion: Not a study

Study: Goldwyn 1977

Reason for exclusion: No original patient data

Study: Goodnight 1984

Reason for exclusion: Case study of 3

Study: Grady 1965

Reason for exclusion: Not about prophylactic mastectomy

Study: Grann 1998

Reason for exclusion: Mathematical simulation

Study: Grann 1999

Reason for exclusion: No original patient data

Study: Griffin 1993

Reason for exclusion: No original patient data

Study: Hamm 1999

Reason for exclusion: No original patient data

Study: Hartmann 1997

Reason for exclusion: Abstract of included article

Study: Herman 1977

Reason for exclusion: No original patient data

Study: Hettle 1980

Reason for exclusion: No original patient data

Study: Hoffman 1979

Reason for exclusion: Surgical technique

Study: Hoffman 1982

Reason for exclusion: About assessing risk

Study: Holgreve 1989

Reason for exclusion: On occult breast cancer at time of prophylactic mastectomy

Study: Holzman 1996

Reason for exclusion: No original patient data

Study: Horton 1988

Reason for exclusion: About assessing risk

Study: Houlihan 1991

Reason for exclusion: About assessing risk

Study: Houn 1995

Reason for exclusion: Physician survey

Study: Hubbard 1978

Reason for exclusion: No original patient data

Study: Humphrey 1983

Reason for exclusion: No original patient data

Study: Isaacs 1996

Reason for exclusion: On genetic testing

Study: Jackson 1984

Reason for exclusion: Animal study

Study: Jameson 1997

Reason for exclusion: Case study of 1

Study: Jarrett 1982

Reason for exclusion: Surgical technique article

Study: Jarrett 1988

Reason for exclusion: Surgical technique article

Study: Jarrett 1990

Reason for exclusion: Surgical technique article

Study: Johnson 1996

Reason for exclusion: On genetic testing

Study: Karp 1999

Reason for exclusion: On genetic counseling

Study: Kauff 2001

Reason for exclusion: On insurance reimbursement

Study: Kelly 1988

Reason for exclusion: About assessing risk

Study: Kesseler 1976

Reason for exclusion: On incidence of bilateral breast cancer

Study: Khouri 1997

Reason for exclusion: Surgical technique article

Study: Klijn 1997

Reason for exclusion: On genetic testing

Study: Klijn 1997b

Reason for exclusion: No original patient data

Study: Kroll 1998

Reason for exclusion: No original patient data

Study: Lanigan 1987

Reason for exclusion: Surgical technique article

Study: Lattes 1980

Reason for exclusion: About LCIS

Study: Leis 1971

Reason for exclusion: No original patient data

Study: Leis 1980

Reason for exclusion: On incidence of bilateral breast cancer

Study: Leis 1981b

Reason for exclusion: Surgical technique article

Study: Leis 1987

Reason for exclusion: No original patient data

Study: Leis1983

Reason for exclusion: No original patient data

Study: Lejour 1980

Reason for exclusion: Surgical technique article

Study: Lerman 1996

Reason for exclusion: On patient decision making

Study: Lise 1997b

Reason for exclusion: No original patient data

Study: Lopez 1996b

Reason for exclusion: No original patient data

Study: Lynch 1971

Reason for exclusion: 3 case reports

Study: Lynch 1978

Reason for exclusion: 2 case reports

Study: Lynch 1978a

Reason for exclusion: No prophylactic mastectomy data presented

Study: Lynch 1978b

Reason for exclusion: No original patient data

Study: Lynch 1980

Reason for exclusion: No original patient data

Study: Lynch 1988

Reason for exclusion: No original patient data

Study: Lynch 1991

Reason for exclusion: No original patient data

Study: Lynch 1993

Reason for exclusion: On genetic testing

Study: Lynch 1994

Reason for exclusion: Case reports

Study: Lynch 1997

Reason for exclusion: On genetic testing

Study: Mann 1998

Reason for exclusion: On genetic testing

Study: Massie 1998

Reason for exclusion: Case report

Study: Matton 1987

Reason for exclusion: Surgical technique article

Study: McAvoy 1979

Reason for exclusion: No original patient data

Study: McCaffrey 1993

Reason for exclusion: No original patient data

Study: McCraw 1980

Reason for exclusion: Surgical technique article

Study: McGuire 1981

Reason for exclusion: Surgical technique

Study: Metcalfe 2002

Reason for exclusion: No original patient data

Study: Metcalfe 2002b

Reason for exclusion: No original patient data

Study: Meyer 1986

Reason for exclusion: No original patient data

Study: Mofflat 1988

Reason for exclusion: No original patient data

Study: Mogelvang 1995

Reason for exclusion: No original patient data

Study: Morris 2001

Reason for exclusion: On genetic counseling

Study: Mulliken 1984

Reason for exclusion: No original patient data

Study: Nelson 1989

Reason for exclusion: No original patient data

Study: Nelson 1997

Reason for exclusion: No original patient data

Study: Nemecek 1993

Reason for exclusion: No original patient data

Study: Orlando 1997

Reason for exclusion: No original patient data

Study: Osteen 1995

Reason for exclusion: Surgical technique

Study: Palmieri 1999b

Reason for exclusion: No original patient data

Study: Payne 2000

Reason for exclusion: No original patient data

Study: Pennisi 1975

Reason for exclusion: On incidence of occult breast cancer with prophylactic mastectomy

Study: Pennisi 1976

Reason for exclusion: On fibrocystic disease

Study: Pennisi 1977

Reason for exclusion: No original patient data

Study: Pennisi 1981

Reason for exclusion: Surgical technique article

Study: Pennisi 1984

Reason for exclusion: More recent data on same study included in review

Study: Pennisi 1986

Reason for exclusion: No original patient data

Study: Perez 1979

Reason for exclusion: Surgical technique article

Study: Peterson 1996

Reason for exclusion: On chromosomal aberation detection

Study: Petit 2002

Reason for exclusion: No original patient data

Study: Pilch 1983

Reason for exclusion: Surgical technique article

Study: Piver 1998

Reason for exclusion: No original patient data

Study: Polednak 2001

Reason for exclusion: No original patient data

Study: Radford 1996

Reason for exclusion: No original patient data

Study: Remmel 2002

Reason for exclusion: No original patient data

Study: Ringberg 1982

Reason for exclusion: On incidence of occult contralateral breast cancer

Study: Romm 1981

Reason for exclusion: 9 case reports

Study: Rosato 1976

Reason for exclusion: Surgical technique article

Study: Rosato 1980

Reason for exclusion: Not in English

Study: Rubin 1979

Reason for exclusion: Surgical technique article

Study: Rubin 1984

Reason for exclusion: Surgical technique article

Study: Sakorafas 2002b

Reason for exclusion: About assessing risk

Study: Sandelin 1998

Reason for exclusion: 2 cases of prophylactic mastectomy

Study: Schechter 1985

Reason for exclusion: No original patient data

Study: Schlenker 1978

Reason for exclusion: No original patient data

Study: Schrag 1997

Reason for exclusion: Hypothetical cohort

Study: Schwartz 1983

Reason for exclusion: No original patient data

Study: Seidman 1983

Reason for exclusion: No original patient data

Study: Simmons 1997b

Reason for exclusion: No original patient data

Study: Singletary 1994

Reason for exclusion: On contralateral breast cancer

Study: Snyderman 1984

Reason for exclusion: Surgical technique article

Study: Snyderman 1984b

Reason for exclusion: Surgical technique article

Study: Snyderman 1984c

Reason for exclusion: Surgical technique article

Study: Stefanek 1995b

Reason for exclusion: Pertains to study already included

Study: Stefanek 2001b

Reason for exclusion: No original patient data

Study: Stephenson 1997

Reason for exclusion: No original patient data

Study: Stoll 1989

Reason for exclusion: No original patient data

Study: Teixeira 1996

Reason for exclusion: 4 case reports

Study: Temple 1985

Reason for exclusion: No original patient data

Study: Temple 1991

Reason for exclusion: Surgical technique article

Study: Theogaraj 1973

Reason for exclusion: Surgical technique article

Study: Todd 1977

Reason for exclusion: No original patient data

Study: Unic 1998

Reason for exclusion: About assessing risk

Study: Vorherr 1982

Reason for exclusion: No original patient data

Study: Walton 1986

Reason for exclusion: Case report

Study: Wapnir 1990

Reason for exclusion: No original patient data

Study: Weber 1995b

Reason for exclusion: No original patient data

Study: Winchester 1995b

Reason for exclusion: No original patient data

Study: Wolmark 1985

Reason for exclusion: No original patient data

Study: Wong 1986

Reason for exclusion: Animal study

Study: Woods 1976

Reason for exclusion: Surgical technique article

Study: Woods 1983

Reason for exclusion: No original patient data

Study: Woods 1987

Reason for exclusion: Animal study

Study: Yarbro 1985

Reason for exclusion: On pathophysiology of breast cancer

Study: Yeatman 1997

Reason for exclusion: On incidence of bilateral breast cancer

Study: Young 1966

Reason for exclusion: No original patient data

Study: Ziegler 1991

Reason for exclusion: Case report

Study: von Smitten 2001

Reason for exclusion: No original patient data

Table 01 MEDLINE/CANCERLIT SEARCH (Rows combined with "or"; columns combined with "and")

EXP BREAST NEOPLASMS

ALL PROPHYLAC: OR

ALL PROPHYLAXIS OR

ALL HYPERTROPHY OR

ALL SUBCUTANEOUS

EXP MASTECTOMY OR

EXP MAMMAPLASTY OR

ALL MAMMOPLAST: OR

ALL MAMMAPLAST: OR

LYMPH ADJ NODE ADJ DISSECTION

EXP BREAST NEOPLASMS

PROPHYLACTIC ADJ SURGERY OR

PROPHYLACTIC ADJ SURGERIES OR

PREVENTIVE ADJ RESECTION OR

PREVENTIVE ADJ MASTECTOMY OR

PROPHYLACTIC ADJ TREATMENT#

PROPHYLACTIC (TF)

MASTECTOMY (TF)

EXP BREAST NEOPLASMS

ALL RISK

SU OR EXP MASTECTOMY

GENES, BRCA1 OR

GE OR

GENETIC SCREENING OR

HYPERTROPHY/SU

Table 02 EMBASE SEARCH (Rows combined with "or"; columns combined with "and")

BREAST(W)CANCER

BREAST(W)CARCINOMA

PROPHYLAC?

PROPHYLAXIS

HYPERTROPHY

SUBCUTANEOUS

MASTECTOMY

MAMMOPLAST?

MAMMAPLAST?

LYMPH(W)NODE(W)DISSECTION

PARTIAL/TI,DE

RECURRENCE/TI,DE

COUNSELING/TI,DE

BILATERAL/TI,DECANCER(W)SURVIVAL

CANCER(W)MORTALITY

BREAST(W)CANCER

BREAST(W)CARCINOMA

PROPHYLACTIC(W)SURGERY

PROPHYLACTIC(W)SURGERIES

PREVENTIVE(W)RESECTION

PREVENTIVE(W)MASTECTOMY

PROPHYLACTIC(W)TREATMENT?

PARTIAL/TI,DE

RECURRENCE/TI,DE

COUNSELING/TI,DE

BILATERAL/TI,DE

CANCER(W)SURVIVAL

CANCER(W)MORTALITY

BREAST(W)CANCER

BREAST(W)CARCINOMA

RISK

SURGERY

MASTECTOMY

GENES

GENETIC

HYPERTROPHY

PARTIAL/TI,DE

RECURRENCE/TI,DE

COUNSELING/TI,DE

BILATERAL/TI,DE

CANCER(W)SURVIVAL

CANCER(W)MORTALITY

BREAST CANCER/DE

BREAST CARCINOMA/DE

BREAST NEOPLAST?/DE

PROPHYLAC?/TI,DE

PROPHYLAXIS/TI,DE

HYPERTROPHY/TI,DE

SUBCUTANEOUS/TI,DE

MASTECTOMY/TI,DE

MAMMOPLAST?/TI,DE

MAMMAPLAST?/TI,DE

LYMPH(W)NODE(W)DISSECTION

BREAST CANCER/DE

BREAST CARCINOMA/DE

BREAST NEOPLAST?/DE

PROPHYLACTIC(W)SURGERY

PROPHYLACTIC(W)SURGERIES

PREVENTIVE(W)RESECTION

PREVENTIVE(W)MASTECTOMY

PROPHYLACTIC(W)TREATMENT

BREAST CANCER/DE

BREAST CARCINOMA/DEB

REAST NEOPLAST?/DE

RISK/TI,DE

SURGERY/TI,DE

MASTECTOMY/TI,DE

GENES/TI,DE

GENETIC/TI,DE

HYPERTROPHY/TI,DE

PROPHYLACTIC/(w) MASTECTOMY

Table 03 METHODOLOGICAL QUALITY OF INCLUDED STUDIES

Study:

Study Design:

Selection bias: Was selection bias (or preferential selection in case series) satisfactorily minimized?

Selection bias was satisfactorily minimized if the major known risk/protective factors (confounders/co-interventions) were controlled for to ensure comparability between groups. For case series preferential selection was minimized if there was evidence of a consecutive sample, or a clearly defined patient population to minimize the chance that clinicians selected only patients with favorable outcomes or that patients with better outcomes volunteered (healthy volunteer bias).

Performance bias: Performance bias satisfactorily minimized?

Performance bias was satisfactorily minimized if prophylactic mastectomy was confirmed in an objective way (i.e., medical or surgical records) and not based exclusively on self-report.

Detection bias: Was detection bias satisfactorily minimized?

Detection bias was satisfactorily minimized if the outcome was assessed in a valid way (i.e., validated pre/post instruments for psychosocial measures, medical records for incidence, medical/death records for vital status), in the same way for both groups, and by a blinded

outcomes assessor.

Attrition bias: Was attrition bias satisfactorily minimized?

Attrition bias was satisfactorily minimized if there was there a low dropout rate and/or if dropouts/withdrawals were sufficiently accounted for so that the reviewer was convinced that differential reasons for dropping out did not occur or were accounted for.

Study: Mulvihill 1982

Study Design: Retrospective cohort

Selection bias: No. People are included in this study for 'risk factors' that would not be considered risk factors for breast cancer by today's standards. Major confounders are not controlled for.

Performance bias: Yes

Detection bias: Don't know (not enough details provided)

Attrition bias: Yes

Study: Stefanek 1995

Study Design: Prospective cohort

Selection bias: Yes

Performance bias: Yes

Detection bias: No. There is nothing in this article stating that a validated patient satisfaction instrument has been used. Biases can result from not using a validated patient satisfaction questionnaire that skews towards favorable outcomes (Rubin 1991).

Attrition bias: Yes

Study: Borgen 1998

Study Design: Convenience sample

Selection bias: No. Because the participants responded to advertisements, those who responded could be different in some important way than those who did not respond.

Performance bias: Yes

Detection bias: No. There is possible recall bias from collecting all psychological data postoperatively.

Attrition bias: Yes

Study: Hartmann 1999

Study Design: Retrospective cohort

Selection bias: No. Study does not control for other important preventive measures besides PM that may have been used by this population including oophorectomy and chemoprevention.

Performance bias: Yes

Detection bias: Yes

Attrition bias: Yes

Study: Hatcher 2001

Study Design: Prospective cohort

Selection bias: No. 5% have had genetic test in the decliners vs. 29% in acceptors. We do not know if there are different baseline risks.

Performance bias: Yes

Detection bias: Yes

Attrition bias: Yes

Study: Hartmann 2001

Study Design: Case series

Selection bias: Yes

Performance bias: Yes

Detection bias: Yes

Attrition bias: Yes

Study: Frost 2001

Study Design: Case series

Selection bias: Yes

Performance bias: Yes

Detection bias: No. There is possible recall bias from collecting all psychological data postoperatively.

Attrition bias: Yes

Study: Meijers-Heijboer 2001

Study Design: Prospective cohort

Selection bias: No. While the authors controlled for some factors such as age and

oophorectomy status, adjustment of other important factors is not reported.

Performance bias: Yes

Detection bias: Yes

Attrition bias: Yes

Study: Josephson 2000

Study Design: Case series

Selection bias: Yes

Performance bias: Yes

Detection bias: No. These interviews took place at least 1 year after the procedure (1 took place after more than 3 years, 3 took place after 2 years, and 9 after more than 1 year). Yet, women were asked to recall their satisfaction with the information provided by the surgical/reconstructive team and preoperative genetic counseling. By the authors' own admission on page 354 "there is a risk that the women may not properly recall how and what they experienced at the time."

Attrition bias: Yes

Study: Lloyd 2000

Study Design: Case series

Selection bias: Yes

Performance bias: Yes

Detection bias: No. In qualitative studies, the 'validity' of the domains is, in part, determined by interviewing enough patients and for enough time that informational redundancy is reached. This is not mentioned.

Attrition bias: Yes

Study: Hopwood 2000

Study Design: Case series

Selection bias: Yes

Performance bias: Yes

Detection bias: No. This is entirely retrospective data. Baseline measures have not been collected. There is possible recall bias from collecting all psychological data postoperatively.

Attrition bias: No.

Study: Zion 2000

Study Design: Case series

Selection bias: Yes

Performance bias: Yes

Detection bias: Yes

Attrition bias: Yes

Study: Leis 1981

Study Design: Case series

Selection bias: No. People are included in this cohort who had benign diseases that are not considered risk factors for breast cancer by today's standards.

Performance bias: Yes

Detection bias: No. Valid disease-free survival estimates depend on all patients getting assessed for disease at regular, fixed intervals. It is not mentioned whether this occurred.

Attrition bias: No. There are 69/127 patients who have not been accounted for.

Study: Babiera 1997

Study Design: Retrospective cohort

Selection bias: No. There is a chance of selection bias. Those electing CPM may differ in some important way from the control group and important factors have not been adjusted for in the analysis. For example, there is a median age difference of 7 years between the two groups. Also, it is stated that the decision to have CPM was influenced by histology and family history: " We do not know how histology and family history were different between the two groups."

Performance bias: Yes

Detection bias: No. Incidence in contralateral PM group is given as occult incidence at time of surgery with no subsequent follow-up data provided, whereas incidence in control group is given up to 103 months. This appears to be an apples and oranges comparison. Also, because valid disease-free survival estimates depend on patients in both groups getting assessed at the same fixed intervals, we do not know the validity of these data as intervals are not mentioned.

Attrition bias: Yes

Study: McDonnell 2001

Study Design: Case series

Selection bias: No. The analysis does not sufficiently control for confounding factors, i.e., histology or stage of primary tumor.

Performance bias: Yes

Detection bias: Yes

Attrition bias: Yes

Study: Montgomery 1999

Study Design: Convenience sample

Selection bias: No. Because the participants responded to advertisements, respondents may be different in some important way than the nonrespondents.

Performance bias: Yes

Detection bias: No. There is a possibility of recall bias by asking all quality of life questions after the surgery only.

Attrition bias: No 50 women of 346 did not respond to questionnaire

Study: Peralta 2000

Study Design: Retrospective cohort

Selection bias: No. This study does not adjust for all major confounders.

Performance bias: Yes

Detection bias: No. Valid disease-free survival estimates depend on patients in both groups getting assessed at the same fixed intervals. Therefore, we do not know the validity of these data as intervals are not mentioned.

Attrition bias: Yes

Study: Lee 1995

Study Design: Retrospective cohort

Selection bias: No. The study only adjusts for age, not the other major confounders. Also, the treatment group includes those undergoing contralateral PM as well as those having biopsies. It is unclear how including those with only biopsies may have biased the results.

Performance bias: Yes

Detection bias: No. PM group is combined with those receiving biopsies; therefore, the risk in the PM group is not ascertainable.

Attrition bias: Yes

Study: Horton 1979

Study Design: Case series

Selection bias: No. People were included in this cohort who had benign diseases that are not considered risk factors for breast cancer.

Performance bias: Yes

Detection bias: Yes

Attrition bias: No

Study: Pennisi 1987

Study Design: Case series

Selection bias: No. People are included in this cohort who had benign breast diseases that are not considered risk factors for breast cancer by today's standards.

Performance bias: Yes

Detection bias: Don't know

Attrition bias: No. The 30% loss to follow-up increases risk of attrition bias.

Study: Evans 1999

Study Design: Case series

Selection bias: No

Performance bias: Yes

Detection bias: Don't know. It is uncertain how the estimation of risk is affected by use of the Claus model.

Attrition bias: Yes

Study: Gabriel 1997

Study Design: Case series

Selection bias: Yes

Performance bias: Yes

Detection bias: Yes

Attrition bias: Yes

Study:

Study Design:

Selection bias:

Performance bias:

Detection bias:

Attrition bias:

Table 04 MORTALITY-Bilateral Prophylactic Mastectomy (BPM)

Study: Meijers-Heijboer 2001

Outcome: TREATMENT GROUP:

BPM group:[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis].0/76

COMPARISON GROUP:

Surveillance group: 1/63

RR=0.28 (95% CI 0.01, 6.68) p=0.43

Length of followup: Mean followup of 3.0 +/-1.5 years.

Attrition: None

Study Details: See Table 5 for study population details.

Study: Hartmann 1999

Outcome: WOMEN AT HIGH RISK

TREATMENT GROUP:

BPM: [horizontal ellipsis][horizontal ellipsis][horizontal ellipsis].2/214 deaths

COMPARISON GROUP: [horizontal ellipsis]. 90/403 deaths

Using three different methods to calculate incidence taking into account ascertainment bias, the risk of death was reduced by 81-94%.

Most conservative estimate for high risk:% reduction=80.9% (95% CI 31.4%, 97.7%)

Moderate risk:

BPM:[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis].0 of 425

Predicted incidence of death: 10.4 of 214

% reduction=100% (95% CI 70%, 100%).

Length of followup: The median length of followup was 14 years.

Attrition: None

Study Details: See Table 5 for study population details and definitions of "high risk" and "moderate risk.".

Study: Pennisi 1987

Outcome: 3 of the 1500 BPM/CPM patients died from breast cancer.

No comparison group

Length of followup: 70% followed for 9 years.

Attrition: 30% were lost to followup

Study Details: 1500 patients from 165 plastic surgeons who had subcutaneous PM and were registered with the Subcutaneous Mastectomy Data Evaluation Center.

78 (5.2%) subjects had obscure carcinoma and 51 (3.4%) had LCIS at the time of surgery and were included in the study.

Among the 139 patients who had CPM, 4 (3%) had breast cancer and 5 (3.6%) had LCIS and were included in the study.

300 (20%) had a first-degree relative with breast cancer and 21% had a history of second-degree maternal or paternal relatives with a history of breast cancer.

Skin necrosis occurred in 5% of the patients.

Table 05 INCIDENCE -Bilateral Prophylactic Mastectomy (BPM)

Study: Meijers-Heijboer 2001

Bilateral Prophylactic Mastectomy (BPM)

Incidence: TREAT MENT GROUP:

BPM[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis][horizontal ellipsis][horizontal ellipsis]0/73

COMPARISON GROUP:

Surveillance arm[horizontal ellipsis][horizontal ellipsis]8/63

BPM significantly (P=0.003) decreased incidence of breast cancer at 3 years' follow-up. Hazard ratio=0 (95% C.I. 0.0, 0.36).

Length of followup: Mean followup of 3.0 +/-1.5 years

Attrition: None

Study Details: Using the surveillance group, the authors estimate the five-year risk of breast cancer was 24 +/- 9%.

The ratio of observed occurrences to expected occurrences in the surveillance group was

1.2 (8 vs. 6.7).

Significantly more women in the BPM arm than in the surveillance arm also had an oophorectomy (44 vs. 27 [58% vs. 38%]).

The 139 women were from 70 families.

None of the affected women were from the same family.

MRI detected 6 of the 6 cancers screened.

Mammography detected 2 of the 8 cancers screened.

Study: Hartmann 1999

Bilateral Prophylactic Mastectomy (BPM)

Incidence: Moderate-Risk Women

TREATMENT GROUP:

BPM [horizontal ellipsis][horizontal ellipsis].4/425

COMPARISON GROUP:

Statistically simulated using the Gail model[horizontal ellipsis][horizontal ellipsis] 37.4/425.

Risk reduction= 89.5%.

High risk women

TREATMENT GROUP:

BPM [horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis]. 3/214

3 COMPARISON GROUPS

All simulated from probands' sisters breast cancer rates:

1. All breast cancer from age 18 to follwup[horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis][horizontal ellipsis] 52.9/214

2. All breast cancer from age 18 to followup corrected for ascertainment bias[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis]30/214

3. Only breast cancers that occurred in sisters after probands' diagnosis[horizontal ellipsis] [horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis][horizontal ellipsis][horizontal ellipsis].37.4/214

Using three different methods to calculate incidence taking into account ascertainment bias, the expected incidents among the 214 high-risk probands ranged from 30.0 - 52.9/214

Most conservative estimate was %difference=90.0 (95% CI 70.8, 97.9)

Length of followup: Median length of followup was 14 years

Attrition: None

Study Details: To be classified as high risk, women had to meet one of the following criteria:2 or more first-degree relatives with breast cancer;1 first-degree relative and 2 or more second- or third-degree relatives with breast cancer;1 first-degree relative with breast cancer before the age of 45 and one other relative with breast cancer;2 second-degree or third-degree relatives with breast cancer and 1 or more with ovarian cancer;1 second or third-degree relative with breast cancer and 2 or more with ovarian cancer;3 or more second or third-degree relatives with breast cancer;1 first-degree relative with bilateral breast cancer.

2 women in the high-risk group developed ovarian cancer.

All 7 who developed breast cancer had subcutaneous mastectomies. But there was no significant difference in outcome between the group with subcutaneous mastectomies compared to those who had total mastectomies.

Median time to development of breast cancer was 6 years.

At the time of the study, tissue was available for pathological review for 603 of the women. 2 invasive cancers were identified during the review. 1 of the 2 women had developed breast cancer 3 years after the PM

Study: Mulvihill 1982

Bilateral Prophylactic Mastectomy (BPM)

Incidence: TREATMENT GROUP:

BPM[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis] 0/9

COMPARISON GROUP:

Surveillance [horizontal ellipsis][horizontal ellipsis]0/4

Length of followup: 1 to 12 years

Attrition: None

Study Details: The 2 groups were similar in age, prior attitudes, and knowledge of breast cancer and control measures.

None of the 4 women who chose surveillance had followed minimum of monthly self-examination and quarterly examination by a physician

Study: Hartmann 2001

Bilateral Prophylactic Mastectomy (BPM)

Incidence: Patients with BRCA1/2 mutations

TREATMENT GROUP:

BPM[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis][horizontal ellipsis].0/26

COMPARISON GROUP:

Simulated group #1 using Easton penetrance model. 9.37/26

Risk reduction =100% (95% C.I. 51.0-100.0).

Simulated group #2 using Struewing penetrance model= 6.52/26

Risk reduction = 100% (95% C.I. 54.1-100.0).

Length of followup: 13.4 years (range 5.8-28.5 years).

Attrition: None

Study Details: Subjects are a subset of the 214 high-risk women who were participants in Hartmann's 1999 study. 26 had alterations in BRCA1 or BRCA2.

8 of the original 214 subjects in the cohort had died at time this study began: 2 from breast cancer, 1 from ovarian cancer. The woman with ovarian cancer had deleterious BRCA1 mutation.

Study: Borgen 1998

Bilateral Prophylactic Mastectomy (BPM)

Incidence:

BPM[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis]. 3/370

Length of followup: 0.2-51.5 years with a mean of 14.8 years

Attrition: Not applicable

Study Details: 255 of 370 (69%) reported the discussion to have PM was initiated by their physician, while 108 (29%) initiated the discussion themselves.

Five did not recall who initiated the discussion.

Incidental carcinoma was identified in 14 of the 370 (4%) and they were included in the study.

Study: Horton 1978

Bilateral (BPM) and Contralateral Prophylactic Mastectomy (CPM)

Incidence:

CPM[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis].0/11

BPM [horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis].0/90

Length of followup: Followup 1 month to 10 years, with an average of 3.1 years.

Attrition: None

Study Details: Note: This study contained a small group of CPM patients; however, results are not presented separately. Due to the preponderance of BPM, the study is reported with BPM incidence results.

Study: Pennisi 1987

Bilateral (BPM) and Contralateral Prophylactic Mastectomy (CPM) combined

Incidence: BPM/CPM[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis].6/1500

Length of followup: 70% of the patients were followed for 9 years.

Attrition: 30% were lost to followup

Study Details: 1500 patients from 165 plastic surgeons who had subcutaneous PM and were registered with the Subcutaneous Mastectomy Data Evaluation Center.

78 (5.2%) subjects had obscure carcinoma and 51 (3.4%) had LCIS at the time of surgery and were included in the study.

Among the 139 patients who had CPM, 4 (3%) had breast cancer and 5 (3.6%) had LCIS and were included in the study.

300 (20%) had a first-degree relative with breast cancer and 21% had a history of second-degree maternal or paternal relatives with a history of breast cancer.

Note: This study contained a small group of CPM patients; however, results are not presented separately. Due to the preponderance of BPM, the study is reported with BPM incidence results.

Study: Evans 1999

Bilateral (BPM) and Contralateral Prophylactic Mastectomy (CPM) combined

Incidence: TREATMENT GROUP:

CPM/BPM[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis]. [horizontal ellipsis]0/400 woman years

COMPARISON GROUP:

Statistically simulated using Claus model[horizontal ellipsis][horizontal ellipsis]4 /400 woman years were expected

Length of followup: Study followup covered 400 women years for an average of 2.2 years.

Attrition: None

Study Details: Women were from 10 European cancer centers that offer risk assessment and counseling services to women with a lifetime risk of breast cancer from 25-80% using the Claus data.

Authors stated that follow-up for more than 5 years would be necessary to address the issue of risk reduction.

Note: This study contained a small group of CPM patients; however, results are not presented separately. Due to the preponderance of BPM, the study is reported with BPM incidence results.

Table 06 PHYSICAL MORBIDITY

Study: Gabriel 1997

Outcome: Physical morbidity defined as complications leading to unanticipated surgical interventions following breast implantation in cosmetic, prophylactic and cancer patients:

Complications involved 274 (18.8%) of the 1454 breasts with implants and 321 (18.8%) of the 1703 implants.

Complications were defined only as events requiring surgical interventionsBy 5 years, the number of implants with complications was nearly 3 times as high in cancer and prophylactic groups as the cosmetic group.

Cancer group - 34.0% of 125 (95% C.I. 27.2%-41.3%)

Prophylactic group - 30.4% of 92 (95% C.I. 23.1%-38.4%)

Cosmetic Group - 12.0% of 532 (95% C.I. 9.1%-15.2%)

The three most frequent problems were:

1. capsular contracture- 17.5% of patients

2. implant rupture - 5.7% of patients

3. hematoma - 5.7% of patients

Followup Time: Mean follow-up was 7.8 years with a range of 0 to 7.8 years (5847 person years.)

For analysis, follow-up period was 5 years.

Attrition: None

Study Details: 208 of the 749 (27.8%) underwent 450 additional surgical procedures within 5 years.

91 of 450 (20.2%) of the procedures were anticipated (staged procedures, patient's request for size change or aesthetic improvement) and 359 had clinical indications and were performed in 178 (23.8%) of the women.

Despite number of complications, author cautions that study did not evaluate patients'overall satisfaction with their implants or the effects of these events on patients' overall health status.

Study: Zion 2000

Outcome: 290 of the 591 (49%) had unanticipated re-operations (UR).

For all 591 women, the average UR per person is 0.96 (std dev 1.32).

Reasons for UR were

:22% - immediate post-operative complications

46% - implant-related issues

32% - aesthetic concerns.

Followup Time: Mean follow-up of 14.2 years.

Attrition: None

Study Details: Physical morbidity assessed by review of medical records and patient interviews to assess complications leading to surgical procedures that were not part of the standard breast implantation protocol.

Median time to UR was 1.3 years with 42% occurring within one year of breast reconstruction.

Of 1182 implants originally placed,

432 (37%) were removed and 389 new implants were placed.

Note: Some of these subjects are probably the same as some of the subjects in the Gabriel study.

Study: Stefanek 1995

Outcome: 7 of 14 (50%) reported they had "quite a bit" or "very much" discomfort after surgery.

2/11 patients had silicon implants remove due to tissue rejection and subsequent infections.

Followup Time: Follow-up on satisfaction survey from 6-30 months

Attrition: None

Study Details:

Table 07 QUALITY OF LIFE

Study: Stefanek 1995

Bilateral Prophylactic Mastectomy (BPM)

Outcome: DECISION SATISFACTION

14/14 (100%) reported satisfaction with their decision to have PM.

12/14 (86%) reported they would recommend PM to other women with the same risk.

COSMETIC SATISFACTION

Of the 11 opted to have reconstruction,

7/11 (64%) reported being "quite a bit" or "very much" satisfied with results.

1/11 (9%) reported "somewhat satisfied"

3/11 (27%) were "dissatisfied," reporting results were worse than expected.

SURGICAL RECOVERY SATISFACTION

11/14 (79%) were "quite a bit" or" very much" satisfied with the time to recover physically.

3/14 were somewhat or a little satisfied.

13/14 (93%) were "quite a bit" or" very satisfied" with the time to recover emotionally.

1/14 (7%) was somewhat satisfied.

13/13 (100%) reported satisfaction with support from husband or partner.

CANCER WORRY

Women in the BPM group reported more worry about developing breast cancer than women in either of the other 2 groups that elected not to have BPM (P=<0.01).

Women in the BPM group tended to overestimate their risk (based on the Gail model) compared to the group 'not interested' in PM (P=<0.05)

Followup: FOLLOWUP

Followup on satisfaction survey from 6-30 months

ATTRITION: None

Study Details: Participants were recruited from a group of 164 women with at least one first-degree relative diagnosed with breast cancer, who were seen by a breast surveillance service (BSS) between 1/1988 and 11/1992.

Satisfaction with BPM assessed through postoperative postal questionnaire.Group comparison analysis:

There was little difference in age, family history, or mammography history among the groups. However, 12 of the 14 had had a recent breast cancer event defined as personal biopsy, diagnosis, recurrence or death of a family member, and biopsy of a family member.

Those selecting PM reported doing breast self-exam monthly or more frequently, which was significantly more often than those not interested in PM (P=<0.05).

Study: Mulvihill 1982

Bilateral Prophylactic Mastectomy (BPM)

Outcome: COSMETIC SATISFACTION

All were enthusiastic about the operative results, despite complications in two.

CANCER WORRY

Those who chose mastectomy estimated themselves more anxious and at higher risk than the others.

SEXUALITY

None reported change in sexual activity after BPM.

Followup: FOLLOWUP

1-12 years

ATTRITION

None

Study Details: Of the 9 counseled prospectively, little distinguished the 5 who chose mastectomy from the 4 who chose surveillance.

They were similar in age, prior attitudes, knowledge of breast cancer and of control measures.

None of the 4 women who chose surveillance had followed minimum of monthly self-examination and quarterly examination by a physician

Study: Borgen 1998

Bilateral Prophylactic Mastectomy (BPM)

Outcome: DECISION SATISFACTION

Most women were satisfied with BPM.

21/370 (5%) regretted their decision to have PM, with 19 of them among the 255 for whom the discussion about PM was initiated by their physicians.

Of the 21 with regrets,

10/21 (48%) had major regrets and would not undergo BPM again.

7/21 (33%) had minor regrets.

4/21(19%) did not report level of regrets.

19/21 (90%) of women who were unhappy with BPM results did not have preoperative counseling.

COSMETIC SATISFACTION

Of the 331 who responded about cosmetic results,

116/331 (35%) reported excellent results.

163/331 (49%) reported acceptable results.

52/331 (16%) reported unacceptable results.

Followup: FOLLOWUP

The follow-up years since surgery ranged from 0.2-51.5 years with a mean of 14.8 years

ATTRITION

Not applicable

Study Details: Quality of Life/Satisfaction assessed by survey regarding satisfaction and regrets with BPM. There is no mention of whether the survey was validated.

336 patients were selected from a group of 817 volunteers who responded to an invitation in the popular press to join the National Prophylactic Mastectomy Registry. 34 patients were recruited from the authors' practice or the NY Metropolitan Breast Cancer Group.

Women with LCIS were excluded.

220 of the 370 (59%) reported having at least 1 first-degree relative diagnosed with breast cancer.

255 of 370 (69%) reported the discussion to have BPM was initiated by their physician, while 108 (29%) initiated the discussion themselves. Five did not recall who initiated the discussion.

Mean age of patients with regrets was 45 and group overall was younger than those who were satisfied with BPM.

Incidental carcinoma was identified in 14 of the 370 (4%) and they were included in the study.

Study: Hatcher 2001

Bilateral Prophylactic Mastectomy (BPM)

Outcome: PSYCHOLOGICAL MORBIDITY/ANXIETY

TREATMENT GROUP:

In the 79 women who chose BPM, anxiety decreased significantly from 41/71 (58%) preoperatively to 29/71 (41%) 6 months post-op (p=0.04). and remained low at 18 months post-op.

COMPARISON GROUP

Psychological morbidity showed a trend towards a decrease in the 64 women who declined BPM from baseline 57% (31/54) vs. 43% (23/54) at 6 months. % 14% (95% CI 0, 29) (p=0.08). Changes from baseline 57% (29/52) vs. 18 months 41% (21/52). % reduction=16% (95% CI-2-33) p=0.11.

CANCER WORRY

Significantly more women in the BPM group 24/74 or 32% compared to the No BPM group 6/58 or 10% were likely to believe that it was inevitable that they would develop breast cancer (P=0.03).

SEXUALITY

The degree of sexual pleasure did not change significantly in either group.

BODY IMAGE

Body image questionnaires given at the 6 and 18 month post-operative interviews to accepters showed no difference in median score of 4 for body image on a scale of 0-30 with 0 being the most positive

Followup: FOLLOWUP

Those choosing BPM were interviewed again at 6 and 18 months post-operatively. Those declining or deferring were re-interviewed at 18 months after the first interview

ATTRITION

11 /168 were lost to contact before completing assessment

Study Details: Patients were assessed with 6 questionnaires measuring general health, anxiety, sexual activity, coping, risk perception and body image.

A score of 4 or higher on the General Health Questionnaire (GHQ) defined possible psychological morbidity.

Patients were identified from cohort of 168 women having a family history of breast cancer or having sufficiently high risk factors for BPM to be offered. They were followed prospectively with baseline data being collected prior to having BPM.

The comparison group is women who considered BPM, but declined. Of these, 154 were recruited for the study. Eleven deferred their decisions whose results were not reported.

Baseline statistical analysis included all women who completed the assessment at the first interview. In subsequent analyses, only those women who completed assessments at each time point are included.

Most women in both groups were employed and had children.

The median age of accepters was 38 and for decliners, 40.

Psychological morbidity decreased significantly over time among accepters, and the longer the time from surgery, the greater the decline.29% of the accepters had genetic testing vs. 5% of the decliners.

Study: Frost 2000

Bilateral Prophylactic Mastectomy (BPM)

Outcome: DECISION SATISFACTION

393/562 (70%) were either satisfied or very satisfied with their PM,

69/562 (11%) were neutral

107/562 (19%) were dissatisfied or very dissatisfied.

(Data missing from 10 participants.)

383/572 (67%) indicated they would definitely or probably choose PM again.

There was correlation between lower level of satisfaction and physician's advice being given as the primary reason for choosing PM.

CANCER WORRY

423/572 (74%) reported a diminished level of emotional concern about developing breast cancer.

520/572 (91%) of the women reported no change or favorable effect on emotional stability.

52/572 (9%) reported adverse effect in level of emotional stability.

492/572 (86%) of the women reported no change or favorable effect on stress levels.

80/572 (14%) reported adverse effect in level of stress.

BODY IMAGE

275/572 (48%) reported no change in their level of satisfaction with their physical appearance.

92/572 (16%) reported favorable effects.

206/572 (36%) reported diminished satisfaction with their physical appearance.

429/572 (75%) of the women reported no change or favorable effect in feelings of feminity.

132/572 (23%) reported adverse effect in feelings of femininity.

Variable most strongly associated with patient satisfaction after BPM was satisfaction with body appearance

469/572 (82%) of the women reported no change or favorable effect in self-esteem

103/572 (18%) reported adverse effect in self-esteem.

SEXUALITY

440/572 (77%) of the women reported no change or favorable effect.

132/572 (23%) reported adverse effect in sexual relationships.

Followup: FOLLOWUP

Mean follow-up period was 14.5 years after surgery.

ATTRITION

572 of 609 (94%) completed the questionnaire

Study Details: Patient satisfaction assessed by questionnaire to evaluate long-term satisfaction, and psychological and social function.

The 609 women were a subset of 639 subjects in Hartmann's 1999 study known to be alive and were recruited to complete a study questionnaire after their BPM to evaluate their long-term satisfaction, and psychological and social function.

572 of 609 (94%) completed the questionnaire.

Family history was the most common number 1 reason given for having a BPM, followed by physicians' advice and nodular breasts. Because reason for choosing BPM was not collected pre-operatively, authors are concerned that recall of reason for choosing BPM may have been colored by subsequent experience.

100% of the 19 women who did not have reconstruction reported being very satisfied or satisfied, and using multiple regression analysis showed there was an association between satisfaction and no reconstruction

Study: Josephson 2000

Bilateral Prophylactic Mastectomy (BPM)

Outcome: DECISION SATISFACTION

No women regretted their decision to have PM. They believed they had no choice in the decision since minimizing risk of breast cancer was most important.

All women would recommend BPM with immediate reconstruction to other women in the same situation.

COSMETIC SATISFACTION

3/15 (87%)women thought the cosmetic result was better than expected.

8/15 (53%) did not feel their new breasts were part of their own body.

MEDICAL CARE SATISFACTION

14/15 (93%) women were satisfied with the factual information given by the geneticists.

8/15 (53%) women were satisfied with the surgical/reconstruction information.

9/15 (60%) were satisfied with the support from their surgeons.

SEXUALITY

5/13 (38%) women with partners said that the results of the operation had changed the relationship with the partner.

Followup: FOLLOWUP

13 interviews took place at least 1 year after surgery, 2 at less than 1 year (7 and 8 months).

ATTRITION

2/17 women selecting BPM refrained from being interviewed.

Study Details: Quality of Life satisfaction with BPM as measured by post-operative interviews with 17 women.

Satisfaction with PM as measured by post-operative interviews.

5 of the women spontaneously mentioned the importance of how to emotionally consider and anticipate the loss of their breasts, how the breasts would be changed following the surgical procedure and "taking good-bye" of them, mourning them.

Study: Lloyd 2000

Bilateral Prophylactic Mastectomy (BPM)

Outcome: Results produced 7 significant categories, 6 stages and a seventh-suffering and countering multiple losses-which transcended all 6 stages.

The six stages are:

1.deciding

2.telling

3.experiencing surgery and recovery

4.maintaining womanliness

5.processing the loss

6.moving on

Followup: FOLLOWUP

Participants were between 6 weeks and 3 years post surgery.

ATTRITION

1/ 11 subjects refused to participate

Study Details: Qualitative in-depth interviews were conducted to explore personal experiences with prophylactic mastectomy and ascertain categories or stages women go through who have BPM.

Study: Hopwood 2000

Bilateral Prophylactic Mastectomy (BPM)

Outcome: CANCER WORRY

47 of 49 returned evaluable General Health Questionnaires (GHQ) one-year post-operatively.

8/47 (17%) scored >9 in a range of 0-28 suggesting "case" level distress.

BODY IMAGE

All 49 returned Body Image Scale (BIS) questionnaires one year post-operatively

.6/49 (12%) reported moderately changed or very much change overall in body image on 10 items.

More than half of the women reported a change from little to very much for 3 items.

27/49 (55.1%) felt less sexually attractive

26/49 (53.1%) felt self-conscious about appearances

26/49 (53.1%) feel less physically attractive.

Followup: FOLLOWUP AND ATTRITION

19/49 women had 1- and 2- year assessments.9 /49 had 1-, 2- and 3-year assessme

Study Details: Quality of Life measured by General Health Questionnaire (GHQ) and Body Image Scale (BIS) to assess mental health and body image one year post-operatively.

Participants were recruited from a group of 76 women who had BPM7 of 45 women required further psychiatric help.

3 of the 7 were given antidepressant medication.

Complications from surgery accounted for 4 of the 7 women needing psychiatric help.

Surgical complications e.g. skin necrosis, nipple loss, infection and pain, accounted for some of the highest GHQ and BIS scores.

Study: Montgomery 1999

Contralateral Prophylactic Mastectomy (CPM)

Outcome: DECISION SATISFACTION

Most women were satisfied with CPM.18 of 296 (6%) regretted their decision to have CPM with 11/296 (5%) of them among the 212 who said the discussion about CPM was initiated by the physician.

COSMETIC SATISFACTION

12/111 who had reconstruction had regrets

6/185 who did not have reconstruction had regrets. RR=0.30 (95% CI 0.12, 0.78) (p=0.01)

88/111 (79%) who underwent reconstruction reported their cosmetic results were excellent or acceptable.

18/111 (16%) said cosmetic results were unacceptable, but only 12 of them also had regrets.

5/111 (5%) did not report satisfaction.

6/111 (5.4%) said they would not chose CPM again if they had known the cosmetic outcome.

SEXUALITY

The reasons given by the 18 women with regrets were:

7/18 (39%) cosmetic results

4/18 (22%) diminished sense of sexuality

4/18 (22%) lack of education about alternatives

3/18 (17%) other reasons.

Followup: FOLLOWUP

The follow-up years since surgery ranged from 0.25-43.8 years with a mean of 4.9 years.

ATTRITION

50 women of 346 did not respond to questionnaire

Study Details: Quality of Life/Satisfaction assessed by survey regarding satisfaction and regrets with PM.

346 patients were selected from a group of 817 volunteers who responded to an invitation in the popular press to join the National Prophylactic Mastectomy Registry and who had CPM.

Insurance companies overwhelmingly provided coverage for CPM in 276 women (93%).

Regrets were less common, but not statistically significant, among women with whom the discussion to have CPM was initiated by the physician (11/212 or 5%) than among women who initiated the discussion themselves 7/84 or 8%).

Table 08 SURVIVAL -Contralateral Prophylactic Mastectomy (CPM)

Study: Babiera 1997

Survival: 5-year disease-specific survival

CPM group= 80% (14/18)

N o CPM (Surveillance) = 90% (104/115)

RR=0.87 (95% CI 0.67, 1.12) p=0.28

Followup: CPM group

Median =52 months

(range 17-143 months).

No CPM group

Median = 70 months (range 13-178 months).

Attrition: None

Study Details: The authors conclude that the results suggest that CPM should not be considered as an initial therapeutic option in patients presenting with ILC.

In the CPM group, 39% of the patients had adjuvant chemotherapy, 6% underwent only neoadjuvant therapy, 28% had radiation therapy, and 22% had hormonal therapy as treatments for their primary ILC.

In the COMPARISON group, 31% had adjuvant therapy, 8% had both adjuvant and neoadjuvant therapy, and 28% underwent hormonal therapy as treatment for their primary ILC.

Study: Peralta 2000

Survival: 15-year all-cause survival

CPM group = 64% (41/64)

No CPM group = 48% (87/182) (P=0.26)

15-year disease-specific survival in pts with Stage 0, 1 or 2 breast cancer

CPM group =71% (45/64)

No CPM (Surveillance) = 53% (96/182) (P=0.06).

Followup: CPM group:

Median = 6.2 years

No CPM group:

Median= 6.8 years

Attrition: None

Study Details: Comparison group patients were matched for age, stage of disease at diagnosis, presence of LCIS, chemotherapy and tamoxifen therapy from among 2,852 patients who underwent mastectomy between 1/1/1973 and 9/30/1998 at one institution.

71% having CPM had immediate reconstruction.

Study: Lee 1995

Survival: 15-year disease-specific survival

CPM or biopsy =105 patients

No CPM (Surveillance)=299

There was a statistically significant 15-year survival advantage in CPM or biopsy (P=0.01) after adjusting for age.

Followup: Mean = 6 years

Median= 5.3 years

Attrition: None

Study Details: Patients had unilateral invasive lobular carcinoma (ILC)

Patients in the CPM group were significantly younger and a significantly greater proportion had multifocal lesions than in the No CPM group. Results were age adjusted.

Those getting CPM and those only getting biopsies were lumped together the 'treatment group.' There are no statistical analyses of just the CPM group alone.

Table 09 INCIDENCE IN CONTRALATERAL BREAST - Contralateral Prophylactic Mastectomy (CPM)

Study: Leis 1981

Incidence: At 10 years:

CPM [horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis].4/58

No comparison group

Follow-up Time: Mean = 6 years Median= 5.3 years

Attrition: 69/127 (54%) subjects not accounted for at 10 years

Study Details: 25 of 127 (19.7%) had unsuspected cancer in the contralateral breast at the time of CPM; 11 were invasive and 14 were non-invasive.

Study: Babiera 1997

Incidence: TREATMENT GROUP:

CPM=not reported

COMPARISON GROUP:

No CPM (Surveillance)=3/115 (2.6%)

Follow-up Time: CPM

Median= 52 months

(range 17-143 months).

No CPM

Median = 70 months (range 13-178 months).

Attrition: None

Study Details: The authors conclude that the results suggest that CPM should not be considered as an initial therapeutic option in patients presenting with ILC.

In the CPM group, 39% of the patients had adjuvant chemotherapy, 6% underwent only neoadjuvant therapy, 28% had radiation therapy, and 22% had hormonal therapy as treatments for their primary ILC.

In the COMPARISON group, 31% had adjuvant therapy, 8% had both adjuvant and neoadjuvant therapy, and 28% underwent hormonal therapy as treatment for their primary ILC.

Study: Peralta 2000

Incidence: TREATMENT GROUP: CPM[horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis][horizontal ellipsis]0/64

COMPARISON GROUP:

No CPM (Surveillance) [horizontal ellipsis].36/182

RR=0.04 (95% CI 0.00, 0.62) p=0.02

Follow-up Time: CPM group

Median = 6.2 yrs

No CPM group

Median= 6.8 yrs

Attrition: None

Study Details: Comparison group patients were matched for age, stage of disease at diagnosis, presence of LCIS, chemotherapy and tamoxifen therapy from among 2,852 patients who underwent mastectomy between 1/1/1973 and 9/30/1998 at one institution.

71% had immediate reconstruction.

Study: McDonnell 2001

Incidence: Premenopausal Women:

TREATMENT GROUP:

CPM=6/388

COMPARISON GROUP:

Statistically simulated, adjusted for treatment= 106.2/388

Risk reduction =94.4% (95% C.I. 87.7% - 97.9%).

Not adjusted for treatment=115/388

Risk reduction=94.8% (95% C.I. 88.6% - 98.1%)

Postmenopausal Women

TREATMENT GROUP:

CPM=2/357

COMPARISON GROUP

Statistically simulated, adjusted for treatment=50.3/357

Risk reduction = 96.0% (95% C.I. 85.6% - 99.5%).

Not adjusted for treatment =54/357 96.3%.

Follow-up Time: Median = 10 years

98% of participants were followed at least 2 yrs

Attrition: None

Study Details: Total occurances of contralateral cancers among all women was 8/745

742 of the subjects fit the Anderson model definition of positive family history, which requires one of the three types of pedigrees: parent affected, sibling affected or second-degree relative affected.

3 women who developed contralateral breast cancer after CPM and whose family pedigree was unclear were included to make the calculated risk reductions conservative.

The median time from mastectomy to development of breast cancer was 2 years (range 1-18 years).

"Adjusted for treatment" means adjusted for adjuvant therapy and Tamoxifen

Comparison group was statistically simulated using age-adjusted life tables.

4 of the cancers were diagnosed within 2 years of CPM, suggesting that the cancer may have been present but not detected at that time.

Table 10 DISEASE-FREE SURVIVAL OR RECURRENCE - Contralateral Prophylactic Mastectomy (CPM)

Study: Peralta 2000

Outcome: 15-year disease-Free Survival (Recurrence or secondary primary in contralateral or primary):

TREATMENT GROUP:

CPM group = 55% (35/64)

COMPARISONG GROUP

No CPM = 28% (51/182) (P=0.01).

Followup Time: CPM group:

Median = 6.2 years

No CPM group:

Median= 6.8 years

Attrition: None

Study Details: Comparison group patients were matched for age, stage of disease at diagnosis, presence of LCIS, chemotherapy and Tamoxifen therapy from among 2,852 patients who underwent mastectomy between 1/1/1973 and 9/30/1998 at one institution.

71% had immediate reconstruction.

Study: Leis 1981

Outcome: Disease-free survival at 10 or more years

TREATMENT GROUP

CPM[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis].54/58 (91%)

No comparison group

Followup Time: Mean = 6 years Median= 5.3 years

Attrition: 69/127 (54%) subjects not accounted for at 10 years

Study Details: 25 of 127 (19.7%) had unsuspected cancer in the contralateral breast at the time of CPM; 11 were invasive and 14 were non-invasive.

Study: Babiera 1997

Outcome: RECURRENCE

Local -regional recurrences

TREATMENT GROUP

CPM[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis][horizontal ellipsis]. 0/18

COMPARISON GROUP

No CPM (Surveillance):.10/115

RR=0.29 (95% CI 0.02, 4.76), p=0.39

Distant disease

TREATMENT GROUP

CPM[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis][horizontal ellipsis] [horizontal ellipsis][horizontal ellipsis].3/18

COMPARISON GROUP

No CPM (Surveillance)[horizontal ellipsis][horizontal ellipsis][horizontal ellipsis]25/115

RR=0.77 (95% CI 0.26, 2.28) p=0.63

Followup Time: CPM group

Median =52 months

(range 17-143 months).

No CPM group

Median = 70 months (range 13-178 months).

Attrition: None

Study Details: In the CPM group, 39% of the patients had adjuvant chemotherapy, 6% underwent only neoadjuvant therapy, 28% had radiation therapy, and 22% had hormonal therapy as treatments for their primary ILC.

In the COMPARISON group, 31% had adjuvant therapy, 8% had both adjuvant and neoadjuvant therapy, and 28% underwent hormonal therapy as treatment for their primary ILC.

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