Women who carry a germline mutation in the BRCA1 or BRCA2 (BRCA1/2) gene have a 50%–80% lifetime risk of developing breast cancer and a 10%–40% lifetime risk of developing ovarian cancer (1–4). These high-risk women are being offered various preventive measures, including surveillance, chemoprevention, and prophylactic surgery to reduce their risk of cancer. During a prophylactic bilateral mastectomy or a prophylactic bilateral salpingo-oophorectomy, healthy breast or ovarian tissue, respectively, is removed to prevent the development of a malignancy. However, these procedures do not completely eradicate cancer risk because, often, not all tissue at risk is taken away (5–9). Because of the invasive and irreversible nature of prophylactic surgery, knowledge of its efficacy and the extent of risk reduction are crucial for women considering the procedure.

Several groups have investigated the efficacy of bilateral prophylactic surgery in women with a family history of breast and/or ovarian cancer or in known BRCA1/2 mutation carriers (Table 1). For BRCA1/2 mutation carriers, prophylactic bilateral mastectomy was associated with an 85%–100% risk reduction for breast cancer (10,11), and a prophylactic salpingo-oophorectomy was associated with an 85%–96% risk reduction for ovarian cancer and a 53%–68% risk reduction for breast cancer (12,13).

There are, however, specific methodologic problems associated with research evaluating the efficacy of prophylactic surgery. For example, was ovarian cancer more prevalent in families of women who opted for a prophylactic oophorectomy than it was in families of the comparison group? Might cancer events be overselected because women elected BRCA mutation testing after their cancer diagnosis? Might cancer events be overselected because a woman’s cancer diagnosis was the reason for prophylactic surgery in one of her relatives, while both of them are included in the study? The aim of this commentary is to discuss various biases that may occur in studies that estimate the risk reduction after prophylactic surgery. These insights may help evaluate previous investigations and help plan future efficacy studies.

**ILLUSTRATION OF DECISION-MAKING PROCESS WITHIN A FAMILY**

Studies of the efficacy of prophylactic surgery often include relatives, either because the study is family-based or because the study is center-based, and some members of the same family are counseled at the same center. Bias may arise if familial relationships are ignored in the analyses because individual decisions regarding genetic testing and preventive measures are likely to be influenced by cancer events that occur in relatives. In a hypothetical family (Fig. 1), woman 8 decided to seek advice about her cancer risk because her mother (woman 4) and grandmother (woman 1) had breast cancer and her aunt (woman 3) had ovarian cancer. Because genetic testing was unavailable at the time, she was advised to undergo breast screening. She informed her sisters and they also started screening. As soon as genetic testing for BRCA1/2 mutations became available, woman 8 visited a clinical genetic center. Her mother (woman 4), being the only living relative who had been diagnosed with breast cancer, was asked for permission to test her DNA. She agreed, and because she was found to be a carrier of a BRCA1 germine mutation, woman 8 could be tested. Woman 8 was found not to be a carrier of the mutation. Her sisters did not wish to be tested but continued with breast screening. However, one of her sisters (woman 6), diagnosed with breast cancer some time later, decided to be tested after all and was found to be a carrier. Woman 7 was very upset by the events happening to that sister and began to consider prophylactic surgery. After woman 7 was found to be a carrier, she opted for a bilateral mastectomy. Woman 5 continued breast screening and was not interested in genetic testing.

The scenario above highlights the potential dependency between cancer diagnosis within the family and individual decisions of relatives to undergo screening, DNA testing, and/or prophylactic surgery. If these events are assumed to be independent in studies that include several members of the same family, bias such as confounding by indication and familial-event bias (see below), may arise. Rebeck et al. (14) mentioned that 59% of the women were related to at least one other study subject, and 32% were related to at least four other study subjects; Meijers-Heijboer et al. (11) reported that they included a maximum of four study subjects from the same family. Despite acknowledging the relationship among study participants, neither of these studies (11,14) considered dependency between events within a family. By selecting the appropriate time period for members of one family to be at risk, bias can be prevented. In addition, the validity of efficacy studies may be increased by careful selection of study subjects.

**BIASES ASSOCIATED WITH SELECTION OF STUDY SUBJECTS**

When evaluating the efficacy of prophylactic surgery, the aim is to identify two groups of women who differ in the exposure of interest, namely prophylactic surgery, but who are, or in the...
Table 1. Efficacy of prophylactic surgery in women with a high risk of breast and/or ovarian cancer: overview of published studies*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Study population</th>
<th>Follow-up</th>
<th>Cancer end point</th>
<th>Risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartmann et al. (10)</td>
<td>Retrospective cohort study with external comparison</td>
<td>All women who underwent a BPM at a single center between 1960 and 1993 and who were retrospectively tested for BRCA1/2 mutation status. BPM+, 26 women with known BRCA1/2 mutation status, one woman with unknown status. Comparison with two penetrance models from Easton (1,30) and Struwing (31).</td>
<td>Start BPM+, date of BPM Follow-up: 14 years</td>
<td>BC BPM+, 0 BC/366 person-years* Expected: Easton model, 10 BC Struwing model, 7 BC Easton model, HK = 0 (95% CI = 0 to 0.59) Struwing model, HK = 0 (95% CI = 0 to 0.84)</td>
<td></td>
</tr>
<tr>
<td>Meijers-Heijboer et al. (11)</td>
<td>Retrospective and prospective cohort study</td>
<td>All BC-tree BRCA1/2 mutation carriers monitored for BC/OC at a single center. BPM+, 76 women BPM-, 63 women</td>
<td>Start: BPM+, date of BPM BPM-, date of start of screening Follow-up: 3 years (range = 0–8 years)</td>
<td>BC BPM+, 0 BC/219 person-years BPM-, 8 BC/318 person-years HR = 0 (95% CI = 0 to 0.36)</td>
<td></td>
</tr>
<tr>
<td>Struwing et al. 1995 (25)</td>
<td>Retrospective cohort study with external comparison</td>
<td>Within all families (≥2 OC, ≥1 BC diagnosed before age 50 years) ascertained between 1969 and 1980 at a single center (n = 12). All BC/OC-free first-degree relatives from BC/OC probands (n = 390). BPM+, 44 women BPM-, 346 women</td>
<td>Start: BPM+, date of BPO BPM-, date of family ascertainment Follow-up: 9 years (range = 0–48 years)</td>
<td>OC BPM+, 2 OC/460 person-years O/E general population = 13 (95% CI = 1 to 47) BPM-, 8 OC/1665 person-years O/E general population = 24 (95% CI = 10 to 47)</td>
<td></td>
</tr>
<tr>
<td>Rebeck et al. 2002 (12)</td>
<td>Retrospective cohort study with prospective follow-up</td>
<td>All known BRCA1/2 mutation carriers with no OC history at 11 centers (n = 331). BPM+, 259 women BPM-, 292 women, matched on age (±5 years), mutation, and center (randomly selected)</td>
<td>Start: BPM+, date of BPO BPM-, date of family ascertainment Follow-up: 11 years (range = 0–43 years)</td>
<td>BC BPM+, 21 BC/1059 person-years BPM-, 60 BC/1600 person-years HR = 0.47 (95% CI = 0.29 to 0.77)</td>
<td></td>
</tr>
<tr>
<td>Rebeck et al. 2002 (12) (part 2)</td>
<td>Retrospective cohort study with prospective follow-up</td>
<td>All known BRCA1/2 carriers at 11 centers and no BC history (n = 241). BPM+, 99 women BPM-, 142 women, matched on age (±5 years), mutation and center, randomly selected</td>
<td>Start: BPM+, date of BPO BPM-, date of matched surgical subject Follow-up: 2 years (range = 0–6 years)</td>
<td>OC§ BPM+, 1 OC/191 person-years BPM-, 5 OC/139 person-years HR = 0.15 (95% CI = 0.02 to 1.31)</td>
<td></td>
</tr>
<tr>
<td>Kauff et al. 2002 (13)</td>
<td>Prospective cohort study</td>
<td>All BRCA1/2 mutation carriers (age &gt;35 years) with no BPO or OC history before date of testing at a single center between 1995 and 2001 (n = 170). BPM+, 98 women (BC, n = 69) BPM-, 72 women (BC, n = 45)</td>
<td>Start: BPM+, date of BPO BPM-, date of testing Follow-up: 2 years (range = 0–6 years)</td>
<td>BC BPM+, 3 BC/127 person-years BPM-, 8 BC/120 person-years HR = 0.32 (95% CI = 0.08 to 1.20)</td>
<td></td>
</tr>
<tr>
<td>Kauff et al. 2002 (13) (part 2)</td>
<td>Prospective cohort study</td>
<td>All BRCA1/2 mutation carriers (age &gt;35 years) with no BPO or OC history (BC history allowed) before date of testing at a single center between 1995 and 2001 (n = 131). BPM+, 69 women (BC, n = 40) BPM-, 62 women (BC, n = 40)</td>
<td>Start: BPM+, date of BPO BPM-, date of testing Follow-up: 2 years (range = 0–6 years)</td>
<td>BC BPM+, 3 BC/127 person-years BPM-, 8 BC/120 person-years HR = 0.32 (95% CI = 0.08 to 1.20)</td>
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</table>

*BC = breast cancer; BPM+ = bilateral prophylactic mastectomy; BPM− = no bilateral prophylactic mastectomy; BPO+ = bilateral prophylactic oophorectomy; BPM− = no bilateral prophylactic oophorectomy; OR = odds ratio; CI = confidence interval; HR = hazard ratio; O/E = observed; OC = ovarian cancer.

†If the woman with unknown mutation status was a BRCA1/2 carrier, then one expected breast cancer per 370 person-years and the Easton model HK = 0.11 and the Struwing model HR = 0.15.

§Calculated from numbers in paper.

§Coelomic epithelial cancer in ovary or peritoneum.
Fig. 1. Hypothetical family pedigree (A) and time scales of female family members (B) being tested for BRCA1/2 mutations. Numbers refer to female family members. A) Open circle = living female; filled circle = living female with diagnosed breast or ovarian cancer; circle with diagonal line = deceased female; open square = living male; open square with diagonal line = deceased male; += BRCA1/2 mutation; – = no BRCA1/2 mutation; B number = age at breast cancer diagnosis; O number = age at ovarian cancer diagnosis. B) t = date of death; Scr = date of start screening; BRCA+ and BRCA- = date of genetic testing for BRCA1/2 mutation status (+ = carrier; – = noncarrier); PS = date of prophylactic surgery.

analysis can be made, similar with regard to other factors associated with disease outcome (15,16). Ideally, this could be accomplished in a randomized clinical trial, but randomization for prophylactic surgery is clearly unethical. Thus, observational study designs such as cohort studies are commonly used, but they can introduce several forms of bias.

Confounding by Indication

Selection of an appropriate comparison (i.e., nonsurgery) group for a valid evaluation of the cancer risk reduction after prophylactic surgery is difficult because BRCA1/2 mutation status is associated with a wide range of penetrance estimates (17–19). In our hypothetical family (Fig. 1), it is likely that, if the sister of woman 7 had not been recently diagnosed with cancer, woman 7 may have considered prophylactic surgery. Moreover, had her sister been diagnosed with ovarian cancer rather than breast cancer, woman 7 might have preferred a prophylactic salpingo-oophorectomy. Thus, more cancer in the family leads to more prophylactic surgery, and the type of the prevailing cancer in the family may affect the type of surgery. Consequently, women who choose prophylactic salpingo-oophorectomy may have an inherently greater risk of ovarian cancer than women who do not, possibly resulting from a specific BRCA1/2 mutation (20,21) or to as yet unknown modifying genes. A comparison of surgery and nonsurgery subjects from families with BRCA1/2 mutations and a different baseline risk of ovarian cancer could thus lead to an underestimation of risk reduction from prophylactic salpingo-oophorectomy. Such underestimation would result in a bias referred to as “confounding by indication.”

In their report on breast cancer risk after prophylactic salpingo-oophorectomy, Rebbeck et al. (14) mentioned the possibility of confounding by indication. The authors indicated that analyses stratified by ovarian cancer history were not feasible because 80% of the families had at least one family member with ovarian cancer. However, if an ovarian cancer family history was more frequent in the surgery group than in the nonsurgery group, selection bias would have been likely, and a subset analysis limited to women with an ovarian cancer family history might have been more valid. To date, none of the efficacy studies on prophylactic surgery for breast and/or ovarian cancer have considered possible differences in penetrance between families of BRCA1/2 mutation carriers with and without prophylactic surgery.

Because of the similar underlying genetic cancer risk among siblings, confounding by indication could be reduced by matching women who undergo prophylactic surgery with their sisters who do not. Sister matching was used by Hartmann et al. (22). Investigators should also consider the age difference between sisters and the influence of cancer occurrence in one sister on the other sisters’ decisions regarding prophylactic measures (see the “Biases Associated With Start of Follow-Up” section). An obvious requirement for sister matching would be that the nonsurgery sisters are also proven BRCA1/2 mutation carriers. Because awareness of BRCA1/2 mutation status may be rare among cancer-free sisters, an alternative approach to sister matching could be a comparison of BRCA1/2 mutation carriers with and without prophylactic surgery within groups of families with a clearly specified cancer history (i.e., with or without ovarian cancer) or specific BRCA1/2 mutations.

Breast Cancer Risk Reduction After Prophylactic Bilateral Salpingo-Oophorectomy: Survival Bias From Competing Risk of Ovarian Cancer

When evaluating breast cancer risk reduction associated with prophylactic salpingo-oophorectomy among BRCA1/2 mutation carriers, the occurrence of ovarian cancer may reduce available person-years at risk, especially among those in the nonsurgery group. Although it was suggested previously that this loss to follow-up would imply survival bias (14), survival bias will occur only if loss to follow-up resulting from dying of ovarian cancer changes the risk of breast cancer in the remaining study group. There are two reasons to think that this indeed is the case. First, compared with other BRCA1 mutations, the central region
of the BRCA1 gene has been associated with a higher risk of ovarian cancer and a lower risk of breast cancer (18). If women with mutations in the central regions—suggested by the presence of ovarian cancer in their family—opt for a salpingo-oophorectomy more often than women with mutations in other parts of the gene, their intrinsic risk of breast cancer would be lower than the risk of the comparison group of carriers with mutations throughout the BRCA1 gene, which would result in an overestimation of the breast cancer risk reduction. This bias by indication may be increased by differential loss to follow-up. Women with mutations in the central region of the gene who have not opted for prophylactic surgery may develop ovarian cancer and die from this disease more often than women with other mutations. Thus, the appropriate subgroup in the comparison group may contribute fewer person-years at risk during follow-up. This increase in confounding by indication during follow-up is, in fact, survival bias. If bias by indication is properly taken into account, this potential survival bias will be avoided.

Second, what may apply to confounding by indication may also apply to confounding in general, especially when one genetic mutation is associated with increased risks of two diseases that also share other risk factors. If confounding is not controlled for, dying from ovarian cancer may change the background breast cancer risk of the remaining comparison group.

Tumors Diagnosed at Prophylactic Surgery: Detection Bias

If a clinically undetected tumor is found in tissue removed during prophylactic surgery, the surgery did not prevent tumor occurrence, although it may increase life expectancy. How this possible favorable effect of surgery should be incorporated in the analysis is debatable. On the one hand, the woman cannot attribute person-years as a cancer-free person. On the other hand, had she not opted for surgery, the tumor might not have been diagnosed during follow-up. By counting the event in the surgery group, cancer risk is overestimated and efficacy is underestimated. By excluding the event, efficacy may be overestimated. Thus, for a conservative estimate of the efficacy of the intended prophylactic surgery, the cancer should be counted as an event in the surgery group, as in Rebbeck et al. (12).

In addition, it is critically important to estimate the efficacy of prophylactic surgery after exclusion of the women diagnosed at surgery. Such exclusion might generate a more realistic estimate of efficacy for women who undergo prophylactic surgery and prove to be cancer-free. The final evaluation of the efficacy of prophylactic surgery should be based on survival studies, in which women diagnosed at surgery should clearly be included in the surgery group.

Biases Associated With Start of Follow-Up

To guarantee that the baseline cancer risk of the surgery and nonsurgery groups are similar, the selection of the comparison group (BRCA1/2 carrier, free of cancer, and no prophylactic surgery) should not depend on cancer occurrence. A clear definition of the starting point of follow-up, at which time the subject should be free of cancer, is essential in this context.

Date of Ascertainment of the Family

Before BRCA mutation testing became available in Western countries in 1995, the efficacy of prophylactic surgery was usually investigated in women selected from families with a high incidence of breast and/or ovarian cancers. Within these families, there is the possibility of ascertainment bias (23), which implies an overestimation of cancer risk because cancer events are included in the analysis that occurred before the date the first family member started to be screened or counseled (i.e., the date of ascertainment). For example, cancer risk would be overestimated if women 1, 3, and 4 (Fig. 1) were included in the analyses. Ascertainment biases could be controlled for by starting follow-up from the date woman 8 decided to be screened, the date of ascertainment for this family, or later (see Fig. 1). If follow-up for the nonsurgery group starts at the date of ascertainment, then for the surgery group, the person-years between the dates of ascertainment and surgery—which are cancer-free by definition—should not be excluded, as first depicted by Gail et al. (24). If follow-up starts at date of prophylactic surgery, these cancer-free person-years might be added to the person-years of the nonsurgery group.

For example, Struwig et al. (25) investigated the occurrence of primary serous carcinoma of the peritoneum after prophylactic oophorectomy in a group of 12 families with multiple ovarian cancer cases. All women diagnosed with breast and/or ovarian cancer before the date of ascertainment for the family were correctly excluded, and the cancer-free first-degree family members of the excluded cases were selected into the study. Thus, ascertainment bias was avoided, but it is not clear whether the cancer-free person-years of the surgery group were allocated to the nonsurgery group. That allocation would reduce the cancer risk in the nonsurgery group and subsequently prevent an overestimation of the reduction of cancer risk after preventive surgery. In the study of Meijers-Heijboer et al. (11) person-years were correctly allocated.

Date of BRCA Mutation Test Result: Cancer-Induced Testing Bias

In recent publications (11–13), only women with a proven BRCA1 or BRCA2 mutation were selected for risk reduction analyses to obtain a homogeneous group regarding underlying cancer risk. The addition of this eligibility criterion may lead to testing bias, especially in retrospective cohort studies.

Most women without cancer would generally not consider prophylactic surgery unless they are certain about their BRCA mutation carrier status (Fig. 1, woman 7). Hence, help with the decision-making process regarding prophylactic surgery is often the reason women without cancer seek genetic testing. Consequently, the date of testing generally precedes the date of the prophylactic surgery. However, testing behavior in women who do not seek prophylactic surgery is more complicated. Some women who do not undergo prophylactic surgery may be identified as mutation carriers only because of their cancer diagnosis (Fig. 1, women 4 and 6). Many women who do not consider prophylactic surgery and remain cancer-free may not undergo genetic testing at all (Fig. 1, woman 5) and are, therefore, not selected for study. This differential selection of identified mutation carriers with cancer from the total group of mutation carriers may lead to an overestimation of cancer incidence in the nonsurgery group if the cancer event is included in the analysis. Because of this cancer-induced testing bias, cancer risk reduction might be overestimated.

To evaluate the possible differential selection of the nonsurgery group that might result in cancer-induced testing bias, the mean age of testing for those who develop cancer during follow-up and that for an age-matched sample that remains cancer free,
might be compared. It is also informative to know the chronologic order of the dates of testing and cancer occurrence within the nonsurgery group, as illustrated in the study by Meijers-Heijboer et al. (11). In this study, women were included who visited the Family Cancer Clinic for breast cancer screening between 1992 and 2000. BRCA mutation testing was possible beginning in 1994, and only two of 76 (2.6%) women who underwent a prophylactic bilateral mastectomy received a molecular diagnosis at surgery, i.e., after the start of follow-up. For the women in the nonsurgery group who remained cancer-free, no proportion of women tested during follow-up was given. However, among the eight women who developed breast cancer in the nonsurgery group, four women were tested after their cancer diagnosis. This high proportion suggests that breast cancer is overrepresented among the tested mutation carriers in the surveillance group, which might result in a cancer-induced testing bias, i.e., an overestimation of the risk reduction.

Another example of a situation in which cancer-induced testing bias could occur is found in the retrospective cohort study of Rebeck et al. (12), in which they evaluated ovarian and breast cancer risk after prophylactic oophorectomy in BRCA1/2 mutation carriers. Follow-up of the nonsurgery group started at the date of the matched subjects’ prophylactic oophorectomy—a date at which they were cancer-free. Seventy-one percent of the women in the surgery group were tested more than 1 year after the prophylactic surgery. In one analysis, the date of genetic testing was used as the start of follow-up instead of the date of the prophylactic surgery. The estimated hazard ratio was essentially unchanged. However, it is not clear which date of testing was used for the nonsurgery group in this analysis: the date of testing of their matched subject or their own date of testing. In the last case, an unchanged hazard ratio indeed suggests lack of cancer-induced testing bias. Thus, cancer-induced testing bias could be avoided by starting follow-up from the date of individual test results or later, as done by Kauf et al. (13).

**Date of Prophylactic Surgery: Familial-Event Bias**

The decision by women with an increased risk for breast and/or ovarian cancer to choose prophylactic surgery is often influenced by family events, such as a recently diagnosed cancer or a cancer-related death in a family member (e.g., woman 6 in Fig. 1). Therefore, it may not be enough to start follow-up at the date of testing to avoid bias, if members of the same family are selected into both the surgery and nonsurgery groups.

Suppose women 5, 6, and 7 from the hypothetical family shown in Fig. 1 had decided to undergo DNA testing together with woman 8 (Fig. 2). The women were found to be BRCA1/2 mutation carriers like their mother and, for the time being, they continued with breast cancer screening. When woman 6 was diagnosed with breast cancer, woman 7 felt insecure about screening and opted for a prophylactic bilateral mastectomy, whereas woman 5 continued breast cancer screening. Women 5 and 6 might be chosen as age-matched controls for woman 7, but if follow-up starts at the individual date of testing, the breast cancer diagnosed in woman 6 (which was the direct reason for the prophylactic surgery in woman 7) would be counted as an event in the analysis. Clearly, this “familial-event bias” would result in an overestimation of the breast cancer risk among women in the nonsurgery group and, consequently, in an overestimation of the breast cancer risk reduction after prophylactic bilateral mastectomy.

Thus, if members of the same family are selected into the study population, the date of prophylactic surgery of the surgery subject should be considered in the analyses, as illustrated by Hartmann et al. (22). Three cases of breast cancer were observed in a group of high-risk women who had undergone prophylactic bilateral mastectomy. The expected number of breast cancers among women without prophylactic bilateral mastectomy was 5.9—a number derived from a group of sisters without bilateral mastectomy, from age 18 to the end of follow-up and corrected for age. However, if the number of follow-up years of the control group was included from the date of the proband’s prophylactic bilateral mastectomy, the expected number of breast cancers would be 37.4, which is 30% less. The reduction of breast cancer risk calculated in these two ways did not differ considerably (94.3% versus 92.0%), possibly because the number of observed breast cancers among women in the prophylactic bilateral mastectomy group was still small.

Familial-event bias may not be restricted to studies that are family-based by design, such as the study of Hartmann et al. (22), mentioned above. The matching factors used in many other efficacy studies (i.e., center, mutation, age) may favor the se-

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**Fig. 2.** Hypothetical model of age-specific start of follow-up in a woman with prophylactic surgery (woman 7) and her potential control sisters (women 5 and 6). Scr = age at start of screening; BRCA+ = age at test result for BRCA1/2 mutation; PS = age at prophylactic surgery; Pseudo-PS = age at the date of the prophylactic surgery of the sister; B number = age at breast cancer diagnosis; dotted line = follow-up from age at pseudo-prophylactic surgery; broken line = follow-up from age at BRCA+ test result; solid line = follow-up from age at pseudo-prophylactic surgery, or age at BRCA+ test result, whichever came last; BC = breast cancer.
lection of relatives into the nonsurgery group. This selection may unintentionally increase bias. To avoid familial-event bias, the best choice for start of follow-up is the age at which the control herself was tested or the age of the control at the date of her relative’s prophylactic surgery (i.e., her age at ‘pseudo-surgery,’ Fig. 2), whichever came last. Because women in the comparison group should be cancer-free at this point, in our example, woman 6 should be excluded as a control and woman 5 would remain an eligible control, with her age at pseudo-surgery as the starting point of follow-up.

**CONFOUNDING**

**Efficacy of Prophylactic Bilateral Mastectomy:**

**Confounding Effect of Salpingo-Oophorectomy**

Among premenopausal women from the general population, breast cancer risk is reduced by about 50% after a salpingo-oophorectomy (26,27). An important issue when evaluating breast cancer risk reduction after prophylactic bilateral mastectomy is the possibility that women opting for this prophylactic surgery are more likely to also opt for prophylactic salpingo-oophorectomy. Therefore, prophylactic salpingo-oophorectomy is a strong confounder in studies assessing the efficacy of prophylactic bilateral mastectomy and might even modify the effect. In one study (11), prophylactic salpingo-oophorectomy was included as a time-dependent covariate in a statistical regression model (11). However, if the majority of women in the prophylactic bilateral mastectomy group also opt for a prophylactic salpingo-oophorectomy, this method may produce residual confounding, and an analysis restricted to women who underwent both prophylactic surgeries might be preferable (even though a salpingo-oophorectomy may not be an effect modifier).

**Confounding by Other Risk Factors of Breast and Ovarian Cancer**

The decision to opt for testing or prophylactic surgery may be related to risk factors for breast and/or ovarian cancer. Meijers-Heijboer et al. (28) suggested that parous women may be more inclined to opt for prophylactic surgery than nulliparous women. Because parity is an established factor that decreases breast and ovarian cancer risk, this confounder, if not adjusted for, would result in an overestimation of the efficacy of prophylactic surgery. So far, known risk factors have hardly been considered in efficacy studies, with one exception (14) (see “Breast Cancer Risk Reduction After Prophylactic Bilateral Salpingo-Oophorectomy: Survival Bias From Competing Risk of Ovarian Cancer” section).

It is clear that researchers should adjust for confounders in analyses of the efficacy of prophylactic surgery; however, the method for incorporating changes in risk factors that are direct consequences of prophylactic surgery, such as lack of pregnancies or hormone replacement therapy after a salpingo-oophorectomy, is less straightforward. The adjusted effects of the surgery and of such risk factors might be considered together in the overall analyses. For example, if long duration of hormone replacement therapy increases breast cancer risk in BRCA1/2 mutation carriers, as it does for the general population, then it might be informative to estimate the efficacy of a prophylactic salpingo-oophorectomy followed or not followed by hormone replacement therapy.

**CONCLUSIONS**

Several forms of bias can occur in studies investigating the efficacy of prophylactic surgery in women at high risk for breast and/or ovarian cancer. First, confounding by indication may lead to an underestimation of the risk reduction after prophylactic surgery; for example, the frequency of ovarian cancer in a family may be associated with the decision to opt for a prophylactic salpingo-oophorectomy, whereas ovarian cancer may be less prevalent in the family of nonsurgery subjects. Second, cancer-induced testing bias may occur when studies are restricted to known BRCA1/2 mutation carriers. For example, women not undergoing prophylactic surgery may be identified as mutation carriers only because they develop breast and/or ovarian cancer at some point, whereas women who do not consider prophylactic surgery and remain cancer-free may not undergo genetic testing and are therefore not selected for the study. Third, familial-event bias may arise when the decision to opt for prophylactic surgery is influenced by a recent cancer diagnosis in a close relative, while this relative also is selected into the nonsurgery group. Both the cancer-induced testing bias and the familial-event bias may lead to an overestimation of risk reduction by prophylactic surgery. To date, these potential biases have largely gone unrecognized in efficacy studies.

An ideal study design for determining the efficacy of prophylactic surgery is a prospective follow-up study, but for power considerations, a follow-up study on a cohort that is carefully retrospectively identified and includes those who died, is an acceptable alternative. A cohort exists of BRCA1/2 carriers that are free of the tumor under study at the start of follow-up. It may not be necessary to use a matched design (29), as long as confounders are properly considered in the analysis. Potential effect modifiers are the region-specific genetic mutation and a salpingo-oophorectomy when evaluating the efficacy of a prophylactic mastectomy. Potential confounders are center, age, parity, and other known risk factors of the tumor under study. The common risk factors of breast and ovarian cancer should be carefully examined. Follow-up of the surgery group starts at the age of prophylactic surgery or at the age of the genetic test result, whichever comes last. Follow-up of the nonsurgery subjects also starts at the age of the genetic test result. However, if a relative of the control is included in the surgery group, the age of the control at the time of the relative’s prophylactic surgery is used as the start of follow-up, if this age is greater than the age at testing.

If we consider the evaluation of prophylactic surgery to be essential for evidence-based counseling of women at high-risk for breast and/or ovarian cancer, we should consider the potential biases seriously, particularly because most biases result in an overestimation of the benefit from prophylactic surgery. It might, however, not always be possible to resolve all of the methodologic problems of efficacy studies, or resolution would be only at the expense of a considerable loss of power. In such settings and for studies already published, a more critical discussion about potential biases, including an estimation of their direction and quantitative impact is needed. Only in this way can BRCA1/2 mutation carriers, clinical geneticists, and treating physicians obtain more accurate information about the true extent of cancer risk reduction from prophylactic surgery. This valid estimate of risk reduction may become even more crucial in the future when data become available regarding the efficacy...
of new surveillance methods, such as magnetic resonance imaging, and new chemoprevention agents, such as raloxifene.

REFERENCES


NOTE

Manuscript received August 5, 2002; revised February 14, 2003; accepted April 29, 2003.