Prophylactic Oophorectomy – What is the Effect on Breast and Ovarian Cancer for BRCA+ Women

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PROPHYLACTIC OOPHORECTOMY – WHAT IS THE EFFECT ON BREAST AND OVARIAN CANCER FOR BRCA+ WOMEN

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of prophylactic bilateral oophorectomy in women with documented BRCA1 or BRCA2 mutations.

BACKGROUND

Ovarian cancer is the most common cause of death among women who develop gynecologic malignancies, the second most common gynecologic malignancy, and the fifth most common cancer in women in the United States (Jernal et al. 2003). The majority of primary ovarian tumors derive from epithelial cells, although they can also arise from other cell types (germ cell tumors, sex cord-stromal tumors, and mixed cell type tumors). Epithelial ovarian cancer is the fifth leading cause of cancer-related death in women in the United States (Jernal et al. 2003). Incidence rates, which have remained relatively stable over the past 20 years, are higher in white compared to black women (Mink et al. 2002). The lifetime risk of developing ovarian cancer is 1.4 to 1.8 percent for women living in the United States (Hartge et al. 1994). The peak incidence of ovarian cancer is 56 years, borderline tumors occur approximately 10 years earlier (Memarzadeh et al. 2001). The incidence increases with age up to age 80 and then declines. The mean age at diagnosis of ovarian cancer is younger among women with hereditary or familial disease. Data from the Gilda Radner Familial Ovarian Cancer Registry showed a mean age at diagnosis of 54 versus 61 years in the general population (Piver 2002).

Risk factors identified in epidemiologic studies include Caucasian race, nulligravity, early age of menarche or late age of menopause, family history of ovarian or endometrial cancer, and prolonged duration of ovulation. It is estimated that genetic factors (BRCA mutation, hereditary nonpolyposis colorectal cancer gene) account for 10 percent of ovarian cancer cases (Li et al. 2001). Population-based studies have identified a personal history of breast cancer (particularly at a young age) or a family history of either breast or ovarian cancer as one of the strongest risk factors, increasing a woman's risk of ovarian cancer two to six-fold (Bergfeldt et al. 2002).

Women with a single family member affected by ovarian cancer have a 4 to 5 percent risk, while those with two affected relatives have a 7 percent risk of developing the disease. In contrast, women with hereditary ovarian cancer syndromes, defined as having at least two first-degree relatives with ovarian cancer have a lifetime risk as high as 25 to 50 percent for developing ovarian cancer (Daly et al. 1998).
BACKGROUND, continued

Hereditary ovarian cancers generally occur in women about 10 years earlier than sporadic disease. These neoplasms have been described as a component of several different syndromes: site-specific ovarian cancer, breast-ovarian cancer, and the cancer family syndrome (Lynch syndrome II). Serous adenocarcinoma is the most common histopathology phenotype (Piver 2002).

Studies of kindreds with site-specific ovarian and breast-ovarian cancer syndromes led to the discovery of two genetic susceptibility genes: BRCA1 and BRCA2, which may account for as many as 90 percent of hereditary ovarian cancers. Founder effects of BRCA1 and BRCA2 have been identified in several populations, most notably in Ashkenazi Jewish individuals, where up to 2.5 percent (1 in 40) of the population carry one of four genetic mutations (Struwing et al. 1995a; Abeliovich et al. 1997). In comparison, 1 in 280 people in the general population carry mutations in these genes (Ford et al. 1995).

Over five hundred mutations with diverse phenotypes and degrees of penetrance have been identified in BRCA1 and BRCA2. This allelic heterogeneity confounds our ability to predict the significance of disease for all mutation carriers. The proportion of ovarian cancer cases in the general population that is attributable to BRCA1 has been estimated at 5.7 percent below age 40 years, 4.6 percent between ages 40 and 49 years, and 2.1 percent between ages 50 and 70 years (Ford et al. 1995). There also may be an increased risk for colon cancer (and prostate cancer in male carriers). Fewer ovarian cancers (3.8 percent) are associated with germline mutations in BRCA2.

The absolute risk of ovarian cancer associated with the presence of BRCA gene mutations is unclear; rates ranging from 16 to 60 percent have been published. One report suggested that a woman with a strong family history of breast or ovarian cancer, or both, who also had a germ-line mutation of BRCA1, had a 60 percent lifetime risk of ovarian cancer (Ford et al. 1994). However, other studies of women who did not have a strong family history of cancer have found this risk to be much lower (Struwing et al. 1997; Risch et al. 2001; Brose et al. 2002). As an example, the risk of ovarian cancer by the age of 70 among carriers of either other population-based reports of women with BRCA 1 mutations, the ovarian cancer risk by age 70 was 36 BRCA gene was only 16 percent in one review of Ashkenazi Jewish women (Struwing et al. 1997). In two and 41 percent, respectively (Risch et al. 2001; Brose et al. 2002). Overall, the lifetime risk of developing ovarian cancer in BRCA1 carriers, BRCA2 carriers, and the general population appears to be 40 to 50, 20 to 30, and 1.4 percent, respectively (Boyd 2003).
BACKGROUND, continued

Women at risk for hereditary cancer syndromes should have a thorough pedigree analysis. A geneticist should evaluate the family pedigree for at least three generations, if available, to provide appropriate counseling and informed consent for genetic testing (ASCO 2003).

The management of a woman with a strong family history of ovarian cancer depends upon her age, reproductive plans, and the extent of risk. Plans must be individualized because the value of screening with transvaginal ultrasound, serum CA 125, or other procedures has not been clearly established in women at high risk (Jacobs et al 1999).

Current recommendations for screening women with BRCA1 and BRCA2 gene mutations include transvaginal sonography and serum CA 125 every six to 12 months beginning between the ages of 25 and 35 years (Burke et al. 1997). The utility of oral contraceptive pills in reducing the risk of ovarian cancer in BRCA1 and BRCA2 families is unclear. In one case control study of 207 women with hereditary ovarian cancer and 161 of their sisters as controls, the adjusted odds ratio for ovarian cancer associated with any past oral contraceptive use was 0.5 (95 % CI, 0.3 to 0.8), and use for at least six years was associated with a 60 percent reduction in risk (Narod et al. 1998). Conflicting data were noted in a second population-based case control study of Jewish women in Israel which included 840 women with ovarian cancer, 244 of whom had a BRCA1 or BRCA2 mutation, and 751 controls, 13 of whom were carriers (Modan et al. 2001). Oral contraceptive use appeared to decrease the risk of ovarian cancer in noncarriers but not carriers, while increasing parity was a protective factor for both carriers (12 percent decrease in the odds ratio of ovarian cancer per birth) and noncarriers. Another population-based case control series of 767 women aged 20 to 69 years with epithelial ovarian cancer and 1367 control women examined the risk of cancer relative to family history and duration of oral contraception (Walker et al. 2002). BRCA status was not assessed. Use of oral contraceptives for 48 months in women with a mother or sister with ovarian cancer resulted in a greater reduction in disease-risk than in women whose family history was negative, 88 (95 percent CI, 59 to 97) and 49 (95 percent CI, 35 to 60) percent, respectively. Short-term use (<48 months) was associated with a 28 (95 percent CI, 13 to 41) percent reduction in ovarian cancer risk in both groups. The wide range of risk reduction was due to the small number of women with an affected first-degree relative (33 cases and 24 controls), and because few of these women used oral contraceptives long-term (three cases and nine controls). Lastly, an analysis of six case-control studies including 2768 cases and 6274 controls noted a reduced risk of ovarian cancer with any use of oral contraceptives compared to no use (OR 0.66, 95 percent confidence interval 0.55 to 0.79).
BACKGROUND, continued

CI 0.56 to 0.79) (Bosetti et al. 2002). The protective effect persisted across strata such as age, parity, menopausal status, and family history of breast or ovarian cancer, and was stronger for use greater than 5 years. In the absence of definitive data, it still seems reasonable to recommend oral contraceptive use for premenopausal women at high risk for ovarian cancer (Eisen et al. 2000).

Prophylactic oophorectomy is an option for reducing the risk of ovarian cancer in women with a hereditary disposition for this malignancy. This procedure is considered because of the limited efficacy of current modalities for early detection and the high mortality associated with ovarian cancer. When considering prophylactic oophorectomy, it is important to differentiate between women with a possible rare familial ovarian cancer syndrome and those with the more common presentation of an isolated family member with ovarian cancer, without evidence of a hereditary pattern. The former are candidates for prophylactic oophorectomy while the latter are not.

The efficacy of prophylactic oophorectomy is compromised by the fact that these women remain at risk for developing "ovarian-like" cancers in the peritoneum, also known as papillary serous carcinoma of the peritoneum (Menczer et al. 2003). Papillary serous carcinoma of the peritoneum (PSCP) refers to diffuse involvement of the peritoneal surfaces with a neoplasm identical to papillary serous carcinoma of the ovary; the ovaries may or may not be present. Clinically this malignancy is associated with high mortality, similar to that of stage III epithelial ovarian cancer (Eisen et al. 2000). Three sources for the extra-ovarian malignancies have been proposed: microscopic rests of residual ovary, preexisting carcinomatosis not detected at the time of prophylactic surgery, or multifocal origin of peritoneal tissue, with disease starting de novo in the peritoneum, which shares a common embryonic origin with müllerian duct epithelium. Papillary serous carcinoma of the peritoneum should be considered a phenotypic variant of ovarian cancer that is relatively rare, but diminishes the efficacy of either screening programs or of prophylactic oophorectomy.

The minimum operation required for prophylaxis is a bilateral salpingo-oophorectomy (BSO). This can be performed by laparotomy or laparoscopy; the latter is generally preferable since it is associated with much less morbidity. A methodical survey of the entire peritoneum should be performed along with peritoneal lavage, omental biopsy, a Pap smear of the diaphragm, and liberal biopsies of any peritoneal irregularity at the time of prophylactic surgery (Lu et al. 2000). These recommendations are based upon the experience of gynecologic surgeons at the Cancer Risk and Prevention Service at the Dana-Farber Cancer Institute.
BACKGROUND, continued

As an example, a study of 50 prophylactic oophorectomies in women attending a familial breast and ovarian cancer clinic reported the discovery of four occult malignancies in these patients (Lu et al. 2000). Two of the malignancies were PSCP, the third was a multifocal borderline ovarian cancer, and the fourth, was an intercystic borderline ovarian cancer. None of these tumors was suspected at the time of preoperative ultrasound or CA 125 screening and only one of the four was identified at the time of initial surgical exploration. Three of these women carried the BRCA1 mutation and the fourth had BRCA2.

Multiple sections of ovaries prophylactically removed from women at high risk for ovarian cancer should be examined microscopically for occult carcinoma (Eisen et al. 2000; Leeper et al. 2002). Peritoneal lavage may also show foci of malignancy, although the sensitivity, specificity, and prognostic value of positive lavage cytology have not been determined. Multiple small series of woman at high risk for ovarian cancer undergoing prophylactic oophorectomy, BSO-oophorectomy, or hysterectomy reported finding several women with occult malignancy in the ovary or fallopian tube and most had malignant cells identified in lavage fluid (Colgan et al. 2002; Leeper et al. 2002). One patient had malignant cells confined to the peritoneal lavage specimen with no evidence of carcinoma in the uterus, tubes, or ovaries. No long-term follow-up data are available.

The mean age of diagnosis of hereditary ovarian cancer ranges from 48 to 51 years (Eisen et al. 2000). Timing of prophylactic oophorectomy requires balancing the procedure-related consequences of infertility and premature menopause, against the risk of ovarian cancer; the surgical risks themselves are quite small by comparison. Generally, prophylactic oophorectomy should be performed as soon as childbearing is completed or by age 35, since the benefit may diminish with age. Oophorectomy prior to menopause may be associated with a number of adverse effects including onset of menopausal symptoms (hot flashes, sleep disturbance, and urogenital changes), an increased risk of cardiovascular disease (Colditz et al. 1987), and an increased risk of osteoporosis and fractures.

Women with a hereditary predisposition to ovarian cancer should understand potential alternatives to prophylactic BSO-oophorectomy. One option is intensive screening with CA 125 and ultrasonography, although data regarding the efficacy of this approach are limited.
TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

Prophylactic oophorectomy is a surgical procedure and is not subject to US Food and Drug Administration or other agency approval.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The benefits of prophylactic oophorectomy are postulated to be prevention of or a marked reduction in the incidence of ovarian cancer and mortality due to ovarian cancer. There may also be a reduction in the incidence of breast cancer. Risks include surgical morbidity (bleeding, infection, and pain); post-surgical reduction in quality of life, and procedure related mortality. Premature menopause induced by oophorectomy may result in early menopausal symptoms and an increase in osteoporosis, fractures, and cardiovascular disease.

Two studies were identified which assessed health outcomes in patients with known BRCA1 or BRCA2 mutations (Kauff et al. 2002; Rebbeck et al. 2002) and an additional study was identified evaluating outcomes in patients with strong family histories of breast and ovarian cancer (Struewing et al. 1995b).

The first study to attempt to quantify the effectiveness of preventive surgery was a multicenter study involving the National Cancer Institute (NCI), Creighton University, and the United Kingdom (Struewing et al. 1995b). The prospective incidence of malignancy, especially of tissues derived from coelomic epithelium (primarily ovary, fallopian tube, and peritoneum), was compared between women with similar genetic risk who have or have not undergone oophorectomy. Data from 12 NCI families were reported. Prospective observation ran from the date of family ascertainment until the date of cancer incidence, death, or December 31, 1992. Average follow-up was 4.0 years for subjects who chose BSO and 4.6 years for the controls. The ratio of observed to expected cancers was calculated for both groups of women using Connecticut Tumor Registry data adjusted for age, race, and birth cohort.
TECHNOLOGY ASSESSMENT (TA), continued

Genetic risk based on linkage analysis could not be estimated for most families because most affected individuals were dead and no DNA was available. No information was available on the BRCA status of these women, but it is likely that many of the women in the study carried BRCA disease-associated mutations, given the selection criteria of the study. The limited genetic information, lack of matching, and small number of participants limit the inferences that can be drawn from these data.

Two cohort studies in BRCA mutation carriers were published in the same issue of the New England Journal of Medicine. The first (Kauff et al. 2002) prospectively compared the effect of risk-reducing BSO-oophorectomy with that of surveillance for ovarian cancer on the incidence of subsequent breast cancer and BRCA-related gynecologic cancers in women with BRCA mutations. All women with BRCA1 or BRCA2 mutations identified during a six-year period were offered enrollment in a prospective follow-up study. A total of 170 women, 35 years of age or older who had not undergone bilateral oophorectomy, chose to undergo either surveillance for ovarian cancer or risk-reducing BSO-oophorectomy. Follow-up involved an annual questionnaire, telephone contact, and reviews of medical records. The time-to-cancer in the two groups was compared by Kaplan-Meier analysis and a Cox proportional-hazards model. Of 170 women who met the criteria for entry, 98 chose to undergo BSO-oophorectomy. There were no significant differences between the two groups of patients in terms of mean age, percentage with BRCA1 or BRCA2 mutations, mean number of first- and second-degree relatives with breast, ovarian, fallopian tube, or primary peritoneal cancer, or percentage with a history of breast cancer, systemic chemotherapy, or oral-contraceptive use. More women in the BSO-oophorectomy group had bilateral mastectomy before the start of follow-up (30% versus 14%, p=0.02). The women were on average 47 years old and 61% were BRCA1 carriers. Average follow-up for both groups was 2 years.

This study, while small, includes only women with known deleterious BRCA mutations. The women in the two groups were comparable at inception of the cohort and were followed concurrently. Additionally, the data were analyzed using appropriate time-to-event statistical techniques. Results from this study directly apply to the central issue of this review.

The final study (Rebbeck et al. 2002) retrospectively investigated whether BSO-oophorectomy reduced the risk of cancers of the coelomic epithelium and breast in women who carry germline, disease-associated BRCA1 or BRCA2 mutations. A total of 551 women with disease-associated germ-line BRCA1 or BRCA2
TECHNOLOGY ASSESSMENT (TA), continued

mutations were identified from 11 North American and European registries and studied for the occurrence of ovarian and breast cancer. The BRCA1 and BRCA2 mutation status of all subjects was confirmed by direct mutation testing. The incidence of ovarian cancer was determined in 259 women who had undergone bilateral prophylactic oophorectomy and in 292 matched controls who had not undergone the procedure. Potentially eligible controls were matched with subjects who had undergone prophylactic BSO-oophorectomy according to type of mutation, treatment center, year of birth, and age at oophorectomy. In a subgroup of 241 women with no history of breast cancer or prophylactic mastectomy, the incidence of breast cancer was determined in 99 women who had undergone bilateral prophylactic oophorectomy and in 142 matched controls. There were no significant differences between the two groups of patients in terms of mean age, percentage with BRCA1 or BRCA2 mutations, parity, number of live births, or oral-contraceptive use. More women in the BSO-oophorectomy group used hormone replacement therapy (48% versus 20%, p<0.001). The women were on average 41 years old and 83% were BRCA1 carriers. The length of postoperative follow-up for both groups was at least eight years.

This is the definitive study of prophylactic oophorectomy among women with known deleterious BRCA mutations. It is unlikely that a randomized, clinical trial will be done given the relatively small population of mutation carriers, the high risk of cancer associated with the mutations, the emotional and health issues associated with the intervention, and the widespread use of prophylactic oophorectomy in BRCA1 or BRCA2 mutation carriers. The women in the two groups were comparable at inception of the cohort by design (matching) and were followed concurrently. The major difference between the two groups was the more frequent use of hormone replacement therapy in the oophorectomy group, which is not unexpected as most women experience significant vasomotor symptoms immediately following oophorectomy. It has been standard of care to start women on hormone therapy after oophorectomy. Again, these data were analyzed using appropriate time-to-event statistical techniques.

Unfortunately, none of the studies reported data on mortality or quality of life after oophorectomy.

Level of Evidence: 3

TA Criterion 2 is met.
TECHNOLOGY ASSESSMENT (TA), continued

TA Criterion 3: The technology must improve the net health outcomes.

Incident ovarian cancer or papillary serous carcinoma of the peritoneum (Table 1)

The results of studies that assessed the effect of oophorectomy on incident coelomic epithelial cancers (ovarian, fallopian tube, papillary serous peritoneal carcinoma) are summarized in Table 1. Struewing et al (1995b) reported two cases of intraabdominal carcinomatosis among 44 women followed after oophorectomy compared to 8 cases of ovarian cancer in 346 women who were 1st degree relatives of patients with ovarian cancer and had not undergone oophorectomy. Compared with Connecticut Tumor Registry data adjusted for age, race, and year of birth, there was a 24-fold (95% CI 10-47) excess of ovarian cancer among women who did not have oophorectomy and a 13-fold (95% CI 1-47) excess among women with oophorectomy. The confidence intervals around these estimates are large and no direct statistical comparison was made between the two groups. These results are suggestive of a protective effect of oophorectomy, but the sample was not large enough to demonstrate a statistically significant effect. Furthermore, many of the women in the study may not have carried a high-risk mutation that would tend to weaken the benefit of oophorectomy.

In their prospective cohort, Kauff et al (2002), specifically addressed the question of the effects of oophorectomy in women who carried a BRCA1 or BRCA2 mutation known to cause disease. The 72 women who elected surveillance were followed with twice-yearly serum CA-125 measurements, twice yearly transvaginal ultrasound, and once or twice yearly gynecologic exams. Ovarian cancer was diagnosed in four women and primary peritoneal cancer in one woman. During the 191 woman-years of follow-up in the 98 women who chose to undergo BSO, primary peritoneal cancer was diagnosed in one woman (p=0.04 compared with the surveillance only group). The relative risk for the development of ovarian cancer was 0.15 (95% CI 0.02-1.31). These data are limited by the relatively short follow-up (2 years) in this cohort. The authors attempted to address this by using the Kaplan-Meir curves to project the proportion of women free from ovarian, fallopian tube, or primary peritoneal cancer at five years. Among the BSO group, 98% were projected to be free from a diagnosis of ovarian cancer after five years of follow-up compared with only 83% of the surveillance group.
TECHNOLOGY ASSESSMENT (TA), continued

The final study (Rebbeck et al. 2002) used a retrospective design, but was significantly larger than the study of Kauff et al (551 subjects versus 170 subjects) and had much longer follow-up (>8 years versus 2 years). Six women who underwent prophylactic oophorectomy (2.3 percent) received a diagnosis of stage I ovarian cancer at the time of the procedure; two women (0.8 percent) received a diagnosis of papillary serous peritoneal carcinoma 3.8 and 8.6 years after bilateral prophylactic oophorectomy. Among the controls, 58 women (19.9 percent) received a diagnosis of ovarian cancer after a mean follow-up of 8.8 years. Among the 37 control women who had ovarian cancer for which the stage was known, 11% had stage I cancer, 16% had stage II, 65% had stage III and 9% had stage IV. With the exclusion of the six women whose cancer was diagnosed at surgery, prophylactic oophorectomy significantly reduced the risk of coelomic epithelial cancer (relative risk 0.04; 95% CI, 0.01 to 0.16). If the upper bound of the 95% confidence interval is taken as a conservative estimate, prophylactic oophorectomy reduced the risk of cancer of the coelomic epithelium by approximately 84%. This study is limited by its retrospective design. No standard surveillance approach was used in the intervention or control group, though cases and controls were matched by treatment center and the 11 investigational centers had considerable expertise and research interest in hereditary breast-ovarian cancer.

Despite these data, the impact of prophylactic oophorectomy on survival from ovarian cancer and on overall survival remains undetermined.
### Table 1: Ovarian cancer after salpingo-oophorectomy in patients with BRCA1 or BRCA2 mutations

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Groups</th>
<th>N</th>
<th>Follow-up (years)</th>
<th>RR (95% CI)</th>
<th>Cancer at surgery</th>
<th>Later cancer</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebbeck</td>
<td>Retrospective cohort with matched controls</td>
<td>BRCA1/2 carriers with oophorectomy</td>
<td>259</td>
<td>8.2</td>
<td>0.04 (0.01-0.16)</td>
<td>6 (2.3%)</td>
<td>2 (0.8%)</td>
<td>Age 35-50 0.03 (0.01-0.20)</td>
</tr>
<tr>
<td>2002</td>
<td>From 11 registries, international. Match on BRCA mutation, year of birth, age at oophorectomy, treatment center</td>
<td>BRCA1/2 carriers without oophorectomy</td>
<td>292</td>
<td>8.8</td>
<td></td>
<td></td>
<td>58 (19.9%)</td>
<td>Age &gt;50 0.11 (0.02-0.76)</td>
</tr>
<tr>
<td>Kauff</td>
<td>Prospective cohort with concurrent controls</td>
<td>BRCA1/2 carriers with oophorectomy</td>
<td>98</td>
<td>2.0</td>
<td>0.15 (0.02-1.31) adjusted for multiple outcomes</td>
<td>NR</td>
<td>1 (1%)</td>
<td>Nominal p=0.04. Study also looked at breast cancer outcomes. Thus, they adjusted their CI for multiple outcomes.</td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td>BRCA1/2 carriers without oophorectomy</td>
<td>72</td>
<td>2.1</td>
<td></td>
<td></td>
<td>5 (7%)</td>
<td></td>
</tr>
<tr>
<td>Struwing</td>
<td>Prospective cohort with concurrent controls</td>
<td>Oophorectomy in patient with strong family history of breast/ovarian cancer</td>
<td>44</td>
<td>10.5</td>
<td>NR</td>
<td>NR</td>
<td>2</td>
<td>Observed/Expected 13 (1-47) compared with Connecticut Tumor Registry data</td>
</tr>
<tr>
<td>1995</td>
<td>All are 1st degree relatives of a patient with breast and/or ovarian cancer</td>
<td>No oophorectomy in patient with strong family history of breast/ovarian cancer</td>
<td>346</td>
<td>4.8</td>
<td></td>
<td></td>
<td>8</td>
<td>Observed/Expected 24 (10-47) compared with Connecticut Tumor Registry data</td>
</tr>
</tbody>
</table>

NR = Not reported

BSO – Bilateral Salpingo-oophorectomy
CI – Confidence Interval
PSCP – Papillary Serous Carcinoma of the Peritoneum
Incident breast cancer (Table 2)

The results of studies that assessed the effect of oophorectomy on incident breast cancer are summarized in Table 2. Struewing et al (1995b) reported three cases of breast cancer among 44 women followed after oophorectomy, compared to 14 cases of breast cancer in 346 women who were 1st degree relatives of patients with cancer and had not undergone oophorectomy. Compared with Connecticut Tumor Registry data adjusted for age, race, and year of birth, there was a 7-fold (95% CI 4-12) excess of breast cancer among women who did not have oophorectomy and a 2.7-fold (95% CI 0.5-8) excess among women with oophorectomy. Again, the confidence intervals around these estimates are large and no direct statistical comparison was made between the two groups. These results are suggestive of a protective effect of oophorectomy on breast cancer incidence, but the sample was not large enough to demonstrate a statistically significant effect.

In their prospective cohort (Kauff et al. 2002), Kauff et al specifically addressed the question of the effects of oophorectomy in women who carried a BRCA1 or BRCA2 mutation known to cause disease. Only 131/170 women in the full study were used in the breast cancer sub-study, because 39 had previously undergone bilateral mastectomy. The prevalence of bilateral mastectomy was more common in the oophorectomy group than in the surveillance group (30% versus 14%, p=0.02). All women were recommended to have annual mammographic examinations, to have clinical breast examinations two to four times per year, and to perform breast self-examinations monthly. Breast cancer was diagnosed in 8/62 (12.9%) women in the surveillance group and 3/69 (4.3%) women in the BSO group (p=0.07). The relative risk for the development of breast cancer was 0.32 (95% CI 0.08-1.20). These data are limited by the relatively short follow-up (<2 years) in this cohort. The authors attempted to address this by using the Kaplan-Meir curves to project the proportion free from breast cancer at five years. Among the BSO group, 94% were projected to be free from a diagnosis of breast cancer after 5 years of follow-up compared with only 79% of the surveillance group.
The study of Rebbeck et al (Rebbeck et al 2002) is larger and has much longer follow-up (>10 years for breast cancer outcomes). Twenty-one women who underwent prophylactic oophorectomy (21.2 percent) subsequently were diagnosed with breast cancer compared to 60 (42.3%) women in the control group. Prophylactic oophorectomy significantly reduced the risk of breast cancer (relative risk 0.47; 95% CI, 0.29 to 0.77). Again, this study is limited by its retrospective design, but it is the largest and highest quality of the studies available. Even if the upper bound of the 95% confidence interval is used as a conservative estimate, prophylactic oophorectomy reduced the risk of breast cancer by approximately 23%.
Table 2: Breast cancer after salpingo-oophorectomy in patients with BRCA1 or BRCA2 mutations

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Groups</th>
<th>N</th>
<th>Follow-up (years)</th>
<th>RR (95% CI)</th>
<th>Breast cancer</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebbeck</td>
<td>Retrospective cohort with matched controls</td>
<td>BRCA1/2 carriers with oophorectomy. No mastectomy or prior breast cancer.</td>
<td>99</td>
<td>10.7</td>
<td>0.47 (0.29-0.77)</td>
<td>21 (21.2%)</td>
<td>Age 35-50 0.49 (0.26-0.90) Age &gt;50 0.52 (0.10-2.70)</td>
</tr>
<tr>
<td></td>
<td>From 11 registries, international. Match on BRCA mutation, year of birth, age at oophorectomy, treatment center</td>
<td>BRCA1/2 carriers without oophorectomy. No mastectomy or prior breast cancer</td>
<td>142</td>
<td>11.9</td>
<td></td>
<td>60 (42.3%)</td>
<td></td>
</tr>
<tr>
<td>Kauff</td>
<td>Prospective cohort with concurrent controls</td>
<td>BRCA1/2 carriers with oophorectomy</td>
<td>69</td>
<td>1.8</td>
<td>0.32 (0.08-1.20)</td>
<td>3 (4.3%)</td>
<td>Nominal p=0.07. Study also looked at ovarian cancer outcomes. Thus, they adjusted their CI for multiple outcomes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA1/2 carriers without oophorectomy</td>
<td>62</td>
<td>1.9</td>
<td></td>
<td>8 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>Struwing</td>
<td>Prospective cohort with concurrent controls</td>
<td>Oophorectomy in patient with strong family history of breast/ovarian cancer</td>
<td>44</td>
<td>11.0</td>
<td>NR</td>
<td>3 (6.8%)</td>
<td>Observed/Expected 2.7 (0.5-8) compared with Connecticut Tumor Registry data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No oophorectomy in patient with strong family history of breast/ovarian cancer</td>
<td>346</td>
<td>4.6</td>
<td></td>
<td>14 (4%)</td>
<td>Observed/Expected 7.0 (4-12) compared with Connecticut Tumor Registry data</td>
</tr>
</tbody>
</table>

NR = Not reported

BSO – Bilateral Salpingo-oophorectomy
CI – Confidence Interval
PSCP – Papillary Serous Carcinoma of the Peritoneum
TECHNOLOGY ASSESSMENT (TA), continued

Quality of life

One study (Tiller et al. 2002) assessed the psychological impact of prophylactic oophorectomy in a prospective cohort of women with a strong family history of breast-ovarian cancer. None of the patients knew their BRCA mutation status at the initiation of the study. The Impact of Events Scale was used to assess change in levels of anxiety over three years of follow-up. After three years of follow-up, ten women who had undergone oophorectomy were compared to 73 women who did not have surgery. Prophylactic mastectomy was associated with a significant reduction in anxiety related to ovarian cancer (p=0.029). Among 22 women who had undergone oophorectomy in total, 86% reported a high degree of satisfaction with their decision to have the procedure. The study was small and did not include broader measures of quality of life. Furthermore, women who were most anxious about ovarian cancer were more likely to undergo oophorectomy (p NS) and thus it is not surprising that they had larger reductions in anxiety. Ideally, a broader range of quality of life instruments should be used to assess the change in quality of life associated with oophorectomy in patients with known BRCA mutations.

TA Criterion 3 is met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

There are no established alternatives to oophorectomy for the prevention of coelomic epithelial cancers in carriers of BRCA1 or BRCA2 mutations. The data on the use of oral contraceptives are conflicting (Narod et al. 1998; Modan et al. 2001). There is one case-control study suggesting that tubal ligation may decrease the risk of ovarian cancer in carriers of BRCA1, but not BRCA2 (Narod et al. 2001). Currently, most institutions use regular surveillance with transvaginal ultrasound and serum CA-125 measurements, but surveillance has not been shown to reduce the proportion of ovarian cancers diagnosed in late stages or to affect mortality (Jacobs et al. 1999).

Several decision analyses have estimated the impact of prophylactic oophorectomy on life expectancy in women with the BRCA1 or BRCA2 mutations. In the first, oophorectomy was estimated to decrease ovarian cancer incidence by 50%. Compared with intensive surveillance, this resulted in an average gain of 0.2 to 1.8 years of life gained for a 30-year-old woman (Schrag et al. 2000). In the second
TECHNOLOGY ASSESSMENT (TA), continued

study, which assumed a larger benefit from oophorectomy, prophylactic oophorectomy improved
survival by 2.6 years (Grann et al. 2002). The combination of prophylactic oophorectomy and
tamoxifen resulted in the largest increase in life expectancy (6.3 years). Gains in life expectancy in
both studies declined with age at the time of surgery and were minimal for 60-year-old women,
although there was little loss in life expectancy if the surgery was performed at age 40 rather than age
30.

TA Criterion 4 is met.

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Both open and laparoscopic BSO are established procedures that have been routinely performed at
many medical centers, primarily to treat benign and malignant ovarian tumors. When performed with
care, there is no reason to believe that results will be different outside of investigational settings.

The patient's decision to undergo prophylactic oophorectomy should be made in the context of
adequate counseling, based upon an understanding of actual risk, not upon perceived risk. The
choice must be made knowing that the post-prophylactic risk of developing papillary serous
carcinoma of the peritoneum, closely related to ovarian cancer, while low, is not zero.

TA Criterion 5 is met.
OPINIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center has not reviewed this topic.

Centers for Medicare and Medicaid Services (CMS)

A specific reference to this procedure was not identified through a search of the CMS website.

American College of Obstetrics and Gynecology (ACOG)

ACOG has been asked to provide a position/opinion statement and representation at the meeting.

Association of Northern California Oncologists (ANCO)

ANCO has been asked to provide a position/opinion statement and representation at the meeting.

Medical Oncology Association of Southern California (MOASC)

MOASC has been asked to provide a position/opinion statement and representation at the meeting.
CONCLUSION

It will be many years before a genotypically defined population of women undergoing prophylactic BSO-oophorectomy can be followed in a prospective manner for a sufficient duration of time to define the operation's impact on survival. In view of these circumstances, patients and physicians will have to make clinical decisions based upon incomplete information.

Three studies were identified which assessed the clinical impact of oophorectomy. The first study was small and included patients based on their family history and not on genotyping. The controls were not matched and comparisons were made only by calculating the observed to expected ratio for both breast and ovarian cancer using Tumor Registry data for controls. Incident breast and ovarian cancers both had observed-to-expected ratios that were half as high in the oophorectomy group compared with the control group. However, the confidence intervals for all estimates were large due to the small size of the study. Two studies specifically addressing the effect of oophorectomy in patients with known BRCA mutations were published in 2002. The first was a moderate sized, prospective cohort with about 2 years of follow-up. The relative risk associated with oophorectomy was 0.15 (95% CI 0.02-1.31) for ovarian cancer and 0.32 (95% CI 0.08-1.20) for breast cancer. The larger study included 259 patients who had undergone oophorectomy and 292 matched controls. Average follow-up was over 8 years for both groups. The relative risk associated with oophorectomy was 0.04 (95% CI 0.01-0.16) for ovarian cancer and 0.47 (95% CI 0.29-0.77) for breast cancer. The very strong, consistent reduction in the risk of ovarian cancer makes it extremely unlikely that this is an artifact of study design. The ideal study would be a randomized, clinical trial of oophorectomy, but this is unlikely ever to be done given the results of these studies. The effect on breast cancer is more modest and could reflect underlying selection bias in the case control study. The significantly higher use of hormone replacement therapy in the oophorectomy group is one indication that the groups differ, but this would tend to bias the results towards more breast cancers in the oophorectomy group. It is reassuring that these 3 studies with widely divergent study designs, found a similar 50% reduction in breast cancer incidence.

The evidence that oophorectomy decreases the incidence of breast and ovarian cancer is strong and consistent. Unfortunately there are minimal data on quality of life outcomes and no mortality data. Decision analytic models have attempted to address this deficiency. They consistently project a gain of 1-3 years in life expectancy and even greater gains when quality of life is considered.
CONCLUSION, continued

Women who choose to have prophylactic surgery should be counseled not only about potential efficacy, but also about the limitations of the procedure and potential alternatives. Women who have not completed their families can consider oral contraceptive pills for chemoprophylaxis. Data demonstrating the value of this approach are conflicting in BRCA gene carriers. Prophylactic BSO at age 35 or at the completion of childbearing is a reasonable alternative to intensive screening among women at the highest levels of risk for developing ovarian cancer. A laparoscopic bilateral BSO is the most expedient approach in women who desire oophorectomy. Preoperative counseling and informed consent should review the possibility of developing papillary serous carcinoma of the peritoneum. The possibility of finding an occult malignancy at the time of surgery and subsequent modifications to the planned procedure should also be discussed. Women should understand the consequences of hormonal ablation and should have a strategy in place for hormone replacement therapy in the postoperative period.

RECOMMENDATION

It is recommended that prophylactic oophorectomy for women with known BRCA1 or BRCA2 mutations associated with the breast-ovarian cancer syndrome meets California Technology Assessment Forum (CTAF) TA criteria.

October 8, 2003

REFERENCES


REFERENCES, continued
REFERENCES, continued


REFERENCES, continued

BSO – Bilateral Salpingo-oophorectomy
CI – Confidence Interval
PSCP – Papillary Serous Carcinoma of the Peritoneum


