The role of genetics in the clinical management of ovarian cancer
Olivier, R.I.

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Chapter 4

Additional salpingectomy after previous prophylactic oophorectomy in high risk women: sense or nonsense?

R.I. Olivier¹, M. A.C. Lubsen-Brandsma¹², H.H. van Boven³, M. van Beurden¹²

Departments of Gynaecology¹, and Pathology³, The Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Department of Gynaecology², Academic Medical Centre, Amsterdam, the Netherlands

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Abstract

Objectives: Since BRCA1/2 germline mutation carriers are also at a higher risk of developing fallopian tube carcinoma, resection of the fallopian tubes is currently included at the time of risk reducing surgery. In this study, we comment on the need of additional bilateral prophylactic salpingectomy (BPS) following previous bilateral prophylactic oophorectomy (BPO) in women at high risk of ovarian cancer.

Methods: Retrospectively, the medical files of 42 high-risk women, who had undergone BPO only, were reviewed.

Results: In our centre, risk reducing surgery consisted of BPO only for 42 women. Twenty-seven women received an informative letter in which counselling for additional BPS was offered. In total, 15 women opted for additional BPS. Surgery was performed with a mean interval of 65 months (range 6-101) in 10 BRCA1 carriers, one BRCA2 carrier, one BRCA1 and 2 carrier and three women with non-informative test results. The procedure was readily done by laparoscopy in 13 women and two needed a laparotomy. No post-operative complications had occurred. Histopathological examination revealed no malignancy.

Conclusions: We believe that additional risk reduction of cancer necessitates BPS in BRCA1/2 carriers after previous BPO. BPS after previous BPO was easily performed. Today, physicians should include resection of the fallopian tube at prophylactic surgery in high risk women and should consider additional BPS in women who have undergone BPO only.
Introduction

The average risk in BRCA1-mutation carriers by age 70 is 39% for ovarian cancer and for BRCA2 11%\(^1\). Therefore, these women often undergo bilateral prophylactic (salpingo-)oophorectomy (BP(S)O) to reduce the risk of ovarian cancer\(^2\). The detection of occult fallopian tube carcinoma in BPSO specimens of BRCA1/2 mutation carriers had implications for the surgical procedure\(^4\). Today, bilateral oophorectomy (BPO) should be extended to a bilateral salpingo-oophorectomy (BPSO) as prophylactic procedure\(^2,3\).

In 1997, following the identification of an occult fallopian tube carcinoma in a BPSO specimen, BPSO became the standard prophylactic surgical procedure in our center. A relative of a patient with occult fallopian tube carcinoma requested to undergo BPS after previous BPO and underwent this procedure. In addition, together with the medical ethical board of our institute, it was decided that the above had implications for all women who previously underwent BPO only. In the literature, the need for additional bilateral prophylactic salpingectomy (BPS) after previous BPO has not been addressed before. The aim of this report is to discuss the possible implications for high risk women with their fallopian tubes still in situ.

Patients and methods

Up to 1997, a total of forty-two women at high risk of developing ovarian cancer had undergone BPO. These women were determined to be at high-risk by the following criteria: BRCA1/2 germline mutation carriers or women with breast cancer from a hereditary breast cancer (HBC) family or women from a hereditary breast and ovarian cancer (HBOC) family. Data on the number of breast and/or ovarian carcinomas in the family were unknown.

DNA testing for known BRCA mutations was done either before risk reducing surgery or performed when DNA testing became available for these women. DNA analysis was performed using denaturing gradient gel electrophoresis, denaturing high performance liquid chromatography, protein truncation test, MLPA or mutation-specific tests\(^5\).

If no mutation at that time was identified in a person herself nor in her family, the DNA result was called inconclusive. If no mutation was found, while there was a family member with a proven BRCA1 mutation, she was called a non-carrier. In our institute, prophylactic surgery was also performed before the era of BRCA1 or 2 testing in women who were family member of a HBOC family.

Medical records of 42 women who had undergone a BPO were reviewed (Table 1). Fifteen of these 42 women were not contacted for counselling due to death (n=2), 70 years of age (n=1) or metastatic disease at the time of reviewing the clinical charts (n=5). Two women had metastatic breast cancer and three cases of papillary serous peritoneal cancer were diagnosed 27, 33 and 70 months after prophylactic oophorectomy and are described in detail elsewhere\(^2\). For seven women it was expected that hardly any fallopian tube tissue was left in situ after hysterectomy (n=1) or after previous BPO (n=6). Of these seven women, the histology reports concluded that tubal tissue had been removed with a length of more than 3 cm on both sides. Together with the medical ethical board of our institute it was decided to send an informative letter, in which the possibility of the occult fallopian tube carcinoma was discussed, to the other women, who were eligible for an additional BPS. Twenty-seven women received an informative letter in which counselling was offered. Seven women did not respond to the informative letter.
Three women choose not to undergo another surgical procedure after counselling; one has not made a final decision about salpingectomy and one woman was recently diagnosed with endometrial carcinoma. In total, the mean follow-up of the 27 women who underwent only bilateral oophorectomy was 66 months (range 1-109 months).

<table>
<thead>
<tr>
<th>DNA results</th>
<th>Additional BPS after BPO (N=15)</th>
<th>BPO (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 mutation</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>BRCA1 and 2 mutation</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Non-informative test results</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Not tested</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Non-carrier BRCA1</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Mean age at oophorectomy (yr, range)</td>
<td>42.7 (32-60)</td>
<td>48.7 (32-65)</td>
</tr>
<tr>
<td>Mean follow-up (months, range)</td>
<td>80 (64-112)</td>
<td>66 (1-109)</td>
</tr>
<tr>
<td>Mean age at salpingectomy (yr, range)</td>
<td>47 (37-65)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Salpingectomy

Laparoscopic 13 NA
Laparotomic 2 NA
Interval between BPO and BPS (months, range) 65 (6-101) NA
Age at diagnosis (yr, range) NA 57 (53-64)
Follow-up time to diagnosis (months, range) NA 60 (33-77)

NA: not applicable

For laparoscopy, three or four ports were used, with a 10-12 mm port placed in the midline and 5 mm ports placed laterally. A systematic exploration of the intra-abdominal surfaces and the viscera is performed. Fallopian tubes were removed within a laparoscopic sac using a cutting forceps.

After BPS, gross specimens of the fallopian tubes were step serial sectioned with intervals of 2-3 mm and entirely submitted for histological examination. This is routinely done in our pathology laboratory. Haematoxylin and eosin-stained slides were examined. Importantly, gross examination, before sectioning, included the measurement of the fallopian tubes, after overnight fixation in formalin.

Results

Fifteen women underwent an additional salpingectomy with a mean interval of 65 months after the prophylactic oophorectomy (range 6-101 months). No signs of intra abdominal pathology were observed. Salpingectomy was performed in 10 BRCA1 carriers, one BRCA2 carrier, one BRCA1 and 2 carrier and three women with non-informative test results. The procedure was readily done by laparoscopy in 13 women. One laparoscopic surgery was converted due to adhesions and one woman had a primary laparotomic bilateral salpingectomy, because of expected difficulties with the presence of a Marlex mesh. No major or minor postoperative complications occurred.
The histopathologic examination of the 30 additional removed fallopian tubes did not show any evidence of malignancy nor pre-malignant changes of the epithelium. The mean length of the additional removed fallopian tubes was 4.4 cm (range 1.5-9.0 cm).

**Discussion**

In our centre, a total of 15 women have undergone BPS after previous BPO. No signs of malignancy were found at histopathological examination. To our knowledge, this is the first paper addressing the issue of additional BPS after BPO. With a review of the literature of fallopian tube carcinoma in high risk women, the pros and cons will be discussed.

In the general population, the clinical and histopathological diagnosis of fallopian tube carcinoma is usually made at an advanced stage, despite the fact that fallopian tube carcinoma is characterized by a number of signs and symptoms as compared to ovarian carcinoma patients which have few signs. Prognostic factors in patients with early stage disease seems to differ between the two diagnoses. Advanced fallopian tube carcinomas are often histopathologically indistinguishable from and have a clinical behaviour similar to epithelial ovarian carcinomas. Importantly, patients are often diagnosed at high stage with poor prognosis. Baekelandt et al. recommended that the treatment and follow-up strategies for patients with ovarian cancer can be used in the management of higher stage patients with fallopian tube carcinoma. The incidence of both early and late fallopian tube carcinoma is not clear. An average annual incidence rate of fallopian tube carcinoma of 3.6 per 1 million women is reported in the US. In a screening study of 22000 women participating, three cases of early stage primary fallopian tube carcinoma were diagnosed. This number was higher than expected by national incidences figures.

The association between BRCA1/2 mutations and fallopian tube carcinomas has been recognized by histopathological examination of the prophylactic specimens. A population based study of fallopian tube carcinoma has revealed the presence of BRCA1/2 germline mutation in over 15% of fallopian tube carcinomas. Furthermore, Levine et al reported a mutation frequency of 17%. Brose et al found a 120 fold increased risk of fallopian tube carcinoma in BRCA1 mutation carriers. Compared to a risk in the general population of 0.025 %, the cumulative age-adjusted lifetime risk of fallopian tube cancer was 3.0% . These data strongly support that additional risk reduction of cancer may be achieved with BPS in BRCA1/2 carriers after previous BPO only.

A transition from benign epithelium through carcinoma in situ (CIS) to invasive fallopian carcinoma may be observed. Others have reported dysplastic changes in the fallopian tubes of women predisposed to developing ovarian cancer. In the study by Piek et al, the fallopian tubes of women predisposed to developing ovarian cancer harboured dysplastic changes, indicating an increased risk of developing tubal cancer. Of 12 women with a predisposition for ovarian cancer, six showed dysplasia and five had hyperplasic lesions.

We have examined the slides of fallopian tubes of the 15 high risk women for epithelial hyperplasia, atypia and carcinoma in situ. No pre-malignant lesions or malignancy was detected in our series; the fallopian tubes were completely submitted for histopathological examination. An explanation may be the lower mean age at additional salpingectomy (47 years) in our series. The median age of 151 patients was 61 years at time of diagnosis in the series of Baekelandt et al. Furthermore, the models presented by Hogg et al, could also be an explanation for the lack of dysplasia in our series. Because of rapid progression of the tumour, cancer precursors are not identifiable.
Screening strategies for ovarian cancer, including CA-125 and ultrasound, have been the subject of many studies in the general population and in high risk women. The high false-positive rate of TVUS and serum CA-125 and the failure to detect more than 57% of early-stage disease are cited as the major limitations. Similarly, the screening method may not be effective for the detection of early stage fallopian tube carcinoma. The risk reduction surgery is therefore an important option to consider for high risk women.

For seven women it was expected that hardly any fallopian tube tissue was left in situ after previous gynaecologic surgery. The histology reports concluded that tubal tissue had been removed with a length of more than 3 cm on both sides. Fallopian tubes are approximately 9 to 12 cm in length, extending from the uterine cornu to the infundibulum. In our series, the mean length of the additional removed tubes was 4.4 cm (range 1.5–9.0 cm) and is comparable with our data on the mean length of fallopian tubes removed at BPSO (4.3 cm; range 1.6–8.0; unpublished data). These lengths of the tubes at BPSO could well be explained by several reasons. The infundibulum and the ampullary portion of the fallopian tube account for approximately half of the fallopian tube. The gross examination and the measures are taken at the pathology laboratory after overnight formalin fixation. Because it is a muscular organ, shrinkage will influence the length, with individual variations. We believe that a mean length of 4.4 cm was to be expected and most certainly will include enough tissue from the ampulla.

The fallopian tubes have a dual blood supply, one by a branch of the uterine artery and one branch of the ovary artery. The dissection of the mesosalpinx at time of BPO could have otherwise, all women were postmenopausal and lacking the blood supply from the ovarian artery branch. In postmenopausal women, the vessels may be calcified, have thickened walls and narrowed lumens.

An unresolved issue remains the intramural portion, which is approximately 1 cm in length. Some authors suggest that a preventive hysterectomy should also be performed. However, it is known that fallopian tube carcinomas are more often located in the ampulla than in the istmic portion. Moreover, there are no long-term data to support hysterectomy in addition to bilateral salpingo-oophorectomy to reduce the risk of fallopian tube carcinoma. Furthermore, the complication rate is not negligible.

High risk women are also at risk of developing peritoneal papillary serous carcinomas (PPSC) and women who have undergone BP(S)O remain at risk. The cumulative risk of developing PPSC subsequent to risk reducing BPSO is less than 10%. In our study, there was no difference in follow-up after oophorectomy versus the interval between oophorectomy and additional salpingectomy (66 months versus 65 months respectively, table 1). Although three women, who had undergone only BPO developed PPSC and no PPSC was seen in the group with BPS, the present difference of PPSC may be chance. PPSC is considered as a primary tumour or as a metastasis of ovarian or fallopian tube carcinoma. A population-based study showed clinical similarities between ovarian carcinoma and PPSC, but it was stated that due to biomolecular differences concerning the clonal origin of the tumour, it cannot be ruled out that PPSC is separate entity. We believe that PPSC is part of the model, which consist of high-grade carcinomas, which are not screen detectable and rapidly progress.

The findings of PPSC only in BRCA1 carriers and not in BRCA2 carriers suggest that PPSC risk is higher among BRCA1 germline mutation carriers. BRCA1 carriers have a higher intrinsic ovarian cancer risk than BRCA2 mutation carriers and only few reports publish data on PPSC occurring in BRCA2 carriers. Foulkes et al reported two cases with BRCA2 mutation (mean age 56 years) after hysterectomy and BPSO. Unfortunately no data on follow-up of the cohort was
given. Six BRCA2 mutation carriers (mean age 59 year) versus 4 BRCA1 mutation carriers (mean age 59 years) were found in 22 cases of PPSC by Levine et al, but whether these cases developed after a prophylactic procedure is not mentioned \textsuperscript{14}. Mean age at diagnosis in our series was 57 years, while mean age of four BRCA2 carriers in our series was 51 years. It is too early to conclude that BRCA2 carriers face a lower risk than BRCA1 carriers of developing PPSC and a delayed age of onset might be the reason for our observation.

In conclusion, we choose to offer counselling on additional BPS to high risk women who underwent risk reducing BPO only. Although no (pre-) malignant lesions were found in our series, we believe additional BPS makes sense, because of an additional risk in BRCA1/2 carriers after previous BPO, based on 1) data in the literature, as discussed above, 2) finding of occult fallopian tube carcinoma in previous reports and 3) failure of early detection at screening. Today therefore, physicians should include resection of the fallopian tubes at prophylactic surgery in high risk women and should consider additional BPS in women who have undergone BPO only.
Reference List


