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Tubal epithelial lesions in salpingo-oophorectomy specimens of BRCA-mutation carriers and controls

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Abstract

Objective. A precursor lesion for ovarian carcinoma, tubal intraepithelial carcinoma (TIC), has been identified in BRCA-mutation carriers undergoing prophylactic bilateral salpingo-oophorectomy (pBSO). Other lesions were also identified in fallopian tubes, but different terminology, interpretation, and lack of knowledge of normal epithelium, have hampered to unravel their possible role in carcinogenesis. The aim of this study is to classify tubal epithelial lesions in BRCA-mutation carriers and controls to enable comparison of prevalence, area of localization, and possible malignant potential.

Methods. Two hundred twenty-six BRCA1/2-mutation carriers were included; ovaries and fallopian tubes, embedded completely, were reviewed. Controls included 105 women who underwent BSO for non-malignant reasons. Tubal epithelial lesions included the following categories: hyperplasia, minor epithelial atypia, TIC, and invasive carcinoma.

Results. Tubal neoplasia was identified in 7.1% (invasive carcinoma, 0.9%; TIC, 6.2%) of BRCA-mutation carriers compared to none in controls (p = 0.004, Fisher’s exact test). Hyperplasia and minor epithelial atypia were identified in 41.6% BRCA-mutation carriers and compared to 58.1% in controls (p = 0.005, Pearson’s chi square). Invasive carcinoma and TIC showed preference for the fimbrial ends (p = 0.027, Pearson’s chi square), while hyperplasia and minor epithelial atypia displayed more variation in localization.

Conclusions. Invasive tubal carcinoma and TIC were limited to BRCA-mutation carriers, whereas hyperplasia and minor epithelial atypia were commonly found in both BRCA-mutation carriers and controls. It is suggested that hyperplasia and minor atypia represent variations of normal tubal epithelium instead of premalignant lesions. Furthermore, total salpingectomy is strongly recommended as most but not all TIC occurred in the fimbriae.

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Introduction

Ovarian carcinoma is a highly aggressive disease which is most often diagnosed in an advanced stage. The majority of cases exhibit serous histology which can either be ovarian, fallopian tube, or peritoneal in origin [1]. Until now these three localizations of serous carcinoma are considered as a single disease entity (“ovarian carcinomas”) with respect to treatment and prognosis. Over the last decades the pathogenesis of ovarian carcinoma has been subject to debate. The traditional view of ovarian carcinogenesis assumes that ovarian carcinoma originates from the ovarian surface epithelium (mesothelium), which invaginates into the underlying stroma, resulting in epithelial inclusion cysts that eventually undergo malignant transformation [2].

However, these epithelial inclusion cysts were invariably present in both high risk cases and controls [3–5]. Recently, a predisposition for ovarian carcinoma was discovered in the fallopian tubes of women with a germline BRCA-mutation [6,7]. Prophylactic bilateral salpingo-oophorectomy (pBSO) is performed in the majority of BRCA-mutation carriers, which reduces the risk of ovarian carcinoma by 80% [8,9]. Incidental findings of occult invasive carcinoma and precursor lesions such as serous tubal intraepithelial carcinoma (TIC) were found in prophylactically removed fallopian tubes from women with a BRCA-mutation [6,7]. Recent studies have established that TIC is present in 1–17% of these women [10–17].

Histopathological investigation of fallopian tube specimens of women diagnosed with serous ovarian carcinomas reported the presence of TIC in up to 50% of these women [11,18,19]. Recent morphologic and molecular genetic studies provided compelling evidence that a proportion of primary serous ovarian tumors actually arise from these precursor lesions: unique and identical p53 mutations were found in both the serous ovarian carcinoma and corresponding...
TIC, indicating a monoclonal relation [20–22]. It is hypothesized that (pre)malignant cells of the tubal epithelium may exfoliate into the tubal lumen and migrate by retrograde flow to the abdominal cavity; implantation of these cells onto the peritoneum or ovarian surface might result in the development of serous carcinomas [8,20,23].

Histological entities other than TIC were also described in the tubal epithelium, for which various terminologies were used such as dysplasia, atypical hyperplasia or mucosal epithelial proliferations [15]. Because of difficulties in interpretation it is still unclear whether all these subtypes have a causal role in the development of tubal or ovarian carcinoma. Furthermore, because most studies did not include a proper control group of healthy women without a BRCA-mutation, knowledge of normal tubal epithelium is poor. This knowledge of tubal epithelial lesions in the general population is essential to enable differentiation of true premalignant lesions from lesions representing variants of normal tubal epithelium.

In this study, we report on tubal epithelial lesions in the largest cohort to date of women with a confirmed BRCA 1/2 mutation who underwent pBSO, in comparison to a large control group of women that underwent BSO for non-malignant reasons. Identified prevalences and areas of localization in the tubes will be compared between both groups to enable identification of tubal epithelial lesions representing possible premalignancies and lesions that are most likely variations of normal tubal epithelium. In addition, a scheme for classification of tubal epithelial lesions is suggested.

Materials and methods

Clinical data

Between January 1996 and December 2009, all women with a known germline BRCA1/2 mutation opted for pBSO at the Radboud University Nijmegen Medical Centre (RUNMC), The Netherlands, were identified. Patients with surgery for preoperatively suspected or tubal lesions were not included in this study. The Dutch nation-wide pathology database (PALGA) was used to identify a control group of women who underwent BSO for non-malignant reasons. Identified prevalences and areas of localization in the tubes will be compared between both groups to enable identification of tubal epithelial lesions representing possible premalignancies and lesions that are most likely variations of normal tubal epithelium. In addition, a scheme for classification of tubal epithelial lesions is suggested.

Pathology

All pBSO specimens of BRCA-mutation carriers were completely embedded, according to standard protocol. The fallopian tubes were cross sectioned at 3 mm interval, except for the fimbrial ends that were sectioned longitudinally to enable maximum exposure of the tubal plicae. One haematoxylin and eosin stained section was produced from each paraffin block. Fallopian tube specimens of control cases were not completely embedded. From these fallopian tube representative sections of the fimbria, ampulla and/or isthmus were selected and embedded for histological examination. All available tubal sections were reviewed by two pathologists (MB, JB) with ample experience in gynecological pathology, being blinded for clinical characteristics. Tubal or ovarian epithelial lesions and their locations were recorded. Consensus was reached concerning the criteria for tubal epithelial lesions before the start of the present study. In case of discrepant diagnoses consensus was reached between both pathologists. In the present study, the following entities were distinguished in the fallopian tubes: benign epithelium, hyperplasia, minor epithelial atypia, TIC (tubal intraepithelial carcinoma, non-invasive severe dysplasia and carcinoma in situ), and (occult) tubal invasive carcinoma.

Benign fallopian tube

The normal fallopian tube is lined by non stratified epithelium with a mixture of three cell types (Fig. 1). Ninety percent of the tubal mucosa is layered by secretory and ciliated cells. The third cell type is the intercalated cell, which is inconspicuous and considered to be a secretory cell as well.

Hyperplasia

Tubal hyperplasia is defined as cellular crowding, stratification, occasional tufting of cells, some loss of nuclear polarity, but the absence of nuclear atypia. Cellular crowding is visible when the number of secretory cells exceeds the number of ciliated cells (Fig. 2A).

Minor epithelial atypia

Features for histological diagnosis of minor epithelial atypia are slightly enlarged, rounded nuclei with irregular cell membrane outlines, slightly enlarged nuclear/cytoplasm ratio, nuclei with slight loss of polarity and inconspicuous nucleoli (Fig. 2B). Minor epithelial atypia is not visible at low power magnification. It comprises epithelial lesions that fulfill some but not all of the criteria for TIC.

Tubal intraepithelial carcinoma (TIC)

Tubal intraepithelial carcinoma is identifiable at low power magnification, displaying a row of dark and thickened epithelium. It is characterized by disorganized cellular crowding and nuclear stratification, and consists of secretory cells in absence of ciliated cells. Other features include mitotic figures, high nuclear/cytoplasm-ratio, nuclear pleomorphism with loss of polarity and prominent nucleoli (Fig. 2C).

Tubal invasive carcinoma

Histological features of tubal invasive carcinoma are identical to TIC, but with the addition of an invasive component (Fig. 2D).

Fig. 1. Benign fallopian tube epithelium with secretory and ciliated cells (level of magnification: 200 ×; level of magnification of inset: 400 ×).
Statistical analysis

Pearson’s chi square and, if appropriate, the Fisher’s exact test were used to test associations between categoric variables. The Kruskal–Wallis and Mann–Whitney U test were used to compare medians between different independent samples. All statistical analyses were performed using SPSS software version 18.0 (SPSS Inc, Chicago, IL) and \( p < 0.05 \) (two-sided test) was considered statistically significant.

Results

A total number of 226 women with a confirmed BRCA-mutation were included in the current study (149 BRCA1 and 77 BRCA2 mutations). Also, 105 controls were included. Women with a BRCA-mutation had a median age of 44 years (range 24–70) compared to controls with a median age of 48 years (range 22–60) (\( p = 0.04 \), Mann–Whitney U test; Table 1). The median age specified for type of BRCA-mutation was 42 years for the BRCA1 mutation carriers and 48 years for the BRCA2 mutation carriers. Distribution of menopausal status was comparable for both groups; 40% of the BRCA-mutation carriers were postmenopausal and 32% of the controls (85 of 212 vs 33 of 103; \( p = 0.17 \), Pearson’s chi square; Table 1). Median number of parity was two for both BRCA-mutation carriers and controls, but the BRCA-mutation carriers had more often three or more children compared to controls (Table 1). Breast carcinoma prior to BSO was significantly more often diagnosed in BRCA-mutation carriers compared to controls (81 of 226 (36%) vs 1 of 105 (1%); \( p < 0.001 \), Pearson’s chi square; Table 1).

Table 1

<table>
<thead>
<tr>
<th>Population characteristics</th>
<th>BRCA 1/2</th>
<th>Controls</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>44 (24–70)</td>
<td>48 (22–60)</td>
<td>0.04&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>127 (60%)</td>
<td>70 (68%)</td>
<td>0.17&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>85 (40%)</td>
<td>33 (32%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>14</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td>0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>No children</td>
<td>34 (16%)</td>
<td>23 (24%)</td>
<td></td>
</tr>
<tr>
<td>1–2 children</td>
<td>110 (50%)</td>
<td>60 (62%)</td>
<td></td>
</tr>
<tr>
<td>3+ children</td>
<td>75 (34%)</td>
<td>14 (14%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>History of breast carcinoma</td>
<td>81 (36%)</td>
<td>1 (1%)</td>
<td>&lt;0.00&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sterilization</td>
<td>8</td>
<td>8</td>
<td>0.11&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mann Whitney U test.
<sup>b</sup> Pearson chi square.
seven cases TIC was identified bilaterally and in another seven cases unilaterally. Of the seven cases with unilateral TIC, the contralateral tubal epithelium showed benign epithelium in three cases, hyperplasia in one, and minor epithelial atypia in three. Two cases were identified with invasive tubal carcinoma which occurred unilaterally with contralaterally benign tubal epithelium in one case and occult ovarian carcinoma in the other. In the control group the tubal epithelium was benign in 44 (42%) cases, showed hyperplasia in 37 (35%) and minor epithelial atypia in 24 (23%) cases. No tubal neoplasia (TIC or invasive carcinoma) was found in controls, which was significantly different from the BRCA-mutation carriers (zero of 105 vs 16 of 226 (7%); p = 0.004, Fisher’s exact test). The less severe lesions, hyperplasia and minor epithelial atypia were commonly identified in both BRCA-mutation carriers and controls, although more often in controls (94 of 226 (42%) vs 61 of 105 (58%); p = 0.005, Pearson’s chi square; Table 2). Furthermore, severity of tubal epithelial lesions in women with a BRCA-mutation was significantly associated with higher age (p = 0.001, Kruskal–Wallis test; Table 3). Controls revealed no significant difference in age distribution for tubal epithelial lesions (Table 3).

**Topographic characteristics of tubal epithelial lesions**

In the majority of cases, invasive tubal carcinoma and TIC were identified in the distal fimbria: invasive tubal carcinomas in 100% and TICs in 64% of the cases (Table 4). Tubal neoplasia (invasive carcinoma or TIC) was significantly more often localized in the fimbriae compared to hyperplasia and minor epithelial atypia (11 of 16 (69%) vs 62 of 155 (40%); p = 0.027, Pearson’s chi square; Table 2). As mentioned previously, invasive tubal carcinoma and TIC were only identified in BRCA-mutation carriers and not in the controls. In the BRCA-mutation carriers hyperplasia was seen in the fimbriae in 35% and minor epithelial atypia in 47%, versus 27% and 54% in the controls, respectively. Hyperplasia and minor epithelial atypia, did not occur significantly more often in the fimbriae but displayed more variation in localization (39 of 94 (41%) vs 23 of 61 (38%); p = 0.64, Pearson’s chi square; Table 4).

**Ovarian occult carcinoma**

An occult ovarian carcinoma of 5.8 mm was identified in a 60 year old woman with a BRCA2 mutation, with an occult invasive carcinoma in one of the adjacent tubes. All other cases, from both the BRCA-mutation and control group, showed only benign ovarian pathology.

Of BRCA-mutation carriers, 81 (36%) were diagnosed with breast carcinoma prior to pBSO. In these 81 BRCA-mutation carriers TIC was present in 5% and invasive tubal carcinoma in 2%, compared to respectively 7% and 0% in the 133 BRCA-mutation carriers without prior breast carcinoma. The presence of tubal neoplasia (TIC and invasive carcinoma) was not significantly different for cases with or without a previous breast carcinoma (six of 81 (7%) vs nine of 133 (7%); p = 0.86, Pearson’s chi square). Treatment for breast carcinoma was surgery (36%), or in addition either adjuvant chemotherapy (49%) or adjuvant chemotherapy with tamoxifen (15%). No significant difference was seen between treatment management of breast carcinoma and prevalence of tubal neoplasia (tamoxifen, p = 0.58 (0/12 vs 6/69); chemotherapy, p = 0.18 (2/52 vs 4/29), Fisher’s exact test).

**Discussion**

Our study has identified significant differences in the prevalence and preferred localization of tubal epithelial lesions in a large cohort of 226 BRCA-mutation carriers versus 105 controls. Occult invasive tubal carcinoma and TIC were present in 7.1% of the BRCA-mutation carriers but were absent in control cases. In contrast, tubal hyperplasia and minor epithelial atypia were commonly identified in both BRCA-mutation carriers and controls, although more often in controls. An association was found between increasing age and the presence of more severe tubal epithelial lesions in BRCA-mutation carriers. Furthermore, invasive tubal carcinomas and TICs had a marked preference for the distal fimbrial end, which was not seen for tubal hyperplasia and minor epithelial atypia.

Our divergent results for the different categories of tubal epithelial lesions lead to the suggestion that hyperplasia and minor epithelial atypia do not represent precursor lesions of invasive carcinomas and/or TICs. Previously, it has been suggested that a stepwise epithelial carcinoma progression model can be applied to the tubes [11]. According to this model, occult carcinoma and TIC are preceded by atypic and/or hyperplastic tubal lesions. However, according to the results of the present study the accurateness of this stepwise progression model seems controversial, as prevalence of the specific tubal lesions as well as areas of localization are different for BRCA-mutation carriers and controls. The association found between increasing age and severity of tubal epithelial lesions in BRCA-mutation carriers might be suggestive for the stepwise progression model, but as the less severe lesions are more often identified in controls it seems unlikely that they are part of the oncogenic pathway. It is more likely that the less severe tubal lesions, as hyperplasia, represent normal proliferation of the tubal epithelium. Tubal hyperplasia is more common in younger women, as was suggested by Norquist et al. [24]. The fact that invasive carcinomas and TICs were not identified in controls marks their uniqueness for women at high risk for ovarian carcinoma and therefore their suggested role in carcinogenesis, especially, since controls were older and therefore more TICs and carcinomas would
be expected. In addition, histological findings of hyperplasia and minor atypia were not identified in close proximity with occult invasive carcinoma and TIC [25].

The incidence of invasive tubal carcinoma and TIC in BRCA-mutation carriers in the present study was comparable with other studies including relatively large populations, with a mean overall prevalence of 5.2% for TIC and 6.7% for tubal neoplasia (TIC and invasive carcinoma) (Table 5). Comparing the prevalence of hyperplasia and minor epithelial atypia with previous reports entails more obstacles. Various terminologies have been used by different authors, or only distinct lesions such as occult carcinoma and TIC were recorded. Some extent of tubal epithelial proliferation has been seen in women, mostly premenopausal, without an increased risk of ovarian or tubal carcinoma, and are considered within normal limits of epithelial variation [26]. However, the extent of this normal variation is still somewhat unclear as most studies did not include a control group. The current study provided the first large control group consisting of patients that were operated for various non-malignant reasons. Only two previous studies on epithelial lesions of the fallopian tubes included a control group (Table 5) [25,27]. The study of Shaw et al. included 64 controls who underwent BSO and reported TIC in 3% of their control cases [27]. However, 22% of their controls underwent surgery for synchronously diagnosed carcinoma of the cervix or endometrium which could have biased their results [27]. In our own control group all patients receiving BSO for malignancy were excluded to rule out possible intrusion.

A limitation of the current study is its retrospective nature leading to less extensive sampling of tubal tissue of controls. Therefore, median number of tubal slides available for review in BRCA-mutation carriers versus controls differed, resulting in an inability of completely blinding the pathologist for BRCA status. Tubal epithelial lesions are quite small and the use of a pathological protocol to embed the fallopian tubes in toto is preferred in further prospective research in order not to overlook putative precursor lesions. One of the strengths of our study is that it included the largest cohort of both BRCA-mutation carriers and controls. Age distribution of the cohort was comparable with other studies [12,17,27], both groups were identified in one single institution and all sections were reviewed by the same two gynecologist-pathologists. Before starting this study, a classification scheme for tubal epithelial lesions was developed and consensus was reached on definitions of these epithelial tubal lesions.

Although various epithelial tubal lesions in women at high risk for ovarian carcinoma were described previously, the diagnosis of tubal epithelial lesions is still subject to many difficulties as outlined in a recent report by Visvanathan et al. [28]. They analyzed inter- and intraobserver reproducibility between gynecologic pathologist in diagnosing tubal epithelial lesions which showed to be fair to moderate for TIC, but poor for other tubal epithelial lesions [28]. To bypass definition issues several reports combined terms as occult carcinoma and TIC in their reported incidence number, which further complicates comparison of studies [8,13,27]. The difficulties in interpretation of results stress the importance of a generally used morphologic classification for future research. Our proposed classification scheme could overcome these interpretation difficulties when generally used.

The BRCA-mutation carriers also have an increased risk of developing breast carcinoma which often occurs at an earlier age than ovarian carcinoma [29]. Literature shows some controversy on the influence of prior breast carcinoma and the risk of identifying occult tubal carcinoma in pBSO tissue [8,16]. In the current study prior breast carcinoma did not influence the presence of tubal epithelial lesions, nor did different treatment protocols for breast carcinoma.

It is recommended to perform a pBSO in women with a confirmed BRCA-mutation at the age of about 40 years, which is based on the increased prevalence of tubal or ovarian carcinoma in these women [30]. This is supported by the present study as both identified invasive tubal carcinomas occurred at the age of 55 and 60, respectively. However, in the current study, the precursor lesion, TIC, was identified in two women before reaching the age of 40 years. The median age of TIC was 53 years (range 35–63) and age distribution of identified TIC was shown in Table 6. Whether the identification of TIC before reaching the age of 40 years is a reason to perform pBSO at a younger age needs further investigation. More research is needed on the prevalence of TIC before the age of 40, on the possibility of TIC metastasizing before developing towards carcinoma and, if so, if this is an indication for adjuvant treatment in these women. Recently, ‘radical fimbriectomy’ was suggested as an alternative solution for prevention of tubal or ovarian carcinoma instead of pBSO [31]. However, our study contradicts that only fimbriectomy would be sufficient in preventing these malignancies. We identified only two-thirds of TICs in the fimbrial

### Table 6

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIC</td>
<td>BRCA1 (N = 149)</td>
<td>BRCA2 (N = 77)</td>
<td>BRCA1/2 (N = 226)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age category</td>
<td>N (total N)</td>
<td>N (total N)</td>
<td>N (total N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>0 (9)</td>
<td>0 (1)</td>
<td>0 (10)</td>
<td></td>
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<tr>
<td>35–40</td>
<td>2 (57)</td>
<td>0 (17)</td>
<td>2 (74)</td>
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<tr>
<td>41–50</td>
<td>2 (42)</td>
<td>2 (26)</td>
<td>4 (68)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>5 (41)</td>
<td>3 (33)</td>
<td>8 (74)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Note: Both invasive carcinoma and TIC/CIS can be found in a single patient.

* Excl. = Excluded → cases with identified invasive carcinoma were excluded from this study.
end while one-third occurred in the ampulla or isthmus of the tubes. Removal of the total fallopian tubes after completion of childbearing with a second step removal of the ovaries at a higher age might be a more suitable alternative for pBSO that needs further investigation [32]. In addition, this method could be more safely performed before the age of 40 years as recommended for pBSO, without the adverse effects of early menopause.

In conclusion, the results of the present study emphasize the essence of removing the fallopian tubes in total, as one-third of the identified TICs did not occur in the fimbrial end. Furthermore, the classification scheme used in this study appears to be useful as it differentiates between equivocal tubal epithelial lesions (hyperplasia and minor epithelial atypia) that are commonly present in the general population, from premalignant lesions with an already established role in carcinoma development (TIC and invasive carcinoma). Occult invasive carcinoma and TIC were only identified in BRCA-mutation carriers, whereas hyperplasia and minor epithelial atypia were more often identified in controls. Therefore, it seems unlikely that hyperplasia and minor epithelial atypia are also precursor lesions of ovarian carcinoma. We suggest to interpret tubal hyperplasia and minor epithelial atypia as variants of normal tubal epithelial proliferation.

Conflict of interest statement
No conflict of interest.

Acknowledgment
This study is financially supported by Ruby & Rose Foundation. This is an original study that has not been presented or submitted for publication elsewhere.

References