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Support of the 'fallopian tube hypothesis' in a prospective series of risk-reducing salpingo-oophorectomy specimens

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Abstract ***Objective:*** To determine the prevalence, localisation and type of occult (non)invasive cancer in risk-reducing salpingo-oophorectomy (RRSO) specimens in *BRCA*-mutation carriers and high-risk women from *BRCA*-negative families.
Methods: A consecutive series of RRSO specimens of asymptomatic, screen-negative high-risk women were prospectively collected in our tertiary multidisciplinary cancer clinic from January 2000 until March 2012. All high-risk women in this study underwent genetic testing on *BRCA*-mutations. The surgico-pathological protocol comprised complete resection of ovaries and fallopian tubes, transverse sectioning at 2–3 mm (sectioning and extensively examining the fimbrial end [SEE-FIM] protocol from 2006) and double independent pathology review of morphologically deviant sections.
Results: Three hundred and sixty RRSOs were performed in 188 *BRCA1*-carriers, 115 *BRCA2*-carriers and 57 *BRCA*-negative women at a median age of 44.0 years. Four occult invasive cancers were detected in *BRCA*-carriers (1.3%, 95%-confidence interval (CI) 0.03–2.61), all in *BRCA1*-carriers >40 years of age. All cancers, of which two tubal and two ovarian cancers, were FIGO-stage I/II. Three non-invasive serous intraepithelial carcinomas (STICs) were detected in *BRCA*-carriers (1.0%, 95%-CI 0.00–2.10). In *BRCA*-negative women one

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STIC was found (1.8%, 95%-CI 0.00–5.16), however she carried an unclassified variant in *BRCA2*. Total follow-up after RRSO was 1691 woman-years, in which one *BRCA1*-carrier developed peritoneal cancer (0.3%, 95%-CI 0.00–0.82).

Conclusions: A low prevalence of occult invasive cancer (1.1%) was found in young asymptomatic, screen-negative women at increased ovarian cancer risk undergoing RRSO. This study adds to the advice to perform RRSO in *BRCA1*-carriers before the age of 40. Our findings support the hypothesis of the fallopian tube as the primary site of origin of pelvic high-grade serous cancer.

1. Introduction

Epithelial ovarian cancer aggregates in families. A family history of ovarian cancer confers an increased risk of this disease: the lifetime risk for women with one first-degree relative affected by ovarian cancer is 3.5–7% and increases to 15% when two first-degree relatives are affected.[1] In approximately 10% of all ovarian cancer cases, a deleterious *BRCA1/2* germline mutation can be detected.[2,3] The lifetime risk of developing ovarian cancer in women with a proven *BRCA1*-mutation ranges from 18% to 54% and is 2.4–23% in *BRCA2*-mutation carriers by the age of 70 years.[4,5]

Since the proven ineffectiveness of gynaecologic screening in detecting early-stage ovarian/tubal cancer,[6,7] *BRCA*-carriers are recommended to undergo risk-reducing salpingo-oophorectomy (RRSO). If performed at a young age, RRSO is associated with a statistically significant reduction of the risk of *BRCA*-associated ovarian/tubal cancer (hazard ratio (HR) 0.21; 95%-confidence interval (CI) 0.12–0.39).[8] After RRSO, a residual risk may exist for 'primary' peritoneal cancer; although according to new insights peritoneal cancer is possibly metastatic from tubal intraepithelial carcinoma.[9,10]

Occult cancers have been reported in prophylactically removed ovaries and fallopian tubes in *BRCA*-carriers. Reported rates vary considerably from 2% to 12%[11,12] and seem to be influenced by patients' age at RRSO, symptoms, gynaecologic screening prior to RRSO, the completeness of prophylactic surgery and the extent of histopathological examination. Non-invasive serous tubal intraepithelial carcinomas (STICs) have been identified in 3–12% of the prophylactically removed tubes of *BRCA*-carriers, especially in the fimbrial part.[11,13] No intraepithelial carcinomas have ever been found in ovaries so far, suggesting that ovarian cancer does not have its origin in the ovary itself.[14] The fallopian tube is currently being suggested as the primary site of origin of pelvic high-grade serous cancer[15], which has recently been established in a mouse model.[16]

Aim of this study was to obtain an unbiased estimate of the prevalence, localisation and type of occult (non)invasive cancer in prophylactically removed ovaries and tubes in a consecutive series of *BRCA*-carriers and high-risk women from *BRCA*-negative families attending a tertiary multidisciplinary cancer clinic.

2. Patients and methods

The Family Cancer Clinic (FCC) at the University Medical Center Groningen (UMCG) is a tertiary level clinic for managing women at hereditary or familial high-risk for ovarian (and breast) cancer (H(B)OC). From 1996, clinical and genetic data of all high-risk families have been prospectively registered at the FCC in a combined setting by a clinical geneticist, a gynaecologic oncologist and a surgical oncologist.[17] Genetic testing for *BRCA*-mutations is available to women from H(B)OC families (see criteria in Fig. 1).[18] Women with a confirmed *BRCA*-mutation are being counselled to consider RRSO from the age of 35 (*BRCA1*) or 40 (*BRCA2*), or as soon as childbearing after this age is completed.[18] Women from a H(B)OC family who tested negative for *BRCA*-mutations (further denoted '*BRCA*-negative high-risk women') are also offered RRSO if the estimated lifetime risk of developing ovarian cancer is >10%. After RRSO, women still visit the FCC for breast cancer screening by a surgical oncologist.[19]

A consecutive series of RRSO specimens of *BRCA1*-carriers, *BRCA2*-carriers and *BRCA*-negative high-risk women were prospectively collected in the UMCG between 1st January 2000 and 1st March 2012. Included were asymptomatic women who had a negative gynaecologic screening (pelvic examination, transvaginal ultrasound and serum CA125 measurement) within 1 year prior to RRSO.[7] Excluded were women with ovarian/tubal cancer prior to RRSO and women who underwent salpingo-oophorectomy as part of breast cancer therapy. Main outcome measures were the prevalence and localisation of occult cancer and STIC (primary outcomes), and of atypical hyperplasia (secondary outcome).[20] An anonymous, password-protected database was used to enter the data. Protection of the patients' identity was guaranteed by assigning study-specific, unique patient numbers and codes were only known to two dedicated data managers. According to Dutch law, no further Institutional Review Board approval was needed for this study.

A strict surgico-pathological protocol was applied consisting of complete resection of both tubes and ovaries that were transversely sectioned at 2–3 mm intervals and processed in their entirety.[21] Since Madeiros et al. in 2006 published a protocol for sectioning and extensively