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

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KEYWORDS

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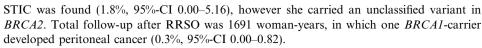
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Conclusions: A low prevalence of occult invasive cancer (1.1%) was found in young asymptomatic, screen-negative women at increased ovarian cancer risk undergoing RRSO. This study adds to the advice to perform RRSO in BRCA1-carriers before the age of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

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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. In approximately 10% of all ovarian cancer cases, a deleterious *BRCA1/2* germline mutation can be detected. 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). 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 cancer¹⁵, 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 'BRCAnegative 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 BRCA1carriers, 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. Since Madeiros et al. in 2006 published a protocol for sectioning and extensively

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