OXFORD

JNCI J Natl Cancer Inst (2021) 113(9): djab037

doi: 10.1093/jnci/djab037
First published online March 12, 2021
Editorial

EDITORIAL

BRCA1/2 and Endometrial Cancer Risk: Implications for Management

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In this issue of the Journal, de Jonge et al. (1) provide the strongest evidence to date that *BRCA1* and *BRCA2* germline pathogenic variants (GPVs) are associated with increased endometrial cancer (EC) risk. Among 5980 women with GPVs within the Hereditary Breast and Ovarian cancer study, the Netherlands (HEBON), they report that GPVs confer increased EC risk versus the general Dutch population (*BRCA1*, standardized incidence ratio = 3.51, 95% confidence interval = 2.61 to 4.72; *BRCA2*, standarized incidence ratio = 1.70, 95% confidence interval = 1.01 to 2.87) and that *BRCA1* GPV heterozygotes experience higher EC risk compared with HEBON participants whose relatives bear GPVs but who themselves tested negative. EC risks were higher among *BRCA1* GPV heterozygotes and for aggressive subtypes, such as those with serous histology or *TP53* somatic mutations. Most previous studies addressing EC risk among *BRCA1* and *BRCA2* GPV heterozygotes have been limited by small sample sizes and/or shorter follow-up (as reviewed in this publication). Although several prior reports have failed to show a statistically significant increased EC risk among heterozygotes, the power of such analyses to detect such risks has often been limited. Notably, 1 large observational study found that both *BRCA1* and *BRCA2* GPVs were associated with increased EC risk (odds ratio of 3.09 and 2.35, respectively) (2), and 2 smaller studies, focused on the serous subtype (3,4), found substantially increased (but almost certainly inflated) risks for this subtype. One recent systematic review and meta-analysis concluded that women bearing GPVs are at statistically significantly higher risk of developing EC, and especially serous EC, which they contend may be part of the "*BRCA1/2* syndrome" (5), whereas another systematic analysis found only modestly increased risks (6). Both reports suggest that the decision to undergo hysterectomy at risk-reducing surgery should reflect personal considerations.

Strengths of the current study include the large sample size, lengthy follow-up, pathology review, and quality of the data and analysis. Nonetheless, futures studies are needed to define absolute risks among the youngest women with *BRCA1* and *BRCA2* GPVs and in racially and ethnically diverse populations.

Dramatic increases in incidence and mortality rates related to EC consequent to the obesity epidemic have garnered attention (7), but opportunities for early detection and prevention of EC in genetically disposed high-risk groups have received less emphasis. Genetic risks for EC pose unique considerations, especially for cancer screening and prevention.

GPV heterozygotes face choices about whether to undergo risk-reducing surgery, the timing of such surgery, and the extent of surgery needed, which may include salpingectomy with deferred oophorectomy, bilateral salpingo-oophorectomy, and potentially, hysterectomy. If incidental cancers are found with risk-reducing surgery, additional quandaries about the need for staging and therapy arise.

Effective surveillance of GPV heterozygotes for EC would need to be long-term; of 19 serous-like ECs in HEBON among carriers, 6 were diagnosed between ages 40 and 60 years and 13 were diagnosed at later ages. Additionally, among women who retain their uteri, EC risk may affect decisions about breast cancer chemoprevention and adjuvant therapy for those affected, because tamoxifen increases EC risk, whereas aromatase inhibitors may lower EC risk (8). Finally, a woman's decision to retain her uterus limits her choice of menopausal hormone therapy to regimens containing both estrogen and progesterone, which increases risk of breast cancer but not EC; estrogen-only options elevate EC risk and would be contraindicated (9). These considerations are critical as early oophorectomy increases risks of chronic diseases and mortality (10,11).

The pathogenesis of serous ECs is poorly understood. Serous ECs are diagnosed 5-10 years later, on average, than endometrioid ECs, and incident rates are higher among African American women, for unknown reasons. It has been hypothesized that serous cancers may develop from the surface endometrial epithelium, rather than from endometrial hyperplasia, the best recognized precursor of the endometrioid subtype (12). In fact, serous endometrial intraepithelial carcinoma (EIC), the presumptive precursor of uterine serous cancers, resembles serous tubal intraepithelial carcinoma (STIC) morphologically; both lesions demonstrate replacement of benign epithelium with high-grade malignant cells that bear *TP53* mutations.

Received: February 19, 2021; **Accepted:** March 5, 2021

Discrete tubal lesions resembling STIC are found concurrently with serous ECs in about 10%-20% of cases (13), and EIC, like STIC, may present with metastatic disease, even without invasion in the uterus or fallopian tube, respectively.

Failure to identify STIC in many cases of high-grade serous tubo-ovarian cancer has prompted speculations that exfoliation of mutated cells from the fimbria of the tube into the peritoneum could account for such cases (14); however, the possibility that "normal appearing" endometrial cells bearing *TP53* mutations or tiny unrecognized EIC lesions could represent another source has not been fully explored. Given the suggestion that serous EC may not respond to standard tubo-ovarian chemotherapy, increased efforts to accurately assign primary sites of serous cancers may have future value in defining treatments (15).

Although de Jonge et al. (1) cautiously conclude that it is inappropriate to routinely recommend hysterectomy at the time of risk-reducing surgery, we consider that this is a suitable subject for review by professional bodies such as the Society of Gynecological Oncology, which should include the viewpoints of women facing these decisions. Importantly, whereas all diagnoses of tubo-ovarian carcinomas prompt discussions with patients about genetic testing, the need for testing after a diagnosis of uterine serous carcinomas is not addressed by guidelines, even when the diagnosis occurs at an uncharacteristically young age. Given the potential that high-grade serous carcinomas arising in the fallopian tube, ovary, endometrium, and peritoneum may all share associations with GPVs and that primary sites are not always discernible, we think that all women receiving these diagnoses should be offered genetic testing for *BRCA1*, *BRCA2*, and other *BRCA*-related genes implicated in homologous recombination repair, at time of diagnosis.

In summary, although the excellent study by de Jonge and colleagues provides solid evidence that *BRCA1* and *BRCA2* GPVs increase EC risk by at least two- to threefold, additional large, high-quality studies in diverse populations are needed, especially among African Americans for whom serous EC rates are notably elevated. Studies to define precise absolute age-specific EC risks for specific GPVs in *BRCA1* and in *BRCA2* and research on the biology of serous cancers are needed to derive evidence-based guidelines.

Funding

None.

Notes

Role of the funder: Not applicable.

Disclosures: In 2019, Dr Foulkes held funds on behalf of a hospital clinical cancer genetic testing laboratory that were provided by AstraZeneca and used to improve variant classification of *BRCA*-related genes. Dr Sherman collaborates on research to develop a test to detect endometrial cancer early, which is funded in part by Exact Sciences.

Author contributions: Writing, original draft—MES, WDF. Writing, review and editing—MES, WDF.

Data Availability

Not applicable.

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