Ovarian Cancer Symptoms Speak Out—But What Are They Really Saying?

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The study by Rossing et al. (8) in this issue of the Journal puts the symptom index to the test to see whether it can “down stage” ovarian cancer. The authors conducted in-person interviews with 812 case patients who had been diagnosed with ovarian cancer and 1313 population-based control subjects from Western Washington state. Information was gathered retrospectively to reflect specific symptoms that these women might have experienced before the date of diagnosis (case patients) or before an assigned comparable reference date (control subjects). Categories of symptoms were drawn from the symptoms index described by Goff et al. (4) and the ovarian cancer consensus criteria (www.wcn.org/articles/types_of_cancer/ovarian/symptoms/consensus_statement.html). The authors used an approximation of these guidelines to define a positive index if any symptom was present daily for at least 1 week with an onset of less than 12 months before diagnosis or the reference date. The authors further analyzed the types of symptoms by surgico-pathological features of the tumor including invasive (n = 574) vs borderline (n = 217) tumors, FIGO (ie, International Federation of Gynecology and Obstetrics) stage, and histological subtypes as a proposed pathway of tumorigenesis. In this model, type I invasive tumors are characterized by slow progression and type II lesions are characterized by early metastasis.

The pattern of symptoms reported among case patients and control subjects was similar to that reported in the literature (1,3,4,9). The study clearly demonstrates that symptoms associated with ovarian cancer were 10 times more likely to occur in women who were ultimately diagnosed with the disease and were present whether they had early- or late-stage ovarian cancer. Symptoms did not discriminate between invasive and borderline tumors or between type I and type II tumors. Symptoms were reported as being present for a relatively short period irrespective of the stage of disease. Among patients with early-stage disease, approximately 27% had symptoms present for at least 5 months before diagnosis. Addition of neither stage nor age statistically significantly improved the positive predictive values for the symptom index, and ultimately, the authors determined that 100 symptomatic women would need to be evaluated to detect one with early-stage ovarian cancer.

The strengths of the study include the in-person interviews and the large number of ovarian cancer case patients. Notably, 220 case patients with early-stage invasive ovarian cancer were included in the analysis, which allows a more valid test of the study hypothesis that ovarian cancer symptoms can signal earlier-stage disease. The study expands upon prior data by providing the positive predictive value of the symptoms index in the general population, which is a more meaningful criterion to compare its performance with other ovarian cancer screening tools.

The study design by Rossing et al. suffers from the same limitations as many previous studies that have relied upon the retrospective reporting of symptoms (9). Although the investigators attempted to interview both case patients and control subjects in a timely fashion relative to the date of diagnosis or an appointed reference date (mean delay = 9 months among case patients and 10 months among control subjects), the retrospective nature of the design raises some doubts. The inherent recall bias among women with ovarian cancer may have inflated the frequency of positive symptom scores in case patients compared with control subjects. Among control subjects, the ability of a woman to recall specific symptoms 10 months before the time of the interview is perhaps a bit optimistic. There is also the potential for survival bias in the cohort of case patients, given that most case patients were interviewed sometime after their diagnosis, which would have excluded women with more aggressive type II disease who succumbed to ovarian cancer before the interview.

The rationale for deviating from what has been defined as a positive symptom index in the literature is not clearly stated. The important difference in the definition of a “positive” index in the study by Rossing et al. is the frequency of the reported symptoms. Goff et al. (4) defined a positive symptom index if a woman had symptoms that occurred more than 12 times per month. The symptom index criteria resulted from a logistic regression analysis of more than 20 symptoms that were validated by prospectively surveying case patients with ovarian cancer and control subjects before surgery or ultrasound or during surveillance in an early-detection program for ovarian cancer (4). The lower frequency of symptoms that was required by Rossing et al. may explain the higher sensitivity in that study than in other studies.
The exceedingly low estimated positive predictive values of a positive symptom index in the study by Rossing et al. is not surprising, given the high frequency of presentation with advanced-stage and the low prevalence of ovarian cancer in the general population. Even when the authors restricted their analysis to patients with early-stage disease, neither the type nor the duration that symptoms were present resulted in a predictive value of any real utility in the detection of ovarian cancer.

The study by Rossing et al. further debunks the falsehood that ovarian cancer is a “silent disease” and continues to raise awareness regarding the symptoms of ovarian cancer. Despite the discouraging conclusion that enhanced symptom recognition is unable to detect early-stage disease, the study provides further validation that ovarian cancer has specific symptoms in the vast majority of patients—whether they have early- or late-stage disease. How this knowledge should affect health-care decisions needs to be further evaluated in the context of a prospective clinical trial. Given the low prevalence of ovarian cancer, the positive symptom index had sensitivity and specificity rates that were similar to other screening tests that have been studied in the general population and judged to be inadequate (10,11). These symptoms may be more useful as a first step in a triage scheme for ovarian cancer detection in a high-risk hereditary cancer population that has a higher prevalence of disease. Even if the positive symptom index did not lead to “down staging” of the ovarian cancers in this study, it is plausible that earlier recognition and evaluation of these symptoms may affect disease outcome by decreasing the tumor burden at diagnosis, which has been shown to enhance patient survival (12).

Importantly, these findings remind us that wide recognition of symptoms alone will not incrementally improve the overall survival from ovarian cancer. Rather, they highlight the urgent need to develop better molecular markers and improved imaging modalities for ovarian cancer screening. The recognition of specific symptoms associated with ovarian cancer has value. However, to truly affect the cure of ovarian cancer, we need better diagnostic tools for asymptomatic women.

References

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