Research Highlights

Highlights from the latest articles in ovarian cancer

Can we accurately predict ovarian cancer from its symptoms?

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Evaluation of: Rossing MA, Wicklund KG, Cushing-Haugen KL, Weiss NS: Predictive value of symptoms for early detection of ovarian cancer. *J. Natl Cancer Inst.* 102(4), 222–229 (2010).

Early detection of ovarian cancer is hampered by the lack of suitable detection systems. Current diagnostic methods are useful in high-risk groups but are not suitable for screening purposes. This study explores the proposition that the patient's symptomology may be sufficiently sensitive and specific to be used as a test for the detection of ovarian cancer *per se*, and possibly for the detection of early-stage cancers. A consensus statement on ovarian cancer symptoms has been produced [1] and a symptom index developed [2] based on persistent symptoms observed in ovarian cancer patients. However, to date, no study has attempted to determine the sensitivity, specificity and positive predictive value of this method and its suitability for detecting early-stage cancers. Personal interviews were undertaken with 812 women who had ovarian cancer and 1313 matched controls using the consensus criteria (symptoms of bloating or feeling full, or with pelvic or abdominal pain or urinary urgency) for at least 1 month, with the onset less than 1 year before diagnosis or contact date. Specificity and sensitivity characteristics of the test were assessed for all ages and all invasive cancers (93.9 and 65.3%), at early-stage (International Federation of Gynecology and Obstetrics [FIGO] Stage I or II: 93.9 and 58.6%, respectively) and late-stage disease (FIGO Stage III or IV: 93.9 and 69.3%, respectively). Similar results were obtained using the Goff symptom index method [2]. The implications of these findings are that only 60–70% of ovarian cancers are detected by this method and the low positive predictive value (1%) obtained questions the usefulness of this test. The positive predictive value is based on the false-positive rate and the incidence of ovarian cancer in the general population; thus, in this context only one cancer would be detected for every 100 positive tests. In order to verify the presence of cancer, surgery would need to be performed as there are currently no other noninvasive methods available and surgery is a costly procedure that is subject to risk. To increase the positive predictive value to 10% would require reducing the false-positive rate to less than 0.5%, an unlikely figure at this point. It was also noted that those patients with a correct prediagnosis were only prediagnosed 5 months prior to diagnosis and that the symptom index was more likely to detect late-stage cancers than early-stage cancers. It is interesting that this assessment of specificity is quite comparable to values obtained with other ovarian cancer tests. While these data would indicate that the test is insufficient as a reliable cancer marker on its own, it may be useful in conjunction with other tests.

References

1 Twombly R: Cancer killer may be 'silent' no more. *J. Natl Cancer Inst.* 99(18), 1359–1361 (2007).

2 Goff BA, Matthews BJ, Larson EH *et al.*: Predictors of comprehensive surgical treatment in patients with ovarian cancer. *Cancer* 109(10), 2031–2042 (2007).

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How effective are current ovarian cancer markers in predicting the onset of ovarian cancer?

Evaluation of: Anderson GL, McIntosh M, Wu L *et al.*: Assessing lead time of selected ovarian cancer biomarkers: a nested case–control study. *J. Natl Cancer Inst.* 102(1), 26–38 (2010).

It is well recognized that the clinical value of a cancer marker for the early detection of ovarian cancer is dependent on two issues: a very low false-positive rate so that unnecessary operations are minimized, and the ability to detect cancer at the earliest stages when it is most treatable. A recent study by Brown and Palmer [1] examining the onset of serous tumors in ovaries from BRCA$^+$ patients noted that the tumors pass through distinct stages. Initially, the tumor resides for several years in the ovary and then spreads rapidly. By the time the cancer is detected it is likely to have already progressed to a later stage by at least 1 year. Thus, to be effective a diagnostic marker must detect cancers greater than 1 year prior to current diagnosis.

The objective of this study by Anderson and colleagues was to establish the lead time for a range of serum ovarian cancer markers to detect the presence of ovarian cancer prior to diagnosis.

Blood samples as part of a large longitudinal clinical trial were provided by 35 postmenopausal women at average risk of ovarian cancer and covering a period of 1–18 years prior to diagnosis of ovarian cancer. Serum samples from matching healthy control women were also examined. Six ovarian cancer biomarkers (CA125, HE4, mesothelin, B7-H4, DcR3 and spondin-2) were measured by ELISA in these samples. Special attention was made to reduce biases related to differential sample collection and known sources of variation. Visual inspection of the longitudinal data of each patient showed that CA125 increased approximately 3 years prior to diagnosis, while HE4 and mesothelin showed a similar time course change but of less magnitude. The first significant change for these markers was not apparent until 1 year prior to diagnosis.

The authors concluded that the likely lead time for the clinical utility of CA125, HE4 and mesothelin as early detection makers of ovarian cancer is less than 1 year, but with a limited discriminatory power. However, it was unclear if this lead time in diagnosis will influence mortality. It was suggested that attempts to identify markers with a greater lead time was a preferred course of action, rather than attempting to develop markers with improved accuracy if they lacked sensitivity to detect early-stage cancers.

Reference

1 Brown PO, Palmer C: The preclinical natural history of serous ovarian cancer: defining the target for early detection. *PLoS Med.* 6(7), E1000114 (2009).

Using *in vitro* cultures of fallopian tube epithelial cells in the study of serous cancers

Evaluation of: Levanon K, Ng V, Piao HY *et al.*: Primary *ex vivo* cultures of human fallopian tube epithelium as a model for serous ovarian carcinogenesis. *Oncogene* 29(8), 1103–1113 (2010).

There is increasing evidence (see [1] for a recent review) that the most aggressive form (type II) of ovarian serous carcinomas arises from the epithelium of the fimbria of the fallopian tube and migrates to the ovarian epithelium where it proliferates. This conclusion is based on a series of cancer-related, time-based, genetic and morphologic associations between serous cancers found in the fallopian tube and the ovary. However, to understand the carcinogenic mechanisms involved in this process requires the development of *in vitro* systems that reflect the development of the cancer *in vivo*.

This study details the characterization of a primary tissue culture procedure of dispersed epithelial cells from fallopian tube fimbria from women with benign gynecological indications. In an attempt to match the cell–cell architecture of epithelial cells *in vivo*, cultures of ciliated and secretory cells were grown at an air–liquid interface on a collagen gel support to form a polarized cell layer with evidence of morphological characteristics (presence of cilia and microvilli, respectively) similar to that seen *in vivo*. A series of lineage-specific markers were used to compare the cultured cells with *in vivo* tissue fimbrial epithelial sections in terms of the morphology of the cilial and secretory cells, their degree of differentiation and tissue polarity. The data presented show convincing evidence of maintained polarity and morphology for up to 28 days in culture. Using this culture system, tissue wounding (scratch) experiments were undertaken to assess the extent to which these cell types in culture can respond to repair. Evidence of proliferation of both ciliated and secretory cells was observed with predominance of secretory cells in the repair process. An assessment of the secreted proteins by mass spectrometry indicated presence of known serous cancer markers. The effects of various agents that induce DNA damage (e.g., irradiation and cisplatinum) showed that these cultures, and in particular the secretory cells, were slow to repair DNA, raising the possibility that these cells are prone to accumulate DNA lesions, which may result in mutations.

This primary culture system bears similarities in terms of polarity, cell type composition and type of secretory proteins to that found *in vivo* and, thus, provides an *in vitro* technique that could assist in the understanding of the carcinogenic process leading to the formation of serous cancers in this and other tissues such as the ovary.

Reference

1 Kurman RJ, Shih Ie-M: The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am. J. Surg. Pathol.* 34(3), 433–443 (2010).