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EDITORIALS

Designing Early Detection Programs for Ovarian Cancer

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Despite the discovery that CA125 and other serum markers increase before the clinical onset of ovarian cancer, it has proven surprisingly difficult to devise a successful screening program for asymptomatic women with ovarian cancer. In this issue of the Journal, Anderson et al. (1) take a valuable step toward the successful design of such a screening program by demonstrating one reason why screening regimens that are based on markers, or panels of markers, can fail. They found that blood levels of CA125, human epididymis protein 4, mesothelin, and three other promising markers did not increase early enough. The markers typically gave a strong signal not more than a year in advance of the symptoms that led to diagnosis, and by this time, many of the cancers had reached an advanced stage of malignancy.

The results of Anderson et al. are not the last word in serum markers or in combinations of markers. Serum markers likely will form a key element in any screening regimen, with the lead time and other parameters of each marker or combination of markers being taken into account. The careful evaluation technique applied in the current study fits into a staged approach necessary for testing performance of early markers of disease (2). Candidate markers emerge from less expensive studies, typically clinical investigations that compare patients with newly diagnosed stage I cancers with women without malignancy. The most promising candidates from the postdiagnosis studies warrant the next step of more realistic comparisons, which use blinded assays of blood that was drawn a year or two before the diagnosis. Unfortunately, many of those biomarkers have a rapid increase in serum concentration late in the course of cancer development or progression, and most will turn out to have little predictive value before symptoms would have led to diagnosis. Markers that prove to be predictive in samples that were collected a year or so before diagnosis then warrant assessment at multiple intervals before diagnosis to trace their time course. Such a retrospective investigation of case patients and control subjects nested in a longitudinal study with serial banked samples, the design used by Anderson et al., offers the second-best evidence of likely performance in a screening program. Only the time-consuming, expensive, and demanding randomized clinical trial can reveal whether an early detection program that includes the biomarkers can save lives.

Current randomized trials are testing the value of different screening programs that are built on combinations of CA125, ultrasound, and risk factor data (such as family history and age). After four rounds of screening 34 261 postmenopausal women for ovarian cancer with both CA125 and ultrasound, investigators of the large US screening trial observed that the predictive value of a positive screen was quite low, approximately 1% (3). Of the 60 screen-detected cancers, 72% had already advanced to at least stage III. In addition, of every 20 women who underwent surgery after a positive screen, just one had cancer. Furthermore, in the UK trial with a slightly different design, positive predictive values from the first round of screening were higher, 35% in the 50 078 women whose risk was assessed with CA125 and risk factor data, followed by ultrasound only if indicated, and 3% in the 50 639 women screened first with ultrasound (4). The effects on mortality in both trials remain to be determined.

We confront daunting arithmetic to avert premature death from ovarian cancer. In the United States, incidence amounts to 13 cases of ovarian cancer per 100 000 woman-years, proverbial needles in the haystack (5). Incidence of ovarian cancer increases with age, to 57 cases per 100 000 women aged 75–79 years. Family history, low parity, and more ovulations over a lifetime further predict risk, with the strongest but least common predictor being a mutation in *BRCA1* or *BRCA2* genes. Among women with higher baseline risks, the predictive value of a positive serum test tends to increase. One can boost performance of an overall screening program by targeting higher-risk subgroups of women for screening or by explicitly combining personal history, host genetics, and levels of serum markers in one prediction model. With advances in understanding etiology, we will also improve the risk models that are useful for screening programs.

We can also improve the performance of a program that is based on a panel of biomarkers by changing what we do after we find a suspicious biomarker result. That is, if highly specific imaging, ideally better than currently offered by ultrasound, followed a suspicious value for a serum marker, then fewer women would undergo surgery. Similarly, less invasive surgery might further reduce harmful side effects. For now, we do not have a proven biomarker, panel of biomarkers, or overall screening program that works well. The current report, with its sobering implications, brings us closer to understanding the crucial elements in designing any effective early detection program for ovarian cancer.

References

1. 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.* 2009;102(1):26–37.
2. Pepe MS, Feng Z, Janes H, Bossuyt PM, Potter JD. Pivotal evaluation of the accuracy of a biomarker used for classification or prediction: standards for study design. *J Natl Cancer Inst.* 2008;100(20):1432–1438.

3. Partridge E, Kreimer AR, Greenlee RT, et al. Results from four rounds of ovarian cancer screening in a randomized trial. *Obstet Gynecol.* 2009; 113(4):775–782.
4. Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol.* 2009;10(4):327–340.
5. Horner MJ, Ries LAG, Krapcho M, et al., eds. *SEER Cancer Stat Fact Sheets*. Bethesda, MD: National Cancer Institute; 2009. http://seer.cancer.gov/statfacts/html/ovary.html. Accessed December 2, 2009.

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