EPIC Early Detection of Ovarian Cancer

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**Running Title:** EPIC Early Detection of Ovarian Cancer

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**Conflicts of Interest:** Steven Skates is a co-developer of the risk of ovarian cancer algorithm. Massachusetts General Hospital has co-licensed software implementing the algorithm.
Abstract: CA125 dominated performance for ovarian cancer early detection amongst four serum biomarkers evaluated in EPIC study pre-diagnostic serum, rising on average 3 years prior to detection. Adding HE4 provided only marginal improvement. This natural history supports annual testing for early detection and highlights the importance of biomarker discovery complementing CA125.

In this issue of CLINICAL CANCER RESEARCH, Terry and colleagues (1) performed a matched case-control study of four serum biomarkers for detection of ovarian cancer prior to clinical diagnosis nested within the European Prospective Investigation into Cancer (EPIC) cohort study. EPIC enrolled over 500,000 women and men from 1992 – 2000 across 10 European countries and followed them to 2005-2008 to assess the influence of diet on cancer incidence. National registries provided comprehensive follow-up of vital status. A one-time blood sample at enrollment formed EPIC’s blood biobank provided by over 200,000 women with over 800 cases of ovarian cancer identified. The four serum biomarkers are CA125, CA72.4, CA15.3, and HE4, the first three discovered in the 1980’s following the breakthrough discovery of monoclonal antibodies, and the fourth in early 2000’s from transcriptional array analyses. The findings confirm previous investigations of ovarian cancer serum biomarkers (2-5) but the significantly much larger EPIC cohort provides substantially more weight and detail to these findings. In this study and the previous studies, amongst the markers investigated CA125 performs the best followed by HE4. The strength of this study is the size of the EPIC cohort, significantly larger than the Women’s Health Initiative (WHI) where a similar biobank and cancer outcomes were available, and from which a related case-control study of candidate biomarkers for ovarian cancer was performed. (5)

The size of EPIC enables division of pre-clinical natural history into multiple strata of time prior to diagnosis giving insight into the distribution of when a biomarker exceeds the standard cut-off. Furthermore, EPIC’s size provided the power for sub-group analysis by stage as a further stratification factor. However, a one-time only sample is limited to assessing the lead-time for a screening rule using a single threshold and does not have the ability to infer the lead-time from longitudinal biomarker screening rules. For example, the risk of ovarian cancer algorithm (ROCA) (6) uses each woman as her own control so that significant increases above a woman’s baseline CA125 flags a second-line screening test as applied in the multi-modal arm of the UK Collaborative
Trial of Ovarian Cancer Screening (UKCTOCS). (7) In addition to assessing lead-time for the four biomarkers with a single-threshold rule, Terry and colleagues (1) provide further insight into the extent to which a combination of markers increases the performance over a single biomarker.

Since EPIC was an observational study with no screening intervention, the nested case-control study can estimate the average time from initial point of rising to clinical detection. Unlike screening studies that intervene on the basis of a blood test followed by ultrasound (7-9) or simultaneously with ultrasound, (10) in EPIC there is no alteration to the preclinical natural history of ovarian cancer. Thus the results from this study (1) provide an unbiased window into the average duration of natural history of ovarian cancer as inferred by the production of CA125 above background levels. A CA125 inferred natural history of ovarian cancer is likely a lower bound for preclinical duration and provides an indication of when ovarian cancer begins to shed CA125 into the general circulation. The three year window observed from when CA125 begins to rise (Figure 1) (1) is an average of the pre-clinical duration over the 810 ovarian cancer cases detected (197 within three years of the baseline blood draw and detection; 613 > 3 years prior to detection). This estimate is similar to the estimate obtained by investigators examining CA125 and other markers in longitudinal preclinical samples from the Carotene and Retinol Efficacy Trial (CARET). (2) However, this average hides the variation between these 810 ovarian cancer cases – a distribution of preclinical durations is surely the case as illustrated in Figure 1 (red arrows). What proportion of the distribution is covered in Figure 1 remains unknown, however this estimate of three years and the range of durations shows a sufficiently wide natural history to support an annual frequency for screening tests to detect ovarian cancer earlier than standard clinical detection. Whether the preclinical duration of early stage disease in cases clinically detected in regional or metastatic stages is sufficiently wide to detect a significant fraction in early localized stage cannot be discerned by this study. An interventional study such as UKCTOCS is required. UKCTOCS did in fact show a significant increase in the proportion of cases detected in early stage. (7) As the authors of the current study (1) indicate, CA125 rises above the standard reference point only around one year prior to clinical detection. Therefore it would be reasonable to infer that a screening program based on a single threshold and annual tests is unlikely to be effective as was observed in the PLCO study where no stage shift nor mortality reduction was observed. (10) Instead, an alternative approach of interpreting CA125 changes over time (11, 12)
which uses each subject as her own control would utilize the rising behavior illustrated in Figure 1 (1) and be more likely to succeed due to the wider window of opportunity it provides. In UKCTOCS,(7) which implemented an algorithm based on this principle (ROCA), stage shift was very significant. Although mortality reduction was only marginally significant as the authors of this study correctly point out, further follow-up may provide more definitive evidence as occurred between two publications three years apart of the European Randomized Study of Screening for Prostate Cancer (ERSPC).(13, 14)

These results offer the hope that with a modest increase in sensitivity by adding biomarkers to CA125, early detection of ovarian cancer may significantly reduce mortality. There are at least three distinct ways additional biomarkers may enhance early detection sensitivity. First, such biomarkers may detect the 20% of ovarian cancers that do not shed CA125. Secondly, novel biomarkers may detect ovarian cancers prior to CA125 based detection. For example, the immune system may amplify the signal from auto-antibodies to ovarian cancer and thereby provide an earlier signal than the signal from proteins shed by ovarian cancer which needs to exceed background circulation levels. Thirdly, concordant rises over time may strengthen a weak CA125 signal and enable earlier intervention in such cases than with CA125 alone. This study addresses the first approach to increasing sensitivity by estimating the additional sensitivity when adding one or more biomarkers to CA125. Only HE4 was statistically significant and its added clinical value was very minor. The corrected concordance (C-statistic or area under the curve) increased from 0.70 to 0.71 with the addition of HE4, and at best by 2% for ovarian cancers detected between 2-3 years after blood draw. A more clinically appropriate metric for early detection of ovarian cancer with a first line blood test is the sensitivity at 98% specificity (SE98). While the increase in SE98 was not given when adding HE4, it is important to note that at 1-2 years prior to detection, a concordance statistic for CA125 of 0.72 corresponds to an SE98 of only 20%. Clearly other markers besides HE4, CA72.4 and CA15.3 that complement CA125 better are needed to increase sensitivity with this approach. And Figure 1 (1) for HE4 does not lend support for expecting HE4 to increase prior to CA125, the second approach by which HE4 may confer an increase. HE4 may still offer increases in sensitivity through the third approach but assessment of this method requires longitudinal samples. Importantly, the minimal increase in sensitivity as shown by this important study (1) and the marginally significant mortality reduction results in
UKCTOCS, highlight the need for biomarker discovery to identify novel markers which complement CA125, either in the spectrum of disease or in time of rise above a subject's baseline.

References:

Legend

Figure 1: Average CA125 levels (solid black) and variation (points) between women prior to diagnosis of ovarian cancer simulated using published estimates showing similar distributions to the smoothed EPIC CA125 values in cases. The solid line shows an average CA125 trajectory with a preclinical increase of three years. Variation between cases results in a distribution of durations of preclinical CA125 increase with longer and shorter durations (red lines) than three years.
Figure 1:

Years prior to diagnosis of ovarian cancer vs. CA125 (U/mL)
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