Personalizing CA125 Levels for Ovarian Cancer Screening

Oliver Dorigo and Jonathan S. Berek

Abstract

Screening trials for the early detection of ovarian cancer in the general population and in patients at a high risk for this disease have so far failed to show a reduction of ovarian cancer–specific mortality. Current screening modalities include pelvic examinations, transvaginal ultrasounds, and cancer antigen 125 (CA125) serum marker levels, which are associated with a high false-positive rate. The last decade has witnessed significant modifications in the interpretation of serum CA125 that extend beyond a static CA125 cutoff point. The Risk of Ovarian Cancer Algorithm (ROCA) incorporates changes of CA125 levels over time and an individual's age-specific risk. Ongoing screening trials have incorporated ROCA, but it is still unclear whether the algorithm will increase the sensitivity and specificity of early ovarian cancer diagnosis. A very recent study analyzed baseline CA125 serum marker levels from high-risk patients included in ovarian cancer screening trials conducted by the Cancer Genetics Network and the Gynecologic Oncology Group. The findings show that the distribution of CA125 serum marker levels in this population is significantly affected by various demographic and clinical factors, in particular menopausal status and oral contraceptive use in premenopausal patients. The data suggest that CA125 cutoff points might have to be stratified for subgroups of patients to reduce false-positive results. These intriguing observations will need to be validated in future screening trials for ovarian cancer.

Various large clinical trials have investigated the efficacy of screening for the early detection of ovarian cancer. The most frequently utilized screening modalities include pelvic examinations, transvaginal ultrasounds (TVS), and cancer antigen 125 (CA125) serum marker levels. To date, however, none of these trials have shown that screening in the general population and in patients at a high risk improves our ability to detect ovarian cancer early and reduce ovarian cancer–specific mortality.

Bast and colleagues were first in identifying CA125 in human ovarian carcinoma cell lines (1). The gene for CA125 was cloned in 2001 and called MUC16 because of the similarities between its product and the mucin family of proteins (2). CA125 is a large transmembrane glycoprotein with a carboxyl terminus, which includes a cytoplasmic tail, a phosphorylation site for proteolytic cleavage, and the transmembrane domain (3). A large portion of the extracellular domain consists of repeat sequences that contain the epitopes OC125 and M11, which are recognized by monoclonal antibodies. The third domain of the CA125 molecule is the amino terminal domain, which is heavily glycosylated during posttranslational modification.

The biological functions of CA125 are complex but overall seem to enhance the malignant potential of ovarian cancer cells. CA125 plays an important role in cellular adhesion, invasion, and intraperitoneal metastasis. Binding of CA125 to mesothelin, as expressed on peritoneal surfaces, can increase the invasive potential of human ovarian carcinoma cells in vitro (4). CA125 can mediate immunosuppression by inhibiting natural killer cell responses in vitro (5).

Clinically, CA125 serum marker levels are used for the preoperative evaluation of patients with pelvic masses, to assess the response to chemotherapy of ovarian cancer patients, and for follow-up of patients after treatment. Various CA125 assays are available that provide reliable and reproducible CA125 measurements. However, serum marker levels of CA125 need to be interpreted with caution. In general, a CA125 serum level of 35 U/mL or below is considered normal, and this cutoff point has therefore frequently been used in clinical trials. However, assays for CA125 have different reagent specificities and cutoff point values. The differences in assay design can lead to variations in the results, and therefore different assays may not be comparable (6). For screening trials that are conducted over a long period of time, changing methodologies may require baseline samples to be retested or be verified in both assays.

The CA125 tumor marker is not specific for ovarian cancer, and the percentage of false-positive results is high.
when used for ovarian cancer screening or diagnosis. CA125 is expressed in various other tissues such as those derived from coelomic epithelium (endocervix, endometrium, and fallopian tube) and in mesothelial cells in the pleura, pericardium, and peritoneum. It is also found in epithelial tissues including from the normal adult ovary, lung, pancreas, breast, stomach, and gall bladder (7). Therefore, CA125 levels can be elevated in benign gynecologic conditions, such as endometriosis, fibroids, and pelvic inflammatory disease, that tend to occur more commonly in premenopausal women. CA125 values increase during pregnancy, with peak levels in the first trimester and postpartum that return to normal about 10 weeks after delivery (8). Furthermore, CA125 levels may be elevated by non-gynecologic conditions including inflammation of the peritoneum, pleura, or pericardium; pancreatitis; liver disease; and tuberculosis. Nongynecologic malignancies derived, for example, from the gastrointestinal system or the breast can increase CA125 levels, particularly in the presence of intraperitoneal metastasis.

Studies have shown that CA125 values are affected by various demographic and clinical factors including age, race, and prior hysterectomy. In general, CA125 levels are lower in postmenopausal than in premenopausal women (9). In African and Asian women, levels tend to be higher than in white women. Other factors, including hysterectomy and smoking, also have been associated with lower CA125 levels, but the data are inconsistent (10).

A very recent study (reported elsewhere in this issue of the journal; ref. 11) analyzed data from 3,692 women who participated in screening studies for ovarian cancer conducted by the National Cancer Institute–sponsored Cancer Genetics Network (CGN) and the Gynecologic Oncology Group (GOG); the CGN and GOG studies included patients at a high risk to develop ovarian cancer on the basis of a positive family history or BRCA mutations. The recent study (11) analyzed the effect of clinical and demographic factors on the distribution of baseline CA125 values in this high-risk population. On the basis of previous data, a cutoff point of 35 U/mL for the CA125 serum level marks the 98th percentile in a population of healthy donors and is frequently used in clinical screening trials. Although this cutoff point has been validated in healthy postmenopausal women, for whom it has a 2% false-positive rate, it has not been shown to be effective for screening in postmenopausal women. The authors identified subgroups of patients in which the 98th percentile cutoff point differed significantly from 35 U/mL. The main results of the analysis showed that menopausal status was the primary clinical factor affecting CA125 levels. Premenopausal women not currently using oral contraceptives (OC) had a significantly higher cutoff point of 50 U/mL whereas premenopausal women currently using OCs had a higher cutoff point of 40 U/mL. On the other hand, the cutoff point for postmenopausal women was 35 U/mL. The authors concluded that the achievement of a 2% false-positive rate in ovarian cancer screening trials for high-risk women will require personalizing the cutoff point for initial CA125 testing primarily on the basis of menopausal status and OC use.

This interesting analysis is an effort to reduce the false-positive rate of CA125-based ovarian cancer screening. The main statistical analysis was based on the CA125 level marking the 98th percentile as the cutoff point for CA125 screening. The 98th percentile was set at 35 U/mL, as determined in early studies that evaluated the baseline levels of CA125 in healthy individuals. Only patients at a high risk were included in both the CGN and GOG studies, however, and the 98th percentile cutoff point for CA125 might not be the most appropriate percentile for this population. This study provides sample estimates of the 98th percentile and uses a linear regression model to estimate the effect of clinical and demographic factors on CA125 cutoff points for this percentile. Although this certainly is a valid analysis, a potentially more comprehensive estimate of the effect of different factors on CA125 cutoff points might have been obtained by using quantile regression (12). It is unlikely, however, that quantile regression would have changed the principal conclusions and possible implications of the study.

The suggestion of personalized CA125 cutoff points for the early detection of ovarian cancer to reduce the percentage of false-positive results is very intriguing. This screening strategy raises several important biological and complex clinical issues that need to be addressed. Increasing the CA125 cutoff point for premenopausal women might decrease the rate of false-positive results, but it is possible that this increased cutoff point would lead to a loss of sensitivity and delay in diagnosis of early ovarian cancer. Further questions pertain to the effect of factors that change the distribution of CA125 serum marker levels within a certain subgroup. For example, current OC use decreased the 50 U/mL CA125 cutoff point of premenopausal women to 40 U/mL. The biological reasons for this difference are uncertain but might be due to the suppressive effect of OCs on benign conditions that can cause an elevation of CA125 levels including ovulation, functional ovarian cysts, endometriosis, uterine leiomyomas, adenomyosis, and menometrorrhagia. On the basis of the proposed personalized CA125 screening strategy, a premenopausal patient on OC would be followed with a cutoff point of 40 U/mL, but should the higher, 50 U/mL cutoff point be assigned to the same patient after termination of OC use? It is also unclear whether the presence or absence of any of the benign conditions listed above should be taken into consideration when personalizing the CA125 cutoff point in either pre- or postmenopausal women. The transition of premenopausal women with a cutoff point of 50 U/mL into menopause will present a similar issue for personalized CA125 levels. How would the time point of reassignment to a different cutoff point category in menopause be defined? Would a stable CA125 level above 35 U/mL but below the cutoff point for premenopausal women be categorized as abnormally elevated when transitioning into menopause?

The implications of personalized CA125 screening values for the early detection of ovarian cancer become
even more complex if one considers the influence of more than one factor that changes the distribution of CA125 levels. What cutoff point should be assigned to a premenopausal woman of Asian ethnicity who currently uses OCs, has irregular menstrual periods, and is a smoker? All these factors were found to be independently associated with lower CA125 levels in the multivariate analysis, but the cumulative effect of any combination of these factors on median CA125 levels is uncertain. More broadly, would the premenopausal cutoff point have to be readjusted to account for changes in any of the variable factors that affect CA125 levels? Ultimately, CA125 cutoff points for screening purposes might have to be personalized not only at baseline according to relevant factors but also may have to be repersonalized over time on the basis of the dynamics of the variability in these factors. It will require a carefully conducted prospective clinical trial to design screening algorithms that incorporate the effect of the different factors.

The Risk of Ovarian Cancer Algorithm (ROCA) has already incorporated the dynamic changes of CA125 levels over time for risk assessment. ROCA is based on the analysis of more than 50,000 serum CA125 levels assayed in 22,000 volunteers followed for a median of 8.6 years (13). Interpretation of CA125 levels based on ROCA takes into account that CA125 levels in women without ovarian cancer are static or decrease over time whereas levels associated with malignancy tend to increase. ROCA uses a computerized algorithm that includes an individual’s age-specific risk of ovarian cancer and her CA125 dynamic profile in estimating her individual risk of ovarian cancer. This algorithm increases the sensitivity of CA125 (86%) for the preclinical detection of ovarian cancer compared with a single cutoff point value because women with normal but increasing levels are identified as being at increased risk. Furthermore, the specificity of CA125 screening is improved (98%), as women with static but elevated levels are classified as low risk. ROCA has therefore already advanced ovarian cancer screening beyond the use of the 35 U/mL CA125 cutoff point for all women. However, further modifications based on personalized clinical and demographic variables identified in the very recent study discussed earlier (11) might further improve the value of CA125-based ovarian cancer screening.

ROCA was used in both the CGN and GOG ovarian cancer screening trials that provided high-risk women for the recent study (11). Two ongoing trials in the United Kingdom, the U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and the U.K. Familial Ovarian Cancer Screening Study (UKFCSS), have likewise incorporated ROCA. In the UKCTOCS trial, more than 202,638 postmenopausal women at average risk were randomized to either control or annual screening. ROCA was used at baseline to triage women into low-, intermediate-, and elevated-risk categories based on their CA125 result. Intermediate-risk women have a repeat CA125 in 6 to 8 weeks whereas women with an elevated risk are referred for a TVS. If TVS shows abnormal results, the patient is considered for referral to surgery. Preliminary data from this trial showed that the multimodality screening algorithm had a sensitivity of 89.8% and specificity of 99.9% in detecting primary invasive epithelial ovarian and tubal cancers (14). Of interest, the positive predictive value was high at 35.1%, resulting in 3 surgeries per correctly diagnosed ovarian cancer. Fifty-eight primary invasive epithelial cancers were detected and 28 (48.3%) of them were stage I or II.

Although the early UKCTOCS data have shown some promising results and lend support to the concept of a personalized CA125 screening algorithm, no other clinical trials have shown efficacy of ovarian cancer screening in the general population. The randomized controlled Japanese Shizuoka Cohort Study of Ovarian Cancer Screening is one of the larger ovarian screening trials that have been reported (15). This trial used annual ultrasound and CA125 serum marker levels to screen 82,487 low-risk postmenopausal women. The numbers of ovarian cancers detected in the screening (27 cancers) and control (32 cancers) arms were not significantly different. Although the proportion of stage I ovarian cancers was greater in the screening (63%) than in the control (38%) arm, the difference was not statistically significant.

The most recently published results of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial have confirmed the lack of effective screening for ovarian cancer (16). PLCO randomly assigned 78,216 women aged 55 to 74 years and at an average risk for ovarian cancer to undergo either annual screening or standard care at 10 screening centers across the United States between November 1993 and July 2001. Patients in the screening arm underwent annual screening with CA125 for 6 years and with TVS for 4 years and were followed for up to 13 years. Ovarian cancer developed in 212 women in the screening arm (5.7 cancers/10,000 person-years) and in 176 women in the control group (4.7 cancers/10,000 person-years); the difference was not statistically significant. There also was no benefit in reduced mortality, with 118 ovarian cancer deaths in the screening group (3.1 deaths/10,000 person-years) compared with 100 such deaths in the standard care group (2.6 deaths/10,000 person-years).

Of concern, a large number of complications resulted from the surgical procedures that were conducted on the basis of positive screening in PLCO including surgical complications in women with false-positive screening results. In PLCO, 3,285 women had false-positive screening results and 1,080 of these women underwent surgery. At least 1 serious complication occurred in 163 (15%) of these 1,080 women, and there were a total of 222 major complications among them or 20.6 complications per 100 surgeries. These data underscore the necessity of increasing the specificity of screening strategies for ovarian cancer and decreasing the rate of false-positive results to avoid unnecessary surgeries and complications.

Despite a number of large, well-designed ovarian cancer screening trials conducted over the last 2 decades, there is currently no screening strategy that has shown a significant reduction in ovarian cancer–specific mortality. Therefore,
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none of the professional organizations including the American College of Obstetricians and Gynecologists, American Cancer Society, U.S. Preventive Service Task Force, and National Comprehensive Cancer Network (NCCN) recommend ovarian cancer screening in the general population. The NCCN recommends screening with CA125 and TVS every 6 months in high-risk women, beginning at 35 years old or at 5 to 10 years prior to the earliest age at diagnosis of ovarian cancer in relatives. No data from clinical trials, however, currently support this recommendation.

The large, ongoing ovarian cancer screening trials in the general population in the United Kingdom. have shown some promising preliminary data, but it is too early to draw meaningful conclusions from these trials. Personalizing CA125 levels beyond the currently used ROCa might be a significant step toward decreasing the percentage of false-positive results and thus avoiding unnecessary surgeries, complications, patient anxiety, and costs. The validation of such personalized CA125 screening with possible adjustment of CA125 cutoff points based on changing clinical and demographic parameters over time will require a prospective clinical trial, especially in a high-risk population. In the meantime, high-throughput technologies including the analysis of serum protein panels have propelled a rapid development of other serum markers including human epididymis protein 4 (HE4), leptin, osteopontin, macrophage inhibitory factor (MIF), IGFII, and apolipoprotein A1 (APO-A1) for ovarian cancer screening. CA125 still outperformed all other markers, however, in 2 recent studies in which the aforementioned and other most promising candidate markers for early detection were compared in preclinical specimens and matched controls from the large PLCO trial (17, 18).

Various combinations of biomarkers either alone or in combination with CA125 are currently being studied in clinical settings and, it is hoped, will improve the efficacy of screening strategies for ovarian cancer. An effective screening strategy for the early detection of ovarian cancer in women at a high risk will be invaluable and will significantly improve the overall prognosis of ovarian cancer patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

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