Factors Influencing Serum CA125II Levels in Healthy Postmenopausal Women

Donna K. Pauler, Usha Menon, Martin McIntosh, Heather L. Symecko, Steven J. Skates, and Ian J. Jacobs


Abstract
Our objective was to identify factors that correlate with CA125 concentrations in healthy postmenopausal women and to introduce recommendations for reporting and interpreting individual CA125 assay results. We analyzed repeated serum CA125 levels, as measured by the CA125II assay, in 18,748 postmenopausal women who participated in the St. Bartholomew’s/Royal London Hospital Ovarian Cancer screening trial from 1986 to 1994 and were not diagnosed with ovarian cancer during the 12-year follow-up period. We found that race is a substantial predictor of normal levels of CA125, with average CA125II concentration from African (median, 9.0; 95% range, 4.0–26.0 units/ml) and Asian women (median, 13.0; range, 5.9–33.3 units/ml) lower than that in Caucasian women (median, 14.2; range, 6.0–41.0 units/ml; P < 0.001). Women with a hysterectomy have lower CA125II values (median, 13.6; range 5.5–39.0 units/ml; P < 0.001), and women with a prior cancer diagnosis other than ovarian cancer have higher levels of CA125II (median, 16.0; range, 6.0–49.0 units/ml; P < 0.003).

Introduction
CA125, a high-molecular-weight glycoprotein that is recognized by the monoclonal antibody OC125, is elevated in most women with ovarian cancer. CA125 is the most extensively studied biomarker for possible use in the early detection of the disease (1–4). Candidate strategies for screening with CA125 use a multimodal approach, using CA125 concentrations as a first-line screen with referral of women to ultrasound if the concentrations are suggestive of a malignancy. Screening decisions based on CA125 most commonly use a single-threshold screening rule that sends a woman to ultrasound if her CA125 concentration exceeds 30 units/ml if postmenopausal, or 25 units/ml if premenopausal. Other more complex algorithms based on CA125 have also been proposed, including those that use information contained in the change or velocity of CA125 (5). Sequential algorithms have been shown to have a high sensitivity (70%) while maintaining high specificity for the detection of preclinical epithelial ovarian cancer (5–10). Whether the single-threshold or longitudinal algorithms are used, proper calibration of a screening algorithm requires knowing the behavior of the marker in a large group of symptomatic women. Screening thresholds (i.e., absolute concentrations or risk levels used to indicate a positive test) are determined directly or indirectly by the behavior of the markers in healthy women, so that specificity can be maintained. If subject-specific characteristics can predict differences in normal levels of CA125, then not accounting for their differences can lead to inequality in their performance at the individual level. For example, a single-threshold screening rule applied to women with lower than normal concentrations of CA125 will result in a screening program that, for them, has specificity higher than and sensitivity lower than that of the general population. Likewise, subjects having higher than average levels of CA125 will have higher sensitivity than average but will bear a larger burden of false positives than the general population. These differences may be small, depending on the differences in normal levels predicted by the characteristics, but even small differences can become substantial with more complex screening algorithms, such as those that use longitudinal algorithms.

More accurate interpretation of CA125 for screening programs requires an understanding of which subject-specific characteristics may influence the assay. Both the mean levels of CA125 within these characteristics and the variability of the assay within these groups are needed to properly calibrate any screening algorithm using the assay. Subject-specific factors are necessary for calibrating a subject’s initial CA125 measurement. For calibrating subsequent CA125 results, the subject’s personal CA125 history and the within-subject component of variability provide a much more accurate determination of whether or not the CA125 value is aberrant.

The primary objective of this study was to identify subject-specific factors that may be substantial predictors of mean CA125 concentrations in a large group of postmenopausal women.
Factors Influencing CA125II

Materials and Methods

Subjects in the present analysis include 18,748 postmenopausal women enrolled in the SB/RLH trial for whom complete data were available for the sixteen subject characteristics recorded in Tables 1 and 2. Women who were diagnosed with ovarian cancer or other cancer (excluding melanoma) or its recurrence during follow-up were excluded from analyses. The subject characteristics in Tables 1 and 2 were tabulated from subject responses to an initial enrollment questionnaire designed in 1986. Oral contraceptive (OCP) use indicates whether a woman used it for more than a 1-year period in her lifetime. HRT indicates the use of estrogen or estrogen/progestin at any point in her life. Hysterectomy, ovarian cyst, and oopherectomy, as used in the Tables, are defined as ever having the condition or procedure. Cancer indicates whether the subject had a previous medical history of cancer (excluding melanoma) that was not active as defined above. Talcum powder indicates whether the woman has ever used talcum powder in the perineum or surrounding area. Smoking and caffeine consumption define whether the woman was currently smoking one or more packs of cigarettes or drinking one or more cups of tea or coffee per day at the time of completion of the baseline questionnaire. Ages of menarche, menopause, and current age were provided by self-report. Median ages and ranges for the 18,748 subjects in the study are displayed in the second and third columns of Table 2.

Although the original first generation CA125 assay, made by a variety of manufacturers and processed at several laboratories, was used throughout execution of the SB/RLH trial, analyses in this report are based on a single reprocessing of stored serum samples by Centocor, denoted CA125II, at a single laboratory site, in 1997. Only normal CA125 measurements from primary screening events were used in this report. Thus, all of the CA125 measurements taken as a result of an initially elevated concentration have been omitted to reduce bias. In total, our analysis consists of 38,155 CA125II measurements obtained from the 18,748 women. Approximately one-half of the women (the control group) contributed only a single initial CA125 measurement, and the other half contrib-

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4 OCP, oral contraceptive.
For factors containing possible values “None” and “Previous,” the parameter estimates equal the difference in log CA125 values for those with a previous history minus those with no history. For the race variable, the parameter estimate is the average difference in log CA125 between the factor (African, Asian, or Other) and Caucasian. Parameter estimates for all age variables represent the change in log CA125 variable for a unit increase. All of the age variables are standardized by subtracting the population mean.

### Table 3: Parameter estimates and Ps

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate</th>
<th>( \exp(\beta) )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2.75</td>
<td>15.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>-0.48</td>
<td>0.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asian</td>
<td>-0.17</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.08</td>
<td>1.08</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>0.01</td>
<td>0.99</td>
<td>0.34</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>-0.05</td>
<td>0.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ovarian cyst</td>
<td>-0.04</td>
<td>0.96</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.07</td>
<td>0.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caffeine consumption</td>
<td>-0.05</td>
<td>0.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.12</td>
<td>1.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age of menarche</td>
<td>0.009</td>
<td>1.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age of menopause, 48 yr</td>
<td>0.007</td>
<td>1.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, 61.05 yr</td>
<td>-0.008</td>
<td>0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Age, 61.05) ( \times ) cancer</td>
<td>-0.007</td>
<td>0.99</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Parameter estimates and associated significance tests from the analysis of log CA125 are displayed in Table 3. The factors of race, age, age of menarche, age of onset of menopause, and previous history of hysterectomy, ovarian cyst, smoking, caffeine consumption, and cancer were all statistically significant predictors of log CA125 (\( P < 0.05 \)). Number of childbirths did not correlate with log CA125 (\( P = 0.34 \)). Previous use of oral contraceptives or talcum powder and previous HRT or oophorectomy did not appear in the best-fitting model for CA125 and were not significant (\( P > 0.05 \)).

The parameter estimates in Table 3 give the change in log CA125 values adjusted for the other factors in the model and can be interpreted as follows. The ages of menarche, menopause, and subject age are coded with respect to 13.1, 48.0, and 61 years of age, respectively. Thus, we can interpret the intercept term, 2.75, as the mean log CA125 level for a 61-year-old Caucasian woman who has never smoked, used talcum, or drunk caffeine, and who has never had children, cancer, an ovarian cyst, or a hysterectomy. All of the other effects are in relation to this baseline group. From Table 3, one can see that the factors of race and previous cancer history have the largest impact on average log CA125. Log CA125 value decreases by 0.48 for African women and by 0.17 for Asian women compared with Caucasian women. A history of cancer increases the log CA125 value by 0.12.

On the basis of the mixed-effects model, the between-subject SD is 0.55 and the within-subject SD, or measurement error, is 0.28 (\( P < 0.01 \) for \( H_e \); between-subject variability equals 0). This yields a total SD (\( \sigma \)) of log CA125 as \( \sigma = 0.62 \). In other words, the variation in log CA125 measurements over different women is twice as large as that from the same woman, even after adjusting for the subject characteristics in Table 3.

The total variability of CA125 is important for interpreting the estimates in Table 3. Because log CA125 is a nonlinear transformation of raw CA125, the variability must be accounted for when transforming the model to the raw scale. On the log scale, the reference group has an average CA125 level (\( \mu \)) of 2.75, but on the raw scale this value becomes \( \exp(\mu)\exp(\sigma^2/2) = 18.9 \) units/ml. The effect size on the raw scale can be interpreted simply. For example, the coefficient \(-0.48\) for African compared with Caucasian implies that log CA125 is 0.48 lower in Africans than Caucasians, and on the raw scale Africans have a value that is \( \exp(-0.48) = 0.62 \) or only 62% of that of Caucasians. Thus, the mean raw CA125 concentration among Africans is 11.70, considerably lower than their Caucasian counterparts.

Fig. 1 displays how average untransformed CA125 values change with race, age, and previous cancer history based on the mean parameter estimates in Table 3. To present the effects, women of average age of menarche (13.1 year), average age of menopause (48.1 year), with no previous children, no previous hysterectomy or ovarian cyst, and who are nonsmoking and not caffeine-consumers were considered. Analogous figures, with these variables set otherwise, would differ only slightly from Fig. 1.

The effects of race, age, and previous cancer history on untransformed CA125 values can be easily seen in Fig. 1. Caucasian women have consistently higher CA125 values. Asian women have on average 16% lower values \([= 1 - \exp(-0.17)]\) than Caucasian women do. African women have the lowest values, which are on average 38% lower than those of Caucasian women. CA125 values tend to decrease with age, with the decrease more sharp in women without a previous cancer diagnosis. Typical CA125 values lie between 13 and 22 units/ml for women of age 50 years. By age 90 years, the average drops to between 7 and 12 units/ml for women without a previous cancer history but never falls below 10 units/ml for women with a previous cancer history.
Standard reports of CA125 often include what is termed the “normal range” of values. Typically the 5th and 95th percentile points of CA125 for an underlying reference population give this range. Parameter estimates that are included in the mean model and estimates of the variation that are based on an underlying normal distribution for log CA125 values can be used to calculate a normal range that is specific for a given set of subject characteristics. On the basis of this method, the normal range of CA125 for a 61-year-old Caucasian woman who has had no previous childbirth, hysterectomy, ovarian cyst, or cancer, who neither smokes nor drinks caffeine, and who achieved menarche at age 13 years and menopause at age 48 years, is 4.6–52.7 units/ml. The normal range for an African woman with the same characteristics is only 2.9–32.6 units/ml. The normal range for the same women who have, instead, a personal history of cancer is slightly shifted upward, at (5.2–59.4) units/ml and (3.3–36.8) units/ml, respectively. These numbers are calculated by first determining the normal reference range for the baseline group \[\exp(2.75 \pm 1.96 \times 0.62)\] and then multiplying each end of the interval by \exp\text{(parameter estimate)}.

Discussion

Our analysis revealed that CA125 levels are significantly lower in postmenopausal women who have undergone hysterectomy but that there is no correlation with unilateral oophorectomy. Even with hysterectomy, the reduction is small and may not be of clinical significance. Similar results were obtained by Grover et al. (15), who found a slight reduction of CA125 levels in postmenopausal women who had undergone hysterectomy but not oophorectomy. In their study population of 915 women with a median age of 55 years, Zurawski et al. (16) found a statistically demonstrable effect only of oophorectomy or hysterectomy on CA125 levels in women under 50. The small reduction in CA125 after a hysterectomy is probably attributable to loss of the tubal, endometrial, and endocervical epithelium, which are known to express the CA125 antigen.

There was a significant increase in CA125 levels in women with a past history of cancer. A previous case control study found that postmenopausal women with raised serum CA125 levels are more likely to have a past history of cancer than do normal controls (7). As CA125 is not a predictor of recurrence in nongynecological malignancies, it was speculated that cancers, especially breast carcinoma, might cause CA125 elevation through a process that is independent of persistent malignancy (7). Our study population included 592 females with a previous history of cancer, and we detected a significant, but small, increase in CA125 in this group. The small reduction of CA125 levels in women with previous benign ovarian cysts provides corroborating evidence of little or no effect of a past history of ovarian cysts on CA125 levels as was found in other studies (17, 18). Women who had given birth to one or more children had a nonsignificant increase in CA125 levels. Westhoff et al. (20) found an effect of parity in their study of 258 post- and premenopausal women. Elevation of serum CA125 has been reported in early pregnancy (18, 20 –23), particularly in the first trimester (22). A sustained increase in CA125 levels after childbirth might be attributable to permanent damage to the blood tissue barriers within the uterus. There was no significant change in levels in women with a previous history of oral contraceptive use, hormone-replacement therapy, or talcum use. Previous studies reporting a correlation of CA125 levels with HRT have been based on small numbers of subjects and have produced conflicting results (15, 24, 25).

No association has been previously reported between CA125 levels and smoking (21, 26, 27). The estimated magnitude of reduction in this study was small, and, hence, the finding of significance could be a byproduct of the large sample size. Also, the definition of a previous smoking history used in the original questionnaire was vague, classifying anyone who...
currently smokes more than one pack of cigarettes per day as a smoker. Questions about personal habits are often biased and subject to high measurement error. The highly significant but small reduction attributable to caffeine might be similarly explained. It is also possible to speculate that smoking and caffeine intake induces liver enzymes that increase the metabolic breakdown of CA125. Previous studies of the correlation of CA125 with age have found either no significant association (15, 28) or significant but small decreases with age (16, 29–31). Our study found a significant decrease in CA125 levels with age.

An important finding of our study was the high correlation of CA125 levels with race. No previous study of CA125 has considered the effects of race; the large sample size of our study population included sufficient numbers of African and Asian women to accurately determine this effect. Differences on the order of 20–50% between races have been discovered in this study to significantly impact the interpretation of cutoff values for normal, especially in the context of screening a healthy postmenopausal population. As trials for ovarian cancer screening get underway to assess the impact of screening on ovarian cancer mortality, there is an urgent need for corroboration of the effect of race on serum CA125 levels.

Finally, the CA125 assay can vary immensely by type (e.g., RIA versus automated enzyme), manufacturer, and generation. In particular, the Centocor CA125II assay used here yields CA125 measures that are several units higher than the Centocor first-generation CA125 assay (32). Davelaar et al. (32) found a tendency of several automated-enzyme assays to measure higher absolute values in the lower CA125 range when compared with the original Centocor CA125 assay, but not with the Centocor CA125II assay. They further supplied regression equations for relating the different common assay measures. Adjustments such as theirs should be applied to CA125 measures from different assays before applying the corrections for influential factors outlined in this article.

References
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