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Combining CA 125 and SMR serum markers for diagnosis and early detection of ovarian carcinoma

M.W. McIntosh[a,*], **C. Drescher**[a], **B. Karlan**[b], **N. Scholler**[a], **N. Urban**[a], **K.E. Hellstrom**[c], and **I. Hellstrom**[b]

[a] Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[b] Pacific Northwest Research Institute, Seattle, WA, USA

[c] Cedar Sinai Medical Center, Los Angeles, CA, USA

Abstract

Objectives—The serum tumor marker CA 125 is elevated in most clinically advanced ovarian carcinomas. Because these elevations may precede clinical detection by a year or more, CA 125 is potentially useful for early detection as part of an ovarian cancer screening program. However, CA 125 is often not elevated in clinically detected cancer and is frequently elevated in women with benign ovarian tumors. CA 125 may be more useful in conjunction with one or more other tumor biomarkers. Additional markers could play a role if, when used with CA 125, they identify some carcinomas missed by CA 125 (i.e., they improve sensitivity), rule out false positives (i.e., improve specificity), or are able to detect the same cancers earlier.

Methods—We have evaluated a composite marker (CM) that combines CA 125 and a previously described soluble mesothelin related (SMR) marker in sera from 52 ovarian cancer cases, 43 controls with benign ovarian tumors, and 220 normal risk controls who participated in a screening program, including 25 healthy women having two serum samples collected 1 year apart. CA 125, SMR, and CM were evaluated for their ability to identify clinical disease and for their temporal stability, which assesses their ability to obtain even greater sensitivity when used in a longitudinal screening program.

Results—CM has the best sensitivity, with specificity equal to CA 125. Importantly, CM has temporal stability at least as high as CA 125.

Conclusion—The CM may outperform CA 125 alone in a longitudinal screening program as well as in a diagnostic setting.

Keywords

Mesothelin; Tumor markers; Cancer screening; PEB algorithm

Introduction

CA 125 can identify 85% of clinically advanced ovarian carcinomas [1–3], and several studies have shown that deviations in CA 125 may occur 18 months or more before clinical diagnosis [4,5]. Thus, monitoring CA 125 could lead to identifying ovarian cancer long before it is clinically apparent. Moreover, the ability of CA 125 to detect cancer early in a screening program is supported by the observation that individual women have temporally stable levels of CA 125 [6], suggesting that specially tailored screening algorithms could lead to detecting

*Corresponding author. Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue MP-900, Seattle, WA, 98109. Fax: +1 206 667 7850., E-mail address: mmcintos@fhcrc.org (M.W. McIntosh).

the disease based on very small deviations in CA 125 levels [7–10]. Presently, a large randomized trial evaluating longitudinal change in CA 125 for ovarian cancer early detection is underway in the United Kingdom [11].

Although CA 125 is the best available single marker for ovarian cancer, its sensitivity and specificity may not be sufficient for screening average-risk postmenopausal women. In particular, it is elevated above reference levels in only 50% of clinically detectable early stage disease [1–3] and is not infrequently elevated in patients with benign ovarian tumors. Adding one or several markers to CA 125 for use as a composite marker (CM) would improve diagnostic performance if sensitivity were improved with no loss in specificity.

Proposals to combine other markers with CA 125 have been made previously, and investigators have evaluated the ability of some established markers to improve the identification of clinical disease [12,13]. Here, we evaluate the performance of a composite marker (CM) consisting of CA 125 and a novel marker SMR [14]. We report and compare the ability of CA 125, SMR, and the CM to distinguish the serum of women with clinically detected ovarian cancer from that of women with benign ovarian tumors and healthy women. In addition, we report the temporal stability of the three markers to assess whether each can improve their sensitivity when used in a longitudinal algorithm [6,15]. We use receiver operating characteristic (ROC) methods to show that the CM has higher sensitivity than either marker used alone, maintaining overall specificity with respect to benign ovarian tumors as well as a healthy screening population. We use correlation analysis to demonstrate that the CM maintains the high temporal stability of CA 125, which implies that its superiority over CA 125 may also hold when used in a longitudinal screening algorithm.

Materials and methods

SMR ELISA assay

SMR was measured by a sandwich ELISA [14] that uses monoclonal antibodies (MAbs) to two different epitopes expressed on molecules expressed by the mesothelin [16,17] and megakaryocyte potentiating factor (MPF) [18] family, including a recently described soluble molecule that has an 82-bp insert in the membrane-associated part of mesothelin and MPF [14]. These molecules are overexpressed in >95% of ovarian carcinomas according to immunohistology, while their expression in normal tissues, except for mesothelium, is low [14]. In concordance with these findings, the gene encoding SMR was found overexpressed in ovarian cancers relative to normal ovarian tissue and tissue from selected other organs and cell lines [19].

Serum specimens

We selected serum from 52 women with ovarian cancer, 43 women having benign ovarian conditions, and 220 healthy women. The cases, randomly selected from our repository, include 31 serous (25 late stage), 2 clear cell (both late stage), 3 endometriosis (2 late stage), 4 mucinous (all late stage), 7 other histology's (4 late stage), and 5 undifferentiated (all late stage). By late stage, we mean stages III or IV.

Specimens were selected at random so that our results are interpretable for their relevance to the diagnosis of the population of ovarian cancer. Numbers of cancer cases and benign disease were chosen to have sufficient power to validate a marker having sensitivity of 10% at high specificity and not powered to evaluate the performance within specific subgroups. As a first step toward evaluating the relevance of our findings for early detection, we also performed measurements on specimens collected serially (1 year apart) from a sample (n = 25) of these healthy women to establish marker temporal stability.

Sera from women with ovarian cancer and benign ovarian tumors were collected before surgical removal of the ovaries. A pathologist examined fixed, paraffin-embedded specimens to confirm the histology for all surgical specimens. The serum from healthy women came from participants in an NCI-funded ovarian cancer screening research trial. Specimen collection and processing protocols were identical for all women regardless of case or control status: subjects donated up to 50 cc of blood, which was processed into sera, plasma, and white blood cell and epithelial cell pellets.

All research subjects were characterized at the time of specimen collection with respect to race, age, menopausal status, and use of hormone replacement therapy (HRT). Women were considered postmenopausal if they reported no menstruation for 6 months, used HRT, or were above 50 and did not report menstrual history. All women using HRT had been taking it for a year or more. Stage and histology were recorded for all cancer cases. Table 1 summarizes these variables for the study population.

Statistical procedures

Quantifying the diagnostic ability of a marker—Receiver operating characteristic (ROC) curves was used to quantify marker performance (see Fig. 1). ROC curves associate the sensitivity of a diagnostic test to the entire range of the possible false-positive rate (FPR). The FPR is equal to one minus test specificity. The area under the ROC curve (AUC) indicates a marker's average sensitivity over the entire ROC curve. We also computed the sensitivity of each marker at 98% specificity, a value more relevant to diagnosis and early detection than the overall sensitivity. Establishing statistical significance of a single marker is performed by the Wilcoxon rank-sum test, also referred to as the Mann–Whitney test. When comparing the ROC curves of two markers, statistical significance is established using a two-sample variant of the test [20]. The Wilcoxon test evaluates the significance of entire ROC curve, and relevance of a specific AUC to early detection or diagnosis is evaluated by evaluating the sensitivity at 98% specificity.

Standardizing markers—To aid interpretation for comparing markers and marker panels, we first transform CA 125 and SMR with the natural log to approximate a normal distribution. We then standardize the markers, so that in the healthy controls, markers have mean 0 and unit standard deviation. Standardization, which affects neither the ROC curves nor the temporal stability of the markers, facilitates the comparison of two different markers because their units of measurement are now comparable (the number of standard deviations above the average normal subject), as illustrated below.

Combining markers—The composite marker (CM) is estimated as a linear combination of the standardized CA 125 and SMR, where logistic regression is used to estimate the weights. The initial logistic regression predicted case status from healthy controls (benign observations omitted), controlling for menopausal status and testing an interaction term between the markers and menopausal status. The interaction term was dropped due to lack of significance. The final logistic regression is summarized in Table 2.

Logistic regression has several properties that make it convenient for applied biomarker research. Logistic regression *P* values evaluate whether the marker combination, compared to CA 125 alone, significantly increases the "distance" between the cases and controls. If the model is correctly specified, the sensitivity of the resulting CM is maximized at all specificities simultaneously [21] (i.e., the ROC curve is optimal), although the theoretically correct model cannot ever be known in practice. We chose a linear combination for ease of interpretation. After establishing significance, we then examine resulting ROC curves (see Fig. 1) and other distance measures (i.e., see Table 3) to evaluate the quality of the composite marker and

whether the improvement is likely to be obtained in areas relevant for diagnosis and early detection.

Evaluating temporal stability—We measured the temporal stability in healthy subjects by computing the Pearson correlation from two time points in 25 of the 220 women participating in our screening program, based on two serum samples obtained 1 year apart. Markers with higher correlation yield improved performance in a longitudinal algorithm [6,9]. For CA 125, SMR, and the CM, Fig. 2 shows the correlation between the first measurement (horizontal axis) and the second measurement (the vertical axis). The high correlation for each of the three markers implies that monitoring markers for their deviation from historical levels using the Parametric Empirical Bayes (PEB) screening rule [9,10] will yield earlier detection than a simpler diagnostic rule that ignores screening history. One cannot claim one marker superior to another based only on its greater temporal stability. The existence of high temporal stability of a marker implies only that its performance can be improved upon in a longitudinal algorithm.

Results

Marker behavior in healthy subjects

For CA 125, SMR, and the CM, we found no statistically significant differences in marker levels with respect to age, hormone replacement therapy (HRT) use, and race. Menopausal status approached statistical significance for CA 125 ($P = 0.08$), but not for SMR ($P = 0.37$) nor for the CM ($P = 0.67$). Table 4 summarizes the levels of CA 125 and SMR for healthy subjects and for women with benign ovarian tumors by menopausal status, and for ovarian cancer cases by stage of disease at diagnosis. The results for CA 125 are consistent with those from larger studies [22].

Marker performance: cases versus healthy controls

Table 4 summarizes CA 125 and SMR on their raw scales, and Table 3 summarizes them and the CM on their standardized scales. Summaries for healthy controls and surgical (benign conditions) controls are given by menopausal status, and levels in cases are given by stage. The overall discrimination ability of each marker (its AUC) to classify cases versus healthy controls, their ROC curves, is summarized on the left side of Table 5. Fig. 1 graphically displays the ROC curves for discriminating cases from healthy controls for postmenopausal subjects.

On their own, both CA 125 and SMR are statistically significant predictors of ovarian cancer compared to healthy controls (Wilcoxon P value < 0.001). On average, CA 125 levels in cases are 5.761 standard deviations above healthy controls (see Table 3). SMR levels in cases are on average elevated by 5.781 standard deviations above healthy controls. The AUC of CA 125 and SMR are 92.5% and 92%, respectively.

Although on average (Table 3) and by their overall ROC curves (left half of Table 5) CA 125 and SMR perform comparably, the ROC curves in Fig. 1 and the summaries in Table 5 show that CA 125 is the better performing marker at the high specificity required for a screening program. For example, at perfect specificity (see Fig. 1), CA 125 identifies 40 of 52 cases (76.9% sensitivity), whereas SMR identifies 22 of 52 cases (42.3% sensitivity). Table 5 summarizes the sensitivity at 98% specificity and shows comparable results, with 78.8% and 59.6% sensitivity for CA 125 and SMR, respectively. Because the performance at high specificity is most relevant for early detection, we conclude that CA 125 is the better single marker.

The CM, estimated by logistic regression, is presented in Table 2. This composite marker, defined as CM = 1.388 × (standardized CA 125) + 0.998 ×(standardized SMR), can now be

treated as a single marker and subjected to ROC analyses. The CM logistic regression is statistically significant for including SMR (likelihood ratio P value < 0.01). Note that although menopausal status was a significant predictor, it does not play a role in the CM because no interaction term exists; only terms involving markers are needed to form the composite marker [21].

We can now see the convenience of using standardized values of the markers when forming the CM. We can interpret the larger coefficient or "weight" for CA 125 to mean that deviations in CA 125 are more suggestive than equivalent deviations in SMR. Specifically, we can say that CA 125 carries 58% = 100 × 1.388/(1.388 + 0.998) of the weight in the composite marker. However, the statistical significance of the logistic regression shows that both markers are significant and important contributors to the resulting CM ROC curve [21].

The statistical significance of the logistic regression suggests that CM will outperform CA 125 and SMR alone. Because significance does not provide an indication of the magnitude of the improvement, we also evaluate summaries of the CM compared to each marker alone. From Table 3, we see that CM in cases averages 8.14 standard deviations higher than healthy controls (column 3), compared to 5.781 in SMR and 5.761 in CA 125, suggesting about a 35% improvement.

A similar magnitude of improvement within early stage disease suggests that the CM may also improve detection of early stage disease. The CM in early stage cases is 5.47 standard deviations above that of healthy controls, which is greater than the elevations found in CA 125 (equal to 3.977) or SMR (equal 3.741). However, the statistical significance or magnitude of any improvement for early stage cancer must be established in additional studies.

The summaries in Tables 3 and 5 and the ROC curve in Fig. 1 show that the improvement may be relevant for screening. Table 5 shows that, at 98% specificity, the CM identifies 86.5% (45 of 52) of the cases, compared to 78.8% (41 of 52) achieved by CA 125 alone (see also Fig. 1). Table 3 shows that the lowest quintile of CA 125 in cases (women in whom markers are least elevated) is only 3.233 standard deviations above normal but the lowest quintile for CM is 4.590 standard deviations above normal.

Marker performance: cancer cases versus benign ovarian tumors

Failure to distinguish benign from malignant disease limits the utility of a marker for both diagnostic and screening purposes. Both CA 125 and SMR are sensitive to benign ovarian tumors and other gynecologic conditions, and as such, we can expect that the CM will be sensitive as well. We therefore evaluated the ability of the CM to distinguish between women with ovarian cancer and women with benign ovarian tumors to establish if its performance in this regard was equal, better, or worse than that of CA 125 alone. For CA 125, SMR, and CM, this aspect of diagnostic performance is measured in the right half of Table 5, which shows reduced average sensitivity, both overall (AUC) and at high specificity, for discriminating between benign disease and cancer cases relative to discriminating cancer cases from healthy controls. For example, the sensitivity declined from 78.8% to 37.2% for CA 125, from 59.6% to 28.8% for SMR, and from 86.5% to 44.1% for CM. All three markers have substantially reduced performance for benign controls compared to healthy controls, but at 98% specificity, the sensitivity of the CM is at least comparable to l to that of CA 125.

Longitudinal marker behavior

Fig. 2 plots standardized markers measured in sera collected 1 year apart for the 25 healthy control subjects who have serial observations available. The correlations are CA 125 = 0.77, SMR = 0.86, and CM = 0.79. All correlations are statistically significant (P < 0.001), implying

temporal stability in all three markers, and differences among them are not statistically significant ($P > 0.35$).

The performance of markers having temporal stability can be improved by taking account of marker history in a longitudinal screening program [6,23], and several longitudinal algorithms have been proposed [7,9,10]. One particular algorithm (the PEB algorithm), intended for use with novel markers, makes use of the simple Pearson correlation of a marker measured at two different time points to generate a screening rule. [9] Because the CM summarizes both markers into a single numeric score, the PEB rule can also be applied to the CM. The potential improvement of the PEB rule can be quantified by computing square root (1 – correlation). This value predicts the improvement in precision that a longitudinal algorithm such as the PEB screening algorithm could achieve [10]. For example, monitoring CA 125 over time, which has a correlation of 0.77, can identify a deviation 48% the size [0.48 = sqrt(1 − 0.77)] of that identified at the same specificity when ignoring screening history. SMR and CM can identify deviations that are 37% and 47% the size, respectively. Thus, as was argued for using CA 125 alone [6], a CM consisting of SMR and CA 125 may be more promising when used in a longitudinal screening program than the CM used one at a time.

Discussion

We evaluated the performance of two markers, CA 125 and SMR, and their composite marker (CM) for several performance characteristics relevant to their potential use in diagnosis and early detection. The best individual marker for diagnosis was found to be CA 125, which performed as published. However, a CM combining CA 125 with SMR was superior to using CA 125 alone to diagnose cancer, and our results suggest that the improvement in sensitivity to cancer may occur in the range of specificity most relevant for early detection and diagnosis. The CM and CA 125 have comparable performance for distinguishing cases from benign disease. In addition, the results suggest that the CM may also improve performance in early stage disease, but since most (80%) of the cases in this study were diagnosed in stages III or IV, larger studies are needed to confirm this conclusion and to more accurately evaluate the magnitude of the performance gain achieved by the CM for this subgroup and overall.

The CM maintains the high level of temporal stability that makes CA 125 particularly suitable for an early detection program., where longitudinal algorithms can be employed. The use of a longitudinal screening algorithm may dramatically improve a marker's performance as first-line screen for ovarian cancer when the marker has high temporal stability. The CM may be able to detect cancer when marker elevations are half the size that can be detected by simpler algorithms that ignore screening history. This calculation is based on the Parametric Empirical Bayes (PEB) screening algorithm that was derived for use of novel markers or marker combinations [10]. Because the temporal stability of the CM was comparable to that of CA 125 and its sensitivity at the same specificity may exceed that of CA 125, the CM could have better performance in screening, but only if the marker CM is found to elevate at least as early as does CA 125. Only after studies are undertaken to assess this property of the CM and confirm its performance at high specificity can we make a definitive statement about the superiority or inferiority of the CM over CA 125 alone for early detection.

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Abbreviations

SMR soluble mesothelin related

MPF megakaryocyte potentiating factor

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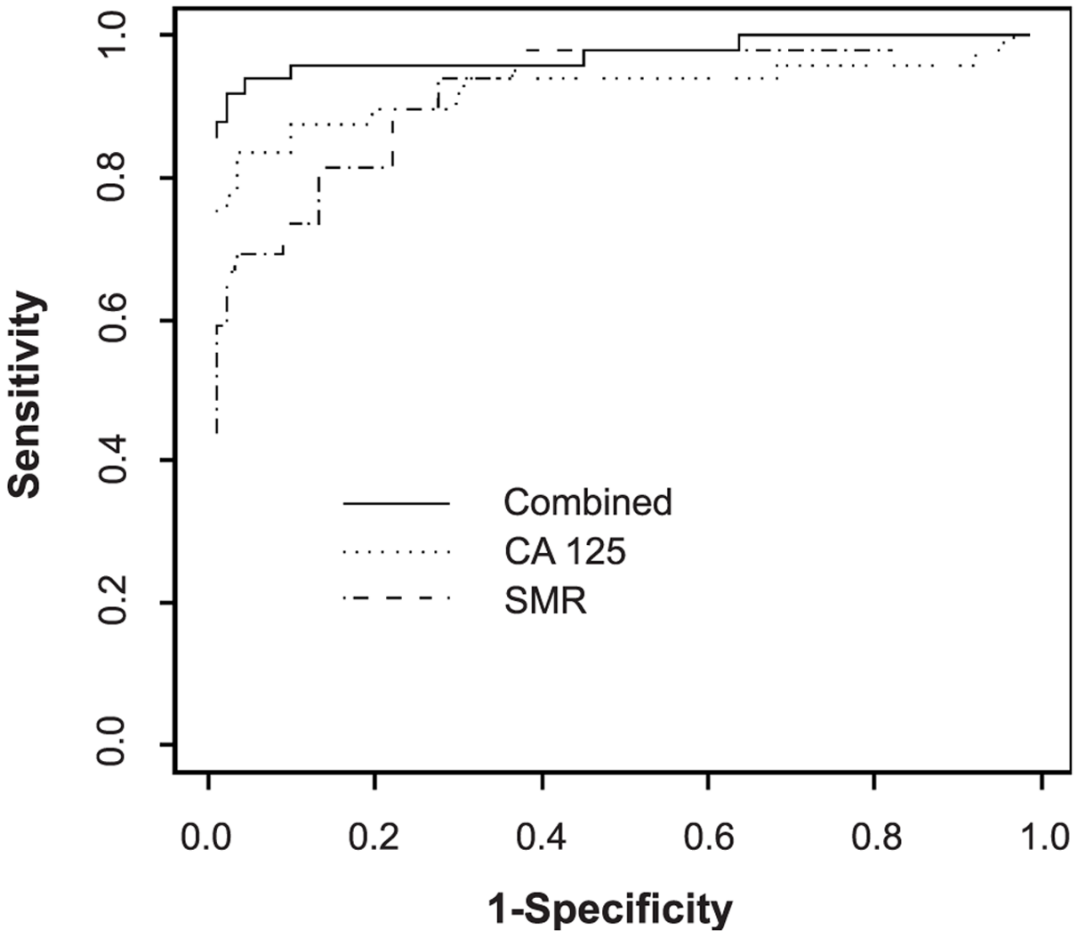

Fig. 1.
ROC curves for SMR, CA 125, and the composite marker (CM) for postmenopausal women only for distinguishing ovarian cancer cases from healthy controls.

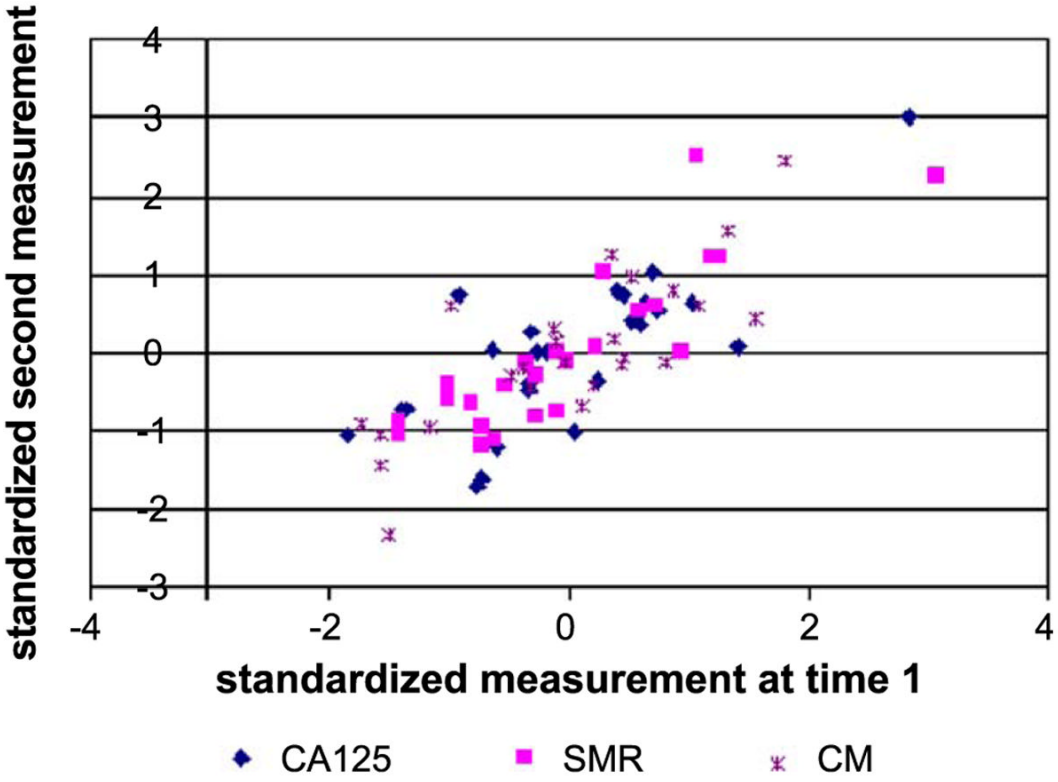

Fig. 2.
Scatter plot showing the correlation between two time points for all three markers. The correlations are 0.77 (CA 125), 0.86 (SMR), and 0.79 (CM). The correlations quantify the improvements that can be made by using the markers in a longitudinal algorithm.

Table 1

Summary description of study subjects who donated specimens for our analysis

	Total	Menopausal status		Race					Stage			
		Premenopausal	Postmenopausal	Native American	Asian	Black	Hispanic	White	I	II	III	IV
Ovarian cancer cases	52	5	47	0	1	1	0	41	7	3	34	8
Benign conditions	43	16	27	2	4	0	1	29	NA	NA	NA	NA
Healthy controls	220	69	151	1	3	0	3	198	NA	NA	NA	NA

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Table 2

Summary of binary regression predicting case status from healthy controls, controlling for menopausal status

	Coefficient	Standard error	*P* value
CA 125	1.388	0.335	0.000
SMR	0.998	0.255	0.000
Menopause	4.427	1.548	0.004

The weights of CA 125 and SMR are used to form the composite screening rule. Note: Markers are combined using their standardized, rather than raw, scales.

Table 3

Summary of standardized markers by health status and menopausal status

	n	Mean	SD	25%	50%	75%
Standardized CA 125						
Healthy						
All	220	0.000	1.000	−0.575	−0.053	0.497
Pre menopausal	129	0.094	1.059	−0.478	0.042	0.573
Post menopausal	91	−0.133	0.900	−0.641	−0.152	0.341
Benign						
All	43	1.779	2.085	0.107	1.557	2.693
Pre menopausal	12	2.115	1.774	1.225	1.522	2.837
Post menopausal	1	1.649	2.206	−0.171	1.557	2.693
Case						
All	52	5.761	3.594	3.233	6.132	8.136
Early	10	3.977	2.809	1.821	5.107	6.143
Late	42	6.186	3.657	3.404	6.395	8.280
Standardized MPF						
Healthy						
All	220	0.000	1.000	−0.630	−0.220	0.515
Pre menopausal	129	−0.081	0.935	−0.676	−0.288	0.493
Postmenopausal	91	0.115	1.080	−0.584	−0.085	0.559
Benign						
All	43	1.956	2.357	0.332	1.526	2.792
Pre menopausal	12	0.951	1.011	0.158	0.471	1.641
Post menopausal	31	2.344	2.616	0.873	1.737	2.923
Case all						
All	52	5.781	4.915	1.579	3.759	9.966
Early	10	3.741	4.737	0.785	2.275	3.530
Late	42	6.266	4.885	1.783	5.033	10.034
Standardized composite marker						
Healthy						
All	220	0.000	1.000	−0.572	−0.116	0.543
Pre menopausal	129	0.029	1.036	−0.553	−0.166	0.646

	n	Mean	SD	25%	50%	75%
Post menopausal	91	0.041	0.952	−0.605	−0.089	0.497
Benign						
All	43	2.613	2.203	0.316	2.368	3.261
Pre menopausal	12	2.295	1.364	0.156	2.191	2.936
Post menopausal	31	2.737	2.461	0.896	2.368	3.517
Case all						
All	52	8.137	4.833	4.590	7.075	11.838
Early	10	5.470	3.960	2.922	4.886	6.8731
Late	42	8.772	4.844	5.192	8.141	12.451

Menopausal status was found as an important predictor of CA 125 but not for other markers, nor the CM. All other variables, including hormone replacement therapy use, age, and race, were not found to significantly modify the marker behavior.

Table 4

Summary of raw marker levels by stage of disease for cancer and menopausal status for controls, within disease status

	Quintiles					
	n	**Mean**	**SD**	**25%**	**50%**	**75%**
Raw CA 125						
Healthy controls						
All	220	11.498	10.023	6.675	9.25	12.900
Premenopausal	129	12.481	11.694	7.100	9.80	13.500
Postmenopausal	91	10.104	6.828	6.400	8.70	11.750
Benign controls						
All	43	75.893	230.357	10.200	24.00	45.900
Premenopausal	12	54.633	65.203	19.825	23.65	50.925
Postmenopausal	31	84.123	269.222	8.600	24.00	45.900
Ovarian cancer cases						
All	52	1346.906	2990.575	62.250	314.05	954.675
Early	10	201.020	183.381	27.950	198.90	315.875
Late	42	1619.736	3274.294	68.875	363.85	1034.400
Raw SMR						
Healthy controls						
All	220	0.150	0.046	0.121	0.139	0.172
Premenopausal	129	0.146	0.043	0.119	0.136	0.171
Postmenopausal	91	0.155	0.050	0.123	0.145	0.174
Benign controls						
All	43	0.245	0.130	0.163	0.219	0.280
Premenopausal	12	0.193	0.048	0.156	0.170	0.224
Postmenopausal	31	0.265	0.146	0.190	0.229	0.287
Ovarian cancer cases						
All	52	0.465	0.296	0.222	0.330	0.692
Early	10	0.351	0.275	0.184	0.255	0.318
Late	42	0.492	0.298	0.231	0.397	0.697

Table 5

Summaries of ROC curves for CA 125, SMR, and the CM for postmenopausal subjects

	ROC area versus healthy controls		ROC area versus benign controls	
	AUC	**Sense (0.98)**	**AUC**	**Sense (0.98)**
CA 125	0.925	0.788	0.801	0.372
SMR	0.920	0.596	0.693	0.288
CM	0.974	0.865	0.838	0.441

AUC represents the area under the ROC curve, and Sense (0.98) represents the sensitivity at 98% specificity of the ROC curve. The AUC differences between SMR and CA 125 are not significant ($P = 0.67$ for healthy controls and $P = 0.85$ for benign controls). AUC improvement of CM over CA 125 for cases versus normal must be implied indirectly by the significance of the logistic regression presented in Table 2.