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ORIGINAL PAPER

Predictors of pretreatment CA125 at ovarian cancer diagnosis: a pooled analysis in the Ovarian Cancer Association Consortium

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Abstract

Purpose Cancer antigen 125 (CA125) is a glycoprotein expressed by epithelial cells of several normal tissue types and overexpressed by several epithelial cancers. Serum CA125 levels are mostly used as an aid in the diagnosis of ovarian cancer patients, to monitor response to treatment and detect cancer recurrence. Besides tumor characteristics, CA125 levels are also influenced by several epidemiologic factors, such as age, parity, and oral contraceptive use. Identifying factors that influence CA125 levels in ovarian cancer patients could aid in the interpretation of CA125 values for individuals.

Methods We evaluated predictors of pretreatment CA125 in 13 studies participating in the Ovarian Cancer Association Consortium. This analysis included a total of 5,091 women with invasive epithelial ovarian cancer with pretreatment CA125 measurements. We used probit scores to account for variability in CA125 between studies and linear regression to estimate the association between epidemiologic factors and tumor characteristics and pretreatment CA125 levels.

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Results In age-adjusted models, older age, history of pregnancy, history of tubal ligation, family history of breast cancer, and family history of ovarian cancer were associated with higher CA125 levels while endometriosis was associated with lower CA125 levels. After adjusting for tumor-related characteristics (stage, histology, grade), body mass index (BMI) higher than 30 kg/m^2 was associated with 10% (95% CI 2, 19%) higher CA125 levels, while race (non-white vs. white) was associated with 15% (95% CI 4, 27%) higher CA125 levels.
Conclusion Our results suggest that high BMI and race may influence CA125 levels independent of tumor characteristics. Validation is needed in studies that use a single assay for CA125 measurement and have a diverse study population.

Keywords Ovarian cancer · CA125 · Predictors · Prognosis · Biomarker

Introduction

Cancer antigen 125 (CA125) is a high molecular weight glycoprotein encoded by the MUC16 gene [1]. It is expressed under normal conditions in epithelial tissues (e.g., breast, lung, genitourinary tract) and overexpressed in epithelial cancers [2, 3]. Circulating CA125 is elevated in more than 80% of women with epithelial ovarian cancer and is the best biomarker to date for the early detection of ovarian cancer [4, 5]. However, the sensitivity and specificity of CA125 as an early detection marker are limited [6], and recent large-scale randomized screening trials reported no significant mortality benefit with CA125 screening versus usual care [7, 8]. Pretreatment CA125 levels are associated with survival and changes in levels have been shown to predict recurrence [9, 10]. Although CA125 is commonly used to monitor women with ovarian cancer for progression, a recent study suggested that active surveillance using CA125 leads to a lower quality of life without increasing survival time [11].

In women without ovarian cancer, CA125 varies with age, race, body mass index (BMI), oral contraceptive (OC) use, hysterectomy, parity, and breast cancer history [12–14]. In women diagnosed with ovarian cancer, CA125 levels are predominantly determined by the extent of disease but also some of the same factors that influence the biomarker in healthy women [15]. Understanding how CA125 varies in women with ovarian cancer both due to the tumor characteristics and independent of tumor characteristics could improve our ability to interpret CA125 values in women with ovarian cancer and provide insight into how CA125 may be associated with progression of disease. Here, we evaluate associations between tumor characteristics, reproductive, and lifestyle characteristics and preoperative CA125 levels in women with ovarian cancer from 13 studies participating in the Ovarian Cancer Association Consortium.

Materials and methods

Study population

This study included women with ovarian cancer from 13 studies participating in the Ovarian Cancer Association Consortium (OCAC), a collaborative group established in 2005 with goal of discovering new genetic variants associated with ovarian cancer [16, 17]. Studies included in this analysis were the Alberta Ovarian Tumor Types Study (AOV) [18, 19], Australian Ovarian Cancer Study (AUS) [20], Belgium Ovarian Cancer Study (BEL) [21], Hawaii Ovarian Cancer Study (HAW) [22, 23], Dr. Horst Schmidt Kliniken (HSK) [24, 25], Hospital-based Epidemiological

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research Program at Aichi Cancer Center (JPN) [26], Women's Cancer Program at the Samuel Oschin Comprehensive cancer Institute (LAX) [27], Malignant Ovarian cancer Study (MAL) [28], Mayo Clinic Ovarian Cancer Case–Control Study (MAY) [29, 30], New England Case Control Study (NEC) [31], Oregon Ovarian Cancer Registry (ORE) [32, 33], Danish Pelvic Mass Study (PVD) [34], and Scottish Randomized Trial in Ovarian Cancer (SRO) [35, 36]. In total, there were 5,538 women with preoperative CA125 values in OCAC. We excluded 147 women with non-epithelial tumors or tumors with unknown origin, 277 patients with borderline tumors, 22 patients with tumors of unknown morphology, and one patient with in situ disease. This resulted in a total of 5,091 women with invasive epithelial ovarian cancer and available CA125 levels. All studies included in this analysis had obtained written informed consent from all study participants and had approval from ethics committees.

Information about demographic, reproductive, lifestyle, and tumor characteristics was collected by individual studies and submitted to a coordinating center that compiled a core dataset, including age at diagnosis, age at menarche, race, family history of breast cancer or ovarian cancer, personal history of endometriosis, menopausal status, hysterectomy, tubal ligation, height, weight 1 year prior to diagnosis, smoking, ever use of OC, history of pregnancy, tumor stage, grade, and histology. Pretreatment CA125 levels were either measured directly as part of an individual study (BEL, JPN, MAL, PVD) or abstracted from medical records (AOV, AUS, HAW, LAX, MAY, NEC, SRO). Information about type of CA125 assay used by different studies is listed in the Supplemental Table 2.

Statistical analysis

We used probit scores to standardize CA125 levels, which varied across studies [37, 38]. Probit scores were calculated using the following equation: $\Phi^{-1} = [i/(n + 1)]$, where Φ is the cumulative distribution function for a standard normal distribution, i is the rank of each participant within a study and n is the number of participants in each study. We estimated the association between exposures of interest and CA125 using univariate and multivariate linear regression.

Epidemiologic and tumor characteristics considered in relation to pretreatment CA125 levels include stage (I, II, III, IV, unknown), histologic subtype (serous, endometrioid, clear cell, mucinous, other), tumor grade (well differentiated, moderately differentiated, poorly differentiated, and undifferentiated), self-reported race (white, black, Asian, other, presumed white, unknown), family history of ovarian cancer (no, yes, unknown), family history of breast cancer (no, yes, unknown), prior history of breast cancer (no, yes, unknown), BMI (<18.5, 18.5–<25, 25–<30, ≥30, unknown), ever OC use (no, yes, unknown), ever pregnant (no, yes, unknown), tubal ligation (no, yes, unknown), prior hysterectomy (no, yes, unknown), and endometriosis (no, yes, unknown), age at menarche, height, and weight 1 year prior to diagnosis. For the purpose of this analysis, race was grouped in three categories: presumed whites have been grouped with whites, black, Asian, and others were grouped as non-white, and unknown were grouped with missing. Residual disease was classified as: no macroscopic disease, macroscopic disease ≤1 cm, macroscopic disease >1 and ≤2 cm, macroscopic disease >2 cm, macroscopic disease of unknown size, tumor not ressected, and unknown.

In univariate models, we adjusted for age at diagnosis (continuous). In order to identify CA125 predictors that are independent of tumor characteristics (stage, histology, and grade), we constructed multivariate models additionally adjusted for stage and a variable for combined histology and grade: high-grade (moderately and poorly differentiated, and undifferentiated) serous, low-grade (well differentiated) serous, high-grade endometrioid, low-grade endometrioid, mucinous, clear cell, and other/unknown). In order to investigate the independent contribution of individual predictors to CA125 levels, we simultaneously adjusted for all the factors that were significant predictors of CA125 in multivariate models. For each predictor, we report the original parameter estimates (coefficients) as well as the percent change in CA125 levels [calculated as [exp (coefficient) − 1]*100]. All the analyses were performed using SAS v9.4 (SAS Institute, Cary, NC). All p values were two-sided, and a significance threshold of $p < 0.05$ was used.

Results

This analysis included a total of 5,091 women diagnosed with epithelial ovarian cancer from a mixture of case–control (population or hospital based) or case only (registry or clinical trial) studies in the USA, Canada, Europe, Asia, and Australia between 1992 and 2016 (Table 1). Cases were predominantly high-grade, advanced stage, and invasive serous though the proportion varied between studies. Among high-grade serous cases, median CA125 levels varied between studies, ranging from 259 U/ml (SRO) to 1590 U/ml (JPN).

In age-adjusted models, height, weight 1 year before diagnosis, age at menarche, hysterectomy, OC use, smoking, and prior history of breast cancer were not significantly associated with pretreatment CA125 levels. Older age at diagnosis, history of pregnancy, tubal ligation, family history of breast cancer, and family history of ovarian cancer were associated with higher CA125 levels, while a personal history of endometriosis was associated with lower CA125 levels (Table 2). After additionally adjusting

Table 1 Characteristics of studies included in the pooled analysis of factors associated with pretreatment CA125 at diagnosis, Ovarian Cancer Association Consortium

Study		Study design	Location	Dates of enrollment	*n*	White race, *n* (%)	Advanced stage**, *n* (%)	High-grade serous *n* (%)	Median (IQR) CA125 among high-grade serous tumors (U/ml)
Alberta Ovarian Tumor Types Study*	AOV	Case only	Canada	1978-2010	372	146 (39)	134 (36)	0 (0)	NA
Australian Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer)	AUS	Case–control	Australia	2002–2006	954	888 (93)	729 (76)	446 (47)	745 (274–1,900)
Belgium Ovarian Cancer Study	BEL	Case–control	Belgium	2007-present	261	259 (99)	176 (67)	155 (59)	524 (136–1,296)
Hawaii Ovarian Cancer Study	HAW	Case–control	USA	1993–2008	217	73 (34)	116 (53)	76 (35)	708 (181–2,462)
Dr. Horst Schmidt Kliniken	HSK	Case only	Germany	2000–2007	114	114 (100)	96 (84)	47 (41)	567 (165–1,234)
Hospital-based Epidemiological research Program at Aichi Cancer Center	JPN	Case–control	Japan	2001–2005	60	0 (0)	39 (65)	12 (20)	1590 (166–3,610)
Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute	LAX	Case only	USA	1989-present	261	240 (92)	213 (82)	178 (68)	681 (227–1,830)
Malignant Ovarian cancer Study	MAL	Case–control	Denmark	1994–1999	425	425 (100)	279 (66)	103 (24)	709 (267–3,220)
Mayo Clinic Ovarian Cancer Case–Control Study	MAY	Case–control	USA	2000–2011	788	761 (97)	619 (79)	514 (65)	738 (268–1,859)
New England Case Control Study	NEC	Case–control	USA	1992–2008	512	484 (95)	291 (57)	308 (60)	806 (235–2,063)
Oregon Ovarian Cancer Registry	ORE	Case only	USA	2007-present	60	56 (93)	42 (70)	30 (50)	1128 (497–2,100)
Pelvic Mass Study	PVD	Case only	Denmark	2004-present	201	0 (0)	151 (75)	69 (34)	728 (269–1,694)
Scottish Randomized Trial in Ovarian Cancer	SRO	Case only	UK		866	0 (0)	713 (82)	272 (31)	259 (89–751)

* Non-serous tumors were oversampled in this study

** Stage III and IV

Table 2 Associations* between demographic, lifestyle, and reproductive characteristics and pretreatment CA125 levels among women with ovarian cancer in the Ovarian Cancer Association Consortium

Predictor	CA125 median (U/ml)	Adjusted for age			Adjusted for age, histology, grade, and stage		
		Coefficient (95% CI)	Percent difference (95% CI)	*p* value	Coefficient (95% CI)	Percent difference (95% CI)	*p* value
Age (years)							
<50	258.0	Ref	Ref		Ref	Ref	
50–60	361.0	0.12 (0.05, 0.20)	13.3 (5.2, 22.0)	0.001	0.02 (−0.04, 0.09)	2.4 (−4.4, 9.6)	0.50
60–70	414.5	0.16 (0.08, 0.24)	17.4 (8.8, 26.7)	<0.0001	−0.03 (−0.10, 0.04)	−3.1 (−9.7, 4.0)	0.38
>70	430.0	0.14 (0.06, 0.23)	15.4 (5.7, 26.0)	0.001	−0.04 (−0.13, 0.04)	−4.4 (−11.8, 3.7)	0.28
Ever pregnant							
No	307.0	Ref	Ref		Ref	Ref	
Yes	451.6	0.12 (0.04, 0.20)	12.6 (3.6, 22.3)	0.01	−0.05 (−0.13, 0.03)	−4.7 (−11.8, 3.0)	0.22
Endometriosis							
No	441.0	Ref	Ref		Ref	Ref	
Yes	222.0	−0.17 (−0.28, −0.06)	−15.7 (−24.6, −5.8)	0.003	0.03 (−0.08, 0.13)	2.8 (−7.4, 14.1)	0.61
Ever OC use							
No	458.5	Ref	Ref		Ref	Ref	
Yes	440.0	0.00 (−0.07, 0.07)	0.2 (−6.7, 7.7)	0.95	−0.05 (−0.11, 0.02)	−4.8 (−10.9, 1.6)	0.14
Tubal ligation							
No	401.1	Ref	Ref		Ref	Ref	
Yes	539.5	0.14 (0.04, 0.25)	15.3 (3.7, 28.2)	0.01	0.05 (−0.05, 0.15)	5.3 (−4.5, 16.0)	0.30
Hysterectomy							
No	424.0	Ref	Ref		Ref	Ref	
Yes	396.0	−0.04 (−0.11, 0.03)	−4.0 (−10.2, 2.7)	0.23	0.01 (−0.05, 0.07)	1.1 (−5.0, 7.6)	0.73
Race							
White	460.0	Ref	Ref		Ref	Ref	
Non-white	298.0	−0.02 (−0.13, 0.09)	−1.7 (−11.8, 9.5)	0.75	0.14 (0.04, 0.24)	15.3 (4.3, 27.4)	0.01
Age at menarche							
<13 years	505.0	Ref	Ref		Ref	Ref	
≥13 years	438.0	−0.06 (−0.13, 0.02)	−5.6 (−12.3, 1.5)	0.12	−0.02 (−0.09, 0.04)	−2.3 (−8.6, 4.4)	0.49
Height (per cm)	N/A	−0.10 (−0.56, 0.36)	−9.8 (−43.1, 43.1)	0.66	−0.27 (−0.69, 0.15)	−23.7 (−50.0, 16.5)	0.21
Weight 1 year prior to diagnosis							
<68 kg	428.0	Ref	Ref		Ref	Ref	
≥68 kg	430.0	−0.01 (−0.08, 0.07)	−0.7 (−7.8, 7.1)	0.86	0.04 (−0.03, 0.11)	3.9 (−3.0, 11.3)	0.28
BMI (kg/m^2)							
<18.5	574.0	0.11 (−0.09, 0.32)	11.8 (−8.9, 37.1)	0.28	0.13 (−0.05, 0.32)	14.3 (−5.2, 37.6)	0.16
18.5–25	419.0	Ref	Ref		Ref	Ref	
25–30	394.0	−0.04 (−0.12, 0.04)	−3.9 (−10.9, 3.7)	0.30	−0.02 (−0.09, 0.05)	−1.9 (−8.5, 5.1)	0.59
>30	492.0	0.06 (−0.02, 0.15)	6.5 (−2.0, 15.8)	0.14	0.09 (0.02, 0.17)	9.8 (1.7, 18.5)	0.02

Table 2 continued

Predictor	CA125 median (U/ml)	Adjusted for age			Adjusted for age, histology, grade, and stage		
		Coefficient (95% CI)	Percent difference (95% CI)	*p* value	Coefficient (95% CI)	Percent difference (95% CI)	*p* value
Family history of breast cancer							
No	451.8	Ref	Ref		Ref	Ref	
Yes	479.0	0.09 (0.00, 0.18)	9.5 (0.1, 19.8)	0.05	0.05 (−0.03, 0.13)	5.1 (−3.1, 14.1)	0.23
Family history of ovarian cancer							
No	456.0	Ref	Ref		Ref	Ref	
Yes	488.5	0.17 (0.02, 0.32)	18.4 (1.8, 37.7)	0.03	0.04 (−0.10, 0.18)	4.1 (−9.3, 19.6)	0.57
Prior breast cancer							
No	417.0	Ref	Ref		Ref	Ref	
Yes	442.0	0.10 (−0.03, 0.23)	10.7 (−3.0, 26.4)	0.13	0.07 (−0.06, 0.19)	6.7 (−5.5, 20.5)	0.29
Smoker							
Never	400.0	Ref	Ref		Ref	Ref	
Current	339.0	−0.03 (−0.14, 0.09)	−2.8 (−13.5, 9.2)	0.63	0.00 (−0.10, 0.11)	0.4 (−9.8, 11.7)	0.95
Past	384.0	0.04 (−0.05, 0.13)	4.2 (−4.5, 13.6)	0.36	0.04 (−0.04, 0.12)	4.2 (−3.8, 12.8)	0.31

* Association between predictor of interest and CA125 probit score

for tumor characteristics, BMI > 30 kg/m^2 was associated with 9.8% (95% CI 1.7, 18.5%) higher CA125 levels, while race (non-white vs. white) was associated with 15.3% (95% CI 4.3–27.4%) higher CA125. Since the majority of non-white participants were Asian, we performed an analysis restricting non-whites to Asians. In the model adjusted for age and tumor characteristics, compared to white women, Asian women had a 16.5% (3.1, 31.7%) increase in CA125 levels. To further address the issue of collinearity between race and study characteristics, we excluded sites that consisted of only one or predominantly one race (BEL, HSK, JPN, MAL) or had no information on race (PVD, SRO), and observed that non-white race was associated with 30.7% (95% CI 18.1, 44.5%)($p < 0.0001$) higher CA125 levels after adjusting for age, histology, and grade. Since similar analyses have been previously published in the NEC study [15], we excluded NEC participants and observed similar associations for BMI > 30 kg/m^2 ($p = 0.004$) and race ($p = 0.001$).

We constructed a multivariate model adjusted for all the factors that were significantly associated with CA125 levels in the age-adjusted models (Table 3). Compared to high-grade serous tumors, CA125 levels were significantly lower for low-grade serous, high-grade endometrioid, low-grade endometrioid, mucinous, clear cell, and other/unknown subtypes ($p < 0.0002$). CA125 levels increased with stage of disease ($p < 0.0001$). The percent change for BMI > 30 kg/m^2 compared to BMI 18.5–25 (9%) and non-white versus white race (14%) was similar to the model adjusted for age and tumor characteristics.

In analyses conducted separately for premenopausal and postmenopausal women, we observed no association between CA125 levels with BMI > 30 kg/m^2 ($p = 0.50$) and race ($p = 0.73$). Among postmenopausal women, BMI > 30 kg/m^2 was associated with 10.8% (95% CI 1.2, 21.2%) higher CA125 levels, while non-white race was associated with 17.7% (95% CI 3.5, 33.8%) higher CA125 levels (Supplemental Table 3). In order to address variation in CA125 measurements within studies, we evaluated the significant associations in studies that measured CA125 on all participants using a single assay (BEL, JPN, MAL, PVD). We observed a significant association between BMI > 30 kg/m^2 with CA125 levels ($p = 0.02$), while the association with race was no longer significant ($p = 0.20$). When we additionally adjusted for residual disease, we observed that BMI > 30 kg/m^2 was no longer significantly associated with CA125 levels (7.6%, 95% CI −0.2, 15.9%), while the association with non-white race remained significant (16.8%, 95% CI 5.8, 28.9%, $p = 0.002$).

To address the differences between tumor types (including differences in CA125 values), we performed sensitivity analysis restricted to high-grade serous tumors. BMI > 30 kg/m^2 was no longer associated with CA125

Table 3 Multivariate adjusted associations between demographic, lifestyle, and reproductive characteristics with pretreatment CA125 levels*

Predictor	Coefficient (95% CI)*	Percent difference (95% CI)	*p* value
Age (years)			
<50	Ref	Ref	
50–60	0.03 (−0.04, 0.10)	3.4 (−3.5, 10.7)	0.33
60–70	−0.02 (−0.09, 0.05)	−1.8 (−8.5, 5.4)	0.62
>70	−0.02 (−0.10, 0.06)	−2.2 (−10.0, 6.2)	0.60
Stage			
I	Ref	Ref	
II	0.24 (0.14, 0.34)	27.0 (14.9, 40.3)	<0.0001
III	0.88 (0.79, 0.97)	141.2 (119.5, 165.0)	<0.0001
IV	1.13 (0.81, 1.45)	209.5 (124.3, 327.1)	<0.0001
Histology/grade			
High-grade serous	Ref	Ref	
Low-grade serous	−0.14 (−0.21, −0.07)	−13.1 (−19.3, −6.4)	0.0002
Unknown-grade serous	−0.10 (−0.22, 0.02)	−9.4 (−19.5, 2.0)	0.10
High-grade endometrioid	−0.21 (−0.33, −0.09)	−18.9 (−28.2, −8.2)	0.0009
Low-grade endometrioid	−0.24 (−0.35, −0.13)	−21.5 (−29.5, −12.5)	<0.0001
Unknown-grade endometrioid	−0.29 (−0.63, 0.06)	−24.8 (−46.7, 6.2)	0.10
Mucinous	−0.62 (−0.74, −0.49)	−46.2 (−52.5, −39.0)	<0.0001
Clear cell	−0.46 (−0.57, −0.35)	−36.6 (−43.2, −29.2)	<0.0001
Other/unknown	−0.18 (−0.27, −0.09)	−16.3 (−23.4, −8.5)	<0.0001
Family history of ovarian cancer			
No	Ref	Ref	
Yes	0.03 (−0.11, 0.17)	3.4 (−10.0, 18.7)	0.64
Family history of breast cancer			
No	Ref	Ref	
Yes	0.05 (−0.03, 0.13)	4.9 (−3.3, 13.9)	0.25
BMI (kg/m^2)			
<18.5	0.12 (−0.07, 0.30)	12.6 (−6.5, 35.5)	0.25
18.5–25	Ref	Ref	
25–30	−0.01 (−0.08, 0.06)	−1.2 (−7.8, 5.9)	0.73
>30	0.09 (0.01, 0.16)	9.1 (1.0, 17.8)	0.03
Ever pregnant			
No	Ref	Ref	
Yes	−0.04 (−0.12, 0.04)	−3.9 (−11.1, 3.8)	0.29
Tubal ligation			
No	Ref	Ref	
Yes	0.03 (−0.07, 0.13)	2.8 (−6.9, 13.4)	0.59
Endometriosis			
No	Ref	Ref	
Yes	−0.05 (−0.16, 0.06)	−5.0 (−14.7, 5.7)	0.34
Race			
White	Ref	Ref	
Non-white	0.13 (0.03, 0.23)	13.7 (2.9, 25.6)	0.01

* Estimates are adjusted for all variables listed in the table

levels in the age-adjusted model ($p = 0.32$) or the model additionally adjusted for stage $p = 0.62$). Non-white race remained significantly associated with CA125 levels both in age-adjusted ($p = 0.05$), and in age and stage adjusted model ($p = 0.04$). Furthermore, compared to high-grade serous cases younger than 50 years of age, those older than

70 years of age had 13.3% lower (95% CI −23.3, −2.0%) in CA125 levels.

Discussion

This pooled analysis included 13 studies in the Ovarian Cancer Association Consortium with pretreatment CA125 which were either measured or abstracted from medical records as well as detailed epidemiologic and clinical data on more than 5,000 women with invasive epithelial ovarian cancer. Our results suggest that BMI > 30 kg/m^2 and race might be associated with CA125 levels, after adjusting for tumor-related characteristics (stage, histology, and grade). We observed predictors of CA125 that are consistent with previously published results, including tumor characteristics (histology, grade, stage) [15], as well as epidemiologic factors (age, high BMI, history of pregnancy, family history of breast cancer, family history of ovarian cancer, endometriosis, tubal ligation, and race) [12, 13, 15]. Most of the previously described epidemiological predictors of CA125 were identified in healthy women [12, 13] and in one study among women with ovarian cancer cases [15]. We hypothesized that the association between epidemiologic factors and CA125 levels is partially independent of, and partially mediated by tumor characteristics. For example, high BMI is associated with increased levels of CA125 in healthy women [12], and BMI also increases risk of endometrioid subtype of ovarian cancer, which itself is associated with lower CA125 levels [15]. By adjusting for tumor characteristics, we identify characteristics that may influence CA125 above and beyond tumor characteristics.

Higher CA125 levels with more advanced disease as well as differences by histologic subtypes has been described previously [15]. While high-grade serous tumors are known to have the highest CA125 levels, differences in CA125 levels between the less common subtypes may not be appreciated. However, the findings of histology and grade-specific estimates of CA125 should be balanced with the possibility that there is some misclassification between subtypes. A recent comparison of grade assessment by two gynecologic pathologists on more than 500 ovarian cancer cases in the Surveillance Epidemiology and End Results Residual Tissue Repository reported only 49% agreement between the pathologists [39]. Similarly, recent studies using molecular markers to distinguish ovarian cancer subtypes suggested that histologic subtype is often misclassified [40]. Most commonly, high-grade serous ovarian cancers are misclassified as high-grade endometrioid. In our study, contamination of the endometrioid subgroup with high-grade serous cases could lead to an overestimate of the CA125 levels for some endometrioid cases.

For epidemiologic factors, most of the significant predictors of pretreatment CA125 that we observed in this pooled analysis in both univariate models (age, parity, family history of breast or ovarian cancer, race) and after accounting for tumor characteristics (BMI, race) have been previously described in the New England Case Control (NEC) study [15]. The results were similar after excluding participants from the NEC study. These data suggest that personal characteristics and exposures beyond tumor characteristics influence CA125 levels in women with ovarian cancer. Interestingly, almost all of these variables were also predictors of CA125 in healthy women who participated in one of the largest randomized ovarian cancer screening trials [12, 13], suggesting that these factors influence CA125 regardless of disease status. Similarities between CA125 predictors and ovarian cancer risk factors in combination with studies showing CA125 can impair immune function [41] suggests that CA125 may have a role in carcinogenesis in addition to being a marker of its progression.

The clinical assay used to measure CA125 varied over time and by site. A few studies measured pretreatment CA125 as part of their study (BEL, JPN, MAL, PVD), while the others abstracted pretreatment CA125 values from medical records. To account for some of this variability, we used a probit score approach which ranks CA125 values within each study to account for variability attributable to between-study differences. However, this approach does not account for any additional variability in the CA125 within study, which is likely more of an issue at sites where CA125 values were abstracted from medical records.

The strengths of our study include its large sample size, detailed epidemiologic and tumor data, and the inclusion of a large number of non-serous histologic types. Questionnaires and clinical data were originally collected for the purposes of large-scale genetic studies at a data coordinating center [42]. For many variables, data have been harmonized across study sites for epidemiologic analyses [43–45].

While our study was limited by the inclusion of existing CA125 values rather than prospective measurements, we observed expected associations between tumor characteristics and pretreatment CA125 levels as well as additional factors that predicted levels. However, validation is needed in a large study using a single assay. In addition, a diverse study population is needed to robustly determine how CA125 varies by race. Identification of predictors of CA125 will aid in the interpretation of its levels for prognosis and screening as well as provide new insights into how CA125 may be involved in the pathogenesis of the disease.

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