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Chronic Medical Conditions and CA125 Levels among Women without Ovarian Cancer

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Abstract

Background: Randomized trials using the biomarker CA125, with or without pelvic ultrasound, have failed to show a clear benefit of general population screening for ovarian cancer. In part this may be due to a lack of information about conditions, besides ovarian cancer, that can alter CA125 levels and affect specificity or sensitivity. We evaluated the association between common medical conditions and CA125 levels among women without ovarian cancer.

Methods: We used data and specimens from 2,004 women without ovarian cancer who participated in the New England Case Control study between 1992 and 2008. Participants completed in-person interviews and donated blood samples at enrollment. We measured CA125 using the CA125II assay and calculated the association between medical conditions and log-transformed CA125 using linear regression.

Results: The median age of participants was 53 years and 1,119 (56%) were postmenopausal. The average CA125 level was 14.5 units/mL for premenopausal and 11.7 for postmenopausal women. Among premenopausal women, CA125 was significantly lower for women with colon polyps ($p=0.06$) and hysterectomy ($p=0.01$) and significantly higher with endometriosis ($p=0.05$).

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CA125 was also significantly higher in premenopausal women with coronary artery disease (CVD) ($p<0.01$, $n=2$ cases) but not among postmenopausal with CVD ($n=79$). Further, among postmenopausal women, CA125 was significantly lower for women with osteoporosis, hypercholesterolemia, and osteoarthritis ($p=0.03$, 0.02 and 0.01 respectively) and higher for women with a history of inflammatory bowel disease ($p=0.04$).

Conclusion: Several chronic diseases are associated with CA125, which could influence the interpretation of CA125 in the context of ovarian cancer screening.

Keywords

Ovarian cancer; Chronic Diseases; CA125

Introduction

An estimated 22,240 new cases, and 14,070 deaths from ovarian cancer occur annually in the United States (1), making it the third most common gynecological cancer in the United States and the leading cause of deaths associated with cancers of the female genital tract. This high mortality largely reflects its tendency to be diagnosed at later stages which is associated with poorer survival (2–4). Development of a reliable screening biomarker would allow earlier detection and intervention, resulting in reduced morbidity and mortality.

Cancer Antigen (CA) 125 is a high-molecular weight glycoprotein and is recognized by the monoclonal antibody OC125 (5). CA125 is used clinically to monitor cancer progression and is a prime candidate for a screening biomarker (6). However, randomized screening trials of CA125 alone, or in combination with transvaginal ultrasound, have not provided clear mortality benefit (4,7). In addition to searching for more sensitive and specific biomarkers, ovarian cancer screening might be improved by taking into consideration cofactors that influence CA125 levels independent of ovarian cancer.

Since MUC16 (the gene that encodes CA125) is expressed in a variety of tissues, including those lining the gastrointestinal, respiratory, reproductive tracts, and body cavities, CA125 levels can vary with a range of exposures and conditions affecting those tissues. These include hysterectomy, parity, oral contraceptive or menopausal hormone therapy use, and history of endometriosis as well as demographic factors such as race, age, body mass index (BMI) (8–14). Medical conditions associated with ascites such as heart failure, tuberculosis, and chronic liver disease may also raise CA125 to levels similar to those detected in women affected by ovarian cancer (11,15–22). In this study, we examined a list of common medical conditions self-reported by women without ovarian cancer to determine associations with CA125 levels.

Materials and Methods

Study population

The present analysis was based on women without ovarian cancer (controls) who participated in the New England Case Control (NEC) study, a population-based study that enrolled newly diagnosed ovarian cancer cases and controls from eastern Massachusetts and

New Hampshire between 1992 and 2008. A detailed account of the study design has been described previously (23). Briefly, the controls were identified through random digit dialing, driver's-license lists, and town-resident lists. A total of 2100 controls (54%) were eligible and enrolled. Nearly all participants (>95%) provided blood specimens at the time of enrollment, and the present study included 2,004 women who had a banked blood sample available for CA125 measurement.

Blood Sample Collection and CA125 measurement

The venous blood samples were collected by trained phlebotomists during the in-person interview in the participants' homes or other convenient locations. The samples were transported to the processing laboratory, usually within 24 hours, where samples were centrifuged and separated into serum, plasma, red blood cells, and buffy coat. Samples were stored at -80°C . CA125 was measured on plasma samples of 100 μL each using the CA125II assay at the Clinical and Epidemiology Research Laboratory (CERLab) at Boston Children's Hospital. The reportable range of the assay was 0.6 to 500 IU/L, with a normal reference interval for females of less than 35 U/ml. We assessed the reproducibility of the assay by including five blinded aliquots of 46 quality control pools. The between batch coefficient of variation (CV) was 1%.

Medical conditions and covariates

All control participants completed an in-person interview. Questions were asked about sociodemographic variables, reproductive and family history, detailed medical history including disease diagnoses, hospitalization, and current medication use. We selected medical conditions based on their known or hypothesized relationship with ovarian cancer or CA125. In addition, we only included medical conditions with at least 5% prevalence. The questions were asked in the following format "Did you have any of the following conditions or surgeries before (a reference date of one year before study enrollment)" and "before (the reference date), did you have any other medical conditions that lasted six months or longer, or any condition you understand to have a genetic basis". Coronary artery disease was defined as myocardial infarction and/or angina. Inflammatory bowel disease included ulcerative colitis and Crohn's disease.

Thyroid disorders were divided into underactive thyroid (hypothyroidism, Hashimoto's thyroiditis or thyroidectomy), overactive thyroid (hyperthyroidism, Grave's disease), others which included thyroid cysts, unknown over or under thyroid, thyroid nodule and thyroid cancer. Gall bladder problems include cholecystitis, cholelithiasis/gall stones and gall bladder surgery. Psychological disorders included anxiety and depression. Obesity was defined as BMI $\geq 30\text{kg/m}^2$. Other medical conditions considered include allergies, appendectomy, asthma/bronchitis, bone fracture, non-ovarian cancers, colon polyps, endometriosis, gastroesophageal reflux/ulcers, headaches/migraines, hypertension, hypercholesterolemia/atherosclerosis, hysterectomy, osteoarthritis, osteoporosis, and uterine fibroids.

Data on covariates known to influence CA125, including age, race, menopausal status/age at menopause, body mass index (BMI, kg/m^2), use of oral contraceptives, hysterectomy,

hormone replacement therapy, smoking status, and parity (8,13,14), were also collected during the interview. Women were classified as premenopausal if they reported that their periods were still occurring, with or without birth control or menstrual regulatory hormones. Women were classified as postmenopausal if they reported their periods had stopped or were only occurring because of menopausal hormones. Women who reported no periods because of a hysterectomy or a medical condition/treatment were classified as premenopausal if they were age <50 and postmenopausal if age ≥ 50 years. The study was conducted in accordance with the guiding principles of human research by the Declaration of Helsinki and the U.S Common Rule. The ethical principles of respect for persons, beneficence, and justice was observed. Informed written consent was obtained from all participants before recruitment into the study.

The study was approved by the Institutional Review Board of Brigham and Women's Hospital Boston, Massachusetts and Dartmouth College, Hanover, New Hampshire.

Statistical methods

We identified two outliers of CA125 defined as greater than two standard deviations from the mean, but those observations were included in the analysis given the accuracy of the assay. CA125 was log-transformed to achieve normal distribution. We assessed geometric mean levels of CA125 associated with medical conditions according to the woman's menopausal status (pre- vs. postmenopausal) at the time of her blood sampling, as differences in CA125 by menopausal status are well established (13).

All models were adjusted for age, race, parity, and smoking. Models conducted in postmenopausal women were additionally adjusted for hormone replacement therapy (HRT). All statistical analyses were performed using SAS 9.2 (SAS Institute, Gary NC, USA).

Results

The average age of participants was 53 years and 60% were over age 50 (Table 1). Most participants were white (97%), 14% were current smokers, and 39% former smokers. The most common medical conditions in this study population were anxiety/depression (24%), history of bone fracture (39%), hypercholesterolemia (15%), hypertension (18%), and obesity (18%).

Among the premenopausal women (Table 2), CA125 was lower in those with a history of colon polyps (−31%; $p=0.06$) and in those with hysterectomy (−23%; $p=0.01$). CA125 levels were higher in women with endometriosis (14%, $p=0.05$) and coronary artery disease (221%, $p<0.01$), although the later was based on a small number of exposed women ($n=2$). Among postmenopausal women, CA125 was higher in women with a history of breast cancer (12%; $p=0.05$) and inflammatory bowel disease (14%; $p=0.04$). CA125 levels were significantly lower in women reporting osteoporosis (−12%, $p=0.03$), hypercholesterolemia/atherosclerosis (−7%, $p=0.02$), and osteoarthritis (−9%, $p=0.01$). Results were similar when the two outliers were excluded.

We analyzed the association between the number of medical conditions and the percent change in CA125 levels (Supplementary Table 1) and observed no consistent patterns of change in CA125 levels with the number of medical conditions in pre- or postmenopausal women. Additionally, we used a multivariable model to simultaneously adjust for all medical conditions that were associated with CA125 in the univariate analyses (Table 3). In premenopausal women, all conditions that were associated with a percent change in CA125 when assessed singly in univariate models (colon polyps, coronary artery disease, endometriosis, and hysterectomy) remained associated after mutual adjustment. With the exception of endometriosis, for which the percent increase was attenuated, the percent change in CA125 after adjustment for multiple medical conditions was similar to that seen in the univariate models. In postmenopausal women, only osteoporosis remained significantly associated with CA125 after adjustment for medical conditions, and the percent decrease in CA125 was similar to that observed for osteoporosis in the univariate model.

We additionally assessed specific medical conditions singly with adjustment for the medication used to treat that condition. For each medical condition, these models produced results similar to those seen in the univariate models (Supplementary Table 2). For example, in postmenopausal women, we assessed medical conditions in relation to CA125 after additional adjustment for medications such as statins for hypercholesterolemia, bisphosphonates for osteoporosis, aminosalicylates (sulfasalazine) and aspirin for inflammatory bowel disease and non-steroidal anti-inflammatory drugs (NSAIDs) for osteoarthritis; adjusting for these medications generally did not affect the percent of change in CA125 for any condition. We did note, however, an attenuation in the percent of increase associated with breast cancer when adjusted for Tamoxifen and Arimidex. We also assessed the association between colon polyps and percent change in CA125 among postmenopausal with and without HRT use and found no difference in the association (Supplementary Table 3).

Discussion

In this study, we assessed the association between several commonly diagnosed medical conditions and CA125 levels in women without an ovarian malignancy. This is the first study to address in an extensive fashion the role of medical conditions on CA125 in the general population using a single assay. Our observations suggest that pathological processes in several organ systems including genitourinary, bone, breast, cardiovascular, and gastrointestinal could affect CA125 levels in women with no evidence of ovarian cancer. In addition, the importance of these systems in influencing CA125 levels varied between premenopausal and postmenopausal women.

We observed increased levels of CA125 in women with a history of coronary artery disease (CAD) with significant association being limited to premenopausal women. However, this observation was based on a small number of cases. Postmenopausal women with CAD also had higher CA125 levels although the difference was not statistically significant. These observations are consistent with previous reports (24,25). Previous studies suggest pericardial, pleura, or peritoneal irritations or reactions from effusions as the potential sources of elevated CA125 in heart diseases including heart failure (26,27). In addition,

heart disease results in overexpression of inflammatory cytokines, especially interleukin-6, which may raise CA125 levels (28–30). Interestingly, we observed lower CA125 levels in postmenopausal women with a history of hypercholesterolemia/atherosclerosis. Our findings are similar to those of Joo and colleagues who reported a significant inverse correlation of CA125 with metabolic syndrome consisting of dyslipidemia, higher total cholesterol and elevated triglycerides (31).

In our study, the association between endometriosis and elevated CA125 was restricted to premenopausal women. Previous studies have observed higher CA125 levels in women with active endometriosis and proposed CA125 as a candidate biomarker for detecting endometriosis (17,32). We did not observe an association between history of endometriosis and CA125 in postmenopausal women. Interestingly, in the PLCO study, a history of endometriosis was associated with significantly lower CA125 in postmenopausal women (7). Since endometriosis is thought to derive from cells exfoliated from the uterine lining, our observation of no association between endometriosis and CA125 among postmenopausal women may simply reflect atrophy of the endometrium and endometriosis that occurs after menopause. Alternatively, the lack of association may reflect prior hormone suppressive therapy or hysterectomy for treatment of endometriosis. Notably, adjusting for these factors in the PLCO study attenuated the inverse association between CA125 and prior endometriosis in that study (8). These results suggested that there is a complex association of endometriosis, its treatment, and menopausal status with CA125 levels.

In our study, hysterectomy was associated with lower CA125 levels in premenopausal women but not in postmenopausal women. Two studies addressing hysterectomy and CA125 in postmenopausal women showed similar relationships (8,14). Further, we previously observed lower CA125 levels in premenopausal and postmenopausal women who had had a hysterectomy in the EPIC cohort, although the association was statistically significant only in postmenopausal women (13). Whether or not postmenopausal women with hysterectomy were taking menopausal hormonal therapy may also be a factor since exogenous hormones likely increase CA125 levels (8,33,34). In our study the average CA125 in hysterectomized postmenopausal women known to have taken hormone therapy was a little higher (12.3 units/ml) compared to those not known to have used HRT (11.9 units/ml; $p=0.28$). The two observations that endometriosis raises CA125 and hysterectomy lowers it in premenopausal women suggest the importance of the uterus (or perhaps more precisely the uterine lining) in the physiology of CA125. CA125 is indeed expressed in the endometrium, and in naturally cycling women, CA125 is highest during the menstrual phase (35,36).

We found two medical conditions related to the colon suggestively associated with CA125 levels. CA125 is expressed in gastrointestinal tract (37–39) and some reports have previously described the association between colorectal cancer, gastrointestinal tumors, and CA125 (40–42). In our study, colon polyps were associated with significantly lower CA125 levels among premenopausal women and suggestively lower levels in postmenopausal women, although we were not able to examine the relationship with prior colon cancer due to small number of women with this condition. Since colon polyps may be precursors to colon cancer, one may have expected to see higher CA125 levels in women with polyps. However, removal of these polyps could have lowered the CA125 levels. It is also possible

that conditions known to be associated with colon polyps, including smoking and obesity, could underlie the association since these exposures can lower CA125 (8). While we adjusted for these potential confounders in our study, the possibility of residual confounding remains. In contrast, the association we observed between higher CA125 and inflammatory bowel diseases among the postmenopausal women may be due to the inflammatory nature of these diseases as CA125 is known to increase in some inflammatory conditions of the gastrointestinal tract (37,43).

We initially observed higher CA125 levels in postmenopausal women with prior breast cancer but the association became attenuated after additionally adjusting for some medications used in treating breast cancer including Tamoxifen and Arimidex. CA125 may be elevated at breast cancer diagnosis and may be used in the management of breast cancer, especially for the advanced metastatic disease (44–46). Pauler and colleagues reported significantly higher CA125 among women with any prior (non-ovarian) cancers in the UK screening study (14).

That both osteoporosis and osteoarthritis were related to lower CA125 among the postmenopausal women is consistent with a correlation previously reported between the degree of bone mineral density loss and CA125 (47). This may reflect declining CA125 level with an increasing hypoestrogenic state. Similarly, an increasing hypoestrogenic state in postmenopausal women may in part underlie osteoarthritis (46) and could explain our observation that postmenopausal women with osteoarthritis have lower level of CA125. As previously pointed out, menopausal hormone replacement can raise CA125 levels (33), this may also increase bone mineral density and reduce the risk for osteoarthritis of the hip (33,48).

We did not find consistent patterns in CA125 levels associated with the number of medical conditions. This is not surprising, as some medical conditions measured here were associated with an increase of the percent change in CA125, while others were associated with a decrease. Consequently, the net change in CA125 corresponding to a given number of comorbidities likely would reflect the commonness of a morbidity, the frequency with which comorbidities migrate together, and the strength and direction of their impact on CA125 levels. Interestingly, however, our data indicated that, in premenopausal women, the influence of individual medical conditions on CA125 levels was similar when adjusted for multiple comorbidities. After adjusting for comorbidities in postmenopausal women, only osteoporosis remained associated with a percent change in CA125 levels, and the observed decrease was comparable to that seen in the univariate model. We found no evidence that treatments associated with various medical conditions measured here changed the association between the medical condition and the percent change in CA125 levels.

Together our results suggest that several common medical conditions may influence CA125 levels in the general population and are worth consideration in the context of measuring CA125 as a screening biomarker. As known, the CA125 levels vary not only due to the influence of medical conditions but also with technical and biologic functions as well as normal inter-individual and within subject biologic variations. In randomized screening trials to date, a single threshold of 35 U/mL is used to classify women as having abnormally high

levels that warrant additional screening. However, adjusting this threshold for abnormal CA125 levels based on personal characteristics may yield a more sensitive and specific test. Several studies have evaluated non-medical factors on a much larger scale (8,13,14). However, our study adds many medical conditions that may be used to further adjust the CA125 screening threshold. The limitations of our study include lack of comprehensive inclusion of all medical conditions that may influence CA125, small sample size, self-reported exposures, lack of validation in medical records, a cross-sectional design that prevents repeated measures of CA125 and precludes assessment of temporality, and lack of racial diversity in the New England population.

Future work should assess the relationship of these and other medical conditions on CA125 in a more diverse population. If confirmed, our findings may help identify factors that could influence false positive and false negative readings for CA125, and ultimately help enhance prevention or detection of ovarian cancer at an early stage with significant prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Demographic factors and medical conditions reported by controls in the New England Case Control Study of Ovarian Cancer, 1992–2008

Characteristic	Premenopausal n=885 n (%)	Postmenopausal n= 1119 n (%)	All participants n=2004 n (%)
Age (years)			
Less than 40	344 (39)	0 (0)	344 (17)
40 to 49	419 (47)	38 (3)	457 (23)
50 to 59	120 (14)	414 (37)	534 (27)
60 years and above	2 (<1)	667 (60)	669 (33)
Race			
White	845 (95)	1096 (98)	1941 (97)
Non-White	40 (5)	23 (2)	63 (3)
Parity			
None	226 (26)	141 (13)	367 (18)
One	154 (17)	103 (9)	257 (13)
Two	287 (32)	339 (30)	626 (31)
Three	150 (17)	241 (22)	391 (20)
Four and above	68 (8)	295 (26)	363 (18)
Smoking status			
Never smoked	460 (52)	491 (44)	951 (47)
Former smoker	292 (33)	483 (43)	775 (39)
Current smoker	133 (15)	145 (13)	278 (14)
Anxiety/Depression			
No	681 (77)	839 (75)	1520 (76)
Yes	204 (23)	280 (25)	484 (24)
Allergies			
No	723 (82)	867 (77)	1590 (79)
Yes	162 (18)	252 (23)	414 (21)
Appendectomy			
No	550 (90)	670 (75)	1220 (81)
Yes	61 (10)	229 (25)	290 (19)
Asthma/Bronchitis			
No	813 (92)	1020 (91)	1833 (91)
Yes	72 (8)	99 (9)	171 (9)
Bone fracture			
No	385 (63)	529 (59)	914 (61)
Yes	226 (37)	370 (41)	596 (39)
Cancer types (Non-ovarian)			
No cancer	843 (95)	950 (85)	1783 (89)
Breast cancer	10 (1)	70 (6)	80 (4)
Basal cell skin cancer	10 (1)	39 (3)	49 (2)

Characteristic	Premenopausal n=885 n (%)	Postmenopausal n= 1119 n (%)	All participants n=2004 n (%)
Melanoma	7 (1)	12 (1)	19 (1)
Others	15 (2)	48 (4)	63 (3)
Colon polyp			
No	603 (99)	760 (85)	1363 (90)
Yes	8 (1)	139 (15)	147 (10)
Coronary Artery Disease			
No	883 (99)	1040 (93)	1923 (96)
Yes	2 (<1)	79 (7)	81 (4)
Endometriosis			
No	821 (93)	1023 (91)	1844 (92)
Yes	64 (7)	96 (9)	160 (8)
Gall bladder disorders			
No	831 (94)	973 (87)	1804 (90)
Yes	54 (6)	146 (13)	200 (10)
Gastroesophageal reflux/Ulcers			
No	847 (96)	998 (89)	1845 (92)
Yes	38 (4)	121 (11)	159 (8)
Headaches/Migraines			
No	771 (87)	982 (88)	1753 (87)
Yes	114 (13)	137 (12)	251 (13)
Hypertension			
No	845 (95)	804 (72)	1649 (82)
Yes	40 (5)	315 (28)	355 (18)
Hypercholesterolemia/Atherosclerosis			
No	854 (96)	854 (76)	1708 (85)
Yes	31 (4)	265 (24)	296 (15)
Hysterectomy			
No	855 (97)	969 (87)	1824 (91)
Yes	30 (3)	150 (13)	180 (9)
Inflammatory Bowel Disease			
No	866 (98)	1067 (95)	1933 (96)
Yes	19 (2)	52 (5)	71 (4)
Obesity			
No	759 (86)	870 (78)	1629 (82)
Yes	126 (14)	240 (22)	366 (18)
Osteoarthritis			
No	851 (96)	894 (80)	1745 (87)
Yes	34 (4)	225 (20)	259 (13)
Osteoporosis			
No	285 (98)	452 (86)	737 (90)
Yes	6 (2)	76 (14)	82 (10)

Characteristic	Premenopausal n=885 n (%)	Postmenopausal n= 1119 n (%)	All participants n=2004 n (%)
Thyroid disorders			
No thyroid disease	781 (88)	864 (77)	1645 (82)
Underactive thyroid disorder	66 (8)	174 (16)	240 (12)
Overactive thyroid disorder	17 (2)	37 (3)	54 (3)
Other thyroid disorders	21 (2)	44 (4)	65 (3)
Uterine fibroids			
No	785 (88)	935 (84)	1720 (86)
Yes	100 (11)	184 (16)	284 (14)

Table 2:

Association between medical conditions and percent change in CA125 levels among pre- and postmenopausal women without ovarian cancer in the New England Case Control Study

Medical Conditions	Premenopausal			Postmenopausal	
	Geometric mean CA125 (95% CI)	% change ^a	P value ^a	Geometric mean CA125 (95% CI)	% change ^a
Anxiety/Depression ^b					
No	15 (15, 16)			12 (12, 12)	
Yes	15 (14, 16)	-3.5	0.41	12 (11, 13)	0.8
Allergies					
No	15 (15, 16)			12 (12, 12)	
Yes	15 (14, 16)	-3.8	0.41	12 (11, 13)	<0.1
Appendectomy ^b					
No	15 (14, 16)			12 (12, 12)	
Yes	15 (13, 17)	-0.9	0.90	12 (11, 13)	-4.5
Asthma/Bronchitis					
No	15 (15, 16)			12 (12, 12)	
Yes	14 (13, 16)	-7.0	0.27	13 (12, 14)	8.7
Bone fracture ^b					
No	15 (14, 16)			12 (12, 12)	
Yes	15 (14, 16)	0.7	0.88	12 (11, 13)	-0.4
Cancer types (non-ovarian)					
No cancer (Ref)	15 (15, 16)			12 (12, 12)	
Breast cancer	17 (12, 23)	12.4	0.49	13 (12, 15)	12.3
Basal cell skin cancer	16 (11, 22)	1.1	0.95	13 (11, 15)	11.5
Melanoma	20 (13, 30)	31.2	0.18	14 (11, 19)	18.8
Others	17 (13, 22)	9.9	0.50	11 (10, 13)	-7.7
Colon polyp ^b					
No	15 (15, 16)			12 (12, 13)	
Yes	10 (7, 15)	-30.6	0.06	11 (10, 12)	-6.6
Coronary Artery Disease					
No	15 (15, 16)			12 (12, 12)	
Yes	45 (22, 94)	221.2	<0.01	13 (12, 14)	5.1
Endometriosis					
No	15 (15, 16)			12 (12, 12)	
Yes	17 (15, 20)	14.4	0.05	11 (10, 12)	-3.8
Gall bladder disorders					
No	15 (15, 16)			12 (12, 12)	
Yes	14 (12, 16)	-10.6	0.14	12 (11, 13)	0.6
Gastroesophageal Reflux/Ulcers					
No	15 (15, 16)			12 (12, 12)	
Yes	16 (13, 19)	3.7	0.68	12 (11, 13)	-1.8

Medical Conditions	Premenopausal			Postmenopausal	
	Geometric mean CA125 (95% CI)	% change ^a	P value ^a	Geometric mean CA125 (95% CI)	% change ^a
Headaches/Migraines					
No	15 (15, 16)			12 (12, 12)	
Yes	14 (13, 16)	-7.7	0.14	12 (12, 14)	4.9
Hypertension					
No	15 (15, 16)			12 (12, 12)	
Yes	16 (14, 19)	8.6	0.35	12 (12, 13)	0.9
Hypercholesterolemia/Atherosclerosis					
No	15 (15, 16)			12 (12, 13)	
Yes	15 (12, 18)	-2.7	0.78	11 (11, 12)	-7.3
Hysterectomy					
No	15 (15, 16)			12 (12, 12)	
Yes	12 (10, 14)	-22.6	0.01	12 (11, 13)	-4.0
Inflammatory Bowel Disease					
No	15 (15, 16)			12 (12, 12)	
Yes	17 (14, 22)	14.2	0.29	14 (12, 16)	14.3
Obesity					
No	15 (15, 16)			12 (12, 12)	
Yes	16 (14, 17)	4.4	0.41	12 (11, 13)	<0.1
Osteoarthritis					
No	15 (15, 16)			12 (12, 13)	
Yes	16 (13, 19)	3.9	0.68	11 (11, 12)	-8.9
Osteoporosis ^c					
No	15 (14, 16)			12 (11, 12)	
Yes	15 (10, 23)	0.2	0.99	10 (9, 11)	-11.6
Thyroid disorders					
No thyroid disease (Ref)	15 (15, 16)			12 (12, 12)	
Underactive thyroid disorder	16 (14, 18)	4.3	0.54	12 (11, 13)	-0.1
Overactive thyroid disorder	15 (12, 19)	-0.7	0.96	12 (11, 14)	2.5
Other thyroid disorders	16 (13, 21)	8.1	0.51	12 (10, 13)	-4.2
Uterine fibroids					
No	15 (15, 16)			12 (12, 12)	
Yes	16 (14, 18)	6.4	0.28	12 (11, 13)	2.5

^a Multivariate model adjusted for age (continuous), race (White/non-White), parity (continuous) smoking status (never, former or current smoker) and hormone replacement therapy (yes/no – only in postmenopausal model)

^b data available from 1998 -- 2008

^c data available from 2003 -- 2008

Table 3:

Percent change in CA125 level adjusted for all medical conditions that were associated with CA125 in univariate models, in pre- and postmenopausal women without ovarian cancer*

Medical Conditions	Premenopausal		Postmenopausal	
	% change	P value	% change	P value
Breast Cancer	NA	NA	9.8	0.23
Colon polyp	-30.2	0.06	NA	NA
Coronary Artery Disease	212.7	0.01	NA	NA
Endometriosis	29.3	0.01	NA	NA
Hypercholesterolemia/Atherosclerosis	NA	NA	-0.6	0.89
Hysterectomy	-27.0	0.01	NA	NA
Inflammatory Bowel Disease	NA	NA	7.7	0.47
Osteoarthritis	NA	NA	-5.8	0.18
Osteoporosis	NA	NA	-11.2	0.04

* Outcome adjusted for conditions shown above and for other covariates (age (continuous), race (White/non-White), Parity (continuous) and smoking status (never, former or current smoker) and hormone replacement therapy (yes/no – only in postmenopausal model)).

NA – conditions that were not significantly associated with percent change in CA125 levels in univariate models were not assessed here