Published in final edited form as:
Gynecol Oncol. 2008 September ; 110(3): 383–389. doi:10.1016/j.ygyno.2008.05.006.

The Epidemiology of CA-125 in Women without Evidence of Ovarian Cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial

Christine C Johnson, PhD[1], **Bruce Kessel, MD**[2], **Thomas L Riley, BS**[3], **Lawrence R Ragard, MD**[4], **Craig R Williams, BS**[3], **Jian-Lun Xu, PhD**[5], and **Saundra S Buys, MD**[6] **for the PLCO Project Team**

[1]Josephine Ford Cancer Center, Henry Ford Hospital, Detroit, Michigan [2]Pacific Health Research Institute and University of Hawaii, Honolulu, Hawaii [3]Information Management Systems, Rockville, Maryland [4]Westat, Rockville, Maryland [5]Biometry Research Group, Division of Cancer Prevention, National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services (DHHS), Bethesda, Maryland [6]Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah

Abstract

Objective—To determine the epidemiology of CA-125 in women without ovarian cancer.

Methods—We analyzed demographic, medical and lifestyle characteristics related to CA-125, measured using the Centocor CA-125II RIA assay, among 25,608 multi-ethnic U.S. women aged 55–74 years enrolled in a cancer screening trial and found to have no evidence of ovarian cancer.

Results—Mean CA-125 level was 11.9 U/ml (SD 8.3); median 10.0 U/ml, interquartile range 8.0–14.0. High levels, using the clinical cut point of ≥ 35 U/ml, were associated with increased age ($p<0.001$) and former smoking ($p<0.021$), while hysterectomy and obesity were protective ($p<0.001$). Mean levels were higher with increasing age ($p<0.001$), ever use of hormone therapy ($p<0.001$), former smoking ($p<0.017$) and history of breast cancer ($p<0.002$), but lower ($p<0.001$) with non-White status, previous hysterectomy, current smoking, and obesity. Current hormone therapy use was not associated with CA-125 in women without a uterus.

Conclusion—In post-menopausal women without ovarian cancer, CA-125 level is influenced by a number of factors, including race/ethnicity, age, hysterectomy, smoking history and obesity.

Keywords

epidemiology; CA-125; race/ethnicity

Corresponding author and reprint requests to: Christine Cole Johnson, Ph.D., M.P.H., Henry Ford Hospital, 1 Ford Place, 5C, Detroit, MI 48202, phone: (313) 874-6672, fax: (313) 874-6656, cjohnso1@hfhs.org.

Conflict of Interest Statement:
None of the authors has a conflict of interest.

Introduction

CA-125 is a tumor antigen that is elevated in the majority of ovarian cancers and has been shown to be increased in some women with early stage disease.[1] Although a single determination of CA-125 does not have the sensitivity, specificity and positive predictive value to be used as a stand-alone screen, CA-125 measurement may be shown to be a valuable part of a multi-modal and/or longitudinal screening algorithm.[2–8] If this approach proves feasible, knowledge of the usual pattern of CA-125 levels among populations of women without ovarian cancer will be a prerequisite.[9]

CA-125 is an antigenic determinant on a high molecular weight glycoprotein encoded by the MUC16 gene, [10;11] that was first recognized by a monoclonal antibody, OC125, and subsequently a series of other antibodies.[12] CA-125 has been shown to be elevated in women with a number of physiologic and pathologic processes including cirrhosis and congestive heart failure and has been reported to vary by age, race, and the presence of benign gynecologic conditions (endometriosis, hysterectomy, hormone therapy use) and other malignancies besides ovarian cancer (breast, colon, pancreatic, lung, gastric, liver cancer).[1;9;13;14]

Most studies of CA-125 have been conducted among cancer patients. While some have studied this marker among general populations, often through analyzing women enrolled in screening studies, many analyses have had relatively small sample sizes and few have been geographically and ethnically diverse. We had available baseline measurements of CA-125 in an exceptionally large, racially and ethnically diverse population of post-menopausal women, residing in multiple locations across the United States. In this population, CA-125 is currently being tested as one modality in a screening trial for ovarian cancer. Our primary goal was to evaluate the epidemiology of CA-125 at baseline measurement in a population examined and found to be without evidence of ovarian cancer, with a focus on the effects of personal characteristics that can readily be obtained clinically including race/ethnicity, age, personal and family medical history, smoking behavior and body mass index.

Materials and Methods

The population under study was selected from the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Cancer Screening Trial. From 1993 through 2001, the PLCO Trial recruited over 150,000 men and women to a randomized controlled trial of screening methods for four cancers and has been described in detail elsewhere.[15] Eligible subjects were from 55 to 74 years of age and not diagnosed previously with prostate, lung, colorectal, or ovarian cancer. Criteria for exclusion included current treatment for cancer other than non-melanoma skin cancer and enrollment in another cancer screening or prevention trial. Beginning on April 15, 1995, individuals who had received a colonoscopy, sigmoidoscopy, or barium enema in the past 3 years were also excluded. Initially, women who by self-report had undergone oophorectomy were ineligible, but in 1996 this restriction was lifted because low accrual of women threatened to jeopardize screening endpoints for lung and colon cancer.

During recruitment, 78,237 women were enrolled and 39,115 were randomized to the intervention arm. Women in this arm, unless they reported a history of oophorectomy, received a baseline CA-125 measurement and transvaginal ultrasound. During the screening process, CA-125 results ≥ 35 U/ml were classified as abnormal (positive) and generated letters to the subject and her physician urging follow-up. Procedures and any diagnoses resulting from abnormal screening results were ascertained by study staff and the entire population was surveyed annually for the occurrence of any cancer diagnoses.

Serum frozen locally was shipped to the Immunogenetics Laboratory at UCLA for testing using the Centocor CA-125II RIA assay, a heterologous, double determinant immunoassay. [16] The capture antibody is the M11 murine monoclonal antibody, and the tracer antibody is the OC 125 monoclonal antibody originally generated by immunization of BALB/c mice with the OVCA 433 ovarian cancer cell line. Quality assurance was done in accordance with the manufacturer's suggested protocol. The coefficients of variation were found to be 4.07% at the lower concentration of 52.7 U/ml and 3.78% at the higher concentration of 106.5 U/ml. The corresponding 95% confidence intervals (CI) were 3.92%–4.22% and 3.64%–3.92%, respectively. These results are in good agreement with those reported by the manufacturer.

Women completing a baseline screen including a questionnaire and a CA-125 test were potentially eligible for these analyses. Analyses were conducted on data available as of July 2004. From the initial women enrolled in the intervention arm, the following were excluded: women without ovaries who were not screened or who were screened inadvertently and those not receiving the CA-125 test/assay, women with a diagnosis of ovarian cancer at baseline or within 2 years of screening or with lack of post-baseline follow-up of up to two years (therefore ovarian cancer status was unknown at 2 yrs post baseline), and women with missing information on one or more of the baseline variables included in the analyses.

Univariate and multivariate logistic and linear regression techniques were used to evaluate whether the study variables were associated with CA-125 level. Distributions of each variable were assessed for outliers. Models were constructed with CA-125 as a binary outcome (≥35 U/ml as a cut point) and as a log-transformed continuous variable. For the log-transformed regression models, parameter estimates are reported along with their exponentiated values, since the latter estimates the ratio between mean CA-125 levels for subjects with a factor versus those without. All model assumptions were checked to assure they were not violated and the data were examined for collinearity among explanatory variables.

The associations between race/ethnicity (White, Black, Hispanic, Asian, Pacific Islander/Native American) and age at screening (55–59, 60–64, 65–69, 70–74 years) and CA-125 were examined as well as other variables including age at last menstrual period as a marker for age at menopause (<40, 40–44, 45–49, 50–54, 55+ years), a personal history of breast cancer, a history of ovarian cancer in first degree relatives, a history of breast cancer in first degree relatives, previous hysterectomy, former or current use of hormone therapy (HT) (yes/no) and body mass index (BMI) (weight/height^2 with normal <25, overweight 25–29, obese 30+). The model also included other variables considered to be potentially associated with CA-125 including history of endometriosis (yes/no), uterine fibroids (yes/no), benign ovarian tumors or cysts (yes/no), partial oophorectomy (yes/no), as well as cigarette smoking status (never/former/current). The analyses were repeated separately for women with and without a hysterectomy as the endometrium is a principal source of CA-125[17]and therefore factors associated with this marker might vary depending on the presence or absence of the uterus.

All aspects of the PLCO study were approved by the Human Rights Committees of each institution and the National Cancer Institute, and written informed consent was obtained from each subject.

Results

There were 34,288 women who were eligible for a baseline CA-125 measurement. Of these, 6,107 did not receive a CA-125 or were ineligible for these analyses due to an ovarian

cancer diagnosis or lack of follow-up. Of the remaining subjects, the 2,573 women with CA-125 testing but incomplete baseline survey data did not differ from the final 25,608 subjects in the analyses with regard to mean CA-125. However there were statistically significantly higher proportions of Black, older and less than high school educated women among those with missing data. Table 1 shows the distribution of the 25,608 women analyzed by race/ethnicity, age group and other variables by ranges of CA-125 levels along with means and medians. Women were predominantly white (90%) and between the ages of 55–64 years (66%), with 26% reporting a hysterectomy, 65% ever using hormone therapy, and 24% with a BMI ≥ 30 (obese). Although the majority was white, minority representation was substantial with 1,132 Black and 900 Asian participants.

The mean CA-125 level was 11.9 (1 SD 8.3) and the median was 10.0 with an interquartile range of 8.0–14.0 U/ml (Table 1). Just over 1.6% of all participants had CA-125 levels of 35 U/ml or greater. An additional 1.1% and 7.4% had levels between 30-<35 and 20-<30 U/ml, respectively. This left nearly 90% of the population having values between 0 and 20 U/ml, with an even distribution in the 0-<10 (44.7%) and 10-<20 (45.2%) groups. Black women had the lowest mean and median CA-125. Mean CA-125 increased with age category, with a decline of percentage of women in the lowest CA-125 category (0-<10 U/ml) as age increased corresponding to increasing percentages in the highest CA-125 category. The earlier the age at menopause, the lower the mean CA-125, and the more likely a woman would fall in the lowest CA-125 category.

Compared to White women, minority women were at lower risk for an elevated CA-125 (35 U/ml or greater), with the adjusted odds ratio (aOR) for Asians (aOR=0.53, 95% confidence interval (CI) 0.28–1.00) of borderline statistical significance ($p<0.051$) (Table 2). Increasing age groups were each associated with a statistically increased risk for a high CA-125. Hysterectomy (aOR = 0.58; CI 0.41–0.81, $p<.001$) and obesity (aOR=0.53; CI 0.39–0.71, $p<0.001$) were associated with lower risk for elevated CA-125. Although early age at menopause was protective in the univariate analyses, there was no evidence of an association of menopausal age with high CA-125 in the multivariate analyses. There was no association with reported history of endometriosis. Women reporting a history of uterine fibroids had an increased aOR of 1.26, although the confidence intervals, 0.97–1.64, included 1.0.

Considering mean levels of CA-125 as an outcome (Table 3), race/ethnicity analyses again using Whites as a reference and adjusting for other variables revealed statistically significant ($p<0.001$) lower mean CA-125 levels for each of the other race/ethnic groups. There was a statistically significant association between increasing age category and higher mean CA-125 levels for each age group ($p<0.0001$). Those women with hysterectomy had lower CA-125 ($p<0.001$). Women with a history of breast cancer, late menopause, former and current hormone therapy use, and former smokers had statistically significantly higher mean CA-125 levels. Obesity and current smoking were associated with statistically significantly lower mean CA-125 levels. Adjusting for other variables abrogated univariate inverse associations between low education, early menopause, endometriosis, uterine fibroids, ovarian cysts and partial oophorectomy as related to CA-125 as a continuous variable.

Repeating these analyses and considering only the 18,955 women who still had their uterus, both former ($p<0.013$) and current ($p<0.0001$) hormone therapy use was associated with increased CA-125 level. Restricting the analyses to the 6,653 women with a previous hysterectomy, only former use of hormone therapy (versus no history of use) was associated with an increased CA-125 as a continuous variable ($p<0.01$).

Discussion

In this study of CA-125 in post-menopausal women with no evidence of ovarian cancer, mean CA-125 level was 11.9, with a very low percentage of women, 1.6%, having values greater than the standard clinical threshold of 35 U/ml. The most striking associations, based on the multivariate parameter estimates (Table 3), were for race/ethnicity, corresponding to 19%, 12%, 8% and 11% lower mean CA-125 levels in Black, Hispanic, Asian and Pacific Islander/Native American women relative to White women, hysterectomy (9% lower mean), current smoking (9% lower mean) and to a much lesser degree obesity (3% lower mean). The higher mean CA-125 levels in women who were older (7%), had a history of breast cancer (5%), late menopause (4%), former smokers (1.4%) and users of hormone therapy (3–4%), were modest. Interestingly, the demographic patterns are complementary to incidence patterns for ovarian cancer, with higher incidence in White and older women.[18]

The most comparable study we could find was data from 18,748 post-menopausal women in a United Kingdom screening trial.[9] However, the focus of their analyses was to develop a parsimonious predictive model rather than our approach of including all variables of interest in our models with the purpose of calculating risk estimates for individual variables. While Pauler et al. included women from 40 to 60 years of age, our study subjects were older, with a range from 55–74 years.

Prior studies generally report a decrease in CA-125 levels with increasing age.[9;13;19–21] It has been consistently demonstrated that CA-125 is higher in pre- versus post-menopausal women,[20] so it is important to consider that our population was all post-menopausal. Our mean and median values for Whites were identical to those in a reference value study of 938 Dutch post-menopausal women with a mean of 12 U/ml and median of 10 U/ml.[20] These authors found a slight decrease in age using categories from <45 years to >65 years, but did not consider any other variables. Another study from the Netherlands indicated a dramatic drop in CA-125 between age categories from 60–70 years in a healthy control group of 370 women, again a univariate analysis.[14] However, Grover et al found no age association in post-menopausal women, and an increase in CA-125 with increasing age in a pre-menopausal and peri-menopausal sample.[22] Pauler et al. demonstrated a slight reduction in CA-125 levels with increasing age adjusted for some of the same variables we used.[9] They reported that the decrease by age was attenuated in women with a previous history of cancer. Our results indicating an increase in CA-125 by increasing post- menopausal age category were based on a very large, diverse, and older sample of women and allowed simultaneous adjustment for numerous collected potentially important variables. If valid, this association could possibly be a consequence of aging processes at the cellular and immunological level. Interestingly, when we analyzed CA-125 using results from the original Centocor assay available for 5371 initially enrolled women aged 60 years and older, the values were lower (age 60–64, mean 9.2 and median 8.0; age 65–69, mean 9.2, median 7.7; age 70–74, mean 9.9, median 8.0), and there was no statistical difference by age categories, suggesting that perhaps the assay used could affect results.

While endometriosis has consistently been found to be associated with CA-125 level, which is expected based on the underlying biology, we did not find this association. This may reflect the limitation that a history of endometriosis was based solely on self report. More importantly, endometriosis often resolves after menopause and therefore a post-menopausal CA-125 might not be expected to be related to a historical diagnosis of this condition.

Another striking finding from these PLCO CA-125 analyses is the differences by racial/ethnic group. These results adjusted for education level as a surrogate marker for socioeconomic status and confirm the prior UK study addressing race/ethnicity as a possible

factor in CA-125 levels in which only 80 Asian and 89 African women out of a total of 18,748 subjects were evaluated.[9] Even so, race was a statistically significant variable with mean CA-125 levels slightly lower (by 1.2 U/ml) in Asians and markedly lower (by 5.2 U/ml) in African relative to White women. In the UK study, the Asian group is most probably predominantly from the Indian subcontinent, whereas in the PLCO study the Asian group is largely comprised of women with Japanese, Chinese, and Filipino heritage.

In our data, hysterectomy was associated with decreased mean CA-125, confirming other work.[9;22] The finding that current hormone therapy use increased CA-125 only in women with a uterus comports with the premise that hormone therapy resulted in stimulation of CA-125 in the endometrium, which is a known source of CA-125 in healthy women.[17] Although some women with hysterectomy who reported having their ovaries had likely also had oophorectomy, the concentration of CA-125 in the healthy ovary is small compared to the endometrium and oophorectomy had no significant impact on CA-125 levels in other studies.[17] [9;23] CA-125 levels vary during the menstrual cycle, suggesting an influence of ovarian steroid hormones. Kurihara et al. demonstrated in a small study that CA-125 was higher among healthy post-menopausal women using hormone therapy than among non-users.[24] Two clinical trials examined CA-125 levels in response to initiation of hormone therapy.[25;26] In both studies there was no effect of current estrogen therapy on CA-125 levels in women with hysterectomies, which corroborates our data. However, for women with a uterus, Karabacak reported that 100 ug/day transdermal estradiol was associated with a significant increase in CA-125, again consistent with our results.[25] In contrast, Cengiz et al. reported that current use of combination of estrogen and progestin resulted in lower CA-125 levels in women with a uterus, while Okon et al. saw no change in their 12 month follow-up study.[26;27] The type of hormone therapy used was not determined in our study, but it is likely that estrogen-only therapy would predominate in the women with hysterectomy and estrogen-progestogen therapy would predominate in women with a uterus.

It is not obvious why current smoking and obesity are associated with a lower CA-125. It is intriguing that Pauler et al. also found a protective effect of current smoking, which they considered was most likely a fluke or possibly due to an effect on liver enzymes and enhanced metabolic degradation of CA-125.[9] Perhaps a higher plasma volume, associated with obesity,[28;29] dilutes the level of serum CA-125. Why former smoking or hormone therapy use may be associated with increased CA-125 is even less clear. A limitation of the baseline questionnaire used in this study is that “former” was not linked to dates or duration, so we cannot reconstruct histories linking the timing of hysterectomy, smoking, and timing and duration of hormone therapy use as related to the date of CA-125 measurement.

Another limitation is that while this population is unusually large and represents geographic and racial/ethnic diversity, it is comprised of women agreeing to participate in a long term cancer prevention screening trial. Potential subjects were recruited using a multitude of approaches, with random mailings accounting for the majority of enrollees.[30] It has been demonstrated that the PLCO population has lower mortality rates than the general population, suggesting they are healthier in general.[31] Analyses of data from one site comparing those enrolled to those invited from within a health care system population demonstrated that 11% of those asked joined the study and suggested that those who were White, in their sixties, with higher income and with fewer co-morbidities were somewhat more likely to participate.[32] Our analyses are therefore likely subject to some degree of selection (volunteer) bias. Further, although the trial deployed numerous strategies to recruit minority subjects [30], the percentages of enrolled women in these groups was lower than the percentages these groups represent in the United States, suggesting that volunteer bias and representativeness may be even more of an issue for non-Whites. This is noteworthy since an important result of our analyses is the lower CA-125 values associated with

minorities. Additionally, there is always the possibility that our results could be affected by unmeasured confounders such as subclinical chronic disease processes or genetic variation and that characteristics such as age and race are markers for some other factor directly affecting CA-125. Finally, it is possible that a small number of women with sub-clinical ovarian cancer remained in the study population.

In summary, CA-125 levels were found to be associated with a number of demographic and medical factors. A notable finding was substantially lower mean CA-125 levels in minority women relative to White women, with levels 8–19% lower. If CA-125 is incorporated in a screening algorithm, these variables may prove to be important in clinical evaluations. Future analyses will consider changes in CA-125 over time using the baseline and measurements available from five subsequent annual screening exams among women without ovarian cancer in this population.

Acknowledgments

The authors gratefully acknowledge the contribution of the study staff at each of the ten screening centers; Westat, Inc.; Information Management Services, Inc.; the central Immunogenetics Laboratory at UCLA; and the study investigators and staff at the National Cancer Institute.

Funding Sources: This work was supported by individual contracts from the National Cancer Institute to each of the ten screening centers and to the coordinating center.

Abbreviations and Acronyms

OR	odds ratio
aOR	adjusted odds ratio
CI	95% confidence interval
SEER	Surveillance, Epidemiology, End Results
HT	hormone therapy
LMP	last menstrual period

Reference List

1. Verheijen RH, Mensdorff-Pouilly S, van Kamp GJ, Kenemans P. CA 125: fundamental and clinical aspects. Semin Cancer Biol. 1999; 9:117–124. [PubMed: 10202133]
2. Duffy MJ, Bonfrer JM, Kulpa J, Rustin GJ, Soletormos G, Torre GC, Tuxen MK, Zwirner M. CA125 in ovarian cancer: European Group on Tumor Markers guidelines for clinical use. Int J Gynecol Cancer. 2005; 15:679–691. [PubMed: 16174214]
3. Bast RC, Badgwell D, Lu Z, Marquez R, Rosen D, Liu J, Baggerly KA, Atkinson EN, Skates S, Zhang Z, Lokshin A, Menon U, Jacobs I, Lu K. New tumor markers: CA125 and beyond. International Journal of Gynecological Cancer. 2005; 15:274–281. [PubMed: 16343244]
4. Karlan BY, McIntosh M. The Quest for Ovarian Cancer's Holy Grail: Can CA-125 still be the chalice of early detection? J Clin Oncol. 2007; 25:1303–1304. [PubMed: 17416848]
5. Baron AT, Boardman CH, Lafky JM, Rademaker A, Liu D, Fishman DA, Podratz KC, Maihle NJ. Soluble epidermal growth factor receptor (sEGFR) [corrected] and cancer antigen 125 (CA125) as screening and diagnostic tests for epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2005; 14:306–318. [PubMed: 15734951]
6. Rosen DG, Wang L, Atkinson JN, Yu Y, Lu KH, Diamandis EP, Hellstrom I, Mok SC, Liu J, Bast J. Potential markers that complement expression of CA125 in epithelial ovarian cancer. Gynecologic Oncology. 2005; 99:267–277. [PubMed: 16061277]

7. Menon U, Skates SJ, Lewis S, Rosenthal AN, Rufford B, Sibley K, MacDonald N, Dawnay A, Jeyarajah A, Bast RC Jr. Oram D, Jacobs IJ. Prospective study using the risk of ovarian cancer algorithm to screen for ovarian cancer. J Clin Oncol. 2005; 23:7919–7926. [PubMed: 16258091]
8. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, Fogel R, Gelmann EP, Gilbert F, Hasson MA, Hayes RB, Johnson CC, Mandel JS, Oberman A, O'Brien B, Oken MM, Rafla S, Reding D, Rutt W, Weissfeld JL, Yokochi L, Gohagan JK. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials. 2000; 21:273S–309S. [PubMed: 11189684]
9. Pauler DK, Menon U, McIntosh M, Symecko HL, Skates SJ, Jacobs IJ. Factors influencing serum CA125II levels in healthy postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2001; 10:489–493. [PubMed: 11352859]
10. O'Brien TJ, Beard JB, Underwood LJ, Dennis RA, Santin AD, York L. The CA 125 gene: an extracellular superstructure dominated by repeat sequences. Tumour Biol. 2001; 22:348–366. [PubMed: 11786729]
11. Yin BW, Dnistrian A, Lloyd KO. Ovarian cancer antigen CA125 is encoded by the MUC16 mucin gene. Int J Cancer. 2002; 98:737–740. [PubMed: 11920644]
12. Whitehouse C, Solomon E. Current status of the molecular characterization of the ovarian cancer antigen CA125 and implications for its use in clinical screening. Gynecol Oncol. 2003; 88:S152–S157. [PubMed: 12586109]
13. Koper NP, Thomas CMG, Massuger LFAG, van der Mooren MJ, Kiemeney LALM, Verbeek ALM. Serum CA 125 concentrations in women of different ages, hormonal statuses, or clinical conditions. Int J Gynecol Cancer. 1997; 7:405–411.
14. Hermsen BBJ, von Mensdorff-Pouilly S, Berkhof J, van Diest PJ, Gille JJP, Menko FH, Blankenstein MA, Kenemans P, Verheijen RHM. Serum CA-125 in relation to adnexal dysplasia and cancer in women at hereditary high risk of ovarian cancer. J Clin Oncol. 2007; 25:1383–1389. [PubMed: 17416858]
15. Gohagan JK, Levin DL, Prorok PC, Sullivan D. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials. 2000; 6S:249S–406S.
16. Buys SS, Partridge E, Greene MH, Prorok PC, Reding D, Riley TL, Hartge P, Fagerstrom RM, Ragard LR, Chia D, Izmirlian G, Fouad M, Johnson CC, Gohagan JK. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. Am J Obstet Gynecol. 2005; 193:1630–1639. [PubMed: 16260202]
17. Zeimet AG, Muller-Holzner E, Marth C, Daxenbichler G, Dapunt O. Tumor marker CA-125 in tissues of the female reproductive tract and in serum during the normal menstrual cycle. Fertil Steril. 1993; 59:1028–1035. [PubMed: 8486169]
18. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer statistics, 2006. CA Cancer J Clin. 2006; 56:106–130. [PubMed: 16514137]
19. Takami M, Sakamoto H, Ohtani K, Takami T, Satoh K. An evaluation of CA125 levels in 291 normal postmenopausal and 20 endometrial adenocarcinoma-bearing women before and after surgery. Cancer Lett. 1997; 121:69–72. [PubMed: 9459176]
20. Bon GG, Kenemans P, Verstraeten R, van Kamp GJ, Hilgers J. Serum tumor marker immunoassays in gynecologic oncology: establishment of reference values. Am J Obstet Gynecol. 1996; 174:107–114. [PubMed: 8571992]
21. Crump C, McIntosh MW, Urban N, Anderson G, Karlan BY. Ovarian cancer tumor marker behavior in asymptomatic healthy women: Implications for screening. Cancer Epidemiol Biomarkers Prev. 2000; 9:1107–1111. [PubMed: 11045795]
22. Grover S, Quinn MA, Weideman P, Koh H. Factors influencing serum CA 125 levels in normal women. Obstet Gynecol. 1992; 79:511–514. [PubMed: 1553167]
23. Grover S, Quinn MA, Weideman P, Koh H. Factors influencing serum CA 125 levels in normal women. Obstet Gynecol. 1992; 79:511–514. [PubMed: 1553167]
24. Kurihara T, Mizunuma H, Obara M, Andoh K, Ibuki Y, Nishimura T. Determination of a normal level of serum CA125 in postmenopausal women as a tool for preoperative evaluation and postoperative surveillance of endometrial carcinoma. Gynecol Oncol. 1998; 69:192–196. [PubMed: 9648586]

25. Karabacak O, Ilgin N, Tiras B, Gursoy R, Himmetoglu O. Influence of exogenous estrogen administration on serum CA-125 originating from the endometrium. Int J Gynaecol Obstet. 2002; 76:169–172. [PubMed: 11818112]

26. Cengiz B, Atabekoglu C, Cetinkaya E, Cengiz SD. Effect of hormone replacement therapy on serum levels of tumor markers in healthy postmenopausal women. Maturitas. 2003; 46:301–306. [PubMed: 14625127]

27. Okon MA, Lee S, Laird SM, Li TC. A prospective randomized controlled study comparing the morphological and biochemical responses of the endometrium to two different forms of 'period-free' hormone replacement therapy. Hum Reprod. 1998; 13:2261–2265. [PubMed: 9756307]

28. Guha PK, Villarreal D, Reams GP, Freeman RH. Role of leptin in the regulation of body fluid volume and pressures. Am J Ther. 2003; 10:211–218. [PubMed: 12756428]

29. Hall JE, Brands MW, Dixon WN, Smith MJ Jr. Obesity-induced hypertension. Renal function and systemic hemodynamics. Hypertension. 1993; 22:292–299. [PubMed: 8349321]

30. Simpson NK, Johnson CC, Ogden SL, Gamito E, Trocky N, McGuire C, Martin J, Barrow S, Lamerato L, Flickinger LM, Broski KG, Engelhard D, Hilke C, Bonk J, Gahagan B, Gren LH, Childs J, Lappe K, Fouad M, Thompson J, Sullivan D. Recruitment strategies in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: The first six years. Control Clin Trials. 2000; 21:356S–378S. [PubMed: 11189688]

31. Pinsky P, Miller A, Kramer BS, Church T, Reding D, Prorok P, Gelmann E, Schoen RE, Buys S, Hayes RB, Berg CD. Evidence of a health volunteer effect in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Am J Epidemiol. 2007; 165:874–881. [PubMed: 17244633]

32. Lamerato LE, Marcus PM, Jacobsen G, Johnson CC. Recruitment in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial: the first phase of recruitment at Henry Ford Health System. Cancer Epidemiol Biomarkers Prev. 2008; 17:827–833. [PubMed: 18398023]

Table 1

CA-125 (U/ml) distribution by selected variables (n=25,608)

		CA-125 Level (n, %)						
	N (%)	**0- <10**	**10- <20**	**20-<30**	**30- <35**	**35+**		
Variable							**Median, (IQR*)**	**Mean (SD) [95% C.I.]**
Total	25,608 (100)	11,434 (44.7)	11,583 (45.2)	1,885 (7.4)	289 (1.1)	417 (1.6)	10.0 (8.0–14.0)	11.9 (8.3) [11.8–12.0]
Race								
Whites	23053 (90.0)	9,944 (43.1)	10,660 (46.2)	1,788 (7.8)	270 (1.2)	391 (1.7)	10.0 (8.0–14.0)	12.1 (8.5) [12.0–12.2]
Blacks	1132 (4.4)	770 (68.0)	307 (27.1)	36 (3.2)	8 (0.7)	11 (1.0)	8.0 (6.0–10.5)	9.3 (6.8) [8.9–9.7]
Hispanics	351 (1.4)	203 (57.8)	130 (37.0)	14 (4.0)	1 (0.3)	3 (0.9)	9.0 (7.0–12.0)	10.2 (6.1) [9.6–10.9]
Asian	900 (3.5)	419 (46.6)	420 (46.7)	41 (4.6)	10 (1.1)	10 (1.1)	10.0 (7.0–13.0)	11.1 (6.3) [10.7–11.6]
Pacific Islander/Native American	172 (0.7)	98 (57.0)	66 (38.4)	6 (3.5)	0 (0)	2 (1.2)	9.0 (7.0–13.0)	10.2 (5.7) [9.4–11.0]
Age (yrs)								
55–59	9075 (35.4)	4,277 (47.1)	4,063 (44.8)	554 (6.1)	78 (0.9)	103 (1.1)	10.0 (7.0–13.0)	11.4 (7.4) [11.2–11.5]
60–64	7874 (30.7)	3,499 (44.4)	3,554 (45.1)	601 (7.6)	90 (1.1)	130 (1.7)	10.0 (8.0–14.0)	12.0 (7.8) [11.8–12.1]
65–69	5472 (21.4)	2,314 (42.3)	2,529 (46.2)	452 (8.3)	75 (1.4)	102 (1.9)	10.0 (8.0–14.0)	12.4 (10.1) [12.1–12.6]
70–74	3187 (12.4)	1,344 (42.2)	1,437 (45.1)	278 (8.7)	46 (1.4)	82 (2.6)	10.0 (8.0–14.0)	12.6 (8.8) [12.3–12.9]
Education								
<12 years	1,387 (5.4)	684 (49.3)	570 (41.1)	91 (6.6)	21 (1.5)	21 (1.5)	10.0 (7.0–13.0)	11.5 (7.2) [11.1–11.9]
High School	16023 (62.6)	7145 (44.6)	7277 (45.4)	1169 (7.3)	167 (1.0)	265 (1.7)	10.0 (8.0–14.0)	11.9 (8.4) [11.8–12.0]
Post High School	8198 (32.0)	3605 (44.0)	3736 (45.6)	625 (7.6)	101 (1.2)	131 (1.6)	10.0 (8.0–14.0)	12.1 (8.4) [11.9–12.2]
Age at Menopause (yrs)								
<40	3332 (13.0)	1,802 (54.1)	1,286 (38.6)	182 (5.5)	24 (0.7)	38 (1.1)	9.0 (7.0–12.0)	10.7 (7.1) [10.4–10.9]
40–44	3265 (12.7)	1,581 (48.4)	1,385 (42.4)	225 (6.9)	29 (0.9)	45 (1.4)	10.0 (7.0–14.0)	11.5 (7.6) [11.2–11.7]
45–49	5789 (22.6)	2,599 (44.9)	2,593 (44.8)	434 (7.5)	59 (1.0)	104 (1.8)	10.0 (7.0–14.0)	12.0 (9.8) [11.8–12.3]
50–54	10,043 (39.2)	4,237 (42.2)	4,758 (47.4)	759 (7.6)	117 (1.2)	172 (1.7)	10.0 (8.0–14.0)	12.2 (7.9) [12.0–12.3]
55+	3179 (12.4)	1,215 (38.2)	1,561 (49.1)	285 (9.0)	60 (1.9)	58 (1.8)	11.0 (8.0–15.0)	12.8 (8.4) [12.5–13.1]
History of Breast Cancer	932 (3.6)	369 (39.6)	460 (49.4)	71 (7.6)	16 (1.7)	16 (1.7)	11.0 (8.0–14.0)	12.5 (8.0) [12.0–13.0]
Family History of Ovarian Cancer	986 (3.9)	440 (44.6)	469 (47.6)	55 (5.6)	8 (0.8)	14 (1.4)	10.0 (7.0–14.0)	11.6 (6.7) [11.2–12.0]
Family History of Breast Cancer	3635 (14.2)	1,683 (46.3)	1,581 (43.5)	279 (7.7)	38 (1.0)	54 (1.5)	10.0 (7.0–14.0)	11.8 (7.4) [11.5–12.0]

		CA-125 Level (n, %)						
	N (%)	**0- <10**	**10- <20**	**20-<30**	**30- <35**	**35+**		
Variable							**Median, (IQR*)**	**Mean (SD) [95% C.I.]**
History of Ovarian Tumors /Cysts	2,489 (9.7)	1,151 (46.2)	1,098 (44.1)	184 (7.4)	22 (0.9)	34 (1.4)	10.0 (7.0–14.0)	11.6 (7.8) [11.3–11.9]
History of Uterine Fibroids	4,704 (18.4)	2,203 (46.8)	2,065 (43.9)	312 (6.6)	46 (1.0)	78 (1.7)	10.0 (7.0–14.0)	11.6 (7.8) [11.4–11.9]
History of Endometriosis	1,471 (5.7)	699 (47.5)	635 (43.2)	115 (7.8)	6 (0.4)	16 (1.1)	10.0 (7.0–14.0)	11.4 (6.3) [11.1–11.7]
Partial Oophorectomy	441 (1.7)	228 (51.7)	178 (40.4)	23 (5.2)	4 (0.9)	8 (1.8)	9.0 (7.0–13.0)	11.0 (7.6) [10.3–11.7]
Hysterectomy	6,653 (26.0)	3,512 (52.8)	2,637 (39.6)	379 (5.7)	51 (0.8)	74 (1.1)	9.0 (7.0–13.0)	10.8 (7.1) [10.7–11.0]
Hormone Therapy Use								
Never	8981 (35.1)	4149 (46.2)	3988 (44.4)	598 (6.7)	90 (1.0)	156 (1.7)	10.0 (7.0–13.0)	11.7 (8.5) [11.5–11.9]
Former	4,341 (17.0)	1,879 (43.3)	1,994 (45.9)	346 (8.0)	56 (1.3)	66 (1.5)	10.0 (8.0–14.0)	12.0 (7.5) [11.8–12.2]
Current	12,286 (48.0)	5,406 (44.0)	5,601 (45.6)	941 (7.7)	143 (1.2)	195 (1.6)	10.0 (8.0–14.0)	12.1 (8.5) [11.9–12.2]
Smoking Status								
Never	14,443 (56.4)	6,320 (43.8)	6,665 (46.1)	1,074 (7.4)	160 (1.1)	224 (1.6)	10.0 (8.0–14.0)	12.0 (8.3) [11.8–12.1]
Former	8,843 (34.5)	3,781 (42.8)	4,109 (46.5)	684 (7.7)	104 (1.2)	165 (1.9)	10.0 (8.0–14.0)	12.2 (8.6) [12.0–12.4]
Current	2,322 (9.1)	1,333 (57.4)	809 (34.8)	127 (5.5)	25 (1.1)	28 (1.2)	9.0 (7.0–12.0)	10.7 (7.2) [10.4–10.9]
Current Body Mass Index**								
Normal	10,608 (41.4)	4,630 (43.6)	4,838 (45.6)	814 (7.7)	122 (1.2)	204 (1.9)	10.0 (8.0–14.0)	12.2 (9.0) [12.0–12.4]
Overweight	8,937 (34.9)	3,956 (44.3)	4,070 (45.5)	649 (7.3)	109 (1.2)	153 (1.7)	10.0 (8.0–14.0)	12.0 (8.5) [11.9–12.2]
Obese	6,063 (23.7)	2,848 (47.0)	2,675 (44.1)	422 (7.0)	58 (1.0)	60 (1.0)	10.0 (7.0–13.0)	11.3 (6.6) [11.2–11.5]

*IQR=Interquartile Range

**Normal defined as BM <25 kg/m^2; Overweight as BM =25–29 kg/m^2; Obese as BM ≥30 kg/m^2

Table 2

Crude and adjusted* odds ratios for selected variables and elevated CA-125 (≥35 U/ml)

Variable	OR (95%CI)	p value	aOR (95%CI)	p value
White	--	--	--	--
Black	0.57 (0.31–1.04)	0.066	0.66 (0.36–1.22)	0.183
Hispanic	0.50 (0.16–1.56)	0.233	0.54 (0.17–1.70)	0.296
Asian	0.65 (0.35–1.22)	0.183	0.53 (0.28–1.00)	0.051
Pacific Is/ Native Am	0.68 (0.17–2.76)	0.591	0.78 (0.19–3.17)	0.730
Age 55–59 yrs	--	--	--	--
Age 60–64 yrs	1.46 (1.13–1.90)	0.004	1.49 (1.14–1.93)	0.003
Age 65–69 yrs	1.65 (1.26–2.18)	<0.001	1.66 (1.25–2.20)	<0.001
Age 70–74 yrs	2.30 (1.72–3.08)	<0.001	2.30 (1.69–3.12)	<0.001
High School degree	--	--	--	--
<12 education	0.91 (0.58–1.43)	0.694	0.96 (0.61–1.51)	0.866
Post High School	0.97 (0.78–1.19)	0.745	0.91 (0.73–1.13)	0.400
Age at Menopause 50–54 yrs	--	--	--	--
<40 yrs	0.66 (0.46–0.94)	0.022	1.11 (0.71–1.72)	0.650
40–44 yrs	0.80 (0.58–1.12)	0.191	0.98 (0.69–1.39)	0.902
45–49 yrs	1.05 (0.82–1.34)	0.698	1.09 (0.85–1.40)	0.479
55+ yrs	1.07 (0.79–1.44)	0.674	1.09 (0.81–1.48)	0.567
History of Breast Cancer	1.06 (0.64–1.75)	0.828	0.99 (0.60–1.66)	0.979
Family History of Ovarian Cancer	0.87 (0.51–1.48)	0.598	0.85 (0.49–1.45)	0.547
Family History of Breast Cancer	0.90 (0.67–1.20)	0.463	0.87 (0.65–1.16)	0.348
History of Ovarian Tumors/Cysts	0.82 (0.58–1.17)	0.277	0.86 (0.60–1.24)	0.434
History of Uterine Fibroids	1.02 (0.80–1.31)	0.857	1.26 (0.97–1.64)	0.078
History of Endometriosis	0.65 (0.39–1.08)	0.094	0.73 (0.44–1.22)	0.237
History of Partial Oophorectomy	1.12 (0.55–2.27)	0.756	1.42 (0.69–2.95)	0.345
Hysterectomy	0.61 (0.47–0.79)	<0.001	0.58 (0.41–0.81)	0.001
No Hormone Therapy	--	--	--	--

Variable	OR (95%CI)	p value	aOR (95%CI)	p value
Former Hormone Therapy	0.87 (0.65–1.17)	0.360	0.88 (0.66–1.18)	0.386
Current Hormone Therapy	0.91 (0.74–1.13)	0.397	1.02 (0.81–1.28)	0.865
Never Smoker	--	--	--	--
Former Smoker	1.21 (0.99–1.48)	0.069	1.23 (1.00–1.51)	0.047
Current Smoker	0.78 (0.52–1.15)	0.207	0.81 (0.55–1.22)	0.316
Normal Weight**	--	--	--	--
Overweight	0.89 (0.72–1.10)	0.273	0.88 (0.71–1.10)	0.260
Obese	0.51 (0.38–0.68)	<0.001	0.53 (0.39–0.71)	<0.001

* statistics estimated using logistic regression; aOR adjusted for all other variables on the table

** Normal defined as BMI <25 kg/m^2; Overweight as BMI =25–29 kg/m^2; Obese as BMI ≥30 kg/m^2

Table 3

Regression coefficients for selected variables and log transformed CA-125 as a continuous variable*

	Univariate			Multivariate**		
Variable	**Parameter estimate**	**Parameter exponentiated**	**P value**	**Parameter estimate**	**Parameter exponentiated**	**P value**
White	--	--	--	--		
Black	−0.243	0.784	<0.001	−0.208	0.812	<0.001
Hispanic	−0.140	0.870	<0.001	−0.126	0.881	<0.001
Asian	−0.060	0.942	<0.001	−0.084	0.920	<0.001
Pacific Is/ Native Am	−0.137	0.872	<0.001	−0.120	0.887	<0.001
Age 55–59 yrs	--	--	--	--		
Age 60–64 yrs	0.036	1.037	<0.001	0.041	1.041	<0.001
Age 65–69 yrs	0.053	1.055	<0.001	0.058	1.060	<0.001
Age 70–74 yrs	0.070	1.073	<0.001	0.073	1.075	<0.001
High School graduate	--	--	--	--	--	--
<12 years	−0.035	0.965	0.005	−0.002	0.998	0.878
Post High School	0.009	1.009	0.137	−0.007	0.993	0.232
Age at Menopause 50–54 yrs	--	--	--	--	--	--
<40 yrs	−0.114	0.892	<0.001	−0.017	0.984	0.150
40–44 yrs	−0.058	0.944	<0.001	−0.009	0.991	0.378
45–49 yrs	−0.021	0.979	0.005	−0.004	0.996	0.570
55+ yrs	0.046	1.047	<0.001	0.043	1.044	<0.001
History of Breast Cancer	0.046	1.048	0.002	0.046	1.047	0.002
Family History of Ovarian Cancer	−0.010	0.990	0.473	−0.011	0.989	0.426
Family History of Breast Cancer	−0.011	0.989	0.168	−0.015	0.986	0.066
History of Ovarian Tumors/Cysts	−0.022	0.978	0.021	0.007	0.993	0.473
History of Uterine Fibroids	−0.029	0.971	<0.001	0.009	1.009	0.250
History of Endometriosis	−0.028	0.972	0.018	−0.004	0.996	0.721
Partial Oophorectomy	−0.082	0.921	<0.001	−0.024	0.976	0.265

Gynecol Oncol. Author manuscript; available in PMC 2013 August 15.

	Univariate			Multivariate**		
Variable	**Parameter estimate**	**Parameter exponentiated**	**P value**	**Parameter estimate**	**Parameter exponentiated**	**P value**
Hysterectomy	−0.112	0.894	<0.001	−0.100	0.905	<0.001
No Hormone Therapy	--	--	--	--	--	--
Former Hormone Therapy	0.027	1.028	<0.001	0.031	1.031	<0.001
Current Hormone Therapy	0.0233	1.024	<0.001	0.040	1.041	<0.001
Never Smoker	--	--	--	--		
Former Smoker	0.015	1.015	0.016	0.014	1.014	0.017
Current Smoker	−0.111	0.895	<0.001	−0.094	0.910	<0.001
Normal Weight***	--	--	--	--		
Overweight	−0.010	0.990	0.108	−0.004	0.996	0.493
Obese	−0.050	0.951	<0.001	−0.030	0.970	<0.001

* statistics estimated using linear regression

** adjusted for all other variables on the table

*** Normal defined as BMI <25 kg/m^2; Overweight as BMI =25–29 kg/m^2; Obese as BMI ≥30 kg/m^2