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Pathologic Findings Following False-Positive Screening Tests for Ovarian Cancer in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial

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Abstract

Objective—In the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), ovarian cancer screening with transvaginal ultrasound (TVU) and CA-125 produced a large number of false-positive tests. We examined relationships between histopathologic diagnoses, false-positive test group, and participant and screening test characteristics.

Methods—The PLCO ovarian cancer screening arm included 39,105 women aged 55-74 years assigned to annual CA-125 and TVU. Histopathologic diagnoses from women with false-positive

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Research highlights

- Serous cystadenomas were the most common ovarian false-positive (FP) finding (28%)
- Leiomyoma and paratubal cysts were the most common non-ovarian FP findings (33% and 30%)
- 4% of women were diagnosed with non-ovarian cancers, mainly associated with elevated CA-125

tests and subsequent surgery were reviewed in this analysis: all CA125+ (n=121); all CA125+/TVU+ (n=46); and a random sample of TVU+ (n=373). Demographic and ovarian cancer risk factor data were self-reported. Pathologic diagnoses were abstracted from surgical pathology reports. We compared participant characteristics and pathologic diagnoses by category of false-positive using Pearson χ^2 , Fisher's exact, or Wilcoxon-Mann-Whitney tests.

Results—Women with a false-positive TVU were younger ($P < 0.001$), heavier ($P < 0.001$), and reported a higher frequency of prior hysterectomy ($P < 0.001$). Serous cystadenoma, the most common benign ovarian diagnosis, was more frequent among women with TVU+ compared to CA-125+ and CA-125+/TVU+ ($P < 0.001$). Benign non-ovarian findings were commonly associated with all false-positives, although more frequently with CA-125+ than TVU+ or CA-125+/TVU+ groups ($P=0.019$). Non-ovarian cancers were diagnosed most frequently among CA-125+ ($P < 0.001$).

Conclusions—False-positive ovarian cancer screening tests were associated with a range of histopathologic diagnoses, some of which may be related to patient and screening test characteristics. Further research into the predictors of false-positive ovarian cancer screening tests may aid efforts to reduce false-positive results.

Introduction

Ovarian cancer is the most lethal gynecologic cancer in the United States, accounting for approximately 14,600 deaths in 2009 (1). Most ovarian cancers are disseminated at presentation which portends a poor prognosis (2). However, ovarian tumors identified at an early stage are associated with over 90% five-year survival (2); therefore, development of an effective method for early detection of ovarian cancer may improve outcomes substantially. Several ovarian cancer screening trials have been conducted to assess early detection approaches, but initial results have demonstrated low specificity resulting in a high number of false-positive screening tests (3-7).

In the first four rounds of screening in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, less than 2% of the 3,387 women with an abnormal transvaginal ultrasound (TVU) and/or abnormal serum CA-125 screening test were diagnosed with invasive ovarian or peritoneal cancer (6). Surgery is the most definitive means of investigating an abnormal ovarian cancer screening test, but it is invasive, expensive, and can pose a significant risk to the patient. Thus, the frequency of false-positive tests in PLCO is unacceptably high. Characterization of the pathologic diagnoses associated with false-positive screening tests may suggest approaches for improving test performance. Accordingly, we performed a detailed analysis of the pathologic findings associated with false-positive TVU and CA-125 tests in PLCO.

Methods

PLCO Trial

PLCO is a multi-center, randomized, two-arm clinical trial designed to evaluate the effect of prostate, lung, colorectal, and ovarian cancer screening on disease-specific mortality. Detailed descriptions of the PLCO study design and the ovarian cancer screening component have been reported previously (3,6,8). PLCO participants were enrolled from November 1993 to December 2001. Women were eligible to participate if they were 55-74 years old, had not been previously diagnosed with lung, colorectal, or ovarian cancer, had not previously undergone a pneumonectomy or total colectomy, and were not receiving cancer treatment (except for nonmelanoma skin cancers). Women who had undergone bilateral oophorectomy prior to enrollment were ineligible to participate in the ovarian screening component.

All participants provided informed consent, and the study was approved by local institutional review boards. Participants were randomized either to annual serum CA-125 testing for 6 years with annual TVU for 4 years or to usual care. This analysis utilizes information from the first 4 screening years only.

Screening Tests

Blood samples collected at screening visits were processed and frozen at -70°C within 2 hours of collection. Serum CA-125 was measured using the Centocor CA-125II radioimmunoassay (Centocor, Inc, Malvern, PA). A CA-125 level ≥ 35 U/mL was considered abnormal and suspicious for ovarian cancer (CA-125+).

TVU was performed using a 5-7.5 MHz transvaginal probe. Ovaries and cysts were measured in three dimensions, and volumes were calculated using the prolate ellipsoid formula ($\text{volume} = 0.523 \times \text{width} \times \text{height} \times \text{thickness}$). Cysts were characterized according to solid area (none/mixed/solid), septal structure (none/ $\leq 3\text{mm}$ / $> 3\text{mm}$), outline (smooth/irregular/papillary), and wall thickness ($\leq 3\text{mm}$ / $> 3\text{mm}$). Criteria for classifying TVU exams as abnormal and suspicious for ovarian cancer (TVU+) included: ovarian volume $> 10\text{cm}^3$; cyst volume $> 10\text{cm}^3$; identification of intracystic solid or papillary areas; or detection of mixed solid/cystic components. Abnormal screening results were reported to participants and their primary physicians, who then decided on subsequent management. As a result, some participants who had one or more abnormal screening results remained in the trial, but never underwent surgery.

Study Subjects

At enrollment, 39,105 women were randomized to the intervention arm, of whom 4,852 were excluded due to prior oophorectomy, leaving 34,253 women eligible for ovarian cancer screening. A total of 3,387 women had an abnormal ovarian screening test (Table 1). Women were categorized into groups based on whether they had an abnormal CA-125 or TVU test during the first 4 screening years. Women with one or more abnormal CA-125 tests and no abnormal TVU tests were classified as CA-125+. Women with one or more abnormal TVU tests and no abnormal CA-125 tests were classified as TVU+. Women with one or more abnormal CA-125 tests and one or more abnormal TVU results were classified as CA-125+/TVU+, regardless of whether the CA-125 and TVU tests were abnormal in the same or different screening years.

Medical records for women with one or more abnormal screening tests were collected by PLCO screening centers, and information regarding diagnostic procedures and subsequent diagnoses was abstracted using standardized forms. There were 1,125 women who underwent a diagnostic procedure after an abnormal ovarian screening test in the first four rounds of screening and were not diagnosed with invasive ovarian, peritoneal, or fallopian tube cancer (i.e., false-positives, Table 1).

Data Collection

At enrollment, participants completed a questionnaire to collect information on demographics, anthropometry, family history of cancer, and medical and reproductive histories. A family history of breast or ovarian cancer was defined based on reported history in a first-degree relative. Age at surgery was taken from the surgical pathology report.

De-identified pathology reports were abstracted by two pathologists who were masked to screening test results (where possible) using a pre-tested form. Available reports from all women in CA-125+ and CA-125+/TVU+ groups were abstracted, as well as reports from a random subset of 400 women in the TVU+ group. Baseline questionnaire or screening test

characteristics did not differ between women in the TVU+ group who were and were not included in the pathology review (data not shown). Pathologists abstracted data regarding the type of surgical specimen, anatomic site, cystic features, and 25 types of ovarian and extra-ovarian pathologic diagnoses. A masked, random sample of 12 reports underwent duplicate abstraction to assess inter-observer agreement, which was evaluated using a simple Kappa statistic. Agreement between pathologists was substantial ($\kappa=0.71$, $P < 0.001$).

Out of 581 pathology reports selected for analysis, 25 were not provided by screening centers for data abstraction, and 16 were unusable because they were illegible or lacked information on surgical specimens. Data were abstracted from 540 reports: 46 of 47 (98%) CA-125+/TVU+; 121 of 134 (90%) CA-125+; and 373 of 400 (93%) TVU+ (Table 1).

Statistical Analysis

Participant characteristics, medical history related to ovarian cancer risk, and pathologic diagnoses were tabulated overall and stratified by false-positive test group. Calculations for leiomyoma, endometrial or endocervical polyp, adenomyosis, and endometrial hyperplasia excluded women who reported a previous hysterectomy. Characteristics of the last abnormal TVU or CA-125 test prior to surgery were compared by pathologic diagnoses.

Pearson χ^2 and Fisher's exact tests were used to evaluate differences in the distribution of categorical variables by false-positive test group. The Wilcoxon-Mann-Whitney test was used to evaluate differences in the distribution of continuous variables by false-positive test group. Statistical analyses using two-sided tests were performed using StataSE 11 (STATA, College Station, Texas) and SAS v9.1 (SAS, Cary, North Carolina).

Results

Participant Characteristics

Of the 540 women included in this analysis, 46 had abnormal results for both screening tests (Table 1), including 23 for whom both tests were abnormal within the same study year. Surgery consisted of a bilateral oophorectomy for the majority of women, and was less frequent in the TVU+ group when compared to CA-125+ and CA-125+/TVU+ groups (CA-125+/TVU+ - 76%, CA-125+ - 75%, TVU+ - 64%, $P=0.039$). Unilateral oophorectomy was performed for a smaller proportion of women, and was more common among the TVU+ group (CA-125+/TVU+ - 15%, CA-125+ - 8%, TVU+ - 21%, $P=0.006$). Various other procedures were performed with much lower frequency. The mean age at surgery was 64.1 years (standard deviation=5.6, range 55 – 77 years). Women classified as TVU+ were slightly younger and had a higher body mass index (BMI) compared with other women (age at surgery: $P < 0.001$; BMI: $P < 0.001$; Table 2). Prior hysterectomy was reported by 30% of the TVU+ group as compared with 22% of CA-125+/TVU+ and 14% of CA-125+ groups ($P < 0.001$, Table 2). History of a benign ovarian tumor or cyst was also reported more frequently by TVU+ women ($P=0.010$), whereas a history of endometriosis was most frequently reported by CA-125+/TVU+ ($P=0.029$, Table 2). Distributions of other demographic and ovarian cancer risk factors were similar by false-positive group (Table 2).

Histopathologic Diagnoses

A total of 1119 findings were reported for the 540 participants for whom pathology reports were reviewed. Frequencies of the histopathologic findings, overall and stratified by false-positive group, are shown in Table 3.

Ovarian diagnoses—Benign neoplastic ovarian diagnoses were reported for 45% of women. These lesions were most frequent among the TVU+ group and least frequent among

CA-125+ ($P < 0.001$, Table 3), reflecting higher frequencies of serous and mucinous cystadenomas, teratomas, and borderline ovarian tumors among women with a false-positive TVU. Serous cystadenomas were diagnosed in the largest proportion of women (28%), followed by fibromas and thecomas (7%), mucinous cystadenomas (6%), and teratomas (5%). Additionally, 5 (1%) women were diagnosed with borderline ovarian tumors (4 serous, 1 mucinous).

Non-neoplastic ovarian findings were also common, particularly simple ovarian cysts (16%) and inclusion cysts (13%). Functional cysts (mainly follicular or corpus luteum cysts) were detected in 5% of women. Women diagnosed with functional cysts were not younger or more likely to report hormone use (data not shown). The overall frequency of non-neoplastic ovarian findings did not vary by false-positive group ($P=0.130$, Table 3).

Non-ovarian diagnoses—Non-ovarian neoplastic findings were reported for 26% of women. Leiomyoma was the most common, reported for 33% of women who reported not having undergone a prior hysterectomy. Additionally, 19 women were diagnosed with nonovarian cancers, including cancers of the endometrium ($n=15$), cervix ($n=1$), colon ($n=1$), and adenocarcinomas of unspecified primary sites ($n=2$). The frequency of non-ovarian cancers was highest among women classified as CA-125+ at 11% ($P < 0.001$, Table 3). The false-positive test associated with each cancer is shown in Table 4.

Non-ovarian non-neoplastic diagnoses were common among all false-positive groups, though most frequent among CA-125+ ($P=0.038$, Table 3). Common findings included paratubal cysts (30%), polyps (18%), and adenomyosis (17%). Endometrial hyperplasia was diagnosed in 23 (6%) women, 6 of whom were diagnosed with atypical endometrial hyperplasia (CA-125+, $n=5$; TVU+, $n=1$).

Pathologic diagnoses in women with a history of benign gynecological conditions—To determine whether a history of benign ovarian cysts or tumors, uterine leiomyomas, endometriosis, or previous hysterectomy was correlated with a particular pathologic diagnosis, we tabulated diagnoses stratified by these conditions. Women who reported a previous hysterectomy had a higher frequency of serous cystadenomas when compared with women without a previous hysterectomy (37% vs. 24%, $P=0.002$). Pathologic diagnoses did not vary by other conditions (data not shown).

Abnormal CA-125 characteristics—We examined the last abnormal CA-125 test prior to surgery among CA-125+ and CA-125+/TVU+ groups, but the distribution of CA-125 was unrelated to specific pathologic diagnoses (data not shown). The median value of the last abnormal CA-125 test prior to surgery was 45 U/mL (standard deviation=54, range 35 - 433 U/mL).

Abnormal TVU characteristics—Only one of several possible criteria was required to classify a TVU as abnormal and suspicious for ovarian cancer, leading to a high frequency of missing data for some features (missing data: ovarian volume - 16%; cyst volume - 34%; solid component - 26%; septal structure - 32%; cyst wall features - 32%). Using available data, we examined characteristics of the last pre-operative TVU among women in TVU+ and CA-125+/TVU+ groups. The median volume of the largest ovary per woman was 17.9 cm³ and the median volume of the largest cyst per woman was 31.0 cm³. A cyst wall thickness of > 3mm was present in 8% of women, septal structure > 3mm thick was present in 9% of women, intracystic papillations were present in 11% of women, and a mixed solid/cystic component was present in 20% of women.

Large ovarian volume was associated with a diagnosis of cystadenoma (median ovarian volume, any cystadenoma vs. other diagnosis: 28.1 cm³ vs. 14.2 cm³, $P < 0.001$) due in part to large ovarian volume among women with a mucinous cystadenoma (median ovarian volume, 42.0 cm³); patterns between other pathologic diagnoses and TVU characteristics were less clear (data not shown).

Discussion

In PLCO, approximately 20 surgeries were performed for each ovarian cancer detected by CA-125 and TVU screening (3,6), demonstrating a high frequency of false-positive tests. In this report, we described the histopathologic diagnoses associated with false-positive CA-125 and TVU tests and their relationship to participant and screening test characteristics. This description of false-positive screening tests is a first step towards understanding factors related to the poor specificity of ovarian cancer screening in PLCO. Specific knowledge of which benign conditions are associated with abnormal CA-125 and TVU tests is necessary in order to implement improved screening techniques that can distinguish between ovarian cancers and these false-positive findings.

Our results suggest that certain groups of women may be prone to false-positive CA-125 or TVU tests. For example, we found that prior hysterectomy was most frequent among the TVU + group. Studies have demonstrated that hysterectomy characteristics, such as surgical method or retention of the ovaries, were associated with findings that prompted for re-operation (9-11). Women in the TVU+ group were also slightly younger and had higher BMI compared with other women. The higher frequency of abnormal TVU examinations among younger women may reflect the inverse association of ovarian volume with age (12-14). Women in the CA-125+ and CA-125+/TVU+ groups underwent bilateral oophorectomy more frequently, probably reflecting the fact that elevated CA-125 does not pinpoint the anatomical source of production, whereas an abnormal TVU finding can be localized to one ovary. Further research on the association between personal characteristics and the risk of a false-positive ovarian cancer screening tests is needed to expand our understanding in this area, and to suggest approaches for triage of screening abnormalities.

Benign neoplastic ovarian findings were most common among women in the TVU+ and CA-125+/TVU+ groups. Consistent with other reports, the most common benign neoplastic ovarian diagnosis was serous cystadenoma. Serous cystadenomas were the most common benign ovarian neoplasm in two case series of middle-aged and older women (15-16). The University of Kentucky Ovarian Cancer Screening Project (UKOCSP) also reported that serous cystadenoma was the most common diagnosis among women who underwent surgery after abnormal screening results (7). By convention, cysts measuring > 1 cm are considered cystadenomas. Cystadenomas can be quite large and may become symptomatic, especially in cases of torsion, rupture, or adhesion to adjacent structures, and removal of large cysts among older women is routine even if suspicion of malignancy is low. However, it is commonly held that serous cystadenomas are unrelated to cancer, and some have argued these lesions may not be neoplasms at all (17).

Women were also diagnosed with solid or partly cystic benign tumors, including fibromas, thecomas and teratomas. Although benign ovarian teratomas are most common among women younger than 30 years old (15,18-19), the frequency observed in PLCO was consistent with other studies: benign teratomas were diagnosed in 5% of women in the UKOCSP screening study, and 7% to 16% of older women in case series (15-16,19). Paratubal cysts and other non-neoplastic non-ovarian pathologic findings were also diagnosed, though there were few consistent patterns by false-positive group. In many

instances, these diagnoses may have been recorded on the pathology report as incidental findings in otherwise normal specimens.

Although most findings were benign, 4% of women were diagnosed with non-ovarian malignancies. This is within the range reported by other ovarian cancer screening studies that used CA-125 and ultrasound: 2% of women in the UKOCSP, 4% of women in the CA-125 and ultrasound arm the UK Collaborative Trial of Ovarian Cancer Screening, and 1% of women in the Shizuoka Cohort Study of Ovarian Cancer Screening (4-5,7). Non-ovarian cancers were found more often among women in the CA-125+ group. The association between elevated CA-125 and colorectal metastases, endometrial cancer, and cervical cancer has been reported previously (20-22); our finding confirms that the incidental discovery of such tumors may be a consequence of ovarian cancer screening with CA-125. It is unclear whether earlier detection altered the outcomes for these women.

Screening also identified potential cancer precursors, including endometrial hyperplasia and atypical endometrial hyperplasia, a precursor of endometrioid endometrial carcinoma (23). Additionally, 1% of women were diagnosed with borderline ovarian tumors. Most serous borderline tumors pose limited patient risk, though the biological potential of a subset may be of more concern (24). Similar to the non-ovarian cancers, diagnoses of borderline ovarian tumors and endometrial hyperplasia, were more common among women with elevated CA-125.

Although the majority of diagnoses underlying the false-positive diagnoses are typically not life-threatening, we cannot assess the influence that patient concerns or non-specific symptoms may have had on the decision to operate. In the UKOCSP many ovarian cysts resolved spontaneously, and ovarian cancer was rare among women whose abnormal cystic findings persisted (7). Autopsy studies of postmenopausal women have shown that small adnexal masses are common among older women, further suggesting that most of the diagnoses we have described are not unusual for women of this age group (25-26).

This analysis was limited by a reliance on original pathology diagnoses from multiple institutions. Additionally, we only analyzed a sample of pathology reports from women in the TVU+ group. However, these women were similar to all eligible TVU+ women with respect to medical, demographic, and screening test characteristics, suggesting that the sample was representative. Fewer than half of women with a positive screening test underwent surgery, and fewer women with an abnormal CA-125 test underwent surgery than women with an abnormal TVU test (6). Individual reasons for proceeding to surgery are unknown; if the reason was related to the underlying pathologic entity then the findings described here may not be representative of all false-positives in PLCO.

Strengths of our analysis include its basis within a large cancer screening trial that utilized the two most common ovarian cancer screening tools. Additionally, diagnoses were abstracted by two gynecologic pathologists with good agreement, and availability of extensive medical and lifestyle data allowed us to characterize ovarian cancer risk factors among women with false-positive results.

In summary, our results show that benign neoplastic ovarian findings were diagnosed more commonly after false-positive TVU examinations, whereas non-neoplastic findings were common among all three false-positive groups. Characteristics such as age, BMI, and prior hysterectomy may be related to false-positives, and require further study. By detailing the conditions associated with false-positive screening tests in a large postmenopausal population, this study may aid efforts to improve test properties and reduce false-positives.

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REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* Jul-Aug;2009 59(4):225–49. [PubMed: 19474385]
2. Horner, MJRL.; Krapcho, M.; Neyman, N.; Aminou, R.; Howlander, N.; Altekruse, SF.; Feuer, EJ.; Huang, L.; Mariotto, A.; Miller, BA.; Lewis, DR.; Eisner, MP.; Stinchcomb, DG.; Edwards, BK. SEER Cancer Statistics Review, 1975-2006. National Cancer Institute; Bethesda, MD: 2009.
3. Buys SS, Partridge E, Greene MH, Prorok PC, Reding D, Riley TL, et al. 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* Nov;2005 193(5):1630–9. [PubMed: 16260202]
4. Kobayashi H, Yamada Y, Sado T, Sakata M, Yoshida S, Kawaguchi R, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. *Int J Gynecol Cancer* May-Jun;2008 18(3):414–20. [PubMed: 17645503]
5. Menon U, Gentry-Maharaj A, Hallett R, Ryan A, Burnell M, Sharma A, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol* Apr;2009 10(4):327–40. [PubMed: 19282241]
6. Partridge E, Kreimer AR, Greenlee RT, Williams C, Xu JL, Church TR, et al. Results from four rounds of ovarian cancer screening in a randomized trial. *Obstet Gynecol* Apr;2009 113(4):775–82. [PubMed: 19305319]
7. van Nagell JR Jr. DePriest PD, Ueland FR, DeSimone CP, Cooper AL, McDonald JM, et al. Ovarian cancer screening with annual transvaginal sonography: findings of 25,000 women screened. *Cancer* May 1;2007 109(9):1887–96. [PubMed: 17373668]
8. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials* Dec; 2000 21(6 Suppl):273S–309S. [PubMed: 11189684]
9. Zalel Y, Lurie S, Beyth Y, Goldberger S, Tepper R. Is it necessary to perform a prophylactic oophorectomy during hysterectomy? *Eur J Obstet Gynecol Reprod Biol* May;1997 73(1):67–70. [PubMed: 9175692]
10. Holub Z, Jandourek M, Jabor A, Kliment L, Wagnerova M. Does hysterectomy without salpingo-oophorectomy influence the reoperation rate for adnexal pathology? A retrospective study. *Clin Exp Obstet Gynecol* 2000;27(2):109–12. [PubMed: 10968347]
11. Plockinger B, Kolbl H. Development of ovarian pathology after hysterectomy without oophorectomy. *J Am Coll Surg* Jun;1994 178(6):581–5. [PubMed: 8193751]
12. Sherman ME, Lacey JV, Buys SS, Reding DJ, Berg CD, Williams C, et al. Ovarian volume: determinants and associations with cancer among postmenopausal women. *Cancer Epidemiol Biomarkers Prev* Aug;2006 15(8):1550–4. [PubMed: 16896048]
13. Pavlik EJ, DePriest PD, Gallion HH, Ueland FR, Reedy MB, Kryscio RJ, et al. Ovarian volume related to age. *Gynecol Oncol* Jun;2000 77(3):410–2. [PubMed: 10831351]
14. Vural F, Vural B, Yucesoy I. Reproductive aging and ovarian volume. *Int J Gynaecol Obstet* Oct; 2005 91(1):73–4. [PubMed: 16039657]
15. Bennington JL, Ferguson BR, Haber SL. Incidence and relative frequency of benign and malignant ovarian neoplasms. *Obstet Gynecol* Nov;1968 32(5):627–32. [PubMed: 4316585]

16. Koonings PP, Campbell K, Mishell DR Jr, Grimes DA. Relative frequency of primary ovarian neoplasms: a 10-year review. *Obstet Gynecol Dec*;1989 74(6):921–6. [PubMed: 2685680]
17. Seidman JD, Mehrotra A. Benign ovarian serous tumors: a re-evaluation and proposed reclassification of serous “cystadenomas” and “cystadenofibromas”. *Gynecol Oncol Feb*;2005 96(2):395–401. [PubMed: 15661227]
18. Comerci JT Jr, Licciardi F, Bergh PA, Gregori C, Breen JL. Mature cystic teratoma: a clinicopathologic evaluation of 517 cases and review of the literature. *Obstet Gynecol Jul*;1994 84(1):22–8. [PubMed: 8008317]
19. Killackey MA, Neuwirth RS. Evaluation and management of the pelvic mass: a review of 540 cases. *Obstet Gynecol Mar*;1988 71(3 Pt 1):319–22. [PubMed: 3347414]
20. Gadducci A, Tana R, Cosio S, Genazzani AR. The serum assay of tumour markers in the prognostic evaluation, treatment monitoring and follow-up of patients with cervical cancer: a review of the literature. *Crit Rev Oncol Hematol Apr*;2008 66(1):10–20. [PubMed: 17964182]
21. Chung HH, Kim JW, Park NH, Song YS, Kang SB, Lee HP. Use of preoperative serum CA-125 levels for prediction of lymph node metastasis and prognosis in endometrial cancer. *Acta Obstet Gynecol Scand* 2006;85(12):1501–5. [PubMed: 17260229]
22. Judson K, McCormick C, Vang R, Yemelyanova AV, Wu LS, Bristow RE, et al. Women with undiagnosed colorectal adenocarcinomas presenting with ovarian metastases: clinicopathologic features and comparison with women having known colorectal adenocarcinomas and ovarian involvement. *Int J Gynecol Pathol Apr*;2008 27(2):182–90. [PubMed: 18317225]
23. Lacey JV Jr, Sherman ME, Rush BB, Ronnett BM, Ioffe OB, Duggan MA, et al. Absolute risk of endometrial carcinoma during 20-year follow-up among women with endometrial hyperplasia. *J Clin Oncol Feb* 10;2010 28(5):788–92. [PubMed: 20065186]
24. Seidman JD, Soslow RA, Vang R, Berman JJ, Stoler MH, Sherman ME, et al. Borderline ovarian tumors: diverse contemporary viewpoints on terminology and diagnostic criteria with illustrative images. *Hum Pathol Aug*;2004 35(8):918–33. [PubMed: 15297960]
25. Dorum A, Blom GP, Ekerhovd E, Granberg S. Prevalence and histologic diagnosis of adnexal cysts in postmenopausal women: an autopsy study. *Am J Obstet Gynecol Jan*;2005 192(1):48–54. [PubMed: 15672002]
26. Valentin L, Skoog L, Epstein E. Frequency and type of adnexal lesions in autopsy material from postmenopausal women: ultrasound study with histological correlation. *Ultrasound Obstet Gynecol Sep*;2003 22(3):284–9. [PubMed: 12942502]

Table 1

Number of women with abnormal ovarian cancer screening tests in PLCO.

Description	Overall	CA-125+/TVU+	CA-125+	TVU+
Abnormal ovarian cancer screening test	3387	108	927	2352
Underwent diagnostic procedure and not diagnosed with invasive ovarian, peritoneal, fallopian tube cancer	1125	47	134	944
Pathology report abstracted	540	46	121	373

Table 2
 Characteristics¹ of selected PLCO subjects with a false-positive ovarian cancer screening test.

	Overall N=540	CA-125+/TVU+, N=46	CA-125+ N=121	TVU+ N=373	P-value ²
Age at surgery (years), mean (SD)	64.1 (5.6)	64.8 (6.1)	65.6 (5.4)	63.5 (5.5)	<0.001
Body mass index (kg/m ²), mean (SD)	26.5 (5.0)	25.4 (4.2)	24.8 (4.5)	27.2 (5.1)	<0.001
Race, %					0.586
White, non-Hispanic	93	96	95	92	
Other	7	4	5	8	
Number of live births, %					0.144
0	10	15	7	11	
1-2	32	41	36	30	
3 or more	58	43	58	60	
Family history of ovarian cancer ³ , %	4	0	2	5	0.149
Family history of breast cancer ³ , %	18	14	16	20	0.510
Personal history of breast cancer, %	4	4	7	3	0.100
Prior hysterectomy, %	30	22	14	36	<0.001
History of uterine leiomyoma, %	24	25	22	24	0.916
History of benign ovarian tumor or cyst, %	10	2	5	13	0.010
History of endometriosis, %	7	16	4	7	0.029
Prior oral contraceptive use, %	52	48	47	54	0.274
HRT use, %					0.527
Never	30	35	26	30	
Former	16	9	18	17	
Current	54	57	55	53	
Cigarette smoking, %					0.650
Never	55	57	54	56	
Former	37	37	41	36	
Current	8	7	5	9	

¹ Except for age at surgery, all characteristics were self-reported at enrollment

² Comparing variable distribution by CA-125+/TVU+, CA-125+, or TVU+ false-positive test group.

³History in a first-degree relative.

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Table 3

Histopathologic findings after a false-positive ovarian cancer screening test in PLCO¹.

	Overall N=540	CA-125+/TVU+ N=46	CA-125+ N=121	TVU+ N=373	P-value ²
	%	%	%	%	
No pathologic abnormality	5	2	12	3	<0.001
Ovarian					
<i>Benign neoplastic</i>	45	46	14	55	< 0.001
Serous cystadenoma	28	22	6	35	
Fibroma/thecoma	7	2	5	8	
Mucinous cystadenoma	6	11	0	7	
Teratoma	5	9	1	6	
Borderline ovarian tumor	1	7	0	1	
Brenner tumor	1	0	1	1	
Endometrioid cystadenoma	1	0	1	1	
<i>Non-neoplastic</i>	39	52	37	37	0.130
Simple ovarian cyst	16	24	7	19	
Inclusion cyst	13	15	20	10	
Endometriosis of ovary	6	11	3	6	
Functional cyst	5	7	4	5	
Stromal hyperplasia	1	0	2	1	
Endosalpingiosis	1	0	2	1	
Other	1	2	2	1	
Non-ovarian					
<i>Neoplastic</i>	26	41	36	21	< 0.001
Leiomyoma ³	33	47	36	29	
Cancer	4	2	11	1	
Adenoma	1	4	3	0	
<i>Non-neoplastic</i>	55	46	64	53	0.038
Paratubal cyst	30	15	31	32	
Polyps ³	18	17	22	16	

	Overall N=540	CA-125+/TVU+ N=46	CA-125+ N=121	TVU+ N=373	P-value ²
	%	%	%	%	
Adenomyosis ³	17	11	20	17	
Hydrosalpinx	6	7	3	6	
Endometrial hyperplasia ³	6	8	10	4	
Endosalpingosis	1	7	1	1	
Endometriosis	1	4	2	1	
Simple cyst	1	0	0	2	
Other	5	4	10	3	

¹ Cells display the percentage of women with each type of diagnosis. Some women had multiple diagnoses.

² Comparing percentage of women with neoplastic ovarian, non-neoplastic ovarian, neoplastic non-ovarian and non-neoplastic non-ovarian diagnoses by CA-125+/TVU+, CA-125+, or TVU+ false-positive test group.

³ Denominator does not include women who reported previous hysterectomy (n = 160).

Table 4

Screening results for non-ovarian cancers.

	CA-125+/TVU+	CA-125+	TVU+
	N	N	N
Type of cancer			
Endometrial	1	10	4
Colon	0	0	1
Cervical	0	1	0
Unspecified adenocarcinoma	0	2	0