Published in final edited form as:

Obstet Gynecol. 2013 January ; 121(1): 25–31.

Assessing the Risk of Ovarian Malignancy in Asymptomatic Women With Abnormal CA 125 and Transvaginal Ultrasound in the Prostate, Lung, Colorectal, and Ovarian Screening Trial

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Abstract

Objective—To estimate the risk of ovarian malignancy among asymptomatic women with abnormal transvaginal ultrasound or CA 125 and to provide guidance to physicians managing these women.

Methods—A cohort of women from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial with abnormal ovarian results at the initial (T0) and subsequent (T1+) screens were analyzed to estimate which findings were associated with high risk of ovarian cancer. Risks of cancer of greater than 10% were designated as high and risks of 3% or less as low.

Results—For the T0 screen, two high-risk categories were identified: CA 125 of 70 or more with negative transvaginal ultrasound (positive predictive value [PPV] 15.9%, CI 14.7%–17.7%); and positive for both CA 125 and transvaginal ultrasound (PPV 25.0%, CI 23.3%–27.3%). For T1+ screens, three high-risk categories were identified: negative transvaginal ultrasound with change in CA 125 greater than 45 or more (PPV 29.0%, CI 28.3%–30.3%); increase in size of cyst 6 cm or greater with negative CA 125 (PPV 13.3%, CI 10.5%–18.0%); and positive for both tests (PPV 42.9%, CI 40.0%–46.0%). High-risk criteria for T0 provide a sensitivity of 60%, specificity 96.2%, PPV 19.7%, and a negative predictive value (NPV) of 99.3%. T1+ criteria yielded a sensitivity of 85.3%, specificity 95.6%, PPV 29.6% and NPV 99.7%.

Conclusions—High risk categories for predicting risk of cancer in women with abnormal CA 125, TVU or both at initial and subsequent screens have been identified. The large number of women in this study, the four year complete follow-up, and very small number of invasive cancers in the low risk categories provides guidance for clinical decisions regarding need for surgery in these women.

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Financial Disclosure: The authors did not report any potential conflicts of interest.

Introduction

Carcinoma of the ovary is the leading cause of death from gynecologic malignancies. Over 21,900 women in the US will develop ovarian cancer annually and 15,460 will die [1]. This high case-fatality rate is largely attributable to the fact that most ovarian cancer is diagnosed in an advanced stage. Because of improved survival in women with early stage cancer, there has been interest in early detection by screening asymptomatic women.

A major problem in screening for a disease with a low prevalence, such as ovarian cancer, is false-positive results. A particular problem for ovarian cancer is that evaluation of an abnormal screen includes, in many cases, an operative procedure for definitive diagnosis. The dilemma in an asymptomatic woman with an abnormal test is two-fold. First, distinguishing between a benign and malignant condition is important in order to avoid surgery in women with benign, asymptomatic conditions. Second, if malignancy is suspected, referral to surgeons with specialized training and/or experience in the operative management of this disease is possible.

In order to evaluate the efficacy of screening for ovarian cancer (as well as prostate, lung and colorectal cancers), the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was initiated in 1992. For ovary the PLCO trial has the following objective: to determine in healthy women aged 55–74 at entry whether screening with CA 125 and transvaginal ultrasound can reduce mortality from ovarian cancer [2]. Results of the initial and subsequent screens and the effect on mortality have been published [3–5]. The primary analysis randomized 34,253 women to undergo screening (intervention) and 34,304 to not undergo screening (usual care). Ovarian cancer was diagnosed in 212 women in the intervention group and 176 in the usual care group. (Rate Ratio [RR]; 1.21; 95% CI 0.99–1.48). There were 118 deaths caused by ovarian cancer in the intervention group and 100 deaths in the usual care group (mortality RR 1.18; 95% CI 0.82–1.71). Of 3285 women with false positive results 1080 underwent surgical follow up; 163 of these women (15%) (95% CI .14.99%–15.22%) experienced at least 1 serious complication, but no known surgically related deaths were recorded. The conclusions were that simultaneous screening with CA 125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality, and that diagnostic evaluation following a false-positive screening test result was associated with complications [5]. Despite this, it is likely that CA 125 and transvaginal ultrasound will continue to be used by some practitioners until dissemination of this information is fully integrated into practice and until other trials of ovarian cancer are completed. In the PLCO trial, the participant's primary physician was responsible for follow up diagnostic tests including need for referral and/or surgical intervention. No specific guidance was provided. As these women were asymptomatic, the low rate of cancer implies that a substantial number of surgeries may have been unnecessary.

The purpose of this study is to estimate the risk of ovarian malignancy among asymptomatic postmenopausal women with abnormal findings on screening tests at initial or subsequent screening years. To provide physicians with some guidance for managing women in this situation, an additional goal is to estimate the risk using clinically relevant thresholds for surgery.

Methods

Design of the PLCO Trial has been described in detail elsewhere [2]. All study sites for the trial obtained IRB approval. In the PLCO trial, a positive screen for ovarian cancer was defined as CA 125 > 35 U/ml; or a transvaginal ultrasound showing ovarian or cyst volume >10 cm³, or solid areas, papillary projections, or mixed components within a cystic ovarian

tumor of any size. The study population for this analysis included women who had both the ovarian screening tests, and had an abnormal screening result for at least one.

The study evaluated the relationship of personal, demographic, and screening result characteristics with ovarian cancer detection, defined as a cancer discovered within two years of a positive screen. Because of the inherent differences in the risk of cancer detection between the baseline (T0) screen and the subsequent annual screens (T1+), analyses were conducted separately. The following characteristics were evaluated as potential correlates of cancer after a positive T0 screen: age, race, family history of ovarian cancer, personal or family history of breast cancer, CA 125 level, maximum ovary or cyst diameter, presence of mixed, irregular, or papillary features, or a solid mass. The analysis of positive screens at T1+ considered these, in addition to the change in CA 125 level and the change in ovary or cyst size from the previous screen.

We constructed distribution tables for each of the characteristics evaluated at initial and subsequent screens (Table 1), including the number and proportion of participants in each classification, the number and proportion with surgical follow-up, and the number and proportion with cancer. Exact confidence intervals (95%) were determined for the estimated probability of cancer detection in each of the characteristic classifications, using the the Clopper-Pearson method. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for malignancy among women with a positive screen were calculated using standard methods. [6]

The underlying principle for this analysis was to employ clinically relevant thresholds to distinguish between high and low risk for cancer. It was first suggested by Jacobs [7] and generally accepted that a rate of one cancer detected for every 10 surgeries would be an acceptable PPV for an ovarian cancer screen. A model for surgical intervention that could, within a reasonable degree of accuracy, have a PPV of 10% or greater and a corresponding NPV of 97% or greater, would be clinically useful. We have designated risks of malignancy of 10% or more as high. Also, from a clinical point of view, a risk of cancer of less than 3% may not warrant surgical intervention but close observation instead, particularly if the patient has co-morbidities and given the 15% surgical complication rate in the PLCO trial false positives. We designated a risk of malignancy of 3% or less as low. For categories of patients where the estimated probability of detecting a malignancy falls between 3% and 10%, or when data limitations leave confidence limits overlapping into this range, we have considered the risk of malignancy as *uncertain*.

Results

39,105 women were randomized to the intervention arm. Women who had their first abnormal suspicious screen and received both tests in that same year, and had at least two years of follow-up are included. 3,224 women met these criteria (Figure 1). 1611 women had an abnormal result at the T0 screen, 543 underwent surgical intervention and 25 invasive cancers were detected. During the T1+ screening years, 1,613 additional women had an abnormal result. Of these, 329 underwent surgical evaluation and 34 additional invasive cancers were detected. None of the 34 women who were detected with cancer in the T1+ screen had positive screens at T0. Five of these women had abnormal non-suspicious transvaginal ultrasounds at T0 and 3 women did not have CA 125 done at T0. The overall probability of cancer detection following an abnormal screen was 1.6% (CI 0.9–2.2) at T0 and 2.1% (CI 1.4–2.8) during T1+.

Table 2 shows an analysis of the relationship of size and morphology of abnormalities found on transvaginal ultrasound to the positive prediction of cancer at T0. If no solid or mixed,

irregular, or papillary components are present, the risk of cancer is low, independent of the size of the abnormality. Similarly, a cyst less than 5 cm has a low risk of being cancer regardless of the morphology. However, a cyst of 5 cm or more with mixed, papillary or irregular components places a woman at uncertain risk. Size and morphology alone do not identify a high risk category.

Predictive values for the combination of CA 125 level and transvaginal ultrasound status are shown in Table 3. If the transvaginal ultrasound is negative, a CA 125 <60 falls in the range of low risk (0.0% CI 0.0%–0.3%), 60–70 is uncertain risk (4.6% CI 2.9%–7.9%), and over 70 is high risk (15.9% CI 14.7%–17.7%). A positive transvaginal ultrasound with a negative CA 125 is low risk (0.7% CI 0.7%–0.8%). A combination of abnormal transvaginal ultrasound and abnormal CA 125 is high risk (25.0% CI 23.3–27.3%).

During T1+ we were able to compare current to previous ovarian/cyst size and CA 125 levels. Table 4 compares transvaginal ultrasound and CA 125 change. As in T0, the combination of abnormal results for both CA 125 and transvaginal ultrasound predicts a high risk for cancer (42.9%, CI 40.9%–46.0%). With a negative transvaginal ultrasound, the magnitude in change in CA 125 is predictive. A change of 25 or less predicts a low risk (0.3% CI 0.2%–0.5%) while a change of 45 or more predicts a high risk (29.0% CI 28.3%–30.3%). A change of 25–45 was low for risk for cancer (1.7% CI 1.4%–2.4%). If the transvaginal ultrasound is positive, increases in CA 125 may indicate an elevated risk for ovarian cancer even when the CA 125 remains normal (<35). In this situation, an increase of >10 trends toward a high risk (10.0% CI 7.9%–13.9%), although lower limit of CI is less than 10%. A CA 125 change <10 predicts a low probability of cancer (0.2% CI 0.15%–0.3%).

Table 5 takes into account changes in cyst or ovarian size in women with abnormal transvaginal ultrasound, but normal CA 125. A change in size of 6 cm or greater suggests the possibility of high risk (13.3% CI 10.5%–18.0%) whereas a change in size <6 cm is low risk.

For T0, using the high risk criteria of transvaginal ultrasound negative with a CA 125 of 70, or a CA 125 and a transvaginal ultrasound positive, the sensitivity for detection of cancer within the PLCO data is 60%, the specificity is 96.2%, PPV is 19.7% and NPV is 99.3%.

For T1+ using three high-risk criteria – transvaginal ultrasound-negative with a change in CA 125 > 45; CA 125 negative, but a change in diameter of ≥ 6 cm; or both CA 125 and transvaginal ultrasound-positive – the sensitivity for detection of cancer within the PLCO data is 85.3%, specificity 95.6%, PPV 29.6% and NPV 99.7%.

Discussion

The PLCO trial demonstrated that screening for ovarian cancer using simultaneous CA 125 and transvaginal ultrasound did not reduce ovarian cancer mortality and was associated with complications following diagnostic evaluation of false-positive screens. [5] Despite this, it is likely that these tests will continue to be recommended because of slow dissemination of findings and/or resistance to incorporate into practice for various reasons. [8]

A screening recommendation for disease with a low prevalence can be problematic because of high false-positive tests. In the PLCO trial of 3285 women with false positive results 1080 underwent surgery (32.9%) as part of diagnostic workup. Among these 1080 women, there were 20.6 complications per 100 surgical procedures [5]

We reviewed screening and follow-up results from the first three years of the PLCO trial to provide some guidance to physicians faced with an abnormal CA 125 and/or transvaginal ultrasound in asymptomatic women. We set arbitrary but clinically meaningful thresholds of cancer risk, with 3% or less being low, 10% or more being high, and between 3 and 10% as uncertain. Women who can confidently be placed in a low risk category could be followed with repeat testing, and surgery avoided especially with a 15% serious complication risk from surgery for false positives. On the other hand, women confidently placed in a high risk category should be considered for surgery unless major co-morbidities preclude. Those in the uncertain category or those whose confidence intervals cross risk categories are more problematic and require physician judgment and an informed patient. While our study cannot definitively estimate the cancer risk in other populations of women, we believe the empirical assessment of risk in this large population of asymptomatic women age 55 and older may provide some useful insights and potentially avoid unnecessary surgery in women inappropriately screened.

Because of the importance of distinguishing benign from malignant conditions in women, a number of scoring systems have been developed to evaluate adnexal masses. These have included systems that incorporate combined information or data from multiple sources such as imaging, risk factors, laboratory data and physician assessment [7,9–16]

A common scoring system is the Risk of Malignancy Index (RMI) [17] that incorporates a clinical prediction rule based on ultrasound, CA 125, and menopausal status. This system reported a sensitivity of 85% and specificity of 97% in a population of 143 women undergoing surgical exploration for an adnexal mass. Subsequent studies [18–20] have reported similar performance while others have failed to equal this performance [21–24]. Several more recent studies have provided guidelines for assessment of adnexal masses for risk of malignancy. Dearking, et al, evaluated the guidelines published by the American College of Surgeons and Society of Gynecologic Oncologists for referral of adnexal masses and noted these perform well in advanced stage disease, especially in premenopausal women [13]. The group from the University of Kentucky has most recently proposed a multivariate index assay that performed better compared to CA 125 and physician assessment [14] and also enhanced the ACOG guidelines for referral when the multivariate index assay replaced CA 125 in the guidelines [15]. However the relevance of these studies to asymptomatic women undergoing screening with CA 125 and transvaginal ultrasound versus evaluation of an adnexal mass is unclear.

This study evaluated criteria to distinguish benign from malignant disease among asymptomatic postmenopausal women who have abnormal transvaginal ultrasound and/or CA 125 as a result of screening. It is important to determine the risk of malignancy to potentially avoid surgery in an asymptomatic woman and to refer appropriately if there is a suspicion of malignancy. No scoring system to determine risk of malignancy has been developed and validated in an exclusively postmenopausal asymptomatic population.

We have shown that it may be possible to establish criteria based on screening test results that could reduce the number of arguably unnecessary surgeries while still remaining sensitive to cancer discovery. However, conclusions from this descriptive analysis are not definitive, and specific data points should be interpreted with caution. For example, the categorization of covariate data in this analysis to reflect low and high risk (e.g., CA 125 <60 and >70, respectively) was empirical, and predictive values observed in these data will likely be overly optimistic when applied in a new population. Even in this large clinical trial, there was limited precision for estimating risk, and identifying optimal cut points in risk, for many of the categories with small numbers of ovarian cancer cases. We therefore strongly

encourage validation and refinement of these results in other populations of postmenopausal women.

However, the large number of women in this study, the four-year complete follow-up and the very small percentage of invasive cancers discovered among the low risk categories should provide some guidance for clinical decisions regarding the need for surgery in asymptomatic postmenopausal women with abnormal findings on CA 125 and/or transvaginal ultrasound. It should be emphasized in conclusion that the use of combination CA 125 and transvaginal ultrasound in asymptomatic women to screen for ovarian cancer using the protocol employed in the PLCO trial does not reduce mortality, does have associated harms, and should not be recommended.

Acknowledgments

The National Cancer Institute funded the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. This research also was supported by contracts from the Division of Cancer Prevention of the National Cancer Institute and by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics National Cancer Institute, National Institutes of Health, Department of Health and Human Services NIH – NO1-CN-75022 and NCI – NO1-CA-75022-70).

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Figure 1.

Flow of patients through the ovarian intervention arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

Distribution of CA 125 Levels at Initial Screen

Table 1

		T0			
		Cancer			
		No		Yes	
		n	%	n	%
Risk (CA-125 Result)					
	<i>Low</i>				
	35–40	114	100	.	.
	40–45	66	100	.	.
	45–50	49	100	.	.
	50–55	27	100	.	.
	55–60	17	100	.	.
<i>Int.</i>	-Subtotal-	273	100	.	.
	60–65	11	100	.	.
	65–70	10	91	1	9.1
	-Subtotal-	21	95	1	4.5
	70–75	4	100	.	.
<i>High</i>	75–80	4	80	1	20
	80–95	6	75	2	25
	95–120	7	100	.	.
	120–150	7	100	.	.
	150–200	4	100	.	.
	200–300	3	100	.	.
	300–500	2	67	1	33
	500+	.	.	3	100
	-Subtotal-	37	84	7	16
	<i>Total</i>	331	98	8	2.4

Table 2

Risk of Cancer at Initial Screen Based on Size and Morphology

		Maximum Ovary or Cyst Diameter								
		0–5 cm			5–7 cm			7+ cm		
		None	Solid	Mixed, Irregular, or Papillary	None	Solid	Mixed, Irregular, or Papillary	None	Solid	Mixed, Irregular, or Papillary
70	Positive screen	537	149	248	153	15	66	56	13	35
	Had surgery	160	39	88	82	9	47	46	11	30
	Percentage of positive with surgery	29.80	26.17	35.48	53.59	60.00	71.21	82.14	84.62	85.71
	Had Cancer	5	4	3	0	0	2	0	1	2
	Percentage of positive with cancer (PPV)	0.93 (CI 0.8–1.1)	2.68 (CI 2.4–3.2)	1.21 (CI 1.0–1.5)	0.00 (CI 0.00–0.50)	0.00 (CI 0.00–4.8)	3.03 (CI 2.4–4.2)	0.00 (CI 0.00–1.3)	7.69 (CI 4.8–13.1)	5.71 (CI 4.5–7.8)
	Percentage of surgery with cancer	3.13	10.26	3.41	0.00	0.00	4.26	0.00	9.09	6.67

CI, confidence interval; PPV, positive predictive value.

Table 3

Risk of Cancer at Initial Screen Based on CA 125 and Transvaginal Ultrasound

	CA-125+ Transvaginal Ultrasound-			CA-125- Transvaginal Ultrasound+	Transvaginal Ultrasound +	Total
	CA-125 35-60	CA-125 60-70	CA-125 70+			
<i>Positive screen</i>	273	22	44		CA-125+ 32	1611
<i>Had surgery</i>	13	3	15		26	543
<i>Percentage of positive with surgery</i>	4.76	13.64	34.09		81.25	33.71
<i>Had cancer</i>	0	1	7		8	25
<i>Percentage of positive with cancer (PPV) --</i>	0.00 (CI 0.00-0.30)	4.55 (CI 2.9-7.9)	15.91 (CI 14.7-17.7)	0.73 (CI 0.7-1.8)	25.00 (CI 23.3-27.3)	1.55 (CI 1.5-1.6)
<i>Percentage of surgery with cancer</i>	0.00	33.33	46.67	1.85	30.77	4.60

Table 4
Risk of Cancer in Subsequent Screens Based on CA 125 and Transvaginal Ultrasound

	CA-125+ Transvaginal Ultrasound–			CA 125– Transvaginal Ultrasound+		Transvaginal Ultrasound+	Total
	CA 125 Difference ≤25	CA 125 Difference 25–45	CA 125 Difference >45	CA 125 Difference ≤10	CA 125 Difference 10–25		
<i>Positive screen</i>	331	115	62	1064	20	21	1613
<i>Had surgery</i>	29	16	25	240	8	11	329
<i>Percentage of positive with surgery</i>	8.76	13.91	40.32	22.56	40.00	52.38	20.40
<i>Had cancer</i>	1	2	18	2	2	9	34
<i>Percentage of positive with cancer (PPV)</i>	0.30 (CI 0.2–0.5)	1.74 (CI 1.4–2.4)	29.03 (CI 28.3–30.3)	0.19 (CI 0.15–0.3)	10.00 (CI 7.9–13.6)	42.86 (CI 40.0–46.0)	2.11 (CI 2.1–2.2)
<i>Percentage of surgery with cancer</i>	3.45	12.50	72.00	0.83	25.00	81.82	10.33

Table 5

Risk of Cancer in Subsequent Screens Based on Change in Cyst or Ovary Size

	CA 125- Transvaginal Ultrasound+			transvaginal ultrasound +	Total
	Maximum Difference < 3	Maximum Difference 3-6	Maximum Difference >=6		
<i>Positive screen</i>	955	114	15	CA 125+ 21	1105
<i>Had surgery</i>	197	38	13	11	259
<i>Percentage of positive with surgery</i>	20.63	33.33	86.67	52.38	23.44
<i>Had cancer</i>	1	1	2	9	13
<i>Percentage of positive with cancer (PPV)</i>	0.10 (CI 0.07-0.2)	0.88 (0.6-1.5)	13.33 (CI 10.5-18.0)	42.86 (CI 40.0-46.0)	1.18 (CI 1.1-1.3)
<i>Percentage of surgery with cancer</i>	0.51	2.63	15.38	81.82	5.02