Examining the Effects of Time to Diagnosis, Income, Symptoms, and Incidental Detection on Overall Survival in Epithelial Ovarian Cancer

Manitoba Ovarian Cancer Outcomes (MOCO) Study Group

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Objective: The primary objectives of this study were to analyze data on time to diagnosis and correlate this with overall survival. We secondarily analyzed the effects of emergency room visits, symptoms, incidental findings, residence, socioeconomic status, and residual disease on overall survival.

Methods: This retrospective population-based descriptive cohort study examined all invasive ovarian cancer cases in Manitoba, Canada, between 2004 and 2010. Clinicopathologic, socioeconomic, and outcome data were collected. Analysis was performed with Cox and logistic regression stratified by early and late stage.

Results: Six hundred eighty-seven ovarian cancer patients were identified, with a final cohort of 601 patients: 210 with early-stage (1/2) and 391 with late-stage (3/4) disease. No presenting symptoms were associated with survival outcome. Poorer survival was associated with increasing age ($P = 0.0016$) and neoadjuvant chemotherapy ($P = 0.0037$). Higher income within the urban setting was also associated with a survival advantage ($P = 0.0037$), whereas initial presentation to the emergency room ($P = 0.0399$) was associated with decreased survival. Finally, for advanced-stage disease, incidental diagnosis had a significantly improved overall survival (hazard ratio, 0.424; 95% confidence interval, 0.27–0.67; $P = 0.0003$), even when accounting for confounding factors. Time from first presentation to diagnosis was associated with survival ($P = 0.0309$).

Conclusions: This study found that time to diagnosis did not negatively impact overall survival, although there was an association. Age, morphology, treatment type, residual disease, medical comorbidities, and income were significant prognostic factors. This is the first study to show a survival advantage to incidentally finding an ovarian cancer. Further research is needed on the outcomes of pelvic examination.

Key Words: Incidental finding, Ovarian cancer, Overall survival, Time to diagnosis

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Epithelial ovarian cancer (EOC) continues to be the most lethal gynecologic malignancy worldwide.[1,2] Although most women are diagnosed as having EOC at advanced stage, early disease has a good prognosis[1,3] leading to screening studies,[4–7] early symptomatic investigations,[8] and symptom based-algorithms.[9,10] None have yet proven useful for improving survival.

Ovarian cancer has been considered a "silent" killer. Goff et al[9,10] showed that 70% of patients had stage 3 to 4 disease, and 95% had symptoms prior to diagnosis. Many cancer societies have advocated prompt assessment for "ovarian cancer"–like symptoms, in the hopes of improved outcomes. The DOvE trial[8] investigated this theory and assessed women with early symptoms by ultrasound and CA-125. They found no change in stage distribution.

Several studies have looked at the effects of time to diagnosis. For example, Lim et al[11] used questionnaires and medical records to determine diagnostic times. They found no differences in time to presentation or diagnosis; however, no survival analysis was performed.[11] Nagle et al[12] used an interview model and correlated this to overall survival; similarly, they did not find any association with time to diagnosis. No study has correlated time to diagnosis based on medical record data to overall survival.

In asymptomatic women, detection is even more difficult. Several screening studies have been performed in large populations.[4–7] All of these studies have resulted in poor predictive values, no changes in stage distribution, and limited effects on survival, balanced with increased surgical harm and large costs. Routine pelvic examinations have been recently brought into question by multiple societies with opposing recommendations.[13–18]

We hypothesize that a longer diagnostic period would be associated with a decreased survival time. Our study analyzes the data from Manitoba, Canada, on the time to diagnosis from presentation of any symptom that may be related to EOC as determined retrospectively from provincial medical records. We then correlate the wait times with overall survival and control for relevant variables. The effects of emergency room (ER) visits, incidental findings, symptoms, residence, socioeconomic status, and residual disease were also evaluated.

METHODS

Data Sources

Invasive ovarian cancer cases diagnosed between January 1, 2004, and December 31, 2010, were identified through the Manitoba Cancer Registry; the morphologies of sex cord and germ cell were excluded. Data extracted from the registry included record type (chart or report only; "chart" patients are patients who are referred to CancerCare Manitoba and have their medical information forwarded, and "report only" patients are patients who are not referred to CancerCare Manitoba), morphology codes, age at diagnosis, American Joint Committee on Cancer (AJCC) staging, postal code, treatment information, and death date. Postal codes were used to identify residence at diagnosis and converted into income quintiles.[19] Data extracted from CancerCare charts included physician encounters, diagnostic procedures, and additional treatment information. Physician notes from encounters included symptom information, which identified when ovarian cancer could first be suspected, and the type of physician at each encounter. American Joint Committee on Cancer staging was the standard staging used in the ovarian registry and matches directly to the FIGO (International Federation of Gynecology and Obstetrics) staging.

Administrative data from Manitoba Health (Physician Claims and Hospital data) were also included. They were used to confirm the physician encounter date for the physician encounter where ovarian cancer was suspected using a standard set of signs/symptoms; the individual physician clinical records were not reviewed. The administrative data were also used to create a measure of comorbidity using the Johns Hopkins ACG System (version 11.0). Date of first presentation was recorded as first point of contact with any health care provider with any symptoms that may have been related to EOC or an incidental finding of EOC (eg, bloating, abdominal pain, change in bowel habit, nausea). Date of diagnosis was defined as evidence of cancer from cytology, imaging, CA-125, or histology. Date of referral encounter was recorded as the initial gynecology-obstetrics appointment. Diagnostic interval was defined as the time from date of first presentation to diagnosis.[20,21]

Analyses

Analyses were performed on 601 ovarian cancer cases that had chart information available. Descriptive statistics for the cohort were calculated. Overall survival after diagnosis was analyzed using time-varying Cox regression models. Predictors included age at diagnosis, AJCC stage at diagnosis, morphology, residence, income, and symptoms at first presentation. Symptoms included abdominal pain, abdominal distension, incidental finding (eg, asymptomatic and discovered through "annual" physical examination or imaging for unrelated condition), bowel symptoms, nausea, decreased appetite, respiratory symptoms, weight change, urinary symptoms, abnormal bleeding, postmenopausal bleeding, palpable mass, weakness, and vomiting. A measure of comorbidity (resource utilization band) was also included, where individuals are grouped by their utilization of the medical system, versus examination based on a specific disease process. Other predictors included whether the gynecologic oncologist encounter was seen before or after first treatment, whether symptoms first presented in the ER, time from first presentation to diagnosis, and treatment.

The predictors of gynecologic oncologist encounter and treatment were time varying, to account for their changing status after and before diagnosis. Survival analyses were stratified by early- and late-stage cancer, because of the large heterogeneity between those groups and the strong relationship between stage and treatment. December 31, 2014, was considered the end-of-study date. Survival was measured as either a death recorded prior to, or on, the end-of-study date, or the individual was censored at the last physician encounter or end-of-study date. Missing residual tumor data were assumed to be missing at random. The mice package in R was used to produce 20 imputations. Imputations were verified by comparing the distributions of observed and imputed data conditional on propensity score.[22] Residual tumor was included in the multivariable model in patients with late-stage disease by splitting the surgery categories into 0 cm, less than 1 cm, and 1 cm or greater.

Analyses were conducted using R version 3.2.1. The rms package was used for time-varying Cox regression models. Restricted cubic splines were used for continuous predictors that violated the assumption of linearity. Predicted values from restricted cubic splines adjusted for other covariates at their mean were plotted. The proportional hazard assumption was evaluated using Schoenfeld residuals. Other diagnostics were performed using residual and influence plots. Likelihood ratio testing was used for model building.

Multinomial logistic regression was used to predict residual disease. Predictors included time to diagnosis, ER visit, incidental finding, and neoadjuvant chemotherapy. The approach suggested by Duffy et al[23] was used to adjust for lead time bias for significant results of incidental findings. This approach requires an estimate of the sojourn time for ovarian cancer (the time where the tumor is asymptomatic but surveillance detectable).

RESULTS

Six hundred eighty-seven ovarian cancer patients were identified in the Registry of CancerCare Manitoba. Eighty-six patients who were not seen in CancerCare Manitoba were excluded. This provided a final cohort of 601 patients for analysis. Only 9% of the 601 patients were initially "diagnosed" as having ovarian cancer with either imaging or CA-125, 78% of the entire cohort was eventually confirmed by histology, and 93% were confirmed by either cytology or histology.

Descriptive statistics for the final cohort by stage are included in Tables 1 and 2. Two hundred ten patients (34.9%) were diagnosed as having early-stage disease, and 391 patients (65.1%) were diagnosed as having late-stage disease. Figure 1 includes a Kaplan-Meier curve plot of the cohort by stage. Those with an unknown AJCC stage had a survival pattern similar to stages III and IV and were assumed to be patients with late-stage disease. None of the presenting symptoms, including abdominal pain, distension, bowel symptoms, nausea, decreased appetite, respiratory symptoms, weight changes, urinary symptoms, abnormal bleeding, postmenopausal bleeding, palpable mass, weakness, or vomiting, were significantly associated with survival; all symptoms were considered equal importance. More than 80% of patients received the diagnosis within 4 months; the median diagnostic intervals are listed in Table 2.

Univariable and multivariable models were analyzed for all variables; only multivariate results were reported here. All analyses were also performed for time to treatment and were parallel to the time-to-diagnosis results and therefore not presented.

In agreement with other studies when looking at results for patients with early-stage disease, only age at diagnosis, residual tumor status, and treatment were significant predictors in the multivariable model (Appendix 1, http://links.lww.com/IGC/xxx): survival decreased as age increased (hazard ratio [HR], 2.133, 95% confidence interval [CI],1.69–2.69; $P < 0.0001$); and survival was lower for patients receiving neoadjuvant chemotherapy compared with adjuvant chemotherapy (HR, 3.696; 95% CI, 1.62–8.44; $P = 0.0019$). Residual tumor of greater than 1 cm had a significantly worse survival than tumors of less than 1 cm or microscopic disease (HR, 5.137; 95% CI, 2.09–12.63; $P < 0.0001$).

For patients with late-stage disease, analysis showed that age was significantly related to survival, with survival decreasing until about age 40 years and then decreasing further after age 70 years ($P = 0.0016$). Morphology was significantly related to survival, with serous carcinoma and clear cell/endometrioid demonstrating significantly higher survival than unclassified epithelial (HR, 0.698 [95% CI, 0.52–0.93; $P = 0.0131$] and 0.423 [95% CI, 0.22–0.83]; $P = 0.0120$, respectively). Neoadjuvant chemotherapy was related to significantly lower survival than adjuvant chemotherapy (HR, 1.633; 95% CI, 1.17–2.28; $P = 0.0037$). Higher income was significantly related to better survival, but only for urban areas (HR, 0.614 [95% CI, 0.44–0.85; $P = 0.0037$] for urban patients and 0.948 [95% CI, 0.65–1.37; $P = 0.7794$] for rural patients). Patients with comorbidities requiring more health resources had significantly lower survival (HR, 1.382; 95% CI, 1.09–1.74; $P = 0.0066$). Patients first presenting symptoms in the ER had significantly lower survival (HR, 1.348; 95% CI, 1.01–1.79; $P = 0.0399$). Time to diagnosis was significantly related to survival (Figure 2; $P = 0.0309$): survival increased between the time of immediate diagnosis to approximately 80 days, and then survival decreased with further time between first presentation and diagnosis (Appendix 2). Predicted 5-year survival for time to diagnosis was 10.8% for 7 days (25th percentile), whereas it was 15.6% for 76 days (75th percentile) while adjusted for covariates at their mean. Grouping histotypes into types I and II ovarian cancers did not provide a better model fit than analyzing individual histotypes.

Our study also identified 67 patients who were diagnosed incidentally. Incidental findings were related to significantly higher survival in patients with late-stage disease (HR, 0.424; 95% CI, 0.27–0.67; $P = 0.0003$) (Appendix 2, http://links.lww.com/IGC/xxx). A similar result was not detected for early-stage disease ($P = 0.5574$) (Appendix 1, http://links.lww.com/IGC/xxx). This advantage was maintained using multivariable analysis accounting for stage, histology, residual disease, age, treatment type, and medical comorbidities. Within this group, 33.3% received the diagnosis based on unrelated imaging (eg, kidney stones, hip fracture) and 66.6% on physical findings, with 36.4% detected on annual/routine physical examination. When

TABLE 1. Baseline characteristics and demographics of patients (n = 601)

	Stage			
	I/II		III/IV/Unknown	
	(n = 210)		(n = 391)	
Variable	**n**	**%**	**n**	**%**
Age, y				
Mean (SD)	59	14	66	14
Stage				
I	137	65	0	0
II	73	35	0	0
III	0	0	200	51
IV	0	0	120	31
Unknown	0	0	71	18
Morphology				
Serous carcinoma	64	30	159	41
Unclassified epithelial	24	11	145	37
Clear cell	23	11	13	3
Endometrioid	41	20	<6	<2%
Mucinous	39	19	9	2
Other	19	9	60	15
Residence				
Urban	126	60	219	56
Rural	84	40	172	44
Treatment				
No treatment	7	3	50	13
Chemotherapy only	9	4	97	24.81
Neoadjuvant chemo	9	4	108	28
Primary debulking + adjuvant	137	65	119	30
Surgery only	48	23	17	4
Residual tumor				
No surgery	16	8	147	38
>1 cm	11	5	105	27
<1 cm	32	15	65	17
0 cm	118	56	55	14
Missing	33	16	19	5
Income				
R1–R3	41	20	96	25
R4–R5	32	15	61	16
U1–U3	82	39	154	39
U4–U5	51	24	73	19
Missing	<6	<2%	7	2

(Continued on next page)

TABLE 1. *(Continued)*

	Stage			
	I/II		III/IV/Unknown	
	(n = 210)		(n = 391)	
Variable	**n**	**%**	**n**	**%**
Comorbidities (Resource utilization band)				
No or only invalid diagnosis	<6	<2%	<6	<2%
Healthy user	0	0	<6	<2%
Low	7	3	14	4
Moderate	147	70	231	59
High	35	17	100	26
Very high	20	10	43	11
Gynecologic-oncologist encounter				
Before first treatment	155	74	271	69
After first treatment	45	21	60	15
Seen, but no treatment	<6	<2%	37	9
Not seen	<6	<2%	23	6
ER				
Yes	40	19	131	34
No	170	81	260	67

1, Poorest; 5, richest; R, rural; U, urban.

adjusting for lead time using a random sojourn time of 1 year, the relationship between incidental findings in late-stage cases and survival was reduced (HR, 0.673; 95% CI, 0.43–1.06; P = 0.0864). It was further reduced when using a random sojourn time of 2.5 years (HR, 0.894; 95% CI, 0.57–1.41; P = 0.6284).

The data were also analyzed for residual disease (0, >1, and <1 cm) as the final outcome for significant variables in early- and late-stage disease, including time to diagnosis, ER visit, incidental finding, and neoadjuvant chemotherapy. None of the results were statistically significant (Appendix 3, http://links.lww.com/IGC/xxx).

DISCUSSION

Many believe that decreasing wait times for diagnosis and treatment of ovarian cancer would improve survival. This has been examined for multiple gynecologic cancers including endometrial,[24,25] cervical,[26,27] and low genital tract,[28]

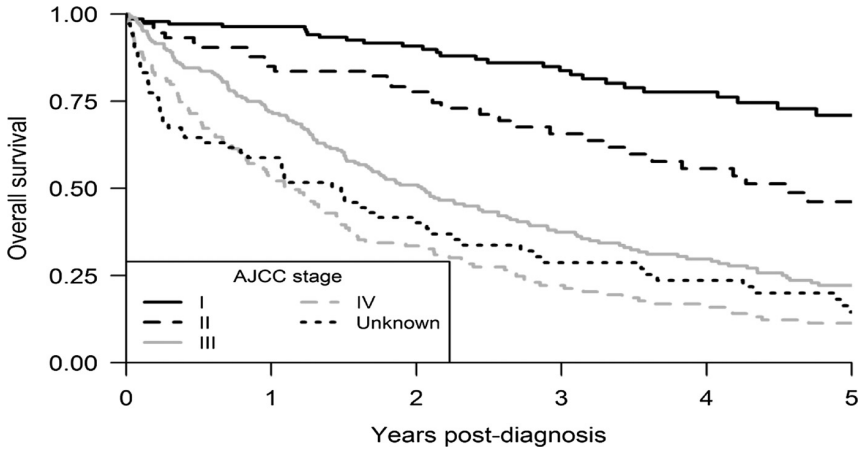

FIGURE 1. Overall survival by AJCC stage.

TABLE 2. Presenting signs/symptoms of patients, death, and follow-up categorized by stage (n = 601)

		Stage			
		I/II		III/IV/Unknown	
		(n = 210)		(n = 391)	
Variable		n	%	n	%
Abdominal pain		74	35.24	161	41.18
Abdominal distension		35	16.67	144	36.83
Incidental		34	16.19	33	8.44
Bowel symptoms		12	5.71	44	11.25
Nausea		6	2.86	37	9.46
Decreased appetite		8	3.81	34	8.70
Respiratory symptoms		<6	<2.5%	35	8.95
Weight change		<6	<2.5%	32	8.18
Urinary symptoms		17	8.10	12	3.07
Abnormal bleeding		17	8.10	13	3.32
Postmenopausal bleeding		14	6.67	16	4.09
Palpable mass by patient		12	5.71	14	3.58
Weakness		8	3.81	17	4.35
Vomiting		<6	<2.5%	20	5.12
Deaths		70		333	
Median diagnostic intervals		77 (29–148)		27 (7–68)	
Follow-up, y	Median (first quartile to third quartile)	3.01 (1.87–4.89)		1.51 (0.53–3.15)	

yet the results remain conflicting throughout gynecologic malignancies and ovarian cancers.

If this declaration were correct, one would expect changes in stage distribution and improvement in survival from screening, yet most studies have shown disappointing results with no changes in stage distribution or survival.[4–7] One might also assume that prompt symptomatic evaluation would lead to earlier detection, as was tested in the DOvE trial.[8] This study assessed 1455 women with early symptoms by ultrasound and CA-125 and found no change in stage distribution. They hypothesized that type I cancers are likely to present in earlier stages and account for most cancers detected early. Early detection in type II cancers has not yet been possible.[8,29]

Several studies have examined time to diagnosis for ovarian cancer. Wikborn et al[2] examined the records of 160 women for initial consult dates; 56% were diagnosed within 4 weeks. Two studies in the United Kingdom did not find that delays in diagnosis were associated with worse survival.[30,31] Lim et al[11] used questionnaires and medical records to determine time from initial symptoms to presentation and diagnosis. The authors found no differences, but no analysis was performed on overall survival.[11] Finally, Nagle et al[12] interviewed 1318 patients to assess time to diagnosis and overall survival. They did not find any association, but did find that incidentally found cancers were more likely to be stage 1 or borderline tumors.[12] To avoid recall/questionnaire bias, as used in previous studies, we used the initial suspicious symptom from patient records to define the time to diagnosis and correlated this to survival.

Our results agree with previous studies, showing that most cancers were diagnosed within 120 days. Similar to Nagle et al,[12] we found that overall survival was not negatively affected by longer time to diagnosis up until 80 days, at which point survival began decreasing with longer diagnostic interval; our

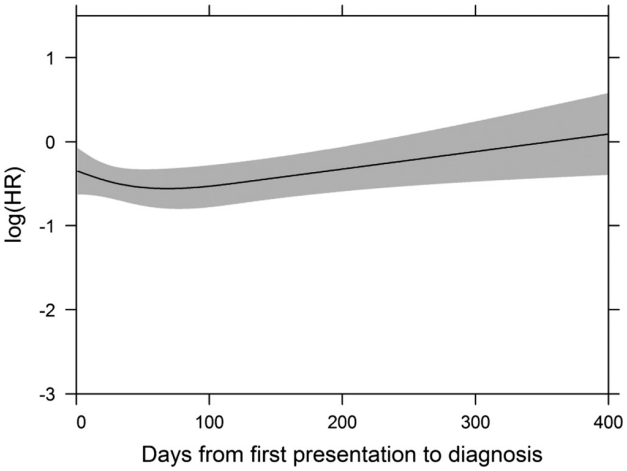

FIGURE 2. Relationship between time to diagnosis and survival in patients with late-stage disease, adjusted for covariates.

statistics were also similar to other data for stage-specific survival.[1,32] We identified that patients who initially presented to the ER had worse overall survival. This is likely due to increased symptoms and aggressive disease and may be associated with long wait times to see primary care practitioners outside the ER. Our study determined that higher urban income conferred a survival advantage for late-stage disease. Whether this relates to patient access, comorbidities, education, or lifestyle requires further investigation.[33] We confirmed that age, morphology, treatment, residual disease, and comorbidities were prognostic factors in late-stage disease for survival, and although these findings are not unique, these analyses validate our database and analysis techniques.

Our study found multiple patients with late-stage disease who had received the diagnosis incidentally with a significant survival benefit. This advantage was maintained on multivariable analysis, even when accounting for stage, grade, histology, and residual disease. One-third of patients with late-stage disease received the diagnosis based on imaging, and two-thirds on physical findings (of which, 36% were detected on physical examination alone). The American College of Obstetrics and Gynecology continues to recommend pelvic examinations,[13] yet the US Preventive Services Task Force and the Canadian Task Force on Preventative Health Care state that there is no evidence of benefit.[14,15] The Society of Obstetrics and Gynecology of Canada states that "The pelvic examination is an integral part of the gynaecological consultation. Competently performing the pelvic examination is an essential skill for all medical professionals."[16] Others argue that annual examinations should be abandoned, but perhaps pelvic examinations with cervical cytology should remain.[17,18] Most of the current recommendations stem from 2 overlapping studies by Padilla et al.[34,35] Both showed that pelvic examinations have limited efficacy; however, increasing experience improved detections rates.[35] Most guidelines recommend pelvic examinations for symptomatic women,[17,18] but none of the policies address the issue of experience and practice; in other words, if experience improves detection rates, then the only way to gain that technical skill is by doing multiple routine normal examinations. Finally, the PLCO (Prostate, Lung, Colorectal and Ovarian) Cancer Screening Trial included bimanual examination in both of its study groups until 1998, when it was abandoned in the screening arm alone. They found a total of 382 ovarian cancers but did not comment on how many were incidentally found in either group, yet claimed that bimanual examination was not useful.[4] Our study is the first study that shows a significant survival advantage to women whose cancer was detected incidentally, even when stage and residual disease are accounted for; however, it may suffer from lead time bias. When including 1-year sojourn time, the predicted 5-year survival was 26.8% for those with incidental findings, and 14.7% for nonincidental findings while adjusted for covariates at their mean. Further study of the utility of pelvic examinations is required before abandoning this practice.

One of the limitations of this study is the inherent problem with accurate collection of data in a retrospective study. Charts may have not captured all appropriate patient characteristics. The study population is heterogeneous, and ethnicity was not recorded. The ability to detect presenting symptoms is certainly limited and difficult to determine from the medical records, as well as challenging to collect for subjective elements such as symptoms. Although we attempted to reduce recall bias by eliminating questionnaires, there is a risk of introducing misclassification bias from this type of study; there may also be a reporting bias on the part of the patient or physician. Finally, power may have been limited because of low numbers and may have affected the power analysis, especially in the "incidental" findings group. We found that the rate of neoadjuvant chemotherapy was 28% and may be considered high for many centres; however, we report on the entire patient population that was served in Manitoba and reflect what was done during the study time frame. We also found that neoadjuvant chemotherapy and residual disease had worse survival for patients with early-stage disease; this result seems unusual; however, we presume that these patients either had suspected advanced-stage disease or were unfit for surgery, resulting in neoadjuvant chemotherapy; by the time they were fit for debulking, their pathological staging was considered only early stage.

This study is the largest population-based study on time to diagnosis examining overall survival. We based our findings on administrative and medical records, from all presentations and billing data, for all providers in Manitoba; although reporting of presenting symptoms is limited and retrospective, this was far more rigorous and less subjective than patient questionnaires and eliminated recall bias. On the other hand, the reported rates of symptoms within our cohort were lower than those in previous symptom analysis.[10,36,37] This suggests that retrospectively examining the medical records, although decreasing recall bias, may be subject to reporting bias. All symptoms that were recorded and examined were also severe enough to warrant a visit to a primary care physician, making them an important starting point for examination, and were consistent with previous retrospective studies on symptom analysis. We examined, and accounted for, residual disease as a confounding factor in our analyses. Because no patient consent was required, we were able to review all eligible patients.

Our study confirms that time to diagnosis did not negatively affect overall survival until 80 days. We also determined that age, morphology, treatment type, residual disease, comorbidities, and income were prognostic factors. Finally, this is the first study to show a survival advantage to incidentally finding an ovarian cancer. This study alone does not show that pelvic examinations are a good screening method but implies that further research on the benefits of pelvic examination, effects of income, and strategies for early diagnosis is needed.

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