Development of an Ovarian Cancer Symptom Index: Possibilities for Earlier Detection

Article *in* Cancer · January 2007

DOI: 10.1002/cncr.22371 · Source: PubMed

9 authors, including:

Barbara A Goff
University of Washington Seattle
274 PUBLICATIONS **9,243** CITATIONS
SEE PROFILE

Charles W Drescher
Fred Hutchinson Cancer Research Center
118 PUBLICATIONS **8,642** CITATIONS
SEE PROFILE

Nicole Urban
Fred Hutchinson Cancer Research Center
193 PUBLICATIONS **14,663** CITATIONS
SEE PROFILE

Shirley Gough
Fred Hutchinson Cancer Research Center
3 PUBLICATIONS **295** CITATIONS
SEE PROFILE

Development of an Ovarian Cancer Symptom Index

Possibilities for Earlier Detection

Barbara A. Goff, MD[1,2]
Lynn S. Mandel, PhD[1,2]
Charles W. Drescher, MD[2]
Nicole Urban, ScD[2,3]
Shirley Gough, BSN[2]
Kristi M. Schurman, BA[2]
Joshua Patras, BS[2]
Barry S. Mahony, MD[4]
M. Robyn Andersen, PhD[2,3]

[1] Department of Obstetrics and Gynecology, University of Washington School of Medicine, Seattle, Washington.

[2] Molecular Diagnostic Program, Fred Hutchinson Cancer Research Center, Seattle, Washington.

[3] University of Washington School of Public Health, Seattle, Washington.

[4] Seattle Ultrasound Associates, Seattle, Washington.

Supported by a grant from the Marsha Rivkin Center for Ovarian Cancer Research (Seattle, WA) and by National Institutes of Health/National Cancer Institute grant P50 CA83636 to N. Urban ("Pacific Ovarian Cancer Research Consortium: Specialized Program of Research Excellence in Ovarian Cancer.").

The contents of this article are solely the responsibility of the authors and do not necessarily represent the views of the Marsha Rivkin Center for Ovarian Cancer Research or the National Cancer Institute.

We thank the Fred Hutchinson Cancer Research Center staff, Marcia Gaul and Vandana Oza, for their administrative support, and Shelly Hager for her software programming support of this study.

Address for reprints: Barbara A. Goff, MD, Division of Gynecologic Oncology, University of Washington School of Medicine, 1959 NE Pacific Street, BB625, Box 356460, Seattle, WA 98196-6460; Fax: (206) 543-3915; E-mail: bgoff@u.washington.edu

Received September 11, 2006; revision received October 4, 2006; accepted October 9, 2006.

BACKGROUND. Currently, screening for ovarian cancer is not recommended for the general population. Targeting women with specific symptoms for screening has been evaluated only recently, because it was believed that symptoms had limited specificity.

METHODS. A case-control study of 149 women with ovarian cancer, including 255 women who were in a screening program and 233 women who were referred for pelvic/abdominal ultrasound, was conducted by inviting women to complete a survey of symptoms. Patients were divided randomly into an exploratory group and a confirmatory group. Symptom types, frequency, severity, and duration were compared between cases and controls. Logistic regression analyses were used to determine which factors independently predicted cancer in the exploratory group and then were used to develop a symptom index, which was tested for sensitivity and specificity in the confirmatory group.

RESULTS. Symptoms that were associated significantly with ovarian cancer were pelvic/abdominal pain, urinary urgency/frequency, increased abdominal size/bloating, and difficulty eating/feeling full when they were present for <1 year and occurred >12 days per month. In a logistic regression analysis, symptoms that were associated independently with cancer were pelvic/abdominal pain ($P < .001$), increased abdominal size/bloating ($P<001$), and difficulty eating/feeling full ($P = .010$). A symptom index was considered positive if any of those 6 symptoms occurred >12 times per month but were present for <1 year. In the confirmatory sample, the index had a sensitivity of 56.7 for early-stage disease and 79.5% for advanced-stage disease. Specificity was 90% for women age >50 years and 86.7% for women age <50 years.

CONCLUSIONS. Specific symptoms in conjunction with their frequency and duration were useful in identifying women with ovarian cancer. A symptom index may be useful for identifying women who are at risk. ***Cancer*** **2007;109:221–7.**

KEYWORDS: ovarian cancer, symptoms, early diagnosis, case-control study.

Ovarian cancer is the second most common gynecologic malignancy in the United States and, unfortunately, the most deadly. This year, it is estimated that approximately 21,000 women will be newly diagnosed with ovarian cancer, and ≈15,000 deaths will result from the disease.[1] One of the reasons for the high fatality rate is that >70% of women with ovarian cancer are diagnosed with advanced-stage disease. Five-year survival rates for women with advanced disease are only from 20% to 30%; however, for women who are diagnosed when disease is confined to the ovary, cure rates are approximately from 70% to 90%.[2]

Although ovarian cancer meets the World Health Organization criteria for a disease that likely would benefit from screening because

DOI 10.1002/cncr.22371
Published online 11 December 2006 in Wiley InterScience (www.interscience.wiley.com).

of the substantial improvement in survival if it is detected early, to date, no studies have demonstrated that screening, even in high-risk populations, has an impact on the morbidity or mortality of the disease.[3–13] Currently, the American College of Obstetricians and Gynecologists recommends against population-based screening for ovarian cancer.[14] The United States Preventive Services Task Force has assigned routine screening for ovarian cancer a grade of *D*, because that group concluded there was fair evidence to recommend its exclusion from a periodic health examination.[15]

In the absence of reliable screening methods, is there anything that clinicians can do to help make an earlier diagnosis of ovarian cancer? Historically, ovarian cancer has been called the *silent killer*, because it was believed that symptoms did not develop until the disease reached advanced stages, when the chance of a cure was poor. However, our previous research indicated that symptoms frequently occur in patients with ovarian cancer.[16] Compared with clinical controls, women with ovarian cancer had abdominal, pelvic, and urinary symptoms that were significantly more frequent, more severe, and of shorter duration than the symptoms reported by women who visited primary care clinics.[17] Our preliminary studies suggest that, in some patients, symptoms may facilitate earlier detection.

The objective of the current study was to evaluate symptoms in women at high risk of having or developing ovarian cancer and to compare those symptoms with symptoms among women with ovarian cancer who were surveyed prior to surgery. We evaluated the frequency, severity, and duration of symptoms in cases and controls, and those variables were used to develop a symptom index. In addition, levels of depression and negative affectivity were examined, because these factors may have an impact on how symptoms are reported.

MATERIALS AND METHODS

Approval for this study was obtained from the Institutional Review Board of the Fred Hutchinson Cancer Research Center and from the hospitals with participating patients. All women signed informed consent. Participants included women who were undergoing surgery for pelvic masses (surgical), women who presented for an ultrasound (US), and healthy, high-risk women who were enrolled in the Ovarian Cancer Early Detection Study (OCEDS). The control groups were chosen specifically, because, like the surgical group, these women were likely to have an increased awareness of symptoms. All participants completed an identical survey asking about the occurrence of 23 symptoms that have been reported with ovarian cancer (Fig. 1). Women rated the severity of each symptom along with the frequency (number of days per month) and duration. Because factors like depression and personality traits can influence how symptoms are reported, all women filled out a self-report depression scale[18] and answered questions that determined the extent of positive and negative affect.[19] The surveys were administered from March 2004 through September 2005.

The timing of surveys was considered to be an important component to minimize recall bias. In the surgical population, all women were surveyed prior to surgery, before they knew their histologic diagnosis. Survey data were correlated with pathology and stage of disease. In the US population, women were surveyed prior to imaging. Symptoms were correlated with US diagnoses. In the OCEDS population, surveys were filled out as part of the ovarian cancer screening visit that was conducted on a quarterly basis. To increase the number of cases, we included 55 women with ovarian cancer who had filled out the same symptom survey as part of a previous study. This group of women was not asked for information regarding depression or negative affectivity.

For analysis, the study participants were divided into an exploratory group and a confirmatory group (Table 1). The exploratory group included all 55 cancer patients from our previous study and a randomly selected group of new patients. All other participants were assigned randomly. There was no significant difference in age or cancer stage between the 2 groups. The exploratory group was used to evaluate odds ratios for the women's self-report of various symptoms of differing frequency, severity, and duration. Those variables that were significant in a bivariate analysis were included in a logistic regression analysis to determine their independent association with cancer. Then, the results of regression modeling were used to develop a symptom index. The model and index were used in our confirmatory group to determine the sensitivity and specificity of the symptom index.

Statistical analysis was performed using SPSS for Windows (version 12.0; SPSS Inc., Chicago, IL). Continuous variables were compared by using independent *t* tests for 2 groups and 1-way analyses of variance with post-hoc tests for >2 groups. Categorical variables were analyzed with the chi-square test (for multiple groups) or the Mann-Whitney *U* test (for 2 groups), and medians were analyzed using the Kruskall-Wallis *H* and median tests. Correlations were determined by using a Pearson correlation. For all

Symptom	Have you experienced this symptom? Is so, please rate the severity: (0=no symptom, 1=minimal, 5=severe)	How many days per month did you experience this symptom?						How long did this symptom persist? (Months)						
		<1	1–2	3–6	7–12	13–19	≥20	<1	1–2	3–4	5–6	7–9	10–12	>12
Pain														
Pelvic (lower abdomen)	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Abdominal	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Back	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Eating														
Indigestion	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Unable to eat normally	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Feeling full quickly	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Nausea or vomiting	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Weight loss	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Abdomen														
Abdominal bloating	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Increased abdomen size	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Able to feel abdominal mass	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Bladder														
Urinary urgency	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Frequent urination	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Bowels														
Constipation	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Diarrhea	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Menses														
Menstrual irregularities	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Bleeding after menopause	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Intercourse														
Pain during intercourse	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Bleeding with intercourse	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Miscellaneous														
Fatigue	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Leg swelling	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Difficulty breathing	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
Other _____	0 1 2 3 4 5	☐1	☐2	☐3	☐4	☐5	☐6	☐1	☐2	☐3	☐4	☐5	☐6	☐7
☐ **No symptoms**														

FIGURE 1. Symptom survey used in this study. Have you had any of the following symptoms in the past year? If you had a symptom, please indicate the severity, and mark in the frequency (number of days a month) and duration (length) of the symptom.

analyses, $P < .05$ was considered statistically significant.

RESULTS

There were 149 women with ovarian cancer, including 55 women with early-stage disease, 88 women with late-stage disease, and 6 women with unknown disease stage. Among the women with early-stage disease, 24 had tumors of low malignant potential (LMP), and 31 had invasive tumors. Among the women with advanced-stage disease, all but 2 had invasive tumors. There were 225 women in the OCEDS group and 233 women in the US group. None of the women in the control groups developed ovarian cancer in the 6 months after completion of the study. Women with ovarian cancer were significantly older than women in the US and OCEDS groups (56 years vs 46 years and 51 years, respectively; $P < .001$), and they had significantly more symptoms (median: cancer group, 8.3 symptoms; US group, 6.3 symptoms; OCEDS group, 5.0 symptoms; $P < .001$). There was no difference in negative affectivity between the groups: Because this represents a personality trait and is relatively stable, this finding was not unexpected. Depression was significantly more common among women who had cancer compared with the other 2 groups. We also correlated depression, negative affect, and age with the total number of symptoms, and we observed that age was correlated negatively with the total number of symptoms women reported (correlation coefficient [r] $= -.12$; $P < .001$), whereas negative affect and depression were correlated positively with the number of symptoms reported ($r = .31$ and $r = .28$, respectively; $P < .001$ for both). Further evaluation revealed that negative affect and depression were correlated signifi-

TABLE 1
Characteristics of the Exploratory and Confirmatory Groups

	No. of women		
Group	Exploratory group	Confirmatory group	Total
OCEDS	127	128	255
US	116	117	233
Cancer	74 (14 LMP)	75 (12 LMP)	149
Early stage	25	30	55
Late stage	47	41	88
Missing stage	2	4	6

OCEDS indicates Ovarian Cancer Early Detection Study; US, ultrasound; LMP, low (or borderline) malignant potential.

* Includes 55 participants from previous a study (Goff et al., 2004[17]).

cantly with symptom severity ($r = .14$ and $r = .26$, respectively; $P < .05$). However, within the cancer group, there were no correlations of these factors with symptom severity. For frequency of symptoms, in all groups, we observed that negative affect and depression were correlated modestly with the frequency of symptoms ($r = .16$ and $r = .22$, respectively; $P < .05$). However, there was no correlation between either negative affect or depression and the duration of symptoms reported.

Development of a Symptom Index in an Exploratory Sample

In our exploratory group, first, we examined correlations among the 23 symptoms. Symptoms that had a correlation coefficient $\geq .70$ were combined into a single variable. Therefore, pelvic and abdominal pain, urinary frequency and urgency, increased abdominal size and bloating, and difficulty eating and feeling full quickly were combined into 4 rather than 8 separate variables. Then, we evaluated the odds ratios associated with reports of symptoms of differing durations, frequencies, and severities. Large odds ratios for the most number of symptoms were obtained from a model in which symptoms were present for <12 months or <6 months and occurred >12 days per month. Adding severity to the model and adding symptoms that occurred >20 days per month or for <4 months' duration did not increase the odds ratios.

Logistic regression models that examined the independent predictive power of symptom reports were run for symptoms of both 6-month and 12-month durations. These are shown in Table 2. Pelvic/abdominal pain and increased abdominal size/bloating consistently contributed to predicting cancer. Computation of the sensitivity and specificity of various symptom indices when comparing cancer between the 2 different control groups revealed that sensitivity ranged from 33% to 47% and that specificity ranged from 61% to 75%. We chose the model that had the greatest sensitivity, which was the model that included the presence of all 6 symptoms (pelvic/abdominal pain, increased abdominal size/bloating, and feeling full/difficulty eating) for <12 months and >12 times per month.

TABLE 2
Results of Logistic Regression for Exploratory Sample. Odds Ration for Cancer Versus Controls

	OR (95% CI)	
Variable	<6 Months*	<12 Months*
Pelvic/abdominal pain	19.1 (2.2–163.1)	23.3 (3.9–163.9)
Increased abdominal size/bloating	11.2 (2.2–58.3)	5.8 (1.4–23.9)
Urinary frequency/urgency	5.3 (.9–30.7)	5.2 (1.0–25.1)
Feeling full/difficulty eating	1.0 (0.1–9.9)	0.9 (0.1–6.3)

OR indicates odds ratio; 95% CI, 95% confidence interval.

* Frequency >12 times/month.

Evaluating the Symptom Index in a Confirmatory Sample

A symptom index was considered positive if a woman had any of the 6 symptoms present for <1 year that occurred >12 times per month. The sensitivity and specificity of the symptom index was assessed in the confirmatory sample for women aged <50 years and women aged ≥50 years. For women aged ≥50 years, the sensitivity was 66.7% with a specificity of 90%. For women aged <50 years, the sensitivity was 86.7% with a specificity of 86.7%. Analyses of sensitivity by stage revealed that the index was positive in 56.7% of women with early-stage disease, in 79.5% of women with advanced-stage disease, and in 80% of unstaged women. We eliminated the LMP tumors in this data set and observed that the sensitivity was 72.3% for women aged ≥50 years and 83.3% for women aged <50 years. When we evaluated sensitivity by stage when LMP tumors were eliminated, the results indicated that sensitivity was 60.0% for early-stage tumors and 79.1% for advanced stage tumors. Figure 2 shows the raw rates at which women in the confirmatory sample reported experiencing each of the 3 sets of symptoms that were included in the index ≥12 times per month in each of our participant populations. Consistent with previously reported analyses, differences between cases and controls in the rate of reporting this frequency of symptoms were statistically significant at the $P < .05$ level in all women.

Logistic regression of the model was also applied to the confirmatory sample stratified by age (Table 3). In this model, depression and negative affect also

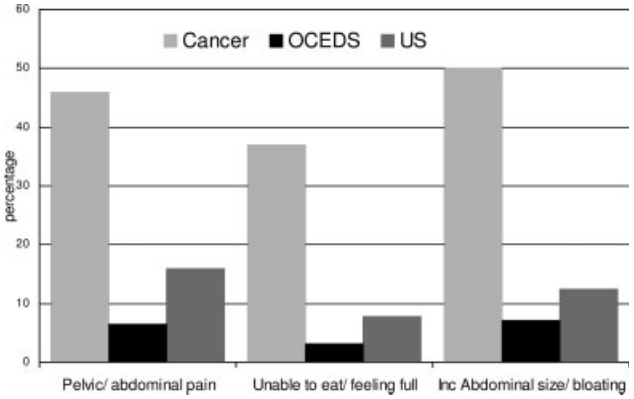

FIGURE 2. Frequency of symptoms reported >12 times per month for duration of <1 year for cases and controls. OCEDS indicates Ovarian Cancer Early Detection Study; US, ultrasound; Inc, including.

were included. Pelvic/abdominal pain and increased abdominal size/bloating predicted cancer in both age groups, whereas negative affect did not. In younger women, depression also was a statistically significant predictor of ovarian cancer.

Evaluating the Symptom Index in the General Population

To estimate how frequently the symptom index would be positive in the general population, we used a database from a previous study in which typical symptoms of ovarian cancer were assessed in 1709 women who presented to a primary care clinic.[17] We evaluated the percentage of women who reported pelvic/abdominal pain, increased abdominal size/bloating, and/or difficulty eating/feeling full. A woman who had any 1 of the symptoms for <1 year that occurred >12 times per month was considered to have a positive screen. Evaluation of this group revealed that 45 of 1709 women (2.6%) tested positive according to the criteria described above and, thus, would have been identified as having symptoms strongly suggestive of ovarian cancer. When they were stratified by age, 36 of 1102 women (3.3%) aged <50 years and 8 of 560 women (1.4%) aged ≥50 years tested positive in this clinic population.

DISCUSSION

Until recently, it was believed that ovarian cancer was an asymptomatic disease.[20–22] In the largest study to our knowledge that evaluated symptoms in ovarian cancer patients, we surveyed 1725 women from the United States and Canada about symptoms and potential delays in diagnosis.[16] We observed that 95% of women with ovarian cancer reported symptoms prior to diagnosis: The most common symptoms were abdominal or gastrointestinal, whereas gynecologic symptoms were the least common. In addition, 89% of women with stage I/II disease reported symptoms prior to their diagnosis. A subsequent case-control study from the Memorial Sloan-Kettering Cancer Center confirmed these results.[23] The authors of that study also observed significant differences in symptoms between ovarian cancer patients and controls, with bloating, lack of appetite, abdominal pain, fatigue, urinary frequency, and constipation occurring significantly more frequently in cases.

Although these studies were important in establishing that symptoms indeed are present in all stages of ovarian cancer, symptoms tend to be nonspecific, and it was not clear whether symptoms of ovarian cancer can be distinguished from those symptoms in women who seek care from primary care providers. To address this question, we surveyed 1709 women who presented to primary care clinics and 128 women who underwent surgery for a pelvic mass. Symptoms such as bloating, increased abdominal size, urinary symptoms, and pelvic and abdominal pain were identified significantly more frequently among women with ovarian cancer than among women in the clinic population.[17]

In addition, cancer patients typically reported symptom occurrence from 20 to 30 times per month, compared with 2 or 3 times per month for controls. The severity of symptoms also was significantly greater in cancer patients, and the symptoms were more recent in onset.

Based on our previous results, for the current study, we surveyed symptoms in women who were enrolled in ovarian cancer early-detection programs, most of whom have heightened awareness of symptoms, and women who were referred for a pelvic/abdominal US, who may have heightened awareness of symptoms for other reasons. The symptoms that women experienced, along with frequency, severity, and duration, were used to determine whether a symptoms index could be developed to identify

TABLE 3
Logistic Regression of Confirmatory Sample (*P* Values)

		P	
Variable	**Total**	**Age <50 years**	**Age ≥50 years**
Pelvic/abdominal pain	<.001	.016	.007
Urinary symptoms	.579	.215	.587
Feeling full/difficulty eating	.010	.957	.988
Increased abdominal size/bloating	<.001	.004	.020
Negative affect	.344	.293	.795
Depression	.208	.020	.928
Age	.028	—	—

women with ovarian cancer. Although we could not eliminate recall bias completely, we did try to minimize its effect by surveying women prior to surgery or US. We observed that symptoms, in combination with their frequency and duration, had a sensitivity of 56.7% for identifying early-stage disease and 79.5% for identifying advanced-stage disease with specificities ranging from 86% to 90%. Our symptom index performed similarly to CA125 for detecting any stage of disease.[3] Studies have demonstrated that CA125, as a single modality, has sensitivity that ranges from 50% to 79% and specificity that ranges from 96% to 99%.[7,24] However, the cost of the symptom index is minimal, which may be useful in selecting women who should have additional diagnostic testing. Ultimately, the objective is to determine whether obtaining serial symptom index measurements and examining the trend will result in earlier diagnosis and improved survival among women with ovarian cancer. The current results suggest that women who complain of abdominal/pelvic pain, increased abdominal size/bloating, or difficulty eating/feeling full quickly that is of $<$12 months' duration and occurs $>$12 times per month should be evaluated for potential ovarian cancer.

To our knowledge, this is the first study to correlate depression and affect with symptom reporting for ovarian cancer. Others, including Croyle and Uretsky,[25] also have demonstrated that, as depression increases, the number of reported symptoms increases. This was true regardless of disease status (cases or controls). We also observed that an indivudal's affect was correlated with the number of symptoms and with reported symptom severity and frequency, but not with symptom duration. It is important to point out that these correlations were only modest. In the logistic regression analysis, there was no association between negative affect and cancer; however, among younger women in our case group, depression was associated significantly with cancer.

Recently, Smith et al evaluated Medicare claims linked to the California Surveillance, Epidemiology, and End Results database. In their study of 1985 women with ovarian cancer and age-matched breast cancer and noncancer clinic controls, patients with ovarian cancer were significantly more likely to have visits for abdominal or pelvic pain, abdominal swelling, and gastrointestinal symptoms in the 6 months prior to diagnosis compared with the control groups.[26] This suggests that there may be a window of opportunity to make an earlier diagnosis for women who have these symptoms. Although it remains unknown whether diagnosing ovarian cancer from 3 months to 6 months earlier will improve prognosis, we do know that, among women in whom an optimal cytoreduction (no macroscopic residual disease after surgery) can be achieved, the cure rate is double that of women who do not undergo optimal surgery (30–40% cure vs 15–20%).[2] The most significant factor associated with optimal cytoreduction is volume of disease at the time of presentation.[27,28] Because ovarian cancer can have very rapid doubling times, 3 months to 6 months may represent a significant interval for diagnosis.

Given the finding that symptoms are present in a significant number of women with ovarian cancer, the question remains: Can we design a method to use symptoms in clinical practice? Because screening asymptomatic women for ovarian cancer is not effective currently, there may be a role for evaluating women who have specific symptoms linked to cancer in an attempt to make an earlier diagnosis. The results from our study suggest that a relatively simple evaluation of symptoms of recent onset and significant frequency should prompt a thorough evaluation for ovarian cancer. Currently, we are in the process of examining the symptom index in a prospective fashion in a primary care setting.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA Cancer J Clin.* 2006;56:106–130.
2. Ozols RF, Rubin SC, Thomas GM, Robboy S.Epithelial ovarian cancer. In: Hoskins WJ, Perez CA, Young R, Barakat R, et al, eds. *Principles and Practice of Gynecologic Oncology.* 4th ed, Philadelphia, Pa: Lippincott Williams & Wilkins; 2005: 895–987.
3. Goff BA, Muntz HG. Screening and early diagnosis of ovarian cancer. *Womens Health Primary Care.* 2005;8:262–268.
4. Menon U, Jacobs IJ, Ovarian cancer screening in the general population. *Curr Opin Obstet Gynecol.* 2001;13:61–64.
5. Paley PJ. Ovarian cancer screening: are we making any progress? *Curr Opin Oncol.* 2001;13:399–402.
6. Van Nagell JR Jr, DePriest PD, Reedy MB, et al. The efficacy of transvaginal sonographic screening in asymptomatic women at risk for ovarian cancer. *Gynecol Oncol.* 2000;77: 350–356.
7. Jacobs I, Davies ASP, Bridges J, et al. Prevalence screening for ovarian cancer in postmenopausal women by CA 125 measurement and ultrasonography. *BMJ.* 1993;306:1030–1034.
8. Liede A, Karlan BY, Baldwin RL, et al. Cancer incidence in a population of Jewish women at risk of ovarian cancer. *J Clin Oncol.* 2002;20:1570–1577.
9. Fishman DA, Cohen L, Blank SV, et al. The role of ultrasound evaluation in the detection of early-stage epithelial ovarian cancer. *Am J Obstet Gynecol.* 2005;192:1214–1221.
10. Skates SJ, Horick N, Yu Y, et al. Preoperative sensitivity and specificity for early-stage ovarian cancer when combining cancer antigen CA-125II, CA 15-3, CA 72-4, and macrophage colony-stimulating factory using mixtures of multivariate normal distributions. *J Clin Oncol.* 2004;22:4059–4066.

11. Petricoin EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet.* 2002; 3:355–366.
12. Jacobs IJ, Menon U. Progress and challenges in screening for early detection of ovarian cancer. *Mol Cell Proteomics.* 2004;3:355–366.
13. National Institutes of Health. Consensus Development Conference Statement. Ovarian cancer: screening, treatment and follow-up. *Gynecol Oncol.* 1994;55(3 pt 2):S4–S14.
14. [No authors listed.]American College of Obstetrics and Gynecology. Committee opinion: routine cancer screening. *Int J Gynecol Obstet.* 1997;59:157–161.
15. US Preventive Services Task Force. *Guide to Clinical Preventive Services.* 2nd ed. Alexandria, Va: International Medical Publishing; 1996.
16. Goff BA, Mandel LS, Muntz HG, Melancon CH. Ovarian carcinoma diagnosis. *Cancer.* 2000;89:2068–2075.
17. Goff BA, Mandel LS, Melancon CH, Muntz HG. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. *JAMA.* 2004;291:2705–2712.
18. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychological Meas.* 1977;1:385–401.
19. Watson D, Clark LA, Tellegen A. Development and validation of brief measure of positive and negative affect: the PANAS scale. *J Pers Soc Psychol.* 1988;54:1063–1070.
20. Young RC. Gynecologic malignancies. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, eds. *Harrison's Principles of Internal Medicine.* 14th ed. New York, NY: McGraw-Hill; 1998:605–611.
21. Clement KD, Connor PD.Tumors of the female reproductive organs. In: Taylor RB, David AK, Johnson TA Jr, Phillips DM, Scherger JE, eds. *Family Medicine: Principles and Practice.* 5th ed. New York, NY: Springer-Verlag, Inc.; 1998: 916–924.
22. American College of Obstetricians and Gynecologists. *1999 Compendium of Selected Publications.* ACOG Educational Bulletin no. 250. Washington DC: American College of Obstetricians and Gynecologists; 1998:665–673.
23. Olson SH, Mignone L, Nakraseive C, et al. Symptoms of ovarian cancer. *Obstet Gynecol.* 2001;98:212–217.
24. Olivier RI, Lubsen-Brandsma MA, Berhoef S, van Beurden M. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. *Gynecol Oncol.* 2006;100:20–26.
25. Croyle RT, Uretsky MB. Effects of mood on self-appraisal of health status. *Health Psychol.* 1987;6:239–253.
26. Smith LH, Morris CR, Yasmeen S, Parikh-Patel A, Cress RD, Romano PS. Ovarian cancer: can we make the clinical diagnosis earlier? *Cancer.* 2005;104:1398–1407.
27. Hoskins WJ, McGuire WP, Brady MF, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol.* 1994; 170:974–979.
28. Hoskins WJ. Epithelial ovarian carcinoma: principles of primary surgery. *Gynecol Oncol.* 1994;55(3 Pt 2):S91–S96.