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Development of an instrument to identify symptoms potentially indicative of ovarian cancer in a primary care clinic setting*

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ABSTRACT

Background: Several recently published studies suggest that screening for symptoms could improve the early diagnosis of ovarian cancer. This report describes the development of a simple and reliable method of collecting symptom information in a primary care clinic. Methods: 1200 women, ages 40 - 87, completed several versions of a draft symptom index (SI) assessment form during their visits to a primary care clinic. Factors associated with a positive SI result were examined. Providers were surveyed about acceptability of the symptom screening procedures. Findings: Variation in the instructions provided to women influenced the rate at which women indicated having symptoms indicative of a positive SI, 5% had positive results when written instructions emphasized listing only current symptoms. Women coming to the clinic because of a current medical concern or problem did have higher rates of positive SI results, as did non-white women ($p < 0.05$). Acceptability by providers was high. Patients could independently complete the SI in 5 minutes. One patient with a positive SI was diagnosed with ovarian cancer and none with a negative SI developed cancer. Interpretation: A quick paper and pencil form can be used to identify women with symptoms potentially indicative of ovarian cancer. Use of such a form for ovarian cancer screening purposes is acceptable to most women and providers in a primary care clinic setting.

Keywords: Ovarian Cancer; Symptoms

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1. INTRODUCTION

Two recent prospective studies suggest that efforts to identify women with symptoms and assure prompt assessment for ovarian cancer using currently available tests (CA-125 and TVS) could result in earlier diagnosis of ovarian cancer [1,2]. Consistent with evidence to suggest that women with ovarian cancer present with symptoms, even when the disease is in its early stages [3-8], and advice from the Gynecologic Cancer Foundation, the Society of Gynecologic Oncologists and the American Cancer Society [9], and a statement by NICE (National Institute for Health and Clinical Excellence) [10] encouraging follow-up of women reporting symptoms. Studies using other methods also suggest that assessment of women with symptoms could reduce time to diagnosis [11,12]. Unfortunately, symptoms that may be indicative of ovarian cancer can be caused by a variety of other conditions. The key to identifying symptoms signaling ovarian cancer appears to be that they are new to a woman and occur frequently [13,14]. In an effort to identify women with symptoms that may be indicative of ovarian cancer and create reliable algorithms for assessment of symptoms necessary for serious study of their potential, we have proposed a decision rule that we call a "Symptom Index" [13,15].

The Symptom Index (SI) is considered positive if women are currently experiencing any one or more of six specific symptoms that are present for less than one year and occur more than 12 times a month. These symptoms include bloating, increased abdominal size, pelvic or abdominal pain, difficulty eating, and feeling full quickly. A case-control study has shown that 57% of women with early stage ovarian cancer and 80% of women with advanced ovarian cancer report symptoms that follow this distinctive pattern at the time of their diagnosis [13]; symptoms in conjunction with other bio-markers may

have a role in earlier diagnosis of ovarian cancer [16].

This report provides preliminary results from a pilot study using a standardized form to prospectively collect SI information at a primary care clinic. The goals of this pilot study were to determine valid methods for the prospective collection of the SI and to assess the feasibility and acceptability such assessments at a primary care visit. We also sought to understand what factors other than ovarian cancer may result in a positive SI.

2. MATERIALS AND METHODS

This pilot effort was conducted at a Women's Health clinic in an urban setting as part of an integrated system of medical centers. This clinic provides both primary care and referral for a group of neighborhood clinics. The clinic performs approximately 24,000 visits annually for 11,500 unique patients. Women were eligible for the study if they were 40 years of age or older, not pregnant at the time of their clinic visit, and had not participated in the study within a 12 months period.

All study activities were reviewed and approved by the institutional review boards of the University of Washington and the Fred Hutchinson Cancer Research Center.

2.1. Procedures

A research nurse identified all women over 40 years of age with scheduled clinic appointments as potentially eligible to participate. Informed consent was obtained from eligible and interested women. In the first phase of the study, 419 women completed an initial version of an SI assessment form with the assistance of the research nurse. Feedback from women participating during this stage of the project was used to understand how women respond to questions about symptoms which allowed us to understand potential false positive or negative responses to the SI, and to improve the design of the data collection instrument.

In the second phase of the study, 781 women were asked to complete one of three versions of the SI data collection form under development. Our goal was to develop an accurate method of symptom data collection that would require minimal implementation effort from clinic staff. After appropriate written instructions were developed, a second format was examined to assess possible differences in the results or the completeness of women's self-reports associated with questionnaire layout.

2.2. Measuring the Symptoms

Initially a tabular form for data collection was used and women were asked "Have you experienced any of the following symptoms?" (**Appendix 1**). With extended use of the SI, it became apparent that the time frame women should use to answer questions about symptoms was unclear. Some women who reported symptoms had experienced them frequently at some point in the past year but those symptoms had since resolved. Reports of such symptoms would increase the false positive rate of the SI because the symptoms are of potential importance only for women who are *currently* symptomatic. The spoken instructions were changed to clarify that the symptoms reported should be occurring at the present time. A total of 101 women completed study forms with spoken instruction to indicate their current symptoms. After IRB approval was sought to change the written instructions, the next 258 participants completed the tabular form with new instructions asking "Are you currently experiencing any of the following symptoms frequently?" These introductory instructions resulted in fewer requests for clarification. Differences in the rates of positive results associated with the change in both spoken and written instructions versus the earlier version of the questionnaire were evaluated.

Two different page layouts of the symptoms questions were also tested. During initial pilot testing the questionnaire was presented using a tabular layout but women frequently left portions blank requiring the nurse to ask if blank spaces indicated no symptoms. In an effort to reduce such difficulties, a second layout was tested using separate questions for each set of symptoms and a more explicit flow pattern (**Appendix 2**). Statistical comparisons of the two formats examining the effect of the questionnaire layout on the rate of SI completion and on SI results were also performed.

2.3. Coding of the Symptom Index

Women were considered to be positive for symptoms if any of the six symptoms occurred 13 or more times per month and were present for less than one year.

2.4. Assessing Other Variables of Interest

In addition to the symptoms question, women completed a questionnaire allowing us to assess age, race/ethnicity, menopausal status, reason for clinic visit, and a variety of general medical conditions that might cause similar symptoms. Women also provided information about any gynecological or medical conditions diagnosed in the past. Gynecological conditions reported included endometriosis, fibroids, and ovarian cysts. General medical conditions included irritable bowel syndrome (IBS), urinary tract infections, acid reflux, diabetes, hypertension, heart disease, and thyroid disease.

2.5. Statistical Methods

STATA statistical software package [version 10.0, Stata

Corporation, College State, TX] was used for these analyses. The characteristics of the study population (n = 1200) were assessed using descriptive statistics, which included the median and range for continuous variables and the frequency and percent for categorical variables. Associations between the instruction or format of the symptoms questions and the results of the Index were assessed using the Fisher's exact test. Exploratory analyses examining the association of symptom index results with demographic characteristics and with self-reported health problems were conducted. All statistical tests were two-sided and considered to be statistically significant at $p \leq 0.05$.

Clinic providers also completed a brief questionnaire assessing the acceptability of the SI assessments being conducted in the clinic, how assessment of symptoms may have influenced their interactions with patients and clinic flow, and their satisfaction with the results of the assessments.

Finally, the names of all participating women were matched to the local cancer registry in an effort to determine whether any of them developed ovarian cancer in the 12 months following their participation in this study.

3. RESULTS

3.1. Eligibility and Enrollment Information

Approximately 72% of women approached about the study completed eligibility and interest form and returned it to the clinic or to study staff. Of those completing forms, 74% indicated that they were eligible to participate. Of those women indicating eligibility, 80% were interested in volunteering to participate in the study and completed study procedures during their clinic visit.

3.2. Characteristics of the Study Participants

The characteristics of the study participants are summarized in **Table 1**. The average age was 55 years (35% of the participants were ages 40 - 49 and 64% were ≥50 years). More than half of the study population reported being post-menopausal. Approximately 87% of the participants in the pilot study were white. Almost half of the clinic appointments for study enrollees were either for evaluation of a current health concern (26%) or for routine follow-up of a health problem reported at an earlier clinic visit (21%). The remaining visits were reported as routine screening appointments; for women over the age of 40, the screening visits were primarily associated with routine screening mammography.

Two (0.17%) of the enrolled women reported a prior history of ovarian cancer but still had an intact ovary, and were retained in all study analyses as they remained at risk for ovarian cancer (data not shown). An additional

Table 1. Patient characteristics.

	Total (n = 1200)
Age	
Mean (SD)	54.6 (9.4)
40 - 49, n (%)	423 (35%)
50+, n (%)	764 (64%)
Not reported	13 (1%)
Menopausal status	
Pre	277 (23%)
Peri	164 (14%)
Post	636 (53%)
Not reported	123 (10%)
Ethnic background	
White	1,041 (87%)
Non-white	148 (12%)
Not reported	11 (1%)
Reason for visit	
Routine screen	608 (51%)
Routine follow-up	252 (21%)
I'm concerned about something	310 (26%)
Not reported	30 (2%)
Gynecological condition	
Endometriosis	18 (2%)
Fibroids	108 (9%)
Ovarian cysts	67 (5%)
Other gynecological problems	84 (7%)
More than 1 of these conditions	101 (8%)
Not reported	822 (69%)
Medical conditions	
Irritable bowel disease	27 (2%)
Urinary tract infections	17 (1%)
Interstitial cystitis	2 (<1%)
Acid reflux	73 (6%)
Diabetes	13 (1%)
Hypertension	72 (6%)
Heart disease	9 (<1%)
Thyroid disease	73 (6%)
More than 1 condition	315 (26%)
None of the listed conditions	336 (28%)
Not reported	263 (22%)

5.58% of women reported a personal history of breast cancer and these women were also deemed eligible to participate and retained in the study sample. All women were able to complete the SI in less than 5 minutes (average 1.5 minutes).

3.3. Effects of Differences in Written and Verbal Instructions and Form Layout on the Results of the Symptom Index

Table 2 summarizes the rate of positivity we observed using the different SI forms. Using the initial symptom data collection instrument and written instructions, approximately 9.3% (95% CI: 6.4% - 11.9%) of the women reported having at least one of the symptoms more than 13 times per month, resulting in a positive Index score. When the spoken instructions were changed and included asking women to describe their *current* symptoms without a change in the written instructions, the rate of positive index results was 7.9% (95% CI: 2.6% - 13.2%). Although it appears that asking women about their "current" symptoms as part of the verbal but not written instructions reduced the rate of positive index results, the rate of positive index results was not statistically significant between the two groups ($p = 0.85$).

After changes in the written instructions, no further spoken instruction was deemed necessary. Two hundred and fifty-eight women responded to the written instructions, "Are you currently experiencing any of the following symptoms frequently?" The rate of positive index results in this group was 5.4% (95% CI: 2.7% - 8.2%).

Changing the symptom data collection instrument from a tabular form to one with individual questions about each symptom and a skip pattern did not change the percentage of women judged to be positive from that of the prior group, given the same written instructions ($p = 0.99$). The rate of women with positive symptoms in the group receiving the flow chart form was 5.7% (95% CI: 3.5% - 7.9%). It should be noted, however, that this test had power to detect only differences of 10% or more.

When a statistical test was performed comparing the third and fourth groups of women combined (that is to say, all women receiving the written instructions asking for current symptoms) with that of the women provided the initial written instructions, the rate of symptom positive results was lower than in the first two groups of women (those who did not receive written instructions specifying interest in current symptoms only [$p < 0.05$]). These results are also presented in **Table 2**.

3.4. Differences in the Clinical Characteristics of Women with and without Positive SI Results

In order to describe the clinical characteristics of women with and without symptoms, the bivariate associations of SI results with the age, race, menopausal status, gynecological and other conditions, and type of clinic visit were explored for all those completing a form that included the written instructions to report only "current" symptoms (n = 680) (**Table 3**). SI results did not demonstrate statistically significant differences according to participant's age, or menopausal status, although younger and premenopausal women were somewhat more likely to have a positive result.

The rate of positive SI results did demonstrate a statistically significant bivariate association with race, with non-white women approximately twice as likely to report symptoms and receive a positive SI result when compared with white women (11% versus 5% respectively, $p = 0.05$). When the non-white group was examined in its sub-categories of Black, Asian, Other, and more than one race, the elevation was not isolated to any specific non-white racial group (data not shown), and, the differences between groups were no longer statistically significant. Women visiting the clinic for a current concern were more likely to have a positive SI result than those coming for follow-up or routine screening (14% versus 6%, and 2% respectively). Non-gynecological conditions were not associated differences in the rates of SI positive results, although 14% of women with IBS and 13% of

Table 2. Description of the study participant groups and percentage of SI positivity within each group.

Group	Description	n	% SI Positive (95% CI)	p values	
Group 1	Participants completed the symptom index with the assistance of the research nurse.	419 (35%)	9.3 (6.4 - 11.9)	Group 1 versus Group 2 N.S.	Groups 1 & 2 versus Groups 3 & 4 (9.0% versus 5.5%, $p < 0.05$)
Group 2	Participants completed the symptom index independently.	101 (8%)	7.9 (2.6 - 13.2)		
Group 3	Participants were instructed to complete the symptom index based on their *current* symptoms.	258 (22%)	5.4 (2.7 - 8.2)	Group 3 versus Group 4 N.S.	
Group 4	Participants completed a new version of the symptom index that used a larger format.	422 (3%)	5.7 (3.5 - 7.9)		

Table 3. Relationship between patient characteristics and results of the symptom index in women who reported "current" symptoms (Groups 3 & 4, n = 680).

Patient characteristic and health condition	Total	Negative SI	Positive SI	p value
Age				0.16
40 - 49	214	198 (93%)	16 (7%)	
50+	463	441 (95%)	22 (5%)	
Menopausal status				
Pre	144	133 (92%)	11 (8%)	
Peri	100	98 (98%)	2 (2%)	0.14
Post	372	349 (94%)	23 (6%)	
Race				
White	602	572 (95%)	30 (5%)	0.05
Non-white	72	64 (89%)	8 (11%)	
Reason for visit				
Routine screen	366	360 (98%)	6 (2%)	
Routine follow-up	125	117 (94%)	8 (6%)	0.001
I'm concerned about something	177	153 (86%)	24 (14%)	
GYNECOLOGICAL CONDITIONS				
Endometriosis				
Yes	11	11 (100%)	0	0.52
No	669	631 (94%)	38 (6%)	
Fibroids				
Yes	56	52 (93%)	4 (7%)	0.54
No	624	590 (95%)	34 (5%)	
Ovarian cysts				
Yes	32	29 (91%)	3 (9%)	0.42
No	648	613 (95%)	35 (5%)	
Other gynecological condition				
Yes	44	37 (84%)	7 (16%)	0.008
No	636	605 (95%)	31 (5%)	
More than 1 of these conditions				
Yes	57	46 (81%)	11 (19%)	<0.001
No	623	596 (96%)	27 (4%)	
MEDICAL CONDITIONS				
Irritable bowel syndrome				
Yes	14	12 (86%)	2 (14%)	0.18
No	666	630 (95%)	36 (5%)	
Urinary tract infections				
Yes	8	8 (100%)	0	0.99
No	672	634 (94%)	38 (6%)	
Acid reflux				
Yes	39	34 (87%)	5 (13%)	0.06
No	641	608 (95%)	33 (5%)	
Diabetes				
Yes	5	5 (100%)	0	0.99
No	675	637 (94%)	38 (6%)	
Hypertension				
Yes	43	42 (98%)	1 (2%)	0.50
No	637	600 (94%)	37 (6%)	
Heart disease				
Yes	6	5 (83%)	1 (17%)	0.29
No	674	637 (95%)	37 (6%)	
Thyroid disease				
Yes	45	41 (91%)	4 (9%)	0.31
No	635	601 (95%)	34 (5%)	
More than 1 of these conditions				
Yes	186	172 (92%)	14 (8%)	0.19
No	494	470 (95%)	24 (5%)	

women with Acid reflux disease were index positive, in a larger population these differences might have achieved statistical significance.

None of the individual gynecological conditions named on our survey were associated with an elevated frequency positive SI results. However, women reporting any of a variety of "other" gynecological conditions (16% versus 5%; $p < 0.01$) and those with more than one gynecologic condition were more likely to have a positive results (19% versus 4%; $p < 0.01$).

3.5. Multivariate Analyses

Multivariate analyses were then conducted on an ad-hoc basis in order to explore whether the statistically significant bivariate association of race and symptoms might be related to differences in personal characteristics or health status. When a multivariate logistic regression model of SI positivity that included race, age, more than one gynecological condition, fibroids, and IBS was tested, the association of race with positive results for symptoms was reduced in size and was not statistically significant. Differences in the rate of SI positivity associated with race may be due to other characteristics of our sample.

3.6. Acceptability to Providers

A survey of the physicians, physician assistants (PAs), and nurses working in the clinic (n = 10) revealed that they felt the SI was "very acceptable" (5.0, sd = 0 among physicians and PAs, and 4.5, sd = 0.58 among nurses). This represented the answers on a Likert scale running from 1 to 5, where 1 was "not at all acceptable" and 5 = "very acceptable". These clinic staff also felt the SI added 1 - 2 minutes to the patient visit, in the 10% to 20% of patients for whom they judged it added any time at all. They also indicated that the symptom information provided was useful to them in their practice (4.3, sd = 0.82 for physicians and PAs and 4.3, sd = 0.58 among nurses). This on a Likert scale running from 1 to 5 where 1 was "not at all useful" and 5 = "very useful".

Participating patients were also linked to the Western Washington SEER registry to determine if they had developed any cancer in the 12 months following study participation. One new case of ovarian cancer was identified. The participant had a positive SI and was diagnosed with ovarian cancer shortly after participating. In this sample no other participants with a positive SI developed ovarian cancer and no patients with a negative SI developed ovarian cancer in this sample.

4. CONCLUSIONS

Recently, many lay media outlets have encouraged women to keep diaries of symptoms as a possible method of early detection for ovarian cancer. In the Diagnosing Ovarian Cancer Early (DOvE) study conducted in Canada, women were recruited though a public media campaign utilizing newspaper, radio, television, and fliers to attract symptomatic women to participate. Remarkably, through this approach, investigators diagnosed ovarian cancer in one per 132 women, which is ten times higher than reported in other studies. Comparison of DOvE patients to those in the general population found a complete resection rate of cancer to be 73% compared to 44%, $p = 0.075$. While this was not statistically significant in this pilot study, the trend was encouraging and suggests that a valid tool to assess symptoms associated with ovarian cancer could be important.

When symptoms are collected prospectively in a clinic setting using the SI, it appears that 5.5% of women report current symptoms associated with a positive result, although as many as 9.7% of women may report having had these symptoms frequently in the past. Thus, it is important to direct women to report only symptoms they are currently experiencing frequently. Predictors of symptoms appear to include the nature of the clinic visit with women reporting current concerns more likely than those visiting for a routine screening appointment to report symptoms. Women with a personal history of gynecological conditions, particularly those with more than one gynecological condition, are also more likely to report currently experiencing symptoms. Those with a diagnosis of acid reflux disease or IBS may also be more likely to report symptoms, although this study did not have power to fully assess this. Further studies are needed to better understand racial or ethnic differences in the reporting of symptoms associated with ovarian cancer.

Study Limitations and Considerations

As expected the low incidence of ovarian cancer led to only one patient in the population developing ovarian cancer. Although this patient was symptom positive, the sensitivity and specificity of the SI tool cannot be assessed in the current study.

The value of this report needs to be understood in context. There have been several efforts to develop algorithms for assessing ovarian cancer symptoms [11-13,17, 18], but few have reported results from use of their index in a study group other than the one in which it was developed , and differences associated with methods of administration of self-report questionnaires have not been previously examined. The symptom index [13] provides a considerably more specific result than other indexes with similar sensitivity and is the first to report results from prospective use in a clinic population. If ovarian cancer screening using symptoms is widely

adopted, maximizing the specificity of screening programs will be important. Until better biomarkers are identified and tested collecting information about symptoms appears to have promise. The Symptom Index (SI) can be easily used in a primary care clinic setting and is acceptable to providers and patients and identifies women with symptoms that are worthy of concern with minimal false-positive results.

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APPENDIX 1

Symptom Questionnaire

Have you experienced any of the following symptoms? Check the box Yes or No. If yes, also check the box for number of days per month and the box for the number of months you experienced each symptom.

Symptom	Have you had this symptom?		If so, how many days per month did you experience this symptom?			How many months did this symptom persist?			
	No	Yes	0 - 5	6 - 12	≥13	<1	1 - 6	7 - 12	≥13
Pain									
Abdominal/pelvic pain	☐0	☐1	☐1	☐2	☐3	☐1	☐2	☐3	☐4
Eating									
Feeling full quickly	☐0	☐1	☐1	☐2	☐3	☐1	☐2	☐3	☐4
Unable to eat normally	☐0	☐1	☐1	☐2	☐3	☐1	☐2	☐3	☐4
Abdomen									
Abdominal bloating or Increased abdomen size	☐0	☐1	☐1	☐2	☐3	☐1	☐2	☐3	☐4
☐8 **None of the above symptoms**									

FOR STAFF USE ONLY. SI Negative: ☐0; SI Positive: ☐1.

APPENDIX 2

Symptom Questionnaire

Are you currently experiencing any of the following symptoms frequently? Check the box Yes or No. If yes, also check the box for number of days per month and the box for the number of months you experience each symptom.

1) Pain: abdominal/pelvic pain

❑$_0$ No				
❑$_1$ Yes →	1a. If yes, how many **days** per month do you experience this symptom?			
	0 - 5 days	6 - 12 days	More than 13 days	
	☐$_1$	☐$_2$	☐$_3$	
	1b. If yes, how **long** have you had this symptom?			
	Less than 1 month	1 - 6 months	7 - 12 months	More than 1 year
	☐$_1$	☐$_2$	☐$_3$	☐$_4$

2) Eating: feeling full quickly or unable to eat normally

❑$_0$ No				
❑$_1$ Yes →	2a. If yes, how many **days** per month do you experience this symptom?			
	0 - 5 days	6 - 12 days	More than 13 days	
	☐$_1$	☐$_2$	☐$_3$	
	2b. If yes, how **long** have you had this symptom?			
	Less than 1 month	1 - 6 months	7 - 12 months	More than 1 year
	☐$_1$	☐$_2$	☐$_3$	☐$_4$

3) Abdomen: abdominal bloating or increased abdomen size

❑$_0$ No				
❑$_1$ Yes →	3a. If yes, how many **days** per month do you experience this symptom?			
	0 - 5 days	6 - 12 days	More than 13 days	
	☐$_1$	☐$_2$	☐$_3$	
	3b. If yes, how **long** have you had this symptom?			
	Less than 1 month	1 - 6 months	7 - 12 months	More than 1 year
	☐$_1$	☐$_2$	☐$_3$	☐$_4$

FOR STAFF USE ONLY. SI Negative: ☐$_0$; SI Positive: ☐$_1$.

