Correlation of cancer risk evaluation and early detection (CADET) scores with abnormal ultrasonographic ovarian findings

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Summary

Objective: To determine the utility of a modified version of ovarian cancer-focused cancer risk evaluation and early detection (CADET) scores as a screening tool for ultrasonographic ovarian findings. *Study design:* Prospective pilot study. *Main outcome measures*: CADET scores were compared with abnormal ultrasonographic ovarian findings of peri- and postmenopausal women who attended their gynecologist for a routine check-up. The women filled in the CADET questionnaire before seeing their gynecologists who were blinded to the CADET results. The women whom they referred for pelvic transvaginal ultrasonographic examination comprised the study group. The results of their scans were compared with their CADET scores. *Results:* Of the 181 peri- and postmenopausal women who were candidates for this study, 154 were referred for ultrasonography, of whom 38 (24%, Group A) had abnormal ovarian scans (30 simple cysts and 8 complex findings). The other 116 (76%) women had normal sonograms (Group B). Demographic characteristics were similar for both groups. Thirteen Group A women (34%) and 52 Group B women (45%) had positive CADET scores (p = NS). The average group CADET scores were also not significantly different (0.8 ± 1.7 for Group A and 1.7 ± 2.5 for Group B). *Conclusion:* CADET scores did not correlate with abnormal ultrasonographic ovarian findings.

Key words: Ovarian cancer; Screening; Symptoms; Early detection.

Introduction

Ovarian cancer is the most lethal form of malignancy of the female reproductive tract and the fifth cause of cancer-related deaths among women, following the breast, lung, colon and pancreas [1]. The incidence of the disease is around 17:100,000 (corrected by age), and 23,000 women in the USA are newly diagnosed with the disease and 14,000 die each year. One of the main reasons for the high death ratio in ovarian cancer is the difficulty in diagnosing it at an early stage [2]. Failure to diagnose ovarian cancer in early stages is currently attributed to the fact that there are no efficient screening tests for early detection of the disease and to the lack of significant clinical symptoms at early stages, which are characteristically non-specific [3]. The rate of complete cure of early diagnosed ovarian cancer is about 90%, but most women are not diagnosed until the disease reaches advanced stages (Stage III or IV) where the estimated cure rate drops to 20%.

Routine transvaginal ultrasound examination, a widely used, noninvasive and inexpensive examination, has been studied extensively as a screening test for the detection of ovarian cancer. False-positive results are common and particularly problematic in pre-menopausal women since ovarian morphology depends on the menstrual cycle phase. Most women with positive screening by pelvic transvaginal ultrasonography will turn out to be free of the disease, and the positive predictive value (PPV) of a screening test among women in an average risk group is 2%. In other words, 98% of women with positive findings will actually be disease free, thus discouraging its application as a screening test in the general population [4]. The PPV of these screening tests, although higher for women in a high-risk group, is still far from satisfying.

The serum marker, CA-125, commonly used to follow-up an already diagnosed patient, has also been proven to be inefficient as a screening tool due to its high percentage of both false positive and false negative rates [5]. Thus, in 1994 the National Institute of Health (NIH) declared that there is no role for screening tests for early detection of ovarian cancer in the general population [6], a position subsequently supported by other organizations [7-9].

On the one hand, reports on early detection of the disease based on clinical signs and symptoms failed to identify a reliable pattern of clinical presentation [10, 11]. On the other hand, a large proportion of ovarian cancers are known to already be symptomatic even at an early stage [7, 12-16]. The problem lies in discovering a way to unify potential symptoms and suggestive clinical findings into a tool for enhancing the yield of a screening process.

The CADET (cancer risk evaluation and early detec-

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tion) software was developed to assist physicians to assess the risk for cancer in a specific patient, based on a detailed self-reported questionnaire. This study aimed to assess the correlation between positive CADET scores and abnormal ultrasonographic ovarian findings in order to establish the utility of the CADET score as a screening tool for ovarian cancer to be used by general practitioners in the community. We hypothesized that if such a correlation did exist, the CADET questionnaire might become a screening tool to be used by general practitioners who do not have routine access to ultrasound (US) examination of their patients. Thus, the CADET score may identify patients who require a more specific investigation for the presence of the disease.

Materials and Methods

Approval for this study was obtained from the "Maccabi" Health Care Services ethics committee. The study population included all peri- and postmenopausal women who saw their community gynecologist for a routine check-up between January 2008 and June 2008, women who filled in the CADET questionnaire pertinent to ovarian cancer before being examined by their gynecologists and who were subsequently referred to routine transvaginal pelvic sonography, were eligible for study entry after signing an informed consent form. Excluded were women who were not examined routinely, not peri- or postmenopausal or did not fill in the questionnaire. All the relevant clinical information on each woman was provided to us by the computerized data base of the health service. The data retrieved from the questionnaire were processed by the CADET software, and a specific score was assigned to each woman based on her responses to the items included in the questionnaire. The treating gynecologists were unaware of the patients' CADET scores when they later interviewed and examined them.

The CADET software is based on an algorithm which ntegrates data on signs, symptoms and risk factors from medical, surgical and oncological textbooks, national cancer organizations and NIH statistical bulletins, MEDLINE publications and epidemiological reports. These data apply to the different stages of various types of cancer, and incorporate an individual's familial and environmental risk factors. The questionnaire includes items on medical history, family history, signs and symptoms, and presence of cancer risk factors [APPENDIX A]. The results are then processed by the software to produce specific cancer risk score [17, 18].

The diagnostic transvaginal pelvic sonographic scans were reviewed by US specialists who are highly qualified in interpreting ovarian pathology. We compared their findings with the CADET scores in order to assess the correlation between positive CADET scores and abnormal ovarian findings on sonography.

Statistical analysis

The Fisher's Exact test was used for assessing proportions and the Student's t test was applied for continuous variables. A two-sided p value < 0.05 was considered as being significant.

Results

A total of 181 peri- or postmenopausal women who went to their gynecologists for routine check-ups were eligible for study recruitment. The final study group consisted of 154 women who were referred for routine US evaluation and whose scan results and CADET scores were available. All the relevant data including patients' age, age at menopause, duration of menopause, US scan results and CADET scores were reviewed.

Table 1. — *Demographic characters of women with normal and abnormal ultrasonographic findings*.

	Group A = abnormal (n = 38)	Group B = normal (n = 116)	p value
Age (years)	58.8 ± 7.0	59.3 ± 6.4	NS
Age at menopause (years)	51.2 ± 4.5	50.3 ± 3.8	NS
Duration of menopause (years)	7.8 ± 7.6	8.7 ± 6.8	NS

Values are presented as mean ± SD; NS, non-significant.

Table 2. — *CADET scores of women with normal and abnormal ultrasonographic findings*.

	Group A = abnormal (n = 38)	Group B = normal (n = 116)	p value
Positive CADET score, n (%)	13 (34)	52 (45)	NS
CADET score ≥ 2.0, n (%)	3 (23)	25 (48)	NS
CADET score*	0.8 ± 1.7	1.7 ± 2.5	NS

* Values are presented as mean ± SD; NS, non-significant.

Thirty-eight of the 154 women (24%) had abnormal ovarian findings on their US examinations (30 simple cysts and 8 complex adnexal findings, Group A), while the other 116 women (76%) had normal US findings (Group B). Demographic characteristics were similar in both groups (Table 1). Thirteen of the 38 Group A women (34%) and 52 of the 116 Group B women (45%) had positive CADET scores (p = NS). The difference in the average CADET score of each group also did not reach a level of significance (0.8 ± 1.7 for Group A and 1.7 ± 2.5 for group B, p = NS). The scores of three of the 13 women in Group A (23%) and 25 of the 52 women in Group B (48%) were in the higher end of the CADET score (≥ 2.0). This difference was not significant (Table 2). Although the CADET score was higher in the sub-group of women with complex adnexal findings (1.95 ± 3.2), it did not reach statistical significance when compared to the score of women with either simple cysts or normal US adnexal findings.

Discussion

The rate of complete cure of early diagnosed ovarian cancer is about 90%, and thus the lack of efficient screening tools for early diagnosis of ovarian cancer is inarguably the major reason for ovarian cancer being the leading cause of death from all cancers of the female reproductive tract. To date, studies which focused on strategies to diagnose ovarian cancer at an early stage failed to identify a specific and reliable symptom pattern. The early clinical signs and symptoms of ovarian cancer are loss of weight, bloating, and abdominal discomfort which are non-specific and it is still unclear if and how it would be possible to incorporate them into a screening tool for expediting the detection of ovarian cancer.

Appendix A

The CADET questionnaire

Please answer all the questions even if your answer is NO.

		YES	NO
FT	Have you ever given birth?		
FTb	Have you ever undergone infertility treatments?		
F7c	Have you ever used oral contraception pills?		
	Have you ever been diagnosed with:		
F18	Endometrial (uterine) cancer		
F18b	Ovarian cancer		
F18c	Breast cancer		
F18d	Colon/rectal cancer		
F22	Multiple cysts in the ovaries		
	Has anyone in your family (parent, sibling, aunt/uncle) ever been diagnosed with:		
F19b	Ovarian cancer		
F19c	Breast cancer		
F19d	Colon/rectal cancer		
	If you were examined for the presence of the breast/ovarian cancer gene was it mutated?		
F20b	BRCA-1		
F20c	BRCA-2		
	Do you feel that you:		
I8	Lost more than 5 kg during the last 3 months without intention to do so		
I8b	Have an unusual lack of energy		
I8c	Have an abnormal degree of constipation		
I8d	Have an unusual lack of appetite		
I8e	Have an abnormal degree of diarrhea		
I8f	Have an abnormal degree of nausea		
I65	Have had an unusual feeling of fullness in the rectum or anus during the past year		
	If you have any abdominal pain or discomfort, which of the following applies:		
J1	Pain that gradually increased over the past few months		
J5	Pain in the lower abdomen		
J9	Abdominal pain that wakes you up at night		
J11	Any other type of abdominal pain		
	Do you feel:		
J15	An unexplained feeling of fullness		
J15b	Bloating, fullness and/or an unusual pressure in the abdomen or pelvic region		
J16	Feeling bloated		
J17	That your meals are not digested well enough		
J18	Pressure in the lower abdomen		
J21	Over-activity of your bowel		
	Did you recently notice any of the following:		
K4	Urgency in urination (difficult or impossible to control the urge to urinate)		
K4b	Pain during urination		
K5	More frequent urination		
	If you have back pains, which applies to you:		
L1	Pain which is only during night time, or more severe pain at night		
L3	Back pain combined with abdominal pain		
L3b	Unusual lower back or abdominal pain		
L4	Pain that is aggravated upon lying down and relieved upon sitting		
L5	Recent onset of pain		
L6	Pain which has recently become more severe		

We assessed the correlation between the replies to a self-reported computer-analyzed questionnaire (CADET software) and US findings in peri- and postmenopausal women who underwent a routine gynecological check-up. We hypothesized that a high CADET score might correlate with abnormal ovarian findings on sonography, and thus identify women at higher risk for developing ovarian cancer. Our results did not bear out the existence of such a correlation. The same proportion of women with abnormal and those with normal ovarian findings on US scans had a positive CADET score. Both groups also had a similar mean CADET score. The differences in the proportion of women in both groups with the higher CADET scores were also not significant.

One explanation for the lack of correlation may lie in the items that were chosen for the patients' questionnaire and the relative weight they were assigned in the CADET score analysis. It should be borne in mind that the CADET score is aimed at identifying women who are at higher risk of developing ovarian cancer and not to predict those who will have abnormal US findings. Women with abnormal ovarian findings on sonographic scans will not necessarily develop ovarian cancer, and women with normal US findings are not exempt from developing ovarian cancer. This is clearly supported by the fact that most of the abnormal ovarian findings in our current study were, in fact, simple cysts which were not suspicious for an existing or future ovarian malignancy. The group of women with a high CADET score (resulting from a higher reported incidence of early signs and symptoms) may well be at higher risk of developing ovarian cancer, even though no abnormal ovarian findings were discovered on their scans. The lack of correlation we found between the CADET scores and abnormal sonographic ovarian findings discourage the use of this tool to replace sonographic scans in the general population. Transvaginal us remains, non sensitive and specific as it is, the only acceptable tool for discovering ovarian abnormalities which require further investigation.

Kim *et al*. used a symptom index as a screening tool to compare ovarian cancer patients and healthy controls [19]. This type of screening has the disadvantage of a recall bias since patients are more likely to recall the appearance of symptoms before the diagnosis of a disease, whereas healthy controls do not pay such attention to temporary inconveniences. Pavlic *et al*. also attempted to use a symptom index as a screening tool [20]. Their study has the disadvantage of enlisting only women who underwent transvaginal US rather than general patients attending the clinic. Another inherent bias in screening by means of a symptom index is the limited number of items in a questionnaire which is based on patient symptoms alone. We attempted to overcome this bias by extending the questionnaire items and by including the complete CADET algorithm incorporating personal and family history and cancer risk factors.

In conclusion, we found that the CADET software could not identify peri- and postmenopausal women who had abnormal US findings. However, a longer follow-up

period should be undertaken in order to disclose the accurate risk of developing ovarian cancer in women with a high CADET score when compared with women with low CADET scores.

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