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# The potential and problems of screening for ovarian cancer

**Y. Yokoyama,** *M.D.*; **T. Higuchi,** *M.D.*; **H. Mizunuma,** *M.D.*

*Department of Obstetrics and Gynecology, Hirosaki University School of Medicine, Hirosaki (Japan)*

**Summary**

Screening for ovarian cancer using tumor markers is simple but often associated with an increased rate of false negatives and a low rate of detection of early stage cancers. The transvaginal ultrasonic method, on the other hand, detects an increased number of Stage I cancers (about 70% of the total cancers detected), but it takes time. Our method is performed in a short time and is most suitable as a screening method. Although there is no established assessment of ovarian cancer screening, we have outlined the potential and the problems associated with it based on the reports published to date and the results of our study.

*Key words:* Screening for ovarian cancer; Transvaginal ultrasonography; Tumor marker.

## Introduction

Ovarian cancer has been believed to have the poorest prognosis among the gynecological cancers. However, recent clinical results on the treatment of ovarian cancer indicate a good prognosis for those detected at an early stage [1]. Consequently, the early diagnosis and treatment of ovarian cancer are considered to be important to improve the therapeutic outcome. There are several methods available for the early diagnosis of ovarian cancers, and tumor markers or ultrasonography are mainly used for screening now. We have used transvaginal ultrasonography (TVS) for screening for some time. In this paper, we discuss the results obtained to date and review the potential and problems of ovarian cancer screening referring to the literature.

## Results of screening using a tumor marker or TVS

Numerous reports on attempts to operate ovarian cancer screening systems have been made, but generally the screening system is inefficient and the number of patients undergoing screening is small. Table 1 shows the screening methods practiced in relatively large patient groups [2-7]. Tumor markers are used independently or in a combination with several markers. Jacobs *et al.* [4] conducted a detailed follow-up study over five to ten years using CA125. They measured CA125 levels in the sera of 22,000 asymptomatic, postmenopausal volunteers aged 45 years and older. They detected 767 women (3.5%) with abnormal serum CA125 levels, defined as 30 U/ml and higher, and found ovarian cancer in 23 of these subjects (3.0%). However, 26 subjects who responded negatively to the CA125 test had ovarian cancers. Therefore, the detection rate of the CA125 test is poor, with only 23 out of 49 subjects (46.9%) with ovarian cancer correctly diagnosed as positive for the disease. Of the 49 patients found with ovarian cancer 16 patients were diagnosed with clinical Stage I disease (32.7%), four patients with Stage II disease (8.2%), 22 patients with Stage III disease (44.9%), and seven patients with Stage IV disease (14.2%), hence the detection rate of Stage I cancer was low.

In contrast, ultrasonography uses a transabdominal method, a transvaginal method or a color Doppler method with the transvaginal method most frequently reported. The group of van Nagell *et al.* [6] has devised a screening method to calculate ovarian volume using the transvaginal method and has investigated in detail. They have defined an abnormal ovary as greater than 20 mm3 in size prior to menopause and greater than 10 mm3 postmenopause and this has become a standard in Western countries. They screened 14,469 asymptomatic women, detected abnormalities in 180 patients (1.2%) and found cancer in 17 patients (0.9%). Eleven patients were diagnosed with Stage I disease (64.7%), and three patients were each diagnosed with Stage II and III disease (17.6%). We have devised and reported a screening method that measures the longest axis of the ovary using a transvaginal method [7]. We examined 51,550 asymptomatic women and by selecting patients with ovaries exceeding 30 mm on the longest axis, detected 5,309 abnormal cases (10.3%) of which 24 women (0.5%) had ovarian cancer. Seventeen patients were diagnosed with stage I disease (70.8%), two patients each with Stage II and III disease (8.3%), one

Table 1. — *Methods and results of screening for ovarian cancer.*

| Author | Methods | Number of total subjects | Number of abnormal subjects | Number of detected cancers |
|---|---|---|---|---|
| Vuento *et al.* [2]* | Color Doppler | 1.364 | 160 | 1 |
| Adonakis *et al.* [3] | CA125 | 2.000 | 18 | 3 |
| Jacobs *et al.* [4] | CA125 | 22.000 | 767 | 23 |
| Jacobs *et al.* [5] | CA125 | 10.958 | 468 | 6 |
| van Nagell Jr. *et al.* [6] | TVS | 14.469 | 180 | 17 |
| Sato *et al.* [7] | TVS | 51.55 | 5.309 | 24 |

*: reference number; TVS: transvaginal ultrasonography.

patient had Stage IV disease (4.2%), and two patients had metastatic cancer (8.3%). The difference in the abnormality rates between the two methods is thought to depend on whether age is considered and whether our method checks for the presence of a functional mass before menopause. It is also thought that the difference in the rate of cancer detection is attributable to the difference in cancer morbidity between Western countries and Japan.

Our screening study is the largest reported. Approximately 70% of the cancers found by TVS were Stage I and this is the main difference from those found by tumor marker screening.

## Problems in the current ovarian cancer screening

The strongest feature of tumor marker screening is the simplicity of the test. A blood sample is the only requirement and this may be obtained quickly and easily. Therefore, the method is suitable for screening a large number of subjects. However, problems in sensitivity and specificity in the measurement and assessment, as well as the expense of the test are problematic. Consequently, a higher rate of false negatives is often associated with tumor marker screening as indicated by the result of Jacobs *et al.* [5]. It is impossible to detect all ovarian cancers of differing histological types using one tumor marker and even a combination of various tumor markers is still insufficient. At present, about one-half of cancers are considered to be detectable by screening with tumor markers.

Ultrasonography, on the other hand, detects an ovarian mass directly and its objectivity is clearer than the tumor marker method in this point. The most common problems associated with ultrasonography are the time taken for the examination and the evaluation criteria. The time of examination is affected by the particular method employed. The transabdominal method seems to be simple but the bladder must be filled and it is unsuitable to image small tumors due to a lack of resolution. In contrast, the transvaginal method must be performed on a pelvic examination table but this is not disadvantageous because uterine cancer screening may also be carried out at the same time and the detection of small tumors is possible within the limits of the resolution. Thus, the transvaginal method is the preferred method for screening at present. The result obtained by the transvaginal method is usually assessed by calculating the ovarian volume depicted or by applying image findings. However, these methods require time for the examination, have problems as a screening method and tend to be avoided by the examiners. Our method of measuring the longest axis alone is performed very quickly and is applicable to screening [7]. It seems appropriate to set the evaluation criterion for ovarian volume at 20 $mm^3$ and over prior to menopause and at 10 $mm^3$ and over postmenopause, and to set the criterion for the longest axis of the ovary at 30 mm and over based on the results obtained so far. It is considered difficult to use image findings in this screening due to the complexity of classification and the difficulty in the interpretation of the findings.

## Potential of ovarian cancer screening

Mackey and Creasman [8] explored the literature written in English in 1995 and evaluated ovarian cancer screening methods using tumor markers (CA125 in particular), transabdominal and transvaginal ultrasonography, and transvaginal color Doppler ultrasonography. They noted that an extensive and long-term study to compare the death rate between women undergoing screening and those not undergoing screening is required before any conclusions may be drawn on the effectiveness of the screening method. The NIH consensus conference in 1995 stated that screening using CA125 or TVS is ineffective in decreasing the death rate from ovarian cancers [9].

Jacobs *et al.* [5] conducted a pilot study to examine the effect of screening using a tumor marker (CA125) and ultrasonography in postmenopausal women aged 45 years and over in the U.K. In the study group (10,958 subjects), screening was performed every year for three years and ovarian cancers were found in 16 subjects in the observation period of seven years while 20 out of 10,977 control subjects were found to have ovarian cancers. The median survival period in the screened group was 72.9 months, which was significantly longer than the median survival of 41.8 months in the control group. Nine deaths occurred in the screened group and 18 in the control group but the difference was not statistically significant. This result has suggested a need for more extensive randomized controlled trials.

These conclusions are to be expected considering that the number of subjects undergoing ovarian cancer screening is still small, tumor marker screening is associated with a high rate of false negatives, particularly for early stage cancers, and ultrasonographic screening takes time. In the current study, we have presented literature published after these conclusions were made and our method using TVS can be expected to be a reliable method for screening for early ovarian cancers (Stage I cancers). Our screening method has not proved to be an effective method due to the low morbidity rate of ovarian cancers in Japan, but it could become effective if the morbidity rate were as high as those in Western countries.

In a study on the cost effectiveness of ultrasonographic screening, Pavlic *et al.* [10] calculated detailed screening costs based on their experience of ovarian cancer screening using TVS performed at their institution since 1988 and concluded that it is beneficial to undergo screening. Whereas their screening method cost more than $600 per person initially, it can now be performed for $25. According to their estimates, the total cost is $80,000 or less, based on the assumption that the cost for screening to detect one ovarian cancer is $25. The tumor detection rate by TVS is one in 1,000 and the treatment cost is only $10,000 because the ovarian cancers detected are mostly Stage I cancers and other

expenses account for $45,500. However, since the cost of treatment of a patient from the discovery of an advanced cancer to death is calculated to be $250,000, transvaginal ultrasonic screening brings a benefit of approximately $100,000.

It is highly unlikely that this calculation is applicable to Japan because the morbidity rate of ovarian cancer in Japan is much lower than those in Western countries. However, the rate of ovarian cancer is expected to increase in Japan in the future and, therefore, it is necessary to establish a more effective method of detecting ovarian cancers at an early stage as one of the measures to deal with this increase. In addition, the following points can be made about the effects of our method of ultrasonic screening; 1) the introduction of ultrasonic screening to general clinical practice as a result of commercialization of the method has increased the detection rate of patients with asymptomatic ovarian cancers, 2) consequently, the ratio of Stage I cancers has exceeded that of advanced cancers and, as the recovery rate of Stage I cancers in our hospital is about 90%, this has led to an improvement in recovery rate, and 3) simultaneous surgery with uterine cancer screening has established the utility of the method as a general gynecological screen.

The usefulness of ovarian cancer screening has not been demonstrated yet. However, our method may be an effective screening method for ovarian cancers if the incidence of ovarian cancer increases in the future.

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Address reprint requests to:
Y. YOKOYAMA, M.D.
Department of Obstetrics and Gynecology
Hirosaki University School of Medicine
5-Zaifu-Cho
Hirosaki 036-8562 (Japan)