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CLINICAL ARTICLE

# Serum CA125 level before the development of ovarian cancer

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**KEYWORDS**
CA125;
Ovarian cancer;
Natural history;
Prospective study

**Abstract**

*Background:* Little is known about the natural history of ovarian cancer with respect to the change of serum CA125 level. *Methods:* The Shizuoka Cohort Study on Ovarian Cancer Screening (SCSOCS) Trial contains approximately 100,000 data on serum tumor marker CA125 prospectively obtained from more than 70,000 women. We reviewed the clinical charts and collected serum samples 2 months to 9.4 years prior to the surgery were available. *Results:* In 396 (95%) of the 419 patients with ovarian cancer, one serum sample was present before the diagnosis (mean, 4.1 years). The change of CA125 level before the diagnosis of ovarian cancer could be clearly separated into two groups according to the length of the following intervals: 47% (107/228) of patients with non-serous-type ovarian cancers develop secondarily from slightly elevated CA125 level (35 $<$CA125 $<$65 U/ml), with a mean interval of 3.8 years. On the other hand, 75% (126/168) of patients with serous-type ovarian cancer seem to develop suddenly from a normal CA125 level (CA125 $<$35 U/ml), with a mean interval of 1.4 years ($p$=0.011). *Conclusions:* The slightly elevated CA125 level is typically present many years before the diagnosis especially in patients with non-serous-type ovarian cancer. However, serous-type ovarian cancer may exhibit a rapid progression possibly through de novo carcinogenesis.
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## 1. Introduction

The natural history of the development of ovarian cancer is not known. It also remains undetermined whether ovarian cancers develop from benign or borderline malignant tumors or arise de novo from the ovarian surface epithelium. There has been considerable interest in the prospect of early detection of ovarian cancer through screening asymptomatic women, in

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both the general and high-risk populations [1]. Over the last decade screening strategies using the serum marker CA125 and transvaginal ultrasound (US) have been refined and encouraging data have emerged on the impact of screening on ovarian cancer survival rates [1]. Rectovaginal examination, US, and the CA125 blood test are three modalities currently used to screen for ovarian cancer, although no universal ovarian cancer screening guidelines are recommended for the general population [2]. Other paper reported that the most effective screening method for ovarian cancer is transvaginal US [3]. At present, however, ovarian cancer screening in the general population using US examinations as well as CA125 blood test is an experimental technique [4]. Developments in the early detection of ovarian cancer are emerging and include blood tests that could lead to identify asymptomatic, early stage ovarian cancer [5].

Epithelial ovarian cancer is virtually accompanied by elevation of serum CA125 level. Although the prevalence of serum CA125 among patients with confirmed ovarian cancer has been established, we know little about the natural history of patients before ovarian cancer is diagnosed with respect to the change of serum CA125 level.

We evaluated a prospectively assembled collection of serum samples to know when serum CA125 level changes prior to the diagnosis of ovarian cancer. The Shizuoka Cohort Study on Ovarian Cancer Screening (SCSOCS) Programme contains more than 100,000 serum samples during 1985 and 2002. A review of the SCSOCS medical records identified 419 women with ovarian cancer and for whom stored serum samples obtained before diagnosis was available.

## 2. Methods

### 2.1. Study design and review of medical records

To establish a new ovarian cancer screening strategy, the SCSOCS Trial started in September 1985 as a part of the Cancer Registration System established in January 1982. The trial was carried out at 212 hospitals in Shizuoka Prefecture in Japan. The participants were living in 35 townships. Cases of ovarian cancer were ascertained by computerized linkage of data with information from the Shizuoka Cancer Registry (SCR). The SCR search covered the period from January 1982 (3 years before the start of the SCSOCS study). Women who visited a hospital for gynecologic examination including cancer screening were invited to participate in the SCSOCS Trial. Eligibility criteria of this part of the SCSOCS included asymptomatic women between the ages of 45 and 85 years and are residents of Shizuoka. From September 1985 to December 2002, a total of about 70,000 women participated. Exclusion criteria were: 1) a history of bilateral oophorectomy and 2) cancer had been diagnosed at any time before registration. The size of the population in the Prefecture that would have been screening eligible is approximately 850,000. Each woman who enrolled received pelvic examinations, serum CA125 determination and transvaginal (occasionally transabdominal) US performed by gynecologists. Each participant filled in a standard questionnaire, which includes age, parity, marital status, use of hormone, current or previous smoking history, and family history of cancer.

If the US scan was normal and serum CA125 value of 35 U/ml or less, no further action was taken. They returned for repeat scans every year (Recall). Women with scan findings of clinical impression of benign disease returned for repeat scans every 3–6 months. Scans were done in a regional hospital by a gynecologist. They were referred for appropriate medical evaluation. Women with abnormal US findings (clinical impression of malignant disease) and/or raised CA125 values ($\geq$35 U/ml) were referred for appropriate further medical evaluation or for surgical investigation by a gynecological oncologist. They had a repeat scan before surgery to confirm the findings. When the CA125 level was above a threshold and the pelvic US was negative the women were invited to a new re-screening round after a 6-month interval (Early Recall). If the CA125 levels and US were considered normal, the interval to the next screening round (routine recall) was one year, and they were again re-invited after a one-year interval (as the 3rd, 4th or 5th screening). Investigators responsible for determining the CA125 levels were aware of the participants' clinical status. All women in the intervention group, including previous non-responders, were re-invited annually unless they requested not to be invited again.

The report of a diagnosis of disease including cancer from a participant was checked against medical records from the hospital where the disease including cancer had been diagnosed. The validity of benign and malignant ovarian masses in the SCSOCS has been found to be in accordance with the registration at the local hospitals. Index cancers were defined as primary epithelial carcinomas of the ovary. The medical records, ovarian ultrasonographic, other radiological studies, and pathologies were reviewed by the investigators. Pathological diagnosis was reviewed retrospectively by specialists, who are experienced pathologists.

In cases of death, the cause was investigated by a review of hospital records and autopsy reports. The status of patients lost to follow-up was checked at intervals with the Death Registry in Shizuoka, so that no instances of death would be missed. Incident ovarian cancer cases occurring in the entire cohort were identified by record linkage to the SCR. This register covers the entire Shizuoka population including diagnoses of ovarian cancer and time of death. New cases of cancer were generally registered immediately after diagnosis. Entries within this registry have proved to be accurate in 96% of cases.

In December 2002, the code was broken and the SCSOCS and SCR were searched to determine both malignant and nonmalignant diagnoses. These registries included entries of all in-patients and all cancer diagnoses made throughout Shizuoka Prefecture. Patients in whom cancer had been diagnosed at any time before registration, according to information from the patient's history and from medical records available to the investigator, were excluded from the study. To obtain information on vital status of registered cases, the SCR has used the following three steps: 1) collation with annual cancer death file, 2) collation with annual death certificate file in Shizuoka, and 3) confirmation of the cases' living status by referring to registers in local municipality offices of inhabitants.

The protocol was reviewed and approved by the institutional review board of the Hamamatsu University School of Medicine. Informed consent for the testing of coded, stored ultrasound pictures and the review of records by appropriate personnel was waived by this institution. To protect the privacy of the patients, their names and unique personal information were not recorded or released. The dates of the sampling and the analyses ranged from 1985 to 2002.

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