Risk of diagnosis of ovarian cancer after raised serum CA 125 concentration: a prospective cohort study

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Abstract

***Objective*—To determine the risk of invasive epithelial ovarian cancer and fallopian tube cancer associated with a raised concentration of the tumour marker CA 125 in asymptomatic postmenopausal women.**

***Design*—Serum CA 125 concentration was measured annually in study participants for one to four years. Participants with a concentration ≥30 U/ml were recalled for abdominal ultrasonography. Follow up was by annual postal questionnaire.**

***Setting*—General practice, occupational health departments, ovarian cancer screening unit in a teaching hospital.**

***Subjects*—22 000 volunteers, all postmenopausal women ≥45 years of age; recruited between 1 June 1986 and 1 May 1990.**

***Intervention*—Surgical investigation if the ultrasound examination was abnormal.**

***Main outcome measures*—Cumulative and relative risk of developing an index cancer (invasive epithelial cancer of the ovary or fallopian tube) after a specified CA 125 result.**

***Results*—49 index cancers developed in the study population during a mean follow up of 6.76 years. The overall cumulative risk of developing an index cancer was 0.0022 for the entire study population and was lower for women with a serum CA 125 concentration <30 U/ml (cumulative risk 0.0012) but was appreciably increased for women with a concentration ≥30 U/ml (0.030) and >100 U/ml (0.149). Compared with the entire study population the relative risk of developing an index cancer within one year and five years was increased 35.9-fold (95% confidence interval 18.3 to 70.4) and 14.3-fold (8.5 to 24.3) respectively after a serum CA 125 concentration ≥30 U/ml and 204.8-fold (79.0 to 530.7) and 74.5-fold (31.1 to 178.3) respectively after a concentration ≥100 U/ml.**

***Conclusion*—CA 125 is a powerful index of risk of ovarian and fallopian tube cancer in asymptomatic postmenopausal women.**

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Introduction

The CA 125 antigen is a glycoprotein with a high molecular weight that is expressed by most epithelial ovarian cancers and is recognised by a monoclonal antibody (OC 125). Since the initial reports of CA 125[1 2] numerous publications have assessed the use of this marker in the management of ovarian cancer. Serum CA 125 concentrations are raised preoperatively in 85% of epithelial ovarian cancers and have an established role in differential diagnosis of ovarian cancer, the monitoring of disease status during treatment, and surveillance during follow up.[3]

The role of CA 125 in screening for early stage ovarian cancer is currently under investigation. We have previously reported the results of a prevalence screen of 22 000 postmenopausal women using a multimodal approach incorporating the sequential combination of serum CA 125 measurement and ultrasonography.[4 5] Although serum CA 125 measurement has limitations of sensitivity and specificity, it probably has a role as one component of a multimodal approach to screening. Serum CA 125 concentrations are raised before the diagnosis of ovarian cancer in a significant proportion of patients.[5 6-9] Furthermore, in prospective studies of screening using serum CA 125 measurement ovarian cancer has been diagnosed at a preclinical stage.[4 5 7] The precise level of risk of ovarian cancer associated with defined serum concentrations has not been reported. Long term follow up and interval screening of the cohort of volunteers from our prevalence screen has provided a unique dataset. On the basis of this information we are able to report the relation between serum CA 125 concentration and subsequent risk of ovarian cancer.

Method

SUBJECTS

In all, 22 000 volunteers were registered with the study between 1 June 1986 and 1 May 1990. Volunteers were recruited via media publicity and several companies' occupational health departments and from the age-sex register of collaborating general practitioners in England, Scotland, and Wales. Eligibility criteria for the study were age ≥45 years and postmenopausal status (more than one year of amenorrhoea). Exclusion criteria were bilateral oophorectomy and ovarian cancer. After the prevalence screen 21 961 volunteers remained eligible, of whom 11 085 selected by computerised random number allocation were invited to participate in annual incidence screens for a further three years. Of these women, 9558 (86.2%) were willing to participate, and on review of their returned datasheets 9344 (84.3%) were still eligible to do so. The 10 876 volunteers who were not randomly selected for further screening were contacted by post, and those who were eligible and did not wish to withdraw from the study (10 120) were followed up annually by postal questionnaire. Women randomised to annual incidence screening were followed up with the questionnaire in years when they did not attend for screening.

CA 125

Venepuncture was performed either in the ovarian cancer screening unit at The Royal London Hospital or in an occupational health department or general practice collaborating with the study. Blood samples taken outside the unit were sent by first class post. All CA 125 assays were performed in the laboratory at the screening unit. Blood samples were centrifuged at 3000

Table 1—*Summary of number (percentage) of volunteers, screens, and women with serum CA 125 concentration ≥30 U/ml*

Group of volunteers	Volunteers	Screens	Mean screens per volunteer	Volunteers with CA 125 ≥30 U/ml	Samples with CA 125 ≥30 U/ml
Total study population	22 000	47 755	2.2	767 (3.5)	1180 (2.5)
Documented index cancer*:					
No	21 951	47 681	2.2	744 (3.4)	1155 (2.4)
Yes	49	74	1.5	23 (47)	25 (34)
One screen only	12 677	12 677	1.0	192 (1.5)	192 (1.5)
More than one screen	9323	35 078	3.8	575 (6.2)	988 (2.8)

*Epithelial cancers of the ovary and fallopian tube.

rpm for 10 minutes and serum separated in 300 µl aliquots for storage at −20°C. CA 125 radioimmunoassays were performed with a commercial kit (Abbott Laboratories, Chicago) according to the manufacturer's instructions. The selection of a CA 125 cut off was a compromise between the objective of high sensitivity and the limits of assay performance. A cut off at 30 U/ml was chosen as this was the lowest CA 125 concentration at which satisfactory assay reproducibility could be achieved at the outset of the study.

SCREENING TESTS

The screening strategy has been described previously.[5] Briefly, the primary screening test entailed venepuncture for serum CA 125 measurement: volunteers with a concentration of ≥30 U/ml were recalled for ultrasonography. If ovarian volume was abnormal (>8.8 ml) referral for surgery was arranged. Details of the results of the multimodal screening strategy will be reported separately. This report relates only to the serum CA 125 results measured at the prevalence screen and at the three or fewer annual incidence screens.

CANCERS

Volunteers were contacted annually either through attendance for screening or by postal questionnaire. The questionnaire asked for information about any hospital attendance during the previous year. When a reply suggested a possible gynaecological malignancy further enquiries were made with the general practitioner and hospital involved and a surgical and a histopathological report obtained. Index cancers were defined as primary invasive epithelial carcinomas of the ovary and fallopian tube. Fallopian tube cancers were included for several reasons. Firstly, stage for stage these tumours have a similar prognosis to epithelial ovarian cancers. Secondly, evidence exists that advanced stage fallopian tube carcinomas may be misdiagnosed as ovarian cancers, and these cancers would therefore be classified as false negative cases. Thirdly, we have previously reported the detection of fallopian tube carcinomas using this screening protocol.[5 10]

ANALYSIS

The expected risk of index cancers was calculated from cancer incidence tables of the Office of Population Censuses and Surveys (now the Office for National Statistics)[11] on the basis of the age distribution of the study population as previously described.[5] The observed risk of index cancers among all study participants measured from the date of the prevalence screen was calculated by dividing the number of index cancers that had developed after a given time interval by the total number of individuals at risk. The risk of index cancers at time interval t after a serum CA 125 concentration satisfying a given criterion (for example, ≥30 U/ml) was calculated from (*a*) the number of index cancers developing within time t of a serum CA 125 concentration satisfying the criterion, divided by (*b*) the total number of individuals with any serum CA 125 concentration satisfying the criterion. When individuals who developed an index cancer had more than one CA 125 screen result the earliest result that satisfied the criterion was used in this calculation.

Cumulative risk curves were constructed by plotting the calculated risk values against time. The relative risk of cancer at a given time interval was calculated from (*a*) the calculated risk value for a specified CA 125 criterion (for example, ≥30 U/ml) at time t, divided by (*b*) the observed risk for the entire population at time t. Confidence intervals for the log risk estimates and log relative risk estimates were calculated using the Taylor series method.[12] Sensitivity was defined as the percentage of volunteers known to have developed an index cancer after a stated length of follow up after their last screen who were screen positive. Specificity was defined as the percentage of volunteers without an index cancer who were screen negative. Positive predictive value was defined as the percentage of screen positive volunteers who had an index cancer.

Results

The study population consisted of 22 000 women with a median age of 56 (range 45-85) years at the time of recruitment. The length of follow up for the volunteers ranged from 4.67 to 9.13 (median 6.68, mean 6.76) years. The postal questionnaire was not returned by 636 (2.9%) volunteers. In all, 49 index cancers had been identified in the study population by 31 July 1995, of which 16 were stage I, four stage II, 22 stage III, and seven stage IV at the time of diagnosis.

All 22 000 volunteers underwent the initial prevalence screen, with 8694, 8638, and 8423 undergoing the first, second, and third incidence screens respectively. In all, 47 755 screening test results for CA 125 were therefore available for this analysis (table 1). Of the 22 000 volunteers, 767 (3.5%) had at least one serum CA 125 measurement ≥30 U/ml during the study, and of the 47 755 serum samples, 1180 (2.5%) had concentrations ≥30 U/ml. Seventy two screens were performed among volunteers, with a subsequent diagnosis of an index cancer in 49 volunteers (36 had a single screen before diagnosis, six had two screens, four had three screens, and three had four screens). The sensitivity of CA 125 for detection of index cancers at one, three, five, and seven years of follow up was 75%, 54%, 48%, and 47% respectively. The overall specificity and positive predictive value of CA 125 were 96.6% and 3.1% respectively.

The cumulative risk of developing an index cancer in the entire study population on completion of the study was 0.0022 and was within the range expected from the data from the Office of Population Censuses and Surveys for a population of the same age distribution (0.0025, 95% confidence interval 0.0019 to 0.0032). In an unscreened population the cumulative risk would increase linearly with time, but owing to the impact of screen detection of preclinical cancers the observed cumulative risk increased steeply during the first year and then reached a plateau. Figure 1 shows the relation between serum CA 125 concentration and cumulative risk of developing an index cancer. Volunteers who did not have a serum CA 125 concentration ≥30 U/ml had a reduced risk of developing an index cancer at all time intervals including the end of the study (cumulative risk 0.0012, 0.0008 to 0.0017) compared with the entire study population (0.0022, 0.0018 to 0.0030). In contrast, the risk to individuals with a raised serum CA 125 concentration at screening was appreciably increased, and the risk was related to the raised concentration. Most of the increase in risk accrued in the year immediately after a raised serum CA 125 concentra-

tion. The risk one year after a concentration ≥30 U/ml, ≥50 U/ml, or ≥100 U/ml was 0.026, 0.083, and 0.149 respectively. On completion of the study the cumulative risk after a concentration of ≥30 U/ml or ≥50 U/ml had increased only slightly (0.030 and 0.089 respectively) and the risk following a concentration ≥100 U/ml was unchanged (0.149).

Relative risks were computed by taking ratios of the risks shown in figure 1. The highest relative risks were for a diagnosis within one year of a raised serum CA 125 concentration. A serum CA 125 concentration ≥30 U/ml was associated with a relative risk of 35.9 (95% confidence interval 18.3 to 70.4) during the year after a screen and 14.3 (8.5 to 24.3) during the five years after a screen. Higher CA 125 cut off concentrations were associated with further increases in the relative risk. For example, a concentration of ≥100 U/ml was associated with relative risks of 204.8 (79.0 to 530.7) and 74.5 (31.1 to 178.3) respectively. Women who did not have a concentration ≥30 U/ml had a reduced relative risk of 0.13 (0.03 to 0.58) and 0.54 (0.32 to 0.91) respectively.

Discussion

RISK FACTORS FOR OVARIAN CANCER

Raised serum CA 125 concentration at a screen in this study was associated with a substantially increased risk of developing ovarian cancer. The risk after a moderately raised concentration (≥30 U/ml) was one order of magnitude greater than after a concentration <30 U/ml, while the risk after a concentration >100 U/ml was more than two orders of magnitude greater. The increased risk for diagnosis of ovarian cancer occurred largely within a year of the raised serum CA 125 concentration. Several factors associated with risk of ovarian cancer have been identified by epidemiological and genetic studies. These include age, parity, oral contraceptive use, family history, and mutation of the BRCA1 gene. The increase in risk associated with age, parity, and a family history involving one relative is small and probably no greater than a threefold to fourfold increase in lifetime risk. The level of risk conferred by a strong family history of ovarian cancer is much greater. For example, in a family with two affected first degree relatives the probability that ovarian cancer is due to autosomal dominant inheritance of a gene such as BRCA1 is 66%. The daughter of an affected relative therefore has a 33% probability of inheriting the predisposing genetic abnormality, and as the penetrance of BRCA1 for ovarian cancer is 44%[13] her lifetime risk of ovarian cancer is approximately 0.15. This lifetime risk of ovarian cancer is similar to the level of risk documented in our study during the year immediately after a serum CA 125 concentration of ≥100 U/ml (0.149). These results establish that raised serum CA 125 concentration is a powerful index of ovarian cancer risk in postmenopausal women.

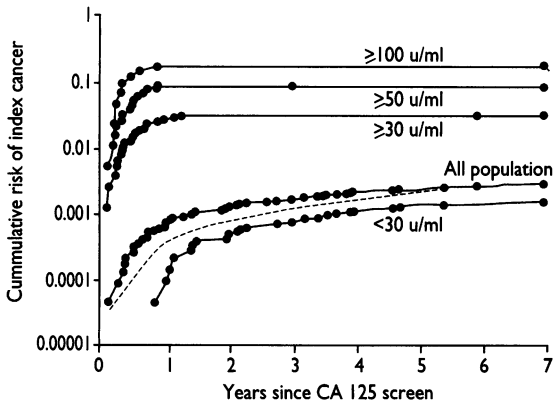

Fig 1—*Cumulative risk of developing index cancer (primary epithelial cancer of ovary or fallopian tube) after serum CA 125 screen. The dotted line represents expected cumulative risk in unscreened population of same age distribution*

Two features of the study design should be emphasised. Firstly, the study involved asymptomatic and postmenopausal women. The prevalence of conditions causing false positive raised serum CA 125 concentrations is higher in premenopausal women and the incidence of ovarian cancer lower than in postmenopausal women. For these reasons the level of risk observed in postmenopausal women is unlikely to apply to premenopausal women with a raised serum CA 125 concentration. Secondly, this study was an interventional screening study. The study design explains the observation that the increase in the risk of diagnosis of ovarian cancer after a raised serum CA 125 concentration was largely within a year of the screen. If the study had been observational the increase in risk would probably have spread over several years. This interpretation is supported by the shape of the curves for expected and observed cumulative risk (fig 1). The total number of observed cases seven years after screening was close to the number expected, but because of the lead time of detection by screening, the slope of the observed cumulative risk was steeper initially. Surgical intervention also explains the lower mean number of screens in volunteers who developed an index cancer (1.5) compared with the rest of the population (2.2) as no further screens were performed after diagnosis of an index cancer.

IMPORTANCE OF RAISED CA 125 IN NON-OVARIAN DISEASE

The importance of a raised serum CA 125 concentration for subsequent diagnosis of disease other than ovarian cancer has not been well documented to date. Of the 767 volunteers with a serum CA 125 concentration ≥30 U/ml, only 49 developed cancer of the ovary or fallopian tube. We have previously reported that on serial sampling, serum CA 125 concentrations in most individuals with initially raised concentrations fall to <30 U/ml.[14] A minority of postmenopausal women, however, have persistently raised concentrations. Not all of these women will develop ovarian cancer, and the cause of the raised concentration in those who do not is currently unclear. The volunteers with one or more serum CA 125 concentrations ≥30 U/ml are therefore being followed up closely to establish whether raised concentration is associated with subsequent development of benign or malignant disease other than an index cancer. There is no doubt that raised serum CA 125 concentration occurs in the advanced clinically apparent stages of several malignancies—for example, breast, lung, and colorectal cancers—but whether raised concentrations can indicate the preclinical stages of these cancers is uncertain. We have not yet identified an association between a raised serum CA 125 concentration and the preclinical stages of any cancers apart from those of the ovary and fallopian tube.

The role of serum CA 125 measurement in screening for ovarian cancer is not yet established. It is clear that serum CA 125 concentration is raised before clinical diagnosis in a significant proportion of ovarian cancers and that a raised concentration is associated with a high risk of ovarian cancer. Satisfactory specificity can be achieved by combining CA 125 with ultrasonography in a sequential screening strategy.[4,5] Recent evidence suggests that it may also be possible to improve sensitivity by estimating the risk from the temporal pattern of CA 125[15] and by the use of tumour markers complementary to CA 125.[16] Ultimately, the value of CA 125 in screening will depend on whether the high risk associated with raised serum CA 125 concentration occurs sufficiently early in the course of the disease for

Key messages

- Serum CA 125 measurement has an established role in monitoring, but not yet in screening for, ovarian cancer
- This study shows that raised serum CA 125 concentration is a powerful index of risk of ovarian cancer in asymptomatic postmenopausal women
- The risk in the year after a serum CA 125 concentration ≥100 U/ml is similar to the lifetime risk to women in high risk families
- The importance of a raised serum CA 125 concentration in relation to risk of other cancers is not yet known
- The role of CA 125 as a component of a screening strategy for ovarian cancer is under investigation, but the impact on mortality is not known

effective intervention to be possible. This issue will be resolved only when the results of the large scale randomised controlled trials that are under way in our own unit and elsewhere are available.

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Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study

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Abstract

***Objectives*—To examine the association of plasma caffeine concentrations during pregnancy with fetal growth and to compare this with relations with reported caffeine intake.**

***Design*—Prospective population based study.**

***Setting*—District general hospital, inner London.**

***Subjects*—Women booking for delivery between 1982 and 1984. Stored plasma was available for 1500 women who had provided a blood sample on at least one occasion and for 640 women who had provided a sample on all three occasions (at booking, 28 weeks, and 36 weeks).**

***Main outcome measure*—Birth weight adjusted for gestational age, maternal height, parity, and sex of infant. The exposures of interest were reported caffeine consumption and blood caffeine concentration. Cigarette smoking was assessed by blood cotinine concentration.**

***Results*—Caffeine intake showed no changes during pregnancy, but blood caffeine concentrations rose by 75%. Although caffeine intake increased steadily with increasing cotinine concentration above 15 ng/ml, blood caffeine concentrations fell. Caffeine consumption was inversely related to adjusted birth weight, the estimated effect being a 1.3% fall in birth weight for a 1000 mg per week increase in intake (95% confidence interval 0.5% to 2.1%). The apparent caffeine effect was confined to cigarette smokers, among whom the estimated effect was –1.6%/1000 mg a week (–2.9% to –0.2%) after adjustment for cotinine and –1.3% (–2.7% to 0.1%) after further adjustment for social class and alcohol intake. Adjusted birth weight was unrelated to blood caffeine concentrations overall (P = 0.09, but a positive coefficient), after adjustment for cotinine (P = 0.73), or among current smokers (P = 0.45).**

***Conclusions*—Smokers consume more caffeine than non-smokers. Blood caffeine concentrations during pregnancy are not related to fetal growth, but caffeine intake is negatively associated with**