Ovarian Cancer Screening

Tom Bourne, Karina Reynolds and Stuart Campbell

INTRODUCTION

THE DEPRESSING statistics relating to the treatment of ovarian cancer are well known. In the United Kingdom this year about 5200 women will develop this cancer, and at least 80% will have died of their disease within five years [1]. In the United States, the overall 5-year survival rate, regardless of stage, is around 36% [2]. The changes in management with regard to surgery, chemotherapy and radiotherapy over the last few years have done little to improve the survival rate for such patients. As a result it has been suggested that the detection of the disease at an earlier stage (i.e. by screening) may solve the problem. This is clearly a gross assumption, especially as so little is known about the natural history of ovarian neoplasia. However, with no breakthrough in the treatment of this cancer imminent, the investigation of possible screening tests must be regarded as a priority. Young et al. [3] have presented the results of two randomised studies of the treatment of stage I disease, demonstrating a disease-free interval of over 5 years for 90% of patients with well or moderately well-differentiated tumours. Length time bias may of course be a factor. However, these data give encouraging support to the view that if the cancer is detected when it is confined to within the capsule of the ovary, the outcome for the majority of women following surgery might be improved.

SCREENING

The low prevalence of ovarian cancer in the general population complicates the development of an effective screening procedure. Furthermore our relative lack of data concerning the initial stages of oncogenesis means that attempts at early detection are directed towards a stage of the disease that has not yet been identified. Clearly the problem is not an easy one. The World Health Organisation (WHO) have promulgated criteria that should be satisfied before a screening programme for a particular disease is started [4].

These criteria include the fact that there should be an early recognisable stage of the disease, and treatment at an earlier stage should improve the outcome. At the present time we have no data to show that treatment of ovarian cancer detected at screening will alter the mortality rate. Screening may preferentially find those cancers in the population with low biological activity (length time bias). An improvement in outcome would therefore not be a reflection of the screening procedure, as women with such tumours would do well regardless. Similarly whilst a cancer may be detected at an earlier stage, the chronological date of death of the patient may remain unchanged (lead time bias). These problems have been reviewed [5], and must be considered in the evaluation of screening programmes for any type of cancer. The answers can only be provided by the results of randomised trials. The issue that needs to be addressed

immediately is whether we are at a stage where such trials are required, and if so, what test or combination of tests should be used

POSSIBLE SCREENING TESTS

Pelvic examination is an important part of the gynaecological examination; however, small ovarian lesions are often missed. Attempts to use culdocentesis have had little success because of the invasive nature of the procedure. Radioimmunoscintigraphy may be used to detect some early disease but practical difficulties preclude its use as a first stage screening test. Consequently attempts to find a possible screening test for ovarian cancer have been limited mainly to the use of defined changes in the concentration of tumour-related antigens in the peripheral circulation and pelvic ultrasonography.

SERUM TUMOUR ASSOCIATED ANTIGENS

Ovarian cancer cell lines have been used as immunogens to isolate tumour-associated antigens which may be released into the peripheral circulation. The most clinically useful has been found to be CA 125. The role of this glycoprotein in the early diagnosis and management of ovarian carcinoma has been extensively reviewed [6]. The serum level of this marker is raised above 35 U/ml in about 80% of all ovarian cancers. However the incidence of elevated levels in patients presenting with stage I disease at surgery is somewhere between 30 and 50%. The best indication of the detection rate of CA 125 for early stage ovarian cancer is given by the data generated from the JANUS study [7]. Sera which had been taken from healthy volunteers were stored, retrieved and tested after 105 women from the cohort had presented with clinical signs of ovarian cancer. Using a cutoff level of 35 U/ml, about 33% of stage I cancers were detected with a lead time of 18 months. It is unlikely that any prospective study will show an improvement on these figures. The specificity of a test based on the measurement of serum CA 125 alone is not optimal. About 35 operations would have to be carried out on women with a positive test result in order to find one cancer. However this odds ratio can be improved substantially either by the use of ultrasound to visualise the ovaries [8], or by using serial measurements of serum CA 125 [9]. Attempts to improve test performance by combining the results from the measurement of several serum markers may optimise specificity, but always at the expense of sensitivity [10]. Conversely, their use to improve sensitivity is likely to decrease the specificity. Many of the papers relating to CA 125 screening fail to state the stages of the cancers that are detected, and are not clear regarding the cutoff values that were used. As a result the specificity of tests for ovarian cancer by the measurement of serum CA 125 is often dealt with in isolation without regard to overall performance. However, regardless of the mode of presentation, the data from the analysis of samples from the JANUS serum bank are unlikely to be improved upon [7]. A test that only has a sensitivity of 33% for the earliest stages of the disease hardly seems a credible first stage screening option, and attempts to improve this aspect are likely to compro-

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T. Bourne et al.

mise specificity still further. What is needed are more sensitive indices of early disease.

Some interesting results have been produced from the measurement of a novel urinary gonadotropin fragment [11]. Another marker, OV-TL 15, which is present in cyst fluid and tissue extracts has demonstrated potentially useful test characteristics [12].

It would be ideal if a simple urine or blood test could be used to detect ovarian cancer in its earliest stages. However, at this time those currently available are limited with regard to sensitivity and specificity. Indeed given the heterogeneity of ovarian carcinoma in general, the isolation of a marker with a raised concentration in the serum or urine of women with early stage disease may prove to be very difficult. To be optimistic, it can be argued that CA 125 can be used in a cost effective way. A proportion of women with cancers in the population would be identified on the basis of raised levels of serum CA 125. As a result a percentage of all cancers would be detected at an earlier surgical stage; this would lead to a limited reduction in mortality and perhaps morbidity from the disease.

ULTRASONOGRAPHY

Transabdominal ultrasound

Screening for ovarian cancer using ultrasound was first proposed by Campbell et al. in 1982 [13]. A close correlation was found between ovarian volumes as measured by abdominal ultrasonography and those found at laparotomy. Subsequently reference ranges were produced for possible use in a screening programme [14]. A large prospective study was initiated [15]. The aim was to use transabdominal ultrasonography to screen about 5000 asymptomatic women every 12 months on three occasions. The detection rate was claimed to be 100%, in the context of the expected prevelance of the disease in the study population. 5 stage I primary ovarian cancers, 4 metastatic ovarian cancers and 379 ovarian masses were found. The odds of finding an ovarian cancer at surgery were about 1 in 67, and the false positive rate was 2.3%. A retrospective analysis of the data showed that if a positive screen is redefined in terms of a volume change at the time of a repeat scan then the odds ratio can be improved to 1 in 50 [16].

At the present time the malignant potential of benign ovarian cysts is not clearly understood. Certainly it has been suggested by several authors that malignant transformation may occur within ovarian endometriosis [17], and from benign to malignant epithelium within serous tumours [18]. If these claims are substantiated, then the removal of benign lesions may be beneficial, leading to a reduction in the number of incident cases of ovarian cancer in the population. It is of interest to note that in the study of Campbell et al. [15] the number of women with an ovarian lesion within the cohort had dropped from 3.6% at the initial screen to 1.2% at the third. No cancers and only 4 benign epithelial tumours were detected at screen 3. In contrast, 91 benign and 6 malignant epithelial tumours were found in the first two screens. It may be that an initially normal scan means that the patient is at low risk of subsequently developing ovarian malignancy. A strategy involving one prevalence screen and one follow-up screen may represent a practicable approach to the problem of population screening. However, until the pathogenesis of ovarian cancer has been more clearly understood it is unreasonable to perform 51 operations on asymptomatic women in order to find one carcinoma. Methods must be found that can be used to reduce the false positive rate. In this way surgery may be avoided amongst women thought to have benign disease.

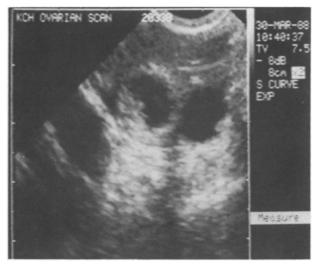


Fig. 1. Borderline serous cystadenocarcinoma within a normal volume ovary. Note the irregular cyst wall and solid projections.

As an alternative masses thought to be benign could be removed using pelviscopy rather than formal laparotomy [19].

Tissue characterisation using abdominal ultrasonography does not seem to be a safe practice. Campbell *et al.* [15] were unable to classify such lesions on the basis of morphological criteria. Andolf, on the other hand, found no cases of malignancy amongst 58 completely anechoic lesions less than 5 cm in diameter diagnosed by abdominal ultrasound [20]. These data suggest an unacceptable degree of uncertainty. However, the better resolution that can be obtained using transvaginal ulrasonography may enable such decisions to be made.

Tranvaginal ultrasound

By placing the ultrasound probe in the vagina, the transducer is positioned closer to the area of interest. As a result higher frequency ultrasound can be used, leading to greatly improved image quality. The technique of transvaginal ultrasonography has been described [21], and the ability to accurately demonstrate ovarian morphology and volume has been validated [22].

Data about ovarian morphology and volume are highly reproducible [23]. The role of transvaginal ultrasonography as a possible screening test for ovarian cancer in women from the general population has been investigated [24]. In this study 1000 asymptomatic women underwent vaginal ultrasonography. All those with a normal initial scan have been rescreened one year later, and no interval cancers have been detected. 9.2% of premenopausal women in the study had an abnormal scan initially; however, when the scan was repeated, only 3.8% had persisting abnormalities. This finding illustrates the fact that, in an ultrasound-based screening programme, any abnormality must be subjected to a repeat scan to avoid the removal of ovaries that are only undergoing transient physiological changes.

As more experience is gained with vaginal probes, it is believed by some that because of the technique's greater resolution, morphological criteria may be used to discriminate between benign and malignant ovarian lesions [25] (Figs 1 and 2). Morphology scores have been developed and applied retrospectively to effectively characterise ovarian pathology [26]. However, the review of old ultrasound pictures and reports may be prone to subjective bias. The application of these scoring systems prospectively in a well designed study should provide some interesting data. The consensus view seems to be that a cystic



Fig. 2. Stage Ia serous cystadenocarcinoma. The volume of the ovary is at the upper end of the normal range. The solid projection into the cavity demonstrated an area of presumed neovascularisation using transvaginal colour Doppler.

lesion which is described as anechoic, simple, unilocular and less than 5.0 cm in diameter is highly unlikely to be malignant.

Vaginal sonography therefore provides improved information about pelvic structures. Although the data are not yet available it is probable that cystic lesions suggestive of cancer will be detected using this technique at an earlier stage than is possible using abdominal probes. Other pelvic disease can also be screened for or investigated using this technique. The uterus can be visualised, and the endometrium measured. A total endometrial thickness of over 0.8 cm in postmenopausal women is highly predictive of significant pathology [27], with the false positive rate associated with such a finding possibly being reduced with the use of transvaginal colour flow mapping [28].

Whilst such high resolution ultrasound may improve the detection rate for early ovarian cancer, we are still faced with a significant false positive rate. Even when applied to a high risk group of women with a higher prevalence of the disease, about 14 operations are needed on women with a positive screen result to find each case of carcinoma [29]. We must therefore still consider other second stage tests to help reduce the amount of unnecessary surgery.

Transvaginal colour Doppler

Changes in tissue vascularity, mediated by angiogenic factors, are fundamental events in normal ovarian physiology [30]. Such changes are also associated with the early stages of oncogenesis [31]. Transvaginal colour Doppler can be used to study these events in a relatively noninvasive way. Flow velocity waveforms obtained from pelvic vessels using pulsed Doppler have specific characteristics that enable them to be identified [32]. Changes in tissue vascularity distal to the point on the vessel sampled are reflected in the Doppler flow characteristics.

Preliminary data suggest that even stage I ovarian carcinomas are associated with changes in vascularity which are detectable by colour Doppler [33], and marked differences in blood flow have been demonstrated between many benign and malignant ovarian cystic lesions [34, 35]. In malignant lesions blood flow can be demonstrated throughout the diastolic phase of the cardiac cycle, probably reflecting a decrease in impedance distal to the point of sampling. It is hoped that the use of this technique

within a screening programme will significantly reduce the false positive rate of the procedure, whilst maintaining sensitivity. However it must be remembered that the use of this technique is in its infancy, and experience of its application to very early ovarian cancer limited.

There are other problems. In postmenopausal women there are few physiological changes occurring within the ovary that may lead to altered vascularity. In premenopausal women this is not the case. Very similar indices of impedance to blood flow are seen in the developing corpus luteum [32] and in the preovulatory follicle [36] as are seen with carcinoma. Criteria for normal blood flow within the ovary have yet to be defined clearly. As with morphological findings, blood flow changes both in the uterus and ovary must be related to the patients menopausal status, ovarian or pituitary cycle, and drug therapy. A repeat assessment should always be performed to exclude vascular changes secondary to normal physiological events. The variety of new machines becoming available will also lead to confusion. Comparative data are required. Until the relative colour sensitivities of different units is obtained, the assessment of what constitutes normal blood flow will be difficult. Any area of blood flow demonstrated by colour Doppler must also be examined by spectral Doppler.

Despite these potential pitfalls, transvaginal colour Doppler may help overcome many of the difficulties related to the early diagnosis of ovarian carcinoma. It has already been shown that it can be used successfully to reduce the false positive rate associated with an ultrasound based screening programme for ovarian cancer. The effect on sensitivity is not yet clear. Its use has also increased the amount of interest in the investigation of factors that mediate the vascular events that occur during oncogenesis. It must be hoped that this will also lead to a greater understanding of ovarian pathophysiology.

WHO SHOULD BE SCREENED?

Reducing the false positive rate is not the only way of improving the overall performance characteristics of a screening test. By directing the test towards a population at particularly high risk, the positive predictive value of the test will improve. This is because amongst those women with a positive test result there will be more cases of the disease in question, in this case, ovarian cancer.

There are many reports that point to family history as being a risk factor for developing ovarian carcinoma [37]. Amongst these families at increased risk there are some where the inheritance pattern appears to be dominant. The lifetime risk of developing the cancer amongst close relatives in these families is about one in two [38]. Whilst such familial cancers probably only constitute about 10% of cancers overall, they are an important group to study. Using genetic linkage studies, it should be possible to identify the gene associated with ovarian carcinoma.

Once a genetic marker of risk has been identified, it could be used to screen the general population. A decision could then be made whether a women should be entered into an ovarian cancer screening programme, or in some cases offered prophylactic oopherectomy.

The other important predisposing factor is reproductive history [36]. Relative infertility is thought to increase risk, whilst use of the oral contraceptive pill may have a protective effect [39]. This is a difficult group to study, as it is virtually impossible to accurately define risk in terms of years of ovulation or exposure to gonadotropins. It is not yet known whether

T. Bourne et al.

treatment with exogenous gonadotropin therapy as part of infertility treatment increases ovarian cancer risk [40].

Whether it is either a desirable or practical option to screen the general population for ovarian cancer is not certain. Probably only women over the age of 50 would be considered due to the age distribution of the disease in the population. If ultrasound were to be contemplated, the facility could be linked to existing mammography services. The same target population would be reached, and capital costs shared. In this way a viable screening strategy might be envisaged.

CONCLUSIONS

Ovarian cancer screening often seems to provoke great controversy whenever the subject is discussed. However, even its most sceptical critics must accept that our current treatment strategies for this disease have not led to a dramatic reduction in the number of deaths due to this cancer. At worst a randomised trial of ovarian cancer screening will show it to have no effect either on the mortality rate for this disease, or on treatment associated morbidity. Even then, a great deal of useful information will have been obtained about ovarian pathophysiology and early cancer. Awareness amongst clinicians and the public about women at increased risk of ovarian cancer will have been heightened, and the genetic background to the disease clarified. At best, screening will be found to make a significant impact on morbidity and mortality amongst those women with cancer, whilst having little physical or psychological effect on the normal population.

It may be that ovarian cancer is not a disease that is amenable to screening. The different stages of the disease may represent entirely different forms of the cancer. In some instances stage III disease may in fact be multifocal disease originating from many sites simultaneously, possibly arising from a genetically primed peritoneum. The lead time of the disease is not known, and although family and reproductive history are known risk factors, we have no idea what predisposes the majority of women to develop this cancer. In view of these related uncertainties the investigation of early ovarian cancer detected at screening, and the study of its pathology, genetics, and immunohistochemistry should be an absolute priority.

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Cancer Registration in Victoria, Australia, 1982–1987

Graham Giles, Helen Farrugia and Bronwyn Silver

THE Victorian Cancer Registry (VCR) became population based in 1982, building upon a hospital based register that had functioned since 1940 and which had covered about 60% of the State's cancer incidence [1]. The VCR is situated in Melbourne where 70% of Victorians reside. With a population of 4.16 million at the last census in 1986 [2], Victoria has a quarter of Australia's population in less than 3% of its geographic area. 22% of Victoria's population is migrant with major contributions from Great Britain (6%), Italy (2.6%), Greece (1.6%) and Yugoslavia (1.4%).

Cancer reporting [including in situ tumours but excluding non-melanocytic skin cancers (NMSC)], is set up under legislation that makes notification mandatory for all hospitals and pathology laboratories. The VCR also receives all death certificates in computer compatible format. As patients may visit more than one hospital and have additional biopsies subsequent to their original diagnosis, further registrations are recorded and linked on the computer system, updating the date of last contact. Information routinely collected includes personal identifiers, sex, dates of birth, diagnosis and death, primary site coded to the International Classification of Diseases Ninth Edition (ICD-9) [3], histology coded to the International Classification of Diseases for Oncology [4], Aboriginality and country of birth. All multiple tumours are recorded on the VCR's computer system but the International Agency for Research on Cancer's guidelines are followed for incidence reporting [5]. The reliability and accuracy of VCR registry data are considered to be high. In 1987, the percentage of cases obtained from death certificates only was 2.7%, and the proportion of cases histologically verified was 90%.

The VCR is housed by the Anti-Cancer Council of Victoria and is seen as a valuable component of the Council's cancer control activities. The Council is able to use VCR data to evaluate the success of its major preventive programs in smoking and sunlight exposure; and screening/early detection programs for breast, cervix and skin cancer. For this reason, the VCR records in situ cervix and breast cancers and collects information on level and thickness for all melanomas. Victoria has recently established a central registry for cervical smear data with a recall system. A similar system for mammographic screening is likely to be introduced in the near future and the cancer registry will be able to assess the impact of these public health measures. In addition, the Council is committed to a cohort study of 50 000 Melbourne residents, 30 000 of whom were born in either Italy or Greece [6], and the VCR will be used to detect cancers occurring in the study population.

Data for the period 1982 to 1987 form the basis of this communication. Data for 1982 were published in Cancer Incidence in Five Continents, Vol V [7] and in Cancer in Australia [8]. Annual data for 1982-1987 have been published in standard reports [9-14]. Incidence data for 1982-1983 have been used for an atlas of Victoria [15]. VCR data have also been used extensively in Canstat a series of pamphlets on cancer epidemiology [16]. As the VCR does not routinely collect data on NMSC, it conducts a quinquennial national household survey to estimate the incidence of treated NMSC [17]. This survey was first conducted in 1985 and was repeated in 1990. The world standardised rates of NMSC in Victoria in 1985 were 497 and 418 per 100 000 males and females respectively. Trends in skin cancer (NMSC and melanoma) have also been reported [18–20]. The VCR is used extensively to facilitate epidemiological and clinical research. Projects include analyses of putative clusters of cancer [21], surveys of surgical management of breast cancer [22], follow-up studies of cervical cytology [23] and analyses of cancer rates in migrants [24].

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