Diagnosing epithelial ovarian cancer: can we detect it earlier?

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Abstract

Ovarian cancer often presents late and the mortality associated with the diagnosis is high. Even with careful clinical examination, many subtle signs may be missed. Observational studies confirm that tubal ligation and hysterectomy confer a protective effect. Screening of low-risk individuals is not yet a useful health intervention. This review evaluates various screening options including clinical examination, biochemical markers, morphological and vascular markers and a combination of tests.

Introduction

Ovarian cancer is often referred to as the 'silent killer' because of late presentation and difficulty in diagnosis. Ovarian cancer is a relatively infrequent diagnosis in southern Africa with an incidence of approximately 5:100 000 women per year.[1] However, in certain older age groups the prevalence increases dramatically. Epithelial ovarian cancer is a more common disease in first world countries with a larger elderly population. The incidence in American women aged 75 to 79 years is very high at 57.3:100 000 women per year.[2]

Even though cervical cancer ranks as the most important cause of cancer death in South Africa, the impact of ovarian carcinoma, particularly in the elderly population, is still very noticeable. Many of the gynaecological cancers, including cervical, endometrial and ovarian carcinoma, can be successfully treated if they are diagnosed at an early stage. However, the diagnosis of ovarian carcinoma is often a death sentence because of late diagnosis. The mortality associated with the diagnosis of epithelial ovarian cancer is invariably high. The mortality/incidence for different gynaecological cancers in the United Kingdom (Office of National Statistics, 2001) is demonstrated in Table I.

Table I: Mortality/incidence for gynaecological cancers in the UK

Disease site	Mortality incidence
Ovary	0.67
Uterine corpus	0.18
Cervix	0.39

This table demonstrates clearly that nearly two-thirds of patients will die after the diagnosis of ovarian cancer, and statistics from the United States between 1991 and 1995 confirm the fact that ovarian carcinoma is the most deadly gynaecological cancer after the age of 45.[2]

There are many reasons for the high mortality associated with ovarian carcinoma. First, ovarian carcinoma is usually diagnosed late due to the inaccessibility of the ovaries. The difficult anatomical position makes clinical signs difficult to detect, and clinical examination is not very helpful in the diagnosis.[3] Because this disease presents in an older age group after childbearing age, these women are often not regularly screened for gynaecological disease. Even with careful clinical examination many subtle signs may be missed, and usually disease is already at an advanced stage at diagnosis.

Histological types

Ovarian carcinoma is a heterogeneous group of diseases and may arise from different areas of the ovarian anatomy. The most important group of tumours in the older age group is the epithelial tumours, which include tumours that are similar to epithelium found in the fallopian tube mucosa (papillary serous cancers), the endometrium (endometriod-type adenocarcinomas) or the endocervix (mucinous adenocarcinomas). Other less frequent tumours of epithelial origin may include clear cell and malignant Brenner tumours (transitional cell carcinomas).

The second group of ovarian malignant tumours is the so-called sex-cord stroma tumours, and these are relatively rare diagnoses. These tumours include granulosa cell

tumours, Sertoli Leydig cell tumours and other rare histological types.

A third group of tumours arises from germ cells and may differentiate into many different types of histological pattern. The most common germ cell tumours include dysgerminomas, teratomas and endodermal sinus tumours.

The last big group of ovarian malignancies is metastatic tumours. Many solid tumours and haematological malignancies may metastasise to the ovaries, and the ovary might be the first place where the histological diagnosis is confirmed. The classical Krukenberg tumour is a metastatic mucin-secreting signet ring cell carcinoma where the primary is in the gastrointestinal tract. Friedrich Ernst Krukenberg described this phenomenon in 1892 when he was only 25 years old.

Of the four big groups of malignant tumours of the ovary, ovarian cancers derived from the coelomic epithelium (epithelial tumours) account for 90% of all cases of ovarian cancer.[4]

In the postmenopausal age group, epithelial tumours predominate and the diagnosis of stromal or germ cell ovarian tumours is rarely made.

Borderline ovarian tumours

Borderline ovarian carcinomas (also sometimes called tumours of low malignant potential) have certain histological features of benign tumours and certain features of malignant tumours.[5] Borderline tumours usually have a better prognosis and are usually diagnosed at the slightly younger age of between 30 and 50 whereas invasive carcinomas are found more commonly after the menopause. Surgery is the mainstay of the management of borderline ovarian cancers, with regular postoperative follow-up.

Surgery for borderline tumours may include unilateral oophorectomy in patients with unilateral disease or an ovarian cystectomy with resection of all peritoneal and omental deposits in patients with bilateral disease. Careful surgical staging is important. After completion of the family, completion surgery with a total hysterectomy and a removal of any ovarian tissue is debatable. However, some authors suggest that late recurrences are reported in retrospective reports and therefore completion surgery is indicated.[6]

Clinical features of invasive epithelial ovarian cancer

Ovarian carcinoma notoriously causes very vague symptoms. A patient may complain of abdominal discomfort with mild to severe distension, but often the symptoms are overlooked or misdiagnosed as indigestion, constipation or simple weight gain. In more advanced cases, nonspecific abdominal pain may become progressively noticeable. Loss of appetite with low-grade nausea and an inability to eat a proper meal may

develop over time when the tumour has invaded the omentum. At the stage where symptoms become noticeable, the tumour is often in an advanced stage with intra-abdominal ascites and omental disease.

Prognostic factors

In general, the prognosis of advanced ovarian carcinoma is poor. The most important prognostic indicator remains early diagnosis. Early detection should improve disease-free survival and overall survival. That makes the search for better diagnostic tools essential. Other clinical factors that may influence the prognosis include residual disease after cyto-reductive surgery and the patient's age and performance status at diagnosis.[7,8,9] The pre-operative volume of ascites and abdominal distention is also a marker of the prognosis.

Certain histological types (e.g. clear cell) are associated with more aggressive disease.[10] The differentiation of the tumour and the extent of anaplastic change within the tumour predict the outcome. Certain genetic factors including tumour ploidy also determine the prognosis.[11]

Aetiology

Epithelial ovarian carcinoma is a heterogeneous group of tumours and aetiological factors are not very well elucidated. Age is an important factor and at least 50% of tumours occur after the age of 63. Obesity increases the risk of ovarian carcinoma and the higher the body mass index, the higher the risk.[12,13] Postmenopausal hormone therapy is associated with an increased detection rate of ovarian cancer.[14] Recently, data from the Million Women Study Group found that hormone replacement therapy increases the risk of ovarian carcinoma by up to 20% (relative risk 1.2, 95% confidence interval 1.09–1.32).[15] Ten per cent of ovarian carcinomas may be associated with a genetic predisposition. These tumours often present in families with multiple individuals affected by cancer, and the two most common genetic abnormalities are the BRCA 1 and 2 gene mutations.[16] Lynch II syndrome and familial site-specific ovarian cancer are two more examples of genetic syndromes with increased risk for ovarian cancer.[17] Reproduction may also play a role in the aetiology, and there is some suggestion that fertility drugs, including clomiphene citrate, may increase the risk for ovarian carcinoma slightly.[18]

Primary prevention

Primary prevention of a disease means the elimination of the risk of exposure to known carcinogens. To reduce ovarian carcinomas would therefore include strategies to prevent obesity. Observational studies confirm that tubal ligation and hysterectomy reduce the risk for development of epithelial ovarian cancer. From this, one can deduce that the uterus and fallopian tubes may act as a conduit for external carcinogens that move up through the uterine cavity and the fallopian tubes to reach the ovaries. When this route for carcinogens is blocked, it has a protective effect.[19]

Secondary prevention

Secondary prevention of ovarian carcinoma entails two different strategies. The first strategy is the screening of low-risk individuals and the second strategy is the identification of high-risk populations.

Secondary prevention by means of screening of low-risk individuals is not always a straightforward and easy health intervention. In order for a screening programme to be successful, the World Health Organization criteria for a successful screening programme should be kept in mind.

- The disease should be an important health problem. (From the South African perspective, ovarian carcinoma may not be a top health priority because of a fairly low incidence; however, in health environments where infectious diseases have been successfully controlled, ovarian carcinoma becomes a proportionally more important health problem.)
- There should be a suitable test for detecting pre-malignant disease or early invasive cancer. (In this regard, ovarian carcinoma presents a unique problem because a good screening test is not currently available.)
- There should preferably be a recognisable early or latent phase of the disease. (There is no known pre-malignant precursor for ovarian carcinoma, and so far there has been no clear benefit in terms of cost saving and life-year saving by screening for ovarian carcinoma.)

The concepts of sensitivity and specificity of a test need to be considered, where sensitivity is the proportion of cancers detected by a positive test and specificity is the proportion of those without cancer identified by a negative test. Usually a test with a high sensitivity will have a lower specificity, and vice versa. In order for ovarian cancer screening to have clinical application, the test must be adequately sensitive and should ideally detect pre-clinical or early disease, which makes timely intervention possible and may improve outcome.[20] The lead time of the marker is important because screening intervals should be practical. The lead time of cervical cytology to detect abnormalities before invasive carcinoma can sometimes be between 10 and 20 years, which gives a window of time wherein intervention may be done. Ovarian cancer screening can only be successful if the test has a high specificity because a positive test will invariably lead to further management; currently it means surgery. If a positive predictive value of 10% is the aim, a minimum specificity of 99.6% is required. Even if the specificity reaches 98%, 50 operations need to be done to diagnose one cancer.

Possible screening tests

In the search for a good screening tool, various options have been investigated, including the following:
- Clinical examination
- Biochemical markers
- Morphological markers
- Vascular markers
- Combination of tests

Clinical examination
The so-called 'palpable ovary syndrome' has been regarded as a possible diagnostic tool in the diagnosis of early ovarian carcinoma.[21,22] If an ovary is palpable in the postmenopausal patient, it is considered abnormal and should be investigated further; however, the sensitivity of a pelvic examination only for detection of ovarian carcinoma is unknown.

Biochemical markers
CA125 is a well-known biochemical marker used to monitor treatment of epithelial ovarian cancers. CA125 is secreted by coelomic and Müllerian epithelium, and a cut-off value of 30–35 units per millilitre is generally accepted for postmenopausal patients.[23] CA125 is raised in 50% of cases with Stage I ovarian carcinoma and is raised in more than 90% of cases with advanced disease. A lead time of approximately 1.5–1.9 years has been described from the time that the CA125 becomes elevated to the time of detection of clinical disease. This marker was initially described by Dr Robert C Bast and is widely used in clinical practice today.[24,25] However, CA125 is a fairly nonspecific marker and may be raised in various non-cancer conditions (see Table II).

Table II: Non-ovarian cancer causes for raised CA 125 levels

Benign	Malignant
TB	Pancreas
Cirrhosis	Lung
Endometriosis	Breast
Fibroids	Endometrium
Pneumonia	
PID	
Pregnancy	

Moss reported in 2005 on a group of 221 women with raised CA125.[26] Twenty per cent of these patients with abnormal CA125 had an ovarian malignancy; however, 80% of cases were due to non-ovarian malignant disease (26%), benign ovarian disease (14%), leiomyomas (9%) and other disease.

Recently, expression of markers such as p53 and p21[waf1/cip1] has been studied in epithelial ovarian cancers to see whether they may indicate prognosis.[27] Despite showing expression in pathology specimens of epithelial cancers, there is no useful screening test available yet.

Other biochemical markers that have been tested (without convincing success) are summarised in Table III.

Table III: Other biochemical markers

- CA72-4,[28] TAG 72
- M-CSF,[29] OVX1,[30] LPA
- Prostasin,[31] Osteopontin[32]
- Inhibin[33]
- Kallikrein
- SMO 47

New biochemical markers are investigated on a regular basis, and hopefully a sensitive and specific test will be available in the near future.

Morphological markers
Ultrasound is a well-established strategy for early detection of ovarian carcinoma.[34] The classic signs for ovarian malignancy are presented in Table IV.

Table IV: Ultrasound features suggestive of malignancy

- Solid or cystic and solid mass
- Papillary growths on inner or outer surfaces
- Multi-locular cysts
- Thick cyst walls
- Bilaterality
- Ascitic fluid present

Using ultrasound to diagnose adnexal masses can be very confusing and often lacks reproducible terminology and standards.[35] Weighted scoring systems that assess morphology and/or ovarian volume have been published.[36,37] Even though certain features of malignancy have long been recognised as risk factors for malignancy, standard terminology and an accurate scoring of abnormal findings remain problematic. In an effort to address this problem, the International Ovarian Tumour Analysis (IOTA) group published guidelines in 2000 to standardise terminology.[38] This multinational research group aimed to standardise ultrasound examination in adnexal tumour evaluation. Certain morphological features are described in detail, including features such as septae, solid components, papillary projections and surface features. Even though these features have been defined, it remains difficult to use isolated morphological characteristics to predict risk of malignancy adequately. A follow-up report published as an abstract in 2003 concluded that in patients with adnexal masses, a multi-model approach is better than any single morphological scoring system and computer modelling may in future be used to help simplifying complex ultrasound findings.

The difficulty with using ultrasound as a predictor of malignancy is the wide inter-observer variability that is dependent on the equipment used during study and the skill of the operator. Clinical decisions are not standardised and appropriate criteria for determining malignancy have

not been described. Despite all these problems, ultrasound remains one of the most useful tools in predicting malignant disease but care should be taken not to overtreat benign adnexal pathology.

Vascular markers
Invasive cancer causes neovascularisation to supply the growing tumour with oxygen. These blood vessels are abnormal and have less smooth muscle in the vessel wall and therefore have less resistance to flow. Tumour vessels often have a lower pulsatile index.[39] Doppler and vascular features of adnexal masses may be very useful in evaluating the risks for malignancy. Scoring systems for different Doppler images have been described.[40]

Combination of tests
Multi-modal screening with different screening strategies shows the best promise. The UK group of Jacobs showed that sequential CA125 and transvaginal ultrasound might achieve a specificity to detect ovarian carcinoma of 99.9% with a positive predictive value of 26.8% (four operations/one case of ovarian carcinoma).[41,42] A risk of cancer (ROC) algorithm was devised by the same research group in which they included age and serial CA125 profiles.

Results from the long-awaited and very well-designed United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) have recently been published.[43] A very large group of women was randomised to three groups in a ratio of 2:1:1. Half of the participants (n = 101 359) were randomised to no intervention while the rest were divided between two screening strategies. One group (n = 50 640) had yearly CA 125 measurements (interpreted with a risk of cancer algorithm) followed by transvaginal ultrasound if abnormal. This was referred to as the multimodal screening (MMS) group. Another group (n = 50 639) underwent yearly transvaginal ultrasound. For detection of invasive epithelial ovarian and tubal carcinomas, there was a significantly better specificity for MMS when compared to the ultrasound-only group.

More than 40% of all the invasive ovarian cancers were diagnosed at Stage 1, which hopefully will translate into better survival. The morbidity cost measured as the number of operations needed to diagnose one invasive cancer was 35 operations per case in the ultrasound group and only three operations per case in the MMS group. The authors concluded that the sensitivity for both screening strategies was encouraging. The final conclusion on whether screening will change mortality still needs further study.

In reaction to these results, the group from Leuven in Belgium responded by calling the results "encouraging".[44] The group noted that there was a high detection of benign pelvic pathology that led to surgical intervention. The group commented that "many unnecessary interventions in women with benign masses could have been prevented by clear instructions on conservative management and by

implementing the best methods available to discriminate between benign and malignant masses". This highlights the difficulty in managing presumed benign adnexal pathology in a litigious society. Surgical intervention is often requested by the patient despite advice and reassurance from the treating clinician.

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial running in the United States aims to include 155 000 men and women, and the screening tool for cancer of the ovaries is CA125 combined with transvaginal scanning.[45] The results of this trial should be available in the next 5 to 10 years.

With present knowledge, there is no effective screening tool that will reduce mortality due to ovarian cancer. However, large prospective trials do support the efficacy of screening strategies including transvaginal ultrasound and serial CA125 to detect epithelial ovarian cancer.

At present, the most promising strategy will combine tests in a serial fashion. A first-line biochemical test can be followed by morphological assessment.

Proteomics

Low molecular weight serum protein profiling with spectrometry holds promise for the future.[46] A specific protein profile may reflect ovarian cancer, and this technology holds potential to diagnose very early ovarian carcinoma accurately. However, the problems with translating the findings of proteomics research into useful clinical practice are numerous.

Conclusion

A high index of suspicion and thorough diagnostic workup are essential when a patient presents with vague abdominal symptoms. Vaginal examination of asymptomatic postmenopausal women is neither sensitive nor specific enough to act as a screening tool for ovarian cancer. Transvaginal ultrasound combined with CA125 offers hope, but we are still waiting for scientific evidence to confirm this as a screening tool that will reduce mortality.

Management of incidental findings of adnexal masses in postmenopausal patients should take place according to a specified protocol. One useful protocol is described in the RCOG (Royal College of Obstetricians and Gynaecologists) guideline number 34.[47]

Successful screening in a low-risk population has so far been disappointing. No single test or combination of tests has yet demonstrated a reduction in mortality. Despite this, however, there are promising prospects.

To answer the question, epithelial ovarian cancer: can we detect it earlier? Yes, we can!

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