Ovarian carcinoma: Classification and screening challenges

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Primary ovarian cancer is the leading cause of death from gynaecological malignancy and the sixth most common cause of cancer death in Australian women. Our understanding of the underlying pathophysiology of epithelial ovarian cancers is incomplete, which poses difficulties for screening, diagnosis and treatment. This review summarises the current knowledge and debate regarding classification of epithelial ovarian cancers, including a proposed new classification system. Current screening methods and the evidence behind them are also presented. The outcomes of large, ongoing trials are awaited to provide more conclusive evidence regarding the effectiveness of screening for ovarian cancer.

Introduction

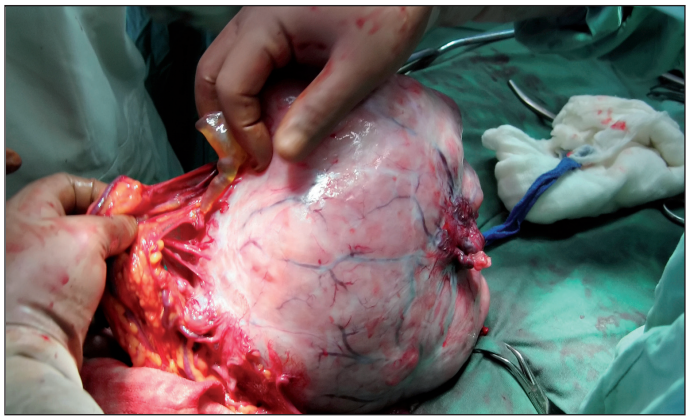
Primary ovarian cancer is the leading cause of death from gynaecological malignancy, and the sixth most common cause of death from cancer in Australian women. Mortality is high, with five year survival rates of only 42%. Ovarian cancer is staged according to the extent of disease spread. Stage I disease is confined to the ovaries, while stage II involves extension into the pelvis. Stage III is characterised by disease with peritoneal implants outside the pelvis or nodal involvement of retroperitoneal or inguinal lymph nodes. Stage IV describes disease with distant metastases. Symptoms are non-specific and often occur late in disease such that 53% of women diagnosed with ovarian cancer present with stage IV disease. Since five year survival drops from 86.1% for stage I disease to only 7% for stage IV disease, early diagnosis is important. [1,2] Unfortunately, the current lack of knowledge regarding the pathophysiology of ovarian cancer poses challenges for the classification of these cancers and therefore the implementation of optimal screening programs.

Classification of epithelial ovarian cancers

Primary ovarian malignancies are broadly classified as either epithelial, germ cell or sex cord stromal, with over 90% being of the epithelial type. [2] Germ cell and sex cord stromal tumours show different pathogenesis, epidemiology, clinical management and outcomes and are not addressed in this review.

The classification of epithelial ovarian carcinomas remains somewhat controversial in that the current system may not adequately describe the underlying cellular origins, pathological process or disease prognosis. [3] These tumours are generally classified as one of four major types according to their morphology – serous, mucinous, endometrioid and clear cell, with each of these histological types representing an organ of the female reproductive tract. Serous and mucinous types resemble fallopian tube and endocervix respectively, while endometrioid and clear cell tumours resemble the endometrium. Tumours can be further typed according to whether they are benign cystadenomas, malignant carcinomas or tumours of low malignant potential, also termed borderline tumours or atypical proliferative tumours. [4]

The cellular origin of epithelial ovarian carcinoma is not entirely understood and this poses difficulties for accurate classification. The wide-held belief is that these tumours arise from ovarian surface epithelium or, more specifically, from inclusion cysts formed from invaginations of the epithelium which lose their continuity with the surface. [4] Ovarian epithelium is derived from the embryonic coelomic mesothelium, as is the peritoneum, pericardium and pleura. However, it is controversial as to whether this adequately explains the histological similarity of ovarian tumours to organs derived from the Müllerian ducts. The Müllerian ducts are classically thought to arise from invagination of the coelomic epithelium, which might explain their histological similarities. However, histological analyses of human embryos have suggested that this may not be the case entirely. It appears that the development of the Müllerian duct may be closely related to that of the Wolffian duct, with Müllerian duct growth being independent of the invagination of coelomic epithelium. Cells of the Müllerian epithelium can be readily distinguished from coelomic cells and Wolffian cells. [5] Debeau [6] hypothesises that epithelial ovarian carcinomas may in fact be of Müllerian origin. Similarly, Kindelberger *et al.* [7] suggest that ovarian carcinomas, particularly those of the serous subtype, may arise from the fimbriae of the fallopian tube.



Removal of a large ovarian tumour.

In addition to the existing controversy regarding cellular origins, the advent of molecular genetic testing technologies has led to increased debate regarding the accuracy of the traditional classification system. Shih and Kurman [3] propose an updated classification to take into account the clinicopathological behaviour, tumour progression and molecular genetics of epithelial ovarian carcinomas, with the aim of providing a better framework for research into screening and treatment strategies.

They propose a novel tumour progression model whereby tumours are broadly grouped as type I or type II tumours. Type I tumours are generally low-grade and arise from precursor lesions with known molecular genetic alterations. These include low-grade serous carcinoma, mucinous carcinoma, endometrioid carcinoma and clear cell carcinoma. Type II tumours include high-grade serous carcinoma, undifferentiated carcinoma and malignant mixed mesodermal tumour (carcinosarcomas), and are characterized by having no known precursor lesion and poorly defined genetic alterations, aside from a common *p53* mutation. Such tumours often present as advanced stage IV tumours at the time of diagnosis and presumably undergo rapid growth from an occult lesion to a clinically detectable carcinoma. Table I outlines the classification and characteristics of type I and type II tumours. There is a notable difference in the known genetic mutations between type I and type II tumours, suggesting separate underlying pathogenic processes. This may provide a possible avenue for future screening, diagnosis and treatment investigations. [3] This classification system has not gained widespread acceptance for the

Table 1. A novel classification system - type I and type II epithelial ovarian carcinomas, their precursor lesions and common genetic mutations. [3]

	Tumour Type	Precursor Lesion	Molecular Genetic Mutations
Type I	Low-grade serous carcinoma	Serous cystadenoma/ adenofibroma; borderline serous tumour	BRAF and KRAS (~67%)
	Mucinous carcinoma	Mucinous cystadenoma; borderline mucinous tumour	KRAS >60%
	Endometrioid carcinoma	Endometriosis; endometrioid adenofibroma; borderline endometrial tumour	Loss of heterozygosity or mutation in PTEN (20%); β-catenin gene (16-45%); KRAS (4-5%); microsatellite instability (13-50%)
	Clear Cell Carcinoma	Endometriosis; clear cell adenofibroma; borderline clear cell tumour	KRAS (5-16%); microsatellite instability (~13%); TGF-β RII mutation (66%)
Type II	High-grade serous carcinoma	Not yet identified	P53 mutations (50-80%); amplification and overexpression of HER2/neu gene (10-20%) and AKT2 gene (12-18%)
	Undifferentiated carcinoma	Not yet identified	Not yet identified
	Malignant mixed mesodermal tumour (carcinosarcoma)	Not yet identified	P53 mutations (>90%)

classification of ovarian malignancies.

Evidence-based review of screening processes and limitations of screening

According to the World Health Organisation (WHO), screening programs should be supported by sufficient scientific evidence and the screening initiative should incorporate education, testing, clinical services and program management. There should be quality assurance, informed consent, equitable access, confidentiality and respect for autonomy. Additionally, the benefits of screening should not outweigh the harm. [8]

Ovarian cancer is a disease with high mortality which may be decreased by early intervention since five year survival is in excess of 80 % when the disease is confined to the ovaries. [2] Although ovarian cancer screening is a recognised need, there are a number of challenges in fulfilling the abovementioned WHO criteria. Limited knowledge of the natural history of the disease has thus far prevented the identification of suitable populations for screening.

Until further research can confirm the tumour progression model proposed by Shih and Kurman, [3] a true precursor lesion is yet to be clearly identified. A number of biomarkers have shown promise in samples from known ovarian cancer patients but few have been thoroughly studied in the preclinical phase as screening tools. Blood tests for the tumour marker CA125 and pelvic ultrasound have been the most studied screening techniques. In combination, they can detect a significant proportion of preclinical cancers and may improve survival. However, our understanding of the biology of ovarian cancer cannot yet fully describe how or whether stage I disease progresses to stage IV disease. [9] Thus, it remains unclear as to whether early detection and intervention would to be able to alter the natural history of the disease, nor has there been evidence as yet to demonstrate that screening decreases mortality. Other challenges relate to sensitivity, specificity, cost, exact screening protocol, acceptability and compliance. [10,11]

CA125 blood tests and pelvic ultrasound have been the most widely studied screening tools for ovarian cancer, with large-scale trials still underway. CA125 is an antigen expressed by foetal coelomic and amniotic epithelium. In adults, it is found in tissues derived from coelomic epithelium (pleura, pericardium and peritoneum) and Müllerian epithelium (tubal, endometrial, cervical). While ovarian epithelium does not normally express CA125, expression is often a feature seen in inclusion cysts and metaplasia. The cut-off for a positive screen is > 35 U/L, which is present in over 50% of patients with stage I disease and over 90% of patients with more advanced disease. [10] Studies have also shown that CA125 may be detectable in the preclinical phase, with elevated levels found in 25% of stored samples collected five years prior to diagnosis of ovarian cancer. [12]

Unfortunately, the false positive rates associated with CA125 testing on its own are quite high since elevations are also seen in cancers of the prostate, breast, bladder, liver and lung, and benign diseases such as diverticulitis, fibroids, endometriosis, ovarian cysts and tubo-ovarian abscess. [10]

Pelvic ultrasound is aimed at detecting early morphological changes. Unfortunately, there is no standardised scoring index for ultrasound findings but many are based on ovarian volume, outline, presence of papillary projections and cyst complexity (number of locules, thickness of septae, wall structure and echogenicity of fluid). In terms of these criteria, papillary projections have the highest and simple cysts and septal thickness have the lowest correlation with malignancy. There was hope that Doppler scanning could provide better sensitivity and specificity by differentiating between benign and malignant lesions on the basis of blood flow and vascular resistance, but due to the degree of similarity between the two, this was not proven to be effective. [10] While transvaginal ultrasound offers better visualisation of the ovaries compared to transabdominal ultrasound, it still cannot be used to clearly distinguish between benign and malignant lesions. [2]

Due to the likely short time interval between malignant change and widespread disease, particularly in high-grade tumours, screening efficacy is questionable. A recent study by Brown and Palmer [13] analysed serous cancers found after prophylactic bilateral salpingo-oopherectomies in BRCA1 carriers. They found that these cancers spend approximately four years as in situ stage I or stage II cancers and a further one year as stage II and III before becoming clinically apparent. For most of this occult period, the cancers are less than 1 cm in diameter and not grossly visible. Thus, to detect serous carcinomas before stage II, disease testing would need to detect tumours of 1.3 cm with a specificity of 50%, and tumours of less than 0.4 cm with a specificity of 80%. To achieve a 50% reduction in mortality with an annual screen, they postulate that screening would need to detect tumours as small as 0.5 cm in diameter. As such, although there is a relatively long occult period, current screening with CA125 and pelvic ultrasound is not adequately sensitive nor specific. It is likely that population screening will require additional cancer-specific biomarkers or novel approaches.

Ideally, the specificity of screening tests for ovarian cancer should be high to minimise morbidity from invasive testing in false-positive women. There are currently no reports on quality of life in such women. It is generally agreed that a screening test must have at least 10% positive predictive value (PPV), that is, no more than nine false positives for every one true positive. Given a population incidence of 40 cases per 100,000 population per year for ovarian cancer, tests would require a sensitivity of 75% and specificity of 99.6% to achieve a PPV of 10%. As this is a challenge for any single biomarker, it is likely

that any screening protocol will require a combination of tests. [10]

Another challenge in ovarian cancer screening is determining appropriate target population groups for screening. Most ovarian cancers occur sporadically with the only risk factor being age over 50 years. Women at increased risk of developing ovarian cancer only account for 5-10% of ovarian cancers, and include women with a family history of ovarian cancer, BRCA1/2 carriers and HNPCC carriers. Their risk can be considerably high, with a cumulative risk of 39% by age 70 in BRCA1 carriers. [10] Screening in these women is generally recommended from age 35, although this practice is not supported by evidence. Genetic counselling is also required where a known gene mutation exists. [14] The difficulty with screening these women is that they are usually younger and often have a variety of physiological (menstrual cycle variations) and benign (endometriosis, ovarian cysts) conditions which affect CA125 levels and ultrasound findings. Studies are required to assess whether serial CA125 measurements may be useful in such groups. [10]

Most biomarkers are initially tested in women with clinically diagnosed and usually advanced stage cancers. While they may show high sensitivity in these populations, the challenge is to find a biomarker which is also elevated in preclinical disease. [10] As CA125 is currently the best studied biomarker, it is likely to form a part of screening protocols in the near future. A number of studies have aimed to assess its effectiveness as a screening tool. Jacobs *et al.* [15] assessed the performance of CA125 followed by ultrasound in screening for ovarian cancer. They recruited 22,000 postmenopausal, female volunteers aged over 45 and measured their CA125 level. Abdominal ultrasound was performed if the level was ≥30 U/ml and abnormal ultrasound results were referred for surgical investigation. Of the 22,000 women, 40 required surgical investigation – eleven of these had disease while the remaining 30 had benign or no lesions present. Of the 21,959 women who had a negative screening result, eight subsequently presented clinically with ovarian cancer (false negative) and 21,951 had not developed clinical cancer in the two year follow up period. Sensitivity was thus 99.9%, PPV 26.8% and apparent sensitivity was 78.6% at 1 year and 57.9% at two years. As this was a prevalence study, information regarding the value of this screening protocol as ongoing screening was not available. However it does suggest that a screening interval of just 1 year may be required, which has potential implications on the cost, acceptability and compliance of screening. [11,15,16] In 2003, Skates *et al.* [17] used data from the Jacobs trial [15] to show that serial CA125 measurement interpreted with risk calculation was more effective in screening for ovarian cancer than a single, fixed cut-off measurement for CA125. The risk calculation is an estimate of the probability of having preclinical ovarian cancer and takes into account age and pattern of CA125 values. For a target specificity of 98%, the risk calculation achieved a sensitivity of 86%, whereas use of a fixed cut-off was only 62% sensitive. [17]

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) is a large, ongoing trial to assess the effectiveness of ovarian cancer screening on mortality. While the final results are still several years away, the results from the initial screen are promising. Over 200,000 post-menopausal women were randomly allocated to either receive no screening, annual CA125 with second-line transvaginal ultrasound, or annual transvaginal ultrasound alone. The sensitivity, specificity and positive predictive value for all primary ovarian and tubal cancers were 89.4%, 99.8% and 43.3% for multimodal screening and 84.9%, 98.2% and 5.3% for ultrasound screening respectively. There was a significant difference in specificity but not sensitivity between the two modalities. [18] Since PPV should be greater than 10% for an effective screening test to minimise morbidity from investigating false negatives, multimodal screening appears to be superior. Of the 87 malignancies found across both groups, there was no stage distribution difference found between the groups – overall, 48.3% were stage I or II. All of the cancers found in the ultrasound group were found from abnormalities on the first screen whereas only 78.6% of cancers from the multimodal screening arm were found on the initial test and 21.4% from an initial indeterminate screening result that required further testing, resulting in a delayed diagnosis for these women. Despite this, multimodal screening did result in fewer repeat tests and almost nine times fewer operations per cancer found. Results are awaited of further screening to assess ongoing sensitivity, specificity and PPV. [18]

Conclusion

In summary, ovarian cancer remains an important health issue with a number of challenges remaining for screening and diagnosis. Consensus is needed regarding a classification system – this is likely to require further study into the pathological basis of disease in serous ovarian cancer. Following this, efforts to find screening modalities which are sensitive, specific, cost-effective, acceptable and which lower mortality are required. This may be possible by refining CA125 and ultrasound modalities or it may require a novel approach. The main issues with screening stem from the lack of a clearly defined precursor lesion, and a lack of evidence to suggest that screening reduces mortality. Consequently, screening of the general population for ovarian cancer in Australia is currently not recommended.

Conflicts Of Interest

None declared.

Acknowledgements

Dr. Jason Abbott, Royal Hospital for Women, Randwick for selection of topic for review.

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