CHAPTER 85

Gynecological Malignancies: Prevalence, Early Diagnosis and Preventive Strategies from a Physician's Perspective

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ABSTRACT

By 2025, 19.3 million new cancer cases are expected to be diagnosed each year. Gynaecological cancers include cancers of the female reproductive tract, namely of the cervix, ovary, fallopian tube, uterus, vulva and the vagina.

Among gynaecological cancers, cervical cancer is the most common cancer in women, accounting for 4% of all cancers diagnosed in 2012. A sub-set of genes, called oncogenes and tumor suppressor genes promote the growth of cancer. Mutation in these genes can be acquired (e.g., through smoking, aging, environmental influences) or inherited. Almost all cervical cancers and some cancers of the vagina and vulva are caused by a virus known as Human Papilloma virus (HPV).

Ovarian cancer is considered to be the most fatal of all gynaecological malignancies in the developed world.[1] One of the paramount reasons for increased fatality from this disease is due to its late presentation.

The increasing incidence of obesity in the developed and developing world has significant implications for health. The direct relationship between obesity and gynaecological cancers is well established. There appears to be a linear increase in endometrial cancer risk with increasing body mass index (BMI).[2] Vulval cancer, although relatively uncommon, is one of the most psychologically disabling genital tract cancers.

Table 1: The efficiency of a screening test

Screening result	True disease classification of apparently well population	
	Diseased persons	**Persons without disease**
Positive	With disease and with positive test (true positive)	Without disease and with positive test (false positive)
Negative	With disease and with negative test (false negative)	Without disease and with negative test (true negative)
Total	Total unknown cases of disease	Total persons without disease

Sensitivity = diseased persons with positive test / All persons in population with disease; Specificity = non-diseased persons with negative test / All persons in population with disease

There are many factors that cause gynecological cancers. Screening and awareness of early signs and symptoms can result in the early detection of these cancers when treatment is more likely to be successful and a complete cure is a possibility. Diet, exercise and lifestyle choices play a significant role in the prevention of cancer. Additionally, knowledge of family history can increase the chance of prevention or early diagnosis by determining if someone may have a gene which makes them susceptible to cancer.

The United States Commission on Chronic Illness (CCI) conference on preventive aspects of chronic disease, held in 1951, defined screening as "the presumptive identification of un-recognized disease or defect by application of tests, examination, or other procedures which can be applied rapidly. Screening tests sort our apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment." (Commission on Chronic Illness 1957)

In a screening test there is no specific exposure or indication to suggest that the individual has any disease. For example, routine testing of prostate specific antigen (PSA) in the male population.

Screening can be of different types such as mass screening where there is no selection of the screening population, or selective screening or multi-phased screening.[3]

Prior to developing a screening test, it is important to understand when we can screen a disease. The disease in question should be an important health problem. It may sometimes be difficult to define what an "important" health problem is. There should be an accepted and effective treatment available, if people with the disease are identified through screening. The disease should have a recognizable latent or early prodromal phase. There should be adequate facilities for diagnosis and treatment. Screening should lead to prevention of disease progression following early detection and treatment and this should play a major impact on morbidity and mortality from the disease. There should be an accurate screening test with high sensitivity and specificity with an agreement of what is considered to be a positively screened case (Table 1).

Worldwide, cervical cancer remains the fourth most common malignancy in women accounting for 7% of all cancer related deaths in women.

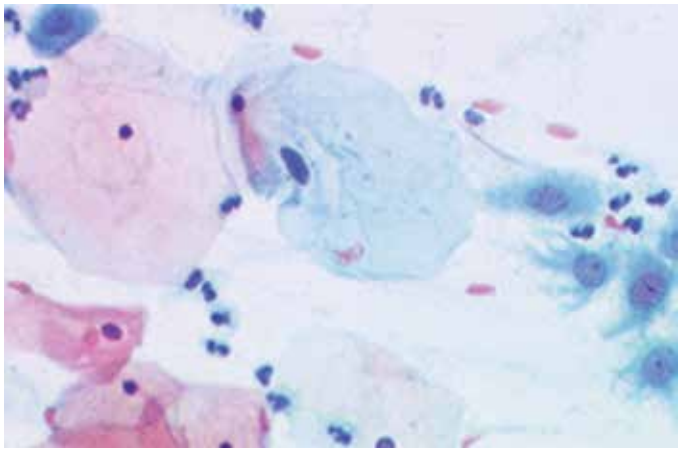

Fig. 1: Normal Smear

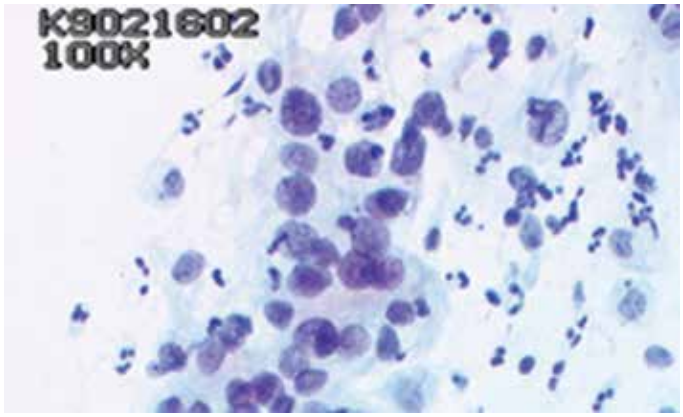

Fig. 2: Severe Dyskaryosis

Over three-quarters of all new cases of cervical cancer are diagnosed between the ages of 25 and 64 years. It is the most common cancer in women below the age of 35 years. The age specific incidence rates show two peaks, the first in women aged 30-34 and the second in women aged above 55 years. The primary recognised cause of cancer of cervix is human papillomavirus infection (HPV). HPV 16 and 18 are considered to be high risk (HR) for developing cervical cancer.[4,5] It is considered preventable as it has a recognizable precancerous condition and an accepted treatment modality for this precancerous stage. Therefore, the principles of screening can be applied to this condition (NCIN, 2008).

The World Health Organization (WHO) International Association for Research on Cancer (IARC) identifies 13 types of HPV strains as oncogenic. These high risk types of HPV are: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, have been shown to directly cause cervical cancer. Adenocarcinomas are more commonly associated with HPV types 18 and 45 principally rather than type 16, which is the commonest HPV type for SCC (squamous cell carcinoma) of the cervix with lymphovascular space invasion (LVSI).[5]

In United Kingdom, the NHS Cervical Screening Program (NHSCSP) is widely recognized to be one of the most successful cancer prevention programs in the world. Following the implementation in 1988 of a comprehensive, quality-assured, cytology-based program, there has been a progressive decline in the incidence of, and mortality from, cervical cancer. Since its introduction, the number of cervical cancer cases has decreased by 7% year on year. The program aims to reduce the number of women who develop invasive cervical cancer (incidence) and the number of women who die from it (mortality). It does this by regularly screening all women at risk so that conditions which might otherwise develop into invasive cancer can be identified and treated earlier (Figure 1). Thus the incidence of cervical cancer has dramatically decreased over the years in the screened population.[6]

CLINICAL TIP: SYMPTOMS OF CERVICAL CANCER

Though cervical cancer may be asymptomatic and a dyskaryotic smear (Figure 2) may be the first abnormal finding, the commonest symptoms are listed below:

- Inter-menstrual bleeding
- Post coital bleeding
- Postmenopausal bleeding
- Unpleasant Vaginal discharge
- Dyspareunia
- Rarely haematuria or backache (advanced disease)

CLINICAL TIP: URGENT REFERRAL

- Referrals for colposcopy from primary care for women with high index of suspicion for malignancy on screening should be made via the two-week rule (TWR) to the gynaecological oncology team.
- Screening is not appropriate for women who have symptoms, and conducting a cervical screening test may delay the proper diagnostic process in such cases. If the woman is symptomatic, such as experiencing bleeding between periods or after sex, she needs to consult her GP straight away.

The effectiveness of the program can also be judged by coverage. This is the percentage of women in the target age group (25 to 64) who have been screened in the last five years. If overall coverage of 80 per cent can be achieved, the evidence suggests that a reduction in death rates of around 95 per cent is possible in the long term.

Recently the direct cause and effect between HR-HPV infection and the development of cervical cancer has been clearly established, with almost 100% of cervical cancers containing HPV DNA.[7] Women with no evidence of HR-HPV infection are extremely unlikely to develop cervical cancer in the short to medium term. Hence use of HPV screening as a tool to triage women who are at high and low risk of developing cervical cancer has been recently introduced in the screening program.

Prevention strategies may be hugely relevant in recourse poor countries with the highest disease burden and absence of universal cervical screening program.

Risk factors for HPV infection include number of sexual partners, a relatively recent new sexual relationship and

a history of previous miscarriage. Among HPV positive women, early age at first intercourse, long duration of the most recent sexual relationship and cigarette smoking are associated with development of CIN 3 (high grade squamous intra-epithelial neoplasia).[8]

Smoking has been associated with an increased risk of SCC. A recent study by Parkin et al, suggested 7% of cases in 2010 were associated with smoking.[9] A recent meta-analysis suggests a 50% increased risk of SCC in current smokers.[10] Low socio-economic status has also shown to be a risk factor; with the risk multiplying by almost three times in most deprived areas.

A meta-analysis found risk of invasive cervical cancer in current users of combined oral contraceptive pills (COC) increases by 7% for each year of use.[11] The risk increase for five years of use is approximately 40%. The risk increase is temporary, and risk returns to the level of a never-user after 10 years of stopping use. Like with smoking, the direct cause and effect from COC on cervical cancer is complicated by confounding sexual behavior.

Women with HIV/AIDS have a six times increased risk of developing cervical cancer and women who have undergone organ transplant have twice or more the risk, strongly suggesting that immunosuppressant plays an important role.

HR HPV testing has recently been introduced in the UK National Cervical Screening Program, both as a primary triaging investigation for low grade and borderline abnormality as well as a test of cure following treatment for high grade cervical dyskaryosis. Whilst the ARTISTIC (A Randomized Trial of HPV Testing in Primary Cervical Screening, n=25,000) trial has shown that routine HPV testing did not add significantly to the effectiveness of liquid based cytology (LBC) screening, primary HPV triaging has a higher negative predictive value.[12]

HPV vaccines are sub-unit vaccines made from the major protein of the viral-coat or capsid of HPV. Virus-like particles (VLPs) mimic the structure of the native virus but do not contain any viral DNA. There are currently two different HPV vaccines, Cervarix® contains VLPs for two HPV types (16 and 18 – bivalent vaccine) and Gardasil® contains VLPs for four HPV types (6, 11, 16 and 18 – quadrivalent vaccine). HPV vaccines are highly effective at preventing the infection of susceptible women with the HPV types covered by the vaccine. In clinical trials in young women with no evidence of previous infection, both vaccines were over 99% effective at preventing pre-cancerous lesions associated with HPV types 16 or 18.[13] Current studies suggest that protection is maintained for at least ten years. Based on the immune responses, it is expected that protection will be extended further; long-term follow-up studies will provide further evidence regarding efficacy. Some other high-risk HPV types are closely related to those contained in the vaccines and vaccination has been shown to provide some cross-protection against infection by these types. Gardasil® is also 99% effective at preventing genital warts associated with vaccine types in young women. A vaccination schedule of 0, 1, and 4-6 months is appropriate for both vaccines for girls being vaccinated at the age of 15 years and above. All three doses should ideally be given within a 12-month period. If the course is interrupted, it should be resumed using the same vaccine. It should not be repeated, ideally allowing the appropriate interval between the remaining doses. For girls aged less than 15 years of age Joint Committee on Vaccination and Immunization (JCVI) recommended a schedule of 0, 6-24 months for both vaccines. It is hoped that the vaccination program will avert 70% or more squamous cell cancer of the cervix by preventing HPV infection.[14]

Since the mid1970s the incidence of ovarian cancer in women over 65 has increased by more than 40%. Worldwide, there are more than 239,000 new cases of ovarian cancer diagnosed each year.[1]

Epithelial ovarian cancer continues to be the most fatal of the female genital tract cancers in developed countries as majority of the patients are diagnosed at advanced stages with tumours of high grade, so the value of diagnostic and prognostic markers is limited. However, contrary to the commonly held perception, ovarian cancer is neither an asymptomatic disease nor a so-called 'silent killer'. The initial presenting symptoms are often associated with other conditions, especially abdominal and gastrointestinal disorders, till they become very obvious in advanced stage disease. Hence a better understanding of symptoms associated with ovarian cancer is required to adopt the correct screening strategies for early detection of disease.[15]

Most women will have had symptoms for months before seeking help. Unexplained fatigue, weight loss or change in bowel habit in women over 50 years old should also prompt further investigation and consideration of ovarian cancer.[16]

Nulliparity, personal and family history of cancer are some of the risk factors associated with developing ovarian cancer. Women who have had cancer of the breast, uterus, colon, or rectum have a higher risk of developing ovarian cancer as there is a greater likelihood that they carry the cancer predisposing genes.

Studies have suggested that postmenopausal women who take oestrogen hormone replacement by itself (oestrogen without progesterone) for 5 or more years have an increased risk of developing ovarian cancer. The overall increased risk was by 30% to 40% over the usual incidence. This risk is reversed on stopping hormone replacement therapy.[17]

The average woman has a 1.5-2% lifetime risk of developing ovarian cancer. For those carrying cancer predisposing gene mutations, this risk is increased. A strong family history of certain cancers may indicate the presence of hereditary gene mutations.

Women with a strong family history of ovarian or breast cancer have an increased risk of carrying a BRCA gene

Table 2: Symptoms of ovarian cancer according to disease stage (courtesy CRUK)			
Symptoms associated with spread of disease	**Early Stage**	**Disease spread beyond the ovary**	**Late stage disease**
	• Lower abdominal pain • Abdominal bloating or feeling of fullness	• Irregular periods or post menopausal bleeding • Lower abdominal pain • Back pain • Urinary frequency • Constipation • Dyspareunia • A swollen abdomen • Feeling of fullness or loss of appetite	• Loss of appetite or a feeling of fullness in the abdomen • Nausea/vomiting • Constipation • Tiredness • Shortness of breath • Abdominal distension

mutation which predisposes them to developing the disease. Women with a family history of cancer of the uterus, ovary, colon or rectum may have an increased risk of carrying a mismatch repair gene mutation (genes MLH1, MSH2, MSH6 or PMS2). This is termed Lynch Syndrome or Hereditary Non-polyposis Colorectal Cancer (HNPCC) and carriers have an increased risk of ovarian cancer as well as other cancers.

Heritable mutations in BRCA1 and BRCA2 genes account for approximately 8% to 13% of newly diagnosed ovarian cancer cases, which is probably under-reported, as routine genetic testing after diagnosis is still not widely prevalent. The risk of developing ovarian cancer by the age of 70 in women carrying a BRCA 1 mutation is approximately 35%-60% and in women carrying a BRCA 2 mutation the risk is 10% to 27%. In comparison, women with Lynch Syndrome (Hereditary Non-polyposis Colorectal Cancer (HNPCC/Lynch syndrome), have a 12% risk of developing ovarian cancer and a 60% lifetime risk of both uterine and colon cancer.[18] Similar to BRCA1 and BRCA2, changes in these genes can cause very early onset cancers, with some of the cancers occurring as early as age 25. These women and other female members of their family should be counselled about undergoing genetic testing. The use of COCPS in ovulation suppression in the early years and offering risk reduction surgery in the form of prophylactic bilateral salphingectomy after completion of family and oopherectomy from the age of 40, are some of the strategies being employed to prevent cancer developing in this high risk group of patients. Routine general population screening for ovarian cancer is not currently recommended. However, offering salphingectomies rather than tubal occlusion at the time of sterilisation seem to be one of the proposed preventative strategies being employed in reducing the risk of ovarian cancer in the future.

Recent hypothesis propose the development of ovarian high grade serous carcinoma by direct shedding and implantation of pre-cancerous serous tubal intra-epithelial cells (STIC cells) from the fimbria on the ovarian surface and accelerating to cancer development due to chromosomal instability and by free reactive oxygen radicals.[19]

The National Institute for Health Care and Excellence (NICE) guidelines in the United Kingdom recommends initiating investigations for any women over 50yrs with suspected ovarian malignancy by performing a baseline Serum CA-125 and pelvic trans-vaginal ultrasound scan.

Currently the best known tumour marker used for screening, predicting and monitoring surveillance of ovarian cancer is cancer antigen -125 (CA-125). The normal range for CA-125 is < 35 IU/L. CA-125 is raised above the normal range in serous epithelial and endometrioid ovarian cancer. CA-125 can be elevated in other cancers such as endometrial, breast, pancreatic, gastrointestinal, and lung cancers. CA-125 is also raised in benign gynaecological conditions such as pregnancy, inflammation, endometriosis, menstruation, and pelvic inflammatory disease.[20] In women with pelvic mass, an elevated result has a sensitivity of 72% and specificity of 78% for ovarian cancer.[21] Of early stage patients, only 50% have increased CA-125 compared with 90% of advanced stage patients. This means that CA-125 is not a good candidate for early screening of EOC.[22] CA-125 is often not elevated in mucinous, clear-cell and borderline tumours. Hence developing an accurate biomarker will significantly improve clinical outcome and possibly survival from this cancer.

Majority of the genetic abnormalities associated with ovarian cancer are not inherited, but are acquired during a woman's lifetime. The commonly noted 'somatic' or acquired mutations observed in epithelial ovarian cancer include mutations in tumour suppressor genes (such as p53 and PTEN), and genes for signaling molecules such as KRAS and the kinases.[23]

In the United Kingdom, a scoring system used in distinguishing ovarian masses is the risk of malignancy index (RMI). This is an algorithm based on the sum score of the product of trans-vaginal scan findings, CA-125 level in blood and the menopausal status and has been developed to distinguish between patients with benign

and malignant pelvic masses. A RMI of 250 or more has 85% sensitivity and 97% specificity in distinguishing between benign and malignant ovarian masses, with an area under the receiver operating characteristic (ROC) curve of 0.83.[24,25]

Endometrial carcinoma is the commonest gynaecological cancer in the developed world, with a rising incidence in the developing world. Worldwide in 2012, 527,600 women were diagnosed with uterine cancer. The mortality rate was 1.7 to 2.4 per 100,000 women.

Obesity delivers a two to five fold increase in the risk of endometrial cancer in both pre- and postmenopausal women. The increase in the risk of developing endometrial cancer in obese patients is likely to be due to increased oestrogen dependent endometrial stimulation. Type 1 endometrial cancers account for the majority of the tumours and are oestrogen dependent endometrioid cancers with a good prognosis while type 2 cancers present later and carry a worse prognosis.

The increasing incidence of obesity in the developed world has significant implications for health and health economics. In 2008, a Department of Health census for England and Wales showed that 1 in 4 adult women were obese. One of the important reasons postulated for this changing prevalence, is the ever increasing number of overweight, obese and morbidly obese women in the post-menopausal age group. There appears to be a linear increase in endometrial cancer risk with increasing Body Mass Index (BMI) a threshold effect has also been noted, with an increase only among obese women with a BMI of 30 kg/m^2 or higher. There is a 4-fold increase in the risk of developing endometrial cancer in obese patients due to increased oestrogen dependent endometrial stimulation. Surgical management of obese and morbidly obese women with early stage endometrial cancer is extremely challenging due to the associated increased morbidity.[26]

Some of the endogenous risk factors associated with the development of endometrial cancer are increasing age, central obesity, physical inactivity, early menarche, late menopause, nulliparity, polycystic ovarian syndrome, family history, oestrogen-secreting tumours, diabetes mellitus, hypertension, history of breast cancer and Lynch syndrome. Women with Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), have an altered gene that increases the risk of bowel cancer and uterine cancer. Women with this gene have a 30–60% risk of developing uterine cancer over their lifetime. They are screened for bowel cancer and may also have tests to check for early signs of endometrial cancer. Women with a rare genetic condition called Cowden syndrome have an increased risk of benign (non-cancerous) tumours and also some cancers. This includes uterine cancer, but the increase in risk is small. Oestrogen receptor modulators and hormonal therapy used in treatment of breast cancer can cause a theoretical increase in the development of uterine cancer.

The overall five year survival rate in uterine cancer across all stages is currently around 80%.[2] Majority of women will present early in the course of the disease when cure is more likely, so physicians need to be vigilant for symptoms suggesting this (Table 2).

The hallmark symptom of endometrial cancer is post-menopausal bleeding (5%-10% of all symptomatic patients will have underlying cancer) with bleeding occurring at least one year after the last menstrual period in the presence of other evidence of ovarian failure. In pre-and peri-menopausal women, endometrial cancer presents with inter-menstrual bleeding often on a background of irregular, dysfunctional menstruation suggesting an-ovulation. Pain, vaginal discharge and pyometra are rarer presentations of endometrial cancer and tend to be secondary to advanced malignancy.

The pathogenesis of development of endometrial cancer is the gradual progression from simple endometrial hyperplasia to complex endometrial hyperplasia without atypia and then to complex endometrial hyperplasia with architectural atypia, followed by progression to early invasive malignancy.

In women who wish to preserve fertility and conserve their uterus, such histological changes can be attempted to be reversed by treating with intra-uterine progesterone system like the mirena IUS and high dose progesterone.

Oestrogen levels are lower during pregnancy and when breast-feeding. The risk of endometrial cancer is lower in women who have had children. Breastfeeding for more than 18 months also decreases the risk of endometrial cancer. Taking contraceptives that combine estrogen and progestin (combination oral contraceptives) decreases the risk of endometrial cancer. The protective effect of combination oral contraceptives increases with the length of time they are used, and can last for many years after oral contraceptive use has been stopped. While taking oral contraceptives, women have a higher risk of blood clots, stroke, and heart attack, especially women who smoke and are older than 35 years. Physical activity at home (exercise) or on the job may lower the risk of endometrial cancer.[27] At present clinical interventions like gastric bypass surgery and other dietary modifications in the morbidly obese patients are being undertaken to understand their potential long term benefits in reducing the risk of developing endometrial cancer in the future.

The baseline investigations in women with suspected endometrial cancer are a transvaginal ultrasound scan and an endometrial biopsy. Transvaginal ultrasound scan is an accurate and precise screening method for endometrial cancer. A meta-analysis of 35 studies using a 5 mm threshold to define abnormal endometrial thickening showed that 96% of women with cancer had endometrial thickness greater than 5 mm; the study reported a negative likelihood ratio of 0.08.[28] Transvaginal ultrasound was also highly reliable in identifying postmenopausal women with vaginal bleeding who were unlikely to have underlying malignancy (endometrial

thickness of <5 mm), which would mean that unnecessary endometrial sampling could be avoided.

A definitive diagnosis of endometrial cancer is histological with endometrial tissue sample being obtained either in the gynaecology outpatient setting using a Pipelle curette or by hysteroscopy and dilatation and curettage under general anaesthesia. A systematic review of different diagnostic evaluations showed that Pipelle biopsy leads to a high overall diagnostic accuracy when an adequate specimen is obtained (post-test probability of endometrial cancer of 81.7% for a positive test and 0.9% for a negative test).[29] However, diagnostic hysteroscopy and directed endometrial sampling is the gold standard for ruling out endometrial malignancy where a distorted, irregularly thickened endometrial cavity is noted on ultrasound scan.

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