Early Detection Of Gynaecological Cancer

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Review Article

ABSTRACT
The burden of gynaecological cancer is increasing at an alarming rate. To reduce the burden of the disease, major efforts have focused on prevention through screening or improvements in treatment. Over the past 5 decades, screening for cervical cancer has significantly reduced mortality in the developed world with the introduction of liquid based cytology and HPV testing. Whether screening for ovarian cancers impacts on its mortality is still unclear. Screening for endometrial cancer is only recommended in women at risk as part of the Lynch syndrome families. Currently, screening for endometrial cancer is not advocated as most women present with symptoms in early disease with better survival outcomes. Vulval and vaginal cancers are too rare to justify mass screening.
INTRODUCTION

The Cancer Research UK estimated that there were 21,493 new cases of gynaecological cancer and 7,747 cases of deaths in 2014 (Table 1) [1]. It is important to increase our knowledge about the causes of cancer and interventions to prevent and manage the disease among healthcare professionals. Reviewing endometrial, cervical, ovarian, vaginal and vulval cancer and their associated risk factors, means of prevention and early detection and the signs and symptoms can alert clinicians to the potential risks and the detection methods available. Cancer can be reduced and controlled by implementing evidence-based strategies for prevention, early detection and timely management of patients with cancer. This article gives an overview of gynaecological cancer screening and risk assessment and to recommend ways of incorporating gynaecological prevention and detection measures into clinical practice.

Table 1: Gynaecological cancer statistics in 2014 [1]

<table>
<thead>
<tr>
<th>New cancer cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uterine</strong></td>
<td>9324</td>
</tr>
<tr>
<td><strong>Cervical</strong></td>
<td>3224</td>
</tr>
<tr>
<td><strong>Ovarian</strong></td>
<td>7378</td>
</tr>
<tr>
<td><strong>Vulval</strong></td>
<td>1313</td>
</tr>
<tr>
<td><strong>Vaginal</strong></td>
<td>254</td>
</tr>
</tbody>
</table>

ENDOMETRIAL CANCER

Epidemiology

It is the fourth most common cancer in women and the most common gynaecological cancer ahead of ovarian cancer and cervical cancer [2]. Almost two thirds of uterine cancers occur in women aged 55-75 with a peak in the rates for women in their early 70s [3]. Obesity is a significant risk factor for adenocarcinoma of the endometrium, with the effect more pronounced in postmenopausal women.

In the UK, 77% of uterine cancers are endometrioid adenocarcinomas, 7% are clear cell and papillary serous carcinoma and 6% carcinosarcoma [3]. Some tumour groups are more common in either younger women (sarcomas) or older women (clear cell and papillary serous carcinoma) [3].

Risk factors

Risk factors for endometrial carcinoma [4]:

- Increasing age
- Early menarche and late menopause
- Nulliparity
- Unopposed oestrogen (obesity, polycystic ovarian disease/syndrome (PCOS), oestrogen only HRT)
- Tamoxifen use
- Hypertension, diabetes mellitus
- Chronic anovulation (PCOS, subfertility)
- Personal history of breast cancer
- Family history of hereditary non-polyposis colorectal cancer (HNPCC) – 22% to 50% lifetime risk
- Endometrial hyperplasia with atypia
Hyperplasia without atypia rarely progresses to endometrial cancer. Hyperplasia with atypia is a precancerous condition that may progress to overt malignancy.

**Table 2:** Type of endometrial hyperplasia and rate of progression to cancer [5].

<table>
<thead>
<tr>
<th>Type of hyperplasia</th>
<th>Rate of progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple endometrial hyperplasia</td>
<td>1%</td>
</tr>
<tr>
<td>Complex endometrial hyperplasia</td>
<td>3%</td>
</tr>
<tr>
<td>Atypical Simple</td>
<td>8%</td>
</tr>
<tr>
<td>Atypical Complex</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Screening**

There is no established population screening programme for endometrial cancer. Screening is therefore limited to high risk individuals with a hereditary predisposition. Women with breast or colon cancer may have a higher genetic risk of gynecological malignancies. Approximately 2–4% of endometrial cancer are attributable to Lynch syndrome (HNPCC or hereditary nonpolyposis colorectal cancer) and up to 10% in women diagnosed under the age of 50 [6]. This is an autosomal dominant syndrome caused by germline mutations. It confers a 40-60% risk of endometrial cancer [7]. BRCA1 gene mutation, in addition to the well-known increased risk of ovarian cancer, has been associated with an increased endometrial cancer risk [7]. If there is a personal or family history of cancer (i.e. Suspected Lynch syndrome), then discuss this with the cancer genetics services. Note that patients under 50 years of age with endometrial cancer may be the index case for such families and the other members should be screened for colorectal cancer.

**Presentation and referral**

Postmenopausal bleeding (PMB) is the most common presentation and all women with PMB warrant urgent investigation [6]. It is important to reassure women that only 10% of those presenting with PMB will have endometrial cancer [8]. Any patients with an abnormal smear suggesting a glandular abnormality or endometrial cancer should be seen at a colposcopy clinic or referred for urgent investigation [6].

All patients with suspected endometrial cancer are to be referred within 24 hours to a gynaecology rapid assessment clinic. This should ideally be a ‘one-stop clinic model’ with transvaginal ultrasonographic scanning (TVUSS) and endometrial biopsy available on the same day.

**Table 3:** Causes of postmenopausal bleeding [9]

<table>
<thead>
<tr>
<th>Causes of postmenopausal bleeding:</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial or cervical polyps</td>
<td>2-12</td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>5-10</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>10</td>
</tr>
<tr>
<td>Exogenous oestrogen</td>
<td>15-25</td>
</tr>
<tr>
<td>Vaginal atrophy</td>
<td>60-80</td>
</tr>
</tbody>
</table>
Initial diagnostic investigations

As in all clinical situations, the investigation of postmenopausal bleeding involves obtaining a thorough history and performing pelvic examination followed by assessment of endometrial thickness by transvaginal ultrasound scan (TVUSS) (abdominal scan only if TVUSS is not possible). Perform an endometrial assessment and biopsy if the endometrial thickness is 5mm or more \(^6\). If the symptoms are persistent, biopsy is indicated even if the endometrial thickness is less than 5mm.

**The endometrial cut off – How thick is too thick?**

To date, four meta-analyses have been published. Each has used different methods to determine the accuracy of TVS in diagnosing endometrial abnormalities in women with PMB. The most cited meta-analysis by Smith-Bindman et al. included 5892 women from 35 prospective studies that compared to the endometrial thickness measured at TVS to the presence or absence of endometrial carcinoma on histology \(^{10}\). At ≤5 mm cut-off, the overall summary mean weighted estimates of the sensitivity for detecting endometrial cancer was 96% for a 39% false-positive rate. This would reduce a pre-test probability of 10% for endometrial cancer to a post-test probability of 1%. Therefore, expectant management (without the need for tissue sampling) is recommended for these women.

One of the studies by Smith-Bindman et al. has shown that in a postmenopausal woman with vaginal bleeding, the risk of cancer is approximately 7.3% if her endometrium is thick (> 5mm) and < 0.07% if her endometrium is thin (< or = 5 mm) \(^{11}\). An 11mm threshold yields a similar separation between those who are at high risk and those who are at low risk for endometrial cancer. In postmenopausal women without vaginal bleeding, the risk of cancer is approximately 6.7% if the endometrium is thick (> 11mm) and 0.002% if the endometrium is thin (< or = 11 mm) \(^{11}\).

**Asymptomatic endometrial polyps**

The prevalence of polyps in women with postmenopausal bleeding ranges from 13% to 50% \(^{12}\). Most lesions are benign, but some may be pre-malignant (simple or complex hyperplasia with cytological atypia) or malignant \(^{12}\). Malignant pathology is identified in 0.5% to 4.8% of polyps found in postmenopausal women \(^{12}\). However, polyps are a known risk factor for the subsequent development of endometrial cancer.

**Diagnostic biopsy of endometrium**

Endometrial sampling and or hysteroscopy can be performed as an outpatient procedure. The endometrial sampling using pipelle is safe, accurate, and cost effective outpatient procedure as it avoids general anaesthesia with high sensitivity and specificity for detection of endometrial hyperplasia and endometrial malignancy \(^{12}\). If the cavity view is suboptimal or the biopsy inadequate, this procedure may need to be repeated under a general anaesthetics.

**Staging investigations**

The aim of imaging is to define the depth of myometrial invasion and to assess for extrauterine disease, particularly lymph node involvement \(^{6}\). It should include:

- MRI pelvis and abdomen to include the para-aortic nodes
- CT chest (and abdomen if not included on MRI scan)
- For atypical endometrial hyperplasia, an MRI pelvis should be arranged and managed as endometrial cancer if there is a suspicion of invasion
All imaging is to be reviewed at the specialist multidisciplinary team (MDT) meeting prior to surgery.

Contrast-enhanced MRI has been shown to be more accurate in assessing the extent of myometrial and cervical invasion than ultrasonography, CT or non-enhanced MRI. Its accuracy is about 91% \(^{[13]}\). MRI could identify patients who are at highest risk for metastatic disease and who would need more radical surgeries and surgical nodal evaluations \(^{[13]}\).

**CERVICAL CANCER**

**Epidemiology**

Worldwide, cervical cancer is the most common gynaecological cancer, and the third most common cancer in women, accounting for 9% of all female cancer \(^{[6]}\). Cervical cancer has the highest incidence in women aged 30–35 years with more than 60% of cases affecting women under 50 years old \(^{[6]}\).

Ninety per cent of cervical cancers are squamous cell carcinomas and the other 10% are adenocarcinomas. Squamous cell carcinoma arises from the metaplastic squamous epithelium of the transformation zone and adenocarcinoma arises from the columnar epithelium of the endocervix (Figure 1).

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**Figure 1:** Schematic representation of the transformation zone

**Risk factors**

Cervical cancer and its precursors have been associated with several epidemiologic variables (Table 4). These risk factors basically increase the likelihood of exposure to high risk Human Papilloma Virus (HPV) type 16 and 18 \(^{[14]}\). HPV is a major case of the main type of cervical cancer.
Table 4: Risk factors for cervical cancer

<table>
<thead>
<tr>
<th>Risk factors for cervical cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Young age at first sexual intercourse (&lt;20 years old)</td>
</tr>
<tr>
<td>• Multiple sexual partner</td>
</tr>
<tr>
<td>• Sexual partner with multiple sexual partners</td>
</tr>
<tr>
<td>• Young age at first pregnancy</td>
</tr>
<tr>
<td>• High parity</td>
</tr>
<tr>
<td>• Lower socioeconomic status</td>
</tr>
<tr>
<td>• Smoking</td>
</tr>
</tbody>
</table>

Screening and prevention

The HPV vaccine is part of the NHS childhood vaccination programme and is routinely offered to secondary school girls aged 12 and 13. A vaccine called Gardasil is used in the NHS cervical cancer vaccination programme. It protects against the types 16 and 18 of HPV, between them responsible for more than 70% of cervical cancers in the UK [15]. A bonus of using Gardasil to prevent cervical cancer is that it prevents genital warts too. The HPV vaccine is currently given as a series of two injections within a six- to 24-month period. Studies have already shown that the vaccine protects against HPV infection for around 10 years, although experts expect protection to be for much longer [15].

HPV vaccination does not replace cervical cancer screening. Women between the ages of 25 and 64 are invited for regular cervical screening under the NHS Cervical Screening Programme (NHSCSP). Women aged 25–49 are invited for routine screening every 3 years, whereas those aged 50–64 are invited for routine screening every 5 years [15]. The current standard screening modality within the NHSCSP is liquid-based cytology, which represented a cost-effective alternative to Papanicolaou smears.

Presentation and diagnosis

Patients with symptoms such as postcoital bleeding, intermenstrual bleeding, postmenopausal bleeding or offensive bloodstained vaginal discharge with or without a suspicious cervix, and irrespective of smear result, should be referred to the gynaecologist for further investigations which may include colposcopy or examination under anaesthetic (EUA) with cervical and endometrial biopsies [6].

The colposcopy unit assesses and sends cytological and histological biopsies, An EUA may be performed at the unit if considered appropriate. Intra-epithelial squamous and glandular neoplasia is managed, if appropriate, at the local colposcopy unit by local excision [6]. Invasive malignancy is referred to the cancer centre. Patients with advanced disease may present initially to either an urologist or a general surgeon with ureteric obstruction or bowel complications. These patients should be referred to the gynaecological oncology team for further management [6].
OVARIAN CANCER

Epidemiology

Ovarian cancer is currently the second most common gynaecological cancer and the fifth most common malignancy in women [6]. It is the biggest gynaecological killer of UK women. Over 80% of ovarian cancer cases are diagnosed in women over the age of 50. The highest age-specific incidence rates are seen in women aged 80-84 years at diagnosis [6]. The majority of women (60%) present with advanced disease with little prospect of cure. Only a small percentage of women confident at spotting the symptoms of the disease.

Risk factors

- Increasing age
- Family history of ovarian cancer: a first degree relative with ovarian cancer increases risk to 5%, 2 relatives: 7% [16]
- Personal history of breast cancer – ovarian cancer risk is 24% higher in breast cancer survivors than the general population [16]
- Nulliparity – Ovulation causes structural changes to the ovary which may stimulate cancer development, and hormonal factors may compound this or have their own independent effects [16]
- Use of postmenopausal hormone replacement therapy (HRT) – ovarian cancer risk is 53% higher in long term (5+ years) oestrogen-only HRT users and 17% higher in long term combines HRT users [17]
- Family history of breast cancer or Lynch syndrome – Ovarian cancer risk is up to 65% higher in women with BRCA1 mutation, and up to 35% higher in women with BRCA2 mutation. [18] Around 7% of women with Lynch syndrome develop ovarian cancer by age 70 [18].

Factors reducing the risk

- Increasing parity
- Breast feeding
- Oral contraceptive pill (reduce the risk by 25-28%) [19]
- Hysterectomy or tubal ligation – 30% lower risk [20]

Screening

Screening is not currently routinely recommended. Options under investigation include transvaginal ultrasound and serum CA-125 [6].

Genetics

If there is a personal or family history of cancer (e.g. Suspected Lynch syndrome, BRCA), then discuss with the cancer genetics services.

Patients who have a personal history of breast cancer, a relative with ovarian or male breast cancer must be offered a referral to the cancer genetics service for BRCA testing.

Approximately 10–15% of all epithelial ovarian cancer is associated with germline BRCA1 or BRCA2 mutations [6]. It is reported over 40% of all women identified as having BRCA1/2 mutations, do not have a significant family cancer
history. Women with high-grade serous and endometrioid histological sub-types are associated with higher rates of BRCA1 or BRCA2 germline mutations.[6]

Presentation and referral

In England at present, only 26% of cases are diagnosed through the 2 week wait (2ww) urgent referral pathway with 29% of emergency presentation [6]. The significantly lower survival rates for ovarian cancer observed are generally attributed to later diagnosis, with as many as 70% of ovarian cancers already at an advanced stage (FIGO stage III or IV) at the time of diagnosis, making them more difficult to treat [6].

CA-125 and HE4

Approximately 80% of patients with advanced ovarian cancer have elevated CA-125 in the blood serum. However, no more than 50% of patients with clinically detectable stage I disease have elevated CA-125 levels.

Serum HE4 (Human epididymis protein 4) concentrations along with CA-125 concentrations may provide higher accuracy for detecting epithelial ovarian cancer [21]. Researchers also found HE4 to be elevated in more than half of the ovarian cancer patients who did not have elevated CA 125 levels. Combination of markers provided slightly improved cancer diagnostic sensitivity for the detection of ovarian cancer.

Calculating the risk of malignancy index

<table>
<thead>
<tr>
<th>Feature</th>
<th>RMI score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrasound features:</strong></td>
<td></td>
</tr>
<tr>
<td>Multilocular cyst</td>
<td>0 = none</td>
</tr>
<tr>
<td>Solid areas</td>
<td>1 = one abnormality</td>
</tr>
<tr>
<td>Bilateral lesions</td>
<td>3 = two or more abnormalities</td>
</tr>
<tr>
<td>Ascites</td>
<td></td>
</tr>
<tr>
<td>Intra-abdominal metastases</td>
<td></td>
</tr>
<tr>
<td><strong>Menopause status</strong></td>
<td>1 = premenopausal</td>
</tr>
<tr>
<td></td>
<td>3 = postmenopausal</td>
</tr>
<tr>
<td><strong>CA-125 level</strong></td>
<td>U/ml</td>
</tr>
</tbody>
</table>

RMI score = ultrasound score x menopausal score x CA-125 level in U/ml

Patients with RMI of 250 or greater are considered at high risk of ovarian cancer and should be referred to the centre for further management.

Assessment in primary care

CA-125 blood serum level (normal level less than 35IU/ml) should be measured and urgent pelvic ultrasound carried out in women with persistent abdominal distension or feeling full and or loss of appetite or pelvic or abdominal pain or increased urinary urgency and or frequency [6].

Best Practice Early Detection Pathways: Ovarian cancer has recommended that if either of these results is abnormal, the patient is referred via the 2ww system. If symptoms persist or worsen despite a normal CA-125 blood serum level and a negative ultrasound scan, refer to secondary care.
The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)

The UKCTOCS is an international ovarian cancer screening trial. It was the first evidence to suggest that screening for ovarian cancer may save lives. Two methods of screening were tested, one based on serum CA-125 (called multimodal strategy) and a second, annual transvaginal ultrasound (TVS) strategy \(^{22}\).

The current report is not sufficient for the decision to be made regarding setting up a national screening programme for ovarian cancer. Researchers need to follow-up the trial participants for 3 years more before the full impact of screening on reducing deaths from ovarian cancer is known.

Initial diagnostic investigations

- Clinical assessment.
- Tumour markers: – CA-125, CA 19-9, CEA, CA-153. Alpha fetoprotein (AFP) and beta hCG in women less than 40 years.
- Ultrasound scan: – TVS should be undertaken and adnexal masses can be evaluated using the International Ovarian Tumour Analysis (IOTA) simple rules which detail five ultrasonic features to predict malignant or benign features (Figure 2).
- If the pelvic mass is clinically or sonographically indeterminate, then further imaging is required to further characterise the mass:
  - MRI scan
  - Level III (Expert) ultrasound.

**Figure 2**: Ultrasound features used in the International Ovarian Tumor Analysis (IOTA) simple rules, illustrated by ultrasound images. B1-B5 benign features; M1-M5 malignant features \(^{23}\).
The decision whether to treat at a cancer unit or refer to the cancer centre is based on the ultrasound findings and or calculation of the risk of malignancy index (RMI) for all patients with an ovarian cyst or mass.

**VAGINAL CANCER**

**Epidemiology**

Primary cancer of the vagina is rare and accounts for less than 2% of gynaecological cancers in the UK [6].

**Screening**

There is no routine screening for vaginal cancer.

**Presentation and diagnosis**

Presentation and diagnosis symptoms depend largely on the size and site of the tumour and to some extent on the age of the patient.

The majority of patients present with [6]:

- post-menopausal bleeding or discharge
- pain, discomfort or dyspareunia
- urinary symptoms including dysuria, frequency and retention
- defaecatory problems such as tenesmus and rectal bleeding

A minority is asymptomatic, with the cancer detected at routine pelvic examination at the time of cervical screening, colposcopic examination or in routine gynaecology [6].

**Asymptomatic patients with abnormal vaginal cytology**

Vaginal intra-epithelial neoplasia (VaIN) is usually asymptomatic and detected at the time of cytological review or colposcopy. It may be multifocal, but most commonly affects the upper vagina.

VaIN may act as a pre-malignant precursor to invasive squamous cancer of the vagina, VaIN3 may progress to invasive cancer. Microinvasive or invasive carcinoma may be found in association with VaIN3, or occasionally occurs even after treatment for VaIN3 [6].

Treatment is dependent on the site and accessibility of the lesion. It may be treated with excision using sharp dissection, laser or cutting diathermy [6]. Alternatively, ablation with diathermy, hyfrecator or laser may be performed [6]. GA may be required to permit adequate access. There may be a place for brachytherapy in some situations [6]. Long-term follow-up is required, particularly in immunosuppressed individuals.

**Staging and other investigations**

- Colposcopic assessment and biopsy and/or EUA with/without biopsy
- Excision or wedge biopsy as appropriate
- Cystoscopy
- Radiology
  - MRI of pelvis
  - CT scan of the chest and abdomen
CT-positron emission tomography (PET-CT) prior to radical radiotherapy to assess nodal involvement

VULVAL CANCER

Epidemiology

Vulval cancer is rare and it represents 4% of gynaecological malignancies \(^{[24]}\). It is ranked as the 20th most common female cancer \(^{[25]}\). It is a disease affecting predominantly elderly women and is uncommon below the age of 50 years \(^{[25]}\). Some 90% are squamous cell carcinomas, while less common histological types are melanomas, adenocarcinomas, basal cell carcinomas, verrucous carcinomas and sarcomas \(^{[6]}\). The inguinal and femoral nodes are the primary sites of regional spread and involvement to pelvic nodes are considered as distant metastasis.

Screening

The is no evidence to support screening and unselected population for vulval cancer. Precursor lesions include VIN, Paget’s disease of the vulva and lichen sclerosis. Surveillance of women with this condition is of value \(^{[24]}\). A detailed cervical cytology history should also be obtained, and if necessary a smear should be performed, as women with vulval carcinoma are at increased risk of cervical malignancy.

Diagnosis and referral

Early diagnosis is important to reduce the morbidity of treatment and to improve survival. Factors that can aid the GP in making an appropriate referral include \(^{[6]}\):

- The disease is more common in post-menopausal women. However, there is a rise in incidence in women in their 40s related to HPV infection.
- Tumours may be asymptomatic, although women will often present with vulval pain, soreness, burning or pruritus.
- Any vulval symptoms should be taken seriously and prompt an examination.

Patients with any of the following should be referred to the local rapid access clinic using a 2 week wait referral form \(^{[24]}\):

- unexplained vulval lump
- vulval ulceration or bleeding
- persistent vulval pruritus or pain.
- persistent warts

If invasive disease is suspected, patients should be referred to the local gynaecological cancer specialist for further assessment. Patients who are found to have a vulval malignancy should have their histology reviewed and care discussed at the centre multidisciplinary team (MDT) meeting.

Clinical information

A detailed history and the date of their last cervical smear should be recorded. Patients should be examined by someone who is familiar with appearance of vulval cancer and preferably to undergo vulvoscopy examination. If an obvious abnormality is seen then a biopsy can be performed \(^{[24]}\).
CONCLUSION

Early detection saves lives. Cervical cancer screening is the most successful programme in gynaecological cancer. Ovarian cancer screening is not proven to be cost effective yet. However, it may be considered in high risk groups. Endometrial cancer screening may be considered in women at risk of Lynch syndrome families. Vulval and vaginal cancers are too rare to justify screening. These prevention and early detection efforts, which require neither major expenditure nor reorganisation, succeed best when patients are well informed and have a relationship with their health care professionals who follow screening and detection recommendations appropriate in their own lives.

DECLARATION OF CONFLICTING INTEREST

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REFERENCES