Scaling up the screening

Gynaecological cancers require standardisation of clinical care across Europe, urge Dr Tahir Mahmood and Professor Peter Hornnes, of the EBCOG...

The management of gynaecological cancers predominantly involves cancers of the ovary, body of the uterus, cervix of the uterus, and cancers of the vulva and vagina. In some European countries, gynaecological surgeons also manage women presenting with breast cancer. There is a huge variation in the standards of care offered to women suffering from such cancers across the member states of the European Union[1,2,3] as measured by incidence or by five year survival data following diagnosis and treatment. The European Board and College of Obstetrics and Gynaecology (EBCOG) advocates the development of unified standards of care across Europe, and this would be underpinned by adopting a unified accreditation system for service providers and also by supporting high-quality equitable postgraduate training programmes.

Gynaecological cancers account for one-sixth of female cancers, with an estimated 942,000 new cases worldwide per year, or 18.6% of all incidents of cancers; they are the cause of 15.3% of cancer deaths in women.[4] Therefore, prevention of cancer and early diagnosis is an increasingly important issue.

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Ovarian cancer

Worldwide ovarian cancer is the sixth most common cancer among women, with an estimated 204,000 new cases; the incidence rates vary from a low of 2/100,000 women in Algeria to a high of 15/100,000 in Poland. General incidence rates are relatively higher in the European population, with rates of ovarian cancer generally increasing exponentially with age, with a sharp increase after about 40 years, with almost 85% of cases occurring in women aged over 50 with mortality/incidence ratio of 56%. Ovarian cancers account for more deaths than all other gynaecological cancers put together. The incidence in younger women has remained fairly stable and may be declining.

Endometrial cancer

The seventh most common cancer among women worldwide is endometrial cancer, with an estimated 199,000 new cases. Endometrial cancer is relatively more common in developed countries; in most European populations the incidence begins to rise steadily five to 10 years before the menopause and reaches a peak usually around 65-70 years. The incidence rates of endometrial cancer vary from a low of 0.9/100,000 women in Oman to a high of 18.8/100,000 in white women in the USA. The highest rates have been observed among women in North America, Europe, Australia/New Zealand and Israel. Since the mid-1980s, there has been a steady increase in incidence among women over 60. Endometrial cancer is a model of hormonal carcinogenesis.

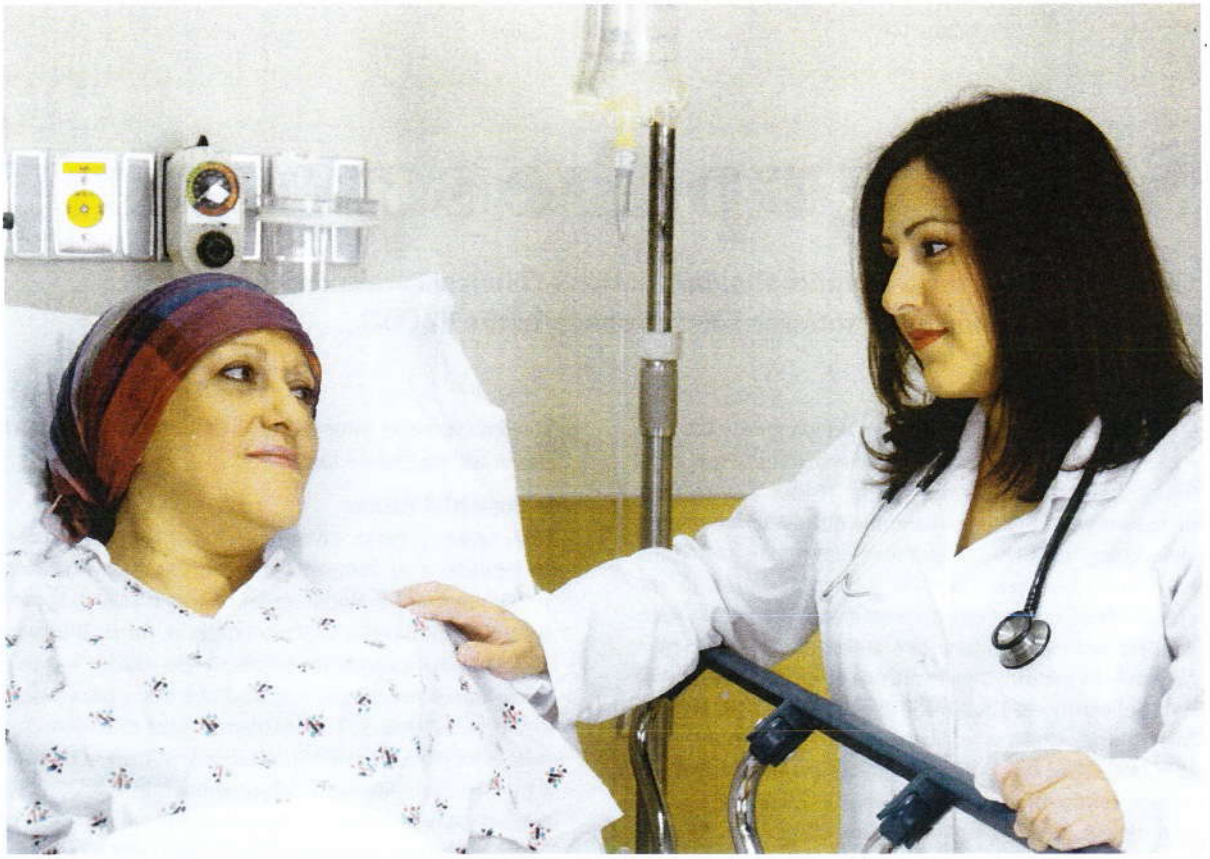
Cervical cancer

Cervical cancer is the second most common cancer among women worldwide with an estimated 493,000 new cases, 83% of which occur in developing countries. In most European populations the incidence of cervical cancer begins to increase at 24 years and the risk increases rapidly to reach a peak, usually at around 35-39. Incidence rates are generally lower in developed countries in Europe and North America, with good five year survival rates.

Overall incidence and mortality have declined considerably during the past 40 years in Western Europe. For example, in the UK the age standardised incidence rates of cervical cancer declined by around 46% during the period 1975-2004 and mortality rates declined by around 63%.

The decline has been attributed to a combination of factors, including improved genital hygiene, improved treatment modalities and the beneficial effects of organised population-based cytological screening programmes.

A persistent infection with an oncogenic HPV type virus is now recognised as a causative factor for preceding pre-cancer changes and cervical cancer. A number of co-factors have been identified as possible modifiers of HPV infection during the developmental stages of cervical cancer (Table 1). The HPV immunisation programme makes cervical cancer one of the most preventable forms of cancers on a global scale.



Screening the asymptomatic population for early disease and pre-malignant conditions is an established strategy for early detection and prevention of cancer

Vulvar and vaginal cancers

Vulvar and vaginal cancers are rare throughout the world and constitute less than 5% of all gynaecological cancers. Both predominantly occur in older women with a steep rise in incidence after 60+ years (incidence of vulvar cancer of 4.2/100,000 and vaginal cancer of 0.7/100,000 women) and by age 85+ (30.5/100,000 and 4.1/100,000 women, respectively). Five year survival rates vary significantly by stage of disease and age at diagnosis. The five year survival rate for vulvar cancer ranges between 31-98%, as compared to 42-72% for vaginal cancers.

Recently, there has been some increase in the rates of vulvar cancer among young women (aged <50 years) in many countries that has been linked to increasing incidence of vulvar intraepithelial neoplasia (VIN), which is caused by persistent infection of oncogenic HPV type.

Screening for gynaecological cancers

The aim is to detect disease early in order to facilitate effective treatment. Screening offers improved prognosis for some cases, less radical treatment for others and potential resource savings for society. Screening can reduce the risk of developing a condition or a condition's complications, but it does not offer a guarantee of protection.

The five year survival for patients diagnosed with ovarian cancer stage 1 is >80%, but this falls to 22% and 14% for advanced cancer stages 3 and 4, respectively. However, the majority of these patients present late when the disease has spread outside the ovary. Current screening strategies are based on serum tumour markers such as CA 125 and/or ultrasound imaging of the ovaries. In the postmenopausal age group, although approximately two out of three cases of ovarian carcinoma could be detected by annual serum CA125 measurement, only one-third would be detected in the early stage; therefore, CA125 measurements are unsuitable as a single screening test for ovarian cancer. Lately a number of combination assays have shown high rates of sensitivity for detection of disease; however, data from larger longitudinal studies are awaited before implementing new screening strategies.

In addition to estimation of a serum CA125 blood test, ultrasound scan can also be used either as a sole screening method or as a secondary test after primary screening with CA125. However, early studies in women over 40 resulted in an unacceptable number of operations for each case of ovarian cancer detected. Currently, a large UK randomised controlled trial of ovarian cancer screening using a multi-modelling method is in progress and its results are awaited. However, among women with a family history of ovarian cancer, it is important to assess their individual risk taking into account their age, parity and use of the pill and the limitations of screening.

For cervical cancer screening, cells are sampled from the cervix using a brush or a spatula. Screening allows early detection of pre-cancer changes, which are amenable to local treatments. There is strong evidence for its effectiveness in reducing incidence and mortality of cervical cancer. Following the introduction of population screening in Finland, Sweden and Iceland in the 1960s, the

Cancer	Risk Factors	Links to reduced risk	Reducing factors
Ovarian	■ Early menarche ■ Sub-fertility ■ Obesity ■ Hormone replacement therapy (HRT) ■ Smoking ■ Nulliparity ■ Family history of breast and colon cancers	■ Greater number of pregnancies ■ Breast feeding (RR 0.5-0.7) ■ Oral contraceptive pill (OR 0.4-0.6) ■ Sterilisation/hysterectomy (OR 0.5-0.7)	■ Diet rich in carotenoids ■ Physical exercise may have a modest protective effect ■ Consumption of vegetables
Endometrial	■ Lynch syndrome ■ Gross obesity ■ Diabetes ■ Oestrogen only HRT >10 years	■ Child bearing ■ Modification of lifestyle: healthy eating, reduce smoking and normal BMI	■ Use of combined oral contraceptive pill halves risk ■ Woman with HNPCC associated cancers related gene mutations
Cervical	■ Early sexual debut and increasing number of partners ■ Smoking ■ High Parity ■ Long-term oral contraceptives pill users ■ Certain HLA antigens ■ Sexually transmitted infections	■ Improved genital hygiene ■ Improved mass population screening ■ HPV immunisation programme	■ Delayed first sexual intercourse ■ Use of condoms can lead to reduced incidence of HPV infection, hence reduction in potential consequences
Vulva and Vaginal	■ History of genital warts ■ Smoking ■ Sexually transmitted infections		■ Awareness campaign ■ Smoking cessation ■ Awareness of sexually transmitted infection

Table 1: A summary of various factors linked to development/reduction of gynaecological cancers

incidence of the disease fell by 50% over 20 years, while Norway (which had a similar population but no screening) saw no change. Cervical screening can be further supplemented by HPV testing, which is found in 95% of the cervical carcinomas and precursor lesions. Data from three NHS centres in the UK – piloting the use of HPV testing in women with early to moderate pre-cancer disease – has shown that allocating these patients to immediate colposcopy on the basis of their HPV status would reduce the need for repeat smears but may increase the number of colposcopies. The past two years have seen the widespread introduction of vaccines against HPV types 16 and 18 in the USA, Europe and Australia. Preliminary trials have confirmed their efficacy in terms of preventing infection by these serotypes. If this is reflected in the reduction of incidence of high grade pre-cancer disease, it would represent the most important advance in the prevention of cervical cancers in the past 30 years, especially in those countries where routine cervical screening is not possible.

The benefits of screening for early diagnosis of cancer of the uterus are unproven. Ultrasound scan assessments of the lining of the uterus, outpatient endometrial sampling and cervical cytology have all been proposed as potential screening tools. Given that the majority of early carcinomas give rise to symptoms and the low pick-up rate for testing asymptomatic women, mass screening is unlikely to be cost-effective. It is important to educate women and their healthcare providers about the significance of postmenopausal bleeding. There are no economic benefits for introducing screening programmes for low volume cancers affecting vulva and vagina.

What are the benefits of screening?

Screening the asymptomatic population for early disease and pre-malignant conditions is an established strategy for early detection and prevention of cancer. Mass screening for cervical cancer fulfils most of these criteria, and establishment of screening programmes in different countries has led to a marked reduction in the incidence of end mortality associated with cervical cancer. Ovarian cancer is the other gynaecological malignancy for which population screening may become justified once the results of the UK trial are available. Although effective treatment is available for early stage disease, a majority of ovarian cancers are usually diagnosed in advanced stages when the prognosis for long-term survival is poor. Mass screening of the low risk population for cancer of the uterus is unlikely to be of benefit as most women present in the early stages with symptomatic disease and have a good prognosis. However, screening of the high risk population is recommended. Screening is not justified for vaginal and

vulvar cancers as they are rare diseases, though increasing awareness of these conditions is important.

How important is education and campaigning to raise awareness?

Across Europe well-established, effective cytology/colposcopy-based screening programmes for cervical cancer exist. However, we are learning more about the role played by HPV oncogenic viruses. HPV vaccination for girls aged 12-13 was introduced into the UK national immunisation programme in September 2008. Subsequently, a two year catch-up drive for vaccinating girls (up to 18 years) was commenced from autumn 2009 for those aged between 16-18 and from autumn 2010 for girls between 15-17. The efficacy of these vaccinations in preventing persistent HPV infection has been found to range between 90-100% and the immunity provided has been shown to last for in excess of six years. Mathematical modelling suggests immunity persists for 20-30 years. Although long-term data is still not available, it is important to point out to the public that immunisations with HPV vaccines would not only reduce the risk of developing cancer significantly but would also have other risk reductions for those cancers that are related to HPV infection such as cancer of oropharynx, vulvar, vaginal cancer and anal cancer as well.

Women should be made aware of the potential risks related to unhealthy living, development of co-morbidity such as diabetes – which increases the risk of endometrial cancer – and be aware of early warning signs such as postmenopausal bleeding, which requires immediate attention and further investigation. For ovarian cancers, women should be made aware of the signs such as loss of appetite, swelling of the abdomen, a feeling of a mass or any other worrying signs, which require a visit to a surgery. Quite often women present late with cancer of the vulva as they feel embarrassed to attend their family doctors even if they are aware of abnormal growths in their private parts. Consumers and specialists should work out what messages need to be conveyed to the public in an easily understandable language, regarding early detection of symptoms, what an average woman should be looking for and how to access services for prevention of the disease and treatment of a condition that they suspect. Table 1 provides a list of factors that increase risks for development of cancers, as well as a list of possible risk modifiers (risk reduction).

The benefits of international collaboration

In order to obtain meaningful results from clinical trials, it is important that multi-centre clinical trials are organised across the globe. Quite often a clinical question requires participation of thousands of eligible women in order to demonstrate the benefits of new interventions, new technology or new treatment modalities. An international collaboration of researchers can reduce the lead time to recruit patients, assess interventions and develop new methods of treating cancers across the globe, which can then become routinely available. Multi-centre international collaborations also allow the undertaking of high-level engagement for testing new drugs, considering genetic aspects of disease development and knowledge sharing. Furthermore, the relatively low incidence of many gynaecological cancers has also meant that until multi-centre international trials are conducted, the benefits of introducing new screening programmes will remain unproven. For example, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) would be recruiting over 200,000 postmenopausal women. Similarly, for the prostate, lung, colorectal and ovarian cancer screening trial (PLCO) in the USA, the target is to recruit 78,000 postmenopausal women. These two trials exemplify why multi-centre trials across the world are needed to resolve the issues around the value of screening, developing new treatments and to assess their cost-effectiveness.

How to improve care of women in Europe

The EBCOG now has 35 countries represented on its council, and is committed to driving improvement in the care of women by streamlining high-quality training programmes across Europe. It is working very closely with the European Society of Gynaecological Oncology to ensure that the hospitals providing care for women with gynaecological cancers are offering a high standard of care by following agreed guidelines and protocols through a multidisciplinary team. These units are accredited on a six yearly rotational visiting programme organised by EBCOG.

The Council has now established a taskforce to develop unified standards of care across Europe. Once these standards of care have been agreed, it will be possible to establish a system of benchmarking provider units within the EU. Such comparative data will be a great stimulus in improving the care of women, firstly by re-organising local services appropriately, and, secondly, by investing more – not only in clinical services but, indeed, developing robust training programmes for the cancer specialists of the future.

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