Incidence, pathophysiology and treatment of cervical cancer

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Cervical cancer is the third most common cancer affecting women. While not in itself a sexually transmitted disease, cervical cancer is linked to the presence of the human papilloma virus, which is sexually transmitted. Survival rates are significantly higher where diagnosis is early, and a national screening programme has reduced mortality in the UK. However, uptake is low in some groups and nurses have a role in increasing uptake.

The NHS cervical screening programme offers screening to all women aged 25 to 65 and screens 3.7 million women each year (Department of Health, 2003). About seven per cent of these have some abnormality requiring follow-up (Wright et al, 2002). In many cases women will be reassured that the abnormality is unlikely to progress and that no treatment – apart from close surveillance – is required. A small number will be told that their problem is more serious, and a proportion of these will be diagnosed with cervical cancer.

Cervical cancer is the third most common cancer in women, with a death rate of 231,000 a year worldwide (Loizzi et al, 2003; Sankaranarayanan et al, 2001). It killed 1,123 women in the UK in 2002 – about 3.7 per 100,000 – (Cancer Research UK, 2004). However, the death rate in developing nations is significantly higher at 5–15 per 100,000 (O’Meara, 2002).

This article discusses the stages of cervical abnormality and examines the role of human papilloma virus (HPV) and cervical intraepithelial neoplasia (CIN). It also examines management of cellular abnormalities and cancer treatment and nurses’ role in raising uptake of screening.

Presentation and risk factors

The cervix is the inferior part of the uterus, which protrudes into the vagina. It is characterised by two types of epithelium: the endocervical epithelium lines the uterus and superior part of the cervix, while the squamous epithelium is located distal to the endocervical epithelium. The two cell types meet in a region known as the transformation zone, where most cellular abnormalities arise. Cervical cancer can develop from the squamous cells or endocervical epithelium, but squamous cell carcinomas are the most common and account for 85–90 per cent of cervical malignancies (Wright, 2001). The mean age of presentation is 54 years, although intraepithelial lesions are often diagnosed at a much earlier age suggesting long latency between cellular abnormality and malignancy (Cannistra and Niloff, 1996).

The most common presenting symptom of cervical cancer is abnormal bleeding, perhaps after intercourse or postmenopause. This may be accompanied by offensive vaginal discharge. Risk factors include (Cannistra and Niloff, 1996):

- Intercourse at an early age;
- Multiple sexual partners (or a sexual relationship with a man who has had multiple partners);
- Smoking;
- Immunosuppression.

Women who present before the cancer becomes too advanced have the best prognosis; cervical screening is effective because cervical neoplasia has a long pre-invasive phase (Goodman and Wilbur, 2003).

Cervical cancer screening

Cervical cancer screening differs from breast screening, which uses mammography to detect cancer in its early stages (Cannistra and Niloff, 1996). Cervical cytology aims to detect precancerous lesions and treat them before they become malignant. The NHS Cervical Screening Programme was launched in the 1990s. Its aim was to cut mortality from cervical cancer by 20 per cent or more by 2000 – a target achieved in 1996 (Smith, 2000).

Cervical smears

In order to detect cellular changes a cervical smear (‘Pap’ smear) is performed. Until recently this was the mainstay of the screening programme, although new technologies have since been introduced.

The cervical smear involves collecting cells from the transformation zone, usually using a combination of endocervical brush and spatula. Samples are smeared on to a slide, fixed with a cytology fixative and then sent for laboratory analysis by cytologists. While simple and relatively inexpensive, the cervical smear is not perfect. False negative results are yielded at least 20 per cent of the time (O’Meara, 2002) – two-thirds of which are caused by sampling or preparation errors. There is also a five per cent false positive rate (Choma, 2003).

Liquid-based cytology

The shortcomings of the smear test led the National Institute for Clinical Excellence to recommend the use of liquid-based cytology (LBC), in which the sample is collected in a similar way, but the head of the spatula is snapped off and rinsed in preservative fluid. This is followed by

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transported to a laboratory where it is processed to remove unneeded material and the resultant cellular suspension is transferred to a slide and stained.

**Abnormal cytological specimens**

Abnormal specimens from cervical smears are defined as:
- High-grade squamous intraepithelial lesions (HGSIL);
- Low-grade squamous intraepithelial lesions (LSIL);
- Abnormal squamous cells of uncertain significance (ASC-US).

The most common abnormal Pap smear finding is ASC-US, which accounts for 5–10 per cent of all smears (Choma, 2003; Goodman and Wilbur, 2003). On further investigation many women with ASC-US have no significant pathology. In such cases the abnormality may be caused by a condition that mimics cervical dysplasia, such as:
- Cellular changes due to tissue damage caused by infection, trauma or radiation;
- Physiological changes secondary to hormonal use and menopausal status;
- A wide range of artefacts resulting from preparation of the specimens (Goodman and Wilbur, 2003).

Seventy per cent of ASC-US and low-grade lesions resolve spontaneously (Kubovchik, 2004). However, LSIL or HGSIL warrant further investigation, generally by colposcopy and biopsy. In colposcopy the cervix is imaged and acetic acid applied to highlight abnormal epithelium. After application of acetic acid, abnormal tissue becomes whitened (Fig 1). Generally the more severe the whitening, the more severe the lesion. Where the edges of the lesion are clearly defined, significant disease is more likely. Where the edges are fuzzy the changes are often precipitated by viral change (Smith, 2000).

**Cervical intraepithelial neoplasia**

Usually a colposcopy performed after an abnormal smear will reveal a lesion from which a biopsy can be taken. Biopsies are graded using the cervical intraepithelial neoplasia (CIN) histological grading system, which quantifies degree of cellular dysplasia ranking from CIN I for mild dysplasia to III for advanced dysplasia (Box 1).

Most women with LSIL have CIN I disease. This generally requires no further treatment because 90 per cent of CIN I abnormalities will not progress (Cooper et al, 2003). These women are followed up with repeat smears and possibly colposcopy (Cannistra and Niloff, 1996). CIN II or III disease will be present in 5–10 per cent of women with LSIL. Women with HGSIL have a 70–75 per cent chance of a CIN II or III lesion and a 1–2 per cent chance of invasive cervical cancer (Wright et al, 2002).

**Human papilloma virus**

Almost all cervical cancers contain traces of the human papilloma virus (HPV), which is also causative in the cellular changes that bring about ASC-US, LSILs and HGSILs. It is thought to infect basal cells within the cervical epithelium gaining access via minor trauma, or at the squamocolumnar junction (Cooper et al, 2003).

There are two sub-types of HPV:
- Low risk – associated with cutaneous infection (such as warts) (HPV 6, 11, 40, 42, 43, 44);
- High risk – associated with infections of the genital tract (HPV 16, 18, 31, 33, 35, 45); HPV 16, 18, 31 and 45 account for about 80 per cent of cervical cancers (Choma, 2003).

About 75 per cent of people of reproductive age have been infected with HPV (Choma, 2003). Primary infection occurs mostly in young adults, and a large percentage of people will be infected by the age of 30 (Helmerhorst and Meijer, 2002). The most important risk factor for the acquisition of HPV is number of sexual partners. HPV infection is mainly asymptomatic and transient. Only 20 per cent of people develop premalignant lesions and only a small percentage of these will become cancerous. Ninety per cent of infections resolve completely within two years without identification of clinically significant lesions (Choma, 2003). It is unclear if the virus is eradicated or merely suppressed to undetectable levels.

Total abstinence from sex is the only way to prevent

**FIG 1. CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN) GRADES I-III**

**CIN I**
Cellular dysplasia only in basal third of epithelium (speckled white area below the OS).

**CIN II**
Cellular dysplasia confined to the basal two-thirds of the epithelium (stratified areas of abnormal tissue in white).

**CIN III**
Cellular dysplasia encompassing over two-thirds of the epithelial thickness, including full thickness lesions (pale irregular areas).

**REFERENCES**


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Managing precancerous lesions

CIN I lesions often resolve spontaneously, and are generally managed by close observation, while CIN II or III lesions require more active intervention. These range from aggressive strategies requiring hospital admission to less aggressive approaches that can be performed as outpatient procedures. Treatment for CIN management has a 95 per cent success rate.

Excisional strategies

The traditional approach was to take a cone biopsy – the removal of a cone-shaped piece of tissue from the wall of the cervix. This ‘cold knife’ biopsy is less common today but is sometimes used for CIN III lesions because it yields a good specimen for the pathologist to examine to determine that the surgical margins are clear. It generally necessitates hospital admission because of the comparatively large amount of cervical tissue removed.

Where possible cone biopsy has been replaced by a less complex procedure called the loop electrosurgical excision of the transformation zone (LEEP), in which the abnormal tissue is excised using an instrument composed of a wire heated by an electrical current. This can be conducted on an outpatient basis. The heated wire can cause some damage to the margins of the biopsy specimen and is not utilised in cases in which there is concern about the histology at the excision margins.

Destructive strategies

The use of radical diathermy or cryotherapy is now limited. Cryotherapy is technically problematic. Laser therapy with a CO2 laser can also be technically difficult. Immediate complications of these treatments are pain and haemorrhage. Patients should avoid sexual intercourse, tampons and douching until the incision is completely healed, which may take several weeks. A small number of women experience cervical stenosis. Post procedure women require frequent smears or colposcopies, as determined by their gynaecologist (Smith, 2000).

Cervical cancer treatment

There are four stages of cervical cancer, stage 1 being the least invasive. Here the cancer is confined to the cervix whereas in stage 4 it extends to the bladder, rectum and distant sites (Box 1). Localised disease is managed by surgery. Widespread disease may require radiotherapy, surgery and chemotherapy. The four-year survival rate from early cervical cancer is 95 per cent, but drops to 0–39 per cent with advanced disease (Rajaram, 1998).

Surgery

For localised disease confined to the cervix, surgery is the treatment of choice. Radiotherapy is equally effective but tends to carry more side-effects.

Surgery involves a vaginal or abdominal hysterectomy. Vaginal hysterectomy is removal of the uterus and cervix through the vagina. It is the less traumatic of the two but may be difficult in those with other gynaecological problems or obese patients. Abdominal hysterectomy involves surgical removal of the uterus, upper part of the vagina, ligaments and connective tissues that hold the uterus in place via an incision in the abdomen. Pelvic lymph nodes are also frequently resected, and an oophorectomy and salpingectomy may be required. Surgical approaches may lead to a number of long-term complications, particularly if radiotherapy is utilised as well. Bergmark et al (2002) found sexual dysfunction to be a major cause of distress, as well as lymphoedema, dyspareunia and the urgent need to defecate.

It is estimated that 10–15 per cent of cervical cancers are diagnosed in women who are still within their childbearing years.

The radical trachelectomy is a specialised surgical procedure which allows preservation of the body of the uterus for young women with early-stage cervical cancer. This is a relatively new approach, and data is being collected to establish its role (Plante and Roy, 2001).

Box 1. Simplified cervical staging system (FIGO) (2001)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Limited to cervix</td>
</tr>
<tr>
<td>II</td>
<td>Extending beyond cervix to upper vagina but not into the pelvic wall</td>
</tr>
<tr>
<td>III</td>
<td>Involving the pelvic side walls, nodes and lower vagina</td>
</tr>
<tr>
<td>IV</td>
<td>Involving bladder, rectum and distant sites</td>
</tr>
</tbody>
</table>
Radiotherapy

radiation therapy has been used successfully to treat carcinoma of the cervix since the early 1900s. Adjuvant radiotherapy is utilised if there is a risk of residual disease postsurgery. Unfortunately, for the management of large cervical lesions the dose of radiation needed to achieve tumour control exceeds the dose tolerated by the normal tissues of the pelvis.

Tumour size is an important predictor of outcome. As tumours increase in size they exceed their blood supply and develop hypoxia and necrosis. This hypoxia results in reduced efficacy of both radiotherapy and chemotherapy. Anaemia is thought to have a similar effect and is therefore a negative prognostic factor in cervical cancer. Hyperthermia, neutron beam irradiation, interstitial brachytherapy and high-dose rate intracavitary radiation have been investigated in reversing the effects of hypoxia but have not resulted in major benefits (Rose, 2001).

The most significant development in improving efficacy of radiotherapy is use of concurrent chemotherapy, which has been found to act as a radiosensitiser. The two treatments are thought to act synergistically via:

- Simultaneous activity of drug and radiation in different phases of the cell cycle and against different tumour subpopulations;
- Radiotherapy decreasing tumour cell repopulation;
- Increased tumour cell recruitment out of resting phase to responsive phases in the cell cycle;
- Inhibition of repair of sub-lethal radiation damage (Loizzi et al, 2003).

Chemotherapy

Disseminated disease is primarily treated by chemotherapy. Survival rates post-recurrence are limited – about 30 per cent of patients die of recurrent disease. Prognostic factors with a negative impact on survival include:

- Recurrence within a previously irradiated area;
- Young age;
- Poor performance status;
- Short time to progression from initial diagnosis (Eralp et al, 2003).

Cisplatin appears to be the most active chemotherapy agent, with response rates of about 20 per cent. Some combination regimens that utilise a greater number of chemotherapy agents have been found to yield higher response rates (50–60 per cent), but this is not necessarily reflected in increased survival. Furthermore, the employment of multiple agents increases the potential for toxicity, which is of particular significance among this population, whose prognosis is poor (Eralp et al, 2003).

Chemotherapy has also been investigated in adjuvant and neoadjuvant settings, but there is no compelling data to support use of either routinely (Loizzi et al, 2003).

Increasing uptake of screening

Most women who develop cervical cancer have never been regularly screened, either because they are citizens of a country that lacks the infrastructure to provide such screening or because there are barriers to their participation in a screening programme (O’Meara, 2002). Within developed countries 30–80 per cent of women diagnosed with an abnormal smear fail to return for follow-up care (Rajaram, 1999). High-risk groups include women belonging to minority ethnic groups, younger women, women on lower incomes and those who are educated to below high-school level. These women also experience decreased survival rates for cervical cancer. For example, the mortality rate among African-Americans is twice that of white women (Choma, 2003).

Lack of uptake of screening programmes by minority ethnic women is a problem. Chiu (2004) describes a project in the UK in which women and health professionals were involved in research to identify and resolve the problems that stopped women from participating.

A key issue was difficulty in understanding and communication between the two groups. Chiu found a clear divergence between the perceptions of the smear-takers and those of the women from minority ethnic groups, which resulted in negative experiences on both sides. In the past there has been an assumption that provision of information is the answer to uptake problems, but this paper identified a pressing need to look more. Close relationships often develop between nurses and their patients, and this places them in an ideal situation to educate women about the purpose and benefit of cervical cancer screening – particularly among women from high-risk groups. Current national guidelines of screening recommendations are given in Box 2.

Conclusion

Cervical cancer is declining in incidence in the developed world, and although no randomised trials have been performed, it is thought that the screening programme is responsible for this decline (Sedlacek, 2002). Treatment for advanced cancer remains problematic and has discouraging response rates. Management strategies must rely on early detection and screening through programmes that are also acceptable to women who belong to minority ethnic groups and who are at high risk. Nurses can play an important role in encouraging women to participate in the NHS cervical screening programme.

### Box 2. Current recommendations of UK cervical cancer screening service

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Frequency of screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>First invitation – cervical cancer is rare under 20 years of age</td>
</tr>
<tr>
<td>25–49</td>
<td>3-yearly</td>
</tr>
<tr>
<td>50–64</td>
<td>5-yearly – cervical cancer is rare in women older than 65</td>
</tr>
<tr>
<td>65+</td>
<td>Only screen those who have not been screened since age 50 or have had recent abnormal tests</td>
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**References**


