Chapter 1

Dysplasia, HPV and cervical cancer

‘In theory, recognition that a pandemic infection is responsible for more than half a million cancer cases each year would attract huge media attention and infection control would become the subject of preventative efforts from the global health agencies. Media attention would likely be particularly acute if the majority of deaths was among women rearing families in the developing world and if the disease were sexually transmitted. A vaccine capable of preventing the disease would be diligently pursued and, once available, promptly distributed for the health and welfare of humankind. Human papilloma virus (HPV) infection fits this scenario; however, HPV has yet to make an impact on either the media or public thinking as outlined in the previous paragraph, even though the link between HPV infection and cervical cancer has been recognised for more than 20 years.’

(Frazer et al. 2006)

Introduction

Our understanding of cervical cancer has increased enormously in recent years, principally through a greater appreciation of the role of the human papilloma virus (HPV). Whilst HPV alone does not cause cervical cancer, it is certainly an extremely important factor. Infection with the virus can trigger a number of cellular changes to the cervix which if left unchecked have the potential to develop into cervical cancer.

This chapter begins with a review of the worldwide incidence of cervical cancer. This is followed by a discussion of the form and function of the normal, healthy cervix and the pathological processes which can occur to disrupt it. The role of HPV in the development of cervical neoplasia is assessed, together with other causative factors. The different stages of pre-cancerous cellular abnormality are outlined, with a description of their cytological and histological grading systems. The final section of the chapter looks at the progression of abnormal cervical cells into carcinoma and describes the main staging system for squamous cell carcinoma of the cervix.

The size of the problem

Cervical cancer is the second most common cancer amongst women worldwide, accounting for more than 273,000 deaths a year – 9% of all female cancer deaths. One in ten female cancers diagnosed worldwide are cancers of the cervix (Ferlay et al. 2004).

The distribution of the disease is not uniform – cervical cancer rates are estimated to vary eight-fold throughout the world, with a seventeen-fold variation in mortality rates
(Ferlay et al. 2004, Sankaranarayanan and Ferlay 2006). This disparity in incidence is principally between developed and developing nations. Globally, cervical cancer accounts for over 2.7 million years of life lost among women between the ages of 25 and 64. When this is broken down by country, 2.4 million years of life lost occur in developing areas, with only 0.3 million in developed countries (Yang et al. 2004).

Within the UK, cervical cancer is the second most common cancer after breast cancer in women under the age of 35, with 625 new cases diagnosed in 2003 (Cancer Research UK 2006). Within Australia 1 in 183 women will develop cervical cancer by the age of 75 (Cancer Council 2006). The incidence and mortality rates of cervical cancer in the UK, USA and Australia are shown in Table 1.1 and some other cervical cancer facts and figures can be found in Box 1.1.

Largely as a result of cervical screening, cervical cancer rates within the developed world are, for the most part, falling. For example, in the UK the mortality rate fell by 60% between 1975 and 2004 (from 7.5 to 2.8 per 100,000 females) (Cancer Research UK 2006). There are a few exceptions to this trend. For reasons which are not really understood the mortality rate for cervical cancer is rising in a number of developed countries such as Spain, Romania and Bulgaria (Cancer Research UK 2006, Office for National Statistics 1999). Where cervical cancer is declining, there has been a concomitant increase in the diagnosis of carcinoma in situ in women under the age of 30 (Quinn et al. 2001). This is also attributable to the success of cervical screening programmes.

Table 1.1 Incidence and mortality rates from cervical cancer in developed countries (per 100,000 women)

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
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<tbody>
<tr>
<td>UK</td>
<td>8.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Australia</td>
<td>6.9</td>
<td>1.7</td>
</tr>
<tr>
<td>USA</td>
<td>7.7</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Source: www.dep-iarc.fr/GLOBOCAN 2002
Taken from National Health and Medical Research Council (NHMRC) powerpoint presentation) http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/FCB2AB9615BCA2571D80078876F/$File/presentation-june06.pdf (accessed 17/6/07)

Box 1.1 Cervical cancer statistics

Cervical cancer statistics: Australia
Cervical cancer is the thirteenth most common cancer in women in Australia
740 women are diagnosed with cervical cancer each year
270 women die of cervical cancer each year in Australia

Cervical cancer statistics: UK
Cervical cancer is the twelfth most common cancer in women in the UK
2800 women are diagnosed with cervical cancer each year
1100 women die of cervical cancer each year in the UK, giving a European age-standardised death rate of 2.8 per 100,000 females and a crude rate of 3.6 per 100,000.
http://info.cancerresearchuk.org/cancerstats/types/cervix/ (accessed 5/7/07)
The healthy cervix

The role of the cervix in a healthy woman is principally concerned with reproduction – it helps to keep the developing foetus in the uterus and has a part to play in the initiation and progression of labour. The mucus produced by the cervix is considered important in female fertility (Moghissi 1972). The cervix is also thought to have a function in the female sexual response (Grimes 1999).

The cervix is cylindrical in shape and lies in the inferior, fibromuscular part of the uterus, accounting for approximately one third of the uterus. The remaining two thirds of the uterus are known as the body or corpus. It is located within the pelvic cavity, posterior to the bladder and anterior to the recto-sigmoid and rectum. It is attached to the bladder by the two vesicouterine ligaments. The tissue lateral to the cervix between the paravesical and pararectal spaces is known as the parametrium. The nerve supply to the cervix is derived from the hypogastric plexus and its blood supply from the internal iliac arteries. Its regional lymph nodes include: the parametrial, external iliac, obturator, hypogastric (internal iliac) and common iliac.

The cervix generally measures about 3–4 cm in length and 2.5 cm in diameter, although its size varies according to age. At its upper boundary, where it meets the corpus of the uterus, there is a narrowing known as the isthmus or internal os. The lower boundary of the cervix is known as the external os and opens into the vagina – indeed, the lower half of the cervix protrudes into the vagina.

Within the cervix itself, the anatomy is subdivided into the endocervix and the exocervix or ectocervix. The endocervix is the name for the upper two thirds of the cervix and the ectocervix the lower two thirds – this is the part that is more easily visualised on colposcopic examination (see Chapter 2).

The ecto and endocervix are lined with two different types of epithelium – the endocervix with columnar glandular epithelium and the ectocervix with squamous epithelium. The squamous and glandular epithelium meet at the squamocolumnar junction (SCJ). The squamocolumnar junction appears as a sharp line with a step due to the difference in the height of the squamous and columnar epithelium.

The cervix undergoes significant changes over a lifetime. Puberty, pregnancy and menopause all serve to alter its structure and location. For example, when a woman reaches puberty the cervix grows and the squamocolumnar junction moves down, exposing the

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*Figure 1.1 Different types of epithelium within the cervix*

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thin, glandular epithelium of the endocervical canal to the acidic environment of the 
vagina. This leads to the destruction of the columnar epithelium which is replaced by 
newly formed **metaplastic squamous epithelium**.

The term *metaplasia* refers to the replacement of one type of epithelium with another. 
The region of the cervix where the columnar epithelium has been or is being replaced by 
the new metaplastic squamous epithelium is referred to as the *transformation zone*. It is 
at the transformation zone that most of the cellular abnormalities associated with cervical 
cancer arise.

After menopause the SCJ moves back up the endocervical canal and the cervix becomes 
smaller. Because the maturation of the squamous epithelium is dependent on oestrogen, 
after menopause the cells do not mature and the epithelium becomes thin and atrophic.

### Types of cervical cancer

There are two main types of cervical cancer. The most common is squamous cell carcinoma 
(SCC) involving the squamous epithelium lining the ectocervix. However, a further 20% 
of cervical cancers are adenocarcinomas involving the glandular epithelial cells which are 
scattered along the endocervical canal (Scorge et al. 2004). A small percentage of cervical 
cancers are also composed of rare histological types such as lymphomas, sarcomas and 
neuroendocrine tumours.

This chapter will concentrate exclusively on squamous cell carcinoma because it is the 
most prevalent kind of cervical cancer. However, adenocarcinoma appears to be growing 
in incidence and is becoming an increasingly significant problem within the developed 
nations (Smith et al. 2000). Cervical adenocarcinoma, its pre-malignant phases and its 
management are discussed in Chapter 2.

### Cervical cytology grading

One important factor which distinguishes cervical cancer from most other cancers is the 
fact that it is preceded by a long pre-cancerous phase. Changes to the cervix begin an 
average of 10 to 15 years before its progression into malignancy. A whole spectrum of 
events may occur before the development of cervical cancer, beginning with cellular atypia, 
then various grades of dysplasia and finally invasive disease. It is this feature of cervical 
cancer which allows the diagnosis and management of cervical abnormalities prior to the 
development of cancer.

The early detection of cervical abnormality relies – certainly within the developed world 
– on obtaining samples of the cervical epithelial cells for analysis. This is achieved by 
taking a Pap smear. Whilst in recent years a number of developments have been made in 
cervical cytology testing, the cervical smear remains the most important cervical screening 
test in the western world. Details of the Pap smear procedure are given in Chapter 2 
and some of the terms used to describe cervical cellular abnormalities are explained in 
Box 1.2.

### The Bethesda System (TBS)

Originally, all cervical smear test cytology samples were graded by the Papanicolaou Class 
System which was introduced in 1943 and used for about 40 years. Since then a number 
of grading systems have been developed in an effort to improve and standardise cervical 
cytology reporting. Perhaps the most important of these is the Bethesda System (TBS). 
‘The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses’ was approved 
at a National Cancer Institute Workshop in the USA in 1988 (Anderson 2004). Develop-
ment of the system had been prompted by much publicised media reports of women dying 
of cancer despite having cervical smears interpreted as normal (Cox 2005). Since then
Box 1.2 Some cytology terms seen on cervical smear reports (see also Table 1.3)

Dyskaryosis: an abnormality of nuclei seen in exfoliated cells, often cells from the uterine cervix, in which the cytoplasm remains unchanged but the nuclei exhibit hyperchromatism, irregularity or enlargement, or an increase in number. (It refers to the nuclear changes seen in cells derived from lesions histologically described as Cervical Intraepithelial Neoplasia or CIN). It is a term now rarely used outside the UK and has been replaced with Squamous Intraepithelial Lesion (SIL) (Johnson and Patnick 2000).

Dysplasia: abnormal development or growth of tissues, organs or cells.

Neoplasia: a pathological process that results in the formation and growth of a neoplasm.

Koilocytosis: a cavitation of cellular cytoplasm, usually as a result of viral infection. It is also sometimes called koilocytic atypia, and is seen as halo-like structures around the nuclei of the abnormal cells. Koilocytosis is not dysplasia but may be considered a ‘pre-dysplastic’ change in some cases.

http://medical-dictionary.thefreedictionary.com

there have been two revisions, one in 1991 and most recently in 2001. This system has subsequently been adopted in its original or a modified form in a number of countries around the world (see Table 1.2).

TBS grades cervical squamous cellular abnormalities from low to high severity. Low grade disease is referred to as low grade squamous intraepithelial lesions (LSIL), and high grade as high grade squamous intraepithelial lesions (HSIL). The next category of dysplasia refers to cancer cells.

The system also has two additional categories known as atypical squamous cells-unspecifi ed (ASC-US) and atypical squamous cells-high grade (ASC-H). These terms were introduced in the 2001 amendments and replaced the previous category atypical squamous cells of undetermined significance (ASCUS – see Box 1.3). It is a classification applied to cells which are not normal but cannot easily be categorised into any of the other groups.

Most women with a diagnosis of ASC-US will on further investigation be found to have no serious pathology. Their cellular changes may have been caused by trauma from benign changes related to tampon use, intercourse, bacteria, yeast, viral infection with Human Papilloma Virus (HPV) or the cellular effects of aging (Cox 2005).

After extensive consultation by the Australian Society of Cytology, Australia also chose to adopt the Australian Modified Bethesda System in 2004. The National Health and Medical Research Council (NHMRC) approved Australian terminology is based on, but has some differences from, the Bethesda System 2001 (NHMRC 1994). The major differences relate to the classification of low-grade abnormalities.

The UK has different terminology for its categories of cervical abnormality, but these can to a greater extent be compared with the Bethesda System categories as illustrated in Table 1.2. The British altered their terminology and classification system in 2002 and brought it closer to TBS. Whilst there could be an argument for the British moving closer still to the Bethesda system, this would clearly have widespread ramifications for the current screening system, necessitating retraining of cytologists, clinicians, nurses and a whole range of ancillary staff including coders and data managers.

Within the developed world most cervical smears taken through screening programmes will turn out to be normal – nine out of ten in the UK. A small number will have pre-cancerous changes which can be treated. Less than 1 in 1000 will demonstrate invasive cancer (Cancer Research UK 2006) (See also Table 1.3).

Cervical histopathology grading

A histological diagnosis is considered to be the ‘acid test’ of a cancer and can provide information about the level of abnormality in the cervical tissue as a whole rather than
Table 1.2 Comparison of cervical cytology staging systems (Rana et al. 2004, NHMRC 2005)

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<tr>
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<tbody>
<tr>
<td>Negative</td>
<td>Negative for intraepithelial lesion or malignancy</td>
<td>Within normal limits</td>
<td>Negative</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Unsatisfactory for evaluation</td>
<td>Unsatisfactory due to — (spec)</td>
<td>Unsatisfactory</td>
</tr>
</tbody>
</table>
| Borderline nuclear change | (1) Atypical squamous cells of undetermined significance (ASC-US)  
(2) Atypical squamous cells possible high grade lesion (ASC-H) | (1) Koilocytes (without changes suggestive of intraepithelial neoplasia)  
(2) Squamous cell changes (not definitely neoplastic but merit early repeat) | (1) Possible low-grade squamous intraepithelial lesion  
(2) Possible high grade squamous lesion |
| Mild dyskaryosis          | Low grade squamous intraepithelial lesion | Mild dysplasia (CIN 1) | Low grade squamous intraepithelial lesion |
| Moderate dyskaryosis      | High grade squamous intraepithelial lesion | Moderate dysplasia | High grade squamous intraepithelial lesion |
| Severe dyskaryosis        | High grade squamous intraepithelial lesion | (1) Severe dysplasia (CIN (3)  
(2) Carcinoma in situ (CIN (3) | High grade squamous intraepithelial lesion |
| Severe dyskaryosis/? Invasive | Squamous cell carcinoma | (1) Severe dysplasia ? invasive  
(2) Invasive squamous cell carcinoma | Squamous cell carcinoma |
Box 1.3 Shades of grey

Cytology is subjective. With subjectivity comes great difference in interpretation, even among expert cytopathologists.

(Cox 2005)

Determination of the different levels of cytological abnormality in a cervical smear specimen is a task performed by a cytologist looking under a microscope. And it is not always easy. The famous Californian photographer, Ansel Adams, always photographed in black and white and identified, for the purposes of his photography, nine different shades of grey. Parallels can be drawn with the reporting of cervical cytology. Whereas the highly normal and the highly abnormal cells are relatively simple to diagnose, it is the grey areas in the middle that are problematic. This category is the abnormal squamous cells of undetermined significance (ASC-US) classification.

It was proposed by some cytologists prior to the 2001 Bethesda update to abolish the ASC-US category but in doing this it was found that some high grade epithelial abnormalities would have been missed. Instead the 2001 review of TBS resulted in a break-down of the ASC-US category into two – ASC-US to include cytologic changes suggestive of a lesion but difficult to interpret fully, and ASC-H in which there are changes suggestive of a high grade lesion but once again inadequate criteria for a definite diagnosis (Smith 2001).

As Cox explains, the problem is that cytology is subjective, and with subjectivity comes difference in interpretation – even amongst cytologists. ‘The ASCUS diagnosis is not reproducible. In fact, ASCUS is not a “diagnosis”, but an interpretation that is very subjective’ (Cox 2005).

The ALTS trial was a large study set up in the USA in order to look specifically at some of the issues associated with the management of low grade cervical lesions (ALTS 2003). Here it was found that only 43% of the Pap tests originally submitted as ASCUS by clinical centre pathologists were interpreted as ASCUS in a blinded review by pathologists involved in the trial (Stoler et al. 2001). It has been suggested that a large number of samples assigned to the ASC category in the USA is from concern over a ‘missing lesion’ and potential litigation that could result from this (Cox 2005).

Table 1.3 Abnormal cytology in NHS cervical screening programmes (as percentage of evaluable cervical smears)

<table>
<thead>
<tr>
<th>Route</th>
<th>UK (Health and Social Care Information Centre Statistics 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>2005–2006</td>
</tr>
<tr>
<td>Negative</td>
<td>93.8%</td>
</tr>
<tr>
<td>Borderline</td>
<td>3.2%</td>
</tr>
<tr>
<td>LSIL/mild dyskaryosis</td>
<td>1.8%</td>
</tr>
<tr>
<td>HSIL/moderate dyskaryosis</td>
<td>0.5%</td>
</tr>
<tr>
<td>HSIL/severe dyskaryosis</td>
<td>0.6%</td>
</tr>
<tr>
<td>Suspected invasive cancer or glandular neoplasia</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

just amongst individual cells. Following the identification of an abnormality on cervical cytology, generally the next stage is to confirm the abnormality by performing a colposcopy. The colposcopy procedure is described in Chapter 2. The following section focuses on cervical histology grading and explains the commonly-used cervical intraepithelial neoplasia (CIN) system.

Whereas cytology grading systems have, to a certain extent, developed independently in different countries, histopathologists tend to use the same system worldwide. Until the 1970s, cervical biopsies were graded as dysplastic, (mild, moderate or severe). The
next category of dysplasia was referred to as squamous cell carcinoma in situ. This is known today as the World Health Organisation (WHO) grading system, but has now been replaced in many countries by the CIN system.

In 1973 Richart introduced the cervical intraepithelial neoplasia (CIN) system which has three levels. The CIN categories are:

- **CIN 1**: mild dysplasia in which the abnormal cells only occupy the basal half of the epithelium.
- **CIN 2**: moderate dysplasia whereby the cells occupy the basal two thirds of the epithelium.
- **CIN 3**: severe dysplasia with almost full thickness involvement of the epithelium by abnormal cells, leaving only a thin mantle of differentiated cells at the surface.

The next level of abnormality is carcinoma in situ (CIS) in which there is full thickness involvement of the epithelium by undifferentiated cells, but the basement membrane is still intact (Richart 1973, Chang 1990). Because both the cytologic and histologic differences between severe dysplasia and cervical carcinoma in situ are often subjective, CIN 3 encompasses both of these categories.

Correlating the cervical cytology result with cervical histology means translating a two-grade system (LSIL/HSIL) into a three grade system (CIN 1/2/3). This can sometimes be problematic for histologists and for this reason some prefer to apply the terms high and low grade lesions to histology samples as well as cytology samples. There is a call from some histologists to revise the whole histology grading system so that it reflects cytological grading more closely (Cooper et al. 1983).

Generally speaking, LSIL will be found to correspond to CIN1 on biopsy. Similarly, HSIL indicate at least CIN2. That said, even within low grade lesions there may be small areas of CIN2 or CIN3 which are not represented on the smear. Thus, the cytological degree of dyskaryosis should be taken to indicate the minimum degree of cellular abnormality that is likely to be present in the histology sample (Johnson and Patnick 2000).

As with cervical cytology, the CIN cervical histology grading system is reliant on humans and is therefore not perfect. The criteria are subjective, with significant levels of intra- and inter-observer variability (Schneider 2003).

### Causative factors in cervical neoplasia

Cervical neoplasia is a disease for which the principle causative agent has been clearly identified. Whilst a number of other factors will influence the progression and development of the disease, the key to cervical neoplasia and cervical cancer is the human papilloma virus (HPV).

Cervical cancer thus joins the 15% of cancers which are attributable to infectious agents (Pisani et al. 1997). Other cancers within this category include Burkitts lymphoma (strongly associated with the Epstein Barr virus), hepatocellular carcinoma (associated with Hepatitis B and C viruses) and gastric cancer (associated with Helicobacter pylori).

HPV DNA is found in 99.7% of cervical cancers and the virus is found in up to 94% of women with CIN. It is currently being debated whether any HPV negative cervical carcinoma exists (Herrington 1999, Walboomers et al. 1999, Schiffman and Castle 2003). Evidence indicating a role for HPV in cervical cancer is now so strong that the International Agency for Research on Cancer (IARC), and part of the World Health Organisation (WHO) – the National Toxicology Program – has officially acknowledged high risk HPV as a known human carcinogen (IARC 1995, US Department of Health and Human Services 2004). HPV is also associated with a number of other cancers such as oral, vulval, vaginal, penile and anal (Kahn and Bernstein 2005).

However, infection with HPV does not inevitably mean that cervical cellular abnormality will develop – indeed, HPV can be detected in up to 46% of cytologically normal women (Scheurer et al. 2005). Why is it, then, that some women are infected with HPV and do not experience any cervical cellular change, whereas others develop CIN, and others still
invasive cancer? The answer is that we do not really know. However, in recent decades our understanding of HPV and its mode of action has increased significantly and is discussed more fully below.

**Human papilloma virus**

Human papilloma viruses are small viruses. Their structure is different from many other viruses in that they are spherical in shape, a little like a golf ball. In order to fully understand the lifecycle of HPV it is necessary to review the normal pattern of cellular regeneration in the skin.

It will be recalled that the innermost layer of the cutaneous epidermis is the basal layer. The cells in this layer are continuously dividing, pushing the older cells up towards the surface. During the process of upward migration the cells lose their capacity to divide and become fully differentiated, mature epithelial cells. At the skin surface they eventually die and are shed in the normal process of skin shedding.

The human papilloma virus is a small virus of approximately 8000 base pairs. In order to become established within a host, HPV requires cells to be actively dividing and differentiating. For this reason the fully differentiated cells on the skin surface are of no use to the virus. The virus requires access to cells at a much earlier stage in their development, whilst they are still in the basal layer.

The HPV genome codes for only eight proteins (Jansen and Shaw 2004, Mahdavi and Bradley 2005). These are divided into ‘early’ (E) and ‘late’ (L), the ‘early’ proteins being expressed during the early stages of the viral infection and the late proteins in the later stages.

The current hypothesis suggests that HPV enters the body through areas of epidermis which are vulnerable and thin, such as the transformation zone of the cervix or anus, or through micro-abrasions in the epithelium produced during sexual activity (Frazer et al. 2006). Once the virus enters the actively-dividing cells of the basal membrane it ‘hijacks’ the cellular resources in order to replicate its own genetic material and express HPV proteins (Frazer et al. 2006). In the meantime it does not disrupt the cells’ normal process of division. On the contrary, because it is so reliant on cellular division continuing for its own multiplication, the virus expresses certain proteins (‘early’ proteins) whose role it is to inhibit cellular differentiation and stimulate continued cellular proliferation (Frazer et al. 2006).

It is not difficult to extrapolate that interfering with cellular replication in this way might also be associated with oncogenesis. And this indeed appears to be the case. E6 and E7 seem to be particularly important in this process. In high risk HPV sub-types, these proteins bind to and inactivate the tumour suppressor gene products p53 and retinoblastoma protein (Kahn and Bernstein 2005), with the clear potential for uncontrolled cell division and ultimately carcinogenesis.

The ‘late’ proteins which are coded by the L1 and L2 part of the genome are the virus capsid proteins, that is, the structural part of the virus. These proteins are not expressed until the virus is much more advanced in its lifecycle and the invaded cell has migrated upwards, closer to the skin surface. Thus, by the time the virally invaded cells reach the surface of the epidermis the viral genome has been replicated by the E proteins and the only remaining step is to apply the viral capsid or ‘coat’ in order to have a fully formed papillomavirus. The virus-laden cells, by now packed with fully formed new HPV are then shed in the normal process of skin shedding, and are ready to infect the next unsuspecting host.

This mechanism of viral invasion and replication is particularly clever in the way it manages to elude the immune system of the host. The virus infects only the cells of the basal layer, thus evading immunologically competent cells in the upper layers of the skin. Furthermore, viral replication and assembly is only completed in the fully-differentiated cell that is destined to die anyway. For this reason HPV infections generate very poor humoral and cell-mediated immune responses. Infections that are not controlled and persist for a long time may cause severe pathologies and ultimately cancer (Jansen and Shaw 2004).
**High and low risk HPV**

There are more than 100 types of HPV which infect humans and 35 of these types infect the human genitalia (Kahn and Bernstein 2005). Human papilloma viruses fall into two main categories: cutaneous and mucosotropic. The mucosotropic group is the relevant group for cervical cancer and viruses in this category can be further differentiated into high and low risk.

**High risk HPV**

HPV strains are named numerically and in the order in which they were discovered. The high risk category includes HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82. Cervical cancer can result from infection by any one of these, but types HPV16 and HPV 18 predominate in many western countries, accounting for 50% and 20% of cases of cervical cancer respectively (Munoz et al. 2004). High risk viruses have varying oncogenic potentials, HPV 16 appearing to have one of the highest. After HPV 16 and 18, HPV 45 and 31 are arguably the most common oncogenic subtypes in many developed countries. HPV prevalence has been found to vary as much as twenty-fold between countries (Clifford et al. 2005). For example, HPV is detected in 2% of Vietnamese women aged 15–69 in Hanoi city (Pham et al. 2003) compared with 90% of women attending an adolescent and STD clinic in Baltimore, MD (Jacobson et al. 2000). Furthermore, different HPV subtypes are found in different proportions according to country (Lowy and Schiller 2006).

High risk subtypes account for the following percentages of the total HPV by region:

- 18% in sub-Saharan Africa
- 5% in Asia
- 10% in South America
- 4% in Europe

The high percentage of high risk virus in Africa and South America explains the increased incidence of cervical cancer within these countries where it is the most common cause of cancer death amongst women (Jacob et al. 2005).

Multitype infections are infections with more than one strain of HPV. These are found in both men and women and tend to be associated with poorer outcomes (Wiley and Masongsong 2006).

**Low risk HPV**

Low risk HPV strains are not associated with cervical cancer but may still be responsible for considerable physical and psychological morbidity. Low risk strains include HPV 6 and 11 which are responsible for approximately 90% of anogenital warts (Kahn and Bernstein 2005). Genital warts may be found on the vulva, perineum and perianal area, vagina and cervix and also on the penis and scrotum in men (see Chapter 11, Box 11.1).

As well as carrying a physical and psychological cost, HPV infection also has significant economic implications. The overall medical cost of HPV-related conditions in the US population aged 15 to 24 is estimated at $2.9 billion a year plus an additional $108.3 million for medical costs associated with cervical cancer and $123.9 million for treatment of external anogenital warts (Chesson et al. 2004).

Infection with low-risk HPV can also lead to a condition called Recurrent Respiratory Papillomatosis (see Box 1.4). This is a rare but debilitating illness affecting the lungs of children and adults alike and often requires repeated surgical intervention in order to maintain lung patency.

Although principally associated with benign cell proliferation, low risk HPV strains may also act as markers for high risk HPV as the two are often found together in the same lesions.
Dysplasia, HPV and cervical cancer

HPV infection symptoms

Aside from HPV 6 and 11, which are associated with the development of genital lesions and genital warts, the majority of HPV infections are asymptomatic and not linked with any gynaecologic examination findings apart from perhaps a slightly higher incidence of cervical erythema. An association between detection of HPV DNA and vaginal discharge, itching, burning, or systemic symptoms has not been found (Mao et al. 2003).

Incidence of and risk factors for HPV infection

HPV is transmitted through sexual contact and is thought to infect three quarters of the reproductive-age population (Scheurer et al. 2005). It is the most commonly diagnosed sexually transmitted infection in developed countries, with an estimated 30 million new cases worldwide each year (Scheurer et al. 2005). Between 64% to 82% of sexually active adolescent girls test positive for HPV (Kahn and Bernstein 2005, Wiley and Masongsong 2006) and the estimated lifetime risk of women acquiring one or more genital HPV infections is at least 75% (Scheurer et al. 2005). As well as being the most common sexually transmitted infection among adolescent girls and young women, HPV is also widely prevalent in young men.

A number of risk factors have been linked with HPV infection. Those which have consistently been found to be associated with an increased risk are age and number of current and previous sexual partners (Scheurer et al. 2005). These and some other risk factors are discussed below.

Age

The highest rates of genital HPV infection occur between 15 and 25 years, then decline steadily after the age of 40 (Wiley and Masongsong 2006). In some populations, there is an increase in non-oncogenic HPV infections in post-menopausal age groups (Herrero et al. 2000). This is possibly the result of acquired immunity, hormonal factors and a lower number of sexual partners (Scheurer et al. 2005).
Number of sexual partners

Genital HPVs are rarely detected in children and in women who are not sexually active but as soon as sexual activity is initiated, incidence rises sharply. The most significant predictor for acquiring infection appears to be the lifetime number of sexual partners. However, because the infection is so prevalent, even having had only one sexual partner carries some risk for infection. Ley and colleagues found that 21% of young women reporting one penetrative male intercourse partner tested positive for HPV DNA (Ley et al. 1991).

Oral contraceptives

A number of studies have found an association between use of oral contraceptives and HPV infection independent of sexual behaviour and other risk factors. The relationship appears particularly significant amongst adenocarcinomas (Madeleine et al. 2001). The mechanism is not really understood but could be related to hormonal influences.

Immunosuppression

People who are immunosuppressed, such as chemically suppressed transplant recipients or patients infected with HIV have higher rates of HPV infection and HPV-associated disease. Immunogenetic factors may play a role in the ability of the immune response to clear HPV infection.

A number of other factors have been associated with an increased risk of HPV infection in some but not all studies. These include:

- herpes simplex virus and vulvar warts
- a history of anal intercourse
- early age at first intercourse
- black or Hispanic women
- tobacco users

(Dell et al. 2000, Scheurer et al. 2005)

Prevention of HPV transmission

Primary prevention of HPV infection needs to address sexual practices – particularly amongst adolescents – reinforcing the asymptomatic nature of HPV infection, the importance of screening and the high risk associated with certain behaviours (e.g. early sexual debut and having many male sexual partners).

Such education programmes would need to involve both males and females – differences in male sexual behaviour could actually explain the differences in cervical cancer rates globally better than the sexual behaviour of women (Castellsague et al. 2002). Men frequently report having had a greater frequency of lifetime sexual partners, more concurrent partners and more contact with sex workers and prostitutes than women (Scheurer et al. 2005).

HPVs are not independently motile agents and it is unlikely that they will make their way to internal genital sites in the absence of penetrative sexual activities. Nonetheless, even non-penetrative intimate touching carries a risk for infection on external sites. Winer and colleagues reported nearly 10% of initially virginal women who subsequently engaged
in any kind of non-penetrative intimate sexual touching of the external genital surfaces tested positive for HPV DNA. In contrast, only approximately 1% (one of 76) of initially virginal women foregoing intimate touching tested similarly positive (Winer et al. 2003).

Evidence about the effectiveness of condoms in preventing HPV infection is inconclusive. Because the virus is often found on areas of the skin not covered by a condom and because condoms may only be applied after some intimate touching has occurred, their efficacy is at best limited. They do, however, clearly protect against pregnancy and other sexually transmitted diseases and thus should still be advocated for these reasons. It has also been suggested that the role of spermicides may be significant in prevention of the spread of the disease (Jacob et al. 2005, Wiley and Masongsong 2006).

### Progression of HPV infection and cervical cancer

The natural history of HPV infection is still not well understood. It is a difficult virus to study because infections may have a short duration and are asymptomatic. There is currently no routine screening for HPV and so it is unclear whether detected infections are recently acquired or long term. It is therefore difficult to obtain data about the progression of infection (Scheurer et al. 2005).

It has already been mentioned that in the majority of women HPV infection is mild, transient and resolves spontaneously, causing no or low grade cellular changes – even in the presence of quite high viral loads (Moscicki 1998, Cooper et al. 2003). However, in a proportion of women it will persist and progress. High risk HPV infections that persist for more than three years are unlikely to resolve spontaneously and convey significant risk of development into high grade squamous intraepithelial lesions. It is estimated 15% of LSIL will progress to HSIL (Cooper et al. 2003).

HSIL, in turn, may behave in a number of ways. As with LSIL, some cases of HSIL resolve if left untreated. Modelling data from the UK suggest at least 80% of HSIL will regress without intervention (Raffle et al. 2003). Another study found one third of women with CIN2 and almost 20% with CIN3 had regressed spontaneously within 12 months (Nobbenhuis et al. 2001). Wright et al. (2003) in their review of the published natural history literature found:

- 43% of CIN2 regresses, 35% persists as CIN2 and 22% progresses to CIN3 or invasive cancer (over an undefined time period)
- 32% of CIN3 regresses, 56% persists as CIN3 and 14% progresses from CIN3 to cancer

Progression can take many years, with statistical models estimating the average interval between HSIL and cancer to be 10 to 15 years. This is in keeping with population statistics. HSIL is most commonly diagnosed among women of 25–29 years, whereas cancer peaks two decades later at 44–49 years (Gustafsson et al. 1997).

Carcinoma in situ (CIS) is thought to present another stage in the dysplastic continuum occurring between HSIL and invasive cancer. Like HSIL, the nature of CIS is probably unpredictable, with some lesions inherently more aggressive than others. CIS is generally diagnosed in women who are 10 to 12 years younger than those diagnosed with invasive cancer, although the exact amount of time necessary for progression is difficult to determine and could be anything from 2 to 20 years (Chang 1990). CIS is treated in a similar way to HSIL.

Ascertaining the mechanism of progression of cervical dysplasia is difficult to do ethically, as illustrated by a New Zealand study of CIS involving a cohort of women who were basically left untreated. This much publicised case initiated the cervical screening programme in New Zealand and is discussed in Box 1.5.

On a cellular level it is now widely believed that cervical dysplasia results from HPV DNA integration into the host cervical cells (Cooper et al. 2003). However, the changes from high grade dysplasia to invasive cancer require additional genetic events thought to
be mediated by the HPV proteins E6 and E7. These proteins can inactivate tumour suppressor genes p53 and pRb and also bring about the suppression of apoptosis (Mahdavi and Bradley 2005).

The events described above are illustrated in Figure 1.2.

**Risk factors in the persistence and progression of dysplasia**

Although our understanding of the cellular changes associated with malignant progression has improved in recent years, the question of why some women with neoplasia develop invasive disease whilst others do not has still not been adequately answered.

A number of studies have addressed this issue and whilst failing to elucidate clear causative factors have suggested apparent co-factors. These epidemiological studies indicate that both environmental and host immunologic factors have a role in disease progression (Scheurer et al. 2005, Soto-Wright et al. 2005, Wiley and Masongsong 2006).
The single most important factor in the development of cervical cancer appears to be persistent cervical infection with an oncogenic HPV type (especially HPV 16 or 18) (Jacob et al. 2005, Lowy and Schiller 2006). Viral load may also be important – an increased viral load is often associated with more persistent infection. Other postulated risk factors include:

1. **Immune status**
   Some commentators have suggested that apart from persistent HPV infection, the principal factors which will bring about progression and transformation are related to the hosts’ immune status. It is thus a failure in immunosurveillance rather than lifestyle factors which brings about malignant change. Identification of the role of the immune system removes some of the blame from the unfortunate cervical cancer victim who has, for a long time, been stigmatised for having a ‘sexually transmitted disease’ (Helmerhorst and Meijer 2002).

   A number of factors indicate that immune status has a part to play in cervical cancer. Women who are immunosuppressed have two to three times the rate of ASCUS, HPV and CIN compared with women who are not immune compromised (Cox 2005). Organ transplant recipients are at particularly high risk of HPV-related dysplasias and cancer. Although the precise reason for this has not yet been identified, it is generally assumed that the therapeutic immunosuppression to prevent organ rejection increases their vulnerability.

   Similarly, a high rate of HPV progression has been observed amongst HIV positive men and women, and is thought to be related to their immunocompromised state (Wiley and Masongsong 2006). This is of particular significance since the introduction of Highly Active Anti-Retroviral Therapy (HAART) which gives HIV/AIDS new status as a chronic disease. The incidence of HPV-related diseases amongst this population has become a significant factor and cervical cancer is now an AIDS defining illness (see Box 1.6).

2. **Smoking**
   Smoking has the second highest association with the progression of cervical dysplasia after persistent HPV infection (Sellors et al. 2003). The relationship between tobacco, HPV-related dysplasias and cancer has been studied extensively, and although the precise causal carcinogenic mechanism remains unclear, positive associations are consistently reported, to the extent that the United States Surgeon General and International Agency for Research on Cancer have judged that active cigarette smoking is causally associated with cervical cancer (Trimble et al. 2005). There is data to show that women with oncogenic HPV and minimally abnormal cervical smears are up to three times more likely to be diagnosed with greater than CIN3 than non-smokers (McIntyre-Seltman et al. 2005).

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**Figure 1.2** The progression to cervical cancer

Dysplasia, HPV and cervical cancer
Cigarette smoking is a risk factor for several tumours and is able to induce its carcinogenic effect in sites not directly exposed to cigarette smoke, such as kidney, bladder and cervix. In the uterine cervix it is possible to detect nicotine derivates such as tobacco nitrosamines and it has been hypothesised that smoking is involved in suppression of the local immune response to HPV infection (Matos et al. 2005). Smoking is associated with metaplasia, neoangiogenesis, and proliferation in epithelium as well as over-expression of p53 and markers of cell proliferation (Wiley and Masongsong 2006). A personal history of smoking in addition to second-hand smoke both appear to play a role in the development of cervical cancer precursors (Soto-Wright et al. 2005).

(3) Oral contraceptive use
The duration of oral contraceptive use and risk of cervical cancer have been shown to have a positive correlation in a number of studies (Smith et al 2003, Vessey and Painter 2006). It has been postulated that the addition of progesterone to human papillomavirus-transfected cervical cells, could lead to oncogenic cell transformation (Hellberg and Stendahl 2005). A personal history of smoking in addition to second-hand smoke both appear to play a role in the development of cervical cancer precursors (Soto-Wright et al. 2005).

(4) Parity
High parity and a large number of pregnancies have been correlated with the development of cervical cancer for a long time (Matos et al. 2005). It has been suggested that multiple pregnancies may have a cumulative traumatic or immunosuppressive effect on the cervix, thereby promoting the progression of HPV infection (Matos et al. 2005). Pregnancy could also induce a hormonal effect on the cervix which further increases the risk of oncogenic progression (Matos et al. 2005).

(5) Other factors
Socioeconomic group, genetic factors, HLA type, other sexually transmitted diseases, number of sexual partners, obesity and dietary factors have all been put forward as potential co-factors for the development of high grade dysplasia and cervical cancer, with varying levels of evidence to support them (Carreon et al. 2005, Modesitt et al. 2005, Zelmanowicz et al. 2005).

Cervical cancer
The function of cervical cancer screening programmes is to detect pre-malignant cervical changes before invasive cancer is able to develop. Unfortunately it would seem that most
of the women who develop invasive cancer have ‘fallen through the net’ with regards to cervical screening. Current estimates suggest that 50% of women diagnosed with cervical cancer have never had a cervical smear and 10% have not had one in the last ten years (Nuovo et al. 2001). Many of these women will have already developed advanced stage disease.

Early stage cervical cancer is generally asymptomatic. It is only as the disease progresses that symptoms occur. Cervical cancer symptoms include post-coital, intermenstrual or post-menopausal vaginal bleeding, back pain, pain in the abdomen, an enlarged abdomen, a lump or frequency of urination. Typically the woman visited her GP with a specific symptom or mentioned the symptom during a visit for another purpose. This resulted in her being referred for a number of diagnostic procedures, although it did not necessarily mark the commencement of the cancer disclosure process. In Markovic’s study, none of the GPs or the specialists conducting the tests raised the possibility of cancer with the women.

This is not to say that the diagnosis was concealed from the women, but rather illustrates that disclosure of a diagnosis of cancer is a multi-layered process. It occurs gradually and involves the participation and interaction of both physician and patient. All the women described their diagnosis being delivered in phases. Initially, physician consultations were characterised by non-disclosure, followed by partial disclosure and finally full disclosure at a time when any ambiguity about what the disease could be had been removed (for example, post-operatively).

Diagnostic and staging investigations

Early stage (asymptomatic) cervical cancer is only likely to be detected through cervical cytology and colposcopy (see Chapter 2). After this a range of investigations will be performed in order to definitively diagnose and stage the disease. These will include many, if not all of those listed below:

- pelvic examination under anaesthetic (EUA)
- sigmoidoscopy
- cystoscopy
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- computerised axial tomography scanning (CAT)
- magnetic resonance imaging scanning (MRI)
- intra-venous urogram or pyelogram (IVU or IVP)
- blood tests
- chest X-ray
- PET scanning

There are a number of staging systems for cervical cancer, but the one which is most widely employed was determined by the International Federation of Gynecology and Obstetrics (FIGO) in the late 1950s, and is known as the FIGO system. Basically stage I tumours are confined to the cervix, whereas stage II to IV extend beyond the cervix (See Table 1.4 and Figure 1.3). According to the FIGO report of 2006, globally 42% of cervical cancer cases are diagnosed at stage I, 30% at stage II, 21% at stage III and 6% at stage IV (Quinn et al. 2006).

FIGO staging is clinically based, principally reliant on determinations made by physical examination, EUA, colposcopy, cystoscopy, sigmoidoscopy, IVP and chest X-ray (Moore 2006). Although it is a system which is widely used throughout the world, it is not without its critics. Opponents feel that it is inaccurate and that modern medical imaging methods such as CT, MRI and PET scanning should be employed in addition to the investigations

### Table 1.4 FIGO classification system for cervical cancer

http://www.cancerhelp.org.uk/help/default.asp?page=2772#0 (accessed 18/6/07)

#### Stage 0
This is more commonly referred to as carcinoma in situ. A carcinoma in situ is one that only involves cells in the tissues in which it began but has not spread beyond this. Carcinoma in situ is a phenomenon which has been observed in other cancers for which there are screening programmes such as breast cancer. CIS is generally treated in the same way as CIN3.

#### Stage I
Stage 1 describes an invasive cancer which is confined to the cervix. It is divided into stage 1A and stage 1B, each of which is further subdivided into two groups:

- Stage IA (microscopic disease)
  - (i) IA1: cancer has invaded cervix tissue by less than 3 mm and is less than 7 mm wide (also known as microinvasive cervical cancer).
  - (ii) IA2: the cancer infiltrates to a depth of 3 to 5 mm but is less than 7 mm wide.

- Stage IB (usually macroscopic disease)
  - (i) IB1: the cancer is no larger than 4 cm and still localised to the cervix.
  - (ii) IB2: the cancer is larger than 4 cm and still localised to the cervix.

#### Stage II
The cancer has begun to spread beyond the cervix but not to the pelvic sidewall. It may involve the upper part of the vagina but not the lower third.

- Stage IIA involves the upper two-thirds of vagina, no parametrial involvement.
- Stage IIB obvious parametrial involvement.

#### Stage III
The cancer has extended though the cervix on to the pelvic wall. On rectal examination there is no cancer-free space between tumour and pelvic sidewall. The tumour involves the lower third of the vagina. All patients with hydronephrosis or a non-functioning kidney are counted as stage III unless known to be the result of other causes.

- Stage IIIA: involvement of the lower third of the vagina; no extension to pelvic sidewall.
- Stage IIIB: extension to pelvic sidewall and/or hydronephrosis or non-functioning kidney.

#### Stage IV
The carcinoma extends beyond the true pelvis or clinically involves mucosa of bladder or rectum.

- Bullous oedema does not allow a case to be designated as stage IV.
- Stage IVA: locally invasive.
- Stage IVB: spread to distant organs.
Figure 1.3 Carcinoma of the cervix uteri: staging cervical cancer (primary tumour and metastases)
described above (Choi 2004, Soutter et al. 2004, Rojas-Espaillant and Rose 2005). Whilst these imaging modalities have indeed been shown to have a role in determining disease status in cervical cancer, they also have their limitations. For example, the sensitivity of CT and MRI in identifying nodal disease has been estimated to be as low as 34% (Heller et al. 1990).

However, this is not the main reason for excluding advanced imaging techniques from the FIGO staging system. Instead, these methods are excluded because they are not readily available in many developing nations. Cervical cancer is not simply a disease of industrialised nations – on the contrary, it is much more of a problem in developing countries (see Chapter 9). The principal function of FIGO staging is to facilitate data collection and comparative reporting of results, not to assign treatment (Moore 2006). In order to allow worldwide comparison between cohorts of women with the disease, the tools required for staging must be accessible to less affluent nations.

And so, in summary, whilst the treating doctor is free to perform whatever investigations are deemed necessary to diagnose and treat the cervical cancer, if the FIGO system is used, any additional information afforded by supplementary testing should not be taken into account in determining its stage.

Prognosis

As with most cancers, stage at diagnosis is the most important prognostic factor in cervical cancer (Garg et al. 2006). Women diagnosed with early stage disease (1A to 1B1) have survival rates of 85 to 100% (Waggoner 2003, Rojas-Espaillant and Rose 2005). Stage IIa tumours also have a good prognosis, with a five-year survival of approximately 90% (Hopkins and Morley 1993). However, once the tumour spreads further than this the prognosis is poorer. The estimated five-year disease-free survival rate after therapy for stage IB2 and IIB disease is 50–70%, for stage III disease is 30–60% and for stage IV disease is 5–15% (Waggoner 2003).

Amongst patients with early stage disease who are treated surgically, a number of other factors have been shown to influence the prognosis of patients diagnosed with cervical cancer including:

(1) Regional lymph node involvement
Inextricably linked with tumour stage, lymph node involvement is the next most important prognostic factor. Indeed, most of the other factors listed below principally impact survival by increasing the incidence of nodal metastasis. Lymph node involvement is associated with a poor prognosis. Patients with negative nodes will have an 85–90% five year survival rate. This figure falls to 20–74% for patients with positive nodes, depending on the number of nodes involved, their location and the size of the metastases (Hatch 1994).

Lymphatic spread is generally via the parametrial, external iliac, obturator and hypogastric (internal iliac) nodes to the common iliac and eventually paraaortic lymph nodes.

(2) Tumour size
For some time it has been recognised that a large tumour is associated with a significantly poorer prognosis amongst women with cervical cancer (Soutter et al. 2004). Burghart et al. (1992) illustrated that women with a tumour volume smaller than 2.5 cm\(^3\) had a five-year survival of 91%, while those with larger tumours (10–50 cm\(^3\)) had a five-year survival rate of 70%. The extent of nodal metastases appears to be directly proportional to tumour size.

(3) Parametrial invasion
Deep cervical-stromal invasion, or extension of the cancer to the vaginal or parametrial margins is a poor prognostic sign. The mode of dissemination into the parametrium is not fully understood and could be through metastatic spread rather than simply by local invasion.
(4) Lymph vascular space involvement
The significance of lymph vascular invasion (LVSI) is controversial, but is thought to signify a high possibility of node positivity and is therefore often used as an indication for lymph node dissection. LVSI is considered to be a poor prognostic factor (Morice et al.).

Conclusion
Cervical cancer is a significant public health issue, particularly in the developing world. It is triggered by HPV infection, which results in various stages of pre-cancerous neoplasia before progressing to invasive cancer. Early detection and treatment of such abnormalities can prevent the development of cancer and is the principle behind cervical screening. Unfortunately, a proportion of women do not participate in such programmes either through choice or lack of availability. Such women are at increased risk of developing advanced cervical cancer. The management of invasive disease is discussed in chapter 2 and in the following 3 chapters.

Frequently asked questions
(1) If I have sex, could I be re-infected with HPV and would that make my cancer recur?
You cannot develop a second primary cervical cancer if your cervix has been removed in your treatment. Furthermore, you may have acquired some immunity to the HPV strain that originally infected you. However, if your cervix remains in situ there could be a theoretical possibility of developing a second primary cervical cancer from another HPV type. Remember, the disease will generally evolve over many years and should therefore be detected through regular cervical screening. There is also a low but increased risk of acquiring other HPV related cancers such as vulval or anal cancer (Edgren 2007). You may wish to discuss this risk with your doctor when you attend for follow-up visits.

(2) My mother died of cervical cancer. Does that increase my risk? Or the risk of my children?
No, there is not considered to be a familial link for squamous cell carcinoma although associations have been drawn between cervical adenocarcinoma and hereditary non-polyposis colon cancer.

(3) Is cervical cancer associated with being overweight?
No, there is no link between cervical cancer and obesity.

(4) Is cervical cancer less common amongst women whose partners are circumcised?
There does now appear to be data to suggest that male circumcision reduces the likelihood of males carrying HPV and affords some protection for their partners against cervical cancer (Castellsague et al. 2002).

(5) Are condoms effective in reducing the incidence of cervical cancer?
Whether condoms protect the cervix remains controversial, and many individuals who claim to use condoms use them inconsistently and often not during foreplay. It is unlikely that use of a condom will prevent HPV infection altogether (Frazer et al. 2006).

(6) I have been diagnosed with an HPV infection. Does this mean that my partner has been unfaithful?
HPV can remain latent for months or years and so infection does not indicate infidelity has occurred.

(7) How many women with high risk HPV will develop persistent lesions?
Between 5–10% of women with high risk HPV will develop persistent lesions (Walboomers et al. 1999).
(8) I have tested positive for the HPV virus. Is there any treatment?
   No, there is not any treatment because the virus resolves spontaneously over time with most women. Ongoing monitoring is considered sufficient action in the case of HPV positivity to ensure that any cytological changes to the cervix are detected early (NHSCSP 2004).

(9) Should my husband be tested for the virus?
   Currently there is no HPV testing for males. Many normal, healthy males will be positive for the virus and the benefits of testing most heterosexual men are unclear (NHSCSP 2004).

Resources

National Health Service (NHS) Cancer Screening Programme: http://cancerscreening.org.uk/index.html
British Society for Clinical Cytology: http://www.clinicalcytology.co.uk/index.asp
British Society for Colposcopy and Cervical Pathology: http://www.bscscp.org.uk/
National Health Service Cervical Screening Programme (NHSCSP): http://www.cancerscreening.nhs.uk/
National Institute for Health and Clinical Excellence (NICE): http://www.nice.org.uk/
National Cancer Institute: http://www.cancer.gov/

References


