Chapter II

Cervical Cancer Biology
2.1 Development of Cancer

Cancer can be generally described as an uncontrolled growth and spread of abnormal cells in the body. Cancer is a class of diseases characterized by out-of-control cell growth which are able to invade other tissues. Normally though through the blood and lymph systems, cancer cells can spread to other parts of the body [58]. Approximately more than 100 different types of cancer are identified, and each category is classified by the type of cell that is initially affected.

The main categories of cancer include [59]:

- **Carcinoma** - Cancer that begins in the skin or in tissues that line or cover internal organs. There are a number of subtypes of carcinoma, including adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma.

- **Sarcoma** - Cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.

- **Leukemia** - Cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood.

- **Lymphoma and myeloma** - Cancers that begin in the cells of the immune system.

- **Central nervous system cancers** - Cancers that begin in the tissues of the brain and spinal cord.

Cell theory is based on three basic principles: (1) cells are the basic units of structure and function in an organism; (2) all living things are composed of one or more cells, (3) the replicating effects of existing cells forms the new cells. When a single cell mature and the body needs, it divides them and produces more number of cells. When it happens out of control (when body does not need), formation of a mass tissue might happens which is termed as tumor. Tumors may be either benign or malignant. Benign tumors cannot create harms to the human body, it can be evacuated from the body and it does not spread to other
parts of the body. These kinds of tumors are not a danger to life. On the other hand, malignant tumors invade and damage the nearby tissues. These cells also can break away from a malignant tumor and enter the lymphatic system or even the bloodstream, which is how cancer can spread to other parts of the body.

The process of cancer development is depicted in Figure 2.1. It has develops in three steps of development process namely initiation, promotion and metastasis. In initiation stage, DNA does not undergo repair by enzymes or undergoes faulty DNA repair. In the second step, promotion of uncontrolled growth and proliferation of mutated cells takes place. The cells lose their normal caliber and start to reproduce. The metastasis stage, invasion of cancerous cells to nearby tissues and the migration of cancerous cells to other tissues through circulatory systems might happen.

![Figure 2.1 Process of Cancer Development](image-url)
2.2. Cervical Cancer

Cervical cancer is a malignant disease which affects the cervix of women. It is one of the commonest cancers which start in the cervix, which is the lower part of the womb. The cervix plays a vital role in the female reproductive system, connecting the upper vagina to the uterus. Normally inner linings of body cavities like stomach and urinary track are covered with the type of cell called epithelial cells. The Epithelial distribution of cervix is shown in Figure 2.2. The upper part close to the uterus is covered by glandular cells and the lower part is covered with squamous cells. The meeting place of these two regions are called transformation zone. Over 90% of cases of cervical cancer arise at the transformation zone, the junction of the squamous epithelium lining the exocervix and the columnar epithelium of the endocervix [60]. Approximately 80 - 85% of cervical cancers are squamous epithelial cell cancers.

Figure 2.2 Epithelial Distribution of Cervix
2.2.1. Squamous Epithelium

The epithelium that covers the vagina, and the cervical vaginal portion of the sexually mature woman, called the squamous epithelium. It measures approximately 0.2 mm thick and is composed of four layers [61] which can be well differentiated as shown in Figure 2.3.

Figure 2.3 Location and Type of Cells in Cervical Cytology
[ Source: H. Friedrich Nauth, Citodiagn_ostico Gineco1_ogico, Hans Friedrich Nauth, 2005.]

**Basal Layer:** It is the innermost layer which is formed by a single layer of cylindrical palisade-wise arranged cells at the base membrane. Germ cells are either round or oval, with large nucleus which occupy much of the cell. The process of regeneration of the epithelium starts at this cell layer. The basal cells are attached to the basement membrane or basal lamina with the help of hemidesmosomes. The basal lamina is an extracellular secretary product of the basal epithelial cells. The main function of this basal lamina is to attach corneal epithelium with the stroma. One destroyed it takes about 6 weeks for basal lamina to regenerate.
**Parabasal Layer:** This tissue consists of several layers of rounded or polyhedral cells, which have a central nucleus and cytoplasm thick with intercellular bridges.

**Intermediate Layer:** It is composed of many layers of attended cells with glycogen-rich cytoplasm, relatively small, central and vesicular nucleus.

**Surface Layer:** This part consists of several layers of attened, polygonalshaped and large cells with thin and bright cytoplasm, without intercellular bridges and pyknotic nucleus.

**2.2.2 Cellular Elements**

The squamous epithelium cell types that are recognized in the cytological smear are as follows.

**2.2.2.1 Superficial Cells**

These cells present the greatest maturation degree; they have a diameter of 50 to 60 μm, they are also eosinophilic (pink stained with eosin) or basophils (blue stained with hematoxylin), as illustrated in Figure 2.4. In this case, the cytoplasm has polygonal shape; it is also clear and homogeneous, and clearly delimited. The cells appear on a one-by-one basis or in groups. In the cytoplasm, occasionally, keratohyaline granules are identified. These cells may have a large nucleus, of approximately 7 μm in which the chromatin structure is easily recognizable, being also regularly and finely distributed, otherwise, cells are small and may present a pyknotic nucleus in which chromatin is condensed by degeneration and is dark-colored uniformly.

![Figure 2.4 Superficial Squamous Cervical Cells](image)
2.2.2.2 Intermediate Cells

They represent the most consistent and largest cell in the vaginal smear. They have a size of about 30 a 50 μm and nuclei around 8 μm (Figure 2.5). They are basophilic, polygonal, rounded shaped and their nuclei are usually vital, but occasionally pyknotic. Intermediate cells can differentiate in large (with glycogen) and small (without glycogen) cells. During pregnancy and under the strong influence of progestins or androgens, these cells show a canoe or boat and wide margin, reason why they are called navicular cells.

![Figure 2.5 Intermediate Squamous Cervical Cells](image)

2.2.2.3 Parabasal Cells

These cells have a diameter of approximately 20 μm and nuclei of approximately 9 μm. Intensely stained, they are basophilic and exhibit an elongated, oval-like and also rounded shape (Figure 2.6). The parabasal cells can be classified as being either large or small.

![Figure 2.6 Parabasal Squamous Cervical Cells](image)
2.2.2.4. Basal Cells

Basal Cells are found in the lower most layer of the squamous epithelium. These cells function to anchor the epithelium to the basement membrane and undergo mitosis for epithelial regeneration. These cells are seen on post menopausal (atrophic) pap smears but never seen on cyclic patient’s Pap smear. These cells have a cytoplasmic diameter of 12 - 14 µm and a nucleus diameter varying between 8-10 µm. The cells have intense basophilic staining and frequently a deteriorated nucleus. If chromatin is preserved, nucleoli may be visible. On occasion the nucleus can appear hyperchromatic from the increased nuclear activity.

2.3 Papillomaviruses and Cervical Cancer

Human papillomavirus (HPV) is one of the most common sexually transmitted infections (STIs) and has been established as the primary cause of cervical cancer [62]. More than 200 types of human papillomavirus (HPV) have been recognized on the basis of DNA sequence. More than 40 of these viruses can be easily spread through direct skin-to-skin contact during vaginal, anal, and oral sex [63]. They are small, double stranded DNA viruses that belong to family papillomaviridae [64].

2.3.1 Historical Context

The acquaintance of papillomaviruses, have been recognized for more than a millennium. Papillomaviruses were first identified in the early 20th century, when it was shown that skin warts, or papillomas, could be transmitted between individuals by a filterable infectious agent. Celsus described three types of warts: acrochordons, usually occurring in children and often disappearing spontaneously; thymion, a vascular papillomatous lesion; and myrmecia, resembling our plantar warts.

In 1922, in Basel, Lewandowsky and Lutz described a rare hereditary condition: epidermodysplasia verruciformis, without thinking of an infectious component of
the disease. Twenty years later it was found to be caused by a papillomavirus infection [65]. Virus particles were first identified ultrastructurally in skin warts in 1949 [66] and in venereal warts in the 1960s [67].

Between 1974 and 1976 zur Hausen and co-workers started to postulate and analyse a possible role of HPV in cervical cancer [68]. In 1976, Meisels and Fortin published two reports outlining that the appearance of koilocytes in cervical smears indicates a presence of a papillomavirus infection [69]. They also suggested that it might be possible to differentiate between benign warty lesions that do not progress to cervical cancer and precursor lesions that do progress to cervical cancer. This idea was supported by the identification of papillomavirus particles in mild dysplastic lesions of the cervix [70].

In 1980, Gissman first reported partial characterization of an HPV from genital warts, which was designated HPV6 [71]. In 1983 and 1984, HPV 16 and HPV 18 were first isolated from cervical cancer, respectively [72].

Modern techniques such as PCR, have confirmed an extremely strong relationship between HPV and cervical cancer. Beginning in the 1980s, scientific investigation began unraveling the molecular biology of human papillomavirus and the actual cellular mechanism of cervical infection and carcinogenesis. The first epidemiologic study of HPV infection was published by de Villiers and coworkers in 1987. This was followed by a large scale of epidemiologic studies that provided solid evidence that HPV is the primary risk factor for cervical cancer [73].

In 1995 the World Health Organisation officially recognized certain papillomaviruses of types 16 and 18 as human carcinogens [74]. HPV has now been found guilty of causing cervical cancer beyond doubt, but it is not sufficient by itself to cause cancer and it needs more than one cofactor.
2.3.2 Human Papillomaviruses (HPV)

Papillomaviruses are double-stranded circular DNA viruses that infect many species. Human papillomavirus (HPV) is a virus from the papillomavirus family that is capable of infecting humans. Like all papillomaviruses, Persistent infection with a carcinogenic papillomavirus (HPV) is a necessary cause of both squamous cell carcinoma and adenocarcinoma. HPVs establish productive infections only in keratinocytes of the skin or mucous membranes. More than 100 types of human papillomaviruses have been identified and approximately half of them infect the genital tract. Many types of HPV have been found in cervical cancers, while others are found rarely or not at all in large series of cancers, which gives rise to the nomenclature of ‘high-risk’ and ‘low-risk’ HPVs. Around 16 HPV types have been classified as high-risk (hrHPV) for carcinogenesis in humans, of which 12 are classified as definitely carcinogenic [75]. HPV16 has a particular high potential for malignant transformation of infected cervical cells [76]. A recent report shows that HPV types 16, 18, 31, 33, 35, 45, 52, and 58 account for 91% of all HPV DNA positive cervical cancers in the world, of which HPV16 and 18 are the most common (71%) [77]. HPV16, 18, and 45 were found in 94% of the adenocarcinomas. One hundred eighteen papillomavirus (PV) types have been completely described, and a yet higher number of presumed new types have been detected according to preliminary data.

It is divided into three regions namely E regions, L regions and LCR regions. E regions represents the coding for early proteins, the L region represents the coding for late proteins and LCR represents the non-coding region as depicted in Figure 2.7.

E1-E7 are responsible for the pathogenicity of the virus, the L region is coding for late structural proteins and the LCR contains the cis-elements necessary for replication and transcription of the viral genome. The E1 and E2 genes are involved in viral replication and genome maintenance.
E1 has helices activity that catalyzes the unwinding of DNA duplex. It also brings the DNA polymerase to the origin of replication, where the E1 and E2 proteins will initiate the replication. E2 also acts as a transcription repressor of the HPV E6 promoter. Although the E4 protein is a product of early gene expression, it is considered to be a late protein with production and localization in the cytoplasm of the upper epithelial layers just prior to full viral assembly and play an important role in the maturation and replication of the virus. The E4 protein also induces the collapse of the cytoplasmic cytokeratin network in human keratinocytes.

Figure 2.7 118 Papillomavirus Types (de Villiers et al. 2004)


HPV is associated with a variety of clinical conditions that range from innocuous lesions to cancer are depicted in Table 2.1.

42
Table 2.1 Human papillomavirus types and clinical manifestations

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>HPV type&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plantar warts</td>
<td>1, 2, 4, 63.</td>
</tr>
<tr>
<td>Common</td>
<td>2, 1, 7, 4, 26, 27, 29, 41, 57, 65, 77, 3, 10, 28.</td>
</tr>
<tr>
<td>Flat warts.</td>
<td>3, 10, 26, 27, 28, 38, 41, 49, 75, 76.</td>
</tr>
<tr>
<td>Other cutaneous lesions</td>
<td>6, 11, 16, 30, 33, 36, 37, 38, 41, 48, 60, 72, 73.</td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis</td>
<td>2, 3, 10, 5, 8, 9, 12, 14, 15, 17, 19, 20, 21, 22, 23,</td>
</tr>
<tr>
<td>Recurrent respiratory papillomatosis</td>
<td>24, 25, 36, 37, 38, 47, 50.</td>
</tr>
<tr>
<td>Focal epithelial hyperplasia de Heck.</td>
<td>6, 11.</td>
</tr>
<tr>
<td>Conjunctival papillomas/carcinomas</td>
<td>3, 22.</td>
</tr>
<tr>
<td>Genital warts (condyloma acuminatum).</td>
<td>6, 11, 16.</td>
</tr>
<tr>
<td>Low-risk cervical intraepithelial neoplasia</td>
<td>6, 11, 30, 42, 43, 45, 51, 54, 55, 70.</td>
</tr>
<tr>
<td>High-risk cervical intraepithelial neoplasia</td>
<td>6, 11, 16, 18, 31, 33, 42, 43, 44, 45, 51, 52, 74.</td>
</tr>
<tr>
<td>Cervical carcinoma</td>
<td>16, 18, 6, 11, 31, 34, 33, 35, 39, 42, 44, 45, 51, 52, 56, 58, 66, 68, 70</td>
</tr>
<tr>
<td>Other genital carcinomas (vagina, vulva, penis and anus)</td>
<td>16, 18, 31, 45, 33, 35, 39, 51, 52, 56, 58, 66, 68, 70</td>
</tr>
<tr>
<td></td>
<td>16, 18, 31, 45, 33, 35, 39, 51, 52, 56, 58, 66, 68, 70</td>
</tr>
</tbody>
</table>

a. a Data from reference 30

b. Order indicates relative frequency; bold type indicates most frequent association
2.4 Risk factors for Cervical Cancer

Risk factors are behaviors or conditions that increase your chance of developing a disease. In other way risk factors are the habits a person possesses which may increase of getting into some special disease or an existing disease get worse than before.

Normally, this risk comes along our way from something we do. For example, smoking increases the chances of developing cancer. Therefore, smoking is a risk factor for cancer. Other times, we cannot do anything about the risk, it just happens. For example, people with the age group of 50 and older are more likely to develop cancer than people under 50. Here age is a risk factor for cancer.

A cervical cancer risk factor is something that increases the likelihood of developing the disease. It is not a guarantee that cervical cancer will develop. Researchers have identified several risk factors increases the individual chance of developing cervical cancer.

Knowing the risk factors and discussing about them will help to make more informed on lifestyle and health care choices. It also helps to focus on those things one can change or avoid like smoking. However, it is still important to know about risk factors that cannot be changed, because it’s even more important for women who have these factors to get regular Pap tests to detect cervical cancer early. Some important risk factors are as follows [78].

2.4.1 Human Papillomavirus Infection

The first and most important risk factor for cervical cancer is infection with a virus known as HPV. It is a group of more than 118 related viruses. It normally affects the cells in the surface of the skin. This virus is most commonly passed from person to person during sexual activity. Among this two important categories are there which are based on how much it creates harms to the humans; “low risk” which are rarely related to cancer and “high risk” which will creates cancer.
HPV is passed from one person to another by skin-to-skin contact such as can occur during sex. Normally the human body will fight against the viruses which are entering into the body. So it is not necessary that all women who have HPV have not the chance of cervical cancer but very few of these women will get into cervical cancer. HPV infection is mainly found in young women and is less common in women over 30.

The Pap test can find cell changes that point to HPV infection. Other tests look for the infections themselves by finding genes (DNA) from HPV in the cells. For some women, the HPV test is used along with the Pap test as a part of screening. While there is no cure for HPV, the abnormal cell growth they cause can be treated. Vaccines have been made that will prevent infection with some types of HPV.

2.4.2 Immune System Deficiency

Women with lowered immune systems have a higher risk of developing cervical cancer. A lowered immune system can be caused by immune suppression from corticosteroid medications, organ transplantation, treatments for other types of cancer, or from the human immunodeficiency virus (HIV), and the virus that causes acquired immune deficiency syndrome (AIDS). When a woman has HIV, her immune system is less able to fight off early cancer.

2.4.3 Smoking

Women who smoke are about twice as likely to get cervical cancer as those who don't. Smoking puts many chemicals that cause cancer into the lungs. These harmful substances are carried in the bloodstream throughout the body to other organs. Tobacco by-products have been found in the cervical mucus of women who smoke. Smoking also makes the immune system less able to fight HPV infections.
2.4.4 Chlamydia Infection

This is a common kind of bacteria that can infect women's sex organs. It is spread during sex. A woman may not know that she is infected unless she is tested for chlamydia when she gets her pelvic exam. Some studies suggest that women who have a past or current infection are at greater risk for cancer of the cervix. Long-term infection can cause other serious problems, too.

2.4.5 Diet

Women with diets low in fruits and vegetables may be at increased risk for cervical cancer. Also overweight women are more likely to develop adenocarcinoma of the cervix.

2.4.6 Birth Control Pills

Long-term use of birth control pills increases the risk of cervical cancer. Research suggests that the risk goes up the longer a woman takes "the pill," but the risk goes back down again after she stops. You should talk to your doctor about the pros and cons of birth control pills in your case.

2.4.7 Intrauterine Devices

A recent study found that women who had ever used an intrauterine device (IUD) had a lower risk of cervical cancer. The effect on risk was seen even in women who had an IUD for less than a year, and the protective effect remained after the IUDs were removed. But IUDs do have some risks. A woman thinking of using an IUD should first discuss the pros and cons with her doctor.

2.4.8 Having Many Pregnancies

Women who have had 3 or more full-term pregnancies have an increased risk of this cancer. No one really knows why this is true.
**2.4.9 Young Age at the Time of First Full-Term Pregnancy**

Women who were younger than 17 years when they had their first full-term pregnancy are almost 2 times more likely to get cervical cancer later in life than women who waited to get pregnant until they were 25 years or older.

**2.4.10 Low Income**

Poor women are at greater risk for cancer of the cervix. This may be because they cannot afford good health care, such as regular Pap tests.

**2.4.11 DES (DiEthylStilbestrol)**

DES is a hormone drug that was used between 1940 and 1971 for some women who were in danger of miscarriages. The daughters of women who took this drug while they were pregnant with them have a slightly higher risk of cancer of the vagina and cervix.

**2.4.12 Family History**

Cervical cancer may run in some families. If your mother or sister had cervical cancer, your chances of getting the disease are 2 to 3 times higher than if no one in the family had it. This could be because these women are less able to fight off HPV than other women.

**2.5 Diagnosis Classification Systems**

There are several systems for classifying premalignant cervical tumors, including cytology and histology. The first system corresponds to the Papanicolaou classification, which has 5 numerical classes or grades (I, II, III, IV, V); this system is purely cytological [79]. In 1961, in the first International Congress of Cytology, held in Vienna, experts agreed about the terms for the three most crucial cytological cervical lesions, namely invasive carcinoma, carcinoma in situ (CIS) and dysplasia, the latter classified as mild, moderate, and severe or severe [80]. In 1967, in order to propose the classification of cervical intraepithelial neoplasia (NIC), this system considered various changes observed in three different degrees of dysplasia, including Grade III severe dysplasia and the previous CIS. (Table 2.2.)
In 90s, a system was proposed at the Bethesda National Cancer Institute U.S. (United States National Cancer Institute). In this system, NIC II and III were assembled in a single group,

"High-grade squamous intraepithelial lesion(HSIL). In 2001, atypical cells were divided into ASC-US (atypical squamous cells of undetermined significance) and ASC-H (atypical squamous cells cannot exclude a squamous intraepithelial high grade lesion). The Bethesda system is recommended by OMS for cytological reports [81].

Table 2.2 Classification Systems. Modified from OMS 2007

<table>
<thead>
<tr>
<th>Papanicolaou</th>
<th>NIC</th>
<th>OMS</th>
<th>Bethesda</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Class II</td>
<td>Atypia</td>
<td>Atypia</td>
<td>ASC</td>
</tr>
<tr>
<td>Class III</td>
<td>NIC I</td>
<td>Mild dysplasia</td>
<td>LSIL</td>
</tr>
<tr>
<td>Class III</td>
<td>NIC II</td>
<td>Moderate dysplasia</td>
<td>HSIL</td>
</tr>
<tr>
<td>Class III</td>
<td>NIC III</td>
<td>Severe dysplasia</td>
<td>HSIL</td>
</tr>
<tr>
<td>Class IV</td>
<td>NIC III</td>
<td>in situ cancer</td>
<td>HSIL</td>
</tr>
<tr>
<td>Class V</td>
<td>Invasive carcinoma</td>
<td>Invasive carcinoma</td>
<td>Invasive carcinoma</td>
</tr>
</tbody>
</table>

2.5.1 Histological Classification: WHO-NIC

In many countries, the NIC classification and the Classification of the World Health Organization (WHO) are widely used in cytological reports, although these systems should only be used in histological reports, including various tissues as follows:

- Mild dysplasia (NIC I, cervical intraepithelial neoplasia-grade I): The extension of the atypical epithelium is limited to the lower third of the epithelium thickness.
- Moderate dysplasia (NIC II, grade II): It affects the lower two thirds of the epithelium thickness.
- Severe dysplasia (NIC III, grade III): The upper third is also involved in the atypia.
• Carcinoma in situ: There are no mature cells migrating towards the surface. The biological significance of these alterations does not differ from severe dysplasia and may therefore be grouped according to the concept on the lesion (NIC III).

2.5.2 Cytological Classification: Bethesda System

Bethesda System diagnostic reports are used for vaginal or cervical cytology and it was introduced in 1988, revised in 1991, and updated in 2001 in order to establish a uniform terminology and standardize diagnostic reports. This system includes epithelial cell abnormalities in squamous cells, glandular and other malignancies.

The categories include:

- Atypical Squamous Cell (ASC)
- Atypia squamous cells of undetermined significance (ASC-US)
- Atypical squamous cells of undetermined significance cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL) (including changes associated with infection by Human Papilloma Virus (HPV) or mild dysplasia (NIC I))
- High-grade squamous intraepithelial lesions (H-SIL), (comprising moderate dysplasia, severe NIC II, NIC III, Ca in situ)
- Carcinoma

2.5.3 Cervical Intraepithelial Neoplasia (CIN)

CIN is the term describing the stages of dysplasia, which means the atypical progressive cytological changes in the layers of squamous epithelium. Invasive squamous cell cervical cancers are preceded by a long phase of preinvasive disease, collectively referred to as cervical intraepithelial neoplasia (CIN). It also represents the presence of abnormal cells seen on the Pap (cervical) smear. These abnormal cells are obtained from the lining of the outer cervix and can range from mild to severe changes. A diagnosis of CIN changes is not cancer. However, the severe form of dysplasia can be considered a precancerous condition and may progress to cancer in several years if not treated.
The concept of cervical cancer precursors dates back to the late nineteenth century, when areas of noninvasive atypical epithelial changes were recognized in tissue specimens adjacent to invasive cancers [82]. The term carcinoma in situ (CIS) was introduced in 1932 to denote those lesions in which the undifferentiated carcinomatous cells involved the full thickness of the epithelium, without disruption of the basement membrane. The association between CIS and invasive cervical cancer was subsequently reported. The term dysplasia was introduced in the late 1950s to designate the cervical epithelial atypia that is intermediate between the normal epithelium and CIS. It has three groups of classification namely mild, moderate and severe which are still used in many developing countries.

By some observations it was found that some of dysplasia regresses, some continues and others progressed to CIS. These observations led to the concept of a single, continuous disease process by which normal epithelium evolves into epithelial precursor lesions and on to invasive cancer. On this basis cervical intraepithelial neoplasia (CIN) was introduced in 1968 to denote the whole range of cellular atypia confined to epithelium. CIN may be categorized into grades 1, 2 and 3 depending upon the proportion of the thickness of the epithelium showing mature and differentiated cells.

CIN1 is considered a low grade lesion. It refers to mildly atypical cellular changes in the lower third (basal 1/3) of the epithelium is often present. This corresponds to infection with HPV, and typically will be cleared by immune response in a year or so, though can take several years to clear. This classification involves mild dysplasia, in which abnormal cells are limited to the first third of squamous epithelium, measured from the basal to the surface layer. In CIN1 there is good maturation with minimal nuclear abnormalities and few mitotic figures.

Undifferentiated cells are confined to the deeper layers (lower third) of the epithelium. Mitotic figures are present, but not very numerous. Cytopathic changes due to HPV infection may be observed in the full thickness of the epithelium (Figure 2.8).
CIN2 is considered a high grade lesion. It refers to moderately atypical cellular changes confined to the basal two-thirds of the epithelium (formerly called moderate dysplasia) with preservation of epithelial maturation. CIN2 is characterized by dysplastic cellular changes mostly restricted to the lower half or the lower two thirds of the epithelium, with more marked nuclear abnormalities than in CIN1.

In CIN3, differentiation and stratification may be totally absent or present only in the superficial quarter of the epithelium. Nuclear abnormalities extend throughout the thickness of the epithelium. Many mitotic figures have abnormal forms. CIN3 is also considered a high grade lesion/Severe dysplasia. It refers to severely atypical cellular changes encompassing greater than two-thirds of the epithelial thickness, and includes full-thickness lesions.

Figure 2.8 Grading of CIN

2.6 Staging System of Cervical Cancer

Staging is the process of finding the depth of cancer spreading. It is the measure of how much the cancer has grown and spread. It is very important to classify the stage of the cervical cancer, since then only we decide the plan of treatment. Cancers normally staged by looking at features of a cancer cells using a microscope or by other tests. A good staging system must be a valid system. Everyone must rely on the staging system and it must be practically applicable.

Staging is important for several reasons:

- Staging helps the doctor plan the appropriate treatment.
- The stage can be used to estimate the person’s prognosis.
- Knowing the stage is important in identifying clinical trials that may be suitable for a particular patient.
- Staging helps health care providers and researchers exchange information about patients; it also gives them a common terminology for evaluating the results of clinical trials and comparing the results of different trials.

2.6.1 The TNM System

The American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) maintain the TNM classification system as a tool for doctors to stage different types of cancer based on certain standards. It is reviewed every 6 to 8 years to include advances in our understanding of cancer.

The TNM system is based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of distant metastasis (M). A number is added to each letter to indicate the size or extent of the primary tumor and the extent of cancer spread.
The T category describes the primary tumor.

<table>
<thead>
<tr>
<th>T</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be evaluated</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (early cancer that has not spread to neighboring tissue)</td>
</tr>
<tr>
<td>T1–T4</td>
<td>Size and/or extent of the primary tumor</td>
</tr>
</tbody>
</table>

The N category describes whether or not the cancer has reached nearby lymph nodes

<table>
<thead>
<tr>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be evaluated</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node involvement (no cancer found in the lymph nodes)</td>
</tr>
<tr>
<td>N1–N3</td>
<td>Involvement of regional lymph nodes(number and/or extent of spread)</td>
</tr>
</tbody>
</table>

The M category tells whether there are distant metastases (spread to other parts of the body)

<table>
<thead>
<tr>
<th>M</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis( cancer has not spread to other parts of body)</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis( cancer has spread to distant parts of the body)</td>
</tr>
</tbody>
</table>

2.6.2 FIGO Staging System

FIGO staging system is purely based on clinical examination, rather than surgical findings. In 1958 FIGO became the official patron of the Annual Report. Volume 12, issued in 1961, became the first report published under its auspices. Table 2.3, shows the FIGO stage in relation to the cytology history. The FIGO stage was grouped into low (1A or 1B), borderline (2A–2B), and high grades (X3A) because this grouping has consequences for therapy, and gives more relevant information about the relation between FIGO stage and screening history.
Table 2.3 FIGO Staging for Cervical Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 0</strong></td>
<td>Carcinoma in situ, preinvasive carcinoma</td>
</tr>
<tr>
<td><strong>Stage I</strong></td>
<td>Invasive carcinoma strictly confined to cervix</td>
</tr>
<tr>
<td>Stage IA</td>
<td>Invasive carcinoma identified microscopically (all microscopically visible lesions, even with superficial invasion, should be assigned to stage IB)</td>
</tr>
<tr>
<td>Stage IA1</td>
<td>Measured invasion of stroma 3.0 mm or less in depth and 7.0 mm or less in horizontal spread</td>
</tr>
<tr>
<td>Stage IA2</td>
<td>Measured invasion of stroma more than 3.0 mm but no greater than 5.0 mm in depth and 7.0 mm or less in horizontal spread</td>
</tr>
<tr>
<td>Stage IB</td>
<td>Clinically visible lesion confined to cervix or microscopic lesion greater than stage IA2</td>
</tr>
<tr>
<td>Stage IB1</td>
<td>Clinical lesions of 4.0 cm or less in size</td>
</tr>
<tr>
<td>Stage IB2</td>
<td>Stage IB2 Clinical lesions more than 4.0 cm in size</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td>Carcinoma extending beyond cervix but not to pelvic sidewall; carcinoma involves vagina but not its lower third</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>Stage IIA No parametrical involvement</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>Stage IIB Parametrical involvement</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td>Carcinoma extending onto pelvic wall; the tumor involves lower third of the vagina. All patients with hydronephrosis or non-functioning kidney are included unless known to be the result of other causes</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>Stage IIIA Involvement of lower third of the vagina; no extension of pelvic sidewall</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Stage IIIB Extension to pelvic sidewall and/or hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td>Carcinoma extends beyond true pelvic or clinically involves mucosa of bladder or rectum. Bullous oedema does not allow a case to be designated as stage IV</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>Spread of growth to adjacent organs</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Spread to distant organs</td>
</tr>
</tbody>
</table>

Source: FIGO Committee on Gynecologic Oncology and IGCS Guidelines Committee (2000)