INTRODUCTION

The definition of cervical cancer is a malignancy of the cervix *(Canavan and Doshi, 2000)*.

Cancer of the uterine cervix is largely a preventable disease characterized by a long lead-time, with precancerous lesions gradually progressing through recognizable stages before developing into invasive disease. The disease process is almost certainly curable if it is identified prior to its progression to invasive cancer *(Benedet et al., 2001)*.

The uterine cervical carcinoma is second most common cancer in women (after breast cancer) and the third leading killer (behind breast and lung cancer). It affects about 16/100000 women per year and cause death in 9/100000 per year *(Jemal et al., 2002)*.

The incidence of cervical cancer has been decreasing in western countries due to cytological screening tests but still high in developing countries *(Benedet et al., 2001)*.

Cervical cancer usually affects women of middle age or older but it may be diagnosed in any reproductive-aged women *(Cannistra, 2002)*.

The risk factors of cervical cancer are human papillomavirus infection *(Snijders et al., 2006)*, multiple pregnancies, early sexual life, multiple sexual partners, oral contraceptive, smoking *(Castellsague et al., 2003)*, HIV infection, Herpes simplex virus type 2, Clamydia infection, dietary factors *(Castle et al., 2003)*, and use of the hormonal drug diethylstilbestrol (DES) *(Walboomers et al., 1999)*.

Treatment of cervical cancer (stage IA) is usually by hysterectomy (removal of the wall uterus including part of the vagina). For stage IA2, the lymph nodes are removed as well. An alternative for patients who desire to maintain fertility is a local surgical procedure such as cone biopsy or cryotherapy *(Wright et al., 2002)*.

Early stages (IBI and IIA less than 4cm) can be treated with radical hysterectomy with removal of lymph nodes or radiation therapy. Larger early stage tumors (IB2 and IIA more than 4cm) may be treated with radiation therapy and cisplatin-based chemotherapy, hysterectomy (which then usually requires adjuvant radiation therapy) or cisplatin chemotherapy followed by hysterectomy *(Decker et al., 2004)*.

Advanced stage tumors (IIB-IVA) are treated with radiation therapy and cisplatin-based chemotherapy. Late-stage (IVB) cervical cancer is treated with radiotherapy, chemotherapy and drugs to relieve pain *(Wright et al., 2002)*.

AIM OF THE WORK

The aim of this work is to study the characteristics of cervical cancer in some governorates in Egypt.

ANATOMY AND HISTOLOGY OF THE CERVIX

The term cervix (taken from the Latin, meaning "neck") is the most inferior portion of the uterus protruding in the upper vagina measuring in adult nulligravida from 2.5 to 3cm in length and 2.5cm in diameter *(Liewellyn-Jones, 2005)*.

The vagina is attached obliquely around the centre of the cervix dividing it into two segments: upper (supravaginal portion) and lower (vaginal portion) *(Krantz, 2006)*.

The endocervical canal which is an elliptical cavity, flattened from front to back, measuring in its greatest width 7-8mm, opens in the vagina through the external os while it is connected above with the body of the uterus at the internal os *(Ferenczy, 2007)*.

The vaginal cervix has both an anterior lip and posterior lip where the anterior lip is lower than the posterior lip with the external os in contact with the posterior vaginal wall *(Ferenczy, 2007)*.

The shape of the cervix varies, in nulligravida it is cylindrical while in parous women it is horizontal due to changes occurring as a result of pregnancy (increased in size, version of epithelium contents of the lower endocervical canal and the laceration at the time of delivery) *(Chard and Lilford, 2004)*.

The supravaginal cervix is separated from the bladder by distinct layer of connective tissue (endo-pelvic fascia) called the pubovesicocervical fascia. Laterally at the same level, the cervix is in continuity with the paracervical ligaments which contain the uterine blood vessels, posteriorly, the supravagainal cervix is covered by peritoneum as it reflects of the uterosacral ligaments downwards towards the vaginal apex *(Jeffeoate, 2006)*.

The part of the cervix that projects into the vagina, called ectocervix or portio, is covered by non-keratinized stratified squamous epithelium similar to that of the vagina. The endocervical canal is covered by tall mucus-secreting columnar cells. The junction between these two is termed the squamocolumnar junction *(Kistner, 2007).*

Transformation zone

The squamocolumnar junction is defined as the border between stratified squamous epithelium and mucin-secreting columnar epithelium of the endo-cervix. Morphogentically there are two different squamocolumnar junctions, one termed original squamocolumnar junction and is the site at which the squamous covering of exocervix abuts the endocervical columnar epithelium at time of birth. Most female babies have columnar endocervical epithelium on the portio surface of the cervix, which forms ectropion or cervical ectopy, overtime it is replaced by metaplastic squamous epithelium. As this occurs the histologic squamocolumnar junction moves towards external os. The newly formed junction is called the physiologic junction. The region between both is called the transformation zone, it is histologically characterized by the presence of metaplastic epithelium *(Kurman, 2008)*. This meta-plastic area has, for unknown reasons, unique suscep-tibility to HPV-induced neoplastic transformation, particularly in the anterior and posterior areas *(IARC, 2007).*

EPIDEMIOLOGY AND RISK FACTORS

Epidemiology

Worldwide, cervical cancer is common, and ranks second among all malignancies for women. In 2002, an estimated 493000 new cases were identified globally and 274000 deaths were recorded. In general, higher incidences are found in developing countries, and these countries contribute 83 percent of reported cases annually. Economically advantaged countries have significantly lower cervical cancer rates, and add only 3.6 percent of new cancers. This incidence disparity highlights successes achieved by cervical cancer screening programs in which Papanicolaou (Pap) smears are regularly obtained *(Parkin, 2008)*.

Within the United States, cervical cancer is the third most common gynecologic cancer and the sixth most common solid malignant neoplasm among women. In the US, women have a 1 in 135 lifetime risk of developing this cancer. In 2006, an estimated 9710 new cases and 3700 deaths from this malignancy of US women, African-American and women in lower socioeconomic groups have the highest age-

standardized cervical cancer death rates from this cancer, and Hispanic and Latino women have the highest incidence rates. This trend is thought to result mainly from financial and cultural characteristics affecting access to screening and treatment. The age at which cervical cancer develops is in general earlier than that of other gynecologic malignancies, and the median age at diagnosis ranges from 40 to 59 years. In women aged 20 to 39 years, cervical cancer is the second leading cause of cancer deaths.

Table (1): Cervical Age-Standardized Incidence and Death Rates

	All races	*White*	*African/ American*	*Asian American and pacific Islander*	*American Indian and Alaskan native*	*Hispanic-Latino*
Incidence (%)	8.9	8.7	11.1	8.9	4.9	15.8
Death (%)	2.8	2.5	5.3	2.7	2.6	3.5

(Jemal et al., 2007)

In 2004, an estimated 12.3, 8.2 and 7.1 women in China, U.K. and Japan respectively per 100,000 population with cervical cancer (*http://www.wrongdiagnosis.com, 2009*).

Within Africa, the incidence and prevalence estimates vary widely between geographical regions. The highest incidence rates in the world are in eastern and Sub-Saharan (Southern) Africa, while in Northern Africa the incidence is lower *(GLOBACAN, 2008)*.

Risk factors

Race

Although the incidence of cervical cancer in the United States has declined significantly, the rates among blacks remain about twice as high as those among whites. The incidence is also approximately two times higher for Hispanic Americans and even higher for Native Americans, while most Asian American groups experience rates similar to whites. When socioeconomic differences are controlled for the excess risk of cervical cancer among blacks is substantially reduced, from >70% to <30%. Racial differences are also apparent in survival, with 59% of blacks with cervical cancer surviving 5 years compared to 67% of whites with the disease *(Jemal et al., 2007)*.

Sexual behavior

First intercourse before 16 years of age is associated with a twofold increased risk of cervical cancer compared with that for woman whose first intercourse occurred after age 20 years. Cervical cancer risk is also directly proportional to the number of lifetime sexual partners. Although difficult to separate epidemiologically, there is evidence to indicate that both early age at first coitus and the number of lifetime independent effects on cervical cancer risk *(ACOG, 2008).*

Smoking

Cigarette smoking has emerged as an important etiologic factor in squamous cell carcinoma (SCC) of the cervix. The increased risk for smokers is approximately twofold, with the highest risk observed for long-term or high-intensity smoker. Proposed mechanisms include genotxic or immunosuppressive effects of smoke-derived nicotine and cotinine, present in high levels in the cervical mucus of smokers *(Plummer, 2009).*

Contraceptive use and parity

Study results linking cervical neoplasia and these risk factors are conflicting. It has been reported

that steroid hormones found in COC may affect the HPV genome and increase viral expression of oncoproteins E6 and E7 *(De Villiers, 2008).* During pregnancy, immunosuppression and hormonal influences on cervical epithelium combined with trauma related to vaginal deliveries have been suggested as etiologic factors associated with the development of cervical neoplasia *(Brinton, 2007).*

Immunosuppression

Cell-mediated immunity appears to be a factor in the development of cervical cancer. Immuno-compromised woman (e.g., from renal transplantation or HIV infection) may not only be at higher risk for the disease but also demonstrate more rapid progression from preinvasive to invasive lesions an accelerated course once invasive disease has been diagnosed. HIV-positive woman with cervical cancer may have a higher recurrence risk and cancer-related death rate compared with HIV-negative control subjects *(Frisch, 2009).*

Human papillomavirus

Human papillomavirus is a nonenveloped DNA virus with a protein capsid. It infects epithelial cells exclusively and approximately 30 to 40 HPV types have an agginity for infecting the lower anogenital tract *(Southern, 2007).*

When infection occurs, replication of the viral particle requires mature squamous keratinocytes. An active HPV infection is initiated when the infectious particles reach the basal layer of the epithelium, where they bind to and enter into cells. It has been suggested that for the maintenance of infection, the virus has to infect an epithelial stem cell. The HPV DNA sequence consists of early (E) and late (L) open reading frames *(De Villiers et al., 2007)*.

The critical molecules in the process of viral replication and cellular transformation are the E6 and E7. The E6 and E7 protein products bind tumor suppressor genes p53 and pRB, respectively. Cell transformation with oncogenic HPV subtypes, such as HPV 16 or 18, may be accompanied by the fact that HPV is no longer in an episomal state but rather is integrated into the host genome. Opening of the virus for genomic integration usually occurs in the E1/E2 region. Disruption of E2, which acts as a repressor of

E6/E7, may result in unregulated expression of the transforming E6/E7 proteins and inactivation of p53 and pRB. Variations in the oncogenicity of different HPV subtypes may be due to differences in the binding efficacy of E6 and E7 to p53 and pRB or differences in their ability to inactivate these tumor suppressor genes. Low-risk types do not give rise to such changes *(Moscicki et al., 2009)*.

As a consequence of disruption of these tumor suppressor genes, the dependence on cell cycle control is abolished and normal keratinocyte differentiation is retarded. With HPV integration into the human genome, there is constant activity of viral proteins E6 and E7, leading to increasing genomic instability, accumulation of oncogenic mutations, future loss of cell cycle control, and ultimately cancer. The viral capsule is quite uniform among the HPV types and is formed from the L1 and L2 reading frames, encoding the structural proteins. These capsule proteins are utilized in prophylactic vaccine therapy, whereas various manipulations of either the protein or HPV DNA from E6 and E7 are used in therapeutic immunologic approaches *(Munoz, 2008)*.

More than 100 HPV types have now been

identified. Clinically HPV types are classified as high-risk (HR) or low-risk (LR) based upon their cervical cancer oncogenicity. Low-risk HPV types 6 and 11 cause nearly all genital warts and a minority of subclinical HPV infections. Low-risk HPV infections are rarely, if ever, oncogenic. In contrast, the HR HPV types include 16, 18, 31, 33, 35, 45 and 58 and account for approximately 95 percent of cervical cancer cases worldwide. Other HR HPV types less often associated with neoplasia include 39, 51, 52, 56, 59, 68, 73, and 82 *(Bosch et al., 2005).*

The most common HR HPV types (16, 18, 45, and 31) found in cervical cancer are also the most prevalent in the general population. Specifically, HPV 16 is the dominant cancer-related HPV, accounting for 40 to 70 percent of invasive squamous cell cervical cancers worldwide (*Bosch et al., 2005).* This serotype is also the most common HPV found among low-grade lesions and in woman without neoplasia *(Herrero, 2008).*