REVIEW ARTICLE

NORTH AMERICAN ACADEMIC RESEARCH (NAAR) JOURNAL
2021 OCTOBER, VOLUME 4, ISSUE 10, PAGES 157-177
https://doi.org/10.5281/zenodo.5626839

Updates on Cervical Cancer

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OPEN ACCESS

Accepted October 25,2021
Published October 30,2021

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DOI :https://doi.org/10.5281/zenodo.5626839

Pages: 157-177

Funding: NA

How to cite this article (APA):
Chand Yadav, P., Raj Pandey, S., Thapa, A., Kishor Chaudhary, D., & Kumar Sah, K. (2021. Updates on Cervical Cancer. *North American Academic Research, 4(10)*, 157-177. doi: https://doi.org/10.5281/zenodo.5626839

Conflicts of Interest
There are no conflicts to declare.

ABSTRACT

Cervical cancer is one of the major causes of cancer mortality in females globally, and its epidemiological behavior is similar to that of a low-infectious venereal illness. Early sexual contact and various sexual partners have been demonstrated to have a significant influence on risk. The significant disparities in incidence between nations are also a result of the adoption of screening. While the overall picture of declining incidence and death persists, there are indicators of an increased risk of cervical cancer, most likely related to changes in sexual activity. Tobacco use and human papillomavirus (HPV) 16/18 infection are presently major concerns in a multifactorial, stepwise carcinogenesis concept in the cervix uteri. As a result, it is advised that society-wide preventative and control measures, screening activities, and HPV vaccination be implemented. Cervical cancer screening techniques have advanced from observation of cell morphology to molecular testing. HPV genotyping at high risk and liquid-based cytology are both extensively recommended and utilized worldwide. In the future, procedures that are precise, inexpensive, quick, and simple to use will gain popularity. Cervical malignancies account for about 90% of all cancers in low- and middle-income countries that lack organized screening and HPV immunization programs. Cervical cancer incidence and death have more than halved in high-income nations in the 30 years after the establishment of comprehensive screening programs. Treatment is determined on the degree of the illness at diagnosis and the availability of resources locally, and may include radical hysterectomy, chemoradiation, or a combination of the two. For women with low-risk, early-stage illness, conservative, fertility-preserving surgical techniques have become the standard of therapy.

Keywords: CERVICAL CANCER, EPIDEMIOLOGY, RISK FACTORS, SCREENING

Introduction

Cervical cancer is one of the most common cancers in women. It is the fourth common cancer after breast cancer, colorectal cancer and lung cancer worldwide. Cervical cancer often develops at a reproductive age (44-55 years old)[1].Persistent infection of high-risk human papilloma virus (HR-HPV) is the cause of cervical cancer[2]. According to the histology of cervical cancer, two mainly types have been identified as "squamous cell carcinoma" and "adenocarcinoma", and squamous cell carcinoma is more common[3]. Reproductive tract infections of HPV are considered to be the most common sexually transmitted infections. Usually, the immune

system is strong enough to eliminate HPV infection in the general population, but in some cases, HPVs could persistent and transform the cervical infected cells progression to the precancerous stage due to the viral oncogenes integrated into the host genome and the resulting genome instability. It takes 15 to 20 years to develop from abnormal cervical cytology to early stage invasive cervical cancer. Although this stage involves the chronic development of cervical precancerous lesions, it belongs to the controllable stage of chronic diseases; therefore, it is a critical period for the prevention of early stage invasive cervical cancer[4].

According to the World Health Organization (WHO), 80% of cervical cancer occurs in developing countries, which account for only 5% of global medical resources[5]. In 2016, about 90% of cervical cancer deaths occurred in low- and middle-income countries[6]. High mortality from cervical cancer in low-income countries is attributed to lack of screening and prevention, rather than lack of treatment[7].

Today, it has been developed a perfect preventive strategy for the eradication of cervical cancer. These preventive measures include vaccination with HPVs vaccine and cervical cancer screening as a routine method to determine the precancerous lesion. Risk factors that may contribute to persistent high-risk HPV infection include increased number of sexual partners, the onset of sexual activity at early-young age, impaired immune system, infection with other sexually transmitted diseases at the same time (such as chlamydia, gonorrhea, syphilis and HIV) and smoking[8]. It has been established those different surgical procedures can be used for stage I B and II A cervical cancer. For invasive cervical cancer, the most commonly recommended treatment is radical hysterectomy. The prognostic value of surgical methods was found to be 80% to 90%.

This study determined the surgical treatment of early stage invasive cervical cancer. Our current research try to explore the prognosis of laparoscopic and traditional laparotomy for early stage invasive cervical cancer.

Epidemiology of cervical cancer

Cervical disease is one of the most common female malignant tumors in the world. In 2018, GLOBOCAN (Global Cancer Morbidity, Mortality and Prevalence) estimated 569,847 new cases, of which 7.5% were female casualties, making it the fourth most common cancer-related death. In 2018, the five-year advantage of cervical cancer growth (the number of patients with cervical diseases who did not survive five years later) was estimated at 1,474,265 worldwide, with 100,000 cervical cancer survivors per woman, and the risk of cervical cancer for women aged from birth to 75 was 1.36% worldwide.

Table 1 Epidemiology of cervical cancer worldwide [9]

Parameter	Women
Incidence rate	
Number of new cases	569,847
Number of new cases per 100,000 women	15.1
ASR (W)	13.1

Proportion of all newly diagnosed cancer (apart from skin cancer)	6.9%
Rank among all newly diagnosed cancer (apart from skin cancer)	Fourth
Mortality rate	
Number of casualty	311,365
Number of casualty per 100,000 women	8.2
ASR (W)	6.9
Proportion of all cancer related casualty (apart from skin cancer)	7.5%
Rank among all cancer related casualty (apart from skin cancer)	Fourth
Prevalence rates (Pts. still alive 5 year after diagnosis)	
Absolute number of survivors	1,474,265
Rate per 100,000 women	39.0
Cumulative risk of developing cervical cancer	
From birth until the age of 75	1.36%

Note: ASR (W)=Age standardized world incidence rate per 100,000 women

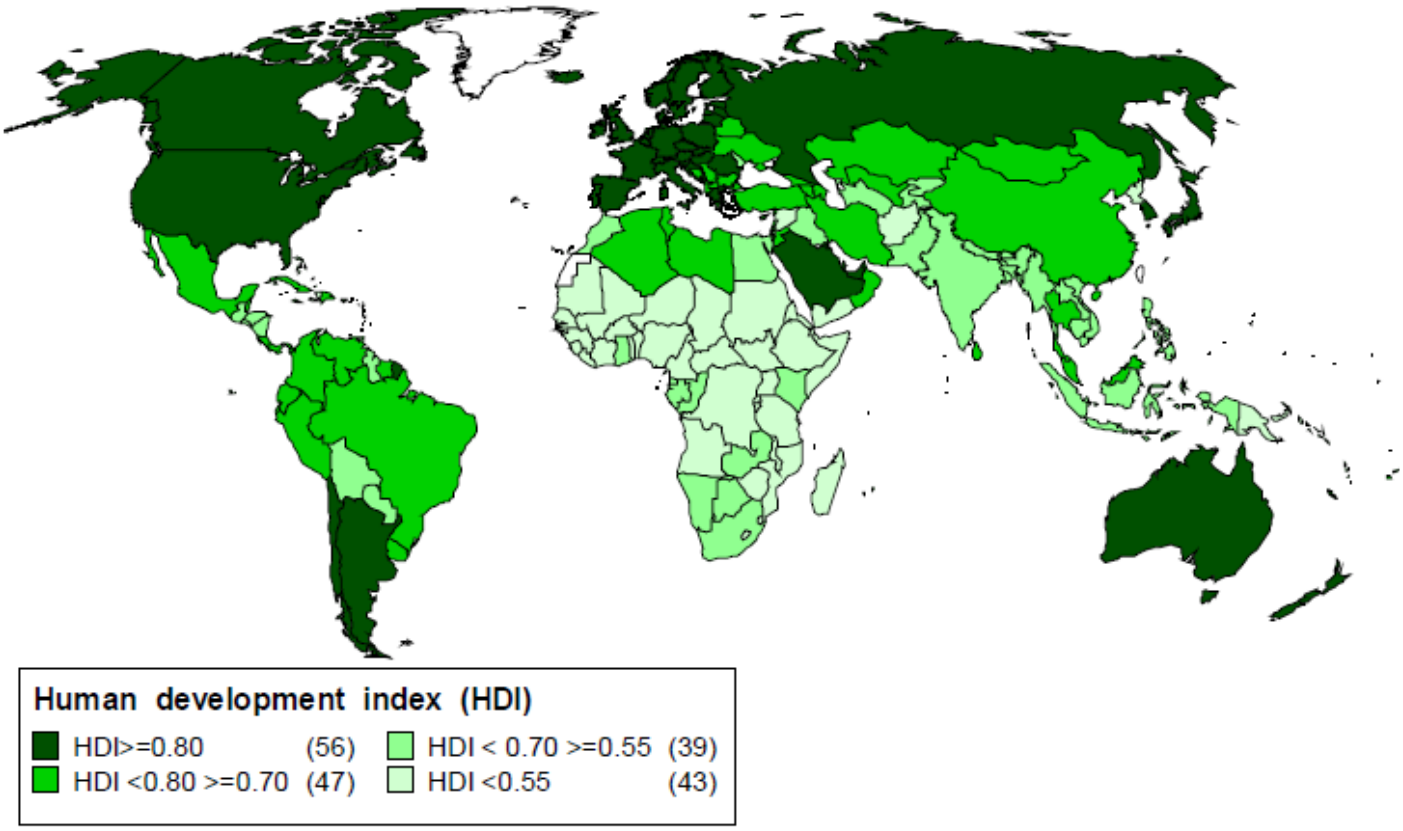
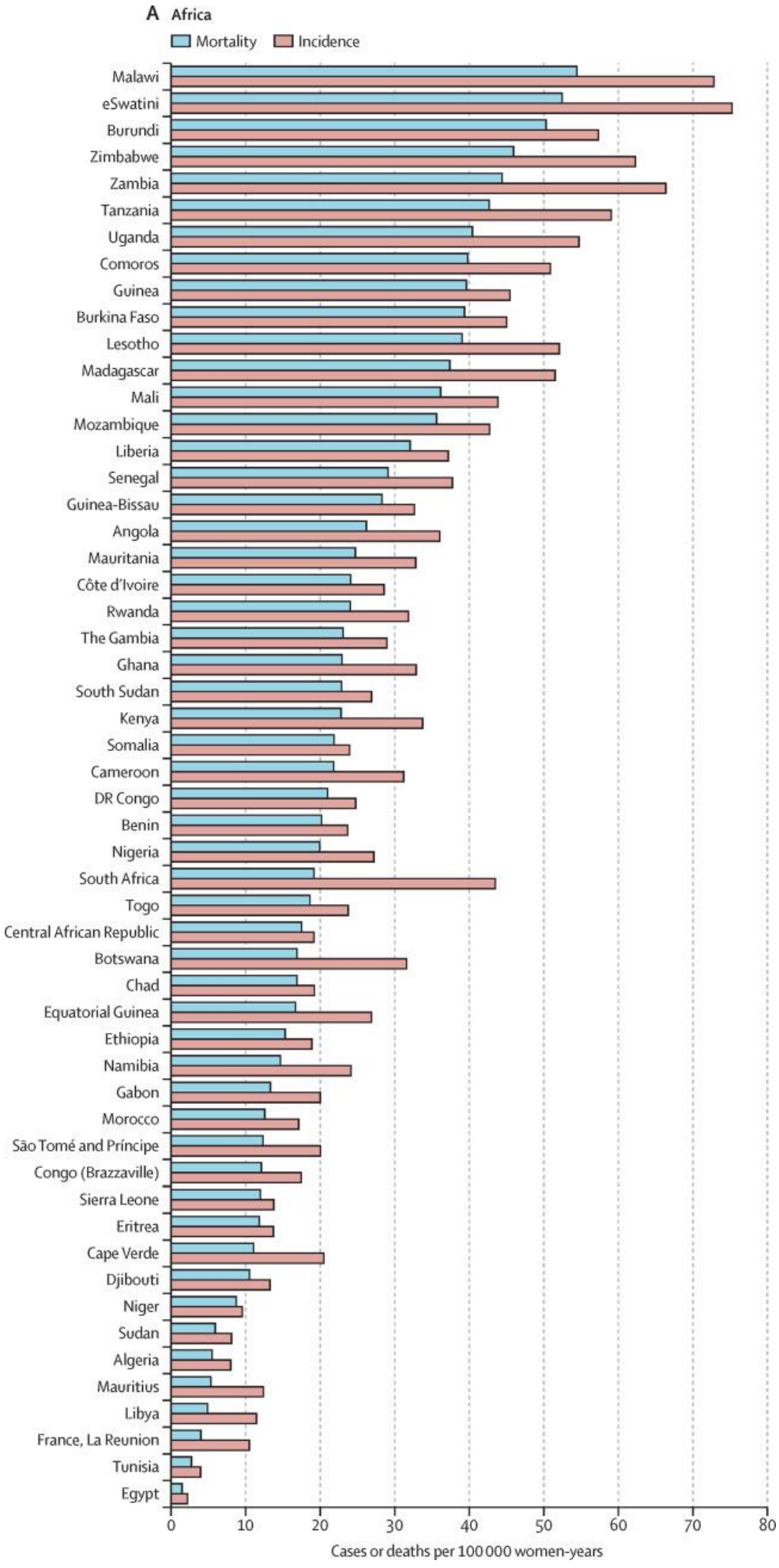


Figure 1. Human development index (HDI) attributed to the 185 countries included in the study of the burden of cervical cancer. Sources: United Nations Development Programme, New York, 2016 and International Agency for Research on Cancer, Lyon, 2018 (Bray F, et al, CA Cancer J Clin 2018).


A Africa
Mortality
Incidence
Malawi
eSwatini
Burundi
Zimbabwe
Zambia
Tanzania
Uganda
Comoros
Guinea
Burkina Faso
Lesotho
Madagascar
Mali
Mozambique
Liberia
Senegal
Guinea-Bissau
Angola
Mauritania
Côte d'Ivoire
Rwanda
The Gambia
Ghana
South Sudan
Kenya
Somalia
Cameroon
DR Congo
Benin
Nigeria
South Africa
Togo
Central African Republic
Botswana
Chad
Equatorial Guinea
Ethiopia
Namibia
Gabon
Morocco
São Tomé and Príncipe
Congo (Brazzaville)
Sierra Leone
Eritrea
Cape Verde
Djibouti
Niger
Sudan
Algeria
Mauritius
Libya
France, La Reunion
Tunisia
Egypt
0
10
20
30
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50
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70
80
Cases or deaths per 100 000 women-years

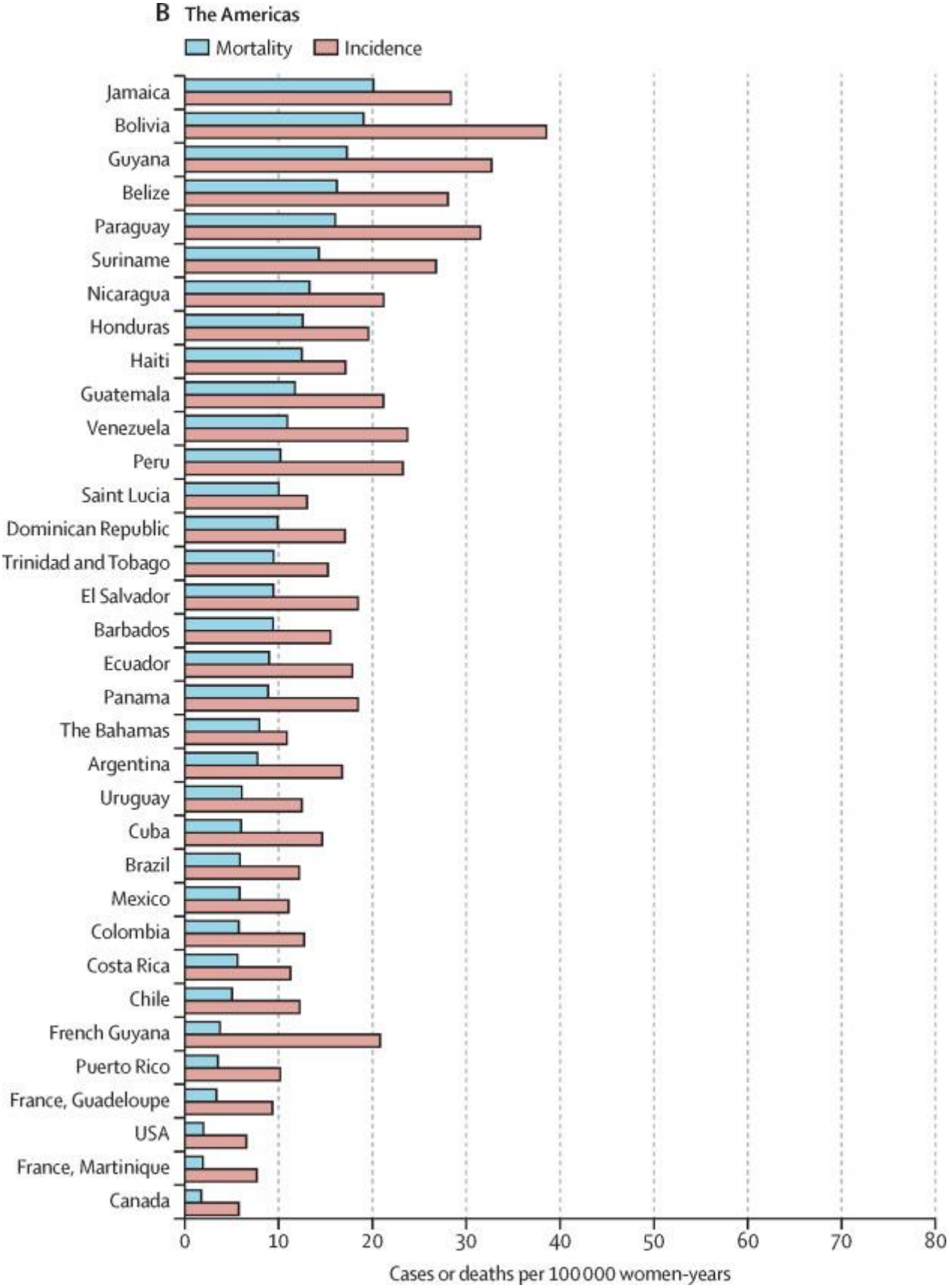

Figure 2: Age-standardized Incidence Rates for Cervical Cancer, Canada and Selected Cancer Registries 1988-1992

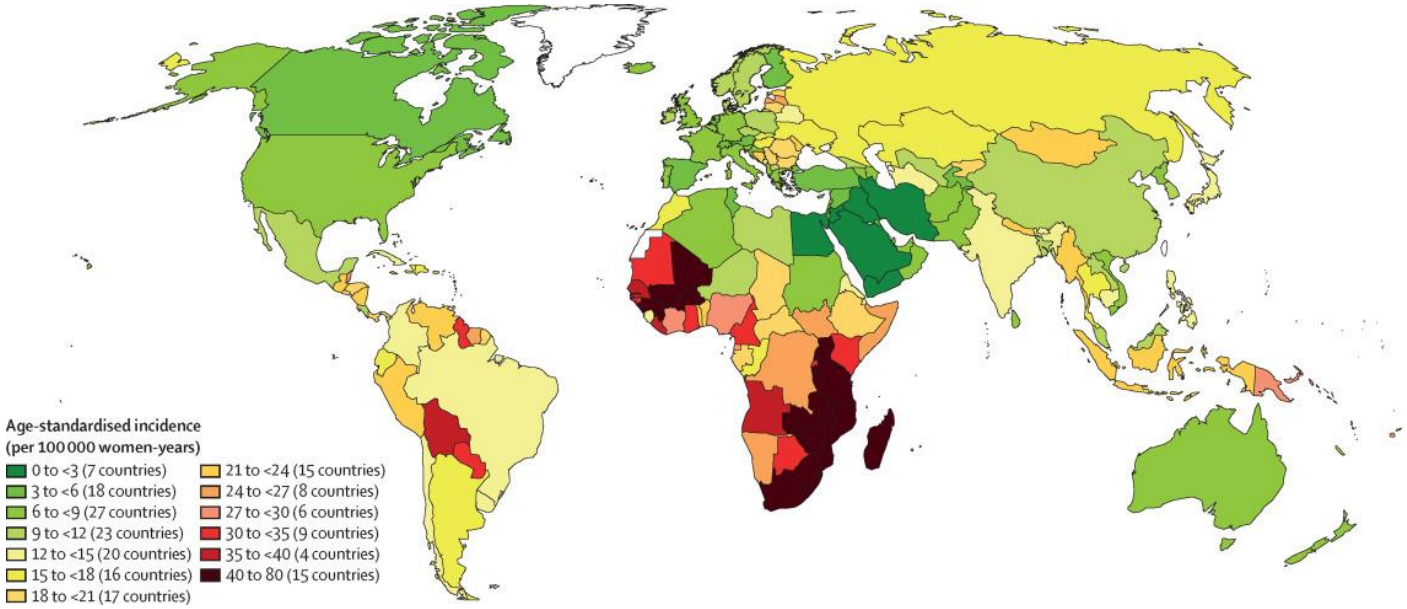

Figure 3: Geographical distribution of world age-standardised incidence of cervical cancer by country, estimated for 2018

Etiology and pathophysiology

HPV is currently identified as the initiation factor in cervical cancer because the virus was identified in 99.7% of cervical malignant tumors [10]. HPVs infection is the world's most widely recognized STI (WHO 2015), sexually active women will be affected sooner or later during their life-time. (American Cancer Society 2014).

Although there is an important link between HPV infection and malignant growth of the cervix, 80%-90% of the HPV infection are short-lived, usually leading to slight cytological abnormal, and are usually difficult to detect within 1-2 years. Successful immune response accounts for the viral clearance. Despite the persistent risk of HPV in 10%-20% of women, about 2% of women suffer from cervical cancer. (American Cancer Society 2014)

At least 150 genotype-specific variants of HPV have been identified, among them 40 types will attack the skin or mucosal epithelium in genital areas. Genital HPV types can be divided into two general categories, depending on the risk of tumor-genesis. low risk HPV types include 6, 11, 42, 43, 44, 54, 61, 72 and 81. Types 6 and 11 accounts for 90%-100% genital warts (condyloma acuminatum/acuminatum) and cause slightly cervical changes, such as mild dysplasia. [10]. High-risk HPV include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82which are considered to be contributed to high-grade cervical lesions and invasive cervical cancer. Types 16 and 18 were found in 70% of cervical carcinoma cases. (Table 1-2)

Table-2 HPV types related with benign and malignant disease (ACS 2014).

Risk	HPV types	Manifestation
High Risk	Type 16 and 18	Low grade cervical lesion. High grade cervical precancerous disease.
		Cervical cancer.
		Cancer of the vagina, vulva, anus and penis
Low Risk	Type 6 and 11	Benign low grade cervical changes.

Human papilloma virus (HPV) is a small envelope-free virus, which contains 72 shells covering the double-stranded cyclic DNA genome (Gearharthart et al., 2015). There are three regions in the HPV genome:

- Encoding the early (E) genes region of cell transformation, such as E1,E2,E4,E6 and E7.
- The late (L) genes region, which encodes structural proteins L1 and L2, produces the capsid.
- long control regions (LCR)for replication and genes regulation.

HPV infection is occurring when basal epithelial cells break and the virus remains latent in the region. Although HPV virus is human specific and has not yet grown in vitro, the infectivity through skin-to-skin contact is considered to be secondary to a large number of new infections every year. Cell-mediated immunity plays an important role in virus clearance. Viral genes are activated when infected well-differentiated keratinocytes leave the basal layer.(33,).The significant difference between low-risk and high-risk HPV types is that after the establishment of the infection, normally low-risk HPV types are maintained as additional chromosomal DNA additives, while high-risk HPV genomes become unified into host cell DNA in harmful lesions. Integrating the viral genome into the genome of host cells is regarded as a sign of threatening transformation. High risk HPV produces viral protein products (E6, E7), which makes the silencing ofp53and active *p*Rb to trigger the host cell immortality. Inactivation of p53 induce cell escape from apoptosis and *p*RB activation disturb the cell cycle checkpoint(fail to programmed cell death), eventually induces chromosomal aberrations (45).

Cervical cancer is described by a very characteristic precancerous phase and can be identified by cytological examination of exfoliated cells (pap smear). Premalignant changes may indicate a series of cervical abnormalities, known as squamous intraepithelial lesions (SIL) or cervical intraepithelial neoplasia (CIN). These early injuries constitute a continuum, which can be divided into low-grade or high-grade SIL or CIN 1, 2 and 3, reflecting undeniable abnormal changes in cervical epithelial cells. CIN-1 often relapses unexpectedly, and CIN-2 and CIN-3 are bound to persist or move forward. Precancerous lesions often occur in metaplastic epithelial cells at the precancerous-columnar junction. Unfortunately, cytological and histological examinations fail to reliably distinguish a few women with cytological abnormalities, which will develop from the vast majority of women with spontaneous regression of abnormalities to invasive cancers.(ACS, 2015; Boardman & amp; Matthews, et al 2014).

The idle time frame between HPV presentation and progression of malignant cervical growth is usually estimated for years or decades. Longitudinal examinations were performed in untreated patients with carcinomas in situ (CIS)lesion, and 30-70% of them developed invasive cancers within the 10-12 years. In about 10% of patients, however, the lesions progresses from in situ to invasive in a period of less than one year(National Cancer Institute 2015). The long-term history of the disease provides an opportunity to screen for precancerous lesions in women so that does not develop into malignant cervical tumors.

Risk factors

Risk factors of cervical cancer include the following

- Sexually transmitted infection

- Reproductive and sexual factors
- Behavioral factors
- Immunosuppressive status

1) Sexually transmitted infections

(1) *Chlamydia trachomatis*infection

Koskela et al. proved that Chlamydia trachomatis infection has increased the risk of cervical squamous cell carcinoma in the past. Chlamydia trachomatis DNA was detected in 40% of invasive squamous cell carcinomas [11]. Sequel of case-control studies conducted in seven countries suggested that serum antibodies to Chlamydia *trachomatis* were associated with an increased overlap in the risk of squamous cell carcinoma. Women with higher immune response titers and women under 55 years of age have increased these hazards. C. *trachomatis* infection may increase the risk of squamous cell carcinoma by expanding the host's vulnerability to HPV infection or increasing HPV mediated effects. The exacerbation of endless Chlamydia trachomatis disease can lead to the production of acceptance of oxygen; subsequently, it can damage DNA and increase the risk of HPV-related carcinogenesis. In addition, women infected with Chlamydia *trachomatis* may have the ability to eradicate HPV disease[12]. Chlamydia can cause endless deterioration, cervical hypertrophy and squamous metaplasia. Metaplasia cells are potential target cells of HPV. In this way, due to Chlamydia disease, cell apoptosis may be inhibited, the top joint of E6/E7 oncogene may exist, and cell defects may occur.[13].

(2) Human immunodeficiency virus

Among women with human immunodeficiency virus (HIV), the risk of infection with high-risk HPV types is higher[14, 15]. Georgette Adiorlolo-Johnson 2010 and others believe that the utilizes harmful HIV testing, HPV DNA testing, histologically confirmed biopsy to support the relationship between cervical malignant growth and high-risk HPV contamination as well as equality in previous studies observed. In addition, there is a strong relationship between HIV infection and malignant growth of cervix in young women, and high-risk HPV DNA was prevalent in HIV positive women. Several members of this group had undergone cervical pap-smear and, without specific immune suppression, HIV-infected women got cervical cancer at a young age. These findings have substantially increased support for the prominent cervical disease relationship among HIV positive populations, which establishes recommendations for annual cervical cytology tests for HIV-infected people.

2) Reproductive and sexual behavior factors

(1) Multiple Sexual partners

People with multiple sexual partners had an increased risk of developing cervical cancer. This increase risk is usually attributed to increased human papilloma virus infection Castellsagu et al2003[16, 17]and Liu et al showed that multiple sexual partners being one of the risk factors of HPV infections for the development of cervical cancer. However, there is no exact number of sexual partners being independent risk for cervical cancer[11].In Edelstein's et al survey, it was suggested that the sexual experience with a older age was associated with a lower age of diagnosis but in early age at onset of sexual relationship is high risk factor for cervical

cancer[18].

(2) Parity

Some studies have shown that full-term pregnancy increases the risk of invasive cervical cancer [19-21]. In addition, high parity increases the malignant risk of women [21]. In the global co-epidemiological survey of cervical malignant tumors, it was found that there was a direct relationship between the risk of cervical diseases and parity, and there was a reverse relationship between the risk of cervical malignant tumors and the age of the women's first pregnancy [22]. Hildesheim et al. inferred that the risk of cervical diseases increases with the increase of the number of births [19]. Delivery is an indicator of CIN 3 in a partnership that has considered development for more than 13 years. In the survey, delivery was also considered to be a risk of cervical malignant growth, especially in women at high risk of HPV. Similarly, no increased risk associated with pregnancy was observed[23].

(3) Oral contraceptive pills.

Current and continuous use of combined oral contraceptives (COC) is associated with increased risk of cervical malignancies [24]. According to the International Collaborative Epidemiological Survey of Cervical Cancer, with the prolongation of oral contraceptives use time, the relative hazards of existing current user increase.[25].Women who used oral contraceptives for five years or more had a higher risk of cervical cancer than women who had never used oral contraceptives. One study found that the risk of using COC less than five years increased by 10% the risk of using OCP (5 – 9) years increased by 60%, and leads to be double risk after consumption of OCP more than 10 years.

However, when women stopped using oral contraceptives, the risk of cervical cancer decreased over time[25-27].

3) Others

(1) Smoking

According to the (Jian-Hong Fang ,Xue- Mei Yui)high-risk HPV positive women who smokes long terms more than 8 years with 18/cigarrate per day are highly susceptible to the increased risk for CIN3 or CIN+. In cases with persistent HPV-infected women, heavy smoking led to a higher risk for CIN3+than those who have never smoked. These findings suggest that smoking increases the risk of high cervical lesions in women with persistent high-risk HPV infection. Among women infected with HPV, current and previous smokers suffer from two to three high squamous intraepithelial lesions (HSIL) or invasive malignant tumors. Latent smoking is also associated with hazards, but to a lesser extent [28]. Synthetic substances in cigarettes, such as nicotine and its metabolites, can cause DNA damage to squamous cells [29].

(2) Obesity

Overweight increases the risk of cervical cancer, and the frequency of hormone-related cervical adenocarcinoma is essential. The results of some case–control and cohort studies showed association between

cervical cancer and obesity as estimated to be 1.40 (95% CI: 1.08, 1.71) and 1.08 (95% CI: 0.60, 1.52), respectively.

Nevertheless, more evidence, based on large prospective cohort studies, is needed to provide convincing findings on whether or not BMI is related with an increased risk of cervical cancer[30].

4) Immunosuppressive women

Immunosuppressive women are at higher risk with cervical cancer compare to immune-comprise women. There is increased prevalence and persistence of HPV infection in immune compromised patients, such as HIV positive, AIDS or post-transplantation women. The immune system plays an important role in destroying cancer cells and slowing down their growth and spread. (ACS 2014). According to Dugue' et all 2015 studies shows that women infected with the immune system using immunosuppressive agents (such as azathioprine) do not seem to increase their susceptibility to cervical disease[31].

Clinical features

Early cervical cancer has been observed to show no harmful symptoms. But more advanced cervical cancer showed various symptoms (Rogers, Siu, Luesley, Bryant, & Dickinson, 2016). These symptoms include vaginal bleeding after intercourse, foul smells of blood and vaginal secretions, postmenopausal bleeding and pelvic pain after intercourse. Symptoms of cervical cancer play an important role in the diagnosis of cervical cancer.

Sign & Symptoms

Symptoms and signs play an important role in determining the stage of cervical cancer. Early stages of cervical cancer have been observed to include abnormal vaginal bleeding and unpleasant odors. The vaginal irregular hemorrhage for example "IMB" (Intermenstrual Bleeding)" and "PCB"(Post Coital Bleeding) is as well the general sign, but in females less than twenty years old, the probabilities of having the cervical cancer while having the Post Coital Bleeding not as much of that of female above the thirty-five years of age. The pain over the part of the cervical might be experienced while the "Sexual Interaction". At the higher phase of the cervical cancer there is huge failure of "hunger", "loss in weight", "pain in pelvic", "pains in back" and "Pains in legs".

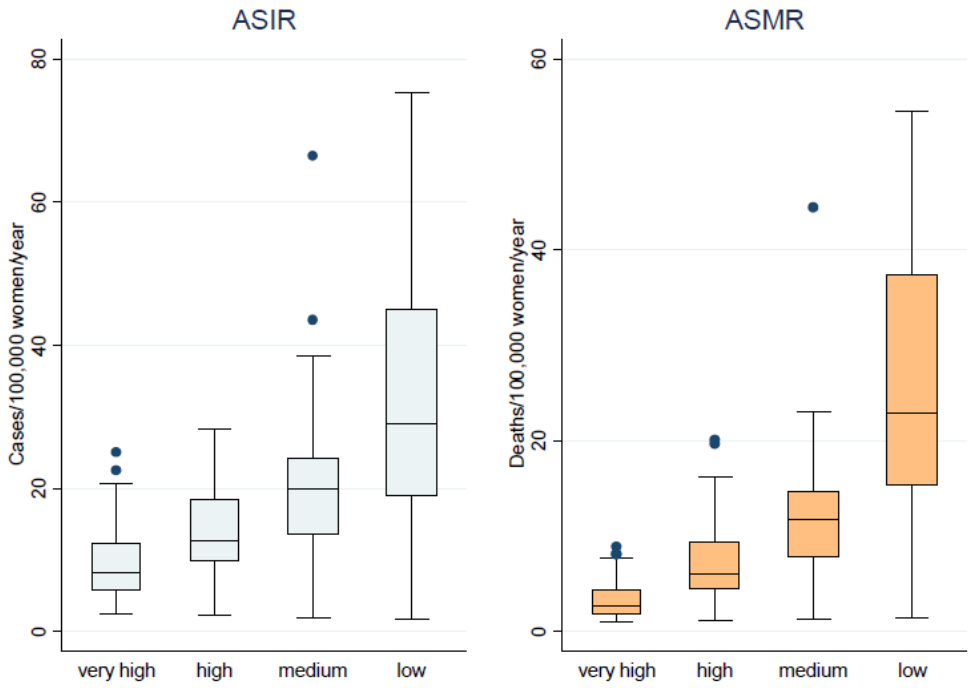

Figure 4. Distribution of the world age-standardised incidence (ASIR, left) and mortality rate (ASMR, right) by category of socio-economic development (expressed by the human development index).

Clinical staging of cervical cancer

The stage of cervical cancer determines its severity; the extent of cancer transmission needs to be recognized. Cancer spreads from the surface of the cervix to deep tissue or other parts of the body leading to very serious disease, which is called "invasive cervical cancer". Women diagnosed with invasive cervical cancer have a survival rate of 70% in about five years. Many women with invasive cervical cancer survive even after five years of diagnosis. Cervical cancer is found to grow very slowly, but in some special cases it can spread quickly. Once a patient is diagnosed with precancerous lesions, she might develop into invasive cervical cancer within 10 to 15 years. [32]. Progress in cervical cancer has been observed at different stages. The different stages of cervical cancer include: stage IA1, IA2, IB, IIA, IB1, IIA1, IB2, IIA2, IIB, III, IVA and IVB.

Table-3 FIGO staging of cancer of the cervix uteri 2018 [33]

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension

IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrical involvement but not up to the pelvic wall

Table-3 (Continued)

Stage	Description
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or Para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or Para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)
III1	Pelvic lymph node metastasis only
III2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

Source: Bhatia et al.

Histopathology

According to 2014 WHO female reproductive organ pathology, the histopathological types of cervical cancer are listed as following:

- Squamous cell carcinoma
- Adenocarcinoma
- Clear cell adenocarcinoma
- Serous carcinoma
- Squamous carcinoma
- Glassy cell carcinoma
- Adenoid cystic carcinoma
- Adenoid basal carcinoma
- Small cell carcinoma
- Undifferentiated carcinoma

Reviewing by few technique is energetic, but this is only the reason for adjusting the staging of cervical cancer. Histopathological grade were as follows: 1. GX: Unable to assess grade 2. G1: well differentiated 3. G2: moderately differentiated 4. G3: Poorly or un differentiated [32].

Two major types of cervical malignancies have been recognized. The most widely recognized cervical cancer is squamous cell carcinoma (SCC), accounting for 80-90% of cervical cancer. SCC is present in squamous cells that spread from the external cervix, and HPV 16 is the most common type associated with SCC [34]. Adenocarcinoma is the second most common malignant growth type of cervix, representing 10-12% of cervical diseases. It often appears from columnar epithelium, a mucous glandular cell aggregation, located in the cervical endometrium and associated with HPV 18, lagging behind HPV 16 [34]. In the past 20 - 30 years, people have seen the expansion in the occurrence of adeno-carcinogenesis. In rare cases, cervical diseases highlights in SCC and adenocarcinoma, which are known as adeno-squamous or mixed cancers (ACS 2014).

Treatment of cervical cancer

Surgical treatment of cervical cancer

Surgery is suitable for the early stage cervical disease. Conization, radical hysterectomy or absolutely simple hysterectomy can be selected according to the stage of disease and the extent of cervical cancer spread.

1)Treatment of Micro invasive cervical carcinoma (FIGO Stage IA)

(1) For Stage IA1

Conization of the cervix is performed unless lymphatic vessel space invasion (LVSI) or tumor cells can be obtained at a careful margin. Complete extra fascial hysterectomy [35]can also be recommended for women who have completed childbirth or older age. Any course of disease, such as stomach, vagina or laparoscopy, can be selected. When LVSI is obvious, pelvic lymphadenectomy should be considered and radical hysterectomy should be adjusted [36, 37]. If pregnancy is required, cervical conization with close follow-up will be satisfactory.

(2) For Stage IA2

Because there is a slight risk of lymph node metastasis in these cases [37-40], pelvic lymphadenectomy is performed despite radical hysterectomy of type B or progressive radical hysterectomy [41, 42]. Under generally safe conditions, basic hysterectomy or tracheotomy, pelvic lymphadenectomy or sentinel lymph node center assessment may be satisfactory surgical treatment. When a patient wants to be pregnant, she may be given a decision: (1) cervical conization and laparoscopic (or extra peritoneal) pelvic lymphadenectomy; or (2) radical hysterectomy, vaginal or laparoscopic tracheotomy and pelvic lymphadenectomy [43, 44].

(3) Follows up.

In time for 3 months to 2 years of cervical smear examination, in the next 3 years from 6 months to months, it is recommended that after the treatment of minimally invasive cancer follow up is required. After five years of general follow-up, patients can return to the standard screening plan in accordance with the national guidelines[35]**.**

2) Surgical treatment for invasive cervical carcinoma (FIGO Stage IB1, IB2, and IIA1)

Surgical treatment is a useful method for the treatment of stage IB1, IB2 and IIA1 injuries. It usually includes radical hysterectomy of type C and pelvic lymphadenectomy [45-47]. Surgical procedures may be open or negligible, such as laparoscopy or robotics compared with traditional laparotomy.

(1) For FIGO Stage IB1

FIGO stage IB1 is generally considered safe, with criteria of maximum tumor width less than 2 cm, cervical stromal seizures less than half, and no suspicious lymphatic concentration on imaging. The standard protocol is radical hysterectomy of type C, but in these cases adjustable radical hysterectomy may be considered. Because of the high recurrence of lymph node involvement, pelvic lymphadenectomy should be reliably included in [41, 42].

For patients undergoing radical hysterectomy, pelvic nerve preservation is recommended because the fundamental fixation remains unchanged, because pelvic wounds of autonomic nerves (such as inferior gastric nerve, visceral nerve and pelvic plexus) often result in obstruction of urination and sexual ability, and subsequent disintegration of quality of life (QOL)[48, 49]**.**

For young women who want to retain their fertility, radical trachelectomy can be performed, proving that the IA2-IB1 stage tumor estimates are incomplete or equivalent to a maximum diameter of 2 cm [50]. The cervix next to the parametrium is evacuated by anastomosis between the uterus and the end of the vagina. Trachelectomy should be performed through an open stomach, vagina or through a minimal protrusion course. When arranging the vaginal method, the pelvic nodes is first discharged by laparoscopic surgery and sent to the coagulation section to confirm the cynicism of the junction, and then continues to undergo radical vaginal resection. On the other hand, nodes may first be investigated by routine pathological strategies, and radical resection is performed as a second medical procedure after a week.

(2) For FIGO Stage IB2 and IIA1

Surgery or radiotherapy can be chosen as a basic treatment for cervical diseases in FIGO stage IB2 and IIA1, depending on other patient variables and neighboring assets, because they have comparable outcomes. The advantages of surgical treatment are: (1) it is reasonable to determine exactly the stage of operation according to histopathological findings, thus giving each patient individualized treatment after operation; (2) it is possible to imagine the treatment of diseases that may not be treated by radiotherapy; (3) it is possible to imagine maintaining ovarian capacity. The same can be achieved in the radiation field by-pass drainage tube in the high ovary intra operative reverse positioning, and should be required. Protecting ovaries and sexuality makes medical procedures a favorite model for younger women. Type C radical hysterectomy involves basic techniques for the treatment of cervical malignancies, including uterus, parametrium, upper vaginal and paracolpium emptying, and pelvic lymphadenectomy. For adjacent connective tissue, the most important bladder tendons (anterior and posterior), horizontal major tendons, and dorsal sacral and rectovaginal ligaments are cut from the uterus and fully separated from their attachment to the uterus. Lymphadenectomy establishes one of the bases of this procedure, and the extent of local lymphadenectomy includes parametrial nodes, obturator node, external, internal and normal iliac nodes.

The mapping of sentinel lymph nodes (SLN) in cervical diseases has not yet been tested, and more evidence is needed to incorporate SLN into the agenda practice. It may play some roles in the malignant growth of cervix at the beginning time, such as FIGO IA stage, IB1 and IB2 [51-53]. The accuracy of sentinel lymph nodes can

be expanded by double labeling with blue and radio colloids [54, 55]. Indocyanine green with near infrared procedure has been used in mechanical medical procedures and laparoscopy. If LVSI is available, pelvic lymphadenectomy should be considered. The repetition rate of hysterectomy and early cervical cancer growth patients through negligible protrusion process was higher than that of open method [56].

(3) FOR FIGO Stage IB3 and IIA2

In stage IB3 and IIA2, tumors are larger and have high risk factors, such as positive lymph nodes, positive paramtria or positive margins, which increase the risk of repetition and require adjuvant radiation after medical procedures. Other risk factors have increased the risk of pelvic duplication, although excluding nodes, including tumor distances maximizing 4 cm, LVSI and external 33% cervical matrix seizures[57, 58]. In this case, adjuvant whole pelvic irradiation can reduce the rate of neighborhood disappointment, and improve the free survival rate and patients treated with medical surgery alone [58]. However, dual therapy increases the risk of severe atrophy.

Therapeutic approaches must then be based on the availability of assets and cancer and patient-related components. At the same time, concurrent platinum-based chemo radiation (CCRT) is the preferred treatment option for IB3-IIA2 injury. Since post-operative adjuvant therapy generally involves overall survival, progression free survival, adjacent and unacceptable recurrence [45, 59, 60], visualization is becoming more and more active for CCRT rather than radiotherapy alone.

In areas where radiotherapy offices are rare, neoadjuvant chemotherapy (NACT) is used to: (1) reduce the ranking of tumors to improve the extreme therapeutic effectiveness and well-being of medical procedures; (2) inhibit micro metastasis and inaccessible metastasis. There is no consensus on whether it improves predictive contrast and standard treatment[61, 62].

Medical procedures after NACT continue as described earlier, such as radical hysterectomy and pelvic lymphadenectomy. The more common problem is to determine the signs of adjuvant therapy, which are often comparable to those of basic surgery[59, 60]. However, it must be remembered that NACT may mistakenly assume that everything is related to the world. Cover pathological findings and influence the assessment of adjuvant radiotherapy/CCRT symptoms in this way. NACT surgery is best preserved in research environments or in areas where radiotherapy is not available. This is especially effective for patients with very low tumors or adenocarcinomas, who have a low response rate [63].

Robotic radical hysterectomy

Innovations in robotics encourage the use of negligible, prominent procedures to treat and evaluate patients with timely, progressive and repetitive cervical cancer (Ramirez et al., 2010). Compared with conventional laparoscopic instruments, the use of automated frameworks in preset research facility exercises is associated with faster execution time, higher accuracy, better adaptability, faster stitching and fewer errors. Complex activities, such as radical hysterectomy, as explained by Nick et al. 2012, tend to develop this method in an increasingly efficient way, which can lead to difficulties in obtaining a larger number of laparotomy specialists

in a shorter period of time in traditional laparoscopic examinations.

Chemotherapy and radiation therapy

In the United States, nearly 4,000 of the 13,000 women with cervical cancer die each year. Different treatments for cervical cancer have been designed. First, chemotherapy is recommended for the treatment of cervical cancer. However, if chemotherapy alone does not show any positive measures, the combination of chemotherapy and radiotherapy is recommended for the treatment of cervical cancer, especially invasive cervical cancer [64]. First, chemotherapy and radiotherapy for invasive cervical cancer were used for treatment of cervical cancer[65]. After radiotherapy combined with chemotherapy, almost 70% of patients with invasive cervical cancer were found to be cured. However, many patients with cervical cancer find cervical cancer again after appropriate treatment.

However, in some cases, surgical treatment is also recommended to treat cervical cancer correctly. Radical hysterectomy is used for early treatment of women with cervical cancer. Radical hysterectomy is usually performed under laparoscopy to achieve better results. In order to determine the importance of laparoscopic radical hysterectomy, many studies have been carried out [66]. In one such study, 26 patients with early cervical cancer were randomly selected and divided into two groups: one group received radical hysterectomy and the other group received chemotherapy. Studies have shown that 85% of patients receiving radical hysterectomy show a rapid recovery, while 56% of patients receiving chemotherapy have a better recovery. According to observation, the patient has undergone radical hysterectomy and often suffers from post-operative pain. Analgesics are prescribed for this purpose [67]. However, even after analgesics, 30% of patients do not feel relaxed. Removal of the discharge tube often leads to difficulty in recovery. Therefore, the conclusion drawn from this study is that radical hysterectomy is considered to be a better recommended treatment for early cervical cancer than chemotherapy. Therefore, laparoscopic radical hysterectomy has proved to be a more effective treatment for early cervical cancer [68]. The combination of chemotherapy and surgery (radical hysterectomy) has proved to be an effective treatment for invasive cervical cancer. IB and IIB invasive cancers are thought to be treated with this combination therapy. 349 cases of IB and IIB cervical cancer were randomly selected[69]. However, the patient's lymph nodes (combined chemotherapy and radical hysterectomy) were also removed.

Prevention of cervical cancer

Primary prevention (HPV VLP vaccine)

Human papilloma virus (HPV) virus-like particles (VLP) vaccine was introduced as the primary prevention for eradicating the cervical cancer. The vaccine is designed to fight HPV 16 and HPV 18. Vaccines contain only microbial "capsid proteins" and no "nucleic acid" microorganisms, so no virus imitation take place. There are three types of HPV vaccine.

The first "cervarix®" vaccine with viral type is used as an element of HPV 16 and 18. Both vaccines stimulate the immune system response and promote neutralizing antibodies. They are safer, more tolerable, and

may stop at least 70% of all persistent "cervical cancer" incidents because 70% of "cervical cancer" is impure to HPV 16 and 18.

The second is the "Gardasil®" with viruses, such as those from human papilloma virus types 6 and 11, which produce low-risk species of "Kondyloma" and human papilloma virus 16 and 18.

The third “Gardasil®9,” vaccine with viral types is used as an element of HPV types 31, 33, 45, 52, and 58 in addition to HPV 6, 11, 16, and 18. It protects against pre-cancer and cancer of cervix, vulva, and vagina; anal pre-cancer and genital warts. (National Cancer Institute 2018)

The last two vaccines target anogenital warts caused by HPV 6 and 11 in addition to the above-mentioned malignant and premalignant lesions. All the vaccines are recombinant vaccines composed of virus-like particles (VLPs) and are not infectious since they do not contain viral DNA. For girls and boys aged 9–14 years, a two-dose schedule (0.5 mL at 0 and 5–13 months) is recommended. If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose is recommended. For those aged 15 years and above, and for immune compromised patients irrespective of age, the recommendation is for three doses (0.5 mL at 0, 1, 6 months). (World Health Organization)

Secondary prevention: cervical cancer screening

Cervical cancer was once considered the leading cause of cancer in the United States. Until 1955-1992, the rate declined by 70% due to Pap smear screening and community-based understanding. It is said that the annual decrease is 3%, but the amount remains at a high level[70]. According to the latest estimates of the American cancer community, nearly 12,710 recent incident of insidious cancer will be detected in 2011, of these almost 4,290 mortalities would be estimated. (American Cancer Association 2010).

Secondary prevention of cervical cancer is routine screening by using cytological testing and HPV testing. The function of cervical screening is to expose, observe and heal precancerous lesions. Planned screening courses aimed at identifying "cervical dysplasia" to stop cervical cancer have proven to reduce cancer incidence. According to Albrow, Kitchener, Gupta and Desai (2012), the planned screening process will also enhance early detection of cervical cancer and reduce the number of women, thus making diagnosis at a higher stage of infection, thereby reducing problematic cure and good endurance rates. Traditionally, cervical screening is actually carried out by observe the abnormal exfoliative cells(pap smear)invented by a pathologist named Papanicolau Nicolas,.. Recently, cytological testing has changed to liquid-based . Nowadays, human papilloma virus detection is essentially a screening course as a classification method for (ASCUS) and (CIN 1), as well as an evaluation of treatment after (CIN2-3/CIS), (AIS) and (CARG).

Shastri et al. (2013) were screened according to "visual examination". The investigator makes use of the “Acetic Acid” on the “Cervix” and if the areas of the acetic turn into white then the test is +ve (Positive).

Cervical cancer is more easily avoided by screening, especially for women having pre-cancerous cervical lesion "asymptomatic" that can be quickly and successfully cured before diagnosis. With the improvement of screening methods, the mortality rate of cervical cancer in developed countries has decreased. But in developing

countries there is lack of these resources. But there are still almost 2,70,000 estimated death, of which 85% are from developing nations and the increased mortality is identified due to the lack of high-quality screening of precancerous lesion and treatment resources which are also deprived of good infrastructure.

When cervical cancers diagnosed and cured at the initial stage, almost 80% of patients diagnosed at the initial stage receive appropriate treatment. In developing countries, cervical cancer is mainly detected in the extremely delayed stage, because they do not have good screening and treatment technologies, in contrast to developed countries, which are incessantly able to diagnose and cure cervical cancer at its initial stage, usually in the precancerous stage. Several treatments used for the precancerous lesions, include cryotherapy, which involves the use of less fever, which can destroy irregular tissues. This technology does not require electricity, making it a cheap and affordable technology that can be used by low-income countries. "LEEP" (Loop electrosurgical excision process) is another approach, including the use of lean cables to remove affected areas. Although slightly costlier than cryotherapy, “LEEP” improves performance because it allows tissue removal for "biopsy" to allow additional examinations and reduce the tendency of advanced cervical cancer[70].

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