eISSN (Online): 2598-0580

Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Epidemiology and Risk Factors for Cervical Cancer

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ARTICLE INFO

Keywords:
Cervical Cancer
Risk
Epidemiology

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.32539/bsm.v5i7.326

ABSTRACT

Cervical cancer in Indonesia in 2018 ranks second in cancer in women in Indonesia with an incidence rate of 348.809 cases with a mortality rate of nearly 60% of the incidence, namely 207.210 deaths. Deaths from cervical cancer are projected to continue to increase and are estimated to reach 12 million deaths by 2030 if not treated properly. The incidence of cervical cancer in Indonesia is estimated to have 180.000 new cases per year and the death rate is thought to reach 75% in the first year. This death is mainly associated with the majority of newly diagnosed patients who are already at an advanced stage (70% of cases) and are already at the terminal stage at the time of diagnosis.

1. Introduction

The latest data on the global cancer burden released by the International Agency for Research on Cancer (IARC) in Geneva on 12 September 2018 estimates an increase in new cancer cases of 18.1 million cases with a death rate of 9.6 million deaths from cancer.[1] Cancer cervix is still a major problem and burden in the world. It is estimated that in the world every 2 minutes one woman dies from cervical cancer[2], Cervical cancer ranks fourth most common cancer in women in terms of incidence (527.600 new cases) with a mortality rate of more than half its incidence (265.700 deaths) worldwide, after breast cancer and colorectal. This cancer ranks third as a cause of cancer death in women in developing countries. Nearly 90% of deaths due to cervical cancer occur in economically weak populations, where access to early detection and prevention of cervical cancer is very limited, [1,3].

Cervical cancer in Indonesia in 2018 ranks second in cancer in women in Indonesia with an incidence of 348.809 cases with a mortality rate of nearly 60% of the incidence, namely 207.210 deaths[4]. Deaths from cervical cancer are projected to continue to increase and is estimated to reach 12 million deaths by 2030 if not handled properly. The incidence of cervical cancer in Indonesia is estimated to have 180.000 new cases per year and the death rate is thought to reach 75% in the first year. This death is mainly associated with the

majority of newly diagnosed patients who are already at an advanced stage (70% of cases) and are already at the terminal stage at the time of diagnosis[5]. The mortality rate from cervical cancer remains high in low and middle income countries (LMICs = low-middle income country) due to low human resources, difficulties in implementing and sustaining early detection / routine screening programs, accurate diagnosis, and early treatment of cervical precancerous lesions, poverty, and lack of infrastructure [6,7]. The high incidence of cervical cancer in developing countries is due to the ineffectiveness of a comprehensive population-based early detection of cervical precancerous lesions, in addition to low awareness, level of education and public knowledge about the occurrence of this cancer.[8-15]

It takes several years for cervical epithelial changes to progress from the precancerous stage to invasive cancer. Therefore, there is an adequate time period for early detection / screening, and management of this precancerous stage. The Papanicolaou smear test has effectively reduced the incidence and mortality of cervical cancer in countries with good screening programs.[11] But in developing countries, such screening programs have not been able to be implemented due to limited resources of experts, laboratory infrastructure and funds[12] WHO with its global strategy in order to eliminate cervical cancer incidence and mortality rates, especially in low-resource developing countries, recommends a national cervical cancer prevention program with early detection of precancerous lesions "screen and treat" through IVA examinations. Every woman who has had mass sexual intercourse and one visit if she finds a positive IVA test, she will immediately perform ablation of the lesion using cryotherapy. This program has a risk of being overdiagnosed and overtreatment because the IVA examination has limited accuracy, especially when performed by paramedics such as midwives and nurses[16-19]. Several meta-analysis studies found IVA sensitivity rates ranging from 49-98% and specificity rates of 75-91%.[13] Evaluation and interpretation of IVA examination results has high interobserver variability, which is a major obstacle during clinical practice. In the study by Jeronimo et al., Finding that colposcopists had an agreed diagnosis of only 56.8% [14].

Subjectivity in image evaluation can be overcome through automated digital image analysis. Automated systems have the potential to allow less experienced doctors, technicians, and other healthcare providers to provide evaluations that are on par with experts. The servicogram images obtained during the IVA procedure can also be used for quality control, and the clinician can seek expert opinion by sending the images to a specialist doctor who is far away (telemedicine). These images can be archived for reference and future research[15].

To improve the accuracy of the IVA examination, researchers are trying to develop computer-assisted technology to make an accurate diagnosis, one of which is by automating the resulting digital images (servicograms) of the IVA examination to be analyzed through certain algorithms, so that they can help doctors make a more accurate diagnosis. This technology has the advantageous potential for early detection of cervical cancer in IVA examinations for developing countries that have difficulty in resources, especially expert doctors, namely in terms of speed of examination results, anyone can do it even by non-medical personnel because it can be done with a cell phone. and image data can be stored and can do telemedicine for consultation with experts, although currently development is still being done to improve its performance[18-20].

However, in order for cervicalography in conjunction with computer-assisted interpretation to be useful in clinical practice, it is important to further develop a methodology that achieves a specificity above 90% and the highest sensitivity possible. In addition, having several other examinations of the patient during the screening visit helps improve the accuracy of the screening. So it would be useful to develop methods that can integrate the multi-modality information from these tests to achieve high sensitivity and specificity in the classification of cervical diseases[16].

One other strategy to improve IVA testing is to combine it with HPV DNA biomolecular examination which has the best sensitivity and specificity compared

to other screening methods. Recent examination of p16 can also explain the progression of the disease progression of HPV infection so that more rational therapy decisions can be made for patients to prevent cervical cancer in the future. Patient risk factors are also considered to increase accuracy such as history of early first sexual contact, smoking, long-term use of oral contraceptives, history of genital infections, high parity and number of sexual partners[17–19].

Cervical cancer epidemiology and risk factors

Cervical cancer is the fourth most common cancer among women worldwide, with an estimated incidence of 570.000 cases and 311.000 deaths, reported in 2018.[17] It is estimated that around 85% of deaths worldwide from cervical cancer occur in low and middle income countries[18–20], in where the death rate is 18 times higher than in developed countries. It is known that the cause of cervical cancer is the oncogenic subtype of the HPV (Human Papilloma Virus) virus, especially subtypes 16 and 18 [21]. The risk factors for cervical cancer include [22]: sexual activity at a young age, having sex with multi-partners, smoking, having many children, low socioeconomic status, use of birth control pills (with negative or positive HPV), sexually transmitted diseases, and immune disorders [23,24].

According to the IARC Globocan 2018 report, cervical cancer in Indonesia in 2018 ranks second to cancer in women after breast cancer with an incidence of 348.809 cases with a mortality rate of nearly 60% of the incidence of 207.210 deaths.4 Deaths from cervical cancer are projected to continue. increase and is estimated to reach 12 million deaths by 2030 if not handled properly. The incidence of cervical cancer in Indonesia is estimated to have 180.000 new cases per year and the death rate is thought to reach 75% in the first year. This death is mainly associated with the majority of newly diagnosed patients who are already at an advanced stage (70% of cases) and even at the terminal stage at the time of diagnosis. The average incidence of cervical cancer in Indonesia is 23.4% with a mortality rate of 13.9%, as shown in Figure 2.1.[3.4] The mortality rate from cervical cancer remains high in low and middle income countries (LMICs = low-middle income country) due to low human resources, difficulties in implementing and sustaining early detection/routine screening programs, accurate diagnosis, and early treatment of cervical precancerous lesions, poverty, and lack of infrastructure[6,7]. The high incidence of cervical cancer in developing countries is due to the inoperability of a comprehensive population-based pre-cervical cancer lesion detection system, in addition to low awareness, education and public knowledge about the occurrence of this cancer even though this disease can be prevented and can be cured if the patient comes at the time. precancerous lesions or at an early stage[8–10].

Epidemiological studies show that the risk of contracting genital HPV infection and cervical cancer is influenced by various factors. Cervical cancer relies on a variety of additional factors that act alongside the cancer-related HPV strains[17].

Cervical cancer risk factors

Sexual factors

A number of studies clearly show that the risk of contracting genital HPV infection and cervical cancer is influenced by sexual activity. An individual has a greater risk of being infected with HPV if he has multiple sexual partners or is a partner who has had multiple sexual partners. Sexual activity at an early age also increases the risk of HPV infection, as can a history of other sexually transmitted diseases, genital warts, abnormal Pap smears or penile cancer in individuals or sexual partners. Use of condoms may not adequately protect individuals from exposure to HPV because the virus can be transmitted by contact with infected tissue that is not protected by condoms.[17]

All women who are sexually active have a risk of developing cervical cancer or the early stages of the disease regardless of age or lifestyle.[12] In accordance with the etiology of the infection, women who initiate sexual intercourse at a young age are at increased risk of developing cervical cancer because cervical columnar cells are more sensitive Against metaplasia, women who have sex before the age of 18 will have a five-fold

higher risk of developing cervical cancer.[12]

Generally, new mucosal cells mature after a woman is 20 years old and over.[12] At the age of under 16 years, cervical mucosal cells are still immature and susceptible to stimulation, including chemicals that are under sperm.[12] Because they are still susceptible, mucosal cells can change their nature to become cancer.[12] The nature of cancer cells is always changing all the time, namely dying and growing again[12]

With stimulation, more cells can grow than dead cells, so that the changes are no longer balanced.[12] This is different if sex is carried out in women over 20 years of age, where mucosal cells are no longer too susceptible to change.[12]

Apart from sexual activity, age is a determinant of the risk of HPV infection. Most cervical cancers are seen at the squamocolumnar junction between the endocervical columnar epithelium and the ectocervical squamous epithelium. In this area, there are continuous changes in metaplasia and this activity is the biggest risk of HPV infection, especially during puberty and first pregnancy but decreases after menopause. The prevalence of HPV peaks in young adults (ages 18 to 30 years) and decreases in older ages. As many as 46% of women in college may have HPV infection of the genital tract. However, cervical cancer is more common in women over 35 years of age[17]

Sexual partners more than one or sexual partners are at high risk.[13] Changing sexual partners, the possibility of contracting venereal diseases increases, one of which is HPV.[10] The risk of cervical cancer increases 10 times in women with sexual relations of 6 people or more than women who have 1 sexual partners.[10]

Virus factors

Persistent cervical infection (often defined as an infection detected more than once in an interval of 6 months or longer) with oncogenic HPV types (especially HPV-16 and HPV-18) is the most important risk factor for progression to high-grade dysplasis and invasive cancer. The risk of developing cancer depends on the type of HPV. A 4-6 year return control in 1643 women with normal cytology showed that women with a high-risk HPV DNA test on PCR were 116 times more likely to develop CIN 3 than women with a negative DNA test. About 40% of the risk of developing HPV-16 and HPV-18 is greater than that of other types of HPV. [17]

Viral load directly correlates with disease severity. Studies using quantitative type-specific PCR for high-risk HPV and low-risk HPV show that HPV-16 viral load has a high correlation with increased cervical disease severity. Another study using Hybrid Capture II TM showed increased viral load in HPV strains at high risk of highgrade lesions. However, high-risk HPV is capable of inducing malignant tumors even when at low levels.[17]

An important factor that emerges in the development of cervical neoplasia is the role of HPV variation. The HPV variations differ in their biological, chemical and pathogenicity properties. The oncogenicity of specific HPV variants appears to vary geographically as well as with the ethnic origin of the population studied. Based on the L1, L2, and URR regional sequence variations of the HPV-16, five variants have been defined for the HPV-16: Europe (E), Asia (US), Asia-America (AA), Africa-1 (Af1) and Africa-2 (Af2). The Asian-American variant may have increased oncogenic activity compared to European isolates due to increased transcription activity.[17]

Several studies have shown that infection with various types of HPV can occur. Most of the several infections contained two strains of HPV, but samples with two, three, four, or five strains were also seen. The presence of several types of HPV tends to increase with the severity of cervical disease. Several types of HPV, usually with at least one type classified as high risk, were found in 12% of patients with normal cytology and in 35% of patients with mild or moderate dysplasia.[17]

Non-viral factors

The primary immune response to HPV infection is cell mediated so conditions that impair cellular immunity such as kidney transplantation or HIV disease increase the risk of acquiring and developing HPV. The URR HPV region contains a similar sequence

to steroid hormone-induced glucocorticoid responsiveness such as progesterone (the active component of oral contraceptives). Long-term use of oral contraceptives is a significant risk factor for high-grade cervical disease according to several studies. Cervical cancer risk also appears to be influenced independently by other variables including current smoking history and parity. Localized immune suppression of the immune system induced by smoking and the mutagenic activity of cigarette components have been demonstrated in cervical cells, and may contribute to HPV persistence or malignant transformations similar to those seen in the lungs. It appears that smoking is an important independent risk factor for HPV infection for higher rates of cervical disease. Multiple pregnancies were a significant independent risk factor among women with histopathologic evidence of HPV infection at the biopsy speciem and among women with CIN 2/3. other factors such as alcohol consumption and diet have not been established[17,21.]

There is some opinion that sexually transmitted viruses may function as a cofactor in the development of cervical cancer. It has been suggested that co-infection with the herpes simplex virus type 2 can play a role in the initiation of cervical cancer. Cytomegalovirus (CMV), herpes viruses (HHV-6 and HHV-7) have also been detected in the cervix. Coinfection offers an opportunity for the virus to interact with HPV. Recent studies using PCR to detect CMV, HHV-6, and HHV-7 in women with abnormal cytologic test results suggest that these viruses are only an observer and not a cofactor in the development of cervical cancer. Chlamydia trachomatis infection has been linked to cervical cancer, but the meaning of this association is unclear. Some authors suggest that the association between C. trachomatis infection and cervical cancer may be due to the effect of Chlamydia infection on the persistence of high-risk HPV.[17]

Genetic predisposition was found to be a major component of cervical cancer. Genetic heritability was found to influence 27% of the factors underlying tumor development. Heredity can affect many factors that contribute to the development of cervical cancer, including susceptibility to HPV infection, ability to clear HPV infection, and time to disease progression. The effect of the family environment is proven to be 2% and is only found between sisters and not between mothers and daughters

Other risk factors

Cervical cancer risk factors include: [15]

a. High parity increases the risk of cervical cancer in women

   Based on research, parity is a risk factor for cervical cancer with a 4.55 times greater risk of developing cervical cancer in women with parity > 3 compared to parity women [3.10]

b. Consumption of oral contraceptives, the longer the duration of use, the more it increases the risk of cervical cancer.[14]

   Women who have used oral contraceptives for 5 years or more have a greater risk of developing cervical cancer than women who have never used oral contraceptives.[10] Use of hormonal contraceptives for more than 4 or 5 years can increase the risk of developing cervical cancer 1.5 - 2.5 times [10]

   Several studies have shown that oral contraceptives cause women to be sensitive to HPV which can cause inflammation of the genitalia so that they are at risk for cervical cancer.[10] However, the effects of using oral contraceptives are controversial because there are several studies that have failed to find an increased risk in female users or former users oral contraceptives.[10]

c. Immunocompremised patients such as those receiving organ transplants and Human Immunodeficiency Viruses (HIV).[5]

   The immune system plays an important role in the process of destroying cancer cells and inhibiting their growth and spread.[10] The HIV virus in AIDS sufferers will damage a person's immune function so that women with AIDS have a high risk of contracting HPV infection which develops into cancer cells.[10]

In AIDS women, the development of precancerous cells into cancer, which usually takes several years, can occur more rapidly due to immunosuppression.10 This condition can also be found in women who take immune-lowering drugs such as those with autoimmune diseases or women who are undergoing a transplant. body organs.[10]

d. A history of sexually transmitted infections, Chlamydia trachomatis infection is associated with an increased risk of squamous cell cervical cancer whereas Herpes Simplex Virus infection is associated with invasive cervical cancer.

e. Smoking. [5]

Smoking is a major risk factor for precancerous lesions and cervical cancer, women who stop smoking for 10 years will reduce the risk of cancer by 50%.[5] Tobacco contains carcinogens either smoked as cigarettes / cigarettes or chewed.[12]

In women who smoke, the concentration of nicotine in cervical sap is 56 times higher than in serum.12 Nicotine in cigarettes makes it easier for all mucous membranes including mucous cells in the uterus to become aroused.12 This excessive stimulation will trigger cancer.12 Cigarette smoke produces polycyclic aromatic hydrocarbons This heterocyclic nitrosamines has the effect of lowering local immune status so that it can become a co-carcinogen for viral infections.[12]

f. Women who are overweight or obese are at twice the risk of cervical adenocarcinoma than women of normal weight.

g. Nutrition, healthy and nutritionally balanced food will increase antioxidants which are useful for preventing the neoplasia process.[14]

h. Genetically, several genetic polymorphisms affect persistent HPV infection and cervical cancer progression.[14]

Family history such as mother and sister also determines the high potential for cervical cancer.[10] at least the risk increases twofold compared to those who do not have a family history.[10] This occurs because in the family history there is the same immune system, cells carried by hereditary factors as well as immune system and the same infected factors.[10]

i. Use of vaginal cleansers (douching) [10]

A healthy vagina must contain lactobacillus bacteria, which are good bacteria to maintain the acidity of the vagina so that germs don't easily infect.[10] The habit of using vaginal fluids (douching) will eradicate these bacteria so that the vagina is more susceptible to infection.[10]

According to the American College of Obstetricians and Gynecologists (ACOG), the habit of washing the vagina with an antiseptic in the form of vaginal washing can increase the risk of cervical cancer.[10] This causes the genital skin to become wrinkled and kills the bacillus doderlain bacteria in the vagina which produces lactic acid to maintain vaginal PH , thereby stimulating changes in cells that end in the incidence of cancer that inhabit the vagina. [10]

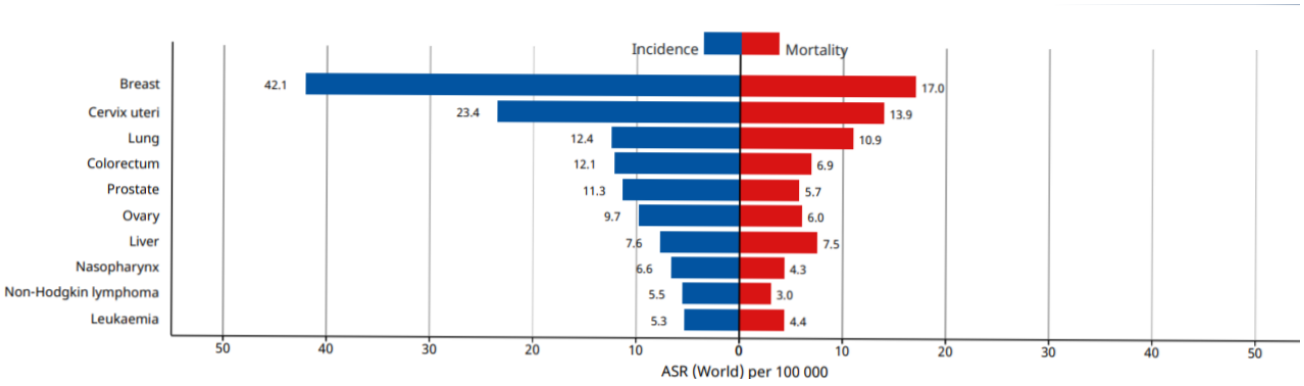

Figure 1.Incidence rate and mortality rate of cervical cancer in Indonesia 201822

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