Chapter 5

Incidence, Risk Factors, Diagnostic Criteria and Prevention Methods in Cervical Cancer

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Abstract

In this section, cervical cancer, incidence, risk factors, diagnostic criteria in cervical cancer, cervical cancer prevention methods have been given.

Cervical Cancer is estimated that cancers will increasingly become the most important causes of mortality and morbidity all over the world within the following 10-20 years. Struggle against cancers has many difficulties and when they are combined with aging population, the increase in cancer prevalence becomes inevitable, regardless of the present or future precautions or investment levels. The changes expected to occur in demographics of the population within upcoming 20 years, even though global cancer rates do not change, means that the incidence of new cancer cases which was 12.7 million in 2008 will reach 21.4 million in 2030 and approximately two thirds of the all cancer diagnoses will be made in countries with lower and medium income level [1].

In different parts of the world great differences are observed related to leading cancer types in terms of either cancer prevalence or death rates. According to World Bank’s cancer morbidity and mortality data, geographic differences in dispersion and spread of cancer are shown in a review performed with income groups. In countries with above-medium and high income the most often diagnosed cancer types are prostate cancer in males and breast cancer in women [1].
Lung and colorectal cancers are the second most prevalent cancer types in both genders. Although these cancers represent the most frequently seen cancer-associated deaths in these countries, in reality the lung cancer is the most prevalent one among the causes of cancer-related deaths. The absolute burden of cancer is far less in countries with lower income. In these countries, although the lung and breast cancers are the most prevalent diagnose-and-cancer related death types, the cervix, stomach and liver cancers are also among the leading cancer types. All of these are cancers that possess etiology-related infection [1].

Countries with medium income are at medium level in terms of cancer burden. In countries with below-medium income, the most prevalent three cancer types are lung, stomach and liver cancers in males; breast, cervix and lung cancers in women. In other words, they seem similar to those in low-income countries (liver, colorectal and esophageal cancers are also important). Below-medium income group is seen in the most crowded countries such as China and India. Therefore, the number of cancers and cancer-related deaths is considerably high in this group [1].

In both genders the lung cancer rates (total) are the highest at West Pacific Region, followed by European and American Continent. The lowest rates are seen at Africa Region. In Africa Region the cervix uterine cancer has the highest incidence in women followed by the women in Southeast Asian Region. The lowest cervical cancer incidence is seen in women living in East Mediterranean Region [1].

According to GLOBOCAN 2008the three cancer types seen in women worldwide are breast, cervix and colorectal. Among the gynecologic cancers the uterus cancer is in the sixth row and ovary in the seventh row. At the same report when the cancer mortality is reviewed, while the breast, lung and cervical cancers occupy the first three rows, ovary cancer is in the seventh row [2]. In our country, according to 2006 data of Department of Fight Against Cancer, Ministry of Health, the cervical cancers comprise the 5 of 100.000 cancers seen in women [3].

According to The Association of Public Health Professionals report (2012) entitled “Non-Contagious Diseases in Turkey”; in 2006 the most frequently seen cancer type in women was breast cancer with 36.9 per 100.000; when gynecological cancer incidence was review the uterus corpus cancer was sixth in row with 7.8 per 100.000, ovary cancer was seventh with 6 per 100.000 and cervical cancer was tenth with 4.7 per 100.000. At the same report, when the cancer-related deaths in women (Turkey-2009) were examined it was observed that ovary cancer was in the seventh row with 5%, uterus cancer was ninth with 2.9% and cervical cancer was tenth with 2% [4].
Cervical cancer, one of the fertility-period problems in women, is the second most frequently seen cancer type in women following breast cancer and 80% of them appear in underdeveloped countries. Cervical cancers comprise 15% of the female cancers seen in underdeveloped countries and 4.2% in developed countries [5,6]. In below-Sahara African countries the cervical cancer is among the leading cancer-related cause of death among women. Five-year survival rate at cervical cancer is 73%; it is 74% at women below 40 years of age and 69% at women over 40 [1].

**Risk Factors at Cervical Cancer**

In fact, all women are at risk of cervical cancer. However, individual risk factors increase this factor. Majority of these risk factors are closely related to unfavorable health behaviors. But most of the women are unaware that these unfavorable ways of behavior are directly associated with cervical cancers.

The factors increasing the risk for cervical cancer are;

**The Risky Ways of Behavior Identified in Literature**

- Coitus at an early age (< 16 years of age), polygamy,
- Sexual intercourse with a polygamist,
- The first gestational age at 20 years old and below,
- The first childbirth age at 20 years old and below,
- The number of deliveries is three and over,
- Having a sexually transmitted disease (especially, Human Papilloma Virus, type 16-18, Herpes Simplex type II and HIV),
- Smoking,
- Age,
- Race (black women),
- Presence of other untreated vaginal infections,
- Presence of immunosuppression [7-14].

**The Risky Ways of Behavior Being Investigated in Literature**

- The menarche onset before 15 years of age,
- Presence of a history of cervical cancer at mother or sister,
- Not performing regular pap test, not going to health controls regularly,
- Nourishment poor in vegetables-fruits (vitamin C, beta-carotene and folate insufficiency),
- Having poor hygiene, reduced socio-economic
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level,

- Not using contraceptive pills for more than five years [7-16].

Coitus at an Early Age and Polygamy/Sexual Relationship with a Polygamist

Studies demonstrate that starting the sexual intercourse at an early age plays an important role in the etiology of cervical cancer. Especially, the risk for development of cervical cancer is high in those who marry at the early ages (16 years of age and below). The risk for cervical cancer is two folds higher in women who marry before 16 years of age compared to those marry after 20 years of age [17]. The possible reason is explained through making young woman's cervix suitable in terms of cellular alteration by the squamous columnar junction that has not completed its development yet. Besides, at earlier ages the secondary immunologic response to HPV is not enough [18].

Sexual activity takes place at the forefront of risk factors related to cervical cancers, because disease most often appears in married women, those who marry at early ages and those involve in so many sexual intercourses. Briefly, multiple-partnership increases the risk for catching infection [17]. Especially, single women with multiple partners are exposed to sexually transmitted infections longer time [15,19]. The number of partners they intercourse with is related to the number of women these partners intercourse with [15].

The Numbers of Pregnancy and Fertility

The incidence of cervical cancers increases with the number of pregnancy and childbirth. The number of pregnancy over three, the first pregnancy before 20 years of age and the first childbirth at earlier age are shown as important risk factors [15,20]. It was suggested that the relationship between multiparity and cervical cancer might be related to extreme childbirth, still birth, abortion and cervical trauma during childbirth and hormonal status during pregnancy or nourishment behaviors [21]. In our country, wide spread of still births and abortions may lead to densely experienced gynecological problems. These untreated problems may progress to malignancy [22].

Viral Infections

Herpes Simplex Virus (HSV)

Herpes Simplex Virus Type 2, was suggested as an important factor in terms of cervical cancers between 1970s and 1980s. However, in subsequent years, a point of view that this infection is an auxiliary factor in development of the disease has gained weight [23].
Human Papilloma Virus (HPV)

HPV is a DNA virus with double-helix, circular, including 8,000-phase pairs and without envelope; today about 120 distinct types were identified [7]. Human papilloma viruses affect only humans. There are more than 70 HPV types that cause mucosal and genital infections in humans [24,25]. HPVs are basically infecting epithelial cells of the cervix and at the cervical transformation zone (a place where vaginal and cervical epithelial cells intersect) they frequently lead to permanent subdural infection in metaplastic epithelium [12,26]. HPV is categorized as lower risk, medium risk and higher risk group according to its oncologic features. The HPV types in lower oncologic risk group are responsible for cervical lesions and genital papillomas. High-risk HPV types are detected in 99.7% of cervical cancers and in precancerous, squamous intra-epithelial lesions that are considered precursors of cervical cancers [24,27]. The type of sexual behavior increases a woman's risk for catching HPV infection.

Smoking

Tar is the first chemical substance demonstrated to have relationship with cancer. In 1950s it was reported in many broadcastings that vaginal shower materials that contain tar lead to cervical cancers in USA. Smoking is also considered as another cause of being subjected to chemical substances containing tar [7]. Risk rates increase with amount of cigarette smoked. Through cigarette smoking body encounters approximately 4,000 different chemical substances that many of them are considered cancerous. In healthy populations many of these substances are observed in cervical mucosa of smokers [7]. In a number of populations a correlation was detected between smoking habit and sexual behaviors. In addition, chemical substance related to cigarette was found within cervical mucus. These substances are thought to affect development of cervical cancer since they cause DNA damage in cervical cells [11]. In smokers the risk for preinvasive and invasive disease increases. Studies have been shown that the risk for smoking-associated cervical cancer increases 2-3 folds compared to control group [20].

Age

Cervical cancer is more often seen between 30 and 55 years of age [28].

Race

The incidence of cervical cancer is 7.6 per 1000,000 in white women whereas it is 12 per 100,000 in black women. The death rate from cervical cancer in black women is about three folds higher than in white women. However, mortality rates are about 5.7 and 2.2 per 100,000, respectively [8,29].
Other Untreated Vaginal Infections

Some difficulties are experienced when evaluating this group of diseases. The leading causes are most often seen infections and difficulty in establishing them[7]. Madreleine et al. observed in their study that the risk for squamous cell cancer has increased 1.6 fold in patients who diagnosed with chlamydia trachomatous [30].

Immunosuppression

Immunosuppression is defined as a risk factor in development of cervical dysplasia and cancer. The risk for development of invasive cervical cancer in HIV-infected women is about three folds higher compared to uninfected women [7,31]. In HIV-HPV coalescence, HIV causes continuation of lesions with higher degree by disturbing immunologic response to HPV and provides sufficient time for genetic alterations important in onset of cancer caused by HPV [24].

The First Menstruation Age

It is suggested that the short period between early menstruation age and the age at first sexual intercourse is a risk factor for cervical cancer [31].

Genetic

There is a relationship between cervical cancer and genetic transition. An interaction of 27% was found between an underlying factor and genetic structure during development of tumor. Genetics will affect so many factors concerning development of tumor. Among them, resistance to HPV, elimination of HPV, disease development period, etc. can be considered [32].

Failing to Attend Gynecologic Examinations Regularly

Cervical cancer is a disease that can be diagnosed early through gynecologic examinations. Therefore, a conscious approach is required in terms of investigation and treatment of the genital infections before cervical cancer emerges.

Diet and Vitamins

Particularly vitamin C has drawn attention due to the role it played in recovery and its antioxidant characteristics against quitting smoking and immunologic system. Many studies demonstrated that high intake of vitamin Chas decreased the dysplasia and invasive cancer rates. In a study it was reported that low folate intake was related to cervical lesions [33]. Even though nourishment status and diet do not affect eating habits, they make a woman to catch infection easier. The cervical cancer incidence is very low in individuals who eat food rich on vegetables and fruits, especially rich on carotene, because carotenes are defined as antioxidants [34].

Poor Genital Hygiene

Unable to apply menstruation and perineum hygiene efficiently and properly may pose a risk in terms of gen-
ito-urinary infections. This type of infections, when they are identified at an early period but necessary measures are not taken, serious health problems may appear such as infertility and cervical cancers [35,36]. Women’s practices toward cleaning their body and perineum during menstruation period demonstrate differences according to their cultures [37]. It is stated that the pads that are prepared at home and used at each menstruation period are risk factors for cervical cancers [38]. Especially in Muslim countries the vaginal shower practiced due to religious reasons is a risk factor for cervical cancers. The vaginal shower practice is commonly used among women in our country [36]. In addition, it is reported that there is a positive relationship between the frequency of vaginal shower and length of application and the risk for cervical cancers [35,36].

**Socio-Economic Status**

It was reported that cervical cancers were related to lower socioeconomic status in developing countries therefore, disease is more often seen in rural areas and in women with lower income levels [12,39]. The poor socioeconomic status influences hygienic attitudes of individuals negatively, as well as their diet and habits to visit health organizations regularly[15,40]. Furthermore, it is stated that absence of a social security will increase the incidence of cervical cancers by negatively affecting the taking advantage of protective health services and having screening test made.

**Prolonged Time Oral Contraceptive Use**

In early studies it was thought that oral contraceptives (OCCs) did not increase the risk for cervical cancer. But in recent studies the long time contraceptive usage has been found to increase risks [20,41]. There are hormonal receptors in cervical tissues of humans; in those who use OCCs histological alterations occur in the cervical epithelium, immunologic alterations that increase sensitivity to viral factors develop and OCCs lead to a mucus secretion that facilitates mutagen entrance [42].

The results of many studies suggest that contraceptives will increase the risks for cervical lesions and cancers [20,41]. However, this is thought to be related to other epidemiologic factors. For example, oral contraceptive users may have started intercourse at an early age, may have various partners and may be protected by barrier methods [15,20,41]. In other words, the widely accepted consideration is that oral contraceptive users might be more sexually active than non-users and therefore, this may be defined as a co-factor not an independent risk factor [29,31,41]. On the other hand, although a number of researches have investigated the relationship between OCC usage and the risk for cervical cancer, to interpret their results is difficult. Regular cervical examination habit and the frequency of pap-test screening are high in OCC users. This supports the view that cervical cancer does not
worsen in OCC users but it only leads to an increase in the detecting rate of the disease during frequently performed controls [42,43].

The conclusions reached in a study that performed detailed evaluation of the results of 18 case-controls and 4 cohort studies carried out until 1991 and in WHO report can be summarized as follows; at the beginning OCCs were found safe but, especially in more recent studies a positive relationship was observed between long time usage and cervical cancer. The results of the well-controlled studies show that the risk elevates in those who had used OCC for five years or longer. The study mentioned here and a 10-year cohort study that included 17,000 women were sustained for further 12 years and their results were published in 1996 [42,44]. Finds demonstrate that the risk for cervical neoplasia increases in individuals who use OCC prolonged time [22,42].

**The Diagnostic Characteristics of Cervical Cancer**

In cervical cancer, the first complaints are generally bleedings in the form of staining right after intercourse. There may not be too many complaints in the early periods of cervical cancer. Majority of the women are unaware of the disease until it completely progresses and starts to interrupt the function of other organs; there is no complaint about pain at the early stages. After cancer cells shaped at the cervical region, they gradually progress within years and grow in a manner to transform surrounding normal cells and tissues into cancer. They cause some complaints after they have achieved a certain size. However, cancer cells might be widely scattered within the time passed until complaints develop.

In individuals with cervical cancer;
- Abnormal uterine bleeding and vaginal discharge occur,
- During inspection cervical lesion may appear as a tumor or ulceration; however the cancer within cervical canal may be hidden,
- During bimanual examination cervix may be felt like a barrel,
- Positive vaginal cytology should be verified by biopsy [45,46].

**Protection from Cervical Cancer**

Among woman cancers the cervical cancer is at the second row after breast cancer and at the fourth row in terms of mortality. As in other cancer types, it is more often seen in undeveloped and medium-level developed countries [2]. In our country according to the 2006 data of Department of Fight Against Cancer, Ministry of Health, the cervical cancers comprise the 5 of 100,000 cancers seen in women [3]. Among the gynecologic cancers it oc-
occupies the third row after endometrium and over [3]. In women the cervical cancer is one of the leading cancers that can be prevented through early diagnosis. The steps for protection from cervical cancer are shown in Table 1.

**Table 1:** Steps for protection from cervical cancer.

<table>
<thead>
<tr>
<th>Steps</th>
<th>Ways of Protection</th>
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<tbody>
<tr>
<td>Primary Protection</td>
<td>To raise awareness about cervical cancer</td>
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<tr>
<td></td>
<td>HPV vaccine</td>
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<tr>
<td></td>
<td>Staying away from risky behaviors</td>
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<tr>
<td></td>
<td>Healthy way of living (healthy nourishment, performing regular exercise)</td>
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<tr>
<td></td>
<td>Prefer to use barrier contraceptives</td>
</tr>
<tr>
<td>Secondary Protection</td>
<td>Having screen tests made for cervical cancer (PAP Smear Test, HPV-DNA test, etc.)</td>
</tr>
<tr>
<td></td>
<td>Identifying risky groups in terms of cervical cancer</td>
</tr>
<tr>
<td>Tertiary Protection</td>
<td>Providing appropriate therapy methods and rehabilitation services</td>
</tr>
</tbody>
</table>

**Primary Protection in Cervical Cancer**

**Raising Awareness**

January has been defined as the awareness month for cervical cancer [4]. In this month various types of scientific and social activities are arranged to raise awareness about cervical cancer.

**HPV Vaccine**

The vaccination studies initiated in 1993 have been put in use since 2000. HPV vaccine has been included in routine vaccination calendar in many countries, notably in USA, Canada, Australia, Germany, France and Israel. But in our country quadrivalent vaccine received certificate in 2007 and bivalent vaccine in 2008 [47]. HPV vaccines were developed against the most dangerous HPV types (16 and 18) and also against types 6 and 11 which are responsible for 90% of genital papillomas in healthy girls and women; they provide 100% protection against HPV types 16 and 18. However, these HPV types are effective in only 70% of cervical cancers. Vaccination should be carried out before the target population run into infection so that vaccines can be effective at the highest level. Therefore, the HPV vaccine series should be completed before the sex life starts. FDA recommends that HPV vaccine be applied to all women (between 9 and 26 year of age) not encountered with the virus before. Applied vaccine will not replace the cervical cancer screening or PAP-smear practice and these screenings must be made regularly [47-49].

**Keeping Away from Risky Behaviors**

In literature, keeping away from the following risky behaviors in terms of cervical cancer is recommended [50-53].

- Early sexual intercourse age (< 16 years of age),
- Polygamous sex life,
• To have sex with an individual with polygamous sex life,
• Age of the first pregnancy and childbirth below 20 years,
• Presence of a sexually transmitted disease (especially, HPV type 16-18, HSV type II and HIV),
• Smoking,
• Presence of other untreated vaginal infections,
• Using OCC longer than 5 years,
• Alcohol consumption.
• Using Barrier Contraceptive Method (diaphragm, condom and spermicide)

It was determined that the risk for cervical cancer was lower in women using barrier method [51], however in diaphragm users the risk for invasive cervical cancer has decreased [52]. The protective effect is stronger in cases where the length of method usage was prolonged. Slattery et al. determined that barrier methods have reduced the risk for cervical cancer only in women with multiple sex partners [53] and reported that when physical barriers were used with spermicides their effects enhanced [54].

The Secondary Protection in Cervical Cancer

Early Diagnose–Screening

The screening in cervical cancer is based on cytological screening. In Western countries, significant decreases were observed in mortality and incidence rates (60% and 80%, respectively) in population-based screenings [2]. Today, the Pap-smear Test is recommended by World Health Organization (WHO) as a screening test that has high selectivity, has been tested for a long time and suitable to computer-assisted assessment. Other than this test, the visual inspection with acetic acid, visual inspection with Lugol iodine solution, HPV test and Liquid-based cytological test are suggested as alternative screening tests [50].

The recommended cervical cancer screenings may vary according to American Cancer Association (ACA), WHO and countries’ health facilities. According to ACA’s recommendations related to cervical cancer screenings [55];

• The cervical cancer screening must begin at 21 years old.
• Women between 21 and 29 years old should receive Pap test every 3 years. (In this age group if there is an abnormal pap test result a HPV test is recommended).
• Women between 30 and 65 years old should have a Pap test and HPV test made every 5 years.

• Women 65 years old and above must be screened in terms of cervical cancer, if they had regular cervical cancer screening test made previously and no abnormal result was found. Women younger than 65 years old and have serious cervical pre-cancer history must be retested even though 20 years have passed from first diagnose. Women whose uterus - not related to cervical cancer- (cervix included) had been excised, should be screened if there is no cervical cancer or serious pre-cancer history.

• Women should participate in screening program recommended for the age group even though they had received HPV vaccine.

WHO's Recommendations for Cervical Cancer Screening [56]

• Screening should start at women 30 years old and above. Younger women must be included in screening program if they are in high risk group. Women below 25 years of age do not take place in the target population in terms of cervical cancer.

• For a woman the best age range to be screened is between 35-45 years.

• Women over 50 years of age must be screened every five years.

• If there is sufficient resource, to have screening done every three years is appropriate for women between 25 and 49 years.

• Annual screening is not recommended for any age group.

• A screening test is recommended for women over 65 years old if the results of the last two tests are negative.

In our country [57]

• During screening the absolute target is to perform PAP-smear for all women between 35 and 40 years of age at least once.

• The cervical cancer screening program starts at 30 years of age.

• PAP-test should be done once every five years for women between 30 and 65 years old.

• At the age of 65, if the results of the last two tests are negative women may be removed from the program.

Conclusion

As a result, compared with the incidence of cervical cancer among common cancer among women maintains its importance. The identification of risk factors for cervical cancer is important in terms of early detection, primary and secondary prevention.
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