

Risk Factors for Cervical Cancer: Diagnosis and Management

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Abstract:- Cervical cancer is the fourth cause of cancer worldwide, and is a common cause of cancer in the low-income countries. Risk factors for cervical cancer include Human papillomavirus (HPV) infection, smoking, low immune system and oral contraceptives. HPV is implicated in virtually all cervical cancer. Vaginal bleeding, bleeding after sexual intercourse, vaginal mass may indicate the presence of malignancy. In advanced disease, metastasis may be present in the abdomen, lungs and elsewhere. Diagnosis by cervical screening, biopsy, squamous cell carcinoma(80-85%),and adenocarcinoma cervical cancer(15%).FIGO,staging system is based on clinical examination rather than surgical findings.Treatment of cervical cancer consist of surgery,chemotherapy, and radiotherapy, but varies worldwide. For surgery to be curative, the entire cancer must be removed (exenternation).Prognosis of cervical cancer depends on the stage of the cancer. High survival rates for women with microscopic formof cancer. Prevention includes, Pap smear screening, twice yearly Pap tests can reduce up to 90% of cervical cancer in Australia, barrier methods, use of condoms and vaccination against HPV 16 and 18 is effective up to 8 years. Consumption of vitamin A, vitamin B 12,VitaminVitaminE and beta-carotene has beneficial effect.

Keywords: Cervical cancer, Risk factors, Human papilloma virus, Diagnosis, Screening

I. Introduction

Cervical cancer is cancer arising from the cervix. It is due to the abnormal growth of cells that have the ability to invade or spread to other parts of the body[1,2].Worldwide, cervical cancer is fourth-most common cause of cancer and deaths from cancer in women[3].In 2012,528,000 cases of cervical cancer were estimated to have occurred with 266,000 deaths[3].It is the second- most common cause of female specific cancer after breast cancer, accounting for about 8 % of both total cancer cases and total cancer death in women[4].Malaysian National Cancer Registry, 2007,reported 747(4.6%) cervical cancer[5].In low-income countries, it is the most common cause of cancer[6].The annual direct medical cost of cervical cancer prevention and treatment prior to introduction of human papillomavirus(HPV) vaccine was estimated at six billion[7].Risk factors for cervical cancer include HPV infection appears to be involved in the development of more than 90% of cases, smoking, a weak immune system, birth control pills, starting sex at a young age, and having many sex partners[8,1].About 90% of the cervical cancer cases are squamous cell carcinoma,10% are adenocarcinoma, and small number are other types[9].Early on, typically no symptoms are seen. Later symptoms may include abnormal vaginal bleeding, pelvic pain, or pain during sexual intercourse [1].While bleeding after sex may not be serious, and it may also indicate the presence of cervical cancer [10] .Diagnosis is typically by cervical screening followed by the biopsy. Medical imaging is then done to determine whether or not the cancer has spread [1].Treatment of cervical cancer may consist of some combination of surgery, chemotherapy, and radiotherapy [1].Five year survival rates in the United States are 68 % [11].Outcomes, however, depend very much on how early the cancer is detected[9].The paper reviews the risk factors, diagnosis, management, and the current screening program for cervical cancer implemented worldwide.

II. History and Epidemiology

In 400 BCHippocrates noted that cervical cancer was incurable.In 1925 Hinselmann invented coloscope.Papanicolaou developed Papanicolaou technique in 1925.Papanicolaou and Traut introduced Pap smear in 1941.Aylesbury spatula was developed to scrape the cervix, collecting the sample for the Pap smear in 1946.First successful in-vitro cell line HeLa derived from biopsy of cervical cancer of Harrinetta Lacks in 1951.Haral zurHausen and Grisam found HPV DNA in cervical cancer and genital warts;Hausen later won the Nobel Prize for his work[12].In 1988, Bethesda System for reporting Pap results was developed. In 2006, first HPV vaccine was approved by FDA[13].

Epidemiologists working in the 20th century noted that cervical cancer behaved like a sexually transmitted disease. In summary: Cervical cancer was noted to be common in female sex workers. It was rare in nuns, except those who had been sexually active before entering the convent (Rigoni 1841)[13,rpt].It was more common in the second wives of men whose first wives had died from cervical cancer. It was rare in the Jewish women[14].In 1935,Syvertson and Berry discovered a relationship between RSV(Rabbit Papillomavirus) and skin cancer in Rabbits.HPV is species-specific and therefore cannot be transmitted to rabbits)[13].These historical observations suggested that cervical cancer could be caused by a sexually transmitted agent. Initial research in the 1940s and 1950s attributed cervical cancer to smegma(e.g..Heinset *al.*1958,[15].During the 1960s and 1970s it was suspected that infection with herpes simplex virus was the cause of the disease's was seen as likely cause because it is known to survive in the female reproductive tract, to be transmitted sexually in a way compatible with known risk factors, such as promiscuity and low socioeconomic status[16].Herpes simplex viruses were also implicated in other malignant diseases, including Burkitt's lymphoma, Nasopharyngeal carcinoma. Merck's disease and the Lucke renal adenocarcinoma.HV5 was recovered from cervical cells [13].

A description of human papillomavirus (HPV) by electron microscopy was given in 1949, and HPV DNA was identified in 1963.It was not until the 1980s that HPV was identified in cervical cancer tissue[17].It has since been demonstrated that HPV is implicated in virtually all cervical cancer. Special viral subtypes implicated are HPV 16,18,31,45 and others[18].With worldwide research in the mid-1980s HPV vaccine was developed, approved by U.S.Food and Drug Administration(FDA) and marketed by Merck &Co. under trade name Gardasil[19].

Epidemiology

In the United States an estimated 12,900 new cervical cancers and 4,100 cervical cancer deaths will occur in 2015[20].In the U.S. it is the eight-most common cancer of women. The median age at diagnosis is 48 .Hispanic women are significantly more likely to be diagnosed with cervical cancer than the general population[21].In 1998,about 12,800 women were diagnosed and 4,800 died[22].Among cancers of the female reproductive tract it is less common than endometrial cancer and ovarian cancer. The rates of new cases in the United States was 7 per 100,000 women 2004[23].Cervical cancer deaths decreased by approximately 74% in the last 50 years, largely due to widespread PAP smear screening[7].

In European Union(EU),about 34,000 new cases per year and over 16,000 deaths due to the cervical cancer occurred in 2004[24].In the United Kingdom(UK) cervical cancer is the 12th most common cancer in women, around 3,100 women were diagnosed with the disease in 2011,and accounts for 1% of cancer deaths(around 920 died in 2011).With 42 % reduction from 1988-1997,NHS(National Health Service) implemented screening program has been highly successful, screening the highest-risk age group(24-49 years) every three years, and those ages 50-64 every 5 years[25].

In Canada an estimated 1,300 women will have been diagnosed with cervical cancer in 2008 and 380 will have died [26].Australia had 734 cases of cervical cancer(2005).The number of women diagnosed with cervical cancer has dropped on average by 4.5 % each year since organized screening beginning in (1991-2005)[27].Regular twice yearly Pap tests can reduce the incidence of cervical cancer up to 90% in Australia, and save 1,200 Australian women from dying from the disease each year[28].In India, the number of people with cervical cancer is rising, but overall the age-adjusted rates are decreasing. Usage of condoms in the female population has improved the survival of women with cancer of the cervix [29,30].

III. Risk factors

Infection with some types of HPV is the greatest risk factor for cervical cancer, followed by smoking [31].HIV is also a risk factor[31].Not all the causes of cervical cancer are known,however,and several other contributing factors have been implicated[32].

HPV Infection

Human papillomavirus type 16,and 18 are the cause of 75% of cervical cancer cases globally, while 31 and 45 are the causes of another 10 % [33].Women who have many sexual partners or who have sex with men who have had many other partners have a greater risk[34].Of the 150-200 types of HPV known 15 are classified as high-risk types that include:16,18,31,33,35,39,45,51,52,56,58,59,68,73,and 82.another three as probable high-risk-26,53,and 66,and 12 are low risk types:6,11,40,42,43,44,54,61,70,72,81 and CP6108[35].

Genital warts, which are a form of benign tumor of epithelial cells, are also caused by various strains of HPV. However, these serotypes are usually not related to cervical cancer. It is common to have multiple strains at the same time, including those that can cause cervical cancer along with those that cause warts [13t].Infection with HPV is generally believed to be required for cervical cancer to occur [36].

Smoking

Cigarette smoking both active and passive increases the risk of cervical cancer. Among HPV-infected women, current and former smokers have roughly two to three times the incidence of invasive cancer. Passive smoking is also associated with increased risk, but to lesser extent[20].Smoking has also been linked to the development of cervical cancer[37].Smoking can increase the risk in women a few different ways, which can be by direct and indirect-methods of inducing cervical cancer[37].A direct way of contracting this cancer is a smoker has a higher chances of CIN3 occurring which has the potential of forming cervical cancer[37].When CIN3 lesions lead to cancer, most of them have the assistance of the HPV virus but that is not the always the case, which is why it can be considered a direct link to cervical cancer[38].

Heavy smoking and long-term smoking seem to have more of a risk of getting CIN3 lesions than lighter smoking or not smoking [39].Although smoking has been linked to cervical cancer,it aids in the development of HPV which is the leading cause of this type of cancer[40].Also, not only does it aid in the development of HPV,but also if women is already HPV-positive, she is at even greater likelihood of contracting cervical cancer[40].

Use of Contraceptives

Long- term use of oral contraceptives is associated with increased risk of cervical cancer. Women who have used oral contraceptives for 5 to 9 years have about three times the incidence of invasive cancer, and those who used them for 10 years or longer have four times the risk [37].

Pregnancies as Risk Factor

Having many pregnancies is associated with an increased risk of cervical cancer. Among HPV-infected women, those who had seven or more full-term pregnancies have around four times the risk of cancer compared with no pregnancies, and two or three times the risk of women who have had one or two full-term pregnancies[37].

IV. Clinical Manifestations

Cervical cancer typically develops from precancerous changes over 10 to 20 years[3].Early stages of cervical cancer may be completely free of symptoms[8,22].Vaginal bleeding, contact bleeding, one most common form bleeding after sexual intercourse, or rarely, a vaginal mass may indicate the presence of malignancy. Also, moderate pain during sexual intercourse and vaginal discharge are symptoms of cervical cancer. In advanced disease, metastasis may be present in the abdomen, lungs and elsewhere. Symptoms advanced cervical cancer may include: loss of appetite, Weight loss, fatigue, pelvic pain, back pain,leg pain, swollen legs, heavy vaginal bleeding, bone fractures, and/or rarely leakage of urine or feces from vagina [41].Bleeding after douching or after a pelvic examination is a common symptom of cervical cancer [42].

V. Diagnosis

Diagnosis of cervical cancer is typically by cervical screening followed by biopsy. Medical imaging is then done to determine whether or not the cancer has spread [1].

Biopsy

The Pap smear can be used as a screening test, but is false negative in up to 50% of cervical cancer cases[43].Confirmation of the diagnosis of cervical cancer or precancer requires a biopsy of the cervix. This is done through a colposcopy, a magnified visual inspection of the cervix aided by using a dilute acetic acid (e.g.vinegar) solution to highlight abnormal cells on the surface of the cervix [8].

Cervical Lesions

Cervical intraepithelial neoplasia, the potential precursor to cervical cancer, is often diagnosed on examination of cervical biopsies by a pathologist. For premalignant dysplastic changes, cervical intraepithelial neoplasia grading is used. The naming and histologic classification of cervical carcinoma precursor lesions has changed many times over the 20th century. The World Health Organization classification[44],system was descriptive of the lesions, name naming them, mild, moderate, or severe dysplasia or carcinoma in situ(CIS).The term, cervical intraepithelial neoplasia (CIN) was developed to place emphasis on the spectrum of abnormality in these lesions, and to help standardize treatment[44].It classifies mild dysplasia as CIN1,moderate dysplasia as CIN2,and severe dysplasia and CIS as CIN3.More recently,CIN2 and CIN3 have been combined into CIN2/3.These are the frequently pathology reported biopsy results.

These should not be confused with Bethesda system terms for Pap smear (cytopathology) results include:

- *.Low-grade Squamous Intraepithelial Lesion (HSIL)
- *.High-grade Squamous Intraepithelial Lesion (HSIL)

*.An LSIL Pap smear correspond to CIN1,and HSIL may correspond to CIN2 and CIN3,however they are the results of different tests, and the Pap smear results need not to match the histologic findings[44].

Cancer and Subtypes Cancer and Staging

Histologic subtypes of invasive cervical carcinoma include following [45].Though the squamous carcinoma is the cervical cancer with most incidence, the incidence of adenocarcinoma of cervix has been increasing in recent decades, that include:[8].

- a) squamous cell carcinoma (about 80-85%)
- b)adenocarcinoma(about 15% of cervical cancers in the UK)[46].
- c) adenosquamous carcinoma
- d) neuroendocrinetumor
- e) glassy cell carcinoma
- f) villoglandular adenocarcinoma

Noncarcinoma malignancies which can rarely occur in the cervix include melanoma and lymphoma. The FIGO(International Federation of Gynecology and Obstetrics stage does not incorporate lymph node involvement in contrast to the TNM(T/tumour,N/node,and M/metastasis) staging for other cancers[13].

Staging

Cervical cancer is staged by FIGO,staging system, which is based on clinical examination, rather than surgical findings. It allows only these diagnostic tests to be used in determining the stage:*palpation,inspection,colposcopy,endocervicalcurettage,hysteroscopy,cystoscopy, proctoscopy, intravenous urography, and X-ray examination of the lungs and skeleton, andcervicalconization*[13].

VI. Management

Management- treatment of cervical cancer consist of combination of surgery, chemotherapy, and radiotherapy[1],but it varies worldwide, largely due to access to surgeons skilled in radical pelvic surgery, and the emergence of “fertility-sparing therapy” in developed nations. Because the cervical cancers are radiosensitive,radition may be used in all stages where surgical options do not exist. Micro invasive cancer (stage IA) may be treated by hysterectomy.For stage IA2,the lymph nodes are removed, as well. Alternatives include local surgical procedures such as loop electrical excision procedure or cone biopsy. For IAI disease, a cone biopsy (cervical conization) is considered curative [47].If cone biopsy does not produce clear margins(findings on biopsy showing that tumor is surrounded by cancer free tissue, suggesting all of the tumor is removed),one more possible treatment option for women who want to preserve their fertility is a trachelectomy[48,49].

A radical trachelectomy can be performed abdominally or vaginally and opinions are conflicting as which is better [50-52].A radical abdominal trachelectomy with lymphadenectomy usually only requires a two- to three days stay hospital stay, and most women recover very quickly(about six weeks).Complications are uncommon, although women who to conceive after surgery are susceptible to preterm labor and possible late miscarriage[53].Wait at least one year is generally recommended before attempting to become pregnant after surgery[54].Recurrence in the residual cervix is very rare if the cancer has been cleared with trachelectomy.Yet women are recommended to practice vigilant prevention and follow-up care including Pap screening/colposcopy,with biopsies of the remaining lower uterine segment is needed(every 3-4 months for at least 5 years) to monitor for any recurrence in addition minimizing any new exposure to HPV through safe sex practices until one is actively trying to conceive[55].

Larger early stage tumors (IB2, and IIA more than 4 cm) may be treated with radiation therapy and cisplatin-based chemotherapy (which then usually requires adjunct radiation therapy),or cisplatin chemotherapy followed by hysterectomy. When cisplatin is present, it is thought to be the most active single agent in periodic diseases[56].Advance stage tumors (IB-IVA) are treated with radiation therapy and cisplatin-based chemotherapy.US Food and Drug Administration(2006) approved the use of a combination of two chemotherapy drugs,hycamtin and cisplatin, for women with late-stage (IVB) cervical cancer treatment. Combination treatment has significant risk of neutropenia, anemia, and thrombocytopenia side effects [57].For surgery to be curative, the entire cancer must be removed with no cancer found at the margins of removed tissue on examination under microscope(exenteration)[58].

VII.Prognosis

Prognosis depends on the stage of the cancer. The chance of a survival rate around 100% is high for women with microscopic forms of cancer[59].With treatment, the five- year relative survival rate is about 72%.These statistics may be improved when applied to women newly diagnosed, bearing in mind that these outcomes may be partly based on the state of treatment five years ago when women studied were first

diagnosed[60].With treatment,80 to 90% of women with stage I cancer 60 to 75% of those with stage II cancer are alive 5 years after diagnosis. Survival rates decreases to 30 to 40% for women with stage III cancer and 15% or fewer of those with stage IV cancer 5 years after diagnosis [61].

According to the IFG0, survival improves when radiography is combined with cisplatin-based chemotherapy [62].If the cancer metastasizes to other parts of the body, prognosis drops dramatically because treatment of local lesions is generally more effective than whole-body treatments such as chemotherapy. Interval evaluation of the women after therapy is imperative. Recurrent cervical cancer detected at its earliest stages might be successfully treated with surgery, radiation, chemotherapy, or combination of the three. About 35% of women with invasive cervical cancer have persistent or recurrent disease after treatment [53].

Average years of potential life lost from cervical cancer are 25.3% [63].Around 4,600 women were projected to die in 2001 in the US of cervical cancer, and the annual incidence was 13,000 in 2002 in the US,as calculated by SEER.Thus,the ratio of deaths to incidence is about 35.4% [63].

VIII.Prevention

Pap Smears -Screening

Pap smear screening every 3-5 years with appropriate follow- up can reduce cervical cancer incidence by 80% [24].Abnormal results may suggest the presence of precancerous changes, allowing examination and possible preventive treatment. The treatment of low-grade lesions may adversely affect subsequent fertility and pregnancy [20].The European guidelines(2010),the age at which to start screening ranges between 20 and 30 years, preferentially not before 25 or 30 years, and depends on the burden of the disease in the population [64].In the United States screening is recommended to begin at age 21,regardless of age at which a woman began sex pr other risk factors [65].Pap smears have not been effective in developing countries. This in part because many of these countries have impoverished health care infrastructures [66].

Liquid- based cytology is another potential screening method. Although it was probably intended to improve on the accuracy of the Pap test, its main advantage has been to reduce the number of inadequate smears from around 9 % to 1% [67,66].

Barrier Methods

Barrier protection and/or spermicidal gel use during sexual intercourse decreases cancer risk [20].Evidence on whether condoms protect against HPV infection is mixed, but they may protect against genital warts,(precursors to cervical cancer)STI,HIV,and *Chlamydia*,which are associated with greater risks of developing cervical cancer [68].

Vaccination

Two HPV vaccines (Gardasil and Cervarix) reduce the risk of cancerous or precancerous changes of the cervix and perineum by about 93% and 62 % respectively [69].The vaccines are between 92% and 100 effective against HPV 16 and 18 up to at least 8 years [20].HPV vaccines are typically given to age 9 to 26 as the vaccine is only effective if given before infection occurs, and vaccines have been shown to be effective for at least 4 to six years, and whether a booster dose will be needed is unknown [70,71].In Japan since 2010,young women have been eligible to receive cervical cancer vaccination for free [72].Vitamin supplements intake, vitamin A, vitamin B 12,vitamin Vitamin E,and beta-carotene is associated with a lower risk [73,74].

IX.Conclusion

Cervical cancer is the common cause of death after breast cancer in women. Papillomavirus (HPV) infection, smoking and low immune system is the common risk factors. Early detection and treatment of precancerous lesions have better prognosis. Prevention includes screening (Pap test), protective sex, and vaccination.

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