Review Article

HISTORICAL PERSPECTIVE OF CERVICAL CYTOLOGY: A REVIEW

Abid Rashid[*], Umbreen Naz[**], Adnan Sarwar[***], Muhammad Mudassar Ashraf[****], Zahid Manzoor[*****], Shaukat Hussain Munawar[******], Maisam Ali Shahid[*******], Ahsan Sarwar[********]

[*]Directorate of Medical Sciences, Government College University, Faisalabad, Pakistan

[**]Department of Obstetrics and Gynecology, Punjab Medical College, Allied/Civil Hospital, Faisalabad, Pakistan

[***]Department of Medicine (Medical Unit), Punjab Medical College, Allied/Civil Hospital, Faisalabad, Pakistan

[****]Department of Eastern Medicine, Directorate of Medical Sciences, Government College University, Faisalabad, Pakistan

[*****]Faculty of Medicine and Allied Medical Sciences, Isra University Islamabad, Pakistan

[******]Al-Manara College of Pharmacy, Multan, Pakistan

[*******]Department of Urology, Allama Iqbal Medical College, Jinnah Hospital, Lahore, Pakistan

[********]Department of Pathology, University of Agriculture, Faisalabad, Pakistan

ABSTRACT:

The research work on cervical cytology moved on a speed in 1920 after discovery of pap smear screening by Papanicolaou. Cervical carcinoma, the 2nd most common cancer worldwide in women, is found in all countries perspective of weather developed, under-developed or developing. Most women with cervical cancer and advanced disease result in low cure rates. Among different risk factors of cervical carcinoma, the major ones include low socio economic and high parity status. Approximately two Lacs deaths occur per year due to cervical cancer accounting for 8.5% of all deaths in cancerous women worldwide. Majority of deaths can be prevented by screening program and training the patients when the disease is pre-invasive. A remarkable fall in mortality has been observed in regions where a comprehensive screening for CIN has been carried out.

KEYWORDS: Cervix, Carcinoma, Mortality, Screening, Parity.

BACKGROUND:

HISTORY:

Historical background dates back to history of man. Dysplasia was first used as a term by Reagan et al 1953. Surface differentiation of carcinoma in situ was shown in 1976-78.[1,2] Pre-invasive lesions of cervix (Cx) have been recognized for over 100 years.[3] In mid 1920s principles of colposcopy were described. Papanicolaou after whom pap smear is named, did much work on cervical cytology in 1920.[4] Papanicolaou and Trant claimed about the role of cervical cytology in detecting the pre-invasive disease of the cervix.[1,2]

The knowledge of historical background of cervical cytology will be helpful in planning, implementing and evaluating a program for prevention of cervical cancer in low resources settings. Greater challenges are faced as a primary prevention approach to cervical cancer, which can be controlled by safe sex practices like regular use of condoms. Although female and male condoms provide some protection, skin-to-skin contact still allows for infection with human papilloma virus (HPV). A woman can be protected from the most common cancer-producing HPV types by an effective vaccine. However, types may vary by geographic region and the degree of oncogenicity of various types remains unclear. Even if an effective multivalent vaccine becomes available for protection of women from the major oncogenic types of HPV, the vaccination programs may be cost

Corresponding Author:
Dr. Umbreen Naz, Department of Obstetrics and Gynecology, Punjab Medical College, Allied/Civil Hospital, Faisalabad, Pakistan.
E-Mail: umbr@yahoo.com

prohibitive and may cause delayed benefits only after 20 to 30 years of prophylactic vaccination.[5]

History of cervical cancer screening

For an effective and efficient screening, the natural history of the disease should be known which develops our interest in historical perspectives of cancers of cervix. On basis of screening it is expected that the mortality from the cancer will be reduced by early detection of the disease. The development of an invasive cancer will be prevented if detection of precursors is achieved through an effective screening. Thus, effective screening programs will result in a reduced cancer incidences as well as reduced cancer mortalities. Knowledge about the natural history of a disease will facilitate us in deciding about the appropriate ages to start and stop the screening program, and about the optimal frequency of re-screening the persons who were negative.[6]

Screening is the test or examination to find out a disease like cancer, diabetes and viral infections in persons with symptoms or even not having a symptom. Pap test was the first screening test used for the cancers and was developed by George Papanicolaou as a research method in understanding the menstrual cycle. Papanicolaou found this test very potential for early detection of cervical cancer and he presented his great finding in 1923. In start, many doctors were skeptical about it. Then, American Cancer Society (ACS) promoted this test in early 1960s and it became a widely used test. Since that time, the death rate from cervical cancer in the United States has declined by about 70%.[4]

Short history of discoveries, policies and developments about cervical cytology (based on Wikipedia) has been given in Table 1 and Table 2.

INCIDENCE

Worldwide, Cervical cancer is both the fourth-most common cause of cancer and death from cancer in women worldwide. About 528,000 cases of cervical cancer occurred in 2012 with 266,000 deaths; which was almost 50%. This was about 8% of the total cases and total deaths from cancer. Nearly 70% cases of cancer of Cx occur in developing countries. It is the most common cause of death from cancers in low-income countries.[7] Whereas, the widespread use of cervical screening programs in developed countries has reduced cervical cancer rates dramatically.[8] In medical research, the most famous cell line known as HeLa was developed from cervical cancer cells of a woman named Henrietta Lacks.[9]

Cervical cancer, the commonest cancer among women, worldwide is one of the main causes of mortality and morbidity amongst gynecological tumors. The south Asian region harbors one fourth of the burden of cervical cancer.[10] Cervical cancer is 8th most common type of carcinomas in American women.[11] In United States only, 13,000 cases of invasive cervical cancer and approximately 0.5 Lac cases of cervical carcinoma in situ (i.e. localized cancer) are diagnosed yearly.[12] Incidence of carcinoma in situ is estimated to be about four times that of invasive cancer.[13]

Each year about 2800 women are diagnosed with cervical cancer in United Kingdom (UK) which is the 12th most common cancer in UK women and as many as 1100 women die there from this disease. In England only, cervical cancer was diagnosed in approximately 2300 women in 2003.[6] In 2007, about 2828 new cases of cervical cancer were diagnosed in UK which accounts for 2% of all cancers in females. Lifetime risk of a female developing cervical cancer has been estimated as 1 in 136 in UK calculated in February 2009 based on incidence mortality data for 2001-2005.[5]

Life time risk associated with cervical cancer is about 3% in developing countries and about 1.1% in developed countries. Cervical cancer in developing countries comprises of around 15% of all cancers in females. The highest age specific rate in all race and age groups have been reported in African women in the age range of 66-69 years with the rate of 152.5/100,000.[9]

In India alone, 132000 new cases and 74000 deaths have been estimated each year and cervical cancer cases in such countries present with advanced disease result in low cure rate. Whereas, the situation in Pakistan is largely unknown due to scarcity of epidemiological data. Cervical cancer has been found responsible for 3.6% of cancer related

mortalities in Pakistan. Situation is worse in Pakistan as only 5% of Pakistani women had awareness of screening and 2.6% had pap smear screening once a life. It constitutes 8.7-11% of all malignant diseases in this country.[5] High incidences of cervical tumor in poor countries of the world reflect the impact of inequity of access to health care resources.

ETIOLOGY:

Early programs of prevention from cervical cancer were based on the premise that diseases of Cx develop from precursor lesions, which progress from mild to moderate and then to severe CIN and later on to cervical cancers.[5] Many studies show that cancer of Cervix is strongly associated with sexual activity.[15] Other risk factors include age, young age at Ist intercourse < 20 years, multiple sexual partners, high parity, low socio-economic status, smoking Human Papilloma virus (HPV) infection and immunosup pression.[16] Higher parity and lower social and economic status are the major risk factors.[17]

A female is considered to be in higher risk group of developing cervical cancer if:[18]

- She had more than 3 partners (sexual) in her lifetime,
- Certain strains of HPV including types 16, 18 and 31 are the ones most likely to produce cancer.
- She had her first sexual intercourse before 18 years of age.
- She had papilloma virus (genital warts) or other venereal diseases
- Her sexual partner had intercourse with a woman having abnormal pap smears or cervical cancer or having genital warts
- She or her partner smokes
- Her mother took diethylstilbestrol (DES) during pregnancy associated with her birth
- She had a previous pap smear showing abnormal or suspicious cells
- She had a poor diet intake
- She had immune system suppressing infections like AIDS

Thus, following measurement must be taken to prevent cancer of cervix:[18]

- Stay with one partner (be monogamous)
- Either of the partner should not smoke
- Eat fruits and vegetables
- Take folic acid and multivitamins
- Get regular screening (pap smears) every year
- Wait at least for 21 years age before having sex

COMPLICATIONS:

(A) Malignant Potential of CIN:

Most early cervical intraepithelial Neoplasia (CIN) lesions will regress spontaneously if untreated[4]; Nevertheless, CIN refers to a lesion that may progress to invasive carcinoma. This concept was introduced in 1963, when Richard indicated that all dysplasias have the potential for pregression.[19,20]

Table 1. Key development about cervical cytology over the years

Year/period	Key developments
19th century	Identification of cervical cancer as a sexually transmitted disease. Introduction of surgery for treating the disease.
Early 20th century	Cervical cancer was found common in female sex workers and in women whose husbands having multiple sexual partners particularly with prostitutes.
1920s	Papanicolaou developed his eponymous technique. The colposcope was developed.
1940s	Pap smear screening begins.
1980s	Linkage of Human Papillomavirus (HPV) was developed with cervical cancer. Tobacco use was linked to cervical cancer.
2000s	First Human papilloma virus (HPV) vaccine was released.

Table 2. Timeline events of cervical cytology

Year/period	Event
400 BCE	First description of cervical cancer
1834	Identification of cervical cancer as a sexually transmitted disease.
1842	Italian epidemiologist Domenico Rigoni-Stern noticed that cervical carcinoma occurred only in married or mating women.
1898	Operation of radical hysterectomy including removal of the parametrium and pelvic lymph nodes was developed.
1925	Foundation of the colposcope, a device used to examine the cervix, vagina and vulva for signs of disease.
1928	Georgios Papanicolaou developed a cervical cytology smear test (today called Pap smear) to d etect cancer cells.
1946	A wooden spatula (aylesbury spatula) with an extended tip, was introduced to scrape the cervix, collecting the sample for the Pap smear.
1951	First successful in -vitro cell line, HeLa, was derived from biopsy of cervical cancer.
1953	Adenocarcinoma in situ (AIS) of the uterine cervix was first described.
1983	HPV 16 was identified in precursor lesions of genital cancer.
1984	Cigarette smoking was found to increase risk of cervical cancer.
1985	Presence of HPV DNA in cervical cancer cells was demonstrated which lead to the development of preventive vaccines.
1988	The Bethesda system (TBS) was introduced as a system for reporting cervical or vaginal cytologic diagnoses. It was considered as standardization of screening results.
1989	Villoglandular adenocarcinoma of the cervix (a rare type of cervical cancer) was first described.
1989	Loop electrosurgical excision procedure (LEEP), for the surgical treatment of CIN, was first described.
1990	Launching of the Breast and Cervical Cancer Mortality Prevention Act which provided nationwide access to free or low-cost breast and cervical cancer screenings to underserved women.
1996–1999	Two new liquid-based Pap tests were approved by United States FDA which in comparison to the traditional method provided a clearer, easier to read sample for pathologists to review under a microscope.
1998	Researchers began human testing of a possible vaccine to prevent cervical cancer.
1999	Study shows that widespread screening reduces cases of advanced cervical cancer in older women.
1999	Chemotherapy radiation combination was alertly recommended for invasive cervical cancer.
1999	DNA test was approved to detect HPV.
2006	United States FDA approved Gardasil, a vaccine that prevents infection with the two high-risk strains of human papillomavirus (HPV). Gardasil is approved for girls and young women aged 9 to 26.
2007	Study suggests that the act of performing a Pap smear produces an inflammatory cytokine response, which may initiate immunologic clearance of HPV, thus reducing the risk of cervical cancer.
2009	Gardasil (HPV vaccine) was found to be over 90 percent effective in preventing cervical cancer in women aged 24 to 45 who received all three vaccine doses, and who are not infected by the virus.
2010	Young women in Japan become eligible to receive cervical cancer vaccination for free. However, in 2013 the local Health Ministry withdraws the vaccine recommendation for girls due to several hundred adverse reactions to the vaccines reported.
2013	Adding targeted drug bevacizumab (Avastin) to standard chemotherapy was found to improve survival for patients with relapsed and advanced cervical cancers.

(a) Progress from CIN-1 to CIN-III:

Studies of progression from mild dysplasia (CIN) to CIN-III are blighted by the difficulty in accurately determining the grade of the initial lesion. CIN I progress to CIN II in 26% of women within 2 yrs. It is estimated that approximately 10–15 % of mild to moderate dysplasia progress to invasive cancer if not treated.[20-22] About 60% of CIN 1 regress without the need for treatment.[23] It was noted that women with mild dyskaryosis had 16-47 times more incidences of invasive disease as compared to general population.[23]

(b) Progression from CIN III to Invasion:

1. The Malignant potential of CIN III is amply demonstrated by McIndoe et al (1984). About 36% of women developed invasive cancer after CIN III in 20 yrs. The length of time for this progression varies, in few months to 20 years. Without any treatment, 30-50% cases of severe cervical dysplasia may lead to invasive tumor. However, risk of cancer is lower for the mild dysplasia.[21,22]

(B)Invasive Ca Cervix:

It is regarded as preventable sexually transmitted disease. In its natural history, the cervical cancer normally progresses from ranging degree of dysplasia, in situ carcinoma to the invasive cancer. Through cytological screening (Pap smear), reduced incidence of invasive cancer and associated mortality and morbidity has been reported thereby.[4,19,20,24]

Morbidity and Mortality:

Mild dysplasia slowly progresses to severe (CIN) and carcinoma and may take 10 – 15 years to develop invasive cervical cancer. These pre-invasive lesions are easy to treat. Thus, majority of deaths can be prevented by screening program and training the patients when the disease is pre-invasive.[21,22] Five year survival rate for advanced cervical cancer is 48% which for pre-invasive cervical disease is 100%.[25]

The global estimates are 452000 new cases each year and 234000 deaths each year due to carcinoma of Cx in year 2000.[25] About 190000 deaths occur worldwide per year as a result of cervical cancer which accounts for 8.5% of all deaths due to cancer in women. In US approximately 4800 deaths occurred from this disease in 2002 which accounts for 1.5% of all cancerous deaths in females. So as a result of organized cervical screening the incidence and mortality of cervical cancer have been falling.[13] A marked fall in mortality from cervical invasive disease has been seen in Iceland, Denmark, Sweden & Finland and even in some regions of Scotland, Korea where a comprehensive screening for CIN is carried out.[26]

CONCLUSION:

Cervical carcinoma is commonly found all over the world and is one of the major causes of mortality in cancerous women. Low socio-economic and high parity status are the main risk factors. Mortality rate can only be controlled by training the patients and implementing screening programs in pre-invasive conditions of disease. A good control on this type of tumor has been observed in regions where comprehensive screening is being carried out. A lot of work is needed in Pakistan and other developing countries regarding planning and implementation of screening and training programs of women in rural and urban areas.

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