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Review Article

Cervical Cancer; a Nightmare for Womanhood: Review of Recent Advances

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Abstract

Cervical cancer is one of the commonest gynecological cancer affecting women. It is also one of the commonest cancers of females that can be detected and treated completely at precancerous stages. Despite of this, so many cervical cancer cases they die every year. The main purpose of this study is to know recent advances in screening, prevention as well as management of cervical cancer at an early stage, so as to reduce the burden of deaths resulting from this disease.

Methods: The literature regarding cervical cancer was searched from various English language journals and published peer-reviewed articles on Pubmed, MEDLINE, Embase and Google Scholar till 2015.

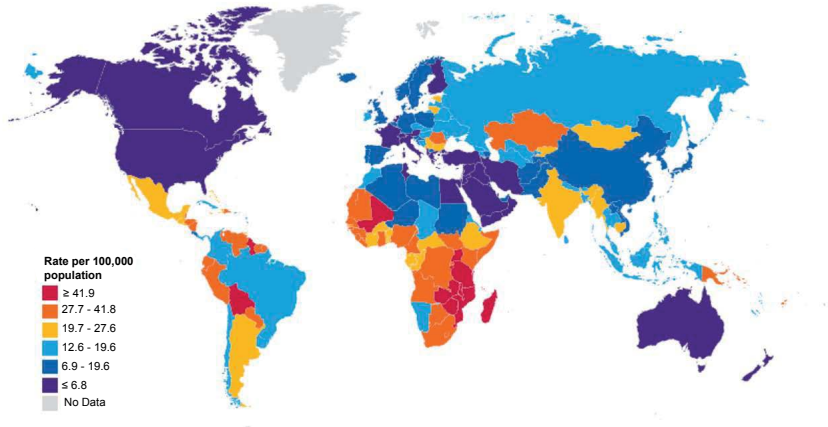
Keywords: Cervical cancer, Human Papillomavirus, Screening, Vaccine

Introduction

Cervical cancer is world's one of most deadliest – but easily preventable cancers of women, responsible for more than 2,70000 deaths annually, of which 85% occur in developing countries [1]. It is the fourth most commonly diagnosed cancer in women in 2012, with an estimated 527,600 new cases worldwide [2]. With rising population and aging, number of cervical cancer cases is expected to increase 1.5-fold by 2030 [2].

Incidence

According to the recent figures the global annual incidence of cervical cancer is around 529,800 new cases, with 275,100 deaths [3] (Figure 1) depicts the global incidence rates of cervical cancer (2012). Cervical cancer in United States was earlier leading cause of death from cancers, currently; it is 3rd in frequency as cause of death among gynecologic cancers [4]. According to most recent figures of 2011 - 2012, 109 women were diagnosed with cervical cancer and around 4,092 women died from it in United States [5]. However, in last 40 years, number of cases and deaths from



*Per 100,000, age standardized to the World Standard Population. Source: GLOBOCAN 2012.

Figure 1. International Variation in Uterine Cervix Cancer Incidence Rates*, 2012

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cervical cancer has reduced significantly. This fall is largely result of regular Pap smear screening in women, which detects cervical pre-cancerous stages [4].

In India cervical cancer is one of leading causes of cancer mortality among women 30 to 69 years of age, accounting for 17% of all cancer deaths [6]. India has a population of around 365.71 million women >15 years of age, who are at risk of developing cervical cancer. Current estimates reveal 132,000 new diagnosed cases and 74,000 deaths annually in India, accounting for nearly 1/3rd of global cervical cancer deaths [7]. Hence, at current incidence rates, annual burden of new cases in India is projected to rise to 225,000 by 2025 [6]. Furthermore, Indian women have a 2.5% cumulative lifetime risk and 1.4% cumulative death risk from cervical cancer [8]. The incidence rises in 30-34 years of age and peaks at 55-65 years, with a median age of 38 years (age 21-67 years) [8]. Little progress was achieved between 1980 and 2010, in reducing cervical cancer mortality in India: 37 women died for every 100 new cases in 1980 compared with 32 for every 100 new cases in 2010 [9]. High mortality rates are largely the result of 70% of cervical cancer cases in India being diagnosed at an advanced stage (stage III or IV) [10]. Hence, there is need of early diagnosis and treatment of cervical cancer to reduce the overall burden of this disease.

Risk Factors

Human papillomavirus (HPV): Almost all (99.7%) cervical cancer cases are result of persistent infection with high-risk type HPV. There are 15 high-risk (oncogenic) HPV, with just two, 16 and 18, responsible for 70% of all cervical cancers [11]. HPV commonly spreads through sexual contact; it can spread without sex, by skin-to-skin contact with an infected area of body [12]. Most of these infections are transient and 90% resolve spontaneously within 2-5 years. On an average, a newly diagnosed HPV infection in young women lasts from 8-13 months [13].

Other factors for cervical cancer:

Other factors either increase risk of developing cervical cancer, by increasing HPV infection or by increasing risk of developing cervical cancer following a high-risk infection. These are as follows:

- Sexual activity: Most common route of spread of HPV infection is through sexual contact, especially early onset sexual activity, multiple partners, high-risk sexual partners [11] and failure to use condoms [14].
- Compromised immune system: A weak immune system, as a result of HIV or by drugs causing suppression of immune response, places women at high risk for HPV infection and cervical cancer [12].
- Teenage pregnancy: A first term pregnancy in women <17 years of age, doubles risk of cervical cancer later in life, as compared to women with first term pregnancy at age 25 and older[12].
- Multiple pregnancies: Women with 3 or more pregnancies are at an increased risk due to hormonal changes or weak immune system during pregnancy [12].
- Family history: Woman with mother/sister having cervical cancer has 2-3 times risk of developing cervical cancer than women without family history [11].
- Oral contraceptives: Long-term use (>-5 years) increases risk of cervical cancer [12].
- Smoking: Smoking also increases risk of squamous cell cancer by exposing body to cancer-causing chemicals and also by weakening immune system [12].
- Dietary habits: A diet deficient in fruits, vegetables, as well as being overweight, increases risk of cervical cancer [12].
- Diethylstilbestrol (DES): DES increases risk of adeno-carcinoma in cervix, especially in women whose mothers took DES when pregnant [12].

Screening Guidelines

Screening guidelines for early diagnosis of cervical cancer are given by two groups [15-18] (Table 1) (Table 2).

Screening Guidelines		
	ACS/ASCCP/ASCP	**USPSTF**
	Recommendations apply to both conventional and liquid-based cytology	
When to Start	Age 21	Age 21
Intervals	Ages 21-29: Cytology alone every 3 years Ages 30-65: HPV and cytology “co-testing” every 5 years is preferred OR Cytology alone every 3 years is acceptable	Ages 21-29 years: Cytology alone every 3 years Ages 30-65: HPV and cytology “co-testing” every 5 years for women who want to extend their screening interval OR Cytology alone every 3 years
When to Stop	Women older than age 65 following adequate negative prior screening (Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 years after diagnosis.)	Women older than age 65 who have had adequate negative prior screening *(as defined below)* and who are not otherwise at high risk (Adequate negative prior screening is defined as 3 consecutive negative cytology results or 2 negative co-tests within 10 years before cessation of screening, with the most recent occurring in the past 5 years.)
Post Total Hysterectomy	Women who have had a total hysterectomy (with removal of the cervix) should not be screened unless there is a history of CIN2 or more severe diagnosis in the past 20 years, or a history of cervical cancer ever	Women who have had a total hysterectomy (with removal of the cervix) should not be screened unless there is a history of high-grade precancer or cervical cancer

Table 1. Compares current (2012) recommendations of two different groups: the U.S. Preventive Services Task Force (USPSTF) and multidisciplinary partnership among American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology (ACS/ASCCP/ASCP) for screening of cervical cancer.

Population	Women21 -65	Women 30 - 65	Women <21yrs	Women >65yrs who have had adequate prior screening and are not high risk	Women after hysterectomy with removal of cervix and with no history of high-grade precancer or cervical cancer	Women <30yrs
Recommendation	Screen with cytology (Pap smear) every 3 years. Grade: A	Screen with cytology every 3 years or co-testing (cytology/ HPV testing) every 5 years. Grade: A	Do not screen. Grade: D	Do not screen. Grade: D	Do not screen. Grade: D	Do not screen with HPV testing (alone or with cytology). Grade: D

Risk Assessment	HPV infection is associated with nearly all cases of cervical cancer. Other factors that put a woman at increased risk of cervical cancer include HIV infection, a compromised immune system, in utero exposure to DES, and previous treatment of a high-grade precancerous lesion or cervical cancer.					
Screening Tests	Screening women ages 21 to 65 years every 3 years with cytology provides a reasonable balance between benefits and harms. Screening with cytology more often than every 3 years confers little additional benefit, with large increases in harms. HPV testing combined with cytology (co-testing) every 5 years in women 30 to 65 years offers comparable balance of benefits and harms, and is therefore reasonable alternative for women in this age group who would prefer to extend screening interval.					
Timing of Screening	Screening earlier than age 21 years, regardless of sexual history, leads to more harms than benefits.					
Interventions	Screening aims to identify high-grade precancerous cervical lesions to prevent development of cervical cancer and early-stage asymptomatic invasive cervical cancer. High-grade lesions may be treated with ablative and excisional therapies, including cryotherapy, laser ablation, loop excision, and cold knife conization. Early-stage cervical cancer may be treated with surgery (hysterectomy) or chemoradiation.					
Balance of Harms and Benefits	Benefits of screening with cytology every 3 years substantially outweigh harms.	Benefits of screening with co-testing (cytology/HPV testing) every 5 years outweigh harms.	Harms of screening earlier than age 21 years outweigh benefits.	Benefits of screening after age 65 years do not outweigh potential harms.	Harms of screening after hysterectomy outweigh benefits.	Potential harms of screening with HPV testing (alone or with cytology) outweigh potential benefits.

Table 2. Clinical Summary of U.S. Preventive Services Task Force Recommendation for Cervical cancer screening.

Histopathologic Types of Cervical Carcinoma

- Squamous cell carcinoma (66%): Arises in squamous epithelial cells of cervix.
- Adenocarcinoma (28%): Arises from mucus-producing glandular cells of endocervix.
- Rarer types (6%) [19]: Adenosquamous carcinoma, neuroendorine carcinoma.

Gross Appearance

There are three categories of gross appearance of cervical carcinoma:

1. Exophytic lesions: Most common form and arises on ectocervix. Grows to form large, friable, polypoidal masses that bleed profusely.
2. Infiltrating lesions: Presents as stony hard cervix with minimal or invisible lesion on cervix.
3. Ulcerative lesions: Presents as an ulcer over cervix, often replacing whole of cervix.

Clinical Features

Early symptoms

1. Profuse, thin, watery, blood tinged discharge,
2. Intermittent, painless metrorrhagia or spotting – Classic symptom,
3. Postcoital / post-douching bleeding or spotting.

Symptoms of Advanced disease

1. Bleeding episodes become heavier, frequent and last longer,
2. Post-menopausal bleeding,
3. Referring pain to flanks or legs due to involvement of ureters, pelvic wall, sciatic nerve routes,
4. Dysuria, hematuria - due to bladder involvement,
5. Rectal bleeding, obstipation - due to rectum involvement,
6. Edema lower extremities (one/both) due to lymphatic and venous blockage by pelvic wall disease,
7. In severe cases uremia as a result of bilateral ureteric compression and damage of kidney due to back pressure.

Dissemination and Spread

Direct local extension and lymphatic spread are main routes of spread of cervical cancer. Hematogenous dissemination is rare and occurs commonly with more advanced disease or unusual types, such as adenosquamous or neuroendocrine tumors.

Direct Extension

Direct extension involves uterine body, vaginal walls, parametrium, peritoneal cavity, bladder, or rectum. Ovarian involvement by direct extension is very rare; ovarian metastases occur in 0.5% of squamous and 1.7% of adenocarcinomas. Lateral spread of cervical cancer may involve ureters. About one third of patients with stage IIIB have ureteral obstruction, and about 5% have bilateral obstruction [20]. It may spread posteriorly to involve rectum or uterosacral ligaments. Anteriorly it spreads to involve bladder, but this is rare in absence of large-volume tumors.

Lymphatic Embolization

Lymphatic spaces involvement causes lymphatic embolization to regional lymph nodes. It is commonly seen with large volume

tumors and or if many lymphatic spaces are involved. Lymphatics from cervix drain into external iliac, hypo gastric, obturator, and common iliac nodes [21]. Anterior channels pass behind bladder and drain in external iliac nodes. Posterior channels drain directly into common iliac and Para-aortic nodes and superior rectal nodes.

The best study of lymph node involvement in cervical cancer was done by Henriksen which is as follows [22]:

Primary Group

1. Parametrial nodes: Small lymph nodes traversing parametria,
2. Paracervical/ureteral nodes: Located above uterine artery where it crosses ureter,
3. Obturator or hypogastric nodes surrounding obturator vessels and nerves,
4. Hypogastric nodes, along hypogastric vein near its junction with external iliac vein,
5. External iliac nodes: group of 6-8 nodes,
6. Sacral nodes.

Secondary Group

1. Common iliac nodes,
2. Inguinal nodes: Deep and superficial femoral lymph nodes,
3. Periaortic nodes,
4. Supraclavicular nodes.

The stage wise risk of pelvic lymph node metastasis [23-25]

Stage IA1 - 0.6% Stage IA2 - 7% Stage IB1 - 8% Stage IIA - 12% Stage IIB - 29% Stage IIIA - 17% Stage IIIB - 27% Stage IVA - 47%

Hematogenous Spread

Poorly differentiated, aggressive types are more likely to spread by hematogenous route. Hematogenous spread usually occurs through invasion of veins rather than arteries [26]. About 1-2% of women with cervical carcinomas show lung metastases, and 5- 35% develop pulmonary metastases [27-31]. Other common sites of hematogenous metastases are liver (3%) [21], bone (16%) [28] and bowel. Small bowel metastases can also result from direct extension from Para-aortic lymph node or from intraperitoneal dissemination [21] (Table 3).

TNM and FIGO Classifications for Cervical Cancer

Regional lymph nodes (N):

NX: Regional lymph nodes cannot be assessed

N0: No Regional lymph node metastasis

N1: Regional lymph node metastasis

Distant Metastasis (M):

M0:No distant metastasis

M1: Distant metastasis (including peritoneal spread; involvement of supraclavicular, mediastinal or para-aortic lymph nodes; and lung, liver or bone).

Stage-Wise Therapy

Stage 0 cancer

Carcinoma in situ (stage 0) is treated with local ablation/ excisional measures (cryosurgery, laser ablation and loop

TNM	FIGO	**Surgical-Pathologic Findings**
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ (pre-invasive carcinoma)
T1	I	Cervical carcinoma confined to the cervix (disregard extension to the corpus)
T1a	IA	Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less; vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion ≤ 3.0 mm in depth and ≤ 7.0 mm in horizontal spread
T1a2	IA2	Measured stromal invasion > 3.0 mm and ≤ 5.0 mm with a horizontal spread ≤ 7.0 mm
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T1b2	IB2	Clinically visible lesion > 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T2a2	IIA2	Clinically visible lesion > 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctional kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	III B	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctional kidney
T4	IV	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)
T4a	IVA	Tumor invades mucosa of bladder or rectum (bullous edema is not sufficient to classify a tumor as T4)
T4b	IVB	Tumor extends beyond true pelvis

Primary tumor (T)

Table 3: Depicts TNM classification and the FIGO staging system for cervical cancer.

excision) with lifelong follow-up. For ectocervical lesions; loop electrosurgical excision procedure (LEEP)/ laser therapy or conization / cryotherapy is advised. For lesions involving endocervical canal; laser/cold-knife conization can be recommended in women wanting to retain reproductive functions. Total abdominal hysterectomy is advised in post-reproductive age group and when cancer extends to inner cone margin.

Stage IA1 cancer

Treatment of choice is surgery. Total abdominal hysterectomy, radical hysterectomy, and or conization are accepted procedures. Lymph node dissection is usually not required if depth of invasion is <3 mm with no lymphovascular space invasion. According to National Comprehensive Cancer Network (NCCN) guidelines, pelvic radiation therapy is currently category 1 recommendation for stage IA and negative lymph nodes after surgery with high-risk factors (large primary tumor, deep stromal invasion or lymphovascular space invasion)[32].

Stage IA2: Radical hysterectomy (type II) with pelvic node dissection [33].

Stage IB, or IIA cancer

Stage IB1: Radical hysterectomy and bilateral pelvic lymphadenectomy with or without chemoradiotherapy.

Radiation therapy**:** External-beam pelvic irradiation combined with intracavitary applications of dose of 80Gy to point A.

Stage IB2 and IIA: The treatment options include;

- Radical Radiation therapy (External plus intracavitary).
- Radical hysterectomy (Type III) with bilateral pelvic lymphadenectomy
- Chemoradiotherapy.

Adjuvant therapy after radical surgery

- High risk cases: Nodal metastases with positive surgical margins: Adjuvant chemo-radiotherapy with external pelvic radiation along with weekly Cisplatin chemotherapy.
- Intermediate risk: Deep invasion of cervical stroma, parametrial extension, lymphovascular space invasion: Adjuvant radiation therapy.
- Low risk: All other patients: No adjuvant therapy recommended.

Stage IIB, III A or IIIB cancer

Radiotherapy is treatment of choice. Results from many large, randomized trials reveal dramatic improvement in survival rate with chemoradiotherapy [34-36]. Hence, use of Cisplatin-based chemotherapy in combination with radiation has become standard of care for management of women with locally advanced cancer [32].

Stage IVA and IVB

For advanced disease palliative therapy is mainstay. Radiation therapy for control of bleeding and pain, whereas systemic chemotherapy for disseminated disease is recommended [32].

Recurrence of Cervical Cancer

Cervical carcinoma recurrences are commonly seen at 40-45 years of age. Stage-wise recurrence rate: FIGO stage IB- 10%, for stage IIA - 17%, stage IIB- 23%, and stages III and IVA - 42% and 74% respectively [37]. The reported recurrence rate by tumor size is: tumors <2 cm 1.2% while for tumors >2 cm 21% [38,39]. Most common sites of pelvic recurrence are cervix, uterus, vagina, parametria, bladder, ureters, rectum, and ovaries [40]. Most frequent distant sites are paraaortic lymph nodes (81%), lungs (21%), and supraclavicular lymph nodes (7%), and incidence relates with stage of disease: 0-3% in stage IA, 13-16% stage IB, 22-31% stage IIA, 22-26% stage IIB, 32-39% in stage III and 75% in stage IVA [41].

Clinical features of recurrence are often non-specific characterized by weight loss, inferior limb edema, pelvic/lower limb pain, vaginal bleeding, respiratory symptoms and increase of supraclavicular lymph nodes. Triad of weight loss, leg edema and pelvic pain is a pathognomic of recurrent disease. Majority of recurrences occur within 18-24 months from time of diagnosis [42].

Treatment of choice for recurrent cervical cancer is based on type of primary therapy received, recurrence site (local, regional, and/ or distant), disease-free interval, symptoms. Treatment with Bevacizumab plus Cisplatin and Paclitaxel or Topotecan and Paclitaxel was approved by FDA in 2014 for persistent, recurrent, or metastatic cervical cancer [43,44]. Statistically significant improvement in overall survival rate and increased rate of tumor shrinkage was noted in women treated with Bevacizumab plus chemotherapy in comparison to chemotherapy alone [45]. According to study the overall survival was 17 months with Bevacizumab and chemotherapy, whereas it was only 13.3 months with chemotherapy alone [46-48].

Cervical Cancer in Pregnant Women

Cervical cancer is most common gynecological malignancy during pregnancy. Incidence varies from 0.1-12 per 10,000 pregnancies [49] whereas incidence of cervical intraepithelial neoplasia (CIN), varies between 1.30 and 2.7 per 1000 pregnancies [49].

Treatment of cancer cervix during pregnancy is most difficult and challenging as pregnant uterus itself is affected. Also rarity of this disease makes large trials or randomized studies impossible. Still many clinical guidelines [50-52] as well as a *Lancet* series paper have been published [53] in order to reach a consensus on treatment of cervical cancer during pregnancy.

Pre-invasive disease

Main treatment of pre-invasive disease during pregnancy is observation. Pregnancy does not affect cervical lesions, and progression to invasive is usually rare (0-0.4%) [54]. Colposcopy and directed biopsies can be safely performed during pregnancy, but endocervical curettage is absolutely contraindicated [55].

Invasive disease

Treatment: Treatment depends mainly on gestational age, disease stage, histology and women's need. When preservation of pregnancy is not required, standard treatment with radical hysterectomy (with fetus in utero) and chemo-radiotherapy are

both feasible options. When cervical cancer is diagnosed during first trimester, conservative approach is followed till second trimester. During third trimester, fetal maturity is awaited and classical caesarean section followed by standard treatment is recommended. During second trimester, interventions including lymphadenectomy, conization, trachelectomy and neoadjuvant chemotherapy can be considered [56].

Stage IA

Conization can be done, but the optimal time to perform during pregnancy is between 14 and 20 weeks of gestation.

Stage IB1, tumor size ≤2 cm

Radical trachelectomy can be considered in stage IB1 disease with a tumor size ≤2 cm, and no nodal involvement [57]. There are few published case reports of antepartum trachelectomy, with a fetal loss rate of 33% within 16 days of surgery [53,58,59]. Major concern with this procedure is perioperative and postoperative bleeding, and also decreased blood supply to uterus if uterine arteries are sacrificed [58]. Alternatively, trachelectomy can be replaced by conization with tumor size ≤2 cm and negative nodal status [60].

Stages IB1, tumor size >2 cm and higher stages

When conservative surgical treatment during pregnancy is not possible, neo-adjuvant chemotherapy can be given until fetal maturation, followed by radical hysterectomy in postpartum period [61]. Cisplatin 50-100 mg/m^2 every 3 weeks have been proposed as standard treatment during pregnancy [53]. Carboplatin can also be given as it has a more favorable toxicity profile with less nephrotoxicity and ototoxicity, but with similar efficacy [62]. Based on toxicity profile and experience in ovarian cancer, Paclitaxel with Cisplatin or Carboplatin can also be recommended during pregnancy [56,63]. For safety of fetus all chemotherapy drugs should be avoided during first trimester that is during period of organogenesis [64].

Neonatal outcome after chemotherapy in-utero

In a prospective analysis of 70 children exposed to chemotherapy in utero, long-term follow up was reassuring (median follow up of 22.3 months) [65]. General cognitive development was found to be within normal range for most children except those who were born preterm.

Impact of Cervical Cancer on Quality of Life

Cervical cancer affects both physical and emotional wellbeing of a woman. Being diagnosed with cervical cancer, going through its treatment, and dealing with the stresses puts a woman into a hormonal and emotional tailspin. Shock, fear, self-blame, powerlessness, and anger are the most common emotions experienced by women with abnormal Pap test results [66]. Diagnosis of a precancerous lesions or cervical cancer is emotionally very traumatic for women, and can affect their relationships and intimacy with partners [67,68]. Up to 90% of women after cancer may experience loss in Quality of Life and sexual difficulties [69-71]. Also cervical cancer treatments, such as surgery, chemotherapy and radiation, can result in a distortion of body image and deeply affects one's confidence of sexual attractiveness [72,73]. Moreover, while the psychological factors have been studied in both retrospective and prospective studies [74,75], the role of biological factors have been marginally addressed with the exception of radiotherapy damages [76,77]. It is time that physicians should improve their skills in discussing sexual implications to better understand woman's need [78]. Hence, a woman with abnormal Pap smear report and those with diagnosed cervical cancer require lot of counseling, patience and time to make them strong enough to deal with the disease and its treatment.

Newer Approach

HPV Vaccines: Two vaccines approved by FDA (Gardasil and

Females Males		
Recommended Age Ranges	• Administer at 11-12 years of age, along with other age-appropriate vaccines, such as tetanus, diphtheria, and acellular pertussis (Tdap) and meningococcal conjugate (MCV4) vaccines • May be administered as early as 9 years of age	
Catch-up Vaccination Recommendations	• Routinely provide catch-up doses through age 26 to females who have not completed the 3-dose HPV vaccine series	• Routinely provide catch-up doses through age 21 to males who have not completed 3-dose HPV vaccine series. • Provide catch-up doses to males through age 26 who meet any of the following conditions: -Immuno-compromised as a result of infection (including HIV), disease, or medications -Has sex with other men -Wants to be vaccinated and does not meet the above two criteria
Doses	• 3 doses of Quadrivalent HPV4 vaccine (Gardasil) or • 3 doses of Bivalent HPV2 vaccine (Cervarix)	• 3 doses of Quadrivalent HPV4 vaccine (Gardasil)
Precautions and Contraindications	• Precaution: Moderate or severe acute illness • Contraindication: Anaphylaxis to a vaccine component (i.e., yeast) or following a prior HPV vaccine dose. • **Contraindication: Pregnancy**	
Administration	• 0.5 ml, administered intramuscularly, preferably in deltoid • observing them for 15 minutes following vaccination, since syncope has been observed in adolescents receiving immunizations.	
Recommended Intervals	• Dose 1: Preferably at 11-12 years of age • Dose 2: 2 months after first dose, with a 4-week minimum interval • Dose 3: 6 months after the first dose, with a 12-week minimum interval between Dose 2 and 3, and a 24-week minimum interval between Dose 1 and 3 If minimum intervals above are not met, re-administer Dose 2 and/or 3. If intervals are longer than minimum intervals, follow routine dosing intervals for series catch-up. Do not restart the series.	

Table 4: HPV Vaccination Recommendations by Advisory Committee on Immunization Practices.

Cervarix) are highly effective in preventing infection with HPV. Gardasil targets HPV 6, 11, 16 and 18 and Cervarix acts against types 16 and 18. Gardasil is safe for use in females (and males) ages 9 to 26 and Cervarix in females 9 to 25 years [79].

Revised ACIP Recommendations Call for Vaccination of Males In 2011, the Advisory Committee on Immunization Practices (ACIP) recommended that males, in addition to females, should routinely receive three doses of HPV vaccine at 11-12 years of age [80-82] (Table 4).

Targeted Therapy: Treatment with drugs that target gene changes in cells causing cancers is often called targeted therapy. They are different from chemotherapy drugs in the sense that they attack cancer cells only without causing damage to normal cells [83]. Pazopanib is a targeted therapy drug that blocks effect of certain growth factors on cancer cells. This drug is basically a kinase inhibitor and inhibits several kinase proteins (VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-A, PDGFR-B, FGFR-1, FGFR-3, Kit, Itk, Lck, and c-Fms). These proteins either promote tumor cells to grow and divide or help form neo-angiogenesis. By blocking these proteins, Pazopanib may help stop growth of cancer cells and can be used for cervical cancer management [84].

Still there is a long way to go to prevent development of this dreadful disease in women. Early screening and detection can help in reducing the overall burden of cervical cancer in near future.

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