

Review Article**Cervical Cancer in the Philippines: Epidemiology, Prevention and Treatment**

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ABSTRACT Cancer of the cervix is the most common gynecologic malignancy in the Philippines. It is consistently associated with high-risk human papillomavirus (HPV) types, particularly types 16 and 18. Identified co-factors for the development of cervical cancer include low socioeconomic status, smoking, parity of 6 or more, oral contraceptive pill use, young age of first intercourse and risky sexual behaviors. Pap testing, on the other hand, has been proven protective. Cervical cancer screening programs available in the Philippines include Pap smears, single visit approach (SVA) utilizing visual inspection with acetic acid (VIA) followed by cryotherapy, and colposcopy. Prophylactic HPV vaccination of both quadrivalent and bivalent vaccines has already been approved in the Philippines and is gaining popularity among the Filipinos. However, there is still no national or government vaccination policy implemented. Guidelines in the management of cervical cancer are provided by the Society of Gynecologic Oncology of the Philippines, Inc (SGOP), with radiation therapy concurrent with chemotherapy being the standard of treatment. Current researches are directed toward improving preventive and therapeutic approaches to cervical cancer.

KeyWords: cervical cancer, epidemiology, cervical cancer screening program, HPV vaccination

Introduction

Cervical cancer has been identified as a fatal but preventable disease. In industrialized countries, the use of Pap testing for cytology-based screening has been highly effective in decreasing the incidence of cervical cancer. However, in the Philippines, burden of cervical cancer remains moderately high, where an existing health infrastructure has not been sufficiently developed to support cytology-based screening programs. Currently, the use of alternative screening modalities, such as visual inspection of the cervix aided by acetic acid (VIA) with or without magnification, is under evaluation. Prophylactic human papillomavirus (HPV) vaccination has likewise been considered as an additional strategy in cervical cancer prevention.

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Prevalence of Cervical Cancer in the Philippines

Cervical cancer remains to be the most common gynecologic malignancy and the most common cause of cancer-related deaths among Filipino women. From 1980 to 2005, the incidence of cervical cancer remained stable [1], with an annual age-standardized incidence rate of 22.5 cases per 100,000 women [2]. Based on the Filipino cancer registry, there were 7,277 new cases of cervical cancer diagnosed in the year 2005. Seventy-five percent of these were diagnosed at a late stage. The overall 5-year survival rate was 44%. There were 3,807 deaths reported, with a mortality rate of 1 per 10,000 women [1].

At the Philippine General Hospital (PGH), the country's government tertiary center reporting the highest number of new cervical cancer cases, 466 new cases were seen in the year 2006. Among these cases, more than half (52%) were diagnosed as stage I II (Figure 1) [3]. With respect to the histologic types, 68% of the cases were squamous cell carcinoma, 21% adenocarcinoma, 3% adenosquamous and 8% of other histology [3].

Prevalence of HPV in the Philippines

Persistent infection with high-risk HPV types has been established to be a necessary cause of cervical cancer. In the study by Ngelangel, et al (1998), the reported prevalence of all HPV types among Filipino women with cervical cancer is 93.8% in squamous cell carcinoma and 90.9% in adenocarcinomas [4].

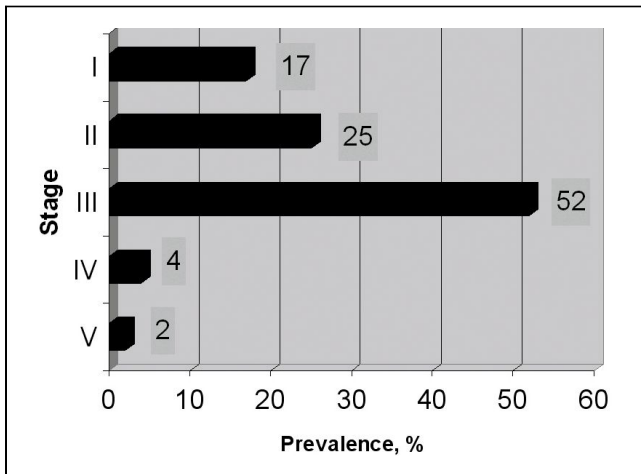


Fig. 1 Stage Distribution of Cervical Cancer [3]^a

^a Stage V represents patients referred to PGH wherein stage could not be fully determined because these patients underwent surgical treatment in another institution prior to referral.

HPV 16 and 18 are the 2 most common high-risk HPV types associated with cervical cancer. HPV 18 has been reported to be relatively more frequent in the Philippines as compared to other countries. Other common HPV types are 45, 52, 51. In squamous cell carcinoma, the most common HPV type is 16, followed by types 18, 45, 52 and 51; whereas in adenocarcinoma, HPV type 18 is the most common, followed by types 16 and 45 (Table 1) [4].

High-risk HPV types have also been identified in cytology studies of Filipino women with normal cervixes. The reported prevalence of HPV in exfoliated cells of these women is 9.2%. The most common type seen is type 45, followed by HPV types 16 and 18 [4].

Co-factors for Cervical Cancer

Epidemiological studies have clearly demonstrated the role of

co-factors in cervical carcinogenesis. In the case control study of Ngelangel, et. al. (1998), factors associated with increased risk of squamous cell carcinoma include low socioeconomic status, smoking, parity of 6 or more and young age of first intercourse. More frequent Pap testing, on the other hand, has been shown to decrease the risk for squamous cell carcinoma [4]. The prevalence of some co-factors in the Philippines is shown in table 2 [5].

Early Age of Sexual Debut

According to the 2005 World Health Organization-Western Pacific Regional Office (WHO-WPRO), the mean age of sexual debut among Filipinos is 14-15 years. About 10% of the young women reported that their first premarital sex experience was without their consent. In 2002, 23% of young adults reported having had a sexual experience, with an estimated 1.6 million (34%) of those aged 15-27 years having had multiple sexual partners [8].

Among sexually active adolescents, knowledge on contraception is poor. Of those surveyed, only 4% of young women can be considered knowledgeable on the subject of contraceptives and family planning. Only 26% of sexually active adolescents admitted to having used contraceptives, with condom use as the most common method. Twenty seven percent (27%) thought that the pill must be taken just prior to or straight after sexual intercourse. An increasing number of female adolescents have also been reported to engage in unprotected commercial sex (17% in 1994 and 30% in 2002). Seventy eight percent (78%) of male adolescents do not use contraceptives, and 6% of these engage in commercial sex [8].

The rapid increase in the number of young adults becoming sexually active translates to an increased risk for sexually transmitted infections (STI). The prevalence of STIs such as gonorrhea and *Chlamydia trachomatis* is high among young people. Human immunodeficiency virus (HIV) infection in females occurs at a younger age group compared to males (47% of infected women are between 20-29 years) [8].

Table 1

Human Papillomavirus Types in Women with Cervical Cancer and in Women with Normal Cytology in the Philippines [4]^a

HPV type	Squamous Cell Carcinoma		Adenocarcinoma		Women with Normal Cytology	
	Number	%	Number	%	Number	%
Negative	20	6.2	3	9.1	346	90.8
Positive ^b	303	93.8	30	90.9	35	9.2
16	130	40.2	8	24.2	5	1.3
18	77	23.8	17	51.5	5	1.3
45	41	12.7	5	15.2	6	1.6
51	10	3.1				
52	10	3.1				

^a Number of patients evaluated was 323 patients for squamous cell carcinoma, 33 adenocarcinoma and 381 women with normal cytology. HPV types included in the table are only the most common identified. ^b For any HPV types

Table 2
Prevalence of Smoking, Oral Contraceptive Use and Total Fertility in the Philippines [5]

Co-factors	Prevalence, %
Current smoking	12.3
Ever use of contraception	13.2
Total fertility rate (per woman)	3

Risky Sexual Behavior

Significant risky behaviors and low knowledge of the Filipinos about STI contribute to increased risk for cervical cancer. In a survey done in 2002, freelance Filipino female sex workers admitted having an average of 5 partners every week with only 30% consistent condom use. Condom use is ascribed to a lot of myths, and there is little or no knowledge on transmission and prevention of STI [6].

High-risk male individuals, namely male sex workers, seafarers and truckers, admit to inconsistent condom use. A multicenter population based survey by Jimenez, et. al. (2000) reported low condom usage among Filipino high-risk males, with its primary usage being for contraception and not as protection against STI [7].

Overseas Filipino workers (OFW) are also considered vulnerable to STI. These individuals admit to inconsistent use of condoms despite engaging in casual sex brought about by factors, such as homesickness, desire for sexual contact, economic pressure to engage in paid sex, and vulnerability to sex trafficking [6].

Cervical Cancer Screening Initiatives

Current Situation of Cervical Cancer Screening

The current cervical cancer screening condition in the Philippines is best described as “convenient-screening” [9]. Of the 389 hospitals surveyed, only 42% offer screening and early detection services for cervical cancer, with only 8% having dedicated screening clinics [2]. The reported Pap smear coverage of Filipino women aged 18-69 years was only 7.7% [5]. Based on the study of the University of the Philippines - Department of Health (UP-DOH) Cervical Cancer Screening Study Group in 2001, only 23% of respondents had received a Pap smear in which 26.6% of these women were from metropolitan Manila and 18.5% were from other areas outside of metropolitan Manila. The women who were more likely to have Pap smears were married, had more children, had a family history of cancer or perceived themselves to be at risk for the disease [10].

Findings from a 1998-2000 community-based cross-sectional study showed that knowledge on cervical cancer was inadequate [9]. The disease was regarded as anxiety-provoking, and serious but moderately curable. Furthermore, even if there was adequate

knowledge and awareness of the benefits of cervical cancer screening tests, the cost of the tests limits a woman from availing of the service [9].

Department of Health Cervical Cancer Screening Program

In February 2005, the Philippine DOH released an Administrative Order to establish a Cervical Cancer Screening Program. This program aims to initiate an “organized” nationwide program that includes sustainable capability building, training, educating, and hiring of health workers on proper VIA, Pap smear, cytology, colposcopy, and pathology [9]. At the primary service delivery level, VIA will be advocated as an alternative screening method for cervical cancer. In the secondary service delivery level, aside from VIA, Pap smear with VIA triage, colposcopy, tissue biopsy, cryosurgery and surgery treatment (total abdominal hysterectomy (TAH) and total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO)) will be made available. All these facilities, plus radiotherapy and chemotherapy will be available at the tertiary service delivery level [9].

The Cervical Cancer Screening Program recommends the following screening guidelines: (1) women 25-55 years old will undergo VIA cervical cancer screening at least once every 5-7 years in areas with no Pap smear capability, otherwise Pap smear will be used; (2) acetic acid wash (3-5%) will be used as the primary screening method at local health units (rural health units; health centers), district hospitals and provincial hospitals with no Pap smear capability; (3) VIA will be used as a triage method before Pap smear at district, provincial and regional hospitals with Pap smear capability; (4) positive or suspicious lesion noted upon screening will be referred immediately; and (5) referral centers for cervical cancer diagnostic tests and treatment will be established in tertiary facilities [9].

Although the DOH screening program is not fully implemented as of yet, sustainability of the program will be ensured through local financing, e.g., subsidy from the local government unit or health facility concerned, Philippine Health financing, or fee for service (user fee) scheme. A standard system of recording and reporting will be developed at service delivery facilities in collaboration with population-based cancer registries. Periodic evaluations will be done to assess the quality of VIA being done, and cytology-based centers will be improved and increased as the country's economics improve. In order to target women about cervical cancer screening and services, there will be an annual public education campaign via mass media and interpersonal communication within each health center.

JHPIEGO Cervical Cancer Prevention Network Program

In 2006, the Johns Hopkins Program for International Education on Gynecology and Obstetrics (JHPIEGO) Global Cervical Cancer Prevention launched the JHPIEGO Cervical Cancer Pre-

vention Network Program (CECAP) at the Philippine General Hospital Cancer Institute. The aim of CECAP is to increase education and awareness about cervical cancer in Filipino women and provide them with access and information to screening and effective treatments through single visit approach (SVA) VIA screening and treatment with cryotherapy for those positive during the same visit, as well as HPV vaccination.

Prophylactic HPV Vaccination

Vaccine Acceptability

Two prophylactic HPV vaccines are registered and marketed in the Philippines, namely, the quadrivalent vaccine (Gardasil) that prevents against HPV types 6, 11, 16 and 18 and the bivalent vaccine (Cervarix) that prevents against types 16 and 18.

Zalameda-Castro and Domingo (2007) conducted a focused group discussion and exploratory survey to determine the acceptability of HPV vaccine. One hundred ninety-five women with daughters 12-15 years were recruited from the Philippine General Hospital Obstetrics-Gynecology Charity Clinic [11]. Only 14.4% of those surveyed had heard of HPV with the television and doctors being the main sources of information. Approximately 56.4% of the women identified HPV as an STI and only 31.8% associated it to the development of cervical cancer. The HPV vaccine was acceptable to 75.4% of women because it would prevent illness, and of these more than half (55%) thought it should be given prior to sexual activity, while 27% thought it should be administered between 12-15 years of age. Many thought that men should also receive the vaccine to prevent them from infecting their partners [11].

Respondents were likewise recruited from the Philippine General Hospital general wards. In ten mothers aged 21-43 years, nine mothers would allow their children to receive the HPV vaccine even if only one out of ten knew about it. Likewise, in ten pediatric patients aged 10-19 years, seven would like to receive the vaccine [11].

The predominant reason for non-acceptance of the vaccine is its high cost. Another concern is the issue that it could promote or encourage unsafe sexual behavior among adolescents. Other cited reasons for non-acceptance were young age, painful injection and sexual inexperience [11].

Prospects for Vaccination Policy and Delivery

The Philippine DOH has not formulated a policy on HPV vaccination, perhaps stemming from the most controversial concern that such formal policy could have a negative impact on sexual behavior of the youth. However, it may be worthwhile to consider the impressions from the Report Card HIV Prevention for Girls and Young Women (the Philippines) as a framework for a prospective Philippine HPV Vaccination Program: (1) minimum legal age

at marriage is 18 years; (2) sex work is illegal but tolerated and common in many areas; (3) there is no budget allocation for sexual and reproductive health services, and where such services exist, they tend to be based on marital status that on age-married youths are regarded as adults for whom services are "acceptable", with discrimination against those who are not married; (4) STI treatment is not free, neither is voluntary counseling and testing; and available data suggest that fewer women access STI testing compared to men [12].

More young people engage in sex at an earlier and often without contraception. These issues call for a comprehensive evidence-based sexual and reproductive health program that takes into consideration the needs of the youth. It should have a clear guideline, which is national in scope that will provide young people with access to health services. Commitment to women's health should incorporate HPV vaccination into the educational curriculum with learning modules to adequately train teachers. The success of HPV prevention for girls and young women will depend on the political will of the government, as well as the support from relevant inter-governmental and non-government organizations (NGOs), and donors.

Research on Deployment of HPV Vaccination

The current DOH Cervical Screening Program includes Pap smear, VIA, colposcopy and tissue biopsy in women aged 25-55 years. If HPV vaccination is integrated into this program, the target population should be extended to include girls and women aged 11-24 years, and those who have not been vaccinated or have not completed the full course.

A national registration system that is linked to a population-based tumor registry could also be implemented to identify a cohort of vaccinated women who can be followed up and compared to unvaccinated cervical cancer cases identified from the tumor registry.

Introduction of an HPV vaccination program can be done in phases across different regions of the archipelago through demonstration research projects. Once the program is operational, evaluation of its short and long-term effects can be done, specifically to evaluate: (1) the knowledge, attitudes, practices and acceptability of vaccination of the target female population and health providers before, during and after implementation to capture behavioral changes and caveats to improve the program and to assess the effectiveness of regular information, education and communications campaigns; (2) the technical issues on vaccine use in the field-vaccine storage, handling, and distribution as well as a nationwide registry; (3) compliance with the three dose vaccine regimen; (4) the health economic impact of vaccination with regard to efficacy and long term safety, and to include the use of new vaccines; (5) the effects on sexual-reproductive health demographics of Filipino adolescents; (6) the effects of cervical screening, although the recommendation for screening has not changed for women who have

been vaccinated; and (7) the impact of HPV vaccination on the incidence of cervical cancer. Evaluation of the HPV vaccination program should be spearheaded by the government with collaborative support from local agencies and international research organizations.

The DOH has not received a proposal for the inclusion of HPV vaccination in its relevant public health programs such as the Expanded Program for Immunization, Women’s Health and Safe Motherhood Program and Cancer Control Program. School-based programs may be the best way to reach the target youth. In this regard, the Department of Education, Culture and Sports (DepEd) may be involved in the HPV vaccination campaign. DepEd’s Population Education Program includes a curriculum on responsible sexual behavior and reproductive health care commencing at the 5th grade elementary school level and up to college. To cover the out-of-school youths that comprise 15% of the 7-24 year age group, community-based programs should be the most appropriate approach.

Guidelines in the Diagnosis of Cervical Cancer

The Society of Gynecologic Oncology of the Philippines, Inc. (SGOP) provides a clinical practice guideline (CPG) for gynecologic oncologists of the country to standardize diagnosis and treatment of gynecologic malignancies. In the diagnosis of cervical cancer, histologic confirmation is necessary. Staging is based on careful clinical evaluation with includes inspection and palpation, preferably under anesthesia, colposcopy, proctosigmoidoscopy, cystoscopy, intravenous pyelography (IVP), chest x-ray and skeletal survey, if necessary. The use of imaging studies such as ultrasound, magnetic resonance imaging (MRI) computed tomography scan (CT scan), positron emission tomography scan (PET scan), PET CT scan and bone scintigraphy may be done to guide in treatment planning but are not used for staging [13]. The International Federation of Gynecologic Oncology (FIGO) classification is the staging system followed.

Treatment and Treatment Outcomes

Complete radiotherapy concurrent with chemotherapy (concurrent chemoradiation) is the standard of treatment. For patients who are unable to receive chemotherapy, radiation alone is acceptable. Standard chemoradiation regimen consists of pelvic external beam radiotherapy concurrent with chemotherapy followed by brachytherapy. Extended field radiotherapy is considered in the presence of paraaortic lymphadenopathy detected by MRI or CT scan or confirmed by fine needle aspiration biopsy or extraperitoneal or laparoscopic lymphadenectomy. Surgical intervention after protracted chemoradiation (of > 8 weeks) is an option.

Surgery, as primary therapy, may be offered for selected early staged disease. For stage IA1 extrafascial hysterectomy with or without bilateral salpingo-oophorectomy is recommended, while

for stage IA2-IIA radical hysterectomy with or without bilateral salpingo-oophorectomy with pelvic lymphadenectomy is recommended. Radical vaginal hysterectomy is also a surgical option but is limited to selected cases of stage IB1-IIA - those with low risk for parametrial or nodal metastasis, tumor size less than 2 cm, with no evidence of metastasis by imaging and metastatic work-up, and with pelvic organ prolapse. Patients who underwent initial surgical intervention may require adjuvant chemoradiation in the presence of surgico-pathologic prognostic factors, namely tumor size > 2 cm, cervical stromal invasion greater than 1/3, positive lines of resection, presence of lymph node metastasis, positive lymphovascular space invasion (LVSI), and presence of endomyometrial invasion. The presence of tumor in the vaginal cuff or less than 2 cm tumor free margin requires additional brachytherapy. In the presence of biopsy-proven metastasis, systemic chemotherapy and individualized radiotherapy is recommended. [13]

Treatment Outcomes

Based on the 2008 annual statistics of the Philippine General Hospital, 75.6% of the new cases of cervical cancer seen were candidates for chemoradiation, and only 11.6% were eligible for surgery (Fig.2) [14].

Among the patients for chemoradiation, only 17.6% were able to complete treatment. Fifty three percent were not able to start treatment at all (Fig.3) [14]. Treatment-related costs of cervical cancer is the main limiting factor as it exceeded twice the average annual income in the Philippines with an average cost of US \$350-1,100 for diagnosis and pretreatment evaluation, US \$1,100-4,850 for surgery and US\$2,100-6,000 for chemoradiation [3].

It is uncommon for patients to complete chemoradiation within the recommended period of 55 days (7-8 weeks). Among the patients treated with chemoradiation, only 22.6% were able to complete treatment within 7-8 weeks. Seventy-two percent completed treatment for more than 9 weeks (Fig. 4). The common reasons for

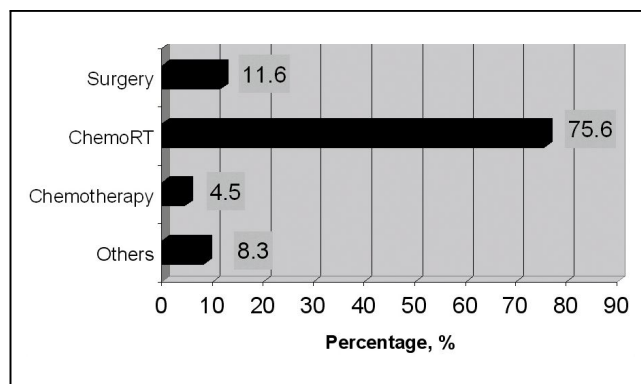


Fig. 2 Therapeutic Interventions for Cervical Cancer [14]^b
^b Others – includes brachytherapy only, bilateral salpingo-oophorectomies followed by chemoradiation, etc.

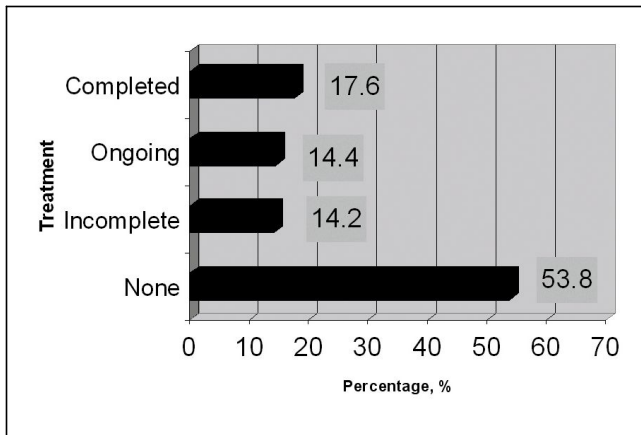


Fig. 3 Treatment Outcome of Patients for Chemoradiation [14]

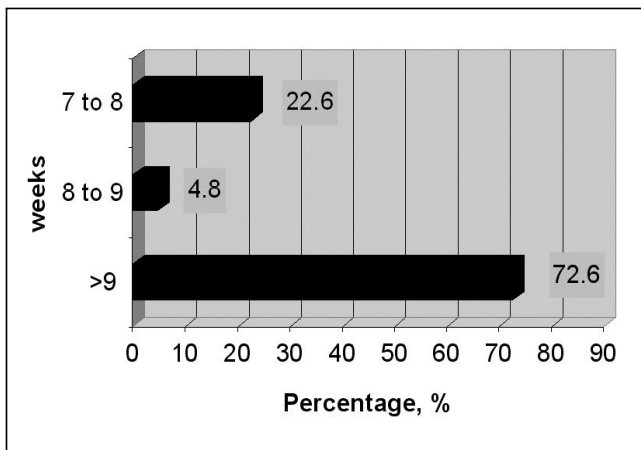


Fig. 4 Length of Treatment with Chemoradiation [14]

prolonged treatment were financial constraints and need to correct treatment-related anemia and electrolyte imbalances. Recurrence or persistence rate of cervical cancer was 37.7% [14].

Current Researches in Cervical Cancer

The Philippines has participated in phase II and phase III clinical trials involving both the quadrivalent and bivalent vaccines. It has become the site of multicenter studies notably the ones on radiotherapy concurrent with Capecitabine and another trial concurrent with Ifosfamide. Genotyping studies of preinvasive and invasive cervical cancers are also being conducted. Lastly, a registry of HPV warts is being performed by the Asia Oceania (Research Organization on) Genital Infections and Neoplasia, Philippine Chapter (AOGIN-RP).

Conclusion

Although the rate of cervical cancer continues to decline worldwide, it remains to be a public health concern in the Philippines. The country continues to face the challenge of implementing an effective cervical cancer screening program that will decrease the incidence of cervical cancer. With the low coverage of Pap testing, use of alternative modalities, such a VIA-cryotherapy programs, seems promising. Implementation of an HPV vaccination policy provides another approach to cervical cancer prevention. Future directions should be towards improving availability of both preventive and curative measures of cervical cancer management to the general population.

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