Cervical Cancer Communiqué
Issue 1 July 2006
EVERY WOMAN IS AT RISK

Cervical cancer affects women everywhere

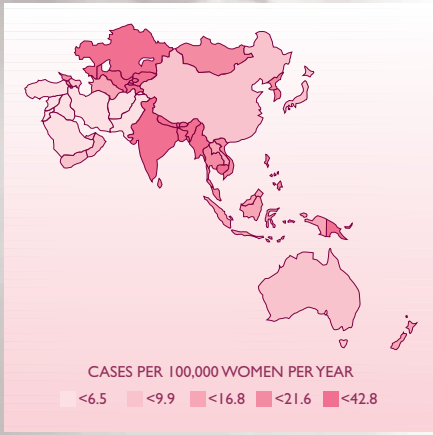

Figure 1. The incidence of cervical cancer in the Asia Pacific region[1]

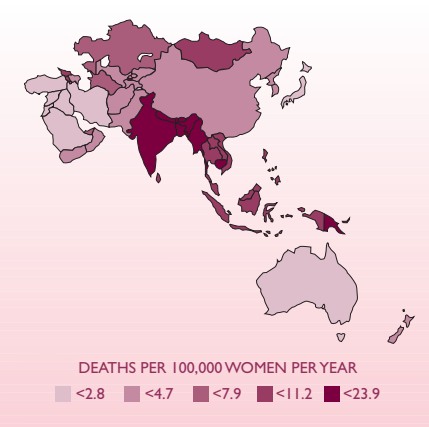

Figure 2. Mortality due to cervical cancer in the Asia Pacific region[1]

Worldwide, a woman dies of cervical cancer every 2 minutes.[1] Indeed, cancer of the cervix is the second most prevalent cancer in women aged between 15 and 44 years. Cervical cancer kills more women than any other form of cancer in the developing world. Generally, the hardest-hit regions are the world's poorest. The incidence and mortality of cervical cancer in Asia Pacific are shown in Figures 1 and 2. In both figures, rates have been adjusted to take into account the age distribution of the population, to ensure that differences between geographical areas do not just reflect variations in the age structure of these populations.

In the Asia Pacific region, 268,000 women are diagnosed with cervical cancer and 144,000 die of this disease every year.[1] The incidence of cervical cancer is by far the highest in Cambodia, India and Bangladesh (Figure 3). In Australia and Japan, the age-standardized rate of incidence is much lower, at 6.9 and 8 women per 100,000, respectively.[1] These regional variations are seen because organized routine screening for cervical cancer does not take place in all countries, or because access to such screening programs becomes difficult in rural areas.

If it is not detected and treated early, cervical cancer is nearly always fatal. The absence of cervical cancer screening programs and lack of disease awareness are most likely at least partly responsible for the higher mortality rates in developing countries. Once a woman presents with symptoms, it is often far too late to treat her effectively. Cervical cancer remains a leading cause of death from cancer in unscreened populations of women in Asia.[1]

Welcome to the first issue of Cervical Cancer Communiqué.

This newsletter is designed to alert the medical community in the Asia Pacific region to the causes and impact of cervical cancer. Understanding how cervical cancer develops is the key to its prevention and Issue 1 describes how this deadly cancer is caused by the common human papillomavirus (HPV), but can be prevented by screening programs. Vaccines that are under development can also potentially prevent this disease. Issue 2 will focus on the vaccines that will soon become available to combat this disease.

What's inside…

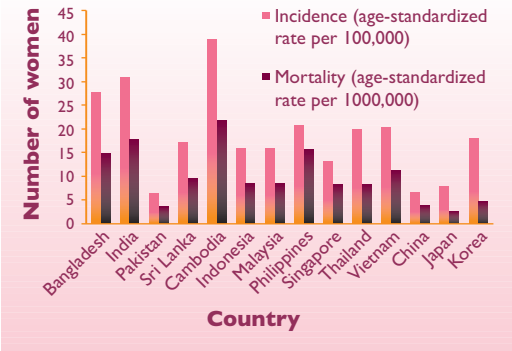

Figure 3. The incidence of cervical cancer in Asia by country[1]

The impact of cervical cancer

All women who have sexual contact are at risk of being infected with oncogenic HPV, which can cause cervical cancer. HPV, which is transmitted by sexual or genital skin-to-skin contact, is a very common virus that will affect 50–80% of women at least once in their lifetime.[2,3] Of these infections, half will be with an oncogenic HPV type.[2,3] Although cervical cancer is only likely to develop after persistent infection with an oncogenic HPV type, these strains may affect both younger and older women. This can be seen in the sample of 2080 Hong Kong Chinese women shown in Figure 4.[4] The reason for this is that during her lifetime, a woman is at risk of new infection with a different HPV type, re-infection with the same HPV type or latent (persistent) infection.

Usually, cervical cancer takes many years to develop, but in some cases progression from initial HPV infection to cervical cancer can take as little as 2 years.[5] In 30% of cases worldwide, cervical cancer strikes women between the relatively young ages of 15 and 44 years (Figure 5).[1] A substantial one-fifth of cervical cancer deaths occur in women under 45 years of age.

Societal burden of cervical cancer

The societal implications are enormous: cervical cancer more often affects the poorest, most vulnerable women, and sends a ripple effect throughout the families and communities that rely on them. At the age at which they are most likely to develop cervical cancer, women are at their peak in the roles of providers, mothers and caregivers.

Being diagnosed with cervical cancer will have a major impact on a woman's quality of life (QOL) due to her suffering from emotional stress, anxiety, physical impairments, diminished sexual response and relationship concerns.[6-8] Even an abnormal cervical cancer screening result, which may be indicative of pre-cancerous lesions, can cause significant anxiety and stress, not only to the patient, but also to her family.[9,10]

> "Cervical cancer is a major health, psychological and social burden in women worldwide"

One measure of disease burden is years of life lost (YLL), which weights mortality according to the age of death.[11] Because of the relative weighting of life at different ages, YLL provides a better measurement of the personal and economic impact of cervical cancer. It reveals how the probability of premature death from cervical cancer affects women in the prime of their lives, often while they are still working and responsible for their children and families. Cervical cancer is the leading cause of cancer-related YLL in the developing countries of South Central Asia.[11] In Japan, Australia and New Zealand, cervical cancer causes more YLL than AIDS, tuberculosis or maternal conditions.

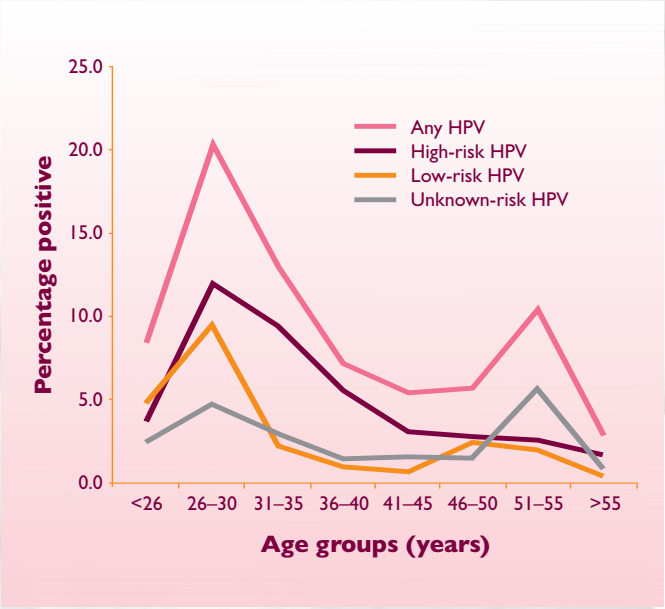

Figure 4. Age-specific prevalence of HPV infection in a sample of 2080 Hong Kong Chinese women[4]

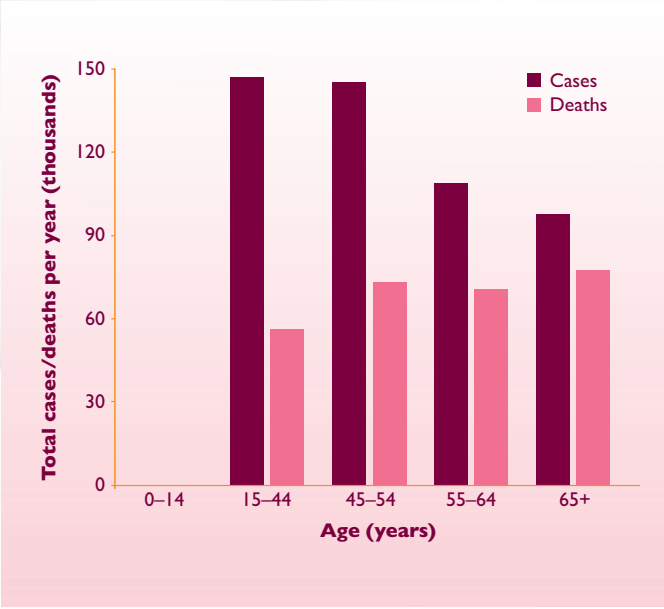

Figure 5. Worldwide age-specific incidence of, and mortality from, cervical cancer[1]

Cervical cancer is caused by the human papillomavirus

The human papillomavirus (HPV) (Figure 6) has been found in 99.7% of cervical cancers worldwide and is the cause of the disease.[12,13] This common virus is easily transmitted by genital skin-to-skin and sexual contact.[2] Approximately 100 types of HPV are specific to humans, at least 30 of which infect the genital mucosa.[14] The HPVs that infect the genital mucosa are classified according to their oncogenic potential and are described as either high- or low-risk.[5,14,15] HPV types 16 and 18 are the most common oncogenic HPV types and are found in up to 70% of cervical cancers worldwide.[15-17] Most HPV infections are transient and clear within a year, but persistent infection with oncogenic HPV types may lead to cervical cancer.[12]

About the virus

HPV particles consist of an outer protein coat, the capsid, which encloses the genetic material, a single molecule of double-stranded DNA. The DNA encodes genes that are expressed early after infection (E proteins) and late after infection (L proteins).[5] The late genes encode the L1 and L2 capsid proteins, which are 'seen' by the host immune system and are thus responsible for HPV immunogenicity.

The E6 and E7 proteins expressed by oncogenic HPV types are responsible for causing cervical cancer.[18] E6 and E7 attach themselves to the host checkpoint proteins pRb and p53 within the cervical cell, preventing their normal task of regulating cell division (p53 is called the guardian of the genome because it induces cells with damaged DNA to self-destruct). Infected cells then reproduce uncontrollably, allowing cells with damaged DNA to reproduce so that they 'mutate' and eventually become cancer cells.

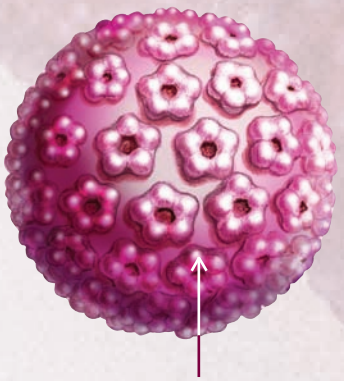

Figure 6. The human papillomavirus

HPV types explained

Papillomaviruses are classified according to sequence differences in the *L1* gene, which is genetically stable and therefore particularly well conserved among all members of the papillomavirus family.[14] This stability, combined with its immunogenicity, also makes the L1 capsid protein an ideal candidate for a vaccine.[19]

> "Oncogenic HPV types 16 and 18 together account for more than 70% of cervical cancer cases"

HPV species show 60–70% homology across the *L1* gene, whereas HPV types have 71–89% homology across the L1 gene.[14] The degrees of similarity or difference between HPV L1 sequences can be represented visually in the form of a phylogenetic tree (Figure 7).

The alpha-papillomavirus genus includes HPV species that infect human mucosal cells. Both oncogenic and low-risk types can be found within this genus, but they generally form distinct species. Low-risk HPV types tend to be most closely related to other low-risk types: for example, HPV 6 and 11, which can both cause anogenital warts, are closely related. Similarly, the oncogenic HPV types 16, 31 and 52 fall into one species, while HPV 18 and 45 fall into another.

The close grouping of oncogenic HPV types may be important for the potential cross-protection that an HPV 16/18 vaccine may provide against other oncogenic HPV types.

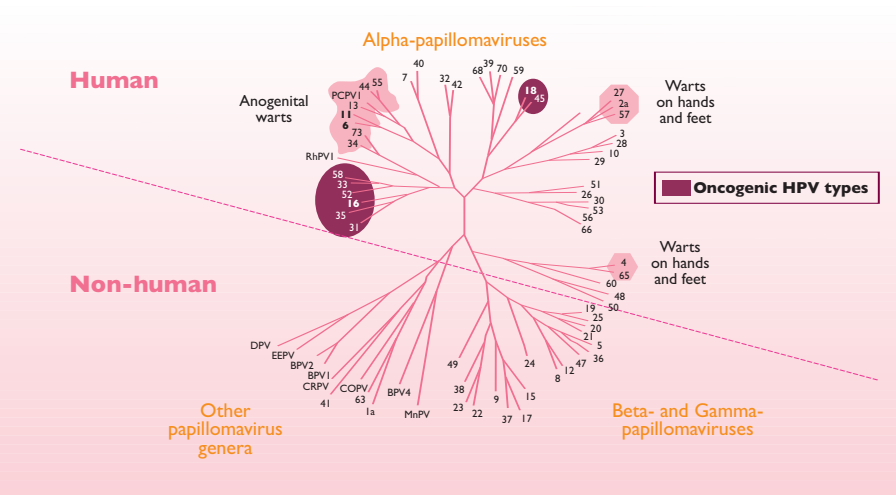

Figure 7. Phylogenetic classification of HPV[14]

From HPV infection to cervical cancer

HPV infects the cells of the basal squamous epithelium that line the cervix via microscopic lesions in the surface of the skin or mucosa.[18] These cells only permit low levels of viral replication and serve as a reservoir for viral DNA. The virus may persist in the epithelium without causing any morphological changes for months or even years.

Persistent infection with oncogenic HPV types may lead to the development of abnormal cells due to the action of viral E6 and E7 proteins on host checkpoint proteins. Cells that appear abnormal under the microscope are classified as atypical squamous cells of undetermined significance (ASC-US), however they may not necessarily have oncogenic significance (Table 1).[20] As infection persists (Figure 8), infected basal cells begin to divide more rapidly than uninfected cells, causing lesions known as cervical intraepithelial neoplasia stage I (CIN I).[18] These basal cells continue to replicate, pushing further into the epithelium, which now shows more severe neoplastic changes (CIN II). If these precancerous cells are not cleared by the immune system, leading to regression, they can infiltrate the entire epithelium (CIN III) and regression becomes unlikely. If abnormal cell growth continues, the oncogenic cells penetrate the basal membrane of the cervix to become an invasive carcinoma.

Usually, women with cervical cancer do not experience symptoms and present only once the cancer has started to spread.[21]

Table 1. Classification of the progressive stages of cervical cancer.[20] *Three different sets of terminology are used to describe cervical samples and specimens. In general, CIN classification is used in histology; ASC-US is a cytological term*

Cytological terms (Pap smear)	Histological terms (biopsy)	
Bethesda system	CIN classification	WHO classification
Normal	Normal	Normal
ASC-US	Inflammatory / reparative responses	Inflammatory / reparative responses
LSIL	CIN I	Mild dysplasia
HSIL	CIN II	Moderate dysplasia
	CIN III	Severe dysplasia; carcinoma in situ
Invasive cervical cancer	Invasive cervical cancer	Invasive cervical cancer

ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; LSIL or HISL, low- or high-grade squamous intraepithelial lesion

Immunology and HPV: Why women can be infected repeatedly

Unlike many other viruses, prior infection with a particular HPV type does not provide women with sufficient immunity against subsequent infections, nor does it reduce the risk of an HPV infection from becoming persistent.[22]

Normally, following HPV infection of the epithelial cells of the cervix, fragments of viral protein (including the L1 capsid) are presented on their surface and on those of recruited antigen-presenting cells (APCs). These attract and activate T-lymphocytes, and a cascade of immunological events is set in motion. The infected cells are destroyed via the cell-mediated host immune response, and viral infection is cleared.[22,23] However, oncogenic HPV types evade this process by inducing the epithelial cells to down-regulate T-lymphocyte responses. As a result, oncogenic HPV infection persists, which may in turn lead to the pre-cancerous changes described above.

Antibody-mediated immunity is mediated by B-lymphocytes. The antibodies they secrete (in HPV's case, against the L1 capsid protein), provide the initial response, as well as the 'immunological memory' that should normally respond to a repeat infection. However, most people who are infected with an oncogenic HPV do not generate effective antibodies to block future infection. This is because HPV replication is restricted to the relatively inaccessible basal epithelial cells. Furthermore, HPV disrupts various cytokine signaling pathways and inhibits expression of viral proteins on the cell surface.[24]

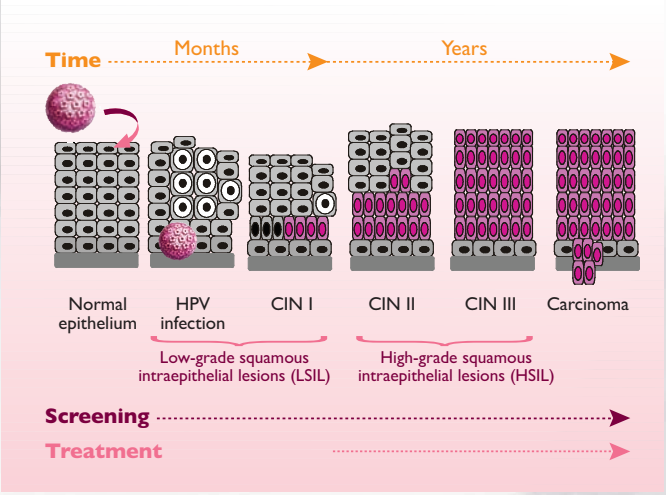

Figure 8. Progression from HPV infection to cervical cancer

Causes of cervical cancer: The usual suspects

The prevalence of different HPV types varies in different countries. Nevertheless, HPV 16 and 18 are the most prevalent oncogenic types worldwide (Figure 9), and together they are found in up to 70% of cervical cancers.[15,17,25] HPV 31, 45 and 52 are also oncogenic, and are found in 11.9% of cervical cancers.[17] HPV types 6 and 11, both low-risk types found in 90% of anogenital warts,[26] are also responsible for 8–10% of low grade cervical abnormality (LSIL).[25]

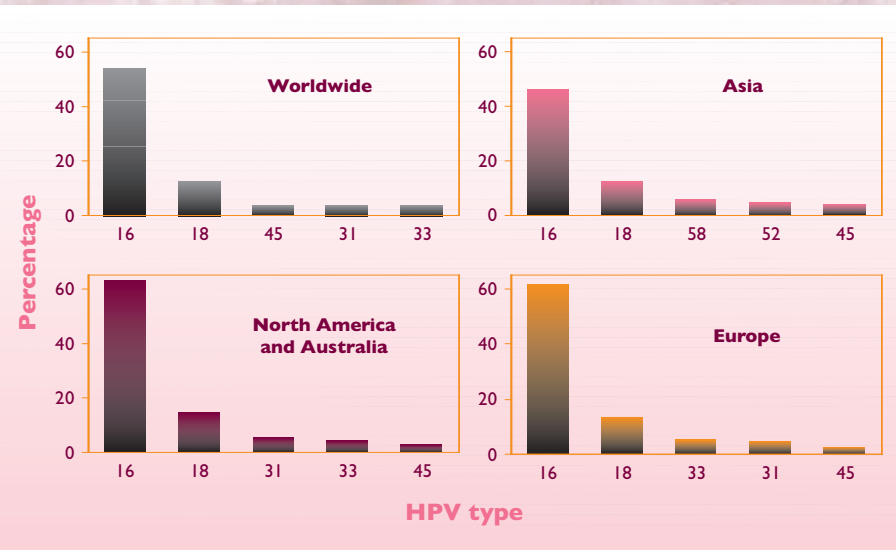

Figure 9. The five most common HPV types found in cervical cancer by region[37]

Although infection with an oncogenic HPV type is the necessary cause of cervical cancer, other risk factors that can contribute to its development and progression include smoking, a large number of sexual partners, first sexual experience at a young age, many pregnancies, the long-term use of oral contraceptives, other sexually transmitted infections like *Chlamydia*, herpes zoster and HIV and a decreased or compromised immune response.[5,27-30]

Cervical cancer is preventable

Because cervical cancer is caused by a virus, it can be prevented in two ways: (i) by preventing HPV infection in the first place by practicing sexual abstinence or by using a potential vaccine, and (ii) by screening for the presence of cervical HPV infection and managing abnormal cytologies or precancerous lesions before cancerous lesions can develop. However, many countries in the Asia Pacific region lack adequate programs for cervical screening that can detect cancer in its early stages. In addition, lack of awareness, rural location or cultural taboos may prevent women from taking advantage of any screening programs that are in place. Vaccinating women against HPV in the future would prevent them from being infected with the virus, and thus reduce their very real risk of developing cervical cancer.

Vaccination is a primary prevention measure

HPV causes 99.7% of cervical cancers,[12] so preventing infection is the best approach to controlling this disease. The most feasible method would be by vaccination, which there is good evidence to show would protect women from this disease.[31-33] Vaccination against HPV types 16 and 18 alone could prevent 70% of potential cervical cancer cases.[15-17]

Currently, the most advanced preventative vaccines in development involve the use of HPV L1 capsid protein pentamers, which self-assemble into non-infectious virus-like particles (VLPs). Two prophylactic vaccine candidates, developed by GSK and Merck, are currently undergoing phase III trials in centres worldwide, including in several Asian countries, and will soon be available.

A recent study of the GSK HPV 16 and 18 vaccine showed that 4.5 years after vaccination, it was still 100% effective against HPV 16- and 18-induced CIN, and produced immune responses that were 17-fold (for HPV 16) and 14-fold (for HPV 18) higher than those produced by natural infection.[33] To prevent HPV infection effectively, a vaccine needs to generate a broad, strong and sustained immune response. The best way to achieve this is to use an effective adjuvant system,[34] as HPV alone is not very immunogenic.[24] GSK's HPV types16 and 18 vaccine contains the proprietary adjuvant AS04, which has been shown to induce a stronger and more long-lasting response than the standard alum adjuvant.[34-36]

Merck's HPV vaccine has recently been approved by the FDA for use in girls and women aged 9 to 26 years in the US. A phase II trial of this vaccine in young women showed that the combined incidence of persistent infection or disease with HPV 6, 11, 16 or 18 fell by 90% in the vaccinated participants, and that this vaccine was safe and immunogenic.[32]

Cervical cancer is preventable (Contd.)

Cervical screening: A secondary prevention measure

Whereas primary prevention involves preventing HPV infection (and hence cervical cancer) from happening in the first place, secondary prevention of cervical cancer involves the detection of existing HPV infection and its subsequent management.

Routine cervical screening is currently the most widely used way to identify precancerous lesions for treatment before they become fatal. The Pap smear test is the most commonly used method of cervical cancer detection and monitoring worldwide. A sample of cells is taken from the surface of the cervix, fixed on a glass slide, stained and examined for cytological abnormalities. Dysplasia is seen as abnormal cellular morphology, including changes in cell size, shape and organization.

Pap smear screening has resulted in a dramatic drop in the incidence of cervical cancer in women aged over 30 years.[1] The risk of developing cervical cancer is reduced by approximately 80% in women who are regularly screened, as any precancerous lesions can be detected and treated.[31]

> "Prevention of cervical cancer is better than cure"

Unfortunately, this test has some disadvantages in that it is expensive (costing US$6 billion per annum in the US alone[31]) and time-consuming.[38] It can also yield false-positive[39] or -negative[40] results, which in turn lead to unnecessary emotional distress or under-treatment, respectively. Non-compliance with screening programs is another disadvantage: in countries that have these programs, approximately 50% of cervical cancers occur in women who do not attend them.[41] More importantly, cervical cancer does not address the underlying cause of cervical cancer and it cannot prevent HPV infection.

Other screening methods include:

- visual inspection with acetic acid (VIA), a simple and relatively inexpensive primary method whereby acetic acid is applied to the cervix to reveal abnormal lesions; treatment by cryotherapy can be performed at the same visit
- colposcopy, usually performed after an abnormal Pap smear result, during which the cervix is examined visually using acetic acid using a colposcope
- oncogenic HPV DNA testing following an abnormal result.

In conclusion, to prevent cervical cancer successfully, a screening program must target an entire population for regular checkups. Of great concern is that in Asia, organized widespread cancer screening programs do not exist or are not adequately utilized by women.

In their own words...

Medical experts in cervical cancer from Asian countries share their experiences of treating patients with the disease.

Dr Genera Manuel-Limson
Gynaecologic Oncologist,
Makati Medical Centre, Manila, Philippines

"Cancer of the cervix is a major health problem in the Philippines because it is the second most common cancer among females. It is also the second most common cause of cancer death among Filipino women.

"It is very important that physicians encourage other physicians to talk about the link between HPV and cancer of the cervix because of the great burden that this disease imposes. HPV infection is a very common viral disease and although generally it is transmitted through sexual contact, one can also get it through skin-to-skin contact.

"There is no organized national screening program in the Philippines.

Screening is usually sporadic and is carried out at family planning clinics, at private clinics and some government institutions. It covers less than 25% of the targeted women. Although in the future a vaccine to prevent cancer of the cervix will be available, we should continue screening women for cervical cancer because there are other types of HPV which may cause infection and probably will lead to cancer of the cervix."

Professor You Lin Qiao

Department Director,
Cancer Institute Hospital,
Chinese Academy of Medical Sciences, Beijing, China

"HPV infection in China is very common, especially in high incidence areas of cervical cancer, where the infection rate is generally about 18%. In some areas, especially Xinjiang, Gansu and Shanxi Provinces, the mortality rate is above 40 per 100,000.

"At the moment, we do not have a nationwide, well-planned and organized cervical cancer screening program. So the screening is mainly initiated by patients themselves. A large number of women have no chance to have such screening.

"When talking about HPV infection, a lot of our clinicians may have communication problems with patients. Patients always ask: how did my infection happen? As long as a woman is sexually active, the chance in her lifetime of exposure to HPV and infection is 70%. We should ensure a patient understands that her current infection does not mean she contracted the infection recently because latent infection with this virus has no symptoms. It can incubate in her body and persist for a long time.

"Now, there is good news: there are several big multinational pharmaceutical groups speeding their research in developing HPV vaccines. The vaccines will soon be approved and available in the market. Prevention through vaccination – this is the most cost-effective way to treat disease. With this, our women's health will be well protected."

Professor Jong-Sup Park

Gynaecologist,
Kangnam St Mary's Hospital, Seocho-gu Seoul, Korea

"Ten years ago, cervical cancer was the first-ranked cancer in Korea, but Pap smear screening led by the government and medical centers means that cervical cancer now ranks fourth among the women's cancers.

"Korean women are able to get Pap smear screening once a year with national medical insurance, but the probability of women going for a check-up is less than 20%. The problem is that women only go to hospital for a check-up after they have got cervical cancer.

"Many people may not know that there is a high correlation between HPV and cervical cancer. A vaccine against human papillomavirus, the cause of cervical cancer, will be commercialized in Korea within the next 1–2 years. I hope young women will have the vaccination to prevent cervical cancer.

"I have a daughter who is a college student. She will be falling in love and marrying someone someday. I do not want my daughter or any young folks to suffer or go through the pain of cervical cancer. I will recommend vaccination to my friends and my daughter because it is effective and will be a magnificent development when the vaccine becomes available."

> "The HPV vaccine will save women who are suffering and in pain, especially mothers, because they hold a very important position in our families. I am so excited and happy with this advancement."
> Professor Jong-Sup Park, Korea

Frequently asked questions

Who is at risk of cervical cancer?

All women who have sexual contact are at risk of being infected with oncogenic HPV, which can cause cervical cancer. This common virus is transmitted not only by actual sexual penetrative intercourse, but also by skin-to-skin genital contact and infection can persist for many years before cancer develops. Cervical cancer can affect women of all ages as early as in their teens, but the mean age of invasive cervical cancer is 50 years.[2]

What causes cervical cancer?

Persistent infection with an oncogenic HPV type such as 16 or 18 can lead to the development of cervical cancer. The progress from initial neoplasia (intraepithelial dysplasia) to cervical cancer may take up to 10–20 years, although in a small number of cases, CIN III develops within 2 years.[5]

What are the symptoms of cervical cancer?

Early cervical cancer is often asymptomatic. In women who are regularly screened, the first sign of disease is usually an abnormal Pap smear result. Symptoms that may occur later could include abnormal vaginal bleeding, abnormal vaginal discharge, low back pain, painful sexual intercourse and painful urination. Metastatic cervical cancer may cause constipation, haematuria, urethral obstruction and symptoms related to the affected distant organ.

Can cervical cancer be prevented?

As it is caused by oncogenic HPV, cervical cancer can be avoided by preventing infection in the first place, either by vaccinating against HPV or sexual abstinence. Two vaccines against the oncogenic HPV types 16 and 18 will become available within the next year. Alternately, regular cervical screening reveals precancerous cells so that they can be removed before cancer develops. This method reduces the risk of developing cervical cancer by 80%.[31]

Can an unvaccinated woman still get cervical cancer even if pronounced 'cured' of a previous infection?

Yes, as she is still at risk of re-infection by a different oncogenic HPV type. She could even be re-infected by the same oncogenic HPV type, as the body's natural immune system is often not stimulated enough following HPV infection to remember the virus and mount a response.[19]

Newsflashes

Upcoming meetings of interest in Asia

Organization	Conference	Where	When
Asia Oceania Research Organization of Genital Infections and Neoplasia (AOGIN)	AOGIN Biennial Meeting: Basic and Advanced Colposcopy Course	Cebu, Philippines	7 September 2006
Asia Oceania Research Organization of Genital Infections and Neoplasia (AOGIN)	Breakthroughs and Issues in HPV Genital Infection and Neoplasia	Cebu, Philippines	8–10 September 2006
International Federation of Gynecology and Obstetrics (FIGO)	XVIII FIGO World Congress of Gynecology & Obstetrics	Kuala Lumpur, Malaysia	5–10 November 2006

What's next in issue 2?

Costs of screening and treating cervical cancer in Asia

Protect women against cervical cancer: HPV vaccines to be launched

Clinical trials of HPV vaccines: efficacy data

Expert opinions

Your questions answered

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This publication has been sponsored by an unrestricted educational grant from GlaxoSmithKline.
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