REVIEW

Cervical Cancer in the Asian Pacific - Epidemiology, Screening and Treatment

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Abstract

Squamous cell carcinoma (SCC) of the cervix continues to be a major problem in many areas of the Asian-Pacific, particularly in the Indian subcontinent and Papua New Guinea, and to a lesser extent in South-East Asia, Korea and Mongolia. In contrast, levels in the developed countries of the region are low, as is also the case for the Muslim countries of Western Asia, and mainland China. Incidence generally mirrora associated mortality, although with some exceptions reflecting facilities and infrastructure for early detection. Over the last 25 years there has been a marked decrease in incidence rates across most of the Asian Pacific, although less pronounced in India than elsewhere, and there are exceptions where the incidence is on the increase. The predominant risk factor is well established to be persistent infection with a high risk 'oncogenic' type of human papilloma virus (HPV), along with multiple partners, other sexually tansmitted diseases and smoking. Consumption of vegetables, in contrast, appears to be protective. Hormonal factors may also play some role. Modifying factors may either impact on neoplasia by directly influencing the processes underlying carcinogenesis, or indirectly by affecting persistence of viral infections. For primary prevention, avoidance of repeated infections and smoking, as well as a high antioxidant intake may be beneficial. Vaccines against HPV also have promise for the future, but a better understanding of the mechanisms underlying spontaneous clearance of both infection and cervical intraepithelial neoplasia (CIN) of different grades is also essential for optimal intervention. For screening, the choice of whether the PAP smear, HPV testing or some form of visual inspection are utilized depends on the resources which are available, all approaches having their own advantages and disadvantages, but with similar sensitivity and specificity. One complication is the increase in adenocarcinoma of the cervix which has been reported in some countries, for which risk factors and most effectice screening may differ from the SCC case. A focus on high risk groups like sex workers might be warranted where financial and technical support are limited. If cervical intraepithelial neoplasias are detected then cryotherapy or the loop electrosurgical excision procedure (LEEP) are effective for their removal. Control of cancer of the cervix, however, demands that a comprehensive approach to screening and management is adopted, necessitating major training of personnel and provision of appropriate resources.

Key Words: Descriptive epidemiology - analytical epidemiology - risk factors - screening - vaccine

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Descriptive Epidemiology

In the country data in the International Association for Cancer Registries/APJCP supplement published after the Khon Kaen annual meeting in 2000, cervical cancer ranked number one in India, Indonesia and Thailand (Gajalakshmi et al., 2001; Sarjadi and Trihartini, 2001; Deerasamee et al., 2001), number two in the Philippines, Malaysia and Vietnam (Anh, 2001; Esteban et al., 2001, Rosemawati and Sallehudin, 2001), intermediate in Pakistan, Mongolia, Korea, Oman and Iran (Ahn, 2001; a;-Lawati et al., 2001; Bhurgri, 2001; Mosavi-Jarrahi et al., 2001; Munkhtaivan et al., 2001), and only number five in Japan (Oshima et al., 2001) and eight or more in China, Jordan and Saudi Arabia (Al Hamdan et al., 2001; Qasem, 2001; Wang, 2001). From GLOBOCAN, squamous cell carcinoma (SCC) of the cervix continues to be a major problem in many areas of the Asian-Pacific, particularly in the Indian subcontinent and Papua New Guinea, and to a lesser extent in South-East Asia, Korea and Mongolia, mortality rates generally reflecting incidence (see Figure 1). However, relative mortality does vary widely, with far fewer patients with cervical cancer surviving in

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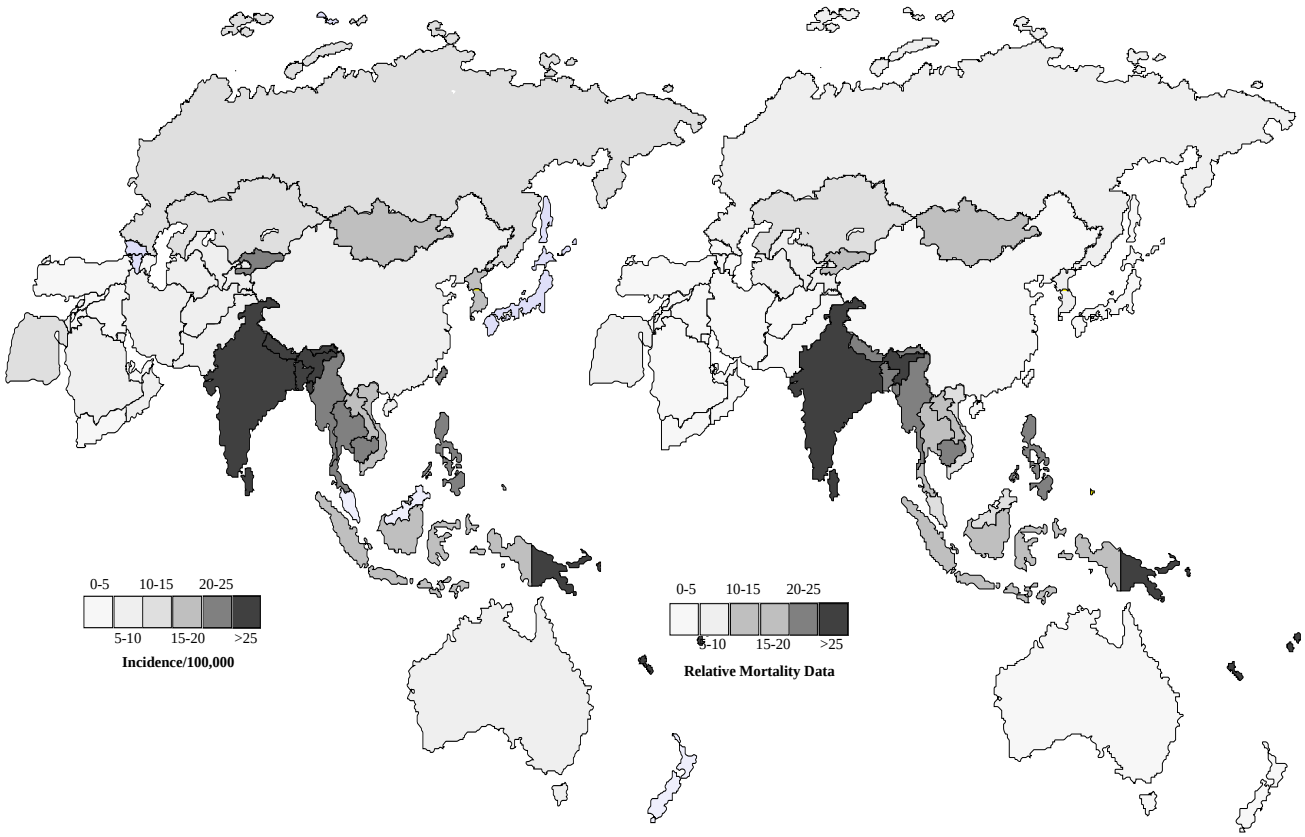

Figure 1. Incidence (a) and Mortality (b) Rates for Cervical Cancer in the Asian Pacific

developing countries than in the developed world. Some rates for 5 year survival are provided in Table 1. Within countries there may also be considerable differences across social groups and in different locations. For example, Aborigines in rural and remote areas of Australia are at significantly higher risk of death from cancer of the cervix than either Aboriginal women in metropolitan areas or non-Aboriginal women in any area (O'Brien et al., 2000).

The age distribution of cervical cancer cases may vary widely with the country, and in high incidence sites individuals in their late 20s and early 30s account for an appreciable amount of the burden (see Table 2). Assuming efficacy of screening for early lesions in the cervix, targeting young women for early detection of cancer development is thus clearly a high priority.

Over the last 25 year period, the incidence rates as reported in Cancer Incidence in Five Continents (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992; 1997; 2002) have shown a marked tendency for decrease in many

Table 1. Five Year Survival Rates for Cervical Cancer Patients

India (Kerala)	47% Sankaranarayanan et al, 1995
Australia	72% Taylor et al., 1996
India (Barshi) (90-91)	40% Jayant et al., 1996
Earlier	27%
India (Bangalore)	41% Kumaraswamy et al., 1998
India (Chennai)	60% Gajalakshmi et al., 2000
Thailand (Khon Kaen)	55% Sriamporn et al., 2004

Table 2. Burden of Cervix Cancers by Age Class*

Registry	25-34	35-44	45-54	55-64	65-74
Tianjin	0.1	0.3	1.0	**3.2**	**4.1**
Madras	4.4	12.4	**18.6**	**14.9**	6.1
Osaka	1.5	4.8	**5.8**	**5.5**	4.9
Manila	2.9	**7.9**	**7.8**	5.3	3.4
Khon Kaen	2.7	**7.2**	**10.2**	**7.2**	1.1
Hanoi	0.7	**2.7**	**3.1**	1.7	1.0
Hanoi	0.7	**2.7**	**3.1**	1.7	1.0

*Incidence/100,000 x percentage of the female population
Data from Parkin et al., 1997

Table 3. Ratios of SCC to Adenocarcinoma of the Cervix Uteri and Endometrium

	AC Cervix	AC Endometrium
China, Tianjin	6.9:1	0.70:1
India, Bombay	11.9:1	0.13:1
India, Madras	56.9:1	0.06:1
Israel, Non-Jews	3.3:1	2.13:1
Japan, Osaka	7.7:1	0.37:1
Singapore, Chinese	5.7:1	0.41:1
Thailand, Khon Kaen	4.5:1	0.24:1
Australia, NSW	3.6:1	0.46:1
Hawaii, Japanese	2.3:1	0.52:1

Data from Parkin et al., 1997

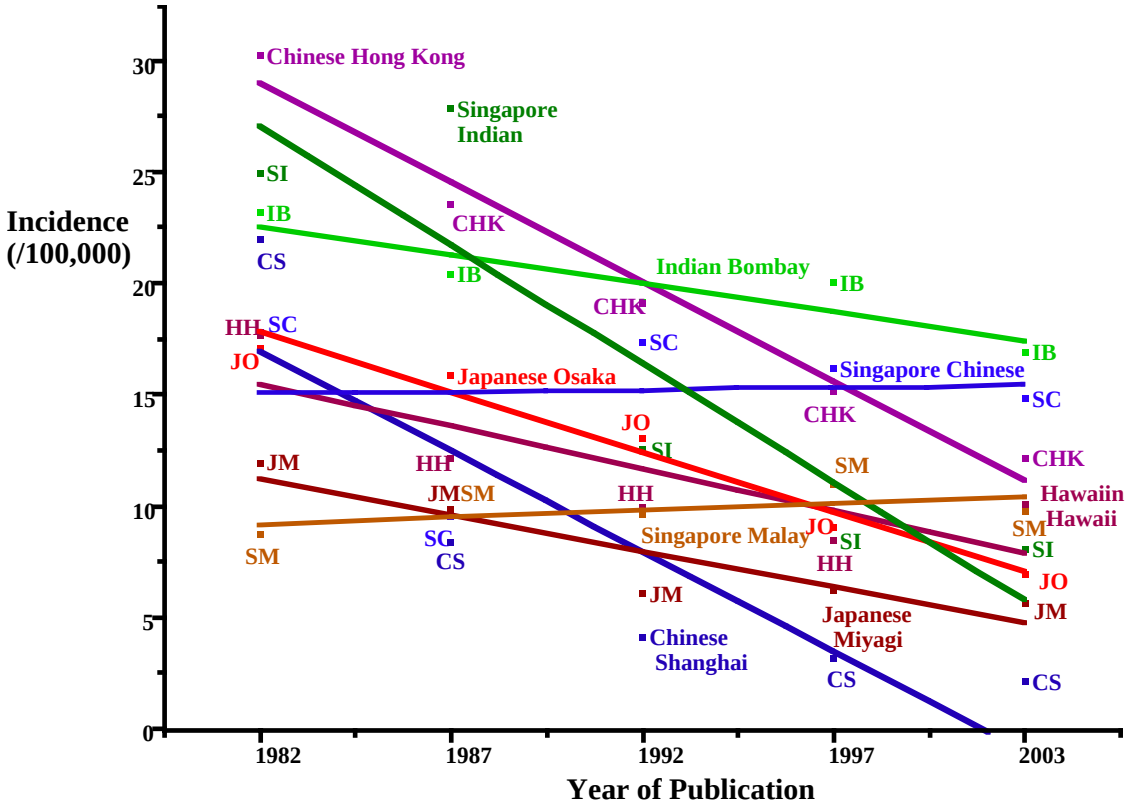

Figure 3. Change in Cervical Cancer Incidence with Time (Data from Cancer Incidence in Five Continents)

Asian countries, although to a much lesser extent in India than elsewhere, and in some populations there has been an increase (see Figure 3). The decline found in countries which have no national screening program in place would point to some natural decrease in risk factor exposure. It should also be remembered, however, that high parity increases the risk of squamous-cell carcinoma of the cervix among HPV-positive women and general decline in parity might therefore partly explain the reduction in cervical cancer recently seen in many countries (Munoz et al., 2002). The situation is also to some extent complicated by the fact that adenocarcinomas of the cervix may also account for a relatively high proportion of total cervical cancer cases, and these may be on the increase (see Table 3). To a certain extent, risk factors may be shared with endometrial cancer, as suggested by their incidence ratios (Table 3). A meta-analysis comparison of squamous cell and adenocarcinomas of the cervix, revealed the latter to be less associated with smoking (Berrington de Gonzalez et al., 2004).

Causal and Modifying Factors

Histogenesis of Cervical Cancer

The development of squamous cell carcinomas in the cervix is generally thought to proceed via cervical intraepithelial neoplasia (CIN) (Richart, 1968; 1990). As early lesions, atypical squamous cells of undetermined significance (ASCUS) indicate an increased risk of low-grade and high-grade squamous epithelial lesions (LSIL and HSIL) (Cheung et al., 2004). LSIL is included in CIN 1 in the Bethesda system, the result of workshops held at the US National Cancer Institute (1989; 1993), while HSIL encompasses the more advanced CIN-2 and CIN 3 (see Figure 4).

General

The main 'cause' of SCC of the uterine cervix is persistent infection with one of the 'oncogenic' human papilloma viruses (HPVs) (zur Hausen, 2002), although co-factors may be necessary for initiation and to allow the virus to generate lesions which progress to cervical cancer. A great deal is known about the pathogenesis of viral involvement (Longworth and Laimins, 2004) and genomic integration sites of human papillomavirus genomes in epithelial dysplasia and invasive cancer of the female lower genital tract have been reviewed recently (Wentzensen et al., 2004). The prevalence of high risk forms of the virus in Asian populations is well documented (Ghim et al., 2002; Anh et al., 2003; Shin et al., 2003).

In high risk groups like sex workers, the rates for both

Table 4. Coincidence of Early lesions and HPV Infection in Sex Workers

	LSIL	HSIL	HPV	HR-HPV
Sex Workers	15.6	2.9	77.4	55.9
Controls	2.9	0.6	27.6	14.3

Data from Mak et al., 2004

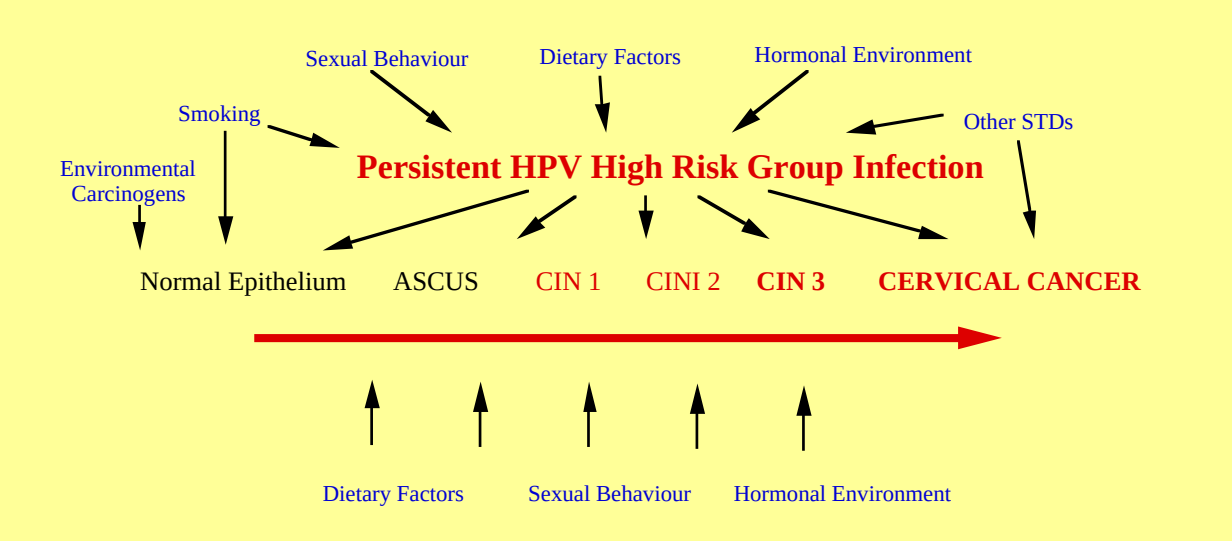

Figure 3. Modifying Factors Impacting on Cervical Neoplasia and Persistence of HPV Infection

early lesions and HPV infection are high (see Table 4)(Mak et al., 2004). Although incidence rates of cervical cancer are presently low, Muslim women are as susceptible as Hindus to HPV (Duttagupta et al., 2004). Different levels of viral integration are correlated with lesion grade (Hudelist et al., 2004) and in one study of cases with CIN-2/3 confirmed by biopsy, over a 6 month period both loss and gain of virus were encountered, but final positivity correlated with outcome in terms of lesion development (Crum et al., 2004). HPV-16-immortalized genital cells are known to be responsive to the genotoxic action of known chemical carcinogens (polycyclic hydrocarbons, alkylating agents or cigarette smoke condensate) (DiPaolo et al., 1996), including examples found in cigarette smoke (Nakao et al., 1996). Furthermore, inflammation may be associated with high-grade lesions in women infected with oncogenic HPV (Castle et al., 2001). Chlamydia trachomatis infection is also a possible co-factor in the etiology of squamous cervical cancer, and its effect may be mediated by chronic inflammation (Smith et al., 2002b).

Infection with human papillomavirus precedes the development of low and high grade squamous intraepithelial lesions and the effect of genital HPV infection on CIN development is highly influenced by oncogenic viral type and high viral load (Ho et al., 1998). A sustained high viral load is consequently informative for progression to a high-grade lesion (van Duin et al., 2002). For the latter the risk is greatest in women positive for the same type of HPV on repeated testing (Kjaer et al 2002). Most infections clear spontaneously, however, and a large proportion of the women who were HPV-positive appear to have cleared the infection after one year (Sellors et al., 2003). The rate appears to be slower with high risk forms. Thus the reported median time to clearance of infection with oncogenic strains is 9.8 months, as compared to 4.3 months with non-oncogenic strains (Giuliano et al., 2002a). Surgical treatment of CIN usually results in clearance of HPV infection within 3 months and human papillomavirus DNA testing may be useful as a rapid intermediate end point for monitoring the efficacy of treatments (Elfgen et al., 2002). On average, HPV DNA detection persists longer than related cytologic abnormalities (Schiffman et al., 2002).

Similarly to the virus itself, human papillomavirus (HPV)-associated cervical intraepithelial neoplasia(CIN) lesions in normal women may spontaneously regress, but a small number obviously do persist and progress to invasive cancer. Neutralizing antibodies against oncogenic human papillomavirus are a possible determinant of the fate of low-grade cervical intraepithelial neoplasia (Kawana et al., 2002) and cellular immunity to HPV-16 E7 is significantly associated with clinical and cytological resolution of HPV-induced CIN (Hopfl et al., 2000). Cell mediated immune responses to E7 peptide correlate significantly with regression of disease and with resolution of viral infection within 12 months (Kadish et al., 2002).

Specific Risk and Beneficial Factors

Sexual Behaviour

a) Direct Influence on Cervical Cancer Development.

Abnormal smears and high risk HPV have been found to be significantly more prevalent in sex workers than in controls in Belgium, Japan, Mexico and Thailand (Ishi et al., 2000; Juarez-Figueroa et al., 2001; Thomas et al., 2001b; Mak et al., 2004), It has been suggested that HSV-2 infection may act in conjunction with HPV infection to increase the risk of invasive cervical carcinoma on the basis of an analysis of seven case-control studies (Smith et al, 2002a), although in other studies, it was concluded that the virus did not play a role in cervical carcinogenesis (Lehtinen et al., 2002; Tran-Than et al., 2003). As noted above, other sexually transmitted diseases could also play roles as co-factors. For example squamous cell SCC, but not AC risk increases with increasing C. trachomatis antibody titers (Smith et al., 2004).

b) Influence on HPV Infection. Incident infection with carcinogenic HPV has been shown to be highest in sexually active women aged 15-19 years, and risk factors are

consistent with a sexually transmitted infection. Lifetime number of sexual partners is associated with oncogenic HPV infection. In contrast, non-oncogenic HPV infection appeared to be associated with recent sexual activity, suggesting a more transient nature (Giuliano et al., 2002b).

Hormones

a) Direct Influence on Cervical Cancer Development. Long-term use of oral contraceptives could be a cofactor that increases risk of cervical carcinoma by up to four-fold in women who are positive for cervical HPV DNA (Moreno et al., 2002). However, it has been concluded that there is no evidence for a strong positive or negative association between HPV positivity and ever use or long duration use of oral contraceptives (Green et al., 2003)

b) Influence on HPV Infection. Included in factors that may predispose to persistent, oncogenic HPV-16 or -18 infection are estrogens, or progestins in the presence of estrogens (Thomas et al., 2001a).

Smoking

a) Direct Influence on Cervical Cancer Development. Cigarette smoking is a factor, which, independently of HPV infection, influences the treatment outcome of CIN (Acladius et al., 2002). The finding that burning wood in the kitchen as also a risk factor is interesting in this context (Velema et al., 2002). Smoking is associated with both CIN1 and CIN2-3, and cigarette by-products may affect the early evolution of HPV-related lesions, possibly by increasing the rate of cell turnover (Harris et al., 2004). Among women attending a colposcopy clinic, the risk of detection of high grade lesions increases with the spouse's cigarette-smoking habit (Tay and Tay, 2004). Also lifetime exposure to environmental tobacco smoke was established as a major factor in cervical neoplasia in non-smoking women in Taiwan (Wu et al., 2003). The overall conclusion of an IARC multi-center study was that smoking increases the risk of cervical cancer among HPV positive women (Plummer et al., 2003).

b) Influence on HPV Infection. Smoking may also promote early cervical carcinogenic events by increasing duration of oncogenic HPV infections and decreasing the probability of their clearance (Giuliano et al., 2002c).

Diet

a) Direct Influence on Cervical Cancer Development. It has been suggested that high plasma levels of antioxidants may reduce the risk of cervical lesions independent of HPV infection (Goodman et al., 1998). Lycopene and perhaps vitamin A may play a protective role in the early stages of cervical carcinogenesis. (Kanetsky et al., 1998) and vitamins C and E (alpha-tocopherol) appear to independently exert protective effects against development of CIN (Ho et al., 1998). The latter vitamin was found to be significantly inversely associated with grade of cervical dysplasia (Giuliano et al., 1997). In another study, dietary intake of foods rich in total vitamin A, and particularly those with high-retinol content, reduced the risk of in-situ cervical cancer, and at the highest level of intake appeared to inhibit progression to invasion (Shannon et al., 2002).

b) Influence on HPV Infection. In one study, concentrations of serum beta-carotene, beta-cryptoxanthin, lutein, and alpha- and gamma-tocopherol were significantly lower among women two times HPV positive compared with either two times HPV negative or one time HPV positive (Giuliano et al., 1997). Circulating vitamin B12 levels also demonstrated an inversely associated with HPV persistence after adjusting for age, age at first intercourse, marital status, cigarette smoking status, race, and body mass index. No significant associations were observed between HPV persistence and dietary intake of folate, vitamin B12, vitamin B6, or methionine from food alone or from food and supplements combined or from circulating folate in another case, however(Sedjo et al., 2002).

Pharmaceutical Intervention

a) Direct Influence on Cervical Cancer Development. Lower alpha-tocopherol levels in in women with cervical intraepithelial neoplasia have been reported (Palan et al., 2004), consistent with findings of decreased antioxidant concentrations and increased oxidative stress (Sgambato et al., 2004). Women with high circulating concentrations of cryptoxanthin and tocopherol may be at a reduced risk of atypical squamous cells of undetermined significance (ASCUS) and cervical dysplasia (Goodman et al., 1998; 2000). The cervix in fact has many advantages as a target for chemoprevention of squamous cell carcinogenesis, since premalignant lesions are readily identifiable and can be followed (Mitchell et al., 1995). Direct application of preventive agents is feasible, with the possibility of repeated biopsy. As a marker, Ki-67 immuno-quantitation in CIN 1 or CIN 2 has strong independent prognostic value for progression (Kruse et al., 2003).

Regarding trials which have already been performed, intravaginal dehydroepiandrosterone was found to be safe and well tolerated and to possibly promote regression of low-grade cervical lesions (Suh-Bergmann et al., 2003). In a preliminary study in India, vitamin E supplementation inhibited progression of CIN I and I (Ganguly et al., 2001). A statistically significant regression of CIN in patients treated with indole-3-carbinol orally compared with placebo has also been reported (Bell et al., 2000), although in another study, the antioxidant beta-carotene did not enhance the regression of high-grade CIN, especially in HPV-positive subjects (Keefe et al., 2001).

b) Influence on HPV Infection. Antiviral agents like Cidofovir have potential for treatment of severe HPV-induced proliferative lesions in the cervix, as well as in other sites of the body (Snoek et al., 2001). Intramuscular injections of interferon beta are effective for treating recurrent HPV, particularly when associated with CIN (Gonzales-Sanchez et al., 2001). Topical immunotherapy is also conceivable (Hengge et al., 2001). It has been argued that chemopreventive agents to decrease HPV viral protein

Table 5. Data for Comparisons of Screening Modalities

Country		Sensitivity	Specificity	PPV	NPV
Africa[1]	VIA	76.8	85.5	9.4	99.5
	VILI	91.7	85.4	10.9	99.8
India[1]	VIA	55.7	82.1	-	>98
	VIAM	60.7	83.2	-	>98
	Pap	29.5	92.3	-	>98
Iran[2]	Pap	72.0	90.2		
	VIA	74.3	94.0		
Finland[3]	HC	85.2	67.2	4.5	99.6
	PCR	74.0	64.1	3.6	99.3
France[4]	HC				99.8
	Pap				99.2
Korea[5]	HPV	92.4	52.4	49.3	93.2
	Pap	76.3	65.8	52.8	84.7
	Both	97.8	36.7	49.2	97.3

1 Sankaranayanan et al 2004, 2 Ghaemmaghami et al., 2004, 3 Kulmala et al 2004, 4 Clavel et al 2001 5 Lee et al 2004

expression warrant particular attention (Follen et al., 2002). Finally, in the future, the possibility of applying specific vaccines will become increasingly feasible and indeed, the first steps have already been taken (Koutsky et al., 2002). If HPV vaccines are successful, the balance of cervical cancer prevention may shifts from traditional screening to primary prevention coupled with HPV testing (Crum et al., 2003).

Screening and Resection

There are three main modalities for screening for early lesions for cervical cancer, in increasing order of requirement for equipment and infrastructure support: visual inspection with acetic acid or Lugol's iodine; the Papanicalou smear; and the HPV test, either by hybrid capture or PCR. Numbers of comparisons have already been made among tests (Danneker et al., ??; Clavel , Lee Ghaemmaghami et al ???, Basu et al., 2003; Sankaranarayanan et al., 2004, Kulmala et al) with generally similar results obtained for sensitivity and specificity (see Table 5). The need for controlled trials for evidence based cervical cancer prevention has been stressed (Franco, 2004). Costa et al., 2000) prompted the authors to conclude that no single test can be adopted to replace the PAP smear in routine clinical studies. Choice of test is complicated by cultural variables and in some cases self-sampling may be of assistance in improving compliance (Dzuba et al., 2002). One device for this purpose has already been tested and shown to give reliable results (Pengsaa et al., 1997), especially in educated women (Sanchaisuriya et al., 2004). Gravitt et al (2001) also demonstrated that a self-collected Dacron swab sample of cervicovaginal cells is a technically feasible alternative to clinician-administered cervical cell collection for studies of the natural history studies of HPV and cervical cancer.

It has been argued that the most effective means for early detection in rural areas of developing countries is direct visual inspection with acetic acid or Lugol's iodine (Wesley et al,. 1997; Sankaranarayanan et al 1998; Chirenje et al., 1999; Singh et al., 2001). Visual inspection can be performed reliably by trained paramedical workers and doctors and is an effective screening option in low resource settings (Bhatla et al., 2004).

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With regard to the type of Pap smear, no significant difference in rates of false positive diagnoses between conventional and liquid-based samples was detected in one study (Mount et al., 2004). However, Sass (2004) found Thin-layer Pap Sure-Path to detect significantly more cases of LSIL and HSIL than conventional smears without compromising specificity. The ASCUS/SIL ratio and unsatisfactory rate declined dramatically. Further evidence in support of the use of the ThinPrep Pap test to enhance the efficiency of cervical cytology screening, has been provided by a focus terms of time taken (Cheung et al., 2003). Reprocessing unsatisfactory ThinPrep Papanicolaou test specimens increases sample adequacy and detection of significant cervicovaginal lesions (Islam et al., 2004). As an adjunct, cervical acid phosphatase adds to the visibility of the Pap test and enables cytoscreeners to significantly improve the detection of positive/abnormal specimens and reduce false negative rates (Markovic and Markovic, 2003-4). Recent results suggest that expression of matrix metalloproteinase 2 can distinguish CIN 1, 2, and 3 grades (Gaiotto et al., 2004) and HPV 16 testing has also been proposed as an adjunct to predict progression to CIN 3 (Tanaka et al., 2004).

In another study, immunohistochemical detection of p16 was more sensitive and specific than the HPV status in cervical lesions using a liquid-based method as well as tissue samples (Yoshida et al., 2004). P16(INK4a) as an adjunct marker in liquid-based cervical cytology (Sahebali et al., 2004) and a putative molecular biomarker of cervical adenocarcinoma whose overexpression appears to primarily reflect HPV-induced cell cycle dysregulation (Schorge et al., 2004). A correlation exists between the expression of p16(INK4a) and pRb in cervical neoplasias (Tringler et al., 2004). Furthermore, aberrant p16 methylation is a biomarker for tobacco exposure in cervical squamous cell carcinogenesis (Lea et al., 2004).

While adenocarcinoma in situ is not as easily recognized as CIN (Renshaw et al., 2004), they share many characteristic features on conventional smears (Ozkan et al., 2004). However, lower protection of cytological screening was found in a case-control study in Italy (Zappa et al., 2004).

With biennial screening, Mitchell et al (2003) estimated that a 46% reduction in the cumulative incidence of invasive adenocarcinoma could be achieved, and with annual screening, a 65% reduction.

Due to high relative sensitivity of the HPV, only very few histologically confirmed high grade lesions are detected among HPV negatives using simultaneous cytology and thus the negative predictive value is particularly good (Nieminen et al 2004). On the other hand, using HPV DNA test alone would lead to multifold amounts of referrals for colposcopy. The screening sensitivity can be further improved by combining cytology with HPV DNA testing, especially for detecting cancer precursors in women older than 60 years. (Lee et al., 2004). Comparison of HPV testing by chromogenic in situ hybridization (CISH) and by hybrid capture (HC) revealed advantages and disadvantages for both (Schiller et al., 2004).

Whatever the methodological approach adopted, opportunistic screening is known to have limited efficacy, with overscreening of a minority as an added disadvantage (Adab et al., 2004). Regarding compliance with testing, more research into cultural determinants would appear to be warranted. In a recent review of the literature on cancer screening, Moore et al (2003) found that very few papers focused on intervention. In one study in South Africa, liteners of a radio-drama were more likely to report attending screening, whereas a photo-comic was ineffective (Risi et al., 2004). The authors concluded that research should concentrate not only on achieving high levels of exposure to health messages, but also on investigating the links between exposure and action.

Resection

It is essential that a comprehensive management system be in place for treatment after screening if the latter is to have any meaning (see Figure 4). For resection of CIN lesions, both cryotherapy and the loop electric excision procedure (LEEP) are widely performed. LEEP avoids the possibility of under-treatment and is associated with an acceptable over-treatment rate, especially for postmenopausal women (Ng et al., 2004). Another advantage is that tissue is available for histopathological assessment, although negative LEEP is associated with a recurrence rate similar to that of a positive LEEP (Livasy et al., 2004). Both HPV and Pap tests perform well in detecting residual or recurrent disease after LEEP and their combination did not increase sensitivity (Sarian et al., 2004). Cyclooxygenase-2 expression predicts recurrence of cervical dysplasia following LEEP (Farley et al., 2004). Concluding a systematic review of the literature Paraskevaidis et al (2004) found a positive HPV test, even in the presence of normal cytology, to accurately predict treatment failure. Similarly in Japan persistent infection with a high-risk type of HPV is a predictor of recurrence (Nagai et al., 2004).Cytology and colposcopy may still be needed in order to rule out false positive and false negative results. Subjects with negative findings at cytology, colposcopy and HPV testing are at negligible risk of recurrence and might return safely to the standard screening protocol (Cecchini et al., 2004).

In the resource rich setting a number of other modalities are applicable. For example, the whole-body FDG PET scan has been shown to be a sensitive imaging approach for the detection of recurrent cervical carcinoma in both symptomatic as well as asymptomatic women (Unger et al., 2004).

Vaccine Development

The HPV types that cause cervical cancer are sexually transmitted, but it should be borne in mind that there is little evidence that infection can be avoided by behavioural

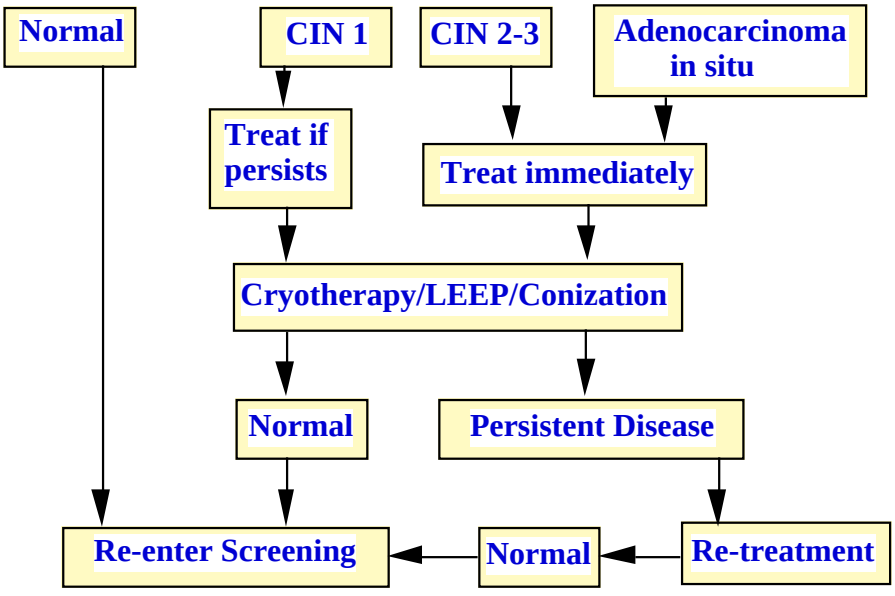

Figure 4. Comprehensive Management of Premalignant Lesions (after Sellors and Sankaranayanan, 2003)

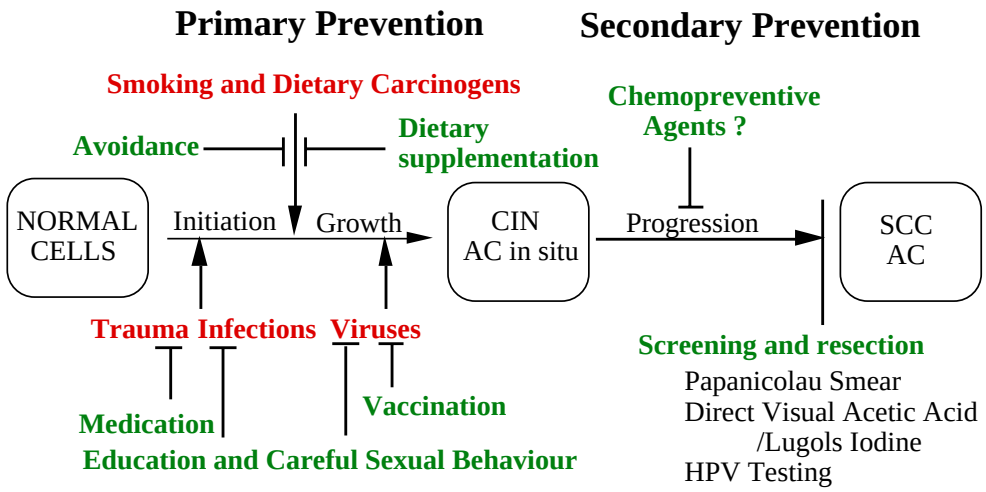

Figure 5. Measures for Primary and Secondary Prevention of Cervical Cancer

changes, such as condom use (Franceschi et al., 2003). The 15 most common types of high risk HPV acoss the world are , in descending order of frequency, 16, 18, 45, 31, 33, 52, 58, 35, 59, 56, 39, 51, 73, 68 and 66 (Munoz et al 2004). Higher than average proportions of type 16 are found in northern Africa, of type 18 in south Asia, of type 45 in sub-Saharan Africa and of type 31 in Central/South America. It has been concluded by Munoz and the IARC collaborative group (2004) that a vaccine including types 16 and 18 could potentially prevent 71% of cervical cancers worldwide, but its impact would be higher in Asia and Europe/North America. In contrast, a vaccine containing the 7 most common HPV types would prevent about 87% of cervical cancers worldwide, with little regional variation. Human papillomavirus vaccines for both prevention and therapy of cervical cancers are no longer a dream (Mandic, Vujkov, 2004) and the first steps have already been taken (Koutsky et al., 2002). If HPV vaccines are successful, the balance of cervical cancer prevention may shift from traditional screening to primary prevention coupled with HPV testing (Crum et al., 2003).Trials have shown vaccines to be acceptable in certain cultural milieus (Lazcano-Ponce et al., 2001; Gudmundsdottir et al., 2003).

Specific strategies have been proposed for both screening and therapeutic purposes (Schreckenberger and Kaufmann, 2004). Transmission of papillomavirus may be prevented by generation of antibodies aganst capsid proteins L1 and L2 that neutralize viral infection (Roden et al., 2004). However, because the capsid proteins are not expressed at detectable levels by infected basal keratinocytes or in HPV-transformed cells, therapeutic vaccines generally target nonstructural early viral antigens.A DNA vaccine linking calreticulin to E7 (CRT/E7) may be a suitable candidate for human trials for the control of HPV infections and HPV-associated lesions (Kim et al., 2004). In a phase I study to evaluate a human papillomavirus (HPV) type 18 L1 VLP vaccine, it was generally well-tolerated and highly immunogenic (Ault et al., 2004). It is important, however, to start as soon as possible simpler trials designed to demonstrate the effectiveness of HPV vaccine in field conditions in developing countries which suffer the major burden of mortality from cervical cancer (Franceschi et al., 2003).

Cervical Cancer Control

From the information which is already available in the research literature, concrete measures for both primary and secondary prevention of cervical cancer can be proposed (see Figure 5). These include safe sexual behaviour, refraining from smoking and increasing intake of vegetables in the general population. For screening, the most appropriate modality for the prevailing economic and social conditions needs to be selected and a conprehensive program put in place to ensure the greatest benefit. However, a recent survey indicated that the recommendations as currently given are met in only very few European countries (Anttila et al 2004) and the situation in most of the developing or partially developed world is even less rosy. Health authorities need to consider stronger measures and incentives than those laid out in the current set of recommendations.

The implications are that public understanding of cervical cancer, psychosocial factors associated with screening, and the potential impact on screening uptake, are all issues which require greater stress (Waller et al., 2004). The importance of education has been stressed, for example to persuade young women to take part in HPV clinical trials (Hoover et al., 2000). The role of biobehavioral factors in the persistence and progression of HPV infection as well as possible interventions to minimize the risk of persistence, as well as primary prevention of HPV continue to be major challenges (Moore et al., 2003).

In the Asian Pacific specific programs like that to increase Pap screening behavior among women in Taiwan need to be emphasized. Intervention mapping, an innovative process of design, guided the development of this program, including a needs assessment identifying factors influencing Pap screening behavior relevant to Chinese women (Hou et al.,

2004). It features methods such as information transmission, modeling, persuasion, and facilitation, and encompasses strategies includlike direct mail communication, role-model stories and testimonials, and a telephone-counseling component. In this type of endeavour particular emphasis should be placed on use of nurses and midwives for both primary prevention and screening (Turkistanlı et al., 2003).

To conclude, the idea of the Practical Prevention Project (Tajima and Moore, 2001), reaching into the community to provide information as well as facilitate access to primary and secondary preventive measures for cervical cancer remains of prime importance.

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