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The male role in cervical cancer

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Abstract
Experimental, clinical, and epidemiological evidence strongly suggests that genital Human Papillomaviruses (HPVs) are predominantly sexually transmitted. Epidemiological studies in virginal and HPV-negative women clearly indicate that sexual intercourse is virtually a necessary step for acquiring HPVs as with any other sexually transmitted disease (STD). men are implicated in the epidemiological chain of the infection. Penile HPVs are predominantly acquired through sexual contacts. Sexual contacts with women who are prostitutes play an important role in HPV transmission and in some populations, sex workers may become an important reservoir of high-risk HPVs. Acting both as "carriers" and "vectors" of oncogenic HPVs male partners may markedly contribute to the risk of developing cervical cancer in their female partners. Thus, in the absence of screening programs, a woman's risk of cervical cancer may depend less on her own sexual behavior than on that of her husband or other male partners. Although more rarely than women, men may also become the "victims" of their own HPV infections as a fraction of infected men are at an increased risk of developing penile and anal cancers. Male circumcision status has been shown to reduce the risk not only of acquiring and transmitting genital HPVs but also of cervical cancer in their female partners. More research is needed on the male role in cervical cancer.

Resumen
Evidencia experimental, clínica y epidemiológica demuestra que los papilomavirus humanos (VPH) genitales son predominantemente de transmisión sexual. Estudios experimentales en mujeres vírgenes y en mujeres VPH-negativas indican de forma clara que el coito es virtualmente un paso necesario para adquirir el VPH. Como ocurre con cualquier otra infección de transmisión sexual (ITS) los varones están implicados en la cadena epidemiológica de la infección. Los VPH en el pene son predominantemente adquiridos a través de contactos sexuales. Los contactos sexuales con mujeres que ejercen el sexo comercial juegan un papel importante en la transmisión de los VPH y en algunas poblaciones estas mujeres pueden convertirse en un importante reservorio de VPH de alto riesgo. Actuando ambos como "portadores" y "vectores" de los VPH oncogénicos los hombres pueden aumentar de forma substancial el riesgo de propiciar cáncer de cérvix en sus parejas. En ausencia de programas de detección precoz, el riesgo de cáncer de cérvix en una mujer puede depender menos de su conducta sexual que de la de su marido u otras parejas sexuales. Aunque más raramente que en las mujeres, los hombres pueden también convertirse en "víctimas" de sus propias infecciones por el VPH, pues una fracción de hombres infectados tiene un riesgo...
Epidemiological studies in virginal and Human Papillomavirus (HPV)-negative women clearly indicate that sexual intercourse is virtually a necessary step for acquiring HPV as detected by HPV DNA and serum antibodies testing. Genital HPVs are predominantly sexually transmitted. As with any other sexually transmitted infection (STI) men are implicated in the epidemiological chain of the infection. Acting both as “carriers” and “vectors” of oncogenic HPVs, male partners may be important contributors to the risk of developing cervical cancer in their female partners. Although more rarely than women, men may also become the “victims” of their own sexual behavior and of their own HPV infections, and a fraction of infected men are at an increased risk of developing penile and anal cancers, two tumors that are strongly related to infection by the same HPV types that cause cervical cancer.

This chapter reviews and summarizes the accumulated evidence showing the importance of the male role in cervical carcinogenesis. We first show ecological evidence correlating sexual behavior patterns with cervical cancer incidence rates in different populations. We also review the evidence for a role of men in HPV transmission and cervical cancer risk.

Sexual behavior patterns and incidence of cervical cancer: An ecological approach

The hypothesis

The extent to which males contribute to the risk of HPV-related cancers in a particular population mainly depends on two factors: the overall pattern of sexual behavior in the population as a whole, and on its related background HPV prevalence. This concept is not new and it was first formally proposed by Skegg and colleagues back in 1982, well before HPV was identified as the causal agent of cervical cancer.1

These investigators hypothesized that, in some populations, “a woman’s risk of cervical cancer will depend less on her own sexual behavior than on that of her husband or other male partners.” Without data on HPV prevalence at hand, they put forward the idea that cervical cancer incidence rates in an unscreened population will vary according to three different sexual behavior patterns. “Pattern A”, would be observed in non promiscuous communities in which both men and women are mainly lifetime monogamous. “Pattern B”, would be the one observed in some Latin American societies in which while women are expected to be lifetime monogamous men have many sexual partners. And “Pattern C”, would be observed in a more permissive society in which both men and women tend to have several partners. Skegg’s model thus predicted that cervical cancer incidence rates would be lowest in “Pattern A” communities, in which men and women are mostly monogamous, and highest in “Pattern B” communities, in which many men have intercourse with a small number of highly promiscuous women, frequently sex workers who constitute a reservoir of HPV infection.

The data: the IARC studies on the male role

Between 1985 and 1993 the International Agency for Research on Cancer (IARC) conducted a series of case-control studies in countries with low, intermediate and high incidence rates of cervical cancer to assess the role of HPV and other STIs in the etiology of this cancer.2-15 Husbands or current stable sexual partners of the women recruited in these studies were also invited, interviewed, and their penile samples tested for HPV DNA detection by state-of-the-art Polymerase Chain Reaction (PCR) techniques. This was accomplished in 1 925 men enrolled in seven case-control studies carried out in Colombia, Brazil, Thailand, The Philippines, and...
Spain. This design allowed, almost 20 years later, the testing of Skegg’s hypothesis by analyzing individually-collected data on HPV infection and sexual practices in adult men and women.

The distribution of the lifetime number of sexual partners in men and women is plotted in Figure 1 for two selected countries that have a 5-fold ratio of cervical cancer incidence rates: Colombia, (age-adjusted incidence rate [AAIR] of 34.4 per 100,000 women), and Spain (AAIR of 7.1). The curve for Colombia, closely resembles that hypothesized in Skegg’s “Pattern B” society, with women being mostly monogamous (around 70%), and men highly promiscuous (55% of men had 20 or more sexual partners). In contrast, the corresponding distribution in Spain, although not identical, is consistent with Skegg’s “Pattern A” society, with the vast majority of women being monogamous (around 90%), and a small fraction of men highly promiscuous (15% of men had 20 or more sexual partners). Clearly, the male to female disparity in terms of number of sexual partners is more marked in high-risk Colombia than in low-risk Spain, confirming thus the contrasting cervical cancer incidence rates predicted by Skegg’s model.

**Figure 1. Distribution of lifetime number of sexual partners in adult men and women in Colombia and Spain**

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**Figure 2. Distribution of age at first sexual intercourse in adult men and women in Colombia and Spain**
In parallel with these findings the distribution of age at first sexual intercourse, a sexual behavior indicator consistently found to be associated with cervical cancer risk even after taking into account HPV, greatly differed between Colombia and Spain (Figure 2). It was remarkable that, for this variable, the between-country disparity was observed both in men (68% versus 24% men initiated sex at age 16 or younger in Colombia and Spain, respectively), and in women (26% versus 6% women, initiated sex at age 16 or younger in Colombia and Spain, respectively).

These studies further found that the prevalence of reported ever contacts with prostitutes (79% in Colombia versus 52% in Spain) correlated also with cervical cancer, as it did the fraction of men’s sexual partners than were prostitutes (28% versus 10% men had more than 50 partners that were prostitutes in Colombia and Spain, respectively).

Concerning HPV infections in men and women the results from these studies show that penile HPV correlates better than cervical HPV with cervical cancer incidence rates. In Colombia, men had a higher HPV prevalence than women (19% versus 15%, respectively). In Spain, HPV prevalences for both men and women were 5 to 6-fold lower than those in Colombia, and men had a lower HPV prevalence than women (3% versus 5%, respectively).

The role of men in cervical carcinogenesis

Male sexual behavior and cervical neoplasia in sexual partners

Although the implication of a sexually transmitted agent in the etiology of cervical cancer has been suggested since the 1940’s,16 most early studies focused on the analysis of female’s sexual behavior and on the testing of female’s biological samples, paying little attention to the potential contribution of men. However, as with any other STD, studies in couples should provide consistent evidence of the venereal nature of HPVs and one would expect higher rates of HPV infection and HPV-related diseases in women who had sexual contacts with promiscuous men than in women who had contacts with non-promiscuous men. Indeed, this was already reported more than 30 years ago by Pri-dan and colleagues who showed for the first time an association between the number of sexual partners of the husband and the risk of cervical cancer among mostly monogamous Jewish women.17

Since the women themselves may also have had multiple sexual partners, the evidence for a role of men in HPV transmission is more clearly shown in studies of couples whose female consort claim to have had no sexual partners other than her husband or stable partner. This was shown for the first time by Buckley and colleagues who found that the risk of cervical cancer among monogamous women greatly increased with the number of sexual partners their husbands had had. Other male factors found to increase risk in this study were an early age at first intercourse, extramarital affairs, and history of STDs.38

The potential importance of the male role was also suggested in early studies of marital clusters. One study reported that subsequent wives of husbands whose previous wife developed cervical cancer had an increased risk of cervical neoplasia,19 and several studies have shown that wives of men with cancer of the penis have a higher incidence and mortality rates of cervical cancer.20-22

Studies showing geographic clustering of cervical and penile cancers,23-26 and studies showing strong correlation between incidence rates of male and female genital cancers,22,26 provided further ecological support on the importance of men in the natural history of cervical cancer.

More recently, data from the Swedish Family Cancer Database showed that husbands of women with in situ or invasive cervical cancer had an excess risk of anal cancer, a recognized HPV-related cancer.27 Anal cancer was also increased as a secondary primary cancer in women with cervical neoplasia.28 Of special interest is also the excess risk found in husbands of cervical cancer patients of both tonsillar cancer and cancer of the tongue, supporting the currently emerging evidence that HPV may be etiologically involved in a fraction of these tumors.29

All together these studies provide thus indirect evidence that: a) cervical and penile cancers share a common infectious etiology, b) both men and women contribute to the transmission of an infectious agent, and c) both men and women may become cancer victims of this viral infection.

Stronger evidence of the male role has been provided by formal case-control studies comparing either direct histories of sexual behavior or clinical evidence of HPV-related lesions in male partners of women with and without cervical cancer.2,13,30-32 Zunzunegui and colleagues showed, for instance, that as compared to unaffected women, women with cervical neoplasia were five times more likely to be married to a man who had had more than 20 sexual partners.30 In another study, women who were the sole sexual consorts of men with pre-existing penile condyloma showed an increased risk of cervical neoplasia.33 Barrasso and colleagues also
reported a high prevalence of HPV-related penile neoplasmia in the sex partners of women with cervical neoplasmia.\textsuperscript{34}

\textbf{Penile HPV DNA and risk of cervical cancer}

After the identification of HPVs as the sexually transmitted agents etiologically linked to cervical cancer, firm evidence for a role of men as carriers and vectors of oncogenic HPVs stemmed from studies that introduced HPV DNA detection in penile samples.

The largest study to date exploring the male role in cervical carcinogenesis is the multicentric case-control study coordinated by the IARC (Lyon, France). As explained in a previous section this large study involved over 1,900 couples that were enrolled in seven case-control studies of cervical cancer carried out in Spain, Colombia, Brazil, Thailand, and the Philippines and in whom exfoliated penile cells were collected in men for HPV DNA detection.\textsuperscript{2,3,5,6,8,9,11,13,15} Pooled data from these studies clearly indicate that the overall penile HPV prevalence clearly increases with increasing lifetime number of sexual partners of the men and with and early age at sexual debut (Figure 3). If we take also into account the sexual behavior of the female consort in the studies conducted in Spain\textsuperscript{2} and Colombia\textsuperscript{13} we can see that penile HPV prevalences were systematically higher in husbands of non-monogamous women than in husbands of monogamous women (Figure 4). Furthermore, the increasing trend between penile HPV and number of sexual partners of men was observed in the partners of both monogamous and non-monogamous women.\textsuperscript{7}

Results for the IARC studies conducted in low- to intermediate-risk countries (i.e., Spain, Thailand and the Philippines), also indicate that the men’s lifetime number of sexual partners, including female prostitutes as sexual partners, is one of the key determinants of cervical cancer risk in their wives. In Spain, the presence of HPV DNA in the husband’s penis conveyed a 5-fold increased risk of cervical cancer to their wives. The odds of cervical cancer among monogamous women increased up to 9.5-fold in relation to the presence of high-risk HPV types in the penis of their husbands. The excess risk associated with HPV type 16 was 6- to 9-fold. Furthermore, the prevalence of penile HPV showed a positive trend with increasing number of sexual partners and with the number of sexual partners who were prostitutes.\textsuperscript{2} In contrast, in high-risk countries such as Colombia and Brazil, no associations with cervical cancer risk were found with penile HPV DNA or with other indicators of male sexual behavior.\textsuperscript{13}

The lack of association between most male-related variables and cervical cancer risk found in high-risk countries could be explained by the fact that in these populations HPV is such a widespread infection that hampers case-control studies to discriminate subjects at a higher risk. In these populations, women’s having sexual contacts with an even limited number of male partners place them at a high risk of acquiring cervical HPV infections and subsequent cervical cancer. HPV DNA detection in the penis of adult men, even if high,
is still a poor reflection of lifetime exposure to HPV. Other biological markers of lifetime sexual promiscuity in men such as seropositivity to *Chlamydia trachomatis* have proved to better discriminate men’s partners at a high risk of cervical cancer, not only in populations at low risk, but also in populations at high risk of cervical cancer.13

**HPV concordance in couples**

Several studies have addressed concordance of genital HPVs in heterosexual couples. Most, but not all, of these studies found a relatively poor correlation of HPV-positivity and types in cervical and penile samples.7,10,36-38 The low agreement may be partly due to technical reasons, since a smaller amount of penile exfoliated cells may be obtained in men relative to the cellular yield obtained from the cervix. In some couples, the partner who has been sampled may not be the relevant one in determining the woman’s risk of HPV persistence and progression to cervical neoplasia. Agreement in HPV findings, however, was also modest in couples where both the wife and husband reported only one lifetime sexual partner.10 In some of these studies the timing of the sampling of penile and cervical specimens at a relatively old age is the likeliest explanation for HPV discordance, since spontaneous regression of HPV infection is common in men and in women who do not develop cervical neoplasia.40 Among women with cervical neoplasia, the relevant infection may have occurred many years earlier, and the relatively low prevalence of penile HPV infection in their husbands suggests that viral shedding of advanced cervical lesions is limited. Also point detection of penile HPV may measure relatively recent exposures to HPVs that may be unrelated to the initiation of cervical neoplasia in the wife.

**Male circumcision, penile HPV, and cervical cancer**

A recent piece of evidence confirming the importance of men in HPV transmission and cervical carcinogenesis comes from the IARC multicentric study on male circumcision.6 This study compared penile HPV DNA prevalence in circumcised and uncircumcised men to estimate a woman’s risk of cervical HPV infection and that of cervical cancer according to the husband’s circumcision status. We found that circumcised men were about three times less likely to harbor HPV in their penis than did uncircumcised men. Consistent with the venereal nature of HPV infections, we found that male circumcision also reduced the risk of both genital HPV infections and cervical cancer in the female partner. As shown in Figure 5 among monogamous women, circumcision status of the husband was associated with a reduced risk of cervical cancer, particularly and most strongly, among women whose male consorts had engaged in high-risk sexual behaviors as measured by an early age at first sexual intercourse, a high lifetime number of sexual partners, and sexual intercourse with women that were prostitutes. Furthermore, as shown in Figure 5, using a computed sexual behavior risk index revealed a statistically significant dose-response relationship between increasing husband’s sexual behavior risk and cervical cancer risk reduction linked to circumcision in their wives. These findings confirmed for the first time the long-suspected hypothesis claiming that male circumcision might reduce the risk of cervical cancer in female partners and underlines the importance of the male in the risk of HPV acquisition and cervical neoplasia in the female partner.

**The male role: Closing the epidemiological chain linking HPV and cervical cancer**

Even though males have traditionally been much less studied than women, in the last decade data from all sorts of epidemiological study designs assessing directly or indirectly the role of men in cervical carcinogenesis have been accumulating. The large IARC studies...
Men and cervical cancer on couples have shed new light on the largely unknown male side of the epidemiological chain of HPV and cervical cancer. Our current understanding is that men who have had multiple sexual partners or who are carriers of HPV DNA may be vectors of high-risk HPV types, placing their sexual partners at a high risk of cervical cancer. The key question though is how men acquire the virus in the penis in the first place. It is now well established that penile HPVs are predominantly acquired through sexual contacts. Sexual contacts with prostitutes play an important role in HPV transmission and sex workers may be an important population reservoir of high-risk HPVs. Through sexual intercourse with high-risk women, HPVs enter the penis which can then be transmitted to the current stable partner or to subsequent sexual partners. Men are thus the vectors of oncogenic HPV types that are usually found in cervical carcinomas. Circumcision is also likely to modulate the risk of penile HPV acquisition, the risk of transmission to the partners as well as the long-term risk of cervical cancer. At the ecological level, populations in which the sexual habits of men greatly differ from those of women, male promiscuity in general, and sexual contacts with prostitutes in particular, is likely. Under these circumstances, a woman’s risk of being infected and develop cervical cancer depends much more on the sexual behavior of her partner than on that of her own.1

**Conclusions**

Experimental, clinical, and epidemiological evidence strongly suggests that genital HPVs are predominantly sexually transmitted. As with any STI men are implicated in the epidemiological chain. Penile HPVs are predominantly acquired through sexual contacts notably, at least in some populations, with prostitutes who become an important reservoir of high-risk HPVs. Act-
ing both as “carriers” and “vectors” of oncogenic HPV's male partners may be important contributors to the risk of developing cervical cancer in their female partners. Male circumcision status has also been shown to influence not only the risk of acquiring and transmitting genital HPV's but also the risk of cervical cancer in women with promiscuous sex partners.

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References


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