

### Editorial

## Understanding the Epidemiology of Genital Infection with Oncogenic and Nononcogenic Human Papillomaviruses: A Promising Lead for Primary Prevention of Cervical Cancer

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Cervical cancer is one of the most common neoplastic diseases affecting women, its combined worldwide incidence is second only to that of breast cancer. In developing countries, however, cervical cancer ranks as the most important of all female neoplasms, whereas in Western, developed nations, it ranks fifth among malignant diseases affecting women (1). An estimated 471,000 new cases of invasive cervical cancer and 213,000 related deaths occurred in 1990 worldwide (2). The highest-risk areas are in southern and eastern Africa, Central America, and tropical South America. Although risk in Western Europe and North America is considered relatively low at fewer than 10 new cases per 100,000 women annually, rates are 10–20 times higher in high-risk countries, where lifetime probabilities of developing invasive cervical cancer can approach 10% (3).

The public health impact of cervical neoplasia extends far beyond the detection, treatment, and follow-up of clinically overt cervical cancer. For each new case of invasive lesion, there are approximately 50 other cases of abnormal cervical smears with low- or high-grade precursor lesions that merit careful monitoring by colposcopic follow-up and eventually biopsy. To this triage burden, one must add an equal caseload of borderline atypias and equivocal smears that need to be confirmed by repeat cytology (4).

Cervical cancer takes a particularly heavy toll among African Americans, native populations, and Hispanic minorities. African-American women have almost twice the incidence and three times the mortality from cervical cancer of white women in the United States. Few cancers exhibit a survival differential due to race as strong as cervical cancer. Five-year survival rates for white patients have continuously improved in the last 35 years, reaching a high of 71% in 1986–1991. Equivalent rates for African-American women peaked at 64% in 1974–1976, and then declined significantly to 56%, a survival rate that is also significantly lower than that for white patients in any period since the early 1970s (5).

Patients with cervical cancer tend to have shorter survival than those with breast cancer. Five-year survival rates for breast cancer, a disease eliciting greater public awareness in North America, are considerably better, at 84 and 69% for white and black women, respectively (5). Moreover, cervical cancer occurs at a relatively earlier age than breast cancer and generally affects multiparous women in the early postmenopausal years.

In high-fertility developing countries, these women are the primary source of moral and educational values for school-age children in their families. The premature loss of these mothers leads to a loss of familial ties, with its attendant social consequences for the community.

The incidence of cervical cancer in Western nations has declined in the past 40 years, primarily as a consequence of the widespread availability of Pap smear screening and of the gradual declines in population fertility. This trend seems to be reversing in recent years, however, particularly in women younger than 50 years (5). This is probably a reflection of the changes in social standards of sexual behavior since the late 1960s, which has led to an increase in the incidence of sexually transmitted diseases in western societies, especially infection with certain types of HPV,<sup>2</sup> the main cause of cervical cancer.

A 1995 IARC monograph classified HPV infection by types 16 and 18 as carcinogenic to humans (group 1). Infection by some other types, such as HPVs 31 and 33, was classified as probably carcinogenic (group 2A), and infection by other types (with the exception of types 6 and 11) was considered possibly carcinogenic to humans (group 2B; Ref. 6). It is likely that, on the basis of emerging evidence in the last two years, HPVs 31 and 33, and perhaps a few other “oncogenic” HPVs, will have their classification status upgraded in future IARC reviews to *bona fide* group 1 agents.

A decade of epidemiological research on HPV and cervical cancer that culminated with the IARC monograph had its worst moments around 1990, when it became clear that the available evidence linking the disease to the virus was largely incoherent. Contrary to what would be expected, first-generation molecular epidemiology studies found that cervical HPV infection was not associated with sexual activity variables (7–9), a paradoxical finding considering that cervical cancer risk is strongly associated with sexual practices. Important measurement errors in ascertaining HPV status had affected these early studies, which led to the seemingly contradictory results (reviewed in Refs. 10 and 11). The solution to the problem came with the advent of PCR protocols, which had enhanced sensitivity and specificity to detect HPV DNA as compared with nonamplified nucleic acid hybridization techniques used in studies published until 1990. Two such protocols using the so-called MY09/11 (12) and the GP5/6 (13) primer sets have been used by most of the studies forming the mainstay of epidemiological evidence reviewed by the IARC (6).

Even with the new PCR protocols, however, the sexually transmitted disease profile of HPV infection has not been uniformly revealed in studies in different populations. These studies indicate that the association between sexual activity and HPV prevalence can be either strong (14–16), moderate (17,

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<sup>2</sup> The abbreviation used is: HPV, human papillomavirus.

18), or even nonexistent (19). Recently, we found evidence that different HPV types might have different degrees of transmissibility by the sexual route. Infection with HPV types deemed of low oncogenic risk was only weakly associated with sexual behaviour among women younger than 40, whereas sexual activity variables were strong predictors of infection with HPV types classified as of high oncogenic risk, regardless of age (20). It is conceivable, therefore, that the variability in results from HPV risk factor surveys might be caused by differences across populations in the relative prevalence of HPV types differing in their transmissibility by the sexual route.

In this issue of *Cancer Epidemiology, Biomarkers & Prevention*, Kjær *et al.* (21) provide strong evidence that this may indeed be the case. They studied risk determinants for genital HPV infection in a random sample of young Danish women (20–29 years) who were free of cervical cytological abnormalities. They used the GP5/6 PCR protocol with oligonucleotide probing of the amplified products to ascertain cervical HPV infection by oncogenic and nononcogenic HPV types. Infection with nononcogenic HPVs was associated neither with age nor with lifetime number of sexual partners. On the other hand, oncogenic HPVs were strongly associated with both of these variables. The only variable strongly correlated with nononcogenic HPVs was condom use, but in a seemingly counterintuitive way; *i.e.*, users, and in particular current users, had higher risk (21). We have observed a comparable effect in a study of female university students in Montreal, Quebec, Canada.<sup>3</sup> Kjær *et al.* (21) make the plausible argument that condom use may not offer an effective barrier protection if it is not used during the entire intercourse and may be a marker for increased frequency of sexual activity per partner or for other unmeasured risk behaviors. Unlike condoms, diaphragms are more likely to exert a more effective protection of the cervix because they are kept in place until after sexual intercourse. In fact, the authors found a moderate protective effect for diaphragms with respect to nononcogenic HPVs (21).

Because their baseline questionnaire did not probe for recent sexual activity, Kjær *et al.* (21) studied the association with recent number of sexual partners in later interviews conducted during follow-up of a subset of the study subjects. This indicated that whereas infection with nononcogenic HPVs continued to be invariant with respect to the information on lifetime partners, it was strongly and positively associated with recent number of partners, a finding that is in line with the emerging notion that infection with nononcogenic HPV types may be more transient, whereas infection with oncogenic HPVs tends to persist and thus be more closely correlated with lifetime sexual activity markers (22, 23).

The best opportunity to study these associations will be afforded by the large, ongoing cohort studies of HPV infection and cervical lesions, including the one conducted by the authors of the Copenhagen study (24). Prospective cohort investigations, particularly those with multiple HPV measurements over time, have begun to unveil the complexity of risk determinants of incident infection by individual HPV types and factors influencing persistence or clearance of infections (25–27).

Few studies of HPV epidemiology have been as large as that of Kjær *et al.* (21). Most previous studies have had limited statistical power to analyze specific or even grouped HPV types as outcome variables. In these investigations, HPV infection was typically analyzed in aggregate form only. This has effec-

tively prevented us from learning about risk factor profiles for different HPV types.

We must recognize an important caveat, however, before we use the information on distinct risk factor profiles for oncogenic and nononcogenic HPVs to further our understanding of the natural history of cervical neoplasia. Despite use of well-tuned PCR protocols, misclassification of HPV infection status may still explain the differences in results between oncogenic and nononcogenic HPVs. The former are positively identified with the use of specific probes, whereas only a few of the latter (*e.g.*, HPVs 6 and 11) are distinguished by positive identification; the remainder (HPV X) are detected by exclusion, for failure to hybridize with any of the type-specific probes. It could be hypothesized that specimens with these untyped HPVs could be false-positive cases, which would lead to a dampening of the statistical association with sexual activity if there had been one with nononcogenic HPVs. This issue also affects the interpretation of data from studies with the aforementioned MY09/11 PCR protocol, which was used in our previous study (20). Kjær *et al.* (21) analyzed the nononcogenic group separately for HPVs 6/11 and HPV X and concluded that they yielded similar patterns of risk factor profiles, a finding that is not consistent with the above hypothesis. In our study in Brazil, we had also split the nononcogenic HPV group into typed and untyped HPVs and treated them as separate outcomes in the analysis. We also found no evidence for distinct risk factor profiles between these two subgroups (20).

Recognition that infection with certain types of HPV is the central cause of cervical neoplasia has created new research fronts in primary and secondary prevention of this neoplastic disease (28). Understanding the remote causes of infection with the clinically relevant HPV types is an important first step in the direction of implementing more effective public health programs aiming at risk reduction. Judging by the thrust of current research in this field, such programs are likely to become an essential component of a multimodal approach to preventing cervical cancer in the future, one that will also include vaccination to prevent HPV infection and screening for cervical disease aided by HPV testing.

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