

## EDITORIAL

### **Is uterine cervical cancer a potentially preventable sexually transmitted disease?**

Uterine cervical cancer is estimated to cause 500,000 deaths each year worldwide, especially in developing countries, where its annual incidence approaches 40 per 100,000 women (1). It is the second commonest malignancy in Papua New Guinea and the commonest among women, especially between the ages of 35 and 55 years (2). Human papillomaviruses (HPVs), members of the papillomavirus subfamily of viruses grouped together by their tumorigenicity and homogeneity of deoxyribonucleic acid (DNA), have been identified as the major aetiological factor in cervical carcinogenesis (3). To date, more than 80 different genotypes of HPV have been described, each showing a particular tropism to specific anatomical sites (4,5). Cutaneous infections of the skin and mucosal infections of anogenital, oral and respiratory epithelia are common with at least 30 genotypes affecting the genital tract (6). HPVs have been divided into three types, of low, intermediate and high risk according to their association with the different grades of intraepithelial and invasive disease. Low-risk HPV types, which include HPV 6, 11, 40, 42, 43 and 44, are usually associated with benign exophytic genital warts, with HPV 6 and 11 being present in 90% of condylomas but only rarely found in association with high-grade squamous intraepithelial lesions (SILs), ie, cervical intraepithelial neoplasia (CIN 2 and 3), and invasive carcinomas. By contrast, intermediate-risk types (particularly HPV 31, 33, 39, 52 and 58) and high-risk types HPV 16, 18, 45 and 56 are associated with flat condylomas, SILs and invasive carcinomas (5). The causal association of HPV with uterine malignant disease and the concept of HPVs of high, intermediate and low risk are both supported by epidemiological case-control studies that have collectively shown a consistent segregation of high-risk and intermediate-risk HPVs with uterine malignancies. It has also been shown that the risk of progression from low-grade to high-grade SIL is greater in patients who have persistent HPV infection and in those with high

viral load, which suggests that prolonged exposure is important in the carcinogenesis (7).

Genomic human papillomavirus DNA is functionally divided into early (E1 to E8) and late (L1 and L2) genes. The early genes are responsible for DNA replication, transcriptional regulation and transformation, whereas the late genes encode the major and minor capsid proteins. Early gene products E6 and E7, which are invariably expressed in carcinomas and tumour-derived cell lines, are recognized as being oncoproteins (8,9). Expression of E6 and E7 of the high-risk HPVs in primary human genital epithelial cells has been shown to produce immortal cell lines which very closely resemble *in vivo* lesions identified as CIN (10). By contrast the HPV E6 and E7 proteins encoded by the low-risk HPVs fail to show this activity. The mechanisms by which E6 and E7 contribute to oncogenesis appear to be related to their ability to form complexes with, and inactivate the normal function of, several cell proteins. HPV E6 inactivates p53 tumour-suppressor protein and E7 forms complexes with several host cellular proteins, including the retinoblastoma tumour-suppressor gene product (pRb), functionally inactivating it (11,12). p53 is responsible for mediating cellular growth arrest in response to DNA damage and regulates programmed cell death (apoptosis) in cells that have undergone irreparable cell injury. Mutations in the p53 gene have been identified as the most common genetic abnormality in human tumours (13).

Clinically and epidemiologically there is evidence that supports sexual behaviour and a sexually transmissible agent in the aetiology of cervical cancer. For instance it has been known for some time now that the cancer is associated with an early age of first sexual intercourse, multigravidity, multiple male sexual partners and the uncircumcised male sexual partner. It has also been well documented that sexual behaviour conducive to acquisition of sexually transmitted diseases

increases the risk of development of the cancer (14). Moreover, there is now accumulating evidence that implicates male sexual practices in the aetiology of this disease. For example, some of the highest rates of cervical cancer occur in regions such as some parts of Latin America where social pressure and tradition result in most women having sexual intercourse before marriage and being monogamous afterwards but their male partners maintaining multiple partners including commercial sex workers even after marriage (15), a situation not dissimilar to that in Papua New Guinea. Furthermore, case-control studies of uterine cancer patients have shown an increased risk of acquiring the cancer in women whose husbands have multiple sexual partners (16,17). An increased risk of cervical cancer has also been associated with a history of sexually transmitted diseases in the husbands of the affected individuals (18,19) as well as in subsequent wives of men previously married to a woman with cervical cancer (20). By contrast, women who use a diaphragm or whose husbands use a condom during intercourse with them have been known to have a reduced risk of cervical cancer (14). A similar protective effect of the condom has been shown in men who use them in extramarital intercourse (18). In a case-control study conducted in Thailand it has been shown that the risk of cervical cancer is strongly associated with the women's husbands having had commercial sex without using a condom when the husbands were less than 30 years old. In the study it was concluded that regular use of condoms by customers of commercial sex workers could reduce the number of invasive cancer cases in the general population by at least 25% (21).

Human papillomavirus infections, including that of high-risk types, are common in Papua New Guinea (22). In a recent study in which we examined cervical smears of 114 women attending the gynaecology clinic at Goroka Base Hospital we found that the overall incidence of HPV was 52%, of which the high-risk types HPV 16 and 18 accounted for 33% of all cases. Carcinoma of the cervix is not only very common in Papua New Guinea but it also contributes considerably to the number of deaths, mostly because the majority of patients present very late to the hospital (2). In

developed countries the death rate from cervical cancer has dropped significantly in the last 40 years mainly due to the widespread use of the Papanicolaou (Pap) test (23). This screening method has been made more sensitive by the addition of tests based on the polymerase chain reaction (PCR) for the detection of HPVs (24). However, these screening methods are expensive and require special expertise and very demanding logistics. Furthermore, following early detection of cervical dysplasia or HPV infection, prevention of invasive disease will require further sophisticated and expensive therapeutic measures of treatment with antiviral and immunomodulatory drugs such as 5-fluorouracil, imiquimod and interferons (25-27), or physical ablation using cryotherapy, electrosurgery or laser therapy (28-30). These forms of treatment do not always work and, besides, none are likely to be available in Papua New Guinea and many other developing countries for a long time to come. Therefore, simple but effective methods are required. Since HPVs are sexually transmitted agents, their spread can be controlled by curtailing the number of sexual partners and by using condoms.

Molecular epidemiological studies have shown that the peak incidence of HPV infection among women occurs between the ages of 20 and 24 years (31,32) indicating an early age of acquisition of the infection. Therefore, to be effective, measures to reduce the incidence of HPV infections need to target the young members of the population. Children and youths should be given health education on sexually transmitted diseases and counseled on the importance of abstaining from sexual activities until a time when they are responsible for their own lives and the lives of those whom they care about. Promiscuity should be strongly discouraged but when premarital and extramarital sex is to take place condoms should always be used; and for this to happen a condom has to be available there and then. Use of condoms in such circumstances should be promoted among youth as fashionable and the right thing ('cool') whereas refusal to use them as irresponsible and antisocial behaviour. Condom use has a significant spin-off of preventing other sexually transmitted infections including

HIV/AIDS. However, for such health education to be effective and behavioural change to take place in a sustainable manner the message should be targeted towards children and young adults before they become sexually active. This is a sensitive matter that will require understanding, cooperation and courage of all stakeholders including parents, teachers, educators, religious leaders and, indeed, society at large. It may also be cost-effective to include such health education in the already existing intervention programs like the peer-mediated health education being conducted by the Papua New Guinea Institute of Medical Research (PNGIMR) that targets youth in the prevention of HIV/AIDS and other sexually transmitted infections. This will add impetus in the war against these diseases, which unquestionably include uterine cervical cancer.

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