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The Section of Infections (INF) has two groups: the Infections and Cancer Biology Group (ICB) and the Infections and Cancer Epidemiology Group (ICE). The research activities of both Groups aim to evaluate the role of infectious agents in human cancers through biological and epidemiological studies.

Using in vitro and in vivo experimental models, ICB is focused on (i) the characterization of the transforming properties of well-established and novel potential oncogenic viruses; and (ii) the evaluation of possible cooperation between viruses and other environmental risk factors, such as ultraviolet (UV) radiation, in promoting cancer development (Viarisio et al., 2018). In addition, ICB collaborates intensively with epidemiologists at IARC and worldwide, offering many laboratory assays for biomarker detection to evaluate the role of infections in human cancer (Donà et al., 2019; Hampras et al., 2019).

The overall strategy of ICE is to improve the epidemiological evidence base with respect to prevention of infection-attributable cancer. This strategy relies on obtaining both high-quality data and biological samples from populations that have been well characterized epidemiologically. Although the strategy of ICE is global, work is naturally focused on low- and middle-income countries (LMICs), which have a disproportionate burden of infection-attributable cancers, and particularly on countries in Africa and Asia. There are currently 11 infectious agents that are classified as carcinogenic by the IARC Monographs, and they are at different stages along the pathway from discovery to public health intervention. Correspondingly, ICE research includes a wide portfolio of study designs that are tailored to specific infectious agents across a spectrum of epidemiological research, from etiology or natural history through global burden assessment to evaluation and modelling of the impact of interventions and/or policy.

ICB and ICE are also participating in several collaborative studies to assess the impact of human papillomavirus (HPV) vaccine in LMICs (see text box) and characterize the role of mucosal high-risk (HR) HPV infection in the etiology of head and neck cancer.

Infections and Cancer Biology Group (ICB)

Role of beta HPV types in the development of cutaneous squamous cell carcinoma

A large number of HPV types have been isolated and fully characterized so far (Rollison et al., 2019a). They are subdivided into genera and species in the HPV phylogenetic tree according to the DNA sequence of the late gene L1. Genera alpha, beta, and gamma comprise the majority of the known HPV types. A subgroup of genus alpha, referred to as mucosal HR HPV types, infect the epithelia of the anogenital tract as well as the upper respiratory tract; these HR HPV types have been clearly associated with a broad spectrum of human cancers, including cervical and oropharyngeal cancers. In addition to the HR HPV types, cutaneous beta HPV types also appear to be implicated in carcinogenesis, although by different mechanisms. Epidemiological and biological studies support the model of synergistic cooperation between cutaneous beta HPV types and UV radiation in the development of cutaneous squamous cell carcinoma (cSCC) (Rollison et al., 2019a). Many findings indicate that beta HPV infection plays a role in an initial phase of skin carcinogenesis, but it is not essential for the viability of the tumour cells once they have become malignant (Rollison et al., 2019a; Tommasino, 2019). Using a beta HPV transgenic (Tg) mouse model, in which E6 and E7 genes can be conditionally silenced via the use of the Cre/Lox system, ICB has recently obtained additional lines of evidence that support this beta HPV-mediated model of skin carcinogenesis (Viarisio et al., 2018). This mouse model has a high susceptibility to UV-induced skin carcinogenesis. Indeed, long-term UV irradiation of keratin 14 (K14) HPV38 E6/E7 Tg mice induced cSCC, although wild-type animals subjected to identical treatments did not develop any type of skin lesions. Accordingly, K14 HPV38 E6/E7 Tg mice accumulate a large number of UV-induced DNA mutations, which increase proportionally with the severity of the skin lesions (Viarisio et al., 2018). In contrast, no mutations were detected in the skin of wild-type animals exposed to the same doses of UV radiation. The mutation pattern detected in the Tg skin lesions closely resembles that detected in human cSCC, with the highest mutation rate in p53 and Notch genes (Figure 1)

Figure 1. Several genes mutated in human skin lesions are also mutated in the ultraviolet (UV) radiation-induced skin lesions of cutaneous squamous cell carcinoma (cSCC) of keratin 14 (K14) HPV38 E6/E7 transgenic (Tg) mice. Heatmap of mutations in genes in normal skin, pre-malignant lesions, and cSCC from different mice (M1–3) reported as significantly mutated in human cSCC. SNV, single-nucleotide variant. Reproduced from Viarisio et al. (2018).

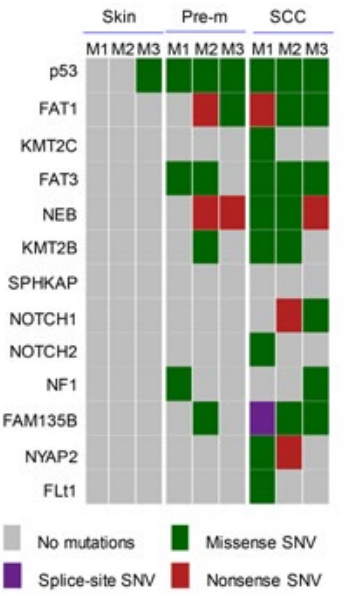
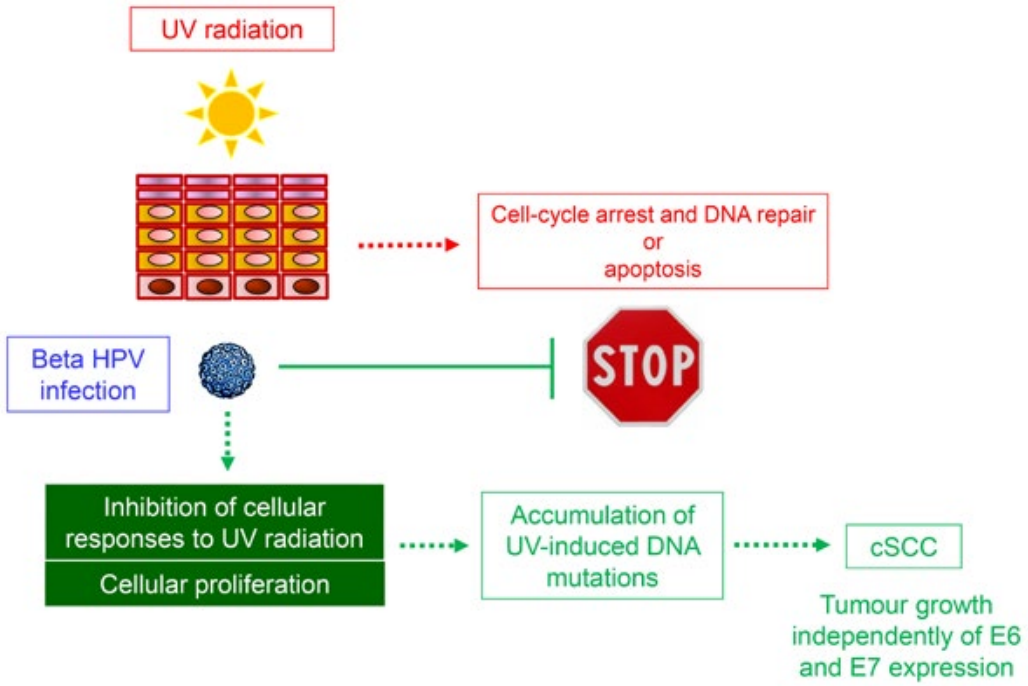


Figure 2. Working model for cooperation between beta human papillomavirus (HPV) types and ultraviolet (UV) radiation in promoting cutaneous squamous cell carcinoma (cSCC). Under normal conditions, UV irradiation of the skin induces DNA mutations in keratinocytes in the basal layer, with consequent (i) cell-cycle arrest and repair of DNA mutations, or (ii) apoptosis, if the DNA damage is unrepairable. Upon beta HPV infection, E6 and E7 expression inhibits the cellular response to UV radiation-induced stress. As a consequence, DNA-damaged cells continue to proliferate, with a high risk of evolving into cancer cells. After inactivation of tumour suppressor genes or activation of cellular oncogenes by DNA mutations, the expression of the viral genes becomes dispensable. Reprinted from Tommasino (2019), Copyright 2019, with permission from Elsevier.



(Viarisio et al., 2018). Silencing the expression of HPV38 E6 and E7 before the long-term UV irradiation prevented the development of any type of skin lesions. In contrast, their loss after the development of UV-induced skin lesions did not have any impact on cancer cell growth.

Together, these findings support the model in which beta HPV E6 and E7 proteins act as facilitators of DNA mutations induced by HPV and UV radiation by targeting key cellular pathways. A plausible hypothesis is that beta HPV types, to efficiently complete their life-cycle in the skin, have developed strategies to maintain infected cells in a proliferative status, even if they have been damaged by UV radiation. By doing so, they strongly increase the probability of infected cells progressing towards malignancy. Because of the irreversible UV-induced DNA damage, the expression of the viral genes may become dispensable for the maintenance of cSCC (Figure 2).

Infections and Cancer Epidemiology Group (ICE)

Modelling cervical cancer control in high-income and low- and middle-income countries

A combination of infectious and chronic disease modelling techniques is helpful to gain insight into HPV infection transmission dynamics and the natural history of cervical cancer, and to design and evaluate prevention programmes (Baussano and Bray, 2019). ICE has developed mathematical models to support the introduction of HPV vaccination and the implementation of HPV DNA-based cervical cancer screening in both high-income countries and LMICs. The findings show that international variations in HPV prevalence, mostly a result of differences in sexual behaviour, have a direct effect on the levels of herd protection and affect the impact of vaccination programmes (Baussano et al., 2018). Overall, HPV vaccination programmes are expected

to be more efficient in populations with sexual behaviour based on traditional norms and lower HPV prevalence (Figure 3). Model-based findings, in combination with empirical data, also demonstrate that the coverage and cross-protection of HPV vaccines required to reduce or eliminate infection vary by individual HR HPV type; HPV 16 infection and the corresponding cancers are the most difficult to eliminate (Lehtinen et al., 2018a, 2019). Finally, on the basis of available data from European HPV DNA-based cervical cancer screening trials, ICE has used the cervical cancer screening model to assess the expected effectiveness of selected vaccination and screening scenarios in different populations (Berkhof, 2018).

HPV genomics

The reasons why only a small minority of HR HPV-infected women progress to cervical cancer remain largely unknown. Furthermore, the 13 established HR HPV types vary enormously in their cancer risk: HPV 16 is uniquely carcinogenic, but the closely genetically related types are much less carcinogenic. These intriguing observations, for which explanations must lie partly in the relatively small (8 kb) HPV genomes, have motivated studies of HPV genomics in the ICE biobank. Indeed, ICE has coordinated a wide variety of epidemiological studies on HPV and cervical cancer around the world, and the resulting biobank is a uniquely ethnically and geographically diverse resource with which to study the genetic determinants of HPV carcinogenesis. A high-throughput HPV 16 whole-genome sequencing platform developed at the United States National Cancer Institute was used to wholly sequence 7116 global HPV 16-positive cervical samples (including 2076 controls, 1878 squamous cell carcinomas, and 186 adenocarcinomas). The resulting global description of HPV 16 genomics (Figure 4) resulted in novel HPV 16 sublineage identification and an evolutionary model for HPV and human co-evolution, including HPV transmission from Neanderthals to modern humans (Chen et al., 2018a). HPV 16 genetic variation was shown to influence risk of cervical cancer: increased cancer risks were seen for the A3, A4, and D (sub) lineages in worldwide regions where they were common (Clifford et al., 2019) (Figure 4).

HPV 16 and risk of anal cancer

The incidence of anal cancer, which is caused by HPV, is increasing at a population level and is elevated in groups with increased anal HPV exposure and/or immunosuppression, particularly HIV-positive men who have sex with men. Compared with HPV and cervical

Figure 3. (a) Relative reduction in HPV 16 prevalence and (b) achievable post-vaccination HPV 16 prevalence among women aged 15–34 years after vaccination of girls aged 11 years in a population with gender-equal sexual behaviour, by coverage and pre-vaccination prevalence. (c) Relative reduction in HPV 16 prevalence and (d) achievable post-vaccination HPV 16 prevalence, among women aged 15–34 years after vaccination of girls aged 11 years in a population with traditional sexual behaviour, by coverage and pre-vaccination HPV 16 prevalence. Reproduced from Baussano et al. (2018). © 2018 IARC/WHO; licensed by UICC.

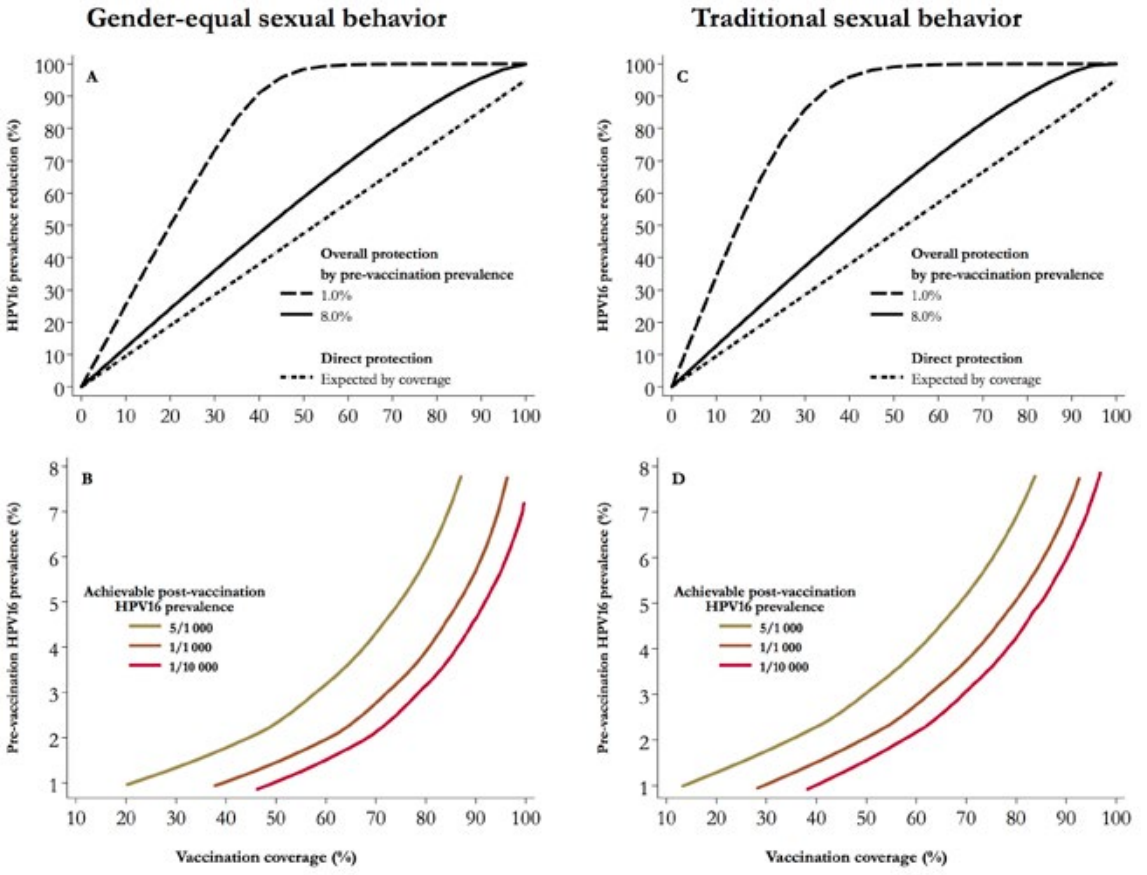
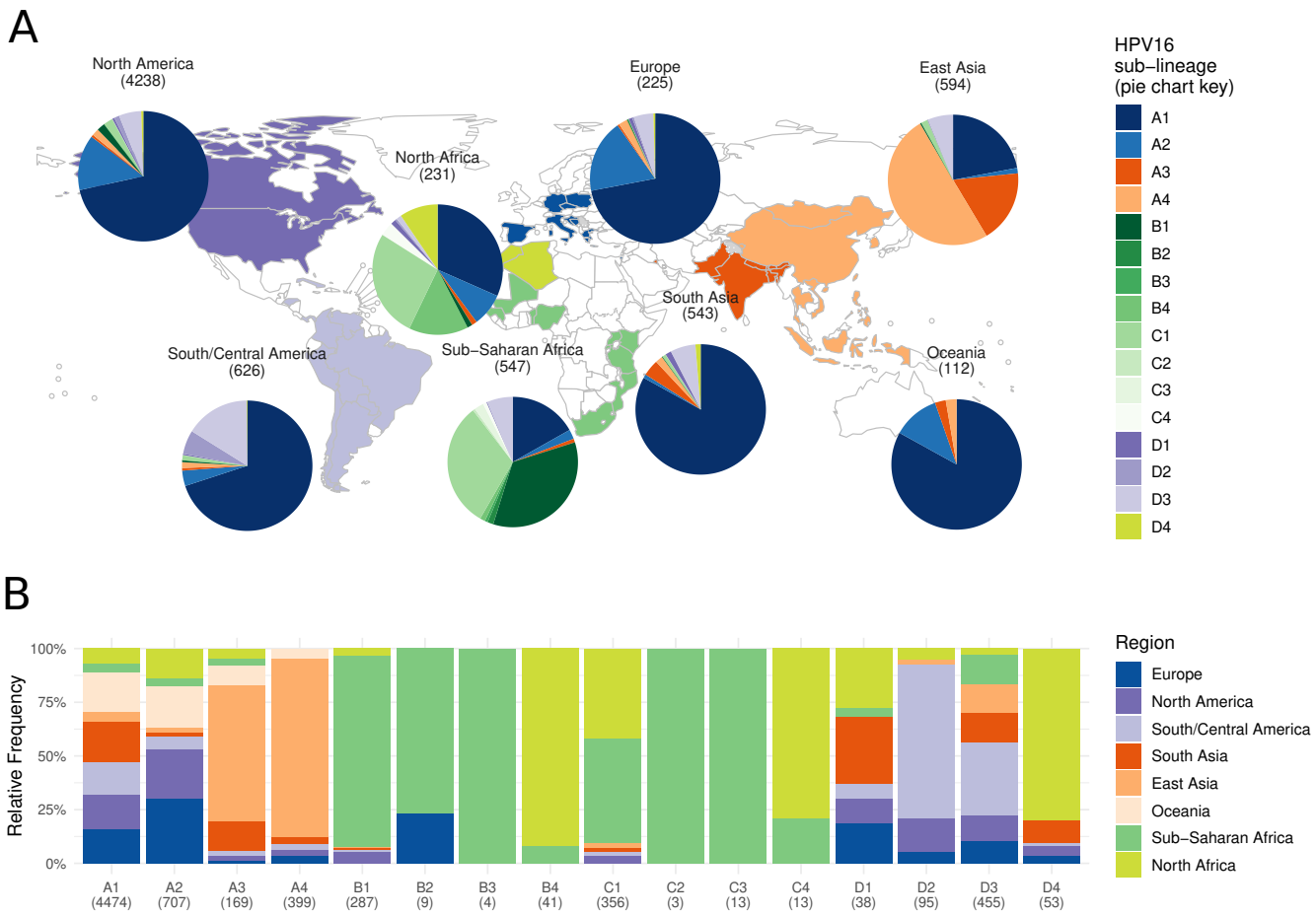


Figure 4. Distribution of sublineages in 7116 HPV 16-positive samples, by geographical region. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city, or area, or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. Reprinted from Clifford et al. (2019), Copyright 2019, with permission from Elsevier.



cancer, much less is known about anal cancer natural history, which is key to informing appropriate prevention approaches. ICE undertook several relevant studies in this regard. First, a meta-analysis across the full disease spectrum from anal HPV infection to cancer confirmed the unique importance of HPV 16 in anal carcinogenesis: HPV 16 predominated over other HPV types in anal cancer, irrespective of HIV status (Lin et al., 2018a) (Table 1). In follow-up meta-analyses or pooled-analyses, notable determinants of anal HPV 16 infection were sexual preference and HIV infection for men (Marra et al., 2019) and cervical HPV 16 positivity for women (Lin et al., 2019), suggesting that HPV-based cervical screening may contribute to anal cancer prevention (Lin et al., 2019). In the APACHES study of the natural history of anal HPV in 500 HIV-positive men who have sex with men in France, anal HPV

Table 1. Number and prevalence (%) of single and multiple infections of human papillomavirus (HPV) types in HPV-positive anal cancer by HIV status. Reprinted from Lin et al. (2018), Copyright 2018, with permission from Elsevier.

HPV type	HIV-negative or unknown	HIV-positive
HPV 16	1333/1554 (86%)	96/144 (67%)
HPV 18	66/1554 (4%)	21/144 (15%)
HPV 33	44/1369 (3%)	12/130 (9%)
HPV 6	54/1415 (4%)	8/124 (6%)
HPV 58	23/1198 (2%)	1/123 (1%)
HPV 35	12/1332 (1%)	0/123 (0%)
HPV 31	19/1338 (1%)	6/129 (5%)
HPV 52	21/1198 (2%)	12/123 (10%)
HPV 11	37/1415 (3%)	10/124 (8%)
HPV 45	10/1329 (1%)	8/125 (6%)
HPV 56	6/1190 (1%)	1/123 (1%)
HPV 39	7/1190 (1%)	8/123 (7%)
HPV 68	4/1190 (< 1%)	10/123 (8%)
HPV 59	2/1190 (< 1%)	5/123 (4%)
HPV 51	11/1190 (1%)	8/123 (7%)
Any HPV	1424/1430 (> 99%)	128/130 (98%)
HPV 16/18	552/629 (88%)	87/118 (74%)
HPV 6/11/16/18	579/629 (92%)	91/118 (92%)
HPV 6/11/16/18/31/33/45/52/58	618/629 (98%)	109/118 (92%)

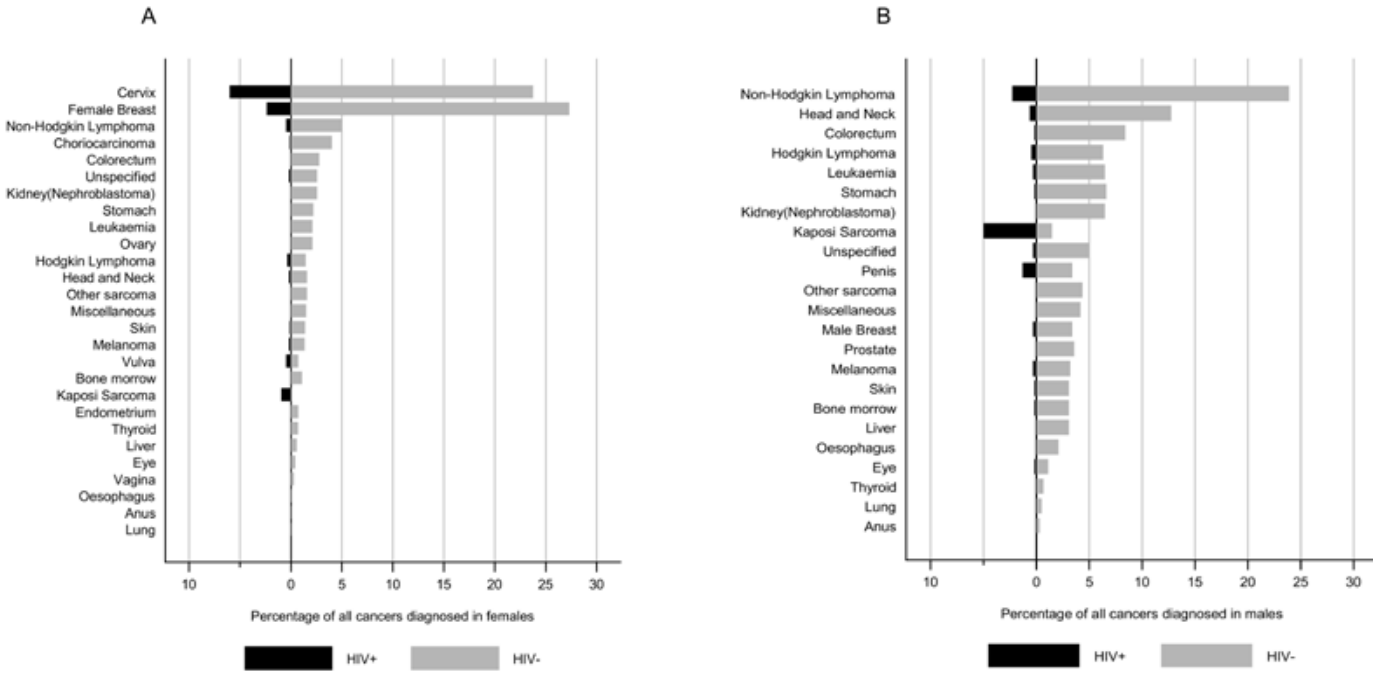
Data are *n*/*N* (%) for overall prevalence.

16 infection was also shown to be the strongest predictor of anal precancerous lesions (Clifford et al., 2018; Combes et al., 2018a).

HIV and cancer risk

HIV-related immunosuppression can worsen oncogenic viral infections, increasing the risk of infection-related cancer. ICE studied the link between HIV infection and a broad spectrum of cancers diagnosed in the era of combination antiretroviral therapy (cART) in Rwanda. People seeking cancer care at Butaro Cancer Center of Excellence were routinely screened for HIV before being confirmed with or without cancer (2656 cases and 1196 controls, respectively). HIV was shown to be significantly associated with diagnoses of Kaposi sarcoma, non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL), as well as cancers of the cervix, vulva, penis, and eye (Figure 5). Associations varied by subtype of NHL or HL, with the association for NHL being limited to diffuse large B-cell lymphoma, particularly plasmablastic lymphoma. No significant associations with HIV were seen with other commonly diagnosed cancer types such as breast, prostate, or colorectal cancer. Overall, 6% of all cancer cases diagnosed at this national referral hospital were estimated to be attributable to HIV infection. In a separate collaboration involving a worldwide consortium of cohort studies, important variations in NHL incidence among HIV-positive people were observed according to geographical region, probably driven by differences in prevalence of oncogenic viruses and/or access to cART (AIDS-defining Cancer Project Working Group of IeDEA and COHERE in EuroCoord, 2018).

Figure 5. Proportion of individual cancer types among all cancers diagnosed at Butaro Cancer Center of Excellence, Rwanda, 2012–2016, by HIV status: (a) women and (b) men. Reproduced from Mpunga T, Chantal Umulisa M, Tenet V, Rugwizangoga B, Milner DA Jr, Munyanshongore C, et al. (2019). Human papillomavirus genotypes in cervical and other HPV-related anogenital cancer in Rwanda, according to HIV status. Int J Cancer. ijc.32491. https://doi.org/10.1002/ijc.32491 PMID:31173641. © 2019 IARC/WHO; licensed by UICC.



Assessing HPV vaccine impact through urine surveys

ICE is engaged in assessing the impact of national human papillomavirus (HPV) vaccination in several low- and middle- income countries (LMICs), such as Armenia, Bhutan, Rwanda, and Uganda. Working in close collaboration with local public health authorities, ICE is conducting a series of baseline and repeat urine surveys, targeting young women before and after the introduction of HPV vaccination, respectively, to follow up type- and age-specific HPV prevalence trends. Data from Rwanda and Bhutan, the first two LMICs to implement national HPV vaccination, show that the prevalence of vaccine-targeted HPV types has decreased significantly as a result of a high-coverage school-based national vaccination programme.

Assessing HPV vaccine impact through urine surveys, Rwanda. © IARC.

Urine collection is a very powerful alternative to standard methods for HPV testing because it is a well-accepted non-invasive procedure, facilitates sample storage and processing, and displays good concordance with cervicovaginal cells for HPV positivity in women. ICE has designed and optimized transferable procedures and skills for designing and conducting repeat urine-based surveys, which may be used by public health authorities in other LMICs to monitor the impact of their vaccination programmes and optimize the allocation of the resources devoted to cervical cancer control.