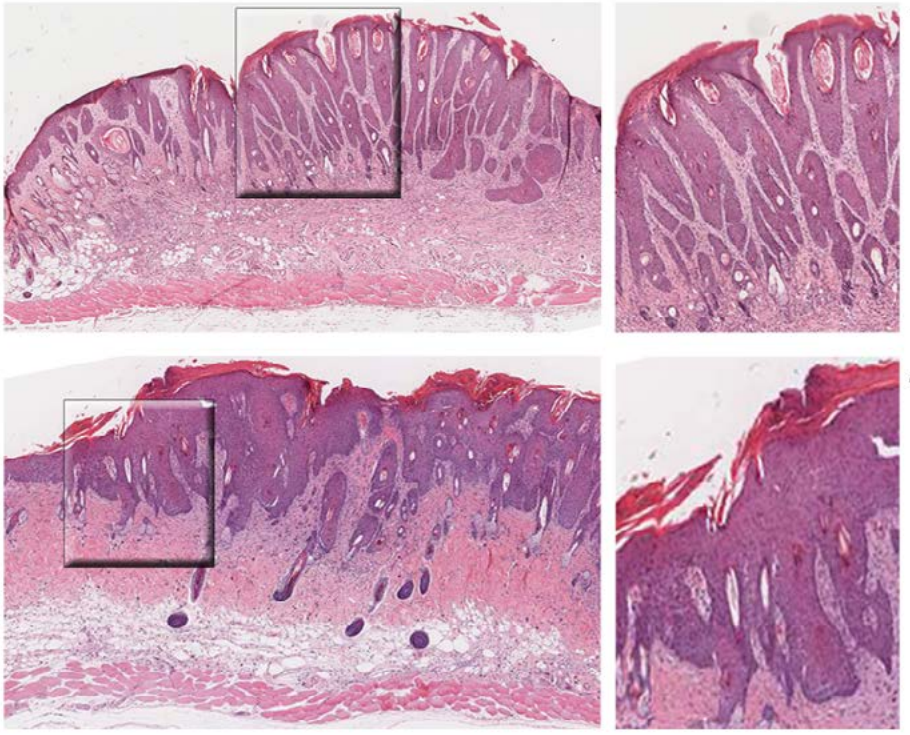

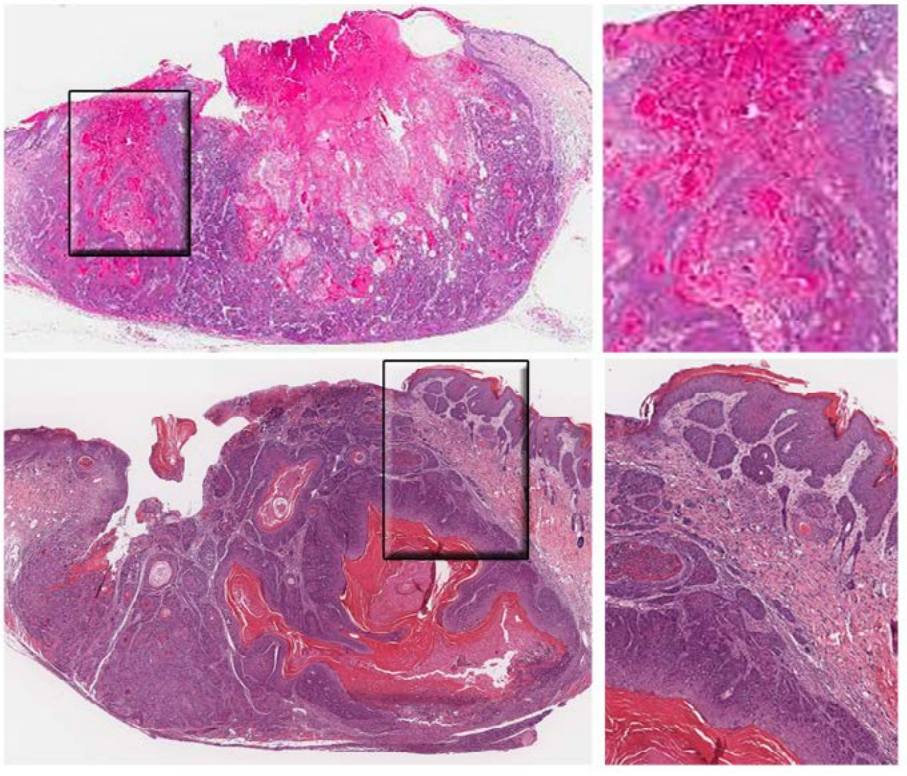

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The Section of Infections (INF) consists of two groups: the Infections and Cancer Biology Group (ICB) and the Infections and Cancer Epidemiology Group (ICE). The research activities of both Groups aim to evaluate the role of infectious agents in human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

ICB uses in vitro and in vivo experimental models and focuses 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 (Hernandez-Vargas et al., 2017; Mattoscio et al., 2017; Pacini et al., 2017). In addition, ICB collaborates intensively with epidemiologists at IARC and worldwide, offering many diagnostic laboratory assays for the detection of more than 200 infectious agents in human specimens (Donà et al., 2016; Anantharaman et al., 2017; Gheit et al., 2017a; Hampras et al., 2017; Moscicki et al., 2017).

ICE focuses on (i) the prevention of cervical cancer through human papillomavirus (HPV) vaccination and HPV-based screening, with a focus on low- and middle-income countries (LMICs) (Schiffman et al., 2016; Vaccarella et al., 2016a); (ii) the natural history of infection-associated cancers, with a particular focus on HIV-positive populations, among whom immunodeficiency tends to worsen the outcome of oncogenic viral infections (Clifford et al., 2017b; Combes et al., 2017b; Franceschi and Clifford, 2017); and (iii) quantitative methods to estimate cancer burden and model the impact of interventions, particularly for infection-associated malignancies (Plummer et al., 2016) and thyroid carcinoma.

In addition, ICB and ICE have several collaborative studies to further characterize the natural history of mucosal high-risk (HR) HPV infection and other oncogenic viruses in the oral cavity, with the final aim of better defining the role of viral infections in the etiology of head and neck cancers.

Infections and Cancer Biology Group (ICB)

Beta HPV types and non-melanoma skin cancer

To date approximately 50 different beta HPV types have been fully characterized, which have been isolated mainly from the skin of healthy individuals. The first beta HPV types were identified in the skin of individuals with a genetic disorder, epidermodysplasia verruciformis (EV), which confers high susceptibility to beta HPV infection and UV-induced non-melanoma skin cancer (NMSC). Many epidemiological and biological findings now support the role of beta HPV in skin carcinogenesis, also in non-EV individuals (Tommasino, 2017; Viarisio et al., 2017a). ICB's previous studies in a transgenic (Tg) mouse model demonstrated that the expression of beta HPV38 early oncogenes, E6 and E7, in the basal layer of the epidermis strongly increases the susceptibility to UV-induced skin carcinogenesis (Viarisio et al., 2017a). Recent findings provide additional support for the role of beta HPV38 in skin cancer development (Viarisio et al., 2017b). Patients with metastatic melanoma harbouring a specific *BRAF* mutation are effectively treated with a BRAF inhibitor (vemurafenib or dabrafenib). However, as a side-effect, a proportion of these patients develop NMSC, which is in part attributed to beta HPV infections in the skin (Tommasino, 2017). Consistently with the scenario in humans, we observed in HPV38 E6/E7 Tg mice that vemurafenib treatment strongly enhanced the development of skin malignant lesions induced by UV (Viarisio et al., 2017b).

In other mechanistic studies, ICB has provided a possible explanation for the cooperation of HPV38 E6 and E7 oncoproteins and UV irradiation in promoting NMSC (Viarisio et al., 2016; Pacini et al., 2017). Indeed, the two viral oncoproteins deregulate cellular pathways known to be activated by stress induced by UV. In normal skin, UV irradiation leads to activation of the inflammasome, with consequent secretion of interleukin 18 (IL-18). In Tg animals, HPV38 E6 and E7 oncoproteins decrease the expression of IL-18 induced by UV irradiation (Viarisio et al., 2016).

UV irradiation also activates, via p53, the expression of Toll-like receptor 9 (TLR9), which in turn senses endogenous ligands generated during the stress, such as damage-associated molecular patterns (Pacini et al., 2017). HPV38 E6 and E7 severely affect the TLR9 expression induced by UV irradiation, altering the functions of p53 (Pacini et al., 2017).

A possible model is that beta HPV types play a role at an early stage of carcinogenesis, facilitating the accumulation of UV-induced mutations in the host genome, which in turn can lead to cellular transformation.

Biology and epidemiology of β-3 HPV types

Recent studies have shown that, in addition to the skin, beta HPV types can be detected in the oral cavity, anal canal, and external genital sites (Donà et al., 2016; Hampras et al., 2017; Smelov et al., 2017a). Beta HPV types are subdivided into five different species: β-1, β-2, β-3, β-4, and β-5. The β-1 and β-2 species comprise the majority of the beta HPV types that are abundantly present in the skin of normal individuals and have been linked to NMSC. In contrast, the β-3

species includes only four HPV types, HPV49, 75, 76, and 115, which appear to infect cutaneous and mucosal epithelia (Hampras et al., 2017). Interestingly, HPV49 E6 and E7 display some functional similarities to mucosal high-risk HPV16 oncoproteins (Viarisio et al., 2016, 2017a). HPV49 or HPV16 E6/E7 Tg mice are highly susceptible to upper digestive tract carcinogenesis upon initiation with 4-nitroquinoline 1-oxide (4NQO), a molecule that mimics exposure to tobacco products. In contrast, wild-type animals as well as β-2 HPV38 E6/E7 Tg mice are not significantly affected by 4NQO treatment. Together, these data highlight biological differences in the beta HPV group. Future molecular and epidemiological studies are warranted to further confirm the mucosal tropism of β-3 HPV types and their possible link to human diseases.

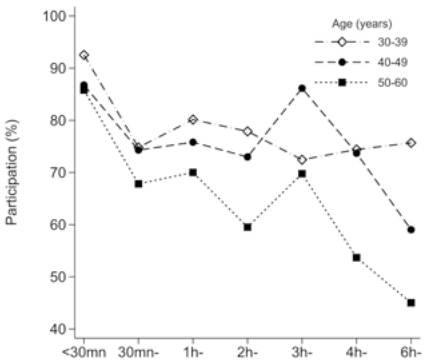
Infections and Cancer Epidemiology Group (ICE)

HPV-based screening and HPV vaccination in LMICs

In Bhutan, HPV testing improved the performance of cervical screening over cytology (Tshomo et al., 2017a), and HPV-based screening of 2500 women using self-collected samples achieved high coverage in rural areas (Baussano et al., 2017c), although the participation rate was inversely related to age and travel time to the screening centre; travelling to the centre was often challenging (Figure 1). In Rwanda, a pre-vaccination cervical cell survey of women older than 20 years revealed a high prevalence of HPV and cervical disease, worsened by HIV (Ngabo et al., 2016). In both countries, a urine survey to monitor vaccine effectiveness already showed decreases in the prevalence of HPV among young women 3 years after the introduction of HPV vaccination (Franceschi et al., 2016).

Using our dynamic HPV transmission model, we predicted that the indirect protection provided by vaccinated individuals to unvaccinated individuals (herd immunity) differs by HPV type and population. Indeed, HPV16 is more difficult to eliminate from the population than the other high-risk types, because of its greater ability to persist and induce

Figure 1. Effect of travel time (on foot) on participation rate in cervical cancer screening in Bhutan in 2016, by age group. Figure reprinted from Baussano et al. (2017a). © Baussano et al., 2017.



Cervical cancer prevention in Bhutan and Rwanda

For a long time, ICE has been engaged in cervical cancer prevention in many low- and middle-income countries. Since 2010, ICE has worked especially with the ministries of health and public hospitals in Bhutan and Rwanda to strengthen screening activities and monitor human papillomavirus (HPV) vaccination.

Several capacity-building initiatives in 2016–2017 have focused on the training of local staff and the transfer of medical technologies. For instance, ICE supported the introduction of HPV DNA-based cervical cancer screening in Bhutan and performed validation studies on HPV test accuracy in Bhutan and Rwanda. Capacity-building initiatives were especially crucial to make the new diagnostic technologies available in typically underserved rural populations. In both countries, training courses were organized and medical equipment provided to improve the diagnosis and treatment of cervical lesions identified during screening.

Finally, ICE helped create computerized medical databases and biobanks of urine samples, cervical cells, and cancer tissue samples and facilitated exchanges between local and international experts at IARC and at international scientific meetings. A few master's students and doctoral students from Bhutan and Rwanda are being supervised by ICE staff, and many more have had the chance to spend short periods at IARC or attend the IARC Summer School.

A Bhutanese nurse on her way to a rural health centre to perform cervical cancer screening. © Chhimi Wangmo.

malignant transformation (Baussano et al., 2017b). Furthermore, HPV control is harder when pre-vaccination HPV prevalence is high (Baussano et al., 2017a). In LMICs where sexual behaviour is based on traditional norms, it is advantageous to introduce vaccination while HPV prevalence in young women is low, anticipating any increase that may occur with liberalization of social attitudes (Baussano et al., 2016).

Variations in HPV prevalence by HIV status and body site

ICE performed large international systematic reviews that showed the predominance of HPV16 in cervical cancer and precancer in HIV-positive women (Clifford et al., 2016a, 2017a). Furthermore, the ICE cervical cancer biobank contributed to a whole viral genome sequencing effort of 5570 HPV16-infected samples, showing that strict conservation of the 98 bp of the HPV16 *E7* gene is critical for cervical carcinogenesis (Mirabello et al., 2017). ICE also showed that HPV infection is infrequent in tonsil brushings of cancer-free children and adults, whereas HPV infection in gargles in adults is rather common (Combes et al., 2017b). Low agreement in paired tonsil brushings and gargles suggests that gargle is not representative of HPV prevalence in the tonsils, where the majority of HPV-related oropharyngeal cancer is located (Lacau St Guily et al., 2017).

Global burden of cancer due to infections

Of 14 million new cancer cases in 2012, approximately 2.2 million (15%) were attributable to carcinogenic infections (Plummer et al., 2016), mainly *Helicobacter pylori*, HPV, and hepatitis B and C viruses. The attributable fractions for infection varied from less than 5% in the USA, Canada, Australia, New Zealand, and some countries in western and northern Europe to more than 50% in some countries in sub-Saharan Africa. HPV alone accounts for 630 000 cancer cases per year (Table 1), 9% of all cancers in women and less than 1% of all cancers in men (de Martel et al., 2017). Cervical cancer accounts for 83% of HPV-attributable cancer cases, two thirds of which occur in less developed countries. Other HPV-attributable ano-genital cancers include cancer of the vulva (8500 cases), vagina (12 000), anus (35 000, of which half occur in men), and penis (13 000) (Table 1). HPV-attributable head and neck cancers represent 38 000 cases, of which 21 000 are oropharyngeal cancers occurring in more developed countries.

Overdiagnosis of thyroid cancer

The experience in cervical cancer led ICE to assess other cancers for which the incidence is rapidly changing, such

Table 1. Number of all cancer cases attributable to human papillomavirus (HPV) and corresponding attributable fraction (%) for all cancers, by cancer site(s), sex, and age group; world, 2012. Table reproduced from de Martel et al. (2017). © 2017 IARC/WHO; licensed by UICC.

HPV-related cancer site (ICD-10 code)	Number of incident cases[a,b]	Number attributable to HPV	Attributable fraction (%)	Number attributable to HPV by sex		Number attributable to HPV by age group		
				Males	Females	< 50 years	50–69 years	≥ 70 years
Cervix uteri (C53)	530 000	530 000	100.0	0	530 000	250 000	220 000	58 000
Anus[c] (C21)	40 000	35 000	88.0	17 000	18 000	6 600	17 000	12 000
Vulva[c] (C51)	34 000	8 500	24.9	0	8 500	2 600	3 400	2 500
Vagina[c] (C52)	15 000	12 000	78.0	0	12 000	2 500	5 200	3 900
Penis[c] (C60)	26 000	13 000	50.0	13 000	0	2 700	5 800	4 400
Oropharynx[c] (C01, C09–10)	96 000	29 000	30.8	24 000	5 500	5 400	18 000	6 000
Oral cavity[c] (C02–06)	200 000	4 400	2.2	2 900	1 500	890	2 300	1 200
Larynx (C32)	160 000	3 800	2.4	3 300	460	420	2 200	1 200
Other pharynx[c] (C12–C14)	78 000	0	0	—	—	—	—	—
Total HPV-related sites	1 200 000	630 000	54.0	60 000	570 000	270 000	270 000	88 000

ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

[a] Source of data: Ferlay et al. (2013). GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: IARC. Available from: http://globocan.iarc.fr.

[b] Numbers are rounded to two significant digits.

[c] These cancer sites were not directly available in GLOBOCAN 2012; therefore, data from the Cancer Incidence in Five Continents, Volume X (CI5-X) database were used to estimate the corresponding number of cases. Source of data: Forman D et al., editors (2013). Cancer Incidence in Five Continents, Vol. X (electronic version). Lyon: IARC. Available from: http://ci5.iarc.fr.

as thyroid carcinomas. ICE provided indirect evidence that the vast increases in the numbers of differentiated thyroid carcinoma in the past two decades are due largely to overdiagnosis of tumours that would not cause symptoms or death during a person's lifetime (Vaccarella et al., 2016b). Increasing use of ultrasonography and other imaging techniques may have been responsible for approximately 470 000 extra cases of thyroid carcinoma in women and 90 000 in men in 12 well-studied high-income countries. Figure 2 shows the progressive rise in the incidence of thyroid carcinoma in young and middle-aged adults in three countries that have been especially affected by the thyroid carcinoma epidemic. Of note, most patients with thyroid carcinoma undergo total thyroidectomy and other harmful treatments.

Figure 2. Rises in age-specific incidence of thyroid cancer per 100 000 women, 1988–2007. The pink area of the curves above the bold dashed line represents the part of disease attributable to overdiagnosis in different periods. Figure adapted from Vaccarella et al. (2016b). Copyright © 2016, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.