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Section of Infections (INF)

The new Section of Infections (INF) comprises two Groups: the Infections and Cancer Epidemiology Group (ICE) and the Infections and Cancer Biology Group (ICB). The reorganisation of the scientific structure of IARC has therefore left the situation of ICE and ICB unchanged, as they were together in the Epidemiology and Biology Cluster before 2009.

Persistent infection with viruses, bacteria and parasites account for approximately 20% of the cancer burden worldwide, with less developed countries being the hardest hit. Infections also represent, or might represent in the future, some of the most preventable cancer causes through immunisation or early detection. Table 1 summarises the infectious agents and the different aspects of the infection/cancer relationship currently under study in INF.

Not all of the topics listed in Table 1 are covered by both Groups. ICB, for instance, is focused on HPV to an even greater extent than is ICE, although it also works on EBV and Merkel cell polyomavirus. Although ICE has never performed large epidemiological studies of non-melanomatous skin cancer, it has collaborated very closely with ICB on the association between cutaneous HPV and squamous cell carcinoma of the conjunctiva.

ICE is more active than ICB in the study of other cancer-associated infections that have either been present in the IARC portfolio for years (*Helicobacter*), or were brought to IARC by the present ICE Group Head (e.g., HIV and HCV). In particular, ICE is a world leader in the study of cancer excess among HIV-positive people. For consistency, some of the long-duration population-based studies previously established in ICE continued with the same extra-mural laboratories they started with. Similarly, the attractiveness of the ICB laboratory has successfully led to extra-mural collaborations with distinguished epidemiologists and clinicians.

With respect to aspects under study, some are exclusive to ICB (e.g., transformation mechanisms) or ICE (worldwide distribution and trends of cancer-associated infections). Collaborations on other relevant aspects (the role of innate and acquired immunity, the impact of different HPV variants) are becoming possible along with the increasing availability at ICB of tests suitable for large-scale application.

Regardless of the infectious agent or the aspect under study, one of the great assets of INF is the collaboration on methodological issues. It has become routine for ICB to provide advice to ICE regarding decisions on biological protocol aspects, and for ICE to provide statistical assistance to ICB in its protocols and publications.

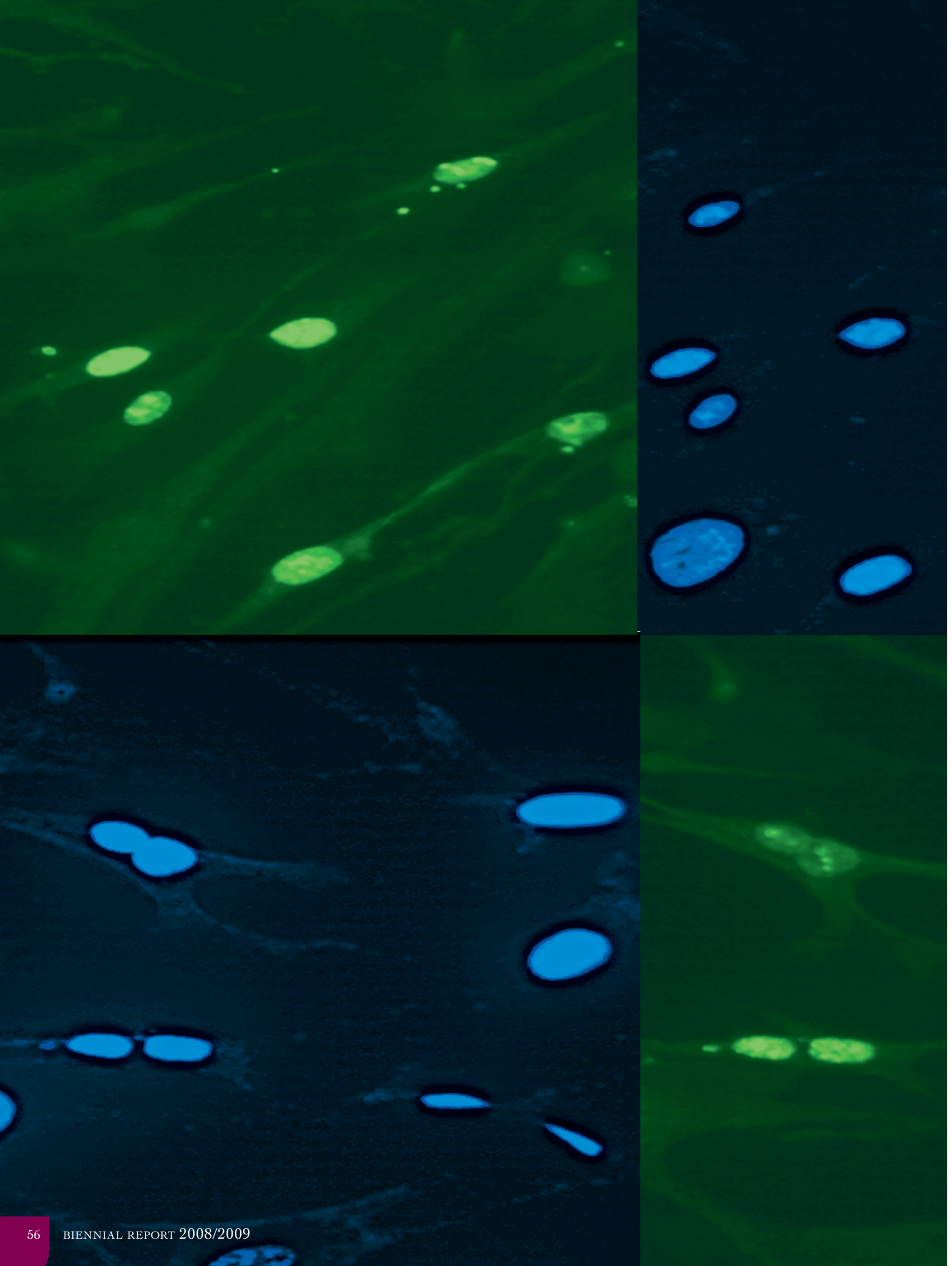
Additional collaborations are ongoing with other Sections, notably the Sections of Early Detection and Prevention (EDP), Nutrition and Metabolism (NME), Genetics (GEN), Environment (ENV), Molecular Pathology (MPA) and Mechanisms of Carcinogenesis (MCA).

The over 100 publications produced by INF in 2008–2009 provide good evidence of the high productivity and width of topics and international collaborations entailed in projects coordinated by INF.

Table 1. Section of Infections Studies

Aspects under study
- Worldwide distribution and trends over time of infections associated with cancer
- Range of tumours associated with infection and strength of the association
- Transformation mechanisms
- Meaning of viral variants
- Role of innate and acquired immunity
- New virological and bacteriological tests for epidemiological studies

Agents included
- Mucosal and cutaneous human papillomavirus (HPV) types
- HIV, in combination with other viruses associated with cancer
- Helicobacter species
- Hepatitis B and C virus (HBV/HCV)
- Epstein Barr virus (EBV)
- Merkel cell polyomavirus



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It is well established that approximately 20% of human cancers worldwide are associated with infectious agents. In addition, new evidence supports the involvement of additional infectious agents in human carcinogenesis, which may add to this total. A sub-group of HPV types that infect the skin are suspected to be involved, together with ultraviolet radiation, in the development of non-melanoma skin cancer (NMSC). In addition, a recently-discovered human polyomavirus, Merkel Cell polyomavirus (MCPyV), is associated with a rare tumour, Merkel cell sarcoma.

The main goal of our Group is to establish a causal role of specific infectious agents in human cancer. Two complementary strategies are currently followed: (i) Functional studies to characterise the biological properties of specific infectious agents using *in vitro* and *in vivo* model systems; and (ii) Epidemiological studies to determine the presence of specific infectious agents in benign and malignant human lesions.

The rationale of our functional studies is based on the fact that viruses directly associated with human cancers have developed several mechanisms to efficiently evade immune surveillance and promote cellular transformation. Therefore, studies in the Group aim to characterise the ability of viruses to de-regulate cellular pathways involved in the immune response and cellular transformation in order to predict their oncogenic potential.

Regarding the epidemiological studies, we have generated novel human papillomavirus (HPV) detection assays with high throughput, sensitivity and specificity. Validation studies have shown that our assays significantly increased the HPV DNA detection rate, especially in multiple infections, in comparison to other well-validated and widely-used HPV detection methods. The development of these novel detection assays allowed us to initiate and complete several epidemiological studies.

Future plans of the Group include (i) extension of the functional studies to emerging oncogenic viruses, e.g. human Merkel cell polyomavirus and related viruses; (ii) developing novel detection assays for additional infectious agents; and (iii) expanding the epidemiological studies in collaboration with other groups from IARC and other institutes, including institutes from low-resource countries.

Cutaneous HPV types

The skin-tropic HPV types from the genus beta of the HPV phylogenetic tree, also known as Epidermodysplasia verruciformis (EV) HPV types, are strongly suspected to be involved in NMSC. However, their direct role in human carcinogenesis is not yet fully proven. In addition, it is not yet known whether, as has been observed with mucosal HPV types, beta HPVs may be sub-grouped into low- and high-risk HPV types. To address these questions, we have initiated the characterisation of the biological properties of the main oncoproteins, E6 and E7, from several beta HPV types. Several experimental models have been used, ranging from primary keratinocytes to transgenic mice.

Our data show that certain beta HPV types (i.e. HPV24, 38 and 49) display transforming activities in comparison to other beta HPV types (i.e. HPV14, 22, 23 and 36), supporting the existence of low- and high-risk HPV types (*Gabet *et al.*, 2008; *Bouvard *et al.*, ongoing study). Studies on HPV38 have resulted in the identification of a novel viral mechanism of inactivation of p53. Unlike HPV16, HPV38 does not induce p53 degradation but rather promotes accumulation of a potent inhibitor of p53 transcriptional functions, _Np73_ (*Accardi *et al.*, 2006). HPV38 E6 and E7 expression in the skin of transgenic mice using K10 promoter induced _Np73_ accumulation, cellular proliferation, hyperplasia and dysplasia in the epidermis (*Dong *et al.*, 2005); *Accardi *et al.*, 2006; *Dong *et al.*, 2008). In conclusion, our functional studies support the role of certain beta HPV types in human carcinogenesis.

Mucosal HPV types and toll-like receptor signalling

Establishment of a chronic infection is a key event for virus-induced carcinogenesis. Several prospective studies, in which HPV-positive women have been followed-up for many years, have shown that HPV16 is able to persist much longer in the host than the other mucosal high-risk HPV types. Thus, the high carcinogenicity of HPV16 may be explained by its greater efficiency than the other mucosal high-risk HPV types in evading the immune system. We observed that the expression of a key player in innate immunity, Toll-like receptor 9 (TLR9), which senses the double-stranded viral DNA, is strongly down-regulated by HPV16 E6 and E7 oncoproteins in several *in vitro* experimental models (*Hasan *et al.*, 2007). Accordingly, immunohistochemical analyses revealed weak TLR9 expression in HPV-positive malignant cervical lesions, while strong TLR9 staining was detected in normal cervical tissues (*Hasan *et al.*, 2007; ongoing studies). E6 and E7 from other mucosal high-risk HPV types, including HPV18, are less efficient than E6 and E7 from HPV16 in down-regulating TLR9 expression, while the mucosal low-risk HPV6 E6 and E7 do not interfere at all with TLR9 transcription. Thus, the ability of the different HPV types to down-regulate TLR9 expression appears to correlate with their ability to persist.

Based on these data, we have extended our studies to cutaneous beta HPV types and other cancer-associated viruses to target the TLR9 signalling pathway.

Prevalence of HPV infections from different anatomical sites in human specimens

We have developed a novel assay for the detection of three different groups of HPV, namely (i) mucosal high-risk HPV types (n=19), (ii) mucosal low-risk HPV types (n=18) and (iii) beta and gamma cutaneous HPV types (n=31) (*Gheit *et al.*, 2006; Gheit *et al.*, 2007; Gheit *et al.*, ongoing study). Due to the high sensitivity and versatility of our HPV detection assay, we were able to perform several epidemiological studies to evaluate the ability of HPV types (i)

to infect a specific anatomical site and/or (ii) to promote carcinogenesis (*Dai *et al*., 2007; *Cazzaniga *et al*., 2008; *Rollison *et al*., 2008). Our data did not provide evidence for the role of the high-risk mucosal HPV types in breast carcinogenesis, but they do suggest a possible involvement of these viruses in a small percentage of oesophageal cancers. In addition, some of the cancer case studies aimed at determining the prevalence of specific mucosal high-risk HPV types in populations that have not yet been analysed (*Gheit *et al*., 2009; *Sideri *et al*., 2009).

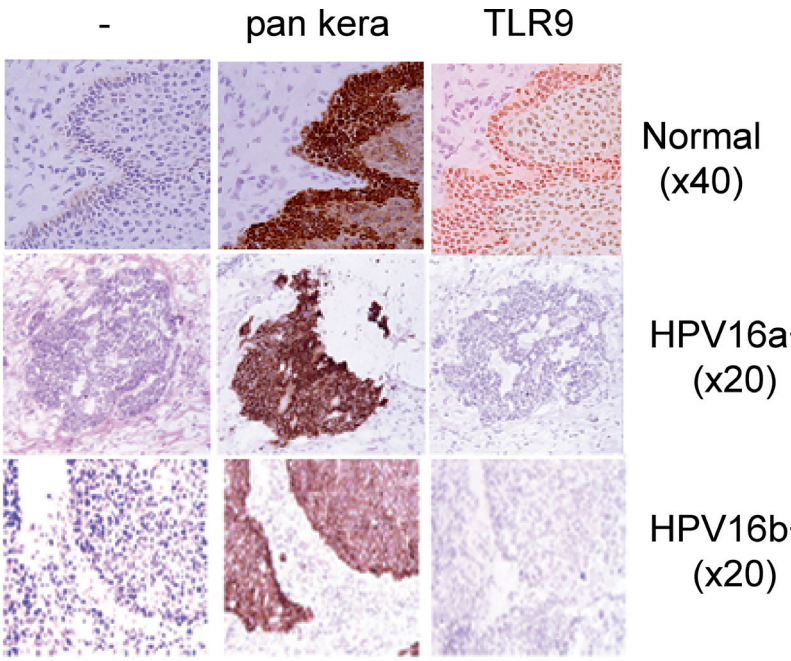

Figure 1. TLR9 is downregulated in HPV16-positive cervical cancers.
Sections of normal and tumoral cervical tissues were stained by immuno-histochemistry for pan keratin or TLR9. No TLR9 expression was detected in cervical cancer of two different donors (HPV16a+ and HPV16b+).

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Human papillomavirus (HPV)

The study of HPV, the necessary cause of cervical cancer, has been the main focus of the Infections and Cancer Epidemiology Group (ICE) in the last two years and has led to 25 published articles, as well as several in press, on related topics.

The successful introduction of vaccines against HPV, as well as HPV-based testing, presupposes accurate knowledge of the infection burden and type-specific distribution of HPV types in different parts of the world. In order to address this issue and fill knowledge gaps on this subject, ICE has carried out in the last two years new population-based HPV prevalence surveys among women with and without cervical cancer in six world areas (*Bardin *et al*., 2008; *Dondog *et al*., 2008; *Keita *et al*., 2009; *Sherpa *et al*., 2009) (Figure 1). HPV testing is also in progress for an additional study site in Iran.

The existence of populations in which HPV prevalence does not diminish in middle-aged women is one of the most important discoveries of the IARC HPV Prevalence Surveys (Figure 2).

Meta-analyses of women with and without cervical cancer, as well as cancers of the anogenital tract, have also been carried out or updated. This has resulted in publications showing that worldwide HPV16/18 prevalence in cervical cancer is indeed more similar than initially expected, lending further credence to the universal efficacy of the HPV vaccines currently available (*Schiffman *et al*., 2009). A meta-analysis on anogenital cancers further suggested that approximately 40% of vulvar, 70% of vaginal and 84% of anal carcinoma may be prevented by current HPV vaccines against HPV16/18 (*De Vuyst *et al*., 2009).

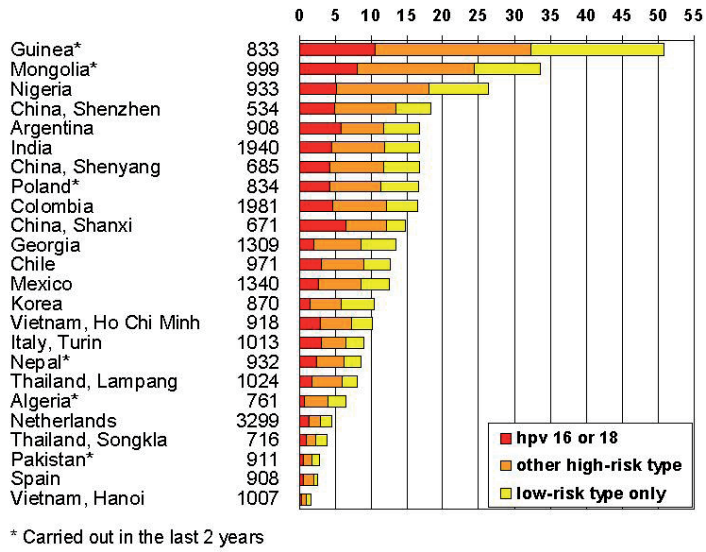

Figure 1. Prevalence of cervical HPV DNA in sexually active women. IARC HPV Prevalence Surveys, 1995-2009.

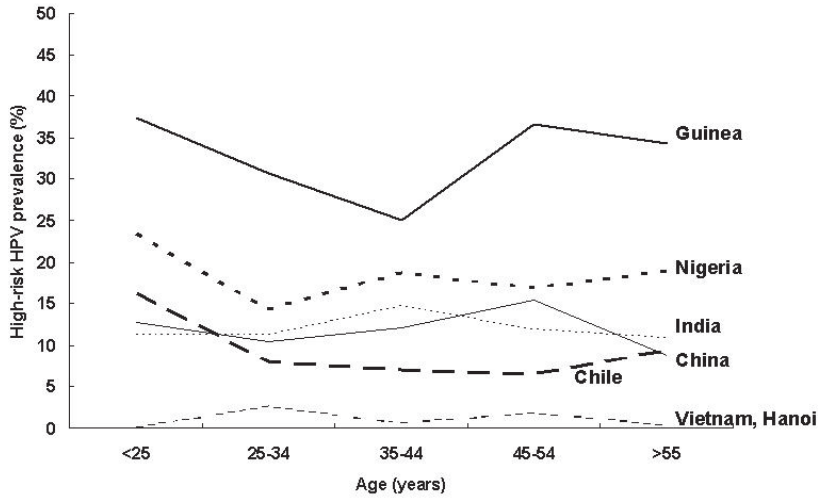

Figure 2. Age-specific prevalence of high-risk HPV types in some less-developed countries. IARC HPV Prevalence Surveys (*Franceschi *et al*., 2006).

International Collaboration on Cervical Cancer

During this period, we have brought to fruition two collaborative manuscripts on the role of sexual behaviour in cervical cancer risk (*International Collaboration of Epidemiological Studies of Cervical Cancer, 2009; *Louie *et al*., 2009). The risk of cervical cancer increased with lifetime number of sexual partners, as expected. We also highlighted, however, the association with early age at first sexual intercourse after careful adjustment for confounding factors. It is conceivable that age at first intercourse is related to invasive cervical cancer risk through HPV acquisition. One possibility is that cervical cancer risk may increase with duration of HPV infection. It is likely that women who have earlier first sexual intercourse are also exposed to HPV earlier, and might have longer duration of infection.

Bayesian models applied to cancer etiology

A natural history model for infection and clearance of HPV infection in the ASCUS-LSIL Triage Study (ALTS) demonstrated that distinct HPV types act as independent agents with no impact on incidence or clearance of other types (*Plummer *et al*., 2007). Further investigation of the determinants of HPV persistence showed that, contrary to some recent claims, newly appearing infections clear equally well among older and younger women (*Maucort-Boulch *et al*., 2009). Therefore, for persistent infection old age is a proxy of "old age" of HPV infection (i.e. a poor prognostic factor).

Human immunodeficiency virus/ acquired immune deficiency syndrome (HIV/AIDS)

Cancer risk in people with HIV/AIDS (PWHA) is a subject of great importance to ICE now that PWHA have improved survival as a result of highly active antiretroviral therapy (HAART). ICE has used record-linkage and cohort studies in Switzerland and Italy to achieve both an adequate study power for uncommon neoplasms (e.g. hepatocellular carcinoma, Hodgkin lymphoma) and accurate information on markers of immunity and use of HAART (10 publications in 2008–2009 and several in press). A second line of research has focused on the way HIV infection modifies the cancer potential of HPV infections in countries at very high-risk for both infections (i.e., Kenya and Uganda) (*De Vuyst *et al*., 2008).

Significantly elevated risks in PWHA versus the general population were found for Hodgkin lymphoma, hepatocellular carcinoma, cancers of the cervix, anus, liver, lip, mouth and pharynx, trachea and lung, multiple myeloma and non-melanomatous skin cancer (*Dal Maso *et al*., 2009). The incidence of non-Hodgkin lymphoma and Kaposi sarcoma were shown to have greatly decreased in the HAART era (*Polesel *et al*., 2008; *Franceschi *et al*., 2008). HAART use was associated with a substantial weakening of the predictive value of CD4+ cell count, supporting the strong efficacy of HAART regardless of the degree of immune impairment when treatment begins. The beneficial effect remained strong up to 10 years after HAART initiation (*Polesel *et al*., 2008; *Franceschi *et al*., 2008). Hodgkin lymphoma risk did not appear to be increasing in recent years among PWHA using HAART, and the best predictive marker was low CD4+/CD8+ ratio (*Clifford *et al*., 2009). In a matched nested case-control study, lower CD4+ cell counts were shown for the first time to be significantly associated with hepatocellular carcinoma risk (*Clifford *et al*., 2008). Excess risks for cervical cancer among PWHA are particularly high in Italy (*Dal Maso *et al*., 2009) as also reported in Spain. Although access to HAART is widespread, cervical screening among HIV-positive women needs to be improved.

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