Section of Infections (INF)

Section head
Dr Silvia Franceschi

The Section of Infections (INF) is comprised of two Groups: the Infections and Cancer Epidemiology Group (ICE) and the Infections and Cancer Biology Group (ICB). ICE and ICB have worked closely together and belonged to the same Section since 2004.

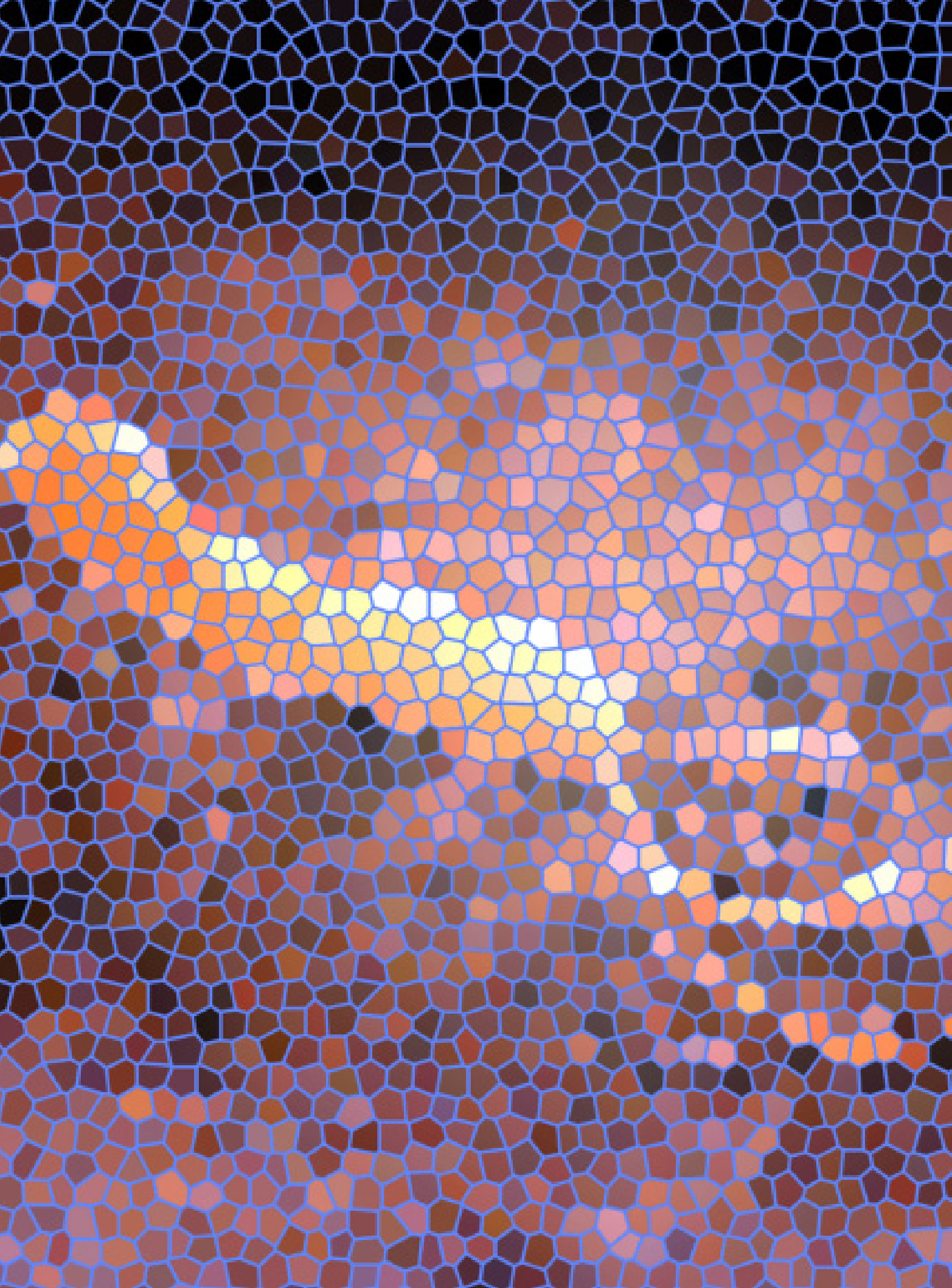
Persistent infections with viruses, bacteria and parasites account for nearly 20% of the cancer burden worldwide, with less developed countries being the hardest hit. Infections also represent, or might represent in the future, some of the most preventable cancer causes through immunization against or early detection and treatment of the infections. The infectious agents studied include 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) and Polyomaviruses although only a few of them will be described in the present Biennial Report.

The two Groups have different emphases in relation to infectious agents. ICB, for instance, is focused on cutaneous HPV to a greater extent than ICE. Conversely, ICE is more active in the study of *Helicobacter* species and HIV. Together the two Groups have initiated new projects of HPV and cancer of the head and neck. This topic is charged with greater methodological problems than HPV and anogenital cancer due to the more limited role of the virus (mainly in cancer of the oropharynx and among non-smokers). The fraction of cancer of the head and neck attributable to HPV has become, however, a crucial issue in respect to the decision to vaccinate adolescent boys against the virus in addition to adolescent girls.

With respect to areas of research, some are exclusive to ICB (e.g. transformation mechanisms) or ICE (worldwide distribution and trends of, as well as fraction of cancer attributable to, carcinogenic infections). New collaborations on other relevant aspects (the role of innate and acquired immunity, the impact of different HPV types and variants) have been initiated thanks to the increasing availability of tests suitable for large-scale application at ICB. Another great asset of INF is the complementary expertise on methodological issues. For example, ICB has expertise in relation to biological protocol issues while ICE is able to provide statistical advice.

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 Cancer Information (CIN).

The over 130 peer-reviewed articles published or accepted for publication by INF in 2010–2011 provide good evidence of the high productivity and the breadth of topics and international collaborations on by INF.



Infections and Cancer Biology Group (ICB)

Group head
Dr Massimo Tommasino

Scientists
Dr Rosita Accardi
Dr Tarik Gheit
Dr Bakary Sylla
Dr Jiping Yue (until July 2011)

Technical assistant
Ms Sandrine McKay-Chopin

Secretary
Ms Annick Rivoire

Visiting scientists and postdoctoral fellows
Dr Halimatou Diop (until April 2011)
Dr Raffaella Ghittoni (until May 2010)
Dr Michelle Iannacone (until August 2011)
Dr Mariafrancesca Scalise (until July 2011)
Dr Ivonne Rubio Sierra (until August 2011)
Dr Marco Stellin (until April 2011)
Dr Patrick van Uden
Dr Jiping Yue (until July 2010)
Dr Claudia Zannetti (until May 2011)

Students
Ms Ginesa Albero Abril (until November 2011)
Ms Iris Cornet
Ms Ikbal Fathallah (until January 2010)
Mr Jordan Ferria (until July 2011)
Ms Aurélie Ferrotin (until September 2011)
Mr Daniele Frangioni (until May 2010)
Mr Mariano Gonzalez Pisfil (until March 2010)
Mr Giuseppe Mariggio (until December 2011)
Mr Seydou MBaye (until December 2010)
Ms Rosa Rubino (until July 2010)
Mr Djamel Saidj
Ms Mariafrancesca Scalise (until October 2010)
Mr Naveed Shahzad
Ms Maha Siouda
Ms Laetitia Tusseau (until September 2010)

It is well established that infections are the cause of approximately 20% of human cancers worldwide (Parkin, 2006). However, new findings indicate that additional infectious agents are involved in human carcinogenesis. A human polyomavirus, Merkel Cell polyomavirus (MCPyV), has been recently discovered and is associated with a rare tumour, Merkel cell sarcoma (Feng et al., 2008). In addition, certain HPV types that infect the skin and belong to genus ß of the HPV phylogenetic tree (Bernard et al., 2010) are suspected to be involved, together with ultraviolet radiation, in the development of non-melanoma skin cancer (NMSC) (Pfister et al., 2003).

The main goal of ICB is to establish a causal role of specific infectious agents in human cancer. Two complementary strategies are currently followed: (1) the characterization of the biological properties of proteins from potential oncogenic viruses using *in vitro* and *in vivo* model systems; and (2) the development of laboratory assays for the detection of infections in human specimens, which can be used in epidemiological studies.

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 the immune surveillance and to promote cellular transformation. Therefore, studies in the Group aim to characterize the ability of viruses to de-regulate cellular pathways involved in the immune response and cellular transformation to predict their oncogenic potential.

Regarding the development of novel diagnostic tools for infections, we have generated new detection assays with high-throughput, sensitivity and specificity for approximately 80 different viruses. The development of these novel detection assays allowed us to initiate and complete several epidemiological studies.

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

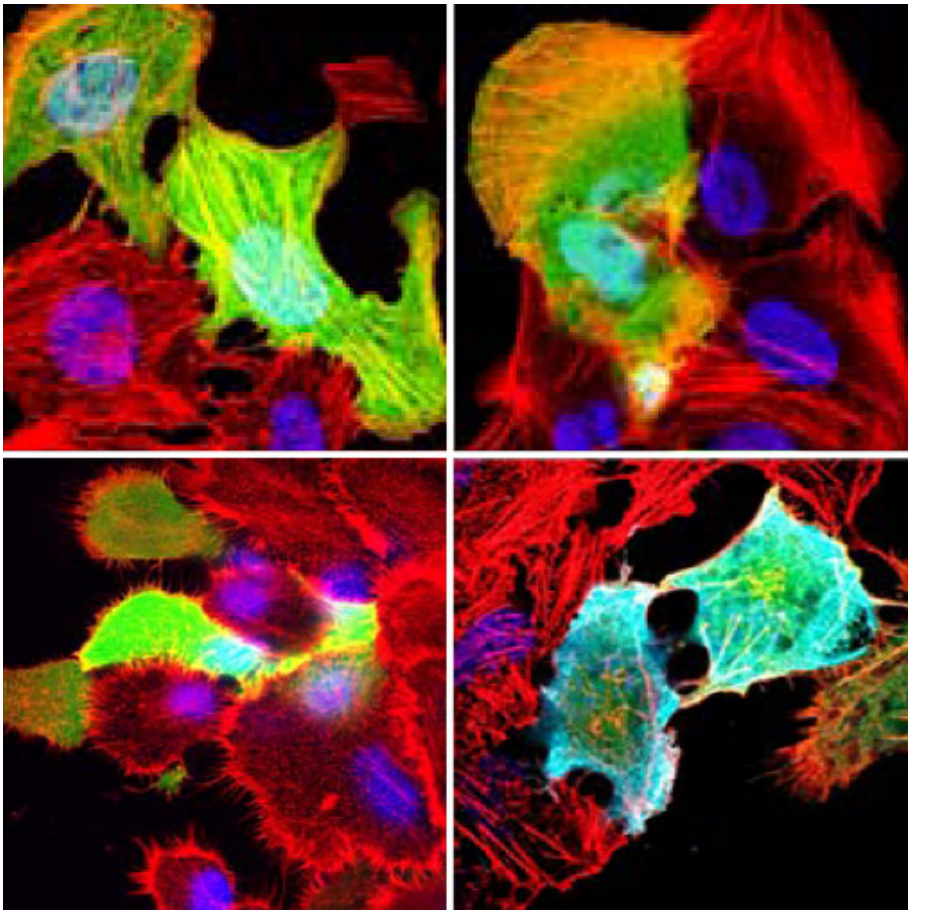


Figure 1. Primary human keratinocytes expressing E7 oncoprotein from cutaneous HPV38 with an altered cytoskeleton

Role of ß cutaneous HPV types in skin carcinogenesis

Epidemiological and biological data have shown that solar exposure and impairment of the immune system are key risk factors for the development of NMSC, which is the most common cancer in fair-skinned adult populations (Pisani *et al.*, 2002). The link with immune status strongly supports the role of an infectious agent in NMSC etiology. Several findings suggest that β HPV types are the most likely infectious agents involved in this disease (Berkhout *et al.*, 2000; de Jong-Tieben *et al.*, 1995; Harwood *et al.*, 2000; Andersson *et al.*, 2008; Waterboer *et al.*, 2008; Casabonne *et al.*, 2007; Karagas *et al.*, 2006; Bavinck *et al.*, 2010); however, their direct role is still under debate. To further evaluate the role of β HPV types in skin carcinogenesis, we have performed several studies to characterize the biological properties of their main oncoproteins, E6 and E7. Several experimental models have been used, ranging from primary keratinocytes to transgenic mice. In particular, we have focused on HPV38 E6 and E7 that were previously shown to induce immortalization of primary human keratinocytes, the natural host of the virus (Caldeira *et al.*, 2003; Gabet *et al.*, 2008). Recently our studies have demonstrated that HPV38 E6 and E7 have the ability to target several cellular pathways involved in cellular proliferation and apoptosis (Hussain *et al.*, 2011; Yue *et al.*, 2011; Accardi *et al.*, 2011). The data show that HPV38, similar to several oncogenic viruses, activates the NF-κB pathway, increasing the resistance of human keratinocytes to tumour necrosis factor α (TNF-α)- and UVB radiation-mediated apoptosis. Accordingly, inhibition of NF-κB signalling resulted in the downregulation of NF-κB-regulated antiapoptotic genes, including cIAP1, cIAP2 and xIAP genes and apoptosis (Hussain *et al.*, 2011).

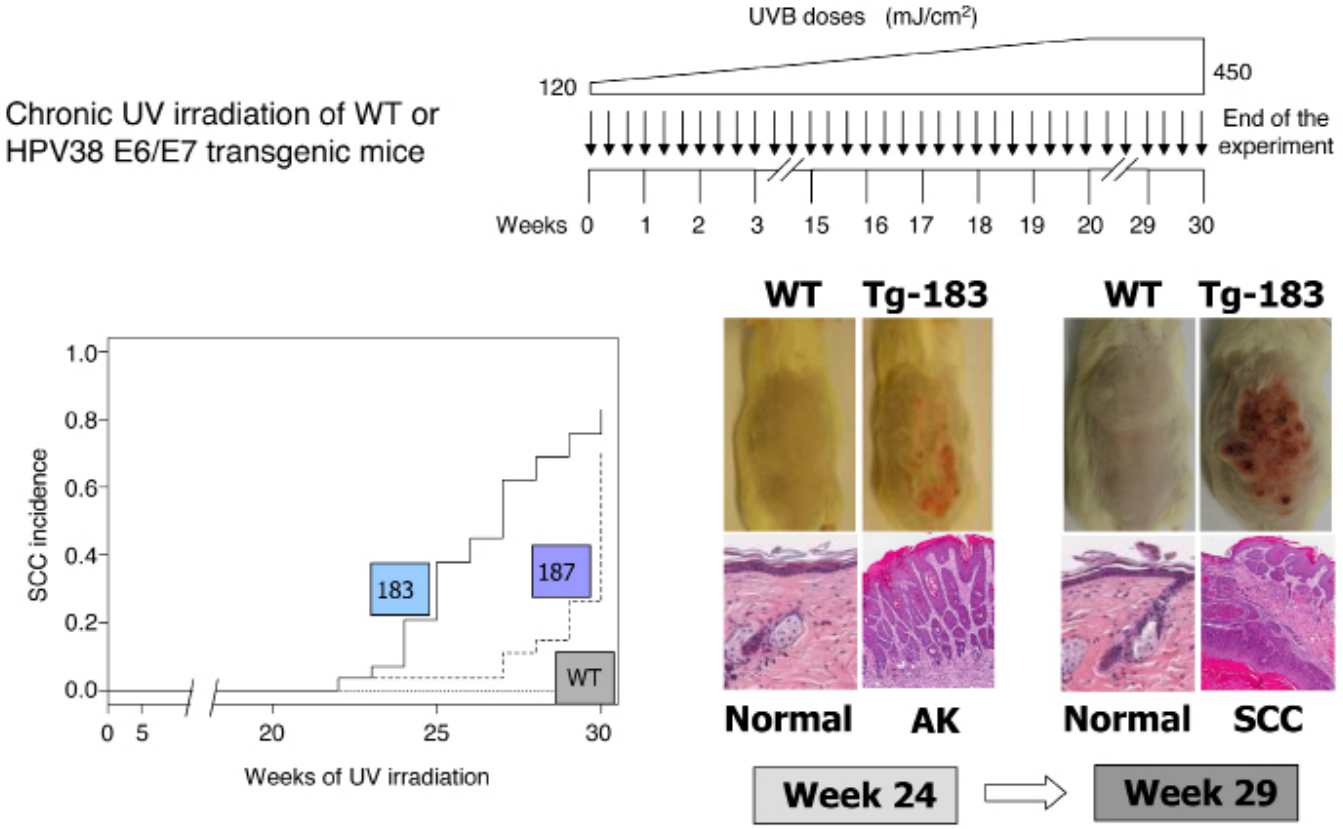


Figure 2. HPV38 cooperates with UV in the development of actinic keratosis-like lesions and squamous cell carcinoma in mice

In an additional study, we have demonstrated that HPV38 E7 induces actin stress fibre disruption and that this phenomenon correlates with its ability to downregulate Rho activity. The downregulation of Rho activity by HPV38 E7 is mediated through the activation of the CK2-MEK-extracellular signal-regulated kinase (ERK) pathway, promoting cellular proliferation. In addition, HPV38 E7 is able to induce actin fibre disruption by binding directly to eukaryotic elongation factor 1A (eEF1A) and abolishing its effects on actin fibre formation (Figure 1) (Yue *et al.*, 2011).

Findings in an animal experimental model provided additional evidence for the oncogenic potential of HPV38. We have observed that expression of HPV38 E6 and E7 in the mouse skin strongly synergizes with UV irradiation in promoting pre-malignant and malignant skin lesions. Indeed, chronic UV irradiation of HPV38 E6/E7 transgenic mice induced the development of actinic keratosis-like lesions, which in humans are considered to be precursors of squamous cell carcinomas (SCC), and subsequently of SCC in a significant proportion of the animals. In contrast, wild-type animals subjected to identical treatments did not develop any type of skin lesions (Figure 2) (Viarisio *et al.*, 2011). Thus, it is clear that the oncoproteins E6 and E7 from β HPV38 significantly contribute to SCC development in the mouse skin, rendering keratinocytes more susceptible to UV-induced carcinogenesis.

Identification of a novel mechanism of inactivation of the p53 functions

Studies on the β HPV types also led to the characterization of a novel mechanism involved in the regulation of the intracellular levels of ΔNp73α, an antagonist of the p53/p73-regulated pathways (Accardi *et al.*, 2011). We observed that HPV 38 E6 and E7 promote the accumulation of the IκB kinase β (IKKβ) in the nucleus, which in turn associate with and phosphorylate ΔNp73α at serine 422, leading to its stabilization and repression of several p53-regulated genes. Inhibition of IKKβ resulted in a rapid degradation of ΔNp73α and a rescue of the p53 functions. Interestingly, we have observed that IKKβ can stabilize ΔNp73α in some breast or head and neck cancer-derived cells. Thus, this event appeared to be important also in non-virus-induced carcinogenesis.

Prevalence of HPV infections in human specimens from different anatomical sites

We have developed novel assays based on Luminex technology 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). Due 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 and/or (ii) to promote carcinogenesis (e.g. Polesel *et al.* 2011; Rollison *et al.* 2008). 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 analyzed (Gheit *et al.* 2009; Sideri *et al.* 2009)

Role of DOK1 tumour suppressor in non-virus and virus-associated cancer

The Downstream of tyrosine kinase (DOK1) is an adaptor tyrosine kinase substrate with a tumour suppressive activity. We have previously shown that *DOK1* gene can be mutated in chronic lymphocytic leukemia (CLL). DOK1 mutated in CLL is a nuclear protein in contrast to the wild-type DOK1 which is cytoplasmic. In addition, a nuclear DOK1 with a mutated nuclear exclusion site is impaired in inhibiting cell proliferation (Lee *et al.* 2004; Lee *et al.* 2007; Niu *et al.* 2006). We also found a nuclear mislocalisation of DOK1 in HPV-immortalized keratinocytes. Thus, the subcellular localization of DOK1 correlates with its tumour suppressive activities. Further studies revealed that the expression of *DOK1* gene is repressed through hypermethylation of its promoter in the majority of healed and neck cancer (HNC) lines analyzed as well as primary human neoplasm including solid tumours (93% in HNC, 81% in lung cancer) and hematopoietic malignancy (64% in Burkitt's lymphoma) (Saulnier *et al.* 2011). In addition, an inverse correlation was observed between the level of DOK1 gene methylation and its expression in tumour and adjacent non tumour tissues. Studies are ongoing to evaluate the potential role of *DOK1* as a prognostic marker in HNC and other cancer types.

The ICB Group is grateful to the following for their collaboration in its projects:

Dr M. Arbyn and Dr J.P. Bogers, University of Antwerp, Belgium; Dr E. Manet, Ecole Normale Supérieure, Fabien Zoulim, INSERM U871, Lyon, Dr U. Hasan, INSERM U851, Pierre-Bénite, France; Dr H. Boeing, German Institute of Human Nutrition, Potsdam-Rehbrücke, Dr G. Dyckhoff, Universitätsklinikum Heidelberg, Professor L. Gissmann, Dr M. Müller, Dr M. Pawlita, DKFZ, Heidelberg, Dr T. Iftner, University of Tübingen, Germany; Dr G. Mosialos, Aristotle University of Thessaloniki, Greece; Dr R. Pillai, Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, India; Dr F. Chiesa and Dr S. Chiocca, European Institute of Oncology, Milan, Dr S. Ottonello, University of Parma, Italy; Dr F.X. Bosch, Dr X. Castellsagué, Dr L. Alemany Vilches, Fundació Privada Institut D'Investigació Biomedica de Bellvitge (IDIBELL), Barcelona, Spain; Dr A. Giuliano and Dr D. Rollison, Lee Moffitt Cancer Center, Tampa, Florida, USA.

Financial support from the following bodies is gratefully acknowledged:

Cancéropôle Lyon Auvergne Rhône-Alpes (CLARA)
La Ligue contre le Cancer, Comité de la Drôme
The European Commission, Seventh Framework Programme

Publications

Accardi L, Donà MG, Mileo AM *et al.* (2011). Retinoblastoma-independent antiproliferative activity of novel intracellular antibodies against the E7 oncoprotein in HPV 16-positive cells. *BMC Cancer,* 11:17.doi:10.1186/1471-2407-11-17 PMID:21241471

Accardi R, Rubino R, Scalise M *et al.* (2011). E6 and E7 from human papillomavirus type 16 cooperate to target the PDZ protein Na/H exchange regulatory factor 1. *J Virol,* 85:8208–8216. PMID:21680517

Accardi R, Scalise M, Gheit T *et al.* (2011). IkappaB kinase β promotes cell survival by antagonizing p53 functions through DeltaNp73α phosphorylation and stabilization. *Mol Cell Biol,* 31:2210–2226. doi:10.1128/MCB.00964-10 PMID:21482671

Andersson K, Waterboer T, Kirnbauer R *et al.* (2008). Seroreactivity to cutaneous human papillomaviruses among patients with nonmelanoma skin cancer or benign skin lesions. *Cancer Epidemiol Biomarkers Prev,* 17:189–195.doi:10.1158/1055-9965.EPI-07-0405 PMID:18199724

Aubin F, Gheit T, Prétet JL *et al.* (2010). Presence and persistence of human papillomavirus types 1, 2, and 4 on emery boards after scraping off plantar warts. *J Am Acad Dermatol,* 62:151–153. doi:10.1016/j.jaad.2009.04.034 PMID:20082896

Balassiano K, Lima S, Jenab M *et al.* (2011). Aberrant DNA methylation of cancer-associated genes in gastric cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Cancer Lett,* 311:85–95.doi:10.1016/j.canlet.2011.06.038 PMID:21831520

Bavinck JN, Neale RE, Abeni D *et al.* (2010). Multicenter Study of the Association between Betapapillomavirus Infection and Cutaneous Squamous Cell Carcinoma. *Cancer Res,* 70:1–10 doi:10.1158/0008-5472.CAN-10-0352.

Berkhout RJ, Bouwes Bavinck JN, ter Schegget J (2000). Persistence of human papillomavirus DNA in benign and (pre)malignant skin lesions from renal transplant recipients. *J Clin Microbiol,* 38:2087–2096. PMID:10834958

Bernard HU, Burk RD, Chen Z *et al.* (2010). Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology,* 401:70–79.doi:10.1016/j.virol.2010.02.002 PMID:20206957

Biver-Dalle C, Gheit T, Drobacheff-Thiebaut C *et al.* (2010). Detection of human papillomavirus DNA in plucked eyebrow hair from HIV-infected patients. *J Invest Dermatol,* 130:2499–2502.doi:10.1038/jid.2010.147 PMID:20520627

Caldeira S, Zehbe I, Accardi R *et al.* (2003). The E6 and E7 proteins of the cutaneous human papillomavirus type 38 display transforming properties. *J Virol,* 77:2195–2206.doi:10.1128/JVI.77.3.2195-2206.2003 PMID:12525654

Casabonne D, Michael KM, Waterboer T *et al.* (2007). A prospective pilot study of antibodies against human papillomaviruses and cutaneous squamous cell carcinoma nested in the Oxford component of the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer,* 121:1862–1868. doi:10.1002/ijc.22885 PMID:17565742

de Jong-Tieben LM, Berkhout RJ, Smits HL *et al.* (1995). High frequency of detection of epidermodysplasia verruciformis-associated human papillomavirus DNA in biopsies from malignant and premalignant skin lesions from renal transplant recipients. *J Invest Dermatol,* 105:367–371.doi:10.1111/1523-1747.ep12320803 PMID:7665914

Fathallah I, Parroche P, Gruffat H *et al.* (2010). EBV latent membrane protein 1 is a negative regulator of TLR9. *J Immunol,* 185:6439–6447.doi:10.4049/jimmunol.0903459 PMID:20980631

Feng H, Shuda M, Chang Y, Moore PS (2008). Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science*, 319:1096–1100. doi:10.1126/science.1152586 PMID:18202256

Gabet AS, Accardi R, Bellopede A *et al.* (2008). Impairment of the telomere/telomerase system and genomic instability are associated with keratinocyte immortalization induced by the skin human papillomavirus type 38. *FASEB J,* 22:622–632. doi:10.1096/fj.07-8389com PMID:17898088

Gheit T, Cornet I, Clifford GM *et al.* (2011). Risks for persistence and progression by human papillomavirus type 16 variant lineages among a population-based sample of Danish women. *Cancer Epidemiol Biomarkers Prev,* 20:1315–1321. doi:10.1158/1055-9965.EPI-10-1187 PMID:21527576

Gheit T, Tommasino M (2011). Detection of high-risk mucosal human papillomavirus DNA in human specimens by a novel and sensitive multiplex PCR method combined with DNA microarray. *Methods Mol Biol,* 665:195–212.doi:10.1007/978-1-60761-817-1_12 PMID:21116803

Gheit T, Vaccarella S, Schmitt M *et al.* (2009). Prevalence of human papillomavirus types in cervical and oral cancers in central India. *Vaccine*, 27:636–639.doi:10.1016/j.vaccine.2008.11.041 PMID:19056450

Ghittoni R, Accardi R, Hasan U *et al.* (2010). The biological properties of E6 and E7 oncoproteins from human papillomaviruses. *Virus Genes,* 40:1–13.doi:10.1007/s11262-009-0412-8 PMID:19838783

Guerrini JS, Bouvard V, Oswald E *et al.* (2011). E6 and E7 proteins from different beta-papillomaviruses types do not interfere in UVB-induced apoptosis of HaCaT keratinocytes. *Exp Dermatol,* 20:71–73.doi:10.1111/j.1600-0625.2010.01197.x PMID:21158941

Harwood CA, Surentheran T, McGregor JM *et al.* (2000). Human papillomavirus infection and non-melanoma skin cancer in immunosuppressed and immunocompetent individuals. *J Med Virol,* 61:289–297.doi:10.1002/1096-9071(200007)61:3<289::AID-JMV2>3.0.CO;2-Z PMID:10861635

Hussain I, Fathallah I, Accardi R *et al.* (2011). NF-KB protects human papillomavirus type 38 E6/E7-immortalized human keratinocytes against tumor necrosis factor alpha and UV-mediated apoptosis. *J Virol,* 85:9013–9022.doi:10.1128/JVI.00002-11 PMID:21715489

Karagas MR, Nelson HH, Sehr P *et al.* (2006). Human papillomavirus infection and incidence of squamous cell and basal cell carcinomas of the skin. *J Natl Cancer Inst,* 98:389–395.doi:10.1093/jnci/djj092 PMID:16537831

Lambert MP, Paliwal A, Vaissière T *et al.* (2011). Aberrant DNA methylation distinguishes hepatocellular carcinoma associated with HBV and HCV infection and alcohol intake. *J Hepatol,* 54:705–715.doi:10.1016/j.jhep.2010.07.027 PMID:21146512

Lee S, Huang H, Niu Y *et al.* (2007). Dok1 expression and mutation in Burkitt's lymphoma cell lines. *Cancer Lett,* 245:44–50.doi:10.1016/j.canlet.2005.10.045 PMID:16338067

Lee S, Roy F, Galmarini CM *et al.* (2004). Frameshift mutation in the Dok1 gene in chronic lymphocytic leukemia. *Oncogene,* 23:2287–2297.doi:10.1038/sj.onc.1207385 PMID:14730347

Niu Y, Roy F, Saltel F *et al.* (2006). A nuclear export signal and phosphorylation regulate Dok1 subcellular localization and functions. *Mol Cell Biol,* 26:4288–4301.doi:10.1128/MCB.01817-05 PMID:16705178

Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer,* 118:3030–3044.doi:10.1002/ijc.21731 PMID:16404738

Parroche P, Touka M, Mansour M *et al.* (2011). Human papillomavirus type 16 E6 inhibits p21(WAF1) transcription independently of p53 by inactivating p150(Sal2). *Virology*, 417:443–448. doi:10.1016/j.virol.2011.05.016 PMID:21791360

Pfister H, Fuchs PG, Majewski S *et al.* (2003). High prevalence of epidermodysplasia verruciformis-associated human papillomavirus DNA in actinic keratoses of the immunocompetent population. *Arch Dermatol Res,* 295:273–279.doi:10.1007/s00403-003-0435-2 PMID:14618345

Pisani P, Bray F, Parkin DM (2002). Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. *Int J Cancer,* 97:72–81. doi:10.1002/ijc.1571 PMID:11774246

Polesel J, Gheit T, Talamini R *et al.* (2011). Urinary human polyomavirus and papillomavirus infection and bladder cancer risk. *Br J Cancer.*doi:10.1038/bjc.2011.519 PMID:22116302

Ribeiro KB, Levi JE, Pawlita M *et al.* (2011). Low human papillomavirus prevalence in head and neck cancer: results from two large case-control studies in high-incidence regions. *Int J Epidemiol,* 40:489–502.doi:10.1093/ije/dyq249 PMID:21224273

Rollison DE, Pawlita M, Giuliano AR *et al.* (2008). Measures of cutaneous human papillomavirus infection in normal tissues as biomarkers of HPV in corresponding nonmelanoma skin cancers. *Int J Cancer,* 123:2337–2342.doi:10.1002/ijc.23795 PMID:18729188

Rubio I, Seitz H, Canali E *et al.* (2011). The N-terminal region of the human papillomavirus L2 protein contains overlapping binding sites for neutralizing, cross-neutralizing and non-neutralizing antibodies. *Virology,* 409:348–359.doi:10.1016/j.virol.2010.10.017 PMID:21074234

Sanchez GI, Kleter B, Gheit T *et al.* (2011). Clinical evaluation of polymerase chain reaction reverse hybridization assay for detection and identification of human papillomavirus type 16 variants. *J Clin Virol,* 51:165–169.doi:10.1016/j.jcv.2011.03.013 PMID:21561803

Saulnier A, Vaissière T, Yue J *et al.* (2011). Inactivation of the putative suppressor gene DOK1 by promoter hypermethylation in primary human cancers. *Int J Cancer.* PMID:21796618

Schmitt M, Dondog B, Waterboer T *et al.* (2010). Abundance of multiple high-risk human papillomavirus (HPV) infections found in cervical cells analyzed by use of an ultrasensitive HPV genotyping assay. *J Clin Microbiol,* 48:143–149. doi:10.1128/JCM.00991-09 PMID:19864475

Shukla R, Yue J, Siouda M *et al.* (2011). Proinflammatory cytokine TNF-α increases the stability of hepatitis B virus X protein through NF-κB signaling. *Carcinogenesis*, 32:978–985. doi:10.1093/carcin/bgr057 PMID:21459755

Sideri M, Cristoforoni P, Casadio C *et al.* (2009). Distribution of human papillomavirus genotypes in invasive cervical cancer in Italy: a representative, single institution case series. *Vaccine*, 27 Suppl 1;A30–A33.doi:10.1016/j.vaccine.2008.12.028 PMID:19480958

Sylla BS, Wild CP (2011). A million africans a year dying from cancer by 2030: What can cancer research and control offer to the continent? *Int J Cancer.* PMID:21796634

Sylla BS, Wild CP (2011). Cancer burden in Africa in 2030: Invest today and save tomorrow. Afr J Cancer. In press.

Textor S, Accardi R, Havlova T *et al.* (2011). NF-κB-dependent upregulation of ICAM-1 by HPV16-E6/E7 facilitates NK cell/target cell interaction. *Int J Cancer,* 128:1104–1113.doi:10.1002/ijc.25442 PMID:20473930

Thépot A, Desanlis A, Venet E *et al.* (2011). Assessment of transformed properties in vitro and of tumorigenicity in vivo in primary keratinocytes cultured for epidermal sheet transplantation. *J Skin Cancer,* 2011:936546. PMID:21188234

Thépot A, Morel AP, Justin V *et al.* (2010). Evaluation of tumorigenic risk of tissue-engineered oral mucosal epithelial cells by using combinational examinations. *Cell Transplant,* 19:999–1006. doi:10.3727/096368910X515854 PMID:20977830

Viarisio D, Mueller-Decker K, Kloz U *et al.* (2011). E6 and E7 from beta HPV38 cooperate with ultraviolet light in the development of actinic keratosis-like lesions and squamous cell carcinoma in mice. *PLoS Pathog,* 7:e1002125.doi:10.1371/journal.ppat.1002125 PMID:21779166

Waterboer T, Abeni D, Sampogna F *et al.* (2008). Serological association of beta and gamma human papillomaviruses with squamous cell carcinoma of the skin. *Br J Dermatol,* 159:457–459.doi:10.1111/j.1365-2133.2008.08621.x PMID:18503604

Yue J, Shukla R, Accardi R *et al.* (2011). Cutaneous HPV 38 E7 regulates actin cytoskeleton structure for increasing cell proliferation through CK2 and the eukaryotic elongation factor 1A. *J Virol,* 85:8477–8494. doi:10.1128/JVI.02561-10 PMID:21697493

Zannetti C, Bonnay F, Takeshita F *et al.* (2010). C/EBPδ and STAT-1 are required for TLR8 transcriptional activity. *J Biol Chem,* 285:34773–34780.doi:10.1074/jbc.M110.133884 PMID:20829351

Zehbe I, Lichtig H, Westerback A *et al.* (2011). Rare human papillomavirus 16 E6 variants reveal significant oncogenic potential. *Mol Cancer,* 10:77. doi:10.1186/1476-4598-10-77 PMID:21702904

Infections and Cancer Epidemiology Group (ICE)

Group head
Dr Silvia Franceschi

Scientists
Dr Gary Clifford
Dr Hugo De Vuyst
Dr Martyn Plummer
Dr Salvatore Vaccarella

Visiting scientists
Dr Catherine de Martel
Dr Joakim Dillner
Dr Anna Giuliano
(until December 2011)
Dr Christian Partensky
Dr Julian Peto
(until December 2010)
Dr Guglielmo Ronco
(until January 2011)

Data managers
Ms Sophie Pallardy (until April 2010)
Ms Vanessa Tenet
Mr Jérôme Vignat

Secretariat
Ms Véronique Chabanis
Ms Sylvie Nouveau
Ms Trudy Perdrix-Thoma (until
September 2010)

Postdoctoral fellows
Dr Bolormaa Dondog
(until September 2010)
Dr Peng Guan
Dr Rebecca Howell-Jones
(until August 2010)

Students
Mr Jean-Damien Combes
Mr Mauro Lise (until March 2011)

Human papillomavirus

The study of human papillomavirus (HPV) infection, the cause of cervical cancer and target of effective vaccines and screening tests, has been the main focus of the Infections and Cancer Epidemiology Group (ICE) in 2010–2011. The IARC HPV prevalence surveys were continued to include additional populations for whom no or very limited information on the burden of HPV or cervical cancer was available (Figure 1). Evidence on the large variability in HPV prevalence was expanded and can inform the prioritization of HPV vaccine introduction in highest-risk countries in times of financial constraint.

Time since first intercourse and the risk of cervical cancer

Young age at first sexual intercourse is an important risk factor for cervical cancer (International Collaboration of Epidemiological Studies of Cervical Cancer, 2009). We envisaged, therefore, a model to elucidate the issue by interpreting the age at first sexual intercourse in terms of proxy of age at first HPV infection and, hence, duration of exposure to the virus (Plummer *et al.*, 2011). This approximation is plausible, as it is known that HPV infection is highly contagious and frequent in many world populations, and first infection with HPV often occurs in women soon after first sexual intercourse.

To reduce the confounding effect of multiple sexual partners, we investigated the relationship between risk of cervical carcinoma and time since first intercourse (TFI) using data on monogamous women only (5074 cases and 16 137 controls) from the International Collaboration of Epidemiological Studies of Cervical Cancer, 2009. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression. In addition, we used age-specific incidence rates in unscreened populations to characterize the age profile of cervical cancer incidence.

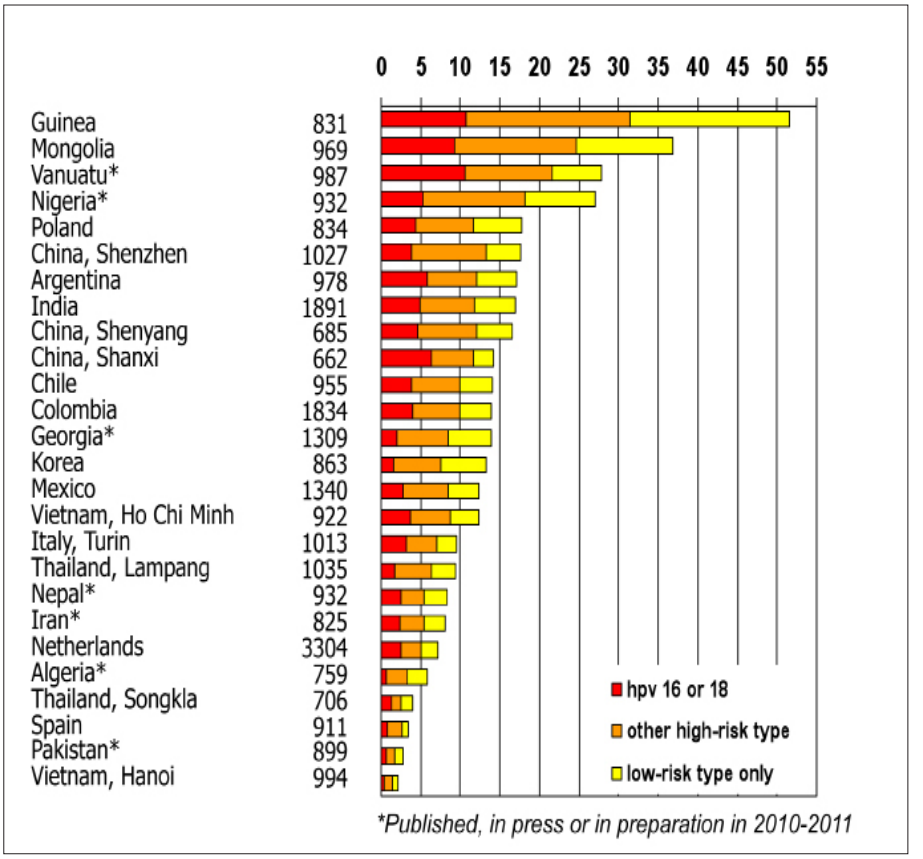


Figure 1. Prevalence (%) of cervical human papillomavirus DNA in sexually active women, IARC Prevalence Surveys, 1990–2011

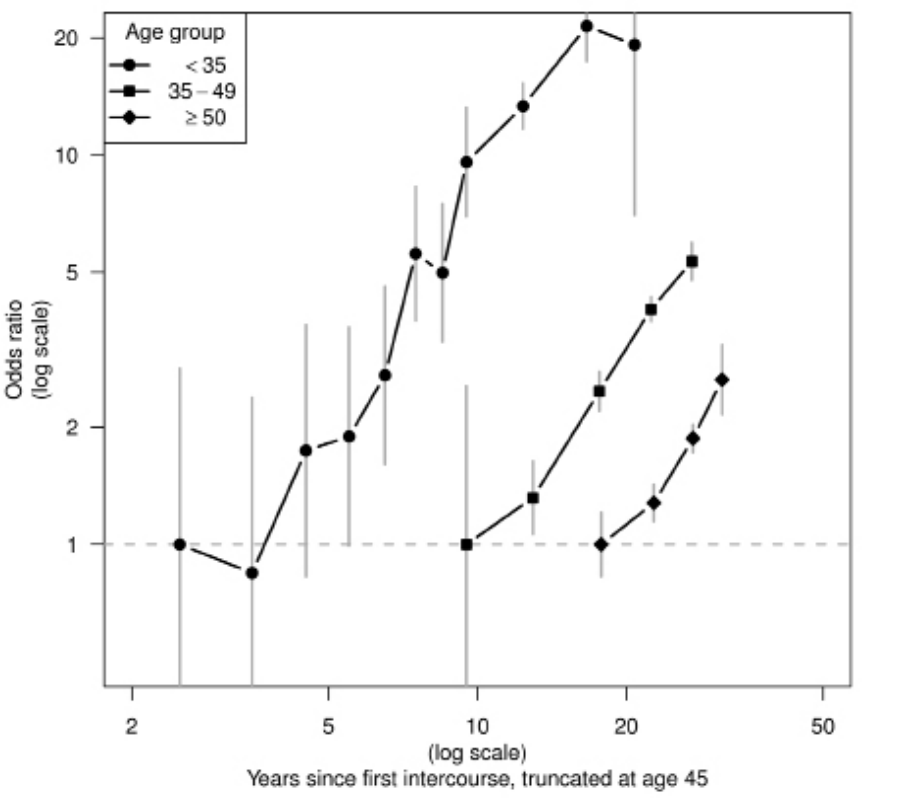


Figure 2. Odds ratios (and 95% floating confidence intervals) for cervical cancer by time since first intercourse stratified by age group (Plummer *et al.*, 2011).

There was no significant difference in slope between the three age strata (χ^2 = 2.67 with 2 degrees of freedom, P = 0.26). The data are thus consistent with a simplified model in which the OR increases as a power of truncated TFI that is constant at all ages. The OR for invasive cervical carcinoma is approximately proportional to the square of TFI (exponent 1.95, 95% CI: 1.76–2.15) up to age 45. Age-specific incidence rates of cervical cancer in unscreened populations are consistent with this model up to age 45, but remain fairly constant at older ages.

We concluded that cervical cancer resembles other cancers caused by strong early-stage carcinogens (e.g. lung cancer and tobacco smoking), with incidence rates proportional to a power of duration of exposure. But cervical cancer also resembles cancers of the breast and other hormone-dependent epithelia, where a similar flattening of age-specific incidence rates is seen at the time menopausal changes start.

Our findings have important implications for immunization strategies against HPV. HPV vaccines have been demonstrated to be highly effective in preventing HPV infection for up to eight years (McKeage and Romanowski, 2011), but the longer term protection is currently unknown. Our model suggests that delaying first exposure to HPV by vaccination would have the same lifelong effect as delaying age at first sexual intercourse. For example, a vaccine against HPV16 and 18 that lasted 15 years would prevent almost all cancers due to these HPV types below age 40 and would reduce the risk almost 5-fold above age 45 (data not shown). Assuming that the vaccine will not be effective against other HPV types, the overall effect would be to reduce all cervical cancer incidence above age 45 by more than 2-fold (Figure 3).

Conversely, our analysis suggests little advantage of vaccinating older women in the prevention of cervical cancer. Women can be infected by carcinogenic HPV at any age (Plummer *et al.*, 2011), but the lifetime cervical cancer risk caused by a new HPV infection will fall sharply with age at infection (Rodríguez *et al.*, 2010).

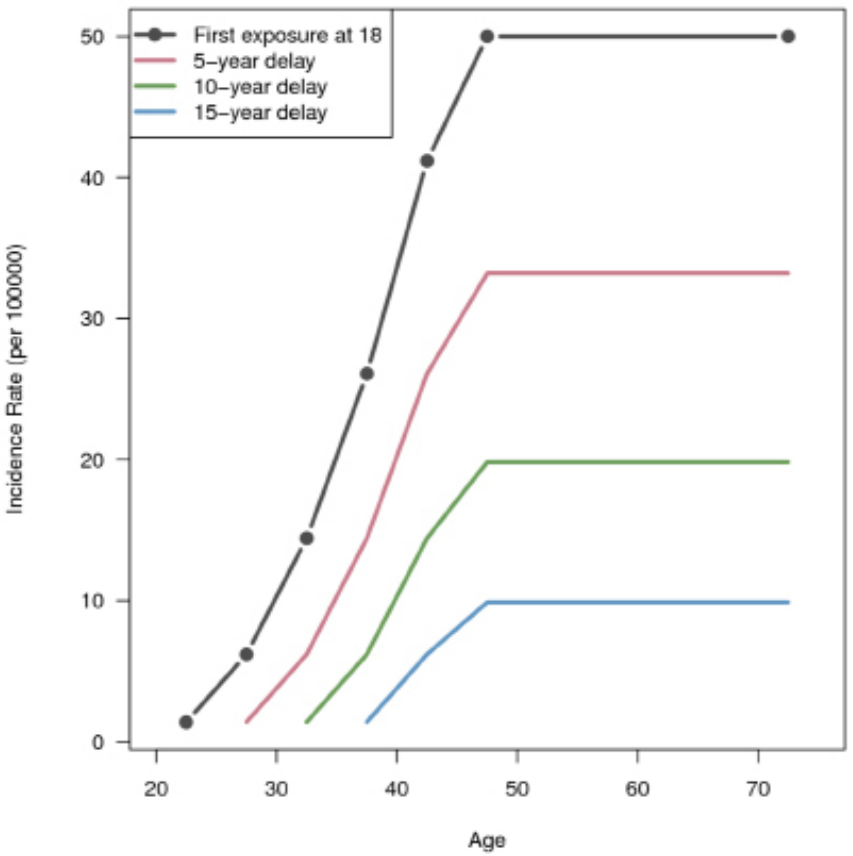


Figure 3. Predicted effect of a vaccine against HPV16 and 18 of limited duration (derived from Plummer *et al.*, 2011)

Random clustering of HPV infections

To understand viral interactions and cross-reactivity of natural or vaccine-induced immunological responses, it is important to assess whether certain combinations of HPV types are more or less likely to be found together, beyond what would be expected by shared sexual transmission and common risk factors.

The ICE has promoted international collaborations that aim to assess the pattern of HPV type clustering in a range of large-scale studies that differ by type of population included (e.g. cancer-free women or men) and HPV detection methods used. These included IARC HPV Prevalence Surveys (mainly low-resource countries) (Vaccarella *et al.*, 2010); The Guanacaste Study of HPV Natural History, Costa Rica (Vaccarella *et al.*, 2011b); The New Technologies in Cervical Cancer (NTCC) screening study, Italy (Carozzi *et al.*, 2011); and The HPV in Men study (United States, Mexico, and Brazil) (Vaccarella *et al.*, 2011a).

An appropriate statistical approach based on multilevel modelling has been developed. We used multivariate logistic regression to model type-specific HPV positivity. The presence of each HPV type was considered as a separate outcome for each woman. The model allows for the inclusion of available covariates such as age, study area and lifetime number of sexual partners. Subject-level random effects represent unobservable risk factors common to all HPV types and allow better adjustment for the complexity of sexual behaviour.

In all study populations considered (see the largest study included, the NTCC, in Figure 4) (Carozzi *et al.*, 2011), high-risk HPV coinfections seemed to occur at random in the female cervix, as well as the male external genitalia. In particular, there was no evidence that HPV16 and 18 are more or less likely to be found in combination with other oncogenic types. The few significant excesses of certain pairs of HPV types that were found could be confidently attributed to artefacts of certain HPV detection methods (e.g. cross-hybridization of similar HPV types) (Vaccarella *et al.*, 2010).

Overall, our collaborative analysis provides evidence that the removal of certain HPV types through vaccination would not result in an indirect increase or decrease in the prevalence of other untargeted types.

Distribution of HPV types in cervical cancer in women infected by HIV

Though data on the prevalence of HPV types in cervical carcinoma in women with HIV are scarce, they are essential to elucidate the influence of immunity on the carcinogenicity of different HPV types, and the potential impact of prophylactic HPV vaccines in populations with high HIV prevalence. We therefore conducted a case-case study in Kenya and South Africa (De Vuyst *et al.*, 2011). During 2007–2009, frozen tissue biopsies from women with cervical carcinoma were tested for HPV DNA using GP5+/6+-PCR assay. One hundred and six HIV-positive (mean age 40.8 years) and 129 HIV-negative women (mean age 45.7) with SCC were included. Among HIV-positive women, the mean CD4 count was 334 cells/μL and 48.1% were on combined antiretroviral therapy. HIV-infected women had many more multiple HPV infections (21.6% of HPV-positive carcinomas) compared to HIV-negative women (3.3%; P < 0.001) and the proportion of multiple infections in HIV-infected women was inversely related to CD4 level.

An excess of HPV18 of borderline statistical significance was shown in HIV-positive compared to HIV-negative cases (Prevalence ratio (PR) = 1.9, 95% CI: 1.0–3.7, adjusted for study centre, age and multiplicity of infection). HPV16 and/or 18 prevalence combined, however, was similar in HIV-positive (66.7%) and HIV-negative cases (69.1%) (PR = 1.0, 95% CI: 0.9–1.2). No significant difference emerged for other HPV types.

Our data are in agreement with a few other smaller studies on the topic. They suggest that current prophylactic HPV vaccines against HPV16 and 18 may prevent similar proportions of cervical cancers in HIV-positive, as in HIV-negative, women provided vaccine-related protection continues after HIV infection.

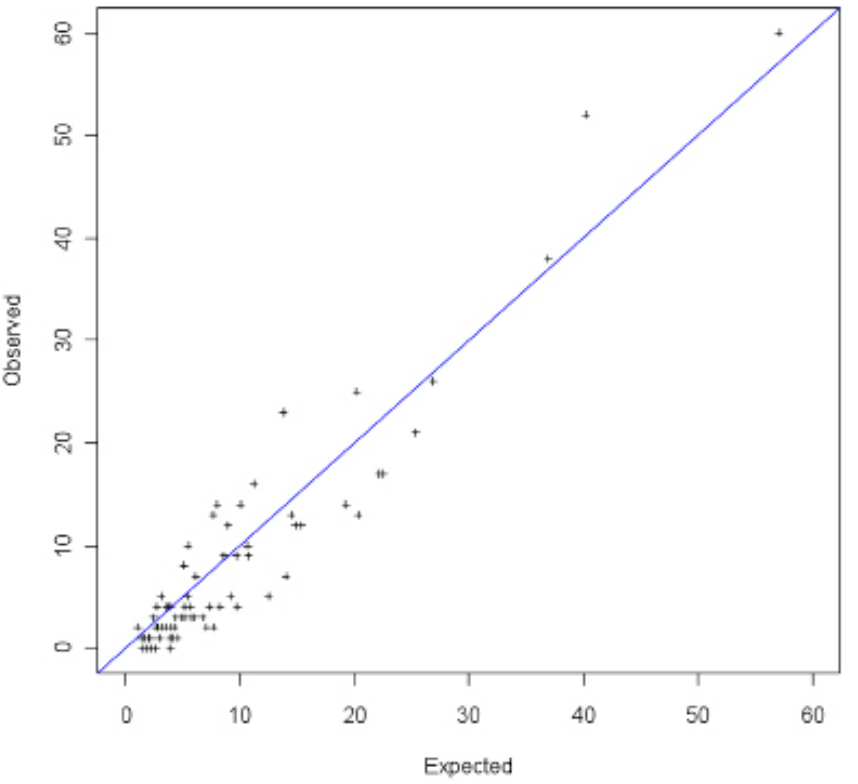
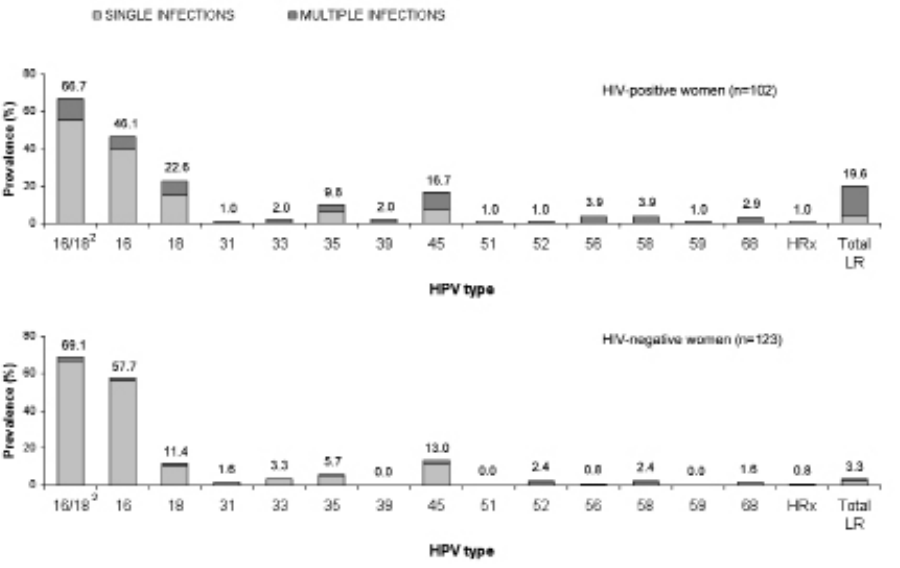


Figure 4. Observed versus Expected occurrence for 2-way combinations of 13 high-risk human papillomavirus (HPV) types. The New Technologies in Cervical Cancer study, Italy (Carozzi *et al.*, 2011)

Plus signs represent occurrences of HPV pairs. HPV pairs located in the upper triangle indicate positive clustering, while those located in the lower triangle represent negative clustering between the HPV types involved. None of the P-values for joint HPV infections were significant at the chosen significance level of 0.01.

Figure 5. Prevalence of human papillomavirus (HPV) in 225 women with cervical squamous cell carcinoma by HIV status and multiplicity of HPV infection (De Vuyst *et al.*, 2011)

10 HPV-negative women were probably false negatives and were excluded; [2]Either 16 or 18 as single infection or in combination with any type as multiple type infection;
HPV: human papillomavirus; HRX: uncharacterized high-risk type; LR: low-risk.



The ICE is grateful to the following scientists for their collaboration:
Studies on HPV and cancer

D. Hammouda, Algeria; D. Loria, E. Matos, Argentina; D. Dorji, U. Tshomo, Bhutan; C. Ferreccio, A. Luzoro, J.M. Ojeda, R. Prado, Chile; M. Dai, N. Li, Y.L. Qiao, R.F. Wu, F.H. Zhao, China; M. Molano, N. Muñoz, H. Posso, Colombia; R. Herrero, France; T. Alibegashvili, D. Kordzaya, Georgia; M. Pawlita, Germany; N. Keita, Guinea; R. Rajkumar, India; N. Khodakarami, Islamic Republic of Iran; F. Carozzi, G. Ronco, Italy; E. Lazcano-Ponce, Mexico; B. Dondog, Mongolia; A.T.L. Sherpa, Nepal; C.J.L.M. Meijer, P.J.F. Snijders, The Netherlands; A. Omigbodun, J.O. Thomas, Nigeria; S.A. Raza, Pakistan; A. Bardin, W. Zatonski, Poland; D.H. Lee, H.R. Shin, Republic of Korea; J. Bosch, X. Castellsagué, S. de Sanjosé, Spain; S. Sukvirach, S. Tunsakul, Thailand; V. Beral, United Kingdom; A. Berrington, K. Irwin, M. Schiffman, J. Smith, USA; B. Aruhuri, I. Frazer, Vanuatu and P.T.H. Anh, N.T. Hieu, Viet Nam.

Studies on HIV and cancer
L. Dal Maso, D. Serraino, Italy; B. Estambale, Kenya; M. Moodley, South Africa; O. Keiser, F. Schöni-Affolter, Switzerland; M. Chung, USA.

Studies on *Helicobacter* species and cancer
J.Y. Scoazec, France; L.J. Van Doorn, The Netherlands.

Case-control studies on different cancer sites
C. La Vecchia, E. Negri, J. Polesel, R. Talamini, Italy.

Financial support from the following bodies is gratefully acknowledged:

Association for International Cancer Research (AICR)
Bill & Melinda Gates Foundation (BMGF)
Fondation de France
Fondation Innovations en infectiologie (FINOVI)
Institut National du Cancer (INCa)
Ligue Nationale contre le Cancer, Comité du Rhône

Publications

Alibegashvili T, Clifford GM, Vaccarella S *et al.* (2011). Human papillomavirus infection in women with and without cervical cancer in Tbilisi, Georgia. *Cancer Epidemiol,* 35:465–470.doi:10.1016/j.canep.2010.12.006 PMID:21292583

Arbyn M, Bruni L, de San José S *et al.* (2011). Prevalence of human papillomavirus infection and burden of cervical cancer in Europe in 2008. In: ESGO Textbook of Gynaecological Oncology. European Society of Gynaecological Oncology. In press.

Ateenyi-Agaba C, Franceschi S, Wabwire-Mangen F *et al.* (2010). Human papillomavirus infection and squamous cell carcinoma of the conjunctiva. *Br J Cancer,* 102:262–267.doi:10.1038/sj.bjc.6605466 PMID:19997105

Bidoli E, Pelucchi C, Zucchetto A *et al.* (2010). Fiber intake and endometrial cancer risk. *Acta Oncol,* 49:441–446.doi:10.3109/02841860903535996 PMID:20148644

Bidoli E, Pelucchi C, Zucchetto A *et al.* (2011). Fiber intake and pancreatic cancer risk: a case-control study. *Ann Oncol.* In press. PMID:21460379

Bohlius J, Schmidlin K, Boué F *et al.*; Collaboration of Observational HIV Epidemiological Research Europe (2011). HIV-1-related Hodgkin lymphoma in the era of combination antiretroviral therapy: incidence and evolution of CD4ß T-cell lymphocytes. *Blood,* 117:6100–6108.doi:10.1182/blood-2010-08-301531 PMID:21368291

Bravi F, Edefonti V, Bosetti C *et al.* (2010). Nutrient dietary patterns and the risk of colorectal cancer: a case-control study from Italy. *Cancer Causes Control,* 21:1911–1918.doi:10.1007/s10552-010-9619-1 PMID:20680437

Bravi F, Edefonti V, Bosetti C *et al.* (2010). Nutrient dietary patterns and the risk of colorectal cancer: a case-control study from Italy. *Cancer Causes Control,* 21:1911–1918.doi:10.1007/s10552-010-9619-1 PMID:20680437

Carozzi F, Ronco G, Gillio-Tos A *et al.* (2011). Concurrent infections with multiple human papillomavirus (HPV) types in the New Technologies for Cervical Cancer (NTCC) screening study. *Eur J Cancer.* In press. PMID:19091544

Carstensen B (2011). Using Lexis objects for multi-state models in R. *J Stat Softw,* 38:1–18.

Castellsagué X, Díaz M, Vaccarella S *et al.* (2011). Intrauterine device use, cervical infection with human papillomavirus, and risk of cervical cancer: a pooled analysis of 26 epidemiological studies. *Lancet Oncol,* 12:1023–1031.doi:10.1016/S1470-2045(11)70223-6 PMID:21917519

Chaabna K, Boniol M, De Vuyst H *et al.* (2011). Geographical patterns of kaposi sarcoma, non-Hodgkin lymphomas and cervical cancer associated with HIV Infection in five African populations. *Eur J Cancer Prev.* In press.

Chen D, McKay JD, Clifford G *et al.* (2011). Genome-wide association study of HPV seropositivity. *Hum Mol Genet,* 20:4714–4723.doi:10.1093/hmg/ddr383 PMID:21896673

Chen D, Truong T, Gaborieau V *et al.* (2011). A sex-specific association between a 15q25 variant and upper aerodigestive tract cancers. *Cancer Epidemiol Biomarkers Prev,* 20:658–664.doi:10.1158/1055-9965.EPI-10-1008 PMID:21335511

Chung MH, McKenzie KP, Richardson BA *et al.* (2011). Cervical HIV-1 RNA shedding after cryotherapy among HIV-positive women with cervical intraepithelial neoplasia stage 2 or 3. *AIDS*, 25:1915–1919. PMID:21716072

Chung SH, Franceschi S, Lambert PF (2010). Estrogen and ERalpha: culprits in cervical cancer? *Trends Endocrinol Metab,* 21:504–511.doi:10.1016/j.tem.2010.03.005 PMID:20456973

Clifford GM, Howell-Jones R, Franceschi S (2011). Judging the carcinogenicity of human papillomavirus types by single/multiple infection ratio in cervical cancer. *Int J Cancer,* 129:1792–1794.doi:10.1002/ijc.25833 PMID:21140454

Dal Maso L, Franceschi S, Lise M *et al.* (2010). Re: Papillary thyroid cancer incidence in the volcanic area of Sicily. *J Natl Cancer Inst,* 102:914–915, author reply 915–916.doi:10.1093/jnci/djq157 PMID:20484104

Dal Maso L, Franceschi S, Lise M *et al.*; Screening of HIV-positive women in Emilia-Romagna (SHER) Study (2010). Self-reported history of Pap-smear in HIV-positive women in Northern Italy: a cross-sectional study. *BMC Cancer,* 10:310. PMID:20565935

Dal Maso L, Lise M, Zambon P *et al.*; AIRTUM Working Group (2011). Incidence of thyroid cancer in Italy, 1991–2005: time trends and age-period-cohort effects. *Ann Oncol,* 22:957–963.doi:10.1093/annonc/mdq467 PMID:20952599

Dal Maso L, Tavani A, Zucchetto A *et al.* (2011). Anthropometric measures at different ages and endometrial cancer risk. *Br J Cancer,* 104:1207–1213.doi:10.1038/bjc.2011.63 PMID:21386846

de Martel C, Franceschi S (2010). Etiology of cancer: Infections. In: Cancer Report of Asian-Pacific Region 2010. Asian Pacific Organization for Cancer Prevention, p. 38–42

de Martel C, Franceschi S Parsonnet J (2011). Tropical Infectious Diseases and Malignancy. In: Guerrant RL, Walker DH, Weller PF, editors. Tropical Infectious Diseases: Principles, Pathogens, and Practice, 3rd Edition. Elsevier, p. 71–75

de Martel C, Franceschi S, Partensky C (2010). Epidémiologie du cancer du pancréas. In: Delpero JR, Paye E, Bachellier P, editors. Cancer du Pancréas. Monographies de l'Association française de Chirurgie. Rueil-Malmaison: Wolters Kluwer France, p. 12–30

de Martel C, Plummer M, Franceschi S (2010). Cholangiocarcinoma: descriptive epidemiology and risk factors. *Gastroenterol Clin Biol,* 34:173–180. doi:10.1016/j.gcb.2010.01.008 PMID:20202771

de Martel C, Plummer M, van Doorn LJ *et al.* (2010). Comparison of polymerase chain reaction and histopathology for the detection of Helicobacter pylori in gastric biopsies. *Int J Cancer,* 126:1992–1996. PMID:19795444

De Vuyst H (2011). Human papillomavirus infection in anal intraepithelial neoplasia and anal carcinoma. *HPV Today*, 23

De Vuyst H, Ndirangu G, Moodley M *et al.* (2011). Prevalence of human papillomavirus in women with invasive cervical carcinoma by HIV status in Kenya and South Africa. Int J Cancer. In press.

De Vuyst H, Parisi MR, Karani A *et al.* (2010). The prevalence of human papillomavirus infection in Mombasa, Kenya. *Cancer Causes Control,* 21:2309–2313.doi:10.1007/s10552-010-9645-z PMID:20938733

Dondog B, Lise M, Dondov O *et al.* (2011). Hepatitis B and C virus infections in hepatocellular carcinoma and cirrhosis in Mongolia. *Eur J Cancer Prev,* 20:33–39.doi:10.1097/CEJ.0b013e32833f0c8e PMID:21166097

Edefonti V, Bravi F, Garavello W *et al.* (2010). Nutrient-based dietary patterns and laryngeal cancer: evidence from an exploratory factor analysis. *Cancer Epidemiol Biomarkers Prev,* 19:18–27.doi:10.1158/1055-9965.EPI-09-0900 PMID:20056619

Edefonti V, Bravi F, La Vecchia C *et al.* (2010). Nutrient-based dietary patterns and the risk of oral and pharyngeal cancer. *Oral Oncol,* 46:343–348.doi:10.1016/j.oraloncology.2009.11.017 PMID:20226721

Foschi R, Pelucchi C, Dal Maso L *et al.* (2010). Citrus fruit and cancer risk in a network of case-control studies. *Cancer Causes Control,* 21:237–242. doi:10.1007/s10552-009-9454-4 PMID:19856118

Franceschi S (2010). Monitoring HPV16/18 immunisation in England and elsewhere. [editorial]. *Br J Cancer,* 103:157–158.doi:10.1038/sj.bjc.6605758 PMID:20628394

Franceschi S (2010). Gastric carcinoma. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO Classification of Tumours of the Digestive System. *IARC Sci Publ*, 48–58

Franceschi S (2010). Hepatocellular carcinoma. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO Classification of Tumours of the Digestive System. *IARC Sci Publ*, 205–216

Franceschi S (2010). Intrahepatic cholangiocarcinoma. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO Classification of Tumours of the Digestive System. *IARC Sci Publ*, 217–224

Franceschi S (2010). Hepatitis C virus: A growing threat to the fight against liver cancer. In: Protection against cancer-causing infections: World Cancer Campaign 2010. Geneva, UICC, p. 12–17

Franceschi S (2011). Global strategy to prevent hepatitis viruses. In: Hepatocellular carcinoma: a global challenge. Nova Science Publishers, inc. In press.

Franceschi S, Dal Maso L (2010). Other microorganisms associated with lymphoid neoplasms In: McGrath I, editor. The Lymphoid Neoplasms, 3rd Edition. Hodder Arnold Health Sciences, London: p. 126–140

Franceschi S, Denny L, Irwin KL *et al.* (2011). Eurogin 2010 roadmap on cervical cancer prevention. *Int J Cancer,* 128:2765–2774.doi:10.1002/ijc.25915 PMID:21207409

Franceschi S, Lise M, Clifford GM *et al.*; Swiss HIV Cohort Study (2010). Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. *Br J Cancer,* 103:416–422. doi:10.1038/sj.bjc.6605756 PMID:20588274

Franceschi S, Lise M, Trépo C *et al.* (2011). Infection with hepatitis B and C viruses and risk of lymphoid malignancies in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Cancer Epidemiol Biomarkers Prev,* 20:208–214.doi:10.1158/1055-9965.EPI-10-0889 PMID:21098651

Franceschi S, Plummer M (2011). Intervention trials. In: Ahrens W, Albrecht R, Pigeot I, editors. Handbook of Epidemiology, 2nd Edition. New York: Springer Science+Business Media, LLC. In press

Franceschi S, Ronco G (2010). The prevention of cervical cancer in HIV-infected women. *AIDS,* 24:2579–2580.doi:10.1097/QAD.0b013e32833f39b2 PMID:20940536

Galeone C, Tavani A, Pelucchi C *et al.* (2010). Coffee and tea intake and risk of head and neck cancer: pooled analysis in the international head and neck cancer epidemiology consortium. *Cancer Epidemiol Biomarkers Prev,* 19:1723–1736.doi:10.1158/1055-9965.EPI-10-0191 PMID:20570908

Gallus S, Turati F, Tavani A *et al.* (2011). Soft drinks, sweetened beverages and risk of pancreatic cancer. *Cancer Causes Control,* 22:33–39.doi:10.1007/s10552-010-9665-8 PMID:20981481

Garavello W, Turati F, Bosetti C *et al.* (2011). Family history of cancer and the risk of laryngeal cancer: A case-control study from Italy and Switzerland. Int J Cancer. In press. PMID:21400506

Gaudet MM, Olshan AF, Chuang SC *et al.* (2010). Body mass index and risk of head and neck cancer in a pooled analysis of case-control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. *Int J Epidemiol,* 39:1091–1102.doi:10.1093/ije/dyp380 PMID:20123951

Gheit T, Cornet I, Clifford GM *et al.* (2011). Risks for persistence and progression by human papillomavirus type 16 variant lineages among a population-based sample of Danish women. *Cancer Epidemiol Biomarkers Prev,* 20:1315–1321.doi:10. 1158/1055-9965.EPI-10-1187 PMID:21527576

Giorgi-Rossi P, Franceschi S, Ronco G (2011). Human papillomavirus prevalence and accuracy of HPV testing to detect cervical intraepithelial neoplasia. Int J Cancer. In press.

González CA, Travier N, Luján-Barroso L *et al.* (2011). Dietary factors and in situ and invasive cervical cancer risk in the European prospective investigation into Cancer and Nutrition (EPIC) study. *Int J Cancer,* 129:449–459.doi:10.1002/ijc.25679 PMID:20853322

Grulich AE, Vajdic CM, Falster MO *et al.* (2010). Birth order and risk of non-hodgkin lymphoma–true association or bias? *Am J Epidemiol,* 172:621–630. doi:10.1093/aje/kwq167 PMID:20720098

Guan P, Huang D, Yin Z, Zhou B (2011). Association of the hOGG1 Ser326Cys polymorphism with increased lung cancer susceptibility in Asians: a meta-analysis of 18 studies including 7592 lung cancer cases and 8129 controls. *Asian Pac J Cancer Prev,* 12:1067–1072. PMID:21790253

Hammouda D, Clifford GM, Pallardy S *et al.* (2011). Human papillomavirus infection in a population-based sample of women in Algiers, Algeria. *Int J Cancer,* 128:2224–2229.doi:10.1002/ijc.25539 PMID:20607828

Heck JE, Berthiller J Vaccarella S *et al* (2010). Sexual behaviors and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. *Int J Epidemiol,* 39:166–181. doi:10.1093/ije/dyp350 PMID:20022926

International Collaboration of Epidemiological Studies of Cervical Cancer (2009). Cervical carcinoma and sexual behavior: collaborative reanalysis of individual data on 15,461 women with cervical carcinoma and 29,164 women without cervical carcinoma from 21 epidemiological studies. *Cancer Epidemiol Biomarkers Prev,* 18:1060–1069.doi:10.1158/1055-9965.EPI-08-1186 PMID:19336546

Khodakarami N, Clifford GM, Yavari P *et al.* (2011). Human papillomavirus infection in women with and without cervical cancer in Tehran, Iran. Int J Cancer. In press.

Krutovskikh V, Partensky C.(2011). Nouvelles perspectives en oncologie: l'épigénétique et les cellules souches cancéreuses [New insights in oncology: epigenetics and cancer stem cells]. Cancer Radiother. In press.

Li N, Franceschi S, Howell-Jones R *et al.* (2011). Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: Variation by geographical region, histological type and year of publication. *Int J Cancer,* 128:927–935.doi:10.1002/ijc.25396 PMID:20473886

Lipworth L, Zucchetto A, Bosetti C *et al.* (2011). Diabetes mellitus, other medical conditions and pancreatic cancer: a case-control study. *Diabetes Metab Res Rev,* 27:255–261.doi:10.1002/dmrr.1162 PMID:21309046

Lise M, Franceschi S, Buzzoni C *et al.* (2011). Changes in the incidence of thyroid cancer between 1991 and 2005 in Italy: a geographical analysis. *Thyroid*. In press.

Lubin JH, Gaudet MM, Olshan AF *et al.* (2010). Body mass index, cigarette smoking, and alcohol consumption and cancers of the oral cavity, pharynx, and larynx: modeling odds ratios in pooled case-control data. *Am J Epidemiol,* 171:1250–1261. doi:10.1093/aje/kwq088 PMID:20494999

Lubin JH, Muscat J, Gaudet MM *et al.* (2011). An examination of male and female odds ratios by BMI, cigarette smoking, and alcohol consumption for cancers of the oral cavity, pharynx, and larynx in pooled data from 15 case-control studies. *Cancer Causes Control,* 22:1217–1231.doi:10.1007/s10552-011-9792-x PMID:21744095

Lucenteforte E, Talamini R, Bosetti C *et al.* (2010). Macronutrients, fatty acids, cholesterol and pancreatic cancer. *Eur J Cancer,* 46:581–587. doi:10.1016/j.ejca.2009.09.024 PMID:19850469

Lucenteforte E, Zucchetto A, Bosetti C *et al.* (2011). Reproductive and hormonal factors and pancreatic cancer risk in women. *Pancreas*, 40:460–463.doi:10.1097/MPA.0b013e31820bf986 PMID:21343831

Marron M, Boffetta P, Zhang ZF *et al.* (2010). Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk in the INHANCE consortium. *Int J Epidemiol,* 39:182–196. doi:10.1093/ije/dyp291 PMID:19805488

Maucort-Boulch D, Plummer M, Castle PE *et al.* (2010). Predictors of human papillomavirus persistence among women with equivocal or mildly abnormal cytology. *Int J Cancer,* 126:684–691. doi:10.1002/ijc.24752 PMID:19609952

McKay JD, Truong T, Gaborieau V *et al.* (2011). A genome-wide association study of upper aerodigestive tract cancers conducted within the INHANCE consortium. [Erratum in PLoS Genet 7] [4] [2011]. *PLoS Genet,* 7:e1001333.doi:10.1371/journal.pgen.1001333 PMID:21437268

McKeage K, Romanowski B (2011). AS04-adjuvanted human papillomavirus (HPV) types 16 and 18 vaccine (Cervarix®): a review of its use in the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic HPV types. *Drugs*, 71:465–488. PMID:21395359

McKenzie KP, Rogers RK, Njoroge JW *et al.* (2011). Cervical squamous intraepithelial lesions among HIV-positive women on antiretroviral therapy in Kenya. *Curr HIV Res,* 9:180–185. doi:10.2174/157016211795945214 PMID:21585334

Okolo C, Franceschi S, Adewole I *et al.* (2010). Human papillomavirus infection in women with and without cervical cancer in Ibadan, Nigeria. *Infect Agent Cancer,* 5:24.doi:10.1186/1750-9378-5-24 PMID:21129194

Partensky C (2010). Pancreatic surgery in France. *Surg Today,* 40:895–901.doi:10.1007/s00595-010-4352-7 PMID:20872190

Pelucchi C, Negri E, Talamini R *et al.* (2010). Metabolic syndrome is associated with colorectal cancer in men. *Eur J Cancer,* 46:1866–1872. doi:10.1016/j.ejca.2010.03.010 PMID:20395126

Plummer M (2011). Lexis: an R class for epidemiological studies with long-term follow-up. *J Stat Softw,* 38:1–12.

Plummer M, Peto J, Franceschi S; on behalf of the International Collaboration of Epidemiological Studies of Cervical Cancer (2011). Time since first sexual intercourse and the risk of cervical cancer. *Int J Cancer.* In press. PMID:21702036

Plummer M, Vaccarella S, Franceschi S (2011). Multiple human papillomavirus infections: the exception or the rule? [editorial]. *J Infect Dis,* 203:891–893.doi:10.1093/infdis/jiq146 PMID:21402540

Polesel J, Franceschi S, Suligoi B *et al.*; Cancer and AIDS Registries Linkage Study Cancer; AIDS Registries Linkage Study (2010). Cancer incidence in people with AIDS in Italy. *Int J Cancer,* 127:1437–1445.doi:10.1002/ijc.25153 PMID:20049835

Polesel J, Franceschi S, Talamini R *et al.* (2011). Tobacco smoking, alcohol drinking, and the risk of different histological types of nasopharyngeal cancer in a low-risk population. *Oral Oncol,* 47:541–545.doi:10.1016/j.oraloncology.2011.03.017 PMID:21478046

Polesel J, Talamini R, Montella M *et al.* (2011). Re: Association of meat and fat intake with liver disease and hepatocellular carcinoma in the NIH-AARP cohort. *J Natl Cancer Inst,* 103:446–448. doi:10.1093/jnci/djq560 PMID:21289300

Polesel J, Talamini R, Negri E *et al.* (2010). Dietary habits and risk of pancreatic cancer: an Italian case-control study. *Cancer Causes Control,* 21:493–500. doi:10.1007/s10552-009-9480-2 PMID:20091114

Raza SA, Franceschi S, Pallardy S *et al.* (2010). Human papillomavirus infection in women with and without cervical cancer in Karachi, Pakistan. *Br J Cancer*, 102:1657–1660.doi:10.1038/sj.bjc.6605664 PMID:20407442

Rinaldi S, Plummer M, Biessy C *et al.* (2011). Endogenous sex steroids and risk of cervical carcinoma: results from the EPIC study. In press.

Rodríguez AC, Schiffman M, Herrero R *et al.* (2010). Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *J Natl Cancer Inst,* 102:315–324.doi:10.1093/jnci/djq001 PMID:20157096

Ronco G, Franceschi S, Segnan N (2011). HPV16 and HPV18 genotyping in cervical cancer screening. *Lancet Oncol,* 12:831–832.doi:10.1016/S1470-2045(11)70195-4 PMID:21865085

Rosato V, Zucchetto A, Bosetti C *et al.* (2011). Metabolic syndrome and endometrial cancer risk. *Ann Oncol,* 22:884–889.doi:10.1093/annonc/mdq464 PMID:20937645

Rossi M, Bosetti C, Talamini R *et al.* (2010). Glycemic index and glycemic load in relation to body mass index and waist to hip ratio. *Eur J Nutr,* 49:459–464. doi:10.1007/s00394-010-0104-0 PMID:20390288

Rossi M, Negri E, Parpinel M *et al.* (2010). Proanthocyanidins and the risk of colorectal cancer in Italy. *Cancer Causes Control,* 21:243–250.doi:10.1007/s10552-009-9455-3 PMID:20012183

Serraino D, Ronco G, Franceschi S (2010). Infections and cancer: the contribution of European research in recent progresses. *Epidemiol Prev,* 34:56–61. PMID:21220819

Sherpa ATL, Clifford GM, Vaccarella S *et al.* (2010). Human papillomavirus infection in women with and without cervical cancer in Nepal. *Cancer Causes Control,* 21:323–330.doi:10.1007/s10552-009-9467-z PMID:20217467

Sullivan SG, Hirsch HH, Franceschi S *et al.*; Swiss HIV Cohort Study (2010). Kaposi sarcoma herpes virus antibody response and viremia following highly active antiretroviral therapy in the Swiss HIV Cohort study. *AIDS*, 24:2245–2252.doi:10.1097/QAD.0b013e32833b7830 PMID:20543658

Talamini R, Polesel J, Gallus S *et al.* (2010). Tobacco smoking, alcohol consumption and pancreatic cancer risk: a case-control study in Italy. *Eur J Cancer,* 46:370–376.doi:10.1016/j.ejca.2009.09.002 PMID:19782561

Tavani A, Scotti L, Bosetti C *et al.* (2010). Aspirin and risk of renal cell cancer in Italy. *Eur J Cancer Prev,* 19:272–274.doi:10.1097/CEJ.0b013e3283394750 PMID:20351553

Turati F, Edefonti V, Bravi F *et al.* (2011). Nutrient-based dietary patterns, family history, and colorectal cancer. *Eur J Cancer Prev,* 20:456–461.doi:10.1097/CEJ.0b013e328348fc0f PMID:21701387

Turati F, Galeone C, Talamini R *et al.* (2011). Coffee, decaffeinated coffee, tea, and pancreatic cancer risk: a pooled-analysis of two Italian case-control studies. *Eur J Cancer Prev,* 20:287–292.doi:10.1097/CEJ.0b013e32834572e7 PMID:21403521

Turati F, Gallus S, Tavani A *et al.* (2010). Alcohol and endometrial cancer risk: a case-control study and a meta-analysis. *Cancer Causes Control,* 21:1285–1296.doi:10.1007/s10552-010-9556-z PMID:20396942

Vaccarella S, Clifford GM, Howell-Jones R *et al.* (2011). Letter to the Editor: Author's reply to: Multiple human papillomavirus genotype infections in cervical cancer progression in the study to understand cervical cancer early endpoints and determinants. *Int J Cance*r 129: 1283–1285

Vaccarella S, Franceschi S, Clifford GM *et al.*; IARC HPV Prevalence Surveys Study Group (2010). Seroprevalence of antibodies against human papillomavirus (HPV) types 16 and 18 in four continents: the International Agency for Research on Cancer HPV Prevalence Surveys. *Cancer Epidemiol Biomarkers Prev*, 19:2379–2388.doi:10.1158/1055-9965.EPI-10-0336 PMID:20826835

Vaccarella S, Franceschi S, Herrero R *et al.* (2011b). Clustering of multiple human papillomavirus infections in women from a population-based study in Guanacaste, Costa Rica. *J Infect Dis,* 204:385–390.doi:10.1093/infdis/jir286 PMID:21742837

Vaccarella S, Franceschi S, Snijders PJF *et al.*; IARC HPV Prevalence Surveys Study Group (2010). Concurrent infection with multiple human papillomavirus types: pooled analysis of the IARC HPV Prevalence Surveys. *Cancer Epidemiol Biomarkers Prev,* 19:503–510.doi:10.1158/1055-9965.EPI-09-0983 PMID:20142247

Vaccarella S, Plummer M, Franceschi S (2011). Reply to Cervantes. *J Infect Dis*, 204:1816–1817. doi:10.1093/infdis/jir627 PMID:21987665

Vaccarella S, Plummer M, Franceschi S *et al.* (2011a). Clustering of human papillomavirus (HPV) types in the male genital tract: the HPV in men (HIM) study. *J Infect Dis,* 204:1500–1504.doi:10.1093/infdis/jir595 PMID:21908729

Zhao FH, Lin MJ, Hu SY *et al.* Cervical Cancer Screening Group in China (2010). Performance of high-risk human papillomavirus DNA testing as a primary screening tool for cervical cancer: a pooled analysis of 17 population-based studies from China. *Lancet Oncol,* 11:1160–1171. doi:10.1016/S1470-2045(10)70256-4 PMID:21075054, erratum in *Lancet Oncol,* 12:11 (2011)

Zucchetto A, Franceschi S, Clagnan E *et al.*; Friuli Venezia Giulia Cancer Registry Working Group (2010). Screening history of women with invasive cervical cancer in north-east Italy. *Eur J Obstet Gynecol Reprod Biol*, 152:200–204.doi:10.1016/j.ejogrb.2010.06.005 PMID:20667643