Special Report: Policy

A review of human carcinogens—Part B: biological agents

In February, 2009, 36 scientists from 16 countries met at the International Agency for Research on Cancer (IARC) to reassess the carcinogenicity of the biological agents classified as "carcinogenic to humans" (Group 1) and to identify additional tumour sites and mechanisms of carcinogenesis (tables 1 and 2). These assessments will be published as part B of Volume 100 of the IARC Monographs.[1]

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infect, respectively, over 300 million and 170 million people worldwide, mainly in Asia and Africa. Chronic infection with these viruses is known to cause hepatocellular carcinoma.[2] Sufficient evidence is available to conclude that chronic infection with HCV can also cause non-Hodgkin lymphoma, especially B-cell lymphoma. In an intervention study, patients with HCV infection and splenic lymphoma who were given the antiviral agent, interferon, showed regression of the lymphoma.[3]

Epstein–Barr virus (EBV) infects almost everyone and causes several types of cancer, including nasopharyngeal carcinoma, one of the most common cancers in southeastern Asia, and Burkitt's lymphoma in children in Africa. New evidence points to a role for EBV in 5–10% of gastric carcinomas worldwide.[4] EBV-positive gastric carcinoma develops early in life and has distinct histopathology, therefore it might belong to a separate clinical entity.[5] In this subset of gastric tumours, presence of the viral genome in a monoclonal form and expression of EBV-transforming proteins are strong evidence for the involvement of EBV.[6]

Data from 22 cohort studies and 80 case–control studies show an association between Kaposi's sarcoma herpes virus (KSHV) and Kaposi's sarcoma, with relative risks higher than 10. Most studies are of transplant recipients and people infected with HIV-1. In both patients who are and are not infected with HIV-1, risk of Kaposi's sarcoma increases relative to increasing titre of antibodies directed against KSHV, which are markers of the viral load.[7,8] Evidence is sufficient to show that KSHV causes primary effusion lymphoma, a rare subgroup of B-cell non-Hodgkin lymphoma. Mechanistic data support an oncogenic role for KSHV in Kaposi's sarcoma and in primary effusion lymphoma—in individuals who are immunocompromised and in those apparently immunocompetent. KSHV is also associated with multicentric Castleman's disease.

Individuals who are infected with HIV-1 have a high risk of cancer. HIV-1 infection, mainly through immunosuppression, leads to increased replication of oncogenic viruses such as EBV and KSHV. Although antiretroviral therapy lowers the risk of many cancers associated with HIV-1, risks remain high.[9]

Cervical cancer is caused by types of human papillomavirus (HPV) that belong to a few phylogenetically related "high-risk" species (alpha-5, 6, 7, 9, 11) of the mucosotropic alpha genus.[10,11] The types found most frequently in cervical cancer (HPV-16, 18, 31, 33, 35, 45, 52, 58) and four types less constantly found (HPV-39, 51, 56, 59) were classified in

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Group 1 agent	Cancers for which there is sufficient evidence in humans	Other sites with limited evidence in humans	Established mechanistic events
Epstein–Barr virus (EBV)	Nasopharyngeal carcinoma, Burkitt's lymphoma, immune-suppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin's lymphoma	Gastric carcinoma,* lympho-epithelioma-like carcinoma*	Cell proliferation, inhibition of apoptosis, genomic instability, cell migration
Hepatitis B virus (HBV)	Hepatocellular carcinoma	Cholangiocarcinoma,* non-Hodgkin lymphoma*	Inflammation, liver cirrhosis, chronic hepatitis
Hepatitis C virus (HCV)	Hepatocellular carcinoma, non-Hodgkin lymphoma*	Cholangiocarcinoma*	Inflammation, liver cirrhosis, liver fibrosis
Kaposi's sarcoma herpes virus (KSHV)	Kaposi's sarcoma,* primary effusion lymphoma*	multicentric Castleman's disease*	Cell proliferation, inhibition of apoptosis, genomic instability, cell migration
Human immunodeficiency virus, type 1 (HIV-1)	Kaposi's sarcoma, non-Hodgkin lymphoma, Hodgkin's lymphoma,* cancer of the cervix,* anus,* conjunctiva*	Cancer of the vulva,* vagina,* penis,* non-melanoma skin cancer,* hepatocellular carcinoma*	Immunosuppression (indirect action)
Human papillomavirus type 16 (HPV-16)†	Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil	Cancer of the larynx	Immortalisation, genomic instability, inhibition of DNA damage response, anti-apoptotic activity
Human T-cell lymphotrophic virus, type-1 (HTLV-1)	Adult T-cell leukaemia and lymphoma	..	Immortalisation and transformation of T cells
Helicobacter pylori	Non-cardia gastric carcinoma, low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma*	..	Inflammation, oxidative stress, altered cellular turnover and gene expression, methylation, mutation
Clonorchis sinensis	Cholangiocarcinoma*	..	..
Opisthorchis viverrini	Cholangiocarcinoma	..	Inflammation, oxidative stress, cell proliferation
Schistosoma haematobium	Urinary bladder cancer	..	Inflammation, oxidative stress

*Newly identified link between virus and cancer. †For other types, see table 2.

Table 1: **Biological agents assessed by the IARC Monograph Working Group**

Group	HPV types	Comments
Alpha HPV types		
1	16	Most potent HPV type, known to cause cancer at several sites
1	18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Sufficient evidence for cervical cancer
2A	68	Limited evidence in humans and strong mechanistic evidence for cervical cancer
2B	26, 53, 66, 67, 70, 73, 82	Limited evidence in humans for cervical cancer
2B	30, 34, 69, 85, 97	Classified by phylogenetic analogy to HPV types with sufficient or limited evidence in humans
3	6, 11	..
Beta HPV types		
2B	5 and 8	Limited evidence for skin cancer in patients with epidermodysplasia verruciformis
3	Other beta and gamma types	..

Table 2: **Human papillomavirus (HPV) types assessed by the IARC Monograph Working Group**

Monograph Working Group
Members
T F Schulz—Co-Chair (Germany), N Mueller—Co-Chair (USA); A Grulich, F Sitas (Australia); K Polman (Belgium); C J Chen, Y Y Fang (China); R Herrero (Costa Rica); B J Vennervald (Denmark); R Mahieux, F Mégraud, F Zoulim (France); H Blum, H zur Hausen (both unable to attend) (Germany); L Banks, A Carbone, D Serraino (Italy); M Matsuoka (Japan); S T Hong (South Korea); M C Kew (South Africa); S de Sanjosé (Spain); I Ernberg (Sweden); B Sripa (Thailand); A Hall, D Forman, R Newton (UK); E Cesarman, D Dittmer, E T H Fontham, P F Lambert, S Moss, E Murphy, M Schiffman, S Stuver, D Whitby (USA)

Conflicts of interest
SDS receives funding from Merck and Sanofi-Pasteur. AG has received funding from and is an advisor for CSL. RM has acted as a consultant for MP Biomedicals. SM served on a speaker's bureau for Otsuka Pharmaceuticals and was a consultant for Altana. NuM is a member of steering committees and a speaker's bureau for Merck and Sanofi-Pasteur. EM owns stock in Genentech. CJC received funding from Bristol-Myer-Squibb.

Invited Specialists
N Muñoz (IARC, France; retired)

Group 1 (table 2). The risk of cancer may be an order of magnitude higher for HPV-16 infection than for other high-risk HPV types. HPV-68 was classified as "probably carcinogenic to humans" (Group 2A) with limited evidence in humans and strong mechanistic evidence. The remaining types of HPV in the high-risk alpha species were classified as "possibly carcinogenic" (Group 2B; table 2). Finally, HPV-6 and HPV-11, which belong to the alpha-10 species, were "not classifiable as to its carcinogenicity to humans" (Group 3) on the basis of inadequate epidemiological evidence and absence of carcinogenic potential in mechanistic studies.

The Working Group recognises the need for further research of cutaneous HPV types of the beta and gamma genera. These widespread HPV types were classified in Group 3 on the basis of inconclusive evidence of causing skin cancer in humans and limited mechanistic data. Exceptions were the beta types HPV-5 and HPV-8, which are "possibly carcinogenic" in patients with epidermodysplasia verruciformis (Group 2B).

Helicobacter pylori infection is associated with gastric cancer,[12] one of the most prevalent cancers worldwide. Prospective epidemiological studies and eradication trials show that *H pylori* infection causes non-cardia gastric cancer.[13] *H pylori* infection also causes B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma; eradication treatment leads to remission of these low-grade lymphomas.[14] Several studies show that individuals with *H pylori* infection have a reduced risk of oesophageal adenocarcinoma compared with those without the infection.[15]

Opisthorchis viverrini and *Clonorchis sinensis*, two liver flukes of the genus *Opisthorchis*, are endemic in northeastern Thailand and many areas of southeastern Asia, respectively. In particular areas, prevalence of infection with liver flukes correlates with incidence of cholangiocarcinoma, and several case–control studies showed a high risk for this cancer.[16,17] Therefore, infections with *O viverrini* or with *C sinensis* were both classified in Group 1.

Schistosoma haematobium is endemic in most countries in Africa and the eastern Mediterranean region; infection with this worm, which causes urinary bladder cancer, is classified in Group 1.

The proportion of cancers caused by infectious agents was recently estimated to be more than 20%.[4] The identification of new cancer sites attributed to these agents means that more cancers are potentially preventable.

Véronique Bouvard, Robert Baan, Kurt Straif, Yann Grosse, Béatrice Secretan, Fatiha El Ghissassi, Lamia Benbrahim-Tallaa, Neela Guha, Crystal Freeman, Laurent Galichet, Vincent Cogliano, on behalf of the WHO International Agency for Research on Cancer Monograph Working Group

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The IARC authors declared no conflicts of interest.

D Blair attended as a Representative of the US National Cancer Institute (Bethesda, MD, USA). F Buonaguro (NCI, Napoli, Italy) and A Fiander (Cardiff University, Cardiff, UK) attended as Observers.

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