The IARC Monographs: Biological Agents and Cancer

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Evaluations and challenges

The *IARC Monographs* programme started evaluating the carcinogenicity of biological agents in 1993 .

- In 2009,Volume 100B considered 11 biological agents.
- In 2011, Volume 104 considered Malaria and 4 polyomaviruses , SV40, and the human BKV, JCV and MCV.

IARC Monographs evaluations of biological agents

Biological agent	IARC Group	*IARC Monographs* volume
VIRUSES		
Hepatitis B virus	1	59, 100B
Hepatitis C virus	1	59, 100B
Hepatitis D virus	3	59
HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59	1	64, 90, 100B
HPV type 68	2A	64, 90, 100B
HPV types 26, 30, 34, 53, 66, 67,69, 70, 73, 82, 85 and 97	2B	64, 90, 100B
HPV types 6 and 11	3	64, 90, 100B
Some HPV of genera beta and gamma	3	64, 90, 100B
HPV types 5 and 8 of genera beta	2B	64, 90, 100B
HIV-1	1	67, 100B
HIV-2	2B	67
HTLV-I	1	67, 100B
HTLV-II	3	67
EBV	1	70, 100B
KSHV	1	70, 100B
SV40 simian polyomavirus	3	104
BK polyomavirus (BKV)	2B	104
JC polyomavirus (JCV)	2B	104
Merkel cell polyomavirus (MCV)	2A	104
BACTERIA		
Helicobacter pylori	1	61, 100B
PROTOZOA		
Malaria (infection by *Plasmodium falciparum* in holoendemic areas)	2A	104
WORMS		
Schistosoma haematobium	1	61, 100B
Schistosoma mansoni	3	61
Schistosoma japonicum	2B	61
Opistorchis viverrini	1	61, 100B
Opistorchis felineus	3	61
Chlonorchis sinensis	1	61, 100B

Concerns with animal cancer bioassays

Due to species specificity, the use of animals as surrogate hosts has not proven very useful for assessing the carcinogenicity of human viruses in humans.

- ❖ Cancer bioassays in the context of natural infection cannot be feasible: most human tumour viruses e.g. HPV, HCV, HBV cannot infect rodents or other animals
- ❖ When infection is feasible, results obtained in cancer bioassays rarely reflect what would happen in humans: e.g. the human BK and JC polyomaviruses have not been demonstrated to induce tumours in humans but are very tumorigenic in rodents.

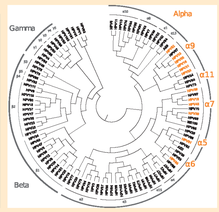
Specificities in epidemiological studies

- ❖ Specific tropism of the infectious agents leads to very specific cancers (e.g. "extranodal NK/T-cell lymphoma (nasal type)" caused by EBV)
- ❖ Difficulty of assessing causality for certain cancer types in which presence of a specific infection is part of the diagnostic criteria (e.g. HTLV1 and ATLL; KSHV and primary effusion lymphoma)
- ❖ Choice of good markers of infection of critical importance; requires clear knowledge of the lifecycle of the agent (e.g. *P. falciparum*)
- ❖ Widespread presence of certain viruses in a healthy population (e.g. EBV and some polyomaviruses): a major problem when studying the potential association of these viruses with human cancer.
- ❖ Specificity of the detection methods is critical (e.g. cross-reactivity between human JC and BK polyomaviruses and with SV40)

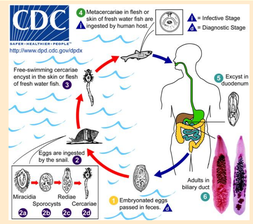
Major findings

Biological agent	Cancers or sites for which there is sufficient evidence in humans	Cancers or sites with limited evidence in humans
Epstein–Barr virus (EBV)	Nasopharyngeal carcinoma, Burkitt lymphoma, immune-suppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin's lymphoma	Gastric carcinoma, lympho-epithelioma-like carcinoma
Hepatitis-B virus (HBV)	Hepatocellular carcinoma	Cholangiocarcinoma, non-Hodgkin lymphoma
Hepatitis-C virus (HCV)	Hepatocellular carcinoma, non-Hodgkin lymphoma	Cholangiocarcinoma
Kaposi sarcoma herpes virus (KSHV)	Kaposi's sarcoma, primary effusion lymphoma	Multicentric Castleman's disease
Human immunodeficiency virus, type 1 (HIV-1)	Kaposi's sarcoma, non-Hodgkin lymphoma, Hodgkin's lymphoma, cervix, anus, conjunctiva	Vulva, vagina, penis, non-melanoma skin cancers, hepatocellular carcinoma
Human papillomavirus type 16 (HPV-16)	Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil	Larynx
Human T-cell lymphotrophic virus, type-1 (HTLV-1)	Adult T-cell leukaemia and lymphoma	
Helicobacter pylori	Non-cardia gastric carcinoma, low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma	
Clonorchis sinensis	Cholangiocarcinoma	
Opisthorchis viverrini	Cholangiocarcinoma	
Schistosoma haematobium	Urinary bladder	
Merkel cell polyomavirus (MCV)		Merkel cell carcinoma
Malaria (infection by *Plasmodium falciparum* in holoendemic areas)		Burkitt lymphoma

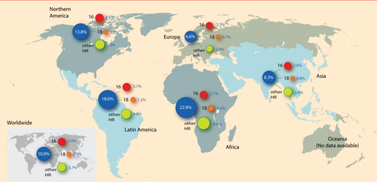
Group	HPV types	Comments
Alpha HPV types		
1	16	Most potent HPV type, known to cause cancer at several sites
1	18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Sufficient evidence for cervical cancer
2A	68	Limited evidence in humans and strong mechanistic evidence for cervical cancer
2B	26, 53, 66, 67, 70, 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	..



Human liver fluke infection is endemic in many countries in South-East Asia. Infection with *Opisthorchis viverrini* or *Clonorchis sinensis* occurs through ingestion of raw or undercooked freshwater fish that contain metacercariae. Chronic infection is associated with cholangiocarcinoma.



HPV DNA crude prevalence 🔵 and high-risk HPV type-specific prevalence (16 🔴 ,18 🟠, other HR 🟢)among women with normal cytology by world region: meta-analysis including 157 879 women from 36 countries (Bosch *et al.*, *Vaccine* 2008; de Sanjose *et al.*, *Lancet Inf. Dis.* 2007)

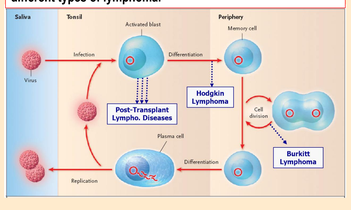


Three major mechanisms of carcinogenesis

Direct carcinogens

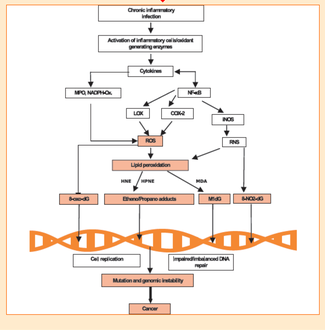
HPV, HTLV-1, EBV, KSHV, MCV

EBV infects B lymphocytes in almost everyone. It can be reactivated from its latent state. Depending on the differentiation status of the infected lymphocytes, EBV reactivation may lead to the development of different types of lymphoma.



Indirect carcinogens: Chronic inflammation

HBV, HCV, *H. pylori*, *S. haematobium*, liver flukes



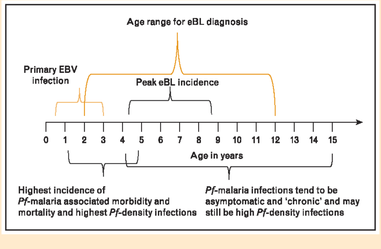
Indirect carcinogens: Immune suppression or deregulation

HIV, holoendemic malaria (*P. falciparum*)

HIV infection increases the incidence of cancers that are all associated with another infectious aetiology

Cancers associated with HIV infection	Evidence in humans	Other infectious agent(s) involved	Evidence in humans
Kaposi sarcoma	Sufficient	KSHV	Sufficient
Non-Hodgkin lymphoma	Sufficient	EBV or HCV	Sufficient
Hodgkin lymphoma	Sufficient	EBV	Sufficient
Cervical cancer	Sufficient	HPV	Sufficient
Anal cancer	Sufficient	HPV	Sufficient
Vulval, vaginal and penile cancer	Limited	HPV	Sufficient
Hepatocellular carcinoma	Limited	HBV, HCV	Sufficient

Both EBV and *P. falciparum* (malaria) infections are necessary for the development of eBurkitt lymphoma



Involvement of co-factors in infection-related cancers

Infection with carcinogenic agents does not always lead to cancer. This feature common to all Group-1 biological agents strongly suggests the involvement of co-factors in the carcinogenic process. Carcinogenesis would result from the interaction of multiple risk factors, including:

- ❖ Host-related factors (e.g. gene polymorphism, immune status)
- ❖ Environmental co-factors
  - ➢ that may lead to reactivation of latent oncogenic viruses such as EBV or KSHV (e.g. chemicals, immuno-suppressive drugs, food, plants or another infection)
  - ➢ acting through other mechanisms (e.g. HPV and UV)

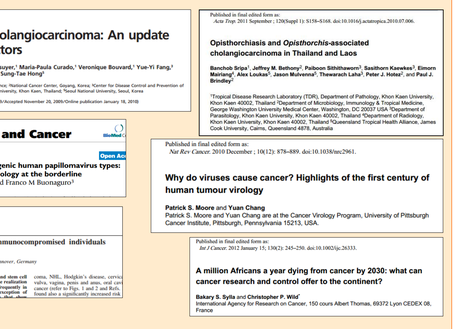
Outcomes and Impact

- ➢ Recognition of *Opistorchis viverrini* as a cancer-associated agent in South-East Asia by WHO

- ➢ Estimation of the global burden attributable to infections based on the evaluations of the Vol. 100B

- ❖ **~16.1%** of cancers attributable to infections (~ 2 million cancer cases of the 12.7 million new cancers that occurred globally in 2008).
  - ✓ proportion is much higher (**22.9%**) in low-resource countries
  - ✓ versus **7.4%** in the developed world
  - ✓ varied from **3.3%** in Australia and New Zealand to **32.7%** in sub-Saharan Africa (De Martel *et al.*, *Lancet Oncology* 2012).

- ➢ More than 270 citations in PubMed for Vol. 100B



- ➢ Stimulation of new research collaboration between the *Monographs* participants within and outside IARC

Research needs

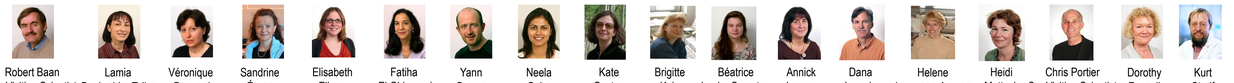
- ❖ Role of multiple infections in cancer (e.g. in sub-Saharan Africa)
- ❖ Role of host-related factors (e.g. gene polymorphism, immune status)
- ❖ Potential importance of variants or subtypes of the infectious agents (e.g. replication-defective mutants of Merkel cell polyomaviruses in human cancer)
- ❖ Role of infection in cancers associated with exposure to chemicals or other agents (e.g. nasopharyngeal carcinoma: salted fish and EBV in southern China)

International Agency for Research on Cancer

World Health Organization

http://monographs.iarc.fr

The *IARC Monographs* Programme staff



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