Infections Causing Human Cancers

Harald zur Hausen
Deutsches Krebsforschungszentrum
69120 Heidelberg
Germany

Infections Linked to Human Cancers:

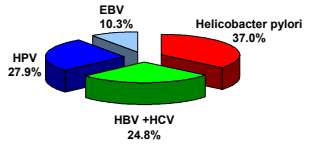
Herpesvirus family:	Epstein-Barr virus (EBV) Human Herpesvirus type 8 (HHV-8)
Papillomavirus family:	close to 20 anogenital HPV types several "cutaneous" HPV types
Hepadnavirus family	Hepatitis B virus
Flavivirus family:	Hepatitis C virus
Retrovirus family:	HTLV-1, human endogenous retroviruses (HERV) ?
Bacteria:	Helicobacter pylori, Helicobacter bilis (?)
Parasites:	Schistosoma haematobium, mansoni, japonicum, Opisthorchis viverrini, Opisthorchis felineus, Clonorchis sinensis

Tumortypes Linked to Infectious Causes

B-cell lymphomas in immunocompromised patients (ca. 50%) and in a subset of T-cell lymphomas Burkitt's lymphomas Nasopharyngeal cancer Hodgkin's disease (30-40%) Gastric cancer (~10%)	EBV
Cancer of the cervix, anal and perianal cancers Vulvar, penile and vaginal cancers Oropharyngeal cancers (ca. 25%) Squamous cell carcinomas of the skin	various HPV types
Hepatocellular carcinomas	HBV and HCV
Adult T-cell leukemia (ATL)	HTLV-1
Seminomas ?	Endogenous human retroviruses
Kaposi's sarcoma	HHV-8
Gastric cancer, gastric lymphoma	Helicobacter pylori
Bladder cancer (Rectal cancer)	Schistosoma haematobium, (japonicum, mansoni)
Cholangiocarcinoma	Opisthorchis viverrini and felineus, Clonorchis sinensis, (Helicobacter bilis ?)

Annual Global Cancer Incidence due to Infections

2 016 920 = 18.6% of total cancer incidence



25% of cancers of the oral cavity
68 572 (HPV)
Cancer of the cervix
493 243 (HPV)

Hepatocellular carcinoma 80%
500 930 (HBV, HCV)

Gastric cancer 80%
747 150 (Helicobacter pylori)

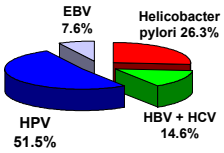
Gastric cancer 10%
93 3937 (EBV)
Nasopharyngeal carcinoma
80 043 (EBV)
Non-Hodgkin's lymphoma 10%
30 057 (EBV)
Hodgkin's lymphoma 30%
18 694 (EBV)

This graph ignores
- anal and perianal cancers (HPV)
- vulvar, vaginal and penile cancers (HPV)
- adult T cell leukemia
- Kaposi's sarcomas and prim. effusion lymphomas
- cancers linked to parasitic infections

Modified from: Parkin et al. Global Cancer Statistics 2002
CA Cancer J. Clinicians 55: 74-106, 2002

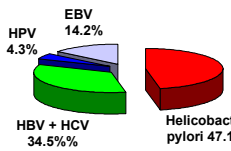
Females: Annual Global Cancer Incidence due to Infections

1 006 544 = 19.9% of total cancer incidence in females



Males: Annual Global Cancer Incidence due to Infections

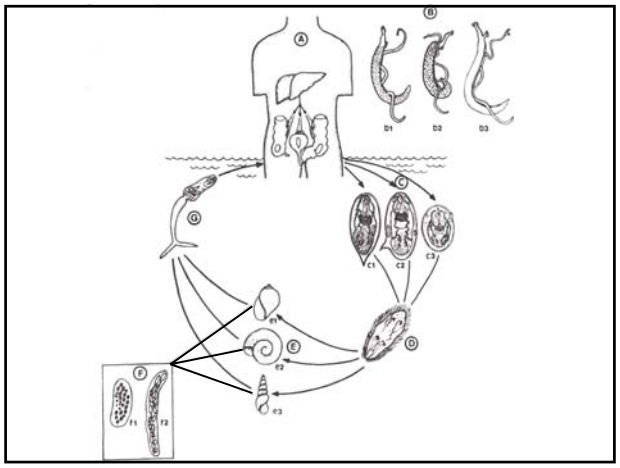
1 025 524 = 17.7% of total cancer incidence in males

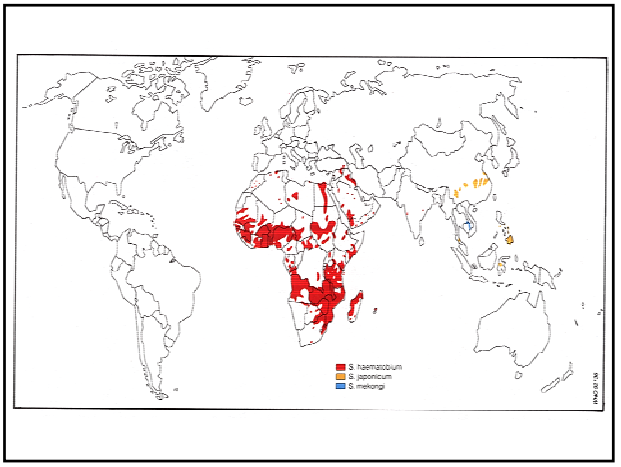


The mechanism by which parasites contribute to carcinogenesis is unknown

In Schistosoma infections non-excreted eggs cause chronic local inflammation.

S. haematobium represents a bladder carcinogen.





In **Schistosoma infections** a number of antigens have been identified with protective potential – immunization studies yielded, however, inconsistent and disappointing results

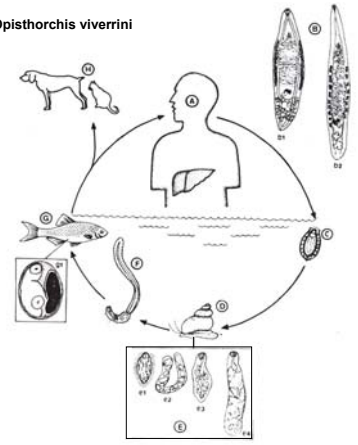
- new vaccines are presently developed against carbohydrate antigens (complex N-glycans);
- recombinant antigen preparations as well as DNA vaccines are also used in preclinical tests with some success.

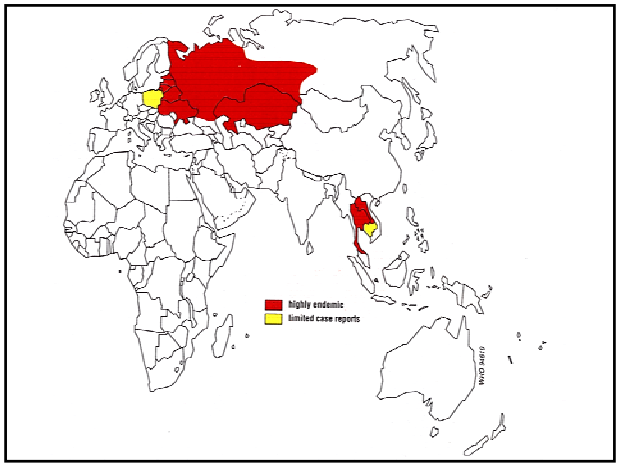
Chemotherapy (Praziquantel) eliminates the parasites.

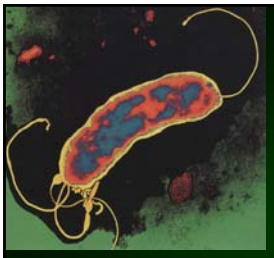
It does, however, not affect transmission of infection

and does not influence the re-infection rates

Life cycle of Opisthorchis viverrini



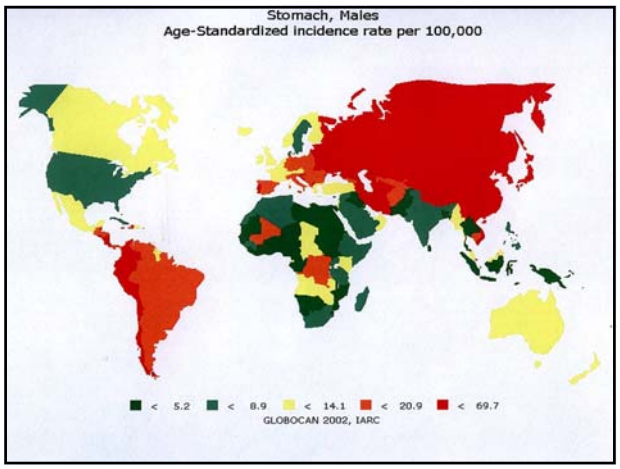


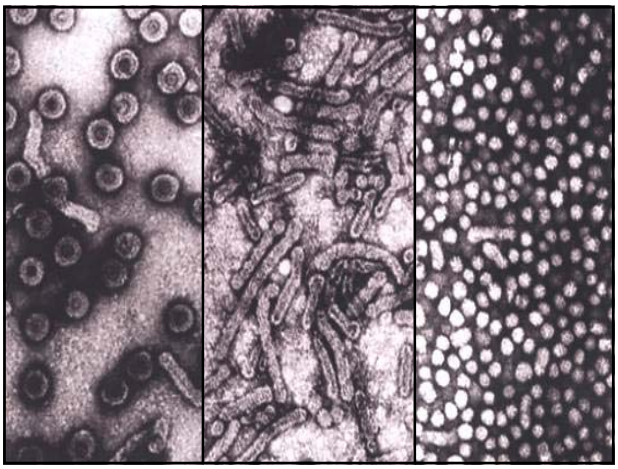


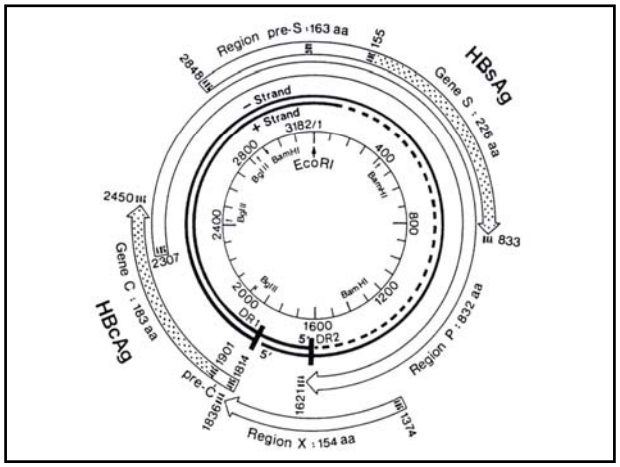
Chronic irritation and specific pathogenicity factors (cag-proteins) seem to play a role In Helicobacter pylori carcinogenesis

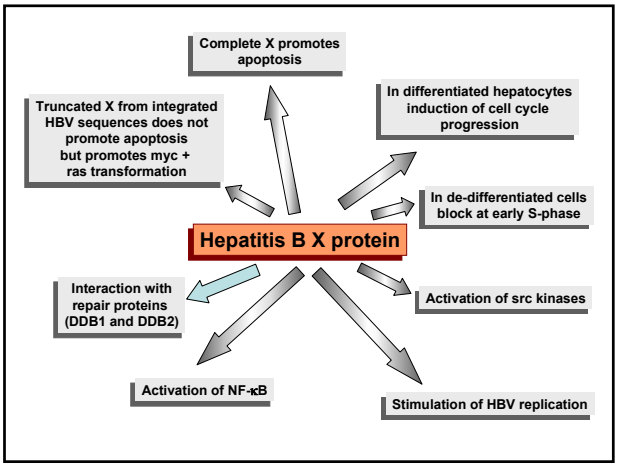
cag-proteins induce c-fos and may stimulate cell proliferation (Meyer-ter-Vehn et al. J. Biol. Chem. 2000.).

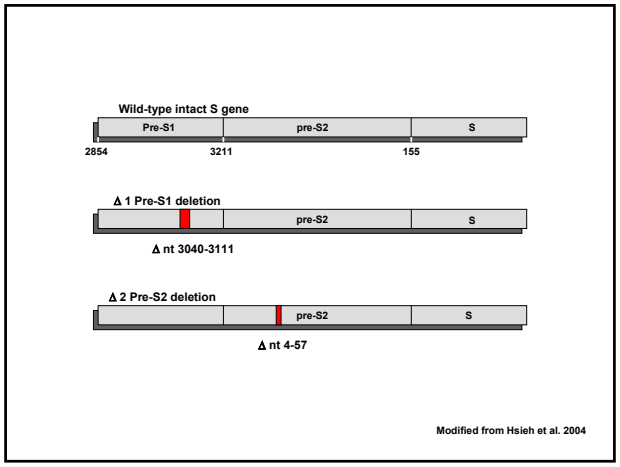
Outer inlammatory protein A (iopA) stimulates interleukin-8 production (Yamaoka et al. PNAS 2000.).











Hepatitis B is responsible for ~80% of hepatocellular carcinomas in the endemic regions of East Asia and Africa.

The virus is mainly transmitted from persistently infected mothers to their babies.

80-90% of the infected children become hepatitis B carriers for lifetime.

After latency periods commonly spanning 40 or 50 years hepatocellular carcinomas may develop, frequently in cirrhotic livers.

Hepatitis B Vaccination

Initially (in 1974) viral antigen (HBs) was purified from the blood of HBV carriers

First clinical trials started in 1975, the vaccine was licensed in 1981.

Since 1986 recombinant vaccines were produced in yeast.

Perinatal vaccination protects 75-80% of children born from HBV-positive mothers against HBV persistence.

Without vaccination 80-90% of them would become virus carriers.

In ~ 5% vaccination fails to induce protective immunity. In these patients the HLA constitution precludes an adequate T-cell response.

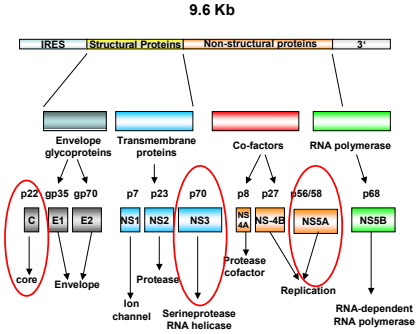
First reports from Taiwan demonstrate a protective effect of hepatitis B vaccination against hepatocellular carcinoma (Kao and Chen, 2002)

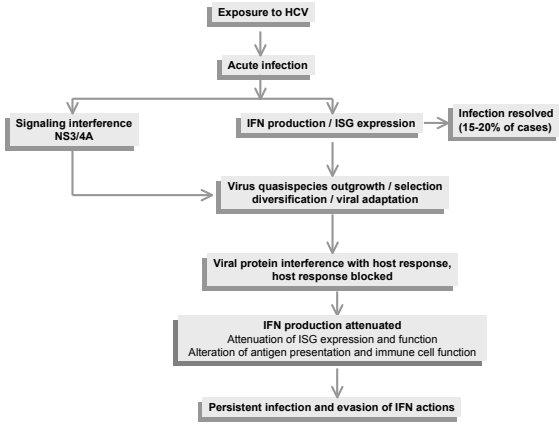
Hepatitis C virus causes approximately 38% of virus-linked hepatocellular carcinomas on the global scale and plays a more important role for this cancer in Europe and the USA than hepatitis B

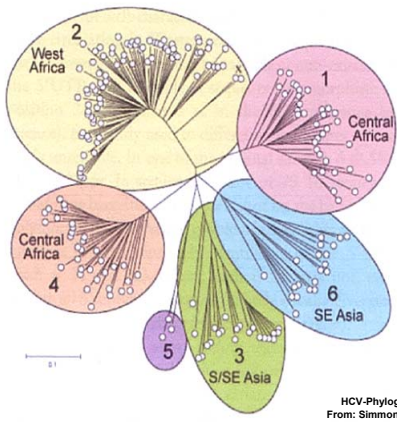
About 2% of the population in the USA and Western Europe are persistently hepatitis C virus-infected.

Main routes of infection are perinatal (10% of babies from infected mothers acquire a persistent infection), sexual contacts, blood transfusions, intravenous drug abuse.

Cancer occurs approximately 20-40 years after primary infection





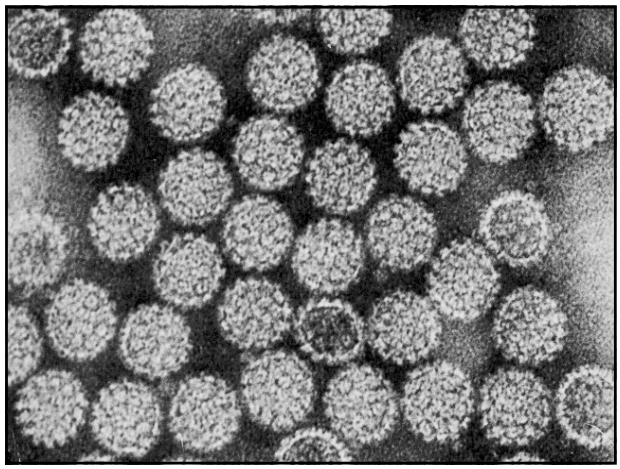


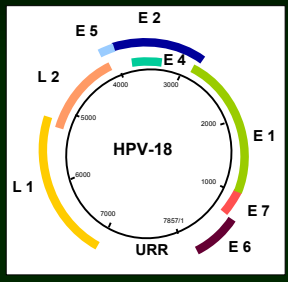
HCV-Phylogenetic tree
From: Simmonds et al., 2005

A vaccine against hepatitis C virus infections is not yet available.

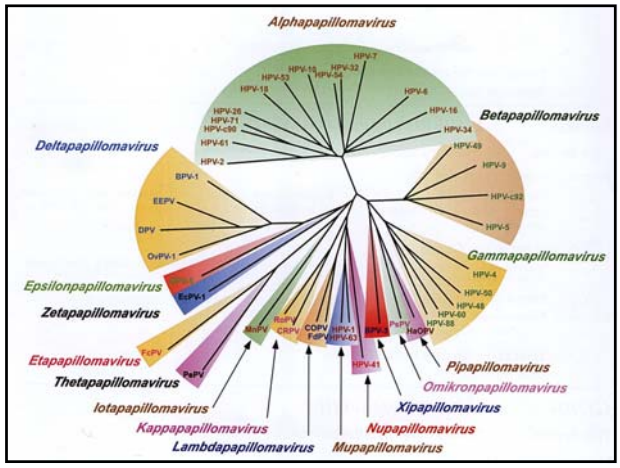
Some hope for a preventive vaccine arises from observations in HCV-convalescent humans and chimpanzees who are protected against re-infection by the same virus.

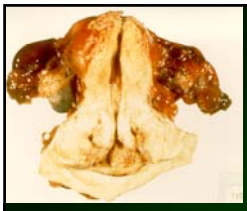
A major problem is posed by the type heterogeneity and a lack of cross-protection against types from other subgroups





viral oncogenes: E6, E7 and E5





High Risk HPV Are the Primary Cause of Cervical Cancer because:

1. Viral genes (E6/E7) are present and uniformly active in cervical cancer cells
2. The E6/E7 genes possess growth-promoting and transforming activity.
3. The malignant phenotype of cervical cancer cells depends on the expression of the viral oncogenes.
4. Epidemiological prospective and case / control studies identify high risk HPV as the major risk factor for cervical cancer

Type of cancer	Papillomavirus types involved	Percent HPV-positive
Cervical cancer	**16**, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 (26, 68, 73, 82)	>95%
Vulva carcinoma		
basaloid	16, 18	>50%
„warty“	16, 18	>50%
keratinizing	16	<10%
Penile carcinoma		
basaloid	16, 18	>50%
„warty“	16, 18	>50%
keratinizing	16	<10%
Vaginal carcinoma	16, 18	>50%
Anal cancer	16, 18	>70%
Oral cavity and tonsils	16, 18, 33	~25%
Nail bed	16	~70%