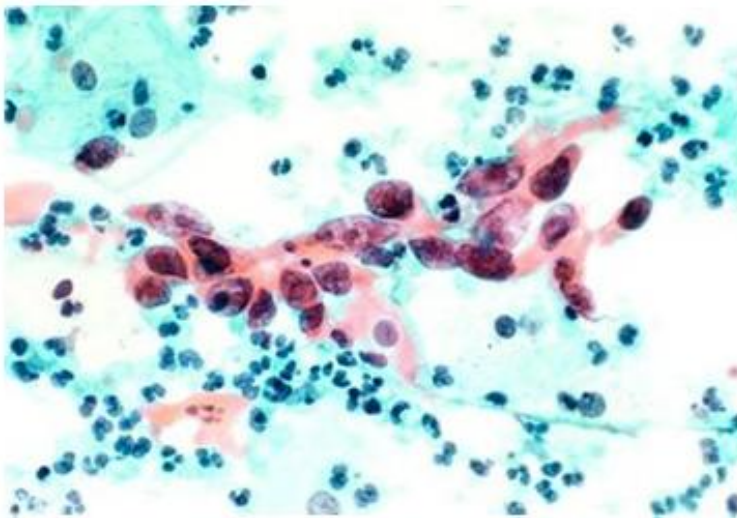
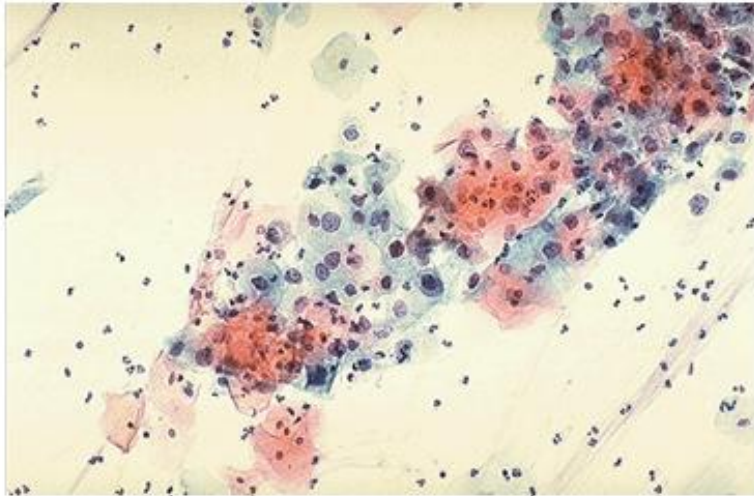
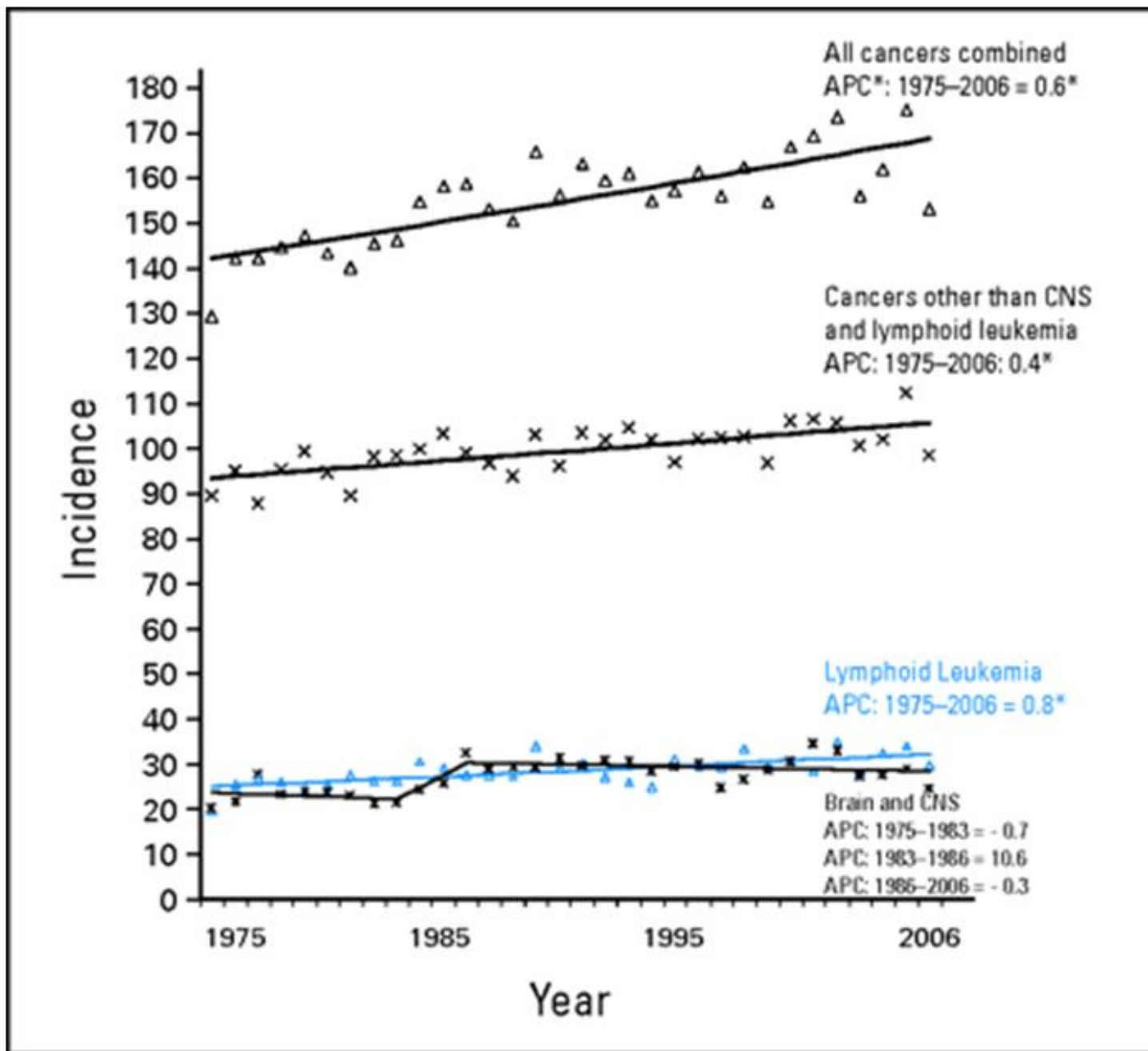


Cancer Prevention as a Challenge for Global Health

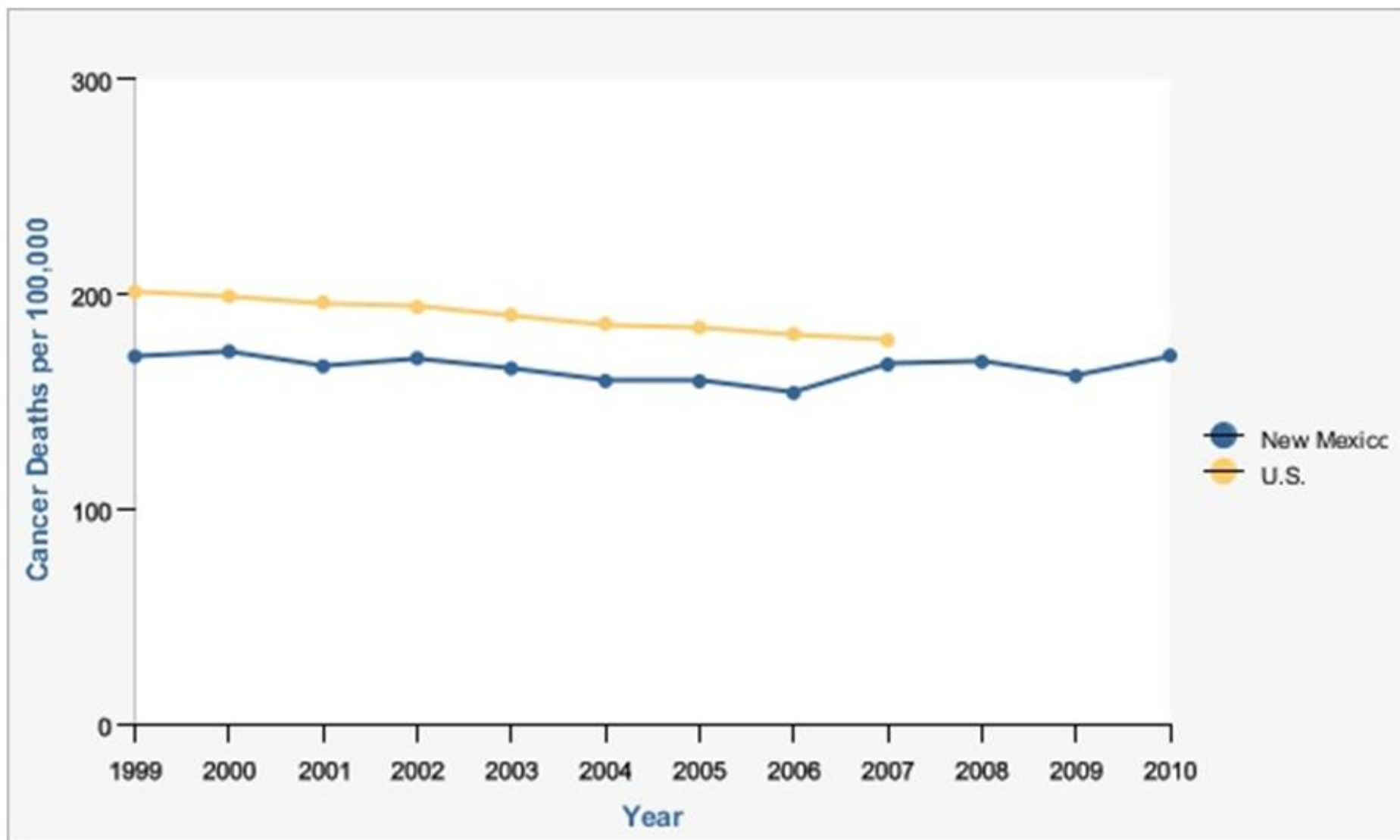
Harald zur Hausen, Deutsches Krebsforschungszentrum
Heidelberg, Germany



Georgios Papanicolaou



Source. SEER 9 USA Statistics



Cancer mortality slightly reduced (USA)

Source`SEER 9 Statistics USA

We are slowly progressing in reducing cancer mortality,

But we lose in reducing cancer incidence (morbidity).

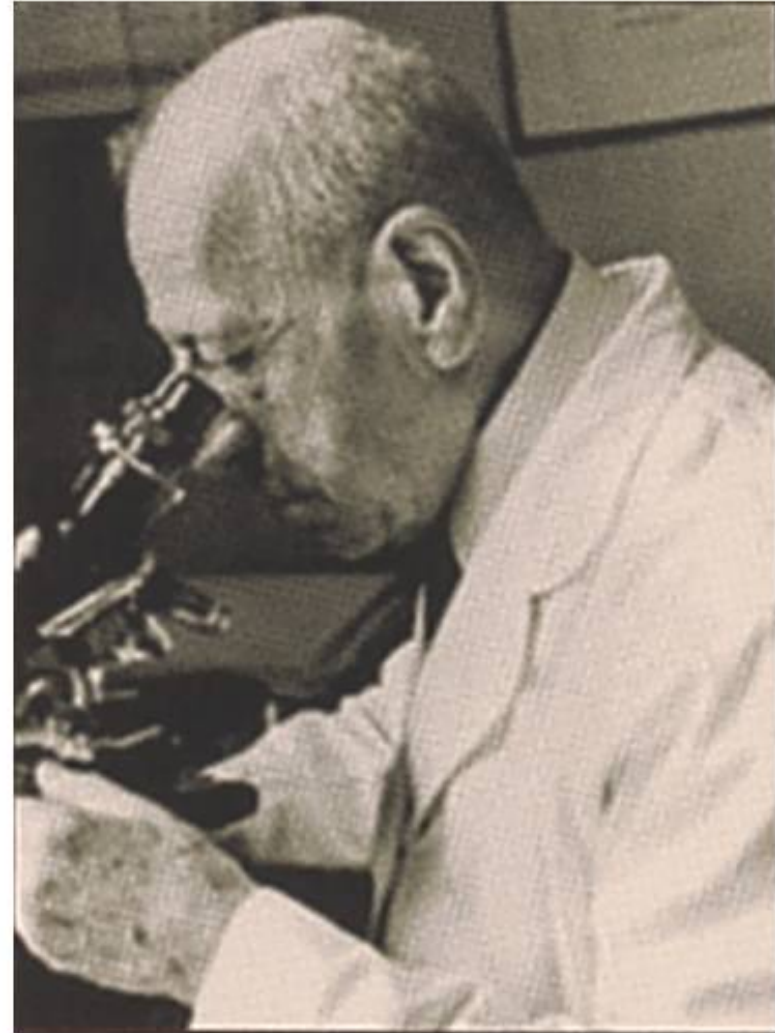
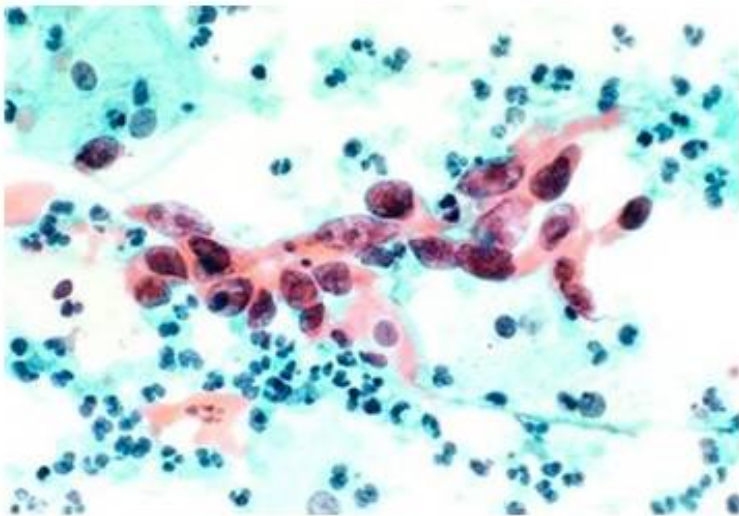
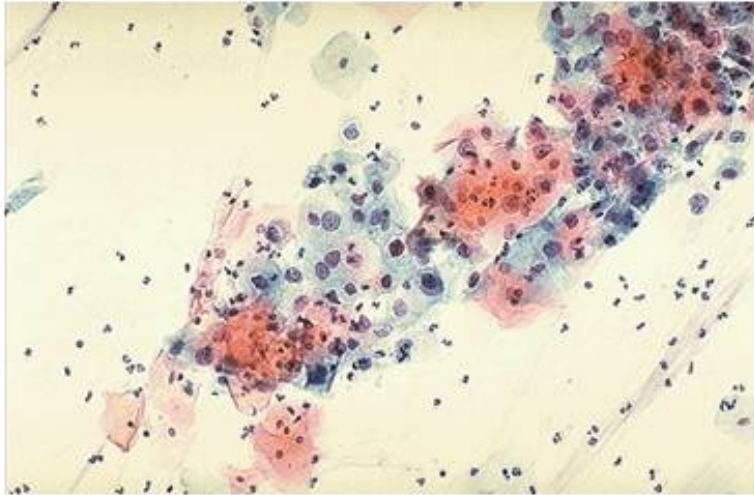
Cancer therapy

Cancer incidence increases globally largely due the worldwide consistent increase in life expectancy.

Slightly more than 50% of human cancers can be cured due to therapeutic interference. The number of therapeutic Interventions, however, increases continuously.

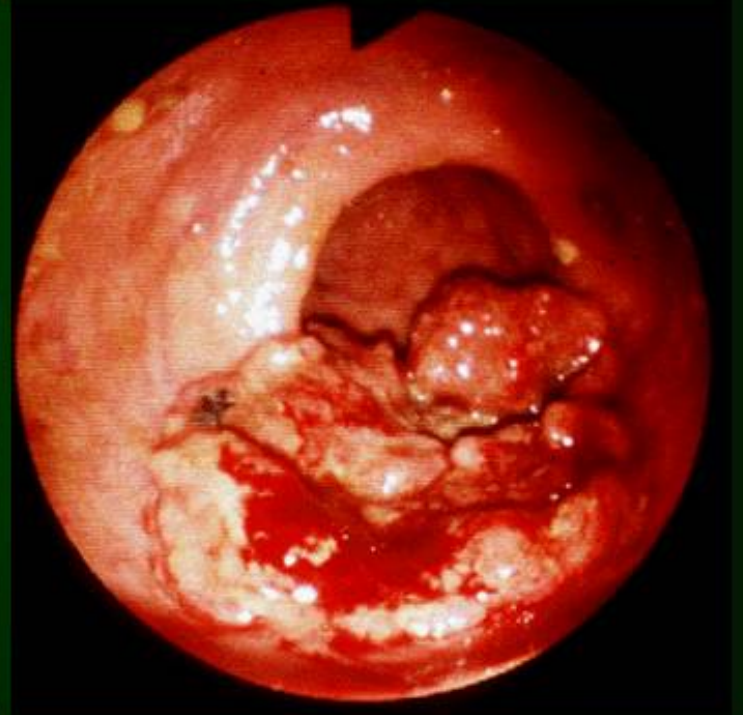
Early diagnosis substantailly reduces the extent of interventions. In certain cancers it results in significant reduction of invasive growth

Surgical intervention after identification of cancer precursor lesions frequently prevents cancer (secondary prevention)



**Georgios Papanikolaou
1883-1962**

Colorectal Cancer



Cancer prevention



Early detection



Cancer therapy



Rehabilitation

Primary prevention avoids the development of cancer and its precursor lesions

A significant reduction of the global cancer epidemic can only be achieved by an efficient primary prevention of cancer.

This requires a change in mentality primarily among physicians, but also among other health officials and health organizations

Cancer prevention (primary prevention) is most cost effective for our society, will be least wearing and will certainly result in long-lasting effects.

It prevents grave and serious interventions and costly subsequent care.

If we wish to achieve an effective long-time control of cancer, then this area of cancer research requires special attention

**Primary cancer prevention requires
the understanding of cancer causes**

**Research in cancer causation is
application-oriented basic research**

Avoidable risk-factors for cancer development:

Change of lifestyle:

Tobacco smoking



No physical exercise



Obesity

Excessive alcohol consumption

Intensive sun exposure

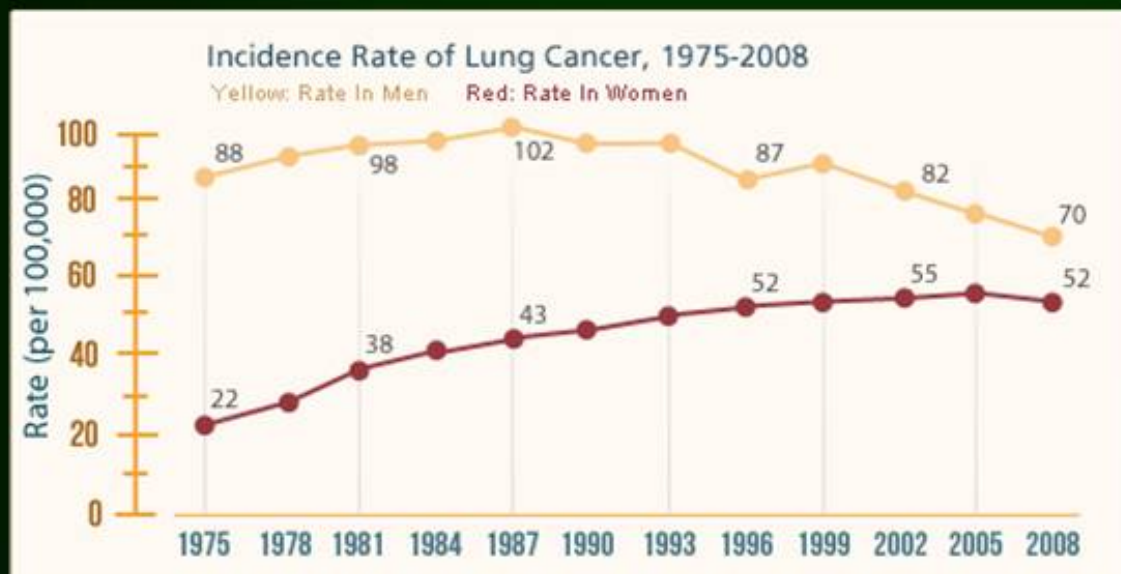


Occupational carcinogens

Tobacco smoking:

Tobacco smoking was initially recognized **in the 1940s by Müller** in Germany as risk factor for lung cancer. In the 1950s **Richard Doll in Oxford and Ernest Wynder in New York** published epidemiological studies on lung cancer causation by smoking.

It took almost 50 years before aggressive advertising against smoking and other restrictive interventions finally revealed effectiveness. At least in males in USA this resulted by now in a significant reduction of lung cancer incidence.



Effective primary prevention is presently possible

For additional specific common human cancers



Some cancer-inducing infections

Diet: e.g. consumption of „red“ meat

**Barely avoidable
cancer risk factors**



**Spontaneous mutations e.g. caused by
environmental carcinogens, radon- and
ionizing radiation**

Hereditary cancer risk factors

**Metabolic diseases with increased
cancer risk (e.g. diabetes)**

Others.....

**Primary prevention of cancer by successful
treatment of persisting infections**

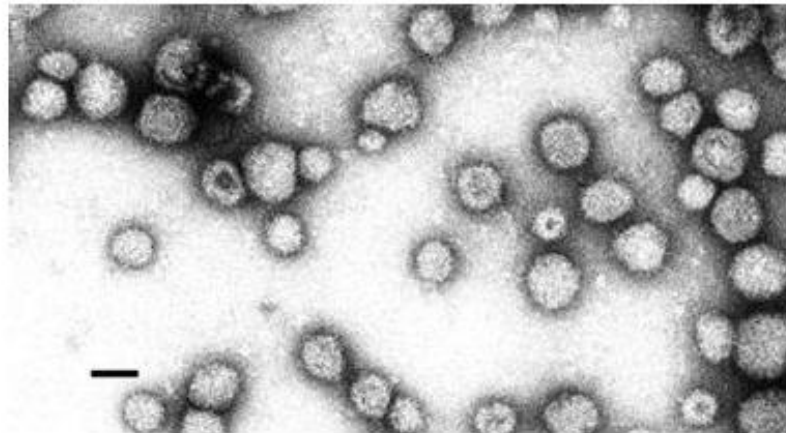
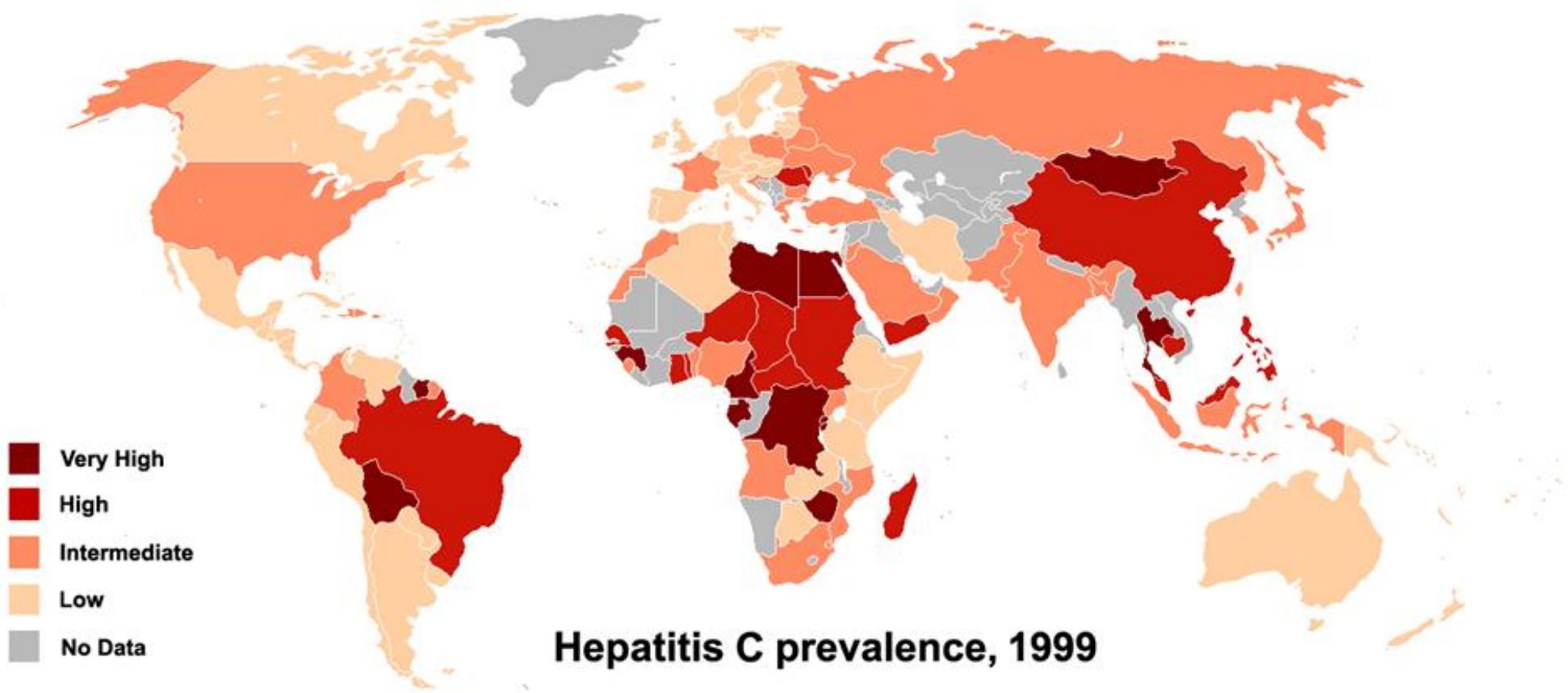
Examples:

Hepatitis C

Schistosoma and liver fluke infections

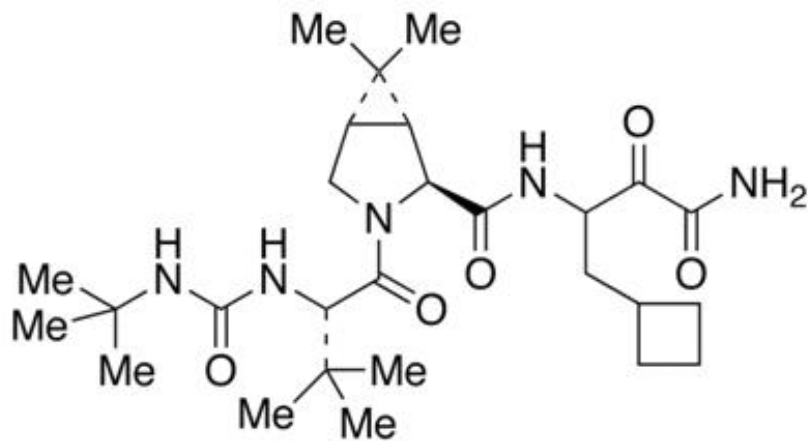
Helicobacter pylori

Human immunodeficiency viruses

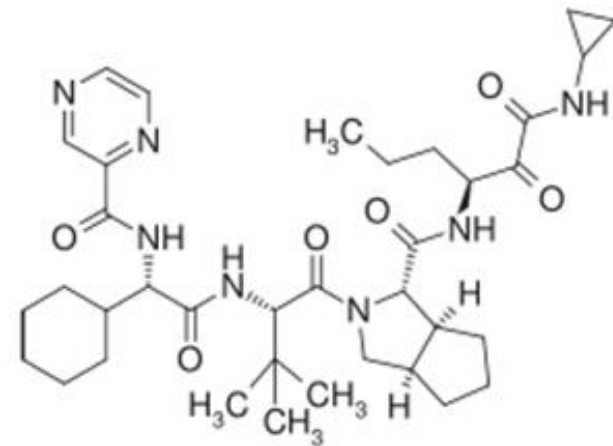


Combining either [boceprevir](#) or [telaprevir](#) with [ribavirin](#) and [peginterferon](#) alfa improves antiviral response for hepatitis C genotype 1.

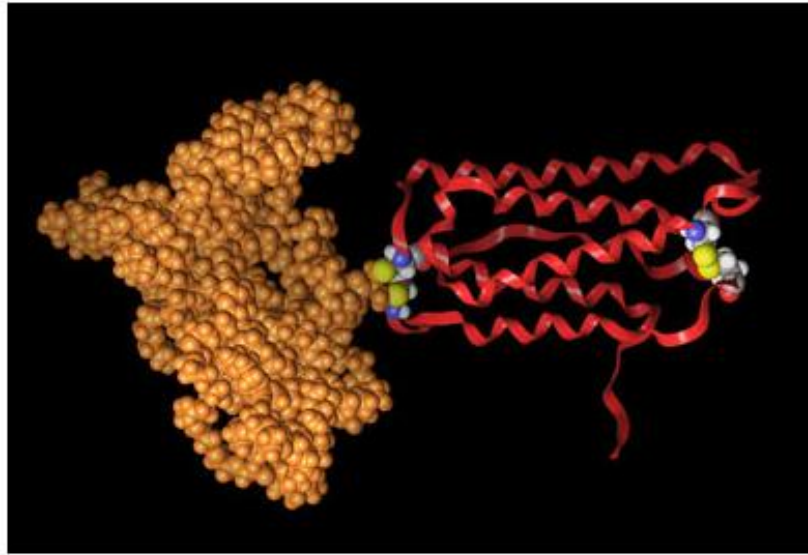
Boceprevir and telaprevir inhibit the virale NS3.4A-protease of Hepatitis C virus (HCV) genotype 1, by reversibly binding to a serine group in the active center of the protease.



Boceprevir

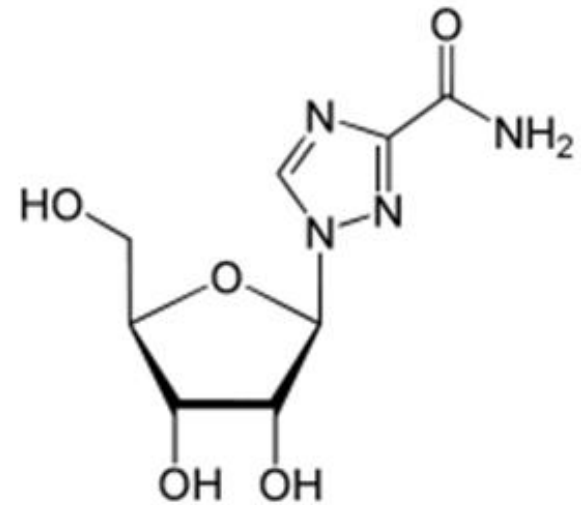


Telaprevir



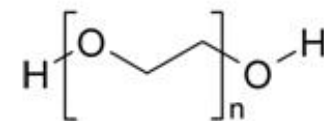
Pegylated interferon

(PEG)



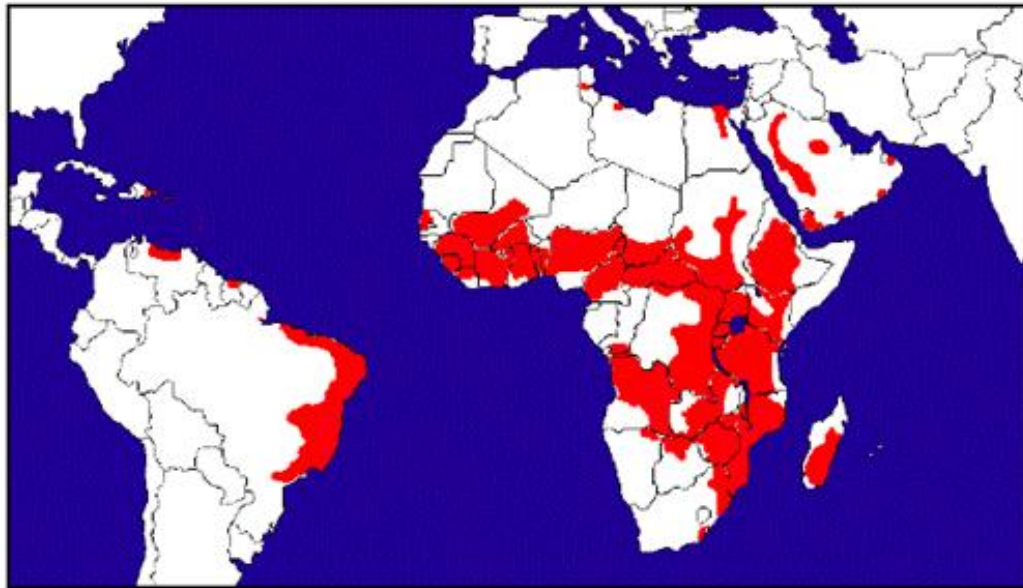
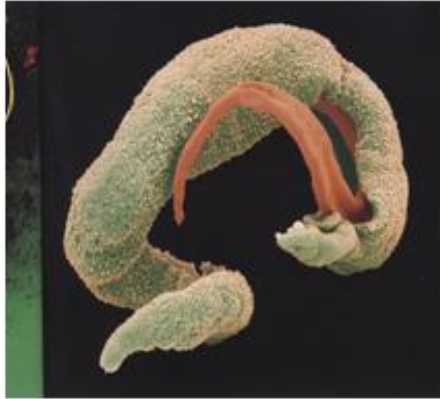
Ribavirin

Pegylation is the process of covalent attachment of [polyethylene glycol](#) (PEG) increase the hydrodynamic size (size in solution) of the agent which prolongs its circulatory time by reducing [renal](#) clearance.

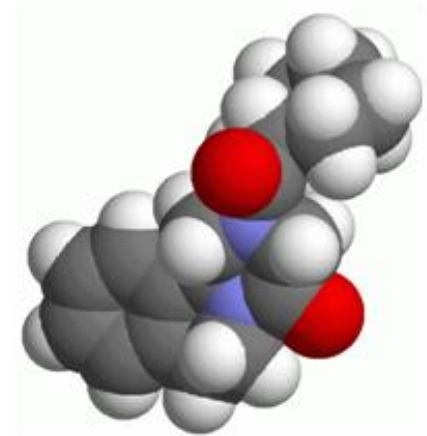
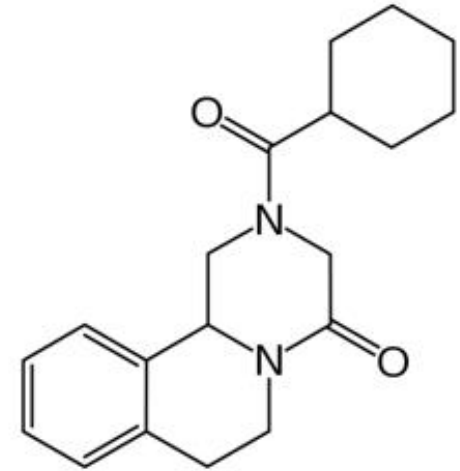


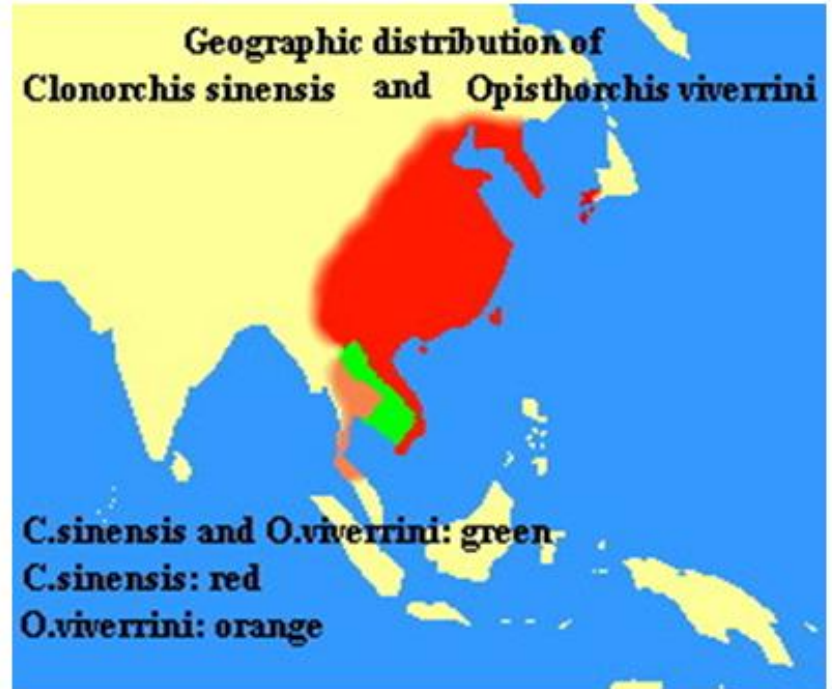
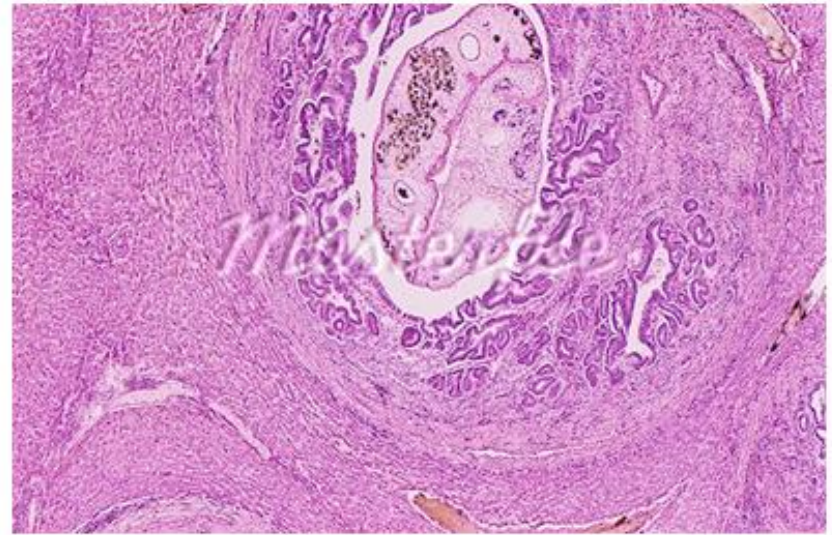
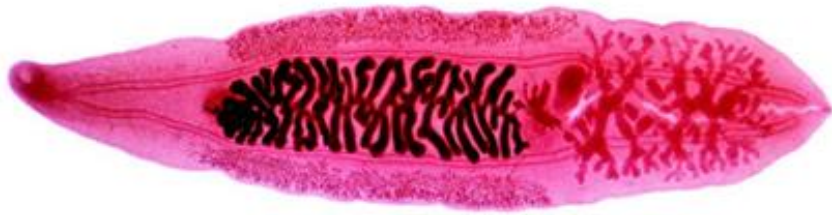
PEG

Schistosoma haematobium causes bladder cancer

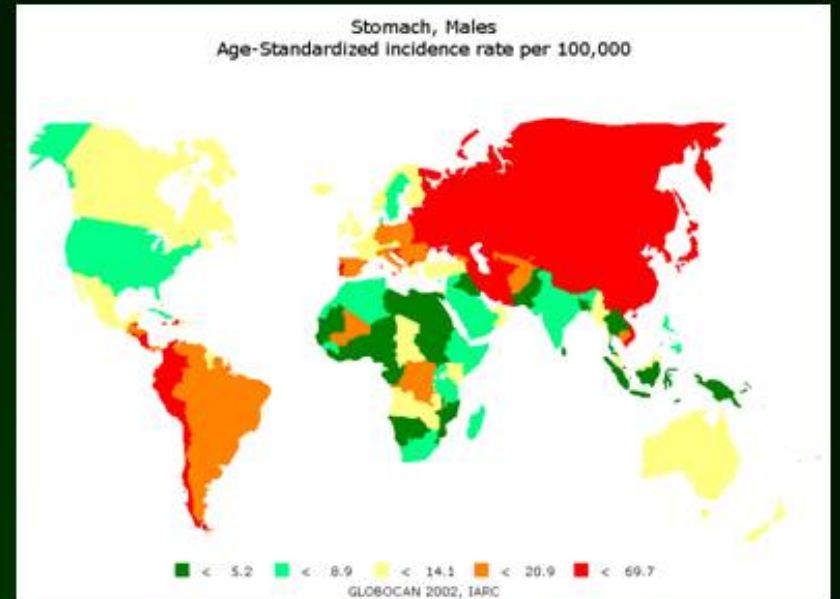
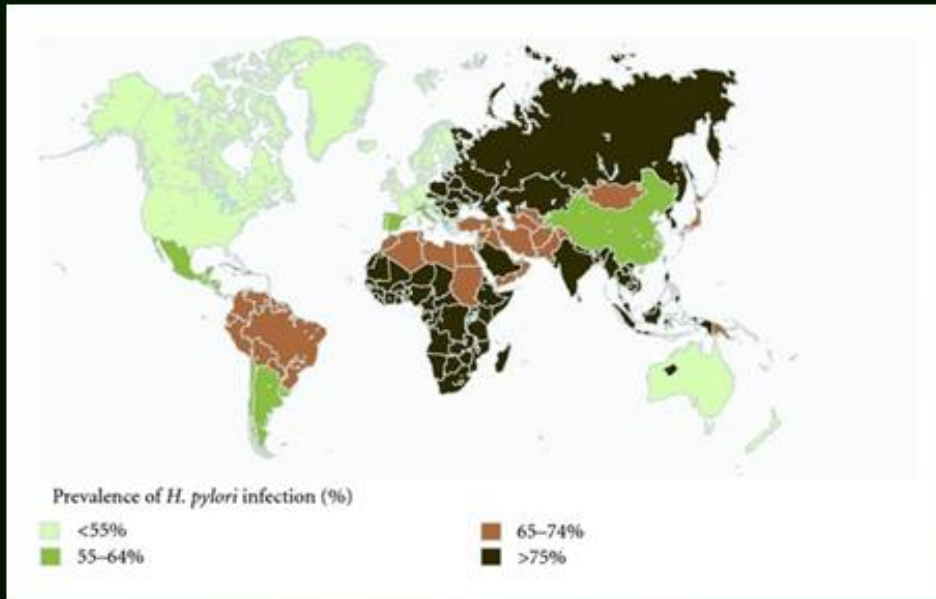


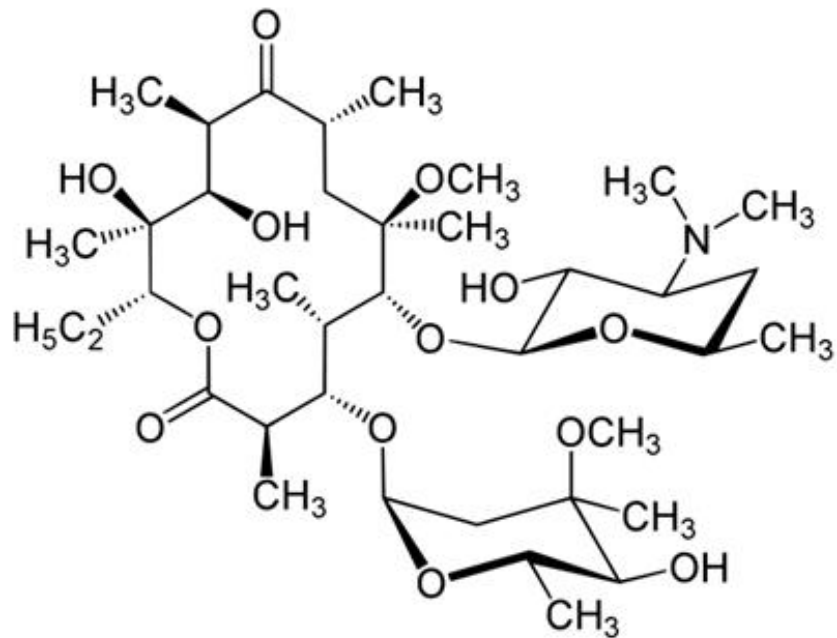
Praziquantel



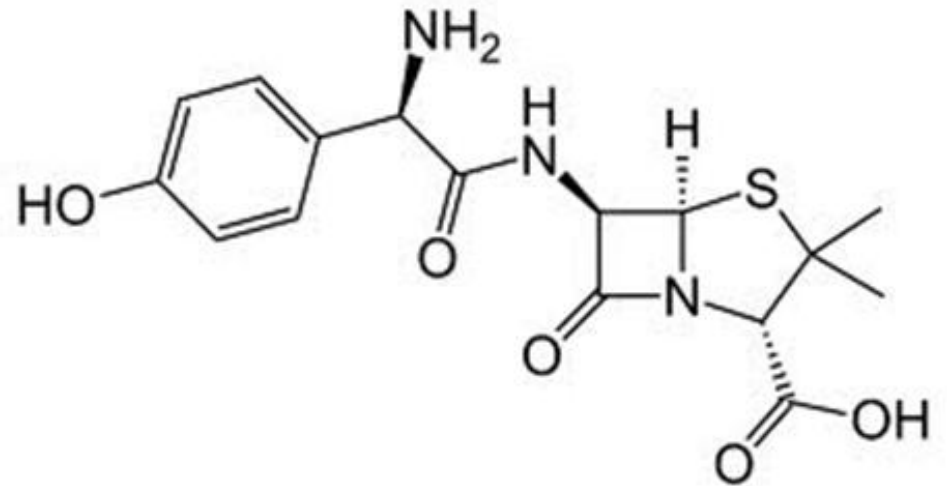


Clonorchis sinensis and Opisthorchis viverrini

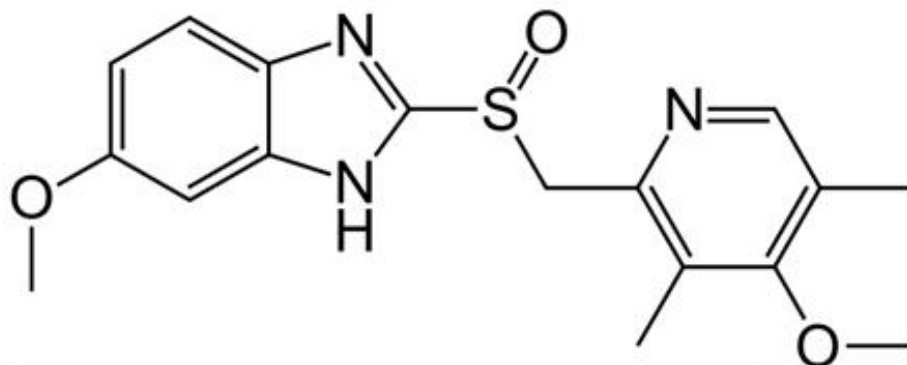




Clarithromycin

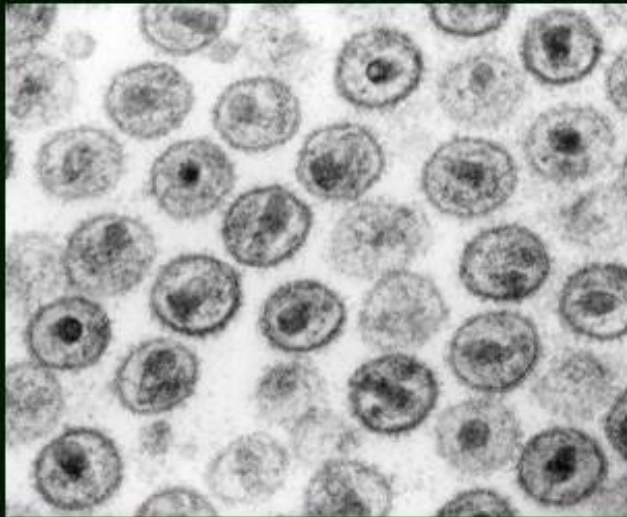


Amoxicillin



Omeprazol (proton pump inhibitor)

**Triple therapy to eradicate
Helicobacter pylori infections
and to treat peptic ulcers.**



Human immunodeficiency infections activate latent Epstein-Barr virus and Kaposi's sarcoma-associated Herpesvirus (HHV-8) resulting in Kaposi's sarcomas and B-lymphomas

Medscape



KS age standardized incidence in males per 100,000: ■ <1 ■ 1-4 ■ 4-22 ■ >22



KSHV seroprevalence rates: ■ <10 ■ 10-20 ■ 30-40 ■ >40 (% positive)

Source: Nat Rev Cancer © 2010 Nature Publishing Group

Highly active anti-retroviral therapy, or HAART

e.G. **Tenofovir /emtricitabine** (a combination of two **NRTIs**, **Ritonavir**, and **Atazanavir**, both latter are protease inhibitors)

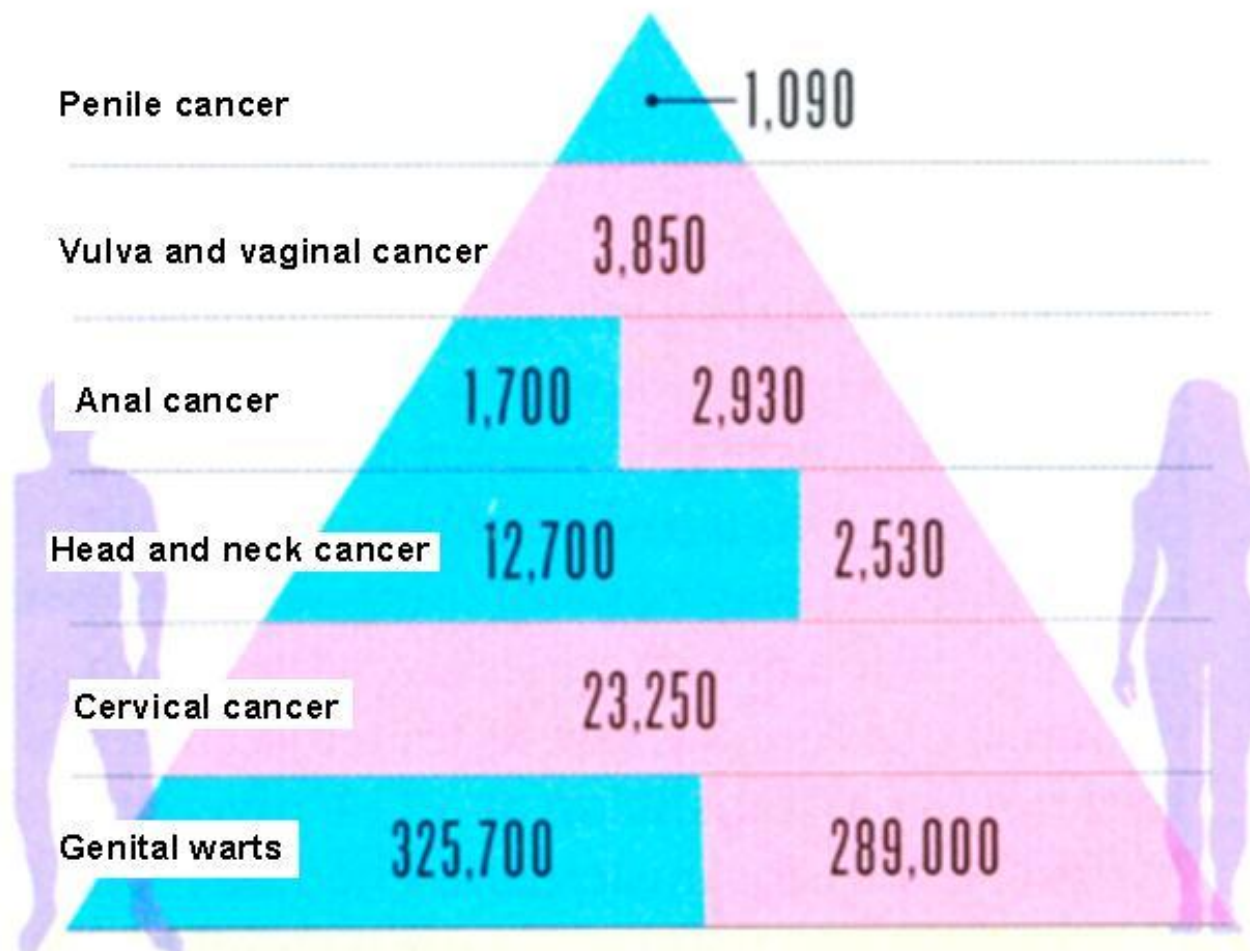
Long-time treatment of AIDS patients with these drugs resulted in a significant reduction of Kaposi's sarcomas and B-cell lymphomas

Prevention of Cancers by Vaccination

A SEX-NEUTRAL BURDEN

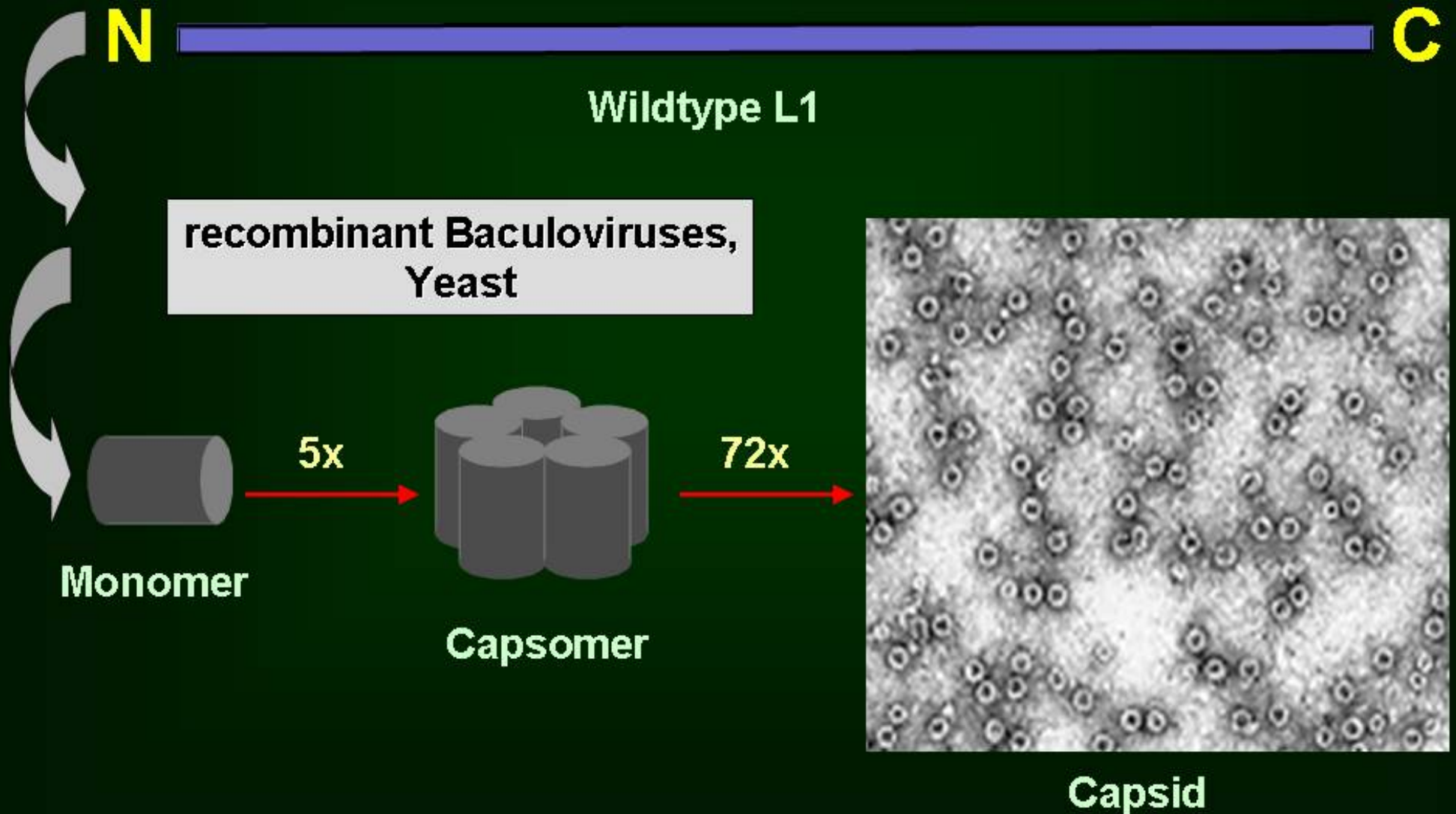
Estimated number of new annual cases of cancers and genital warts in Europe*

Male
Female



* Related to HPV types 6, 11, 16 and 18

HPV L1 VLPs



Results of clinical studies:

- VLP Vaccines induce **high antibody titers**, even without addition of adjuvants;
- Titers are commonly at least **10 times higher** as in **natural infections**;
- **Antibodies persist** for prolonged periods of time;
- **No significant side effect** have been observed;
- **The protective effect for previously not exposed women comes close to 100%** (prevention of infection, prevention of cervical precursor lesions).

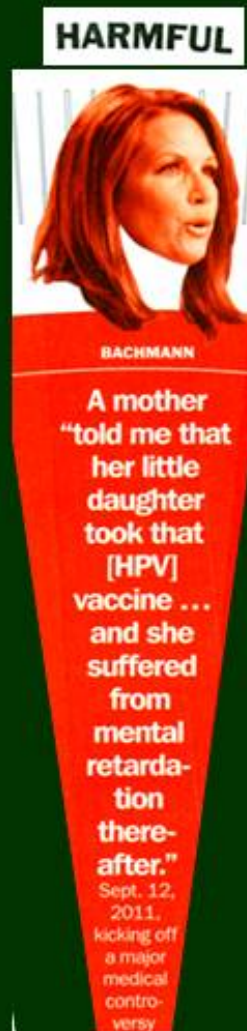
Discussed and Open Questions:

- Which age groups should be vaccinated? Only girls between 9 and 17 or 25 years of age?
- Should vaccination only be applied to PCR- and antibody negative women or is it advisable also for a previously not tested female population?
- **Should the vaccine also be applied to boys and young adult males?**
In case we would only vaccinate boys, in most societies we would probably prevent more cervical cancers than by only vaccinating girls.
- Does vaccination result in a prolongation of intervals for cervical cancer screening?
- Does the application of HPV vaccines to young girls result in earlier sexual activity and increased promiscuity?

The consequences for gynecology / cytology:

- **The screening methods will predictively change in the forthcoming years;**
- **Self-sampling will gradually replace cervical scrapings;**
- **First results are available indicating a better predictive value of HPV testing in comparison to conventional cytology;**
- **Surgical interventions for CIN lesions will substantially decline depending on the percentage of vaccinated women.**

Impact of HPV Vaccination on the USA Presidential Campaign 2012



HPV Vaccine

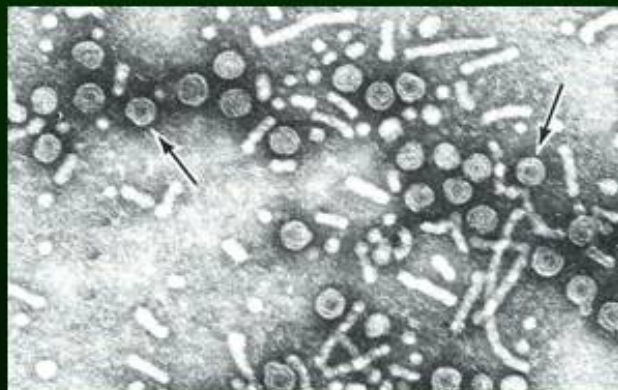
Michele Bachmann attacked Rick Perry in the Republican-primary debate on Sept. 12, 2011, for requiring HPV vaccinations for sixth-grade girls in Texas, then earned criticism for suggesting the next day in a television interview that "that injection" could cause "mental retardation." The American Academy of Pediatrics responded, "There is absolutely no scientific validity to this statement. Since the vaccine has been introduced, more than 35 million doses have been administered, and it has an excellent safety record."

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 30 to 60 years hepatocellular carcinomas may develop, frequently in cirrhotic livers.





Mei-Hwei Chang

**Perinatally vaccinated children reveal a 70% reduced risk for liver cancer in the subsequent 20 years when compared to non-vaccinated control groups
(64 vs. 444 cases)**

**Decreased incidence of hepatocellular carcinoma
In hepatitis B vaccinees: a 20-year follow-up study.**

Chang MH et al.

J Natl Cancer Inst. 2009,101: 1348-1355.

Increased risk for colon cancer – a possible link to infections?

?

?

?



Are there animal pathogenic viruses **non-permissive for replication in human cells, but carcinogenic in humans** ?



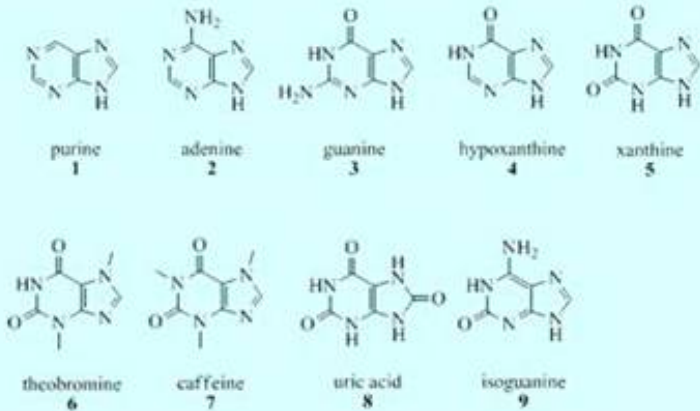
A number of **human pathogenic viruses** (e.g. BK, JC, EBV, High risk HPV, adenoviruses) are non-permissive for animal cells, but **induce carcinomas upon inoculation into animals**

Colorectal Cancer: Protective and Risk Factors

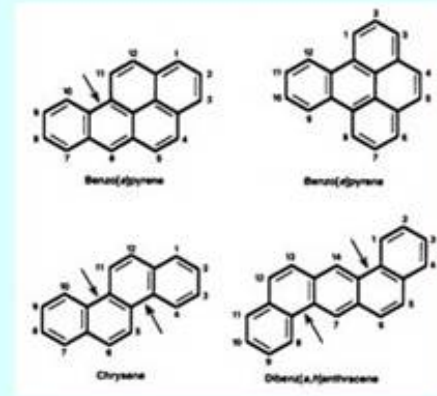
	DECREASES RISK	INCREASES RISK
Convincing	Physical activity ^{1 2}	<div style="border: 1px solid red; padding: 2px;"> Red meat^{3 4} Processed meat^{4 5} </div> Alcoholic drinks (men) ⁶ Body fatness Abdominal fatness Adult attained height ⁷
Probable	Foods containing dietary fibre ⁸ Garlic ⁹ Milk ^{10 11} Calcium ¹²	Alcoholic drinks (women) ⁶
Limited — suggestive	Non-starchy vegetables ⁹ Fruits ⁹ Foods containing folate ⁸ Foods containing selenium ⁸ Fish Foods containing vitamin D ^{8 13} Selenium ¹⁴	Foods containing iron ^{4 8} Cheese ¹⁰ Foods containing animal fats ⁸ Foods containing sugars ¹⁵
Limited — no conclusion	Cereals (grains) and their products; potatoes; poultry; shellfish and other seafood; other dairy products; total fat; fatty acid composition; cholesterol; sugar (sucrose); coffee; tea; caffeine; total carbohydrate; starch; vitamin A; retinol; vitamin C; vitamin E; multivitamins; non-dairy sources of calcium; methionine; beta-carotene; alpha-carotene; lycopene; meal frequency; energy intake	

Chemical carcinogens, produced during broiling, roasting, frying, or curing are considered as main risk factors

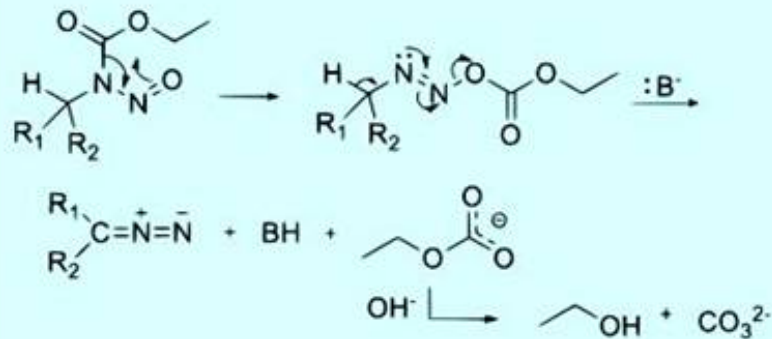
They produce cancers in rodents if applied in 1.000 or 10.000 fold higher concentrations



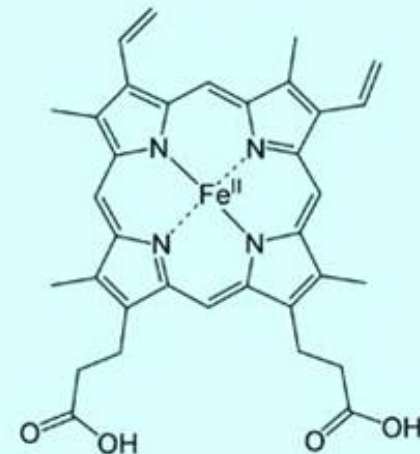
Heterocyclic aromatic amines



Polycyclic aromatic hydrocarbons



N-Nitroso compounds

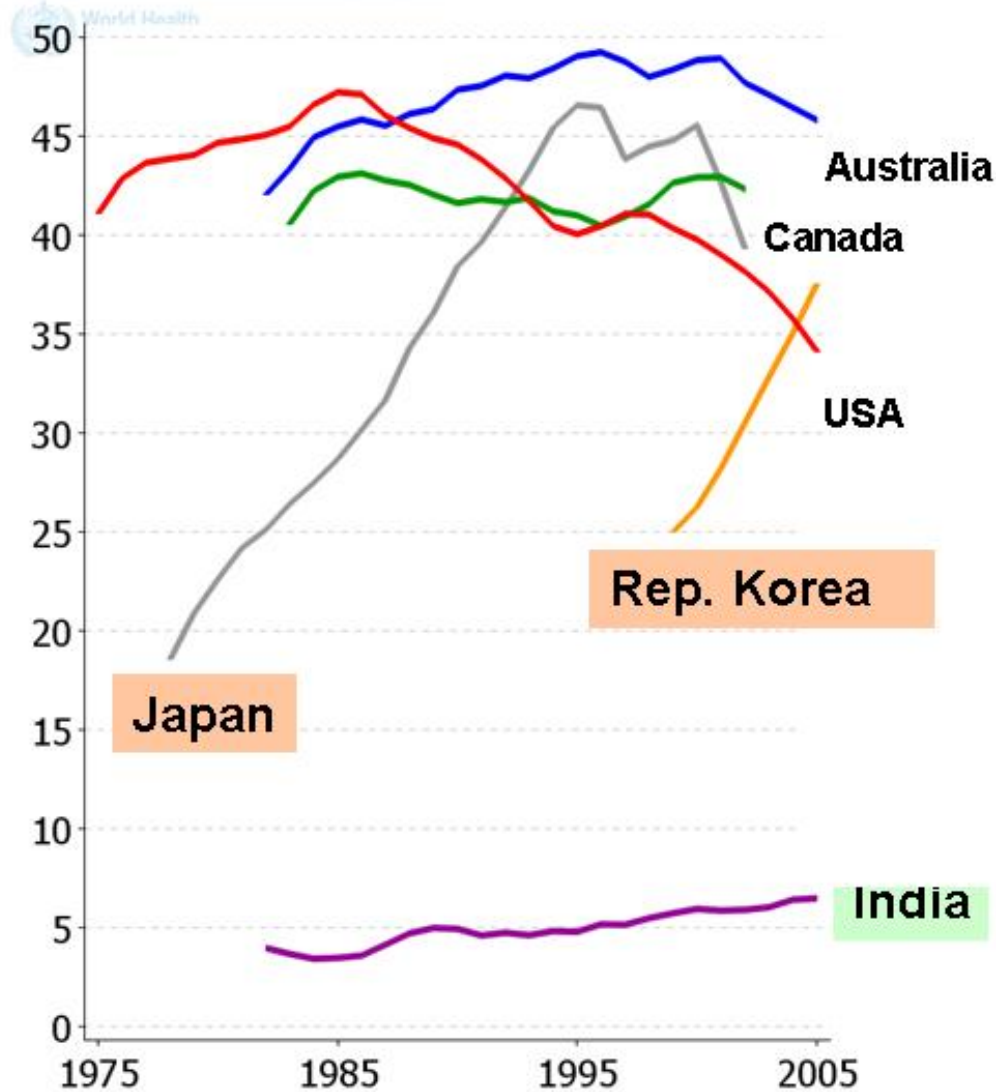


Heme iron

Yet, “white” meat, specifically the consumption of fried, grilled or smoked chicken and fish, is considered as relatively “safe”.

This in spite of the production of similarly high concentrations of heterocyclic aromatic hydrocarbons in the cooking or smoking process.

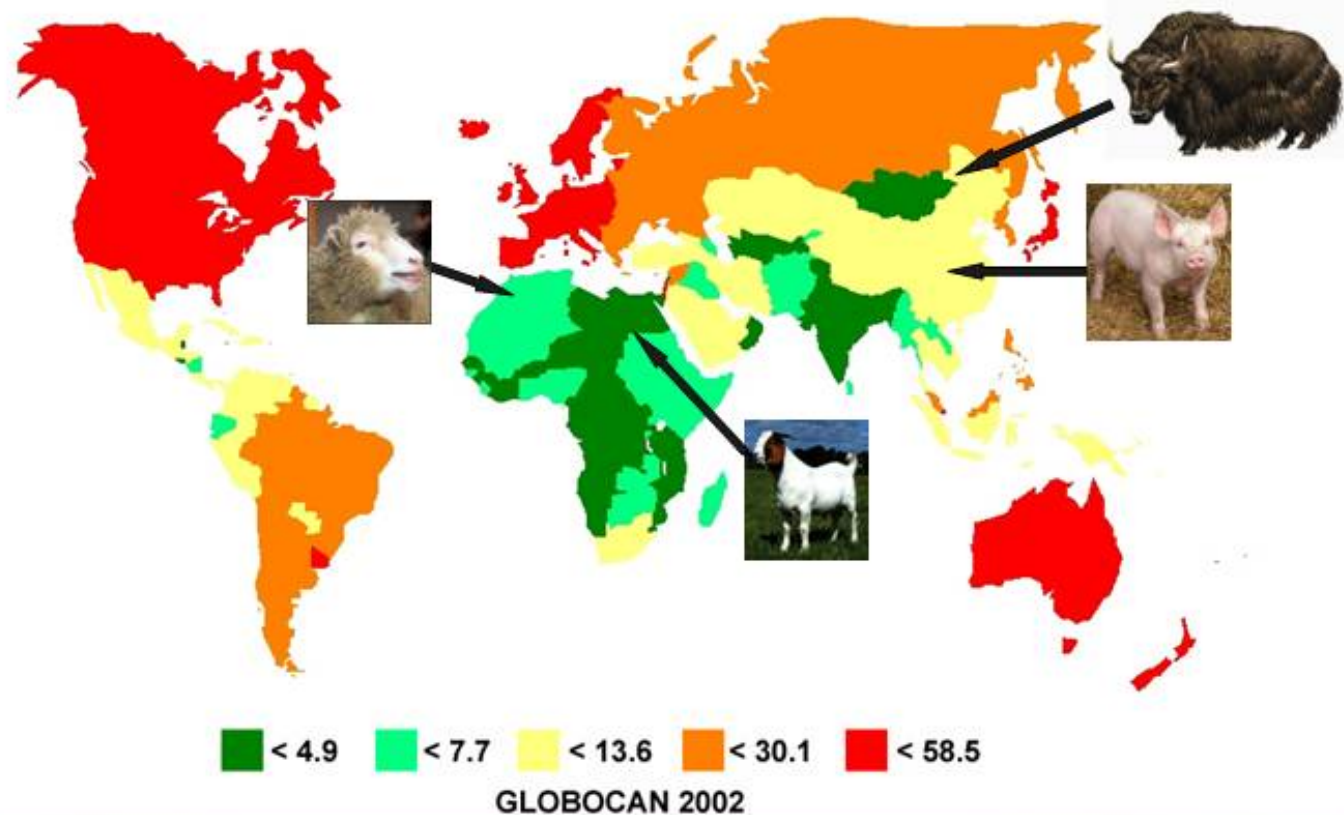




Colorectal cancer Incidence



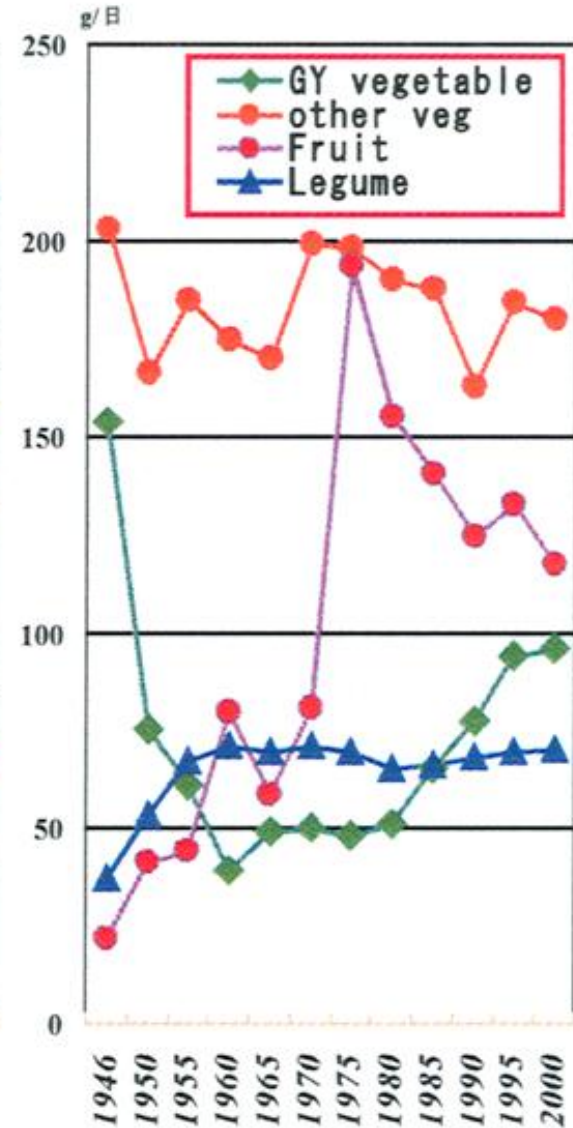
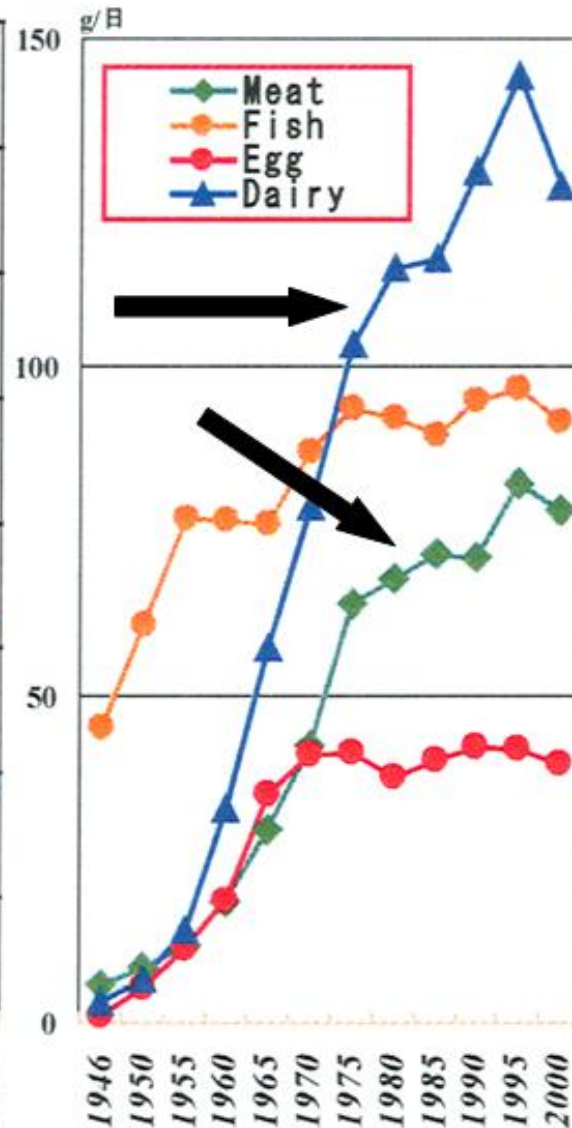
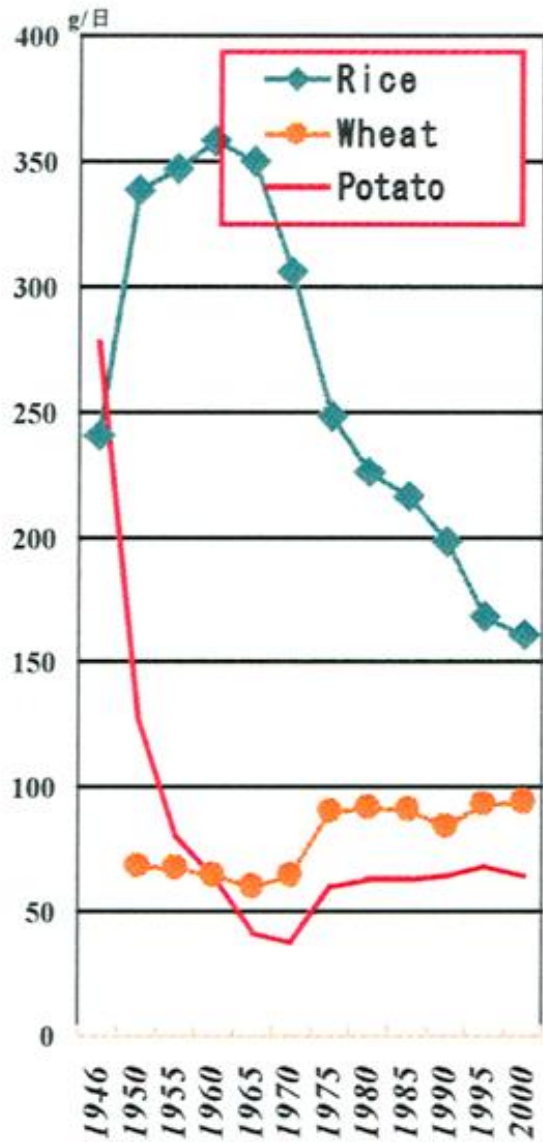
Incidence of Colon and rectum cancer: ASR (World)-Male (All ages)



The higher risk for colorectal cancer after red meat consumption appears to be mainly restricted to beef (*Bos taurus*) diet.

*In some countries the risk is relatively low, in spite of a high proportion of pork (China), mutton (Arabic countries) or Yak (*Bos mutus*) meat (Mongolia) in the diet.*

Dietary Changes in Japan



Dietary changes after World War II in Japan. Decreased rice and increased meat consumption are noteworthy.

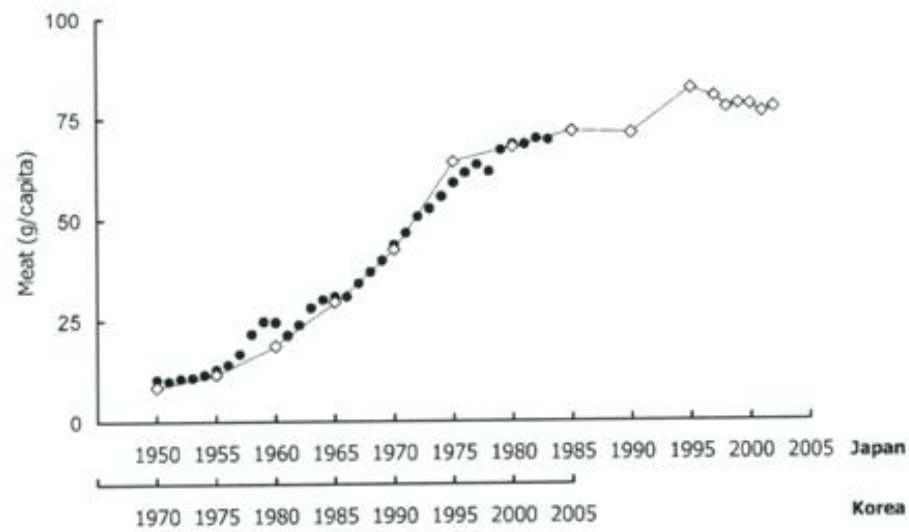


Figure 1 Daily meat consumption in Korea (1970–2003) and Japan (1950–2002). (●), Korea; (◊), Japan.

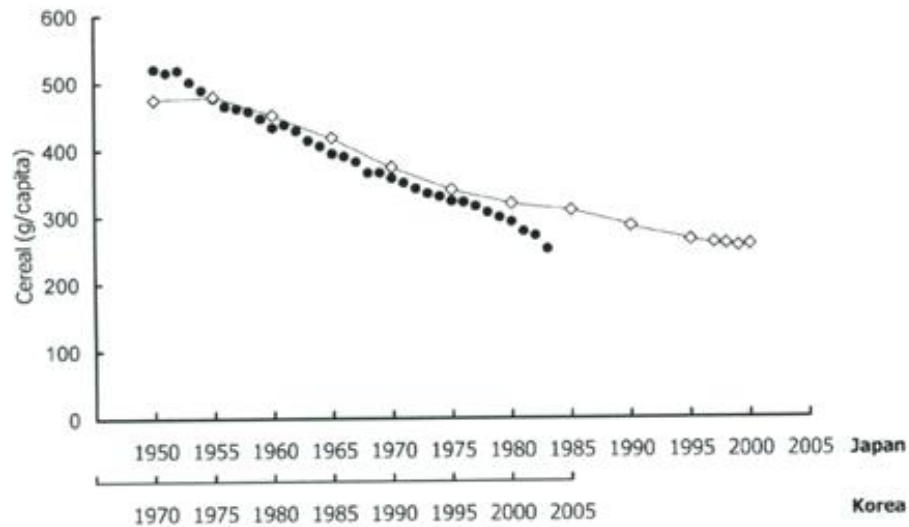
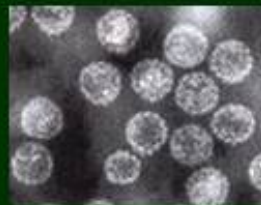
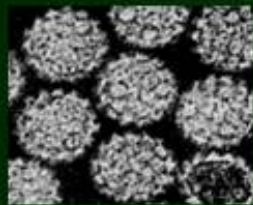


Figure 2 Daily cereal consumption in Korea (1970–2003) and Japan (1950–2002). (●), Korea; (◊), Japan.



**Polyomaviruses, papillomaviruses, and single-stranded DNA viruses
may survive in a protein environment temperatures of up to
80° C for 30 minutes or longer**



**In the better studied humans up to now 10 distinct Polyomavirus types
have been discovered, in cattle thus far only one. Do cattle harbour more
than one polyomavirus type?**

Bovine Viruses Transmissible to Human Cells

Some examples:

A. Potentially carcinogenic and relatively heat-resistant:

Polyomaviruses, Papillomaviruses, Adenoviruses

B. Carcinogenic human members in this virus family:

Herpesviruses, Retroviruses, Flaviviruses

C. Relatively heat-resistant viruses of unknown carcinogenicity:

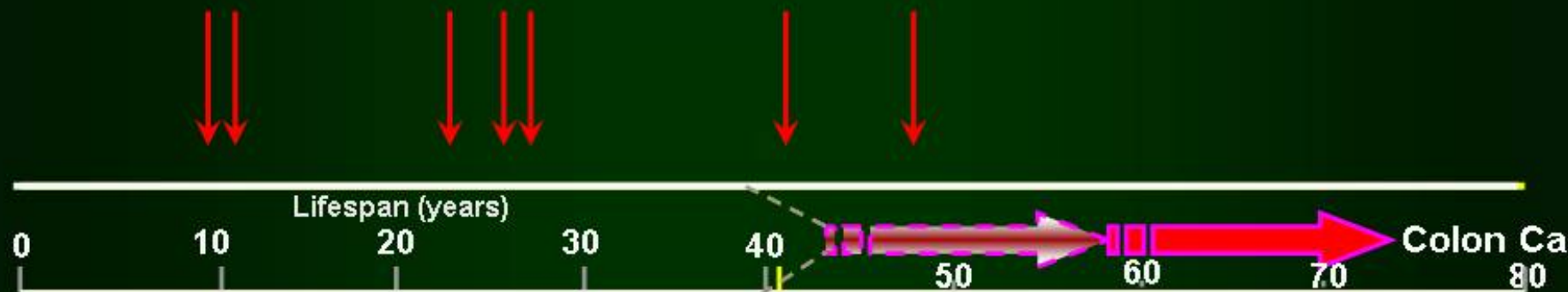
Parvoviruses, Anelloviruses

Additional bovine viruses transmissible to human cells: Bornaviridae, Bunyaviridae, Calici-, Circo-, Coronaviridae, Filoviridae, Orthomyxoviridae, Paramyxoviridae, Picornaviridae, Reo-, Rhabdo- and Togaviridae

**Putative diagram of colon cancer pathogenesis:
non-synchronous interaction and synergism between chemical and biological factors**

**Transient or latent infection by
the putative carcinogenic virus**

Consumption of raw or undercooked red meat (beef)



**Inherited genetic
modifications as
risk factors**

Consumption of cooked or cured red meat (beef)

*Induction of mutations in host cell DNA
by chemical or biological mutagens*

Acquired genetic modifications

Non-oncogenic infections negatively influencing childhood

leukemia risk – a hint for virus / virus interactions ?

Epidemiologic studies indicate that for some cancers their incidence is negatively influenced by infections

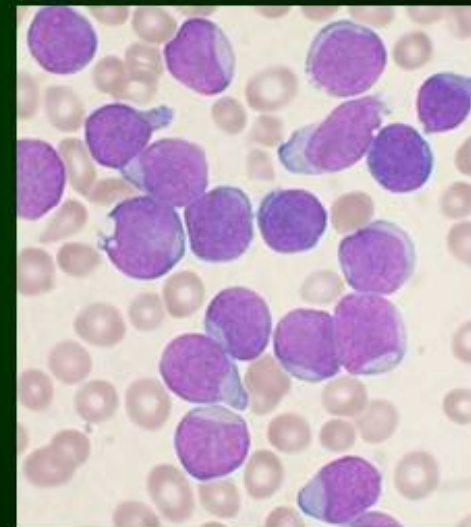
Childhood malignancies

Childhood leukemias

Hodgkin's disease

Childhood brain tumors

neuroblastomas



Repeatedly reported protective factors for childhood leukemias:

Risk factors for childhood leukemias

Multiple infections in early childhood

Rare infections during the first year of life

Underprivileged social status

High socioeconomic status

Crowded household, many siblings

Prenatal chromosomal translocations

Inverse risk with birth order

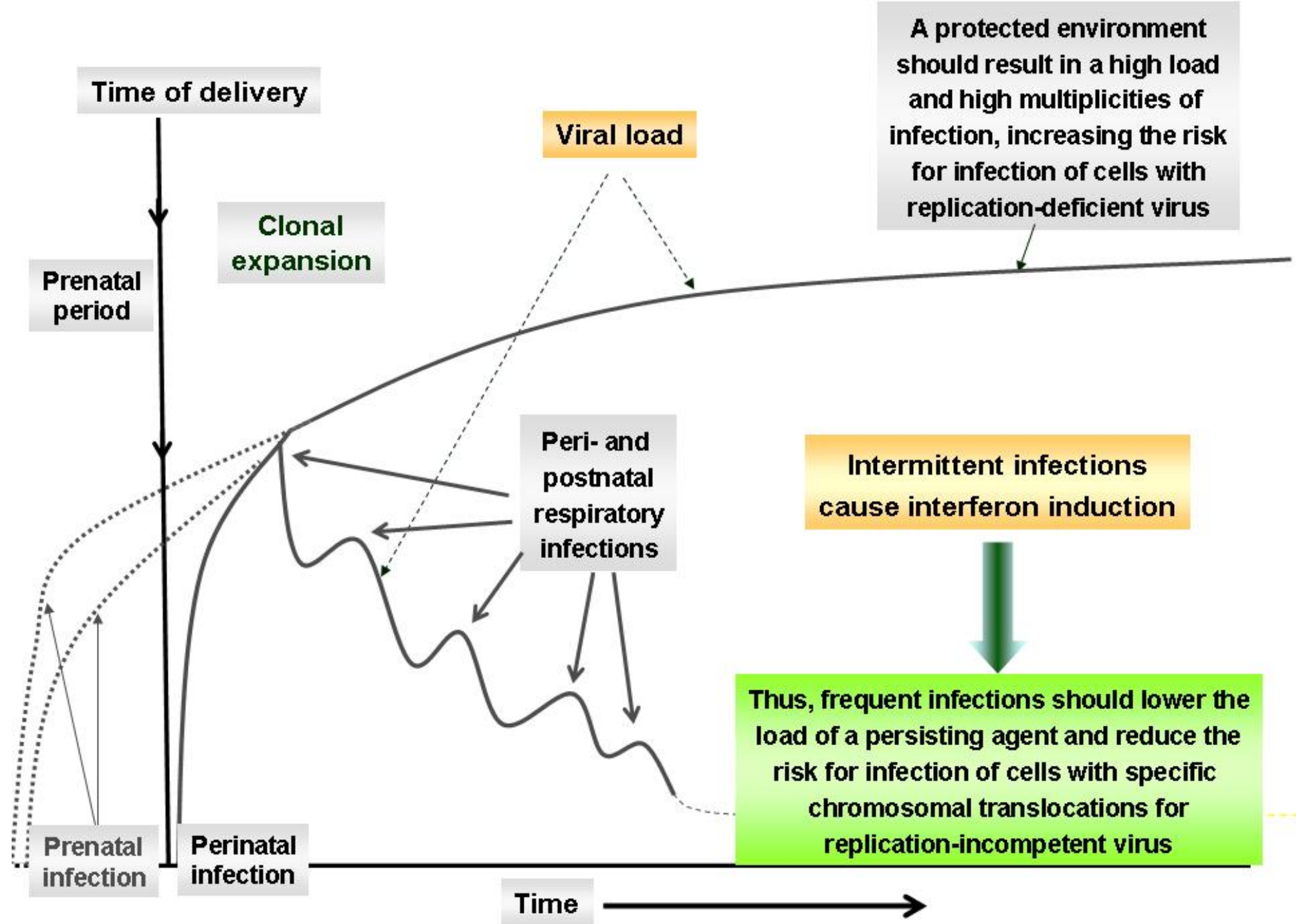
Agricultural occupation of parents

Breast-feeding for more than 6 months

Communicative contacts

Asthma, hay fever, neurodermatitis, contact eczema

Ionizing radiation



A protected environment should result in a high load and high multiplicities of infection, increasing the risk for infection of cells with replication-deficient virus

Intermittent infections cause interferon induction

Thus, frequent infections should lower the load of a persisting agent and reduce the risk for infection of cells with specific chromosomal translocations for replication-incompetent virus

Based on this hypothesis it was rational

- to concentrate the search for infectious agents in childhood leukemias on agents present in peripheral blood cells and in bone marrow
- to look for viruses which respond to human interferons.
- to concentrate on viruses which are also vertically transmitted.

One family of agents fulfilling both criteria are TT viruses

- TT viruses replicate in lymphatic and bone marrow cells
- Treatment of persistently Hepatitis C virus-infected patients with interferon concomitantly reduced the TT virus load
- TT virus DNA can be isolated from umbilical cord blood

**This demonstrates that it remains
important to search for further
infections as risk factors for human
cancers.**

**The identification of infectious
cancer risk factor provides a
realistic basis for primary cancer
prevention**

