Viruses and cancer

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Tumor Viruses

Some naturally occurring tumors in animals are caused by viruses (1908)

Studies of tumor viruses have provided seminal insights into biology and carcinogenesis (e.g. oncogenes, p53)

Viruses are an important cause of cancer in humans

Anti-viral strategies can prevent or treat cancers

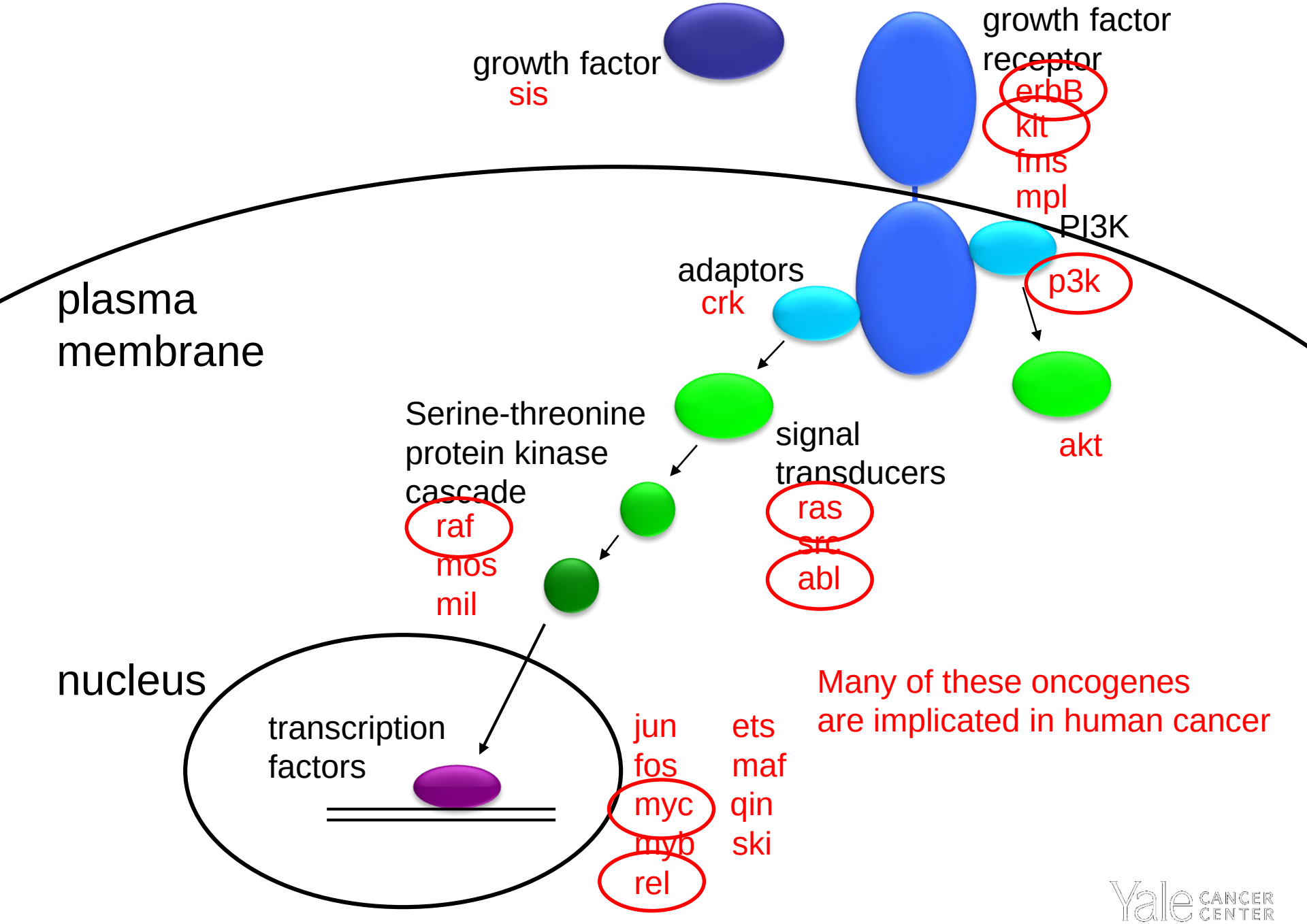
Expression of specific viral genes are sufficient to induce tumor formation

Oncogenes

RNA viruses – retroviruses

DNA viruses –
- polyomaviruses
- papillomaviruses
- herpesviruses

Many retroviral oncogenes encode proteins that comprise cellular growth signaling pathways



These oncogene products are targets for therapy

v-Abl oncogene Bcr-Abl translocation in chronic myelogenous leukemia

Gleevec inhibits tyrosine kinase activity and controls CML

v-ErbB1 oncogene EGF receptor is mutated in lung cancer

Numerous TKI specific for mutant form of EGFR

Braf oncogene Commonly mutated in melanoma

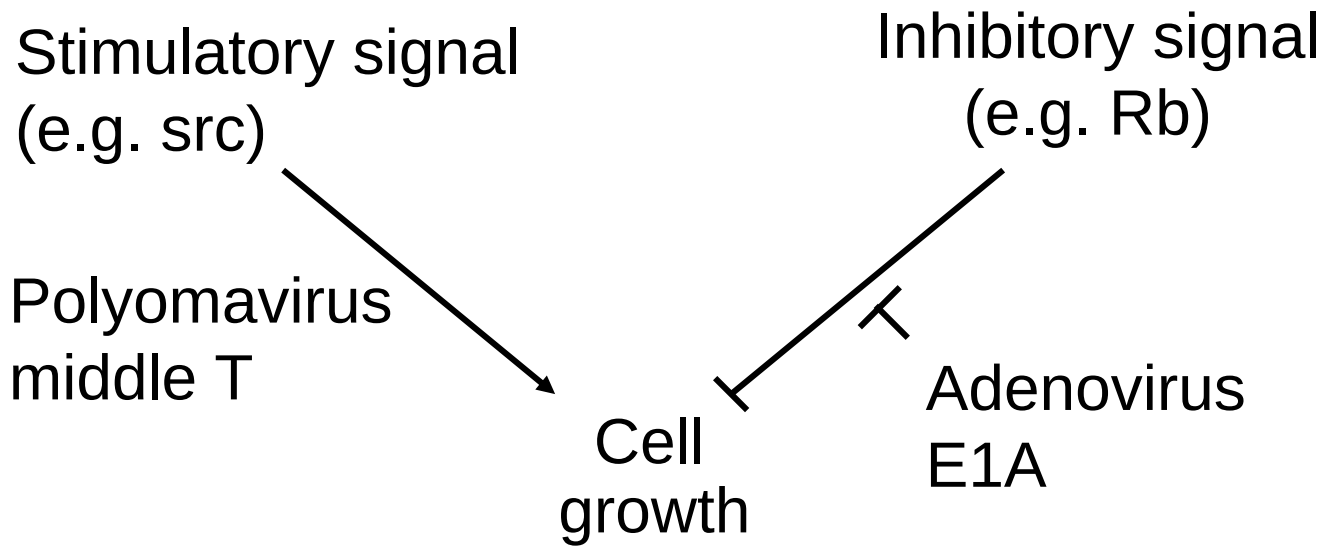
Vemurafemid in patients with these mutations

Responses tend to be short-lived

DNA virus oncogenes products modulate
many of the same pathways
by binding to cellular proteins

Some DNA virus oncoproteins transform cells
by turning on cellular growth stimulatory proteins

Other DNA virus oncoproteins transform cells
by turning off cellular growth inhibitory proteins



Oncoproteins from multiple DNA tumor viruses bind and inactivate same tumor suppressor proteins

Retinoblastoma

- Adenovirus E1A
- Polyomavirus large T antigen
- High-risk HPV E7
- Low-risk HPV bind poorly

p53

- SV40 large T antigen
- Adenovirus E1B 55kDa
- Adenovirus E4orf6
- High-risk HPV E6
- Not low-risk HPV E6

These interactions are important for human cancer

Viruses and human cancer

Difficulties in identifying human tumor viruses

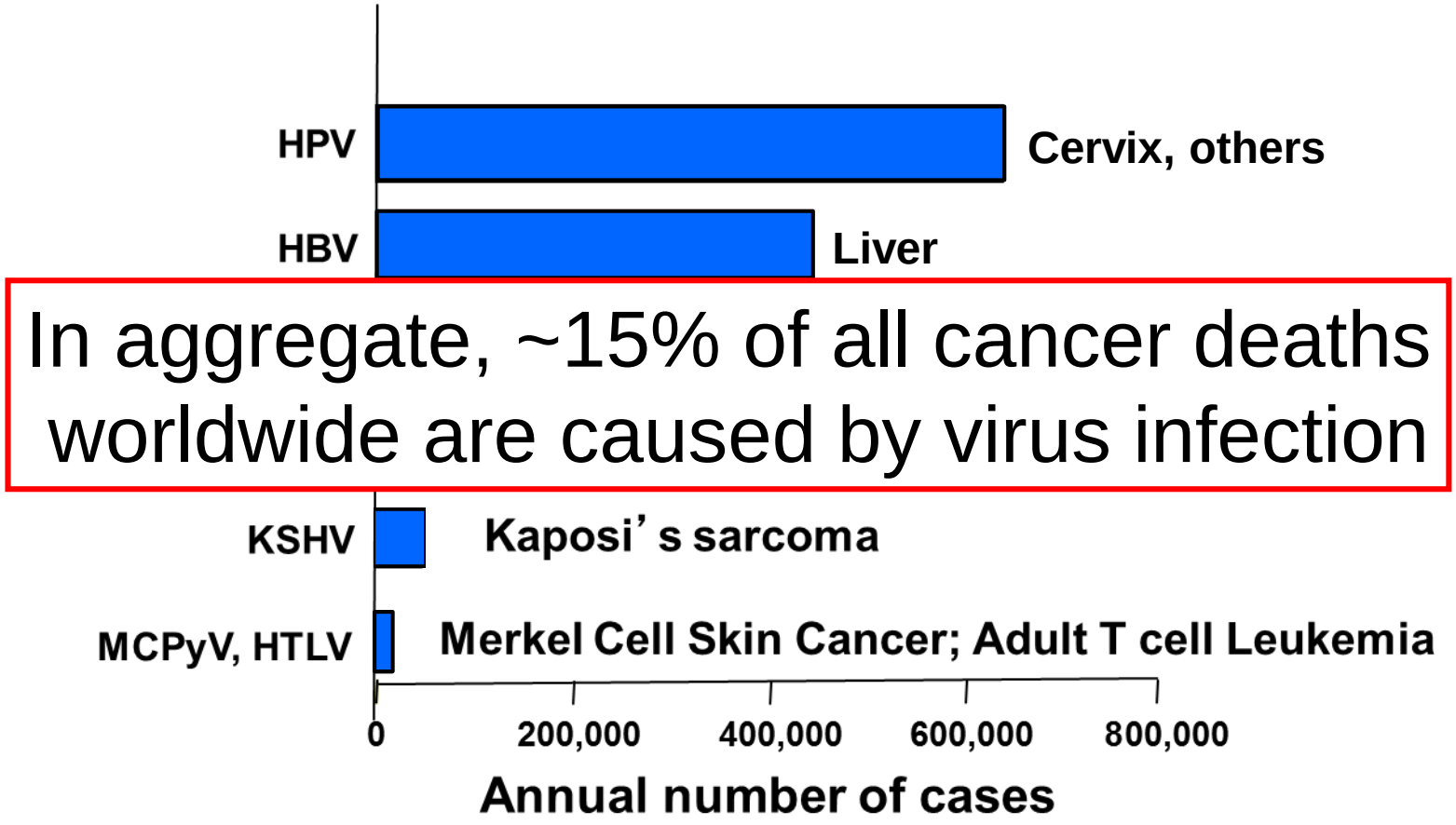
Inefficient

Slow

Not sufficient

No virus present

Human Tumor Viruses



In aggregate, ~15% of all cancer deaths worldwide are caused by virus infection

Adapted from Plummer et al, Lancet Glob Health 4: 609-16, 2016

Are other human tumors caused by viruses?

- EBV
  - Hodgkins disease
  - Gastric carcinoma
- HPV
  - Skin cancers
- Additional viruses?

Viral tumors are more prevalent in the developing world

Poor nutritional and health status

Infections more common

Poor screening programs

Different viral strains

Different host genetics

How do viruses cause cancer?

Encode oncogenes (HPV, herpesviruses)

- Stimulate cell growth
- Induce genetic instability
- Inhibit cell death (apoptosis)

Induce expression of cell oncogene

(some retroviruses vectors used in gene therapy)

Induce chronic inflammation (HBV, HCV)

- Injury, repair, proliferation, mutagenesis

Mechanism of carcinogenesis has important implications for prevention and treatment

Some general principles

Most people infected with
a tumor virus do not get cancer

Progression to cancer often associated
with immunosuppression or immunodeficiency

It takes many years after infection before
the cancer develops

The cancer itself is not contagious

HIV is an honorary tumor virus

Immunosuppression caused by HIV predisposes people to various cancers

AIDS-defining cancers

- Primarily virus-associated
  - Kaposi sarcoma - KSHV
  - Cervical - HPV
  - Aggressive B-cell lymphoma- EBV

Non-AIDS-defining cancers

e.g. lung cancer

Viral etiology provides opportunities for understanding, prevention, and cure

Prevention

Prevent viral infection or spread by various public health measures

Prevent progression to carcinoma or spread of virus to new hosts by anti-viral strategies

Public health measures

Elimination of HBV and HCV from blood supply

Identification of HPV-induced cervical dysplasia by Pap screening and DNA testing

Vaccination against tumor virus infection

Vaccination against hepatitis B virus infection

Safe and effective hepatitis B vaccine that prevents infection and hepatitis

60% vaccine coverage of infants worldwide

>2/3 reduction of risk of hepatocellular cancer in vaccinated children

Treatment

Persistence of viral genes and proteins in cancer cells provide novel, well-defined targets for therapy

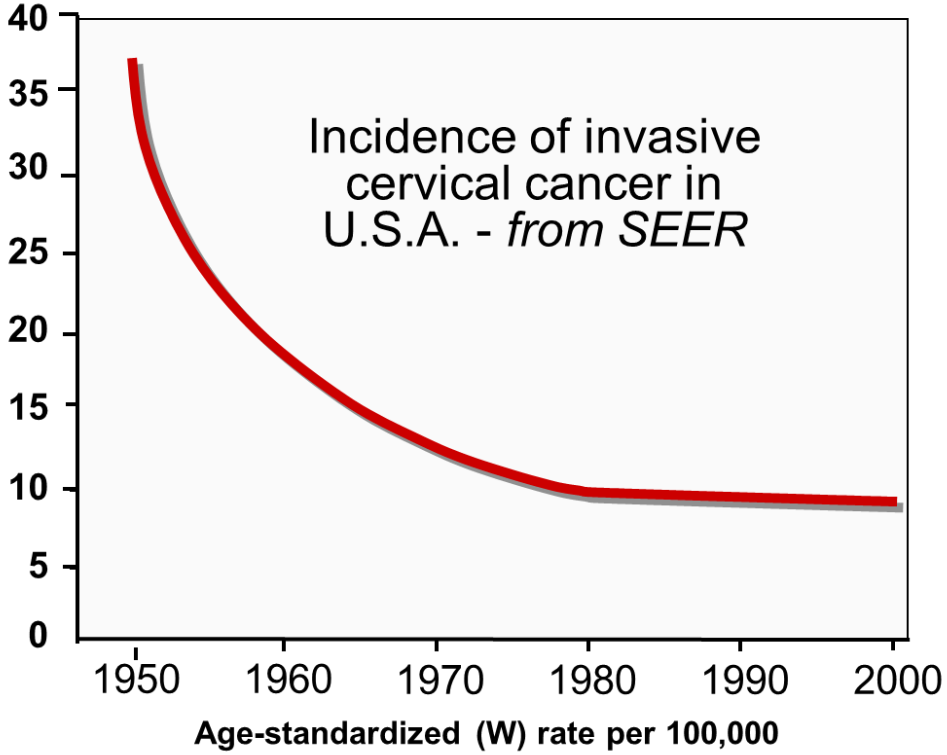
Drugs that inhibit herpesvirus DNA replication can reduce numbers of Kaposi sarcoma lesions.

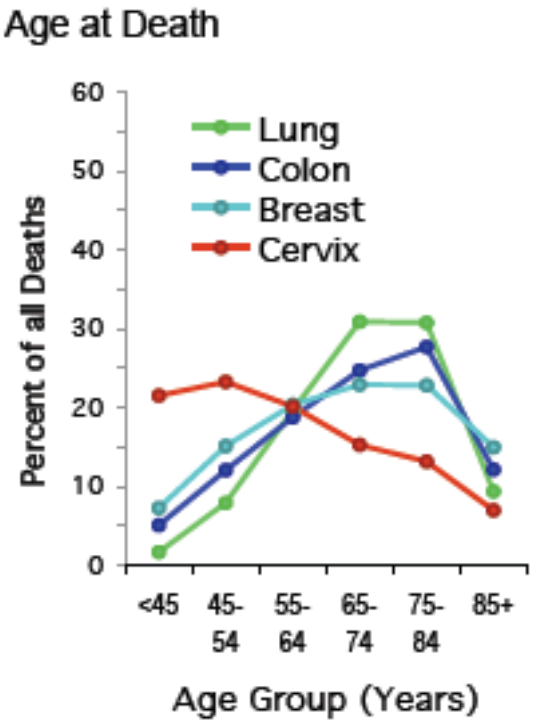
Will HCV cure reduce cancer risk?

Anti-viral drugs target viral proteins that are absent from uninfected cells.

Cervical carcinoma

Most common cause of cancer death in women in developing world





Possible to eradicate most cases
of cervical cancer based on an understanding
of the infectious basis for this disease

Papillomaviruses

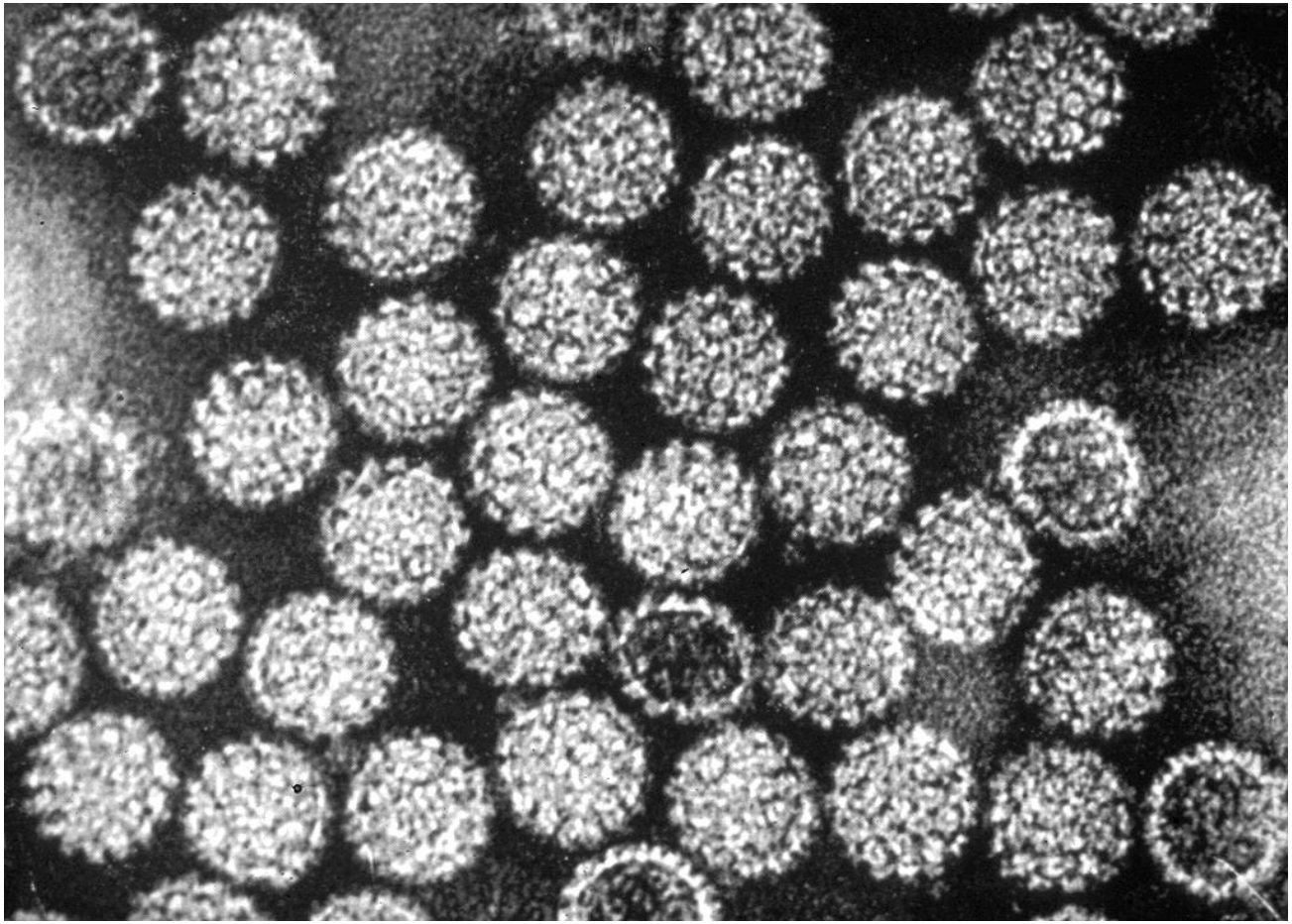
Small non-enveloped viruses

- 8000 base pairs of double-stranded DNA
- encode ~10 proteins

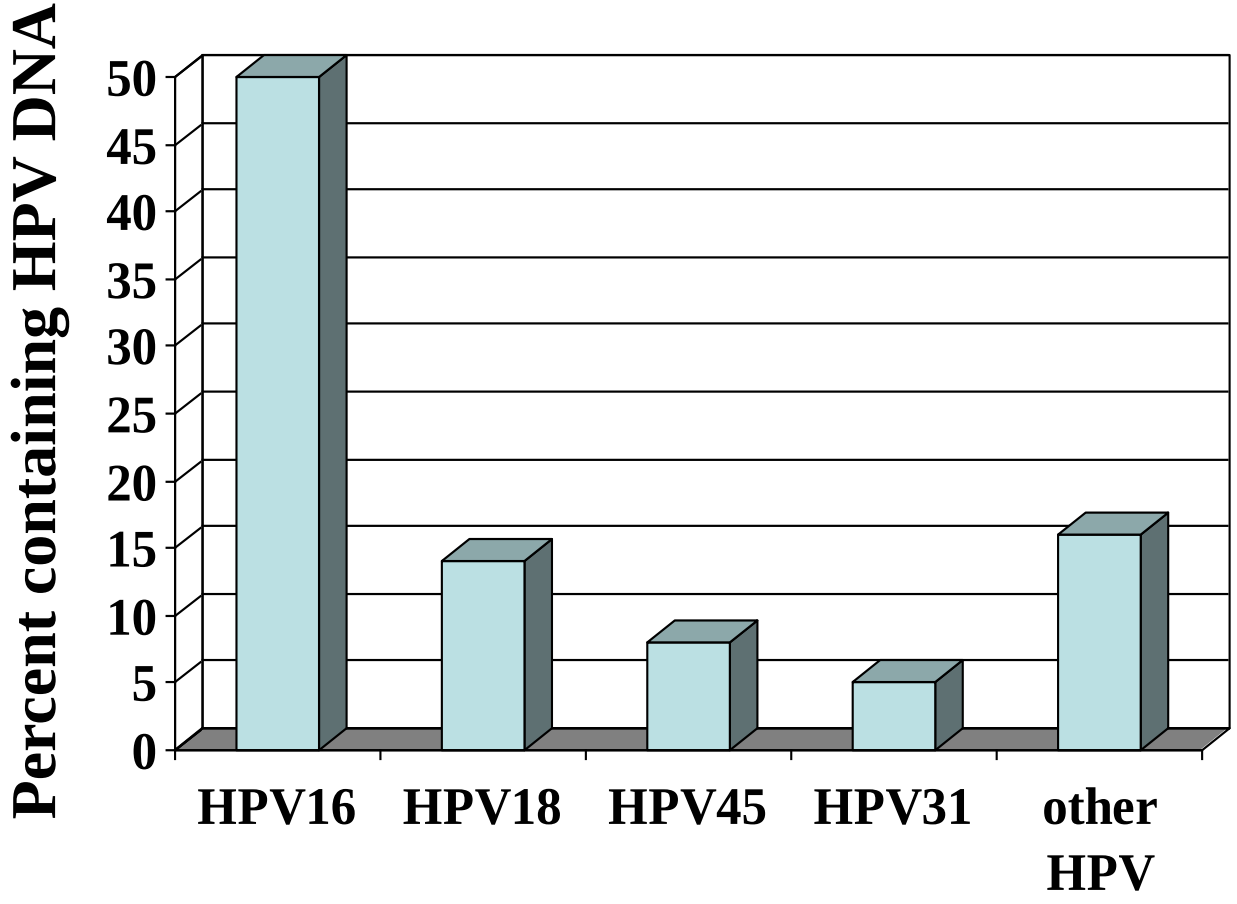
Many different HPV types

- Infect billions of people world-wide
- Specific types associated with specific diseases
- High-risk HPV types associated with cancer

Human Papillomavirus Particles



Virtually all cervical cancers contain HPV DNA



Harald zur Hausen
2008 Nobel Prize

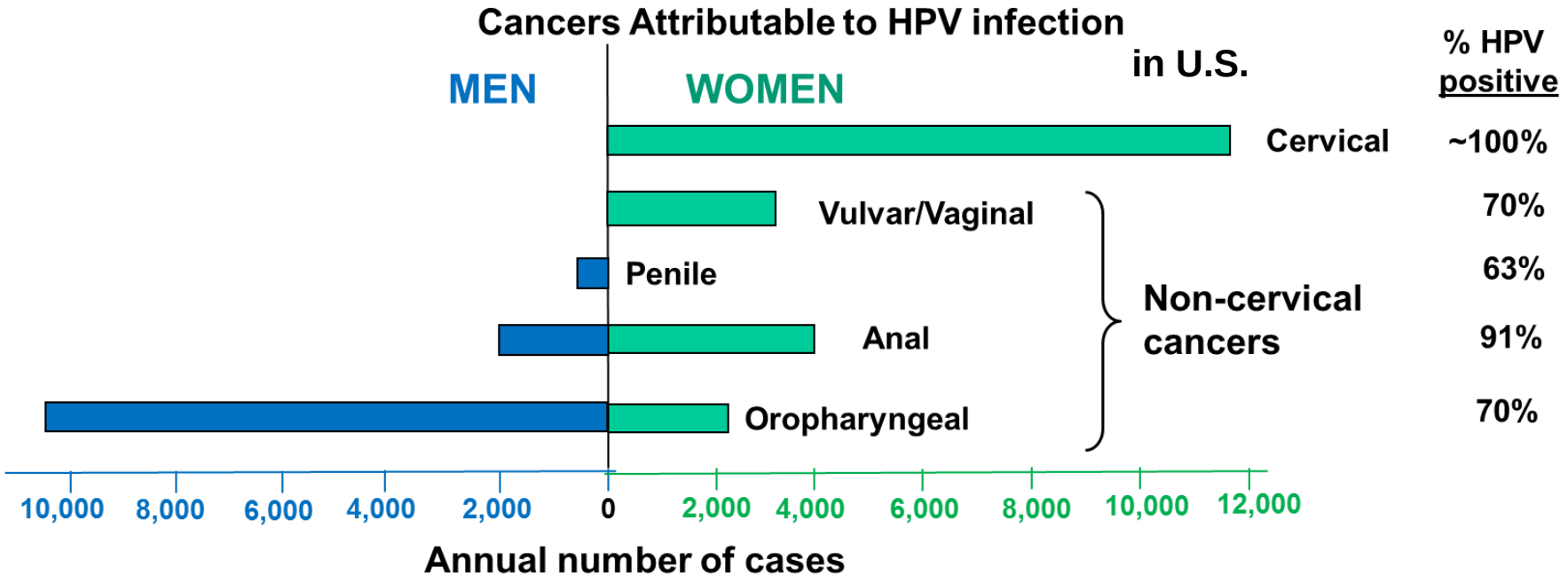
~1000 cases
Bosch, et al., 2000

Epidemiological studies demonstrate that infection with high-risk HPV types confers a greatly elevated risk of cervical cancer

- Many years pass between infection and cancer
- Most infected women do not get cancer

HPV infection is necessary but not sufficient

It's not just cervical cancer



HPV16 by far most prevalent HPV type in non-cervical cancer

Important that males are also vaccinated

Adapted from Van Dyne, et al., MMWR, 2018; https://www.cdc.gov/cancer/hpv/statistics/cases.htm

Two types of HPV vaccines

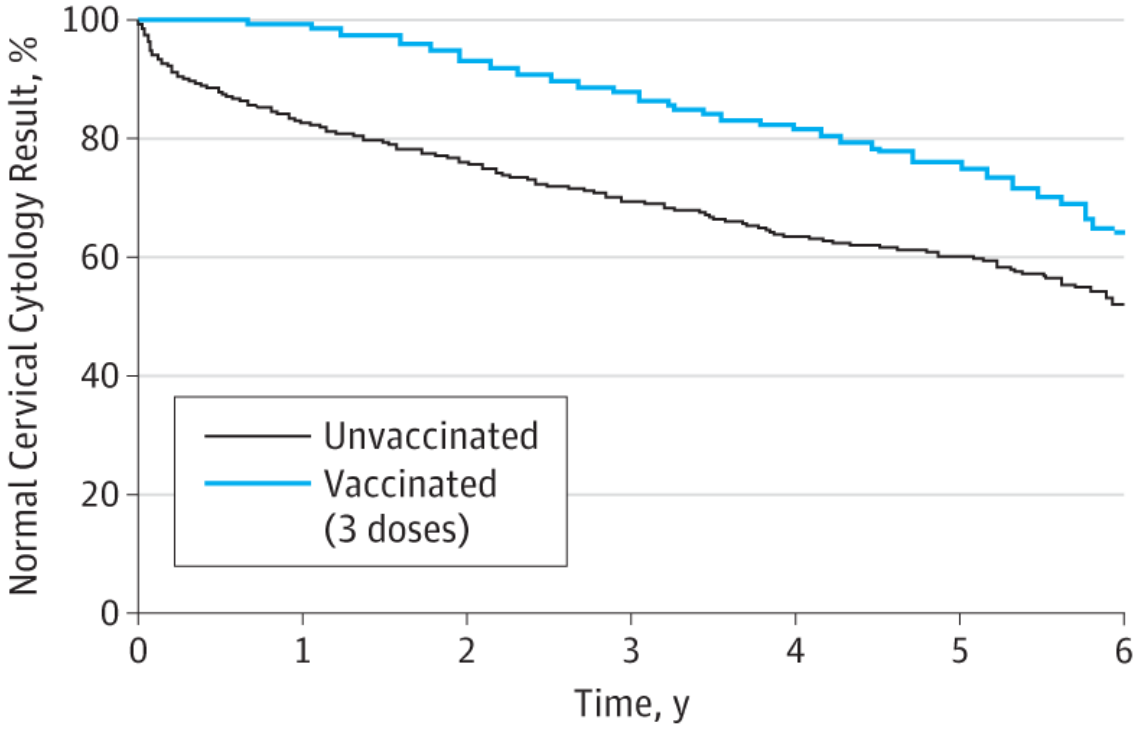
- Prophylactic vaccine (Gardasil, cervarix)
  - Generate antibodies to virus particles
  - Prevent HPV infection
- Therapeutic vaccine
  - Generate killer T cells to viral E6/E7 proteins in cancer cells
  - Treat HPV disease

Prophylactic HPV VLP vaccine

- Virus-like particle assembled from L1 protein
- Multiple HPV types in vaccine
- Contains no viral DNA
- Non-infectious, non-pathogenic
- Can induce robust antibody and cell-mediated immune response
- Prevents persistent HPV16 and HPV18 infection and cervical precancer

The first vaccine designed to prevent human cancer

HPV vaccination reduces incidence of precancerous cervical lesions

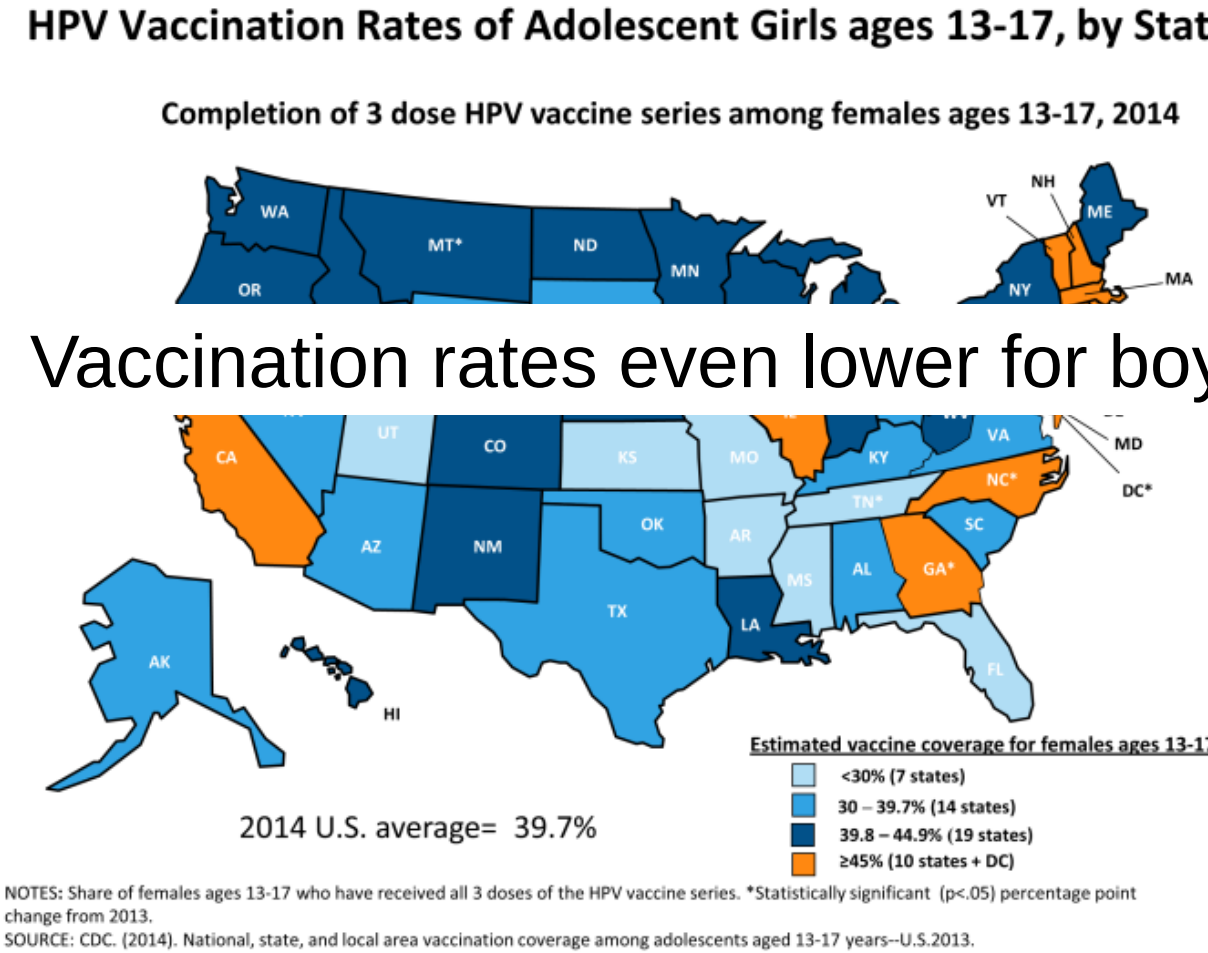


Decreased incidence of genital warts in heterosexual Australian men following HPV vaccine implementation in 2007

Ali et al, BMJ 2013

Herd immunity

In the US, HPV vaccination recommended for all boys and girls between 11 and 12 years old



Vaccination rates even lower for boys

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What are main barriers to HPV vaccination?

Cost
General anti-vax attitude
Fear of side-effects
Social or religious stigma regarding
    sexually transmitted diseases
Lack of school-based or mandatory programs

Health care providers!

Limitations to prophylactic HPV VLP vaccine

VLPs expensive to produce and distribute

No benefit to women already infected

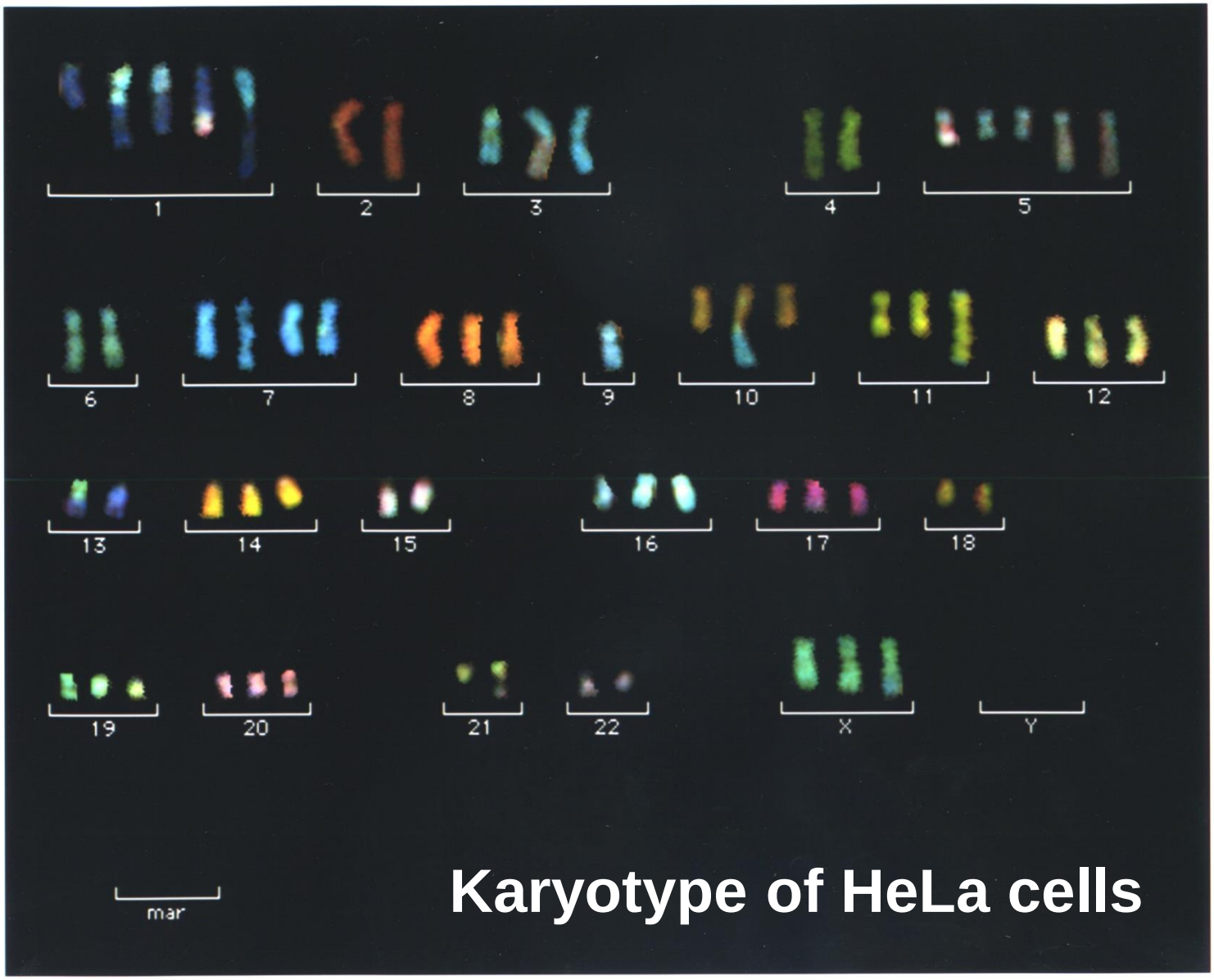
Vaccination rates low in much of the world

Not all high-risk HPV types are in vaccine and there is no cross-protection

- Currently HPV16,18,6,11 and five other high-risk types

Cancer cells accumulate many mutations during carcinogenesis

E6 and E7 induce genetic instability

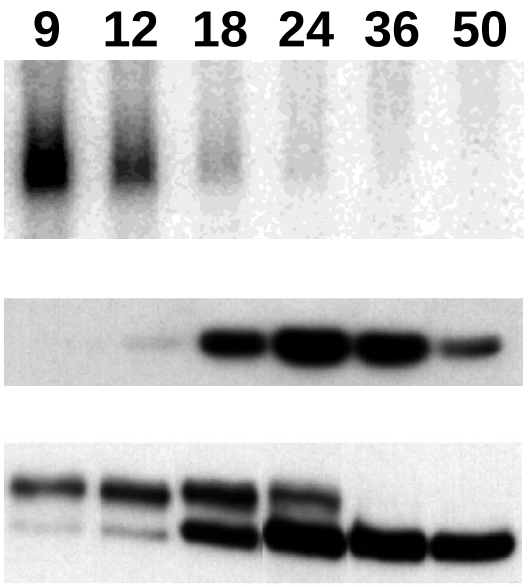


Karyotype of HeLa cells

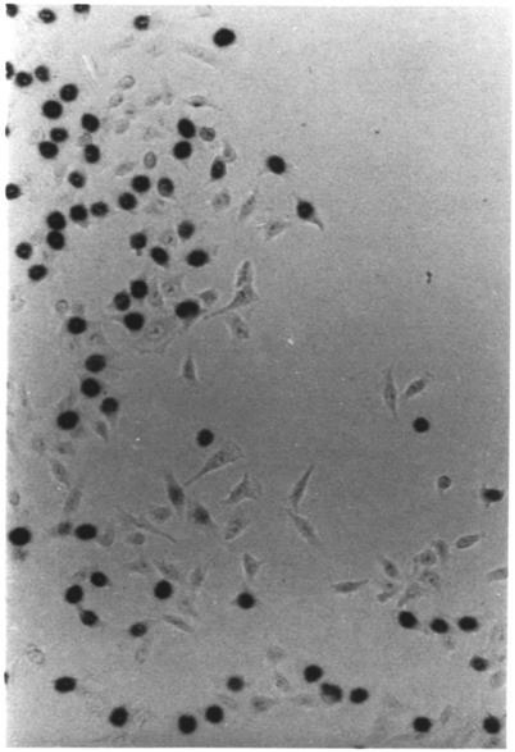
Despite mutations, viral oncogenes are expressed in the cancers

Do these mutations make the cancer cells independent of viral oncogenes?

Repression of HPV E6/E7 oncogenes activates p53 and Rb in cervical cancer cells



Repression of HPV oncogenes causes cervical cancer cells to stop growing



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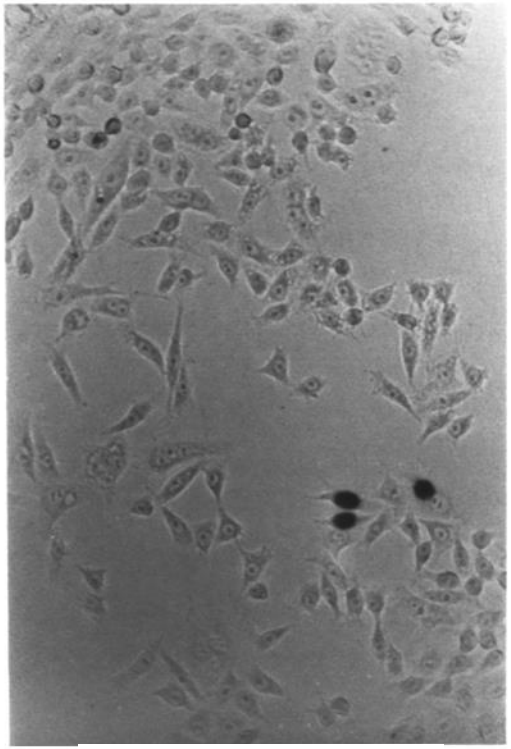

E2 protein

PROLIFERATION OF CERVICAL CANCER CELLS REQUIRES EXPRESSION OF THE HPV ONCOGENES

- Cellular mutations accumulated during carcinogenic progression are not sufficient to maintain the malignant state
- Implies that drugs that inhibit the activity of viral proteins may be therapeutically useful

Strategies for controlling cervical cancer in the 21st century

Prevent infection
- prophylactic vaccination

Identification, monitoring, and treatment of carriers
- Pap smear and HPV DNA testing

Inhibit progression and transmission
- anti-viral drugs that inhibit viral replication

Immune-based treatment of cancer
- therapeutic vaccination

Mechanism-based treatment of cancer
- anti-viral treatments that inhibit expression or action of E6 and E7 proteins

Thank you!

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