Viruses and Human Cancer
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Viruses: The Invisible Enemy
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Overview

1842: Domenico Rigoni-Stern, Verona: no cervical cancer in nuns

Oncogenic viruses in animals were discovered 100 years ago

The first oncogenic human virus (EBV) was discovered in 1964

Oncogenic viruses have taught us much about cancer:

Tumor suppressor p53 first discovered in association with PyV

Oncogenes were first defined in retroviruses

Approximately 15% of human cancer worldwide has a viral etiology

Vaccines against these viruses will significantly reduce the human cancer burden
### Human cancers attributable to infection

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cancer</th>
<th>% lifetime risk in carriers</th>
<th>Annual cases</th>
<th>% all cancers</th>
<th>Main transmission route</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. pylori</em></td>
<td>Stomach</td>
<td>~10.0</td>
<td>592,000</td>
<td>5.8</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Lymphoma (MALT)</td>
<td></td>
<td>11,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>Cervix (HPV-16, 18)</td>
<td>~3.0</td>
<td>492,800</td>
<td>5.1</td>
<td>Sexual</td>
</tr>
<tr>
<td></td>
<td>Ano-genital</td>
<td></td>
<td>53,880</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mouth, pharynx</td>
<td></td>
<td>14,500</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin (HPV-5)</td>
<td>&lt;0.01</td>
<td>~1,000</td>
<td>&lt;0.01</td>
<td>Contact</td>
</tr>
<tr>
<td>HBV and HCV</td>
<td>Liver</td>
<td>~15.0</td>
<td>535,000</td>
<td>5.5</td>
<td>Parenteral</td>
</tr>
<tr>
<td>EBV</td>
<td>Nasopharynx</td>
<td>&lt;1.0</td>
<td>78,100</td>
<td>1.0</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Hodgkin lymphoma</td>
<td></td>
<td>28,600</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Burkitt lymphoma</td>
<td></td>
<td>6,700</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>KSHV (HHV-8)</td>
<td>Kaposi sarcoma</td>
<td>&lt;1.0</td>
<td>66,200</td>
<td>0.9</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>NHL</td>
<td></td>
<td>16,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schistosome</td>
<td>Bladder</td>
<td>&lt;1.0</td>
<td>10,600</td>
<td>0.1</td>
<td>Water, snails</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>ATL</td>
<td>~1.2</td>
<td>3,300</td>
<td>0.03</td>
<td>Milk</td>
</tr>
<tr>
<td>Opisthorchis</td>
<td>Gall bladder</td>
<td>~5.6</td>
<td>2,500</td>
<td>0.02</td>
<td>Water, raw fish</td>
</tr>
<tr>
<td>Merkel PyV</td>
<td>Skin</td>
<td>&lt;0.01</td>
<td>~1,500</td>
<td>&lt;0.01</td>
<td>Contact</td>
</tr>
</tbody>
</table>

(Adapted from Parkin, 2006)
Annual global cancer burden due to infections

2,216,920 new cases = 20.6% of total cancer incidence
(adapted from Parkin et al. 2002, 2006)

>99% cancer of the cervix (HPV)
25% cancers of the oral cavity (HPV)
80% hepatocellular carcinoma (HBV 50%, HCV 30%)
80% gastric cancer (H. pylori)
10% gastric cancer (EBV)
>99% undifferentiated nasopharyngeal carcinoma (EBV)
10% non-Hodgkin lymphoma (EBV)
30% Hodgkin lymphoma (EBV)

This pie chart excludes the remaining 3.6%:
- Anal and perianal cancers (HPV)
- Vulvar, vaginal and penile cancers (HPV)
- Adult T cell leukemia (HTLV-1)
- Kaposi sarcoma and KSHV lymphomas
- Merkel cell carcinoma (MCPyV)
- MALT tumours (H. pylori)
- Cancers linked to helminth infections
Paradox: oncogenic viruses that don't cause human cancer

Adenoviruses: AdV 2, 5 & 12
Highly oncogenic in new born rats due to E1A, E1B, E4 & E5

Polyomaviruses: BKV, JCV
Highly oncogenic in baby hamsters due to large T and small t antigen transformation

HTLV-2: Immortalizes T-cells in culture
Merkel Cell Carcinoma

- Rare, aggressive skin cancer
- Occurs in the elderly
- Transplant recipients and AIDS
- New polyoma virus discovered 2008

Merkel cell carcinoma virus is phylogenetically distant from other human polyoma viruses
Distinguishing tumor viruses from rumor viruses

1972-1974    RD114    Pediatric sarcoma    Feline gamma-retrovirus
1972-present  MMTV     Breast cancer     Murine beta-retrovirus
1992-2004     SV40     Various           Simian polyomavirus
2006-2010     XMRV     Prostate cancer  Murine gamma-retrovirus

Rnase L mutation?
XMRV in stroma, carcinoma or neither?
# Distinguishing tumor viruses from rumor viruses

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Virus</th>
<th>Disease</th>
<th>Virus Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1972-1974</td>
<td>RD114</td>
<td>Pediatric sarcoma</td>
<td>Feline gamma-retrovirus</td>
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<tr>
<td>1992-2004</td>
<td>SV40</td>
<td>Various</td>
<td>Simian polyomavirus</td>
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<tr>
<td>2006-2010</td>
<td>XMRV</td>
<td>Prostate cancer</td>
<td>Murine gamma-retrovirus</td>
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- Rnase L mutation?
- XMRV in stroma, carcinoma or neither?

## Rumors about genuine tumor viruses: KSHV (HHV-8)

<table>
<thead>
<tr>
<th>Year</th>
<th>Disease</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Kaposi sarcoma</td>
<td>True</td>
</tr>
<tr>
<td>1995</td>
<td>Primary effusion lymphoma</td>
<td>True</td>
</tr>
<tr>
<td>1996</td>
<td>Multicentric Castleman’s disease</td>
<td>True</td>
</tr>
<tr>
<td></td>
<td>(PCR, Southern blot, Ag, isolation, serology)</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>Multiple myeloma (PCR)</td>
<td>False</td>
</tr>
<tr>
<td>1997</td>
<td>Sarcoidosis (PCR)</td>
<td>False</td>
</tr>
</tbody>
</table>
Multifactorial causes of cancer
(virus is necessary but not sufficient to cause cancer)

1. Liver cancer (HCC)
   - HBV alone: medium frequency of HCC
   - Aflatoxin in diet: HCC rare
   - HBV + aflatoxin: ~5-fold relative risk in HCC
     (Wild & Montesano 2009)

2. Skin cancer in EV
   - HPV-5, HPV-8 (ubiquitous)
   - Ultraviolet light exposure (on face)
   - Epidermodyplasias verruciformis gene (rare)
Multifactorial causes of cancer

3. Burkitt's Lymphoma in children

Epstein-Barr Virus (EBV)

Holoendemic malaria

C-myc translocation to Ig heavy or light chains 8;14, 8;2 or 8;22

BL cases
Malaria belt
Multifactorial causes of cancer

4. Kaposi's sarcoma (KS)

• 1º cause: KSHV (HHV-8)
• Classical: rare, in elderly men
• Iatrogenic: commoner in immunosuppressed transplant patients
• AIDS-KS, role of HIV: immunosuppression + Tat?
Oncogenic viruses and changes in cancer incidence when AIDS appeared

(Adapted from Rabkin et al. 1992)
Humankind’s Collection of Viruses

Family Heirlooms (co-evolved with host)
- Endogenous Retroviruses
- Herpesviruses
- Papilloma & polyoma viruses
- Hepatitis B virus

Temporary Exhibits (zoonoses, outbreaks)
- Rabies
- West Nile
- Nipah
- Ebola
- SARS

'New' Acquisitions (<12,000 years ago)
- Measles
- Smallpox
- Influenza
- HIV

KSHV is a Maternal Heirloom

- In Africa, 98% KSHV-infected children have KSHV+ mothers but there is no correlation with infection status of fathers (Bourboulia et al, 1998; Dedicoat et al, 2004; Plancoulaine et al, 2004)
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- In Ashkenazi Jews, KSHV genomes co-diversify with mtDNA, but not with Y-DNA (Wilder, Weiss & Boshoff, unpublished)

![Genetic variation in the K1 gene](image_url)
How long has KSHV been present in the Veneto and the Po valley?

Marcello Fogolino

Madonna with San Gottardo and San Giobbe

1508
Mantova
Virus: the invisible enemy or the invisible friend

Could viruses be useful to their hosts?

Non-pathogenic:
- TTV
  - GBV-C co-infection delays progression to AIDS
  - HERV-W in the placental syncytiotrophoblast

Low pathogenic:
- γ-Herpesviruses
  - KSHV & EBV?
- Retrovirus
  - HTLV-1 & HTLV-2?

KSHV: Loss of fitness to host is a rare side effect usually occurring after reproductive age

- Its minor cost in fitness might be offset by a broad advantage to the host in a certain environment
- Analogous to the cost of homozygous lethal genes being outweighed by heterozygous fitness
Interactions between infections: Malaria

Burkitt's Lymphoma

EBV is ubiquitous but BL only occurs where there is malaria

Kaposi's Sarcoma

KSHV prevalence (before AIDS) broadly correlates with malaria

Detrimental

Beneficial?
KSHV and Malaria: Hypotheses

KSHV transmission is enhanced by mosquitos (Ascoli and Coluzzi, 2004)

KSHV might protect against cerebral malaria through secretion of v-MIPs that bind to CCR3 at the blood brain barrier

KSHV is not an ‘emerging infection’ but has been maintained in the human population by positive selection analogous to genetic hemoglobinopathies
Vaccination against tumor virus infection

- HBV SAg recombinant subunit vaccine since 1986: Protects against hepatitis and against liver cancer
- HPV virus-like particle capsid vaccine: Two successful vaccines licensed 2006
- EBV Gp340 envelope glycoprotein: Not taken up by Pharma Cos
- HTLV-1 envelope glycoprotein protects macaques and rabbits from challenge: Not seen by Pharma Cos as a market
- HCV and HIV: Huge markets but no really efficacious vaccines yet
Conclusions

- Oncogenic viruses have given us deep insight into cancer, e.g., oncogenes, tumour suppressor genes
- Cancer is a 'side effect' of persistent virus infections that promote cell proliferation
- Low penetrance of viral oncogenesis: requires cofactors
- Immune deficiencies increase incidence of virus-linked cancers
- ~15% of global human cancer burden has a viral etiology, ~1.6 million cases annually
- Vaccines hold great promise to reduce that burden