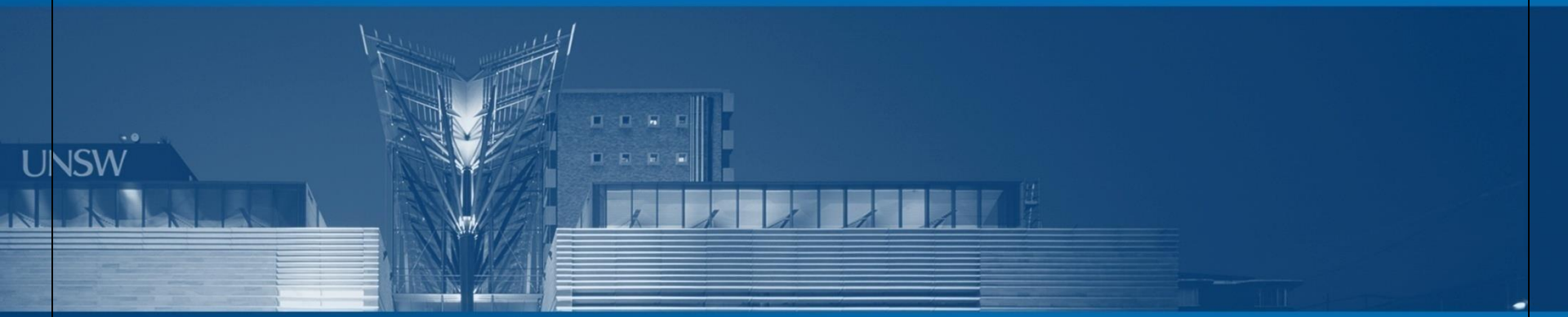


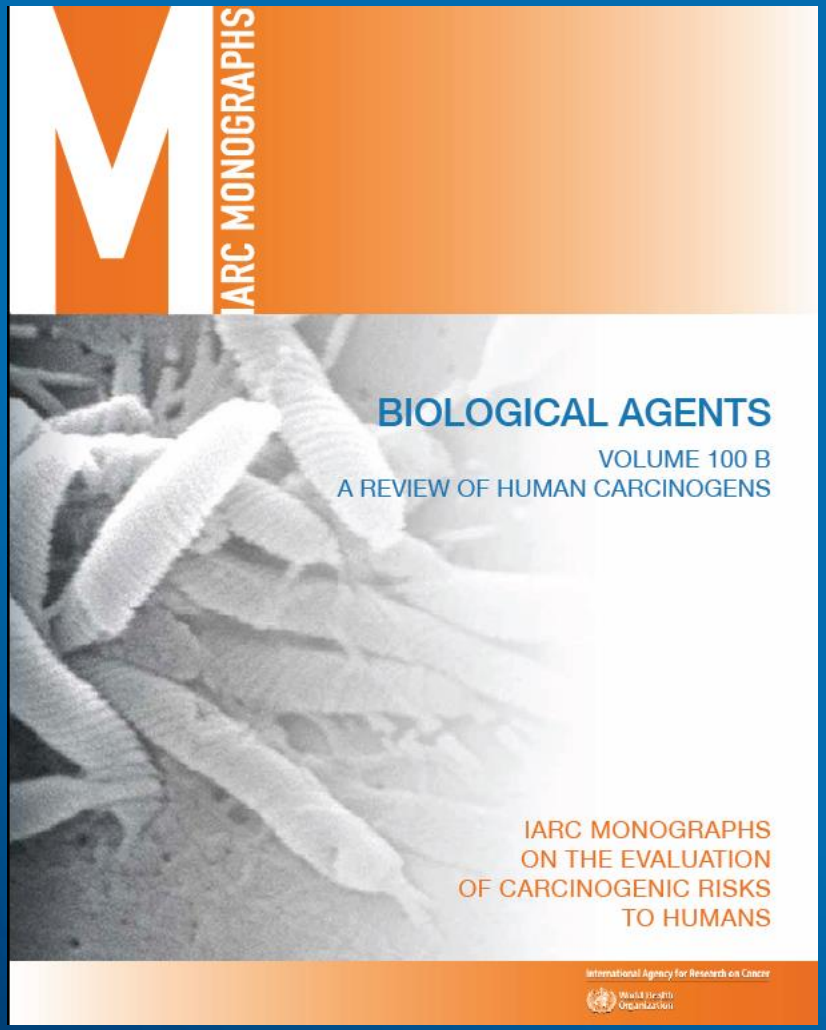
Epidemiology of tumours induced by viruses

Claire Vajdic PhD

Head, Adult Cancer Program
Leader, Cancer Aetiology and Prevention
Adult Cancer Program
Lowy Cancer Research Centre

Talk outline

- 2012 IARC Monograph: Biological agents that cause cancer
  - Focus on viruses
  - Selected epidemiological evidence
- My research on cancers with a viral cause



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IARC Monographs

- 1969+
- Critical reviews of biological and epidemiological data on carcinogenicity by international working groups of independent experts
- Chemicals, lifestyle factors, biological & physical agents and specific occupations
- http://monographs.iarc.fr

IARC Monographs… why?

- Identifying the cause(s) is the first step in cancer prevention
- Scientific justification for measures to reduce human exposure to carcinogens in the workplace and the environment
- Used by authorities to provide effective cancer control programmes
  - Vaccination or early treatment

IARC Monograph definition

A carcinogen:

"an agent that is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity"

"… at any stage in the carcinogenesis process, independently of the underlying mechanisms"

Types of epidemiology studies

- Experimental
  - Randomised trials
- Observational
  - Case reports / case series
  - Ecological / correlation
  - Case-control
  - Cohort

Causal inference

Causation

Changes in one variable *directly causes* changes in the other

Correlation or association

A relationship between two or more variables

Does not imply causation

May be real, or due to chance (random error), bias (systematic error) or confounding

Framework to assess causation: Bradford Hill criteria

Criteria	Evidence in favour of causal effect
Strength	Larger association more likely to be causal
Consistency	Different populations, countries, sampling frames
Specificity	Of cancer type and individuals at risk
Temporality	Exposure precedes cancer (essential)
Biological gradient	Greater exposure should generally lead to greater incidence of the effect
Plausibility	Mechanism between cause and effect makes sense
Coherence	Epidemiological and laboratory findings agree
Reversibility	Removal of factor decreases cancer incidence

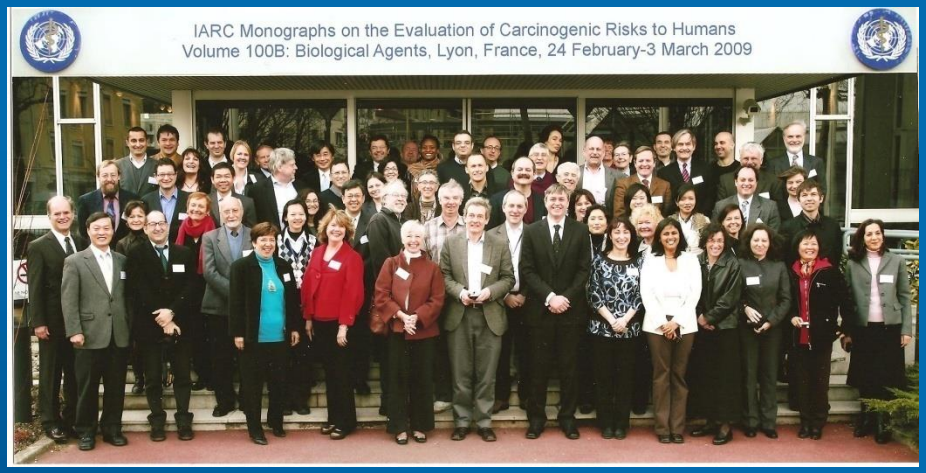
IARC classification system

Scientific, qualitative judgements

Carcinogen	Definition
Group 1	*The agent (mixture)* ***is carcinogenic to humans****.* This category is used when there is *sufficient* evidence of carcinogenicity in humans.
Group 2A	*The agent (mixture)* ***is probably carcinogenic to humans****.* This category is used when there is *limited* evidence of carcinogenicity in humans and *sufficient* evidence of carcinogenicity in experimental animals.
Group 2B	*The agent (mixture)* ***is possibly carcinogenic to humans****.* This category is used for agents, mixtures and exposure circumstances for which there is *limited* evidence of carcinogenicity in humans and *less than sufficient* evidence of carcinogenicity in experimental animals.

IARC Biological agents working group review

- February 2009
  - 36 scientists, 16 countries
- Discussion, vote
- Preliminary report
  - Bouvard et al. *Lancet Oncology* 2009;10:321-322
- 100th Monograph 2012



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Viruses that are direct carcinogens

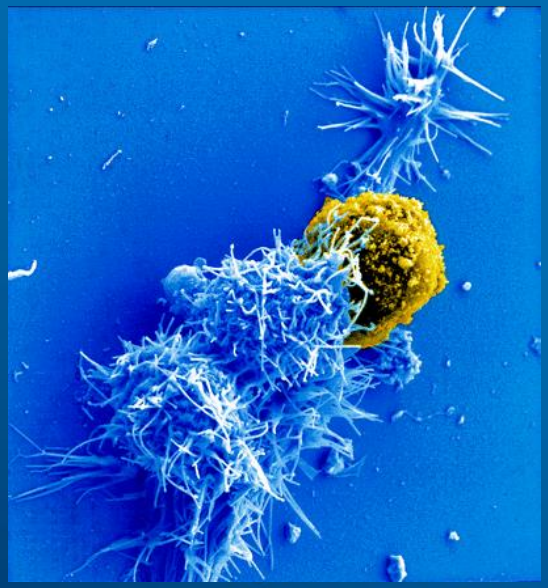
1. Human T-cell lymphotropic virus, HTLV1
2. Epstein-Barr virus, EBV
3. Human herpesvirus 8, HHV8 / KSHV
4. Human papillomavirus, HPV

Criteria

- viral genome or part of it can usually be detected in each cancer cell
- virus can immortalise after the growth of target cells in vitro
- virus expresses several oncogenes that lead to disruption of cell-cycle checkpoints, inhibition of apoptosis and cell immortalisation

HTLV-1

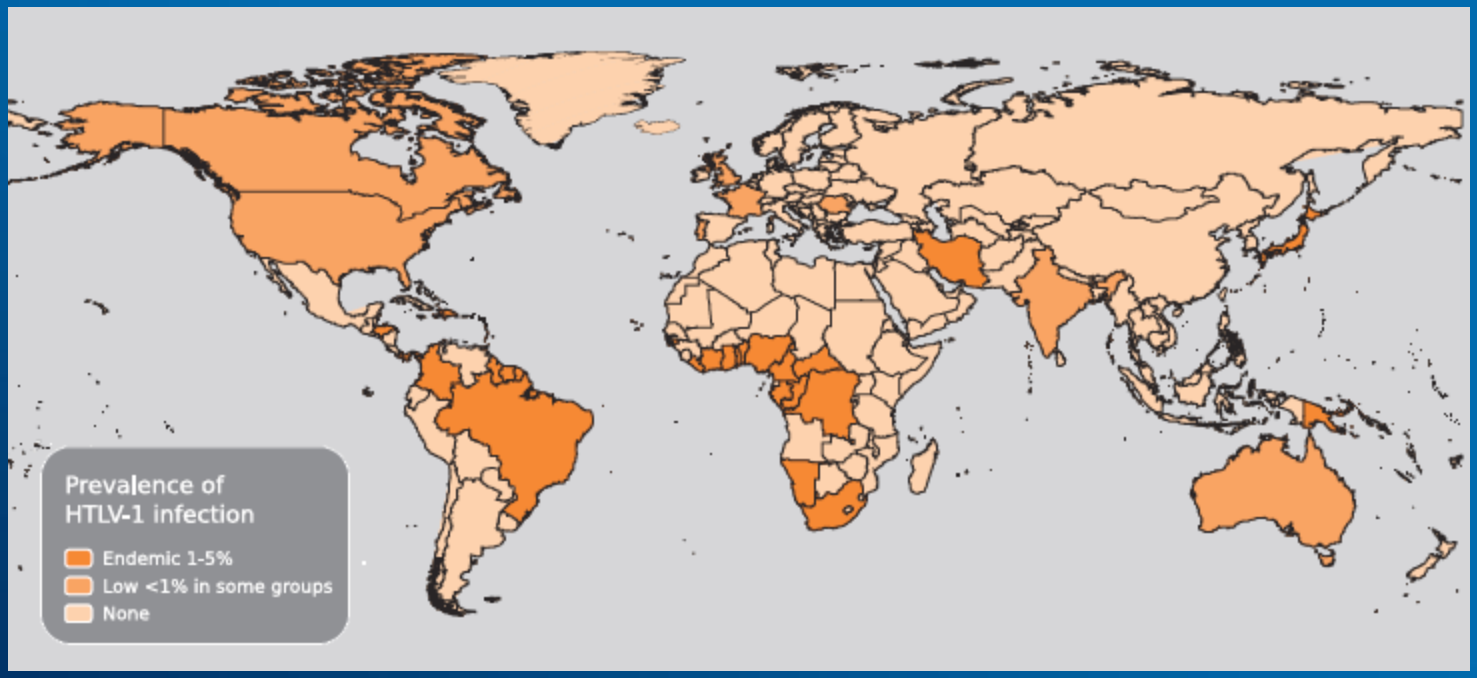
Agent	Sufficient evidence (Group 1)	Limited evidence (Group 2A)	Established mechanistic events
Human T-cell lymphotrophic virus, type 1	• Adult T-cell leukaemia and lymphoma (ATL)	-	Immortalisation and transformation of T-cells



Human dendritic cell and a HTLV-1-infected lymphocyte
Ceccaldi et al *J Virol* 2006;80:4771-80

HTLV-1 & lymphoma: ecological evidence

First human retrovirus implicated in human cancer



ATL occurs almost exclusively in areas where HTLV-1 infection is endemic, such as Japan, the Caribbean and West Africa, or countries with high rates of immigration from these areas

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EBV

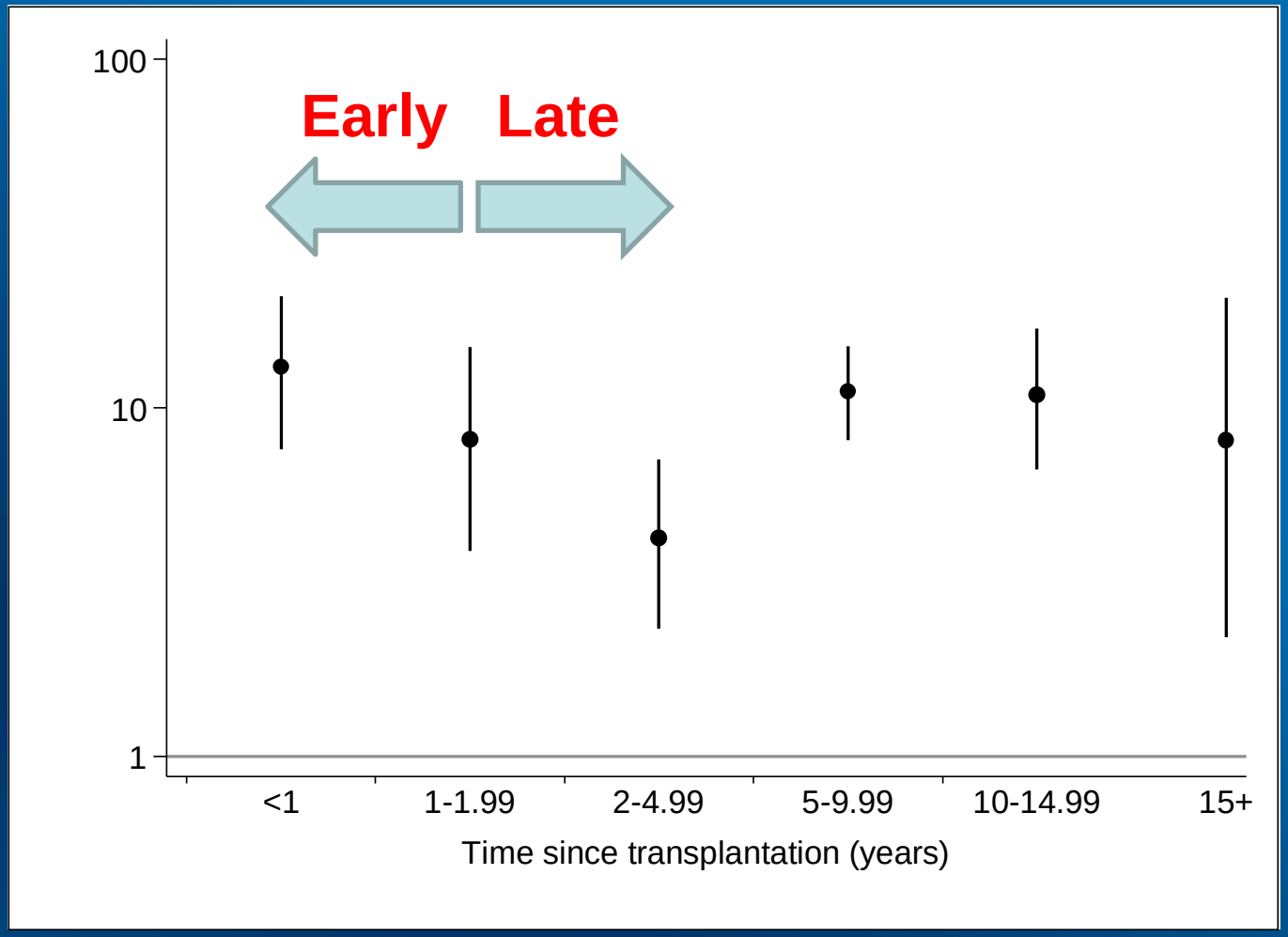
Agent	Sufficient evidence (Group 1)	Limited evidence (Group 2A)	Established mechanistic events
Epstein-Barr virus	• Nasopharyngeal carcinoma (98%) • Burkitt's lymphoma (82%) • Hodgkin lymphoma (46%) • Immune-suppression related non-Hodgkin lymphoma • Extranodal NK/T-cell lymphoma (nasal type)	• Gastric carcinoma (5-10%) • Lympho-epithelioma-like carcinoma	Cell proliferation Inhibition of apoptosis Genomic instability Cell migration

EBV & Burkitt lymphoma (BL): case-control evidence

Study	Cases	Controls	Antibodies against EBV-VCA	Odds ratio (95% CI)	Adjusted factors
Carpenter et al 2008 Uganda 2005-06	325 HIV-ve children with BL	579 HIV-ve children without BL	Low Medium High *P-trend*	1.0 (ref) 3.6 (2.3-5.6) 4.5 (2.3-8.7) *<0.0001*	Age, sex, district, household income, tribe
Mutalima et al 2008 Malawi 1994-99	148 children with BL	104 children without BL	Low Medium High *P-trend*	1.0 4.1 (1.6-10.1) 14.8 (5.8-39) *<0.001*	Age, sex, residence

VCA – viral capsid antigen

EBV infection and immune-suppression related lymphoma: cohort evidence



van Leeuwen et al. *Blood* 2009;114:630-7.

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‘Early’ NHL (n=27)

	n	Adjusted IRR (95% CI)*	*P*-value†
EBV IgG status at transplantation			
Positive/unknown	17	1.00	
Negative	10	**4.66 (2.12-10.36)**	<0.001
Receipt of antiproliferative			
No	6	1.00	
Yes	21	0.50 (0.17-1.23)	0.120
Receipt of calcineurin inhibitor			
No	2	1.00	
Yes	25	1.36 (0.31-5.96)	0.682
Receipt of antibody			
No	17	1.00	
Yes	10	2.39 (1.08-5.30)	0.031

*Adj. for age, sex, EBV status, duration transplantation, receipt of immunosuppressive agents and antibodies; †*P*-values reported for test of homogeneity in nominal covariates;

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‘Late’ NHL (n=79)

	n	Adjusted IRR (95% CI)*	*P*-value†
Age (years)	79	1.02 (1.01-1.04)	0.005
EBV IgG status at transplantation			
Positive/unknown	74	1.00	
Negative	5	**0.92 (0.37-2.28)**	0.849
Time since transplantation			
2-4.99	12	1.00	
5-9.99	43	3.63 (1.91-6.89)	
≥10	24	4.68 (2.29-9.55)	<0.001^
Receipt of antiproliferative			
No	14	1.00	
Yes	65	1.14 (0.63-2.06)	0.647
Receipt of calcineurin inhibitor			
No	10	1.00	
Yes	69	3.04 (1.52-6.07)	0.002
Receipt of antibody			
No	59	1.00	
Yes	20	1.21 (0.73-2.03)	0.456

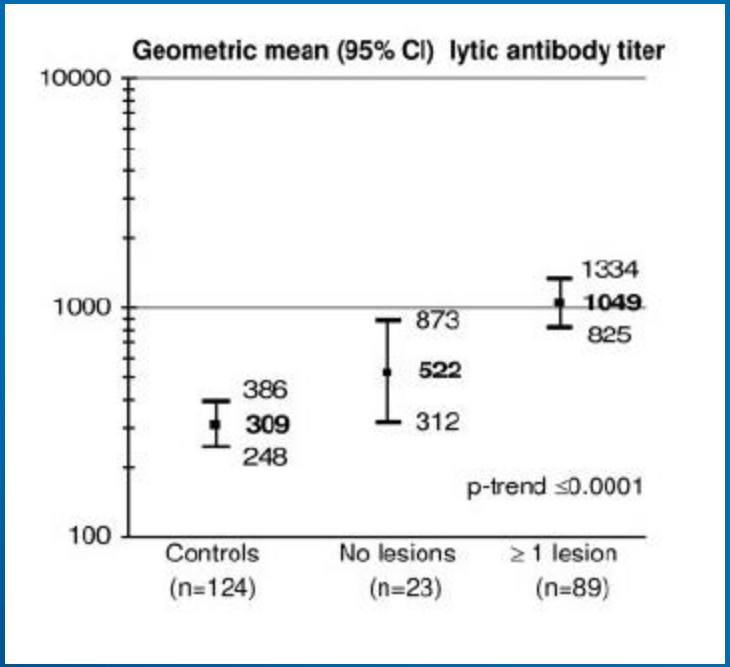
*Adj. for age, sex, EBV status, duration transplantation, receipt of immunosuppressive agents and antibodies; †*P*-values reported for test of homogeneity in nominal covariates; ^*P*-value for test of trend

KSHV / HHV8

Agent	Sufficient evidence of carcinogenesis in humans (Group 1)	Limited evidence of carcinogenesis in humans (Group 2A)	Established mechanistic events
Kaposi sarcoma herpes virus or Human herpes virus-8	• Kaposi sarcoma (100%) • Primary effusion lymphoma	• Multicentric Castleman's disease	Cell proliferation Inhibition of apoptosis Genomic instability Cell migration

KSHV / HHV8 and Kaposi sarcoma

- 22 cohort studies and 80 case-control studies
- All show broadly consistent evidence of an association between KSHV infection and Kaposi sarcoma
- In most studies, the relative risks are >10



Cancer 2006;107:2282–90.

HPV

Agent	Sufficient evidence (Group 1)	Limited evidence (Group 2A)	Established mechanistic events
Human papillomavirus type 16	Carcinoma of the: • Cervix • Vulva • Vagina • Penis • Anus • Oral cavity • Oropharynx • Tonsil	• Larynx cancer	Immortalisation Genomic instability Inhibition of DNA damage response Anti-apoptotic activity

HPV

Agent	Sufficient evidence (Group 1)	Probably carcinogenic (Group 2a)	Possibly carcinogenic (Group 2b)
HPV **18**, **31**, **33**, **35**, 39, **45**, 51, **52**, 56, **58**, 59	• Cervical cancer		
HPV 68		• Cervical cancer	
HPV 26, 53, 66, 67,70, 73, 82			• Cervical cancer
HPV 30, 34, 69, 85, 97			• Cervical cancer
HPV 5, 8			• Skin cancer in patients with epidermodysplasia verruciformis

HPV

Cancer of the cervix almost unknown in nuns

→ 2 hypotheses regarding sexual activity

(1) Early age first intercourse

(2) Sexually transmitted infection

3280 nuns, 20 years
Number of cancers by site[1]

Site	Number
Skin	3
Thyroid	1
Bone	1
Spleen	1
Urinary tract	5
Mouth	3
Parotid	2
Peritoneum	1
Mesentery	1
Digestive tract	42
Liver	4
Pancreas	2
Breast	53
Ovary	9
Uterus	2
Cervix	0

[1]Gagnon F. Am J Obstet Gynecol 1950;60:516-22

HPV

CANCER OF THE CERVIX: A SEXUALLY TRANSMITTED INFECTION?

VALERIE BERAL

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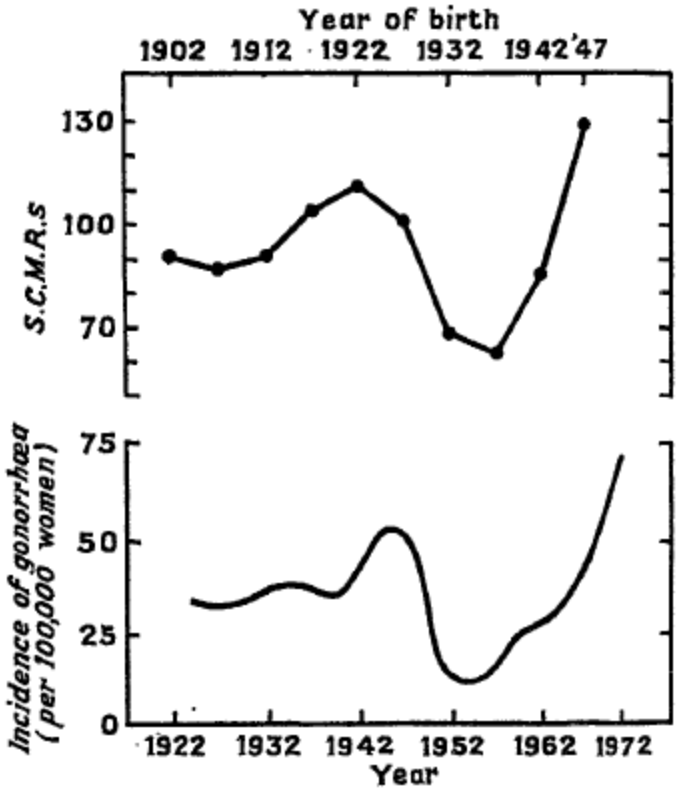

Fig. 1—S.C.M.R.s from cervical cancer among women born between 1902 and 1947 in England and Wales and incidence of gonorrhœa among women in England and Wales, 1925-72.

STANDARDISED MORTALITY RATIOS FOR CERVICAL CANCER BY SOCIAL CLASS AND HUSBAND'S OCCUPATION IN MARRIED WOMEN (ENGLAND AND WALES 1959–63)

Social class	Occupation of husband	S.M.R.
I	All occupations	34
	Clergymen	12
	Scientists	17
	Civil engineers	60
II	All occupations	64
	Teachers	30
	Senior government officials	40
	Publicans and inn keepers	120
	Lodging house and hotel keepers	150
III	All occupations	100
	Clerks of work	40
	Clerks	64
	Crane and hoist operators	159
	Drivers of road goods vehicles	168
IV	All occupations	116
	Shopkeepers and assistants	71
	Gardeners and groundsmen	98
	Fishermen	257
	Deck and engineroom ratings, barge and boatmen	263
V	All occupations	181
	Office and window cleaners	95
	Labourers	222

THE LANCET, MAY 25, 1974

HPV

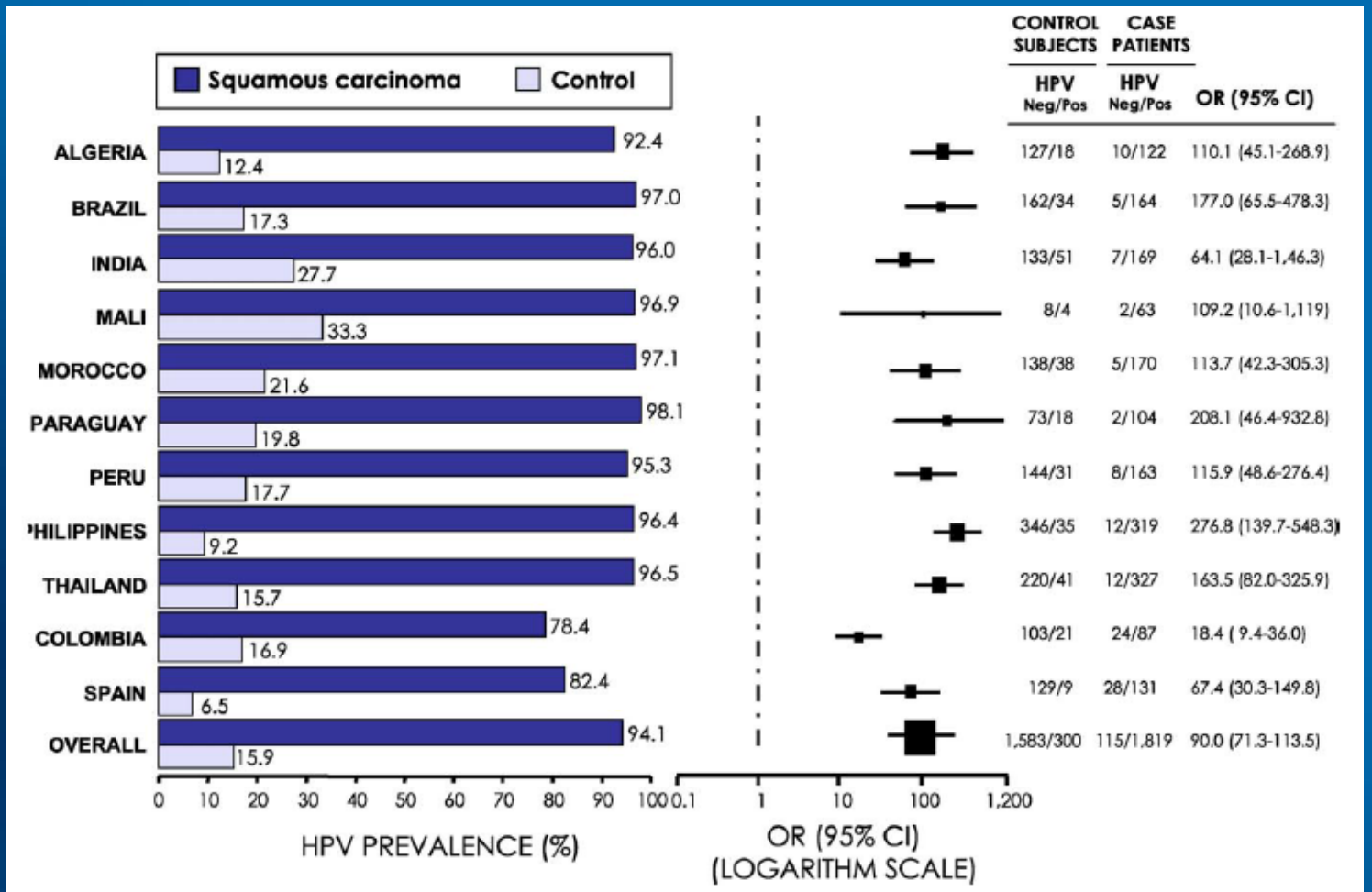

Fig. 3. Left panel: prevalence of HPV-DNA by country among women with squamous cell carcinoma (SCC) and among control women. Right panel: odds ratios (OR) for cervical SCC with 95% confidence intervals (CI). ORs are adjusted by center and age. Adapted and expanded from [13].

Munoz et al. *NEJM* 2003;348:518-27

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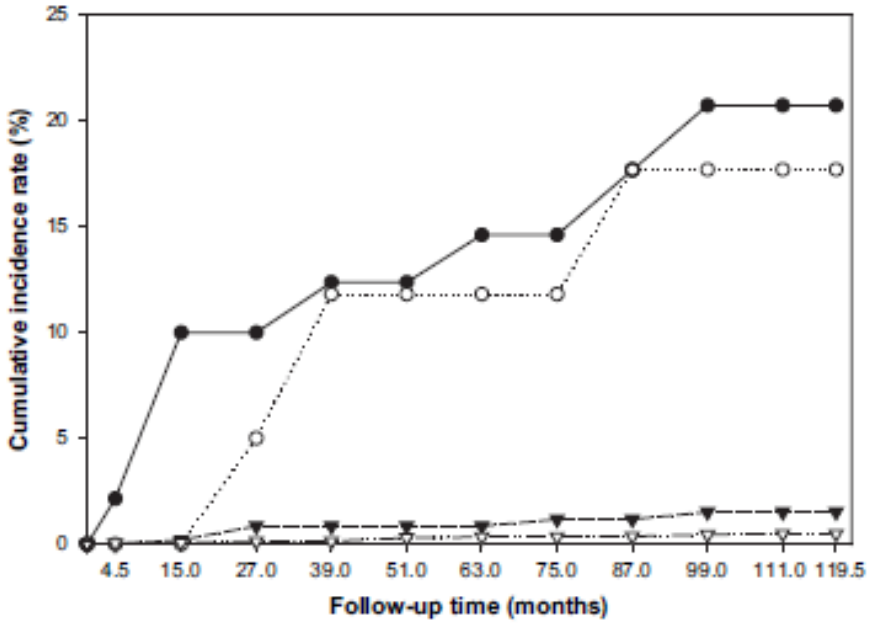
HPV

- US cohort study
- Baseline: HPV DNA test, Pap smear
- Routine cytology follow-up over 10 years for cervical-cancer precursor lesion (CIN3)



No.of women seen during follow-up interval

HPV16+	93	50	39	38	36	39	28	28	27	11	1
HPV18+	38	18	20	14	15	12	9	15	11	3	0
HC2+	890	498	463	419	370	353	310	276	288	127	7
HC2-	11741	6763	6231	5784	5369	4923	4619	4281	4140	2051	133

Fig. 3. Cumulative incidence of cervical intraepithelial neoplasia grade 3 and cancer (≥CIN3) over a 10-year period in 12976 women 30 years old and older with negative cytology at enrollment, according to oncogenic human papillomavirus (HPV) status at enrollment. HPV status is defined hierarchically as: positive for HPV 16 (**closed circles**), else positive for HPV18 (**open circles**), else positive for the non-HPV16/18 oncogenic types in Hybrid Capture 2 (HC2) (**closed triangles**), else oncogenic HPV negative (**open triangles**).

Khan et al. *JNCI* 2005;97:1072-9

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Viruses that are indirect carcinogens

1) By causing chronic inflammation

- HBV
- HCV

2) By causing immune suppression

- EBV
- KSHV / HHV8
- HIV

HBV and HCV

Agent	Sufficient evidence (Group 1)	Limited evidence (Group 2A)	Established mechanistic events
Hepatitis B virus	• Hepatocellular carcinoma (54%)	• Cholangiocarcinoma • Non-Hodgkin lymphoma	Inflammation Liver cirrhosis Chronic hepatitis
Hepatitis C virus	• Hepatocellular carcinoma (31%) • Non-Hodgkin lymphoma	• Cholangiocarcinoma	Inflammation Liver cirrhosis Liver fibrosis

HBV

- Taiwan cohort study, 20-years follow-up after intervention
- Hepatocellular carcinoma incidence by HBV vaccination status at birth

Table 4. Multivariable-adjusted relative risk of developing hepatocellular carcinoma (HCC) between July 1983 and June 2004 in birth cohorts born before vs after the national hepatitis B virus vaccination program*

Variable	Group	Person-years	No. of HCCs	RR (95% CI)	P
Birth cohort	Nonvaccinated	78496404	444	1.00 (referent)	
	Vaccinated	37709340	64	0.31 (0.24 to 0.41)	<.001
Age, y	6–9	32051011	100	1.00 (referent)	
	10–14	41404604	180	1.18 (0.92 to 1.51)	.183
	15–19	42750129	228	1.26 (0.99 to 1.60)	.065
Sex	Female	56129109	140	1.00 (referent)	
	Male	60076635	368	2.50 (2.04 to 3.01)	<.001

* Rate ratio with 95% CIs and *P* values were estimated by Poisson regression analysis. All statistical tests are two-sided. CI = confidence interval; RR = relative risk.

Chang et al. *JNCI* 2009;101:1348-55

HIV

Agent	Sufficient evidence (Group 1)	Limited evidence (Group 2A)	Established mechanistic events
Human immunodeficiency virus, type 1	• Kaposi sarcoma • Non-Hodgkin lymphoma • Hodgkin lymphoma • Cervical cancer • Anus cancer • Conjunctival cancer	• Vulvar cancer • Vaginal cancer • Penis cancer • Non-melanoma skin cancer • Hepatocellular carcinoma	Immunosuppression (indirect action)

HIV

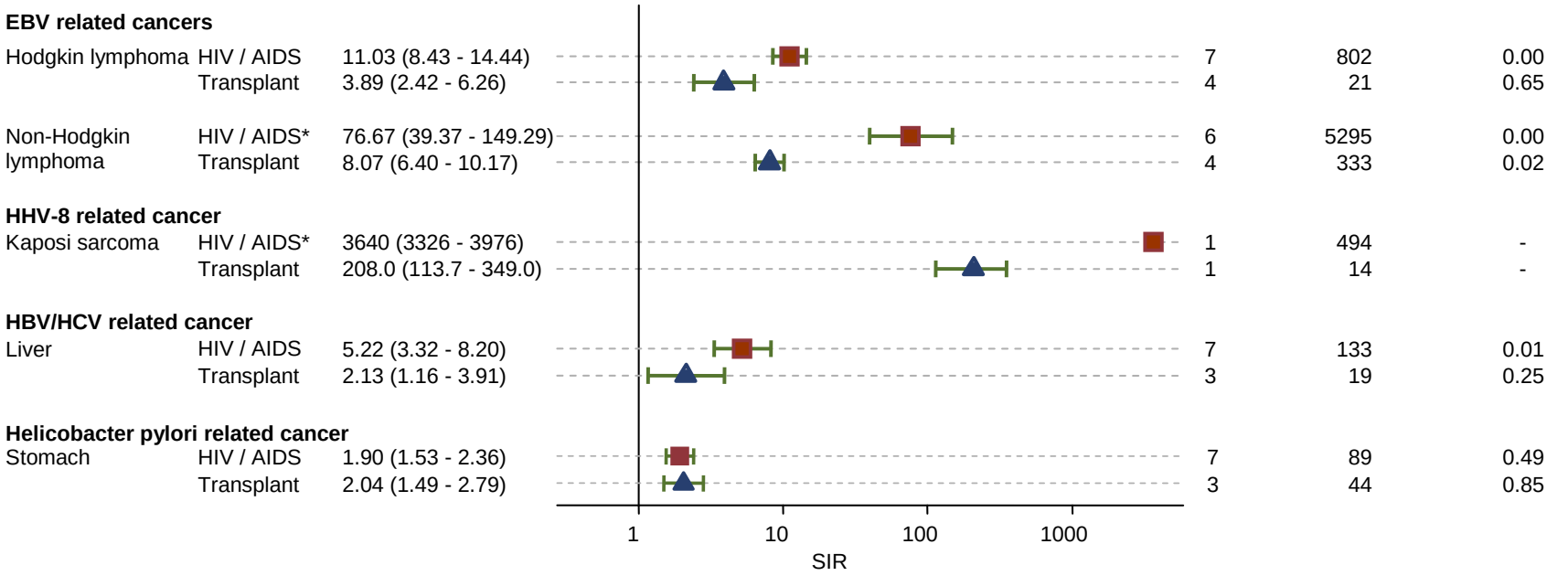

Figure 2: Standardised incidence ratios for cancers related to infection with Epstein-Barr virus, human herpesvirus 8, hepatitis B and C virus, and *Helicobacter pylori* in people with HIV/AIDS and in transplant recipients

EBV=Epstein-Barr virus. HBV=hepatitis B virus. HCV=hepatitis C virus. HHV8=human herpesvirus8. *For AIDS-defining cancers, data from cohorts defined by an AIDS diagnosis included only those individuals who did not have that type of cancer at the time of AIDS.

Grulich et al. *Lancet* 2007;370:59-67

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HIV

Grulich et al. *Lancet* 2007;370:59-67

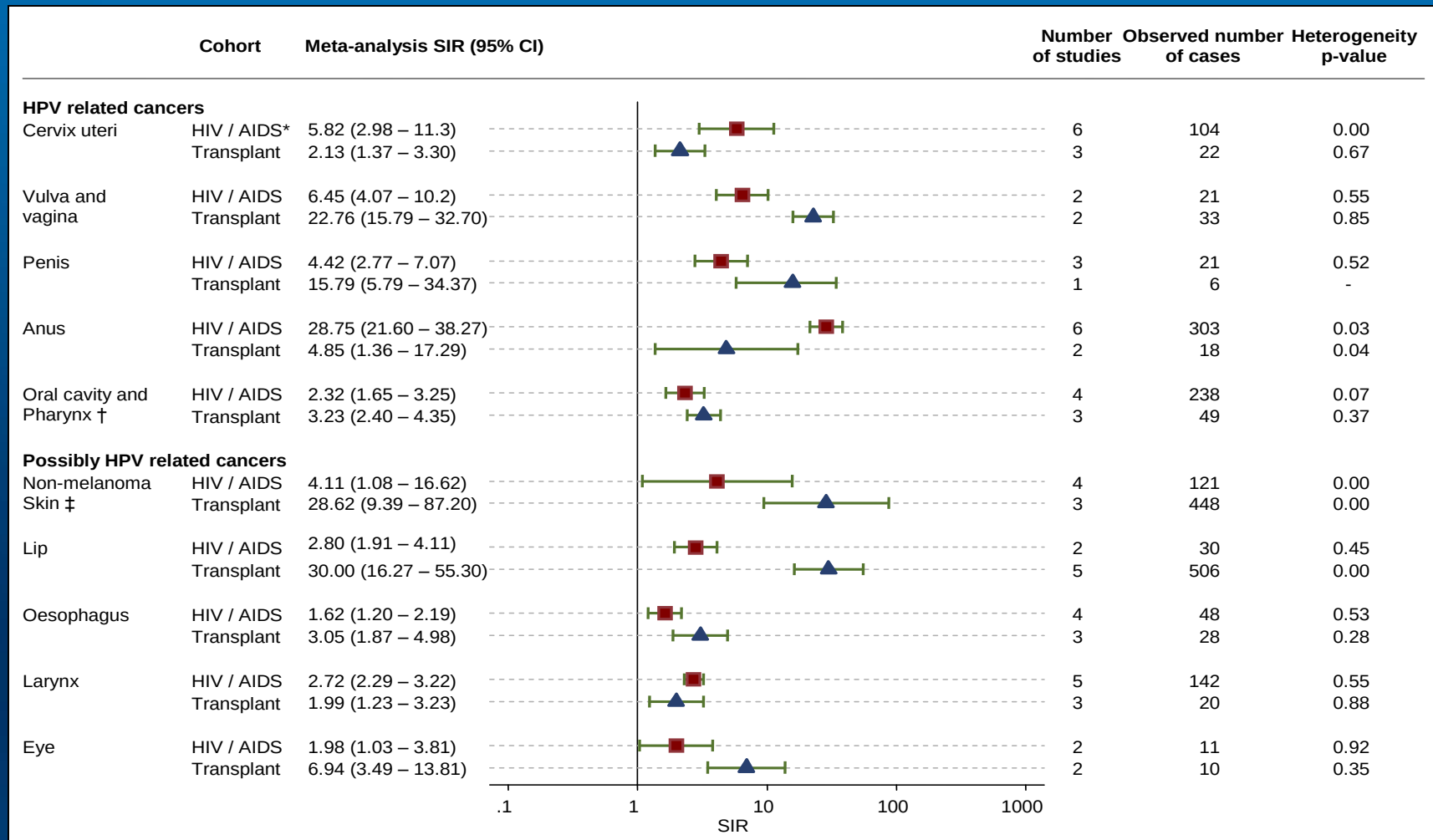

Figure 3: Standardised incidence ratios for cancers related to, or possibly related to, human papillomavirus infection, in people with HIV/AIDS and in transplant recipients

HPV=human papillomavirus. *For the AIDS-defining cancer (cervical cancer), data from cohorts defined by an AIDS diagnosis included only those individuals who did not have cervical cancer at the time of AIDS. †Excluding lip and nasopharynx. ‡Any measure of non-melanoma skin.

Summary

- Epidemiology will continue to have a key role in determining the carcinogenesis of viruses
- Well designed studies are critical
- Now and into the future:
  - combination of traditional and next generation epidemiology
  - improved cancer phenotyping
  - improved identification of co-factors, i.e.
    - The agent itself (variants or subtypes)
    - Host (gene polymorphisms, immune status)
    - Environment (e.g. another infection)

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