

Co-infection and Cancer

New Program Announcement with Review (PAR) Concept

Division of Cancer Control and Population Sciences
Division of Cancer Biology
Division of Cancer Prevention
Center for Global Health
Center to Reduce Cancer Health Disparities

Purpose

- *Enhance mechanistic and epidemiologic research in co-infection* and cancer.*
- *Identify markers for early detection and prevention.*

*Co-infection: the occurrence of infections by two or more infectious (pathogenic or non-pathogenic) agents-either concurrently or sequentially and includes both acute and chronic infections by viruses, bacteria, parasites, and/or other microorganisms.

For the purpose of this FOA, we exclude co-infection with HIV.

Cancer-causing Pathogens: 15% New Cancer Cases*

Viruses	Cancer
Epstein-Barr virus (EBV)	Lymphoma, nasopharynx, leukemia
Hepatitis B and Hepatitis C viruses	Hepatocellular carcinoma
Human papillomavirus (HPV)	Anal, cervical, head and neck, oral, penile, vaginal, vulvar
Human immunodeficiency virus (HIV)	Kaposi sarcoma, AID-related lymphomas

Bacteria	Cancer
<i>Helicobacter pylori</i> (<i>H.pylori</i>)	Stomach

Parasites	Cancer
Liver flukes	Biliary, cholangiocarcinoma, gallbladder, pancreas
Schistosoma haematobium	Bladder

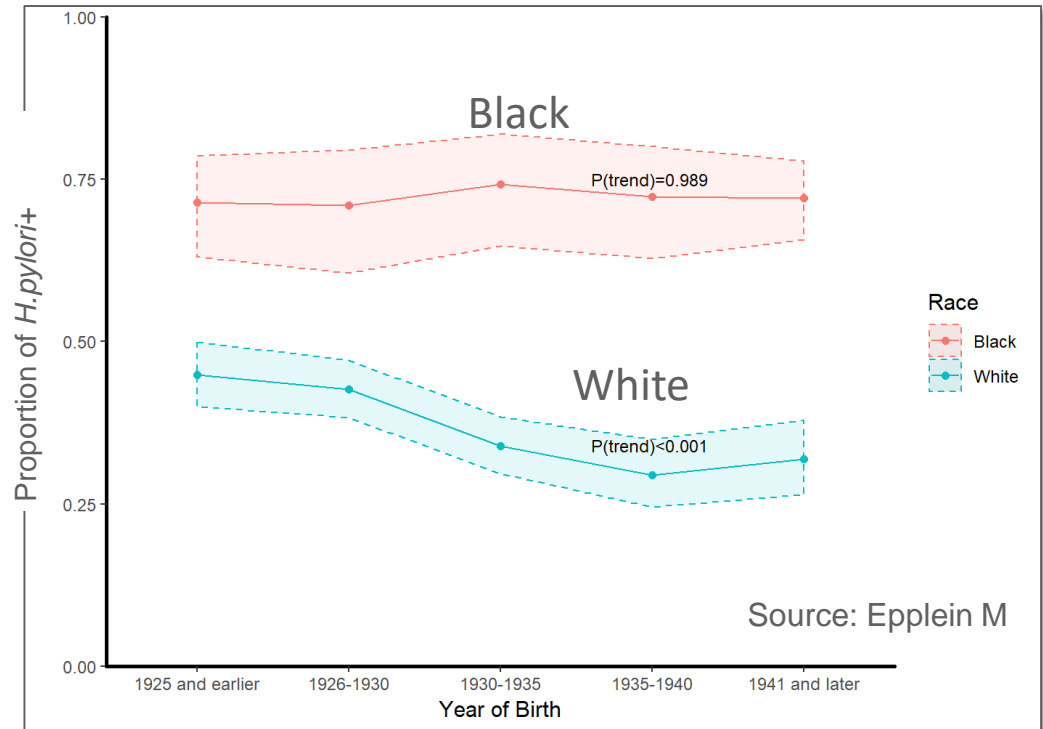
* Plummer, Lancet Global Health 2016

Global and U.S. Prevalence of Carcinogenic Agents

	EBV	<i>H.pylori</i>	HPV	Hepatitis B	Hepatitis C
World ¹	≥90%	~50%	~12%	~4%	~2%
U.S. ²	~80%	~30%	~23%*	≤0.4%	~1%

¹WHO; ²CDC; *High-risk HPV types

U.S. Population	<i>H.pylori</i> prevalence
White	20%
Black	50-80%



Infection-Driven Carcinogenesis

- Most infected individuals are chronic carriers and *rarely* develop the associated cancer
- Infection-driven cancer initiation and progression *may* require additional co-factors
 - What factors act cooperatively with the pathogens to produce cancer?
 - What are the mechanisms that underpin that cooperation?
- **Co-infection**
 - **What is the involvement of other pathogenic agents and non-pathogenic agents in the development and/or progression of cancer?**

Prevalence of Co-infection: *Likely* High

Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical

BJC

British Journal of Cancer (2015) 112, 1866–1873 | doi:10.1093/bjc/dzq000

Epstein Barr Virus and *Helicobacter pylori* Co-Infection Are Positively Associated with Gastric Cancer in Pediatric Patients

Salyakina and Tsinioremas *Human Genomics* 2013, 7:23
<http://www.humgenomics.com/content/7/1/23>



María G. Cárdena

PRIMARY RESEARCH

Open Access

Keywords: EBV; *Helicobacter pylori*; intestinal and diffuse gastric cancer; premalignant lesions; gastritis; c

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- Evidence on co-infection and cancer risk is suggestive.
- Direct role in causation is unknown.
- Mechanisms are speculative.

A Multifactorial Role for *P. falciparum* Malaria in Endemic Burkitt's Lymphoma

Charles Torgbor^{1,2}, Peter Awuah³
David A. Thorley-Lawson^{1,3*}

Cell. 2015 August 13; 162(4): 727–737. doi:10.1016/j.cell.2015.07.019.

Plasmodium Infection Promotes Genomic Instability and AID Dependent B Cell Lymphoma

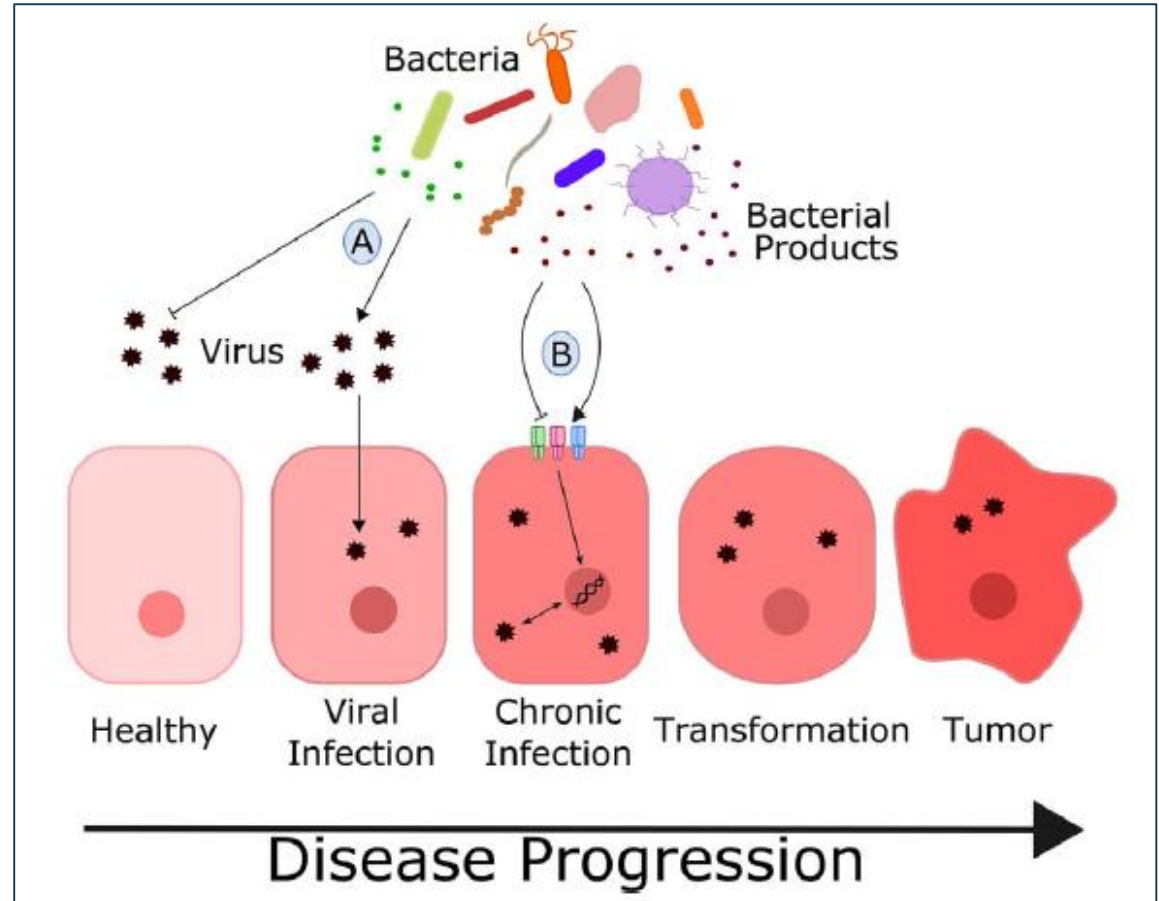
Davide F. Robbiani^{1,*}, Stephanie Deroubaix¹, Niklas Feldhahn^{1,4}, Thiago Y. Oliveira¹, Elsa

Mechanisms of Infection-driven Carcinogenesis

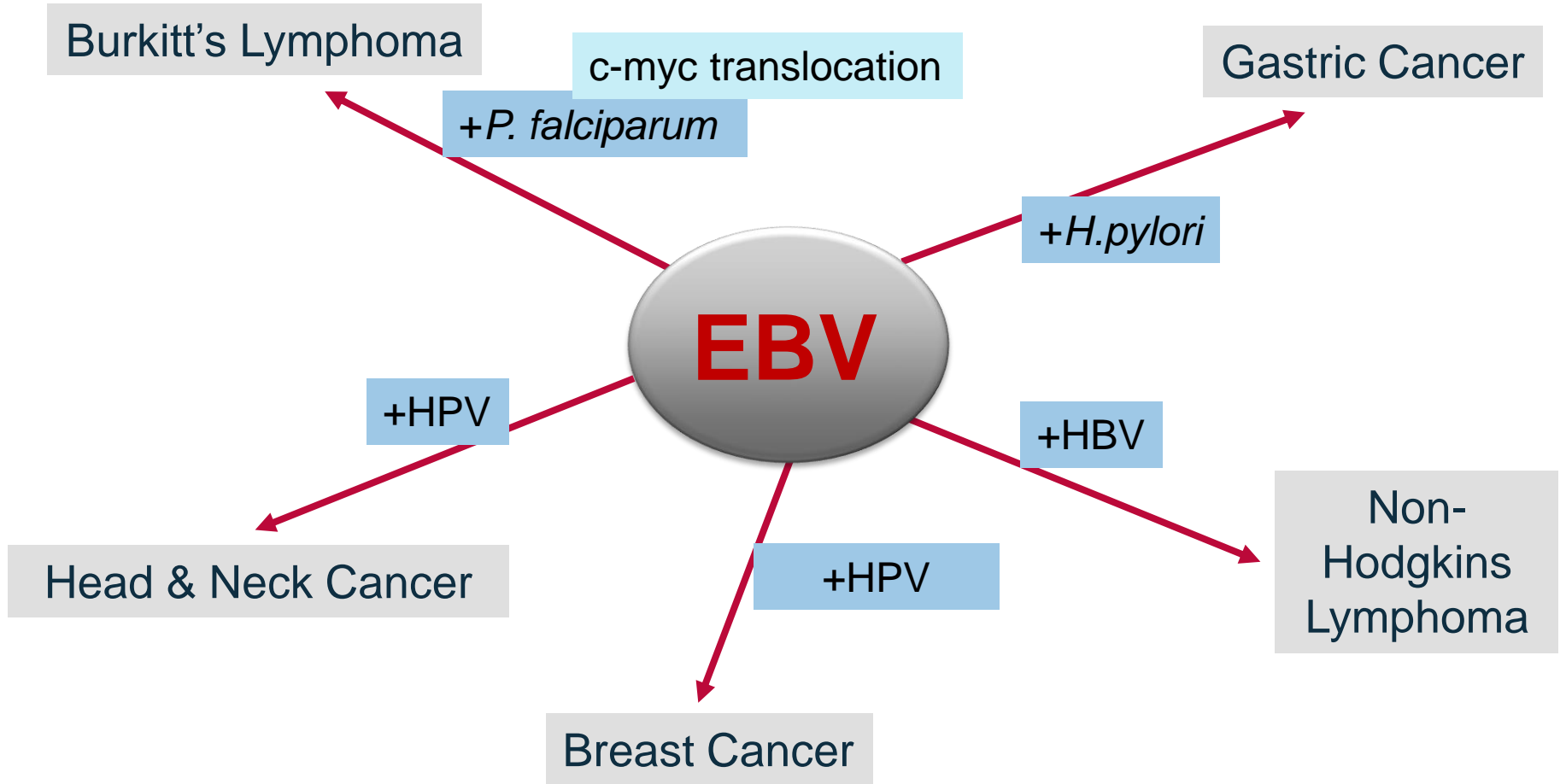
Co-infection: Unclear

Potential Mechanism

- Inflammation
- Host immune responses
- Immune evasion
- Genomic instability
- Altered tumor niche
- Changes in viral integration into hosts' genome
- Episome maintenance



Mechanism Examples



Infection with another infectious agent(s) may be the necessary co-factor for infection-related cancer initiation and progression.

- Etiologic role of co-infection in cancer risk is suspected but largely unknown.
- Mechanisms of co-infection in carcinogenesis is unclear.
- Identification of risk profiles may lead to targeted interventions and prevention strategies.

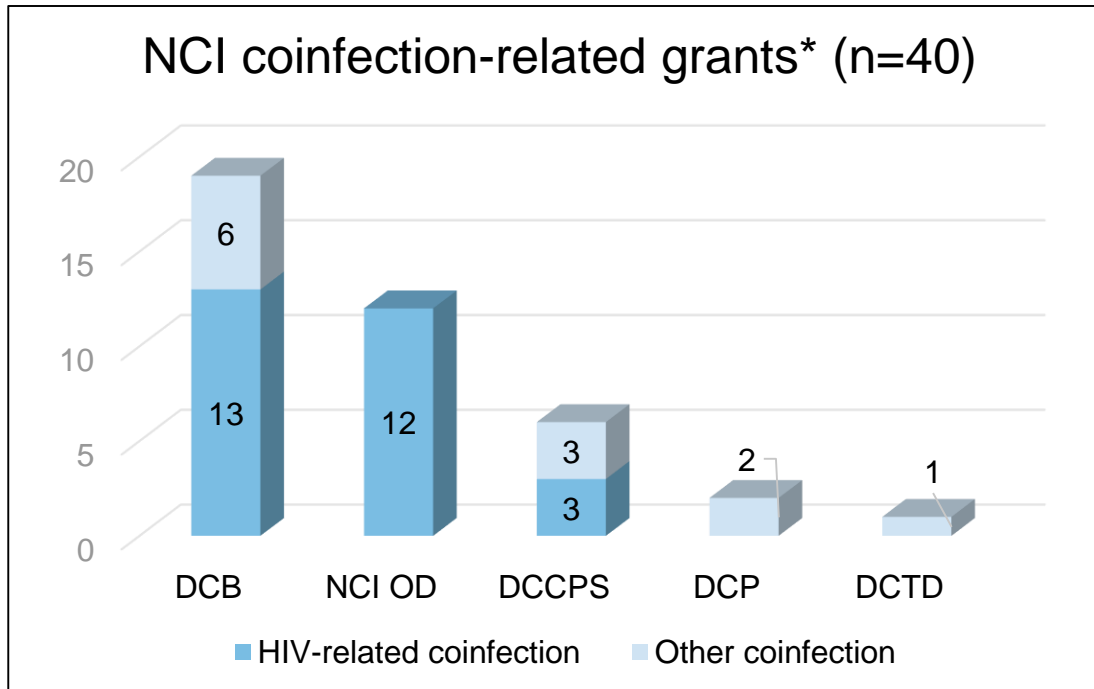
PAR Co-infection and Cancer: Area of Warranted Research

- Responses from Request for Information (NOT-CA-16-067)
- Discussions across NCI
 - Disparities/Inequities
 - Global Health Implications
 - Encourage investigations of co-infection with certain infectious agents (e.g., EBV and *H.pylori*)
 - Exclude Co-infection with HIV

- Identify role(s) of co-infection in cancer susceptibility.
- Investigate mechanisms underlying co-infection and carcinogenesis.
- Determine the effect of timing and type of initial infection and secondary infection(s) on susceptibility to cancer.
- Develop of new models to test mechanisms of co-infection driven cancer etiology.
- Identify molecular signatures of co-infection that distinguish cancer susceptibility.

Proposed Characteristics of PAR and Portfolio Analysis

- Funding Opportunity Announcement: PAR
- Mechanism: R01, R21



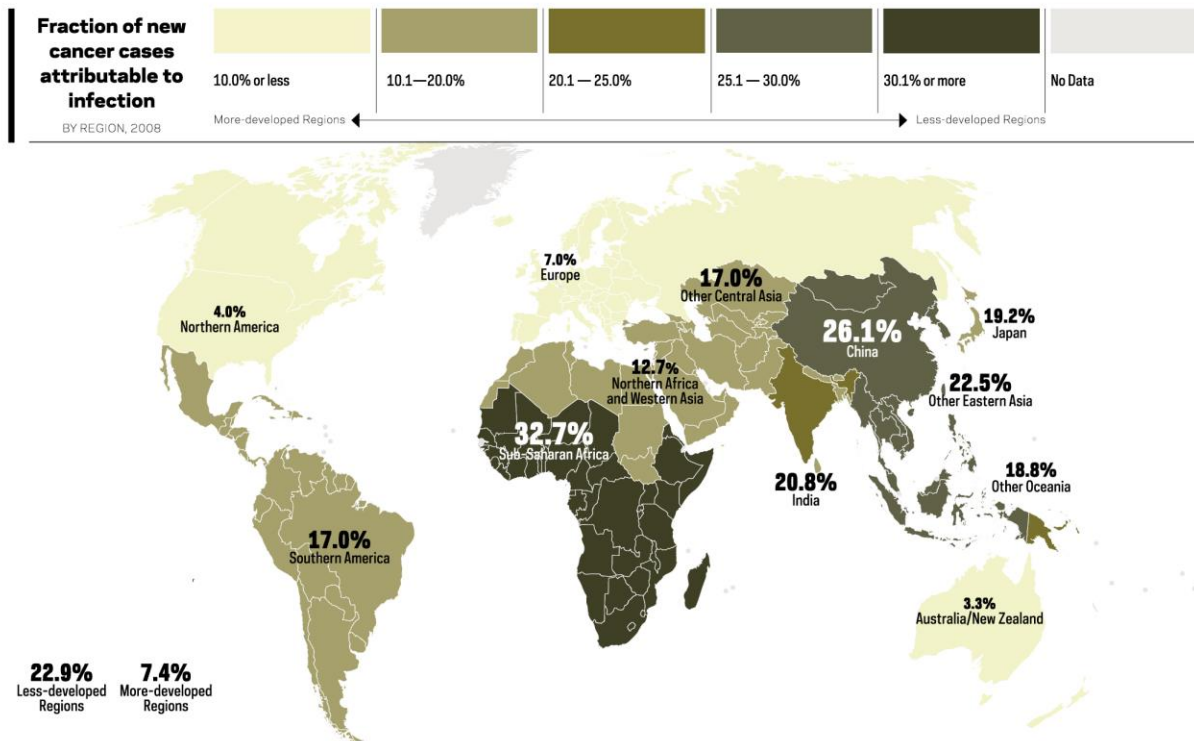
*Active grants only; search date: 3/2019

THANK YOU

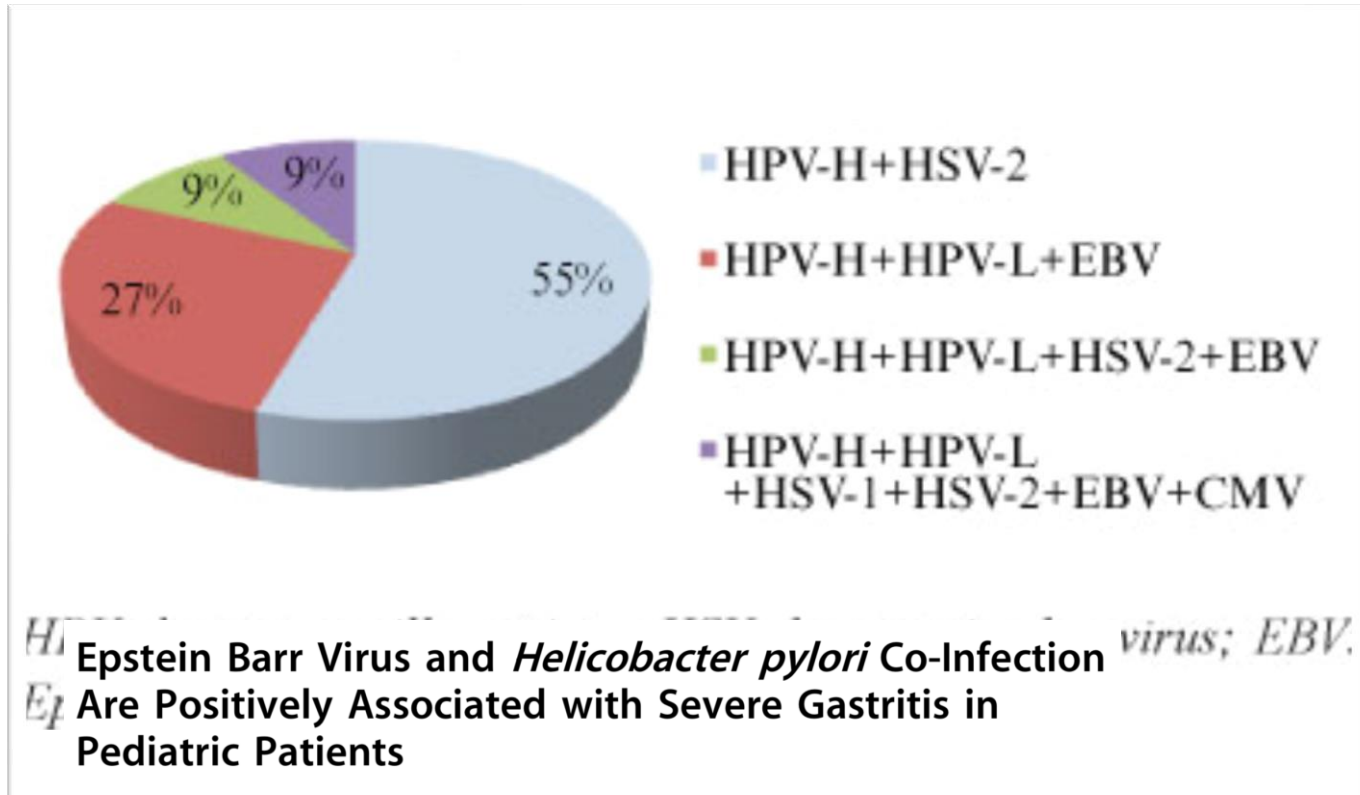
- Divi Rao
- Danielle Carrick
- Gary Ellison
- Mukesh Verma
- Phil Dashner
- Betsy Read-Connole
- Jo Ann Rinaudo
- Sudha Sivaram
- Vidya Vedham
- Anil Wali

A higher proportion of cancer cases are due to infection in lower income countries, particularly in Asia and Sub-Saharan Africa.

Fraction of new cancer cases attributable to infection (by region, 2008)



Invasive Cervical Cancer: Co-infection with HPV



H. pylori virus; EBV.
Epstein Barr Virus and *Helicobacter pylori* Co-Infection Are Positively Associated with Severe Gastritis in Pediatric Patients

María G. Cárdenas-Mondragón, Ricardo Carreón-Talavera, Margarita Camorlinga-Ponce,

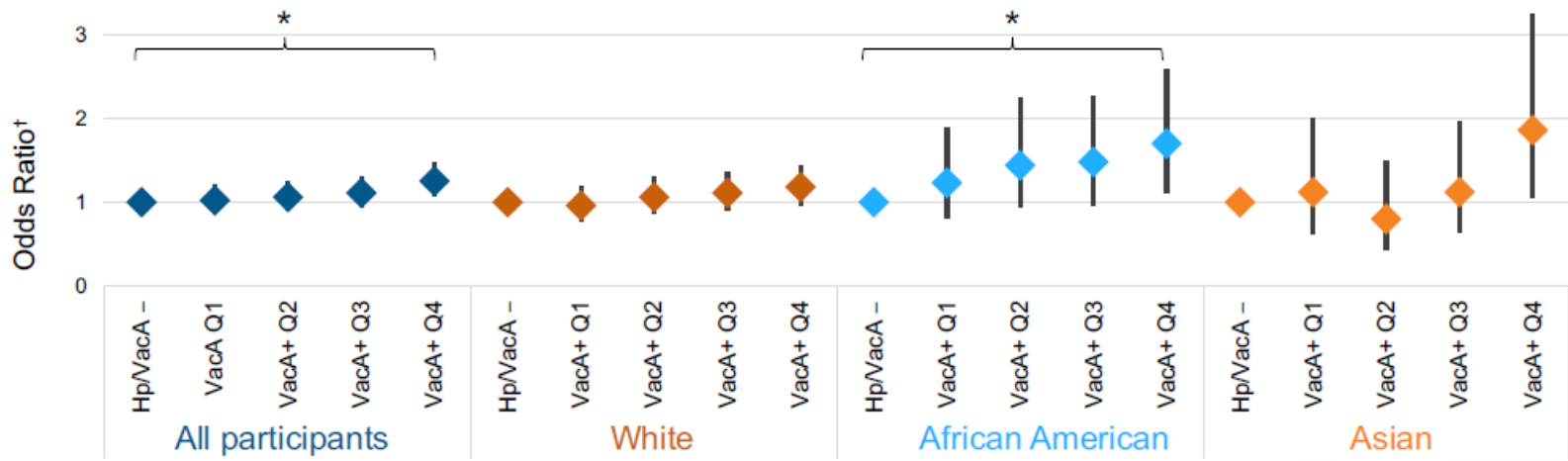
Source: Smith JS, JNCI 2002

HPV: A Necessary but Insufficient Cause

- Established cofactors: tobacco smoking, high parity, long-term hormonal contraceptive use, co-infection with HIV
- Probable cofactors: coinfection with *Chlamydia trachomatis*, herpes simplex virus type-2, immunosuppression, certain dietary deficiencies
- Likely important: genetic and immunologic host factors and viral factors other than type (ie., variants of type, viral load, viral integration)
- High number of sexual partners increases acquisition of oncogenic HPV infections

H.pylori and Colorectal Cancer

Odds of colorectal cancer incidence by strength of antibody response to *H. pylori* VacA, among participants in 10 US cohorts



* p-value for trend <0.01

† conditional logistic regression with cases matched to controls on age, race, sex, and cohort

Gastroenterology

Are people harboring different bacteria based on genetic origin or heritage?

Beyond Established Carcinogenic Infectious Agents

OXFORD

ARTICLE

Antibodies Against *Chlamydia trachomatis* and Ovarian Cancer Risk in Two Independent Populations

Britton Trabert, Tim Waterboer, Annika Idahl Sally B. Coburn, Patricia Hartge, Katrin Hufna, Alexander Mentzer, Beata Peplonska, Mark E. Michael Pawlita, Nicolas Wentzensen

JNCI J Natl Cancer Inst (2019) 111(2): djy084

doi: 10.1093/jnci/djy084
Article



IJC

International Journal of Cancer

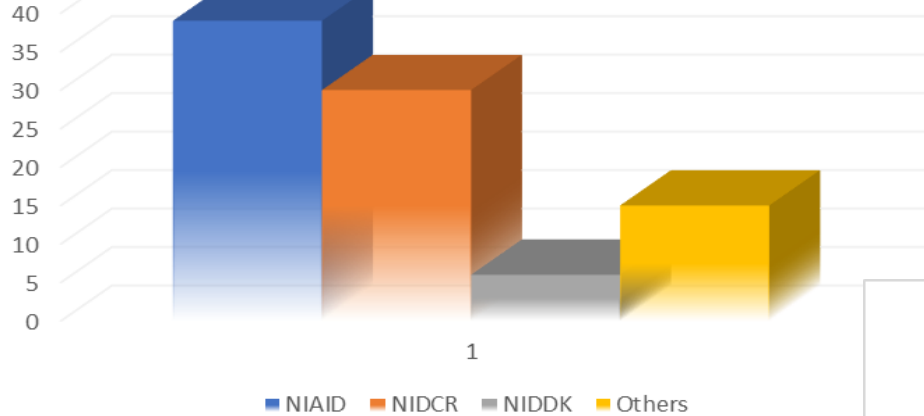
Prospective seroepidemiologic study on the role of Human Papillomavirus and other infections in cervical carcinogenesis: Evidence from the EPIC cohort

Xavier Castellsagué^{1,2}, Michael Pawlita³, Esther Roura^{1,2}, Núria Margall⁴, Tim Waterboer³, F. Xavier Bosch¹, Silvia de Sanjosé^{1,2}, Carlos Alberto Gonzalez⁵, Joakim Dillner^{6,7}, Inger T. Gram⁸, Anne Tjønneland⁹, Christian Munk¹⁰, Valeria Pala¹¹, Domenico Palli¹², Kay-Tee Khaw¹³, Ruanne V. Bamabas^{14,15}, Kim Overvad¹⁶, Françoise Clavel-Chapelon^{17,18,19}, Marie-Christine Boutron-Ruault^{17,18,19}, Guy Fagherazzi^{17,18,19}, Rudolf Kaaks²⁰, Annekatrin Lukanova^{20,21}, Annika Steffen²², Antonia Trichopoulou^{23,24}, Dimitrios Trichopoulos^{23,25,26}, Eleni Klinaki²³, Rosario Tumino²⁷, Carlotta Sacerdote²⁸, Amalia Mattiello²⁹, H. B(as) Bueno-de-Mesquita^{30,31,32}, Petra H. Peeters^{30,33}, Eiliv Lund⁸, Elisabete Weiderpass^{7,8,34,35}, J. Ramón Quirós³⁶, María-José Sánchez^{2,37,38}, Carmen Navarro^{2,39,40}, Aurelio Barricarte^{2,41}, Nerea Larrañaga^{2,42}, Johanna Ekström⁴³, Maria Hortlund⁴⁴, David Lindquist⁴⁵, Nick Wareham⁴⁶, Ruth C. Travis⁴⁷, Sabina Rinaldi⁴⁸, Massimo Tommasino⁴⁸, Silvia Franceschi⁴⁸ and Elio Riboli³⁰

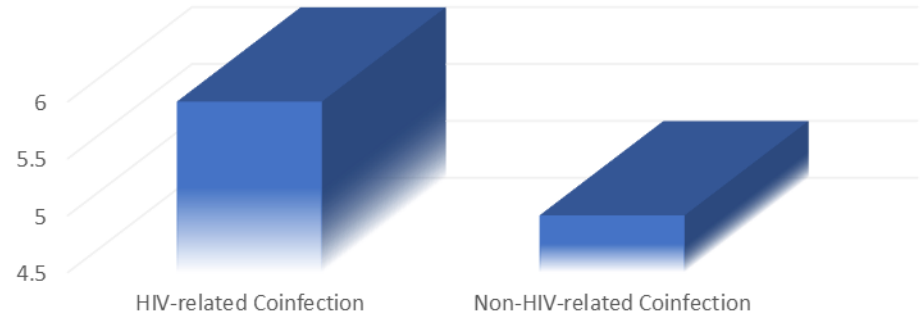
NIH-wide Portfolio Analysis: Infections & Cancer

INFECTION-RELATED GRANTS

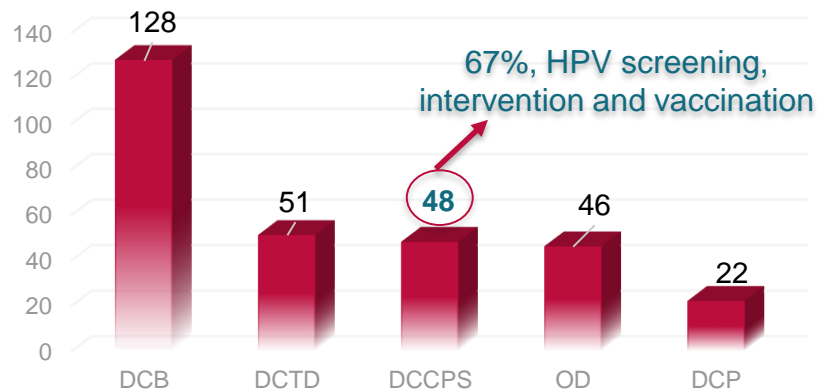
(N=90)



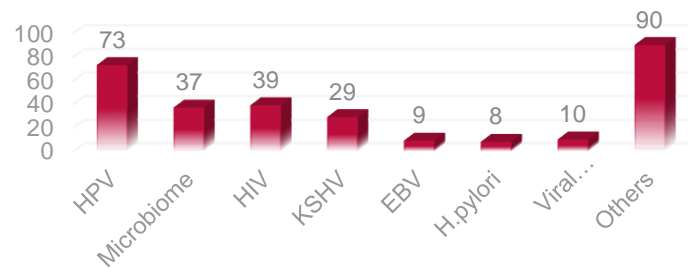
CO-INFECTION GRANTS (N=11)



NCI INFECTION-RELATED GRANTS* (N=295)



INFECTION-RELATED GRANTS, BY INFECTIOUS AGENTS (N=295)



Others: cytomegalovirus, adenovirus, Vesicular Stomatitis Virus, Human T-cell leukemia virus type