



Protein-specific antibodies to *Helicobacter pylori* as a marker of disease risk

NCI Division of Cancer Control and Population Science 2014
New Grantee Workshop

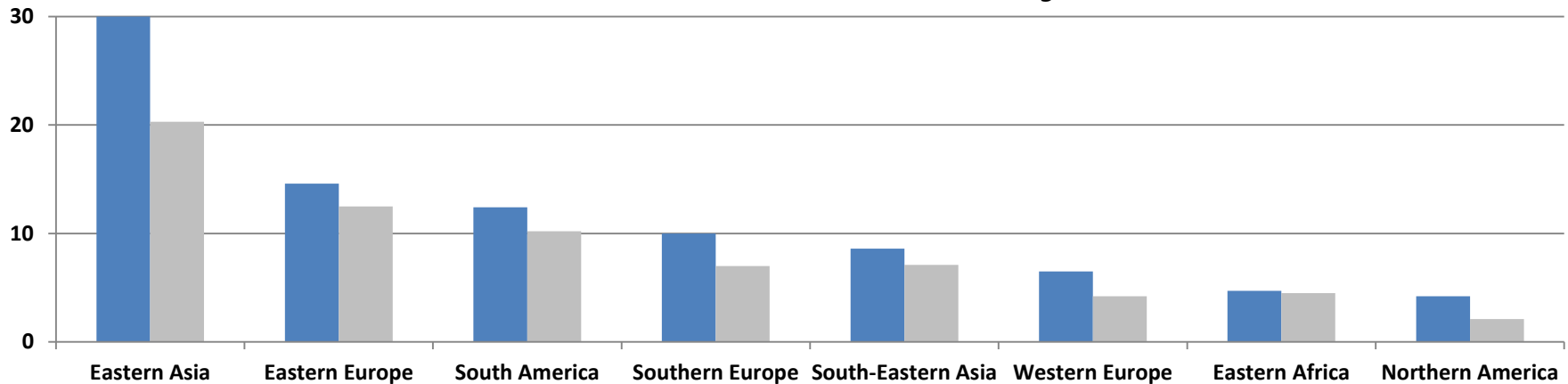
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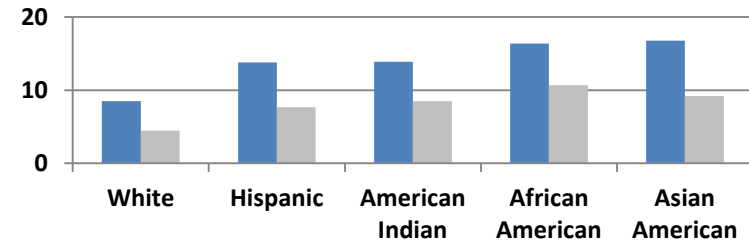
Gastric Cancer

- ▶ 4th most common cancer worldwide (1 million new cases a year)
- ▶ 2nd most common cause of death from cancer

Gastric cancer incidence and mortality in 2008



	Numbers	ASR (W)
World	988,602	14.0
East Asia	601,314	30.0
China	464,349	29.9
Japan	102,040	31.1
Korea	27,098	41.4

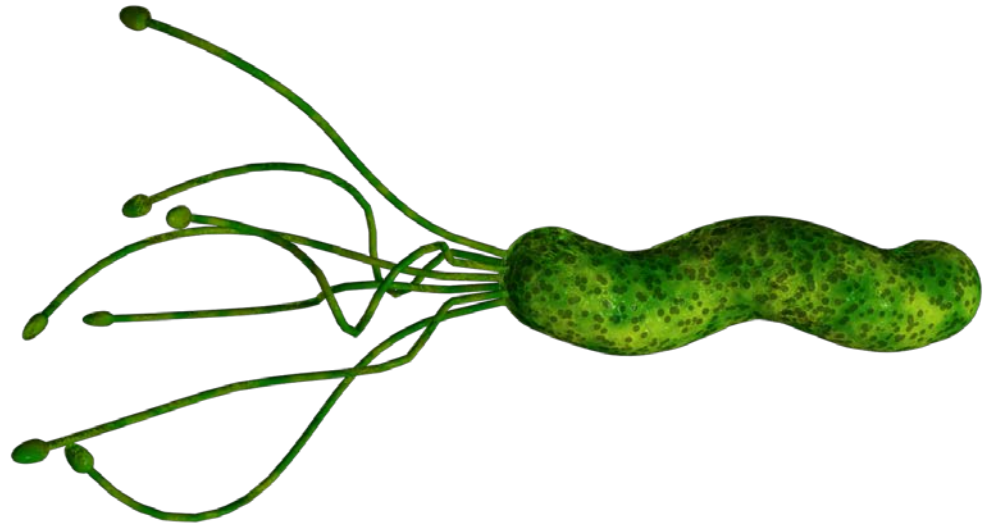


Gastric Cancer Risk Factors

- Age ↑
- Diet
 - Fruits (vegetables) ↓
 - Salt, salty food (red and processed meat) ↑
- Smoking ↑
- Low socio-economic status ↑
- Familial predisposition ↑
 - 2-3 fold increased likelihood

Helicobacter pylori (*H. pylori*)

- Gram-negative, spiral microaerophilic bacterium
- Infects >50% world population
- Mode of transmission is uncertain
 - Humans are the only known reservoirs
- Class I human carcinogen
 - Increases risk of gastric cancer at least 6-fold
 - Single agent responsible for the greatest burden of infection-associated cancers



H. pylori and gastric cancer risk

- Meta-analysis of *H. pylori* eradication trials showed that eradication therapy **reduced gastric cancer risk by 35%**
- Why not mass eradication?
 - Majority of those infected will not develop cancer
 - Antibiotic resistance
 - Potential benefits of infection
- Need: a biomarker to identify those at higher risk
 - CagA
 - In China, the majority of the population are CagA+ *H. pylori*+

K07: *H. pylori* blood biomarker for gastric cancer risk

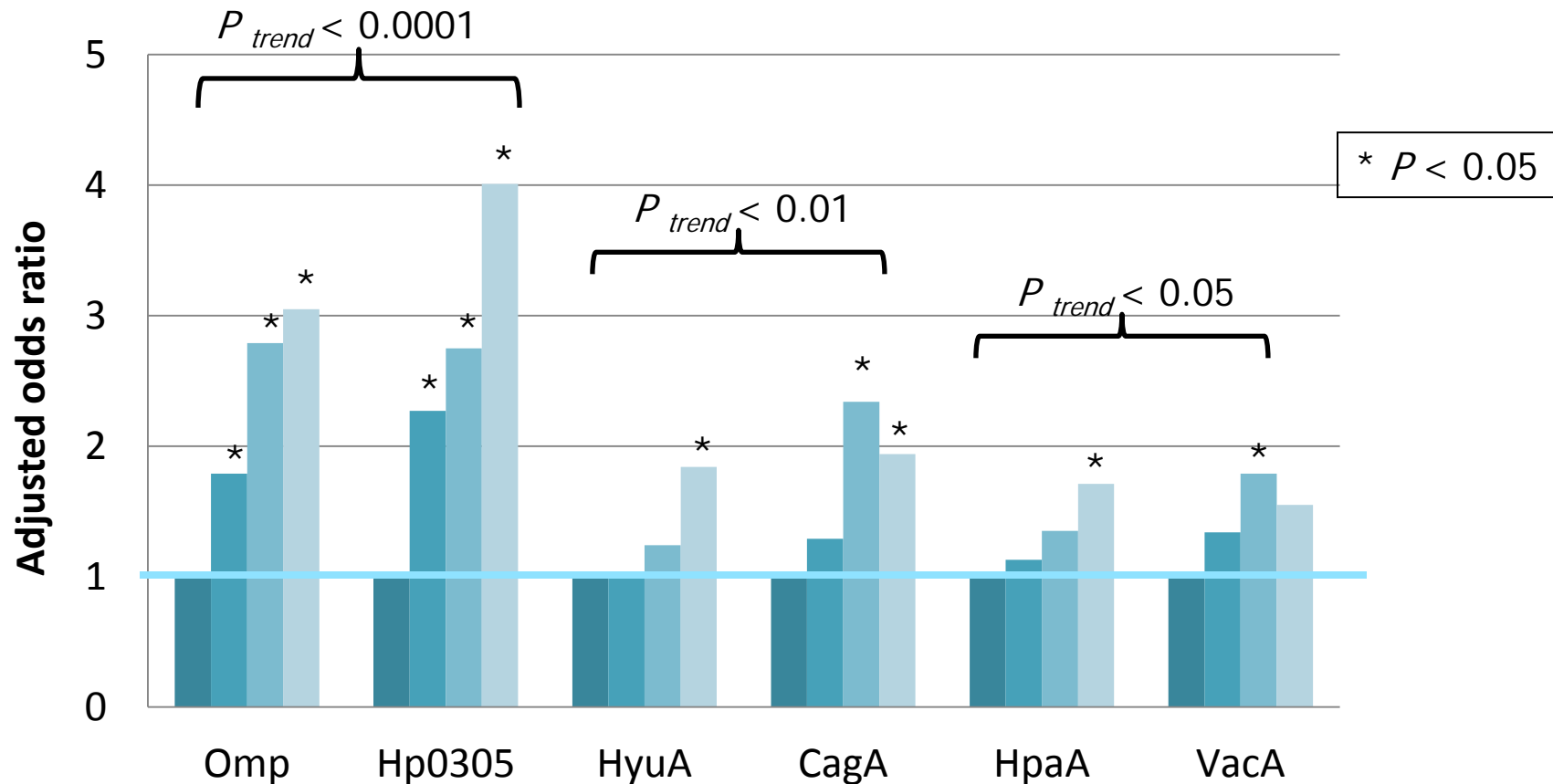
AIM: To examine associations between serum antibodies to 15 *H. pylori* proteins and gastric cancer risk in China, as a potential new risk marker

- Population: Shanghai Men's Health Study
 - Nested case-control study among 61,582 men
 - 40-74 yrs at baseline in 2002-2006
- Outcome: Distal gastric cancer
 - 226 cases and 451 matched controls
- Method: *H. pylori* multiplex serology
 - Developed at the German Cancer Research Center to detect antibodies to 15 *H. pylori* proteins
 - Previously examined in relation to gastric cancer risk in only 1 study, a case-control study in Germany

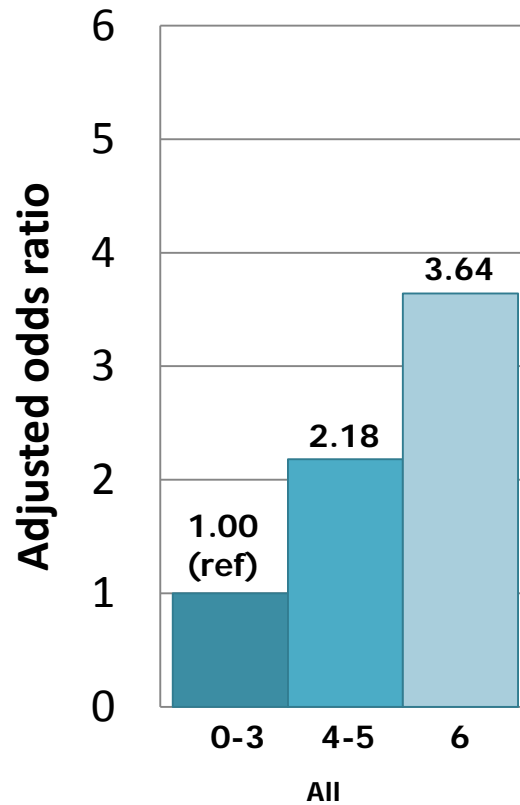
Results

<u>GERMANY</u>		<u>SMHS</u>		<u>SMHS, excluding early cases</u>	
CagA	5.6	CagA	1.7	CagA	3.6
GroEL	4.7	GroEL	1.2	GroEL	1.4
HcpC	3.0	HcpC	1.0	HcpC	1.1
HP 0305	2.3	HP 0305	2.3	HP 0305	2.5
Catalase	2.2	Catalase	1.0	Catalase	1.0
VacA	2.2	VacA	1.6	VacA	2.4
Cag16	1.9	Cag16	1.1	Cag16	1.2
HyuA	1.6	HyuA	1.5	HyuA	1.4
Omp	1.4	Omp	3.0	Omp	4.4
HP 0231	1.1	HP 0231	1.0	HP 0231	1.0
NapA	1.4	NapA	1.3	NapA	1.4
Cad	1.1	Cad	0.9	Cad	1.1
UreA	0.8	UreA	0.9	UreA	1.0
Cag3	1.3	Cag3	0.7	Cag3	0.9
HpaA	0.8	HpaA	1.5	HpaA	1.9

Increasing quartile of antibody level to specific *H. pylori* proteins and gastric cancer risk



Number of sero-positives and gastric cancer risk



R01: *H. pylori* blood biomarker for gastric cancer risk in East Asia

Phase I: Replicate our findings in 8 cohorts from China, Japan, and Korea, utilizing blood samples from 2,000 cases and 2,000 controls

Cohort name	Location	Cohort size	Age	Cases
CHINA				
Shanghai Men's Health Study	Vanderbilt University	61,500	40-74	150
Shanghai Women's Health Study	Vanderbilt University	74,942	40-70	375
Nutrition Intervention Trial - Linxian	Chinese Academy of Medical Sciences	33,000	40-69	300
JAPAN				
Japan Public Health Center-based Prospective Study	National Cancer Center, Japan	90,296	45-74	450
KOREA				
Korean Multicenter Cancer Cohort	Seoul National University	19,688	37-83	300
Korean National Cancer Screenee Cohort	National Cancer Center, Korea	34,211	30+	200
Health Examinees Study	Seoul National University	155,000	40-69	150
Korean Cancer Prevention Study-II	Yonsei University	156,795	21-95	300
Total				2,000

R01: *H. pylori* blood biomarker for gastric cancer risk in East Asia

Phase II: Determine if host factors of inflammation or susceptibility to inflammation add predictive value in assessing cancer risk

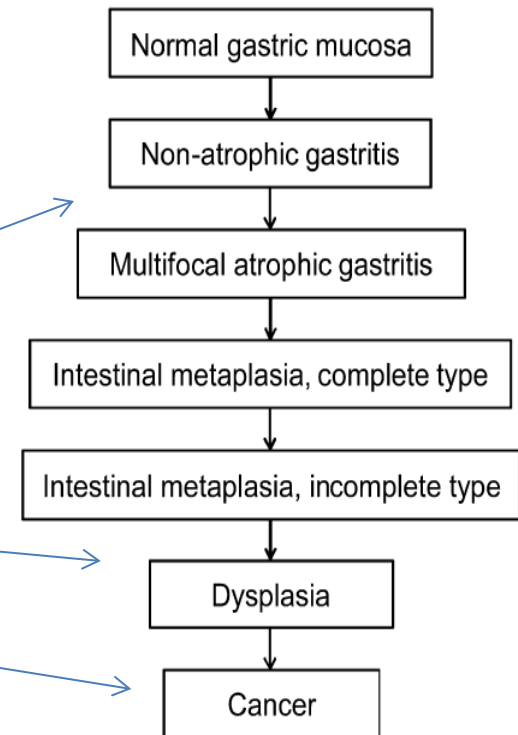
- Urinary prostaglandin- E_2 , the end product of the COX-2 pathway
- Pepsinogen I/II ratio, a measure of degree of gastric atrophy

R01: *H. pylori* blood biomarker for gastric cancer risk in East Asia

Phase III: To build a predictive model for gastric cancer risk in East Asia

Phase IV: To validate the model among individuals with both cancer and precancerous lesions in a high-risk population

- Validation cohort: Linqu County, China intervention trial
 - At baseline individuals provided blood samples and participated in endoscopic screening
 - total N for this project = ~1,590
 - 496 with superficial gastritis or mild CAG
 - 496 with intestinal metaplasia
 - 350 dysplasia
 - 248 gastric cancer



R01: *H. pylori* blood biomarker for gastric cancer risk in East Asia

Public Health Relevance

- Identify individuals with a 10-20% absolute lifetime risk
- Targeted for *H. pylori* eradication therapy
- Individuals with low-risk *H. pylori* excluded for intervention
- Numbers, in China alone:
 - 250 million residents >40 years old; 90% *H. pylori*+

50 million high-risk; 200 million excluded from treatment

R01: *H. pylori* blood biomarker for gastric cancer risk in East Asia

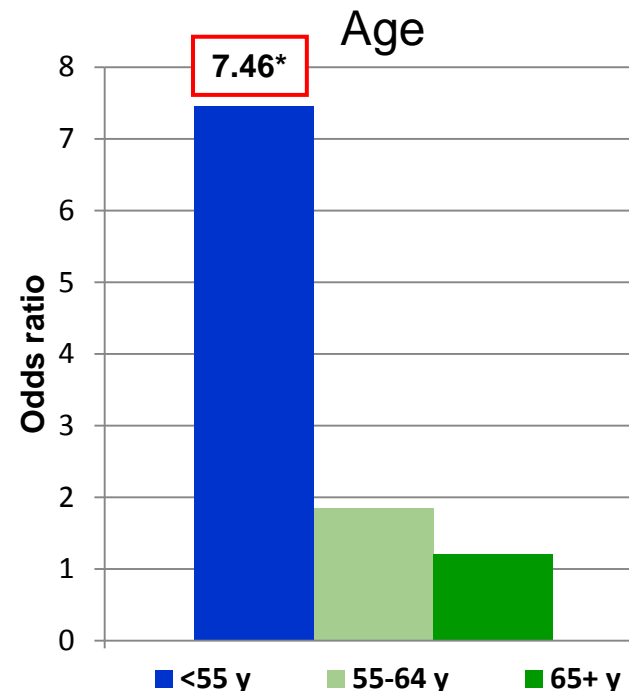
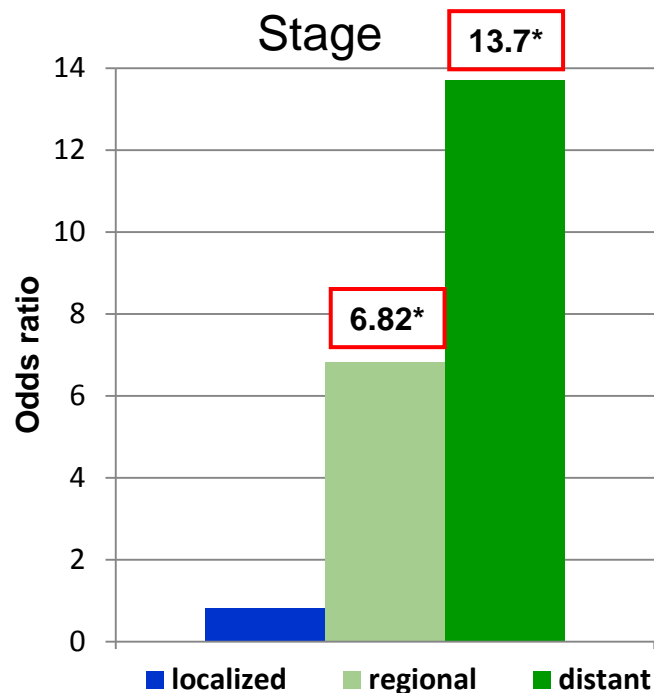
Year 1 (July 1, 2013 – present)

- First meeting of on-site (Vanderbilt) Co-Is Sept. 5, 2013
- Study Protocol draft completed Sept. 15, 2013
- First conference call of international collaborators Oct. 1, 2013
- PI trip to Japan to meet with collaborators Nov. 10-14, 2013
- Study Protocol completed and disseminated Dec. 2, 2013
- Baseline questionnaires collected Ongoing
- Data Use Agreements for each site signed Ongoing
 - Then baseline data to be sent to Vanderbilt and data harmonization begins
- Biospecimen shipment to lab for assaying [Spring 2014]

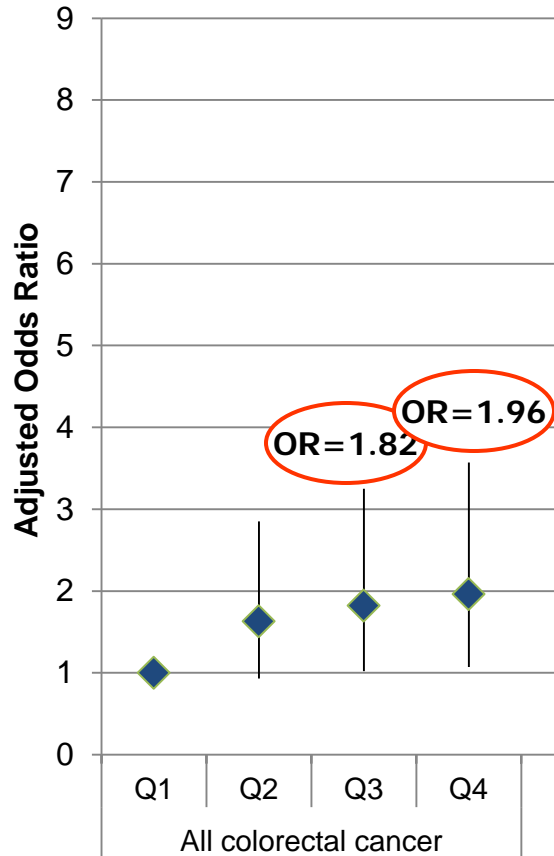
H. pylori and Colorectal Cancer Risk: Preliminary Data/Outcomes



- In a **prospective, nested case-control study** (188 cases, 370 controls), sero-positivity to 5 *H. pylori* proteins increased the odds of colorectal cancer incidence
 - VacA, HP 231, HP 305, NapA, and HcpC (ORs **1.46 to 1.64**)
- These associations were even stronger for **colon cancer**, separately:
 - **VacA OR = 2.22** (1.22 – 4.06)
- There were strong differences in the VacA+ association with colon cancer by:

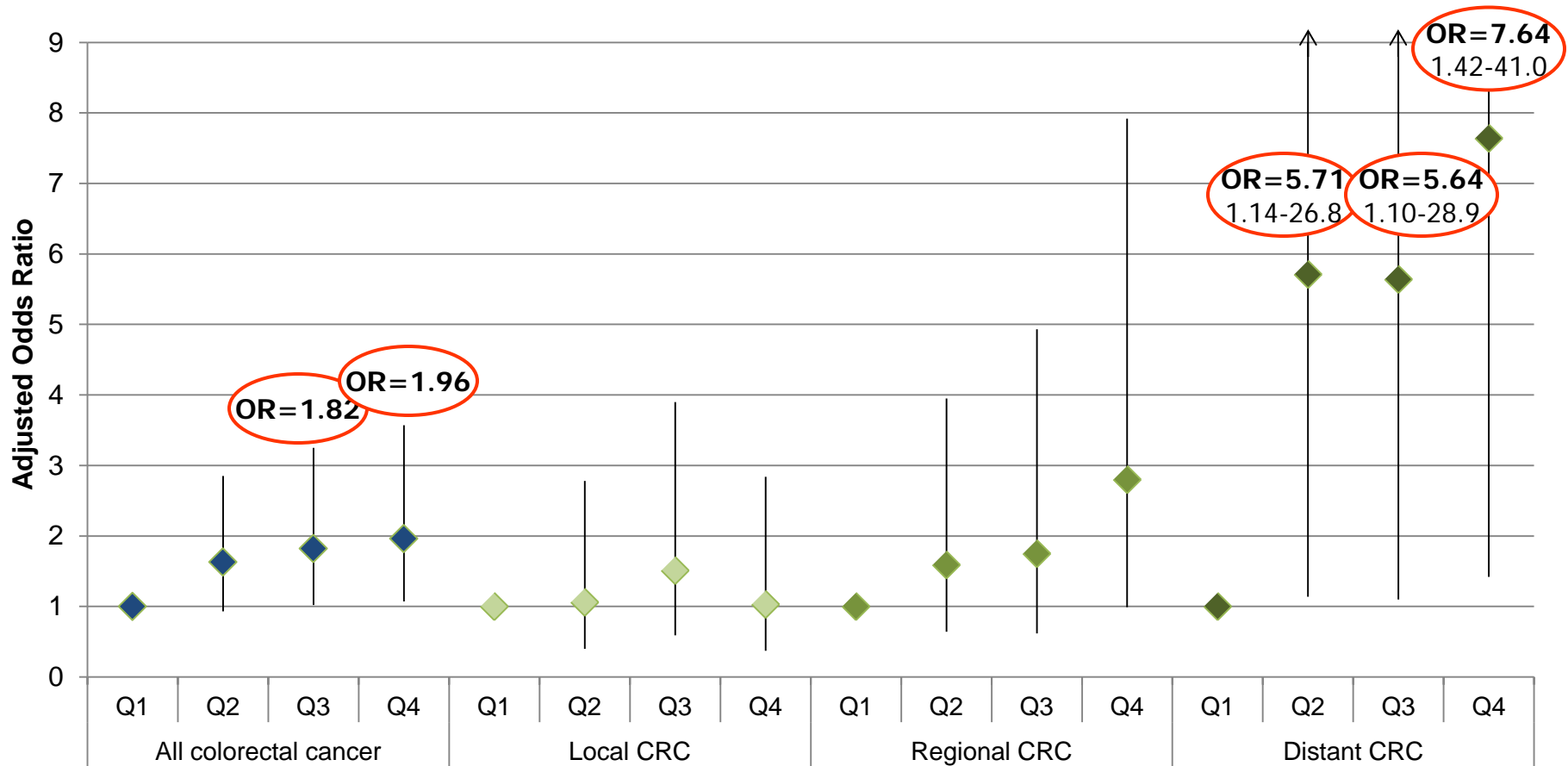


Odds ratios of colorectal cancer risk by quartile of VacA antibodies



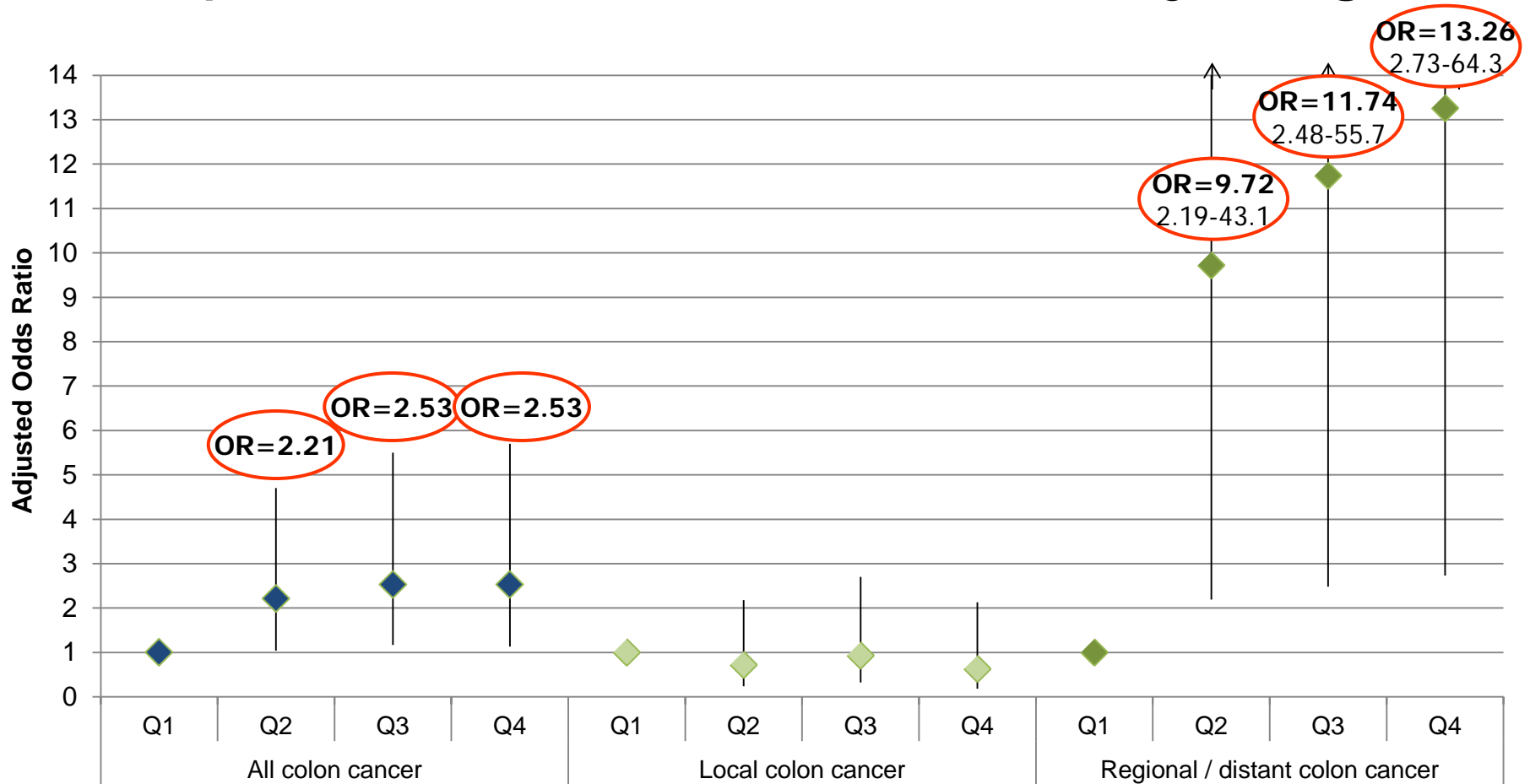
*conditional logistic regression

Odds ratios of colorectal cancer risk by quartile of VacA antibodies, by stage



*conditional logistic regression

Odds ratios of **colon** cancer risk by quartile of VacA antibodies, by stage



*conditional logistic regression

New R01: *H. pylori* protein-specific antibodies and colorectal cancer risk

Consortium of 10 prospective studies comprising >4,000 CRC cases, to definitively evaluate the association by site, stage, age of onset, lag time

Cohort name	Cohort description	Cases
Multiethnic Cohort Study (MEC)	Individuals of Hawaiian, Japanese, African, Latino and Caucasian ancestry from Hawaii and Los Angeles, CA	900
Women's Health Initiative (WHI)	Post-menopausal women from 40 clinical centers nationwide	807
Prostate, Lung, Colorectal, Ovarian Screening Study (PLCO)	Participants in a nation-wide screening trial in 10 large cities across the US (including Honolulu)	718
CLUE II	Residents of suburban Washington County, Maryland	526
Nurses' Health Study (NHS)		400
Physicians' Health Study (PHS)	Medical professionals from over 14 states	250
Health Professionals Follow-up (HPFS)		200
NYU Womens' Health Study (NYUWHS)	Women visiting a breast screening center in NYC	388
Cancer Prevention Studies (CPS)	Healthy individuals from 21 states recruited by the ACS	300
Southern Community Cohort Study (SCCS)	Low-income African Americans and whites in the southeast US, recruited from community health clinics	150



Thank you!

VUMC – Epidemiology

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Southern Community Cohort Study**

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