Cancer Epidemiology

April 2, 2015

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Outline for Today

- Methods and Important Concepts
  - Descriptive Epidemiology
    - person, place, time
  - Causality
    - Most common risk factors for cancer
  - Analytic Studies
    - Cancer Epidemiology model
    - Case-Control, cohort, cross-sectional
- Study examples (registries, secondary analyses, cross-sectional)

Goals of Cancer Epidemiology

- Study risk factor-cancer relationships
  - Generate and interpret data from descriptive and analytic studies
- Draw conclusions regarding the causal nature of risk factors in carcinogenesis
  - Evaluate strength of evidence
  - Summarize the consistency of evidence
- Take action (intervention, etc.) to protect society from exposure if a causal hypothesis is confirmed

As a public health professional, what would you want to know about cancer?

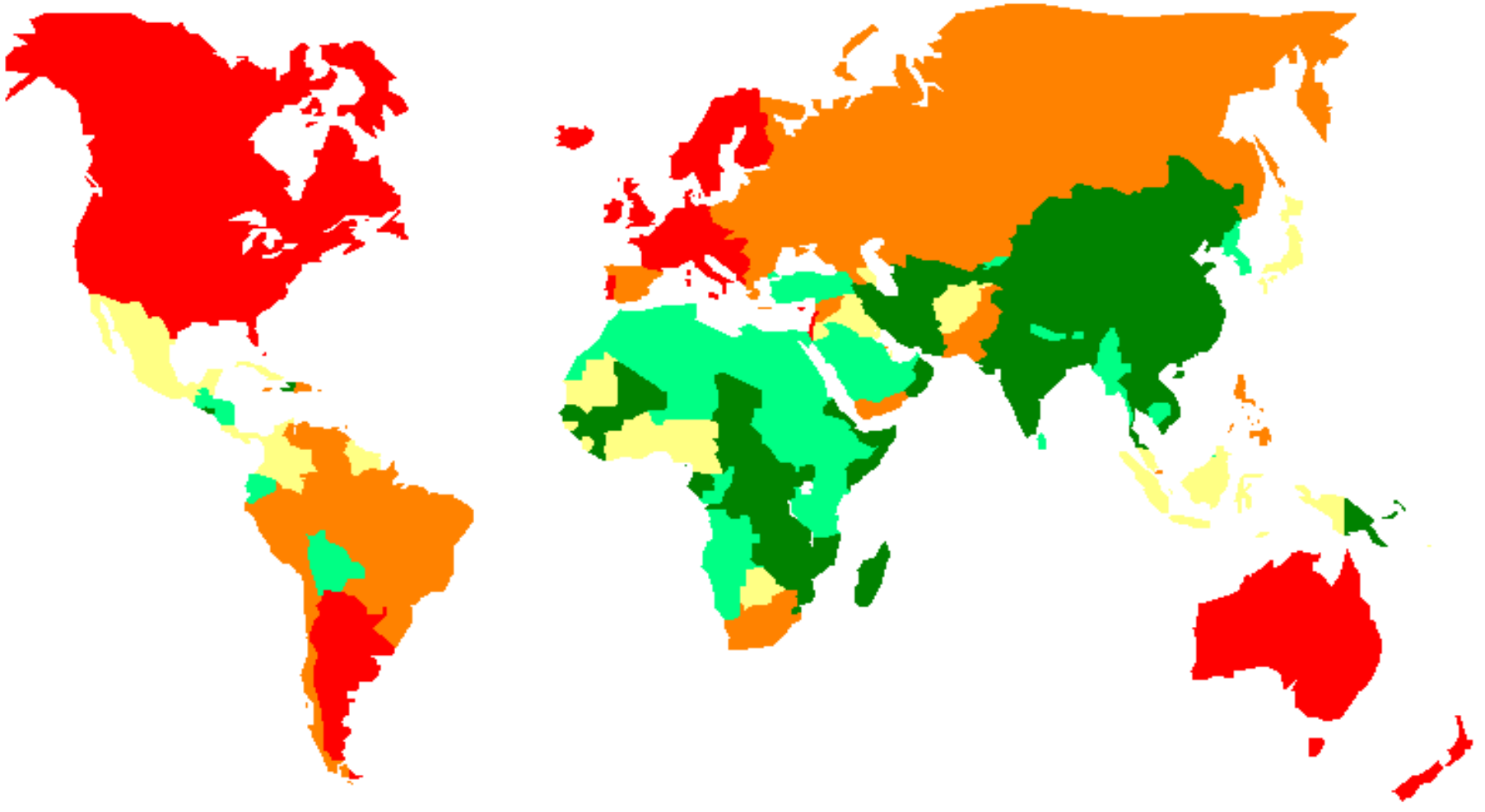
- How big a problem is cancer?
  - descriptive epidemiology
- What causes cancer?
  - analytic epidemiology, etiologic research
- What public health strategies can we take to prevent cancer?
  - translating evidence into policy

Descriptive epidemiology

- Characterize occurrence according to:
  - Person
  - Place
  - Time
- Why is this important?

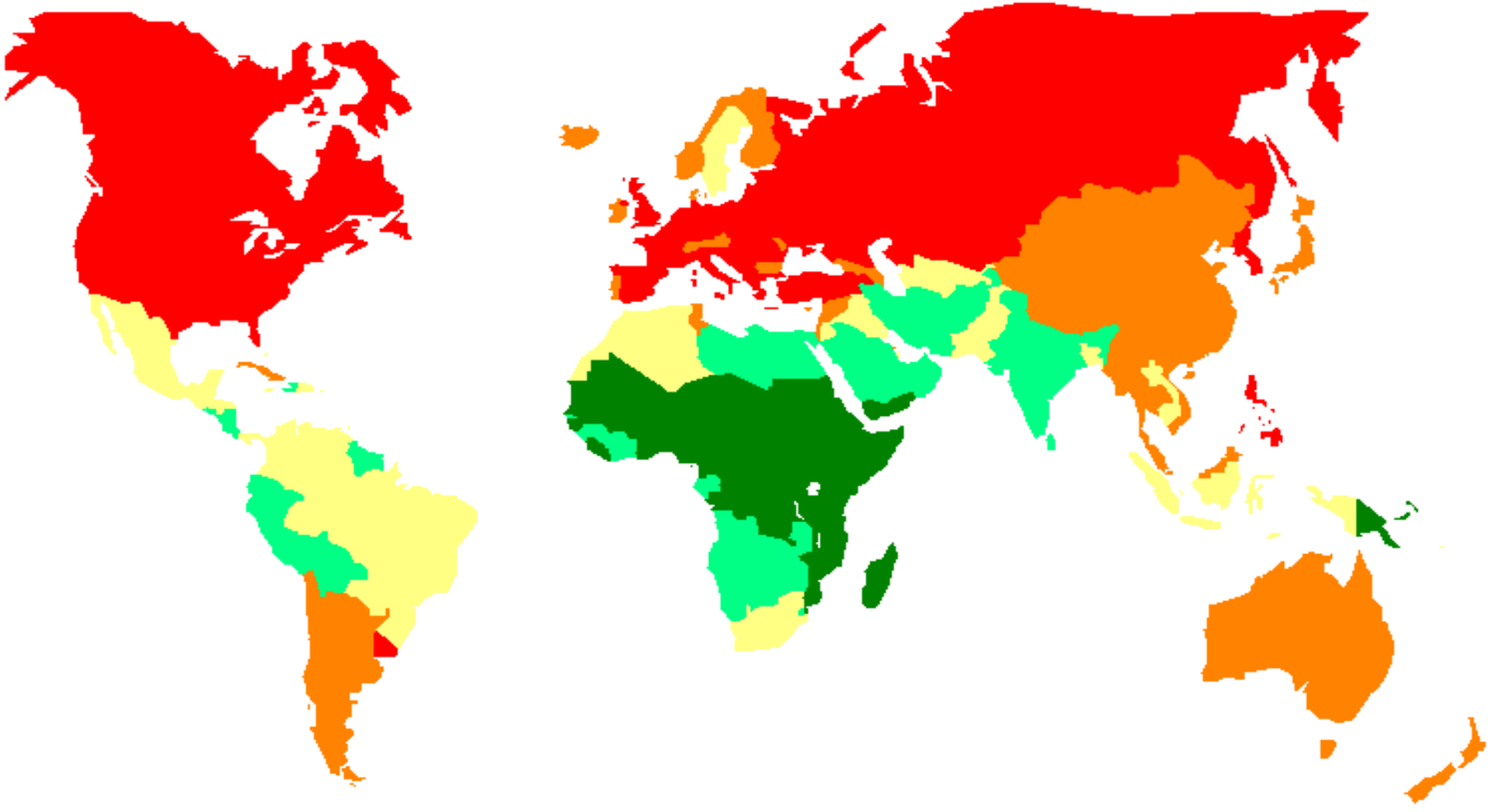
PLACE:
There are global patterns in the occurrence of cancer

Breast
Age-Standardized incidence rate per 100,000



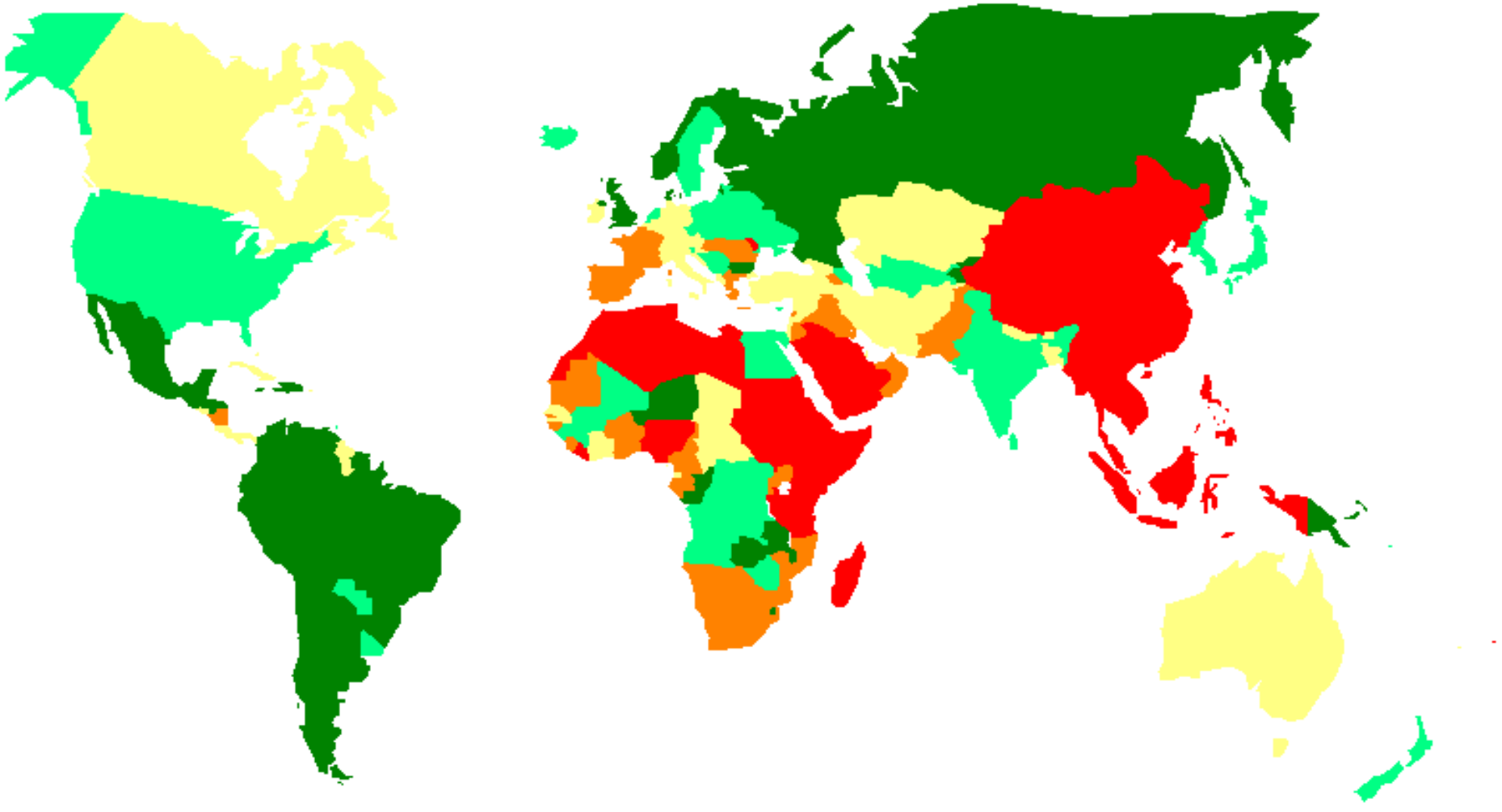
GLOBOCAN 2002, IARC

Lung, Males
Age-Standardized incidence rate per 100,000

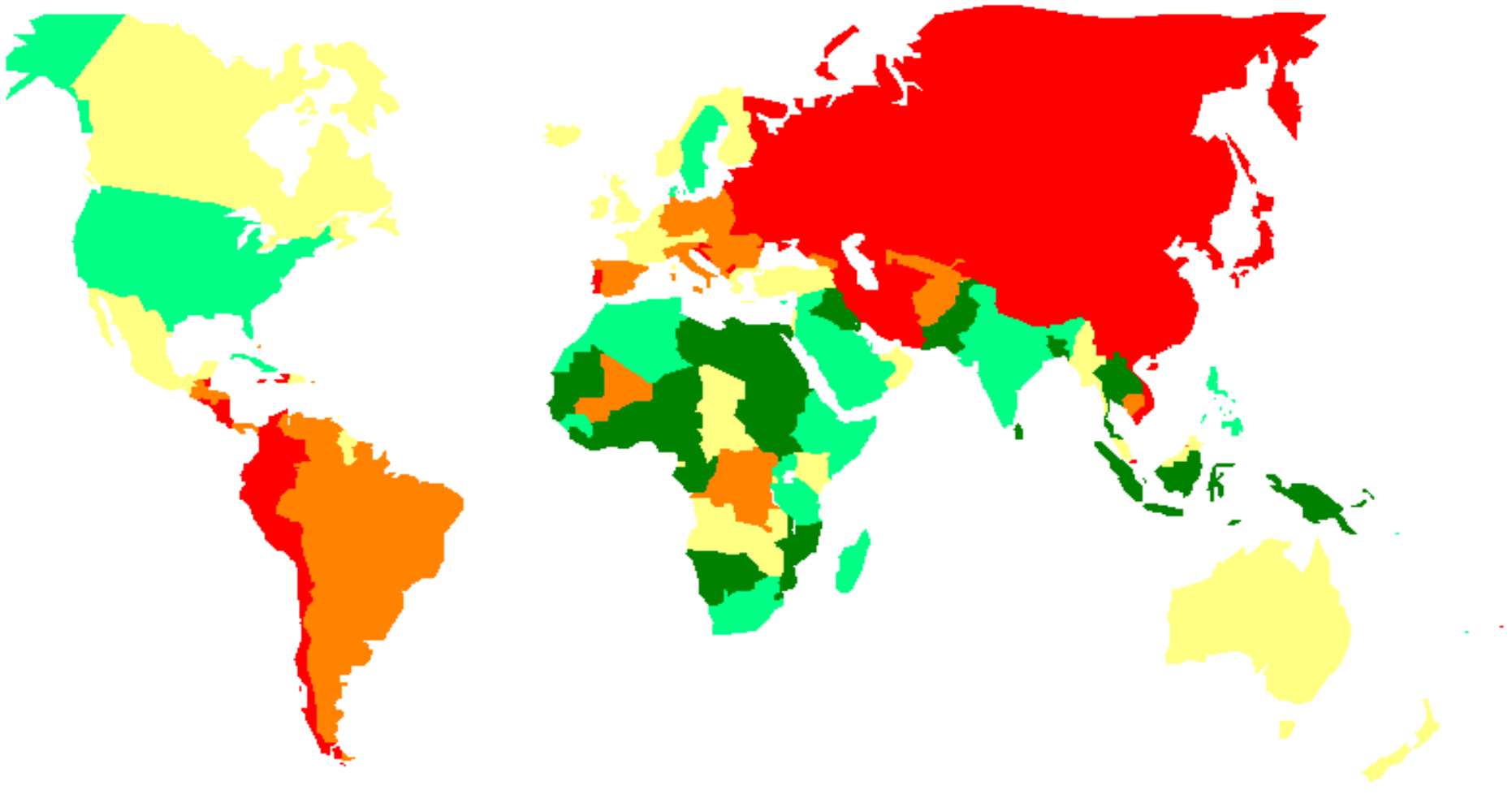


GLOBOCAN 2002, IARC

Nasopharynx, Males
Age-Standardized incidence rate per 100,000



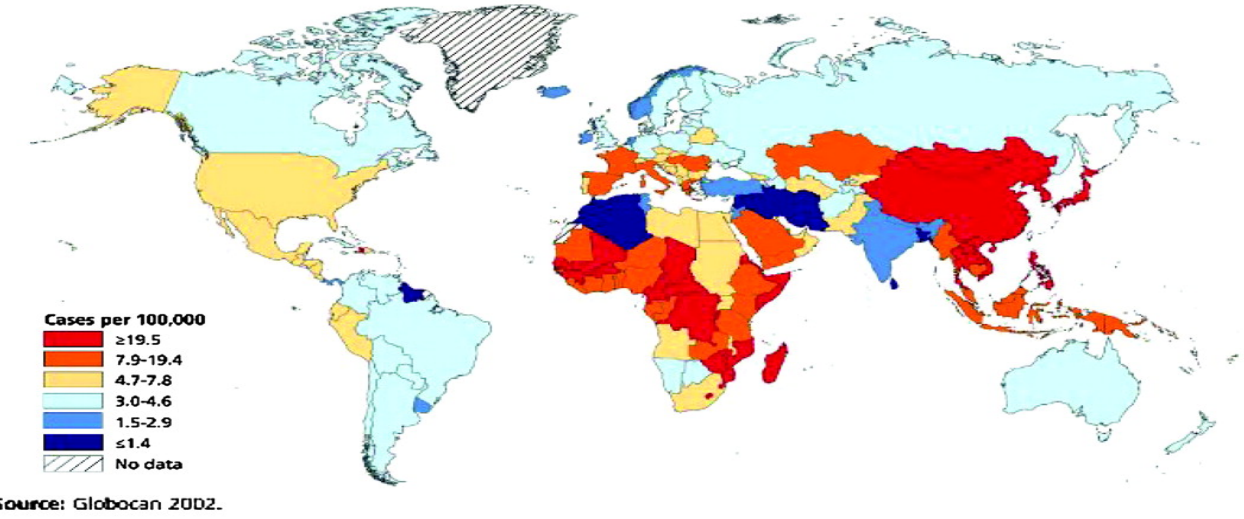
Stomach, Males
Age-Standardized incidence rate per 100,000



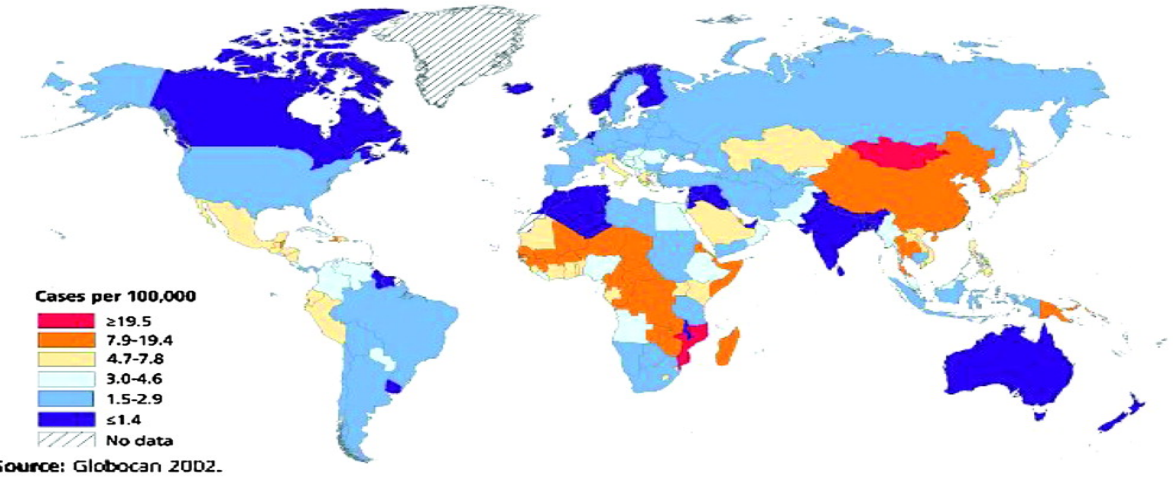
GLOBOCAN 2002, IARC

Liver cancer incidence in males and females.

Males



Females



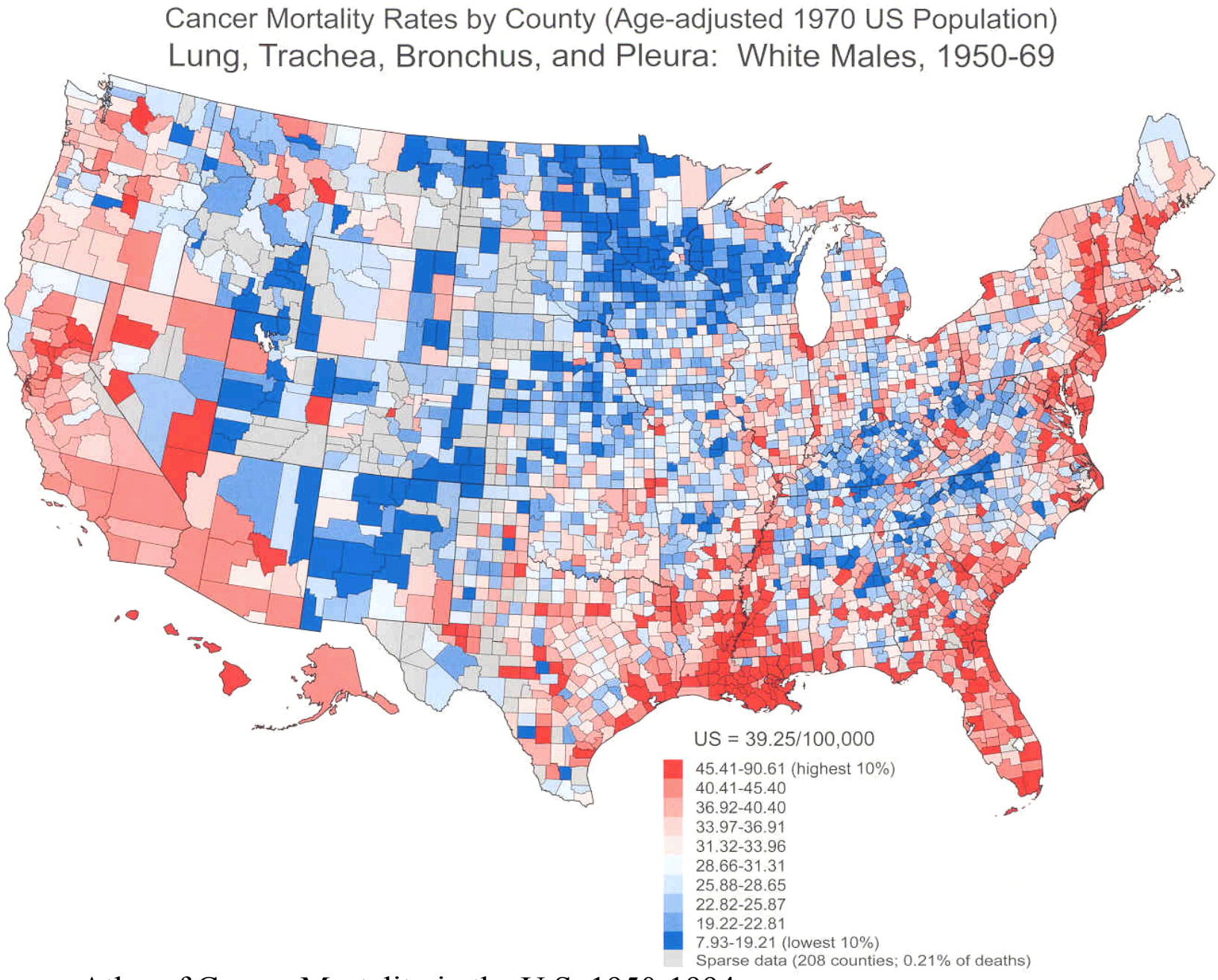
Source: GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide

Thun M J et al. Carcinogenesis 2009;31:100-110

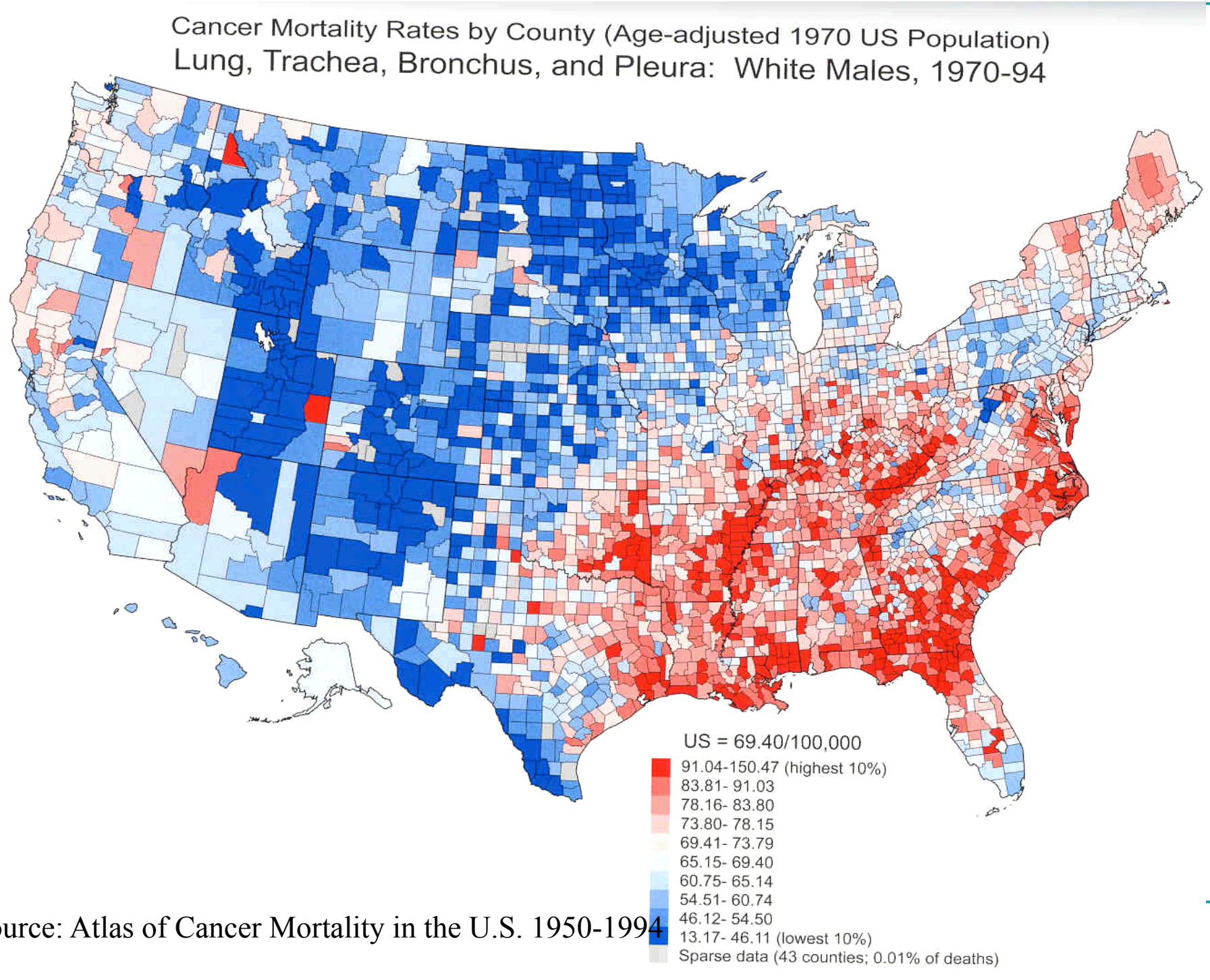
Carcinogenesis

PLACE:
There are national patterns in the occurrence of cancer

Lung, Trachea, Bronchus, and Pleura



Source: Atlas of Cancer Mortality in the U.S. 1950-1994



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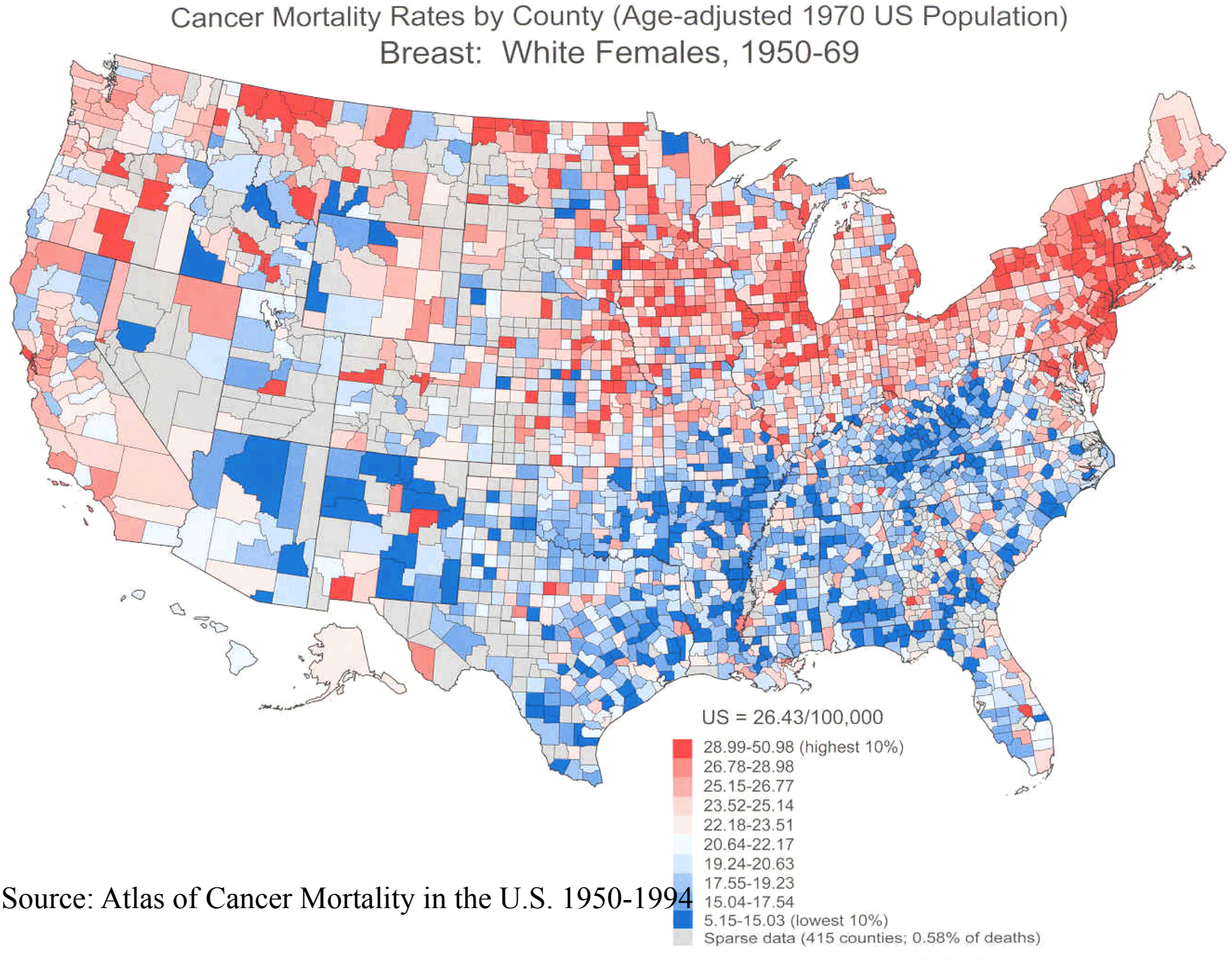

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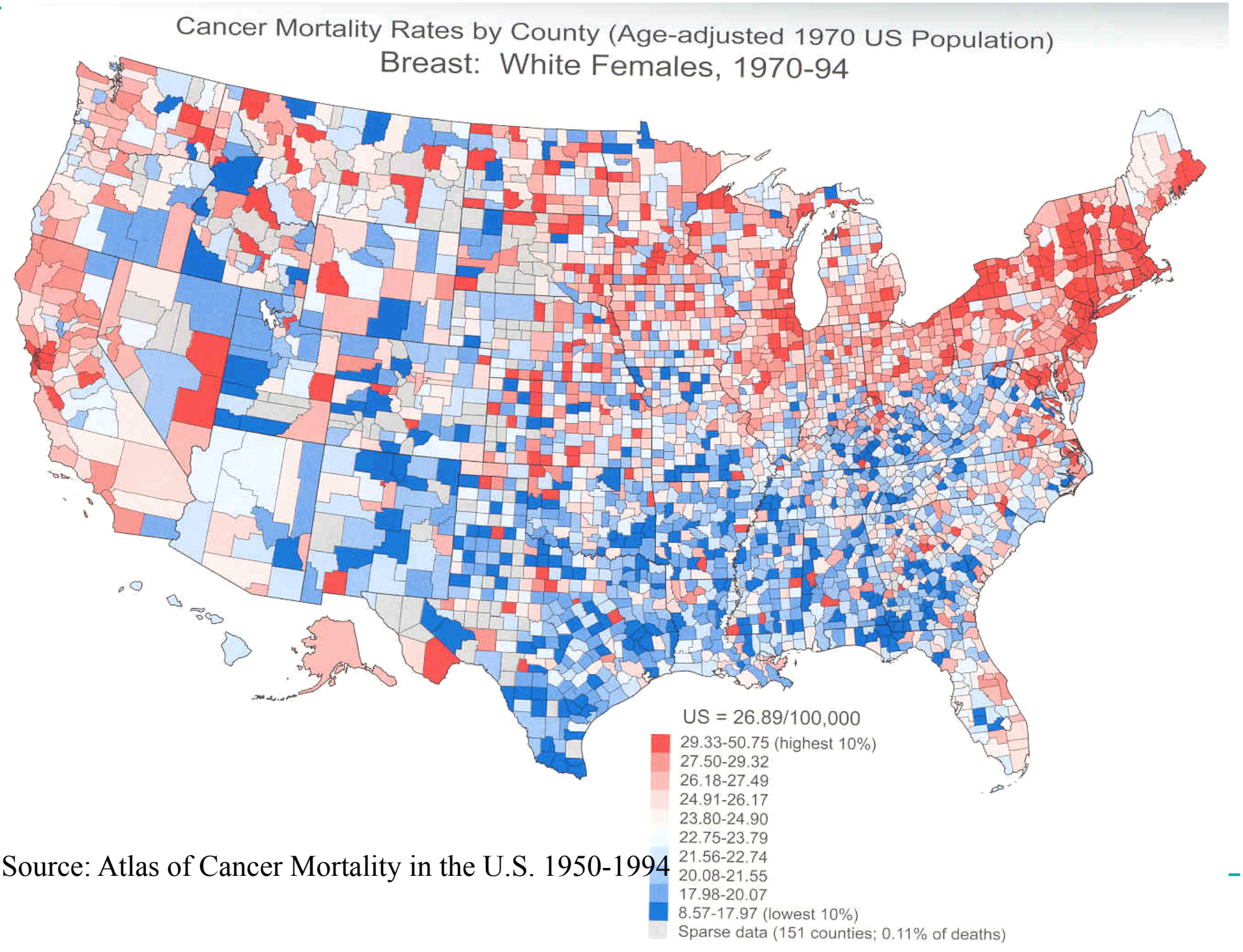
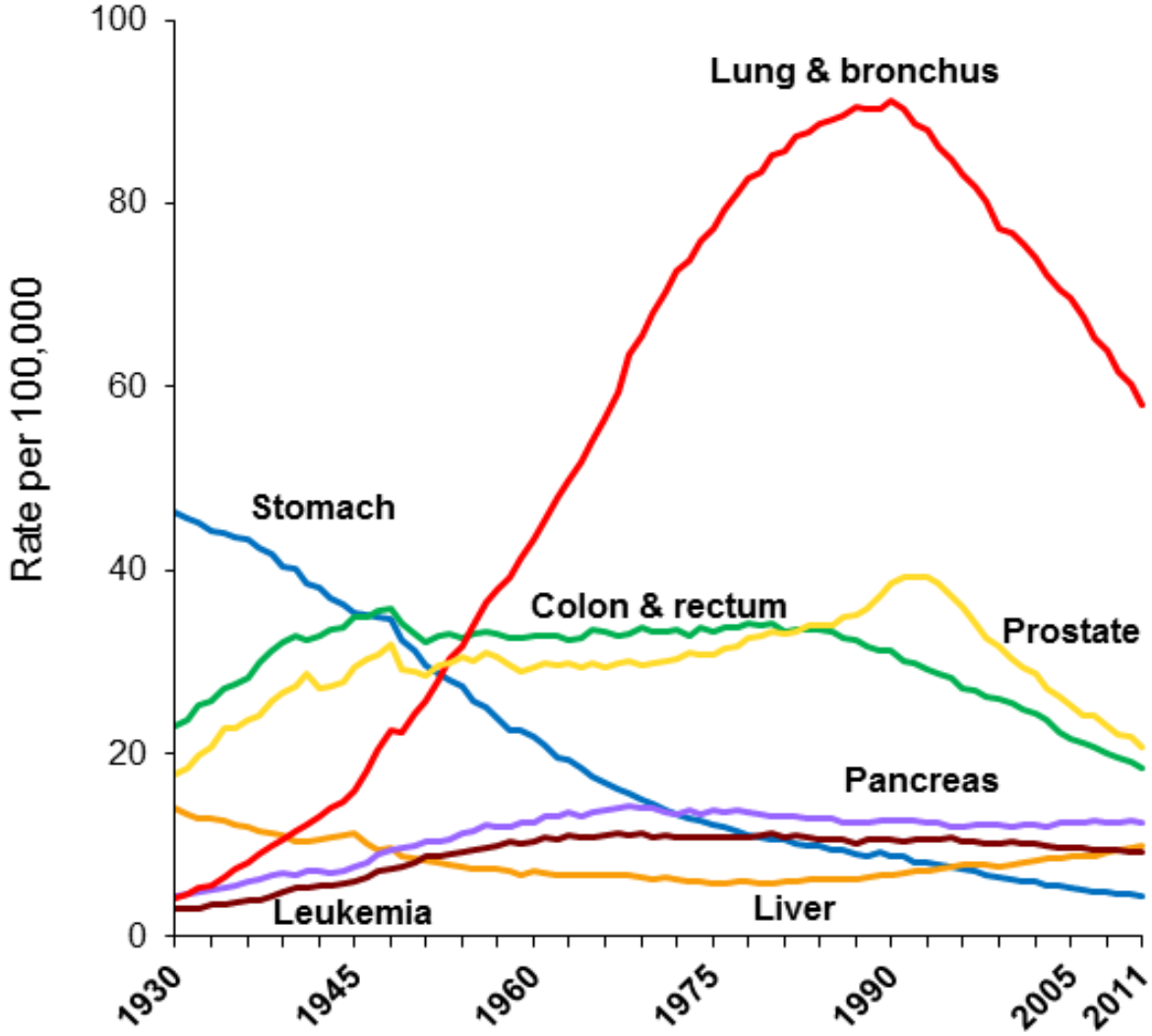
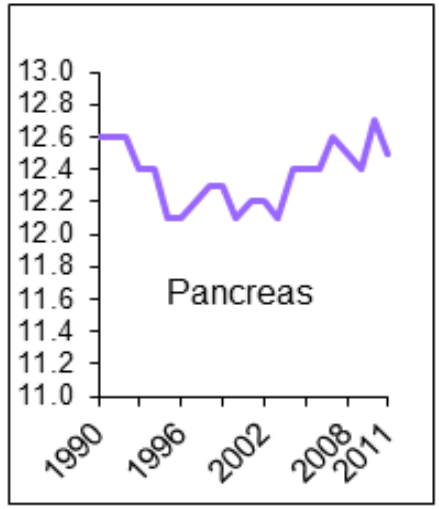


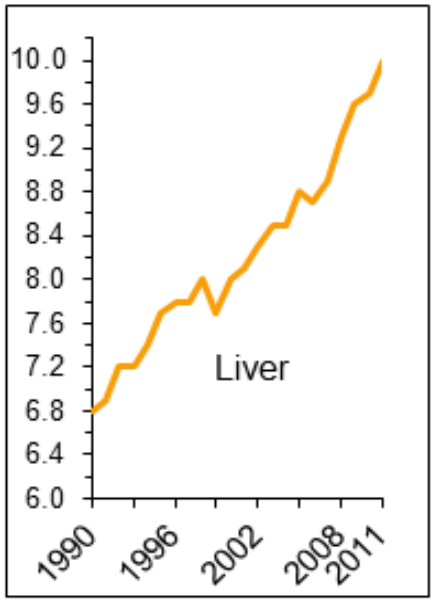
Source: Atlas of Cancer Mortality in the U.S. 1950-1994

TIME:
What are the trends in the occurrence of cancer across time?

Trends in Cancer Death Rates* Among Men, US,1930-2011

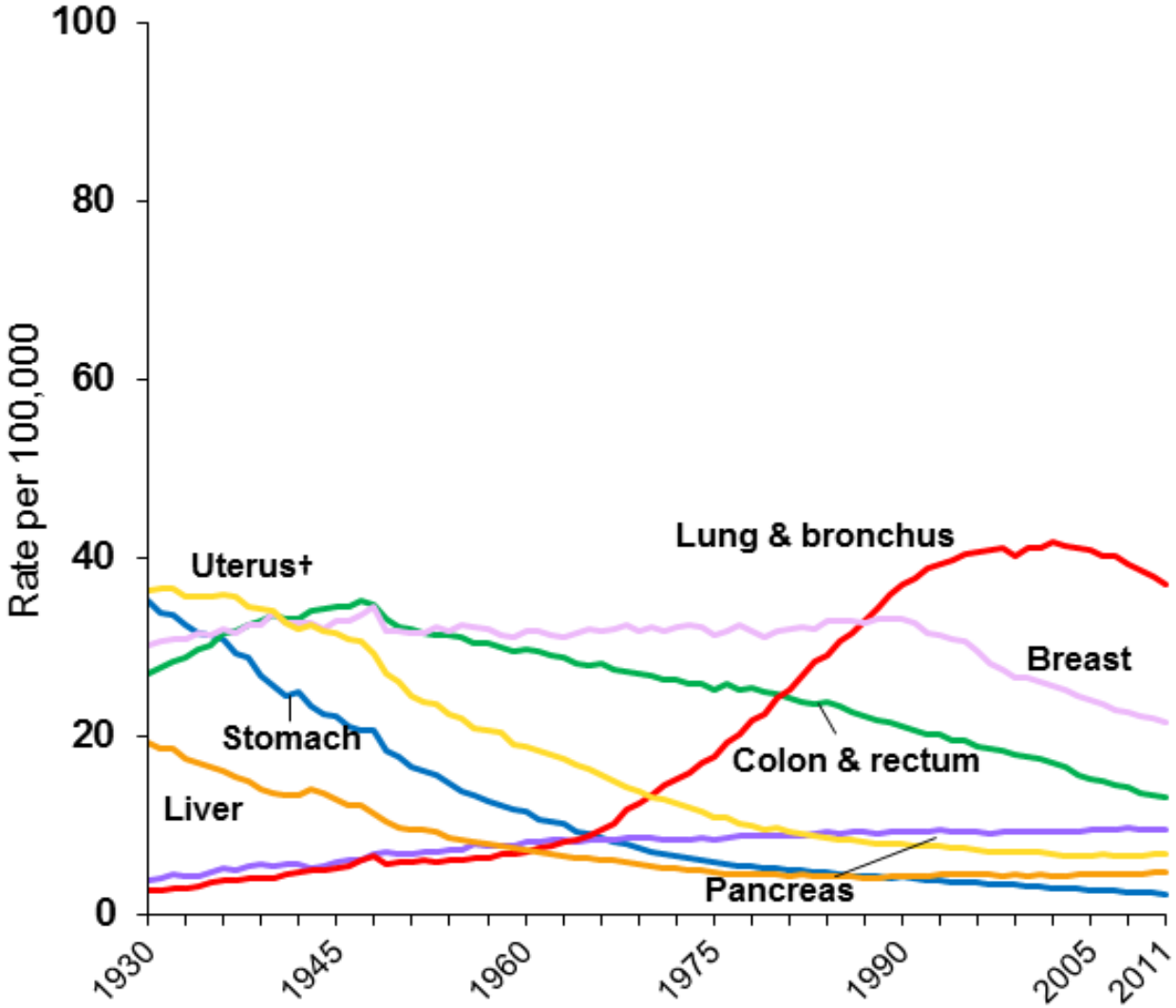


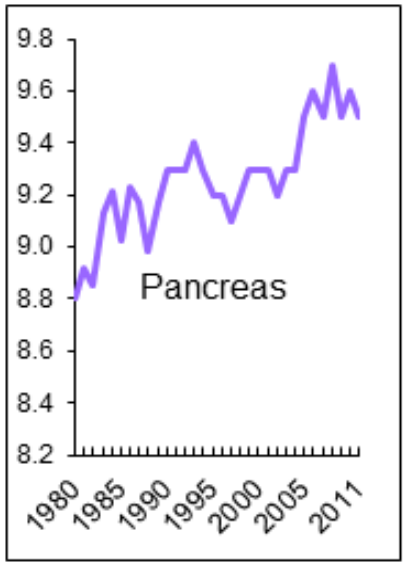


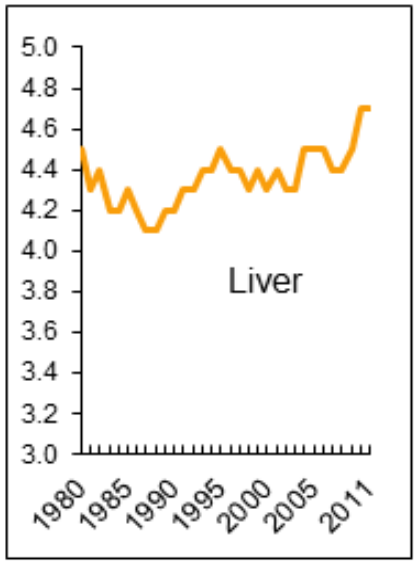


*Age-adjusted to the 2000 US standard population.
Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2014.

Trends in Cancer Death Rates* Among Women, US,1930-2011

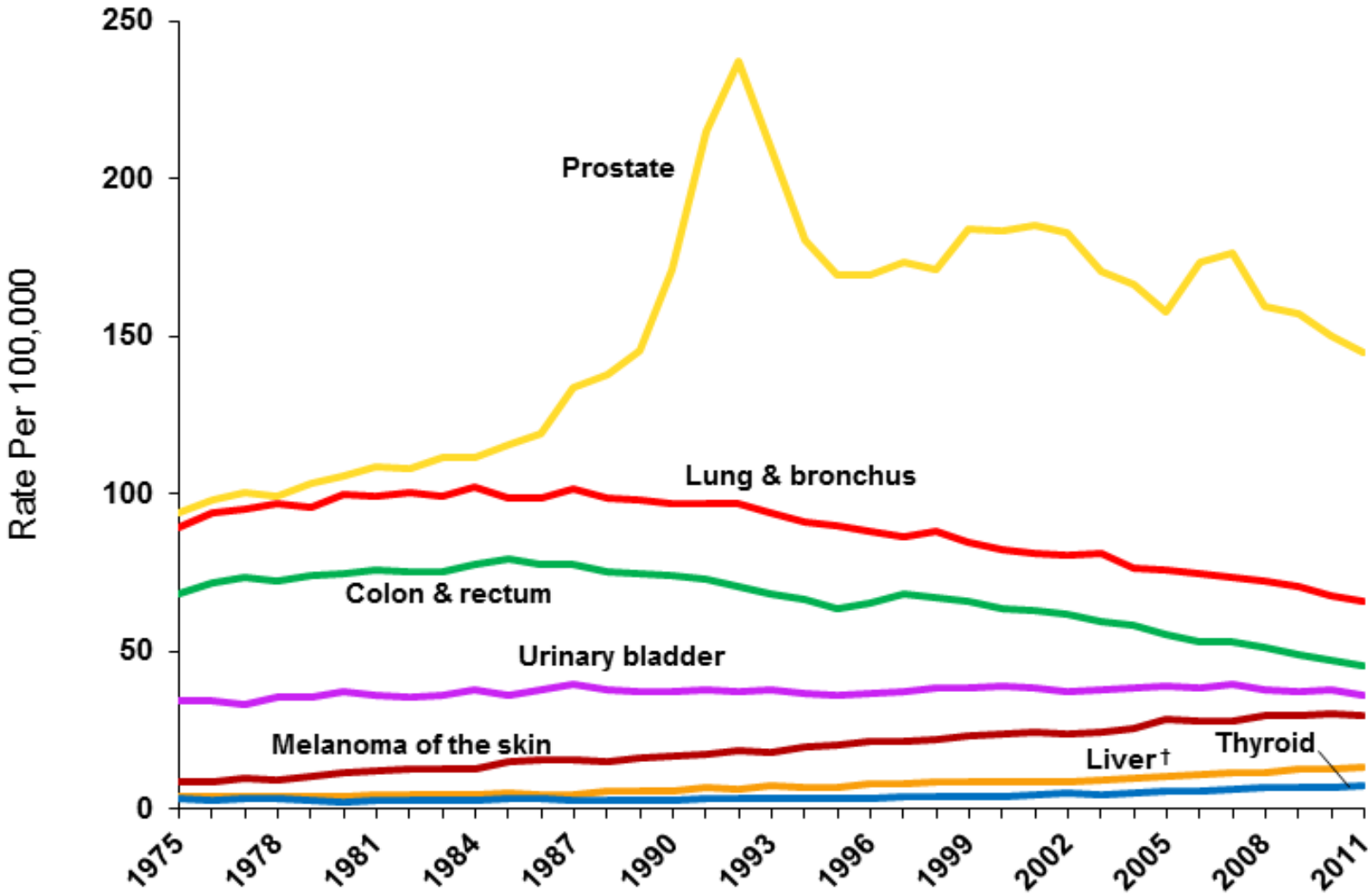






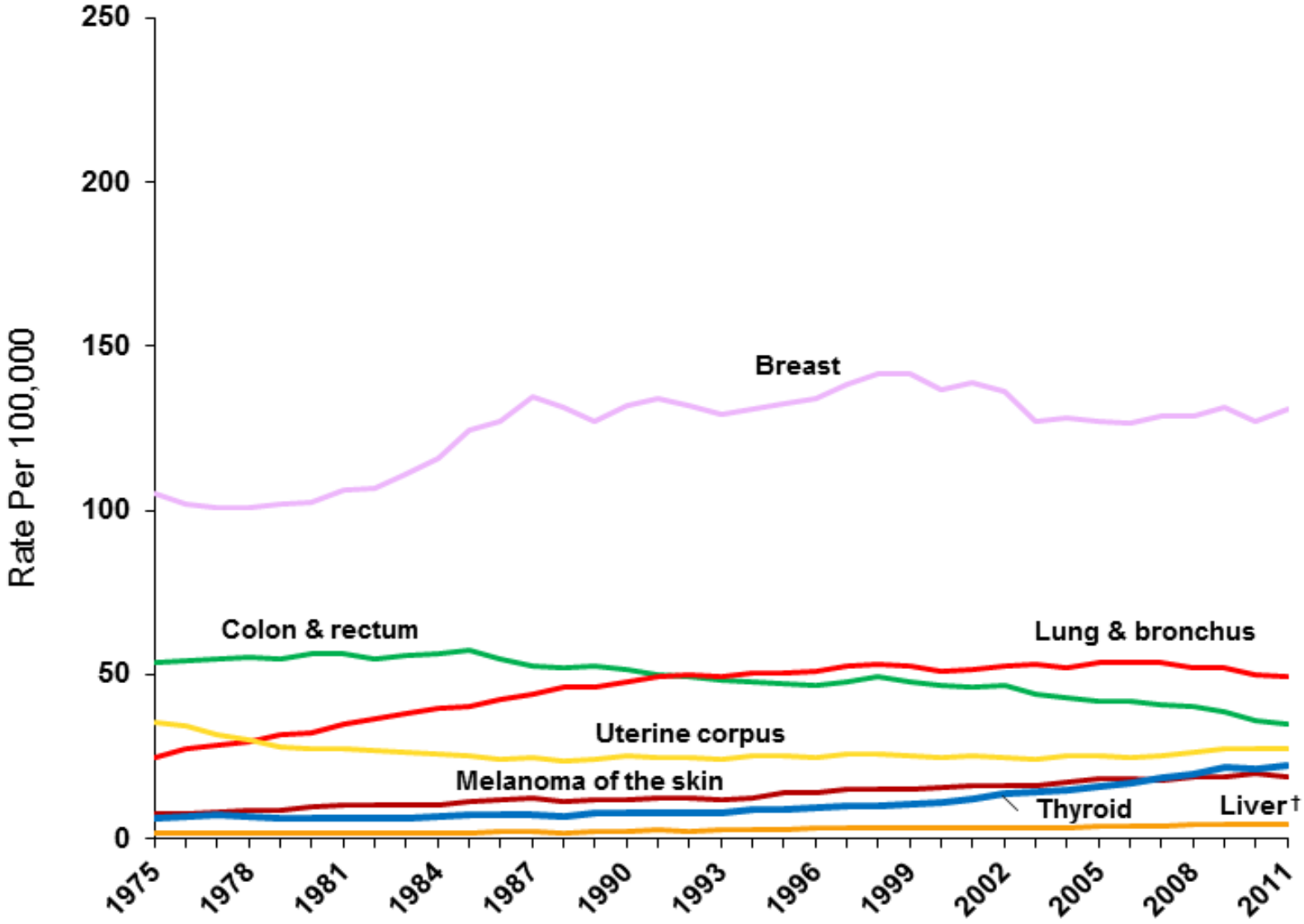
*Age-adjusted to the 2000 US standard population.
†Uterus includes uterine corpus and uterine cervix combined.
Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2014.

Trends in Cancer Incidence Rates* Among Men, US, 1975-2011



*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
†Includes the intrahepatic bile duct.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2014.

Trends in Cancer Incidence Rates* Among Women, US, 1975-2011



*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
†Includes the intrahepatic bile duct.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2014.

PERSON:
Does the occurrence of cancer differ between men and women?

Cancer statistics, 2015

Estimated New Cases

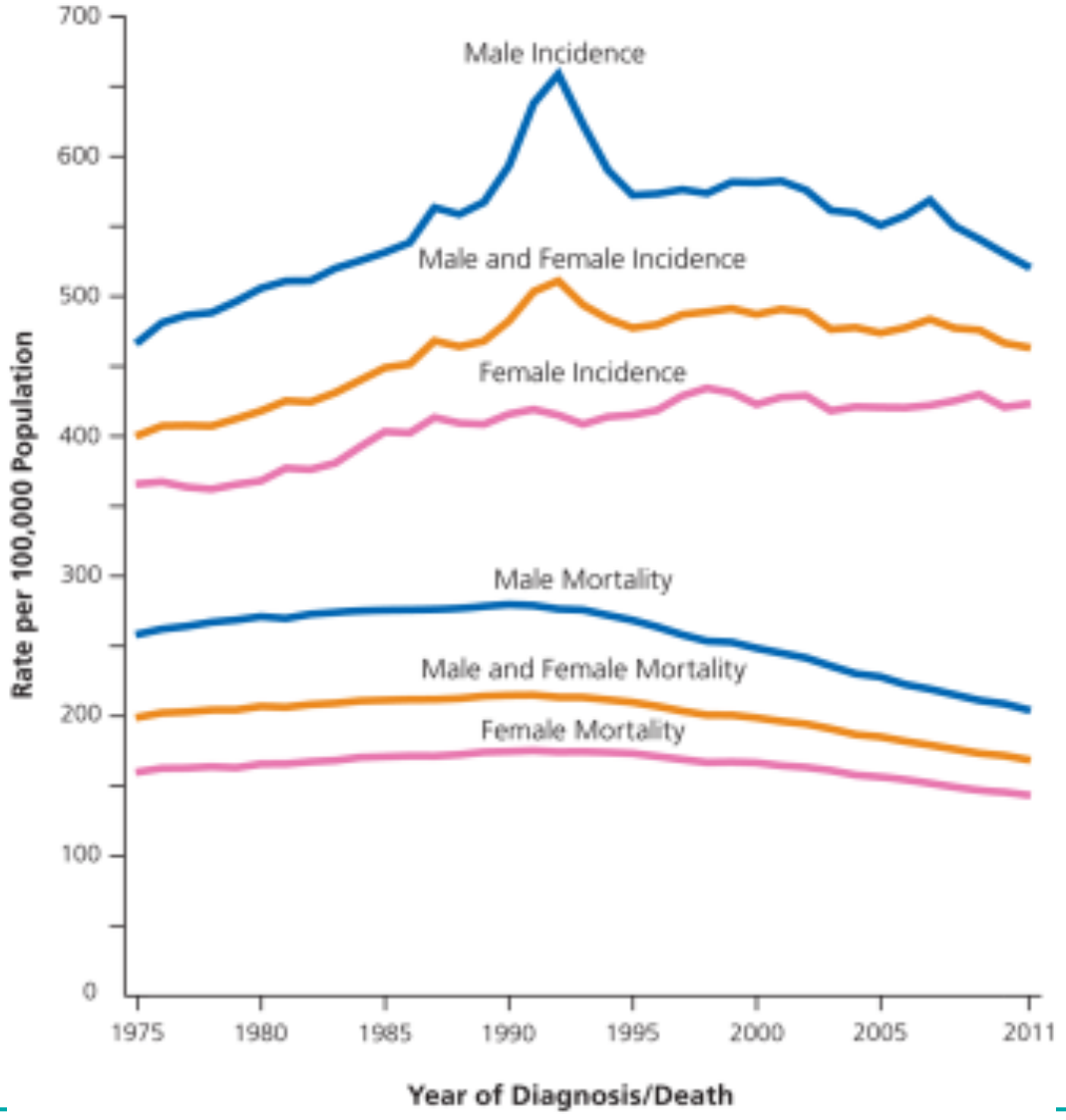
Males				Females		
Prostate	220,800	26%		Breast	231,840	29%
Lung & bronchus	115,610	14%		Lung & bronchus	105,590	13%
Colon & rectum	69,090	8%		Colon & rectum	63,610	8%
Urinary bladder	56,320	7%		Uterine corpus	54,870	7%
Melanoma of the skin	42,670	5%		Thyroid	47,230	6%
Non-Hodgkin lymphoma	39,850	5%		Non-Hodgkin lymphoma	32,000	4%
Kidney & renal pelvis	38,270	5%		Melanoma of the skin	31,200	4%
Oral cavity & pharynx	32,670	4%		Pancreas	24,120	3%
Leukemia	30,900	4%		Leukemia	23,370	3%
Liver & intrahepatic bile duct	25,510	3%		Kidney & renal pelvis	23,290	3%
All Sites	**848,200**	**100%**		**All Sites**	**810,170**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	86,380	28%		Lung & bronchus	71,660	26%
Prostate	27,540	9%		Breast	40,290	15%
Colon & rectum	26,100	8%		Colon & rectum	23,600	9%
Pancreas	20,710	7%		Pancreas	19,850	7%
Liver & intrahepatic bile duct	17,030	5%		Ovary	14,180	5%
Leukemia	14,210	5%		Leukemia	10,240	4%
Esophagus	12,600	4%		Uterine corpus	10,170	4%
Urinary bladder	11,510	4%		Non-Hodgkin lymphoma	8,310	3%
Non-Hodgkin lymphoma	11,480	4%		Liver & intrahepatic bile duct	7,520	3%
Kidney & renal pelvis	9,070	3%		Brain & other nervous system	6,380	2%
All Sites	**312,150**	**100%**		**All Sites**	**277,280**	**100%**

CA: A Cancer Journal for Clinicians
5 JAN 2015 DOI: 10.3322/caac.21254
http://onlinelibrary.wiley.com/doi/10.3322/caac.21254/full#caac21254-fig-0001

Cancer statistics, 2015



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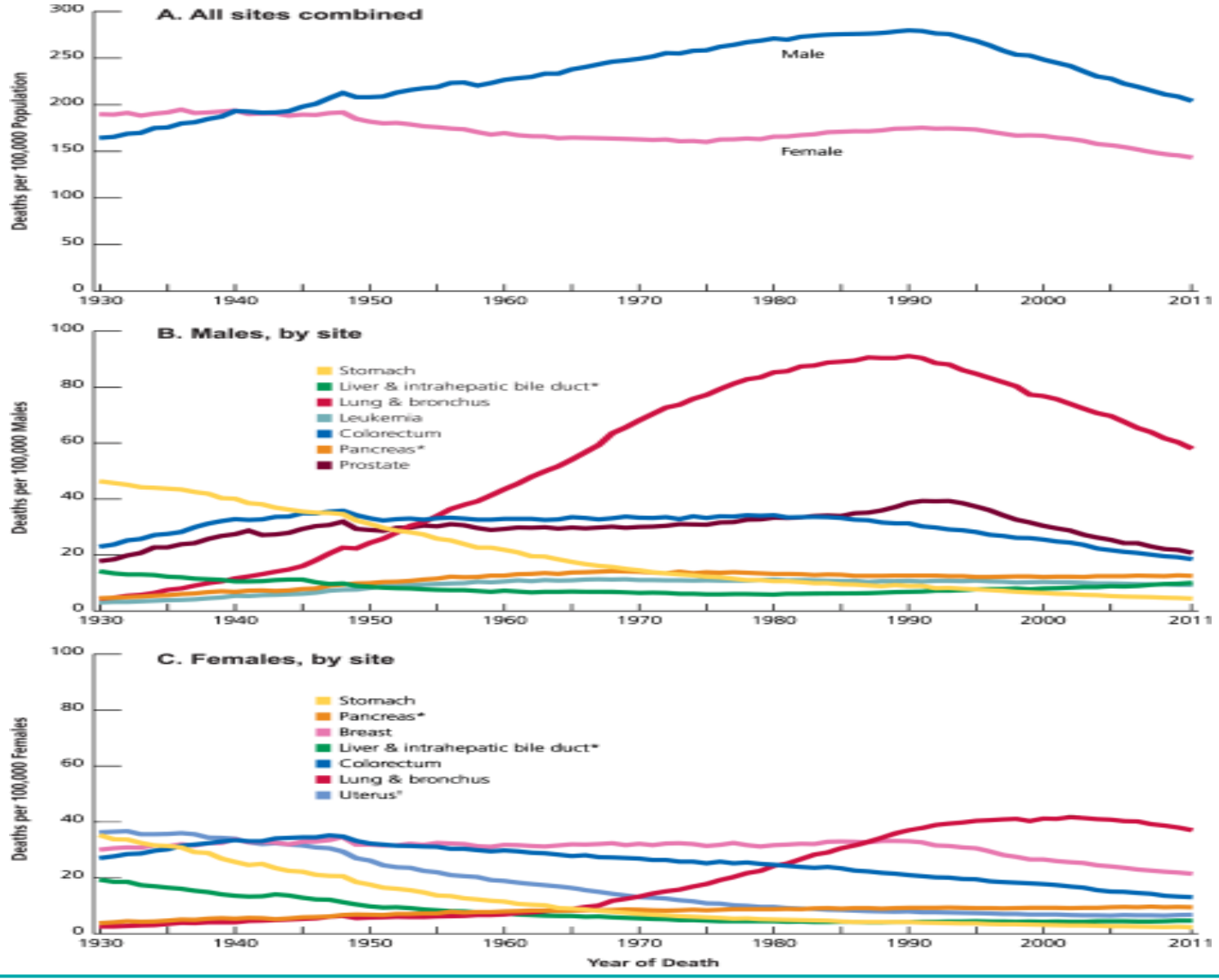
Cancer statistics, 2015



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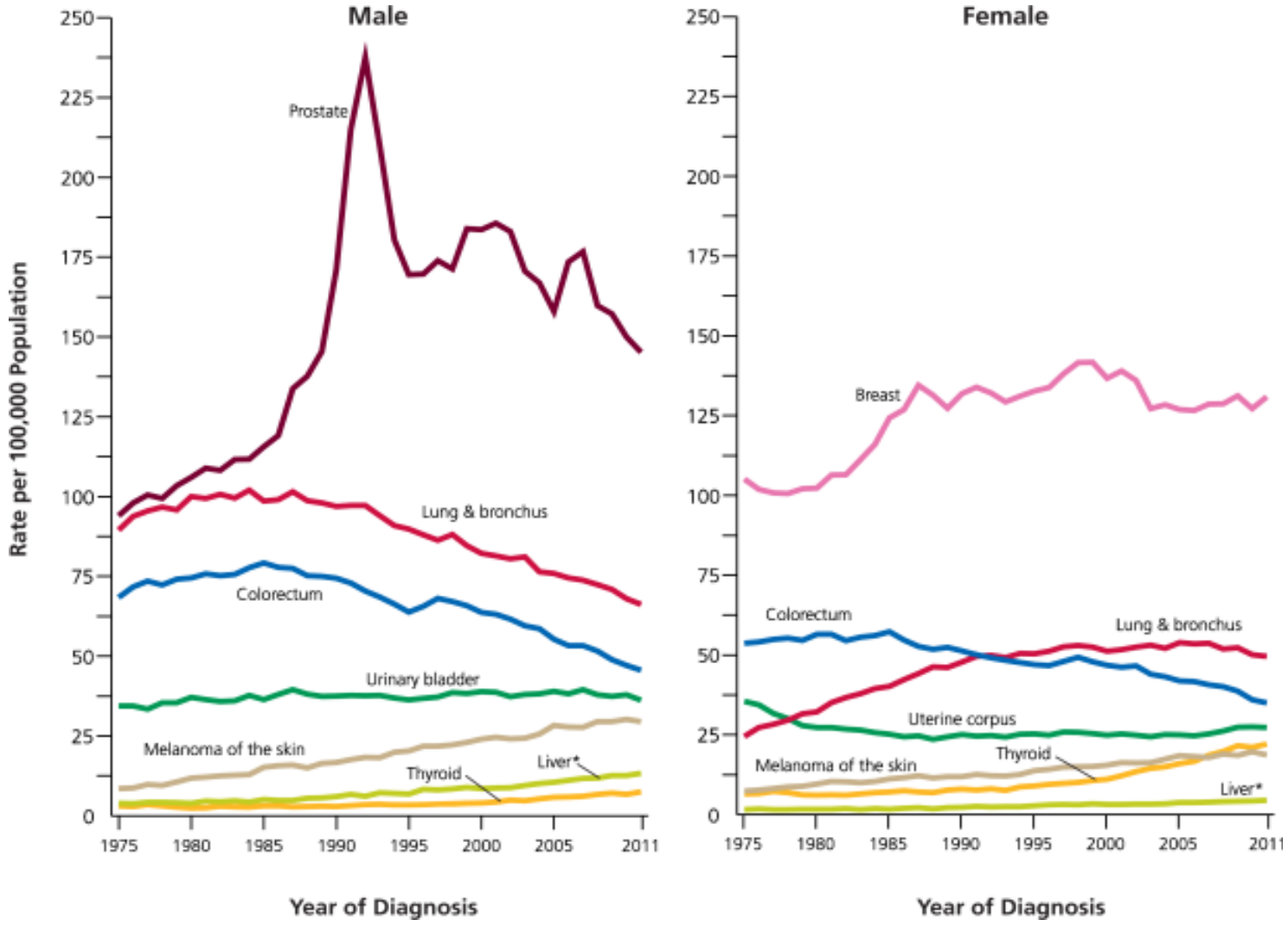

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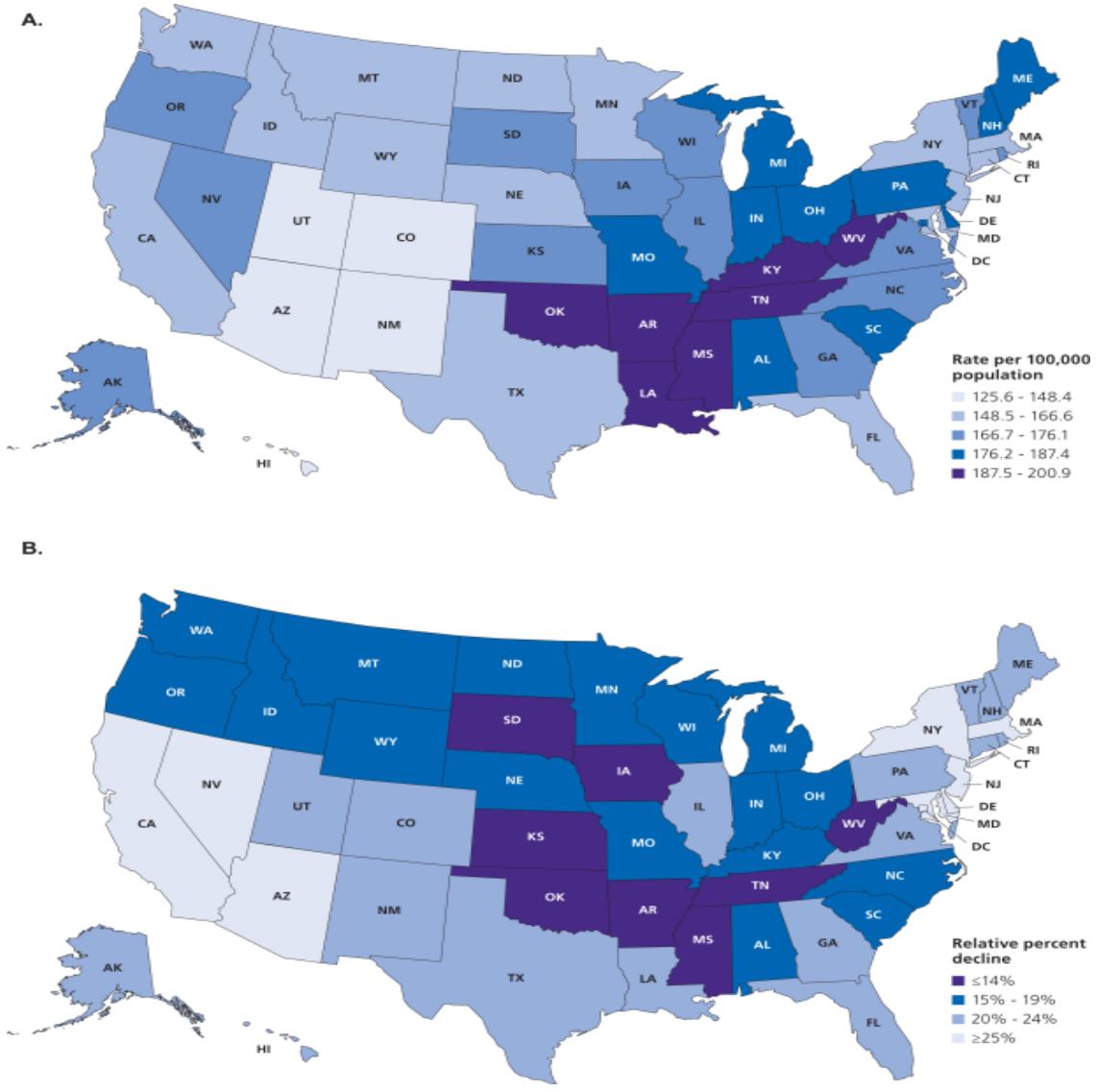
Cancer statistics, 2015



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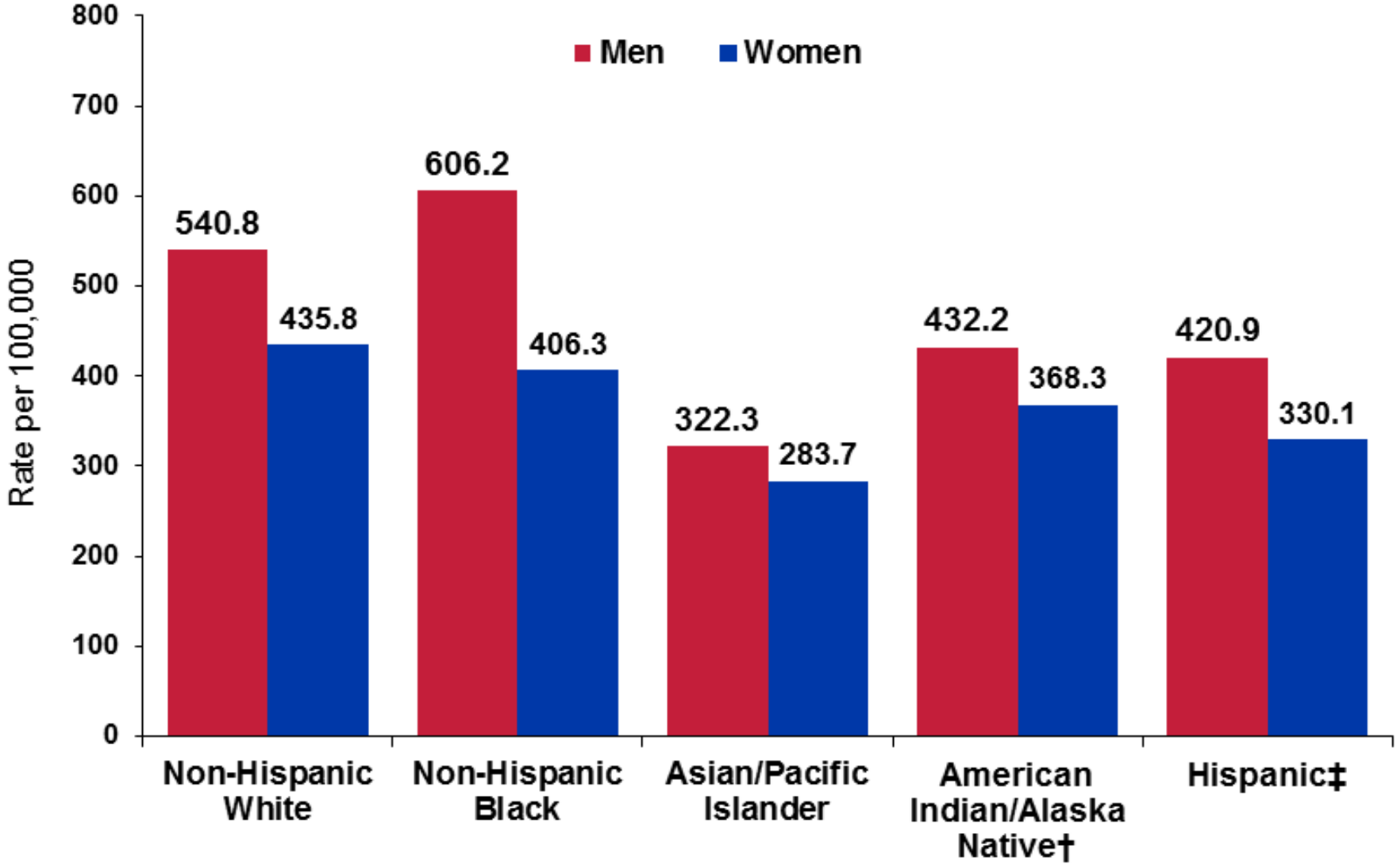
http://onlinelibrary.wiley.com/doi/10.3322/caac.21254/full#caac21254-fig-0004

PERSON:
Does the occurrence of cancer differ by racial/ethnic group?

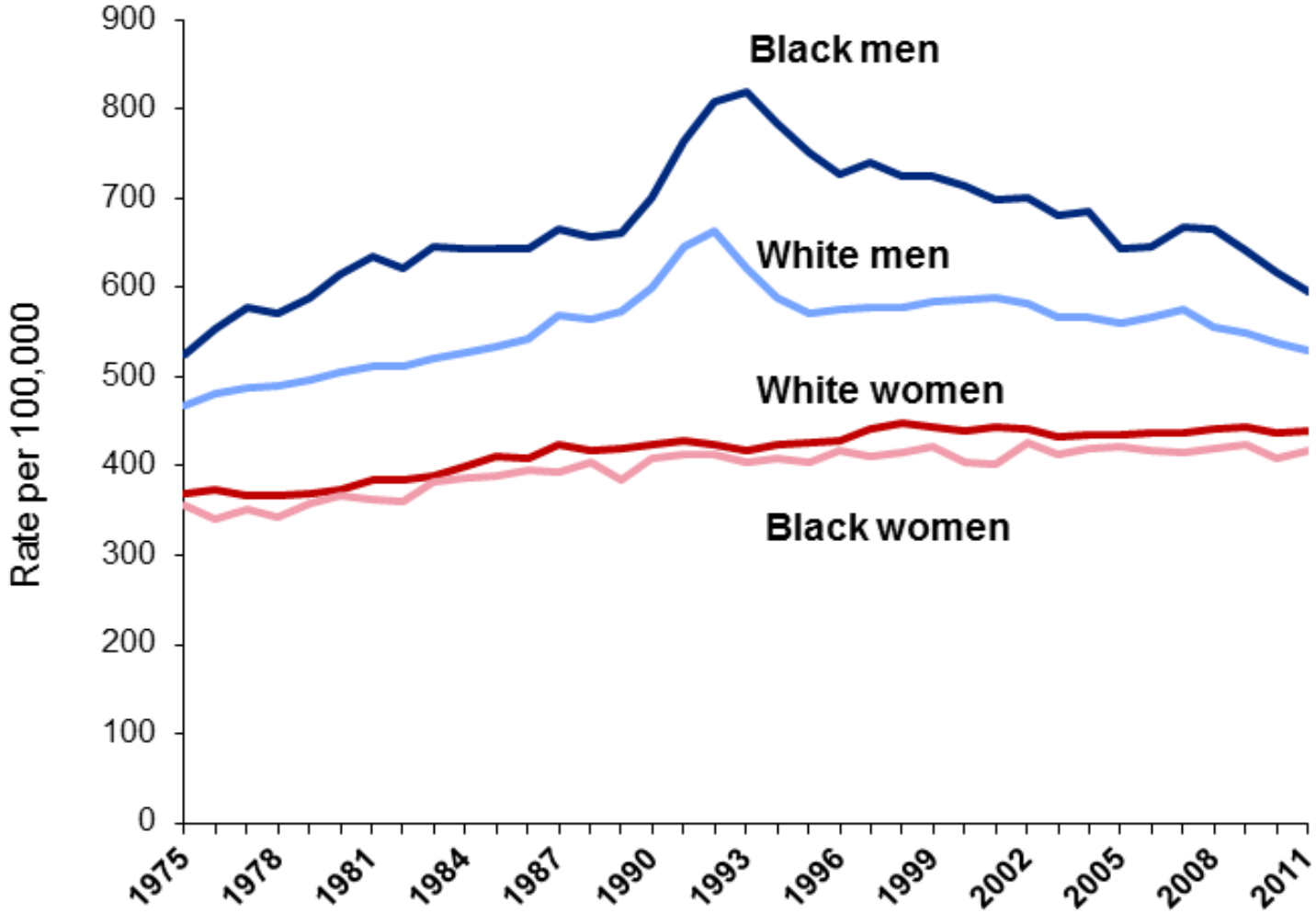

RACIAL AND
ETHNIC GROUPS

Cancer Incidence Rates* by Race and Ethnicity, 2007-2011



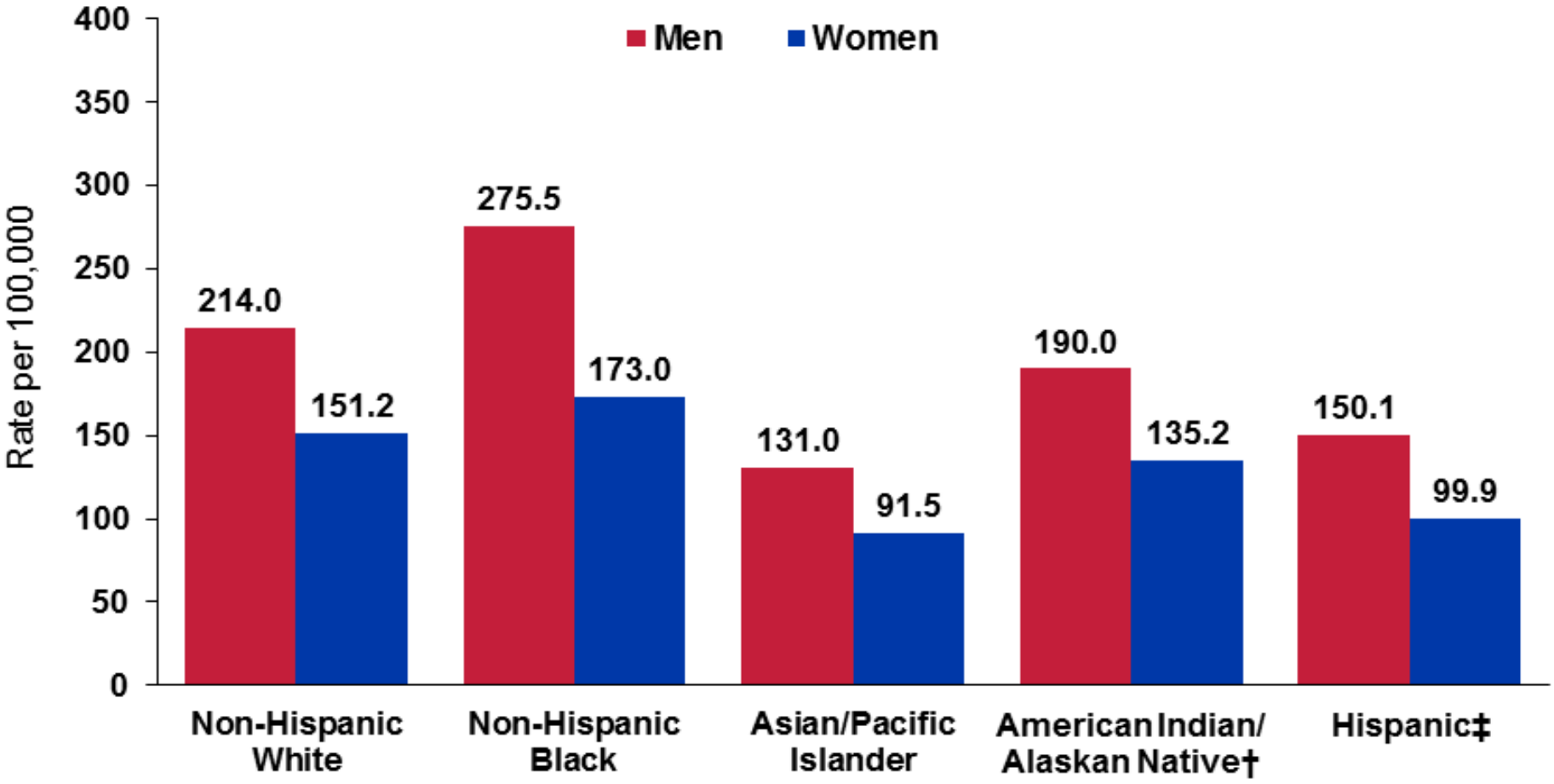
*Age-adjusted to the 2000 US standard population.
†Data based on Indian Health Service Contract Health Service Delivery Areas. Rates exclude data from Kansas.
‡Persons of Hispanic origin may be of any race.
Source: National American Association of Central Caner Registries, 2014.

Trends in Cancer Incidence Rates* by Sex and Race, US, 1975-2011



*Age-adjusted to the 2000 US standard population. Incidence rates are adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2014.

Cancer Death Rates* by Race and Ethnicity, US, 2007-2011



*Per 100,000, age-adjusted to the 2000 US standard population.
†Data based on Indian Health Service Contract Health Service Delivery Areas.
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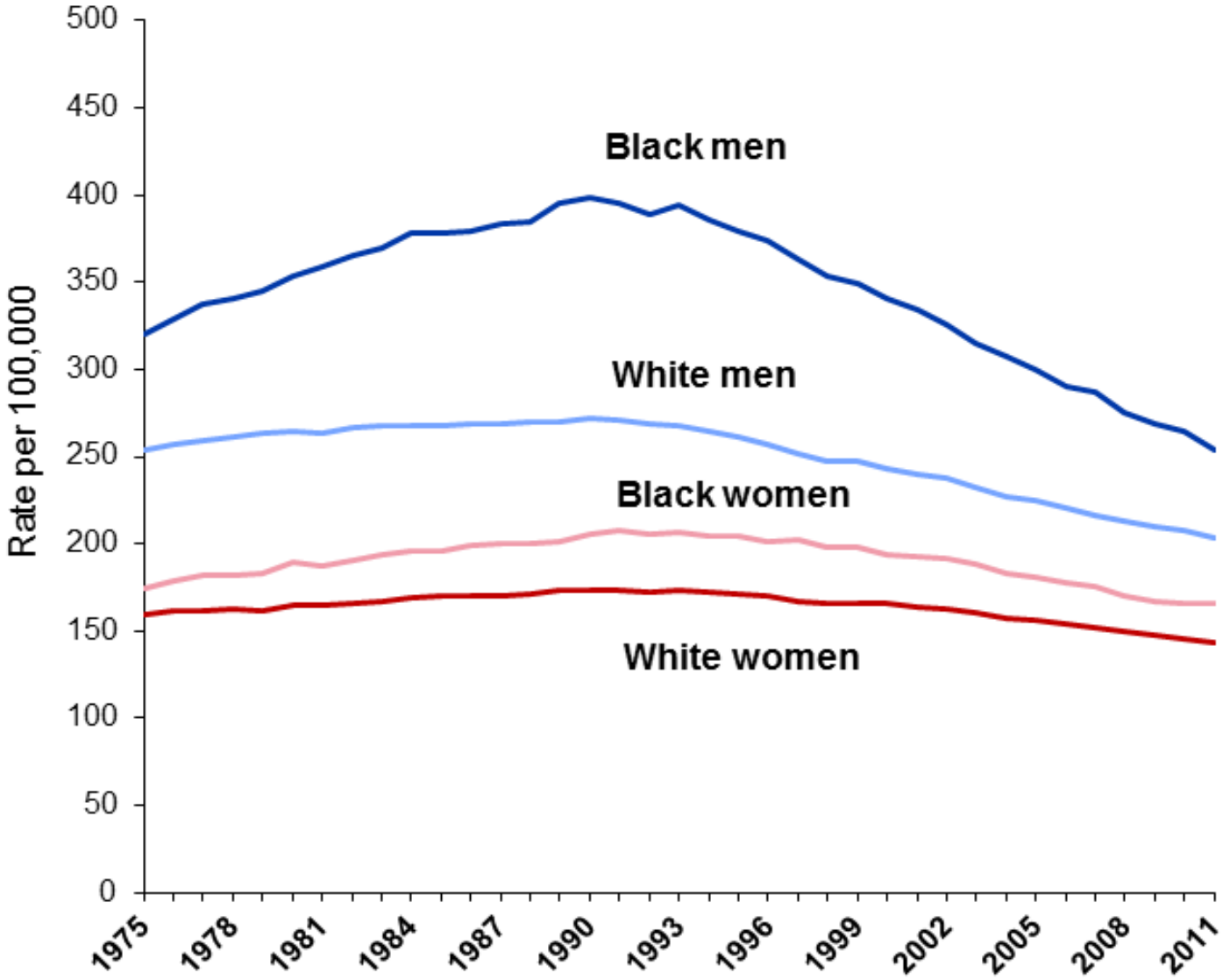
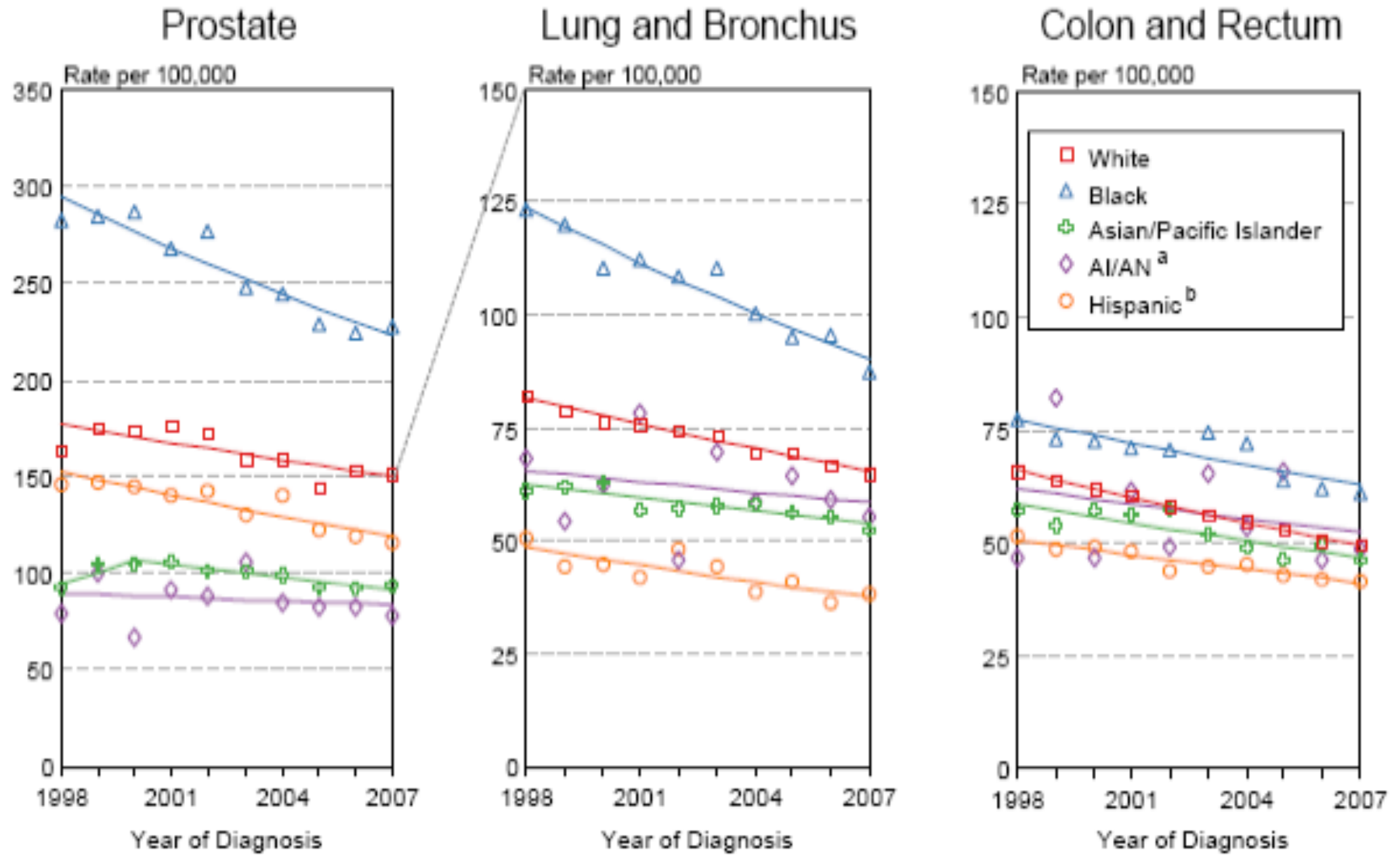
Sources: National Center for Health Statistics, Centers for Disease Control and Prevention, 2014.

Trends in Cancer Death Rates* by Sex and Race, US, 1975-2011

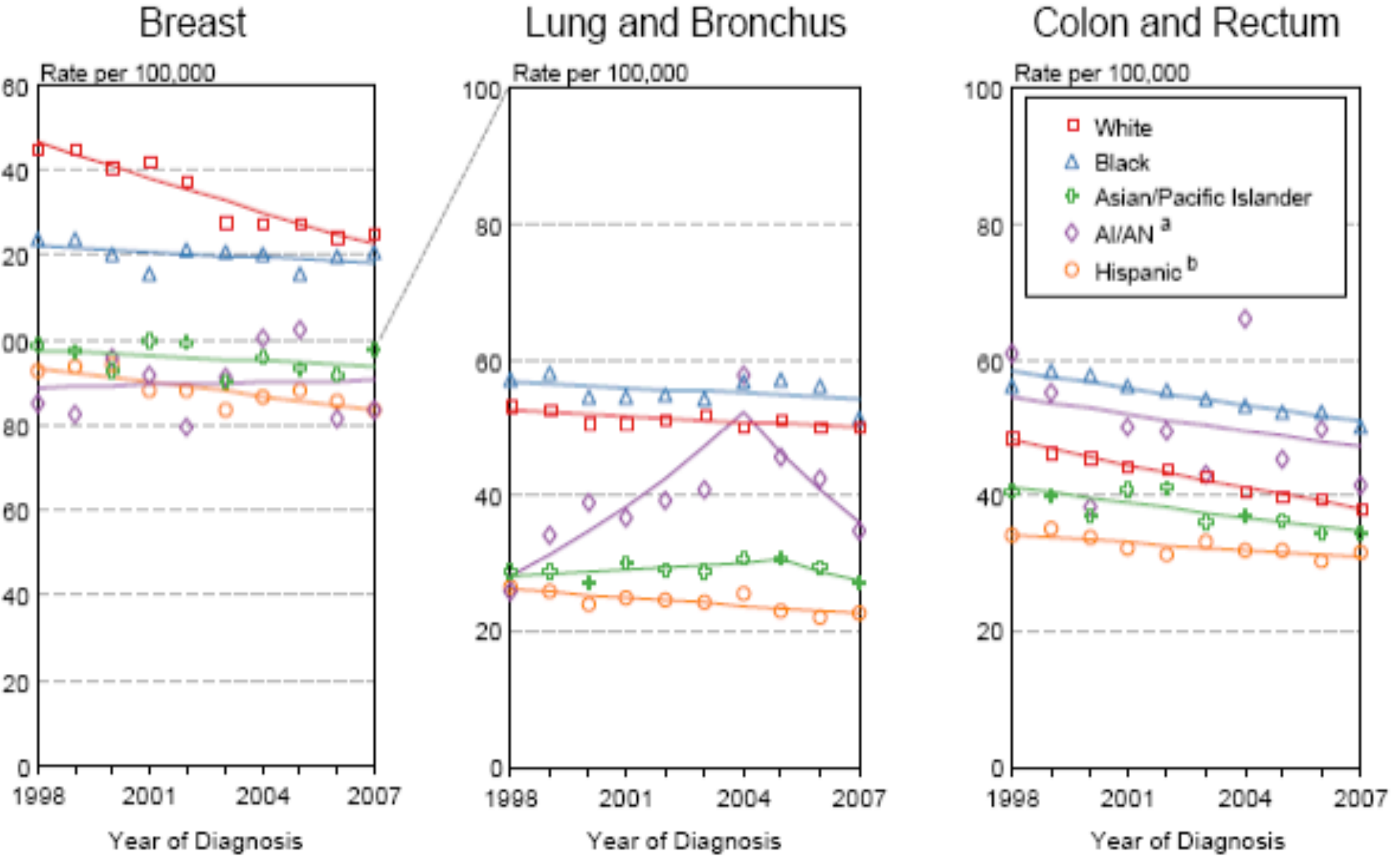


*Age-adjusted to the 2000 US standard population.
Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2014.

SEER Incidence 1998-2007
Males by Race/Ethnicity

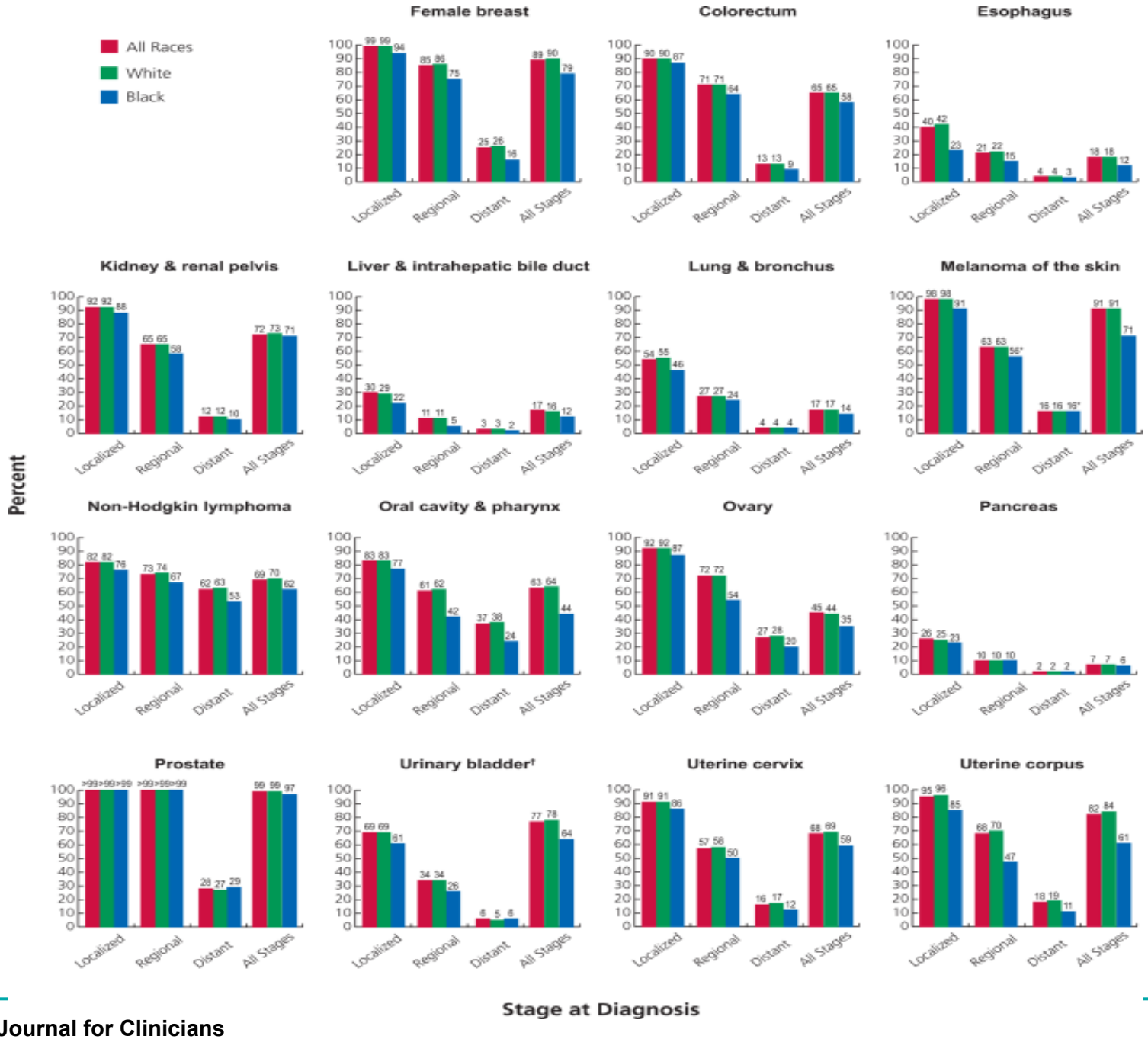


SEER Incidence 1998-2007
Females by Race/Ethnicity



Survival

Cancer statistics, 2015



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Trends in Five-year Relative Survival (%)*, 1975-2007

Site	1975-1977	1987-1989	2001-2007
All sites	49	56	67
Breast (female)	75	84	90
Colon	51	60	65
Leukemia	34	43	57
Lung and bronchus	12	13	16
Melanoma	82	88	93
Non-Hodgkin lymphoma	47	51	70
Ovary	36	38	44
Pancreas	2	4	6
Prostate	68	83	100
Rectum	48	58	68
Urinary bladder	73	79	80

*5-year relative survival rates based on follow up of patients through 2008.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2008, Division of Cancer Control and Population Sciences, National Cancer Institute, 2011.

Cancer Survival*(%) by Race, 2001-2007

Site	White	African American	Absolute Difference
All Sites	66	58	8
Breast (female)	90	77	13
Colon	65	55	10
Esophagus	18	11	7
Leukemia	54	48	6
Non-Hodgkin lymphoma	68	60	8
Oral cavity	62	42	20
Prostate	100	96	4
Rectum	66	59	7
Urinary bladder	79	64	15
Uterine cervix	70	58	12
Uterine corpus	85	62	23

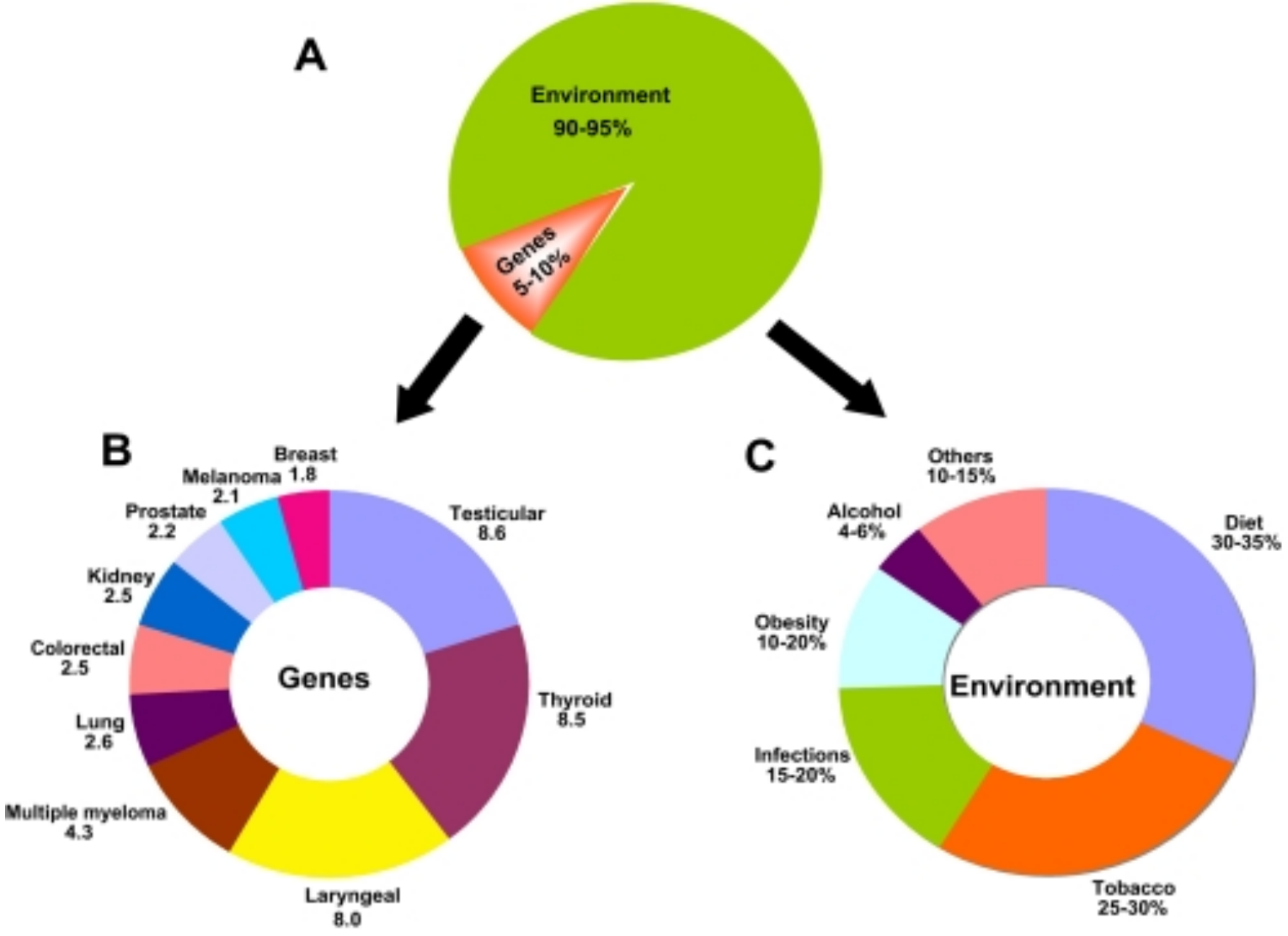
*5-year relative survival rates based on cancer patients diagnosed from 2001 to 2007 and followed through 2008.
Source: SEER 17 registries, Surveillance, Epidemiology, and End Results Program, Division of Cancer Control and Population Sciences, National Cancer Institute, 2011.

What are the major causes of cancer?

Common Causes

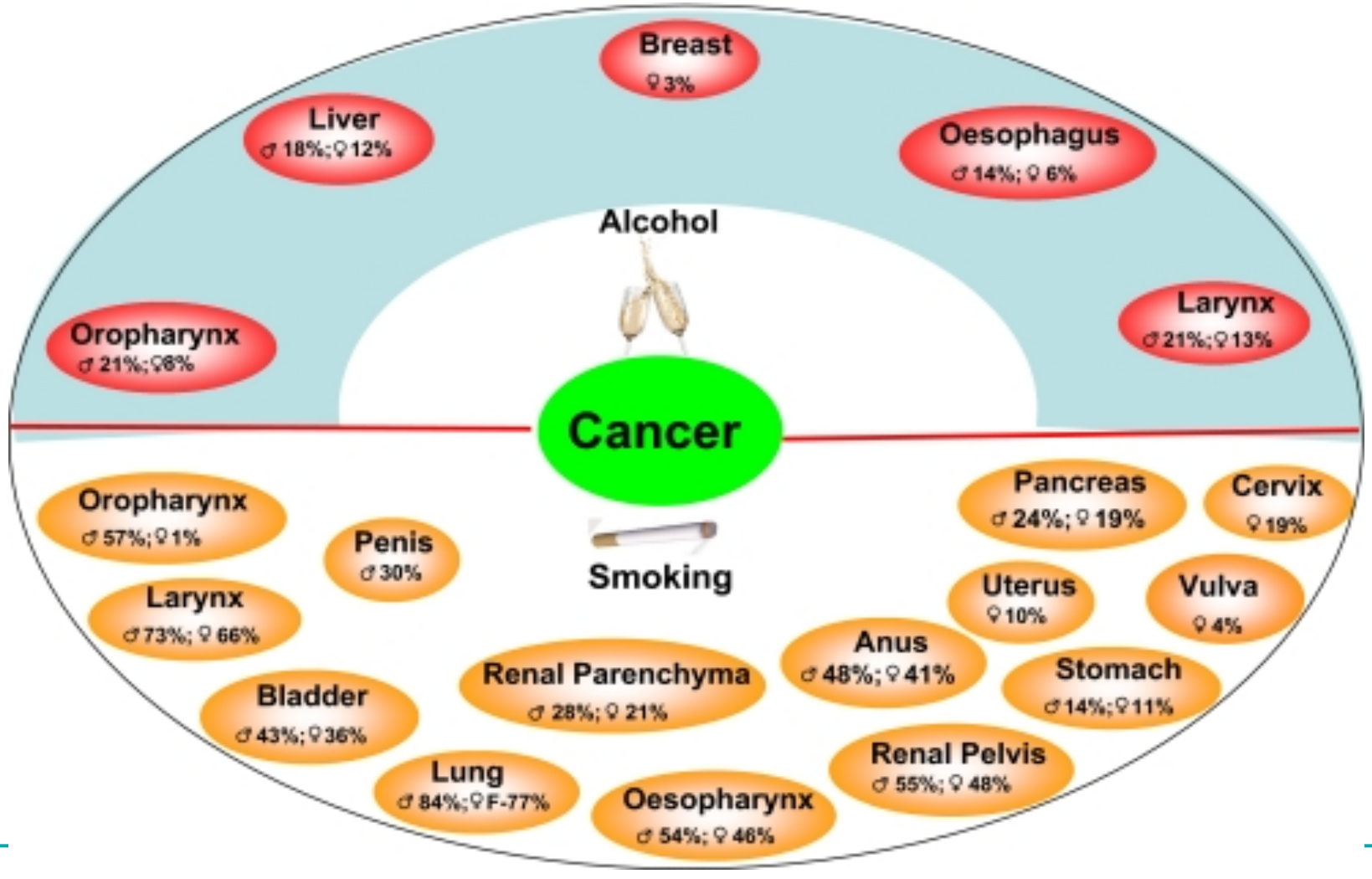
- Tobacco ~ 20%
- Infection~ 15-25%
- Diet ~ 20-30%
- Obesity and Physical Activity ~10-20%
- Pollutants ~ 10%
- Other

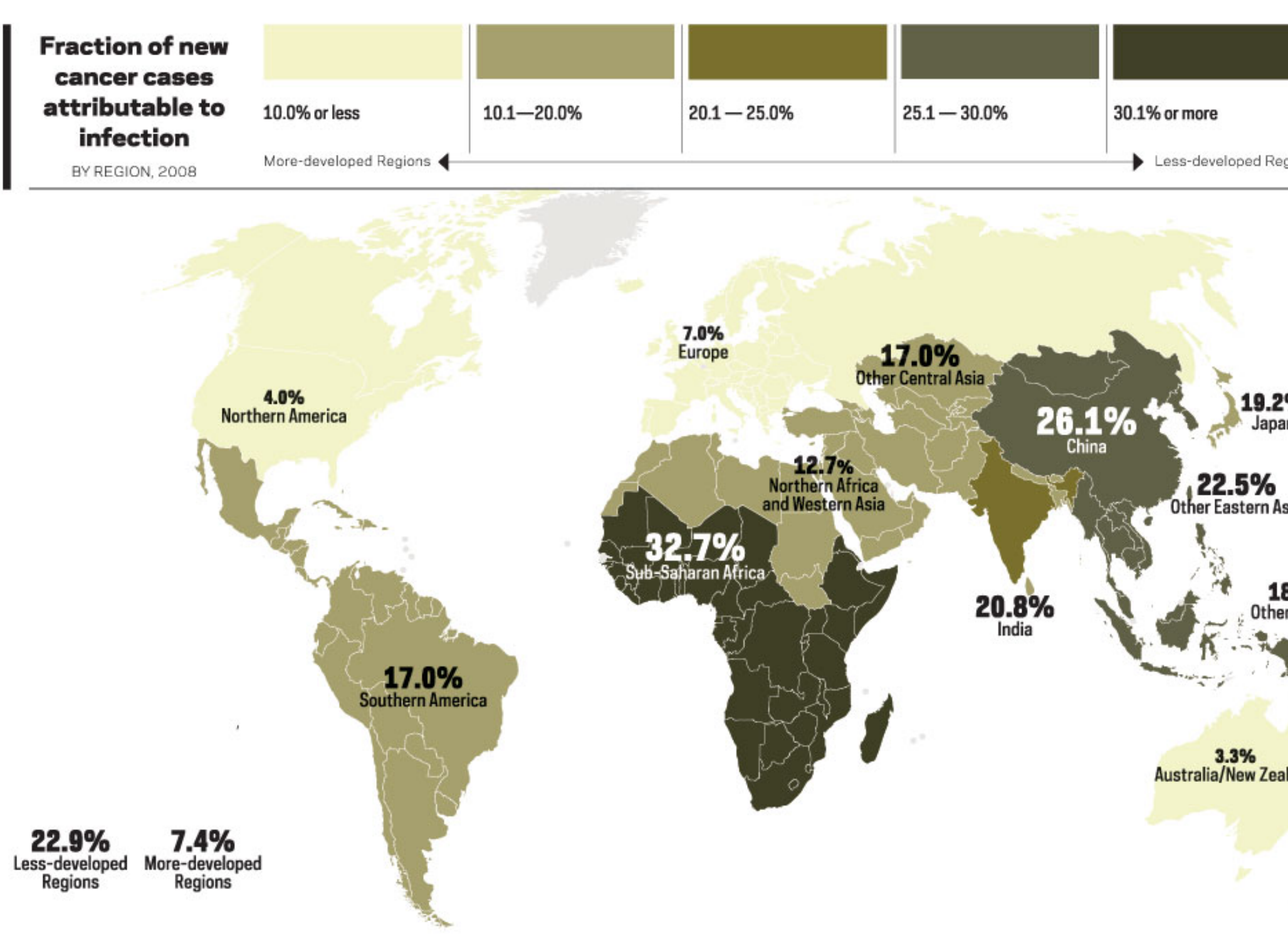
Type of Causes

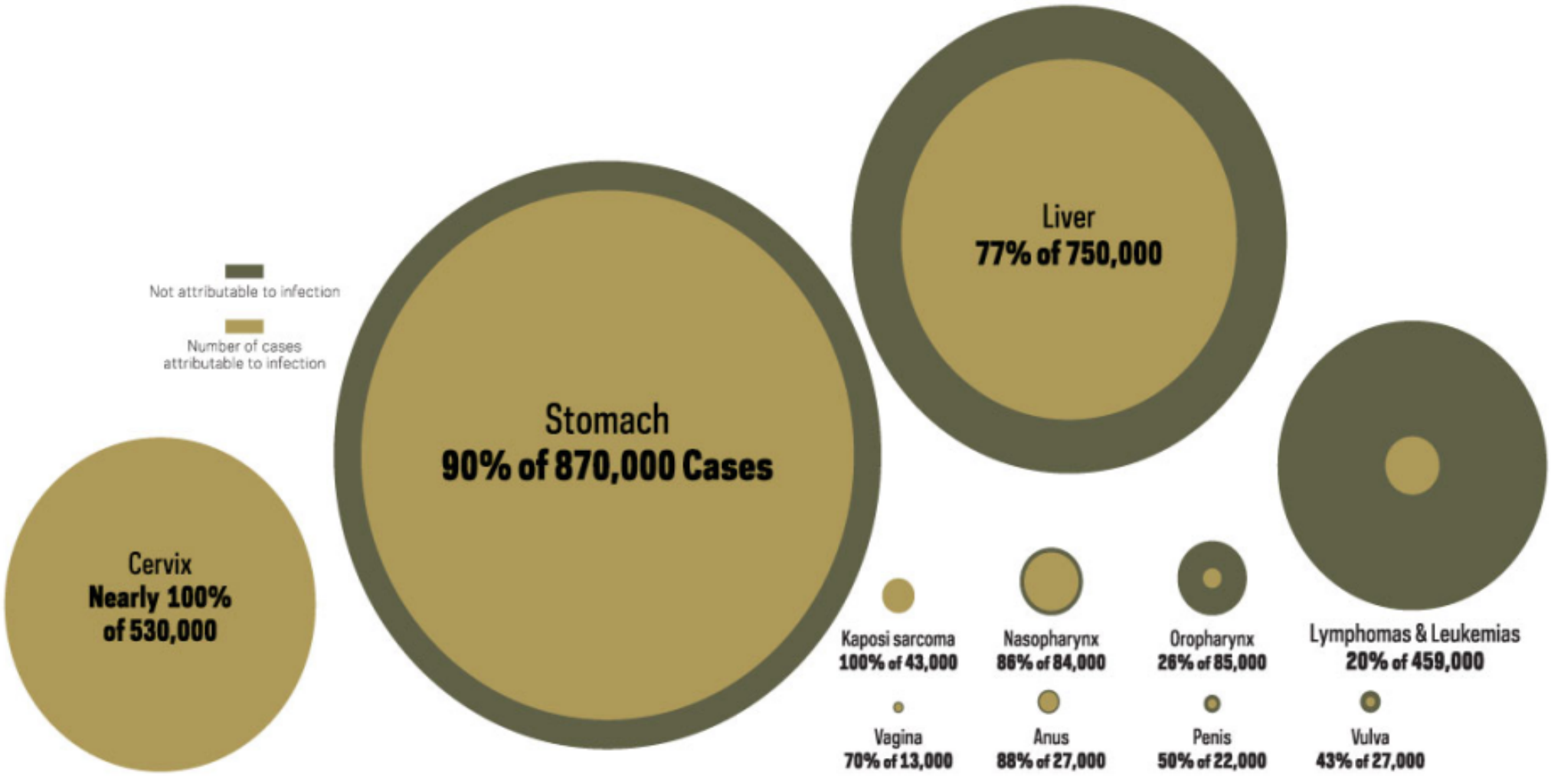


Anand, 2008 MMWR / September 9, 2011 / Vol. 60 / No. 35
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2515569/figure/Fig1/

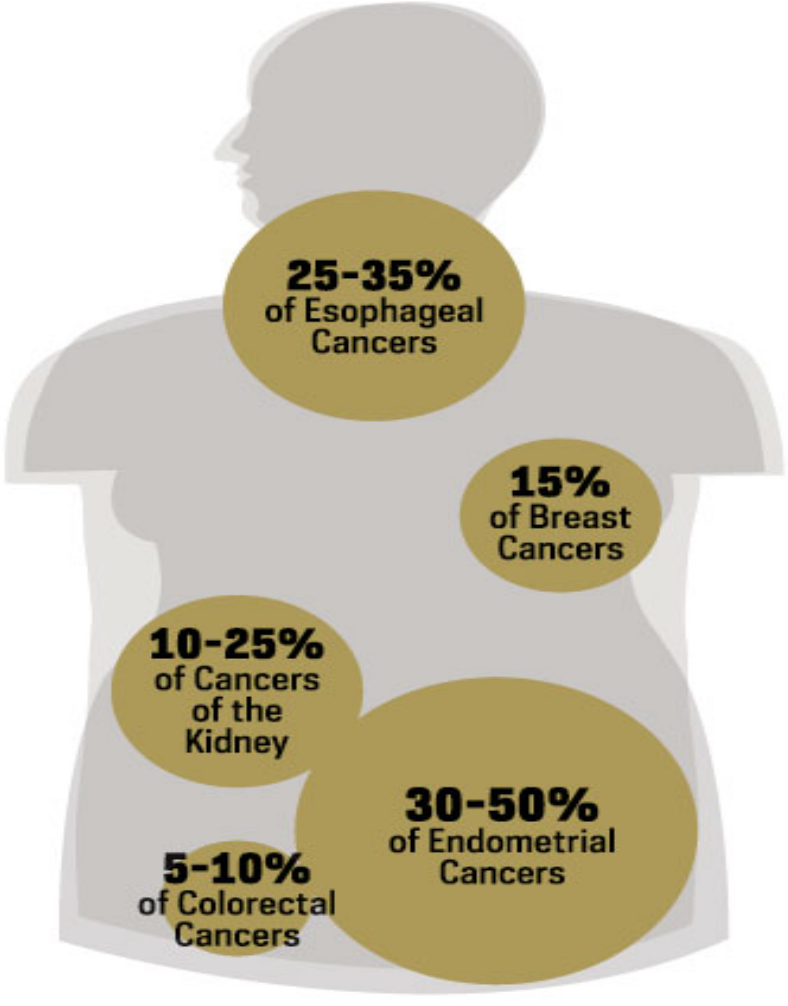
Smoking causes several types of cancer and accounts for 20% of all global cancer deaths

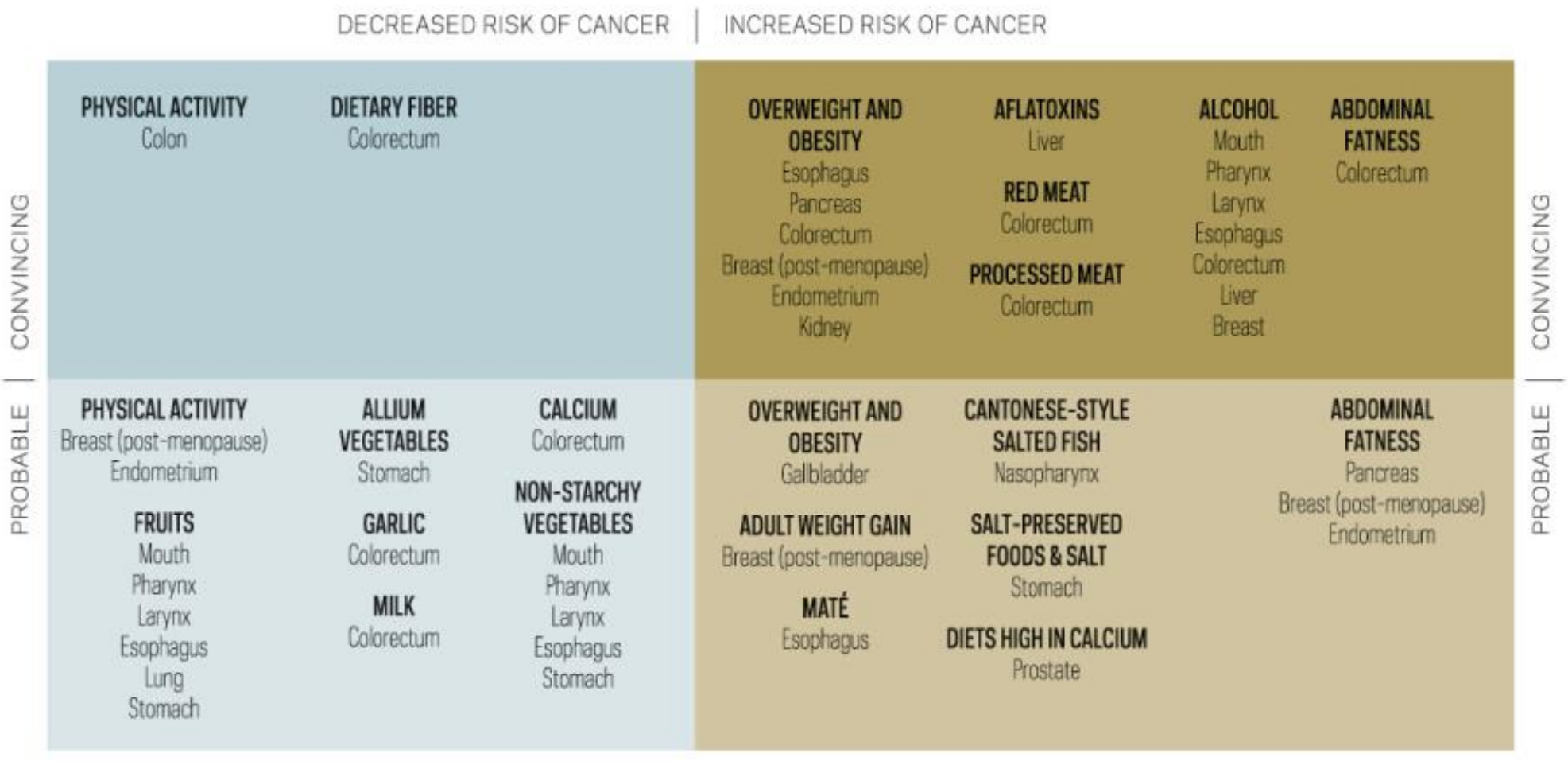



Fraction of new cancer cases attributable to infection
BY REGION, 2008
10.0% or less
10.1—20.0%
20.1 — 25.0%
25.1 — 30.0%
30.1% or more
More-developed Regions
Less-developed Reg
4.0%
Northern America
7.0%
Europe
17.0%
Other Central Asia
26.1%
China
19.2%
Japa
12.7%
Northern Africa
and Western Asia
22.5%
Other Eastern As
32.7%
Sub-Saharan Africa
20.8%
India
17.0%
Southern America
3.3%
Australia/New Zeal
22.9%
Less-developed
Regions
7.4%
More-developed
Regions



Percentage of new cancer cases in high-income countries caused by excess body weight





Environmental Carcinogens

Ananda, 2009

Major inherited susceptibility to cancer

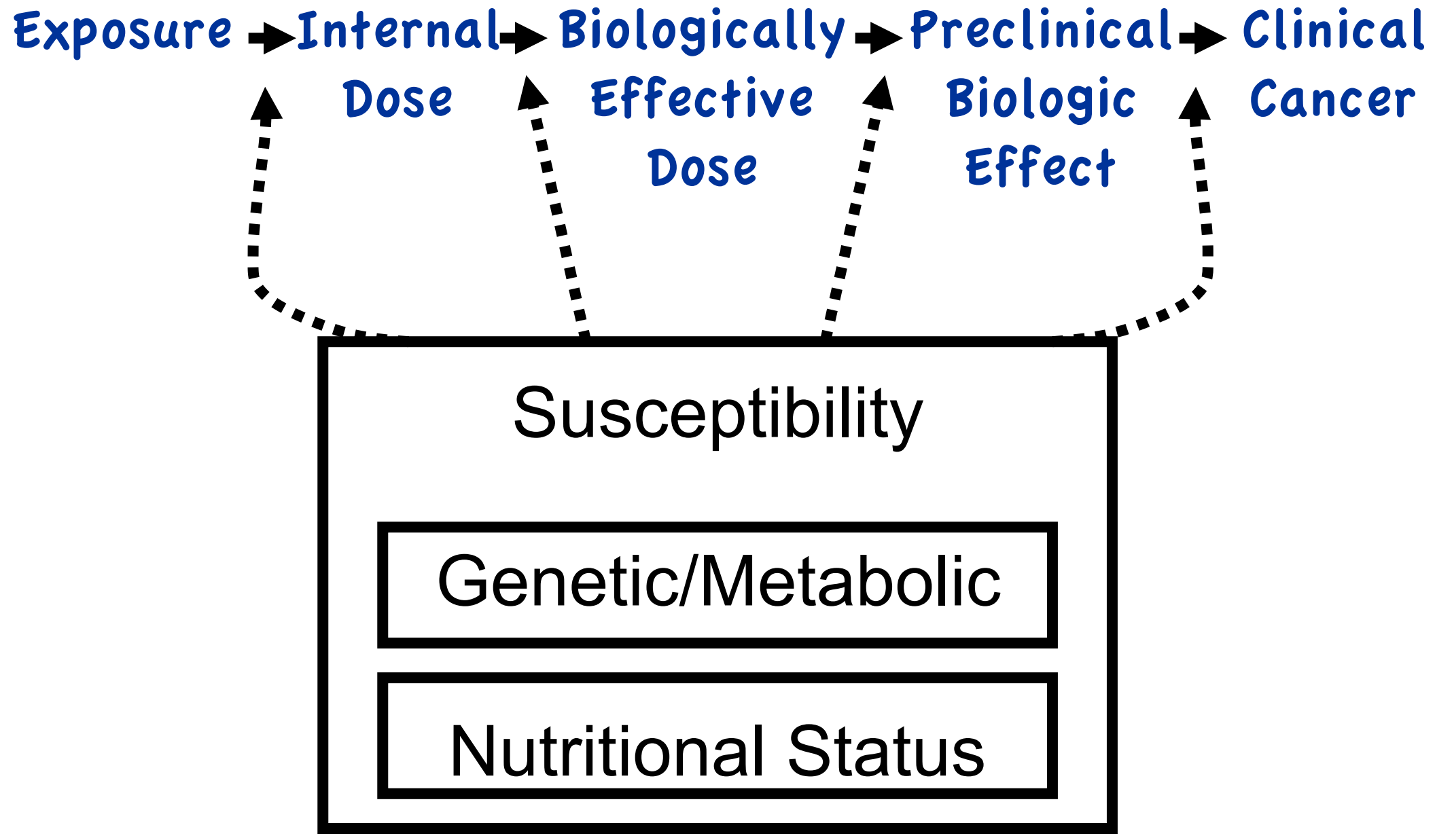
- BRCA1/BRCA2 and breast cancer
- FAP and HNPCC and colon cancer

Source: Boffetta P. Oncogene 2004; 23

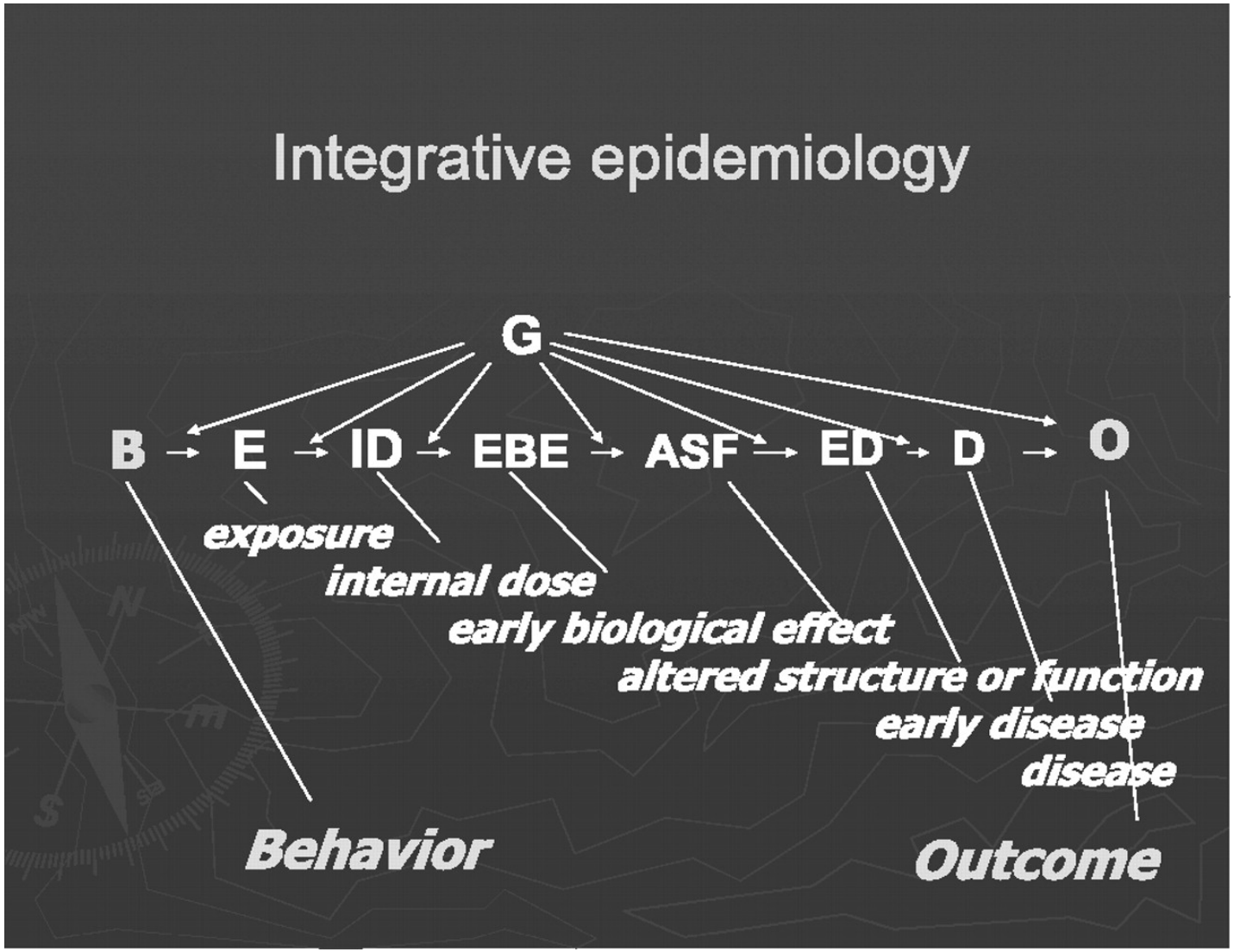
Types of Epidemiologic Studies

- Cohort
- Case-Control
- Cross-Sectional (Prevalence)
- Other

Cancer epidemiology model



Integrative epidemiology is simply the familial molecular epidemiology paradigm with the ‘wings’, behavior, and outcome added.



Caporaso N E Cancer Epidemiology Biomarkers Prev 2007;16:365-366

Biomarkers of Exposure

- Exposure
  - Sources
    - Endogenous
    - Exogenous
- Measure
  - Environmental (benzene, lead, se, aflatoxin)
  - Nutrients (folate, beta-carotene, c, e, d)
  - Infections (HIV, HBV, HCV, HPV, EBV, H. Pylori)
  - Endogenous (hematologic parameters, ER, PR, testosterone)

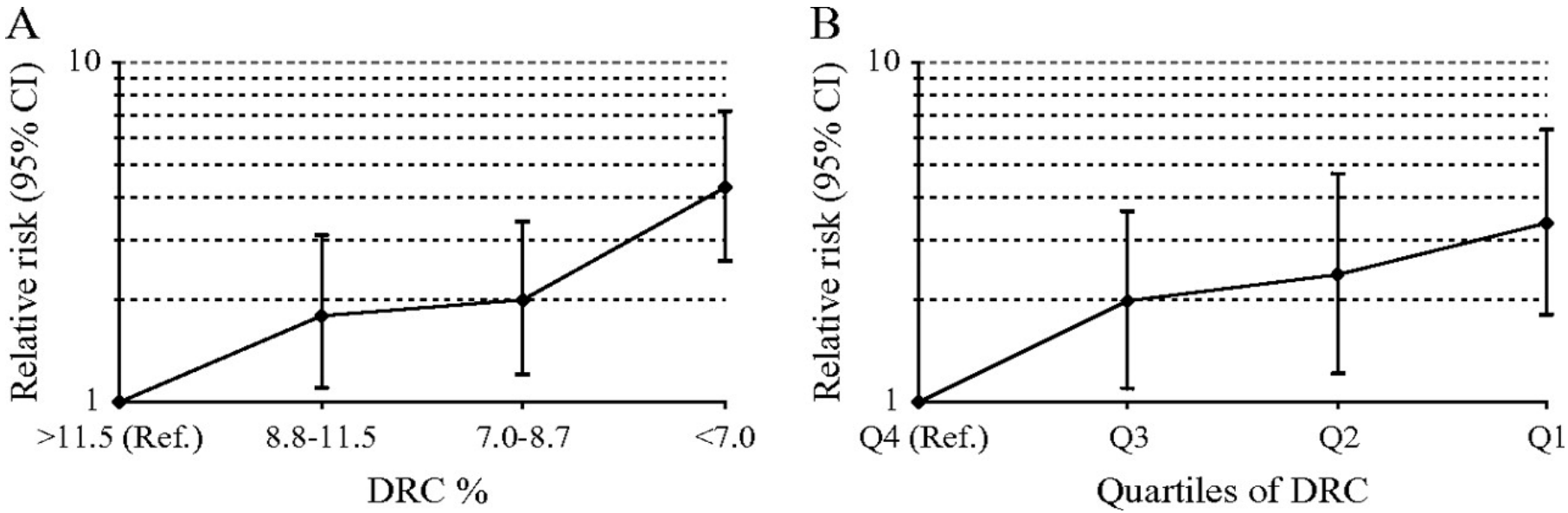
Biomarker of Exposure

- http://sph.unc.edu/superfund-pages/research-projects/biomarkers-of-exposure-versus-effect-improving-the-scientific-basis-for-risk-assessment/

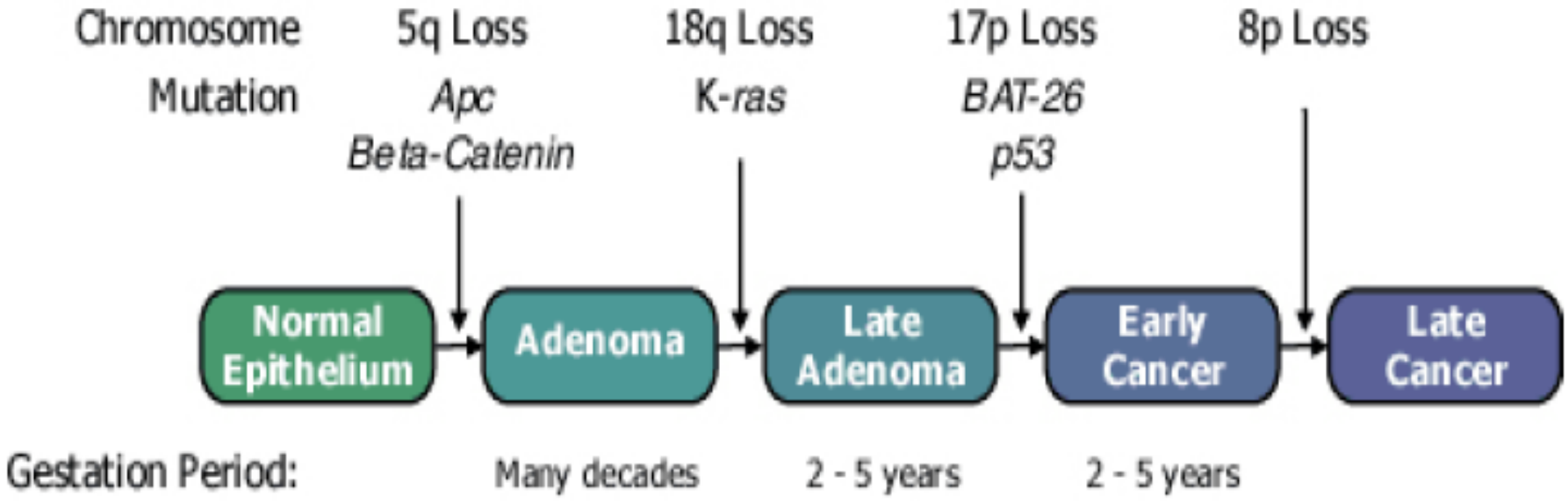
Intermediate endpoints

- Intermediate biomarkers on the continuum between exposure and cancer development.
- Early biologic effects
  - Common measures:
    - tissue toxicity, chromosomal alterations, changes in DNA, RNA and protein expression and alterations in functions relevant to carcinogenesis (e.g. DNA repair, immunological response, etc.)
- Altered structure or function
  - Precursor lesions
  - Apoptosis, proliferation

DNA repair capacity (DRC) and risk of lung cancer.



Boffetta P Carcinogenesis 2009;31:121-126

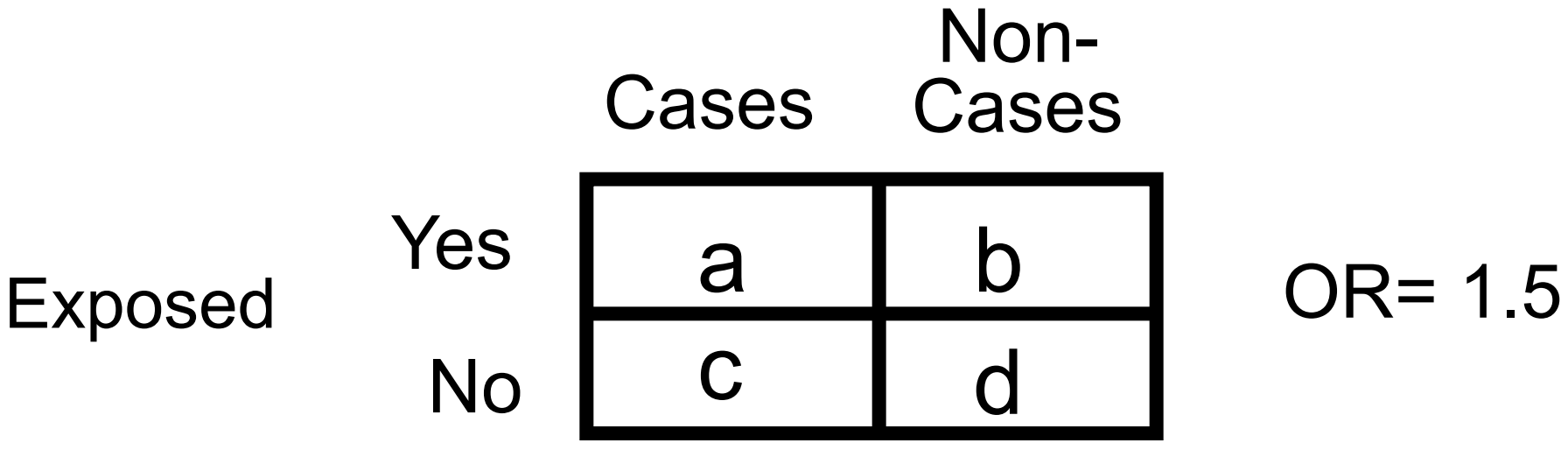


Classical "Vogelgram" developed by Fearon and Vogelstein, demonstrating the multi-step progression of the germ-line Apc mutation to familial adenopolyposis (FAP) and on to full-blown hereditary colorectal cancer

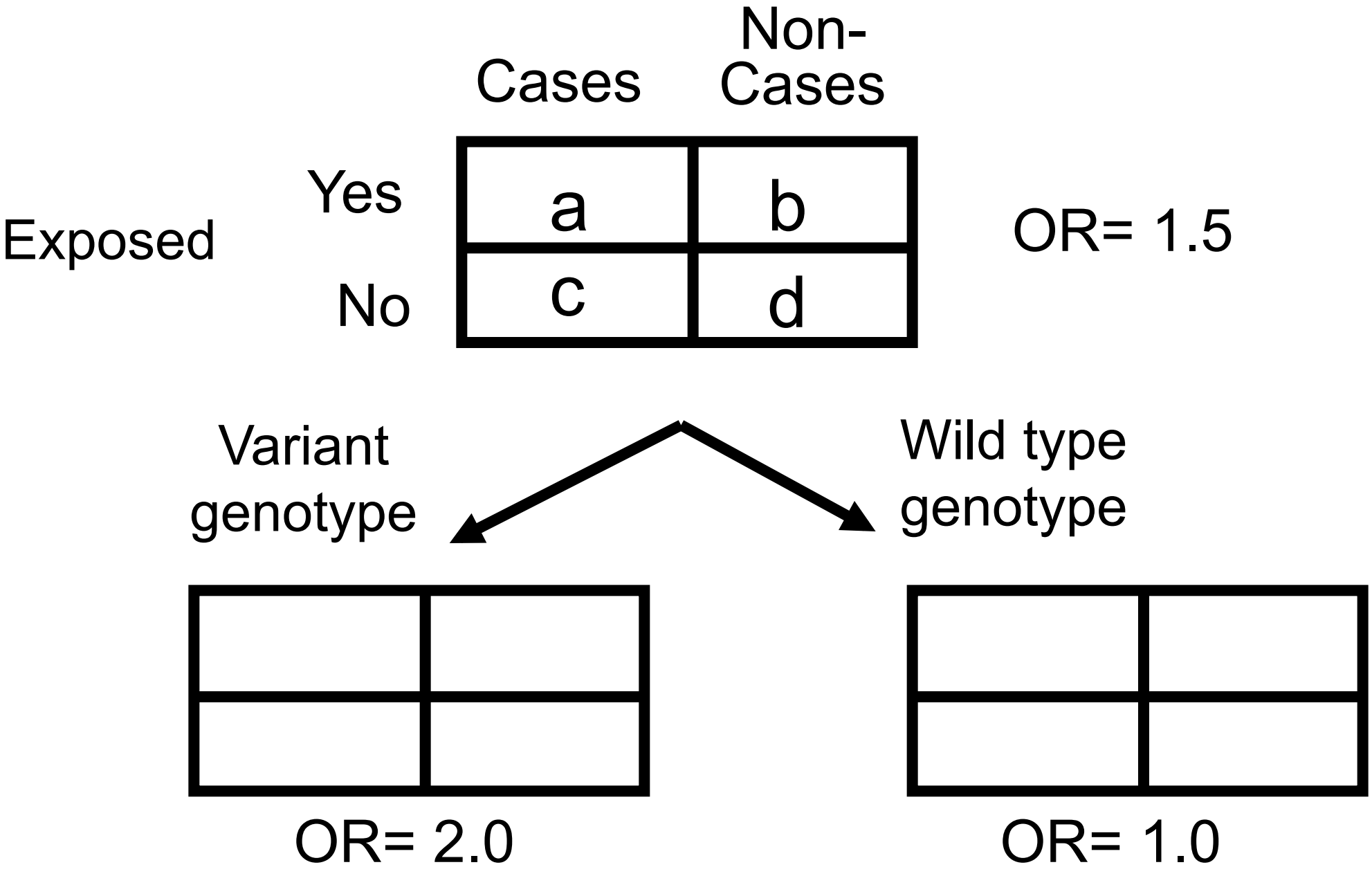
Susceptibility Biomarkers

- Genetic
  - Genotype (germline DNA mutations)
  - Functional /phenotypic (polymorphism)
- Nutritional status
- Infectious status
  - Exposures as co-factors
  - E.g. diabetes and west Nile virus
  - HIV and HSV

Not accounting for genetic susceptibility



Accounting for genetic susceptibility



Smoking and genetic susceptibility:

NAT2 acetylation genotype, cigarette smoking, and bladder cancer risk: meta-analysis (ORs)

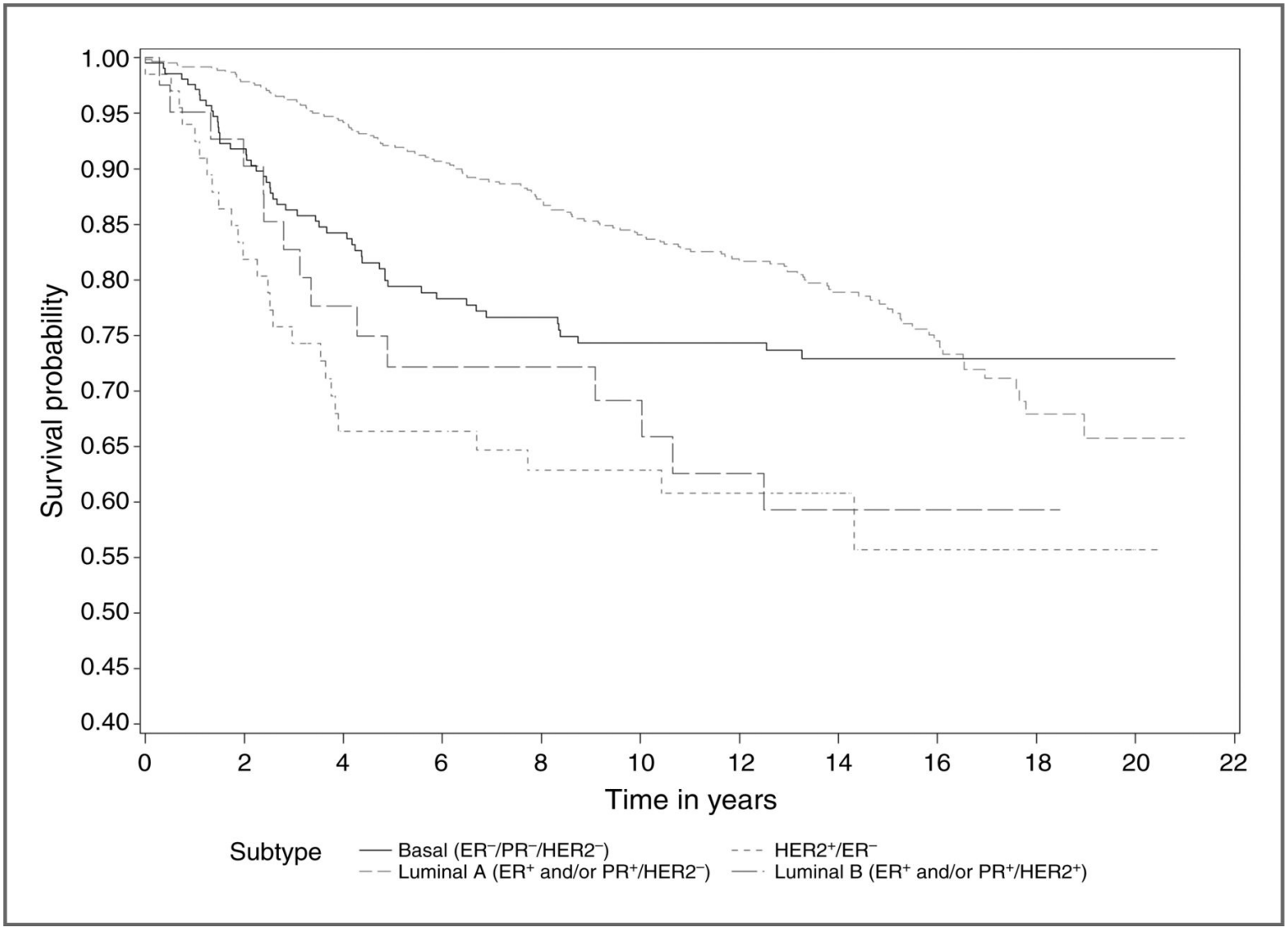
	NAT2 status	
Smoking	Rapid	Slow
Never	1.0	1.1
Ever	1.9	3.2

Source: Marcus PM, et al CEBP 2000; 9: 461

Disease and Outcome

- Tumor markers
  - Somatic mutations
    - KRAS, BRAF, p53
  - Epigenetic markers
    - CIMP, ER, IGF, SFRP
  - Cytogenetics (copy number)
  - Histopathology
- Molecular signatures
  - Risk and prognosis
  - Classes of tumor type

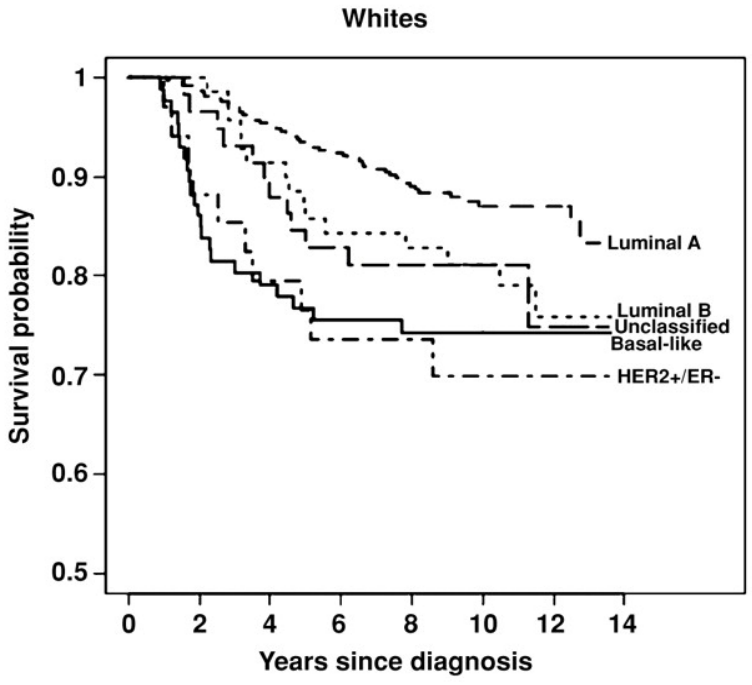
Kaplan–Meier survival curve for breast cancer mortality.

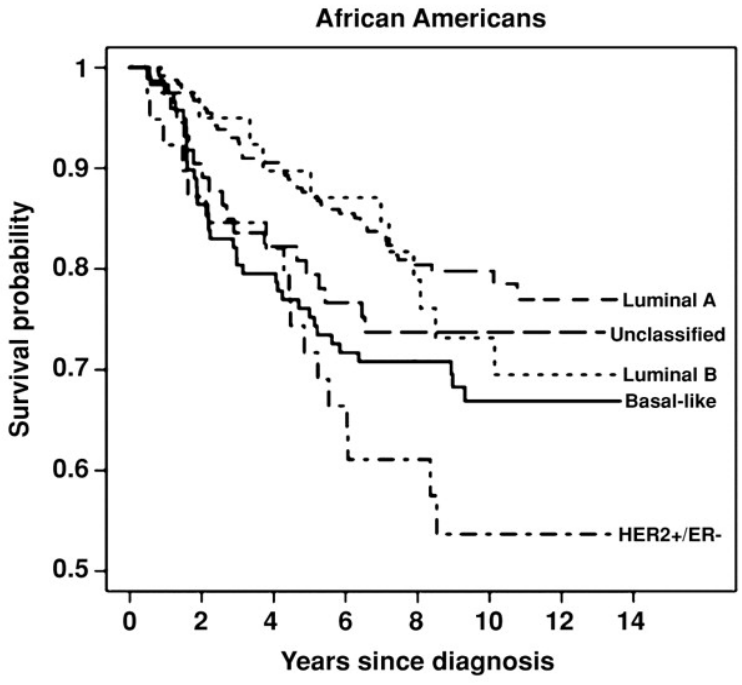


Reina Haque et al. Cancer Epidemiol Biomarkers Prev 2012;21:1848-1855

AACR American Association for Cancer Research
Cancer Epidemiology, Biomarkers & Prevention

Race-stratified Kaplan–Meier plots and race effect estimates for breast cancer–specific mortality by immunohistochemical subtype in the Carolina Breast Cancer Study, 1993–2006.

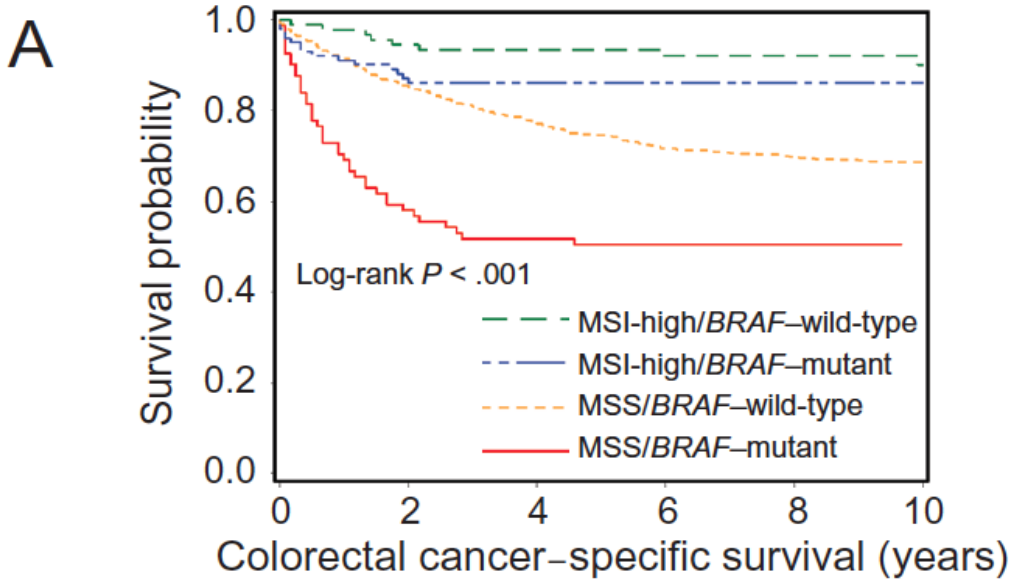


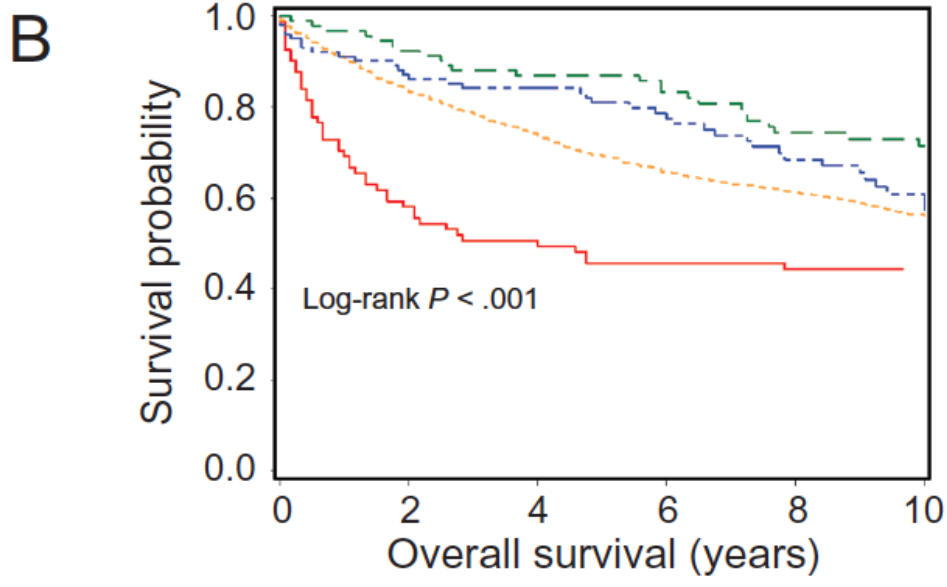


Hazard ratios for the effect of race on breast cancer–specific mortality		
	HR for race (AA vs. white) adjusted for age at diagnosis and date of diagnosis (95% CI)	HR for race (AA vs. white) adjusted for age at diagnosis, date of diagnosis, and stage at diagnosis (95% CI)
Luminal A	1.9 (1.3–2.8)	1.9 (1.3–2.9)
Luminal B	1.4 (0.6–3.1)	1.3 (0.6–3.0)
Basal-like	1.2 (0.7–2.1)	1.3 (0.8–2.3)
HER2+/ER-	1.7 (0.8–3.8)	2.2 (1.0–5.1)
Unclassified	1.4 (0.7–2.9)	1.2 (0.6–2.6)

Katie M. O'Brien et al. Clin Cancer Res 2010;16:6100-6110

Clinical Cancer Research
AACR American Association for Cancer Research

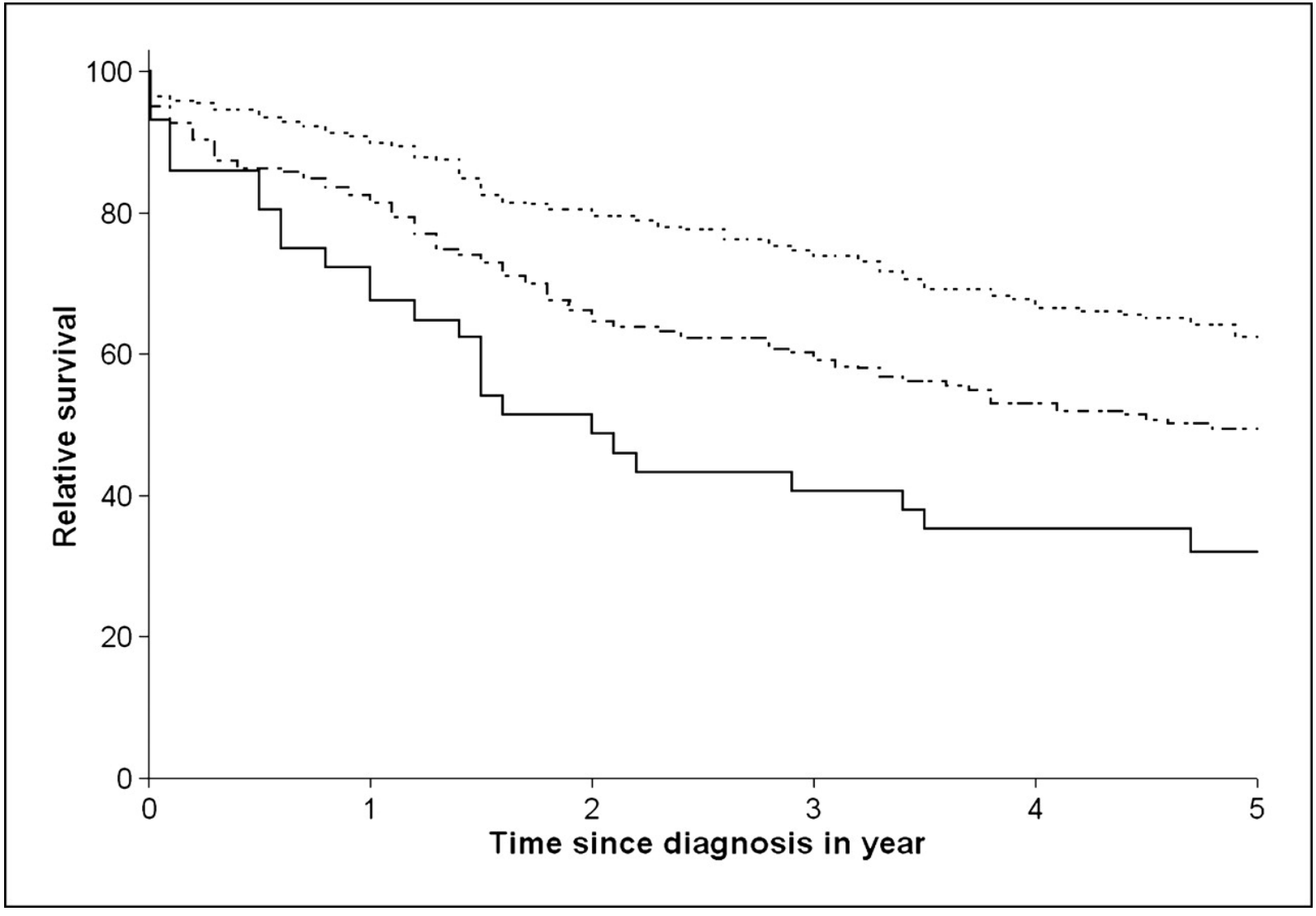




Number at risk

Year	0	2	4	6	8	10
MSI-high/*BRAF*–wild-type	92	85	76	68	56	43
MSI-high/*BRAF*–mutant	101	87	82	65	49	31
MSS/*BRAF*–wild-type	979	815	704	578	494	385
MSS/*BRAF*–mutant	81	47	40	37	32	29

Relative survival according to methylation status in MSS group (P < 0.001).



Ludovic Barault et al. Cancer Res 2008;68:8541-8546

AACR American Association for Cancer Research
Cancer Research

Genetic Epidemiology

- The study of the role of genetic factors in the occurrence of disease in populations with a focus on statistical methods for gene discovery within families
- Human genome epidemiology refers to the continuum of epidemiologic approaches to the human genome from gene discovery to medicine and public health

Genetic epidemiology studies

- Familial aggregation studies
  - Is there a genetic component to the disease, and what are the relative contributions of genes and environment?
- Segregation studies:
  - What is the pattern of inheritance of the disease (e.g. dominant or recessive)?
- Linkage studies:
  - On which part of which chromosome is the disease gene located?
- Association studies:
  - Which allele of which gene is associated with the disease?

Conventional Epidemiologic Studies

- Case-control
  - Genetic variants good because stable indicators of host susceptibility
  - Comprehensive search for several genes
  - Gene-environment interactions
  - Uncommon disease endpoints
- Gene discovery and population based risk characterization

Conventional Epidemiologic Studies

- Cohort
  - Large populations over longer term allow for assessments of changes in biomarkers overtime
    - Gene-environments interactions
- Cross-sectional Studies
  - Assess gene and allele frequency within a population
- Case-only

Examples

- Studies exploring race, age and colorectal neoplasia
  - Race and colorectal cancer survival in two cohorts
    - South Carolina Central Cancer Registry
    - Surveillance, Epidemiology, and End Results (SEER)
  - Race and risk of metachronous polyps
    - Polyp Prevention Study cohort
  - Race and risk of screening polyps
    - SC Colon Cancer Prevention Network cohort

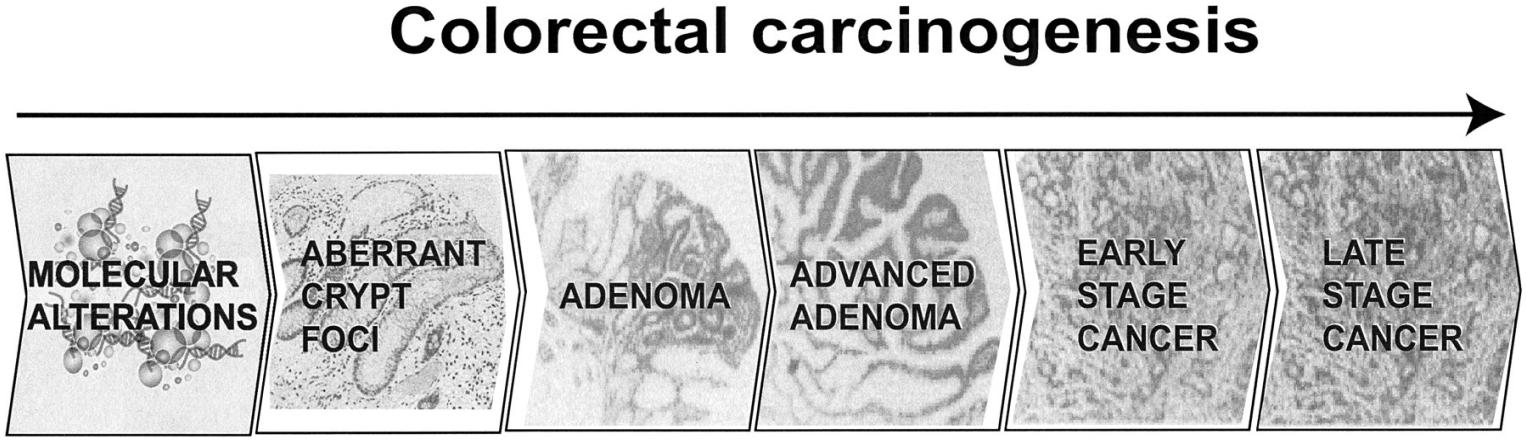
Colorectal cancer and disparities

- Colorectal Cancer Statistics
  - 4th most common cancer diagnosis
  - 2nd leading cause of cancer death
  - ~140,000 new colorectal cancers diagnosed each year;
  - ~ 48,000 deaths annually
  - Incidence rates are decreasing over time
    - Except in those < 50 years of age
- Racial Disparity
  - Blacks have a 20% higher CRC incidence rate and a 45% higher mortality rate

Explaining the Reasons for the Racial Differences

- Socioeconomic
  - Insurance, employment, educational status
- Lifestyle and Behavioral
  - Higher rates of obesity, sedentary lifestyle, smoking
- Clinical
  - Comorbid conditions (e.g. diabetes, metabolic syndrome)
  - Hematologic measures (e.g., platelets, hemoglobin, NLR)
- Biologic
  - Diagnosed at a **younger age** yet **later stage** of disease
  - Tendency toward proximal neoplasia
  - Lower prevalence of MSI+ cancer
  - Higher prevalence of KRAS+ tumors

Cancer is most often a multi-step process



Anderson, W. F. et al. J Natl Cancer Inst 2002;94:1126-1133

JNCI Journal of the National Cancer Institute

Pathways of Carcinogenesis in Sporadic CRC

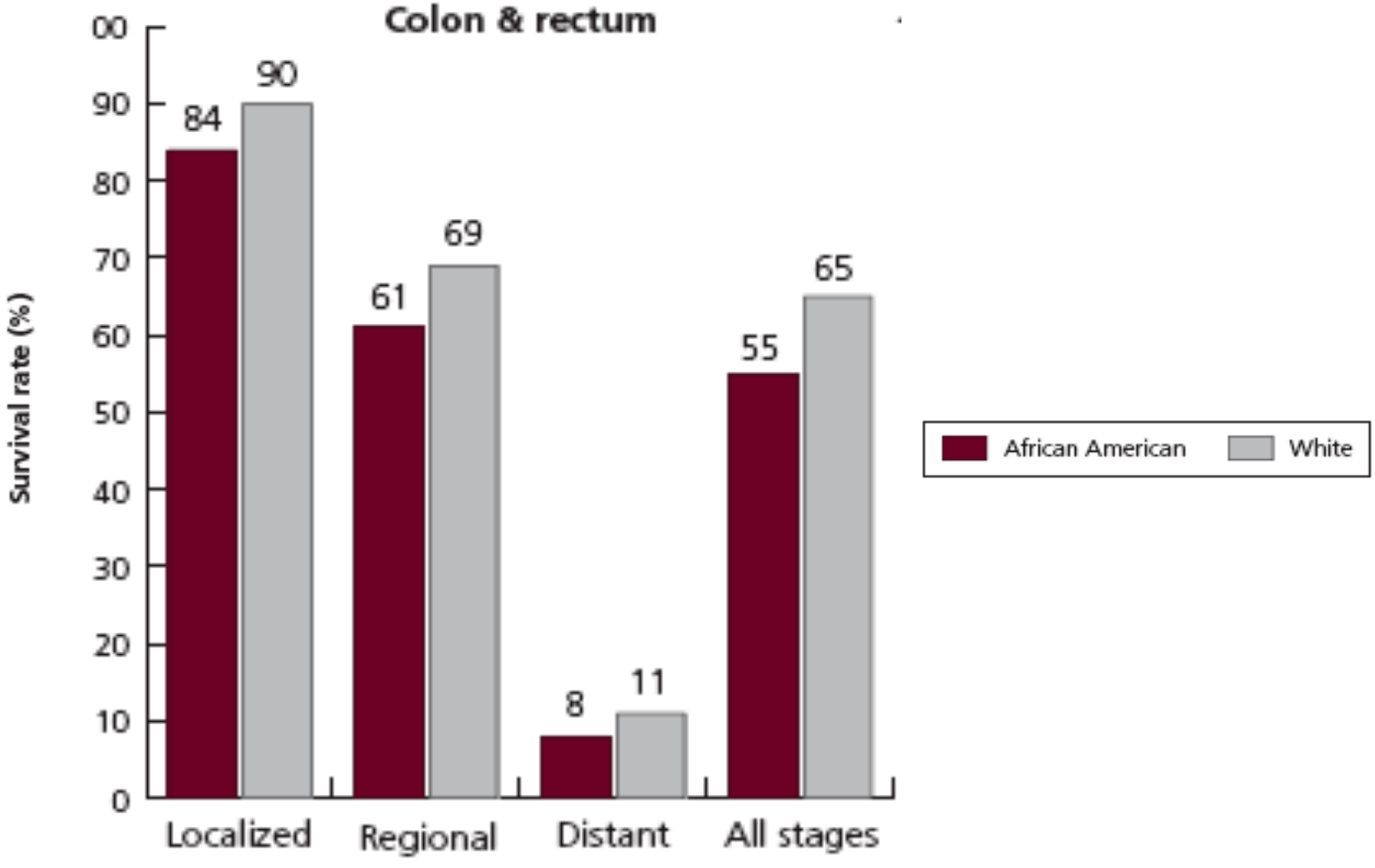
Pathways and pathoimmunomolecular features of sporadic colorectal carcinogenesis.			
Pathomolecular features	**Pathway 1** Chromosomal Instability Pathway (CIN)	**Pathway 2** CpG Island Methylator Pathway I (CIMP-1)	**Pathway 3** CpG Island Methylator Pathway II (CIMP-2)
Colonic location	Distal predominance	85% Proximal colon	Proximal predominance
Precursor lesion	Conventional Adenoma (tubular, TVA)	Serrated Polyp (SSA or TSA)	Serrated Polyp (likely TSA, TVA)
Histologic type	Adenocarcinoma, NOS	MUC-1 Mucinous Adenocarcinoma & component	MUC-2 Signet Cell Adenocarcinoma & component
Epigenetic phenotype	CIMP-	CIMP+	CIMP+
Microsatellite instability	MSS	MSI-H	MSI-L/MSS
Genetic alterations	P53, APC	BRAF	KRAS
Pathoimmunotype (immune infiltrate)	--	Intra-tumoral lymphocytes	Peri-tumoral lymphocytes
Prevalence (estimates)	60%	13-15%	25-27%
Prognosis	Average	Good	Poor
Adapted, in part from, from Issa (2008); Ogino (2010)			

Race and Advanced Stage Colorectal Cancer Survival: Two Studies

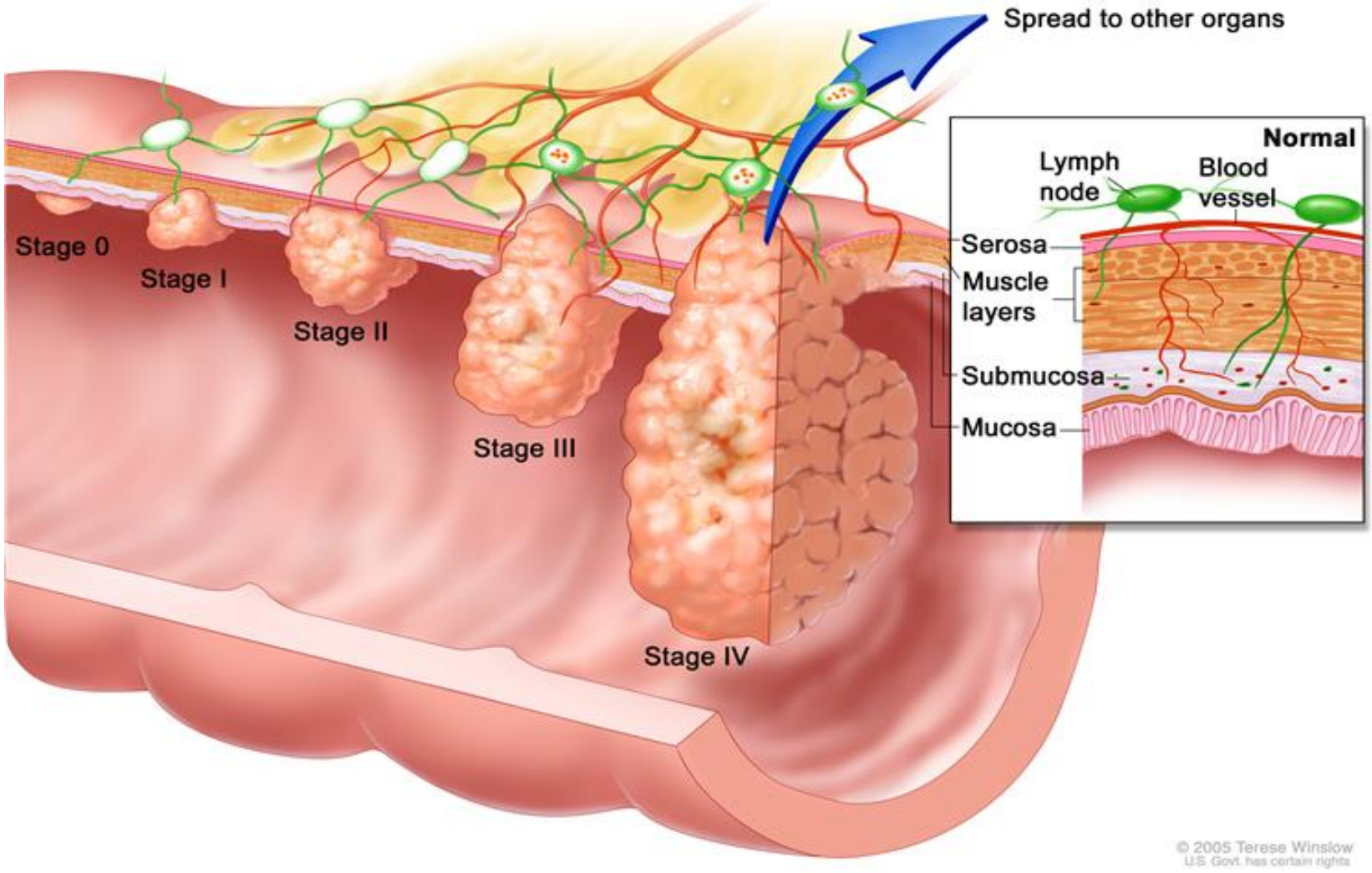
Advanced stage colorectal cancer

- Why focus on advanced stage colorectal cancer?
  - Similar recommended treatment
  - Large relative difference in survival
  - Opportunity to examine changes in survival overtime corresponding to changes in chemotherapuetic regimens

Survival by Stage and Race



ACS, 2013


Spread to other organs
Stage 0
Stage I
Stage II
Stage III
Stage IV
Normal
Lymph node
Blood vessel
Serosa
Muscle layers
Submucosa
Mucosa
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Study 1: South Carolina Central Cancer Registry data

- Population-based data system that collects cancer incidence (newly diagnosed cases) in South Carolina.
- Information on cancer mortality (deaths) is collected by the Division of Vital Registry
- CRC cases 1996-2006 with follow-up through 12/31/2007

Methods

- We computed median survival and corresponding 95% confidence intervals for blacks and whites in **three time periods (pre-2000, 2000-2003, 2004+).**
- Using Cox proportional hazards regression, we computed hazard ratios (HR) and 95% confidence intervals (CIs) to model the hazard of death as a function of race.
- We also assessed the interactions between race and age, gender, and pathologic features on survival.

RESULTS

			2000-2003			2004+		
Age	Gender	Race	n	n_e	M (95%Cl)	n	n_e	M (95%Cl)
<50	Male	White	60	53	15 (11, 24)	**42**	**20**	**25 (20, NA)**
		Black	31	28	15 (7, 28)	**23**	**15**	**16 (12, NA)**
	Female	White	58	50	19 (15, 25)	**45**	**23**	**24 (20, NA)**
		Black	47	45	10 (9, 15)	**40**	**31**	**13 (10, 19)**
50+	Male	White	406	382	14 (12, 16)	330	233	16 (15, 20)
		Black	173	163	11 (9, 13)	131	101	13 (10, 18)
	Female	White	342	320	11 (10, 14)	282	212	12 (10, 14)
		Black	156	141	12 (9, 17)	131	100	12 (11, 15)

Age	Variable		Level	HR[a]	95% CI	P
<50	Gender-by-location					0.01
		Male	Distal	1.0		
			Proximal	0.61	(0.4-0.95)	0.03
			Rectal	0.75	(0.49-1.14)	0.18
		Female	Distal	1.0		
			Proximal	**1.45**	**(1.03-2.05)**	**0.03**
			Rectal	1.09	(0.69-1.72)	0.71
	Grade		Low	1.0		
			High	1.5	(1.17-1.93)	0.001
	Histologic Type		Adenocarcinoma NOS[c]	1.0		
			Other[c]	0.68	(0.47-0.98)	0.04
	Age			0.92	(0.84-1.02)	0.13
	Race		EA	1.0		
			AA	**1.34**	**(1.06-1.71)**	**0.02**

Age	Variable		Level	HR[a]	95% CI	P
50+	Gender-by-Race					0.04
		Male	EA	1.0		
			AA	1.16	(1.01-1.32)	0.04
		Female	EA	1.0		
			AA	0.94	(0.82-1.08)	0.41
	Location		Distal	1.0		
			Proximal	1.25	(1.13-1.38)	0.0001
			Rectal	1.13	(1.01-1.28)	0.041
	Grade		Low	1.0		
			High	1.36	(1.23-1.5)	<0.0001
	Histologic type		Adenocarcinoma NOS	1.0		
			Other	1.01	(0.89-1.16)	0.86
	Age			1.08	(1.06-1.1)	

Summary

- Younger blacks had poorer survival~ HR 1.34
  - Younger women with proximal tumors ~ HR 1.45
    - High prevalence of proximal tumors among black women
- Proximal tumor associated with poor survival
- Disparity is worsening overtime, especially since 2004
  - In patients < 50 years, median survival is 24.5 months in whites and 14.5 months for blacks

Study 2: SEER Registry Data

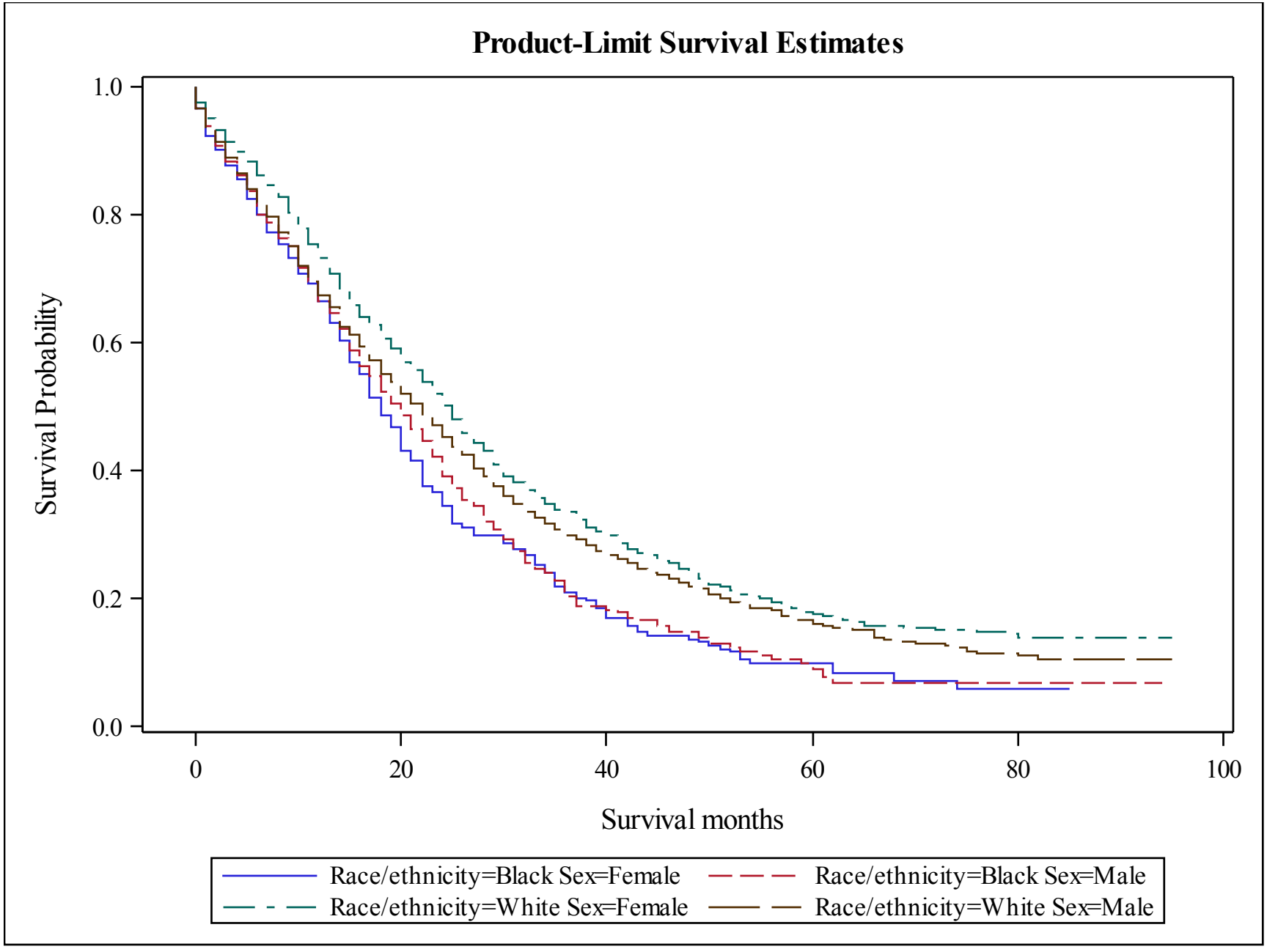
- Study Focus
  - To replicate our findings in larger study cohort **post 2004** in younger and older patients
- Methods
  - The SEER research cohort is comprised of population-based data in 18 geographic areas in the USA
  - We computed median survival and corresponding 95% confidence intervals for blacks and whites from 2004-2011

	< 50			50+		
Characteristic	**Whites**	**Blacks**	**P-value**	**Whites**	**Blacks**	**P-value**
	(n=3611)	(n=830)		(n=20846)	(n=3767)	
Age (years)	44 (18-49)	45 (19-49)	0.131	68 (50-103)	64 (50-108)	<0.0001
Gender, n (%)			0.125			<0.0001
Male	1977 (55)	430 (52)		11298 (54)	1855 (49)	
Female	1634 (45)	400 (48)		9548 (46)	1912 (51)	
Location, n (%)			<0.0001			<0.0001
Distal	1301 (36)	273 (33)		6072 (29)	1156 (31)	
Proximal	897 (25)	314 (38)		8802 (42)	1815 (48)	
Rectal	1413 (39)	243 (29)		5972 (29)	796 (21)	
Tumor Grade, n (%)			<0.0001			<0.0001
Low	2104 (67)	530 (75)		12298 (69)	2413 (77)	
High	1033 (33)	179 (25)		5549 (31)	735 (23)	
Histologic Type, n (%)			0.135			<0.0001
Adeno/NOS	3161 (88)	737 (89)		18714 (90)	3451(92)	
Mucinous	306 (8)	72 (9)		1677 (8)	269 (7)	
Signet Cell	144 (4)	21 (3)		455 (2)	47 (1)	

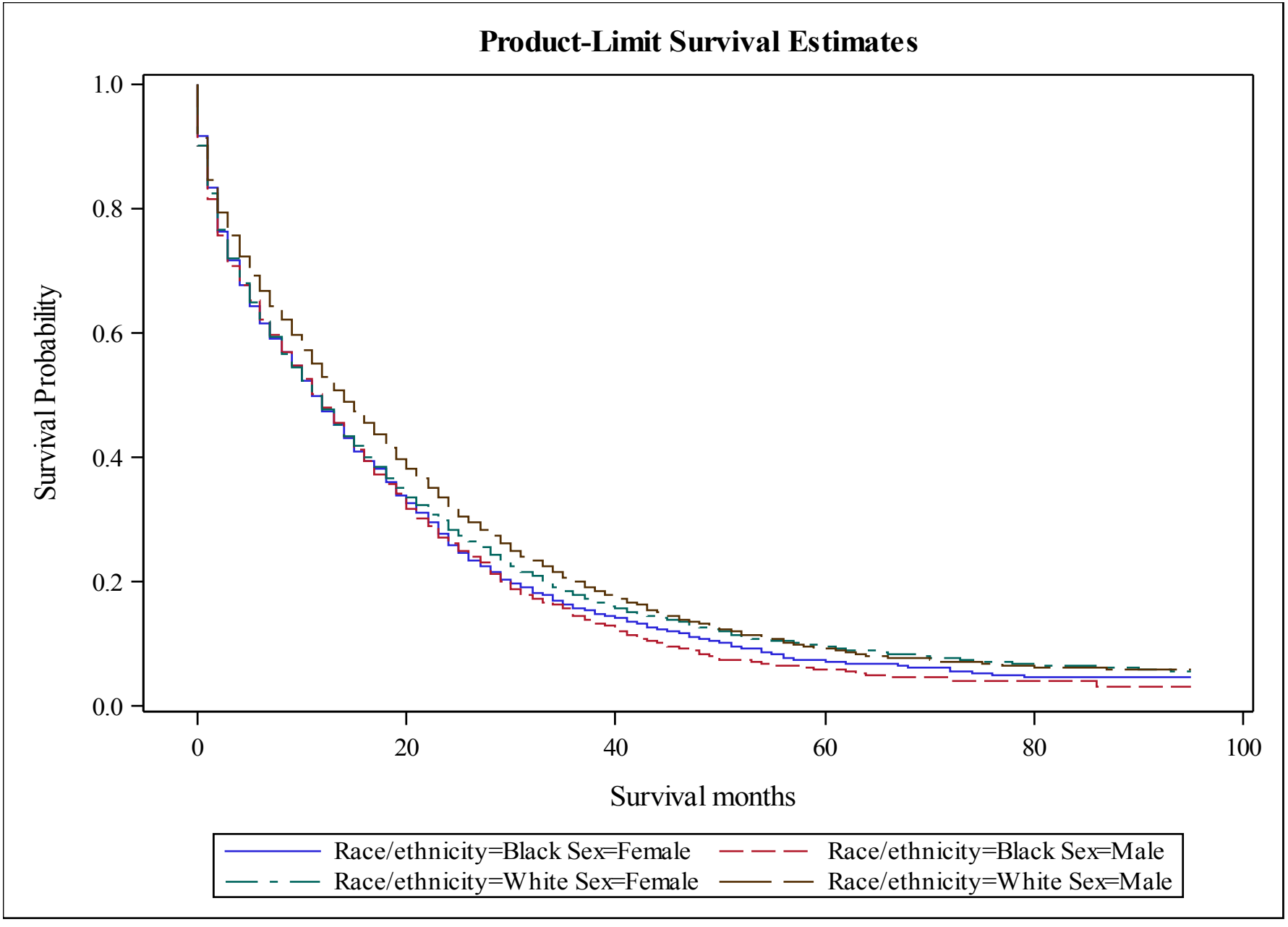
Kaplan-Meier Survival Time Estimates by Age and Gender

Age	Gender	Race	Subjects	# of events	Median	95% CI
<50	Male	Whites	1977	1270	22	(20, 23)
		Blacks	430	303	20	(17, 22)
	Female	Whites	1634	1014	25	(23, 26)
		Blacks	400	287	18	(16, 20)
50+	Male	Whites	11298	8565	14	(13, 14)
		Blacks	1855	1471	12	(11, 13)
	Female	Whites	9548	7401	11	(11, 12)
		Blacks	1912	1502	11	(10,12)

Patients < 50 years



Patients 50+ years



Summary of Results

- Disparity is pronounced in the younger patients.
  - Median survival in < 50 years
    - Women: whites 25 months, blacks 18 months
  - 5-year survival in < 50 years
    - Men: whites 16%, blacks 9.1%
    - Women: whites 17.6%, blacks 10%
- Results parallel what we observed in South Carolina
- Further analyses underway to determine if pathologic features interact with race and age and gender

Study 3: Race and Risk of Metachronous Polyps in Younger and Older patients

General Aim

- Evaluate the association between race and risk of any metachronous adenoma, advanced adenoma, and serrated polyps
- Pooled analysis of three multi-center large bowel adenoma chemoprevention trials

Polyp Prevention Study Cohort

- Pooled Data
  - Antioxidant Polyp Prevention Studies
  - Calcium Polyp Prevention Study
  - Aspirin/Folate Polyp Prevention Study
- Subjects randomized to study agent or placebo
- Colonoscopic surveillance at 1 and 4 years Antioxidant and Calcium studies and at 3 years in the Aspirin/Folate trial

Statistical Analyses

- To assess the association between different types of polyps and race, we estimated risk ratios (and 95% confidence intervals) for one or more adenomas after randomization.
- We defined advanced lesions as adenomas with at least 25% villous component, high-grade dysplasia, or an estimated size of 1 ≥ centimeter

	Age ≤ 50 years			Age > 50 years		
Baseline Characteristic	Black (n=22)	White (n=403)	P [a]	Black (n=179)	White (n=2079)	P [b]
Age—yrs. (SD)	44.0 (6.1)	44.8 (5.0)	0.44	60.9 (7.1)	62.8 (6.8)	0.0006
Male—no. (%)	13 (59)	264 (65)	0.54	107 (60)	1529 (74)	0.00001
Smoker—no. (%)						
Never	9 (40)	178 (44)		71 (40)	702 (34)	
Former	5 (23)	136 (34)		58 (33)	1017 (49)	
Current	8 (36)	87 (22)	0.24	49 (28)	343 (17)	0.0001
Body Mass Index -- no. (%)						
Normal (< 25 kg/m^2)	4 (18)	141 (35)		38 (21)	634 (31)	
Overweight (25-29 kg/m^2)	10 (46)	179 (45)		86 (48)	974 (47)	
Obese (≥ 30 kg/m^2)	8 (37)	82 (20)	0.12	55 (31)	464 (22)	0.007
Alcohol ≥ 0 drinks per week						
Yes— no. (%)	14 (74)	280 (74)	0.99	87 (53)	1370 (69)	0.0001
Diabetes						
Yes— no. (%)	2 (9)	9 (2)	0.05	20 (11)	159 (8)	0.09
High Cholesterol						
Yes— no. (%)	5 (24)	99 (25)	0.94	43 (24)	572 (28)	0.31
Hypertension						
Yes— no. (%)	6 (27)	57 (14)	0.09	99 (55)	717 (35)	0.0001
Family History of CRC						
Yes— no. (%)	3 (16)	139 (38)	0.05	27 (18)	492 (27)	0.03
Baseline Adenoma no., mean (SD)						
No. of prior adenomas[c]	2.18 (2.1)	1.78 (1.6)	0.19	2.40 (1.9)	2.69 (2.9)	0.19
Large (≥ 1 cm)[c]	0.53 (0.7)	0.25 (0.5)	0.01	0.31 (0.6)	0.32 (0.6)	0.99
Advanced[c]	0.52 (0.7)	0.37 (0.6)	0.28	0.44 (0.7)	0.41 (0.7)	0.59
Treatment						
Yes – no. (%)	14 (64)	302 (75)	0.24	119 (66)	1441 (69)	0.43

	≤ 50 years				> 50 years			
Conventional Adenoma	Black (n=21)	White (n=390)	RR (95% CI)		Black (n=172)	White (n=2022)	RR (95% CI)	
Any	10	130	1.0	1.70 (0.99-2.92)	82	958	1.0	1.08 (0.92-1.27)
Advanced Histology	4	19	1.0	5.52 (1.87-14.97)	22	228	1.0	1.25 (0.86-1.90)
Any Advanced	4	26	1.0	4.05 (1.43-11.46)	23	288	1.0	1.05 (0.71-1.56)
Proximal	7	90	1.0	1.72 (0.85-3.49)	63	649	1.0	1.24 (1.00-1.53)
Distal	6	56	1.0	1.93 (0.89-4.24)	49	583	1.0	1.08 (0.84-1.38)
Serrated Polyp								
Any	5	118	1.0	0.75 (0.34-1.62)	35	623	1.0	0.65 (0.49-0.87)
Proximal	2	29	1.0	1.17 (0.28-4.89)	13	206	1.0	0.67 (0.40-1.16)
Distal	4	101	1.0	0.69 (0.28-1.69)	27	518	1.0	0.61 (0.43-0.86)

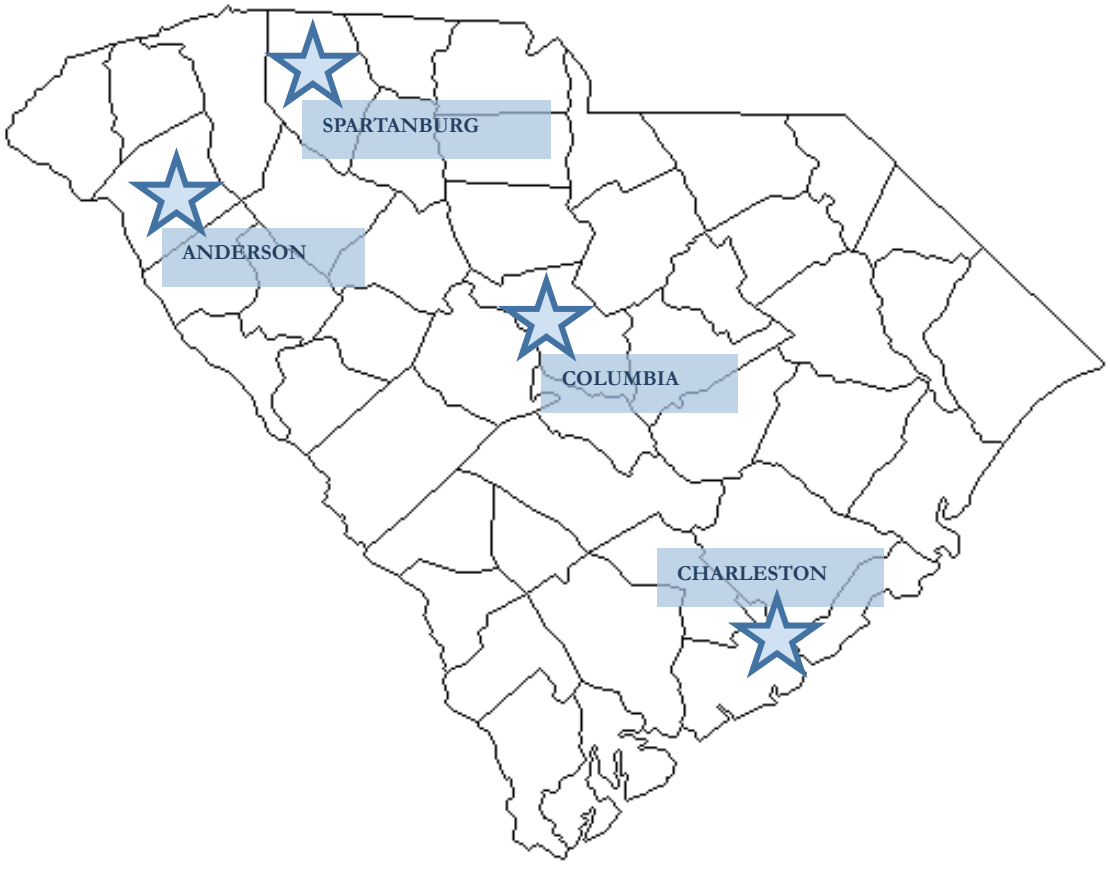
[a] RR for black race compared to white race adjusted for age, sex, study treatment assignment, and follow-up time

Summary

- Younger Patients
  - Blacks have higher risk of metachronous adenomas, especially advanced neoplasms
    - CIN Pathway tumors
- Older Patients
  - Strong inverse relationship with serrated polyps
    - CIMP 1 Cancers, better prognosis
  - Higher Risk of proximal adenomas
  - No differences in conventional adenomas overall
- Limitations
  - Small number of Blacks
  - All patients had adenoma at baseline
  - No histopathologic re-review with change in diagnosis

Study 4: Race and Risk of Large Bowel Polyps in the Poor and Uninsured in South Carolina

South Carolina Colon Cancer Prevention Network



South Carolina FOUNDATION

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HOLLINGS CANCER CENTER
A National Cancer Institute Designated Cancer Center

Spartanburg Regional
GIBBS CANCER CENTER

Study Design & Population Characteristics

- Patients were recruited at one of five free medical clinics within four geographic regions of South Carolina from 11/11 to 8/13 as part of screening program.
- AA between the ages of 45 - 65 years and patients of all other races/ethnicities were between the ages of 50 - 65 years
- Asymptomatic, no personal history of colorectal neoplasia.

Characteristic	European American (n=91)	African American < 50 (n= 15)	African American 50+ (n= 112)	Other Race or Ethnicity (n=18)	P
Age—yrs. (sd)	55.9 (3.8)	48.1 (1.6)	55.0 (3.8)	55.5 (4.4)	0.35
Education					
< High school graduate	21 (29)	3 (25)	27 (28)	2 (12)	
High school graduate	24 (33)	6 (50)	40 (42)	7 (41)	
Any college	28 (38)	3 (25)	29 (30)	8 (47)	0.56
Working status					
Unemployed	59 (81)	10 (83)	53 (55)	9 (53)	
Working	14 (19)	2 (17)	43 (45)	8 (47)	0.002
Male—no. (%)	39 (43)	7 (47)	43 (38)	9 (47)	0.82
Smoker—no. (%)					
Never	37 (41)	9 (60)	52 (46)	6 (32)	
Former	27 (30)	3 (20)	22 (20)	6 (32)	
Current	27 (30)	3 (20)	38 (34)	7 (37)	0.47
Body Mass Index -- no. (%)					
Normal (< 25 kg/m^2)	15 (17)	2 (14)	16 (14)	3 (16)	
Overweight (25-29 kg/m^2)	25 (28)	2 (7)	38 (34)	7 (37)	
Obese (30 kg/m^2 –34 kg/m^2)	28 (31)	1 (7)	21 (19)	5 (26)	
Morbidly Obese (≥ 35 kg/m^2)	22 (24)	9 (64)	37 (33)	4 (21)	0.11
Waist to Hip Ratio ≥ 1	31 (38)	5 (38)	29 (28)	2 (12)	0.14
Sitting per day (6 hours+)	36 (51)	4 (33)	54 (57)	8 (47)	0.39
Alcohol -- ≥1 drinks per week					
Yes— no. (%)	16 (22)	6 (50)	35 (36)	3 (18)	0.06
Diabetes					
Yes— no. (%)	25 (27)	5 (33)	37 (33)	8 (42)	0.62
High Cholesterol					
Yes— no. (%)	45 (49)	8 (53)	52 (46)	10 (53)	0.92
Hypertension					
Yes— no. (%)	60 (66)	9 (60)	84 (75)	15 (80)	0.33
Family History of CRC					
Yes— no. (%)	6 (7)	1 (7)	1 (1)	0 (0)	0.10

Conventional Adenoma								
	Any Conventional Adenoma		**Advanced Conventional Adenoma**		**Large Proximal Conventional Adenoma**		**Large Proximal Advanced Conventional Adenoma**	
	No. (%)	RR* (95% CI)	No. (%)	RR* (95% CI)	No. (%)	RR* (95% CI)	No. (%)	RR* (95% CI)
EA (n=91)	28 (31)	1.0	8 (9)	1.0	2 (2)	1.0	4 (4)	**1.0**
AA (n= 124)	45 (36)	1.15 (0.77-1.73)	14 (11)	1.37 (0.58-3.21)	10 (8)	4.10 (1.02-16.5)	12 (10)	2.20 (0.77-6.25)
Other (n=18)	6 (33)	1.02 (0.49-2.13)	1 (6)	0.61 (0.8-4.56)	0 (0)	--	0 (0)	**--**
Serrated Polyp								
	Any Serrated Polyp		**Advanced Serrated Polyp**		**Serrated Adenoma**		**Proximal Serrated Adenoma**	
	No. (%)	RR* (95% CI)	No. (%)	RR* (95% CI)	No. (%)	RR* (95% CI)	No. (%)	RR* (95% CI)
EA (n=91)	29 (32)	1.0	5 (5)	1.0	7 (8)	1.0	4 (5)	1.0
AA (n= 124)	22 (18)	0.53 (0.32-0.89)	2 (2)	0.25 (0.07-0.94)	3 (2)	0.36 (0.10-1.24)	1 (1)	0.15 (0.42-0.49)
Other (n=18)	5 (28)	0.81 (0.34-1.91	0 (0)	--	0 (0)	--	0 (0)	--

*RR adjusted for age, sex, and geographic location

Summary

- Poor and uninsured patients have
  - A high burden of comorbid conditions and detrimental lifestyle factors
  - Are at high risk of colorectal adenomas (37% adenoma prevalence for CA or SA combined)
- Risk of polyp type differed in whites and blacks
  - Blacks had a higher risk of large proximal CA
  - Blacks had lower risk of SP, advanced SP, and proximal SA
  - Blacks under age 50 were at high risk of
    - Any CA (36%)
    - Advanced CA (14%)
    - Adenoma rates equal or exceeding the prevalence of whites over 50 years

Overall summary of findings

- Higher prevalence of several risk and prognostic factors in blacks compared to whites yet no consistent influence on RR or HR
- Racial differences more pronounced in younger blacks compared to younger whites
- Differences in pathology of neoplasia
  - Higher prevalence of proximal neoplasia in blacks
  - Fewer serrated lesions in blacks (majority SSA)
  - Possible CIN or CIMP-2 phenotype

Future Directions

- **Prospective collection of common risk and prognostic factors**
  - Ancestral markers to careful define African ancestry
  - Lifestyle and behavioral risk factors such as physical activity, smoking
  - Clinical factors such as obesity, diabetes, treatment
- **Molecular and Epigenetic Tumor Profiles**
  - Detailed pathology
  - KRAS, BRAF, P53, APC, MSI+, CIMP Status
  - Tumor heterogeneity, adjacent polyp, metastatic lesions
- **Immune Profiles**
  - Macro- and micro-immune functioning
    - serum (e.g. WBC, HgB, Platelets, Neutrophil, Lymphocyte, Monocyte, etc)
    - Tumor infiltrates (e.g. CD4, CD8, CD45R0, T-bet, CD25, CD56, CD68, CD20), Immune cytokines and chemokine expression
- **Microbiome markers in tumor and normal mucosa**

Collaborators

- Statewide study:
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