McGill | Faculty of Medicine

Department of Epidemiology, Biostatistics, and Occupational Health

May 2017

Cancer Epidemiology and Prevention
Course EPIB 671

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Course EPIB 671: CANCER EPIDEMIOLOGY AND PREVENTION - 2017

Department of Epidemiology & Biostatistics, McGill University
Eduardo Franco (514-398-6032, eduardo.franco@mcgill.ca)

http://www.mcgill.ca/cancerepi/courses/epib-671-summer-session
https://www.dropbox.com/sh/7mnee908zeti5y2/AAB7aGqIkdsjGNYp0Q73bMRoa?dl=0

Session	Date	Topics to be covered	Articles
1	May 15 (Mon)	Introduction, mechanisms of carcinogenesis, tumour biology, descriptive epidemiology	
2	May 17 (Wed)	Causality, epidemiologic approaches and study designs, evidence assessment	Taubes
3	May 19 (Fri)	Causes: tobacco, lifestyle, infections	Schiffman
4	May 23 (Tue)	Causes: diet, occupation/environment; Primary prevention: evidence and knowledge	Gorey
5	May 24 (Wed)	Secondary prevention: biases in screening, assessment of the evidence	
6	May 26 (Fri)	Student Symposium, take-home exam	

Note: All sessions are from 1:00-5:00 pm but please be available to stay beyond 5 pm if necessary.

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Cancer Research Society
Useful links

EPIB 671 (Summer Session)

Files to download for students registered in EPIB 671

1. Course Description and Bibliography: general information about the course, its contents and bibliography (not essential in class but be sure to read before coming to class on Monday)

Course Schedule 2016

Course Description 2016

2. Entire set of slides to be used by Dr. Franco (needed in class to facilitate note-taking):

Slides EPIB671-2015

3. IARC-Monographs-Evaluation Summaries: Appendix material (Not essential but will be frequently alluded to in class)

IARC Monographs [.pdf]

4. Taubes Science269-164s and Taubes Letters: Article by Taubes, Science 1995 and associated letters to the editor (Please read it. It will be discussed in class), Reading Guide and New York Time September 2007

Taubes Science269-164s and Letters [.pdf]

Taubes Reading Guide [.doc]

Taubes NY Times-Sep.2007 [.pdf]

5. JNCI85-958: Article by Schiffman et al., JNCI 1993 (Please read it. It will be discussed in class)

JNCI85-958 [.pdf]

6. Gorey-AJPH-1997: Article by Gorey et al., AJPH 1997 (Please read it. It will be discussed in class)

Gorey-AJPH-1997 [.pdf]

Gorey Article - Reading Guide [.pdf]

7. Chapter 5 - Franco & Rohan: Chapter 5 of Franco & Rohan textbook on the epidemiology of cancer precursors. Contains supplemental information concerning etiologic models and measurement error (Not essential in class but if you have a chance read it before the session on methods, specially if you have not taken an intermediate level epidemiology course)

Chapter 5 - Franco & Rohan [.pdf]

Course webpage (continued)

Biology of Cancer

Cancer Research Society

Useful links

5. JNCI85-958: Article by Schiffman et al., JNCI 1993 (Please read it. It will be discussed in class)
JNCI85-958 [.pdf]

6. Gorey-AJPH-1997: Article by Gorey et al., AJPH 1997 (Please read it. It will be discussed in class)
Gorey-AJPH-1997 [.pdf]
Gorey Article - Reading Guide [.pdf]

7. Chapter 5 - Franco & Rohan: Chapter 5 of Franco & Rohan textbook on the epidemiology of cancer precursors. Contains supplemental information concerning etiologic models and measurement error (Not essential in class but if you have a chance read it before the session on methods, specially if you have not taken an intermediate level epidemiology course)
Chapter 5 - Franco & Rohan [.pdf]

8. CaDetPrev-26-350: Review article by Franco et al., 2002. Contains detailed information concerning guidelines for cancer screening and prevention (Not essential. Useful as reference material to supplement the discussion during the session on screening and prevention)
CaDetPrev-26-350 [.pdf]

9. Chapter by Franco in the Encyclopedia of Cancer 1997: Contains an overview of cancer epidemiology and prevention. Its contents reflect the general layout of the course (Not essential but supplements the discussion on general applications of epidemiology in cancer research)
EncyclopCancerChapter [.pdf]

10. Review article by Franco et al., Sem Cancer Biol 2004 on causal relations in cancer:
SemCaBiol-14-413-2004 [.pdf]

11. Giovannucci-NEJM-1995: Article by Giovannucci et al., NEJM 1995 (Please read it. It will be discussed in class)
Giovanucci-NEJM [.pdf]

12. Recent Past Student Presentations:
Student Presentations-2015 [.pdf]
Student Presentations-2014 [.pdf]
Student Presentations-2013 [.pdf]
Student Presentations-2012 [.pdf]
Student Presentations-2011 [.pdf]

Expanded Purview of Cancer Epidemiology

- **Cancer surveillance:** burden of disease, incidence and mortality trends, cancer clusters
- **Cancer risk:** assessing candidate etiologic factors
- **Cancer prevention:** assessing the validity and the impact of chemoprevention and other preventive approaches
- **Cancer screening:** assessing efficacy, comparing competing technologies
- **Cancer survival:** assessing prognostic factors, determinants of quality of life in terminally ill patients

Milestones in Cancer Epidemiology

- Establishment of first tumour registries (1935, 1943) and development of data quality standards by the IARC and IACR (1970’s)
- Doll & Hill (1950); Wynder & Graham (1950): case-control approach to study cancer causes (cigarettes and lung cancer)
- Surgeon General's Report on tobacco and cancer (1964)
- WHO's IARC founded in 1965; major contributions: CI5C and carcinogenicity monograph series
- Doll & Peto’s report to the US OTA (1981)
- Emergence of molecular epidemiology (late 80's)
- Launching of mega-studies of screening (60's - 80's) and diet (80's)
- Focus on precursor lesions as opposed to clinically invasive cancer (90’s)
- Studies of SNPs and genome-wide association studies (2000’s)

Mutational theory of carcinogenesis

Types of evidence

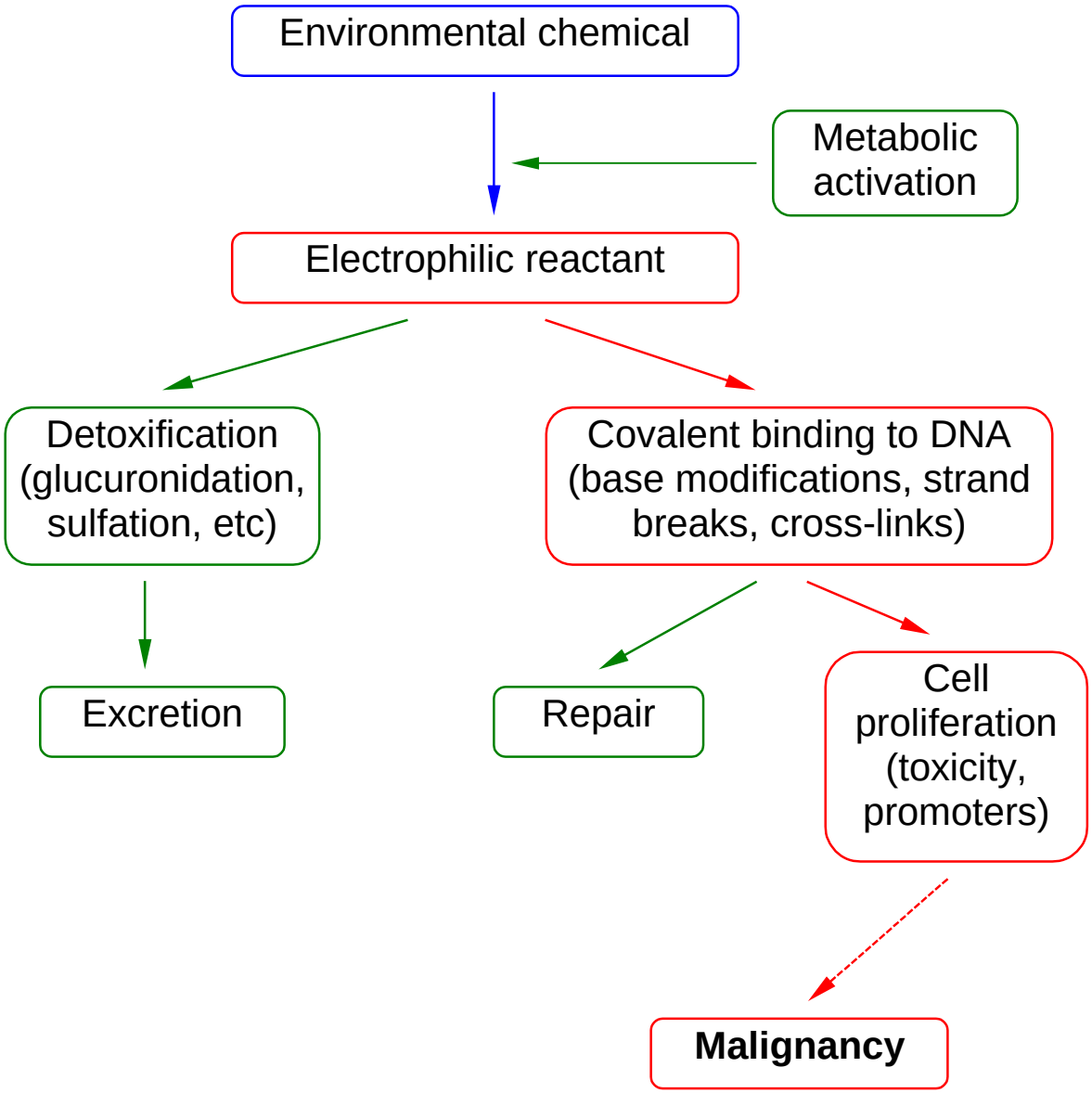
- **Analogy**: Agents that damage DNA are frequently carcinogenic
- **Experimental**: Most carcinogenic agents (initiators) are mutagens
- **Epidemiologic**: Cancer incidence is increased in patients with DNA repair deficiency

Tenets

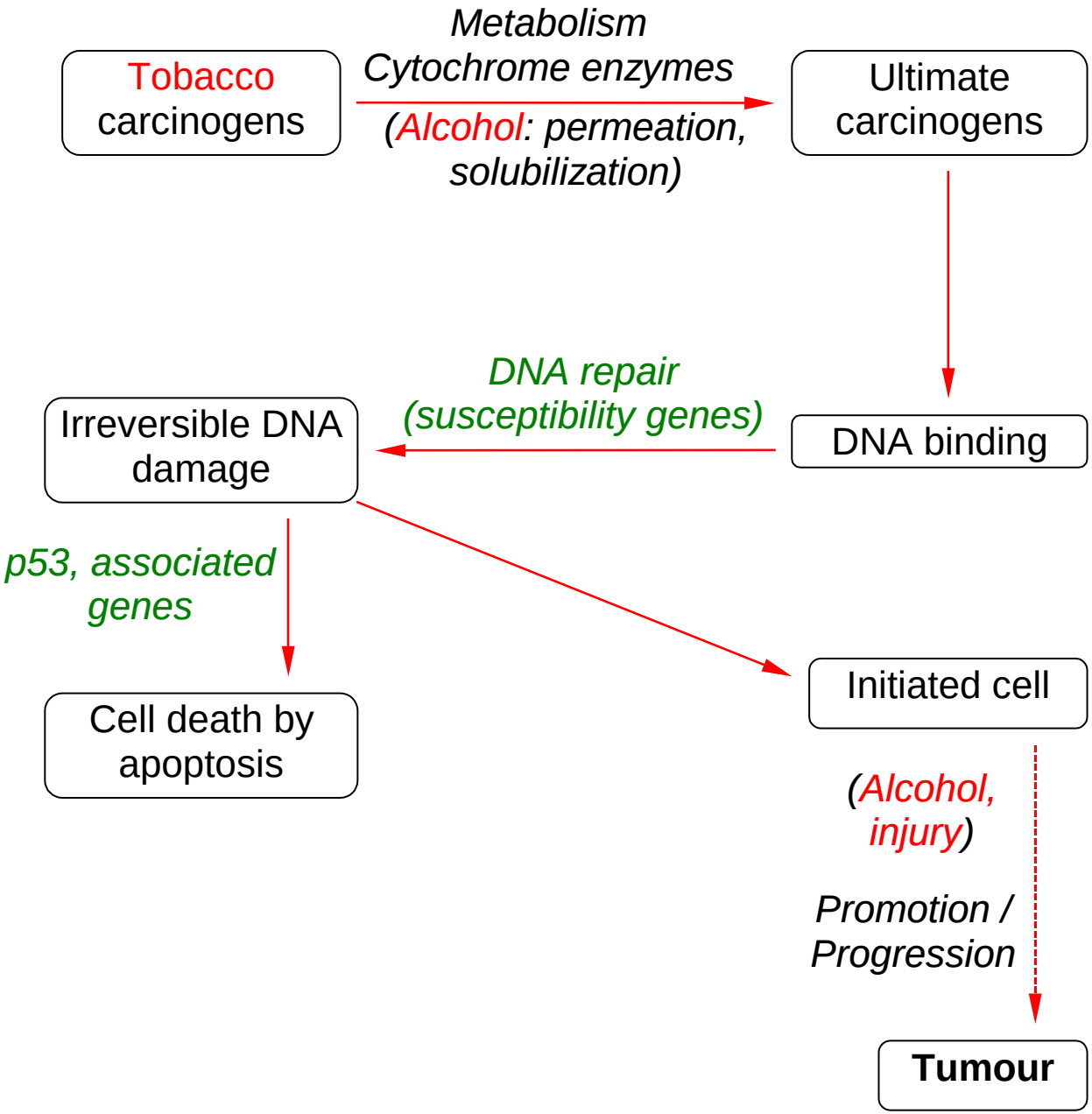
- Progression from normal to malignant involves multiple steps
- Cofactors may either enhance or inhibit carcinogenesis

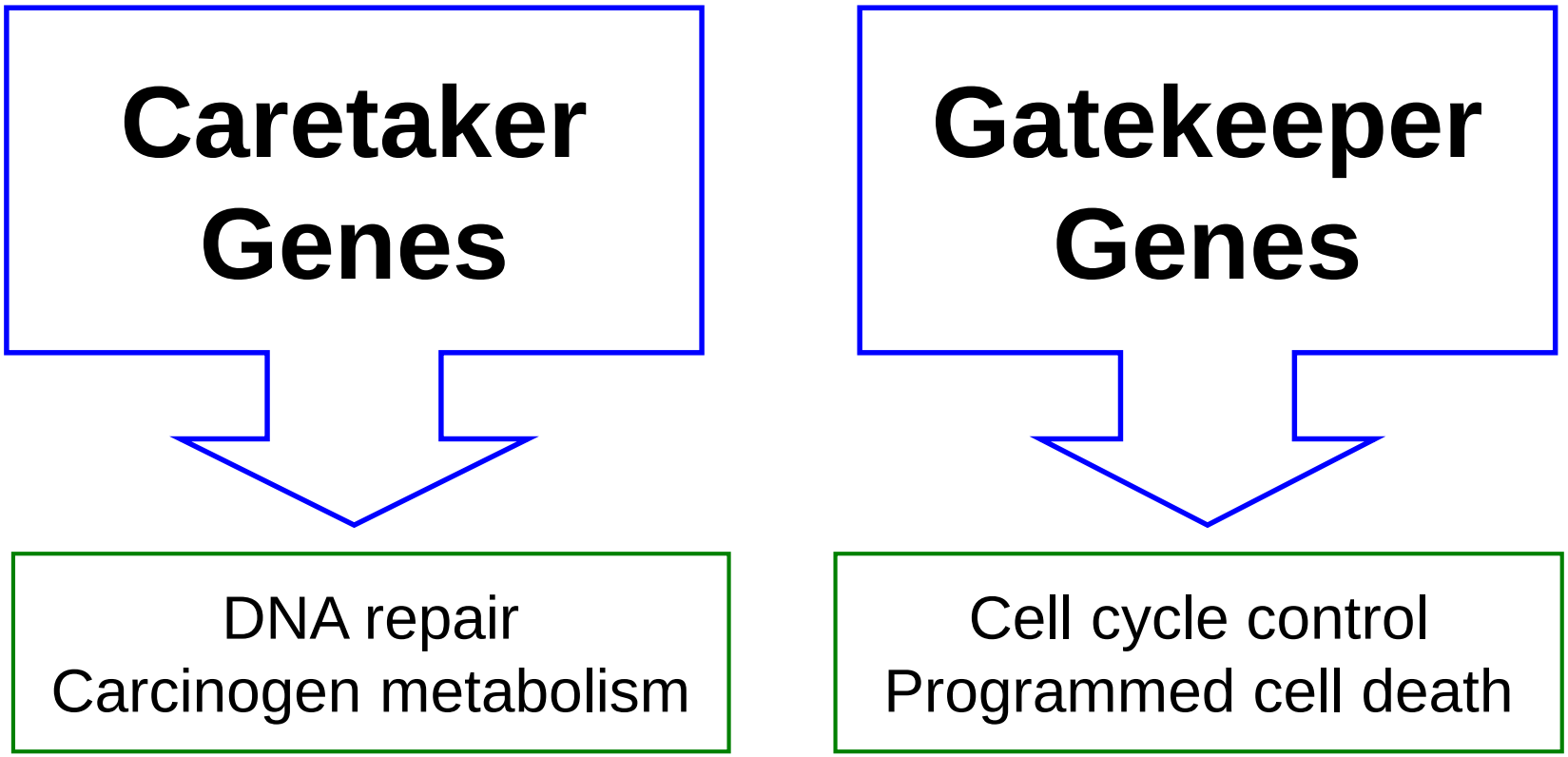
Chemical carcinogenesis

Sequence of events



Mechanisms involved in oral carcinogenesis





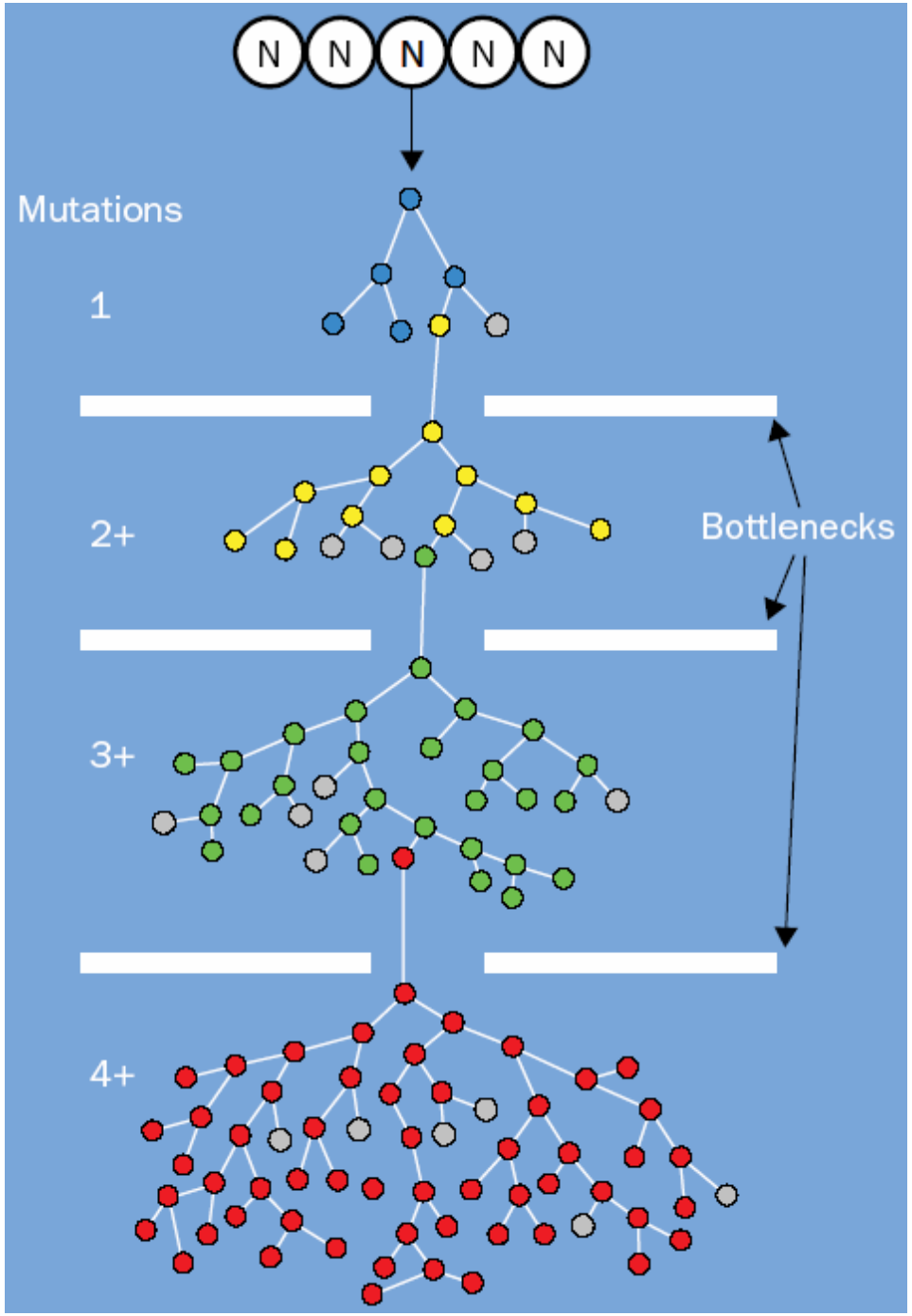
Shields and Harris, 2000

Cancer causation: the Darwinian process

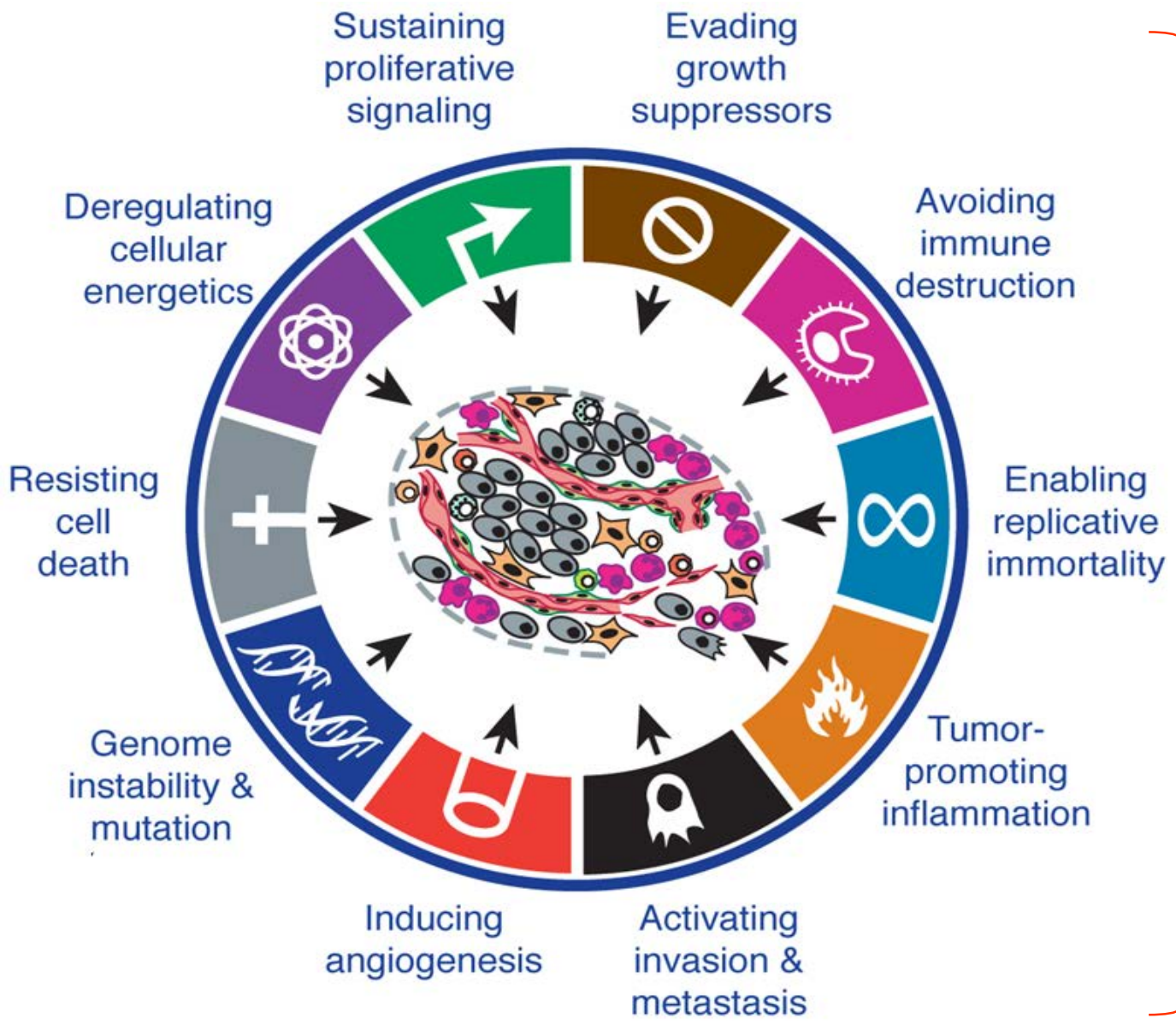
Mel Greaves

Lancet Oncol 2002; **3:** 244–51

“Clonal evolution of a cancer. All cancers evolve by Darwinian principles: clonal proliferation, genetic diversification within the clone, and selective pressure enabling mutant subclones to bridge the bottlenecks (such as anoxia, restricted space and nutrients, apoptosis imposition). Each colour in the figure represents a cell (and its descendent clone) acquiring the first (blue) or additional, sequential mutations. Grey represents dying cells. This diagram greatly simplifies the extensive genetic diversity, complex population structure, and highly variable dynamics of cancer clones. N, normal stem cells.”



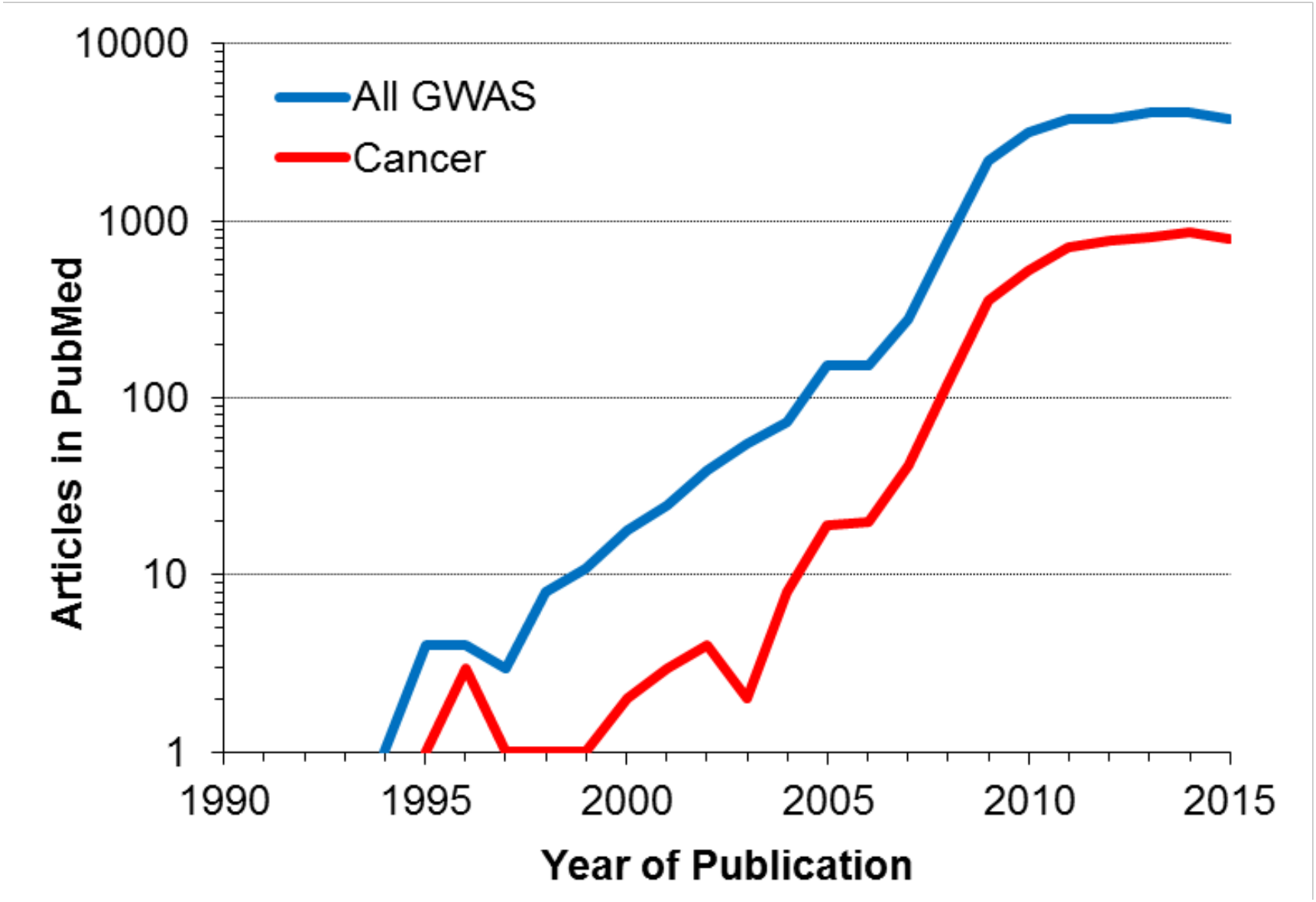
D. Hanahan, RA Weinberg. Hallmarks of Cancer: The Next Generation. Cell 2011

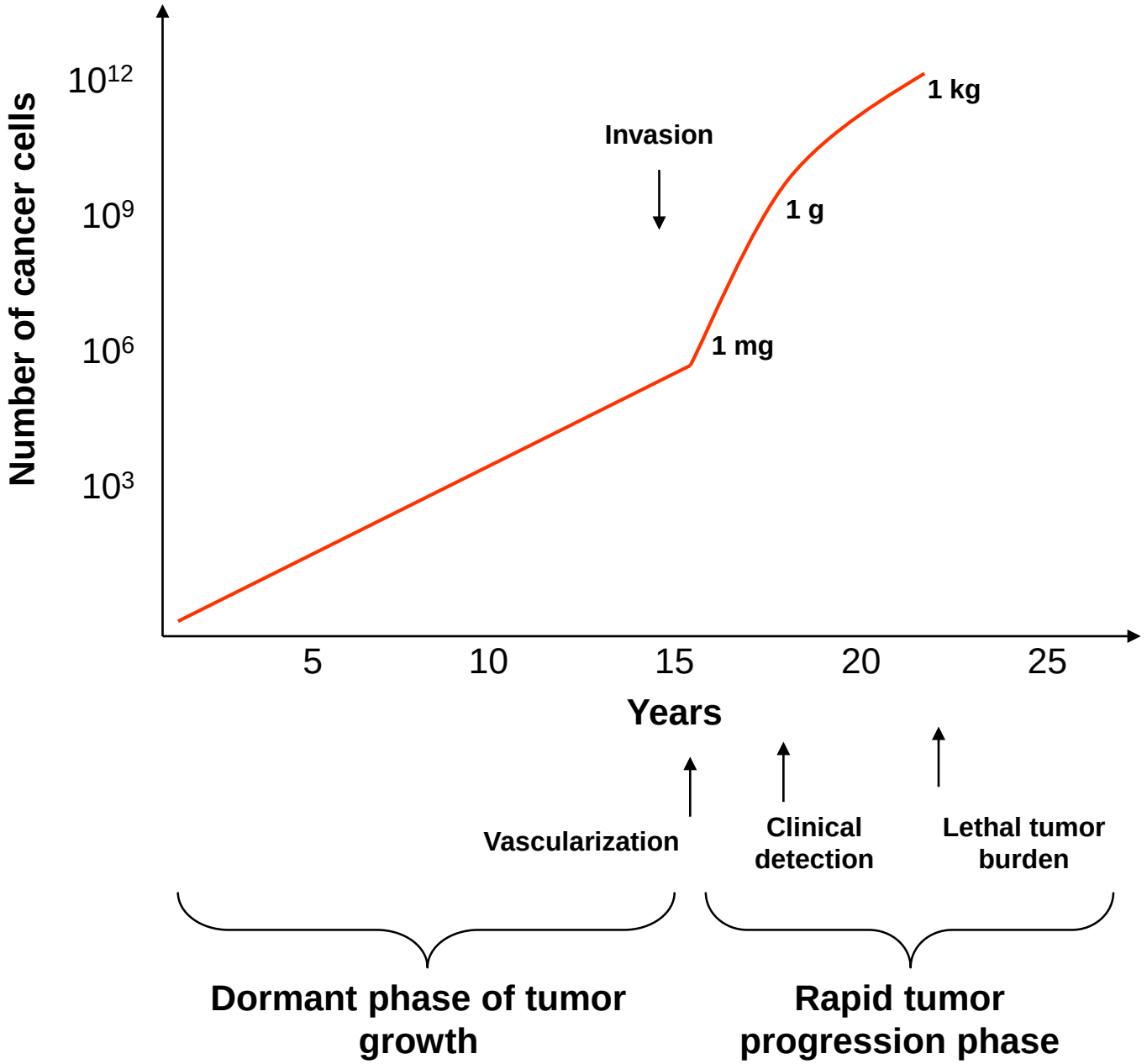


In addition to DNA mutations, phenotypic changes can happen via epigenetic reprogramming and microRNA mediation.

Other mediating factors in carcinogenesis: tumour microenvironment, exosome release by tumour cells.

Genome-Wide Association Studies





Adapted from: Ruddon, 1995

Non-epidemiologic approaches used in assessing the evidence concerning the carcinogenicity of a suspected chemical, physical, or biological exposure or its circumstances (Adapted from Franco et al., Sem Ca Biol 2004)

Approach*	Type of scientific evidence	Level of inference	Type of study	Features
Mechanistic	Analogy	Molecular structure	Structure-activity relationships	Useful to identify potentially carcinogenic compounds based their molecular similarity to known carcinogens
Toxicology	Experimental	DNA, cellular, organ	In vitro short-term genotoxicity assays	Rapid screening system for candidate compounds or exposures
		Organ, whole organism	In vivo animal studies	Provides proof of principle and insights into dose-response effects

* Other supporting in vivo and in vitro data relevant to evaluation of carcinogenicity can also be used, particularly if they provide insights into mechanisms of absorption, metabolism, DNA binding or repair, hormonally-mediated effects, genetic damage, altered cell growth, loss of euploidy, cytopathic changes, and related biological effects.

Epidemiologic approaches used in assessing the evidence concerning the carcinogenicity of a suspected chemical, physical, or biological exposure or its circumstances (Adapted from Franco et al., Sem Ca Biol 2004)

Type of epidemiologic evidence	Level of inference	Type of study	Features
Observational	Non-inferential, descriptive	Case reports	Suggestion of association
	Population	Surveillance of incidence and mortality	Documentation of baseline disease burden, exploratory hypotheses
		Ecologic (correlation or aggregate) studies	Coarse verification of correlation between exposure and disease burden
	Individual	Cross-sectional studies	Correlation between exposure and disease (or marker) without regard to latency
		Case-control studies	Correlation between exposure and disease (or marker) with improved understanding of latency; suitable for rare cancers
		Cohort studies	Correlation between exposure and disease (or marker) with improved understanding of latency; suitable for rare exposures
Experimental	Individual **	Randomized controlled trials of preventive intervention	Most unbiased assessment of correlation between exposure and disease (or marker)

** RCTs may target communities or providers as units of randomly allocated intervention. However, this is done for convenience of study design; in practical terms inference is at the individual level.

Coverage of IARC's "Cancer Incidence in Five Continents" Monographs

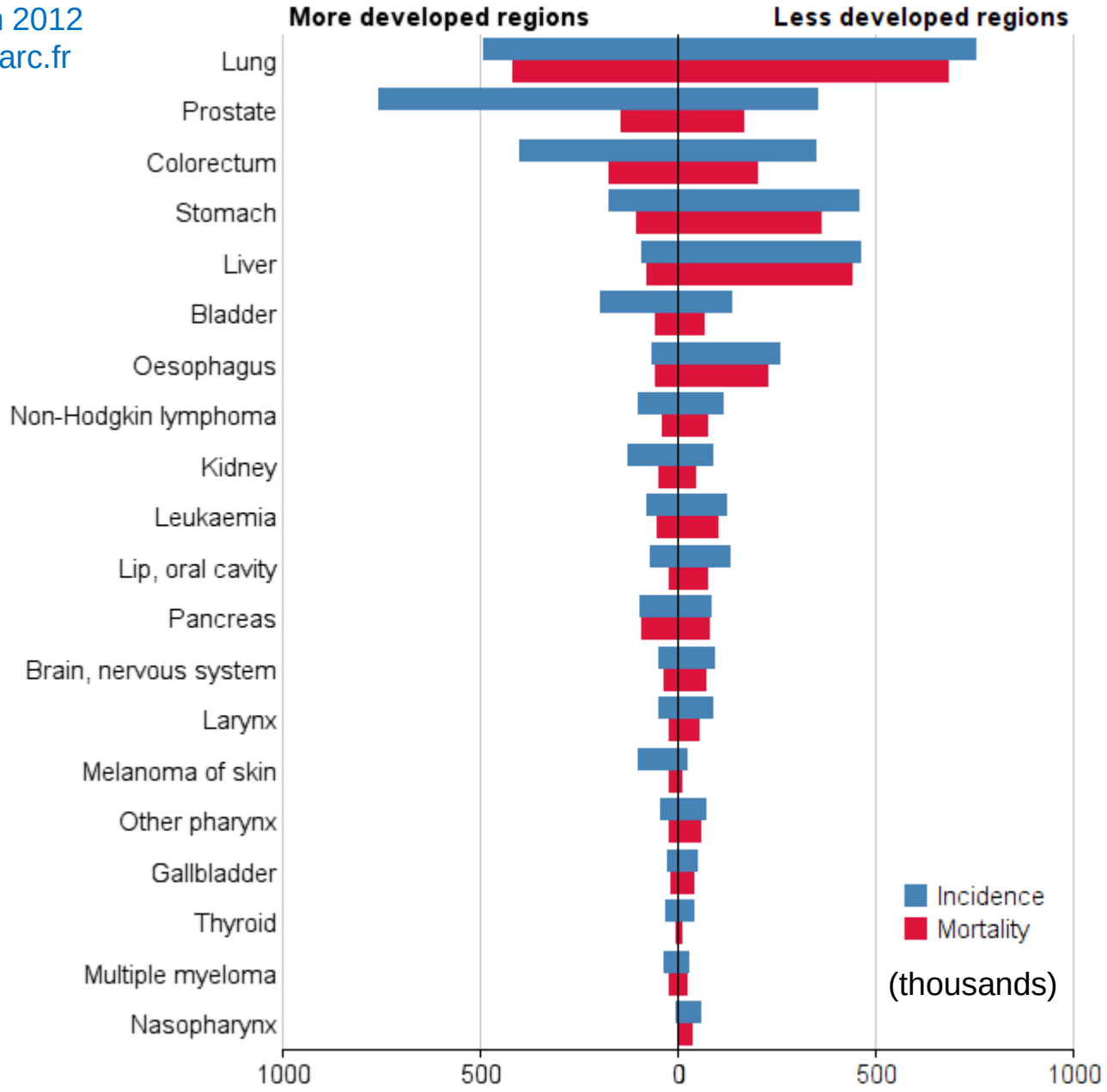
Volume	Year of publication	Registries	Countries	Coverage period (approx.)
I	1966	32	29	1960-62
II	1970	47	24	1963-67
III	1976	61	29	1968-72
IV	1982	79	32	1973-77
V	1987	105	36	1978-82
VI	1992	138	49	1983-87
VII	1997	150	50	1988-92
VIII	2002	186	57	1993-97
IX	2007	225	60	1998-02
X	2012	290	68	2003-07

http://ci5.iarc.fr

Estimated numbers of new cancer cases and deaths in 2012

IARC: Globocan 2012
http://globocan.iarc.fr

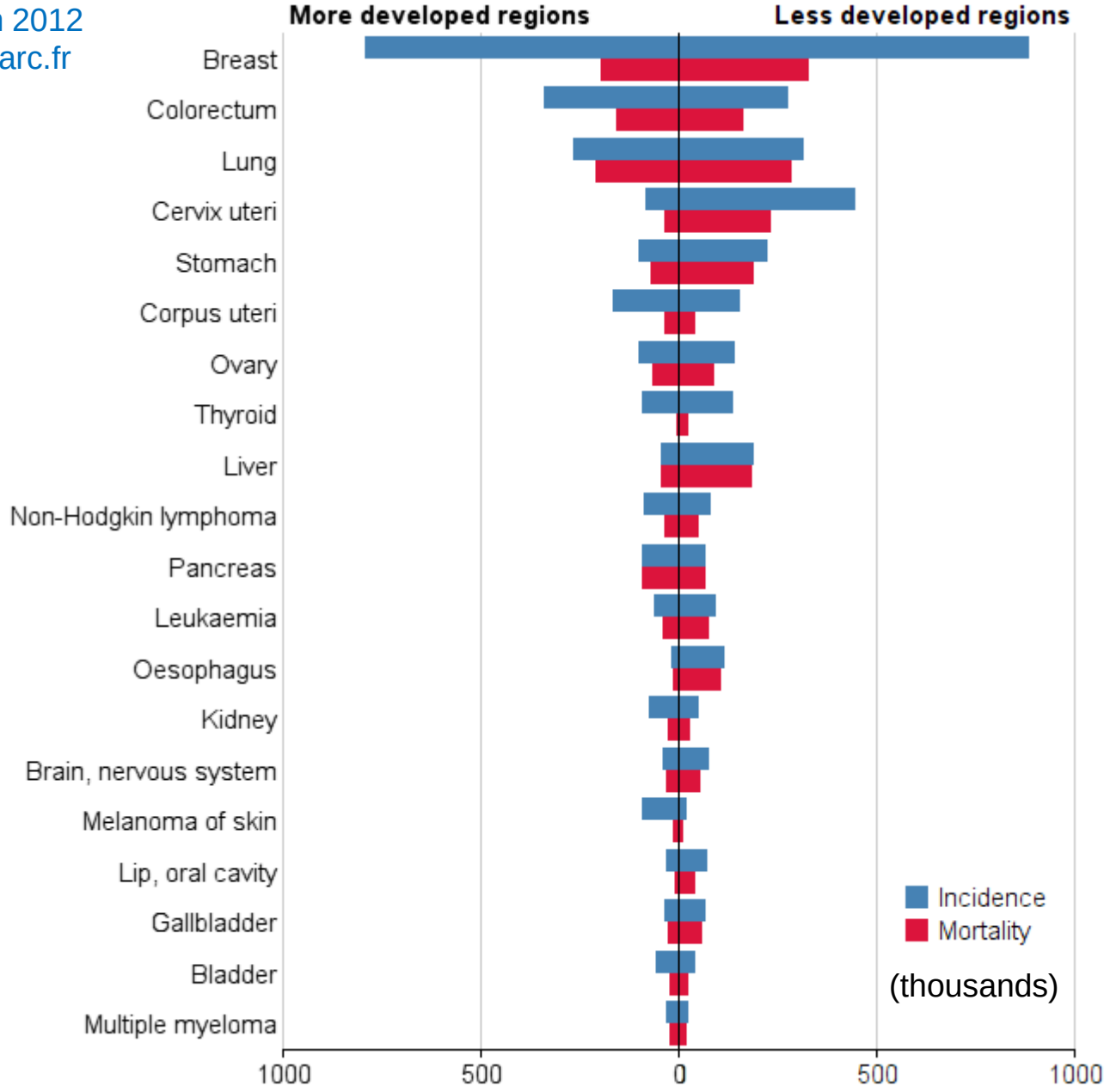
Male



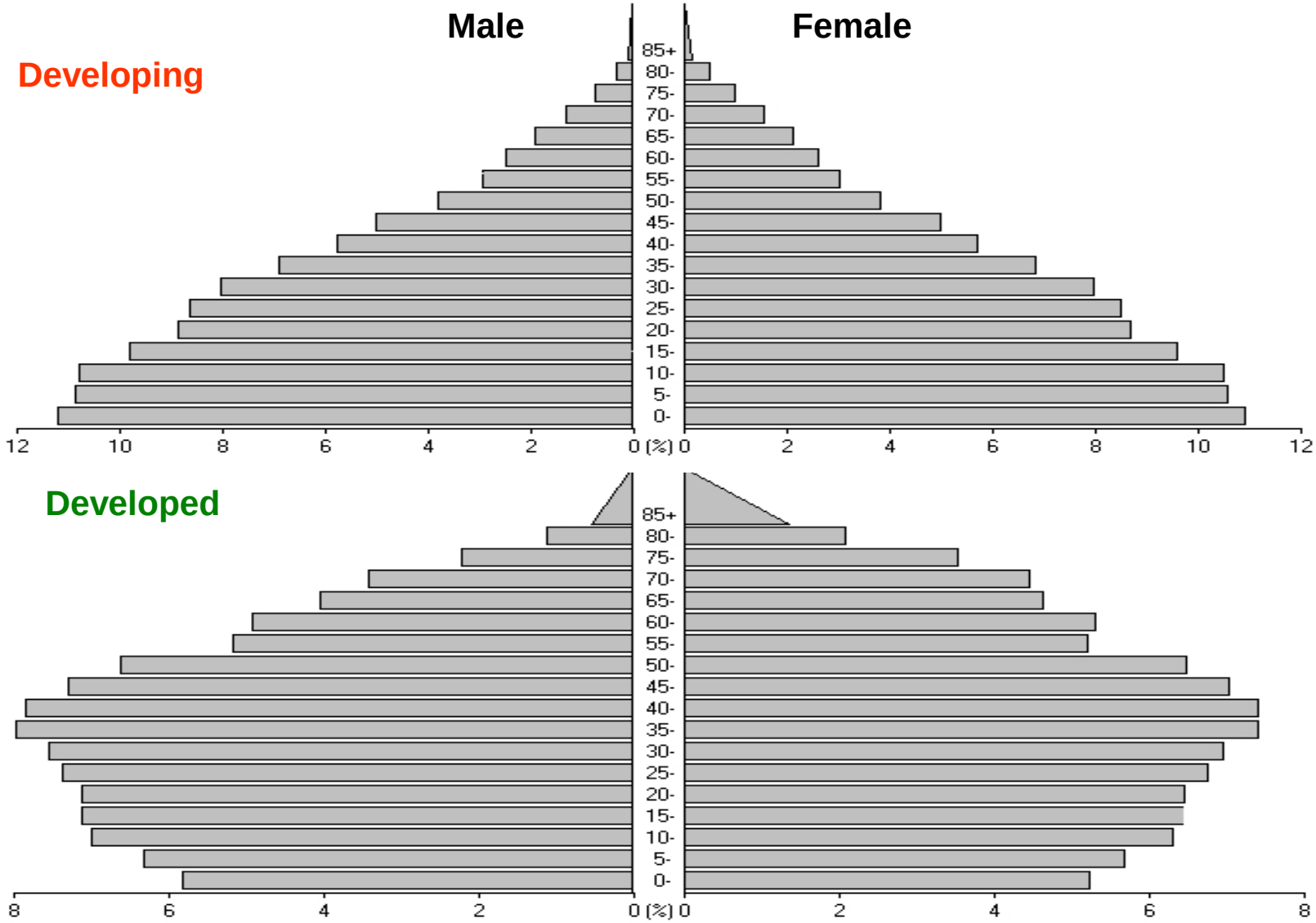
Estimated numbers of new cancer cases and deaths in 2012

IARC: Globocan 2012
http://globocan.iarc.fr

Female



Age structure of developing and developed countries



Proportion (%)

Source: IARC, 2000

Computing age-standardized incidence rates: stomach cancer in men in Scotland in 1978-82

Age in Years	Number of cancers in 5 yrs (*n*)	Number of males in Scotland[a] (*P*)	Age-specific incidence per 100,000 per year[b] (*I*)	Number of persons in standard (world) population (*W*)	Expected cases in standard population[c] (*E*)
0-4	---	90,190	---	12000	---
5-9	---	98,794	---	10000	---
10-14	---	125,477	---	9000	---
15-19	---	132,134	---	9000	---
20-24	1	114,408	0.2	8000	0.02
25-29	2	95,751	0.2	8000	0.03
30-34	3	96,967	0.6	6000	0.04
35-39	12	82,984	2.9	6000	0.17
40-44	29	78,890	7.4	6000	0.44
45-49	75	78,572	19.1	6000	1.15
50-54	133	78,776	33.8	5000	1.69
55-59	211	77,420	54.5	4000	2.18
60-64	250	65,155	76.7	4000	3.07
65-69	406	58,310	139.3	3000	4.18
70-74	413	44,701	184.8	2000	3.70
75-79	289	26,744	216.1	1000	2.16
80-84	181	11,768	307.6	500	1.54
85+	72	5,297	271.9	500	1.36
Total	**2077**	**1,362,338**	**30.5**[d]	**100000**	**21.73**[e]

[a] Average population 1978-1982

[b] Incidence = $I = n \times \frac{100{,}000}{P \times 5}$

[c] $E = \frac{I \times W}{100{,}000}$

[d] Crude rate = 30.5 per 10^5 per year

[e] Standardized rate = 21.73 per 10^5 per year

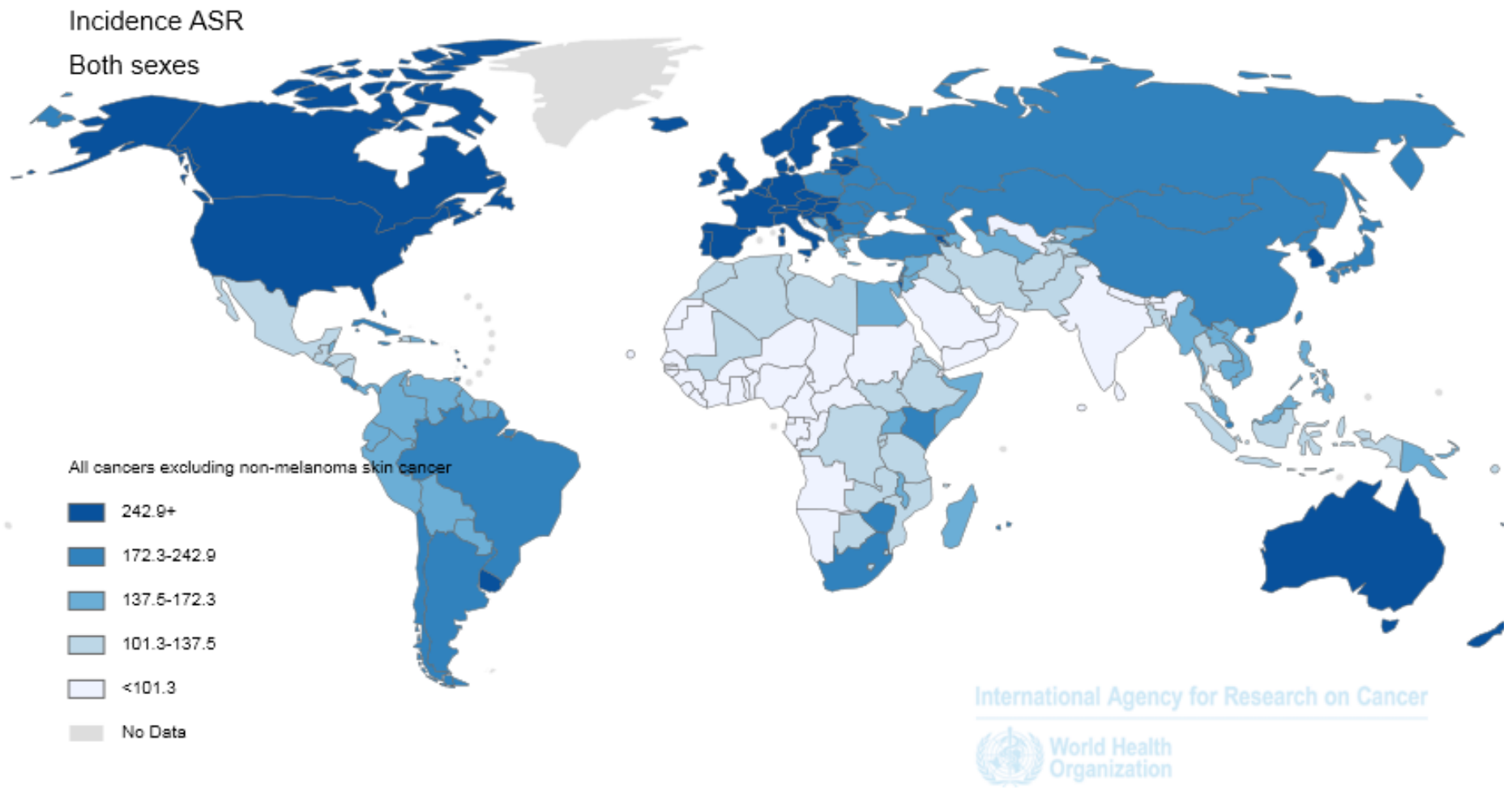
(Source: IARC)

Effect of Choice of Standard Population for Age-adjustment

Gender	Cancer Site	Rate according to standard population		Difference (US-World)
		US 2000	World 1960	
Males	Prostate	177.6	117.7	50.9%
	Lung	82.1	51.5	59.4%
	Testis	5.6	5.1	9.8%
Female	Breast	137.1	99.0	38.6%
	Cervix	8.0	6.3	27.1%
	Vulva	2.4	1.5	56.7%

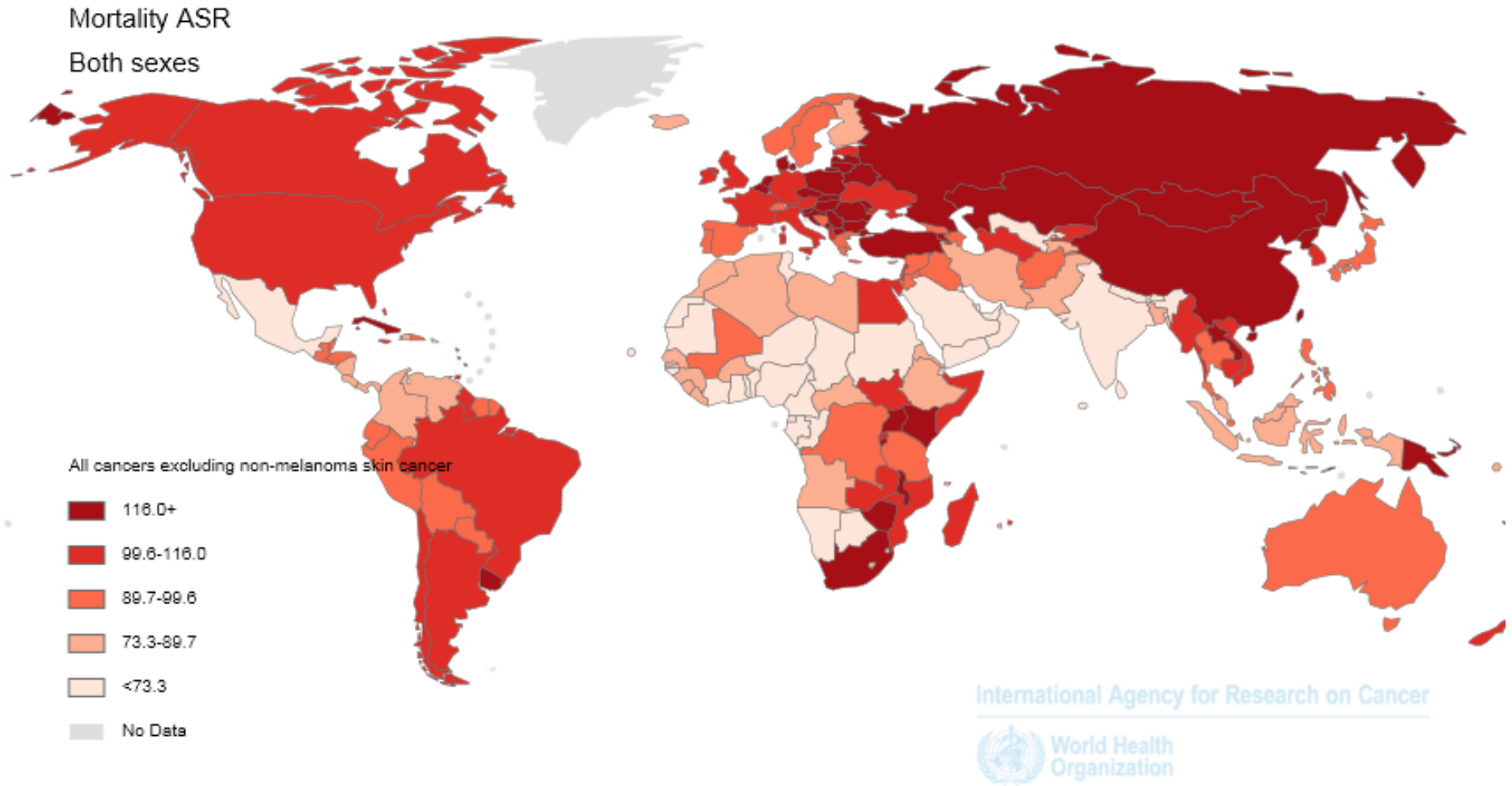
Average age-adjusted incidence rates per 100,000 (1998-2002) in the US SEER program

Age-standardized **incidence** rates (per 100,000) for all cancers combined (except non-melanoma skin cancer) (Source: IARC, Globocan 2012)



IARC: Globocan 2012
http://globocan.iarc.fr

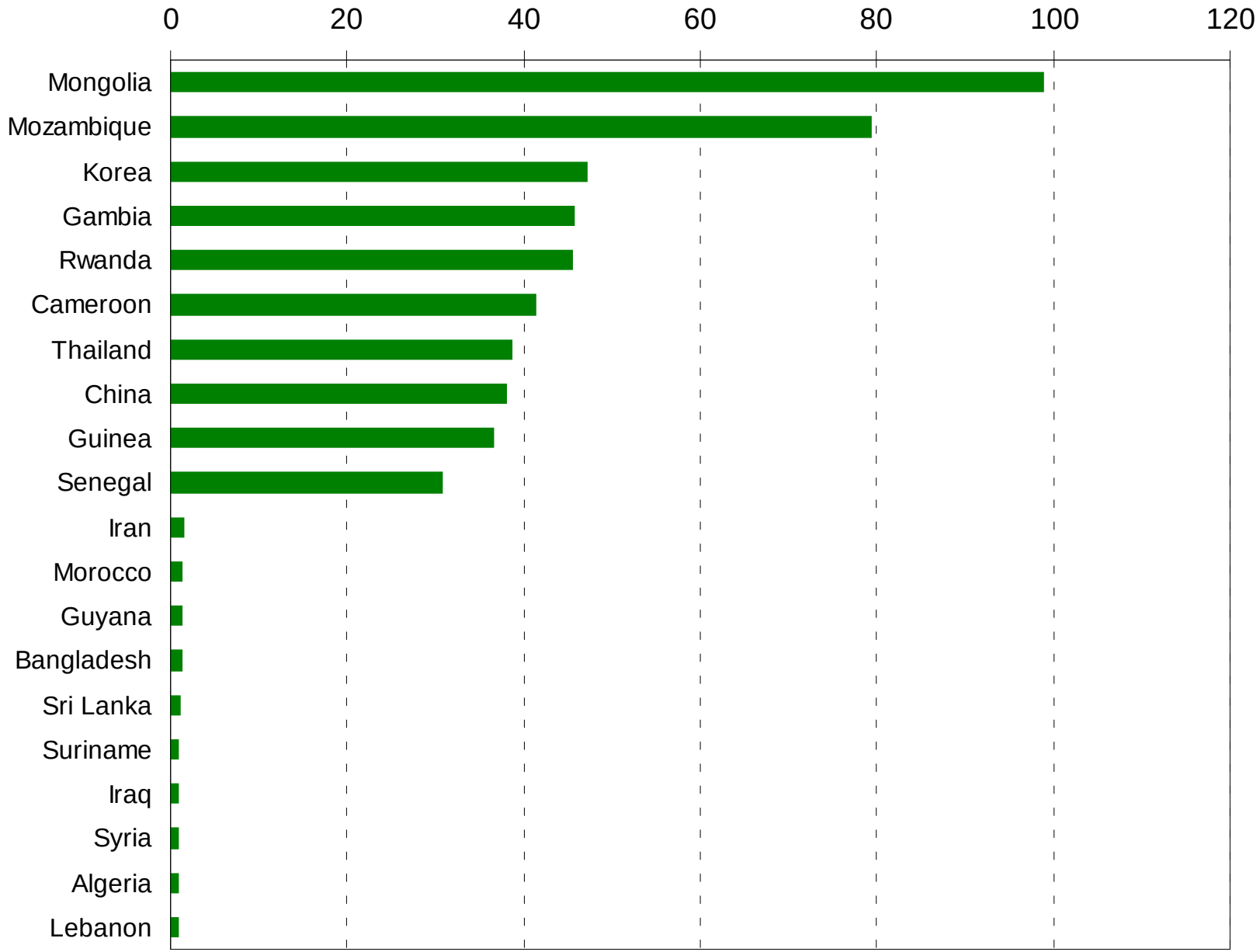
Age-standardized **mortality** rates (per 100,000) for all cancers combined (except non-melanoma skin cancer) (Source: IARC, Globocan 2012)



Source: GLOBOCAN 2012 (IARC)

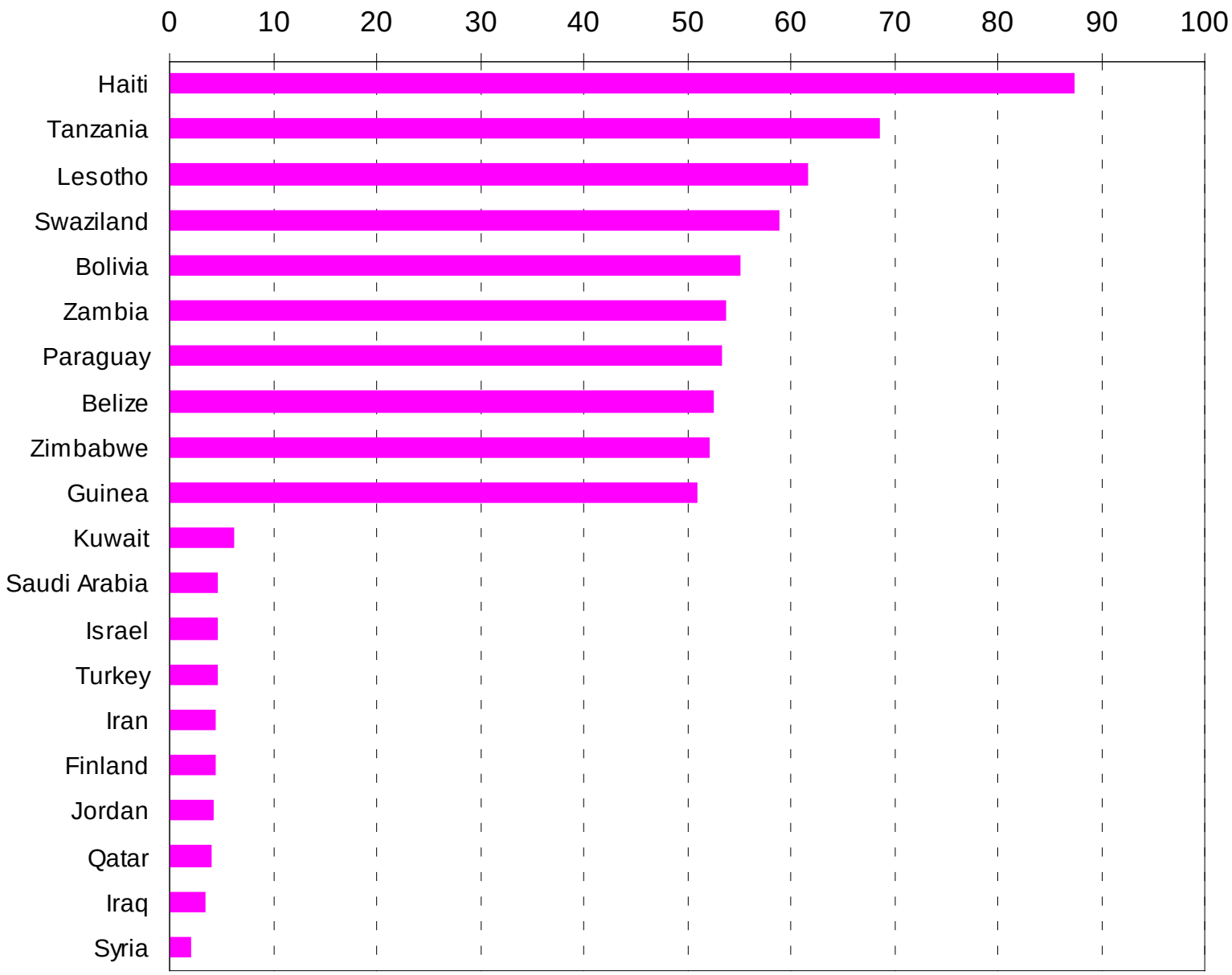
IARC: Globocan 2012
http://globocan.iarc.fr

ASIR (x 100,000), Liver carcinoma; top 10 and bottom 10 countries, Males



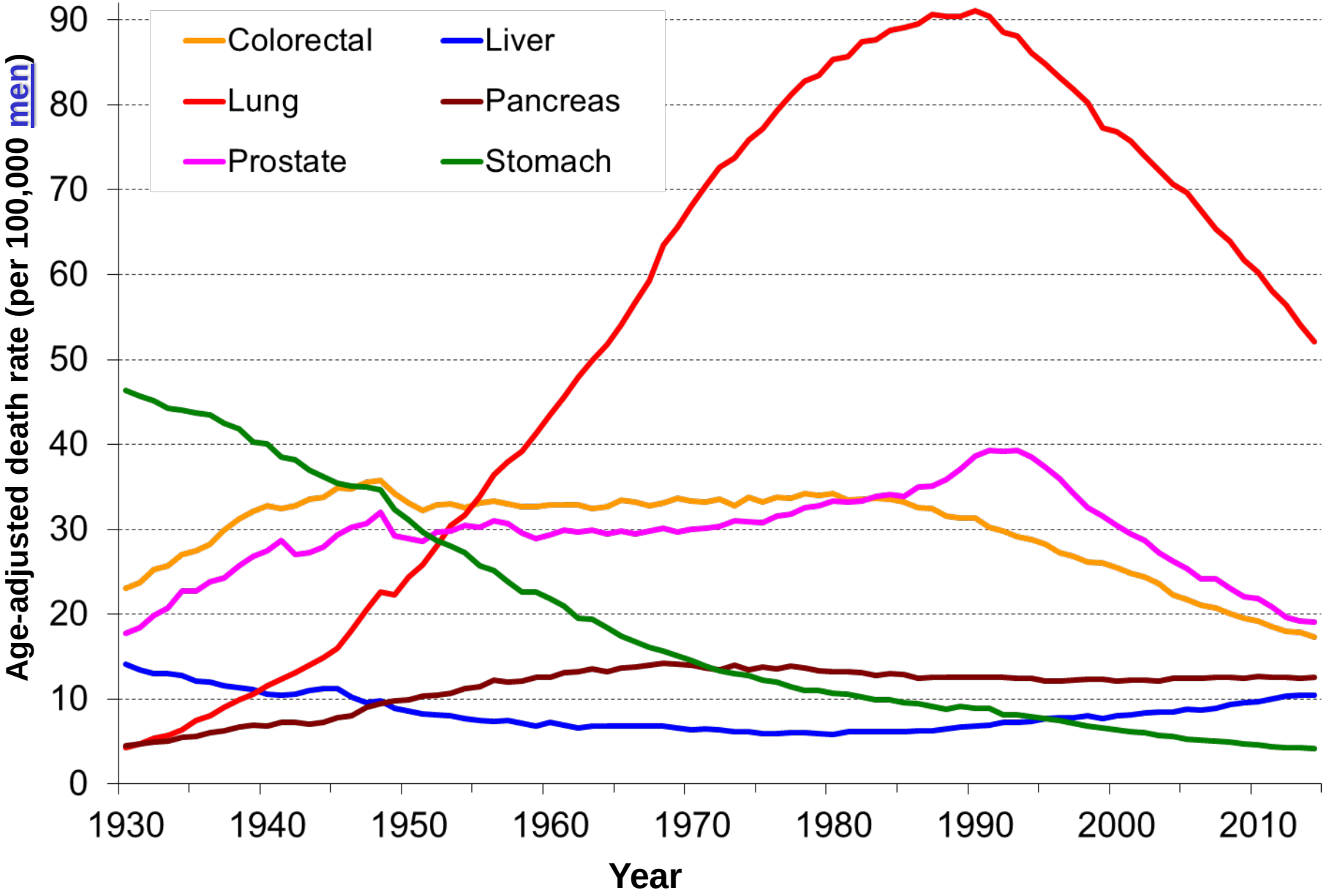
(Source: Globocan 2002)

ASIR (x 100,000), Cervical cancer; top 10 and bottom 10 countries



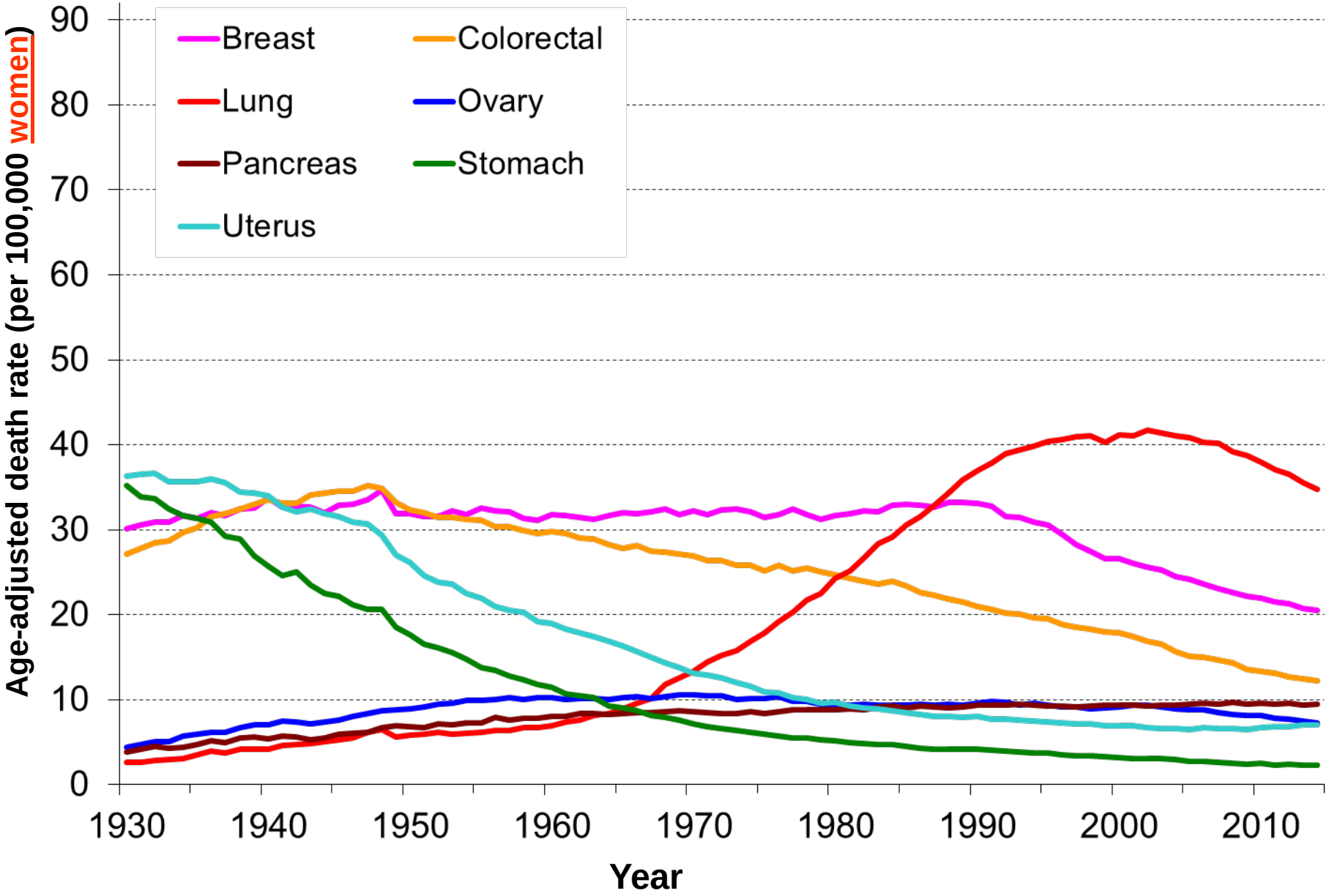
(Source: Globocan 2002)

Cancer Mortality in the U.S according to site (Males)



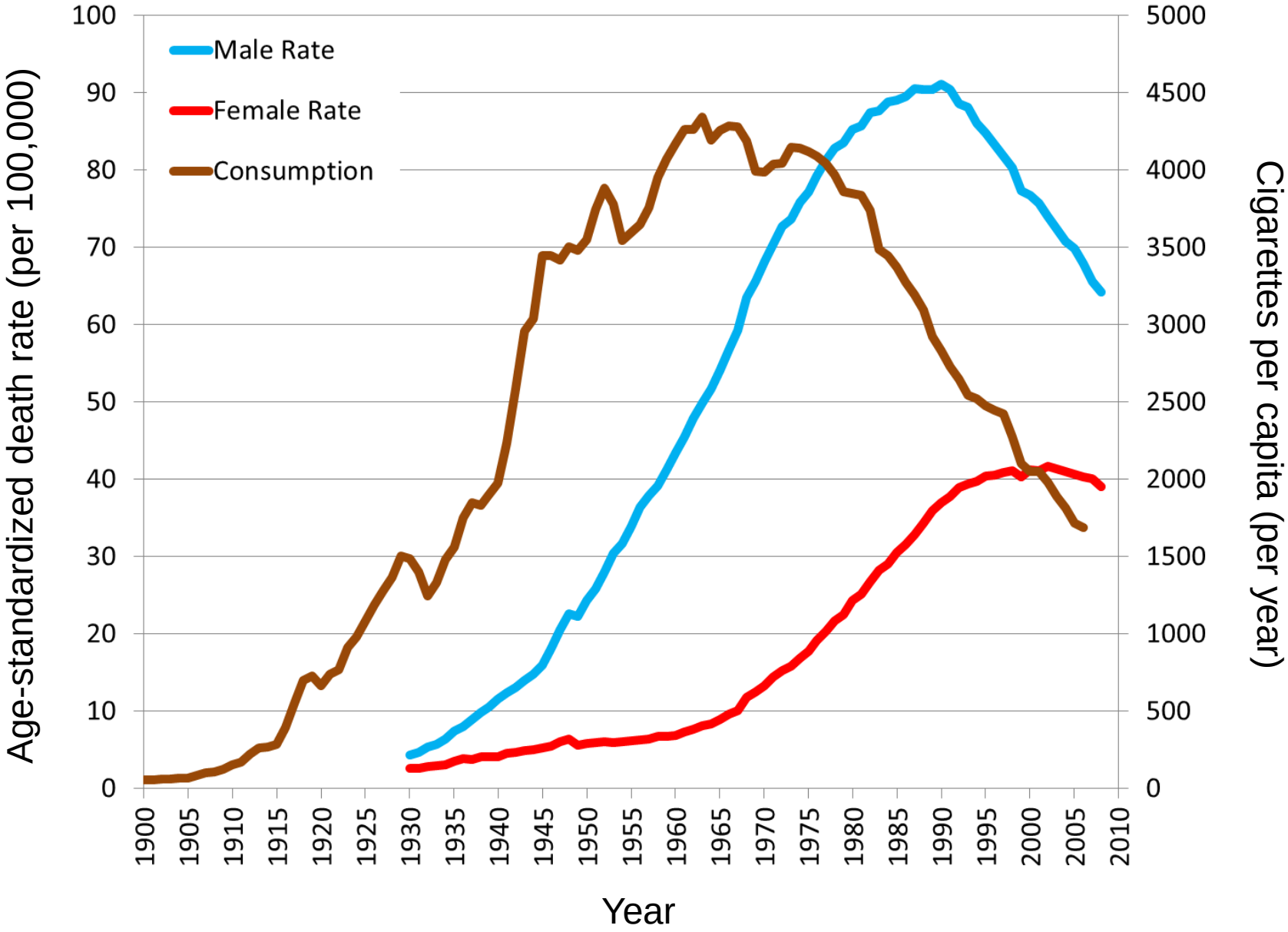
Age-adjusted death rates in the US (2000 population); Source: American Cancer Society, Surveillance Research

Cancer Mortality in the U.S according to site (Females)

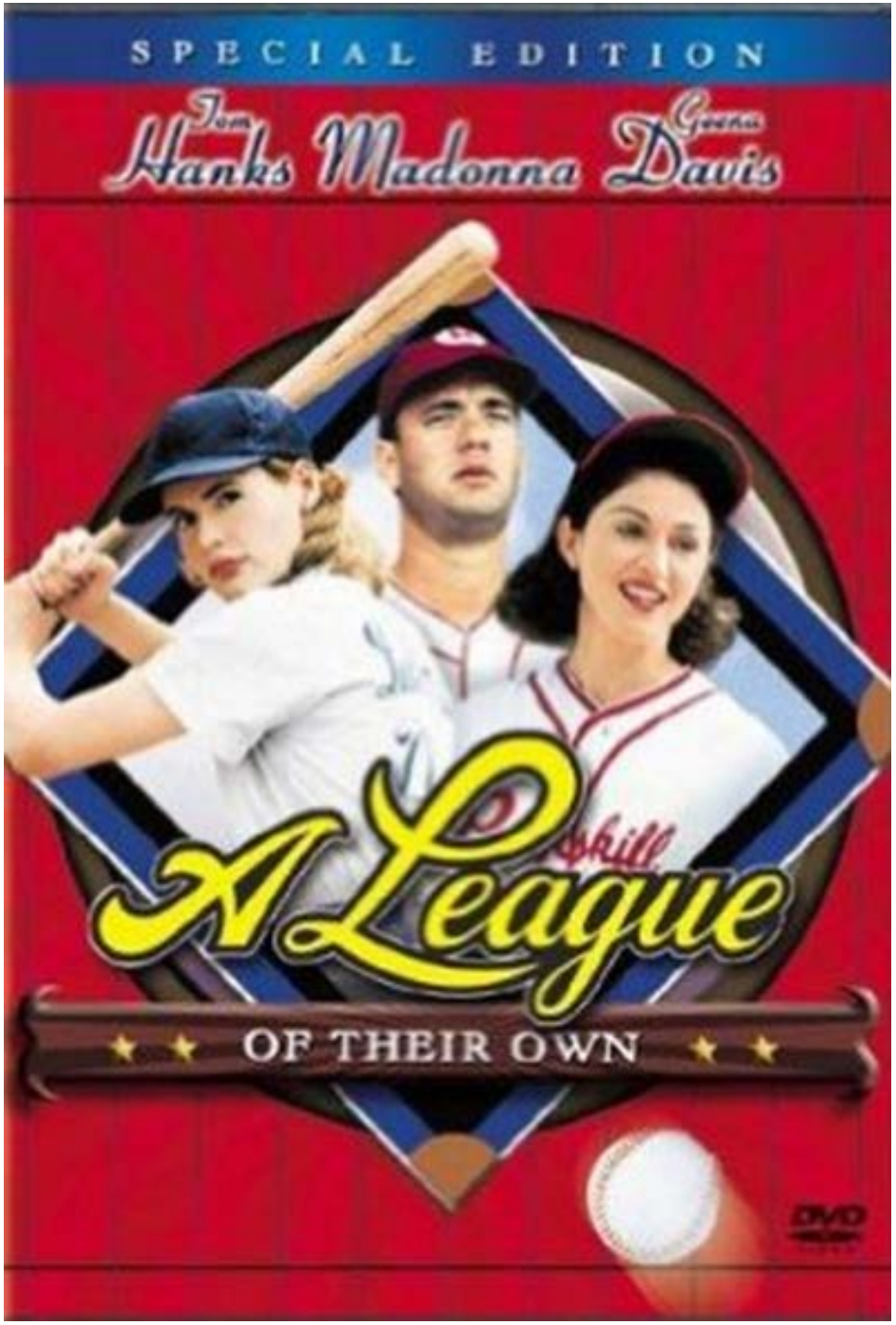


Age-adjusted death rates in the US (2000 population); Source: American Cancer Society, Surveillance Research

Tobacco Consumption and Lung Cancer Mortality in the US



Source: ACS Cancer Statistics; US Department of Agriculture

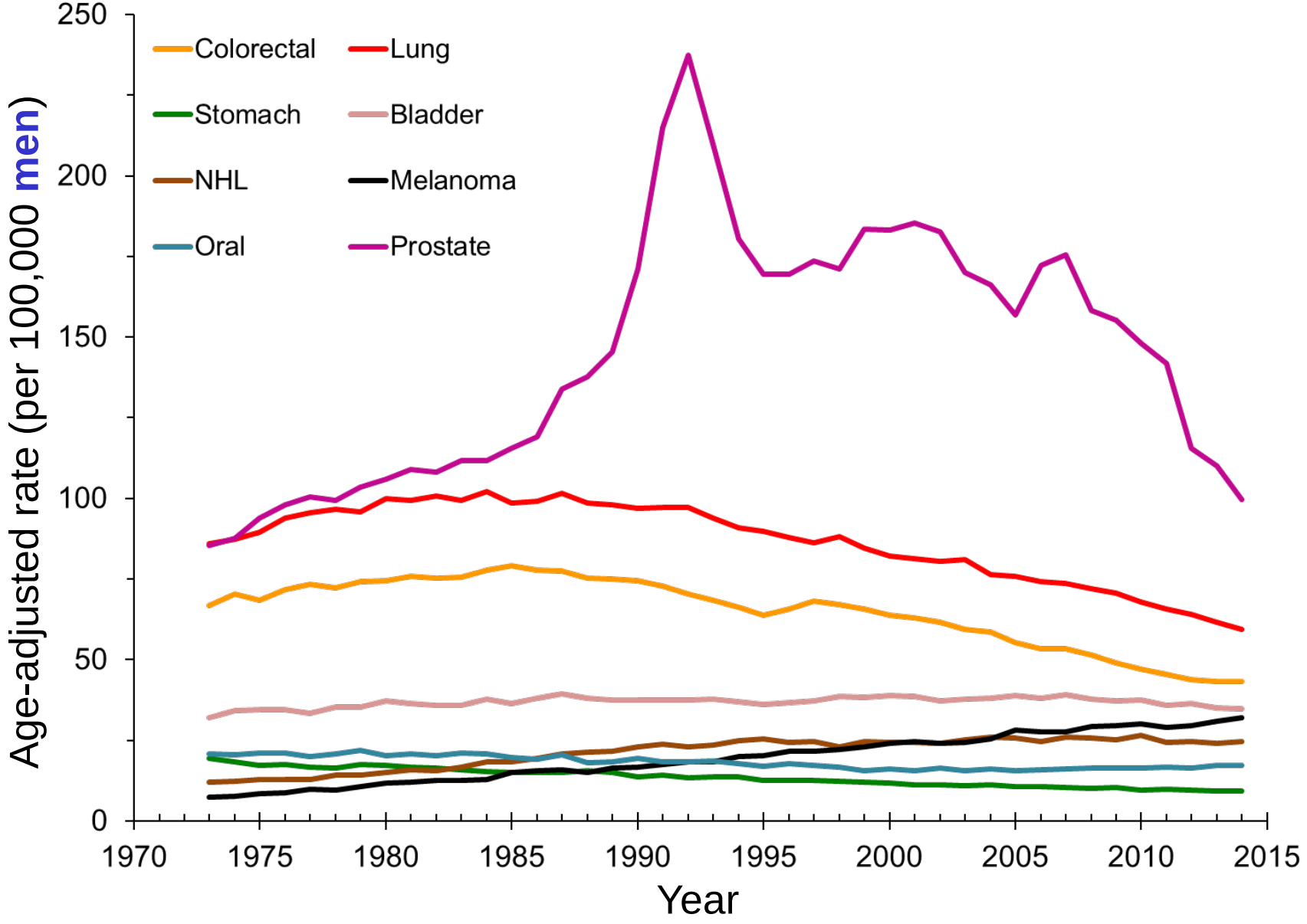


A league of their own

Cast:

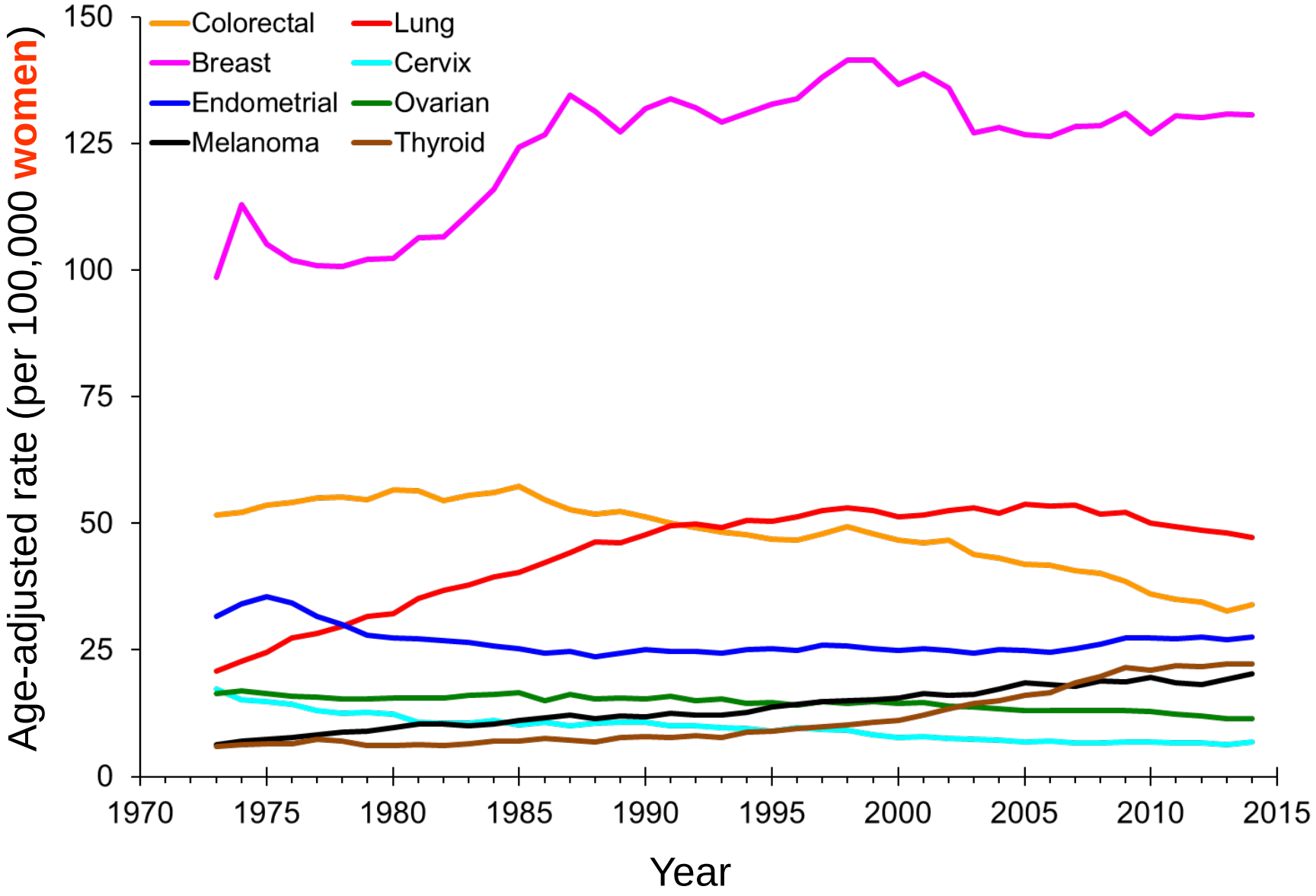
Tom Hanks ... Jimmy Dugan
Geena Davis ... Dottie Hinson
Madonna ... Mae Mordabito
Lori Petty ... Kit Keller
Jon Lovitz ... Ernie Capadino
David Strathairn ... Ira Lowenstein
Garry Marshall ... Walter Harvey
Bill Pullman ... Bob Hinson
Megan Cavanagh ... Marla Hooch - 2nd Base
Rosie O'Donnell ... Doris Murphy - 3rd Base
Tracy Reiner ... Betty Spaghetti' Horn - Left Field
Bitty Schram ... Evelyn Gardner - Right Field
Don S. Davis ... Charlie Collins, Racine Coach
Renée Coleman ... Alice Gaspers - Left/Center Field
Ann Cusack ... Shirley Baker - Left Field

Age-standardized (2000 US population) incidence rates in 9 SEER registry areas



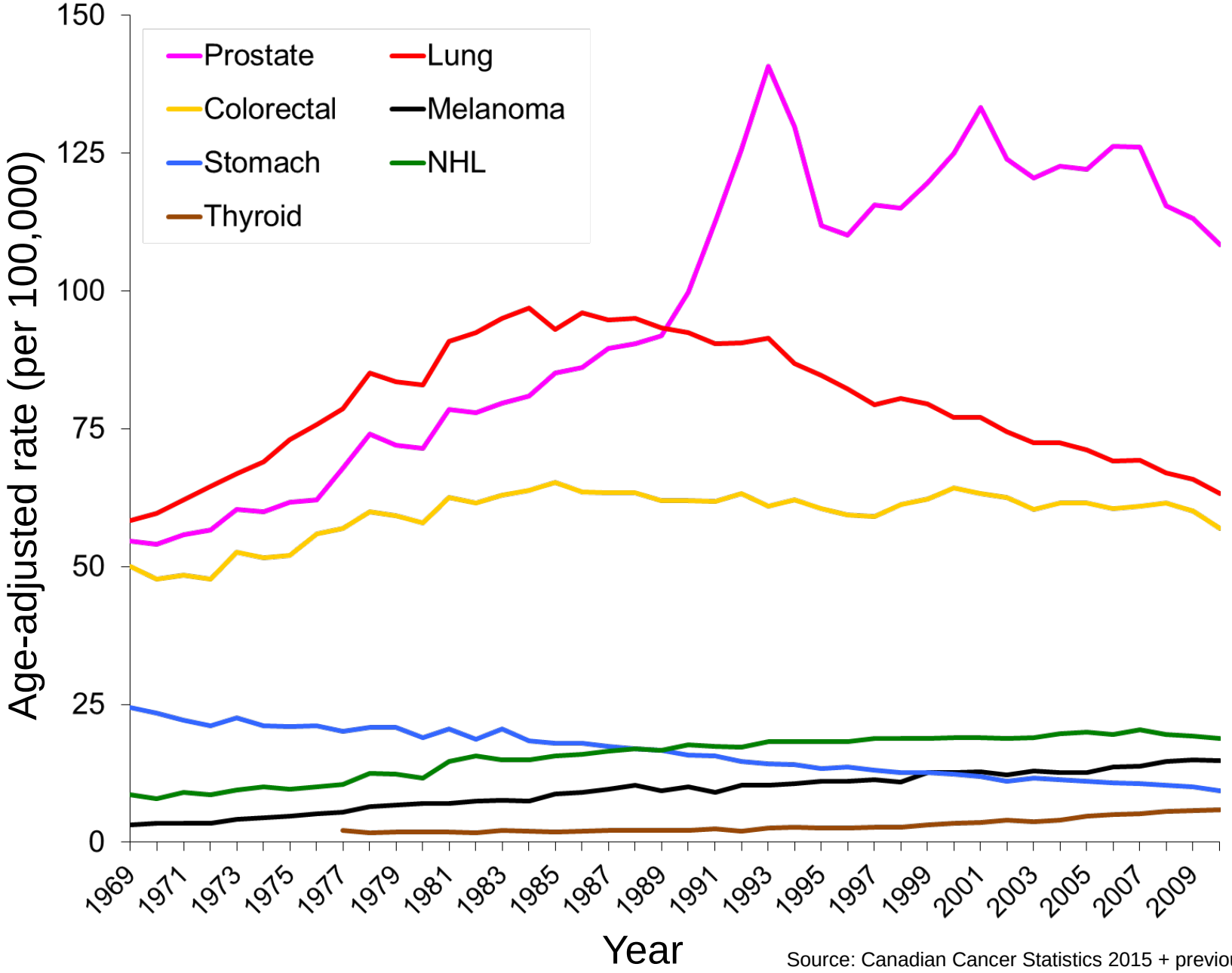
Source: Howlader et al. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017 (accessed May 13, 2017).

Age-standardized (2000 US population) incidence rates in 9 SEER registry areas



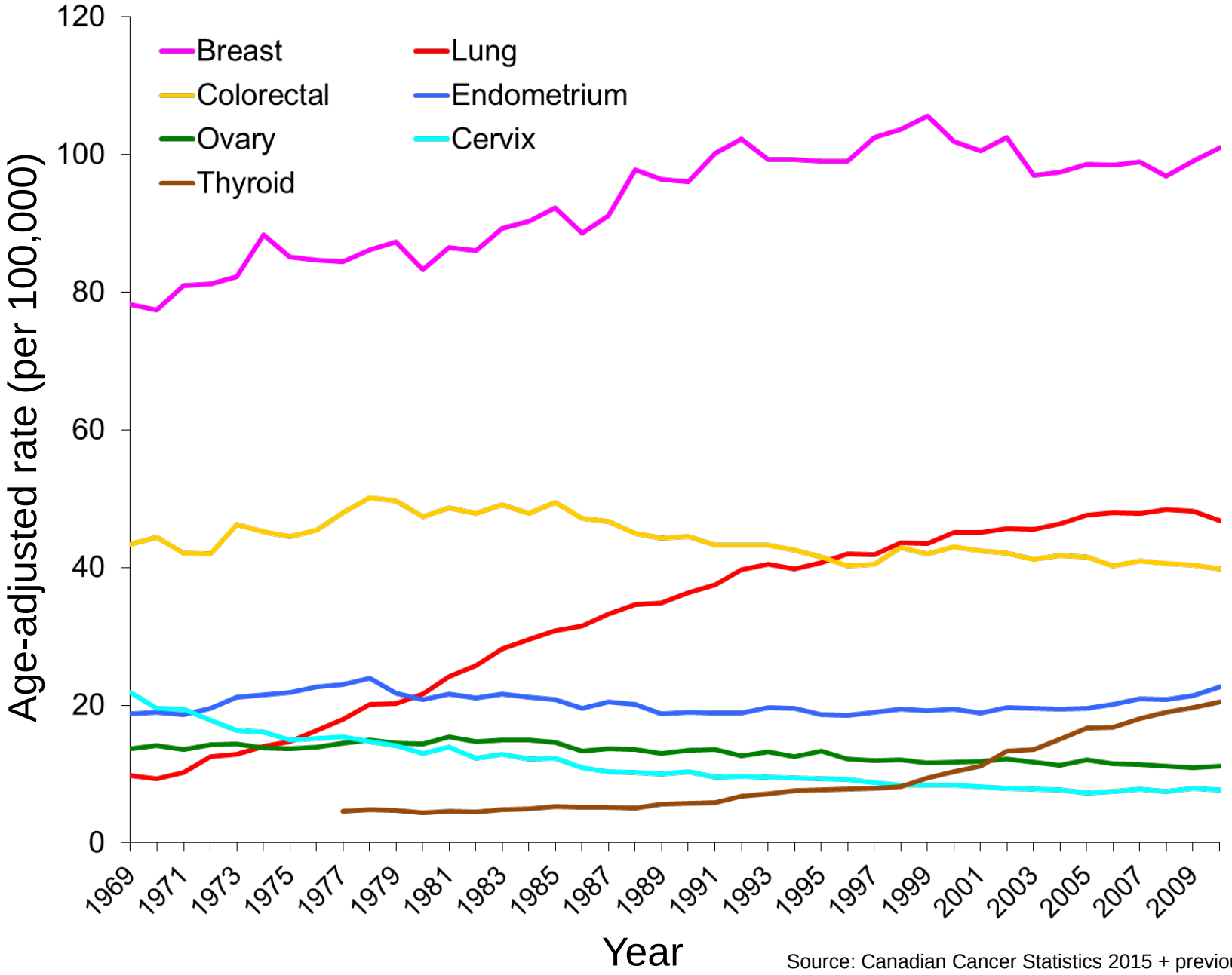
Source: Howlader et al. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017 (accessed May 13, 2017).

Canada: Incidence rates among **men** (age-adjusted to the 1991 Canadian population)

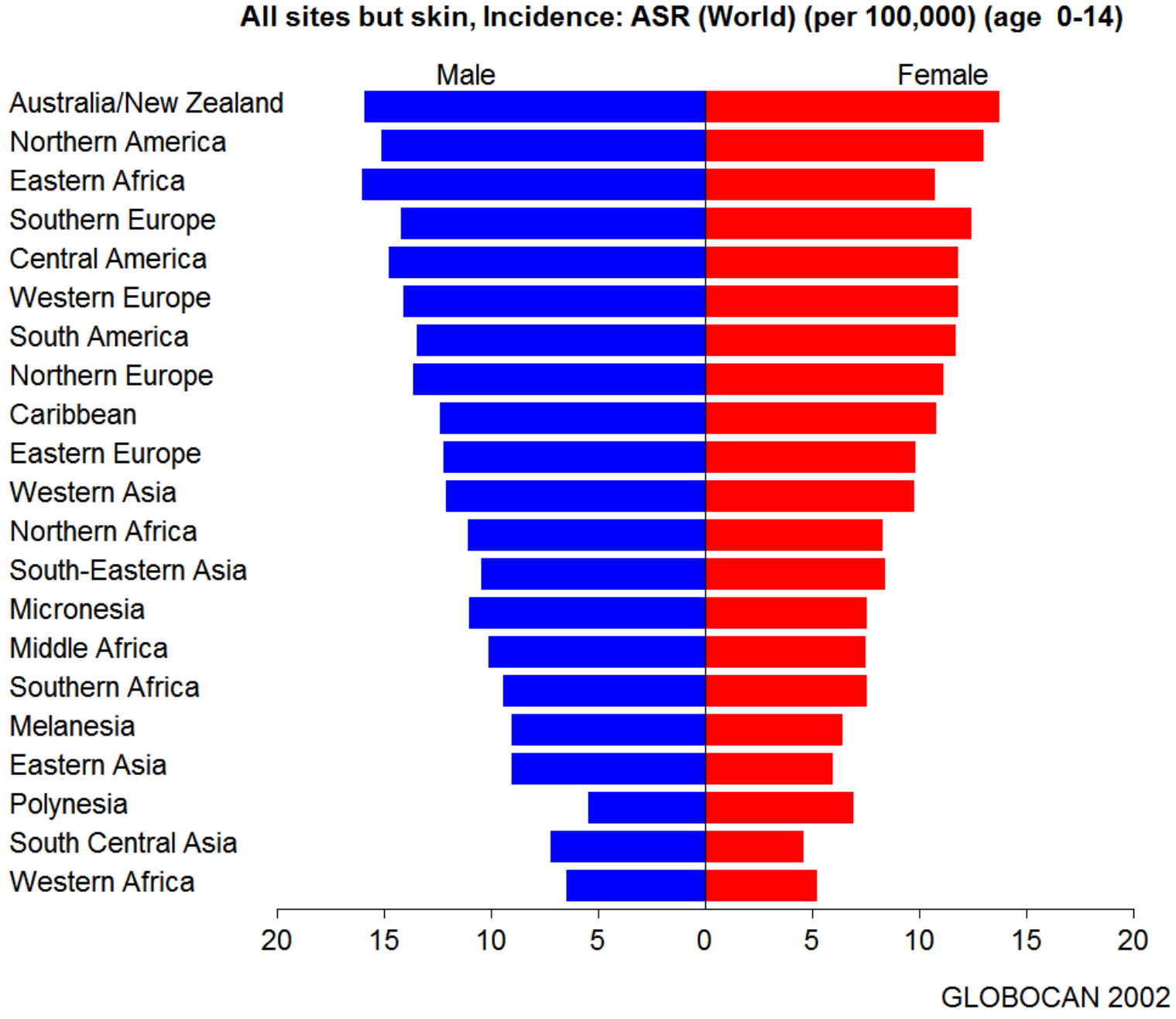


Source: Canadian Cancer Statistics 2015 + previous ones

Canada: Incidence rates among **women** (age-adjusted to the 1991 Canadian population)



Source: Canadian Cancer Statistics 2015 + previous ones


All sites but skin, Incidence: ASR (World) (per 100,000) (age 0-14)
Male
Female
Australia/New Zealand
Northern America
Eastern Africa
Southern Europe
Central America
Western Europe
South America
Northern Europe
Caribbean
Eastern Europe
Western Asia
Northern Africa
South-Eastern Asia
Micronesia
Middle Africa
Southern Africa
Melanesia
Eastern Asia
Polynesia
South Central Asia
Western Africa
20
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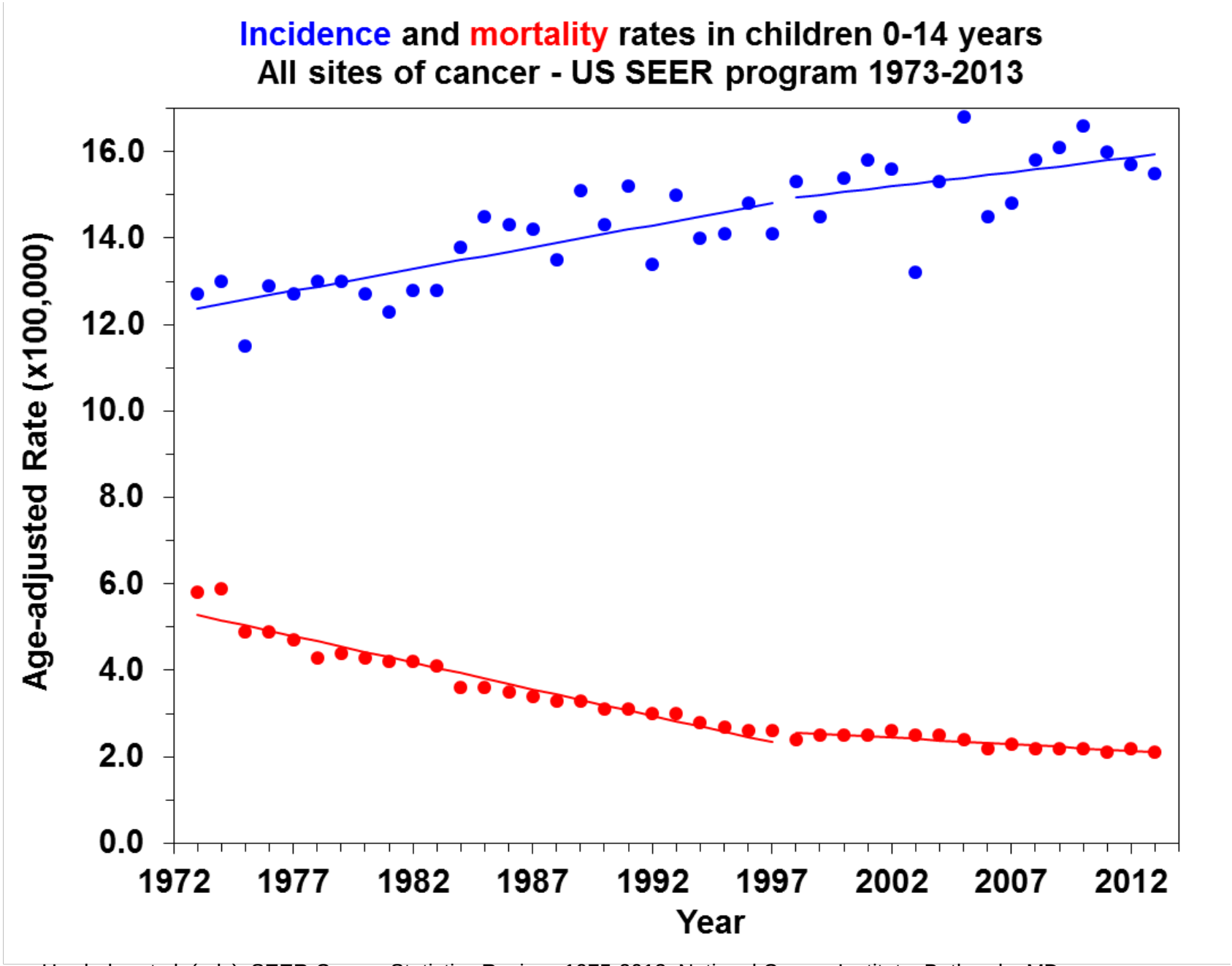
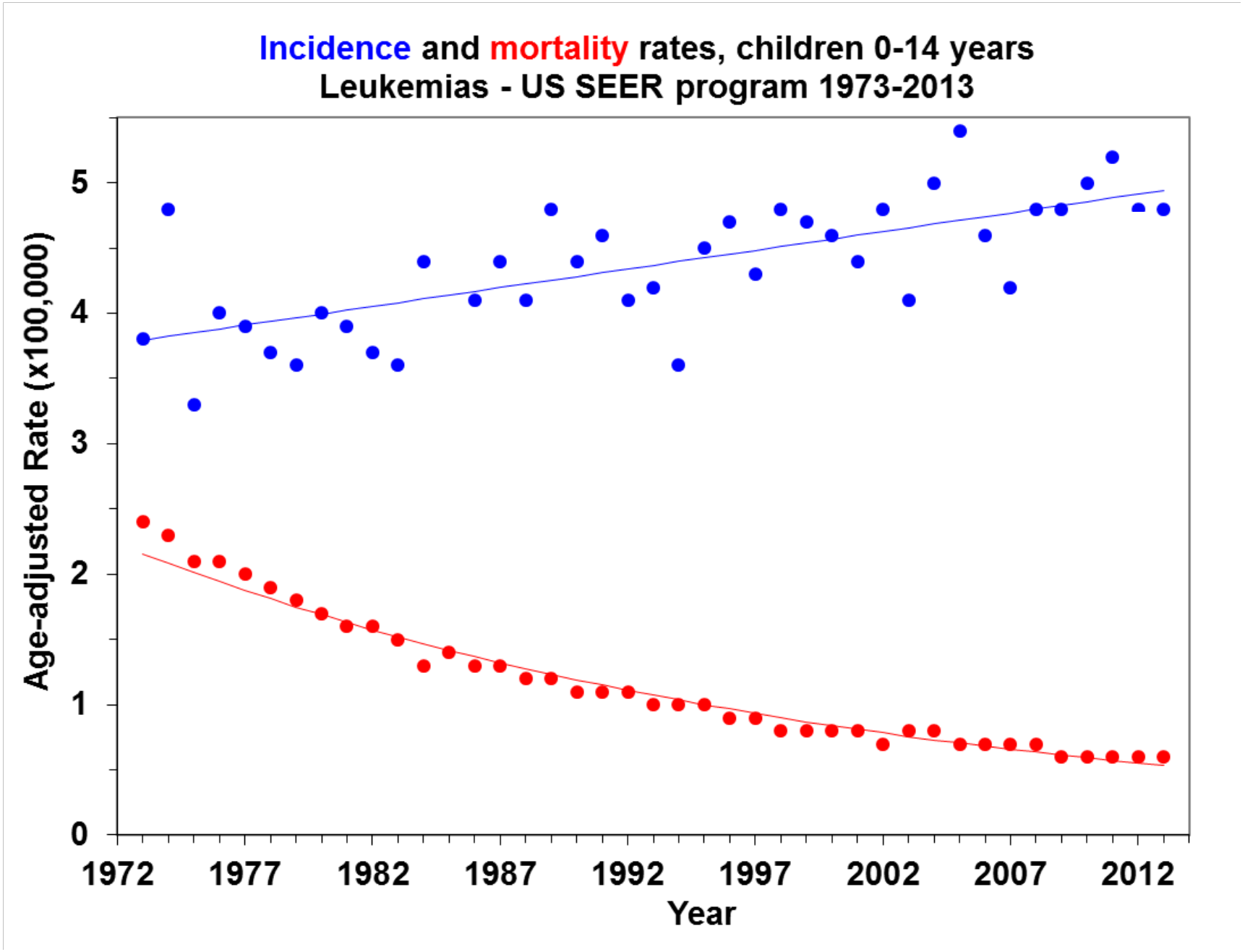
15
20
GLOBOCAN 2002

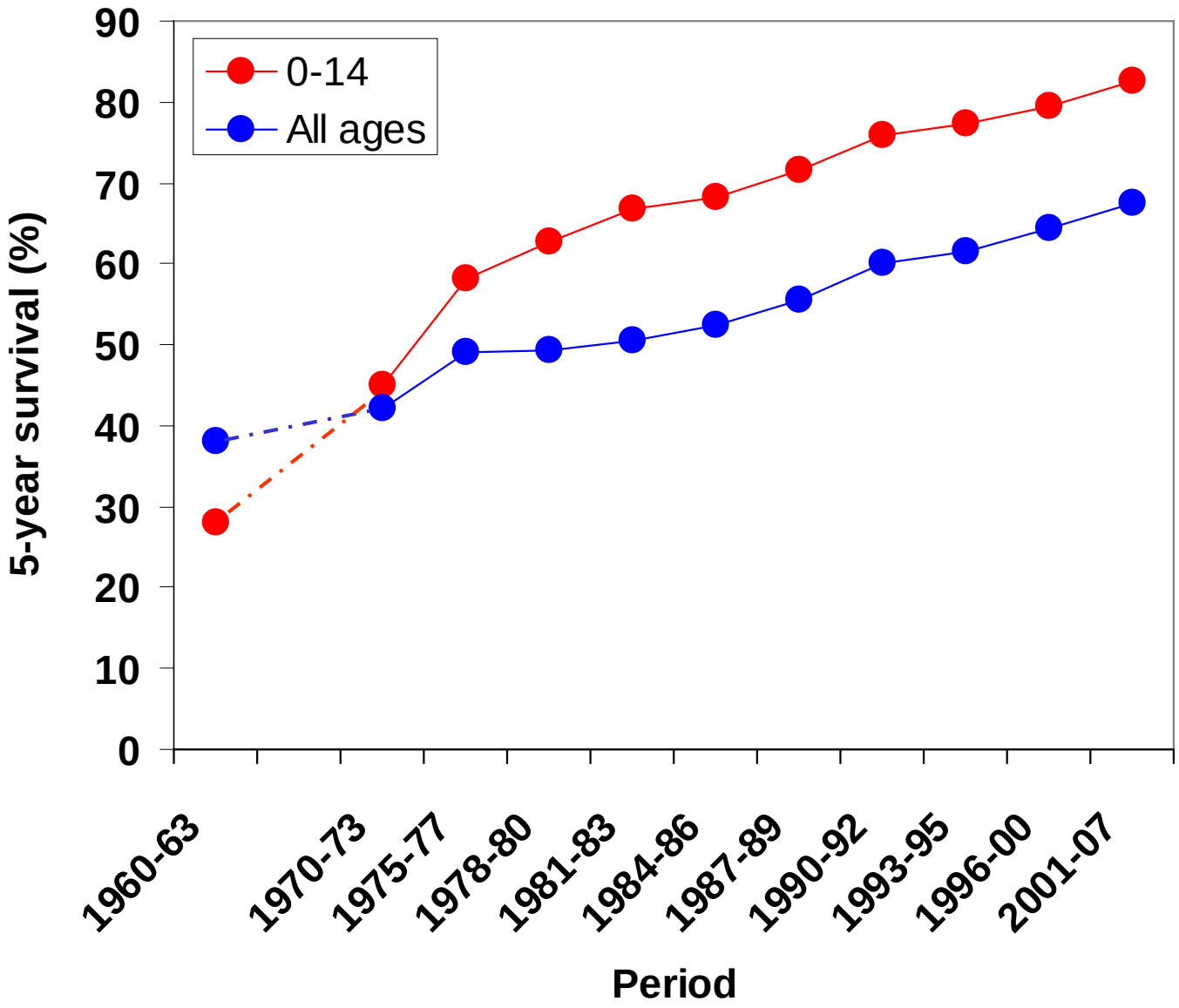


Source: Howlader et al. (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/ (accessed May 5, 2016)



Source: Howlader et al. (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/ (accessed May 5, 2016)

5-year relative survival for all sites of cancer, children versus all ages, US SEER program



Source: Howlader et al (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/

Epidemiologic approaches used in assessing the evidence concerning the carcinogenicity of a suspected chemical, physical, or biological exposure or its circumstances (Adapted from Franco et al., Sem Ca Biol 2004)

Type of epidemiologic evidence	Level of inference	Type of study	Features
Observational	Non-inferential, descriptive	Case reports	Suggestion of association
	Population	Surveillance of incidence and mortality	Documentation of baseline disease burden, exploratory hypotheses
		Ecologic (correlation or aggregate) studies	Coarse verification of correlation between exposure and disease burden
	Individual	Cross-sectional studies	Correlation between exposure and disease (or marker) without regard to latency
		Case-control studies	Correlation between exposure and disease (or marker) with improved understanding of latency; suitable for rare cancers
		Cohort studies	Correlation between exposure and disease (or marker) with improved understanding of latency; suitable for rare exposures
Experimental	Individual **	Randomized controlled trials of preventive intervention	Most unbiased assessment of correlation between exposure and disease (or marker)

** RCTs may target communities or providers as units of randomly allocated intervention. However, this is done for convenience of study design; in practical terms inference is at the individual level.

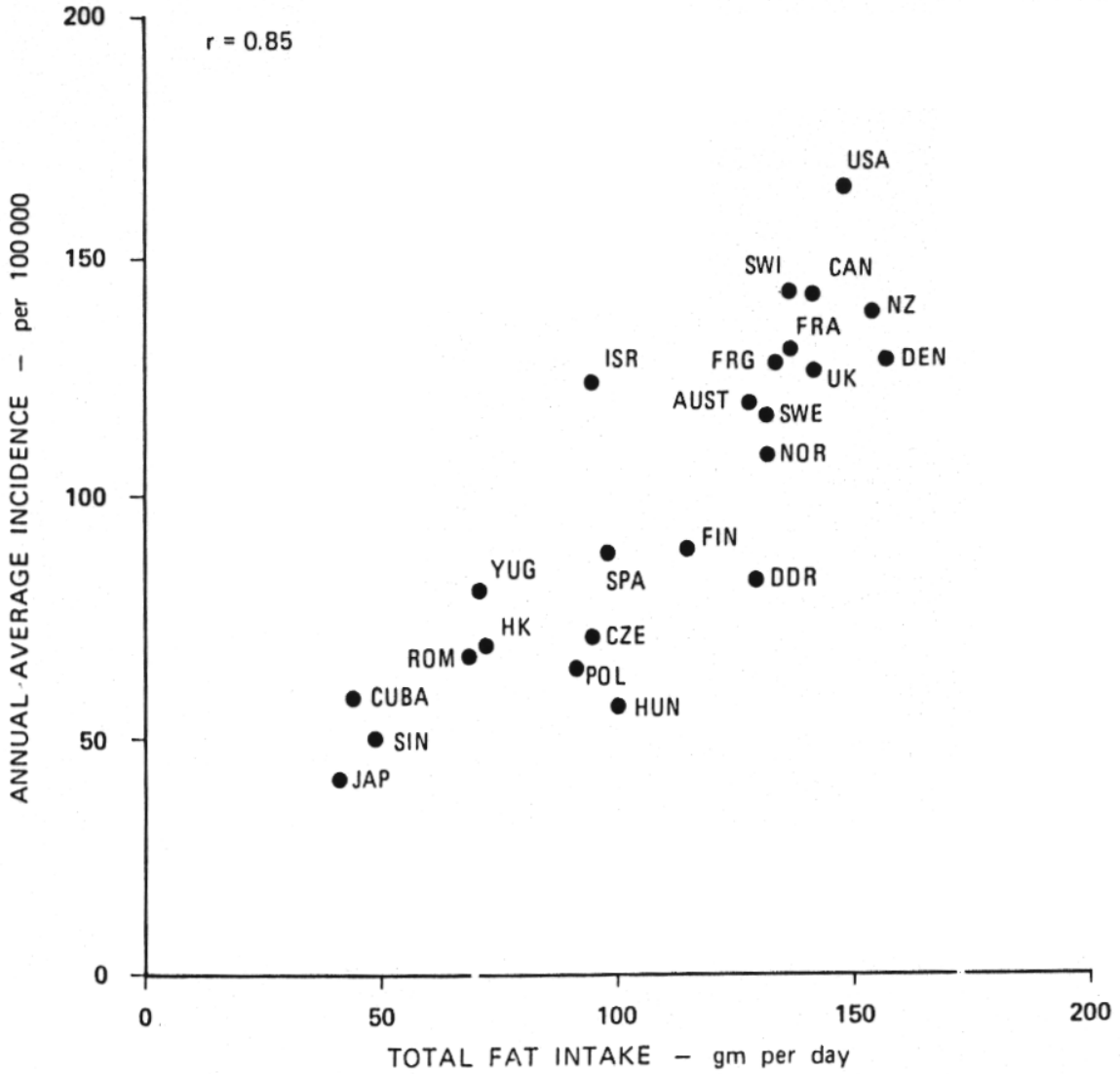


Fig. 1. Correlation of age-standardized incidence of breast cancer in women aged 35–64 years in 1972–1977 in 25 countries with estimated per caput daily fat consumption in 1964–1966. Incidence data are those reasonably representative of whole countries given by Doll and Smith (1982). Data on fat consumption from Food and Agriculture Organization (1971).

From: Armstrong and Mann, 1985

STUDY DESIGNS

- ***Cross-sectional:***

  Disease and risk factors determined simultaneously in a survey.

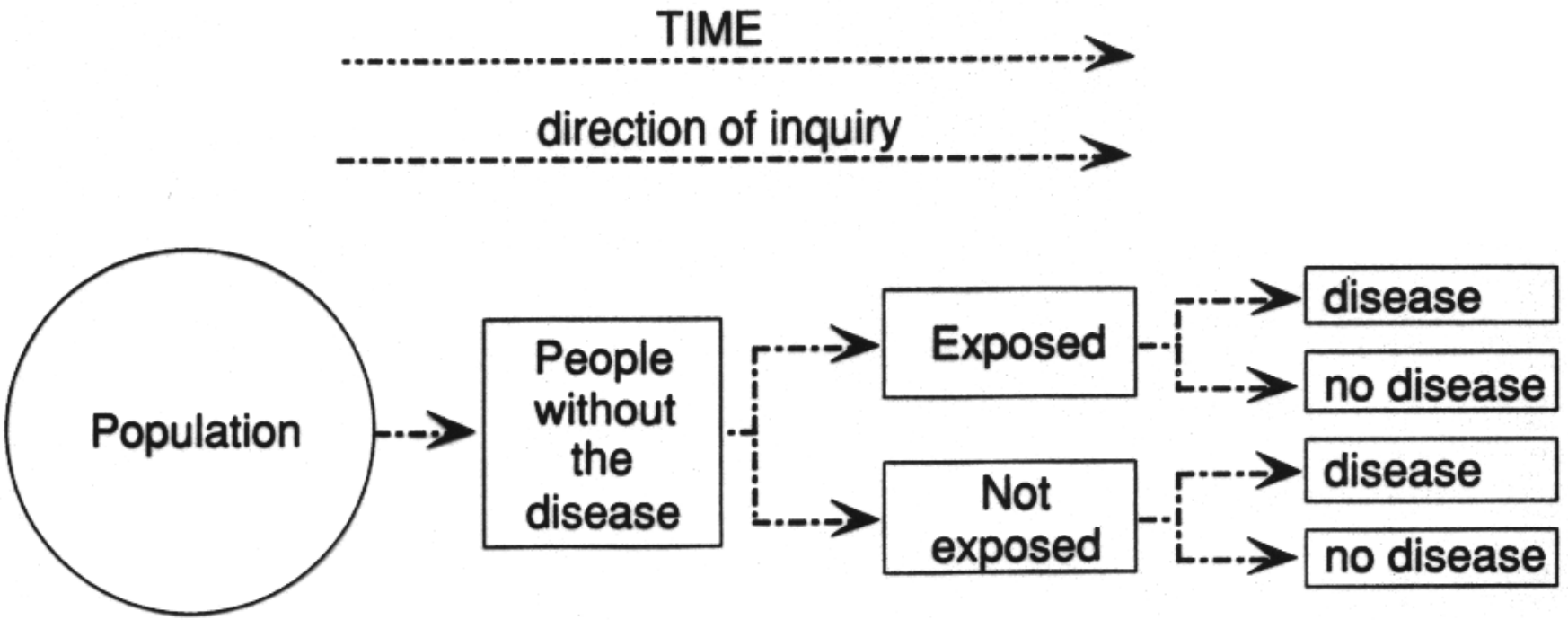
- ***Cohort:***

  Risk factors determined initially and population is followed up to ascertain disease occurrence.

- ***Case-control:***

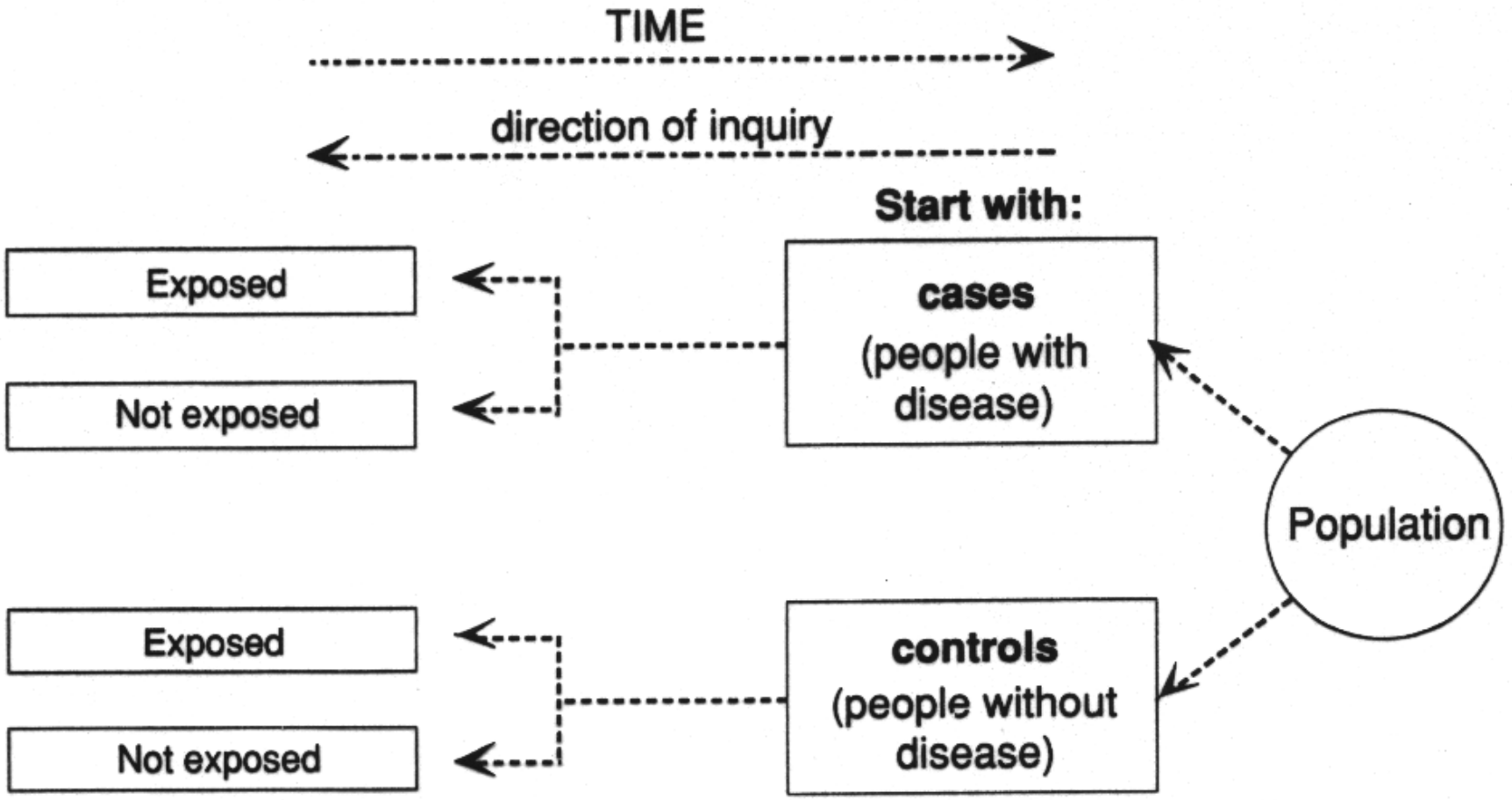
  Disease occurrence determined initially and risk factors probed retrospectively.

Design Layout of a Cohort Study

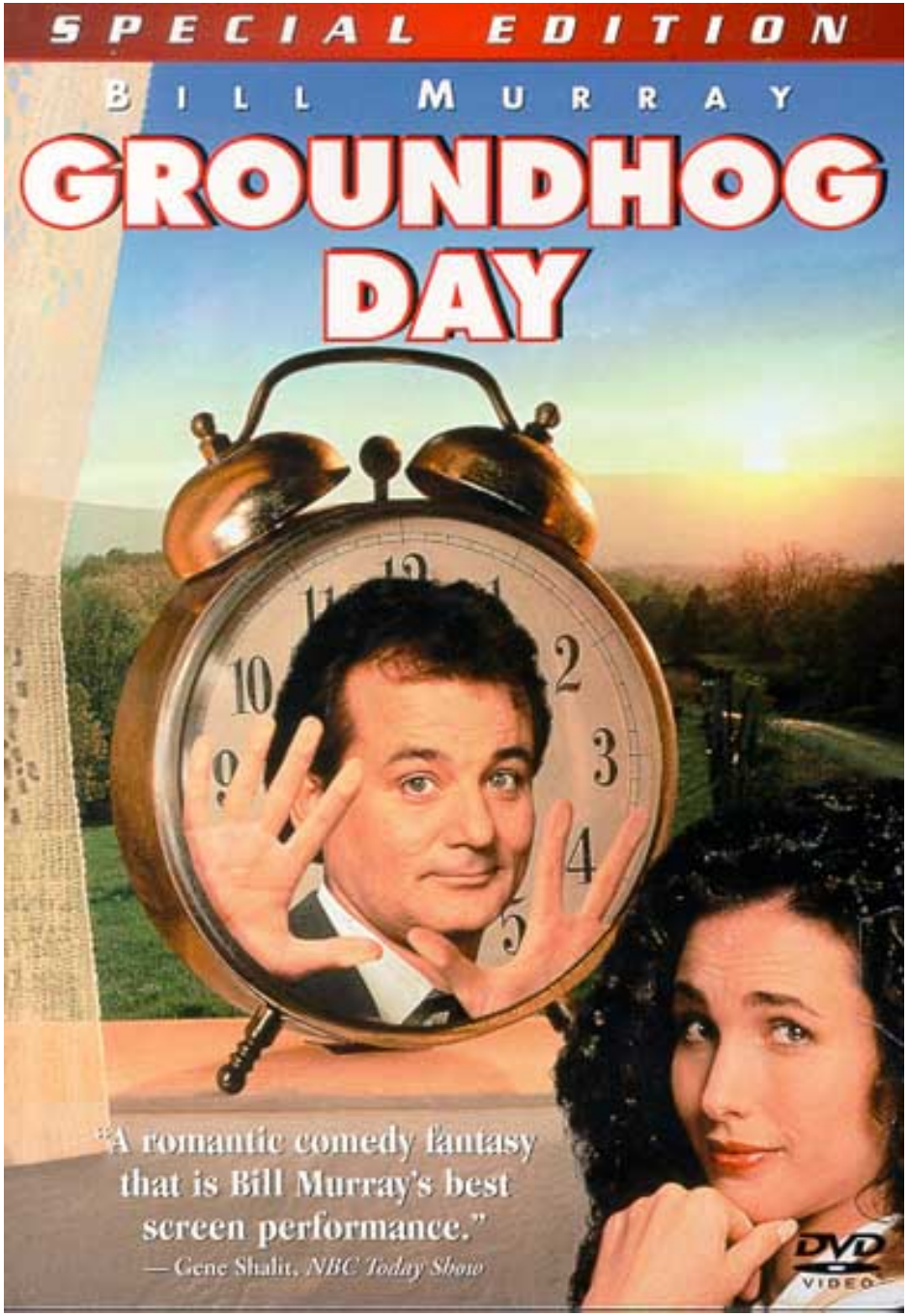


From: Beaglehole et al., W.H.O., 1993

Design Layout of a Case-Control Study



From: Beaglehole et al., W.H.O., 1993



Groundhog Day

Cast:

Bill Murray ... Phil
Andie MacDowell ... Rita
Chris Elliott ... Larry
Stephen Tobolowsky ... Ned
Brian Doyle-Murray ... Buster
Marita Geraghty ... Nancy
Angela Paton ... Mrs. Lancaster
Rick Ducommun ... Gus
Rick Overton ... Ralph
Robin Duke ... Doris the Waitress
Carol Bivins ... Anchorwoman
Willie Garson ... Phil's Assistant Kenny
Ken Hudson Campbell ... Man in Hallway
Les Podewell ... Old Man
Rod Sell ... Groundhog Official

THE RELATIVE RISK AS THE MEASURE OF EFFECT

In a case-control study, why is the odds ratio used to estimate the relative risk of disease given the exposure?

Hypothetical example:

Population at risk (PAR): 10×10^6
Disease incidence: 30×10^{-6} / year
Exposure prevalence: 5%
Study duration: 2 years
RR = 5

Exposure	Cases	PAR	Rate	RR
Present	125	0.5×10^6	125×10^{-6} / yr	**5.0**
Absent	475	9.5×10^6	25×10^{-6} / yr	1.0 (referent)
Total	600	10×10^6	30×10^{-6} / yr	

Case-control study number 1:

All incident cases are contacted; 1 non-diseased control is randomly selected for each case

Exposure	Cases	Controls
Present	125	30
Absent	475	570
Total	600	600

$$OR = \frac{125 / 30}{475 / 570} = \mathbf{5.0}$$ (95%CI: 3.3-7.9)

Case-control study number 2:

A random 25% sample of the incident cases; 2 non-diseased controls are randomly selected for each case

Exposure	Cases	Controls
Present	31	15
Absent	119	285
Total	150	300

$$OR = \frac{31 / 15}{119 / 285} = \mathbf{4.95}$$ (95%CI: 2.5-10.2)

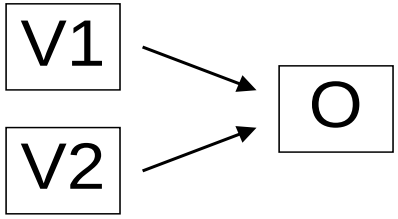
Components of Etiologic Models in Cancer: *Commonly Suspected Relations*

V1 and V2= candidate risk factor variables 1 and 2

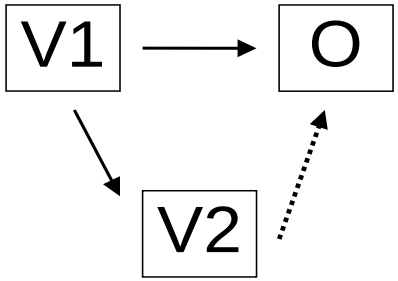
O= cancer outcome

Adapted from Franco et al., 2002

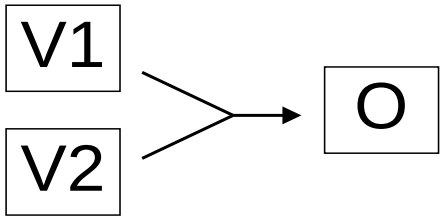
Independence of effects:



Confounding:



Interaction:



Hypothetical example of controlling for confounding

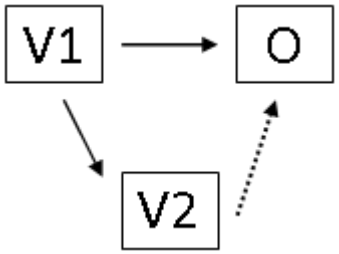
V1 (the real risk factor) has 20% prevalence and increases risk of O (the disease) 10-fold; V2 is not a risk factor but is associated with V1

	Crude V1xO		
	V1+	V1-	Total
O+	60	24	84
O-	140	776	916
Tot	200	800	1000
RR = 10.00			

	Crude V2xO		
	V2+	V2-	Total
O+	53	31	84
O-	267	649	916
Tot	320	680	1000
RR = 3.63			

	Stratum V1+		
	V2+	V2-	Total
O+	48	12	60
O-	112	28	140
Tot	160	40	200
RR = 1.00			

	Stratum V1-		
	V2+	V2-	Total
O+	5	19	24
O-	155	621	776
Tot	160	640	800
RR = 1.05			



Components of Etiologic Models in Cancer: *Less Suspected Mechanisms*

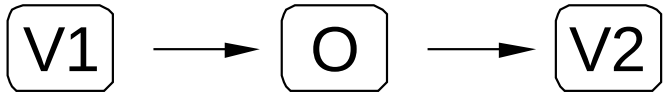
V1 and V2= candidate risk factor variables 1 and 2

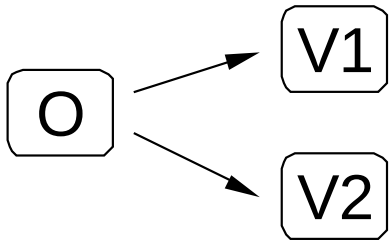
O= cancer outcome

Adapted from Franco et al., 2002

Causal pathway:

Correlates of outcome:





RANDOM MISCLASSIFICATION OF THE EXPOSURE IN A CASE-CONTROL STUDY

True population classification:

EXPOSURE	CASES	PAR	RATE	RR
Present	125	0.5×10^{6}	125×10^{-6}/yr	5.0
Absent	475	9.5×10^{6}	25×10^{-6}/yr	1.0 (Referent)
Total population	600	10×10^{6}	30×10^{-6}/yr	

If exposure correctly ascertained in a case-control study (150 ca + 300 co):

EXPOSURE	CASES	CONTROLS	OR (95%CI)
Present	31	15	4.95 (2.5–10.2)
Absent	119	285	1.0 (Referent)
Total	150	300	

If exposure is ascertained with 20 % error:

EXPOSURE	CASES	CONTROLS
Present	31 (24 ↻, ↻ 6)	15 (57 ↻, ↻ 3)
Absent	119	285
Total	150	300

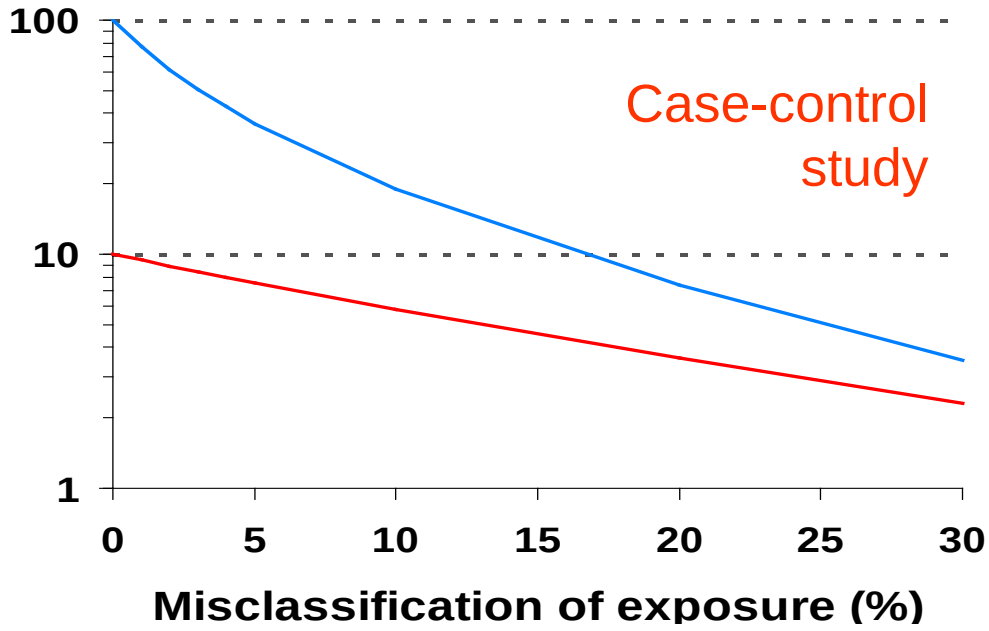
Arrangement with misclassification:

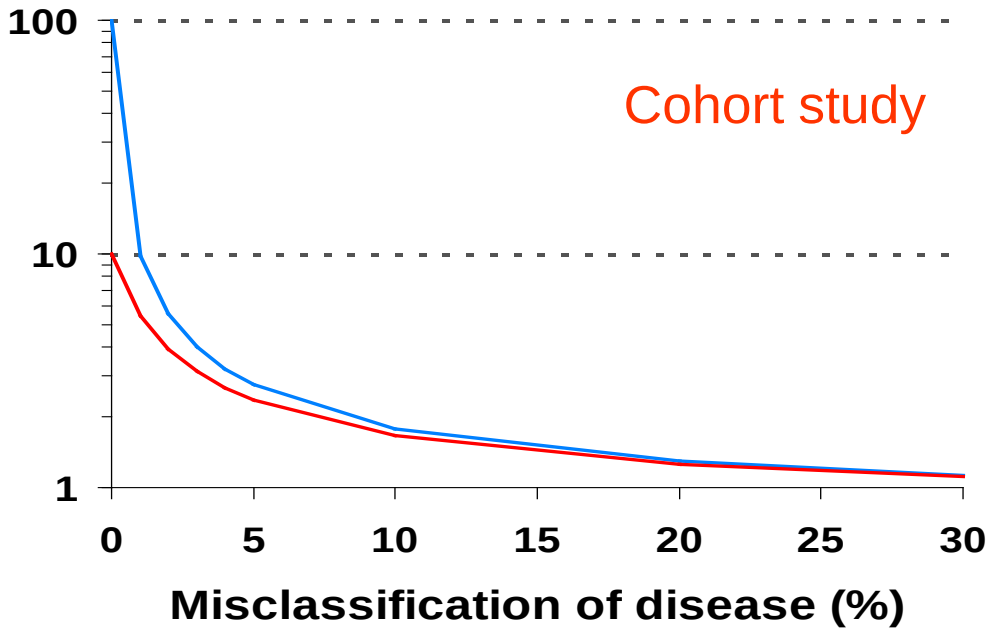
EXPOSURE	CASES	CONTROLS	OR (95%CI)
Present	49	69	1.6 (1.0 – 2.6)
Absent	101	231	1.0 (Referent)
Total	150	300	

Effect of measurement error in epidemiologic studies

Parameter: RR (exp-dis)

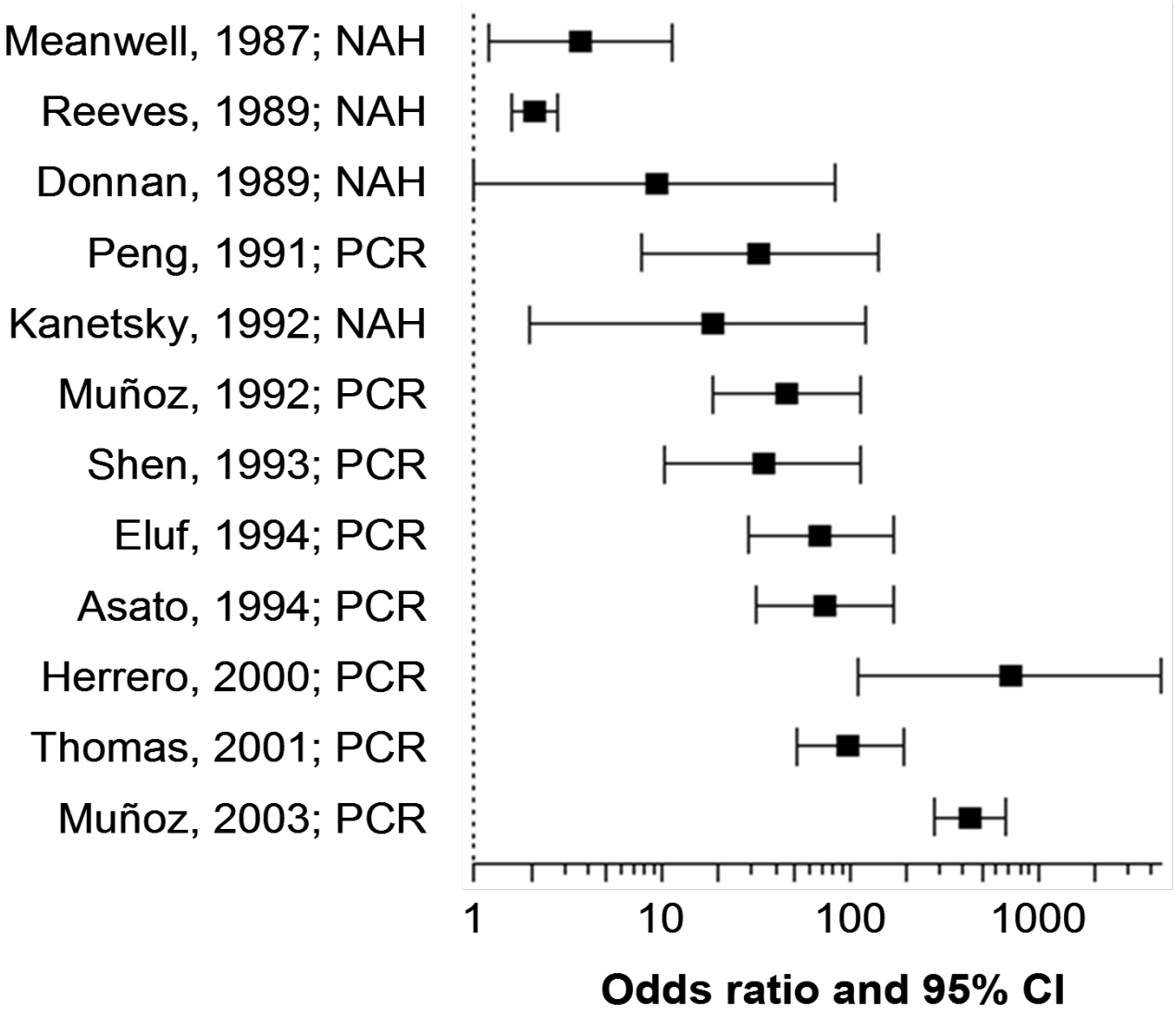
Assumptions:
P(exp)=20%,
P(dis)~2.5%





Adapted from: Franco and Rohan, 2002

Relative risks for associations between HPV and cervical cancer in case-control studies

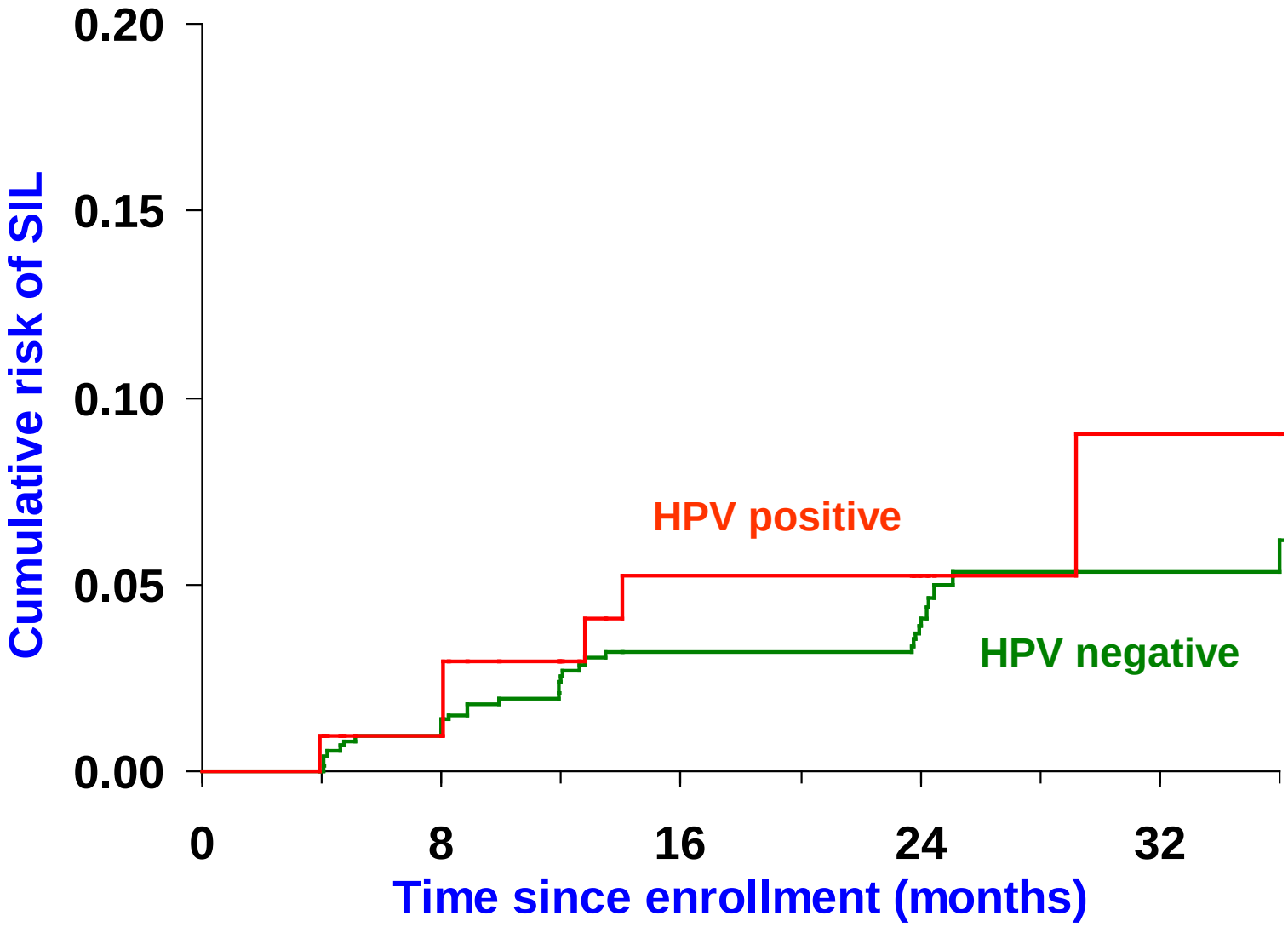


NAH: non-amplified DNA hybridization

PCR: polymerase chain reaction

Franco & Tota, AJE 2010

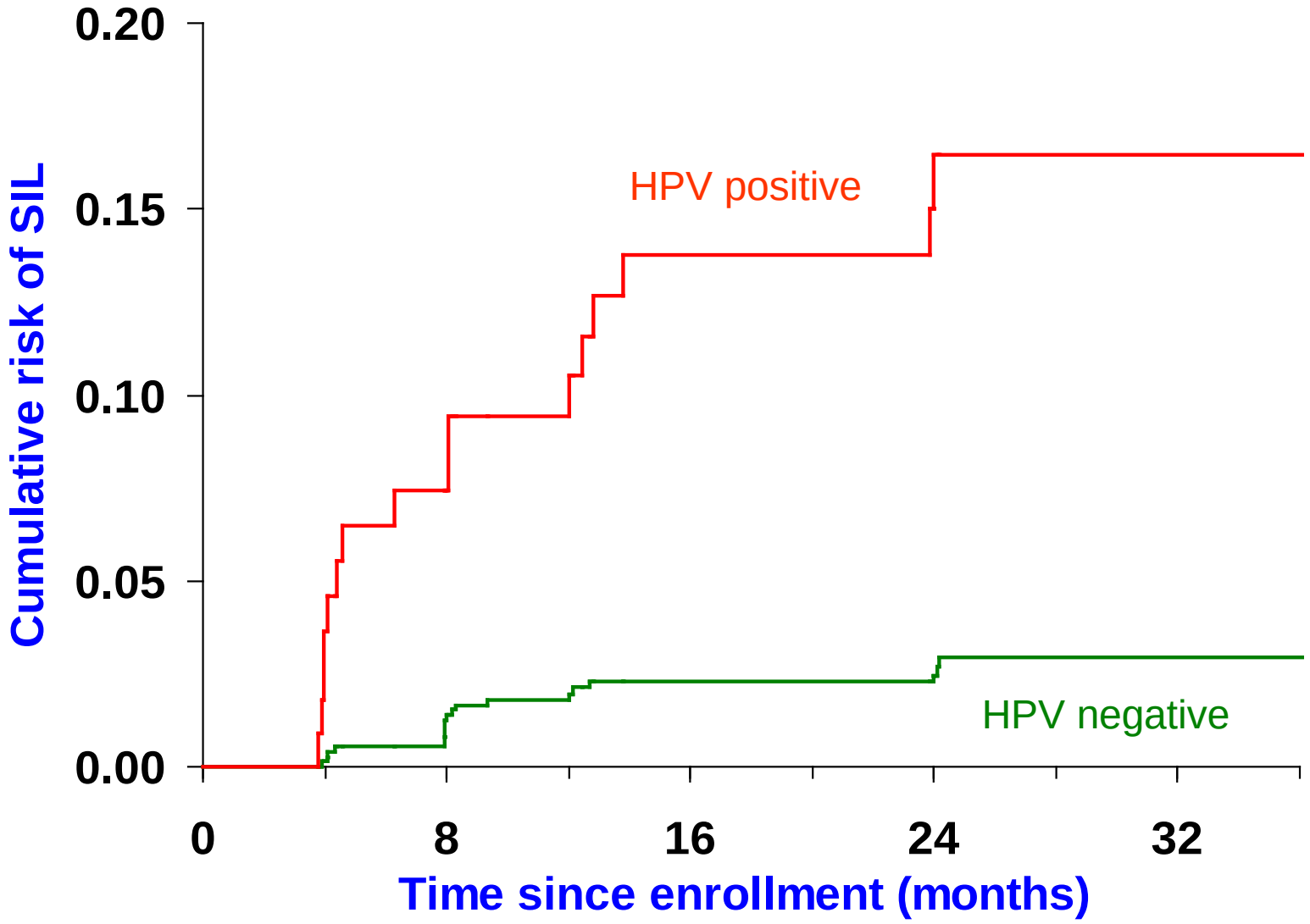
Cumulative incidence of SIL among women with a normal Pap smear at entry **(Local cytology)**



Ludwig-McGill Cohort (August 1997)

Franco & Tota, AJE 2010

Cumulative incidence of SIL among women with a normal Pap smear at entry **(Review cytology)**



Ludwig-McGill Cohort (August 1997)

Franco & Tota, AJE 2010

Features of Epidemiologic Study Designs

Features	Ecologic	Cross-sectional	Case-control	Cohort	Randomized controlled trial
Study of rare outcomes	Appropriate	No	Appropriate	No (unless high risk population is targeted)	No (unless high risk population is targeted)
Study of rare exposures	Appropriate	No	No	Appropriate	Not applicable
Study of multiple outcomes	Appropriate	Appropriate	No	Appropriate	Appropriate
Study of long latency	No	No	Appropriate	Inefficient	Inefficient
Assessment of temporality	Possible	No	Possible	Yes	Yes
Can measure incidence?	No	No	Only if all cases identified	Yes	Yes
Weight of evidence	Very low	Low	High	Very high	Highest
Types of biases	Ecologic fallacy, confounding, detection, misclassification	Selection, recall, confounding, misclassification	Selection, detection, recall, confounding, misclassification	Selection, detection, confounding, misclassification	Misclassification, differential loss to follow-up
Study duration	Very short	Short	Intermediate	Long	Long
Cost	Very low	Low	High	Very high	Highest

Modified from: Beaglehole et al. 1993

Main regression models in epidemiologic studies

Logistic regression model:

- $P (D = 1 \mid x_i) =$
  $\{ 1 + \exp [- (ß_o + ß_1 x_1 + ß_2 x_2 + ... + ß_n x_n)] \}^{-1}$

- **Odds ratio** = $OR = \exp (ß_1 + ß_2 + ... + ß_n)$

Proportional hazards model:

- $h(t) = h_o(t) \exp (ß_1 x_1 + ß_2 x_2 + ... + ß_n x_n)$

- **Hazard ratio** = $HR = \exp (ß_1 + ß_2 + ... + ß_n)$

Progress in Cancer Epidemiology: Advances in Study Design and Statistical Methods

- Stratification and adjustment to deal with confounding and interaction.
- Development of statistical methodology for regression analysis: Cox model, logistic regression, and survival analysis frameworks.
- Convergence of the case-control and cohort study paradigms for studying risk attribution.
- Advances in computing technology making data analysis more efficient.
- Development and continued improvement of record linkage methodology to study occupational, pharmacological and other exposures.
- Development of methods with repeated measurements of exposure and outcomes, allowing the study of early cancer endpoints.
- Development of the statistical modeling framework for the analysis of correlated data (GEEs).
- Contribution of hybrid qualitative/quantitative approaches to assess occupational exposures.
- Establishment of meta-analysis and pooled analysis to study aggregate evidence for associations of low magnitude.
- Improved approaches for studying the role of genetic mutations and gene-environment interactions: case-control, case-only, and kin-cohort methods.
- Multi-phase genome-wide association studies (GWAS) and bioinformatics tools.

Criteria to Establish Causality (Hill, 1965)

Most important:

Experimental evidence
Strength of association
Consistency
Temporality
Biologic gradient

Least important:

Coherence
Plausibility
Analogy
Specificity

EVIDENCE OF CARCINOGENICITY IN HUMANS

(International Agency for Research on Cancer, W.H.O.)

A study is interpreted as implying causality if:

> There is no identifiable positive bias
> Possibility of positive confounding was considered
> Association is unlikely to be due to chance alone
> There is a dose-response relationship

A study provides evidence of no association if:

> There is no identifiable negative bias
> Possibility of negative confounding was considered
> Possible effects of misclassification were weighed
> Has sufficient size to detect a weak association
> Latency was considered in the design

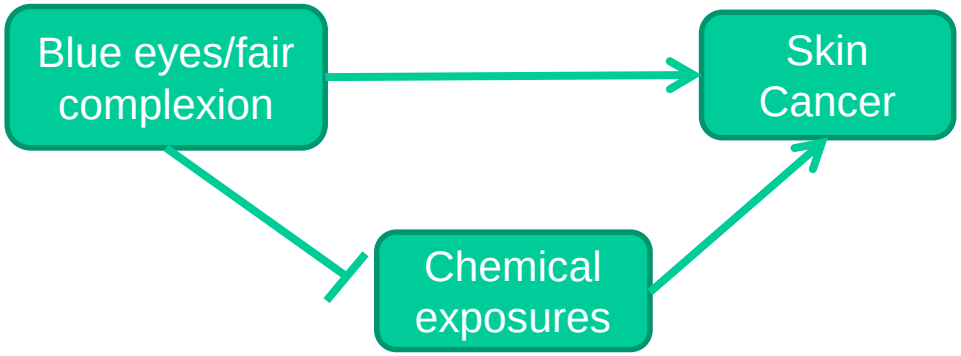
Hypothetical examples of biases and confounding

Positive Bias: A case-control study of in situ endometrial cancer and ERT: hormone users may be screened more frequently and thus have more lesions detected.

Negative Bias: A case-control study of alcohol and cancer where controls came from a hospital population: the latter has an over-representation of patients with digestive or systemic disorders related to alcohol.

Positive confounding: The relation between coffee drinking and pancreatic cancer without proper adjustment for smoking (Trichopoulos NEJM study described in Taubes 1995).

Negative confounding: A retrospective cohort study of skin cancer related to exposures among workers in an industrial setting without properly adjusting for ethnicity.



OVERALL EVALUATION OF CARCINOGENICITY
(International Agency for Research on Cancer, W.H.O.)

Group 1: *Exposure circumstance is carcinogenic to humans. (N=105)*

- Sufficient evidence of carcinogenicity in humans.
- Evidence less than sufficient in humans but sufficient in experimental animals and strong evidence that in exposed humans the agent acts through a relevant carcinogenic mechanism.

Group 2A: *Exposure circumstance is probably carcinogenic to humans. (N=66)*

- Limited evidence in humans but sufficient in experimental animals.
- Inadequate evidence in humans but sufficient in experimental animals and strong evidence that in exposed humans the agent acts through a relevant carcinogenic mechanism.

Group 2B: *Exposure circumstance is possibly carcinogenic to humans. (N=248)*

- Limited evidence in humans and less than sufficient evidence in experimental animals.
- Inadequate evidence in humans but limited evidence in experimental animals with supporting evidence from other relevant data.

Group 3: *Exposure circumstance not classifiable as to its carcinogenicity to humans. (N=515)*

- Evidence inadequate in humans and inadequate or limited in experimental animals.
- Evidence inadequate in humans and sufficient in experimental animals but carcinogenic mechanism in animals does not operate in humans.

Group 4: *The exposure circumstance is probably not carcinogenic to humans. (1)*

- Evidence suggesting lack of carcinogenicity in humans and in experimental animals.

EVALUATION OF CARCINOGENICITY
(U.S. Environmental Protection Agency)

- *Group A* *Human carcinogens*
  Sufficient evidence from epidemiologic studies

- *Group B* *Probable human carcinogens*
  Less than sufficient epidemiologic evidence but sufficient evidence from experimental animal studies
  - B1: Limited epidemiologic evidence
  - B2: Inadequate epidemiologic evidence

- *Group C* *Possible human carcinogens*
  Absence of epidemiologic data and at least one of:
  1. definite response in a single, well-conducted animal study
  2. marginal response in inadequately designed studies
  3. benign tumors only in animal studies and no response in in vitro assays of mutagenicity
  4. marginal response in a tissue with high rate of spontaneous tumor formation

- *Group D* *Not classified*
  Inadequate evidence of carcinogenicity

- *Group E* *No evidence of carcinogenicity*
  No epidemiologic evidence and no evidence in at least two adequate animal tests in different species

Corroboration of Epidemiologic Findings

A golden rule?

- Provides the necessary confidence for public health action
- Provides the knowledge base that serves as foundation for mechanistic studies

Corroboration of Epidemiologic Findings

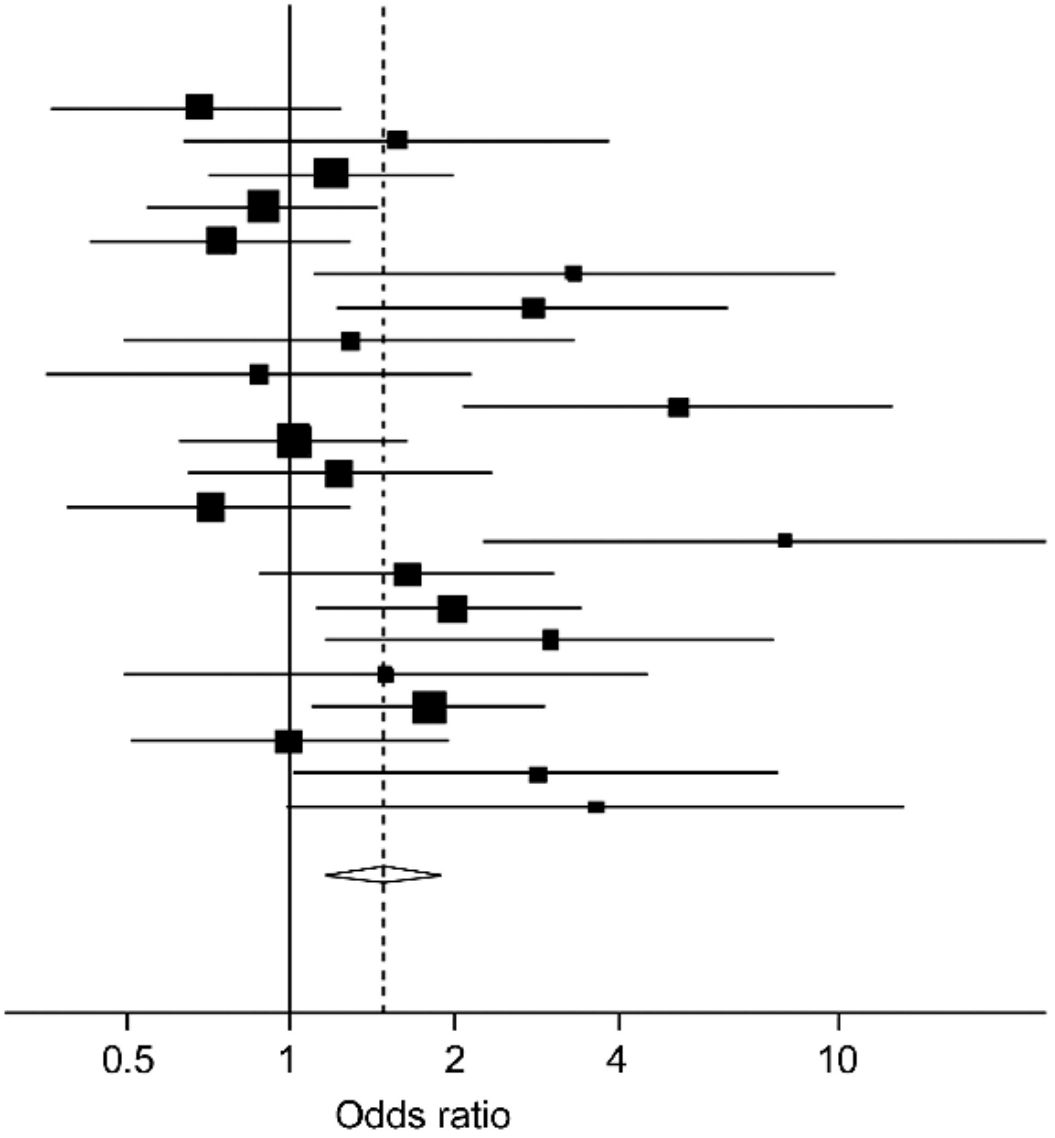
The downside: “epidemics” of repetition

- Newly discovered associations tend to lead to successive attempts at replicating the original findings
- Strong or moderate associations become clear with few replications
- Weak associations can only be examined with a large and diverse base of studies
- False associations may lead to a frivolous barrage of studies: “infectious” effect
- No stopping rules: replication of negative and positive findings will continue to be published for as long as there is interest

Association between p53 codon 72 polymorphism and squamous cell cervical cancers

STUDY	OR	95% CI
Rosenthal et al, 1998	0.68	0.4-1.3
Hayes et al, 1998	1.56	0.6-3.8
Josefsson et al, 1998	1.19	0.7-2.0
Hildesheim et al, 1998[a]	0.89	0.5-1.4
Sonoda et al, 1999	0.74	0.4-1.3
Zehbe et al, 1999[b]	3.32	1.1-9.9
Zehbe et al, 1999[c]	2.79	1.2-6.4
Giannoudis et al, 1999	1.29	0.5-3.3
Dybikowska et al, 2000	0.88	0.4-2.1
Dokianakis et al, 2000	5.07	2.1-12.0
Madeleine et al, 2000	1.02	0.6-1.6
van Duin et al, 2000	1.23	0.6-2.3
Tenti et al, 2000	0.71	0.4-1.3
Makni et al, 2000	8.00	2.2-28.5
Pegoraro et al, 2000	1.64	0.9-3.1
Zehbe et al, 2001[d]	1.97	1.1-3.4
Zehbe et al, 2001[e]	2.99	1.2-7.7
Gustafsson et al, 2001	1.50	0.5-4.5
Pegoraro et al, 2002	1.79	1.1-2.9
Bhattacharya et al, 2002	1.00	0.5-1.9
Arbel-Alon et al, 2002	2.83	1.0-7.8
Nagpal et al, 2002	3.64	1.0-13.3
ALL STUDIES (Random Effects)	1.48	1.2-1.9

Test for heterogeneity: $\chi^2(21df)=52$; p=0.0002



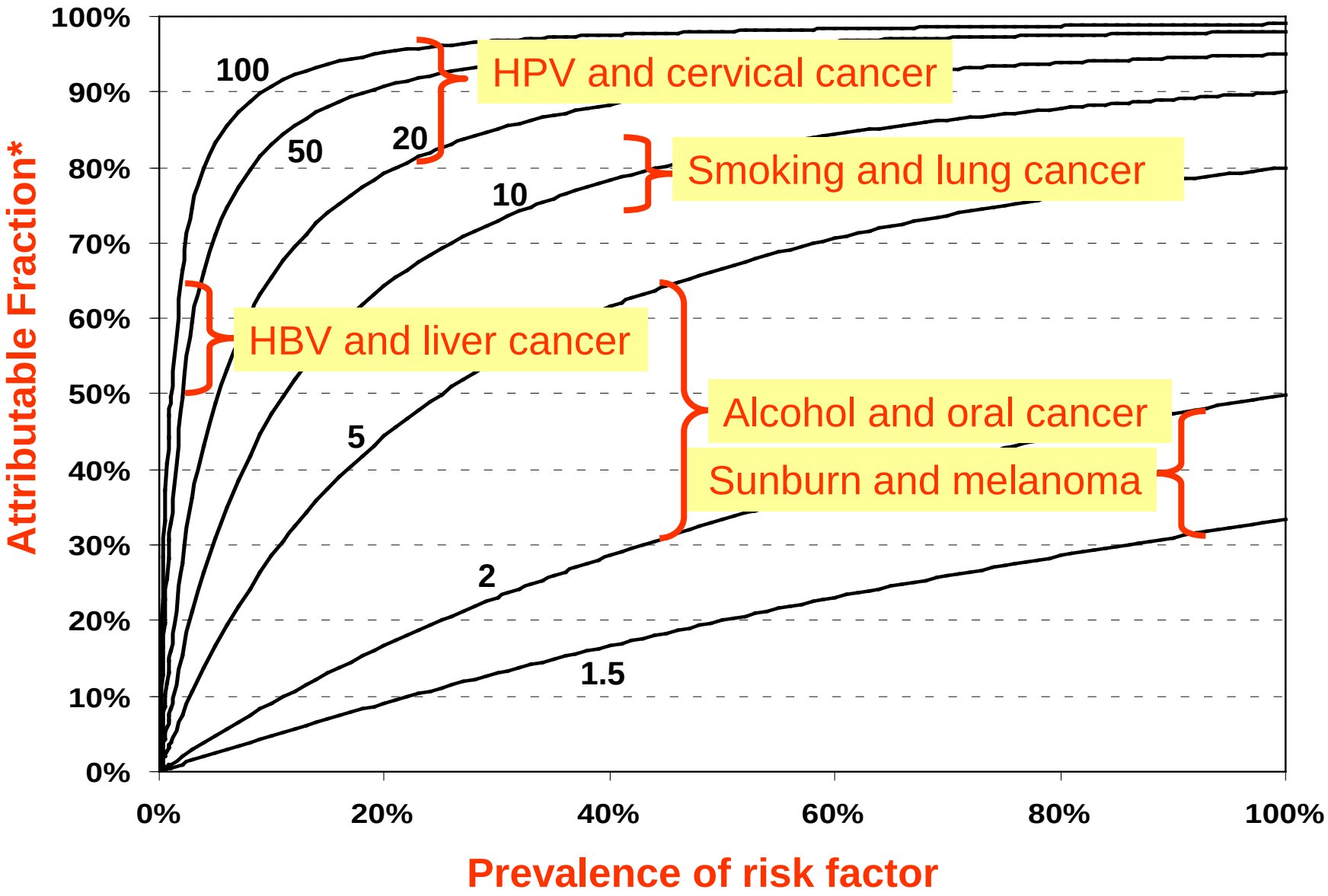
Koushik et al., CEBP 2004

Corroboration of Epidemiologic Findings

The downside: “epidemics” of repetition

- Genetic association studies have become more ambitious:
  - Early studies focused on one or a few candidate SNPs
  - Recent studies target many SNPs and haplotypes using high throughput platforms
- Solution: Bayesian approaches, e.g., false positive report probability *(Wacholder et al., JNCI 2004)*
  - FPRP: Probability of no association given a statistically significant finding for a putative association
  - Based on 3 quantities: prior probability that the association is true, p value for the finding, power of the study

Attributable fraction as a function of the RR and risk factor prevalence in the population *AF=P(RR-1)/[1+P(RR-1)]



Franco & Harper, Vaccine 2005

Proportion of cancers attributed to different factors

Factor	Estimate (%)	Range (%)
Tobacco	33	25 - 40
Diet	30	20 - 60
Infection: viral, bacterial, parasitic	16	7 - 23
Reproductive factors and hormones	7	5 - 10
Ionizing radiation	6	4 - 8
Heredity	5	2 - 8
Occupation	5	2 - 8
Obesity	4	1 - 5
Alcohol	3	2 - 4
UV light	1	0.5 - 1
Pollution	<1	<1 - 2
Medicines	<1	<1- 2
Food additives	<1	-2 - 1

Sources: Doll & Peto, 1981; 1996; Levine et al, 1989; Li et al., 1991; Pisani et al., 1997; Key et al., 1997; Parkin et al., 2006; Rushton et al., 2008; de Martel et al., 2012; Arnold et al., 2015

TOBACCO CONSUMPTION AND CANCER RISK

- **In-depth reviews:**
  IARC Monograph on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 38 (1986), Vol. 83 (2002), Vol. 100E (2012)
  U.S. Surgeon General's Reports: 1979, 1982, 1990

- **Sufficient evidence for a causal relation:**
  Mouth and pharynx
  Nasal cavities and nasal sinuses
  Esophagus (squamous cell, adenocarcinoma)
  Stomach
  Pancreas
  Liver
  Larynx
  Lung
  Kidney (renal cell carcinoma)
  Bladder and renal pelvis
  Uterine cervix
  Myeloid leukaemia
  Ovary (mucinous)

- **Evidence suggesting lack of carcinogenicity:**
  Thyroid
  Endometrium

- **Sufficient evidence for a causal role of parental smoking:**
  Hepatoblastoma in children
  Leukemia (acute lymphocytic)

Risks of male cigarette smokers for dying from lung cancer relative to nonsmokers, in some major cohort studies.

Country	No. of subjects in study	Daily no. of cigarettes	Relative risk*	Reference
USA	440 558	0 1-9 10-19 20-39 ≥ 40	1.0 4.6 7.5 13.1 16.6	Hammond (1966)
Japan	122 261	0 1-9 10-14 15-24 25-49 ≥ 50	1.0 1.9 3.5 4.1 4.6 5.7	Hirayama (1974)
Sweden	27 342	0 1-7 8-15 ≥ 16	1.0 2.1 8.0 12.6	Cederlöf *et al* (1975)
UK	34 440	0 1-14 15-24 ≥ 25	1.0 7.8 12.7 25.1	Doll & Peto (1976)

*** Ratio between the occurrence rate of cancer among smokers and that among nonsmokers.**

Source: Muir et al, 1990.

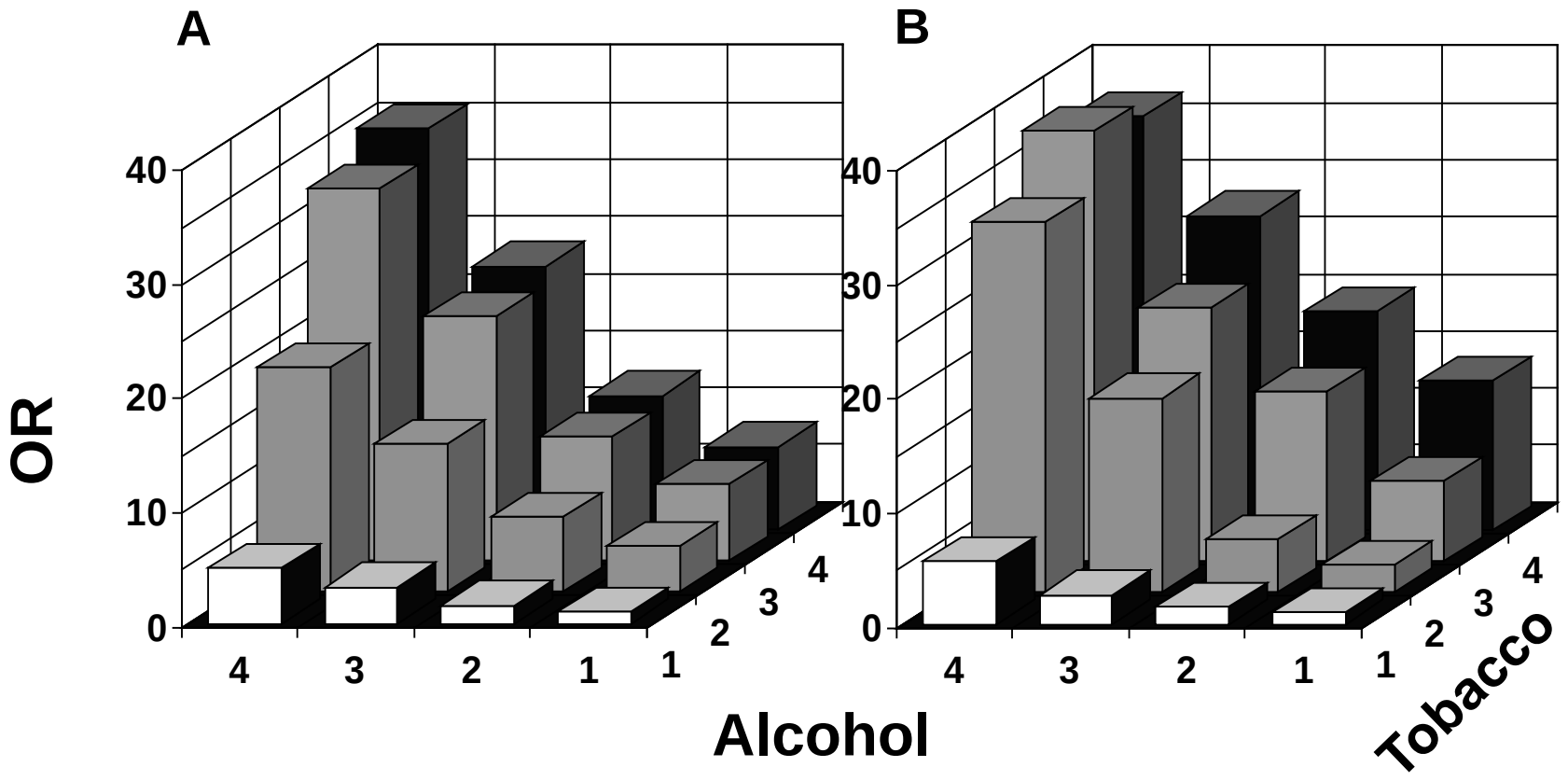
Lung cancer mortality ratios (RR) in ex-smokers of cigarettes, by number of years since stopping smoking[a] (Muir et al, 1990)

Study population	Time since stopping smoking (years)	RR	Reference
British doctors	1-4 5-9 10-14 ≥ 15 Current smoker	16.0 5.9 5.3 2.0 14.0	Doll & Peto (1976); Doll *et al*. (1980)
US veterans[b]	1-4 5-9 10-14 15-19 ≥ 20 Current smoker	18.8 7.7 4.7 4.8 2.1 11.3	Rogot & Murray (1980)
Japanese men	1-4 5-9 ≥ 10 Current smoker	4.7 2.5 1.4 3.8	Hirayama (1975)
Men aged 50 – 69 years in 25 US states (1-19 cigs/day)	< 1 1-4 5-9 > 10 Current smoker	7.2 4.6 1.0 0.4 6.5	Hammond *et al*. (1977)
Men aged 50 – 69 years in 25 US states (> 20 cigs/day)	< 1 1-4 5-9 > 10 Current smoker	29.1 12.0 7.2 1.1 13.7	Hammond *et al*. (1977)

Overall passive smoking-associated RR for lung cancer (Overall weighted average RR = 1.14, 95%CI: 1.00-1.30)

Study (first author)	Year	Place	Type of study[1]	Type of exposure	No. cases	Overall RR (95% CI)	Covariate adjustment	Gender
Wu	1985	USA	CC	home	29[2]	1.2 (0.5-3.3)	Age	female
Wu	1985	USA	CC	work	29[2]	1.3 (0.5-3.3)	Age	female
Dalager	1986	USA	CC	home	99	0.8 (0.5-1.3)	Age, sex, residence	NJ:males LA+TX:both
Humble	1987	USA	CC	home	28	2.6 (1.0-6.5)	Age, sex, race	both
Varela	1988	USA	CC	home	439	1.9	Age, sex, residence, previous smoking history (matching variables)	both?
Butler	1989	USA	COH	home	?	2.0 (0.4-8.8)	Age	female
Janerich	1990	USA	CC	home	191	1.1 (0.8-1.4)[3]	None?	both
Brownson	1992	USA	CC	home	431	0.8 (0.6-1.1)	Age, history of lung disease	female
Stockwell	1992	USA	CC	home	210	1.6 (1.1-2.4)[3]	Age, race, education	female
Fontham	1994	USA	CC	home, work, social	653	1.3 (1.0-1.6)	Age, race, residence, language, tobacco, education, fruits, vegetables, vitamin index, cholesterol, family Hx lung cancer, occupation	female

[1]CC: case-control, COH: cohort.
[2]Adenocarcinoma of the lung.
[3]Pooled weighted average of risks across all levels of smoking exposure.



ORs of upper aero-digestive tract cancer in southern Brazil according to joint exposure to tobacco and alcohol consumption. Results by conditional logistic regression (matching variables: age, sex, study location, and admission period) controlling for race, temperature of beverages, religion, use of a wood stove, and consumption of spicy foods.
Model A assumes independence of effects.
Model B assumes effect modification.
Levels of lifetime alcohol consumption: 1) <1; 2) 1-145; 3) 146-932; 4) >932 kgs; levels of cumulative tobacco exposure: 1) never smoked; 2) 1-25; 3) 26-60; 4) >60 pack-years.

Source: Schlecht et al., Am J Epidemiol, 1999

VIRUSES IMPLICATED AS CAUSES OF HUMAN CANCER

Virus	Group (genome)	Convincingly linked to	Possibly implicated in
Hepatitis B virus (HBV)	Hepadnavirus (3 Kb DNA)	Liver	NH lymphoma (NHL)
Hepatitis C virus (HCV)	Flavivirus (10 Kb RNA)	Liver, NHL	Cryoglobulinemia, monoclonal gammopathy
Human papillomavirus (HPV)	Papillomaviridae (8 Kb DNA)	Cervix, anogenital, oropharyngeal, skin	
Simian virus 40 (SV 40) (also JC and BK viruses)	Polyomaviridae (5 Kb DNA)		Mesothelioma, CNS, osteosarcoma, NHL (SV40?)
Merkel Cell Virus (MCV)	Polyomaviridae (5 Kb DNA)	Merkel Cell Carcinoma	
Human T Lymphotropic viruses (HTLV)	Retrovirus (10 Kb RNA)	T-cell leukemias	
Human immunodeficiency virus (HIV)	Retrovirus (10 Kb RNA)	AIDS-associated malignancies	
Epstein-Barr virus (EBV, HHV-4)	Gamma-herpesvirus (~170 Kb DNA)	NHL, nasopharynx	Hodgkin’s lymphoma, breast, stomach
Herpes simplex virus 2 (HSV-2, HHV-2)	Alpha-herpesvirus (~150 Kb DNA)		Cervix (cofactor?)
Cytomegalovirus (CMV, HHV-5)	Beta-herpesvirus (~230 Kb DNA)		Cervix (cofactor?)
Human herpesvirus 8 (KSHV, HHV-8)	Gamma-herpesvirus (~140 Kb DNA)	Kaposi’s sarcoma	Castleman's disease, Pleural effusion lymphoma
Human herpesvirus 6 (HHV-6)	Beta-herpesvirus (~160 Kb DNA)		NHL (?)

BACTERIA IMPLICATED AS CAUSES OF HUMAN CANCER

- *Helicobacter pylori*: stomach, MALT lymphoma
- *Chlamydia trachomatis*: cervix
- *Chlamydia pneumoniae*: lung
- *Tropheryma whippeli* (Whipple disease bacillus): Intestinal lymphomas
- *Fusobacterium fusiforme* and *Borrelia vincentii*: skin SC carcinomas associated with tropical phagedenic ulcer

EUKARYOTIC AGENTS IMPLICATED AS CAUSES OF CANCER

Protozoa

- *Plasmodium falciparum*: African BL

Metazoan parasites

- *Schistosoma haematobium: bladder (Africa)*
- *Schistosoma japonicum: rectum (China)*
- *Clonorchis sinensis: liver cholangiocarcinoma (SE Asia)*
- *Opistorchis viverrini: liver cholangiocarcinoma (SE Asia)*

MECHANISMS OF MICROBIAL CARCINOGENESIS

Direct (via genome integration or interference with genetic control of cellular proliferation)

- Agent necessary in early and late stages: HPV, HBV, EBV
- Agent necessary in early but not late stages: HSV, CMV

Indirect (influence on immune response, chronic inflammation)

- Decreased immunosurveillance: condylomas in AIDS
- Polyclonal proliferation of initiated cells: lymphomas in AIDS, malaria in Burkitt's lymphoma
- Chronic irritation and inflammation: *H. pylori, C. trachomatis*, helminthic infections

Koch's Postulates as Standard of Evidence of Causation in Infectious Diseases (1890)

(i) The parasite occurs in every case of the disease in question and under circumstances which can account for the pathological changes and clinical course of the disease

(ii) The parasite occurs in no other disease as a fortuitous and nonpathogenic parasite

(iii) After being fully isolated from the body and repeatedly grown in pure culture, the parasite can induce the disease anew

Some reviewers have added a fourth postulate: the requirement to reisolate the microbe from the experimentally inoculated host

Fredricks and Relman, 1996

Criteria used in attributing causality to candidate microbial agents

Evans (1976)
Antibody to the agent is regularly absent prior to the disease and exposure to the agent
Antibody to the agent regularly appears during illness and includes both immunoglobulins G and M
Presence of antibody to the agent predicts immunity to the disease associated with infection by the agent
Absence of antibody to the agent predicts susceptibility to both infection and the disease produced by the agent
Antibody to no other agent should be similarly associated with the disease unless a cofactor in its production

Evans and Mueller (1990)
Geographic distributions of viral infection and tumor should coincide
Presence of viral marker should be higher in cases than in controls
Incidence of tumor should be higher in those with the viral marker than in those without it
Appearance of viral marker should precede the tumor
Immunization with the virus should decrease the subsequent incidence of the tumor

Fredricks and Relman (1996)
Nucleic acid belonging to putative pathogen should be present in most cases and preferentially in organs known to be diseased
Few or no copy numbers should occur in hosts or tissues without disease
Copy number should decrease or become undetectable with disease regression (opposite with relapse or progression)
Detection of DNA sequence should predate disease
Microorganism inferred from the sequence should be consistent with the biological characteristics of that group of organisms
Tissue-sequence correlates should be sought at the cellular level using in situ hybridization
Above should be reproducible

Adapted from Franco et al., Sem Ca Biol 2004

Evaluation of Carcinogenicity to Humans: IARC Monograph Series (1)

Infectious Agent	Volume, year	Evaluation	Group
Hepatitis B Virus (HBV) (chronic infection)	59, 1994	Carcinogenic	1
Hepatitis C Virus (HCV) (chronic infection)	59, 1994	Carcinogenic	1
Hepatitis D Virus (HDV)	59, 1994	Not classifiable	3
Schistosoma haematobium	61, 1994	Carcinogenic	1
Opistorchis viverrini	61, 1994	Carcinogenic	1
Clonorchis sinensis	61, 1994	Probably carcinogenic	2A
Schistosoma japonicum	61, 1994	Possibly carcinogenic	2B
S. mansoni	61, 1994	Not classifiable	3
O. felineus	61, 1994	Not classifiable	3
Helicobacter pylori	61, 1994	Carcinogenic	1
Human papillomavirus (HPV) types 16 and 18	64, 1995	Carcinogenic	1
HPVs types 31 and 33	64, 1995	Probably carcinogenic	2A
HPVs, other types (except 6/11)	64, 1995	Possibly carcinogenic	2B
Human Immunodeficiency Virus (HIV) type 1	67, 1996	Carcinogenic	1
Human T Lymphotropic Virus (HTLV) type I	67, 1996	Carcinogenic	1
HTLV-II	67, 1996	Not classifiable	3
HIV-2	67, 1996	Possibly carcinogenic	2B
Epstein-Barr Virus (EBV)	70, 1997	Carcinogenic	1
Human Herpesvirus (HHV) type 8	70, 1997	Probably carcinogenic	2A

Evaluation of Carcinogenicity to Humans: IARC Monograph Series (2)

Infectious Agent	Volume, year	Evaluation	Group
HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66	90, 2007	Carcinogenic	1
HPVs 6, 11	90, 2007	Possibly carcinogenic	2B
HPV genus Beta	90, 2007	Possibly carcinogenic	2B
Malaria (*P. falciparum*)	104, 2014	Probably carcinogenic	2A
JC Virus (*polyomavirus*)	104, 2014	Possibly carcinogenic	2B
SV40 *polyomavirus*	104, 2014	Not classifiable	3
BK polyomavirus	104, 2014	Possibly carcinogenic	2B
Merkel cell vírus (MCV) (*polyomavirus*)	104, 2014	Probably carcinogenic	2A

Viruses re-assessed by the IARC Monograph Working Group (to be published in Vol. 100B, 2009)

Group 1 agent	Cancers for which there is sufficient evidence in humans	Other sites with limited evidence in humans	Established mechanistic events
EBV	Nasopharyngeal carcinoma, Burkitt's lymphoma, immune-suppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin's lymphoma	Gastric carcinoma,* lympho-epithelioma-like carcinoma*	Cell proliferation, inhibition of apoptosis, genomic instability, cell migration
HBV	Hepatocellular carcinoma	Cholangiocarcinoma,* non-Hodgkin lymphoma*	Inflammation, liver cirrhosis, chronic hepatitis
HCV	Hepatocellular carcinoma, non-Hodgkin lymphoma*	Cholangiocarcinoma*	Inflammation, liver cirrhosis, liver fi brosis
KSHV	Kaposi's sarcoma,* primary effusion lymphoma*	Multicentric Castleman's disease*	Cell proliferation, inhibition of apoptosis, genomic instability, cell migration
HIV-1	Kaposi's sarcoma, non-Hodgkin lymphoma, Hodgkin's lymphoma,* cancer of the cervix,* anus,* conjunctiva*	Cancer of the vulva,* vagina,* penis,* non-melanoma skin cancer,* hepatocellular carcinoma*	Immunosuppression (indirect action)
HPV-16	Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil	Cancer of the larynx	Immortalisation, genomic instability, inhibition of DNA damage response, anti-apoptotic activity
HTLV-1	Adult T-cell leukaemia and lymphoma		Immortalisation and transformation of T cells

Adapted from: Bouvard et al., Lancet Oncol. Vol 10 April 2009; *Newly identified link between virus and cancer

Bacteria and parasites re-assessed by the IARC Monograph Working Group (to be published in Vol. 100B, 2009)

Group 1 agent	Cancers for which there is sufficient evidence in humans	Other sites with limited evidence in humans	Established mechanistic events
H. pylori	Non-cardia gastric carcinoma, low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma*		Inflammation, oxidative stress, altered cellular turnover and gene expression, methylation, mutation
C. sinensis	Cholangiocarcinoma*		
O. viverrini	Cholangiocarcinoma		Inflammation, oxidative stress, cell proliferation
S. haematobium	Urinary bladder cancer		Inflammation, oxidative stress

Adapted from: Bouvard et al., Lancet Oncol. Vol 10 April 2009; *Newly identified link between agent and cancer

HPV types re-assessed by the IARC Monograph Working Group (to be published in Vol. 100B, 2009)

IARC Group	HPV types	Comments
Alpha HPV types		
1	16	Most potent HPV type, known to cause cancer at several sites
1	18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Sufficient evidence for cervical cancer
2A	68	Limited evidence in humans and strong mechanistic evidence for cervical cancer
2B	26, 53, 66, 67, 70, 73, 82	Limited evidence in humans for cervical cancer
2B	30, 34, 69, 85, 97	Classified by phylogenetic analogy to HPV types with sufficient or limited evidence in humans
3	6, 11	
Beta HPV types		
2B	5 and 8	Limited evidence for skin cancer in patients with epidermodysplasia verruciformis
3	Other beta and gamma types	

Adapted from: Bouvard et al., Lancet Oncol. Vol 10 April 2009

IARC estimates of new cancer cases attributable to infections in 2008*

Agent	Developing regions	Developed regions	World	Relative to all cancers
Hepatitis B and C viruses	520,000 (32.0%)	80,000 (19.4%)	600,000 (29.5%)	4.72%
Human papillomavirus	490,000 (30.2%)	120,000 (29.2%)	610,000 (30.0%)	4.80%
Helicobacter pylori	470,000 (28.9%)	190,000 (46.2%)	660,000 (32.5%)	5.20%
Epstein-Barr virus	96,000 (5.9%)	16,000 (3.9%)	110,000 (5.4%)	0.87%
Human herpes virus type 8	39,000 (2.4%)	4,100 (1.0%)	43,000 (2.1%)	0.34%
Human T-cell lymphotropic virus type 1	660 (0.0%)	1,500 (0.4%)	2,100 (0.1%)	0.02%
Opisthorchis viverrini and *Clonorchis sinensis*	2,000 (0.1%)	0 (0.0%)	2,000 (0.1%)	0.02%
Schistosoma haematobium	6,000 (0.4%)	0 (0.0%)	6,000 (0.3%)	0.05%
All agents	1,600,000 (100.0%)	410,000 (100.0%)	2,010,000 (100.0%)	**16.1%**

* De Martel et al., Lancet Oncol 2012;13:607-15

IARC estimates of new cancer cases attributable to infections in 2008*

Region	New Cases	New Cases Attributable to Infection	Population Attributable Fraction
Sub-Saharan Africa	550 000	180 000	32·7%
North Africa and west Asia	390 000	49 000	12·7%
India	950 000	200 000	20·8%
Other central Asia	470 000	81 000	17·0%
China	2 800 000	740 000	26·1%
Japan	620 000	120 000	19·2%
Other east Asia	1 000 000	230 000	22·5%
Latin America	910 000	150 000	17·0%
North America	1 600 000	63 000	4·0%
Europe	3 200 000	220 000	7·0%
Australia & New Zealand	130 000	4200	3·3%
Other Oceania	8800	1600	18·2%
More developed regions	**5 600 000**	**410 000**	**7·4%**
Less developed regions	**7 100 000**	**1 600 000**	**22·9%**
World	**12 700 000**	**2 000 000**	**16·1%**
More developed: Japan, N. America, Europe, Australia, New Zealand Less developed: remaining regions			

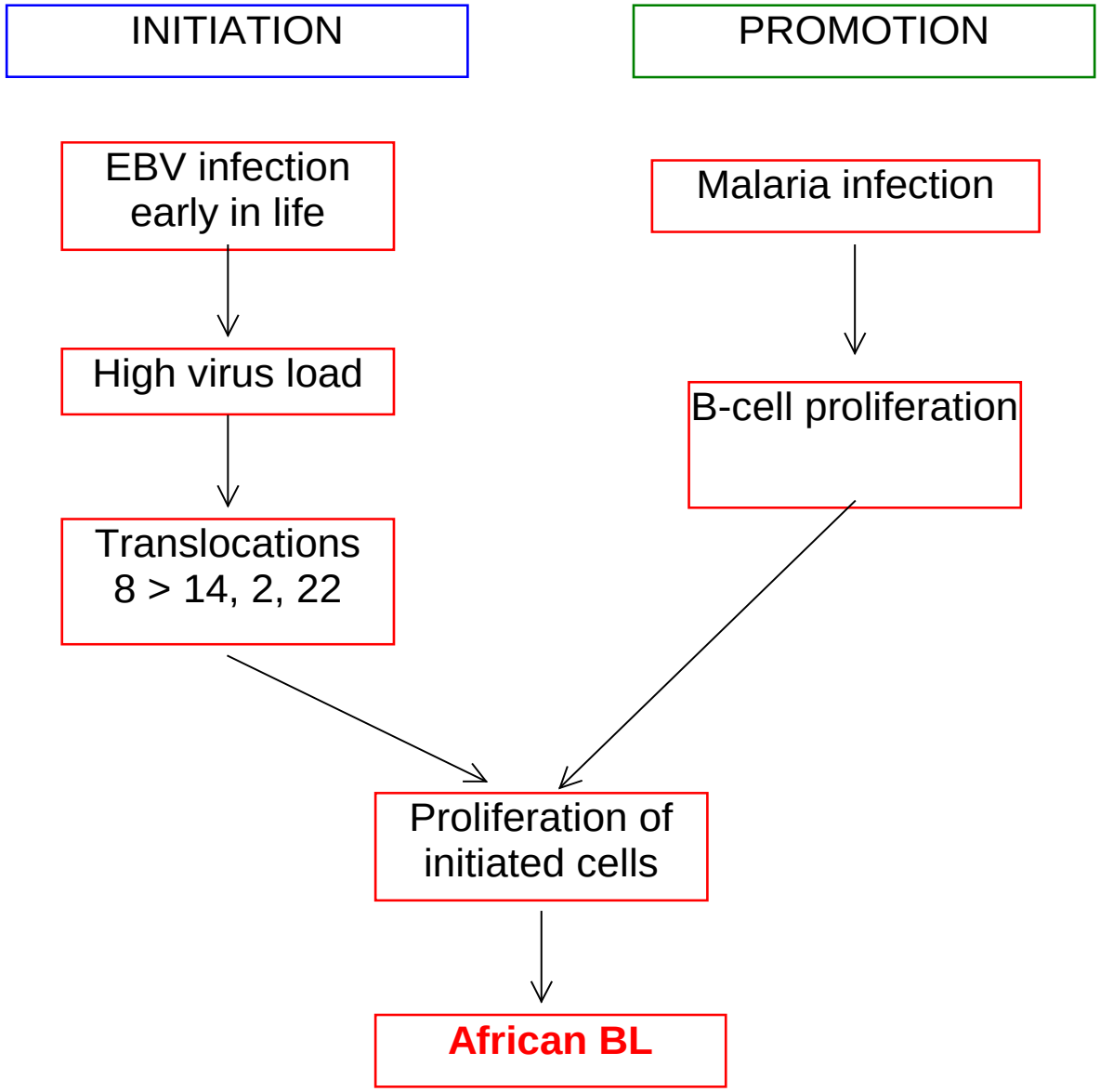
* De Martel et al., Lancet Oncol 2012;13:607-15

Association between HBsAg and HCC in prospective studies

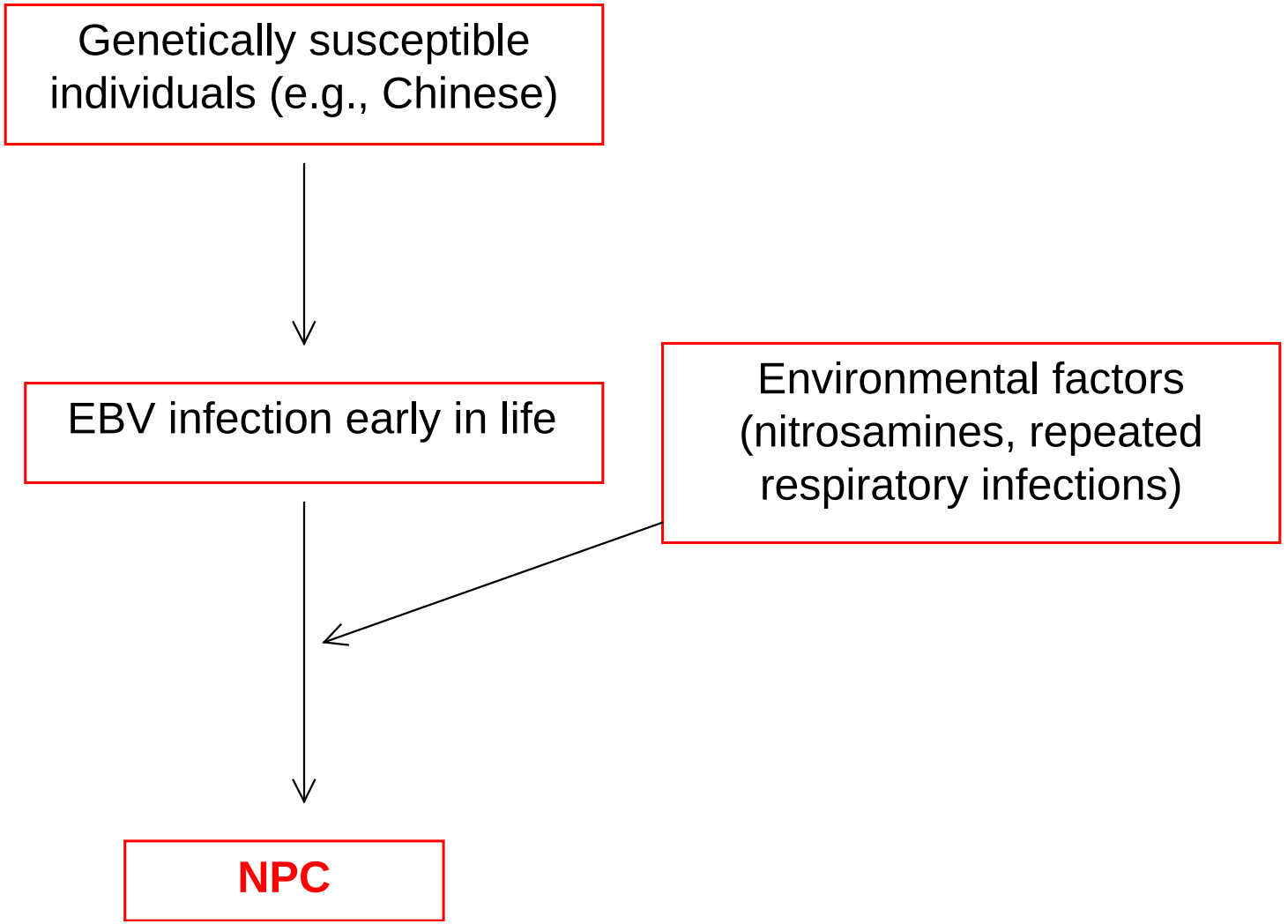
(Pooled RR = 11.61, 95%CI: 9.8 - 13.7)

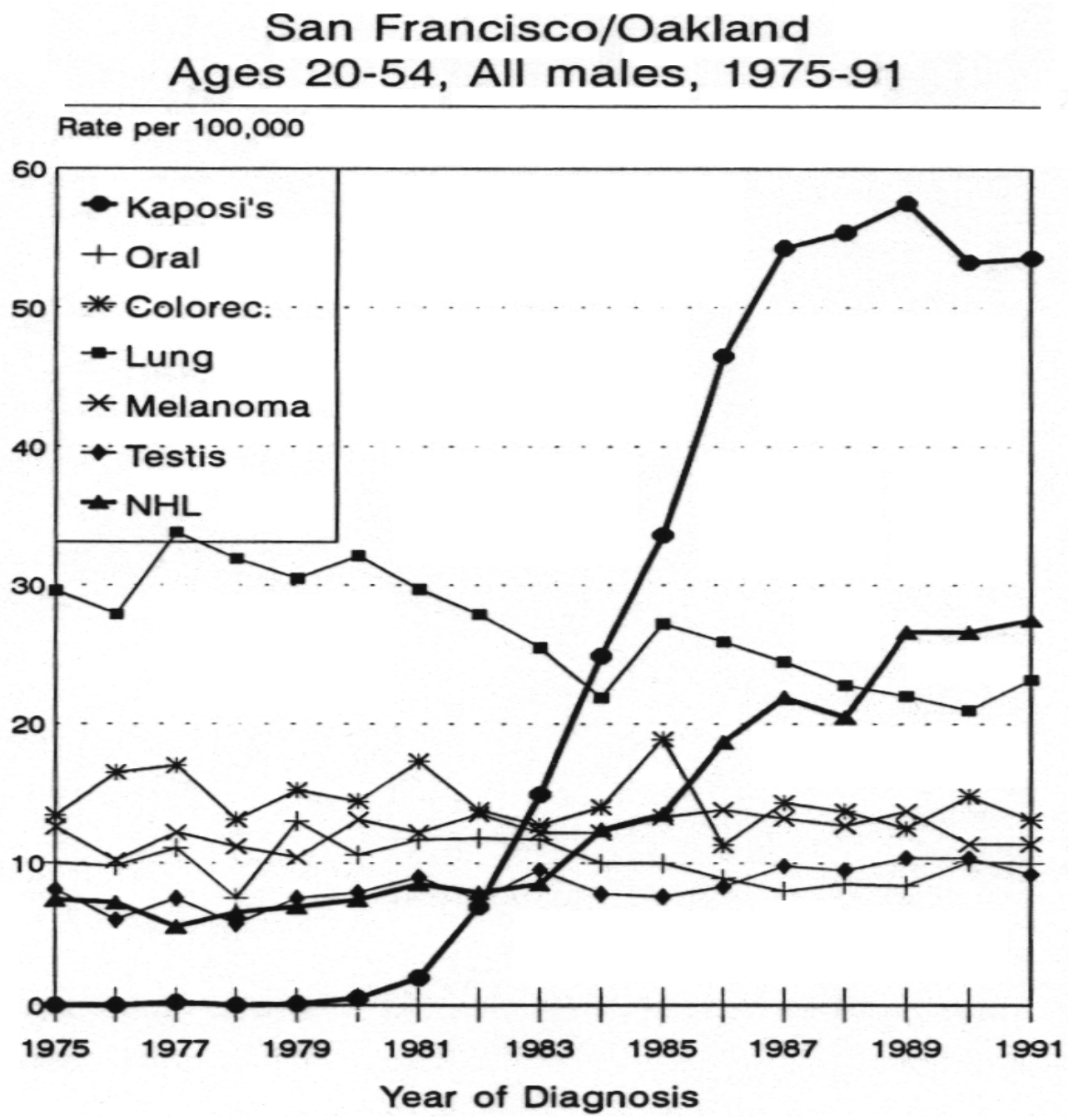
Study	Year	Region	RR	95% CI	
Prince & Alcabes	1982	USA	10	2.7	26
Oshima et al.	1984	Japan	6.6	4	10
Fukao	1985	Japan	30	6	88
Tu et al.	1985	China	6.7	4.2	11
Tokudome et al.	1987	Japan	5.6	1.5	14
Dodd & Nath	1987	USA	27	10	39
Tokudome et al.	1988	Japan	7.3	4.1	12
Ding et al	1988	China	5.3	3.8	7.2
Sakuma et al	1988	Japan	30	1	77
Sakuma et al	1988	Japan	21	9.6	40
Yeh et al	1989	China	39	16	117
McMahon et al.	1990	USA	148	59	305
Beasley & Hwang	1991	China	103	57	205
Ross et al.	1992	China	8.5	2.8	26
Hall et al.	1985	UK	42	13	98

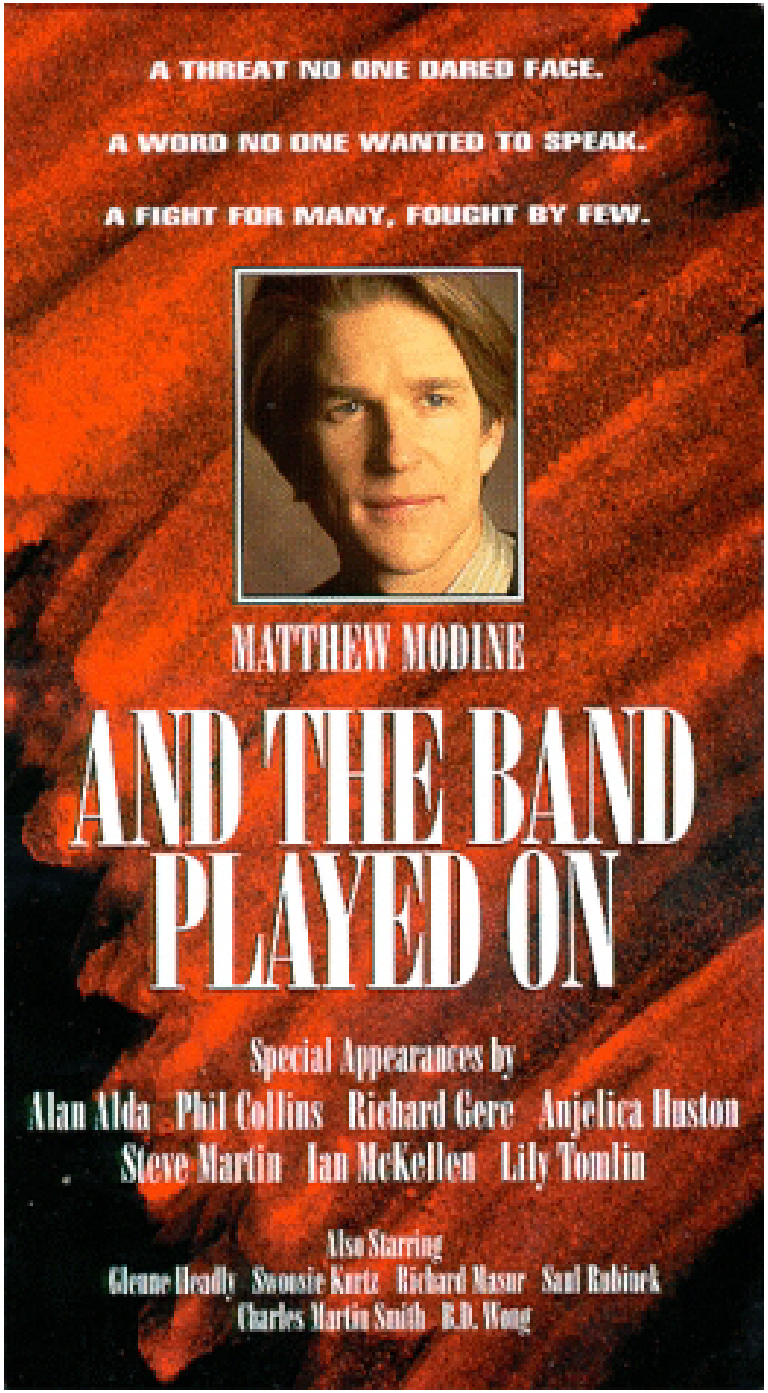
Etiologic model for EBV in Burkitt's lymphoma



Etiologic model for EBV in nasopharyngeal carcinoma




San Francisco/Oakland
Ages 20-54, All males, 1975-91
Rate per 100,000
60
50
40
30
20
10
0
Kaposi's
Oral
Colorec.
Lung
Melanoma
Testis
NHL
1975
1977
1979
1981
1983
1985
1987
1989
1991
Year of Diagnosis

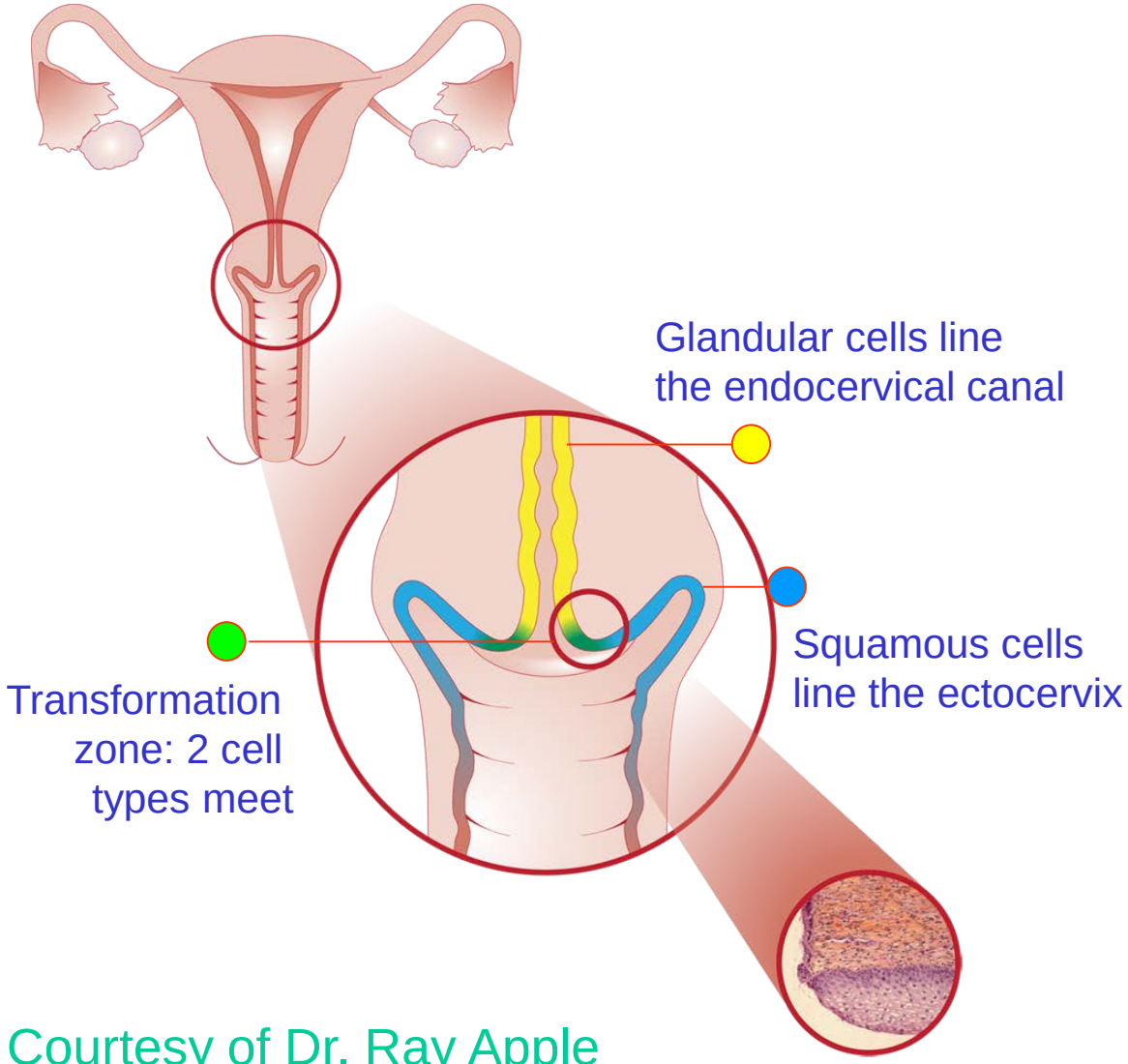


And the band played on

Cast:

Matthew Modine ... Dr. Don Francis
Alan Alda ... Dr. Robert Gallo
Patrick Bauchau ... Dr. Luc Montagnier
Nathalie Baye ... Dr. Françoise Barre
Christian Clemenson ... Dr. Dale Lawrence
Phil Collins ... Eddie Papasano
Alex Courtney ... Dr. Mika Popovic
David Dukes ... Dr. Mervyn Silverman
Richard Gere ... The Choreographer
Ronald Guttman ... Dr. Jean-Claude Chermann
Glenne Headly ... Dr. Mary Guinan
Anjelica Huston ... Dr. Betsy Reisz
Ken Jenkins ... Dr. Dennis Donohue
Richard Jenkins ... Dr. Marc Conant
Steve Martin ... The Brother
Richard Masur ... William W. Darrow, PhD
Dakin Matthews ... Congressman Phil Burton
Ian McKellen ... Bill Kraus
Peter McRobbie ... Dr. Max Essex
Saul Rubinek ... Dr. Jim Curran
Charles Martin Smith ... Dr. Harold Jaffe
Lily Tomlin ... Dr. Selma Dritz
B.D. Wong ... Kico Govantes
Neal Benari ... Dr. Tom Spira

Two types of cervical cancer

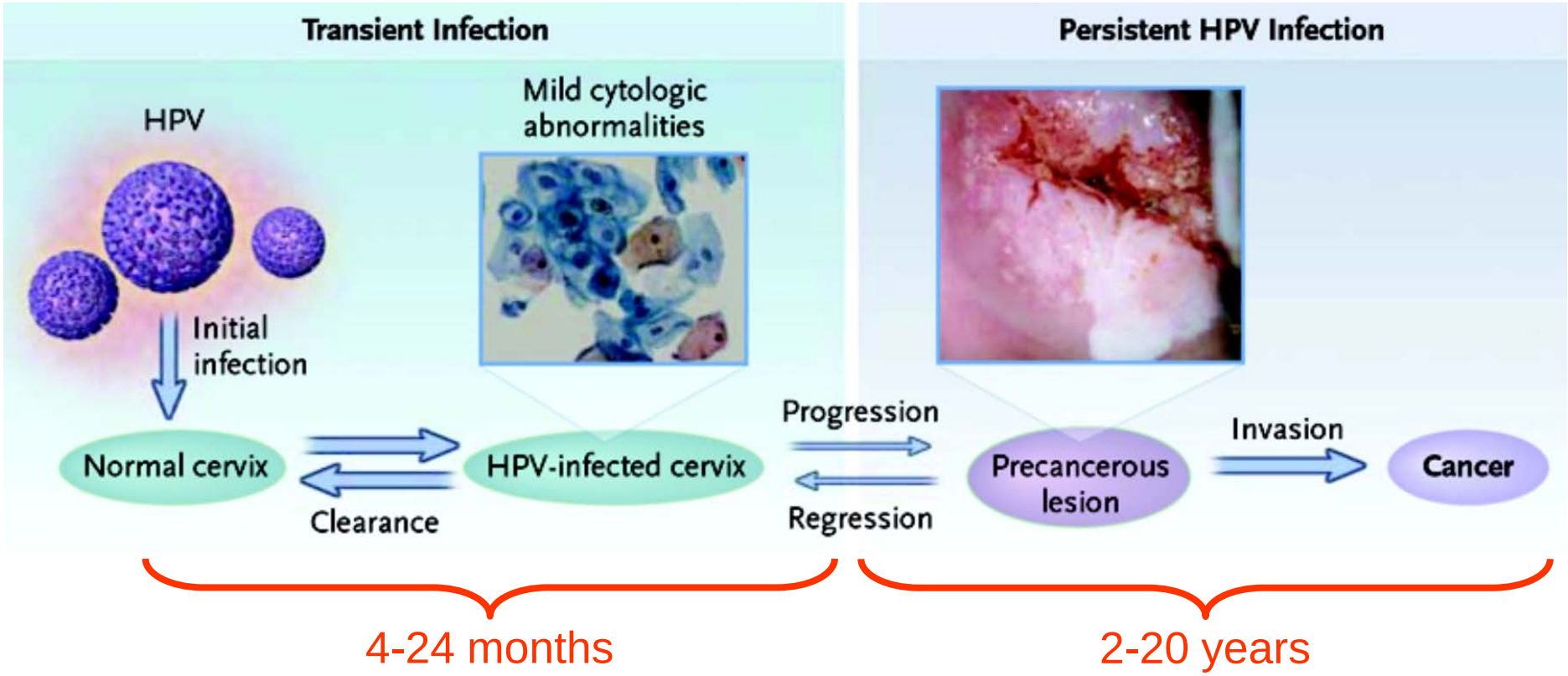


Courtesy of Dr. Ray Apple

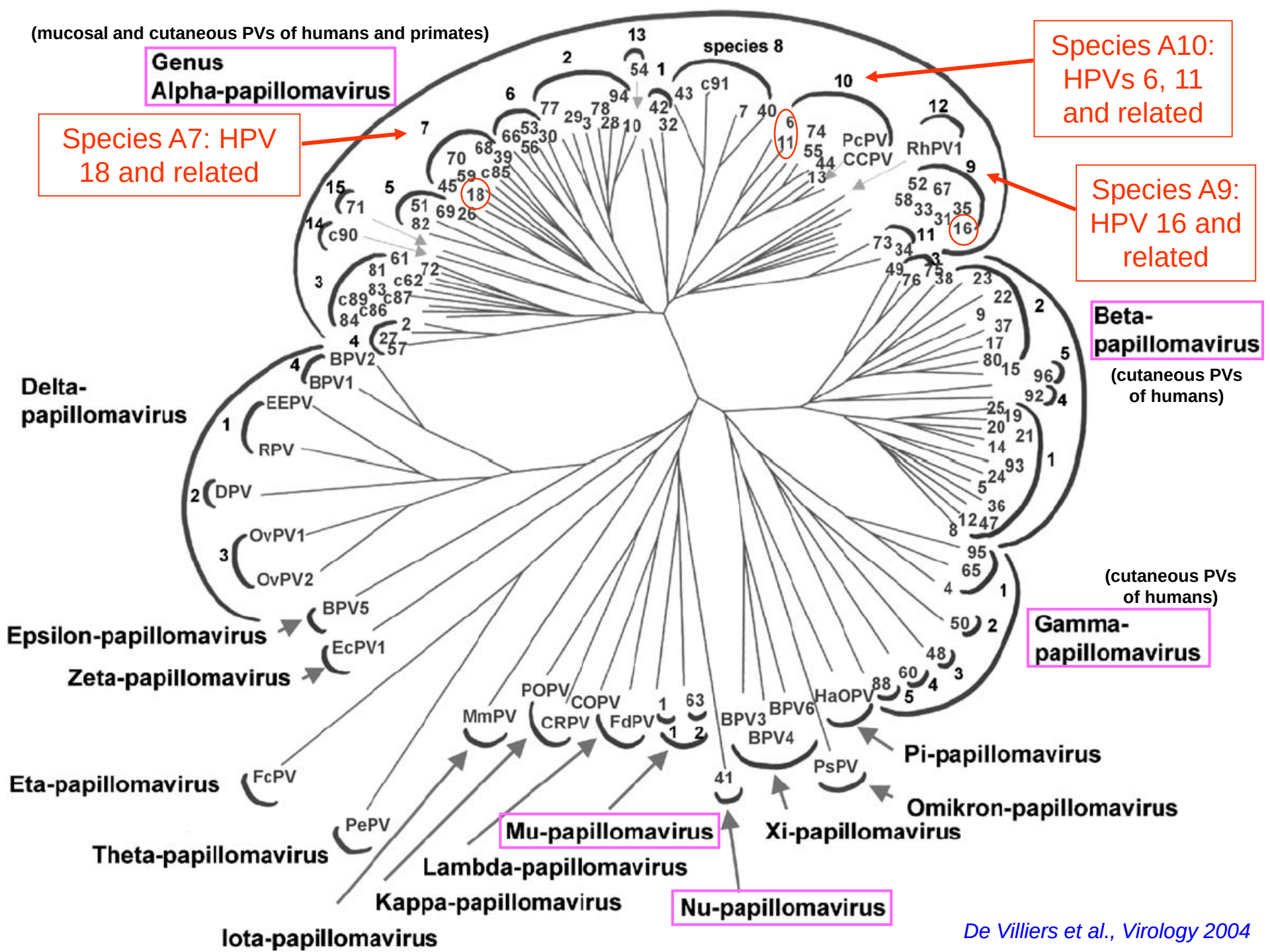
- Squamous cell carcinomas: 75%-80% of all cervical cancers.
- Adenocarcinomas: 20%-25% and incidence continues to increase.

Natural history of HPV infection and cervical carcinogenesis

Cofactors: **Host** (polymorphisms in HLA and other genes), **behavioural** (smoking), **hormonal/reproductive** (OC use, parity, IGF), **STI-related** (HSV, Chlamydia), **nutritional**, **immunosuppression** (HIV, transplantation), **HPV-related** (variants)



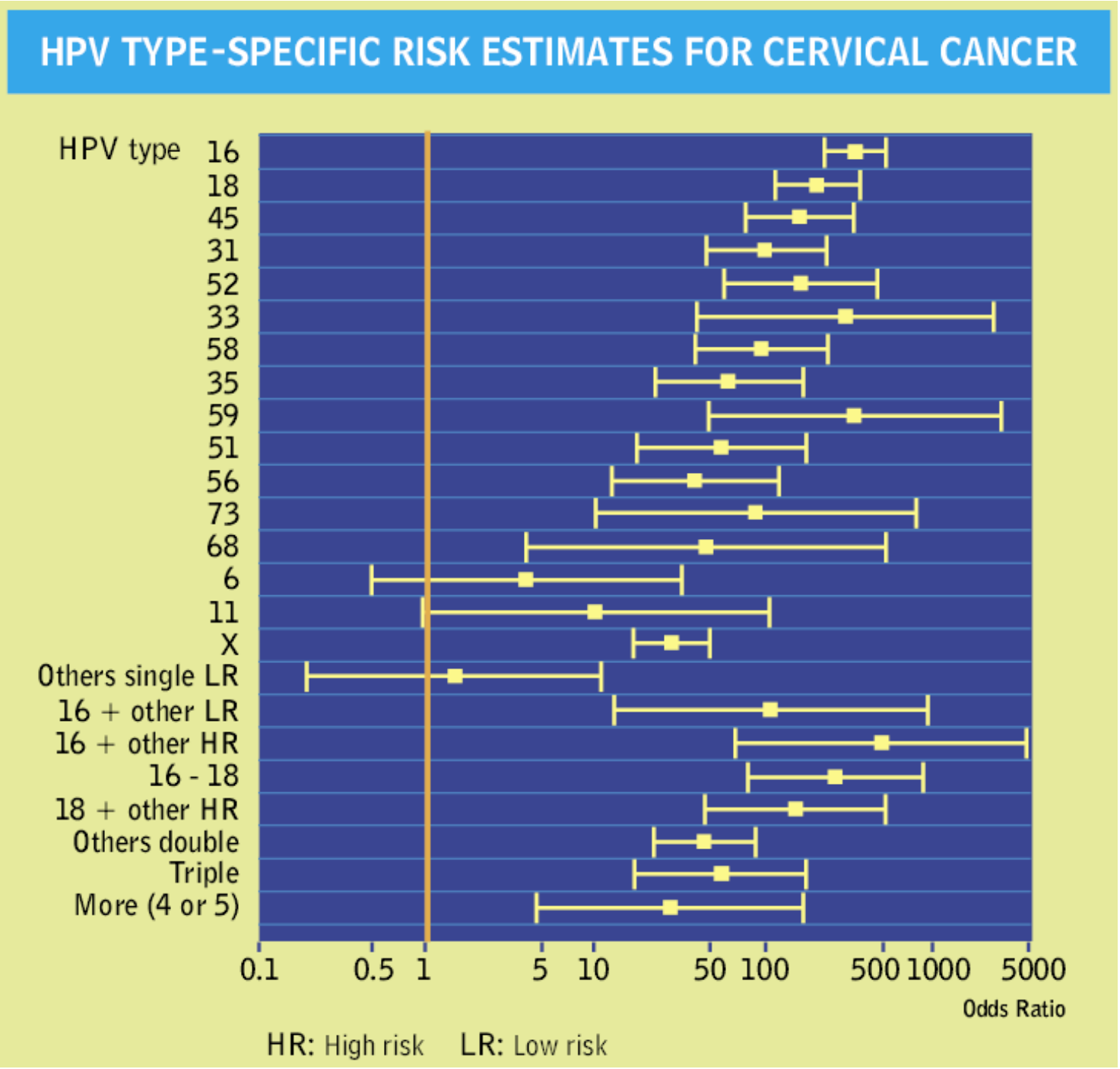
Adapted from: Wright and Schiffman, NEJM 2003; Franco and Harper, Vaccine 2005


(mucosal and cutaneous PVs of humans and primates)
Genus Alpha-papillomavirus
Species A7: HPV 18 and related
Species A10: HPVs 6, 11 and related
Species A9: HPV 16 and related
species 8
PcPV
CCPV
RhPV1
Beta-papillomavirus
(cutaneous PVs of humans)
Delta-papillomavirus
BPV2
BPV1
EEPV
RPV
DPV
OvPV1
OvPV2
Gamma-papillomavirus
(cutaneous PVs of humans)
Epsilon-papillomavirus
BPV5
EcPV1
Zeta-papillomavirus
Eta-papillomavirus
FcPV
Theta-papillomavirus
PePV
Iota-papillomavirus
Kappa-papillomavirus
Lambda-papillomavirus
Mu-papillomavirus
Nu-papillomavirus
Xi-papillomavirus
Omikron-papillomavirus
Pi-papillomavirus
MmPV
POPV
CRPV
COPV
FdPV
BPV3
BPV4
BPV6
HaOPV
PsPV
De Villiers et al., Virology 2004

Relative Risk estimates from the pool of IARC case-control studies:

Muñoz et al., NEJM 2003

Graph kindly provided by the Editors of HPV Today



MECHANISMS OF CARCINOGENESIS FOR DIET

- ***Direct ingestion of carcinogens***

  ⇒ Carcinogens in natural foodstuffs (silica fiber, bracken fern)
  ⇒ Carcinogens produced by cooking (BP, PAHs in charcoal-broiled meats)
  ⇒ Carcinogens produced in stored food by microorganisms (aflatoxins)

- ***Carcinogens formed in the body***

  ⇒ Carcinogens from natural foods (nitrites+amines->nitrosamines, prevented by antioxidants)
  ⇒ Altered intake/excretion (hi fat+hi meat->increase in bile acids->colon ca)
  ⇒ Altered bacterial flora (cholesterol+bile acids->bacteria->carcinogens)

- ***Transport of carcinogens***

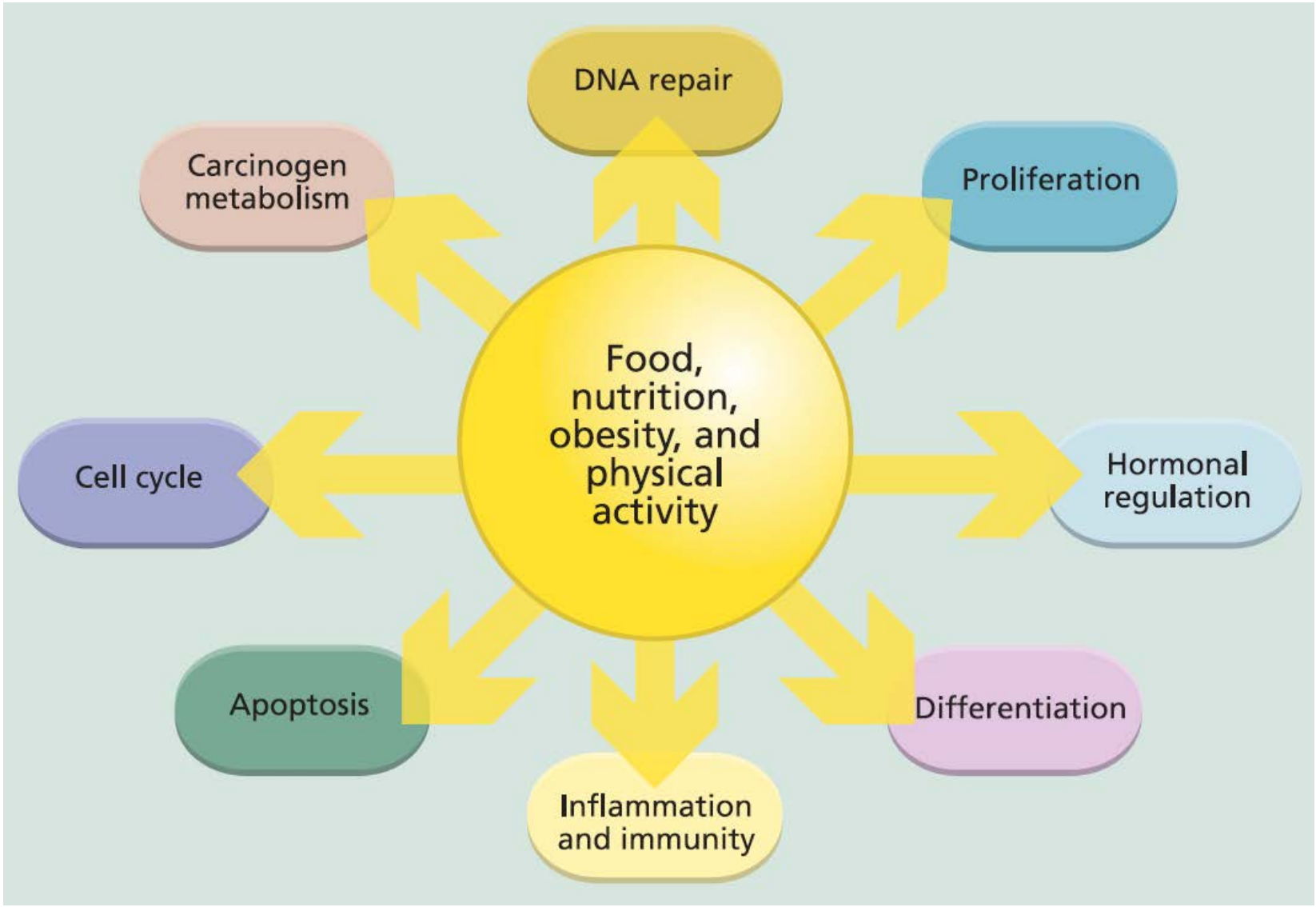
  ⇒ Effect of dilution or adsorption of carcinogens (fiber)

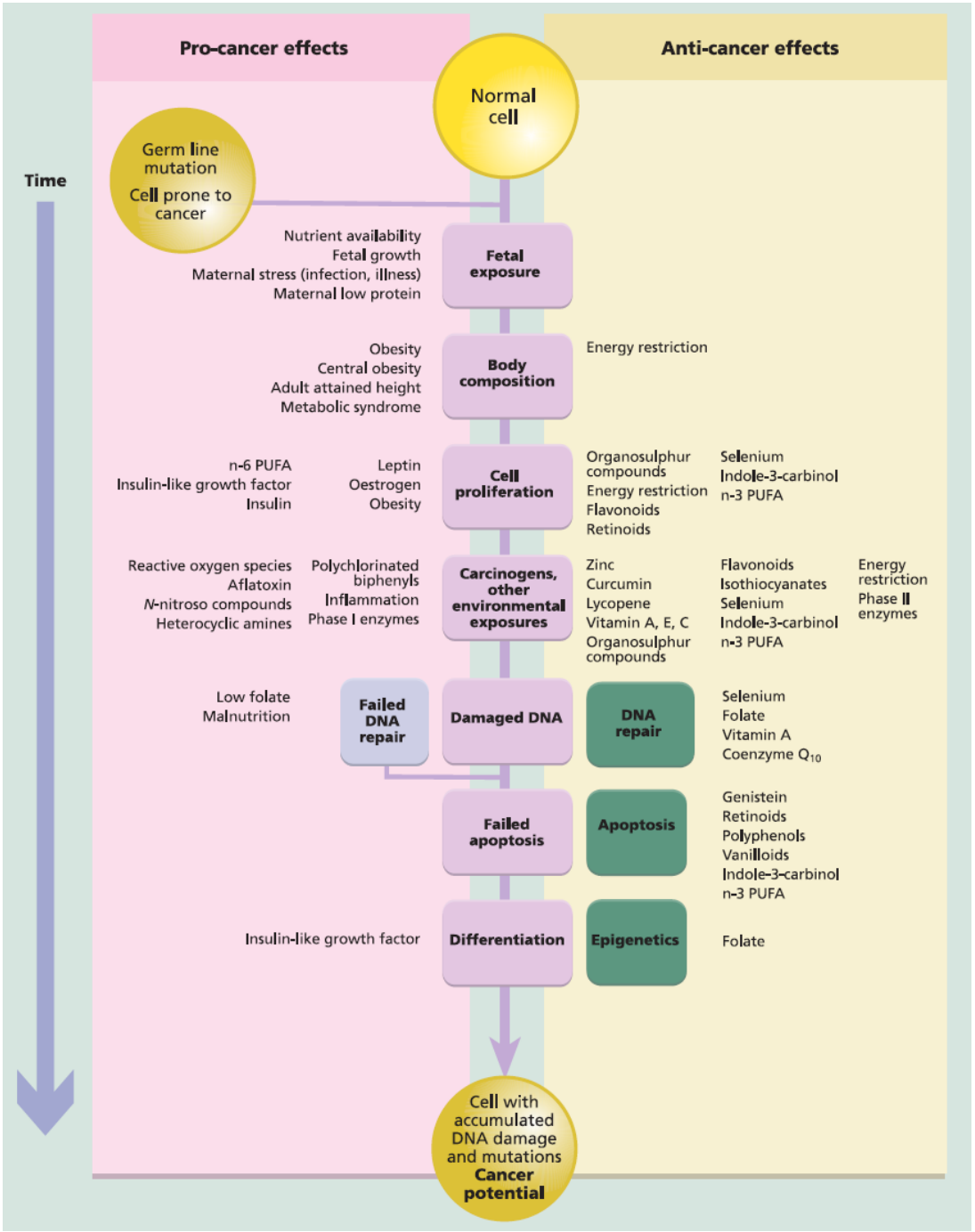
- ***Promotion (vitamin deficiency)***

- ***Storage of carcinogens (fat)***

Summary of conclusions:

World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2007


DNA repair
Carcinogen metabolism
Proliferation
Food, nutrition, obesity, and physical activity
Cell cycle
Hormonal regulation
Apoptosis
Differentiation
Inflammation and immunity



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Physical activity and cancer risk

	DECREASES RISK	INCREASES RISK
Convincing	**Colon[2]**	
Probable	**Breast (postmenopause)** **Endometrium**	
Limited — suggestive	Lung Pancreas Breast (premenopause)	
Substantial effect on risk unlikely	None identified	

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BODY FATNESS, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

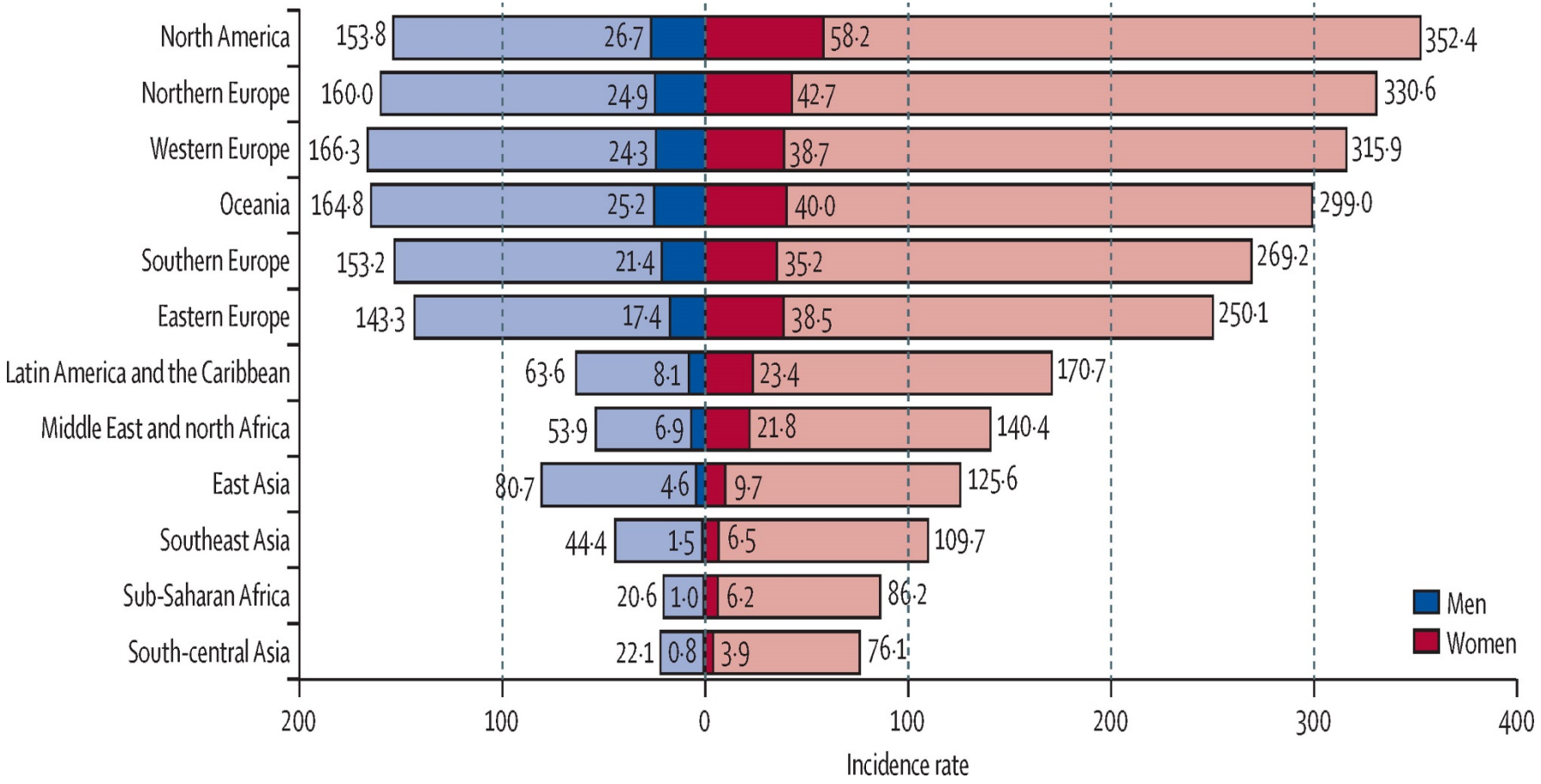
	DECREASES RISK		INCREASES RISK	
	Exposure	**Cancer site**	**Exposure**	**Cancer site**
Convincing			**Body fatness**	**Oesophagus[1]** **Pancreas** **Colorectum** **Breast (postmenopause)** **Endometrium** **Kidney**
			Abdominal fatness	**Colorectum**
Probable	**Body fatness**	**Breast (premenopause)**	**Body fatness**	**Gallbladder[2]**
			Abdominal fatness	**Pancreas** **Breast (postmenopause)** **Endometrium**
			Adult weight gain	**Breast (postmenopause)**
Limited — suggestive			Body fatness Low body fatness	Liver Lung
Substantial effect on risk unlikely	None identified			

1 For oesophageal adenocarcinomas only.
2 Directly and indirectly, through the formation of gallstones.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

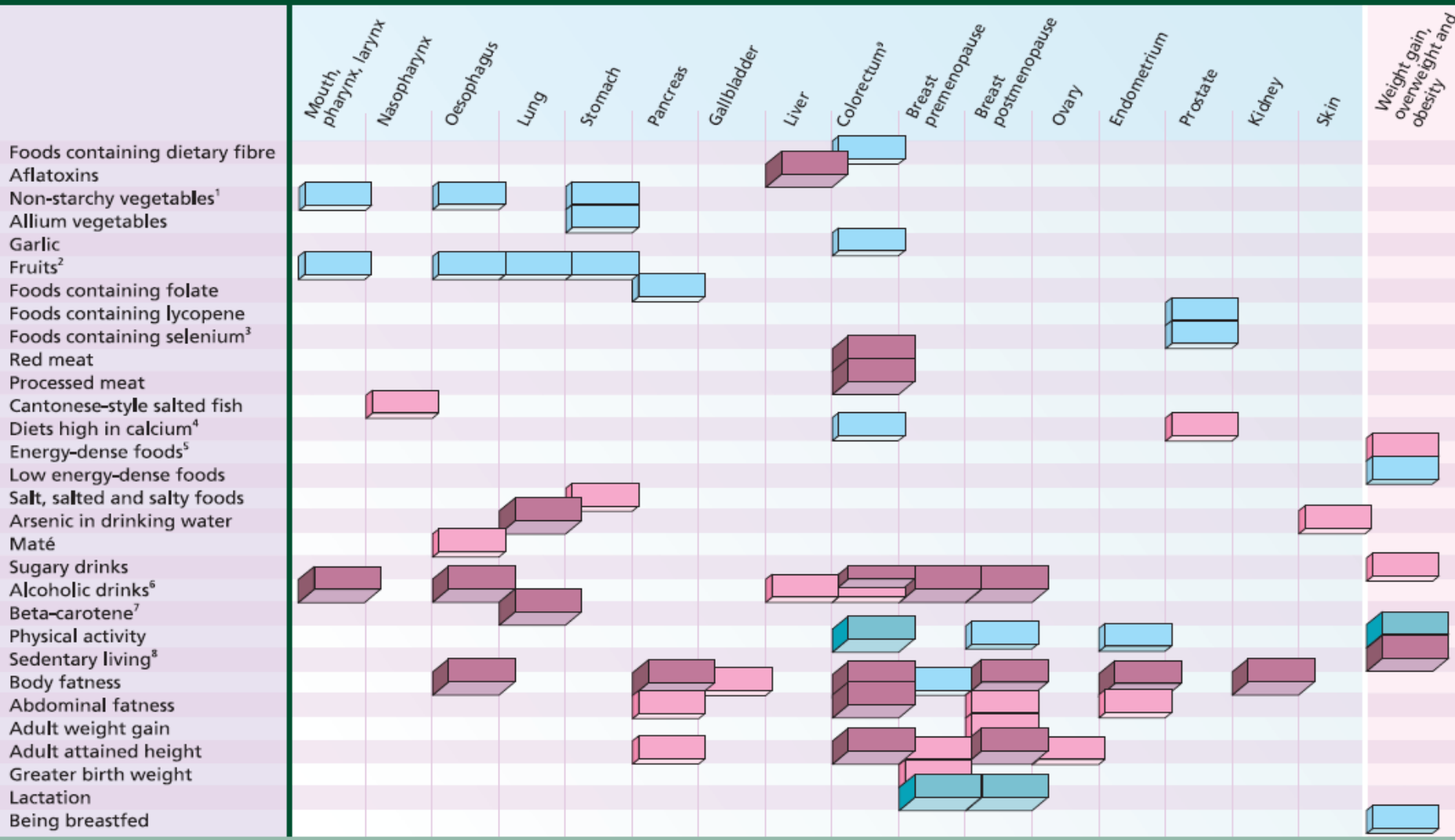
World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2007

Age-standardised incidence rate of high-BMI-related cancers and high-BMI-related cancers attributable to high BMI (per 100,000 people) in 2012



Arnold et al., Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncology 16: 36-46, 2015

Summary of 'convincing' and 'probable' judgements



KEY

- Convincing decreased risk
- Probable decreased risk
- Probable increased risk
- Convincing increased risk

[1] Includes evidence on foods containing carotenoids for mouth, pharynx, larynx; foods containing beta-carotene for oesophagus; foods containing vitamin C for oesophagus

[2] Includes evidence on foods containing carotenoids for mouth, pharynx, larynx and lung; foods containing beta-carotene for oesophagus; foods containing vitamin C for oesophagus

[3] Includes evidence from supplements for prostate

[4] Evidence is from milk and studies using supplements for colorectum

[5] Includes 'fast foods'

[6] Convincing harm for men and probable harm for women for colorectum

[7] The evidence is derived from studies using supplements for lung

[8] Includes evidence on televison viewing

[9] Judgement for physical activity applies to colon and not rectum

World Cancer Research Fund

American Institute for Cancer Research

RELATIVE RISKS OF UADT CANCER ACCORDING TO MATÉ CONSUMPTION. ANALYSIS BY SITE (Pintos et al, Epidemiology, 1994)

Site	Consumption (cuias/day)	Crude RR	Crude 95%CI	Adjusted RR	Adjusted 95%CI
Mouth	Never	1.0	(ref)	1.0	(ref)
	<=1	1.81	1.1-2.9	2.10	1.1-4.1
	2	1.61	0.9-2.8	1.30	0.6-2.7
	>=3	3.31	1.8-6.2	2.82	1.2-6.6
	Trend test (P-value):		0.0002		0.0381
	ever vs. never	1.96	1.3-2.9	1.88	1.1-3.3
Pharynx	Never	1.0	(ref)	1.0	(ref)
	<=1	1.62	0.9-3.1	0.45	0.2-1.3
	2	3.35	1.7-6.5	1.87	0.6-5.9
	>=3	3.53	1.7-7.3	1.32	0.4-4.1
	Trend test (P-value):		$3x10^{-5}$		0.3684
	ever vs. never	2.58	1.6-4.3	0.94	0.4-2.2

* By conditional logistic regression (matching variables: age, sex and admission period). Adjusted analysis included tobacco, alcohol, income, rural residency, 10 dietary variables, and consumption of other non-alcoholic beverages (see text for details). Missing values were excluded.

Age-standardized mortality rates (per 100,000) for lung cancer in urban and rural areas[a].

Registry	Males			Females		
	Urban	Rural	Ratio U:R	Urban	Rural	Ratio U:R
Japan, Miyagi	30.9	28.4	1.1	9.2	8.1	1.1
Czechoslovakia, Slovakia	68.2	70.5	1.0	9.4	6.5	1.4
FRG, Saarland	77.7	63.0	1.2	7.7	6.0	1.3
France, Calvados	46.1	39.6	1.2	3.4	2.9	1.2
France, Doubs	56.9	40.1	1.4	3.3	2.0	1.7
Hungary, Szabolcs	61.8	50.9	1.2	10.3	6.2	1.7
Norway	39.4	24.5	1.6	9.6	5.2	1.9
Romania, Cluj County	35.2	35.3	1.0	6.7	4.7	1.4
Switzerland, Vaud	63.8	56.6	1.1	8.7	5.6	1.6
UK, England and Wales	74.8	56.2	1.3	19.7	15.1	1.3
Australia, NS Wales	55.5	46.8	1.2	12.2	8.3	1.5

[a] **From Muir *et al*. (1987)**

Occupational Exposures Assessed by the IARC

Substance or mixture	Group 1	Group 2A	Group 2B
Physical agents (radiation)	2	1	1
Respirable dusts & fibers	5	0	7
Metals & metal compounds	5	0	5
Fuels & by-products of wood & fossil fuels	5	2	10
Monomers	1	5	8
Intermediates in plastics & rubber manufacturing	1	2	8
Aromatic amine dyes	3	3	13
Pesticides	2	3	17
Polyaromatic hydrocarbons	0	3	9
Chlorinated hydrocarbons	0	4	7
Intermediates in the production of dyes	0	1	7
Azo dyes	0	0	10
Nitro compounds	0	0	10
Others	3	6	10

Occupations and industries implicated for Group 1: Aluminum production, Auramine manufacturing, Boot and shoe manufacturing and repair, Coal gasification, Coke production, Furniture & cabinet making, Haematite mining (underground), Iron and steel founding, Isopropanol manufacturing, Magenta manufacturing, Painter, Rubber industry. For Group 2A: Art glass manufacturing, Cobalt metal manufacturing, Hairdresser or barber, Petroleum refining.

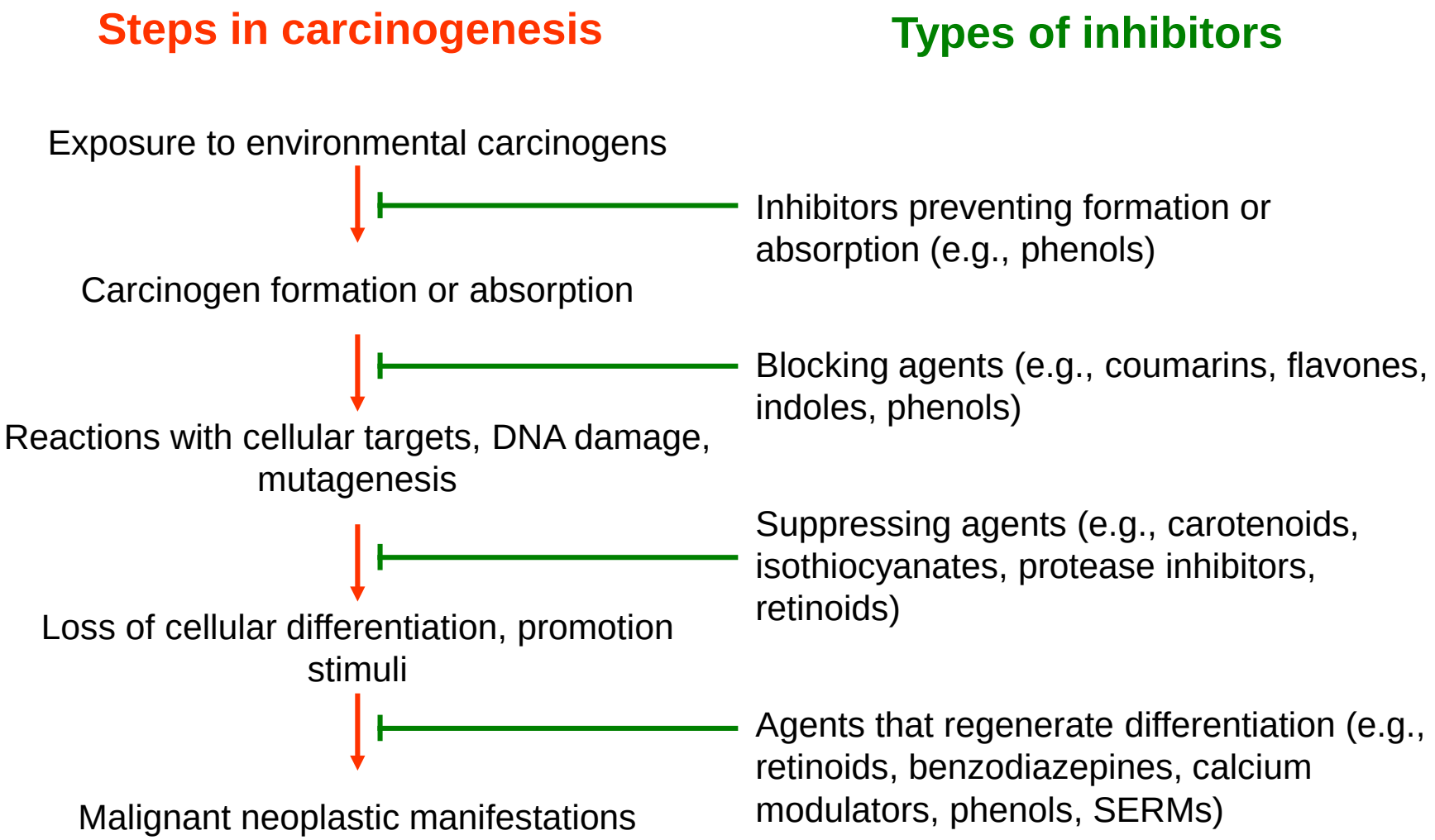
Siemiatycki et al, Environ Hlth Persp, 2004

Levels of Cancer Prevention and Control

Level	Public health goal	Research goal	Intervention
Primary	To reduce incidence of pre-invasive and invasive disease.	To identify risk factors and biological intermediates.	Modification of lifestyle and environmental exposures, immunization, chemoprevention.
Secondary	To reduce the prevalence of pre-invasive and invasive disease; to shift the burden of disease to early stages. Ultimately, to reduce cause-specific mortality.	To identify early signs, morphological and biological precursors of disease.	Screening, either opportunistic or organized; early detection as part of practice guidelines. Both activities imply timely treatment of disease.
Tertiary	To improve the clinical outcome of invasive disease; to prolong survival; to avert premature death.	To identify prognostic factors of disease recurrence and survival.	Tailored management, therapy, and follow-up.
Quaternary	To improve quality of life, minimize suffering, improve palliation.	To identify determinants of pain, disability, cachexia.	Tailored palliative and supportive care and management at end of life.

Adapted from Franco EL. Epidemiology in the study of cancer. In: Bertino JR et al. (eds.), Encyclopedia of Cancer, Vol. 1. Academic Press, San Diego, 1997 (pp. 621-641).

Rationale for Cancer Chemoprevention



Adapted from Greenwald, 1995; 2001

RATIONALE FOR TAMOXIFEN IN BREAST CANCER PREVENTION:

Effect of tamoxifen treatment on the risk of primary contralateral breast cancer in women with postmenopausal breast cancer enrolled in 5 randomized controlled clinical trials*

Author(s) and year	Rate of contralateral breast cancer per 100 women followed per year		
	Tamoxifen Group (N)	Control Group (N)	Ratio T/C
NATO, Nolvadex and Adjuvant trial, 1988	0.43 (564)	0.38 (567)	1.13
Ribeiro and Swindell, 1988	0.34 (282)	0.37 (306)	0.92
Fisher et al, 1989	0.51 (1318)	1.18 (1326)	0.43
Fornander et al, 1989	>0.43 (931)	>0.78 (915)	0.55
Stewart and Knight, 1989	0.27 (282)	0.38 (531)	0.71

*Adapted from Bernstein et al, AJE 135: 142, 1992

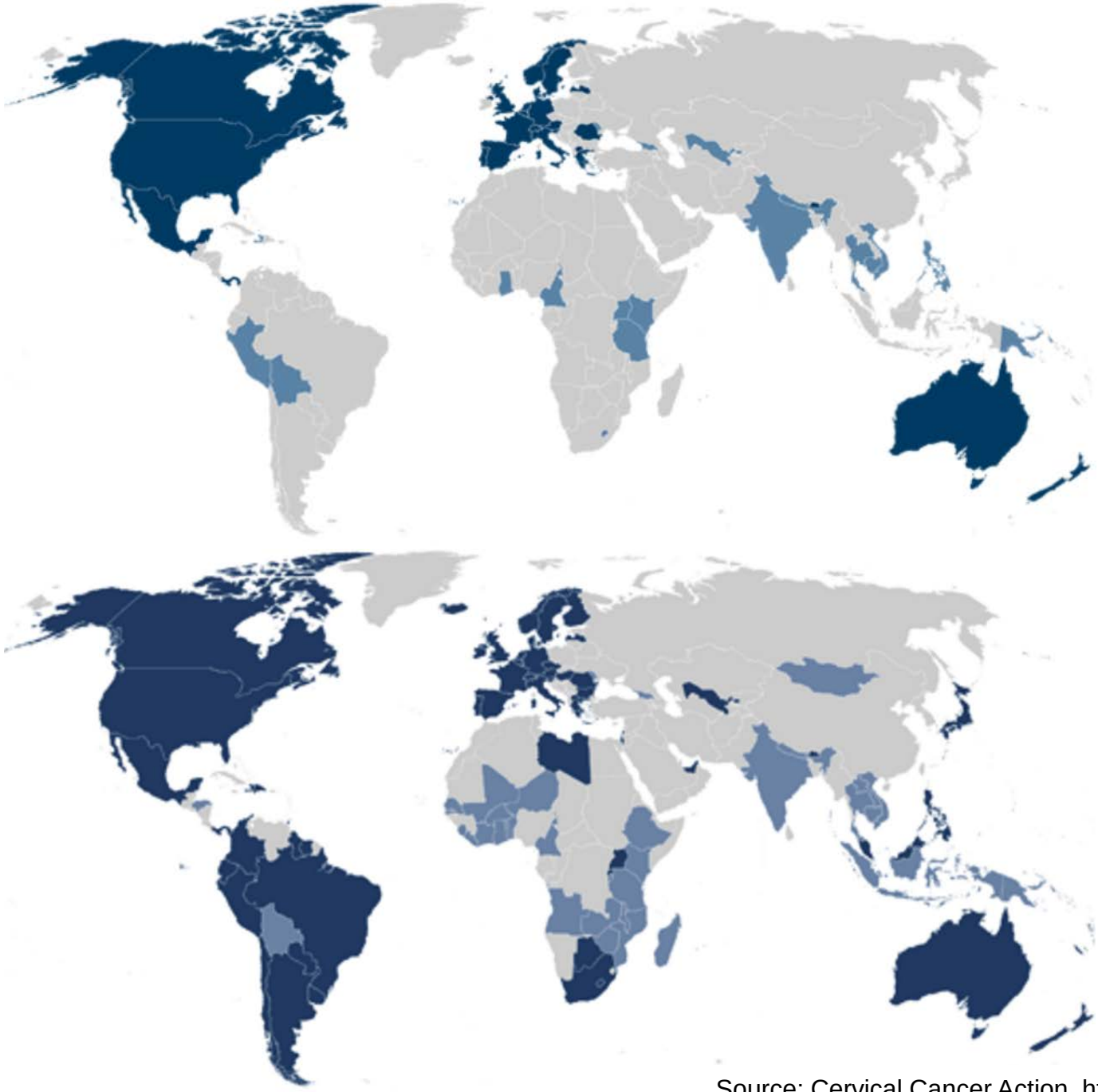
Selected Large Phase III RCTs of Chemoprevention in Cancer

RCT	Intervention	Target population	Outcomes of interest	Findings
ATBC (Alpha-Tocopherol/Beta-Carotene)	Vitamin E (AT), BC, placebo in 2x2 design	29,133 male smokers ages 50-69	Lung cancers, all cancers	Increased lung cancer risk for BC, reduced prostate cancer risk for AT
CARET (Carotene and Retinol Efficacy Trial)	BC, retinyl palmitate, placebo in 2x2 design	18,314 ever smokers, asbestos workers, ages 45-74	Lung cancers, all cancers	Increased risk for lung cancer for BC
BCPT (Breast Cancer Prevention Trial)	Tamoxifen (first SERM), placebo	13,388 women with high-risk of breast cancer	Breast cancer (precancer and cancer), other cancers	50% reduction in breast cancer and 2-fold increase in endometrial cancer
STAR (Study of Tamoxifen and Raloxifene)	2 SERMs	19,747 women with high-risk of breast cancer	Breast cancer (precancer and cancer), other cancers	No increased risk for endometrial cancer (raloxifene)
MAP.3	Exemestane, placebo	4560 post-menopausal women at increased risk of breast cancer	Breast cancer (precancer and cancer)	Substantial risk reduction
SELECT (Selenium and Vitamin E Cancer Prevention Trial)	Selenium, vitamin E, placebo in 2x2 design	35,534 men ages 50 and over	Prostate cancer	No effect or slightly increased risk for vitamin E
PCPT (Prostate Cancer Prevention Trial)	Finasteride (alpha-reductase inhibitor), placebo	18,882 men age 55 and older	Prostate cancer diagnosis	Reduced risk of low-grade cancers, increased risk of high-grade cancers
REDUCE (Reduction by Dutasteride of Prostate Cancer Events)	Dutasteride (AR inhibitor), placebo	8231 men ages 50-75 with PSA 2.5-10)	Prostate cancer diagnosis	Similar to PCPT

NCI PDQ: www.cancer.gov

Main findings from RCTs of HPV vaccination

- High efficacy (>95%) against incident and/or persistent HPV infections by the target types (16/18 or 6/11/16/18) and precancer associated with these types in women 15-26 years of age.
- Protection has continued unabated after 9 years of f/up (~12 yrs for prototype HPV-16 vaccine).
- High titers of neutralizing antibodies among vaccinees.
- Comparable protection among older women and men if not previously exposed.
- No evidence of protection against existing infections; vaccination does not accelerate clearance of infections by target types.
- Evidence of cross-type protection, primarily for HPV 45 and to a lesser extent to HPVs 31 and 33.
- Incidence of adverse events comparable to placebo and within expected background rates in general population.



Global Progress in HPV Vaccine Introduction

Top: 2010
Bottom: 2015

Dark blue: Countries with national programs; Light blue: countries with pilot programs; Grey: no data (vaccines may have been approved for use in the private sector but are not deployed via central coordination)

Source: Cervical Cancer Action, http://www.cervicalcanceraction.org/

Targeted Agents with Established Cancer Risk–Reducing Effect

Intervention (Year)	Cancer Prevented
Hepatitis B vaccine (1997)	Liver cancer *
Tamoxifen (1998)	Breast cancer
Finasteride (2004)	Prostate cancer
Human papillomavirus vaccine (2006)	Cervical cancer **
Raloxifene (2006)	Breast cancer

* Not part of original regulatory approval of intervention; observation after public health implementation of HBV vaccination;
** Expected in 2020 and later.

Modified from: Lippman SM, Lee JJ. Cancer chemoprevention. In: The Molecular Basis of Cancer, 3rd. Ed(s) J Mendelsohn, PM Howley, MA Israel, JW Gray, CB Thompson. Saunders-Elsevier: Philadelphia, PA, 711-720, 2008

The Beta-Carotene Paradox

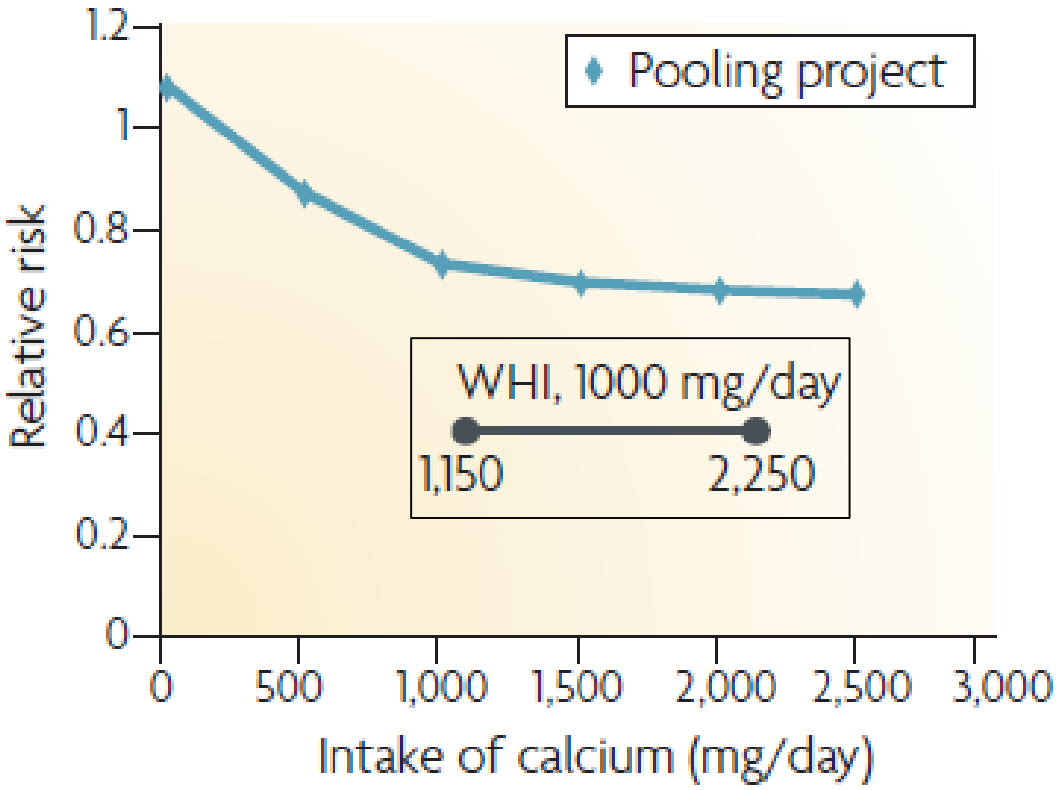
- Observational studies consistently showed that high consumption of vegetables and fruits is associated with reduced risk of many cancers
- Beta-carotene, a vitamin A precursor, has anti-oxidant properties that make it a suitable candidate for chemoprevention trials
- Large RCTs began in the late 80's …

Effect of Beta-carotene administration on the risk of lung cancer and death in two large scale randomized controlled trials.

Study	Design	Outcomes	RR (95%CI)
Alpha-tocopherol/Beta-carotene Trial (ATBC), Finland: 29,133 male smokers, age 50-69 NEJM 330: 1029-1035, 1994	RCT 2x2 design: daily 20 mg BC, 50 IU AT, placebo, 6.5 years	874 lung cancers, 3570 deaths	Lung cancer: 1.18 (1.03–1.36) All deaths: 1.08 (1.01–1.16)
Beta-carotene and Retinol Efficacy Trial (CARET), US: 14,254 smokers+ ex-smokers (M+F), age 50-69, 4060 asbestos exposed males, age 45-74 NEJM 334: 1150-1155, 1996	RCT: daily 30 mg BC + 25 K IU retinyl palmitate, placebo,	388 lung cancers	Lung cancer: 1.28 (1.04–1.57) All deaths: 1.17 (1.03–1.33)

WHI RCT vs. Pooling Project of Calcium Intake and Colorectal Cancer Risk *(Martinez et al., Nature Reviews Cancer 8:694-703, 2008)*

"Participants in the WHI had a mean baseline daily intake of 1,151 mg of calcium, which increased during the course of the trial. Thus, it is possible that the WHI participants attained no additional benefit from further calcium supplementation owing to a high background dietary level."



Cho et al. JNCI 96: 1015–1022, 2004

Wactawski-Wende et al. NEJM 354: 684–696, 2006

Limitations of RCTs in expanding the knowledge base in cancer prevention

- Restricted range of questions to be examined (ethical issues or pragmatism)
- Must respect ethical and clinical practice boundaries
- Overly simplistic or the wrong questions are asked (e.g., beta-carotene in lung cancer)
- Need to rely on surrogate or intermediate endpoints rather than on disease outcomes
- Blind faith in the generalizability of findings

Problems with much of the literature on the effect of cancer prevention strategies

- **Studies based on uncontrolled, non-experimental conditions:**
  - Selection and intervention-assignment biases
  - Lack of suitable control groups
  - Confounding
  - Systematic errors
  - Wrong endpoints
  - Inadequate methods of data analysis

- **Based on editorials and personal experience that:**
  - Lack scientifically rigorous methods to make inferences
  - Cannot be generalized to clinical practice

Systematic overviews of the evidence for cancer prevention methods

» **Comprehensive and updated continuously**
- US National Cancer Institute's Physician's Data Query (PDQ) program

» **Comprehensive and updated sporadically**
- US Preventive Services Task Force
- Canadian Task Force on Preventive Health Care (formerly Canadian Task Force on Periodic Health Examination)

» **Specific reviews initiated by ad hoc specialty groups**
- Cochrane Collaboration
- US Agency for Healthcare Research and Quality (formerly Agency for Health Care Policy and Research)
- Canadian Agency for Drugs and Technologies in Health (formerly Canadian Coordinating Office for Health Technology Assessment)
- UK National Coordinating Centre for Health Technology Assessment
- Several professional and cancer societies

US NCI's Physician's Data Query program: Levels of evidence for statements of efficacy

Level of evidence	Assessment of the evidence by expert review
1	Evidence obtained from at least one well-designed and conducted randomized controlled trial
2	Evidence obtained from well-designed and conducted controlled trials without randomization
3	Evidence obtained from well-designed and conducted cohort or case-control analytic studies, preferably from more than one center or research group
4	Evidence obtained from multiple-time series with or without intervention
5	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

US NCI's Physician's Data Query program: Qualifiers for levels of evidence for efficacy

Type of endpoint	Outcome	Level of evidence
Cancer	Mortality	ai
	Incidence	aii
Intermediate endpoint *	Incidence	b

* A generally accepted intermediate endpoint or surrogate biomarker, e.g., large adenomatous polyps for colorectal cancer, HG-CIN for cervical cancer, lesions detected by spiral CT for lung cancer, etc.

NCI-PDQ program's summaries of evidence for the efficacy of specific prevention strategies for cancer

Cancer	Prevention strategy	Evidence
Breast	Avoidance of combination hormone replacement therapy	1ai, 1aii
	Strenuous exercise for more than 4 hours per week	3aii
	Early pregnancy before age 20 compared to after 35	3aii
	Breastfeeding	3aii
	SERMs (tamoxifen or raloxifene)	1aii
	Aromatase inhibitors or inactivators (in high risk postmenopausal women)	1aii
	Prophylactic mastectomy (in women with a strong family history)	3aii
	Prophylactic oophorectomy or ovarian ablation	3aii
Colo-rectal	Avoidance of excessive alcohol use	3aii
	Avoidance of cigarette smoking	3ai, 3aii, 3b
	Reduction of obesity	3ai, 3aii
	Regular physical activity	3aii
	Use of NSAIDs (celecoxib, rofecoxib) to reduce the risk of adenomas in people with a prior history of a colonic adenoma that had been removed	1b
	Aspirin	1ai, 1aii
	Hormone therapy (estrogen plus progestin) in postmenopausal females	1aii, 3aii
	Estrogen only therapy has no effect.	1ai, 1aii
	Removal of adenomatous polyps (especially for larger polyps)	1ai, 3ai
	Diet low in fat and meat and high in fiber, fruits and vegetables does not reduce CRC risk	1aii, 3aii
	Vitamin Intake shows mixed relationship to CRC incidence	3aii, 1aii
	Calcium supplementation shows inadequate evidence	1aii, 3aii
	Use of statins do not reduce the incidence or mortality from CRC.	1ai, 1aii

http://www.cancer.gov/cancertopics/pdq/prevention

NCI-PDQ program's summaries of evidence for the efficacy of specific prevention strategies for cancer

Cancer	Prevention strategy	Evidence
Lung	Avoidance of cigarette smoking and long-term sustained smoking cessation	3ai, 3aii
	Elimination of secondhand smoke	3ai, 3aii
	Reduction or elimination of exposure to radon, asbestos, arsenic, beryllium, cadmium, chromium and nickel)	3ai, 3aii
	Avoidance of exposure to outdoor air pollution	3ai, 3aii
	Dietary factors and physical activity have uncertain association	3ai
	Avoidance of beta-carotene supplementation among current smokers (no substantive effect on non-smokers)	1ai, 1aii
	Vitamin E supplements do not affect risk	1aii
Prostate	Chemoprevention with finasteride and dutasteride	1aii, 1ai
	Use of vitamin E and selenium show no/inadequate reduction in risk	1aii
	A low-fat diet with fruit and vegetables shows inconsistent results	5
Endometrial	Use of combination of oral contraceptives	3aii
	Physical activity (trend in risk reduction with increasing duration/intensity unknown)	3aii
	Increased parity and lactation	3aii
	Avoidance of hormone therapy (unopposed estrogen use)	1aii, 3aii
	Avoidance of tamoxifen use	1aii
	Controlling of overweightness and obesity	1aii
	Weight loss (insufficient evidence)	3aii
Liver	Prevention of Hepatitis B through immunization (Hepatitis B vaccine)	3aii

http://www.cancer.gov/cancertopics/pdq/prevention

US Preventive Services Task Force (USPSTF)

Grades and definitions for clinical preventive services (adopted July 2012)

Grade	Definition
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.
I	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

Source: http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm (accessed May 2014)

US Preventive Services Task Force (USPSTF)

Levels of Certainty Regarding Net Benefit (adopted July 2012)

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: • The number, size, or quality of individual studies. • Inconsistency of findings across individual studies. • Limited generalizability of findings to routine primary care practice. • Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: • The limited number or size of studies. • Important flaws in study design or methods. • Inconsistency of findings across individual studies. • Gaps in the chain of evidence. • Findings not generalizable to routine primary care practice. • Lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

Source: http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm (accessed May 2014)

Two models of cancer screening

- **Opportunistic:** Prompted by the convenience of a healthcare visit by the patient.
- **Organized:** Prompted by a central public health structure that ensures coverage to all persons considered at risk.

Wilson & Jungner's classic screening criteria

1) The condition should be an important health problem.
2) There should be a treatment for the condition.
3) Facilities for diagnosis and treatment should be available.
4) There should be a latent stage of the disease.
5) There should be a test or examination for the condition.
6) The test should be acceptable to the population.
7) The natural history of the disease should be adequately understood.
8) There should be an agreed policy on whom to treat.
9) The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
10) Case-finding should be a continuous process, not just a "once and for all" project.

Wilson JMG, Jungner G. *Principles and practice of screening for disease*. Geneva: WHO; 1968.

Andermann et al.'s "Synthesis of emerging screening criteria proposed over the past 40 years"

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.

Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bull World Health Organ. 2008;86:241–320.

Screening / early detection
Can you do it? Should you do it?

"Is cure possible in those for whom it is necessary ?" (ovarian cancer: we can't do it but we should do it)

"… and is cure necessary in those for whom it is possible ?" (prostate cancer: we can do it but should we do it?)

Adapted from W.F. Whitmore Jr. Urol Clin North Am 1990;17:689-97

Fulfillment of Wilson & Jungner's Screening Criteria for Various Cancers

Criterion	Cervix	Vulva	Vagina	Ovary	Breast	Mouth	Anal	Colorectal	Melanoma	Lung
Incidence	++	++	+	++	++	+	+	++	++	++
Survival	+	+	+	++	+/-	+	+	+	+/-	++
Natural history adequately understood	++	+	+	+	++	++	++	++	++	+
Recognizable latent stage exists	++	++	++	+/-	++	++	++	++	++	+/-
Suitable test or examination available	++	++	++	+/-	++	++	++	++	++	++
Test acceptable to population	+	++	+	++	+	++	+	+	++	++
Accepted treatment for disease exists	++	++	++	++	++	++	++	++	++	++
Facilities for diagnosis and treatment available	++	++	++	++	++	++	++	++	++	++
Agreed policy on whom to treat as patients	++	+	+	+	+	++	++	++	++	+/-
Potential harms of undergoing screening	+	+	+	+/-	+	++	+	++	+	+/-
Cost-effectiveness	++	?	?	+/-	++	+	+	++	+	+
Case-finding a continuing process	++	++	++	++	++	++	++	++	++	++

Incidence considered in the absence of screening
Harms considers psychological harms and potential morbidity during the entire screening process
Cancers for which organized, guideline-driven screening programs currently exist were considered highly cost-effective. Cancers for which screening guidelines exist for high-risk subgroups only, or in opportunistic settings were considered moderately cost-effective

Tota, Isidean, Franco (in preparation)

Measures and surrogates of improved outcome for determining screening efficacy and effectiveness

1) Decrease in cause-specific mortality
2) Reduction in incidence of advanced cancers
3) Increase in survival
4) Shift in stage to early cancers
5) Enhanced detection of precursor lesions

Strongest, last to obtain

Weakest, first to obtain

Efficacy versus Effectiveness

- **Efficacy:**

  Assessment of screening strategy under ideal conditions of test performance in controlled, investigational settings

- **Effectiveness:**

  Assessment of screening strategy in actual public health conditions that reproduce the complete context of test deployment and post detection intervention

Performance Indices for the Core Screening Technology Based on Cross-sectional Evaluation

Test result	**Lesion present**	**Lesion not present**	Total
Positive	True positives (TP)	False positives (FP)	T+
Negative	False negatives (FN)	True negatives (TN)	T-
Total	L+	L-	N

Performance Indices for the Core Screening Technology Based on Cross-sectional Evaluation

Sensitivity: The probability that the screening test will be positive among those with the lesion

$$Se = TP / (TP + FN) = TP / L+$$

Specificity: The probability that the screening test will be negative among those without the lesion

$$Sp = TN / (TN + FP) = TN / L-$$

Positive predictive value (PPV): The probability that those who are tested positive have a lesion

$$PPV = TP / (TP + FP) = TP / T+$$

Negative predictive value (NPV): The probability that those who are tested negative do not have a lesion

$$NPV = TN / (TN + FN) = TN / T-$$

PPV and NPV are affected by the prevalence of the lesion to be detected in the population

Positive predictive value

$$PPV = Se \times P / [Se \times P + (1 - Sp) \times (1 - P)]$$

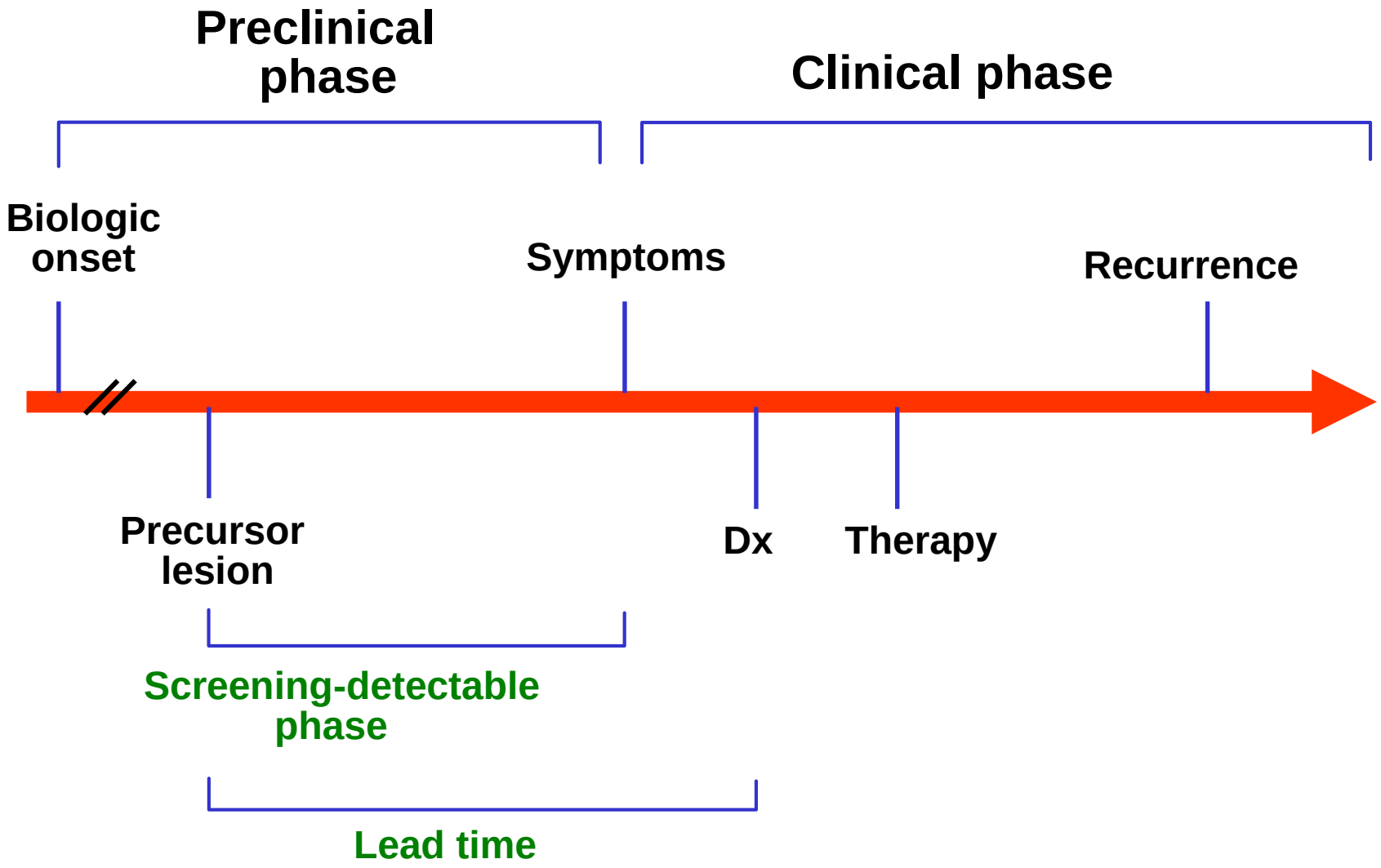
Negative predictive value

$$NPV = Sp \times (1 - P) / [(1 - Se) \times P + Sp \times (1 - P)]$$

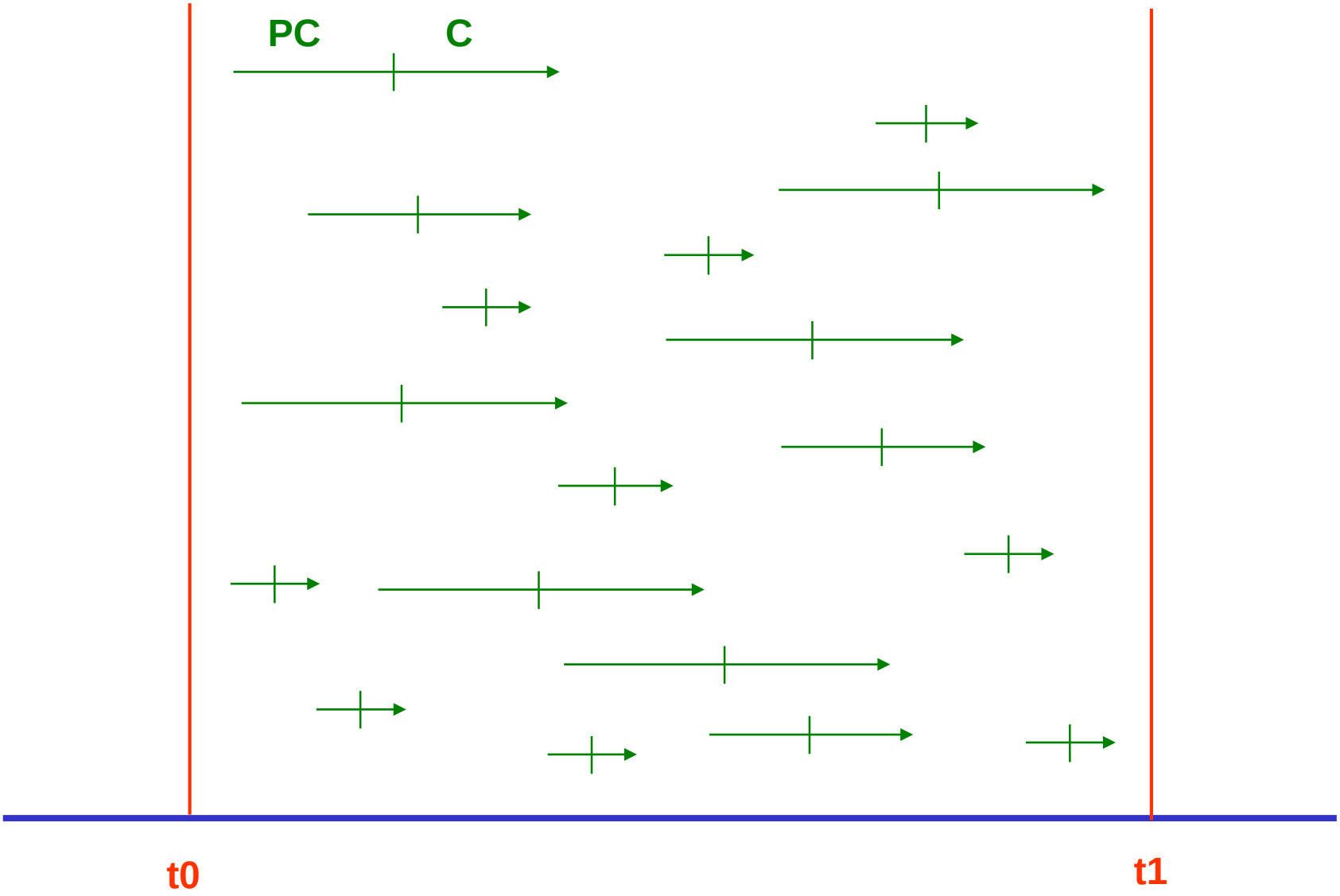
Where Se is the sensitivity and Sp is the specificity of the test and P is the prevalence of the lesion

BIASES IN SCREENING

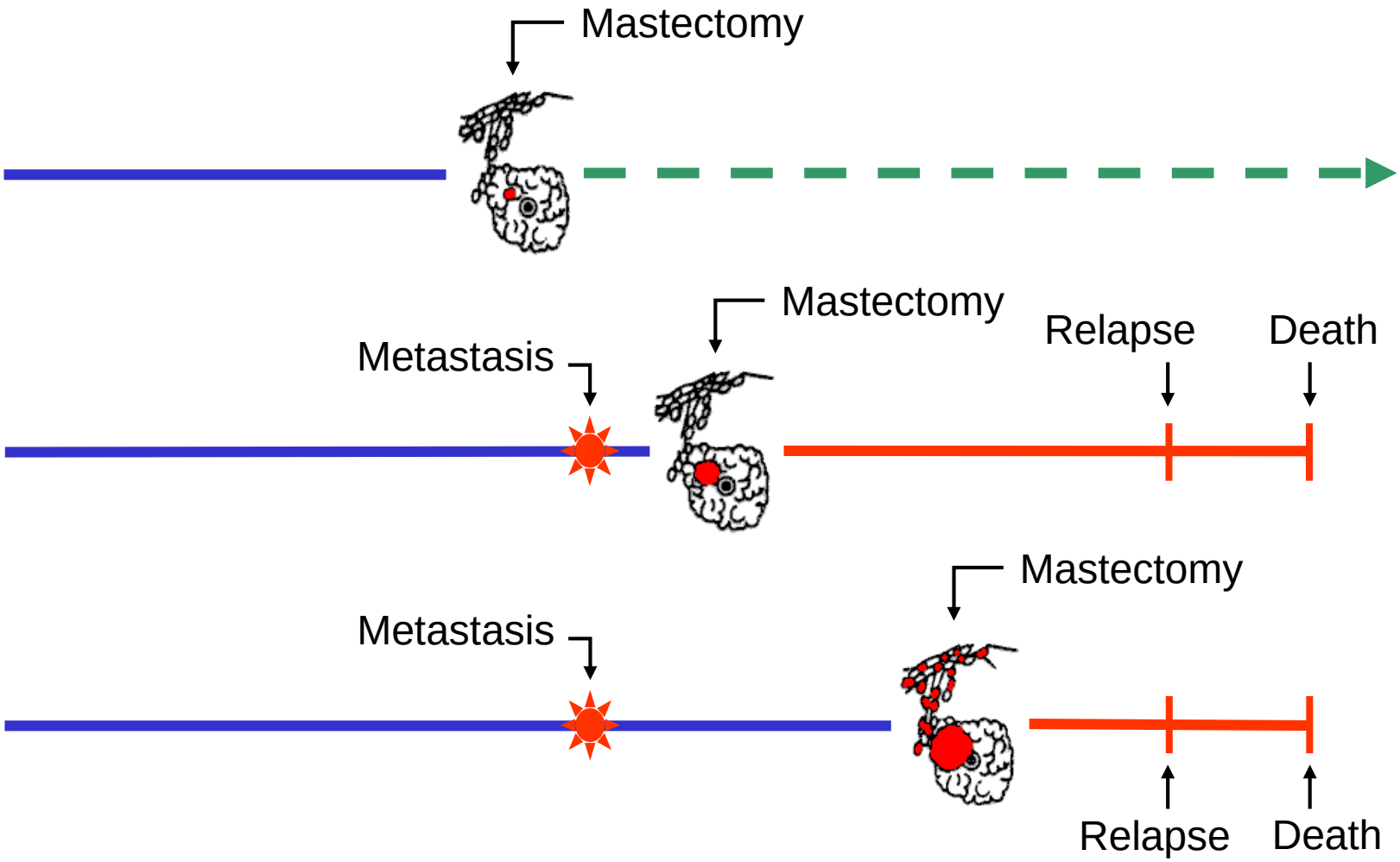
- Selection bias (all designs):
  - Referral (volunteer) bias, length-biased sampling
- Lead time bias (all designs)
- Overdiagnosis bias (all designs)
- Verification bias (all designs)
- False gain in sensitivity due to test combination (Franco, 2000)
- Sticky diagnosis and slippery linkage biases (RCTs) (Black et al., 2002)


Preclinical phase
Clinical phase
Biologic onset
Symptoms
Recurrence
Precursor lesion
Dx
Therapy
Screening-detectable phase
Lead time

Length-biased sampling



Lead time bias



Adapted from: Mittra, 1993

Positive predictive value (%) as a function of sensitivity, specificity, and prevalence of disease to be detected by screening

Prevalence	Specificity	Sensitivity		
		0.8	0.9	0.95
0.005	0.95	7	8	8
	0.99	29	31	32
	0.999	80	82	83
0.001	0.95	2	2	2
	0.99	7	8	9
	0.999	44	47	49
0.0001	0.95	0.2	0.2	0.2
	0.99	0.8	0.9	0.9
	0.999	7	8	9

Verification Bias

When does it happen?

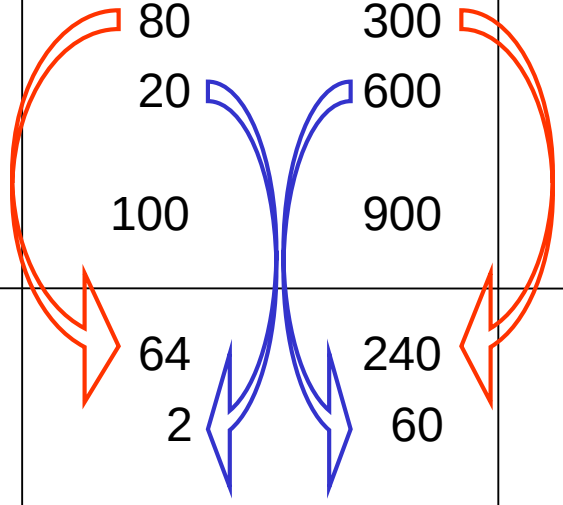
When disease verification is not the same for test+ and test- subjects

- If uncorrected: estimates should be considered relative, not absolute.

Bias due to differential verification based on screening results

Table of screening results if only a sample is tested:
80% for test+* and *10% for test-

		Disease	No disease	Total tested	Not tested	Total
Complete ascertainment	Test +	80	300	380	0	380
	Test -	20	600	620	0	620
	Total	100	900	1000	0	1000
Disease ascertainment in sample	Test +	64	240	304	76	380
	Test -	2	60	62	558	620
	Total	66	300	366	634	1000



Franco, Lab Clin N Amer, 2000

Verification bias

	True values	Biased estimates	Absolute bias
Sensitivity	80%	97%	17%
Specificity	67%	20%	- 47%
PPV	21%	21%	0%
NPV	97%	97%	0%

Franco, Lab Clin N Amer, 2000

Newfoundland Study: Screening performance after correcting for verification bias *(CIN2 or worse)*

Pap threshold	**Uncorrected**		**Corrected**	
	Sensitivity	Specificity	Sensitivity	Specificity
ASCUS+	55.9	61.8	40.2	91.6
LSIL+	38.2	80.5	26.8	96.2

Ratnam et al. CEBP 2000;9:945-51

False Gain in Sensitivity

Whenever an adjunct test is added to a conventional test, even if unrelated to disease.

- If uncorrected: sensitivity gain may be irrelevant even if deemed statistically significant against conventional test alone.

Combination of repeat Pap smear and HPV testing in the triage of abnormal smears

Study	Referral smear	Method	Sensitivity (%)
Cox, 1995	ASCUS	Repeat Pap	73
		HPV	93
		Both	**100**
Wright, 1995	ASCUS or SIL	Repeat Pap	80
		HPV	78
		Both	**96**
Hatch, 1995	SIL	Repeat Pap	75
		HPV	74
		Both	**91**
Hall, 1996	ASCUS or SIL	Repeat Pap	87
		HPV	93
		Both	**100**
Ferenczy, 1996	ASCUS or SIL	Repeat Pap	87
		HPV	77
		Both	**95**

Adding HPV testing to improve the diagnostic sensitivity of repeat cytology in triaging abnormal Paps

1) Only repeat Pap

Cytology alone	CIN	
	+	-
+	145	47
-	41	131

Sensitivity = 78.0%
Specificity = 73.6%

2) Combined repeat Pap + HPV

Cytology + HPV	CIN	
	+	-
+/+, +/-, -/+	164	63
-/-	23	115

Sensitivity = 87.7%
Specificity = 64.6%

HPV positivity rate = 44.9%

Data from Ferenczy et al., AJOG 1996

Adding HPV testing to improve the diagnostic sensitivity of repeat cytology in triaging abnormal Paps

3) Expected frequencies assuming repeat Pap combined with hypothetical random adjunct test (same positivity as HPV)

Cytology+ adjunct test	CIN	
	+	-
+	145 *(+ 45% of 41)*	47 *(+ 45% of 131)*
-	41 *(- 45% of 41)*	131 *(- 45% of 131)*

Cytology+ adjunct test	CIN	
	+	-
+	*163.4*	*105.8*
-	*22.6*	*72.2*

Sensitivity = 87.8%
Specificity = 40.6%

Data from Ferenczy et al., AJOG 1996

Correcting sensitivity and specificity for incremental diagnostic gain contributed by adjunct test

Calculation of expected value: assuming that the adjunct test has no association with cytology or histological diagnosis.

- Can be calculated separately for sensitivity (S) and specificity (W):

$$S_E = S_C + P\,(1 - S_C) \quad \text{for the expected null sensitivity}$$

$$W_E = W_C - P\,(W_C) \quad \text{for the expected null specificity}$$

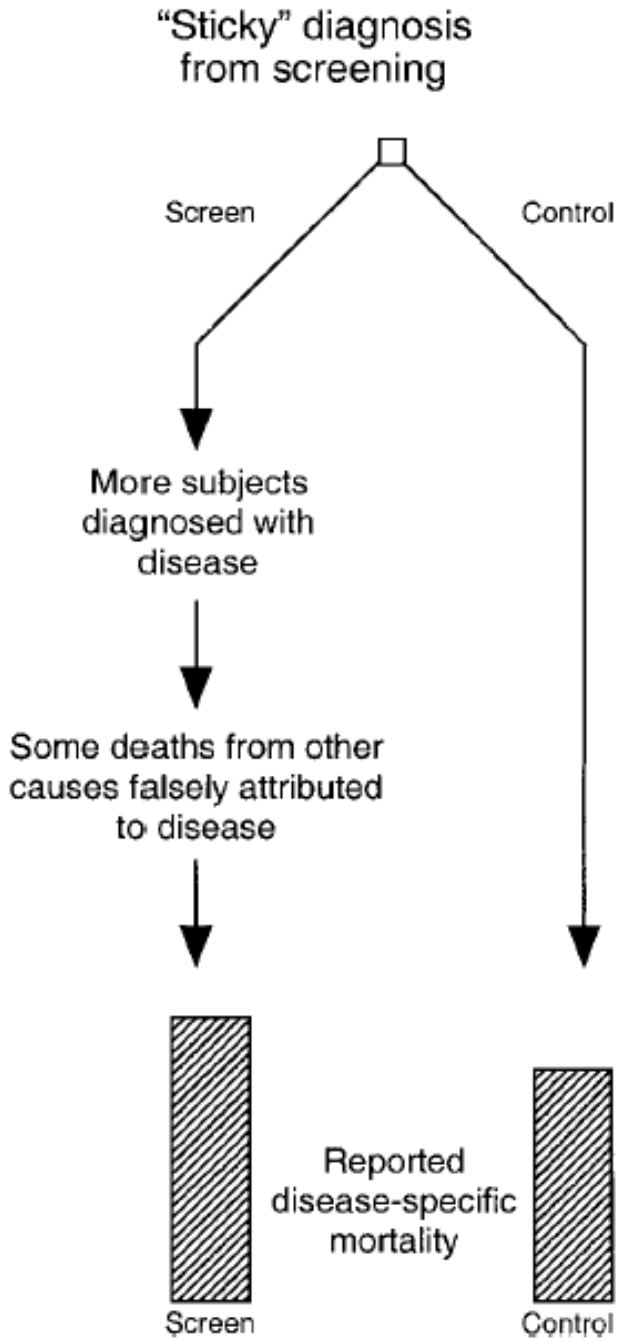
Where S_E and W_E denote the adjusted (for the addition of the new test) sensitivity and specificity, S_C and W_C represent the sensitivity and specificity of cytology alone, and P is the expected positivity rate of the adjuvant test.

Franco & Ferenczy, AJOG 1999;181:382-6

Interpreting gain in sensitivity and loss in specificity when HPV testing is added to Pap cytology in cervical lesion triage

Study	Index	Diagnostic utility (%)			Significance versus	
		Pap alone	Pap+HPV (95%CI)	expected Pap+ chance	Pap alone	expected Pap+ chance
Cox 1992	Sensitivity	44	78 (71-84)	60	yes (+)	yes (+)
	Specificity	92	79 (75-83)	65	yes (-)	yes (+)
Hatch 1995	Sensitivity	76	92 (86-95)	89	yes (+)	no
	Specificity	57	43 (36-51)	27	yes (-)	yes (+)

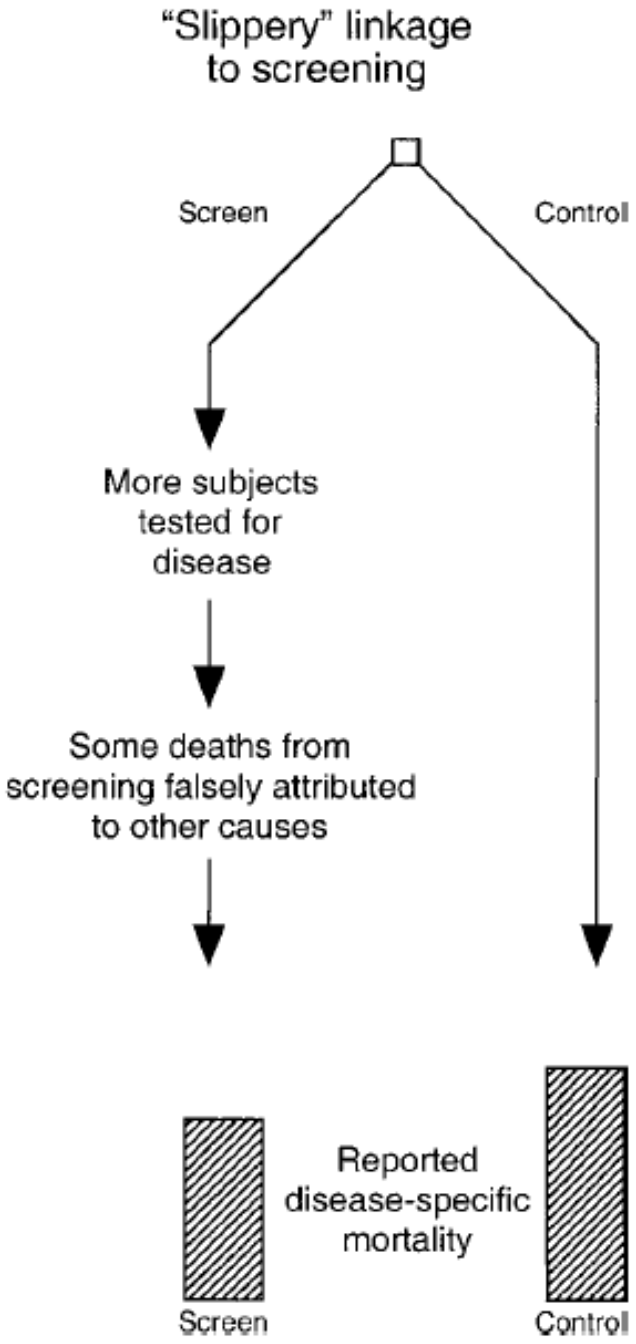
Franco & Ferenczy, AJOG 1999



Sticky Diagnosis Bias

(Black et al., JNCI 2002)

- In an RCT, the target cancer is more likely to be detected in the screened group than in the control group
- Deaths are more likely to be attributed to the target cancer in the screened group
- Example: Excess lung cancer mortality in the screened arm of the Mayo Lung Project

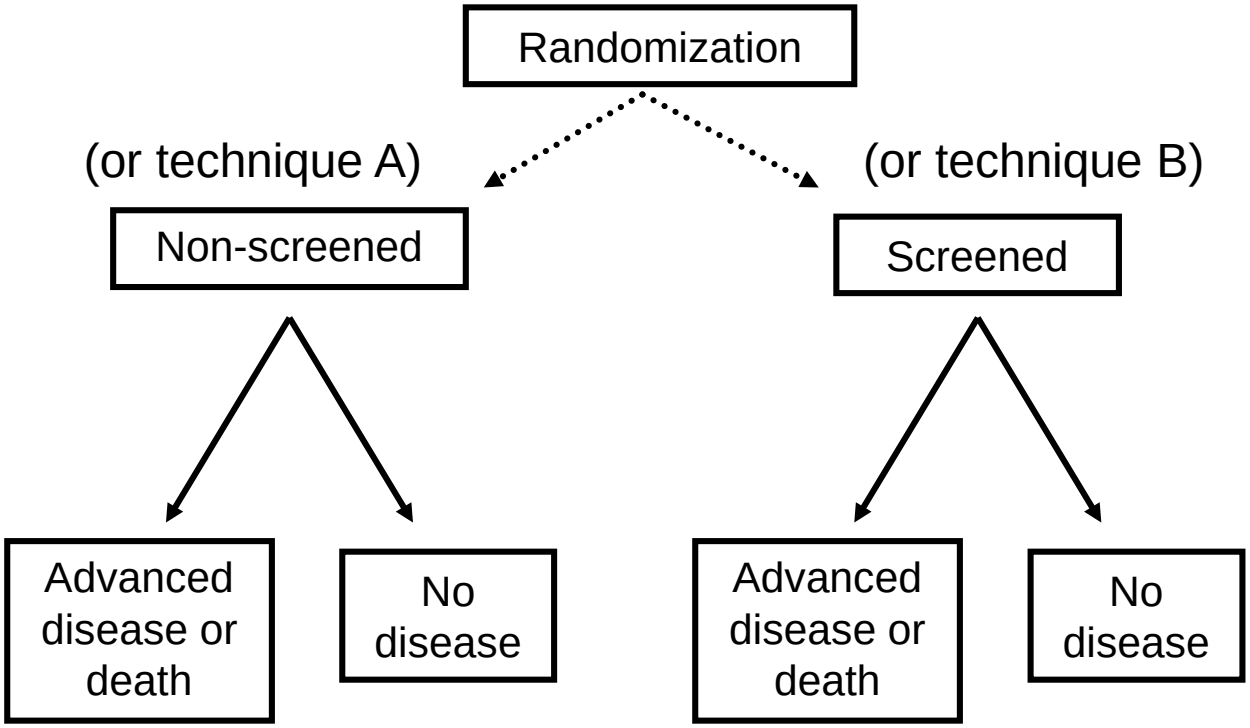


Slippery Linkage Bias

(Black et al., JNCI 2002)

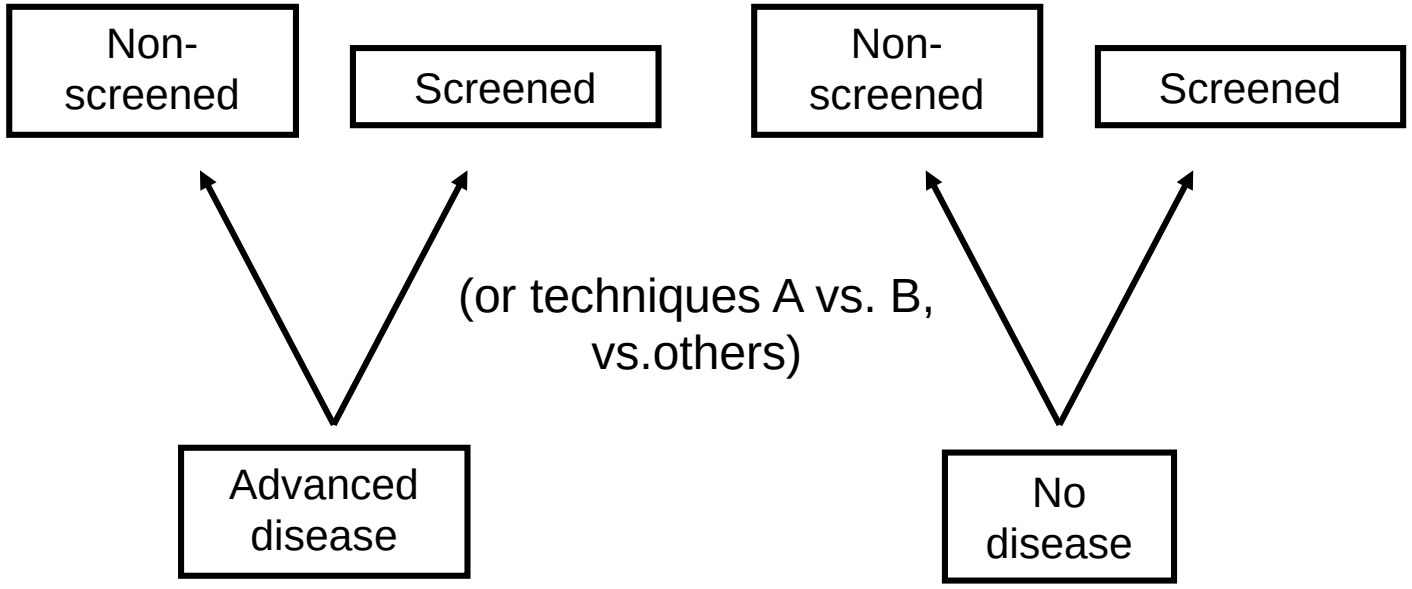
- In an RCT, more subjects undergo invasive procedures and treatment in the screened group than in the control group
- These interventions may lead to deaths which may not be assigned to the screening intervention (i.e., they slip away from appropriate linkage)
- Example: Excess cardiovascular deaths in the screening arm of the Minnesota Colon Cancer Study

Randomized Controlled Trial versus Cohort Study to assess Screening Efficacy



Type	Design	Concerns
RCT	Randomization	Differential dropout Loss to F/up Non-compliance Contamination
Cohort study	No randomization	Selection bias Confounding Differential dropout Loss to F/up

Case-Control Study to assess Screening Efficacy



Type	Concerns
Case-control study	Selection bias Confounding Protopathic bias Differential misclassification of screening Hx via recall bias

Evidence for efficacy of Pap smear screening in cervical cancer

Level 3:

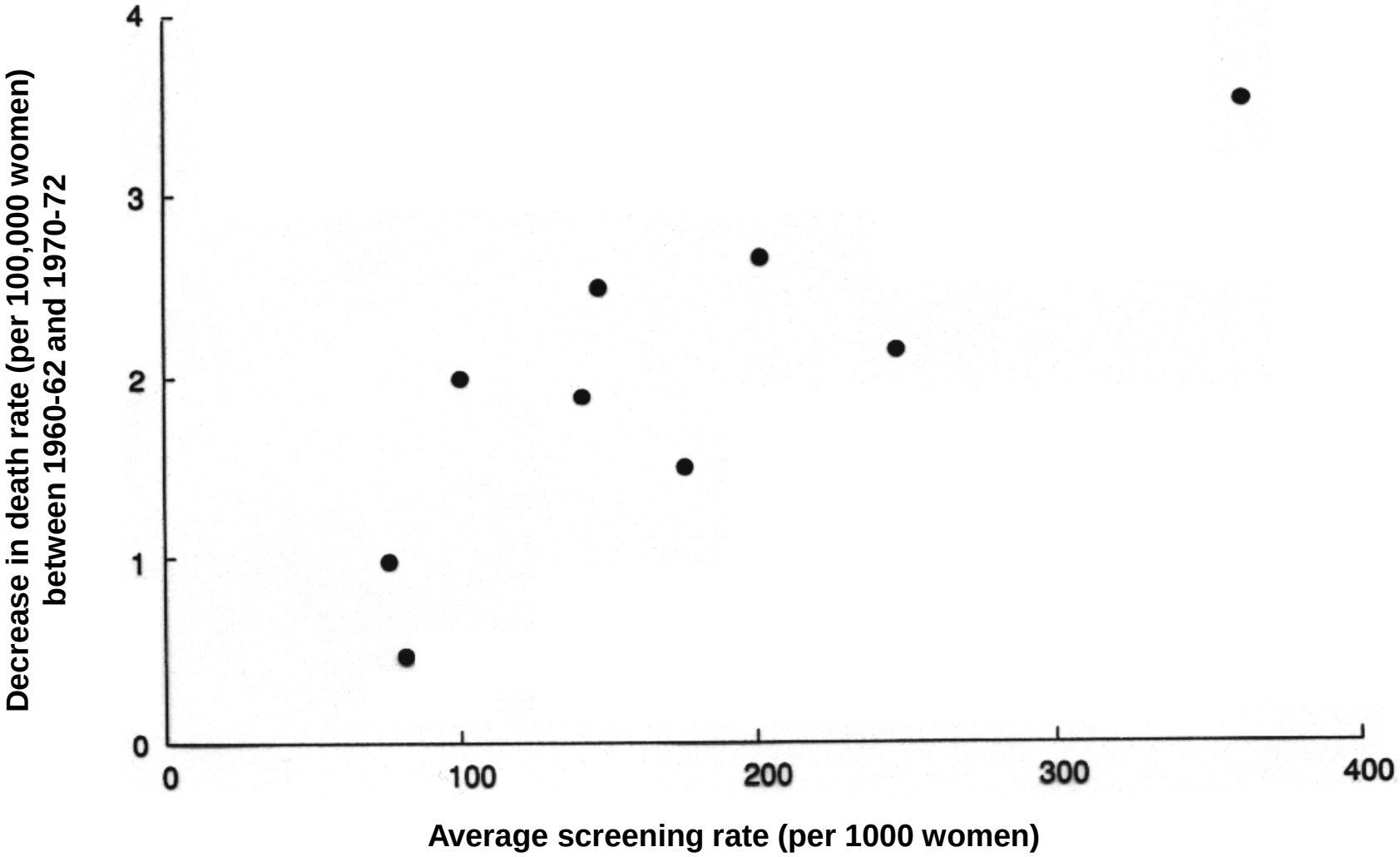
- ✓ Case-control studies indicate that risk of invasive cervical cancer is 2-10 times greater in women who have not been screened.
- ✓ Case-control studies indicate that risk increases with time since last normal smear or with lower frequency of screening.

Level 4:

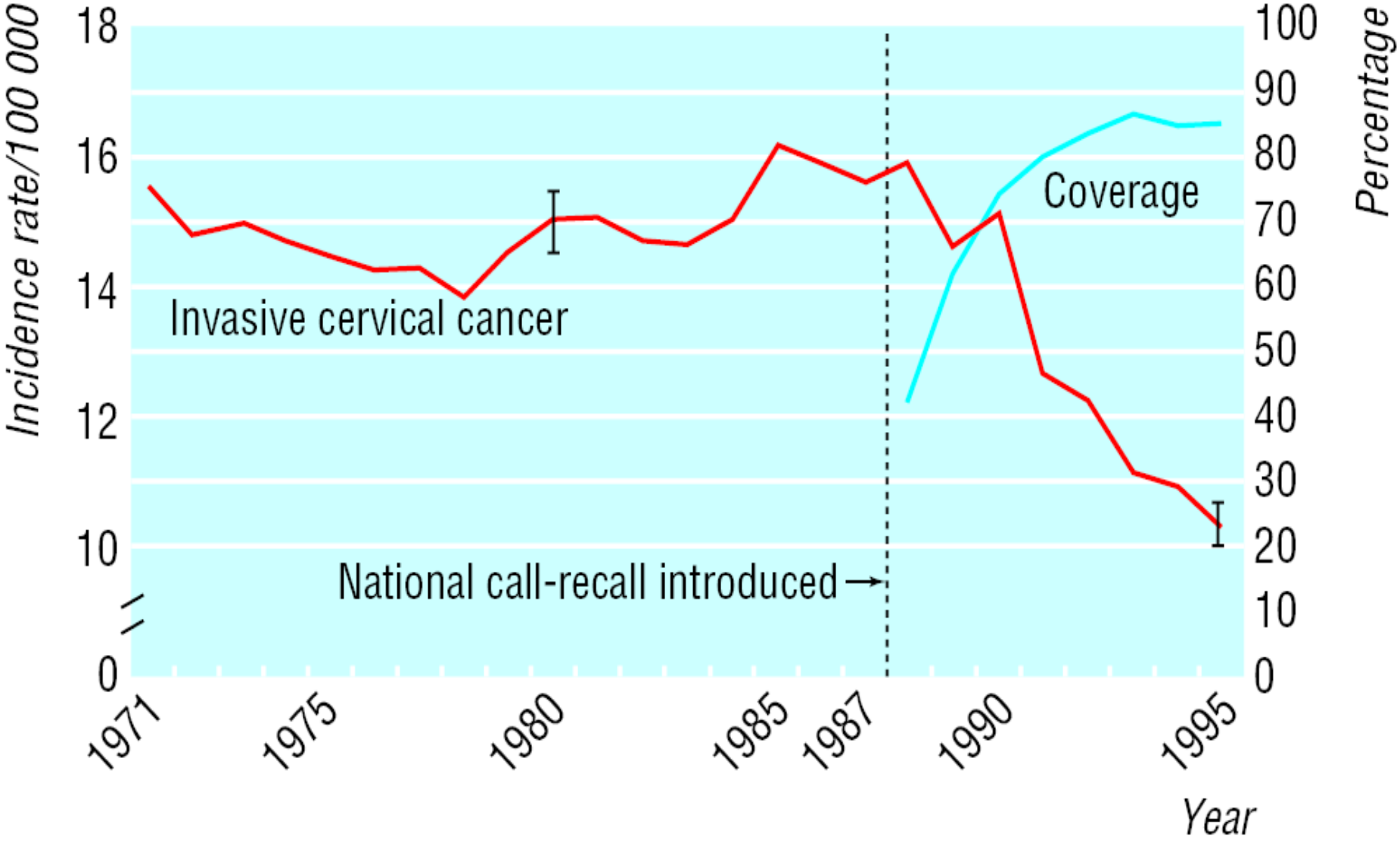
- ✓ Incidence and mortality has decreased sharply following introduction of cytology screening: Scandinavian countries, Canada, and US.
- ✓ Reductions in incidence and mortality seem to be proportional to the intensity of screening efforts, i.e., proportion of population covered: Scandinavian countries and Canadian provinces.

Level 5:

- ✓ Multiple national and international consensus worldwide.



Relationship between intensity of Pap cytology screening and decrease in mortality from cervical cancer in Canadian provinces (Source: Boyes et al., 1977; WHO)



Age standardized incidence of invasive cervical cancer and coverage of screening, England, 1971-95

(Quinn et al., BMJ 1999; 318: 9048)

Relative risks of cervical cancer for cytology screening variables in NCI's Latin American study

	Cases	Controls	RR[a]	95% CI
Ever had a Pap smear				
Yes	381	1015	1.0	
No	372	409	2.5	(2.4-3.3)
Unknown	6	6		
Interval since last Pap smear				
12-23 months	123	384	1.0	
24-47 months	109	345	1.0	(0.7-1.3)
48-71 months	45	84	1.7	(1.0-2.5)
72-119 months	28	66	1.4	(0.8-2.3)
>=120 months	38	73	1.8	(1.0-2.5)
Never	372	409	3.0	(2.3-4.0)
Unknown	44	69	2.1	(1.3-3.4)
Approximate number of lifetime smears				
>= 10	73	254	1.0	
3-9	105	300	1.1	(0.9-1.8)
2	53	158	1.1	(0.8-1.8)
1	167	257	2.2	(1.5-3.1)
0	334	383	3.1	(2.4-4.8)
History of a previous abnormal Pap smear				
No	236	772	1.0	
Yes	50	63	2.5	(1.2-3.6)

[a] Adjusted for age

Adapted from Herrero et al IJE 21: 1050, 1992

How good is Pap cytology in cervical cancer screening?

- Duke Report (Nanda et al., 2000): Considering only studies free of verification bias: sensitivity: 51%, specificity: 98%

- Pooled analysis of European and Canadian studies (Cuzick et al., 2006): sensitivity = 53% (CIN2+) and specificity = 96%

- Cytology screening programmes have to compensate for the low sensitivity by requiring 2-3 annual Pap tests before screening can be done less frequently

- Approximate programme sensitivity for:

  2 consecutive annual Pap tests: 51% + 51% of 49% = 76%
  3 consecutive annual Pap tests: 76% + 51% of 24% = 88%

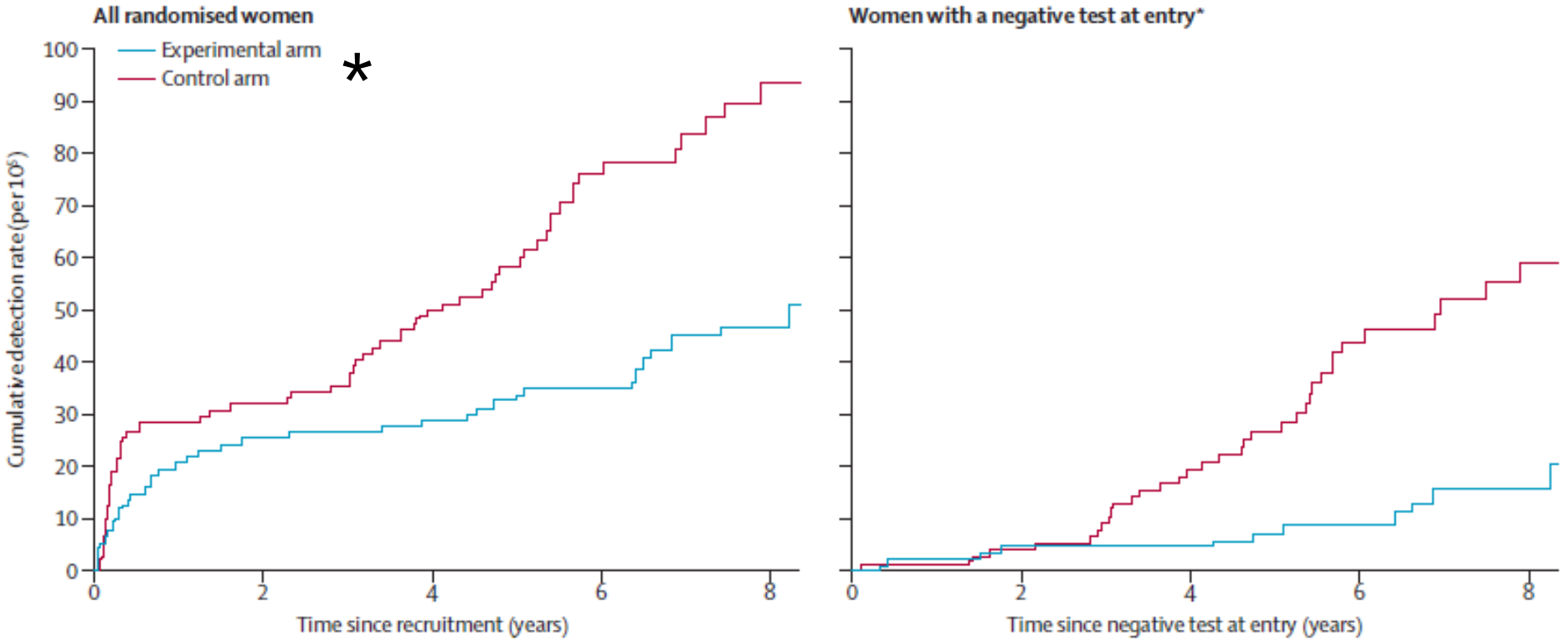
Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

Lancet 2014; 383: 524–32

*Guglielmo Ronco, Joakim Dillner, K Miriam Elfström, Sara Tunesi, Peter J F Snijders, Marc Arbyn, Henry Kitchener, Nereo Segnan, Clare Gilham, Paolo Giorgi-Rossi, Johannes Berkhof, Julian Peto, Chris J L M Meijer, and the International HPV screening working group**

- 4 RCTs: Swedescreen (Sweden), POBASCAM (The Netherlands), ARTISTIC (England), and NTCC (Italy).
- 176,464 women aged 20–64 years were randomly assigned to HPV-based (experimental arm) or cytology-based (control arm) screening.
- Women were followed up for a median of 6.5 years: total of 1,214,415 person-years.
- 107 invasive cervical carcinomas were identified by linkage with screening, pathology, and cancer registries, by masked review of histological specimens, or from reports.

Cumulative detection of invasive cervical carcinoma in the pooled analysis of European RCTs (Ronco et al., Lancet 2014)



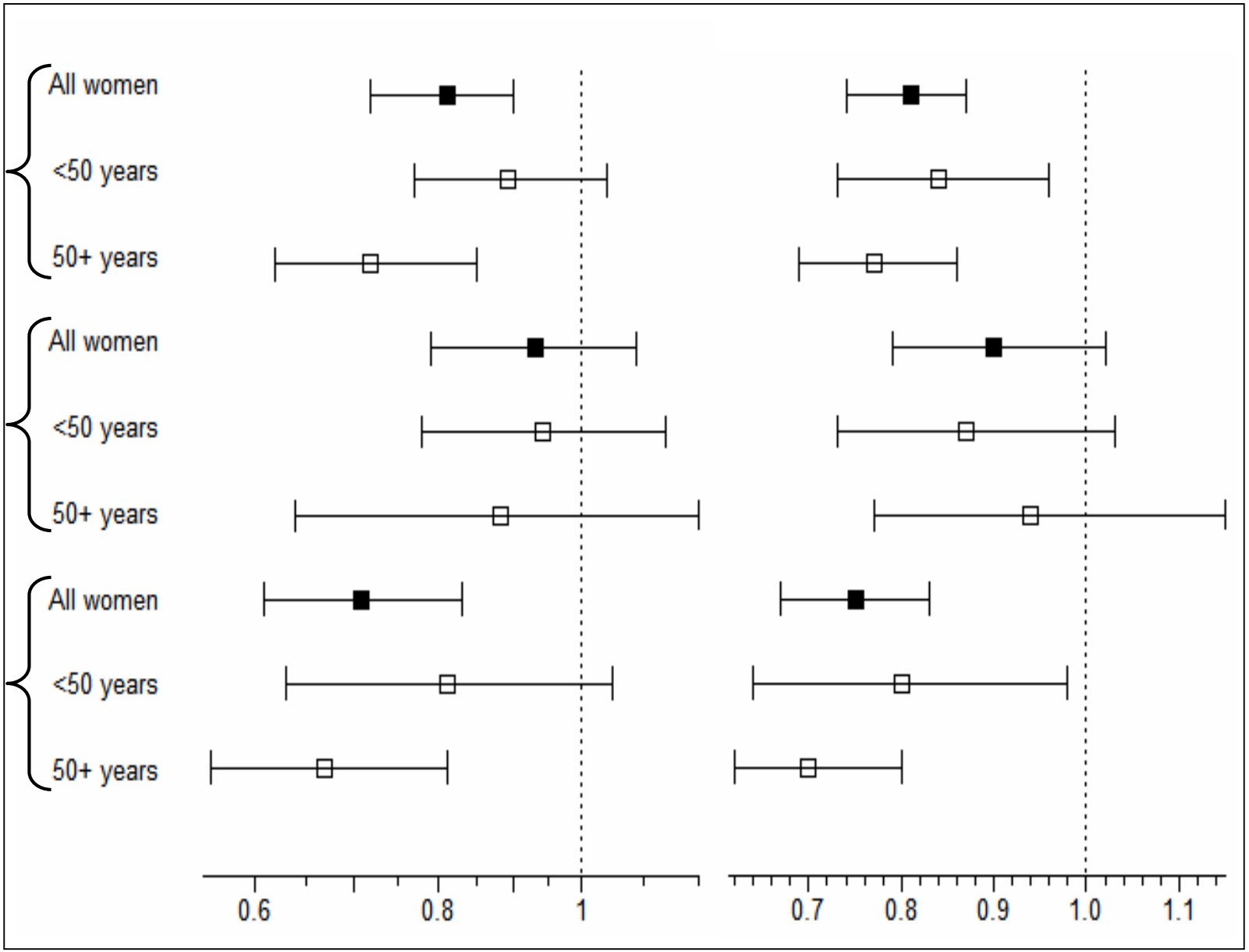
Cancer type	Rate ratio (Exp:Cont) (95%CI)	
All ICCs	0.60 (0.40-0.89)	0.30 (0.15-0.60)
SCC only	0.78 (0.49-1.25)	
Adenocarcinoma	0.31 (0.14-0.69)	

* Experimental=HPV-based; Control: cytology-based

Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography (Review). Cochrane Library 2009, Issue 4

- Objectives: To assess the effect of mammography screening for BrCa on mortality and morbidity.
- Search strategy: PubMed (November 2008).
- Selection criteria: Randomised trials comparing mammography with no mammography.
- Main results: 8 eligible trials identified. One biased trial excluded; 600,000 women included in the analyses.
  - 3 trials with adequate randomisation did not show a significant reduction in BrCa mortality at 13 years (RR=0.90, 95%CI: 0.79-1.02);
  - 4 trials with suboptimal randomisation showed a significant reduction in BrCa mortality (RR=0.75, 95%CI: 0.67-0.83);
  - All 7 trials combined: RR=0.81, 95%CI: 0.74-0.87.

2009 Cochrane review: Summary RRs of BrCa mortality *



* Mammography vs. usual care

7 years follow-up

13 years follow-up

Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography (Review). Cochrane Library 2009, Issue 4

Conclusions:

- Screening likely to reduce BrCa mortality by 15% but at the expense of 30% overdiagnosis and overtreatment.
- For every 2000 women invited for screening throughout 10 years
  - 1 will have her life prolonged and
  - 10 healthy women, who would not have been diagnosed without screening, will be treated unnecessarily
  - > 200 women will experience psychological distress for many months because of false positive findings.

US Preventive Services Task Force - Screening for Breast Cancer

Release Date: November 2009 - Updated: December 2009 – Updated January 2016

- Biennial screening mammography for women aged 50 to 74 years: B recommendation.
- The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between the ages of 40 and 49 years: C recommendation.
- Current evidence is insufficient to assess the additional benefits and harms of screening mammography in women 75 years or older: I Statement.
- Recommends against teaching breast self-examination (BSE): D recommendation.
- Current evidence is insufficient to assess the additional benefits and harms of clinical breast examination (CBE) beyond screening mammography in women 40 years or older: I Statement.
- Current evidence is insufficient to assess the additional benefits and harms of either digital mammography or magnetic resonance imaging (MRI) instead of film mammography as screening modalities for breast cancer: I Statement.

http://www.uspreventiveservicestaskforce.org/uspstf/uspsbrca.htm

Ilic D, O'Connor D, Green S, Wilt T. Screening for prostate cancer. Cochrane Library 2009, Issue 4

- Objectives: To determine whether prostate cancer screening reduces prostate cancer mortality.
- Search strategy: Multiple databases (May 2006).
- Main results: 2 RCTs met inclusion criteria (Quebec, Sweden), 55,512 men included in analyses (ITT), PSA and DRE used alone or in combination in different screening rounds.
    - No significant difference in prostate cancer mortality (RR=1.01, 95%CI: 0.80-1.29);
    - 47% more cancers diagnosed
    - Screening compliance poor in Quebec trial
- Conclusions: Insufficient evidence to support screening for reducing prostate cancer mortality

US Preventive Services Task Force - Screening for Prostate Cancer - Release Date: May 2012

- Recommends against PSA-based screening for prostate cancer: D Recommendation

This recommendation applies to men in the general U.S. population, regardless of age. This recommendation does not include the use of the prostate-specific antigen (PSA) test for surveillance after diagnosis or treatment of prostate cancer; the use of the PSA test for this indication is outside the scope of the USPSTF.

http://www.uspreventiveservicestaskforce.org/prostatecancerscreening.htm

Blunting of effects: Intent-to-treat versus Per-protocol analyses

Labrie F, Candas B, Cusan L, Gomez JL, Belanger A, Brousseau G, Chevrette E, Leveseque J. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. Prostate 2004;59:311-18.

- Screening compliance: Intervention=23.6%; Control=7.3%
- Per-protocol analysis: Prostate cancer mortality reduction comparing screened in both groups versus not screened in both groups: RR=0.39, 95%CI: 0.19-0.65.
- ITT analysis by Cochrane team: RR=1.01, 95%CI: 0.76-1.33

RCTs are prone to dilution effects

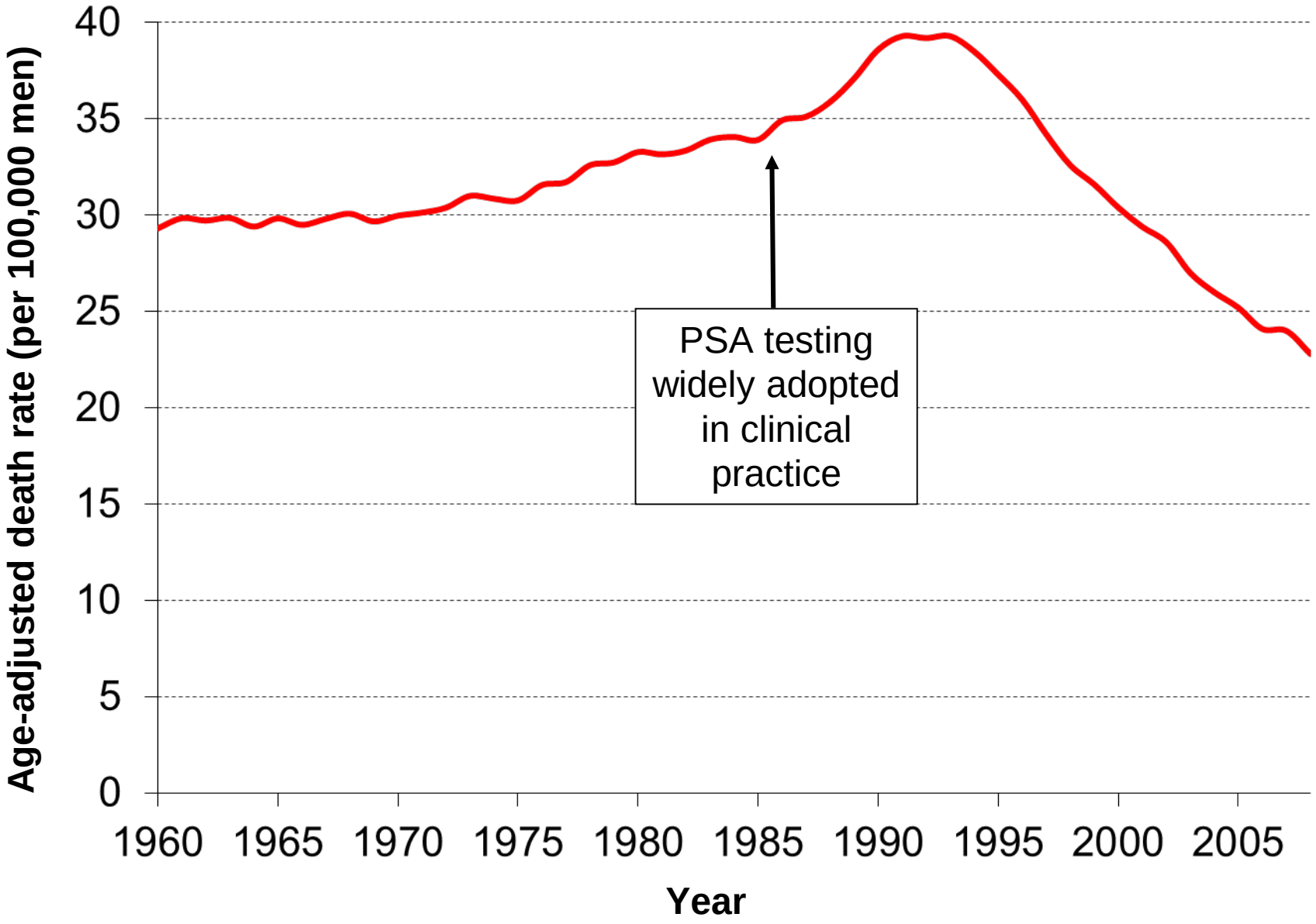
PLCO trial of PSA testing (Andriole et al., NEJM 2009;360:1310-9)

- 76,693 men randomly assigned to annual screening or usual care in 10 U.S. centers.
- Screening intervention: offered annual PSA for 6 years (85% compliance) and DRE for 4 years (86% compliance).
- Control group: Rates of PSA screening were 40%-52% and 41%-46% for DRE.

➢ Prostate cancer incidence: RR=1.22, 95%CI: 1.16-1.29.

➢ Prostate cancer mortality: RR=1.13; 95%CI: 0.75-1.70.

Decline in prostate cancer mortality in the US since the early 90's



Age-adjusted to the 2000 US population; Source: American Cancer Society, Surveillance Research

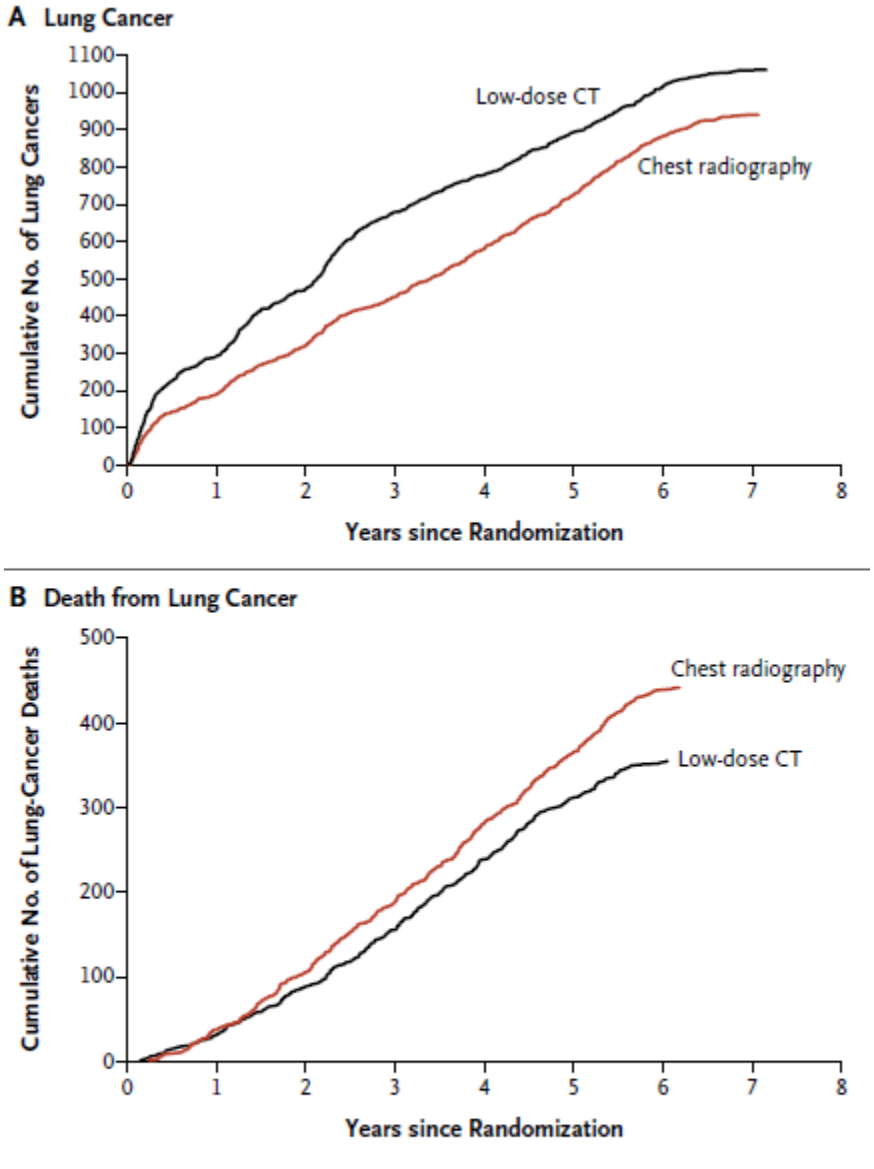


Figure 1. Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer.

The number of lung cancers (Panel A) includes lung cancers that were diagnosed from the date of randomization through December 31, 2009. The number of deaths from lung cancer (Panel B) includes deaths that occurred from the date of randomization through January 15, 2009.

National Lung Screening Trial
N Engl J Med 2011;365:395-409

- 53,454 individuals aged 55-74,
- History of > 30 pack-years, quit within last 15 years if former smokers
- 3 annual screens with low-dose CT or chest x-rays
- Enrolment: 2002-04
- Follow-up: until the end of 2009

Relative reduction in lung cancer mortality: 20% (P=0.004)

Relative reduction in all-cause mortality: 6.7% (P=0.02)

U.S. Preventive Services Task Force's Recommendations*

Cancer	Method	Target Population	Grade
Bladder	Hematuria, urine cytology, urine biomarkers	Adults	I
Breast	Mammography (biennial)	Women aged 50-74	B
		Women 40-49	C
	Breast self-examination	All ages	D
	Clinical breast examination		I
	Digital mammography, magnetic resonance imaging		I
Cervix	Pap cytology every 3 years	Women aged 21-65	A
	HPV testing plus cytology every 5 years	Women aged 30-65	A
Colo-rectal	FOB testing, sigmoidoscopy, colonoscopy	Adults 50-75 years	A
		Adults 76-85 years	C
		Adults > 85 years	D
	Computed tomographic colonography and fecal DNA	Adults 50-75 years	I
Lung	Low-dose computerized tomography	55-80 yrs ever smokers (30 PY)	B
	Chest x-ray, sputum cytology	Asymptomatic adults	I
Oral	Direct inspection and palpation	Adults	I
Ovarian	CA-125, ultrasound, or pelvic examination	Adult women	D
Pancreas	Abdominal palpation, ultrasound, serologic markers	Asymptomatic adults	D
Prostate	PSA test, digital rectal examination	Men of all ages	D
Skin	Whole-body skin examination	Average risk persons	I
Testicular	Clinical examination	Asymptomatic young men	D

*As of 2014

http://www.uspreventiveservicestaskforce.org/uspstopics.htm#AZ

Additional Slides

Supplement to points discussed in the articles to cover the topic of mediated analysis

Using Mediated Analysis to Assess Etiologic Pathways

Epidemiologic Evidence Showing That Human Papillomavirus Infection Causes Most Cervical Intraepithelial Neoplasia

JNCI 85: 958-964, 1993

*Mark H. Schiffman, Heidi M. Bauer, Robert N. Hoover, Andrew G. Glass, Diane M. Cadell, Brenda B. Rush, David R. Scott, Mark E. Sherman, Robert J. Kurman, Sholom Wacholder, Cynthia K. Stanton, M. Michele Manos**

Sexual behaviour

↓

HPV infection

↓

CIN

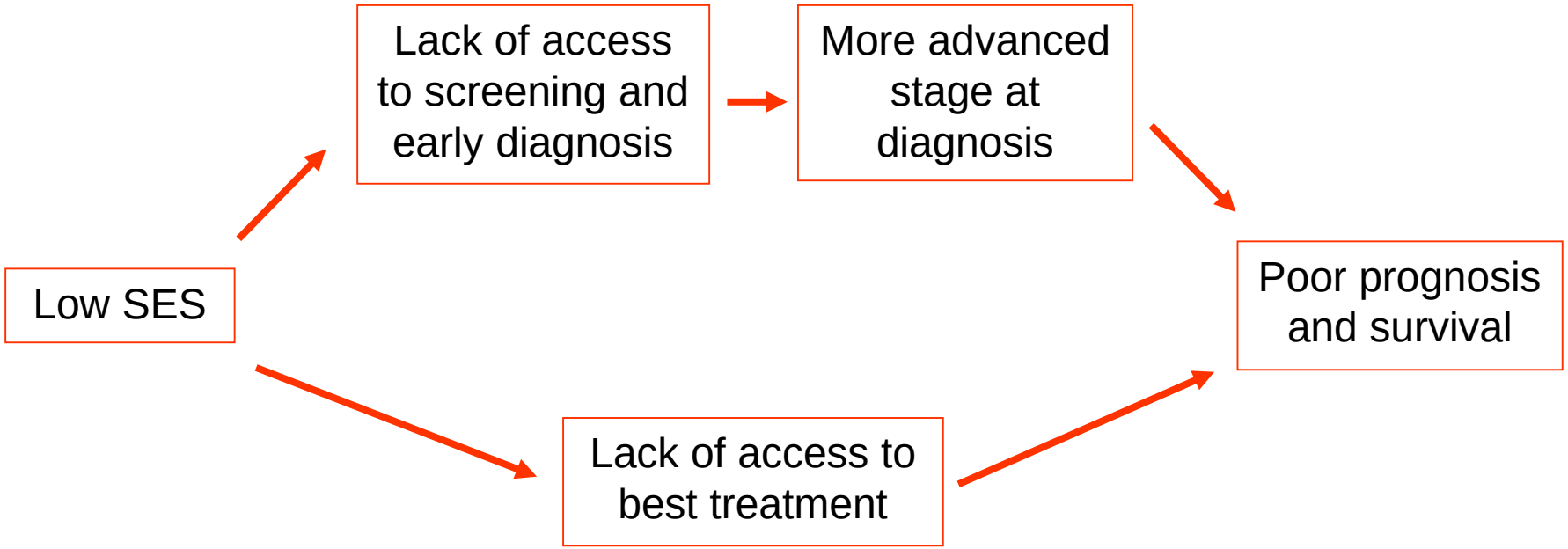
Risk factor	RR #1*	RR #2†	RR #3 (95% CI)‡
Lifetime No. of sex partners			
1	1-	1-	1-
2	1.6	1.6	1.0 (0.5-2.1)
3-5	2.6§	2.4§	1.2 (0.6-2.1)
6-9	4.2§	4.1§	1.8 (1.0-3.4)
10+	4.4§	4.4§	1.8 (1.0-3.3)

From table 2: RR#1: adjusted for age in sextiles

RR#2: adjusted for age, age at 1st intercourse, education, income, smoking, OC use, parity

RR#3: adjusted for age and HPV test results

Gorey KM, Holowary EJ, Fehringer G, Laukkanen E, Moskowitz A, Webster DJ, Richter NL. An international comparison of cancer survival: Toronto, Ontario, and Detroit, Michigan, metropolitan areas. Am J Public Health. 1997 Jul;87(7):1156-63.



Hypothesis: SES has a differential effect on the survival of adults diagnosed with cancer in Canada and the United States

Ontario Cancer Registry and US NCI's SEER program provided a total of 58,202 and 76,055 population-based primary cancer cases for Toronto and Detroit, respectively

SES data for each person's residence taken from population censuses

Compared 1- and 5-yr survival rates by low, middle, and high SES (contextual)

In the US cohort, there was a significant association between SES and survival for 12 of the 15 most common cancer sites (low SES=worse).

In the Canadian cohort, only 3 of the 15 sites showed an association but with no clear trend.

Patients of low-income areas in Toronto experienced a survival advantage for 13 of 15 cancer sites at 1- and 5-year follow-up.

Gorey et al., AJPH 1997

TABLE 3—Cancer Survival Rate Ratios for Residents of Lowest-Income Areas: Toronto, Ontario, vs Detroit, Mich

Cancer Site	1-Year Survival SRR	1-Year Survival (95% CI)[a]	5-Year Survival SRR	5-Year Survival (95% CI)[a]
Women				
Lung–bronchus	1.19	(1.09, 1.29)	1.58	(1.19, 2.10)
Breast	1.06	(1.04, 1.08)	1.30	(1.23, 1.38)
Colon	1.06	(1.01, 1.12)	1.39	(1.20, 1.61)
Bladder	1.19	(1.08, 1.31)	1.46	(1.15, 1.85)
Rectum	1.06	(0.99, 1.13)	1.09	(0.88, 1.35)
Non-Hodgkin's lymphoma	1.07	(0.97, 1.18)	1.27	(0.96, 1.69)
Corpus uterus	1.18	(1.13, 1.23)	1.34	(1.21, 1.49)
Stomach	1.02	(0.87, 1.20)	1.64	(0.93, 2.90)
Oral	1.16	(1.05, 1.28)	1.40	(1.08, 1.81)
Pancreas	1.22	(0.91, 1.63)	1.81	(0.55, 5.93)
Kidney	1.19	(1.07, 1.33)	1.39	(1.04, 1.86)
Ovary	1.12	(1.03, 1.22)	1.38	(1.06, 1.80)
Cervix uterus	1.17	(1.12, 1.23)	1.48	(1.25, 1.76)
Brain–CNS	1.70	(1.27, 2.28)	2.46	(1.12, 5.38)
Men				
Lung–bronchus	1.19	(1.11, 1.27)	1.97	(1.58, 2.46)
Prostate	1.10	(1.08, 1.13)	1.21	(1.11, 1.32)
Colon	1.11	(1.06, 1.16)	1.38	(1.19, 1.60)
Bladder	1.14	(1.09, 1.19)	1.28	(1.11, 1.42)
Rectum	1.04	(0.98, 1.11)	1.13	(0.91, 1.40)
Non-Hodgkin's lymphoma	0.96	(0.87, 1.06)	1.09	(0.83, 1.43)
Stomach	1.28	(1.11, 1.48)	1.73	(1.12, 2.68)
Oral	1.21	(1.12, 1.31)	1.82	(1.45, 2.29)
Pancreas	1.40	(1.03, 1.91)	3.39	(1.32, 8.68)
Kidney	1.16	(1.03, 1.30)	1.54	(1.19, 1.99)
Brain–CNS	1.08	(0.86, 1.35)	1.57	(0.80, 3.09)

Using Mediated Analysis to Assess Prognostic Pathways

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RACE AND GENDER INFLUENCES ON THE SURVIVAL OF PATIENTS WITH MOUTH CANCER

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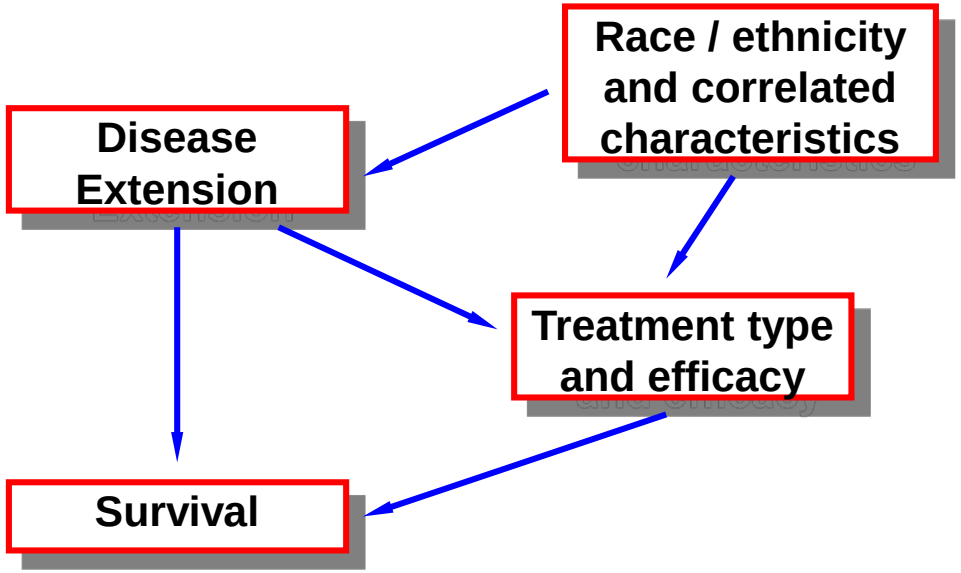


Hypotheses:

- Race/ethnicity associated with stage and treatment
- Association between race/ethnicity and survival is indirect via the prognostic effects of stage and treatment

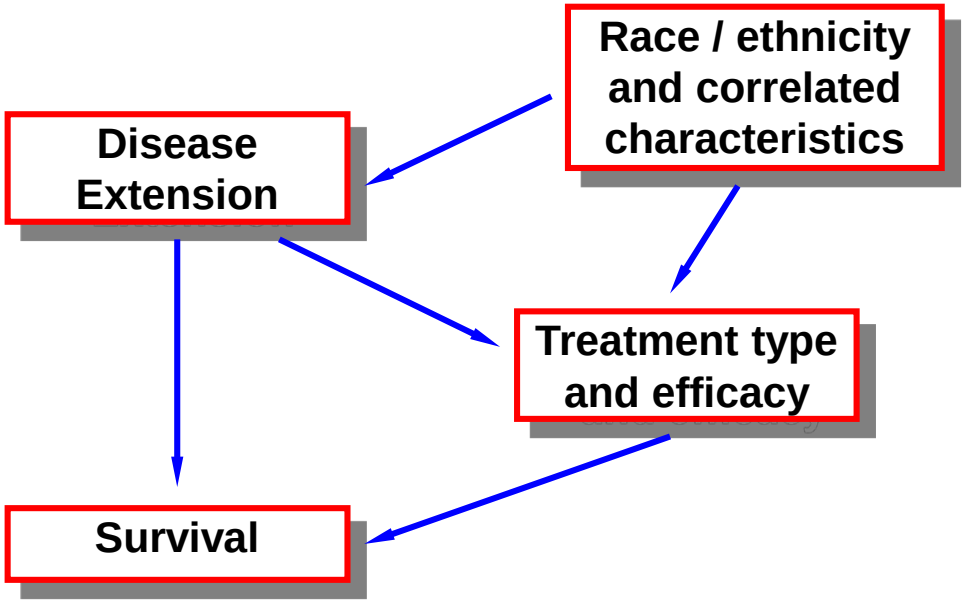
Race-specific (non-white vs. white) hazard ratios* for different clinical outcomes among 1847 patients with lip cancer

Variables adjusted for in the models	Hazard ratios (95% confidence limits) by outcome		
	All deaths	Deaths due to mouth cancer	Mouth cancer recurrence
None	2.46 (1.6, 3.9)	2.30 (1.3, 4.1)	2.08 (1.2, 3.6)
Gender, age, origin	2.32 (1.5, 3.7)	2.29 (1.3, 4.1)	2.11 (1.2, 3.7)
Above plus stage	1.57 (1.0, 2.5)	1.39 (0.8, 2.5)	1.28 (0.7, 2.3)
Above plus treatment	1.44 (0.9, 2.3)	1.17 (0.7, 2.1)	1.01 (0.6, 1.8)

* Cox's proportional hazards regression.

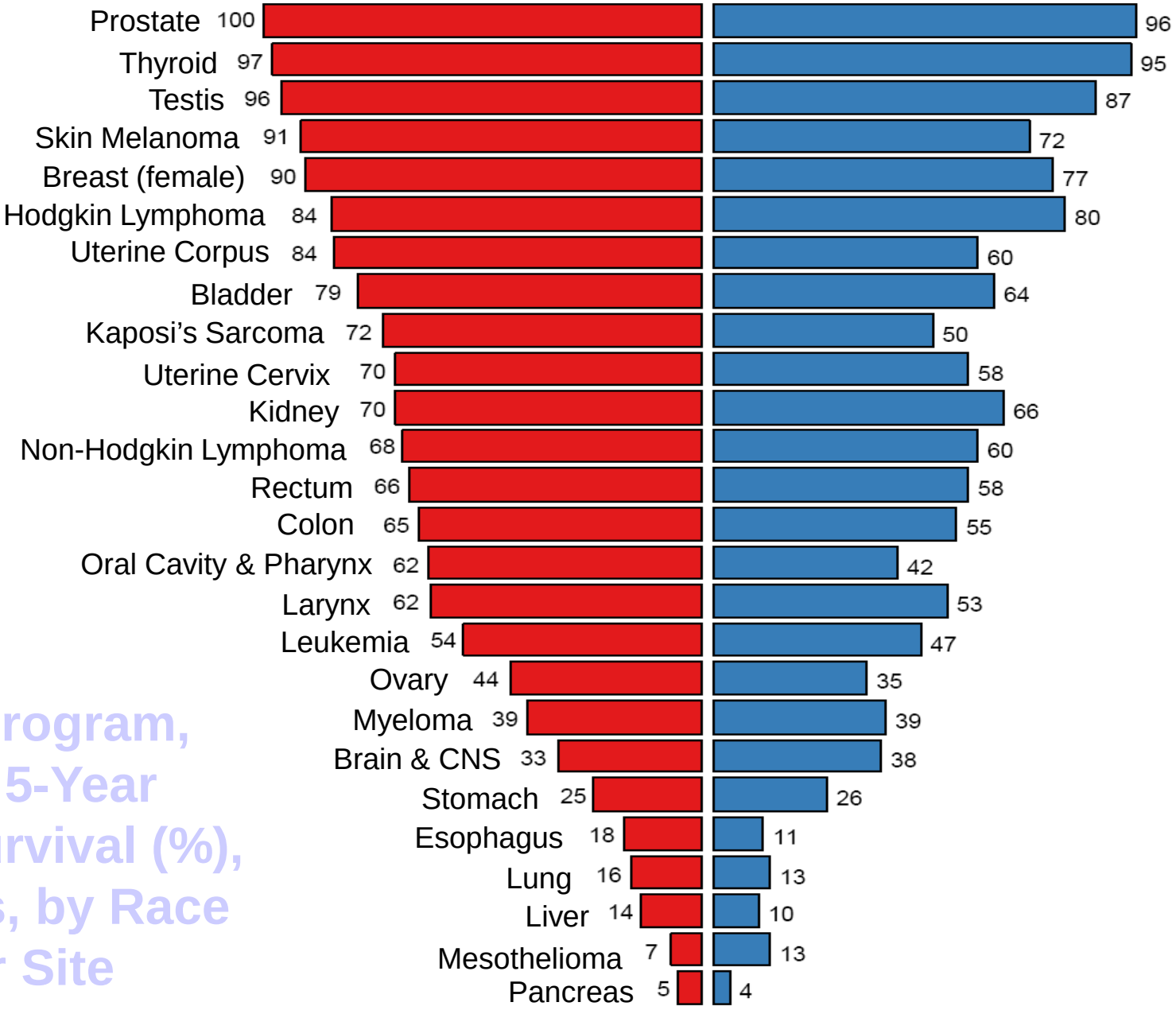
Hypotheses:

- Race/ethnicity associated with stage and treatment
- Association between race/ethnicity and survival is indirect via the prognostic effects of stage and treatment



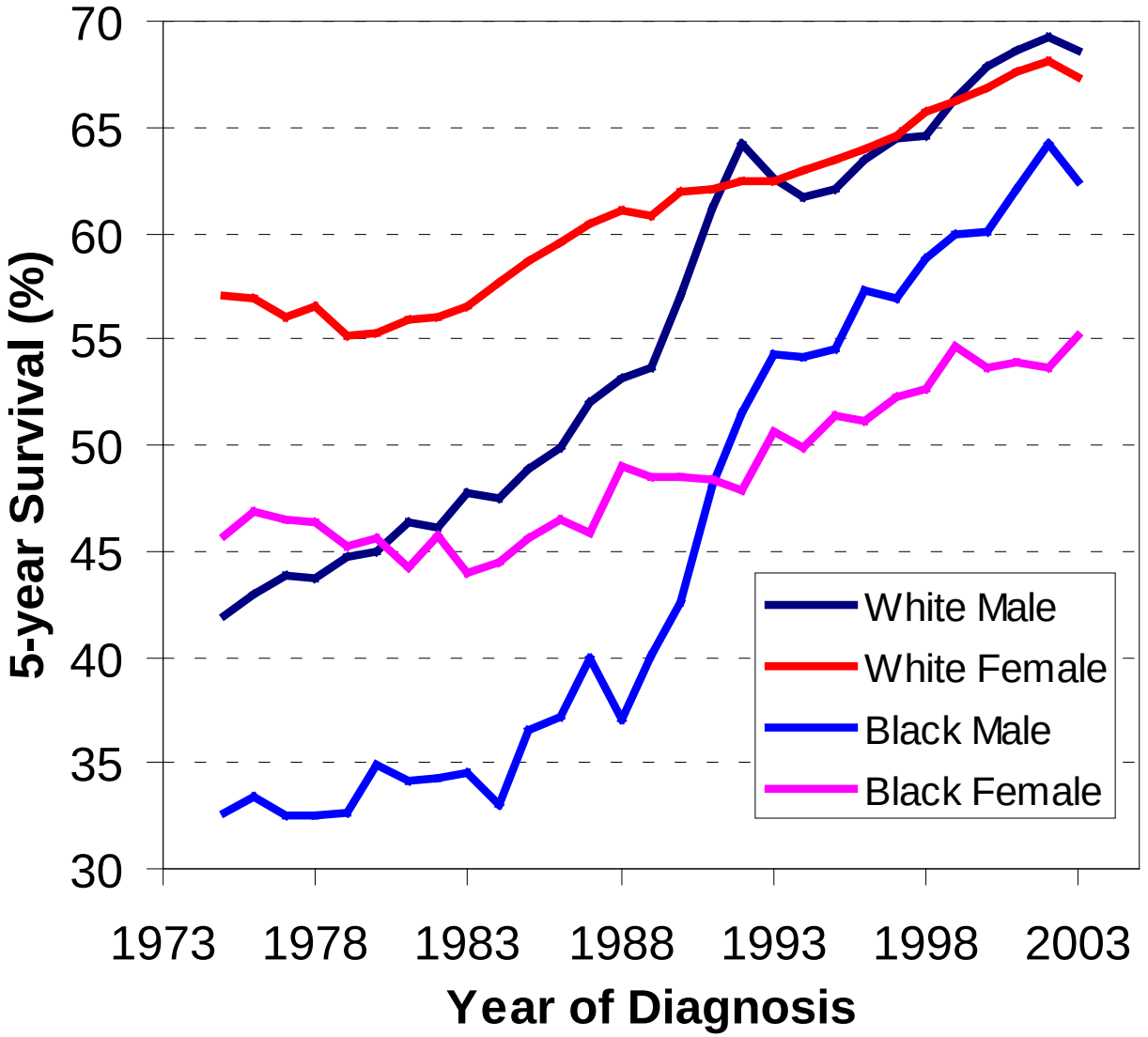
Franco et al., J. Clin. Epidemiol. 1993

US SEER Program, 2001-2007: 5-Year Relative Survival (%), Both Sexes, by Race and Cancer Site



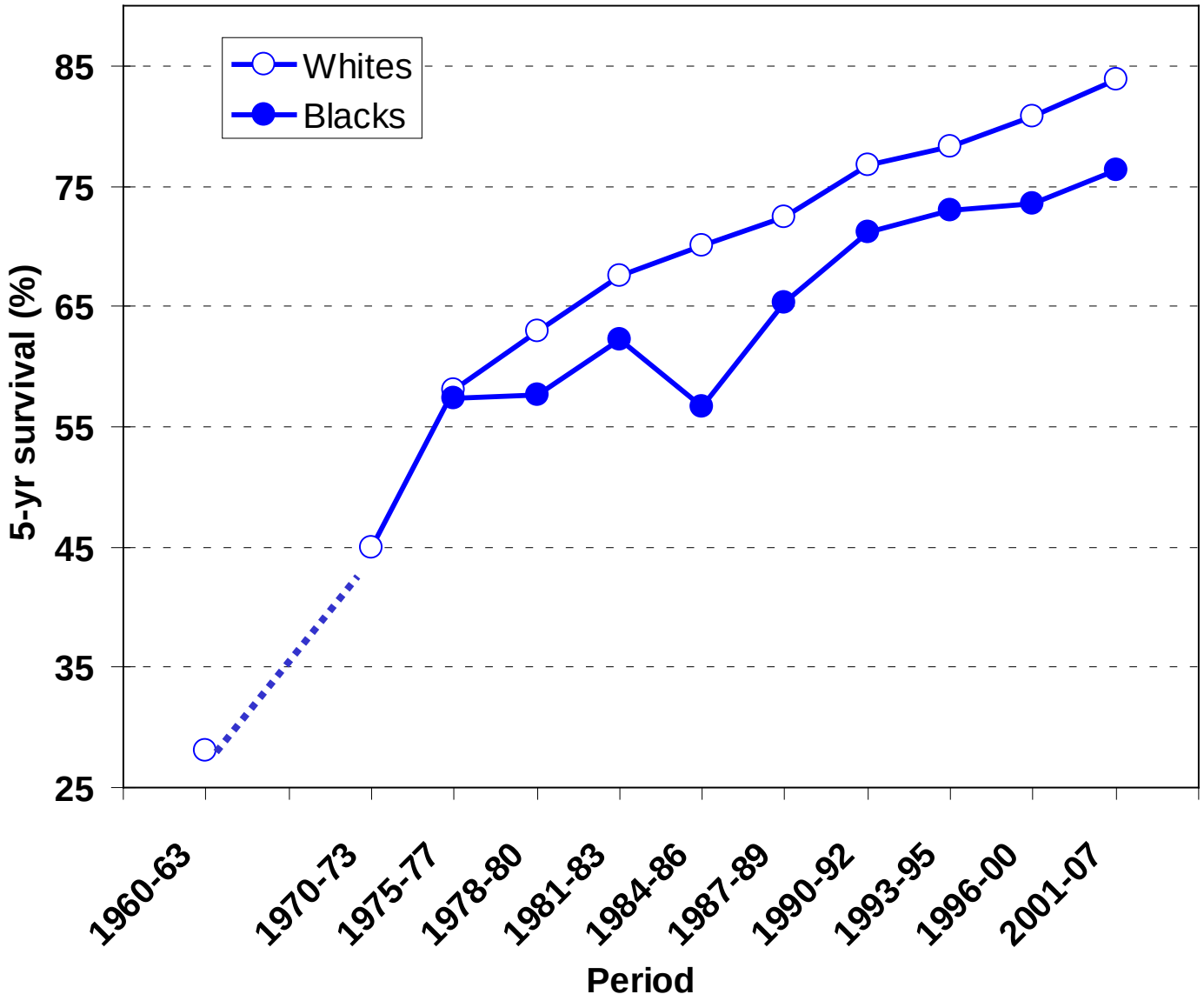
Source: Howlader et al (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/

US SEER program: 5-year relative survival for all sites of cancer, all ages, by gender and race



Source: Howlader et al (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/

5-year relative survival, 0-14 years, all sites, by race
US SEER program



Source: Howlader et al (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/