KIMMEL CANCER CENTER

Cumulative Risk Assessment: Some Thoughts

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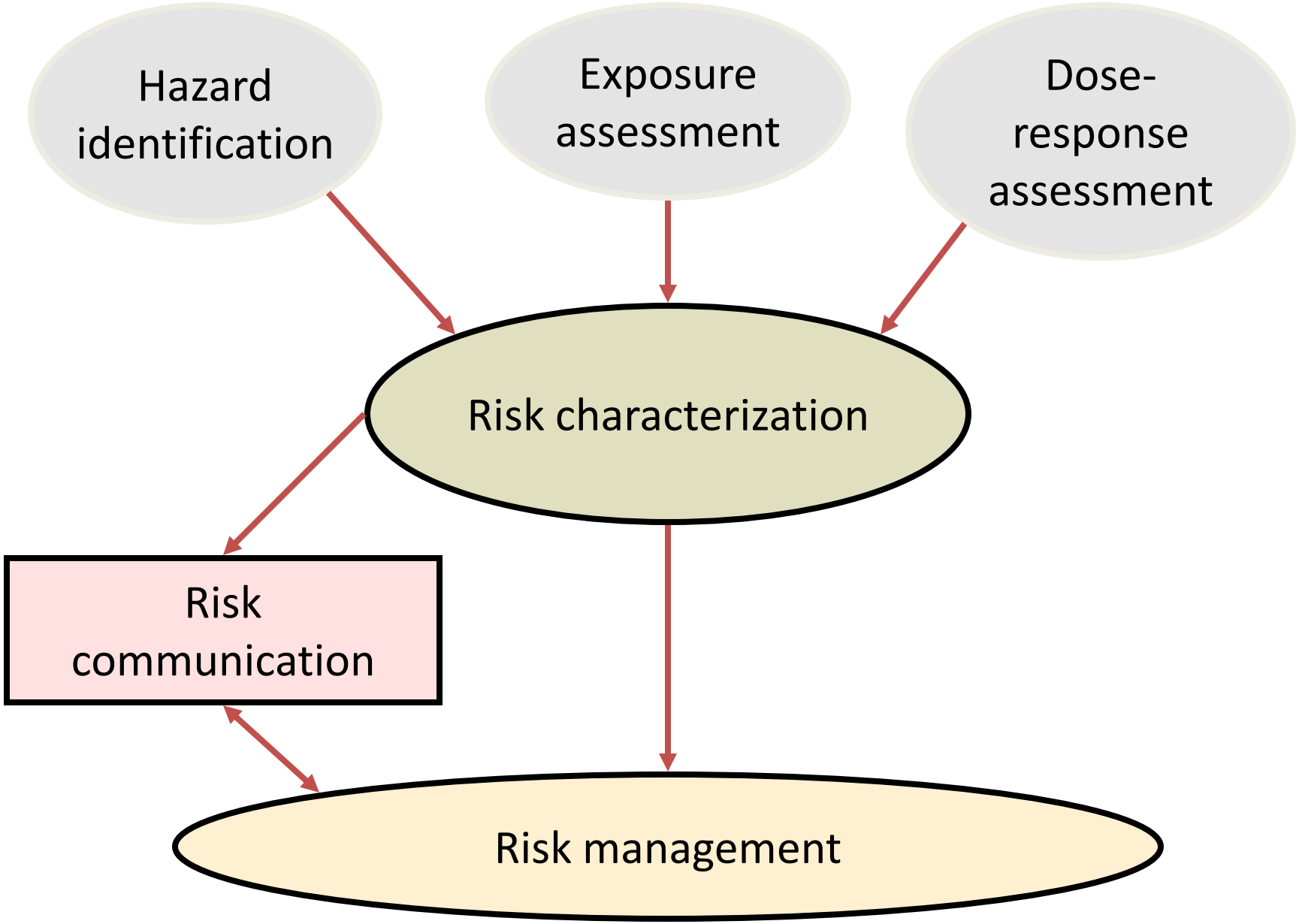
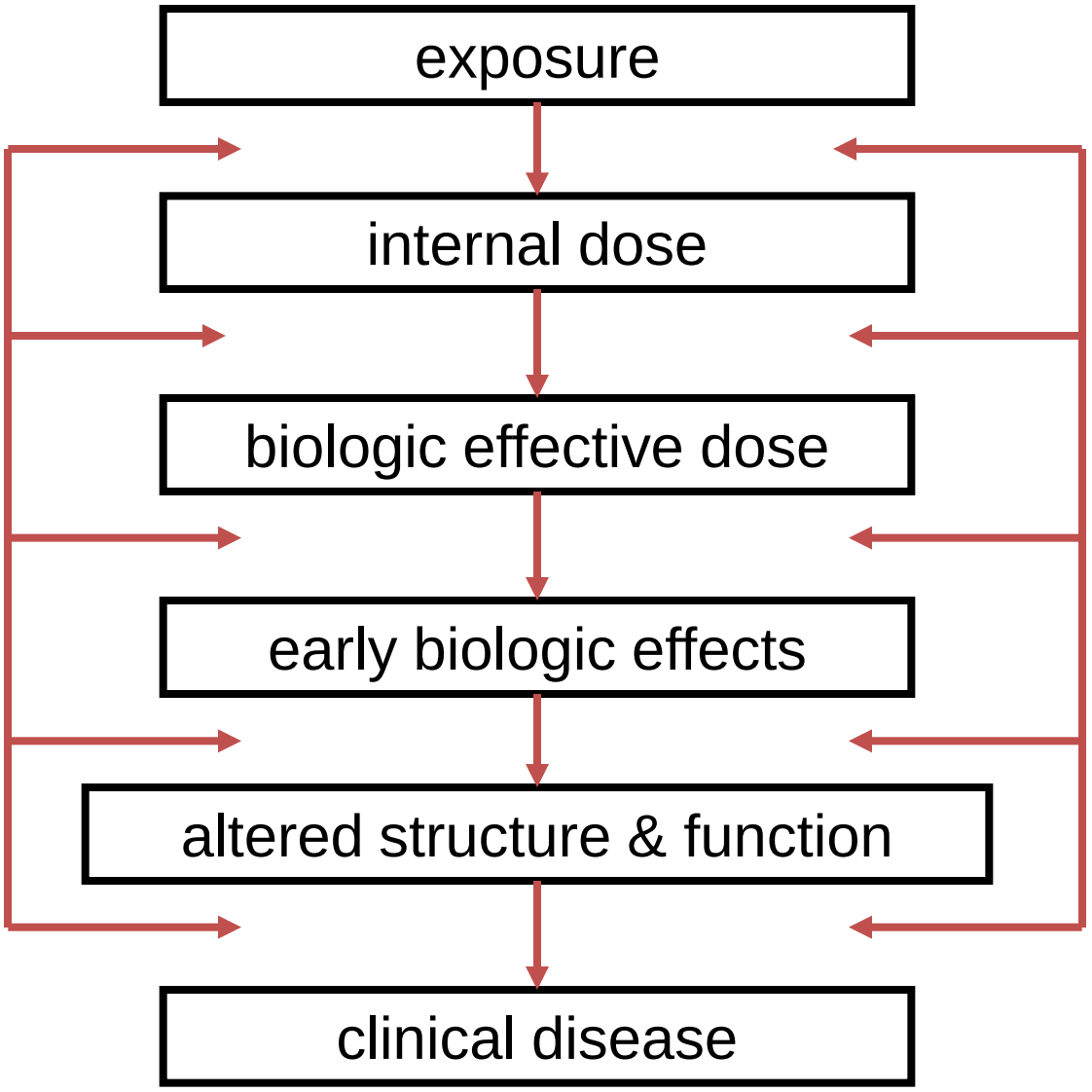
JOHNS HOPKINS MEDICINE


Hazard identification
Exposure assessment
Dose-response assessment
Risk characterization
Risk communication
Risk management

The Toxicological Paradigm

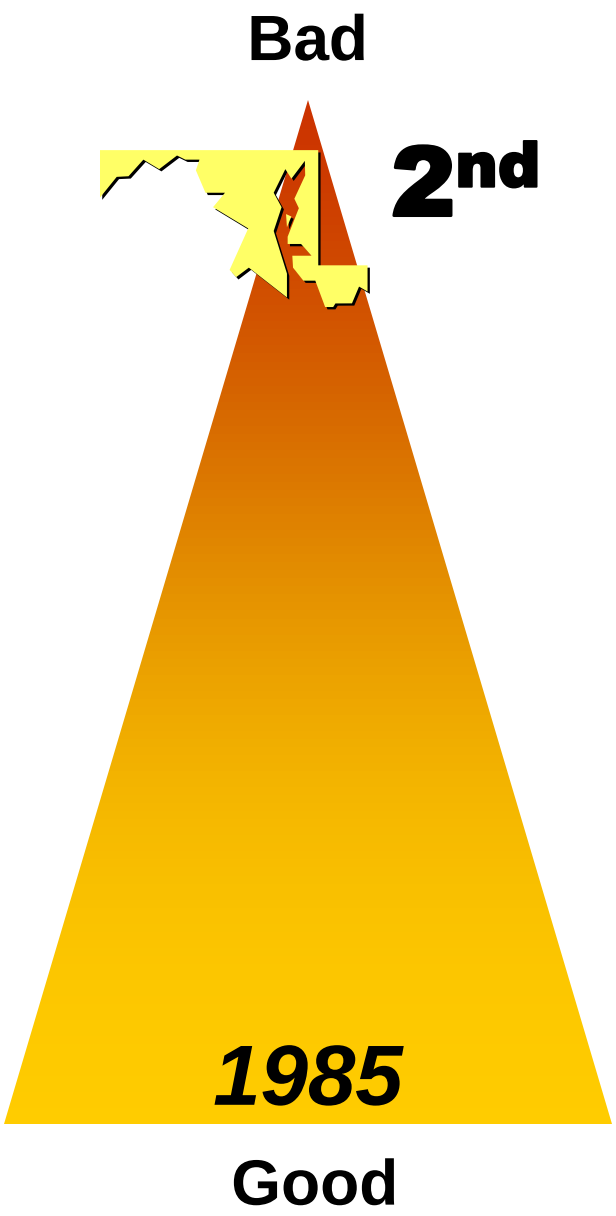


Susceptibility
genetic
factors

Effect
modifiers
diet
habits
health
medication
co-exposure

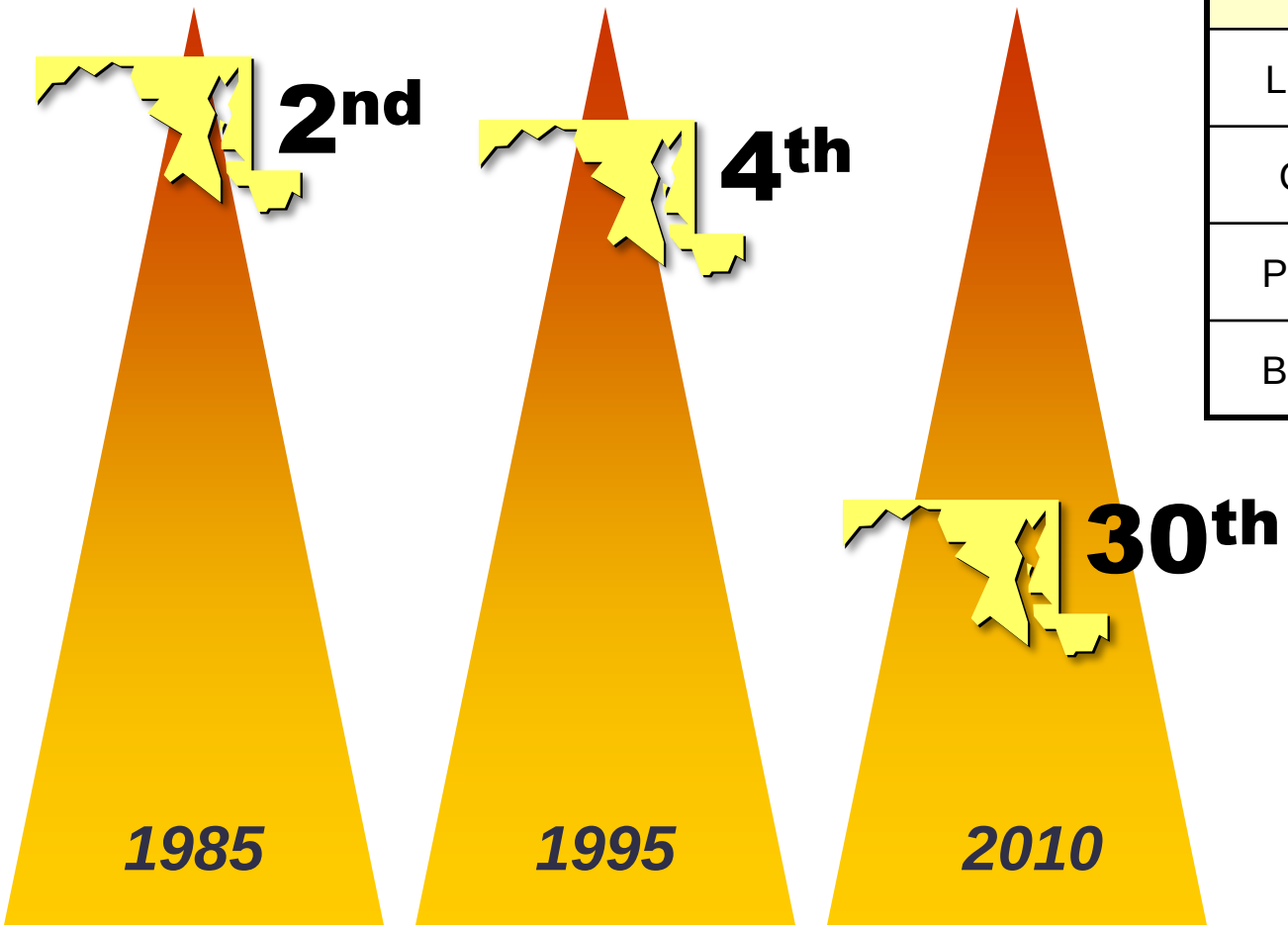
Changing Patterns in Cancer: Maryland

All Cancer Mortality Rank Among States and D.C.



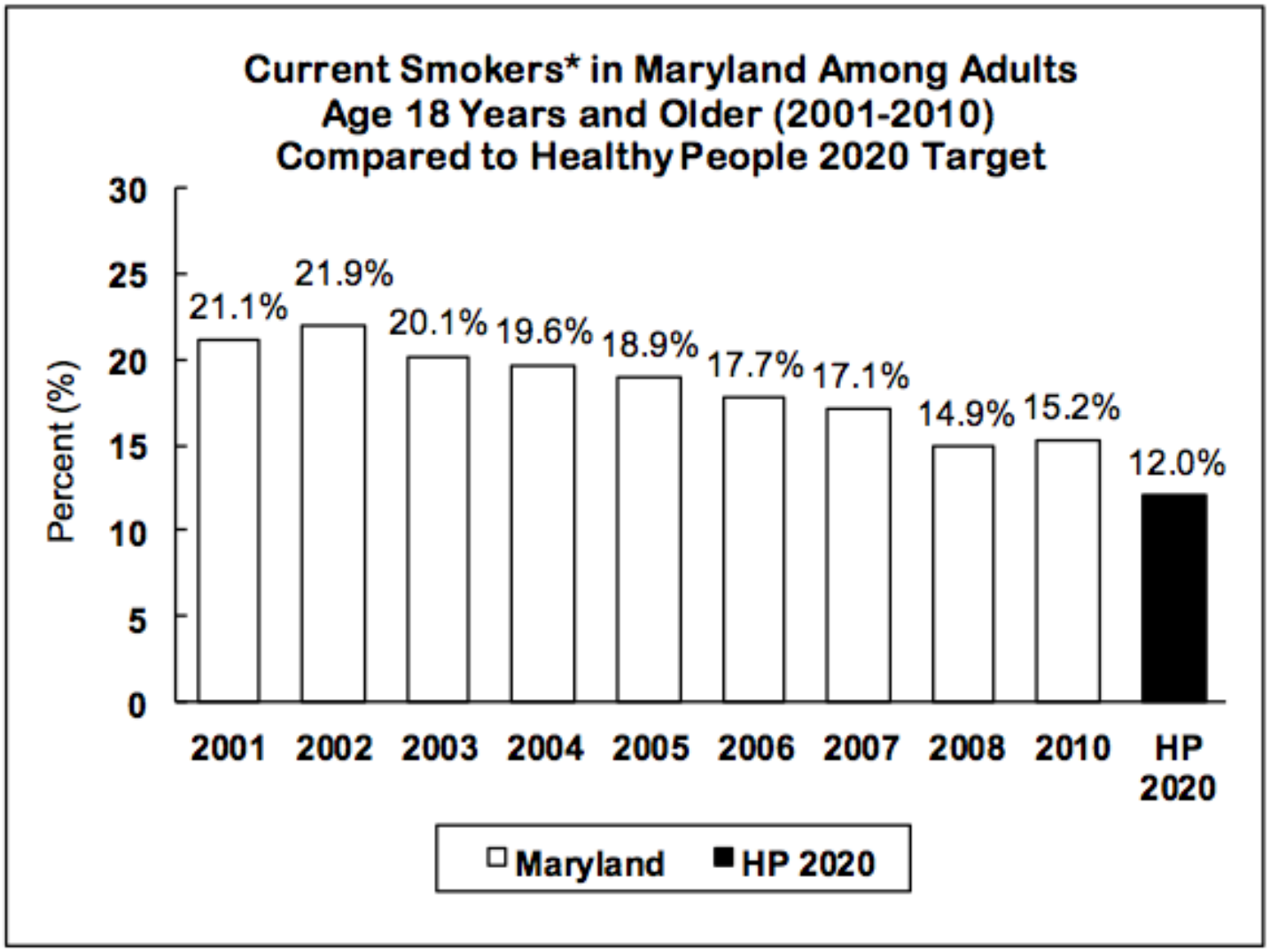
Cancer Site	1985 Rank
Lung/bronchus	8th
Colon/rectum	10th
Prostate (male)	9th
Breast (female)	10th

All Cancer Mortality Rank Among States and D.C.



Cancer Site	2010 Rank
Lung/bronchus	33rd
Colon/rectum	33rd
Prostate (male)	22nd
Breast (female)	5th

Prevalence of Current Smoking in Maryland

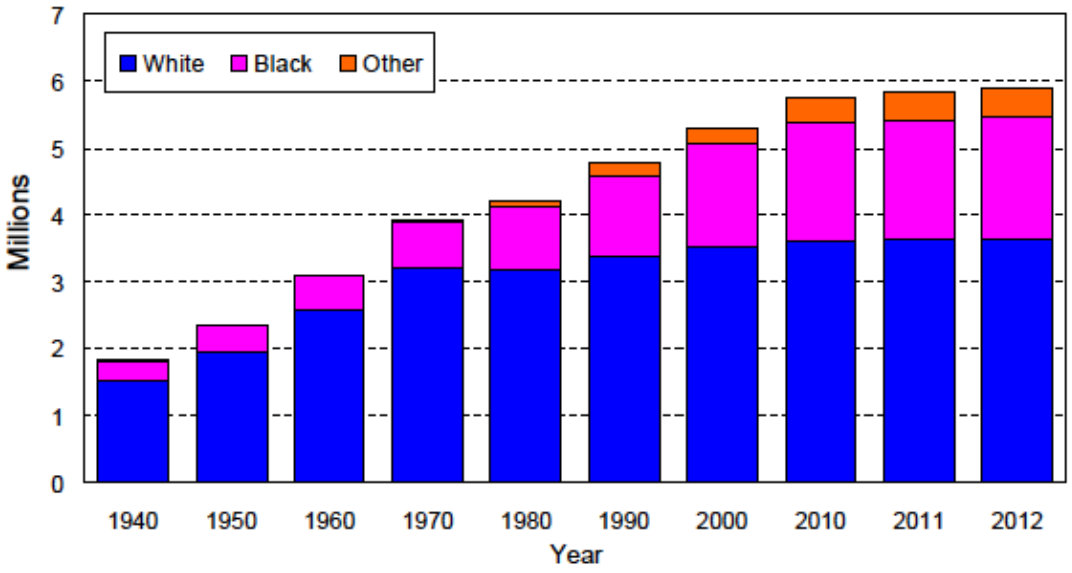


Maryland Cancer Report 2013

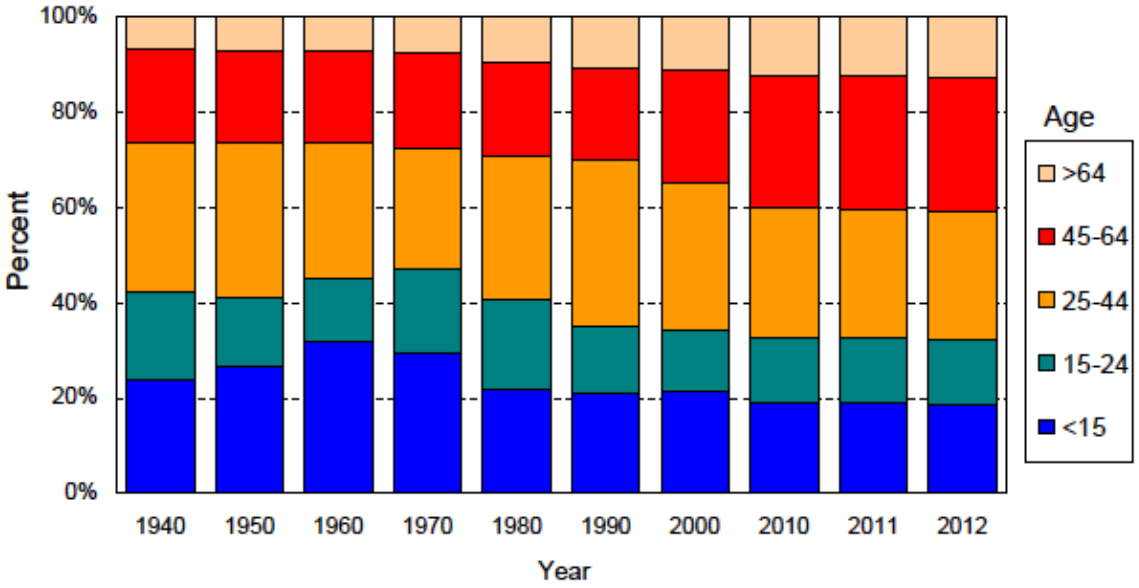
Maryland and Baltimore Metro Region: A Closer Look

POPULATION

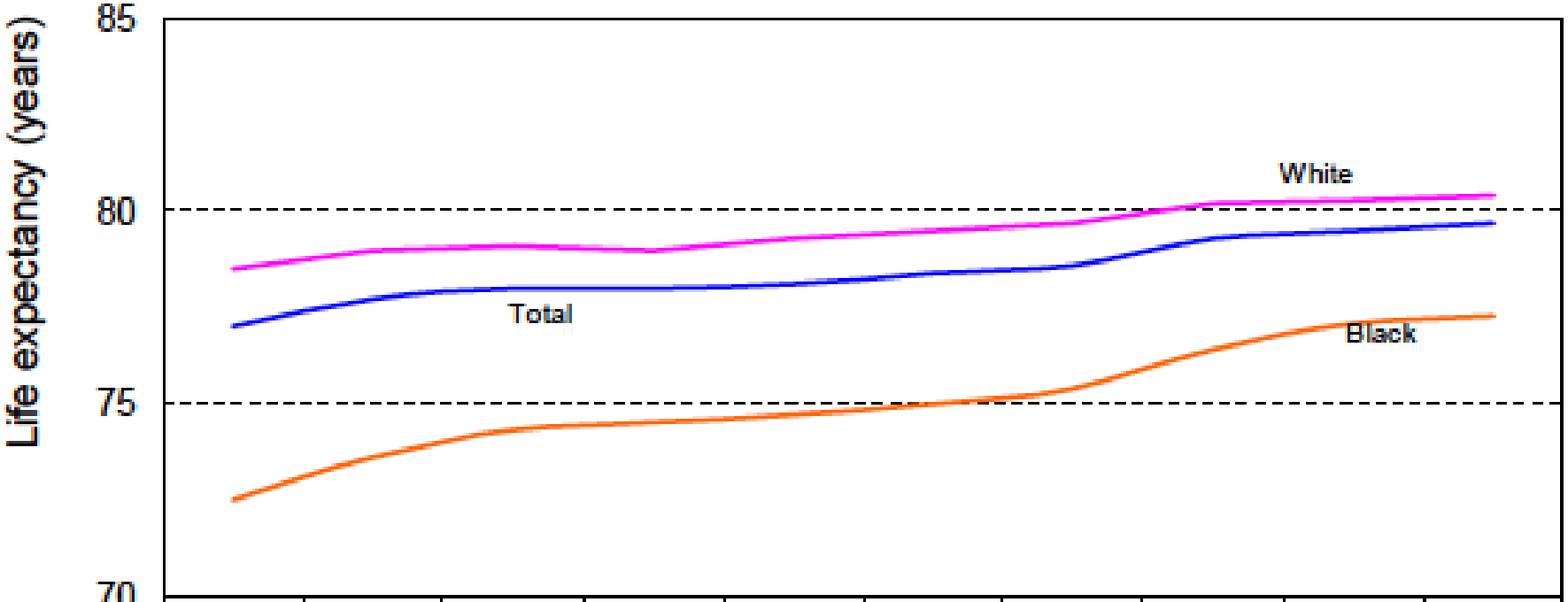
Distribution of the Population by Race, Maryland, 1940-2012.



Distribution of the Population by Age Group, Maryland, 1940–2012.

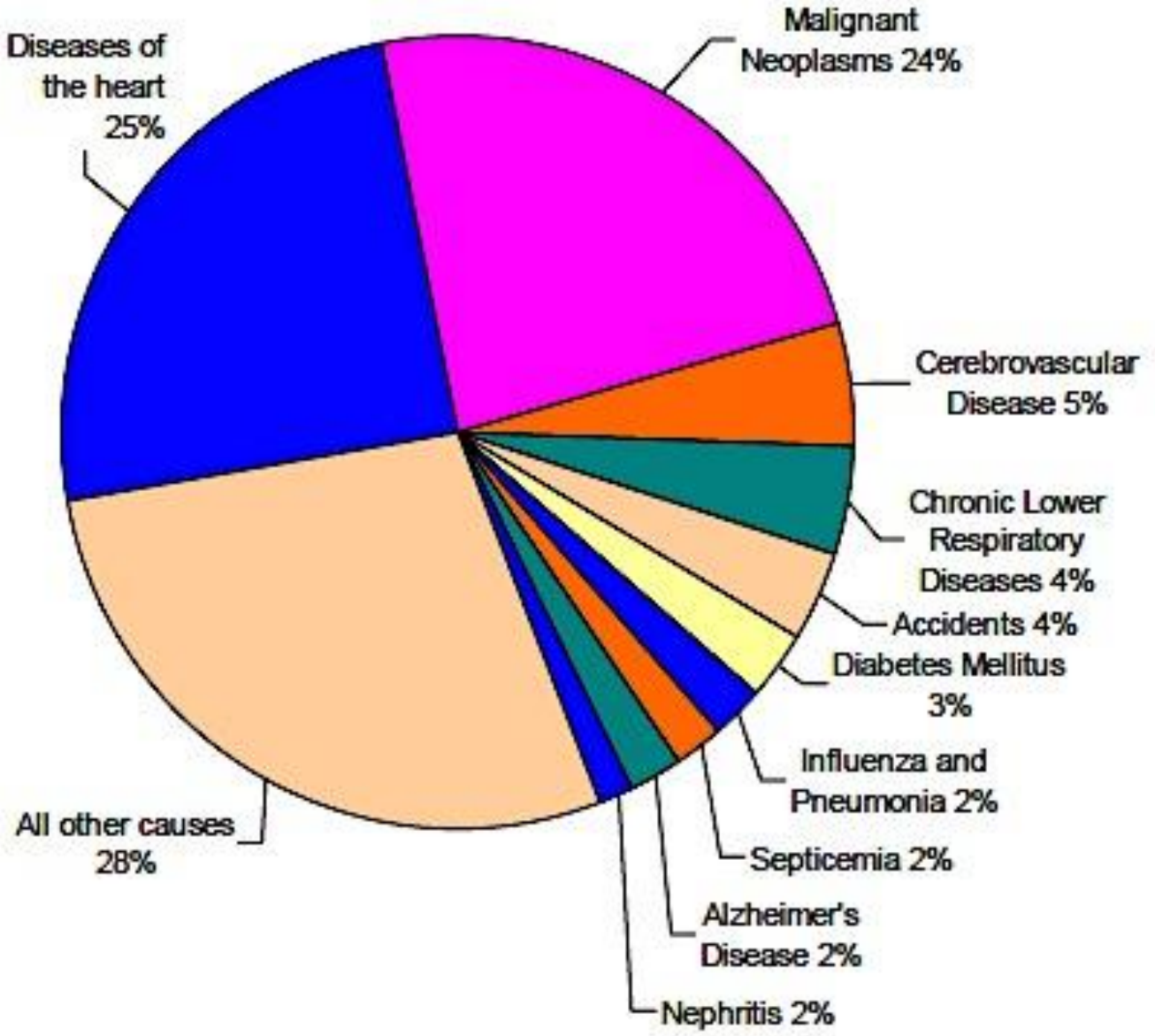


Life Expectancy at Birth by Race, Maryland, 2003-2012.



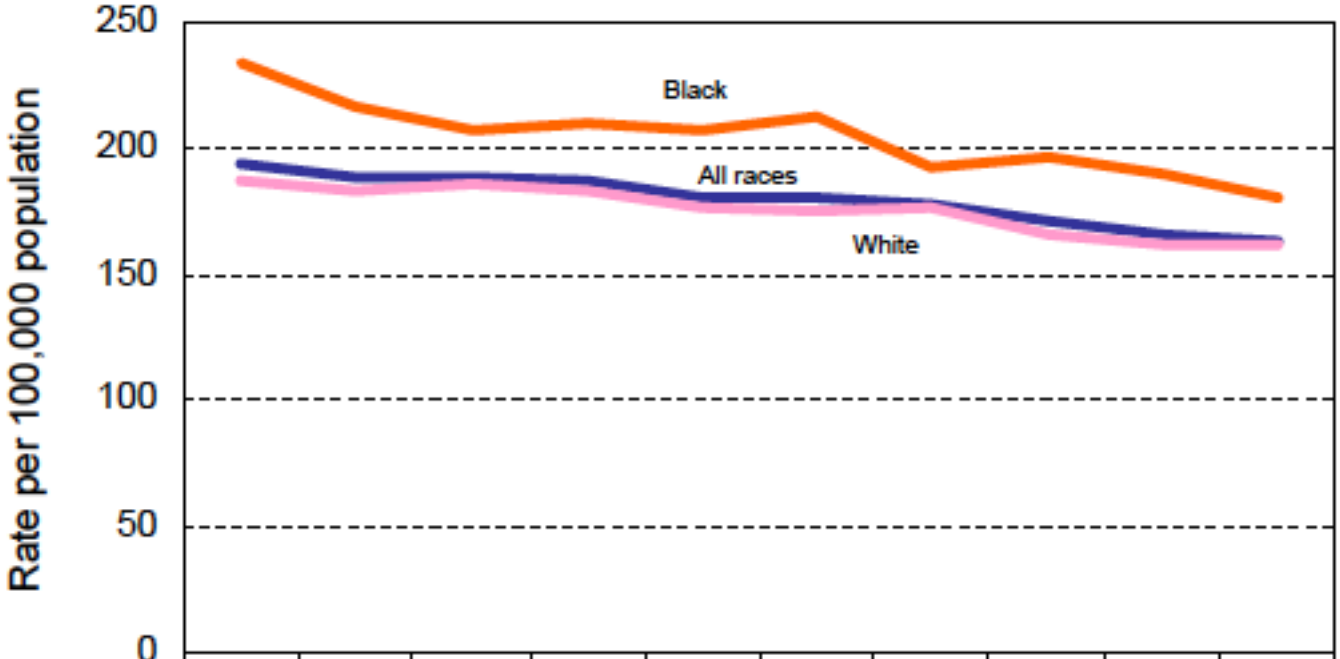
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Total	77.0	77.7	78.0	78.0	78.1	78.4	78.6	79.3	79.5	79.7
White	78.5	79.0	79.1	79.0	79.3	79.5	79.7	80.2	80.3	80.4
Black	72.5	73.6	74.3	74.5	74.7	75.0	75.4	76.4	77.1	77.3

Causes of Death: But now people are living with multiple chronic diseases



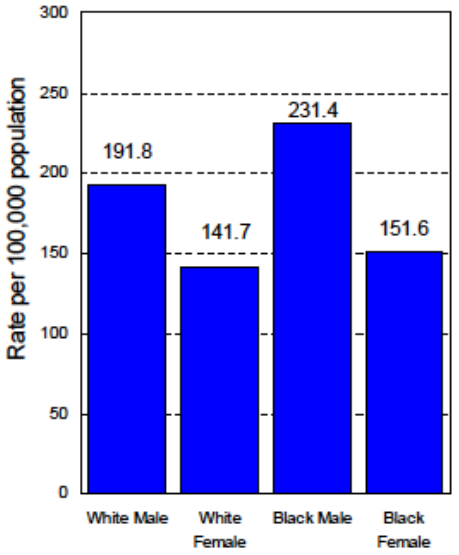
MALIGNANT NEOPLASMS

Age-adjusted Death Rate* for Malignant Neoplasms by Race, Maryland, 2003-2012.



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Total	194.3	188.1	187.9	186.5	180.0	180.6	177.7	170.9	165.7	163.7
White	186.9	183.7	185.7	183.7	176.3	175.0	176.6	166.1	161.3	162.2
Black	234.3	216.7	207.7	210.3	207.3	212.8	193.0	197.0	190.0	180.8

Age-Adjusted Death Rate* for Malignant Neoplasms by Race and Sex, Maryland, 2012.



Life expectancy at birth, by neighborhood Baltimore City, 2002-2006

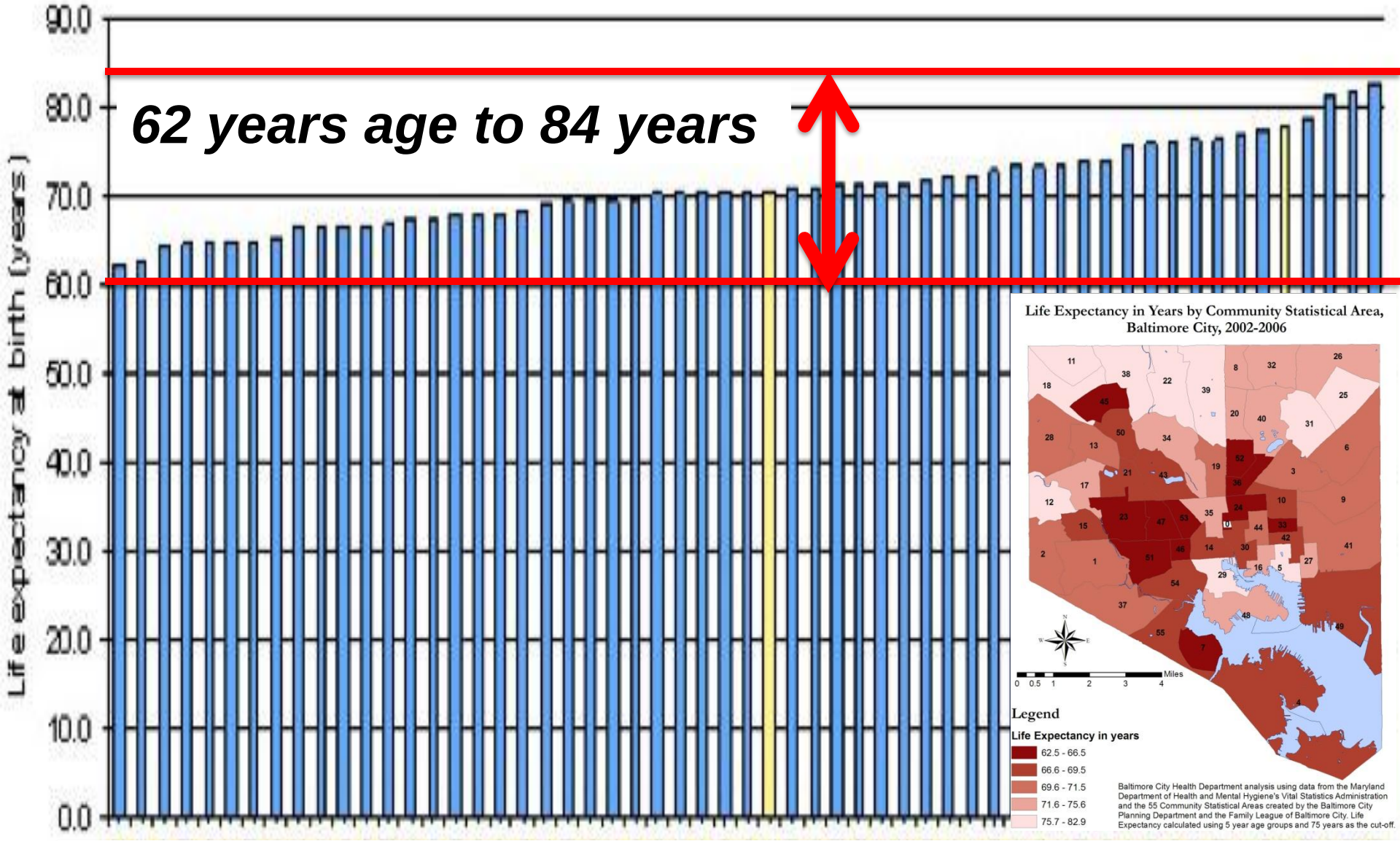
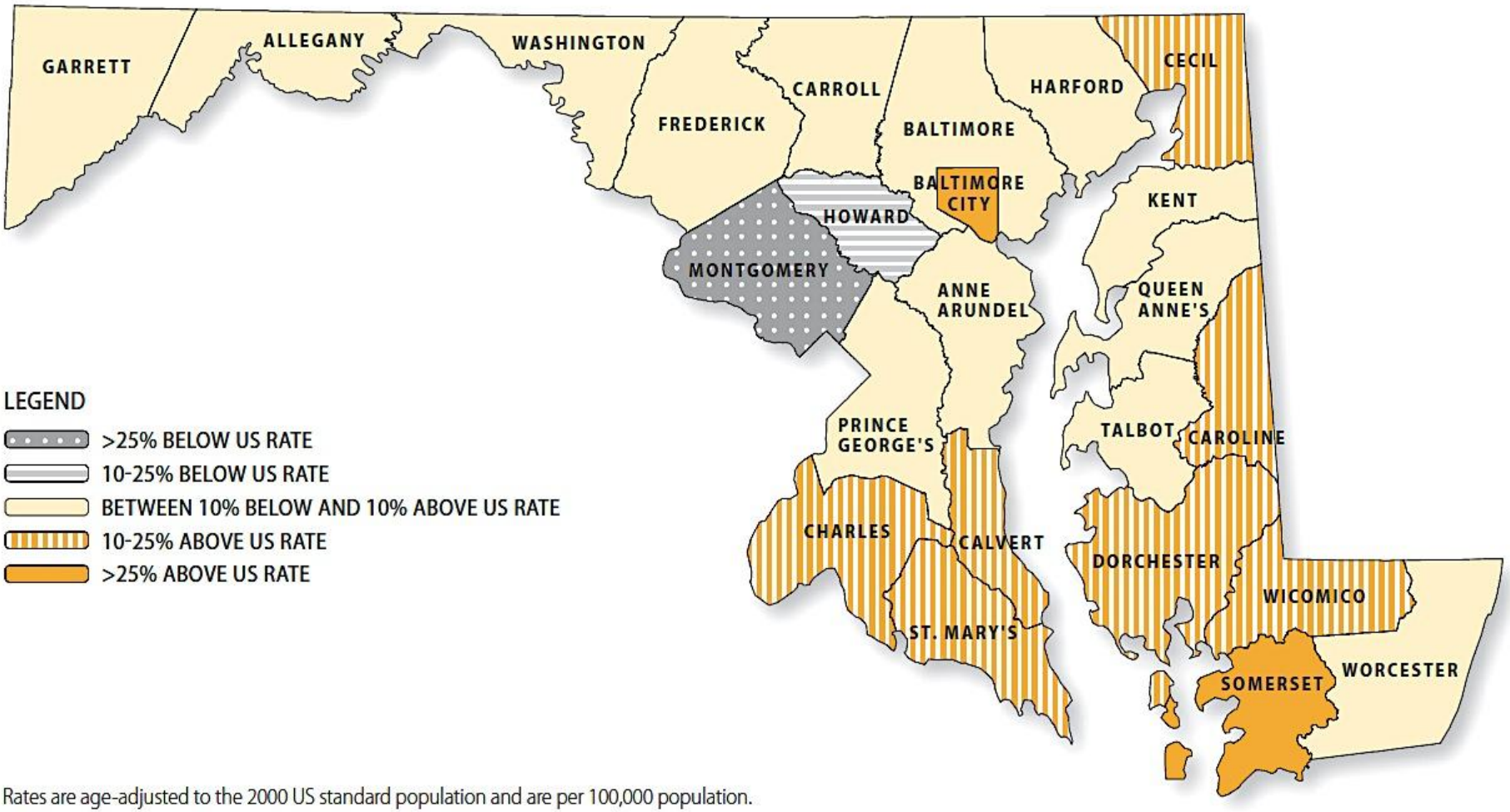


FIGURE **1.8**

Maryland All Cancer Sites Mortality Rates by Geographical Area: Comparison to US Rate, 2002-2006



Rates are age-adjusted to the 2000 US standard population and are per 100,000 population.

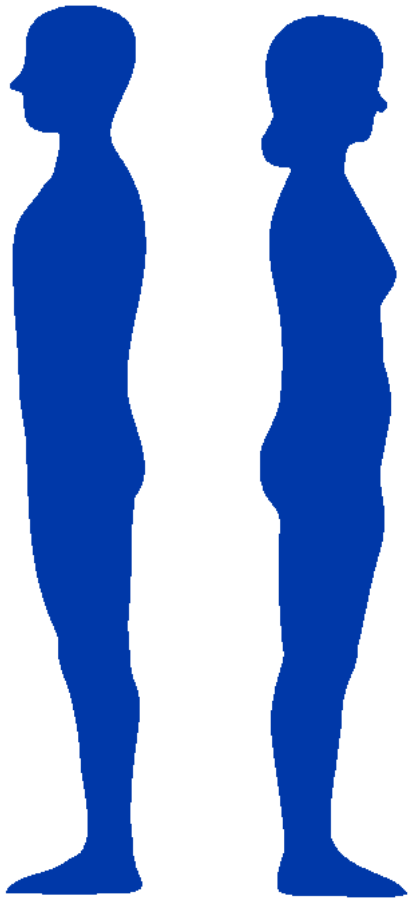
US all cancer sites mortality rate, 2002-2006: 186.7/100,000

Source: NCHS Compressed Mortality File in CDC WONDER, 2002-2006.

Causes of Individual Tumors

Estimated Cancer Deaths in the US in 2013

Men 306,920		Women 273,430	
Lung & bronchus	28%	26%	Lung & bronchus
Prostate	10%	14%	Breast
Colon & rectum	9%	9%	Colon & rectum
Pancreas	6%	7%	Pancreas
Liver & intrahepatic bile duct	5%	5%	Ovary
Leukemia	4%	4%	Leukemia
Esophagus	4%	3%	Non-Hodgkin lymphoma
Urinary bladder	4%	3%	Uterine corpus
Non-Hodgkin lymphoma	3%	2%	Liver & intrahepatic bile duct
Kidney & renal pelvis	3%	2%	Brain/other nervous system
All other sites	24%	25%	All other sites



For the overwhelming majority of cancers we do not know the etiological factors

Agents, mixtures and exposures classified by IARC as Group 1: "Carcinogenic to Humans"

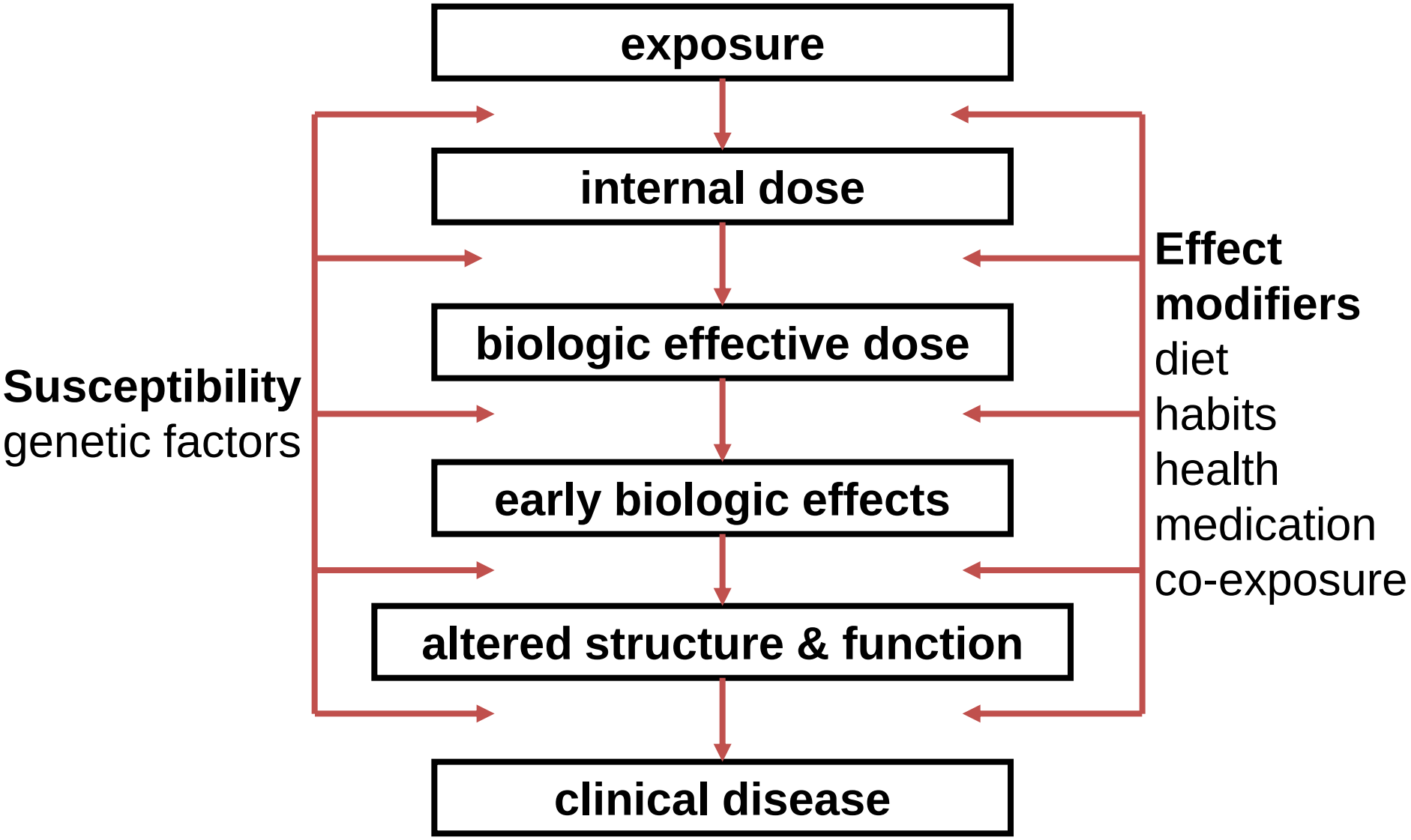
• **Agents and Groups of Agents**	**81**
– Drugs	22
– Environmental chemicals	29
– Radiation	17
– Viruses, bacteria, parasites	11
– Inorganic fibers	2
• **Mixtures**	**12**
– **air pollution (10/2013)**	
• **Exposure Circumstances**	**15**
Total	**108**

IARC Monographs Volumes 1-100 (2010) 109 (2013)

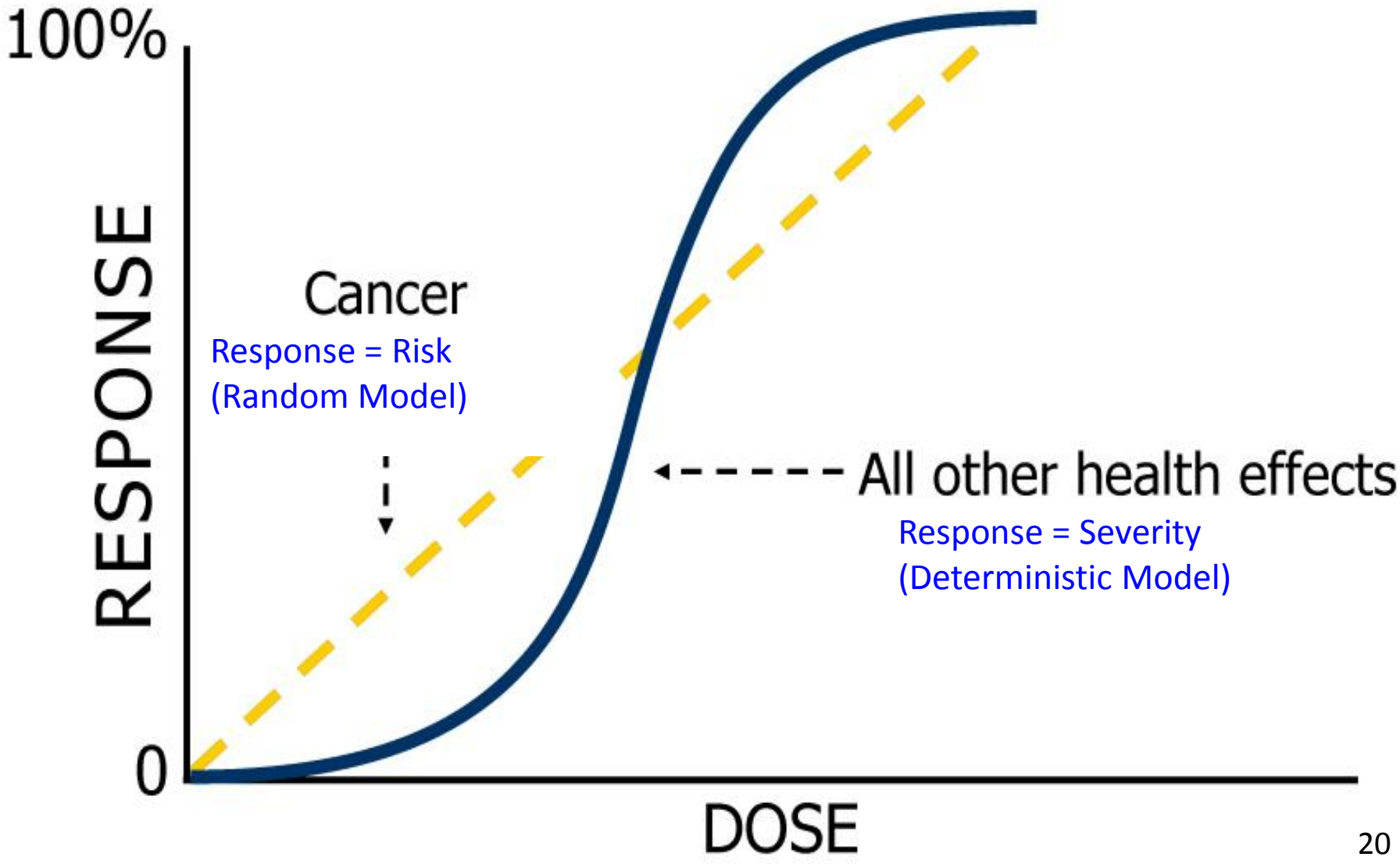
Exposure, Dose, and Response Relations

The Toxicological Paradigm

(biological mechanisms and individual variation)



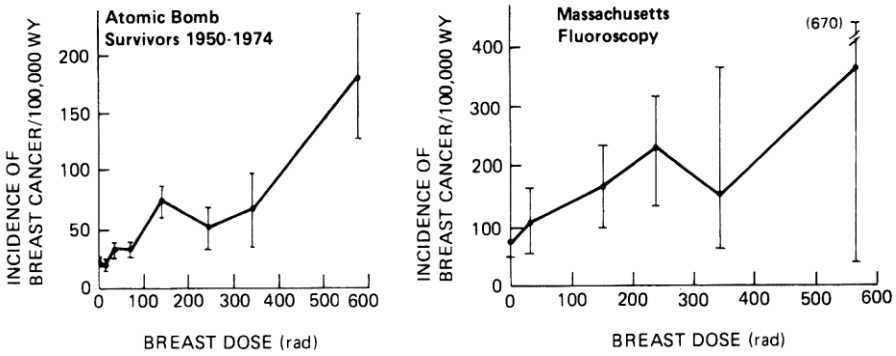
Dose-Response Curves



Random

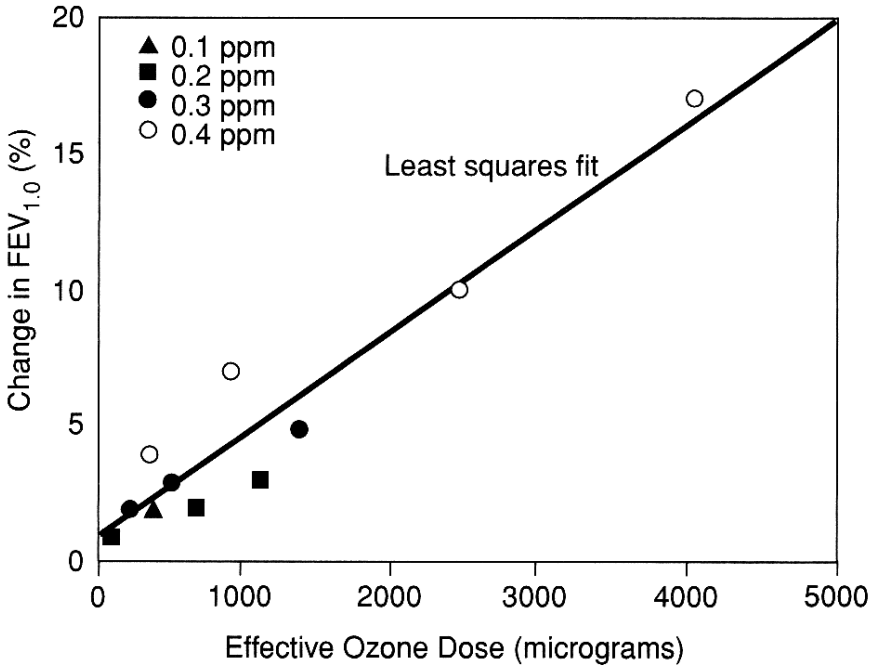
Deterministic

Radiation-induced breast cancer



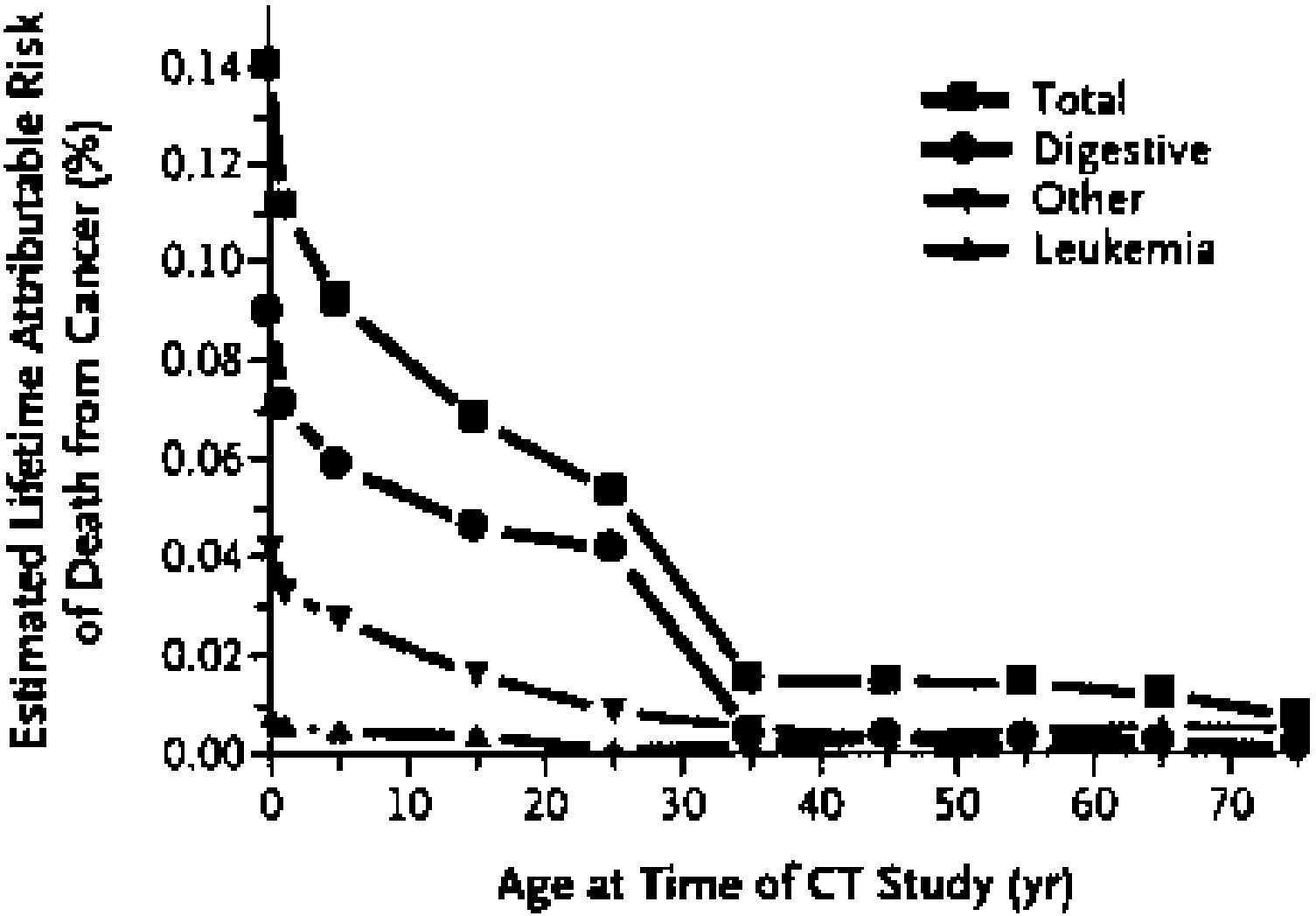
Risk is a function of dose
No threshold
Cancer, genetic effects

Ozone-induced lung dysfunction



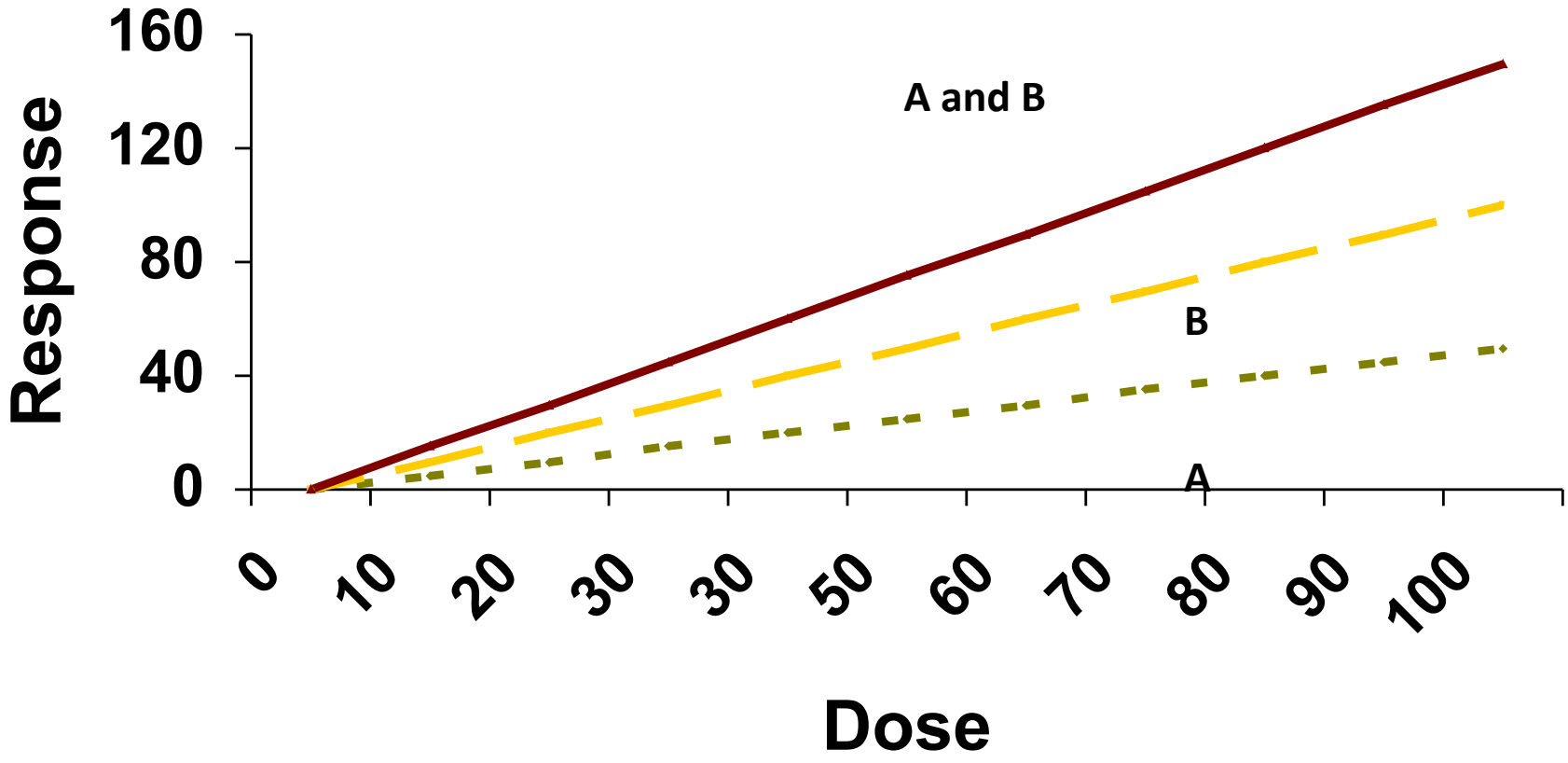
Severity is a function of dose
A threshold is often present
All other effects

Effect of Age of Exposure on Risk

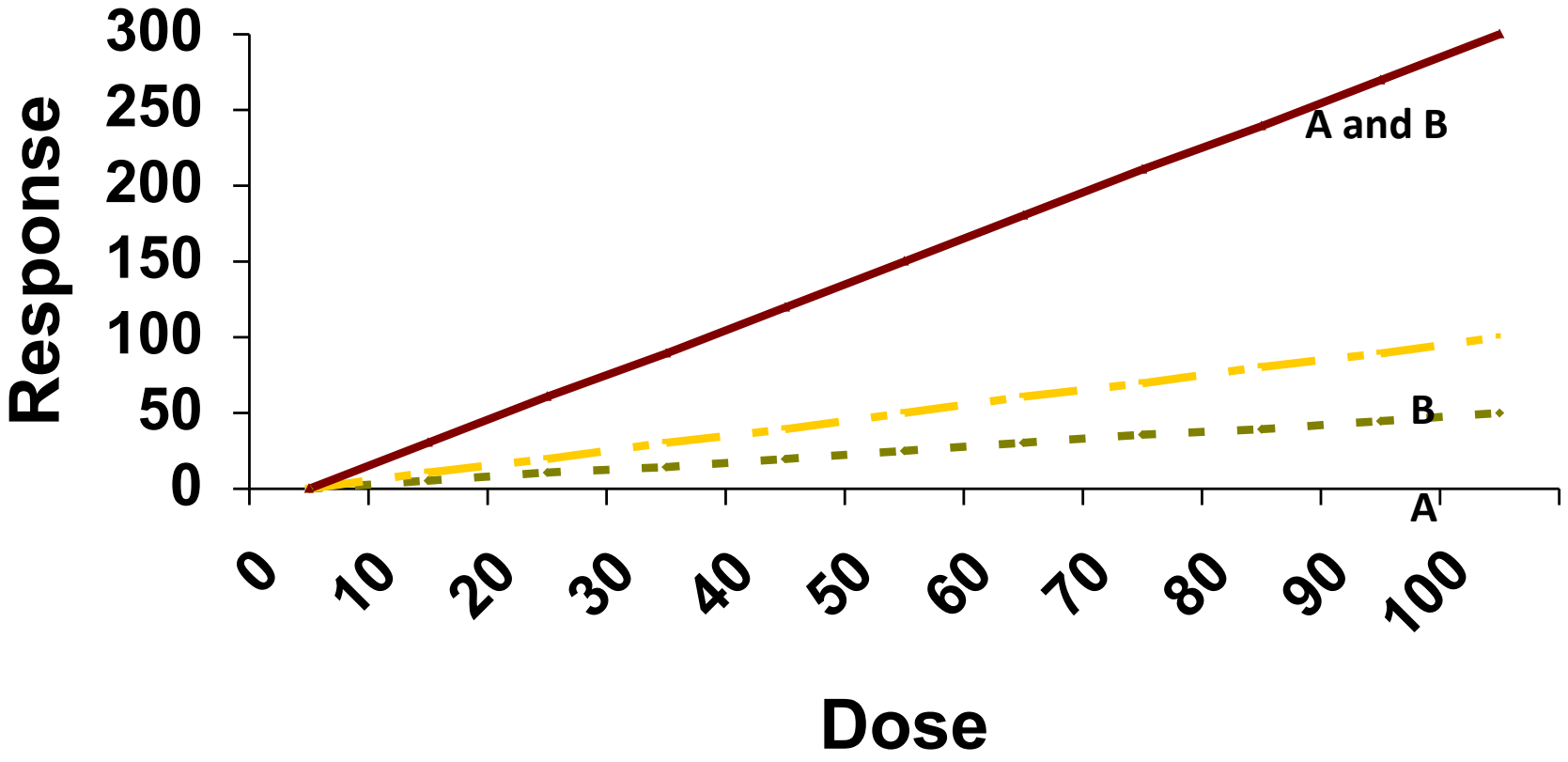


Brenner DJ, Hall EJ. NEJM 357: 2277-2284, 2007

Additivity


Response
160
120
80
40
0
A and B
B
A
0
10
20
30
30
50
60
70
80
90
100
Dose

Synergism


Response
300
250
200
150
100
50
0
A and B
B
A
0
10
20
30
40
50
60
70
80
90
100
Dose

Lung Cancer & Asbestos

Compared with the risk of dying from lung cancer for a nonsmoker not exposed to asbestos

Report of the Surgeon General, 1985

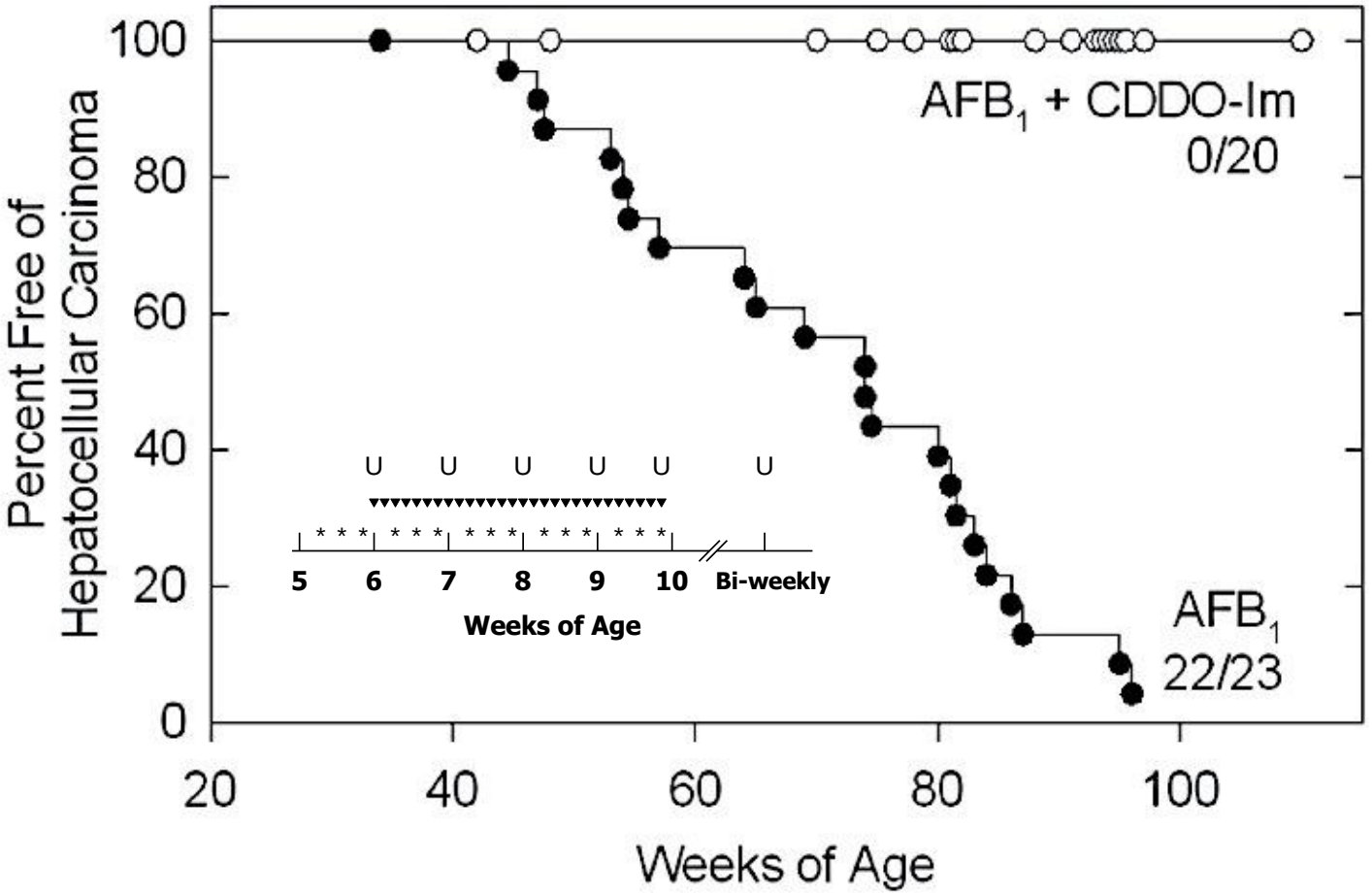
Cohort Study of Liver Cancer in P.R.C.: Viral-Chemical Interactions

- 18,244 urine and blood samples collected from healthy men age 45-65
- 50 liver cancer cases and 247 controls
- Urinary aflatoxin biomarkers measured in blinded samples
- HBV status determined for each subject

Lancet 339: 943-946, 1992
and *C.E.B.P. 3: 3-11, 1994*

BIOMARKERS: HBsAg AND URINARY AFLATOXINS	RELATIVE RISK FOR LIVER CANCER
NO BIOMARKERS DETECTED	**1.0**
HBV (YES) AFLATOXIN (NO)	**7.3**
HBV (NO) AFLATOXIN (YES)	**3.4**
HBV (YES) AFLATOXIN (YES)	**60.0**

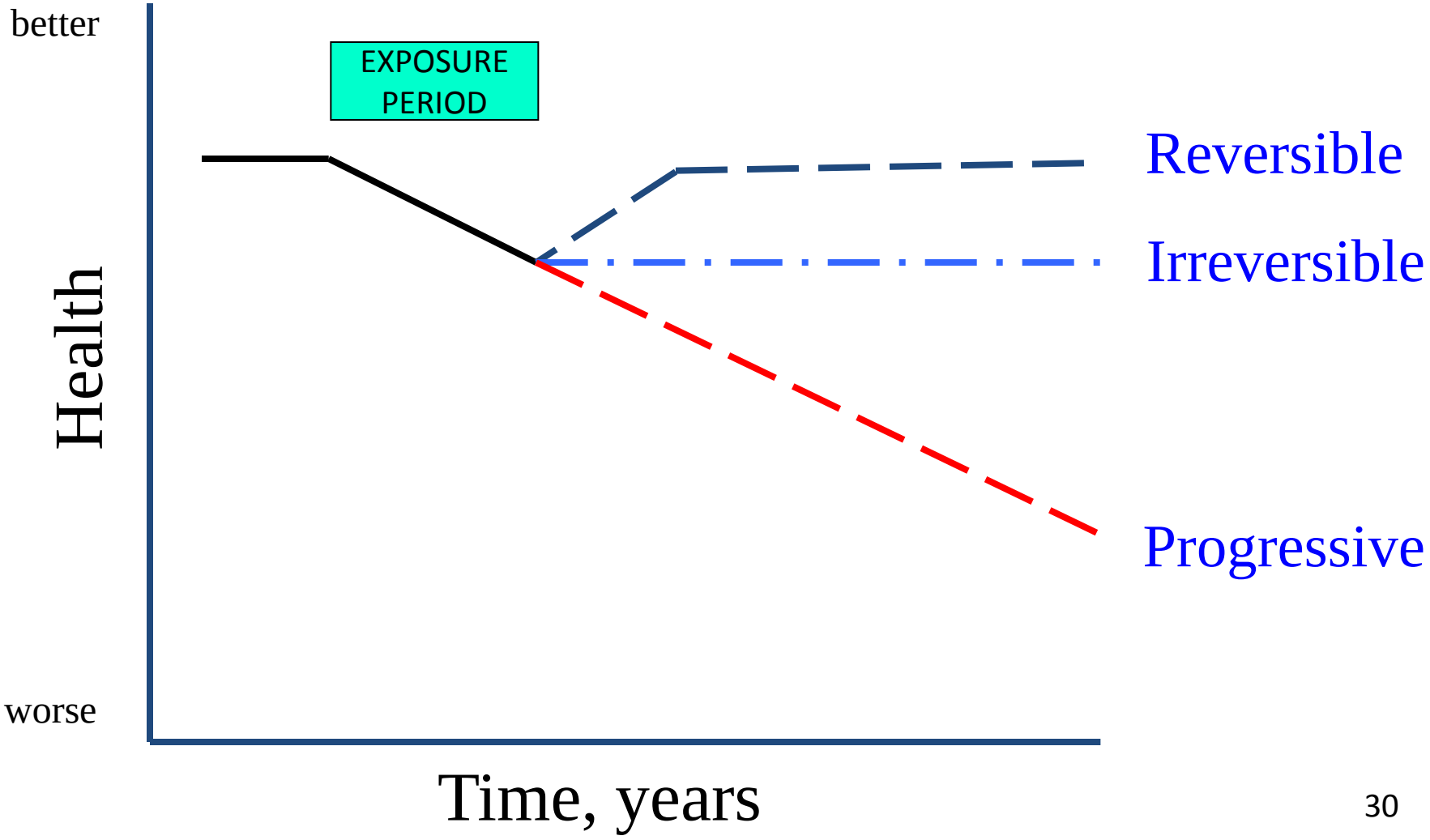
Kaplan-Meier estimates for the proportion of animals free of hepatocellular carcinomas (HCCs).



Exposure in both groups are the same but dose (and outcome) is completely different

Johnson et al, Cancer Prev Res, 2014

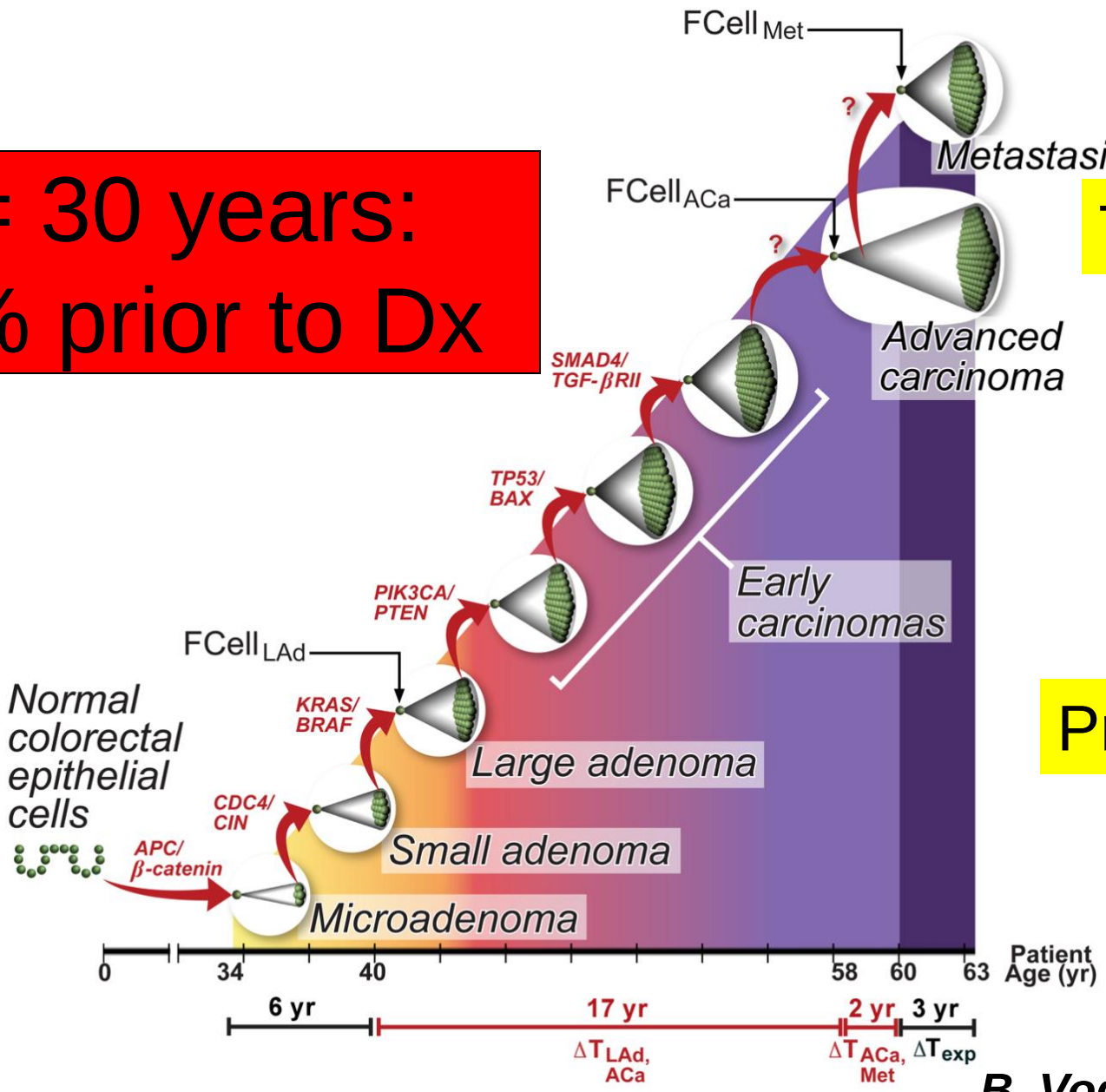
Time-Course of *Response*



The Challenge

Tumor Evolution: Cancers of 2050 Already Initiated

t = 30 years:
90% prior to Dx



Therapy

Prevention

B. Vogelstein, 2011