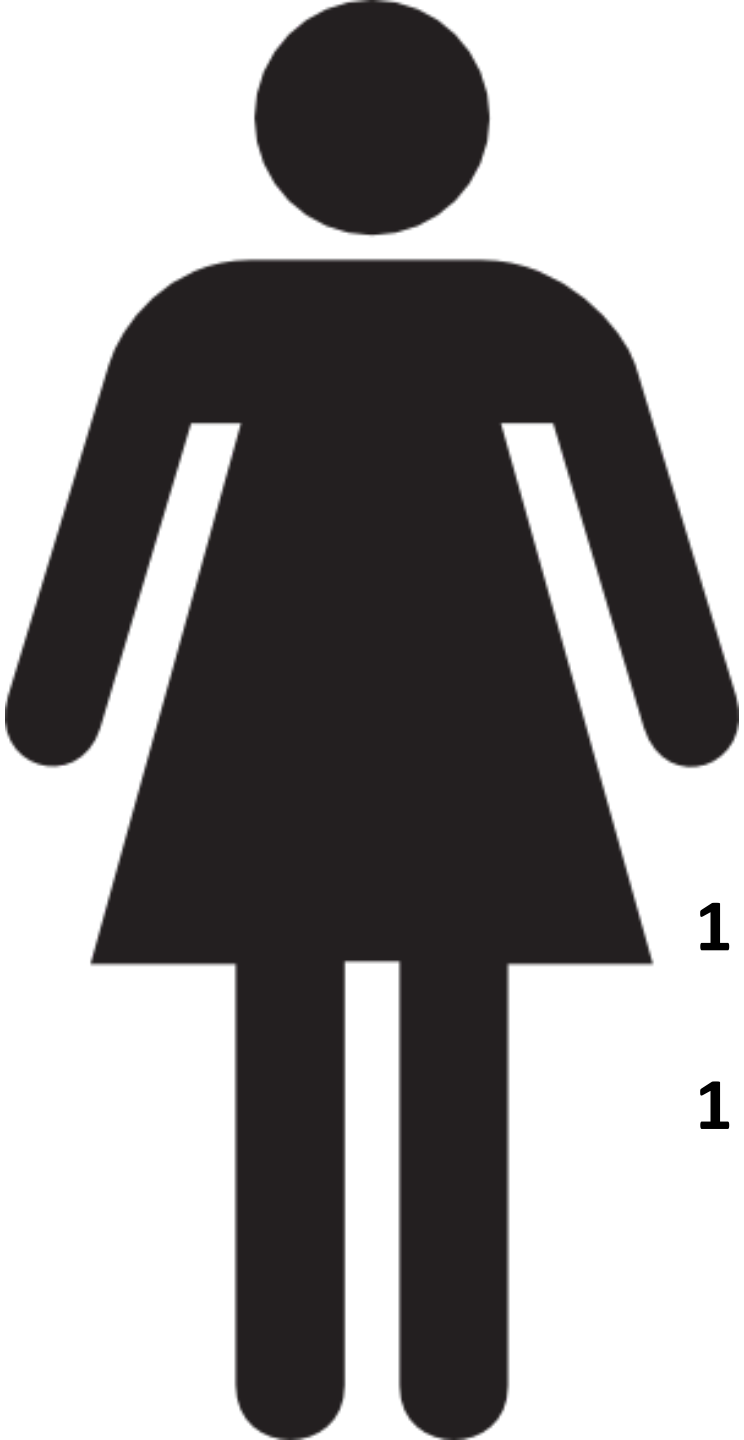
UNIWERSYTET JAGIELLOŃSKI
COLLEGIUM MEDICUM

Szpital
Uniwersytecki
w Krakowie

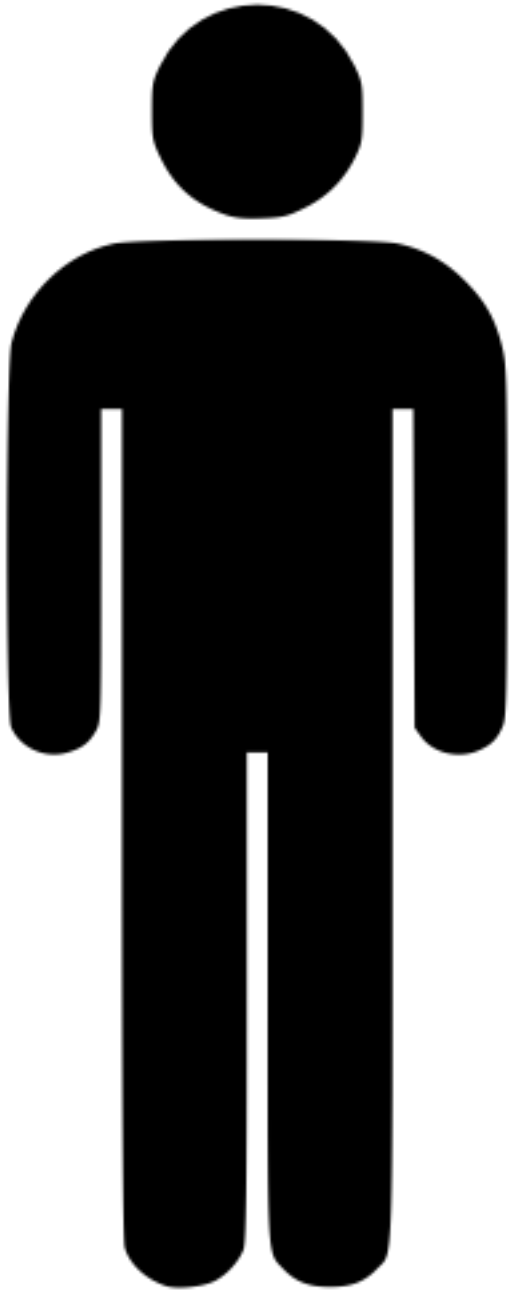
FROM CARCINOGENESIS TO TREATMENT



LIFETIME RISK OF CANCER

1 in 3 will be diagnosed

1 in 5 will die

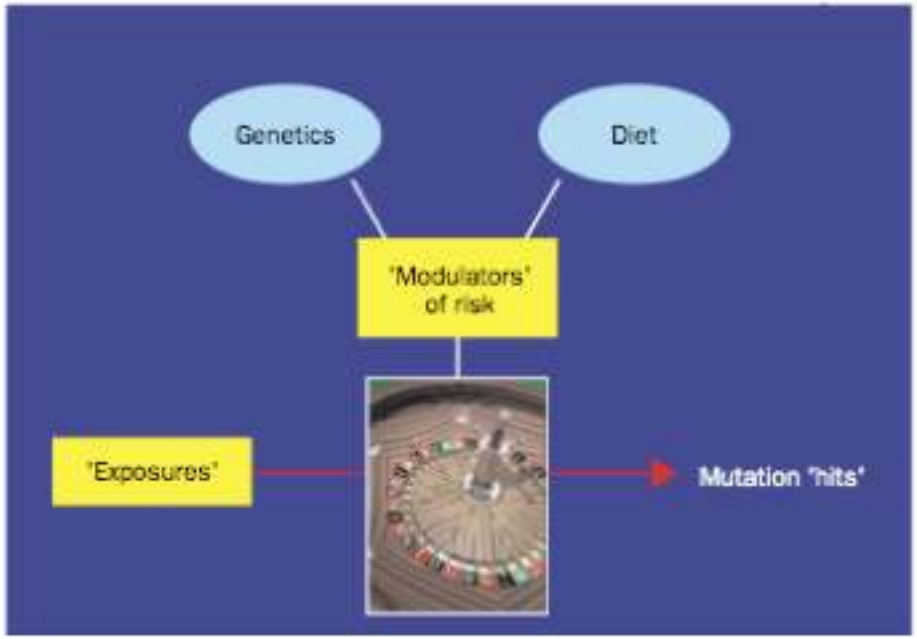


LIFETIME RISK OF CANCER

1 in 2 will be diagnosed

1 in 4 will die

CARCINOGENESIS



Cancer is caused by genetic (inherited and sporadic mutations) and epigenetic disorders

Mutations can be germinal or somatic (induced by carcinogens or spontaneous)

Overall cancer risk is influenced by inherited factors, lifestyle, environment and LUCK

NEOPLASTIC TRANSFORMATION IS MEDIATED BY:

- ONCOGENES (TURNED ON BY MUTATION)
  - *pedal to the metal*
- SUPPRESSOR GENES (TURNED OFF BY MUTATION)
  - no brakes
- DNA-REPAIR GENES (MUTATION LEADS TO GENOMIC INSTABILITY)
  - Incompetent Auto Mechanic

Table 1 Cancer predisposition genes

Gene (synonym(s))[a]	Syndrome	Hereditary pattern	Second hit	Pathway[b]	Major heredity tumor types[c]
Tumor-suppressor genes					
APC	FAP	Dominant	Inactivation of WT allele	APC	Colon, thyroid, stomach, intestine
AXIN2	Attenuated polyposis	Dominant	Inactivation of WT allele	APC	Colon
CDH1 (E-cadherin)	Familial gastric carcinoma	Dominant	Inactivation of WT allele	APC	Stomach
GPC3	Simpson-Golabi-Behmel syndrome	X-linked	?	APC	Embryonal
CYLD	Familial cylindromatosis	Dominant	Inactivation of WT allele	APOP	Pilotrichomas
EXT1,2	Hereditary multiple exostases	Dominant	Inactivation of WT allele	GLI	Bone
PTCH	Gorlin syndrome	Dominant	Inactivation of WT allele	GLI	Skin, medulloblastoma
SUFU	Medulloblastoma predisposition	Dominant	Inactivation of WT allele	GLI	Skin, medulloblastoma
FH	Hereditary leiomyomatosis	Dominant	Inactivation of WT allele	HIF1	Leiomyomas
SDHB, C, D	Familial paraganglioma	Dominant	Inactivation of WT allele	HIF1	Paragangliomas, pheochromocytomas
VHL	Von Hippel–Lindau syndrome	Dominant	Inactivation of WT allele	HIF1	Kidney
TP53 (*p53*)	Li-Fraumeni syndrome	Dominant	Inactivation of WT allele	p53	Breast, sarcoma, adrenal, brain...
WT1	Familial Wilms tumor	Dominant	Inactivation of WT allele	p53	Wilms'
STK11 (*LKB1*)	Peutz-Jeghers syndrome	Dominant	Inactivation of WT allele	PI3K	Intestinal, ovarian, pancreatic
PTEN	Cowden syndrome	Dominant	Inactivation of WT allele	PI3K	Hamartoma, glioma, uterus
TSC1, TSC2	Tuberous sclerosis	Dominant	Inactivation of WT allele	PI3K	Hamartoma, kidney
CDKN2A ($p16^{INK4A}$, $p14^{ARF}$)	Familial malignant melanoma	Dominant	Inactivation of WT allele	RB	Melanoma, pancreas
CDK4	Familial malignant melanoma	Dominant	?	RB	Melanoma
RB1	Hereditary retinoblastoma	Dominant	Inactivation of WT allele	RB	Eye
NF1	Neurofibromatosis type 1	Dominant	Inactivation of WT allele	RTK	Neurofibroma
BMPR1A	Juvenile polyposis	Dominant	Inactivation of WT allele	SMAD	Gastrointestinal
MEN1	Multiple endocrine neoplasia type 1	Dominant	Inactivation of WT allele	SMAD	Parathyroid, pituitary, islet cell, carcinoid
SMAD4 (*DPC4*)	Juvenile polyposis	Dominant	Inactivation of WT allele	SMAD	Gastrointestinal
BHD	Birt-Hogg-Dube syndrome	Dominant	Inactivation of WT allele	?	Renal, hair follicle
HRPT2	Hyperparathyroidism Jaw-tumor syndrome.	Dominant	Inactivation of WT allele	?	Parathyroid, jaw fibroma
NF2	Neurofibromatosis type 2	Dominant	Inactivation of WT allele	?	Meningioma, acoustic neuroma
Stability genes					
MUTYH	Attenuated polyposis	Recessive	?	BER	Colon
ATM	Ataxia telangiectasia	Recessive	?	CIN	Leukemias, lymphomas, brain
BLM	Bloom syndrome	Recessive	?	CIN	Leukemias, lymphomas, skin
BRCA1, BRCA2	Hereditary breast cancer	Dominant	Inactivation of WT allele	CIN	Breast, ovary
FANCA, C, D2, E, F,G	Fanconi anemia	Recessive	?	CIN	Leukemias
NBS1	Nijmegen breakage syndrome	Recessive	?	CIN	Lymphomas, brain
RECQL4	Rothmund-Thomson syndrome	Recessive	?	CIN	Bone, skin
WRN	Werner syndrome	Recessive	?	CIN	Bone, brain

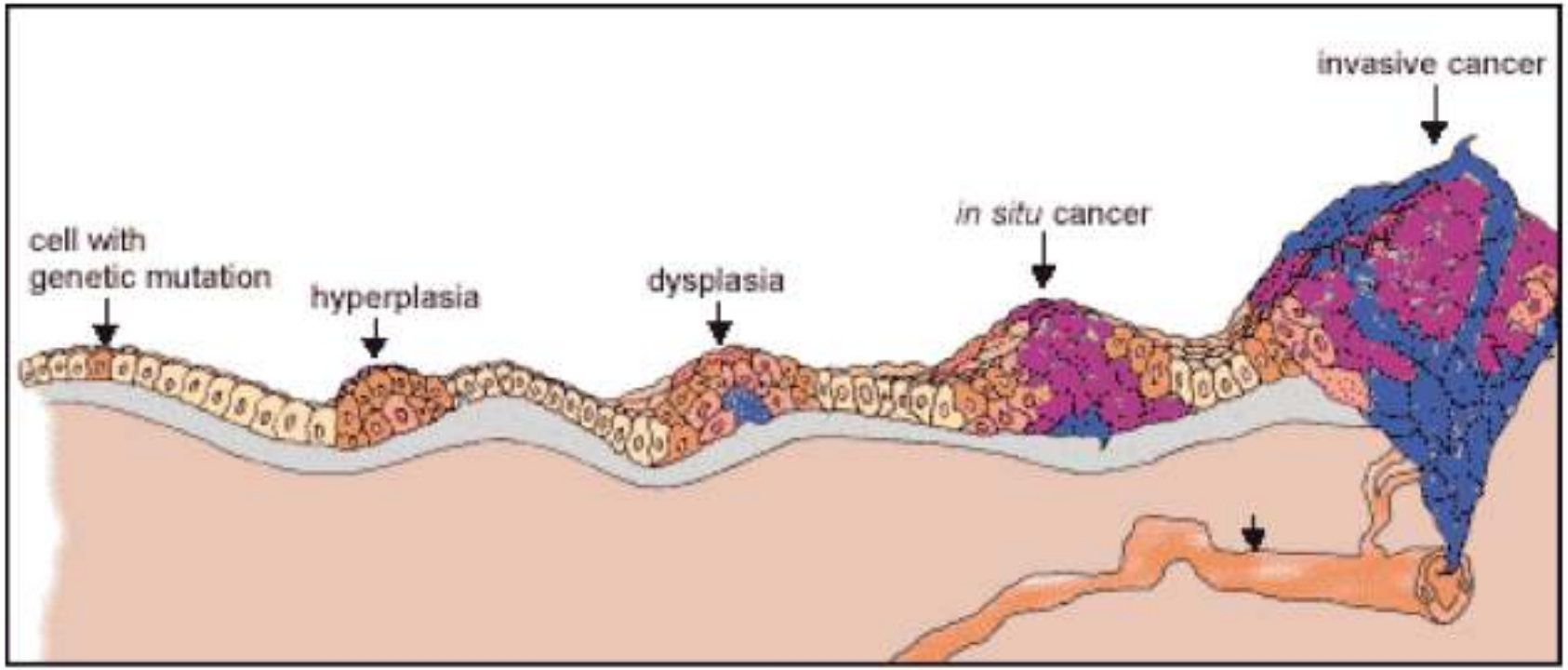
Table 2 Genes that are mutated somatically but not inherited in mutant form

Gene[a] (synonym)	Somatic mutation type[b]	Cancers with mutant gene[c]	Pathway[c]
CTNNB1 (β-catenin)	Activating codon change	Colon, liver, medulloblastomas	APC
BCL2	Translocation	Lymphomas	APOP
TNFRSF6 (*FAS*)	Activating codon change	Lymphomas, testicular germ cell tumors	APOP
BAX	Inactivating codon change	Colon, stomach	APOP
FBXW7 (*CDC4*)	Inactivating codon change	Colon, uterine, ovarian, breast	CIN
GLI	Amplification, translocation	Brain, sarcomas	GLI
HPVE6	HPV infection	Cervical	p53
MDM2	Amplification	Sarcomas	p53
NOTCH1	Translocation	Leukemias	p53
AKT2	Amplification	Ovarian, breast	PI3K
FOXO1A, 3A	Translocation	Rhabdomyosarcomas, leukemias	PI3K
PI3KCA	Activating codon change	Colon, stomach, brain, breast	PI3K
CCND1 (cyclin D1)	Amplification, translocation	Leukemias, breast	RB
HPVE7	HPV infection	Cervical	RB
TAL1	Translocation	Leukemias	RB
TFE3	Translocation	Kidney, sarcomas	RB
ABL1 (*ABL*)	Translocation	Chronic myelogenous leukemia	RTK
ALK	Translocation	Anaplastic large cell lymphoma	RTK
BRAF	Activating codon change	Melanoma, colorectal, thyroid	RTK
EGFR	Amplification, activating codon change	Glioblastomas, non–small cell lung cancers	RTK
EPHB2	Inactivating codon change	Prostate	RTK
ERBB2	Amplification	Breast, ovarian	RTK
FES	Activating codon change	Colon	RTK
FGFR1–3	Translocation	Lymphomas, gastric cancers, bladder cancers	RTK
FLT3, 4	Activating codon change	Leukemias, angiosarcomas	RTK
JAK2	Translocation	Leukemias	RTK
KRAS2, N-RAS	Activating codon change	Colorectal, pancreatic, non–small cell lung cancer	RTK
NTRK1, 3	Translocation, activating codon change	Thyroid, secretory breast, colon	RTK
PDGFB	Translocation	Dermatofibrosarcomas and fibroblastomas	RTK
PDGFRB	Translocation	Leukemias	RTK
EWSR1	Translocation	Ewing's sarcomas, lymphomas, leukemias	SMAD
RUNX1	Translocation	Leukemias	SMAD
SMAD2	Inactivating codon change	Colon, breast	SMAD
TGFBR1, TGFBR2	Inactivating codon change	Colon, stomach, ovarian	SMAD
BCL6	Translocation	Lymphomas	?
EVI1	Translocation	Leukemias	?
HMGA2	Translocation	Lipomas	?
HOXA9, 11, 13; HOXC13,	Translocation	Leukemias	?

MANY MUTATED GENES REGULATE ONLY A FEW INTRACELLULAR PATHWAYS OF CRITICAL IMPORTANCE

TUMOR DEVELOPMENT

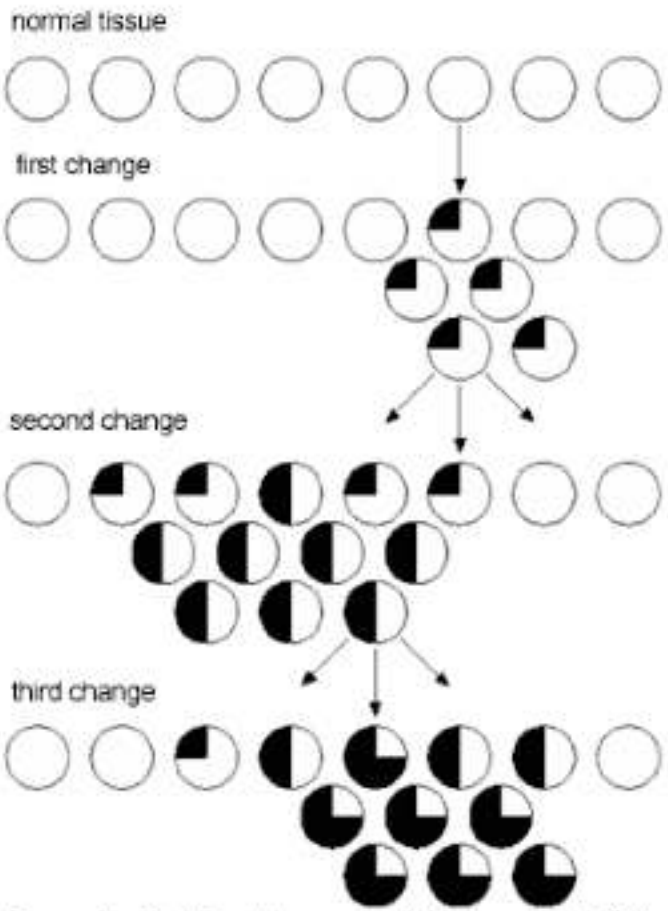
FROM HYPERPLASIA TO INVASIVE CANCER



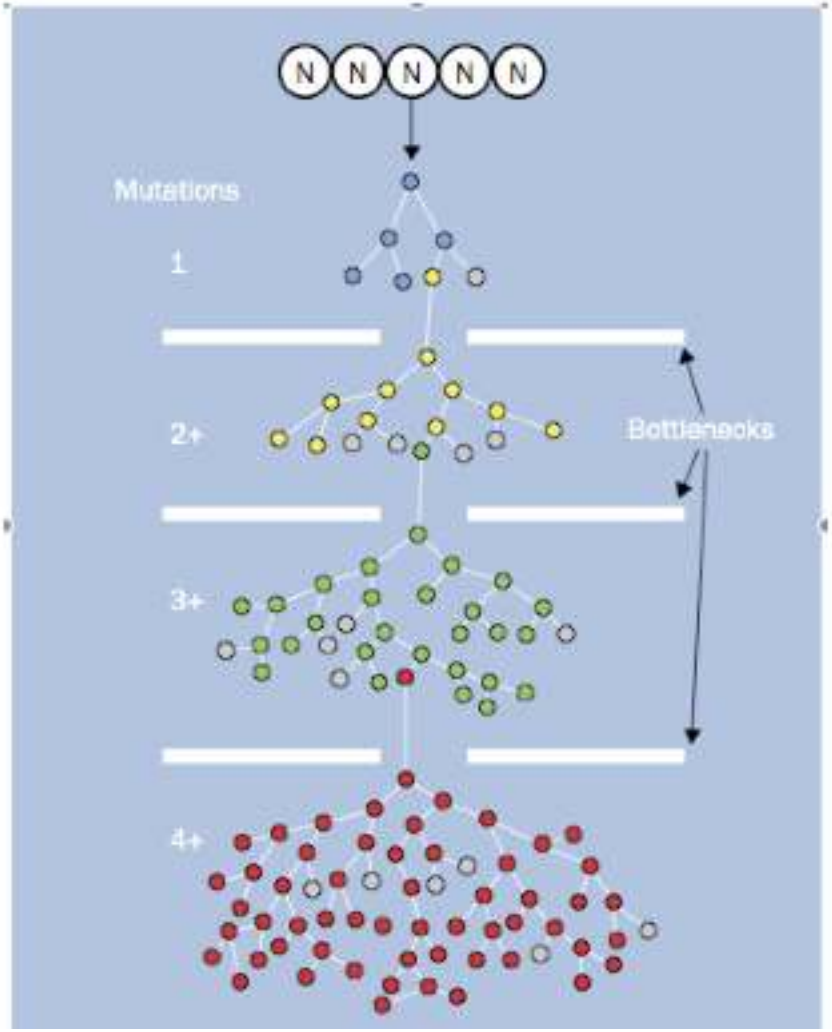
1.000.000.000 cells
~ clinical detection
(historical) approx.
30 cell divisions

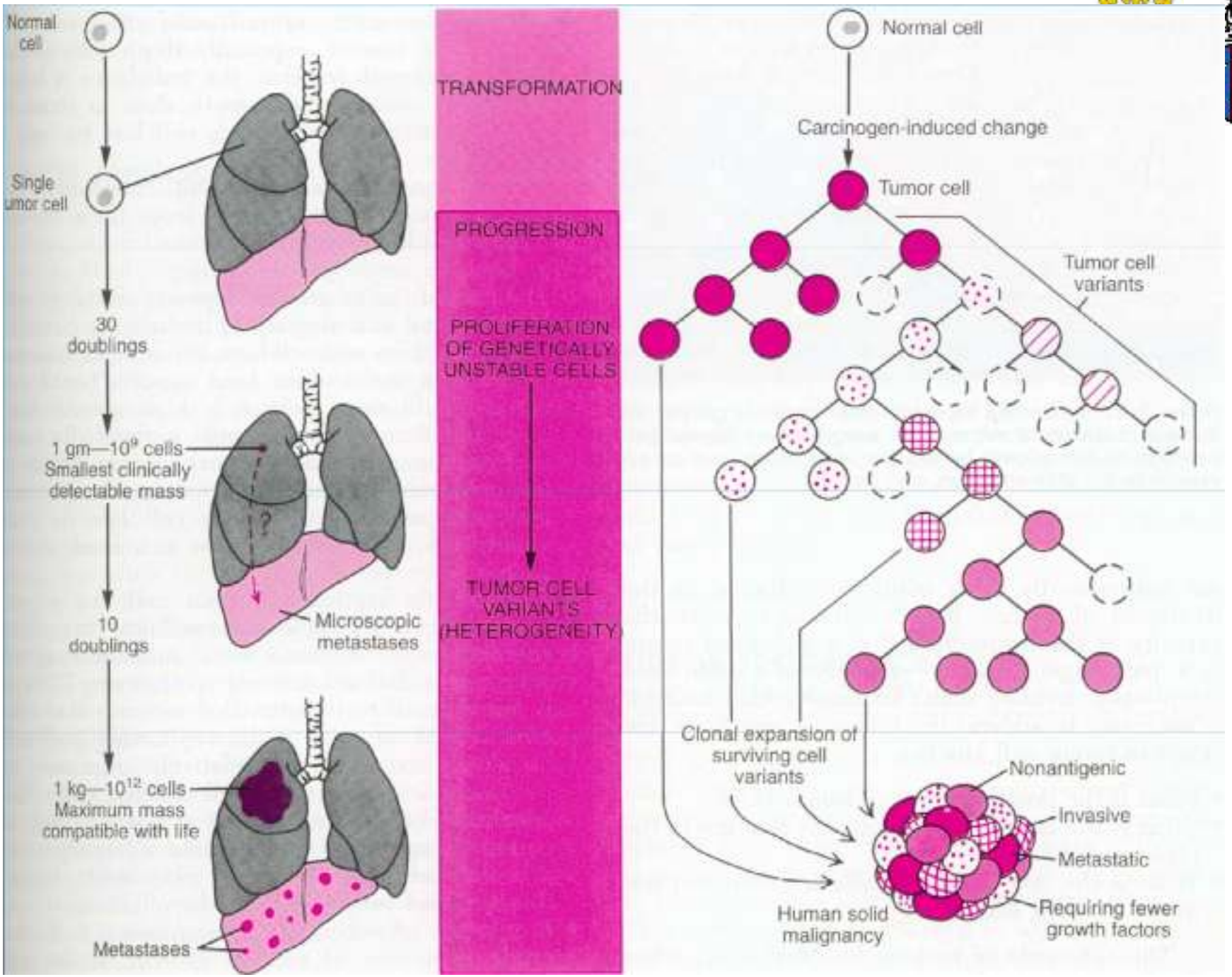
1.000.000.000.000
cells
~ 1 kg
DEATH
approx. 40 divisions

TUMOR PROGRESSION – CLONAL SELECTION IN AGREEMENT WITH DARWINIAN THEORY =*THE FITTEST WILL SURVIVE*

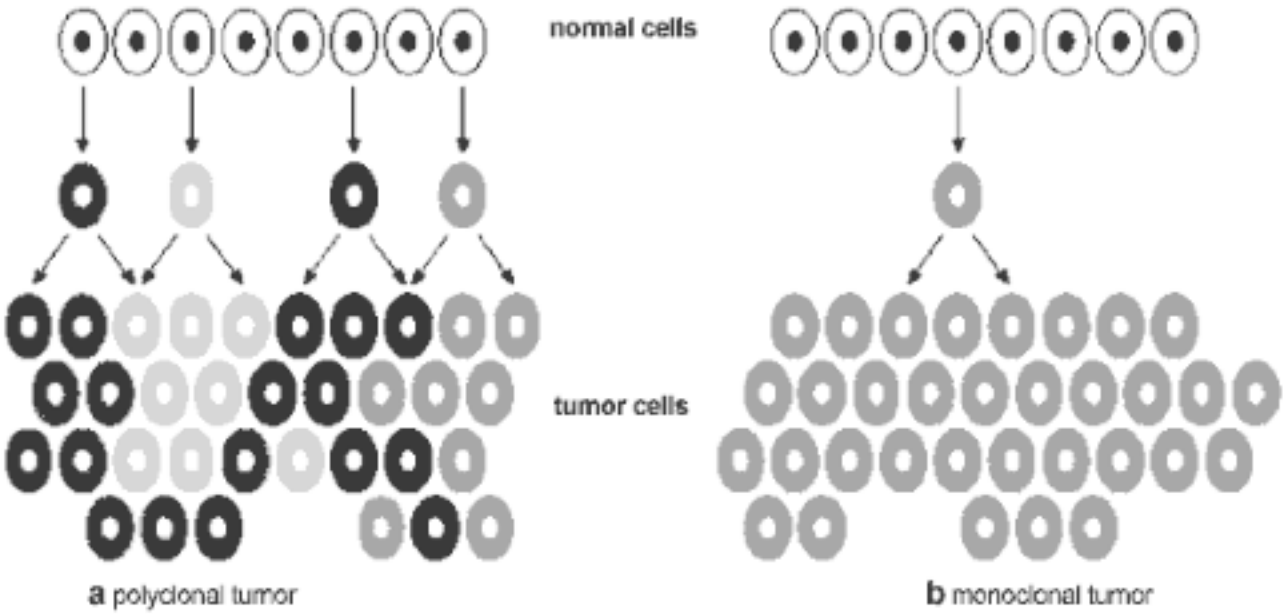


Source: Modified from Varmus, H., & Weinberg, R.A. 1993. *Genes and the biology of cancer*. New York: Scientific American Library.



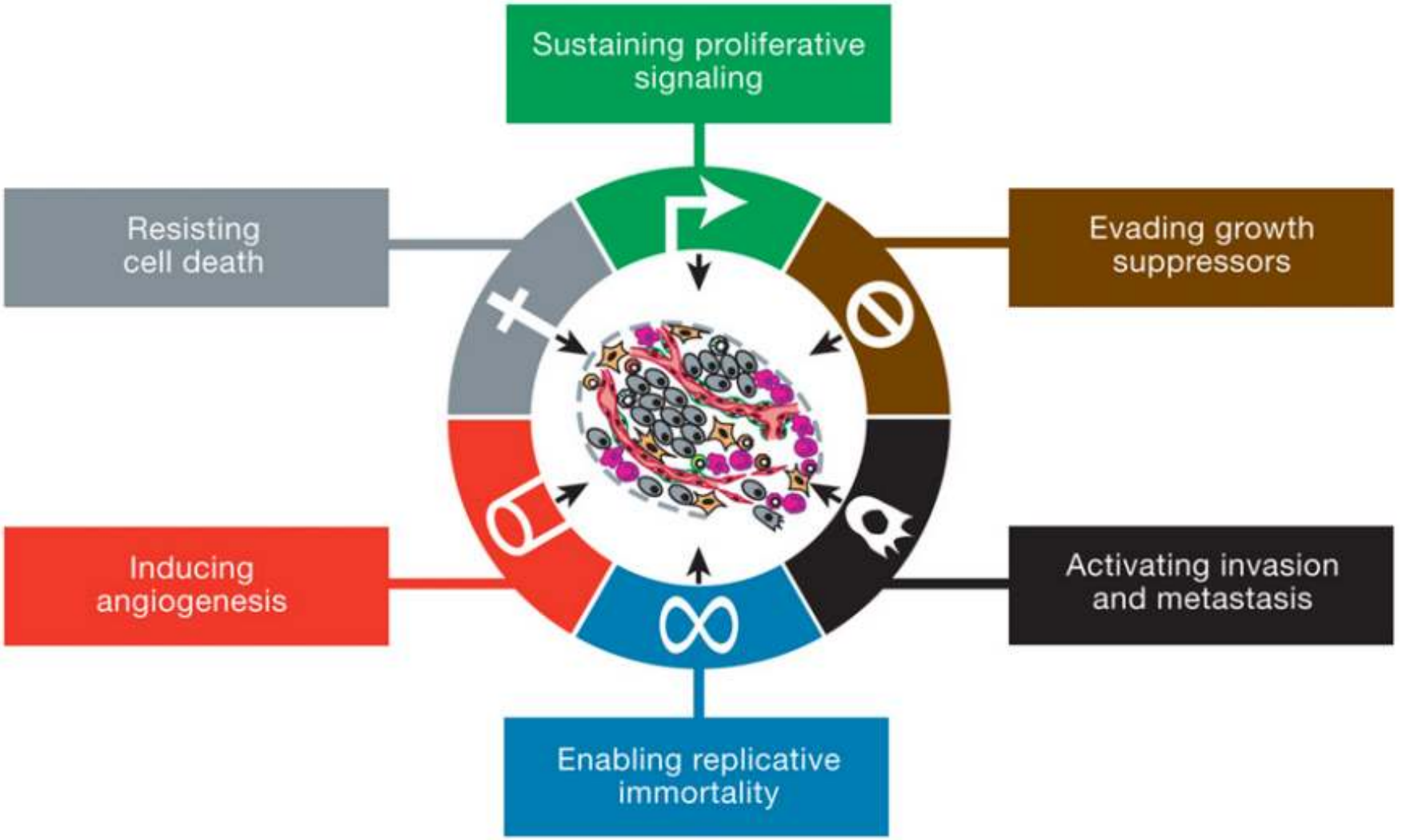

Normal cell
Single tumor cell
30 doublings
1 gm—10⁹ cells
Smallest clinically detectable mass
10 doublings
Microscopic metastases
1 kg—10¹² cells
Maximum mass compatible with life
Metastases
TRANSFORMATION
PROGRESSION
PROLIFERATION OF GENETICALLY UNSTABLE CELLS
TUMOR CELL VARIANTS (HETEROGENEITY)
Normal cell
Carcinogen-induced change
Tumor cell
Tumor cell variants
Clonal expansion of surviving cell variants
Nonantigenic
Invasive
Metastatic
Requiring fewer growth factors
Human solid malignancy

NEOPLASTIC TRANSFORMATION POLYCLONAL OR MONOCLONAL

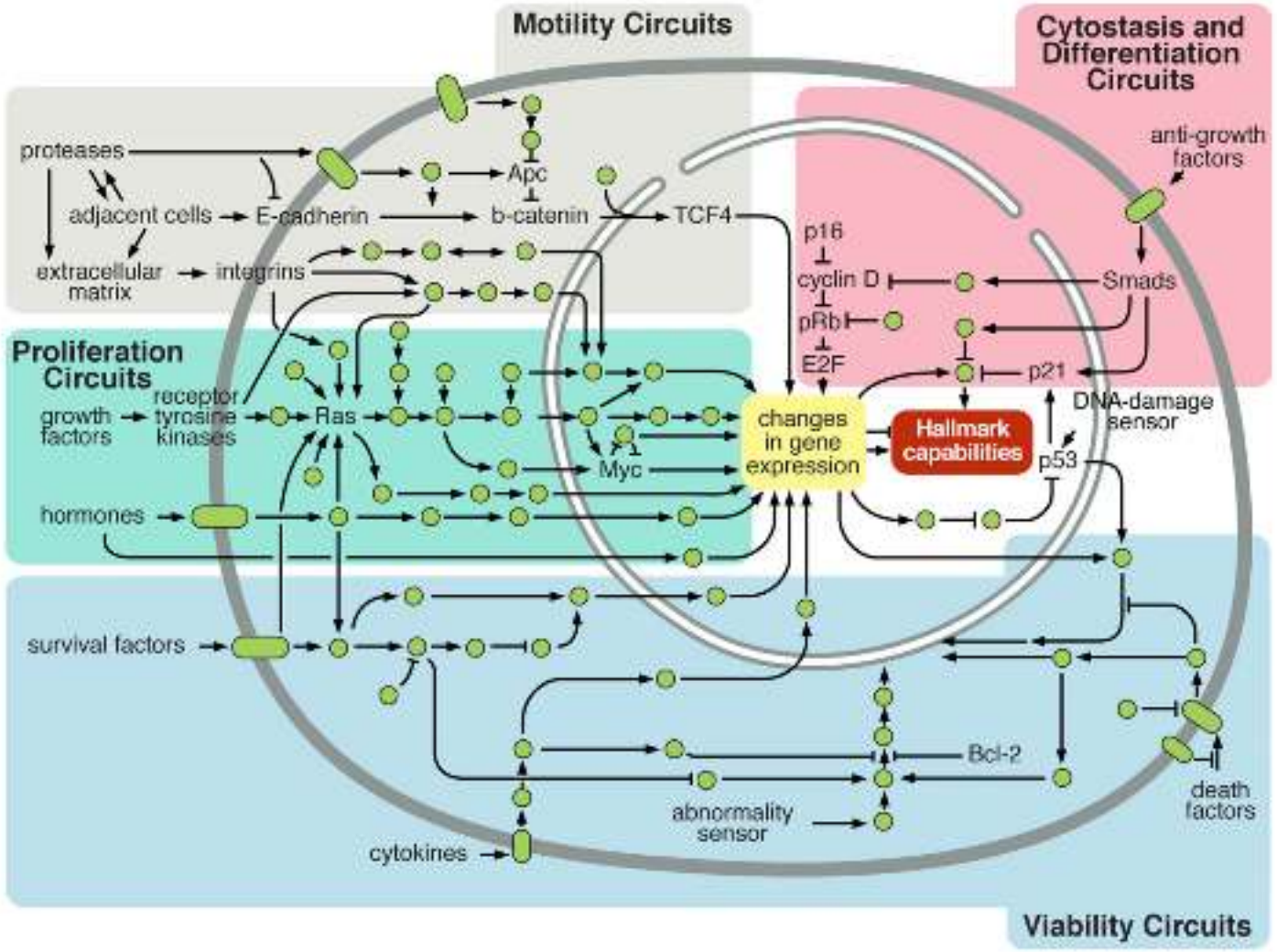


Source: Modified from Varmus, H., & Weinberg, R.A. 1993. *Genes and the biology of cancer.* New York: Scientific American Library.

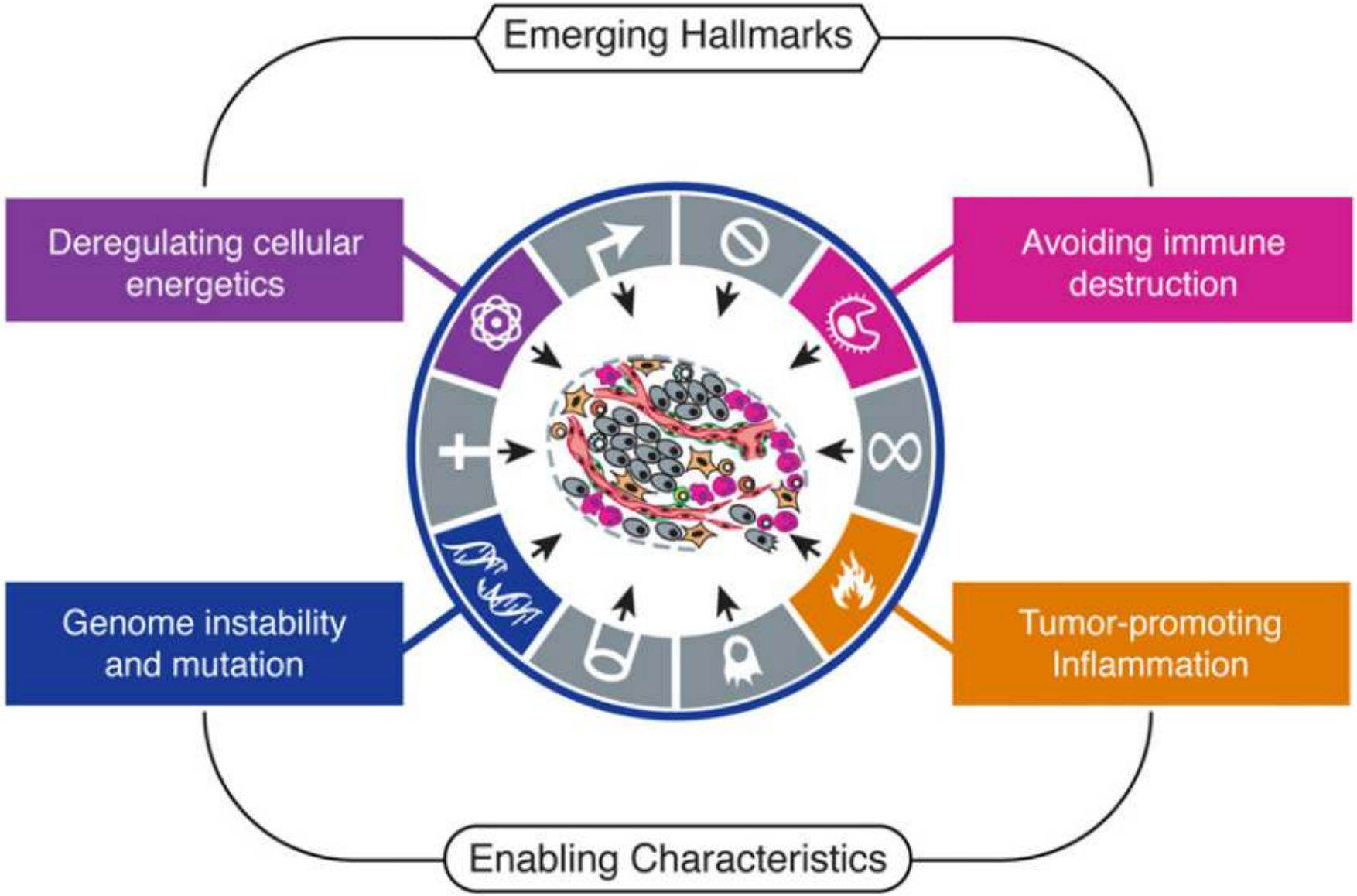
THE HALLMARKS OF CANCER



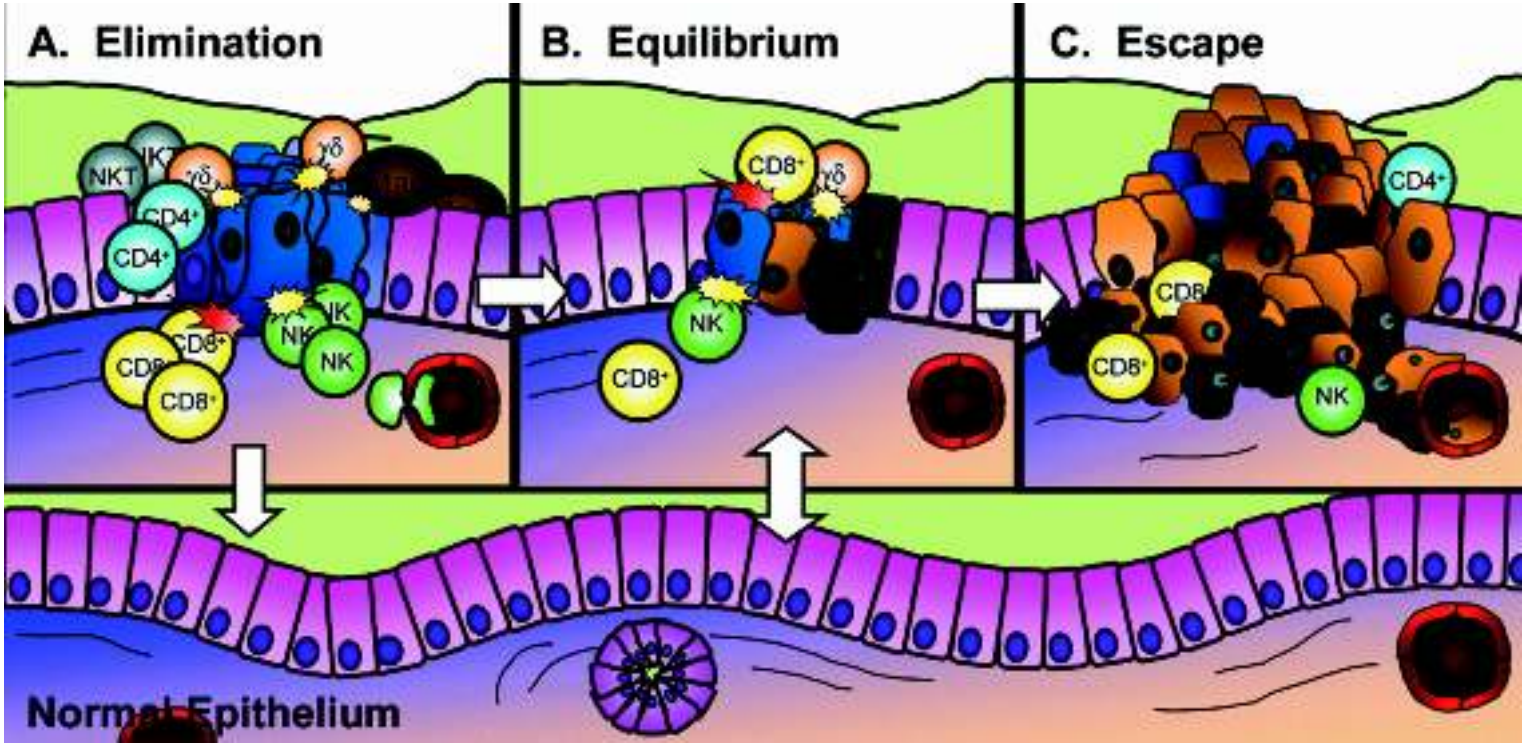
HALLMARKS OF CANCER
intracellular pathways



NOVEL HALLMARKS OF CANCER



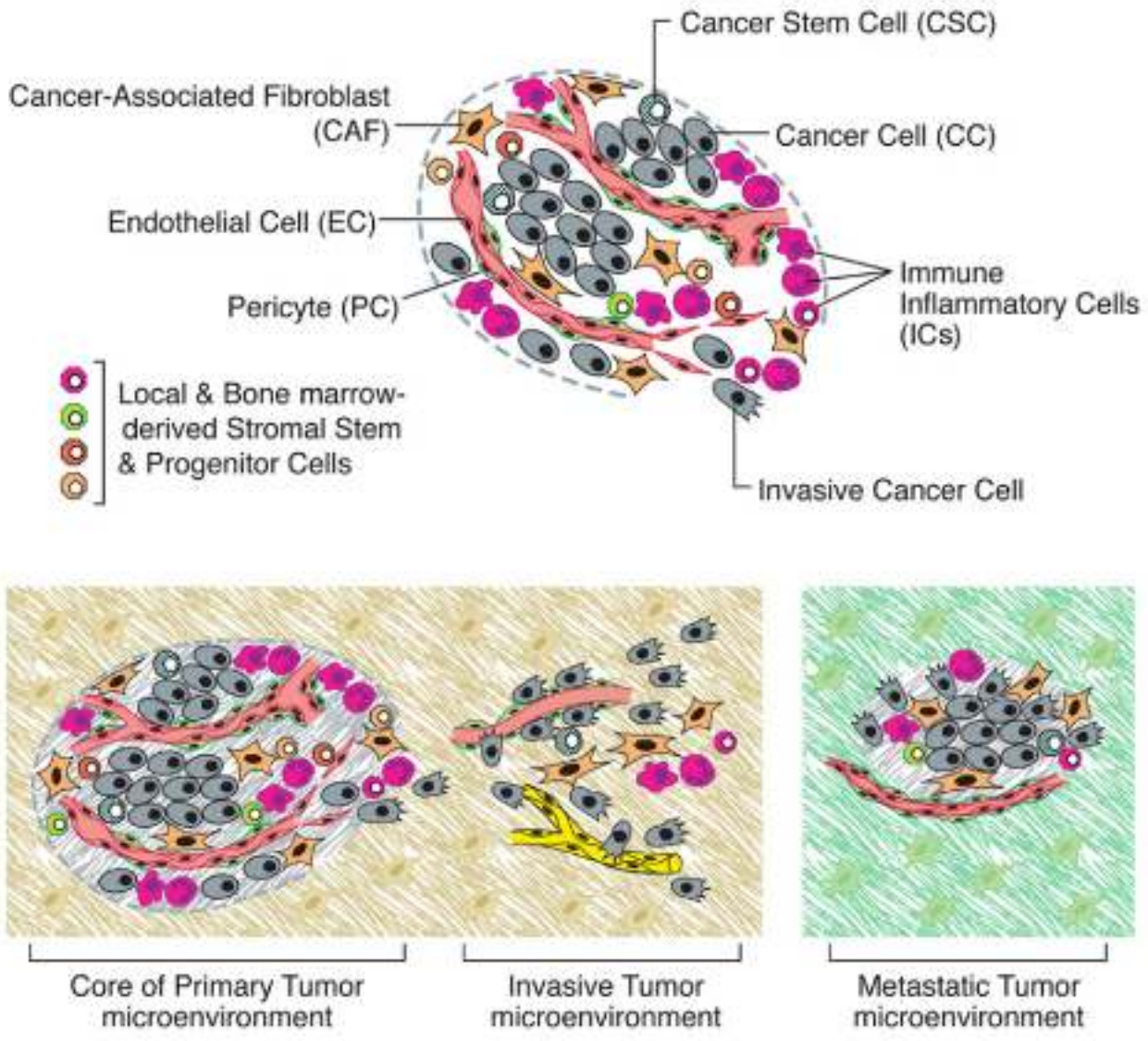
IMMUNE SURVEILLANCE



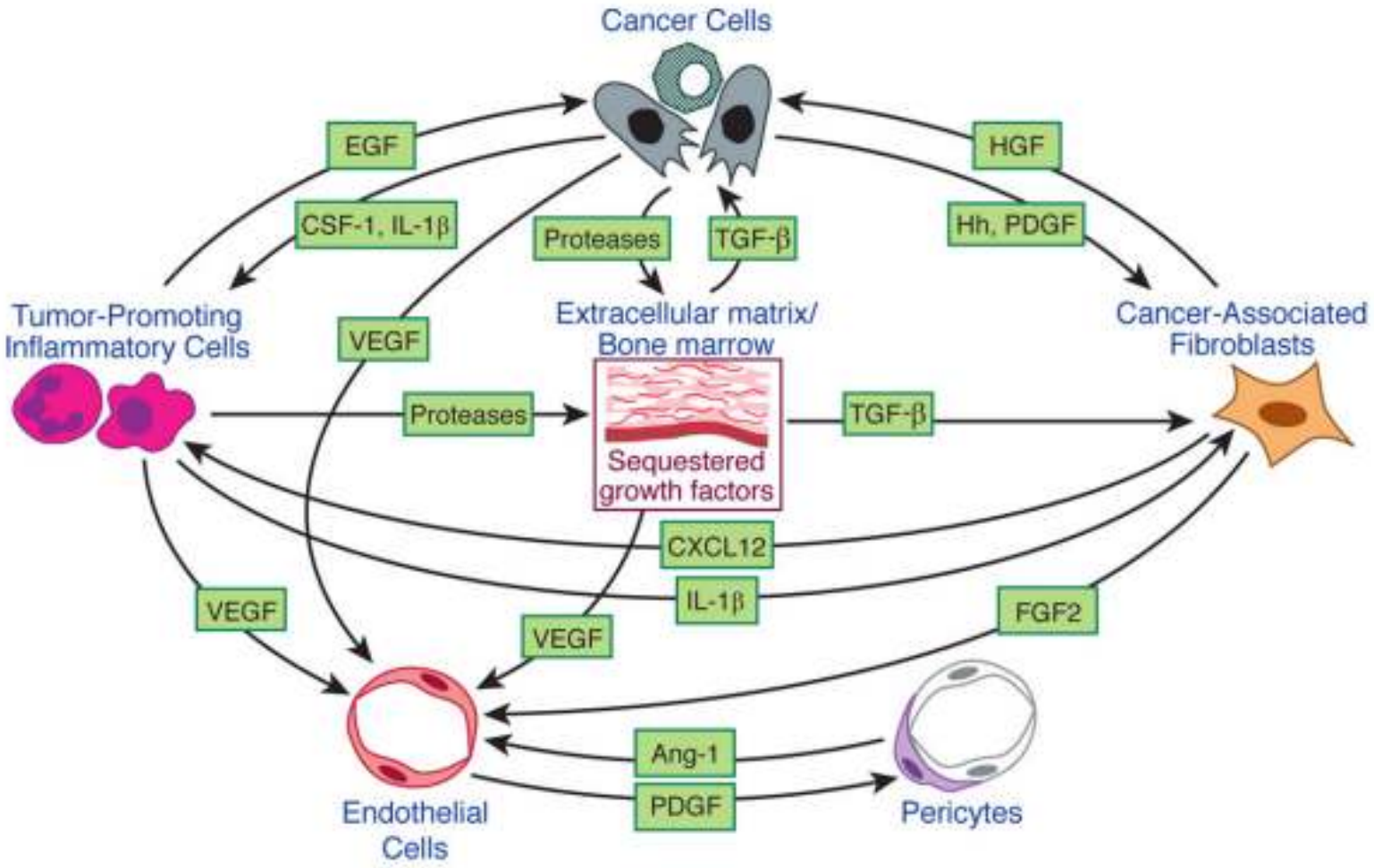
TUMOR ESCAPE MECHANISMS

- loss of MHC class I = not recognizable by T cells
- secretion of soluble MHC class I = supression of NK cells
- secretion of IL-10, IL-6, IL-4, VEGF = general immune suppressio
- upregulation of PD-L1, PD-L2 = direct suppression of T cells

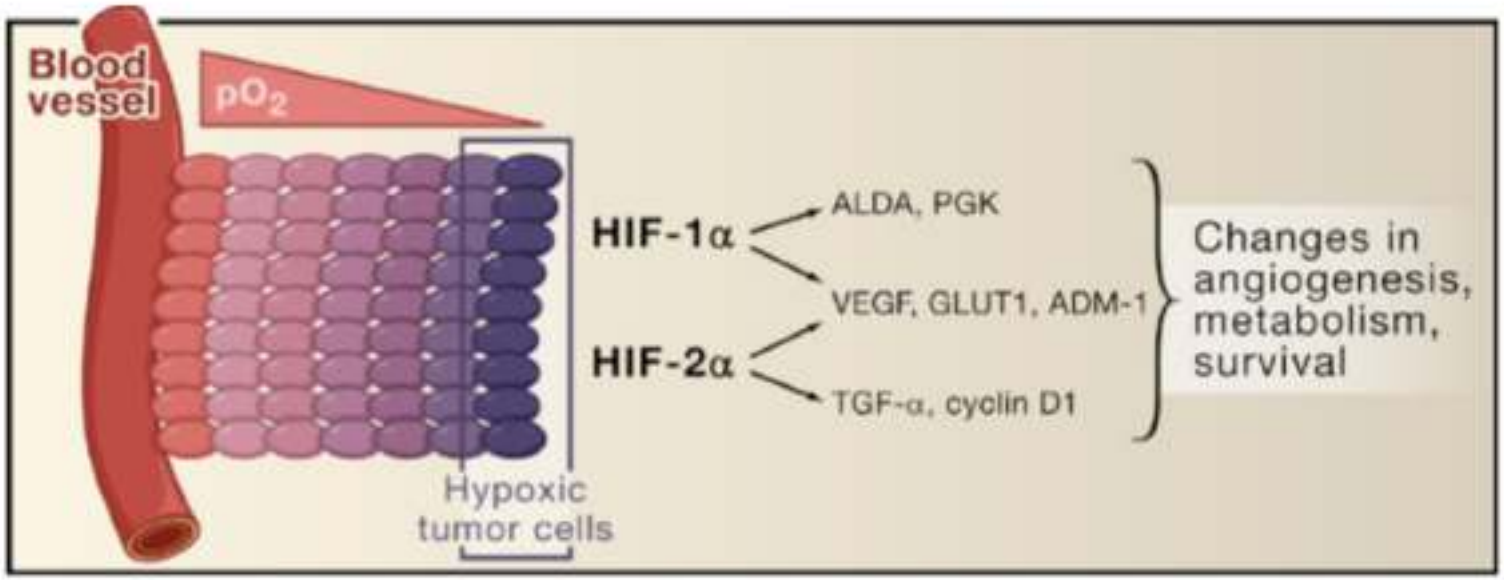
TUMOR - IT IS NOT JUST ABOUT CANCER CELLS

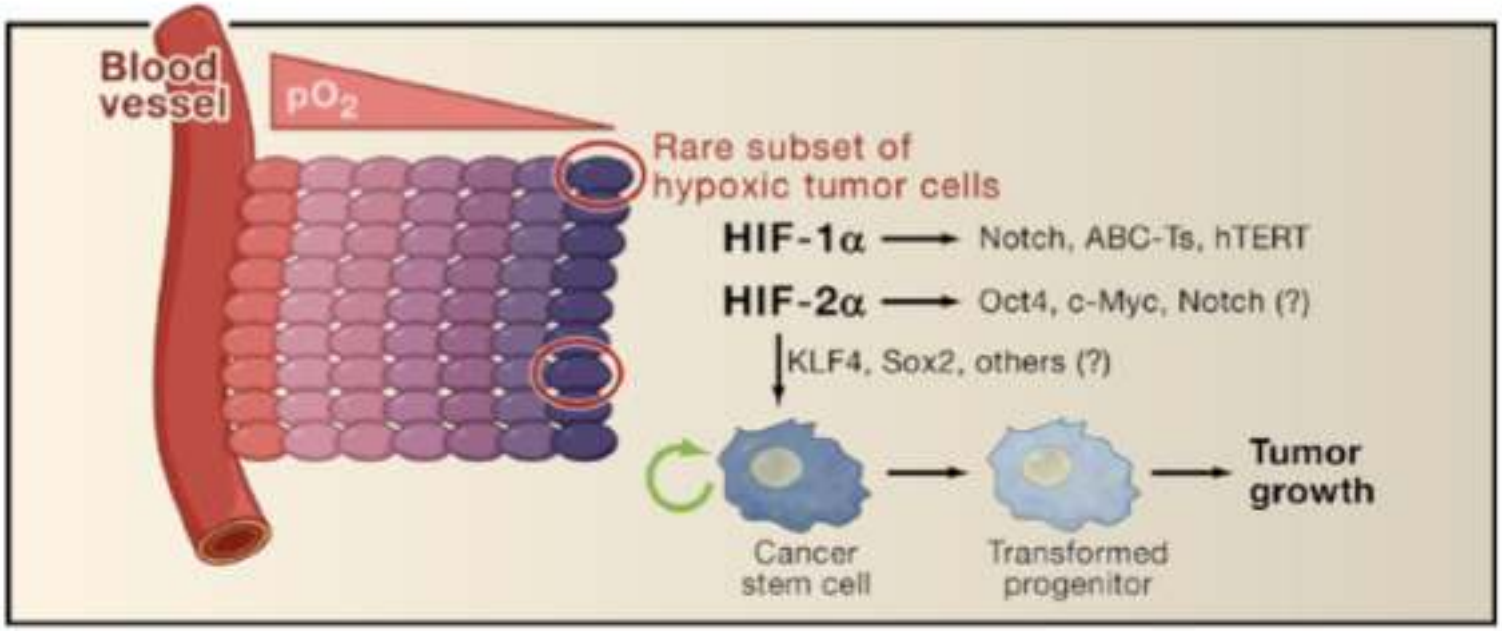


INTRATUMORAL CROSSTALKS LEADING TO PROGRESSION

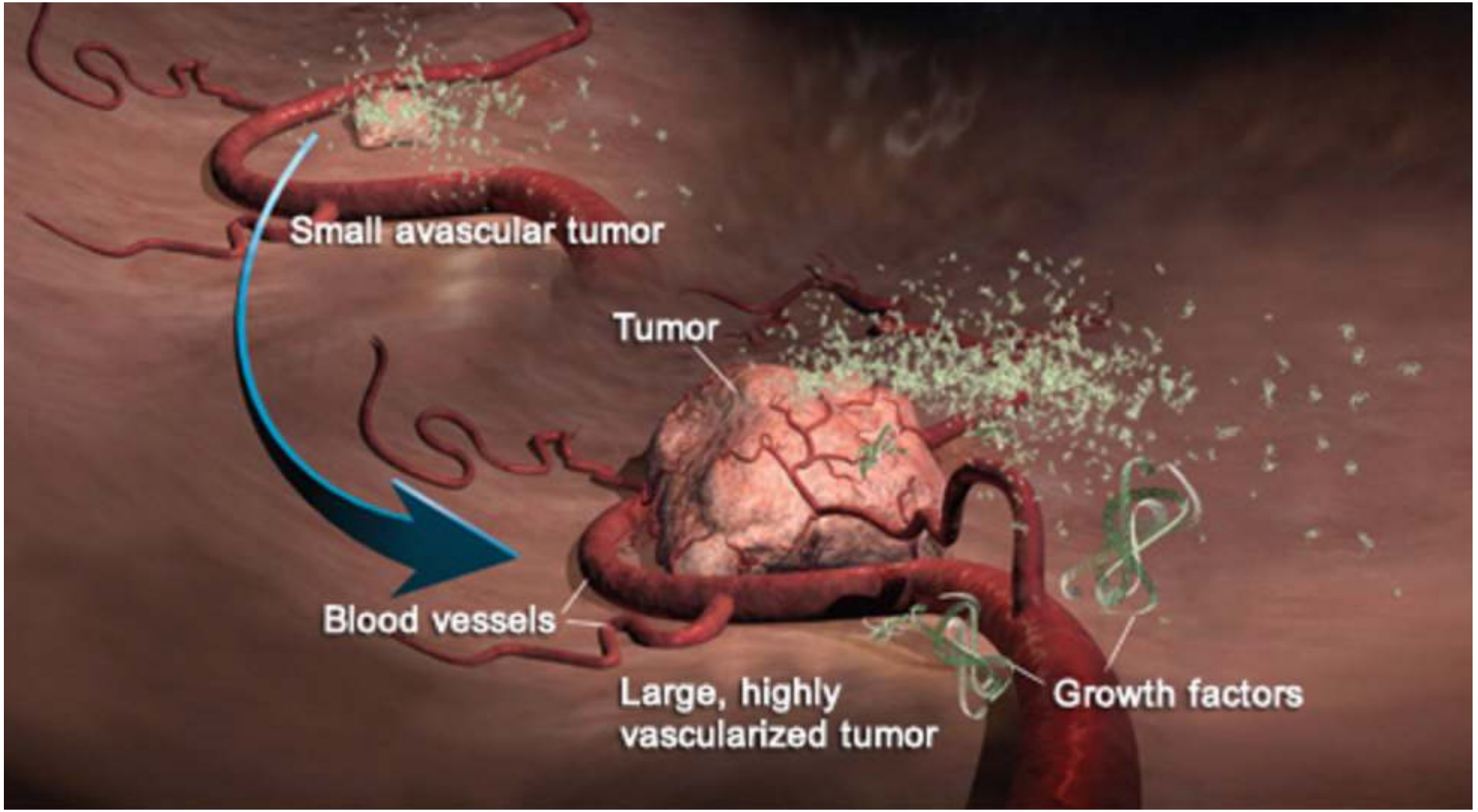


ANGIOGENESIS

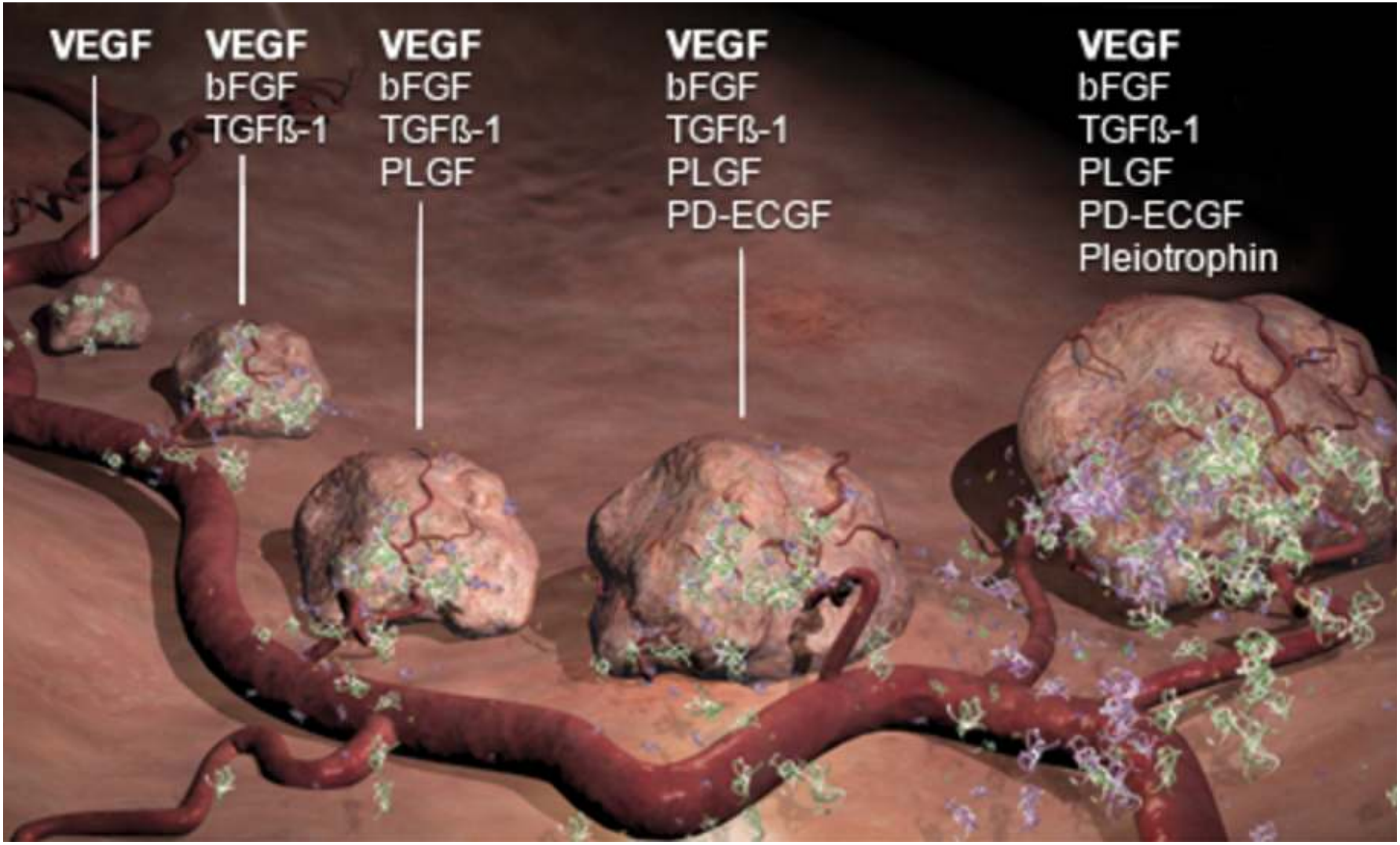


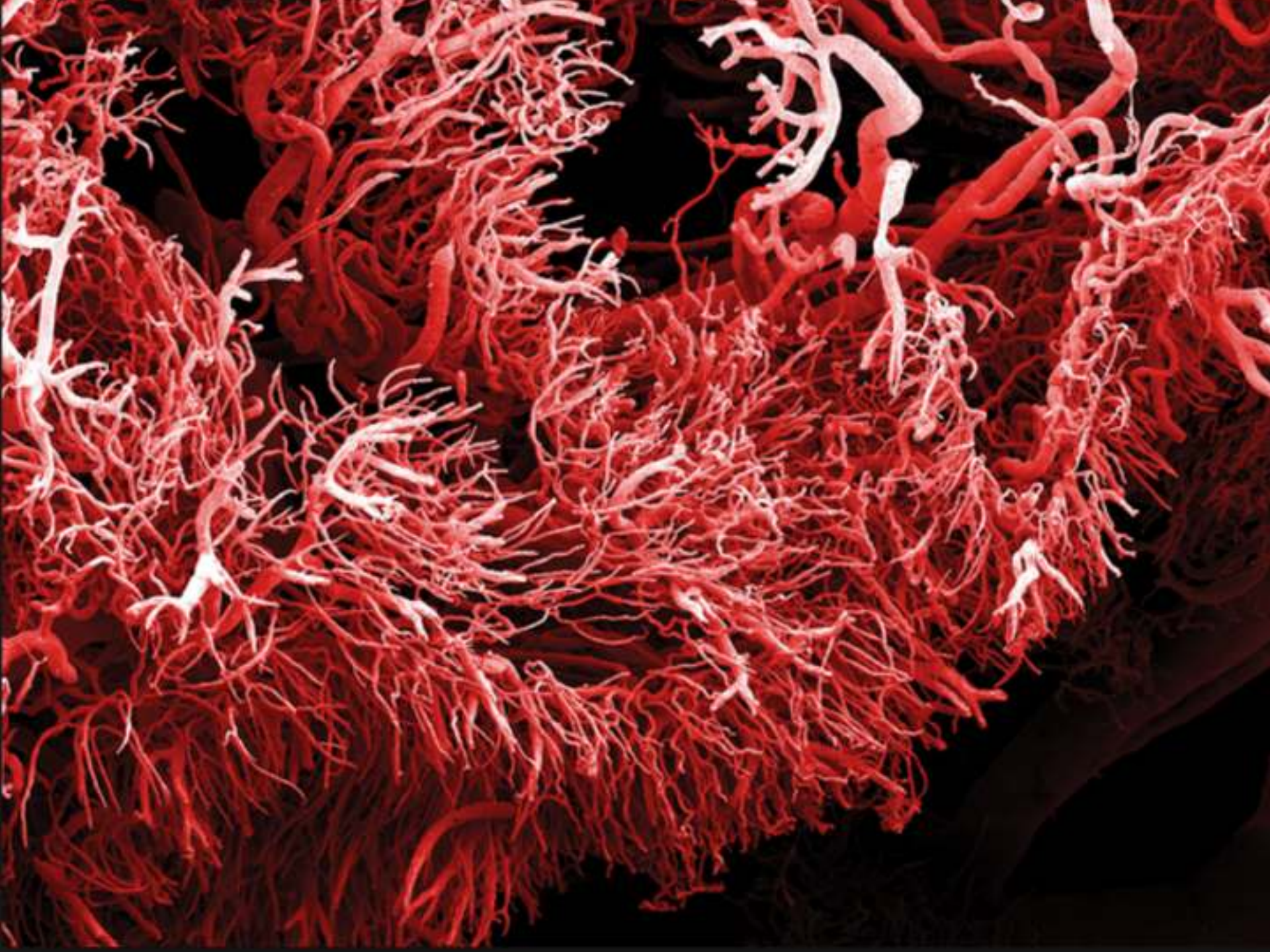


ANGIOGENESIS

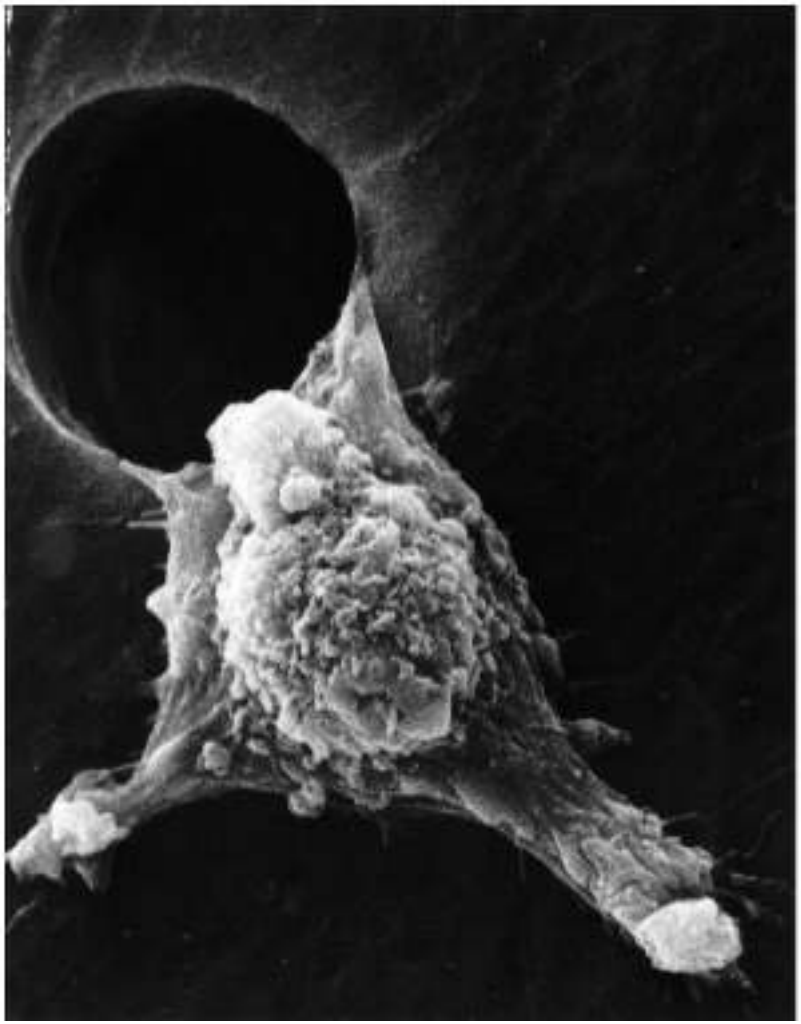


ANGIOGENESIS – PROANGIOGENIC FACTORS

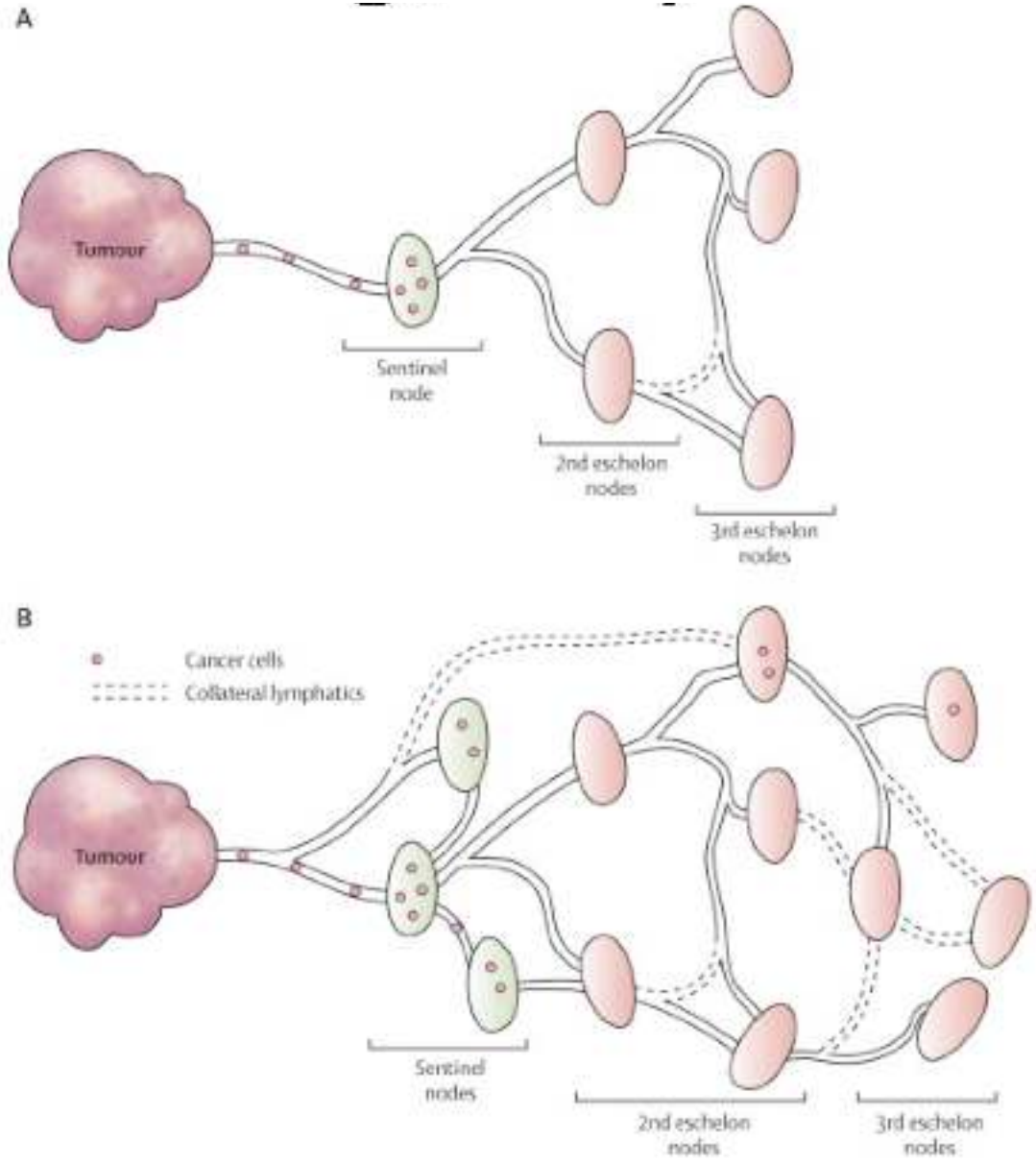


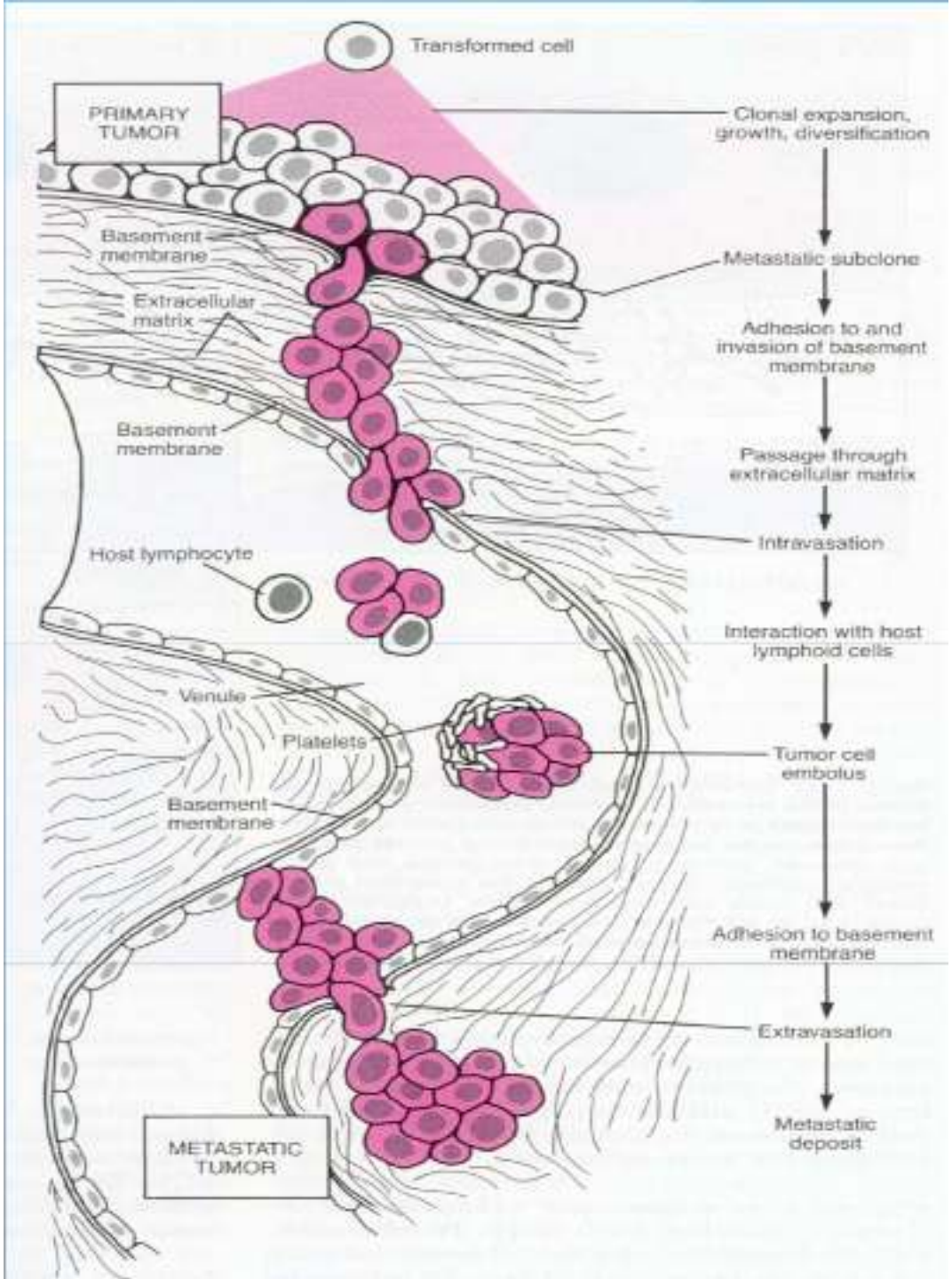


INVASION/METASTASIS

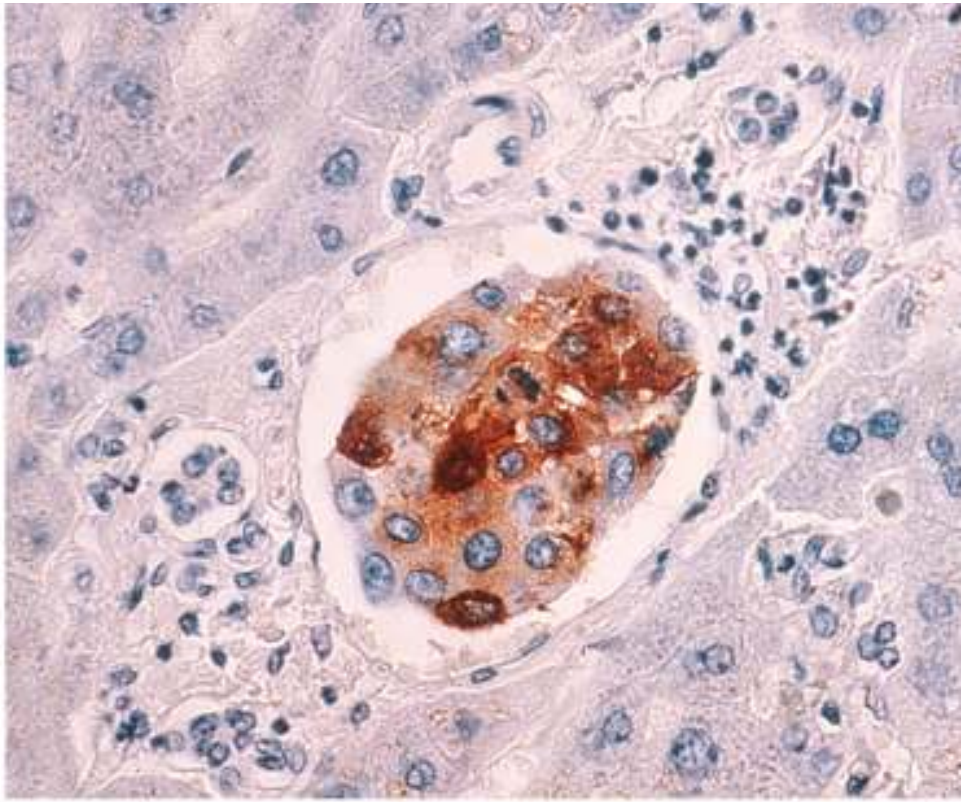


LYMPHANGIOGENESIS - METASTASES IN LYMPH NODES

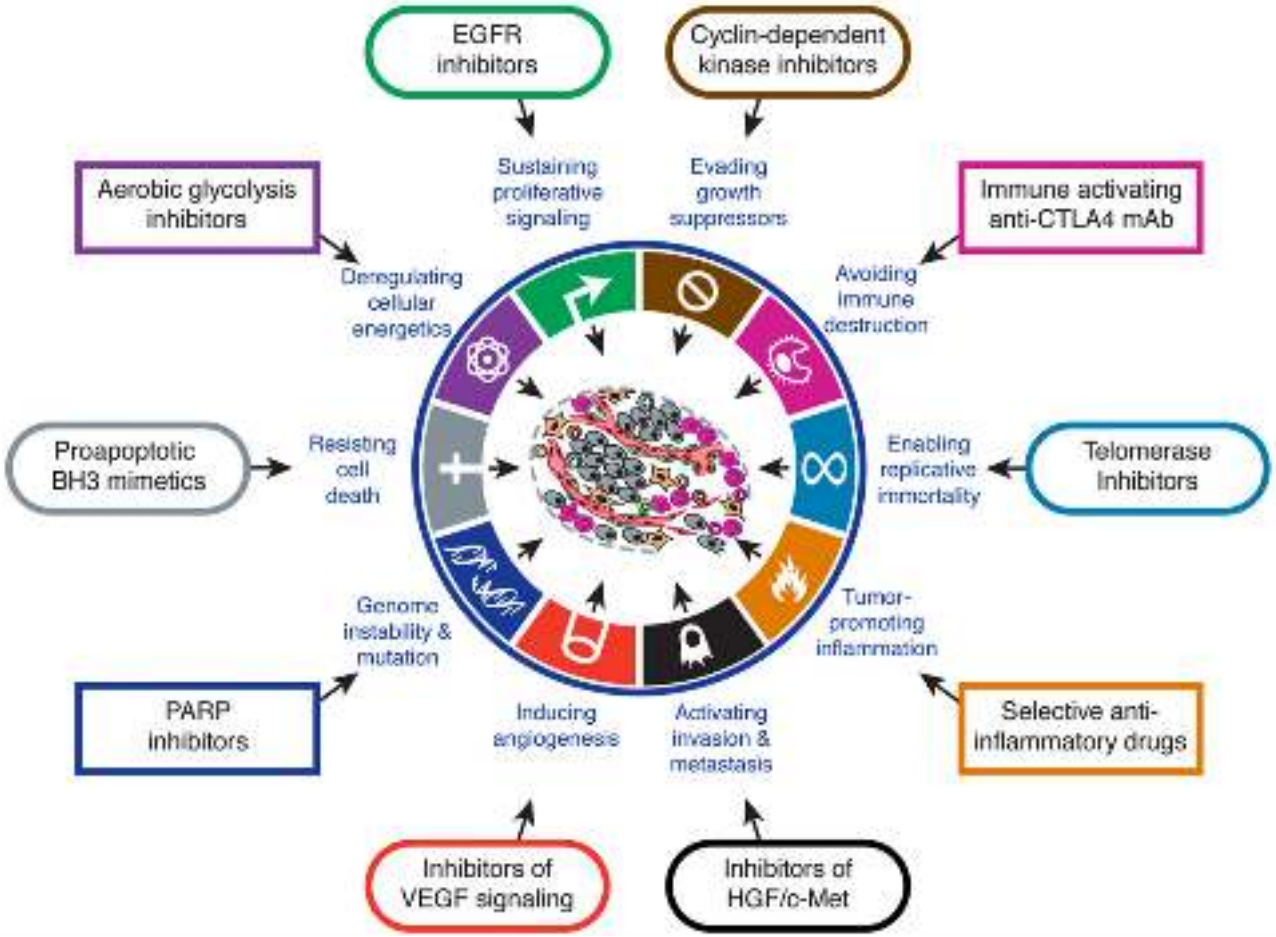



Transformed cell
PRIMARY TUMOR
Clonal expansion, growth, diversification
Basement membrane
Metastatic subclone
Extracellular matrix
Adhesion to and invasion of basement membrane
Basement membrane
Passage through extracellular matrix
Intravasation
Host lymphocyte
Interaction with host lymphoid cells
Venule
Platelets
Tumor cell embolus
Basement membrane
Adhesion to basement membrane
Extravasation
Metastatic deposit
METASTATIC TUMOR

DISTANT METASTASES (LIVER) VIA BLOOD



HALLMARKS OF CANCER – ACHILLES HEEL OF CANCER?

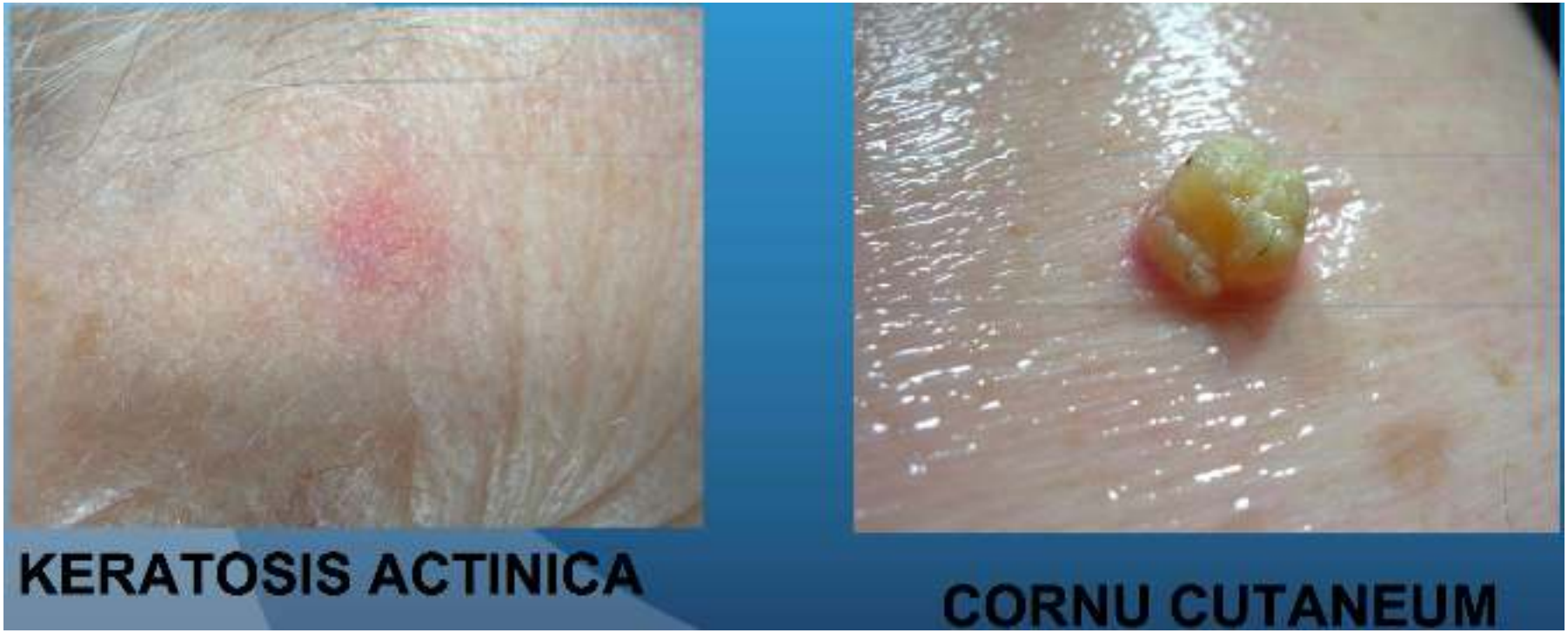


PHASES OF TUMOR DEVELOPMENT

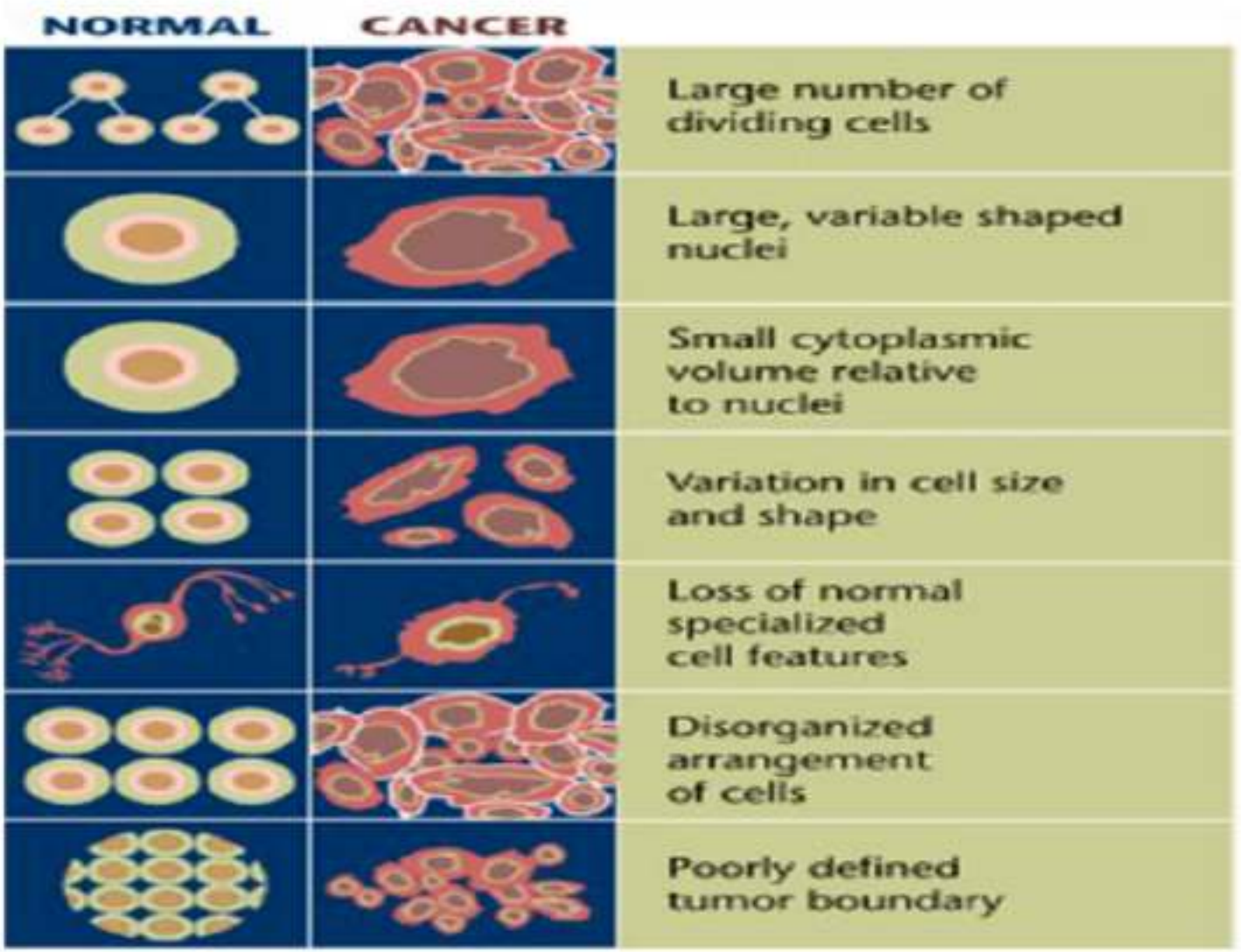
1. INDUCTION – 5-10 YEARS
2. IN SITU – 5-10 YEARS
3. INVASIVE – 1-5 YEARS
4. DISSEMINATION 1-5 YEARS

PRECANCEROUS CONDITION

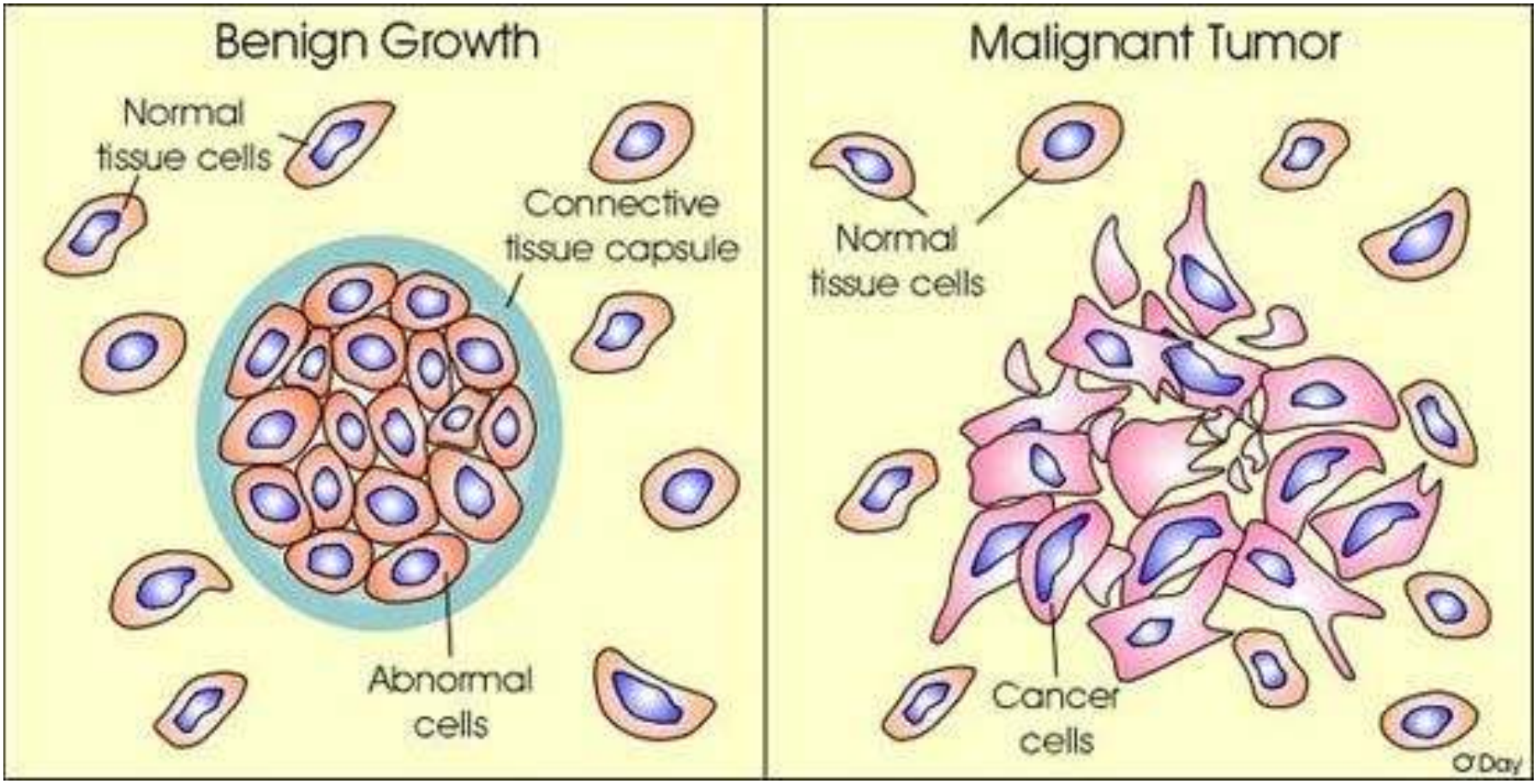
Premalignant lesions are morphologically atypical tissue which appears abnormal under microscopic examination, and in which cancer is more likely to occur than in its apparently normal counterpart.



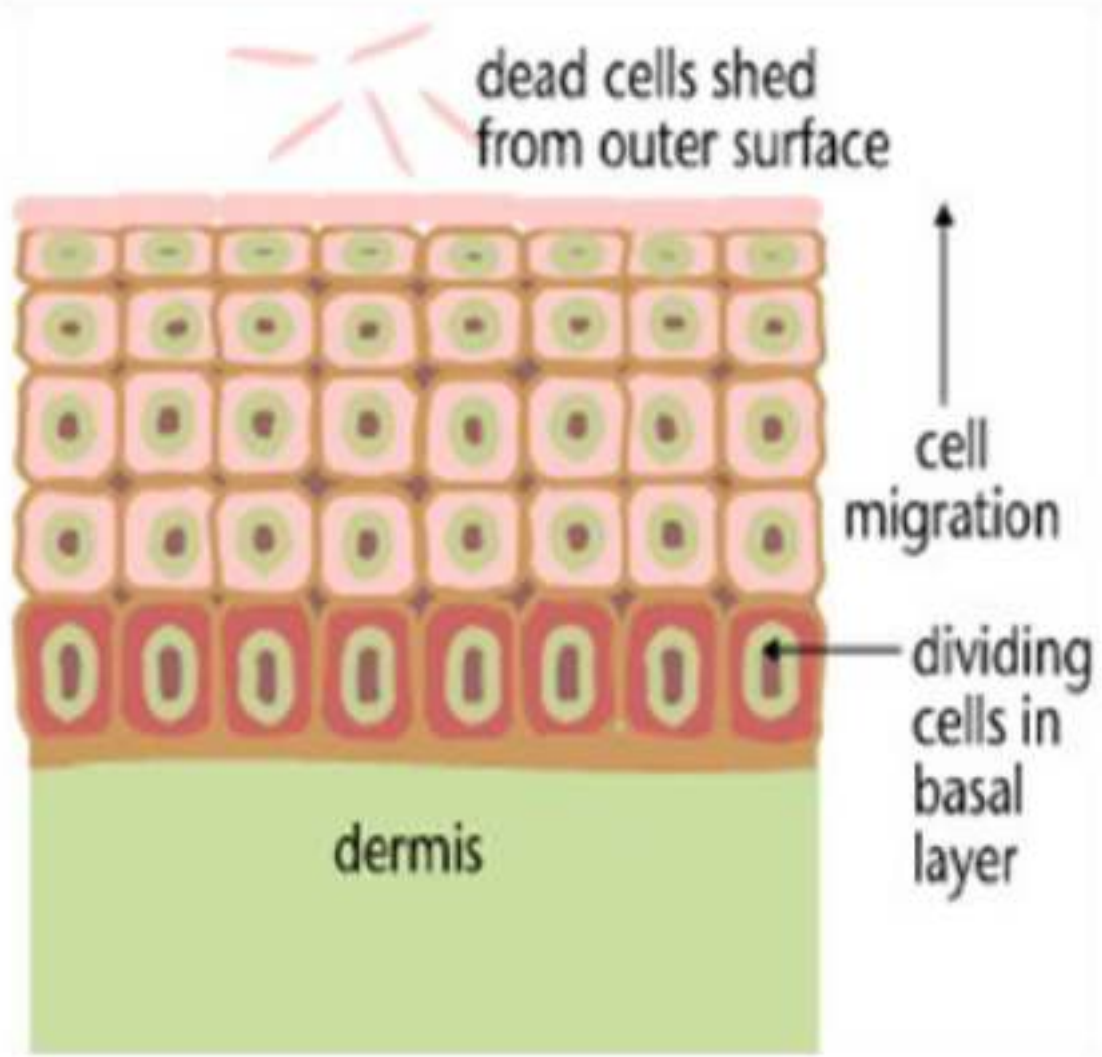
What are the differences in the features of normal and cancer cells?



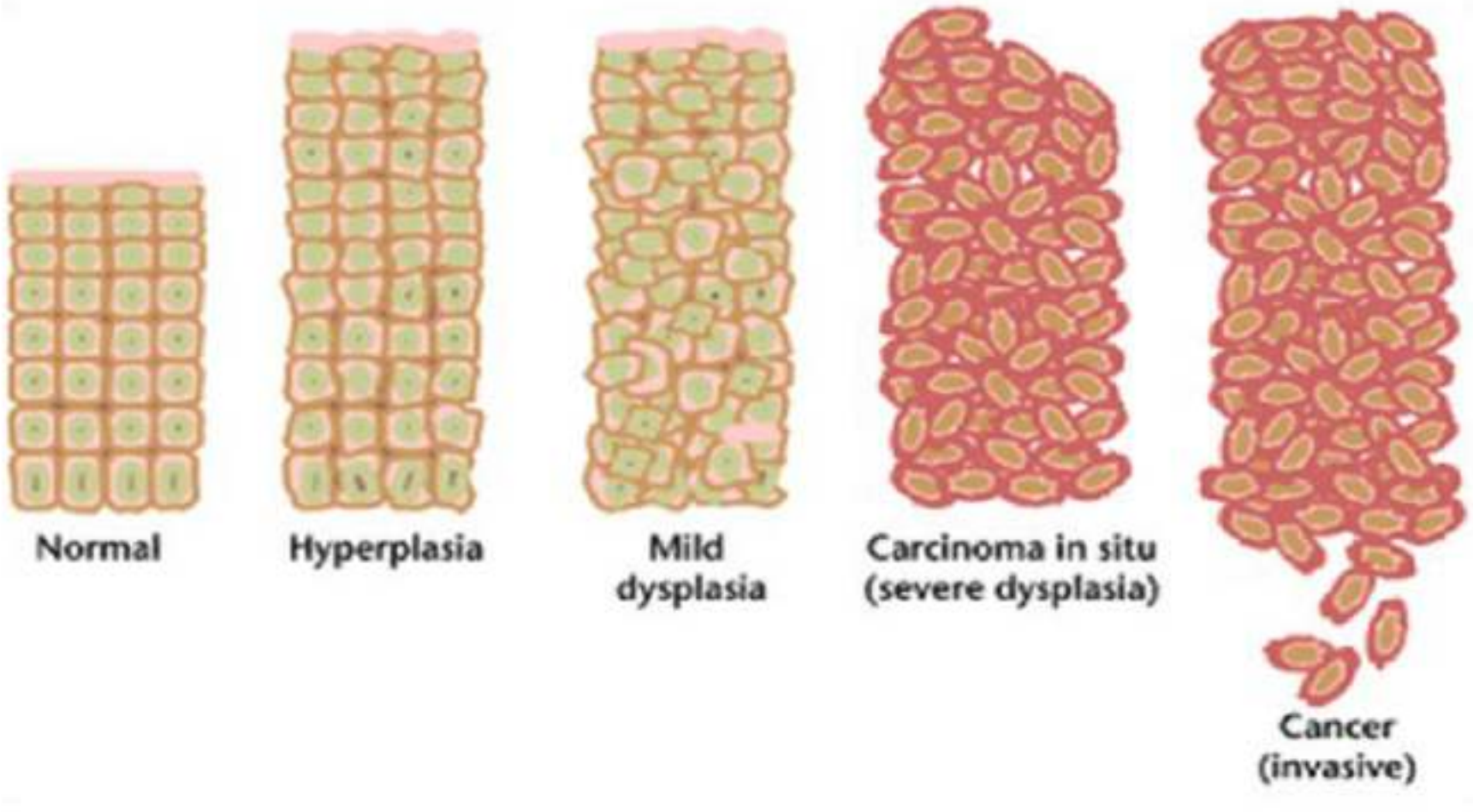
Benign vs Malignant Tumors



Normal cell growth

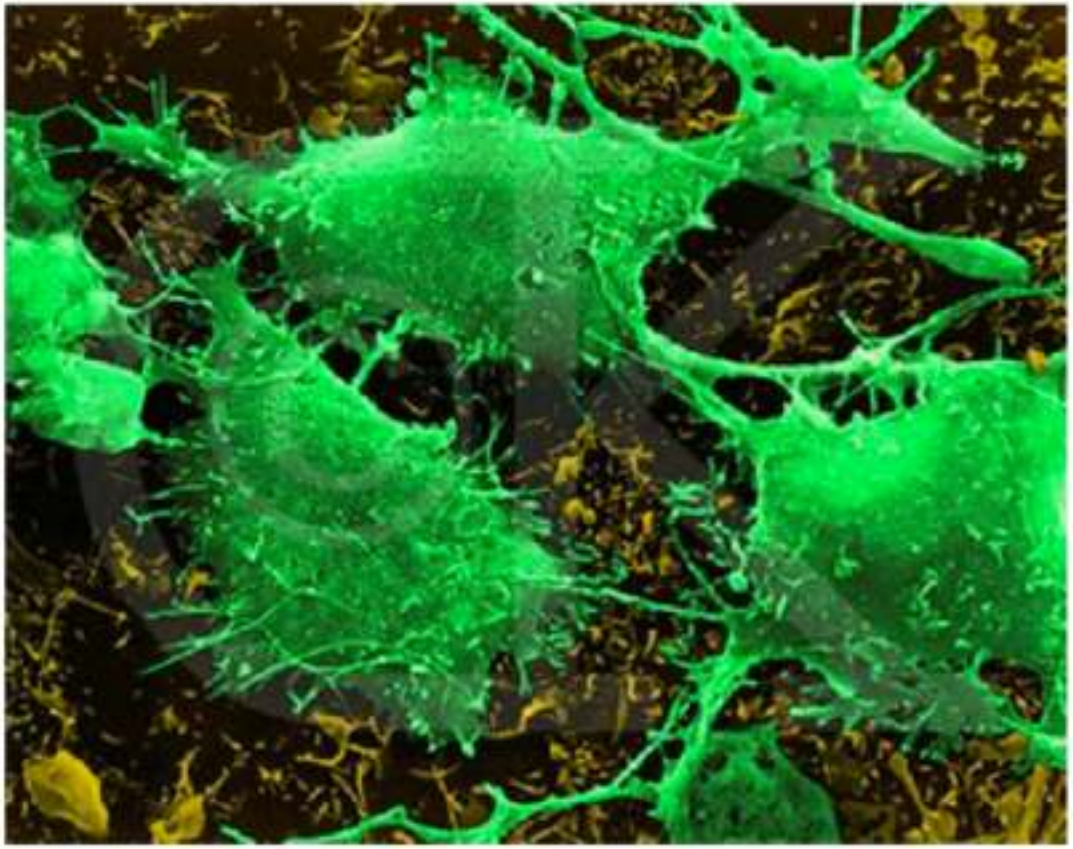


Cancerous growth



Carcinogenesis.
Some factors to consider…

- Heredity
- Immunity
- Chemical
- Physical
- Viral
- Bacterial
- Lifestyle



Heredity

- 5-10% of Cancers
- ?15% of all cancers
- Molecular biology and Human Genome Project

Heredity

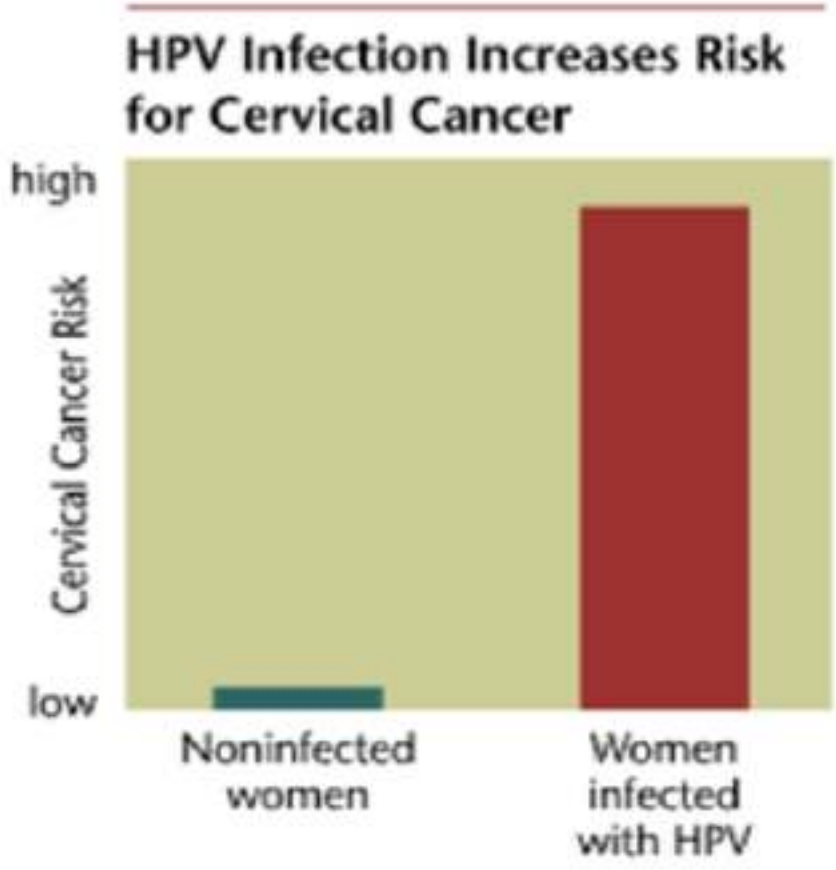
- Genes isolated for several classic familial cancer syndromes:
  - RB1 (retinoblastoma)
  - APC (familial polyposis)
  - Human Non Polyposis Colon Cancer (HNPCC)
  - BRCA 1&2 (breast cancer)
  - p53 (many cancers)

Immunity

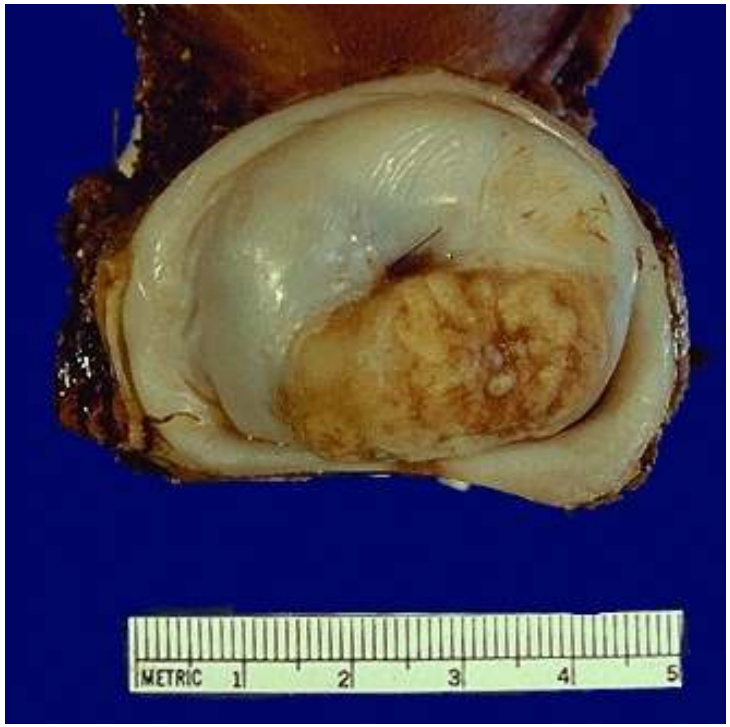
- HIV / AIDS
- Immunosuppression

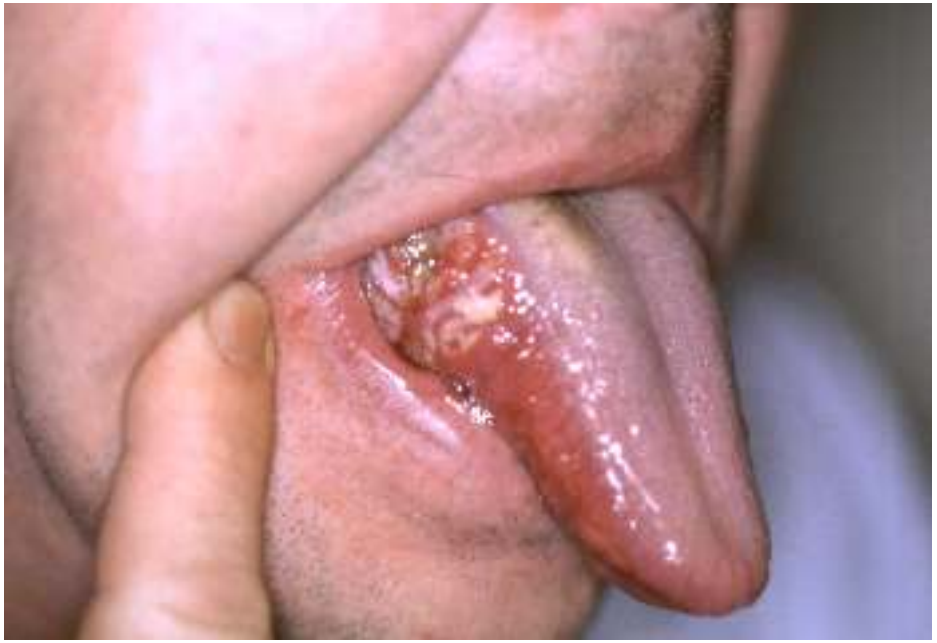
Virus's

- Hepatitis B
- Human T-cell Leukaemia virus
- Epstein Barr Virus
- Human Papilloma Virus (HPV)



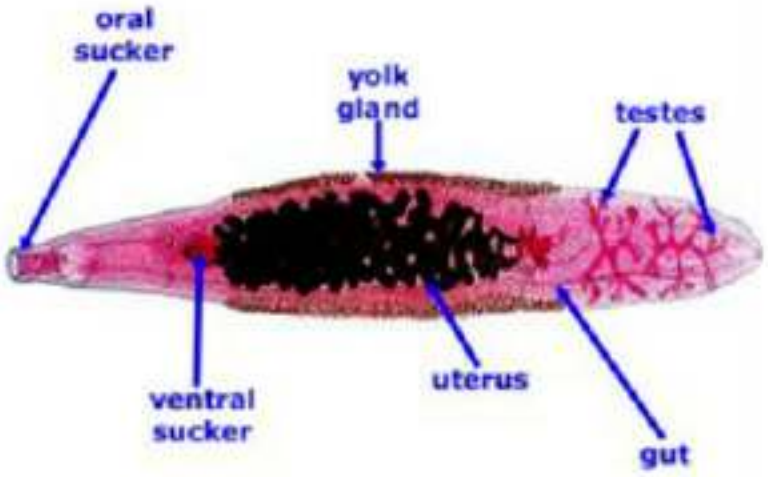
HPV-ASSOCIATED CANCERS





Bacterial

- H. pylori
- Other Parasites:
  - Schistosoma spp
  - Clonorchis sinensis



Estimated Burden of Cancer from Infection Worldwide in 2000

	No. of cases	Agent	% World cancer
Liver	509,000	HBV, HCV, flukes	5.1
Cervix	471,000	HPV	4.7
Stomach	442,000	*H. pylori*	4.4
Kaposi's (HIV related)	134,000	HHV-8	1.3
Non Hodgkin lymphoma	72,000	*H. pylori*, EBV, HIV	0.7
Ano-genital	65,000	HPV	0.6
Nasopharyngeal	63,000	EBV	0.6
Hodgkin disease	33,000	EBV, HIV	0.3
Bladder	10,000	Schistosoma	0.1
Leukaemia	3,000	HTLV1	0.03
Total	1,801,000		17.9

Chemical

- Alcohol
- Asbestos
- Wood dust
- Rubber, plastics, dyes
- Tar / bitumen
- Aflatoxin
- Alkylating agents

- Tobacco

ALCOHOL

- head and neck cancer,
- esophageal cancer,
- liver cancer,
- breast cancer,
- colorectal cancer

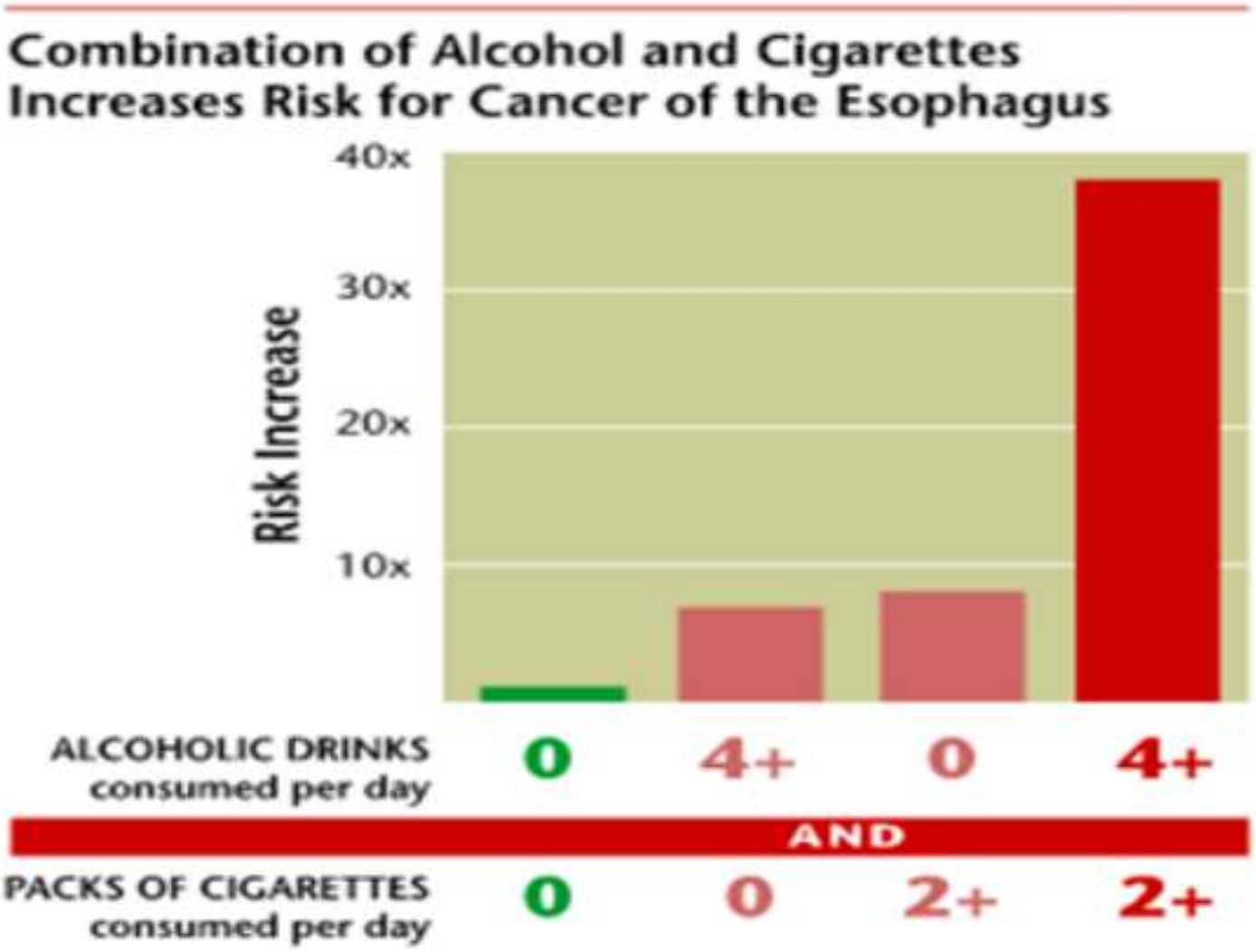
Smoking

- Single biggest cause of cancer
- 25-40% smokers die in middle age
- 9 in 10 lung cancers
- Know to cause cancer in 1950

SMOKING

- **lung cancer**
- **head&neck cancers**
- **pancreatic cancer**
- **kidney cancer**
- **bladder cancer**

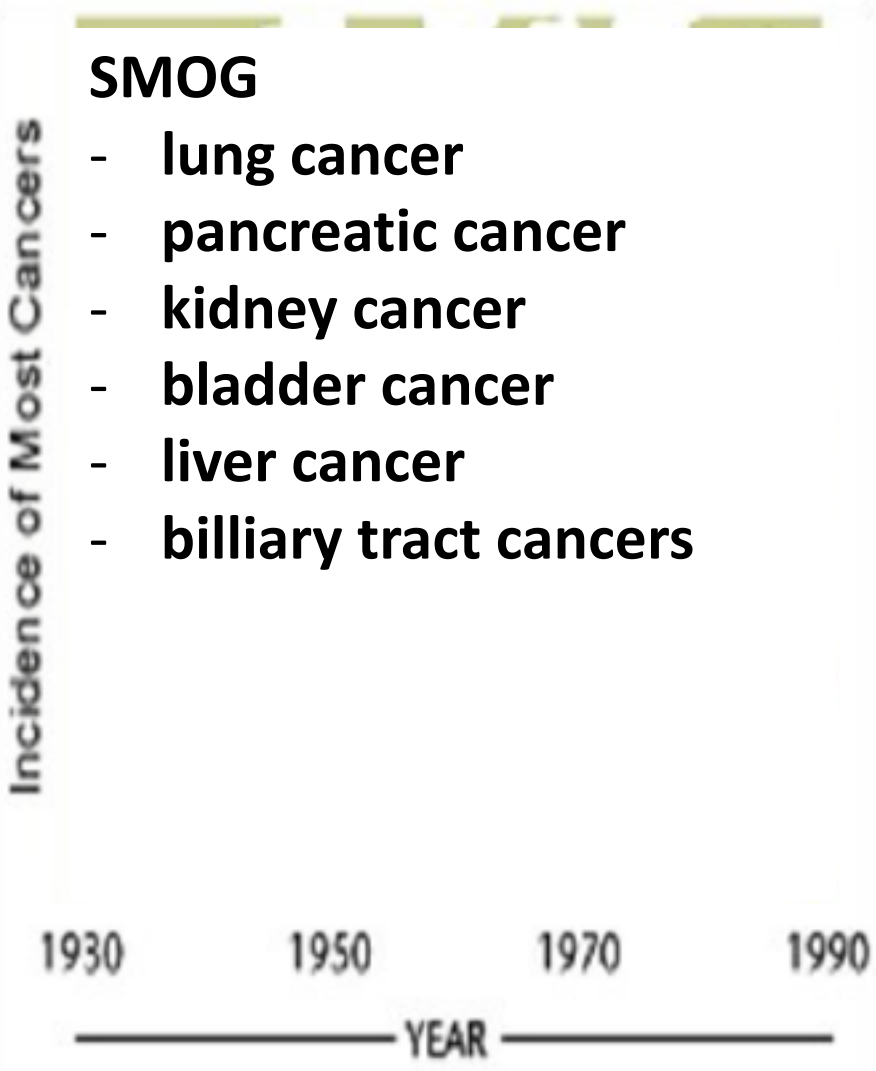
Smoking and alcohol



Industrial pollution

SMOG

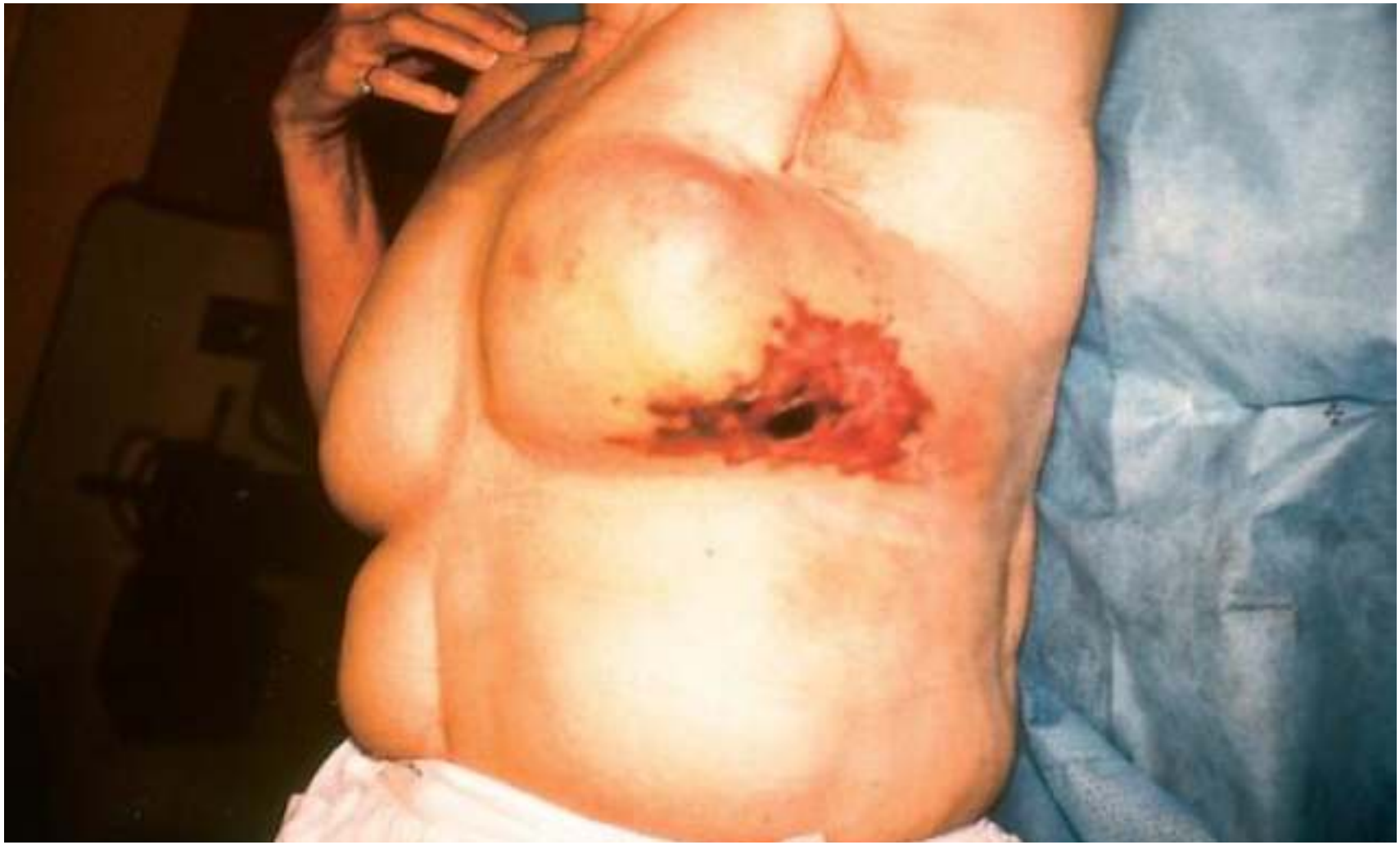
- **lung cancer**
- **pancreatic cancer**
- **kidney cancer**
- **bladder cancer**
- **liver cancer**
- **billiary tract cancers**



PHYSICAL CAUSES

- ULTRAVIOLET RADIATION
  - SUNLIGHT
  - TANNING BED
- IONIZING RADIATION
  - RADON
  - CANCER TREATMENT
- ELECTROMAGNETIC RADIATION
  - CELLULAR PHONES?

RADIATION-INDUCED SARCOMA



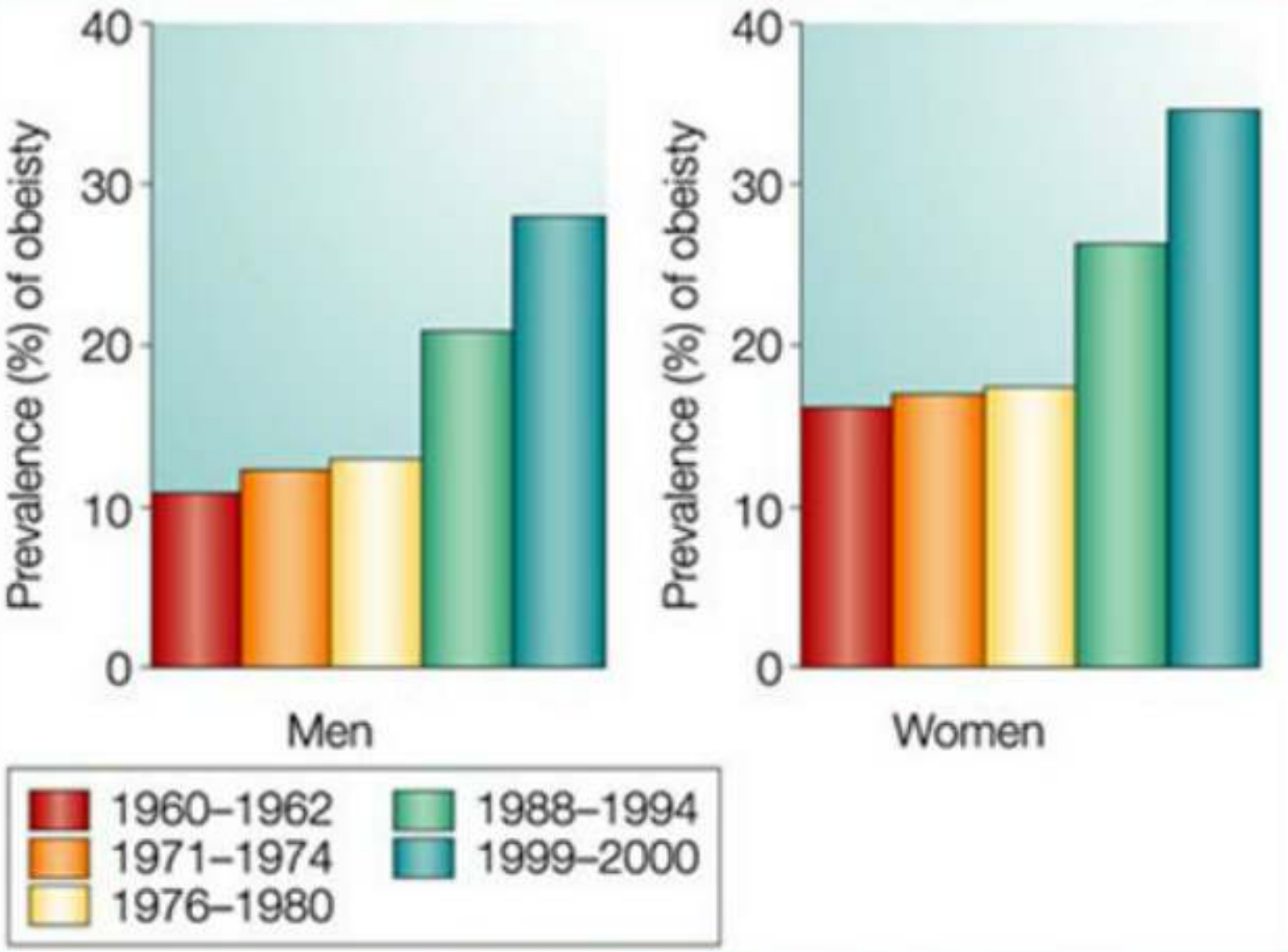
Obesity

Lifestyle:

- Highly caloric diet, rich in fat, refined carbohydrates and animal protein
- Low physical activity

Consequences:

- **Cancer**
- Diabetes
- Cardiovascular disease
- Hypertension



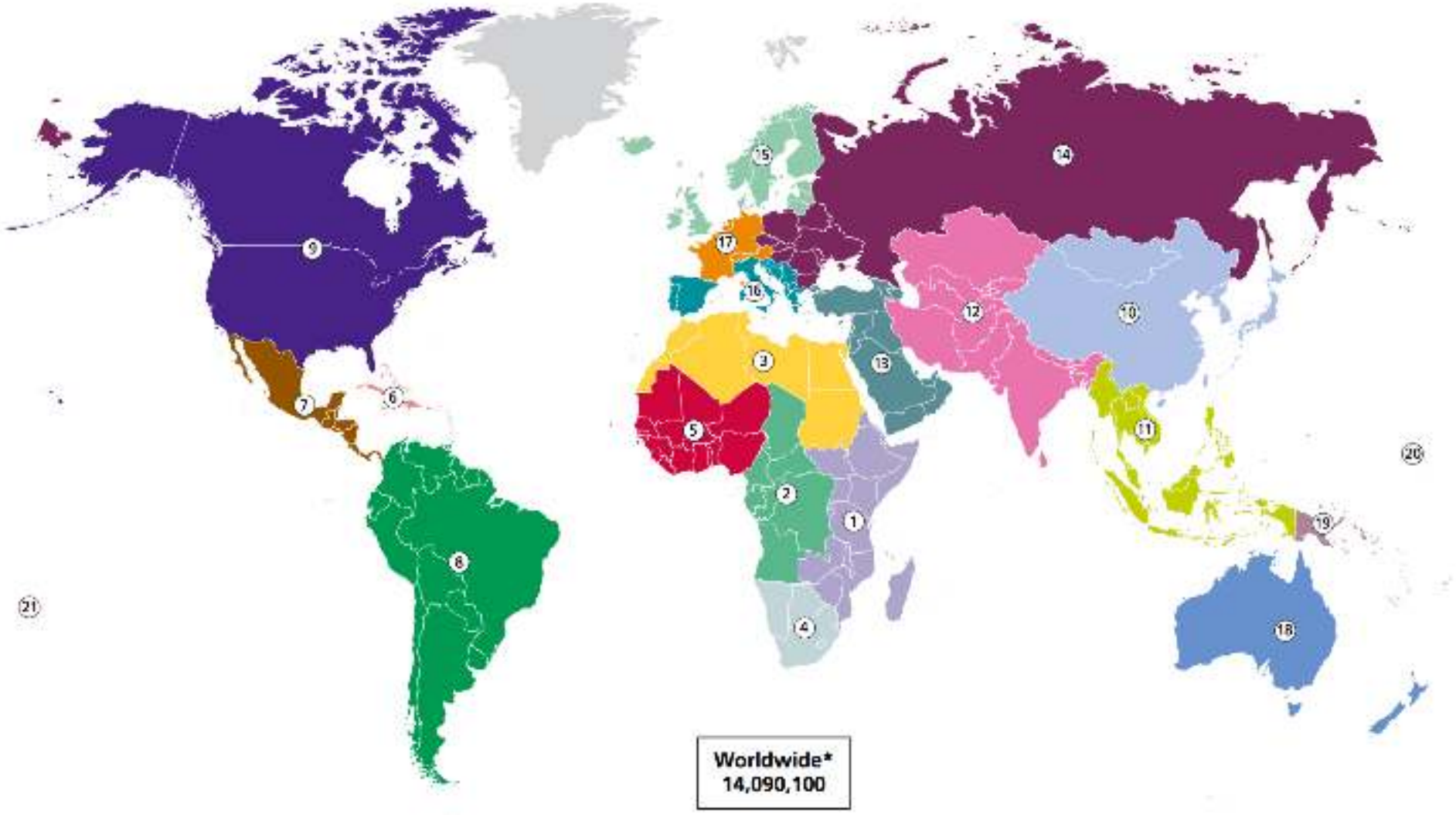
OBESITY-ASSOCIATED CANCERS

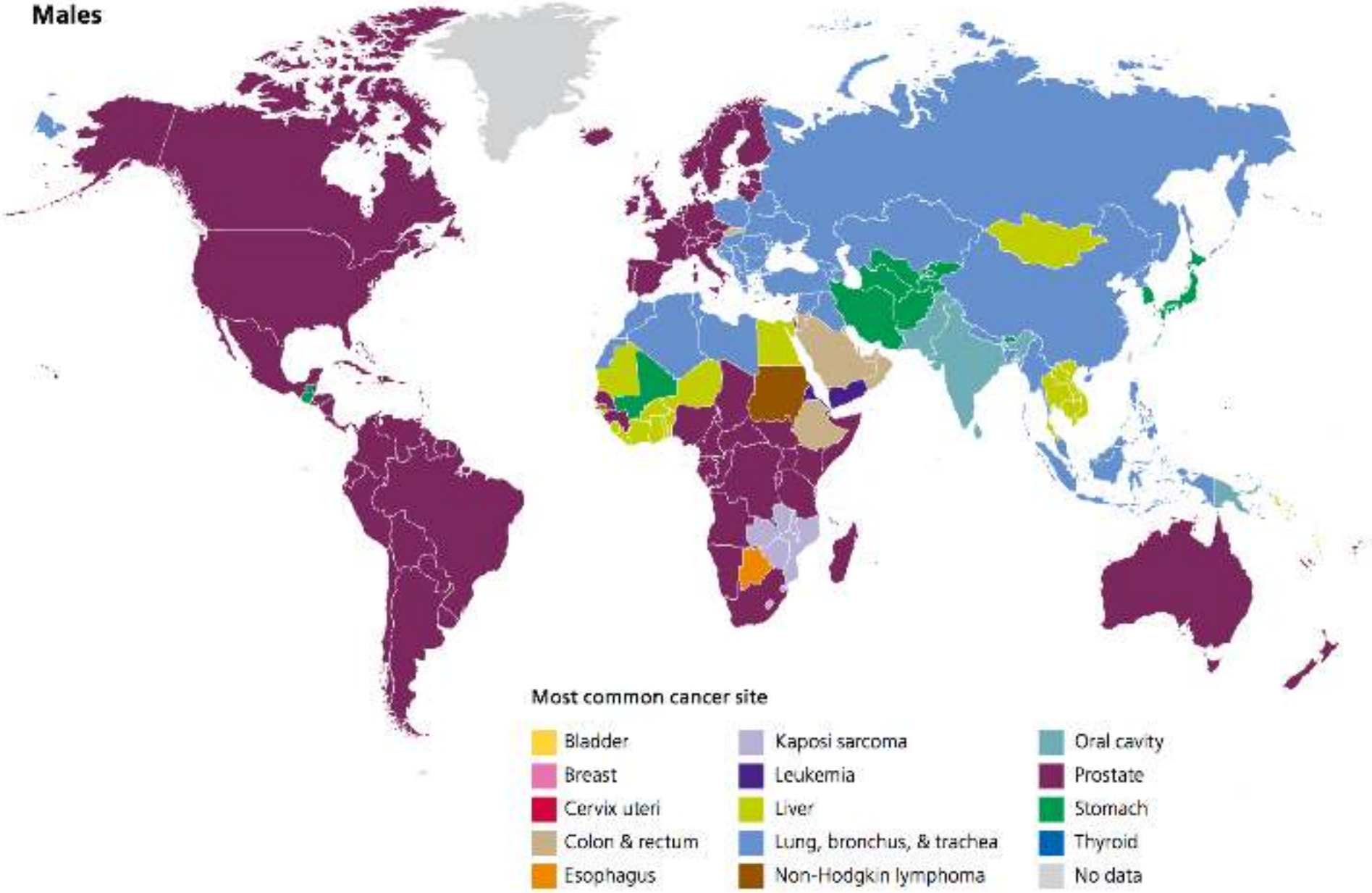
- Esophagus
- Pancreas
- Colon and rectum
- Breast (after menopause)
- Endometrium (lining of the uterus)
- Kidney
- Thyroid
- Gallbladder

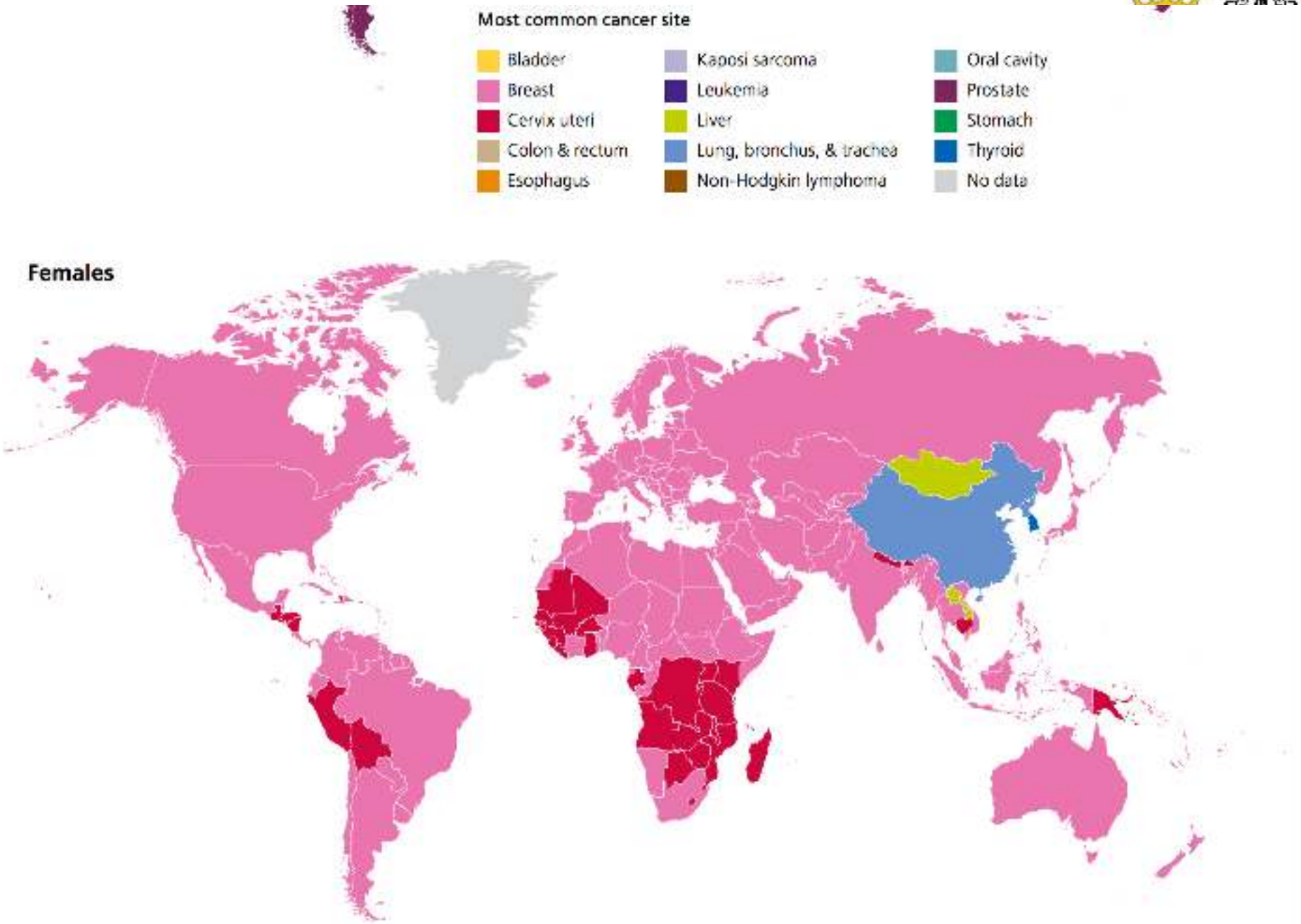
- THE MAJORITY OF MALIGNANT TUMORS IN ADULTS GROWS SLOWLY
- USUALLY A FEW DAY/WEEK DELAY IN DIAGNOSIS DOES NOT WORSEN PROGNOSIS AND TREATMENT EFFICACY
- TWO WEEKS FOR SYMPTOM IMPROVEMENT BEFORE INITIATION OF SPECIFIC CANCER DIAGNOSIS
- THE EARLIER THE BETTER- IN TERMS OF CURE AND LONG-TERM PROGNOSIS

CANCER EPIDEMIOLOGY

Estimated Number of New Cancer Cases by World Area, 2012*

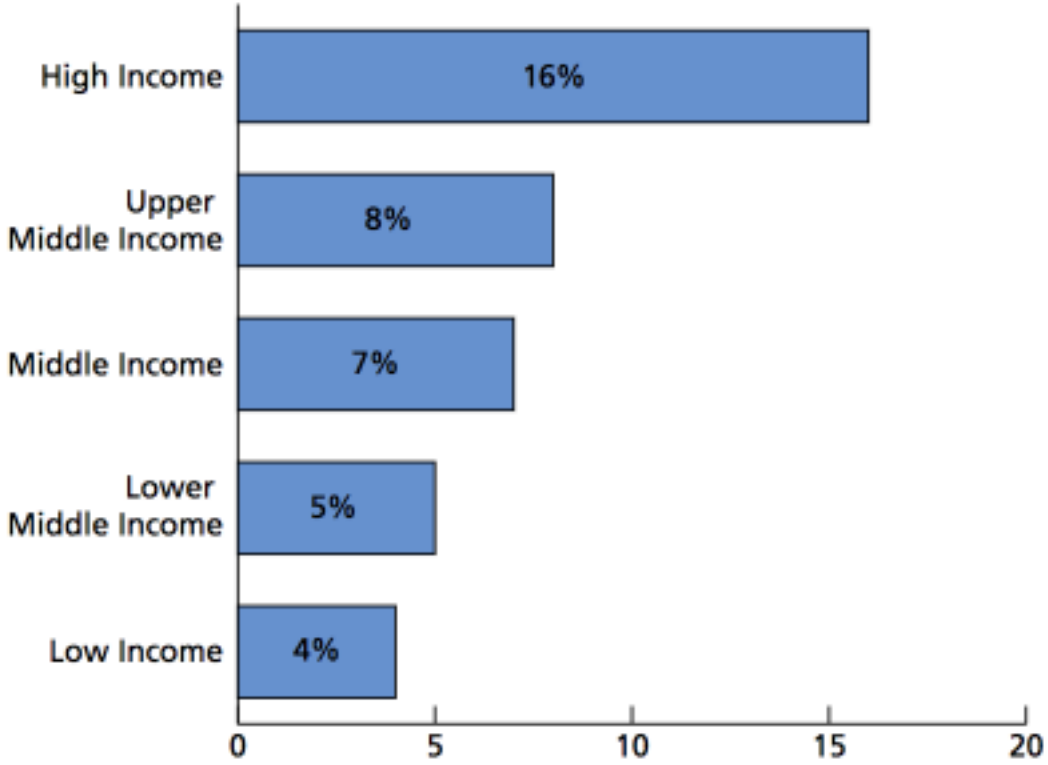



Males
Most common cancer site
Bladder
Breast
Cervix uteri
Colon & rectum
Esophagus
Kaposi sarcoma
Leukemia
Liver
Lung, bronchus, & trachea
Non-Hodgkin lymphoma
Oral cavity
Prostate
Stomach
Thyroid
No data



Source: GLOBOCAN 2012.

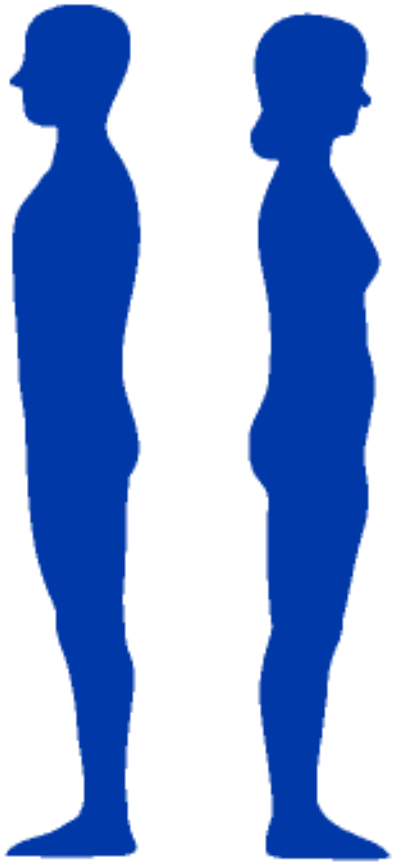
Figure 4. Percent of Population 65 Years of Age and Older by Country Income Level, 2013



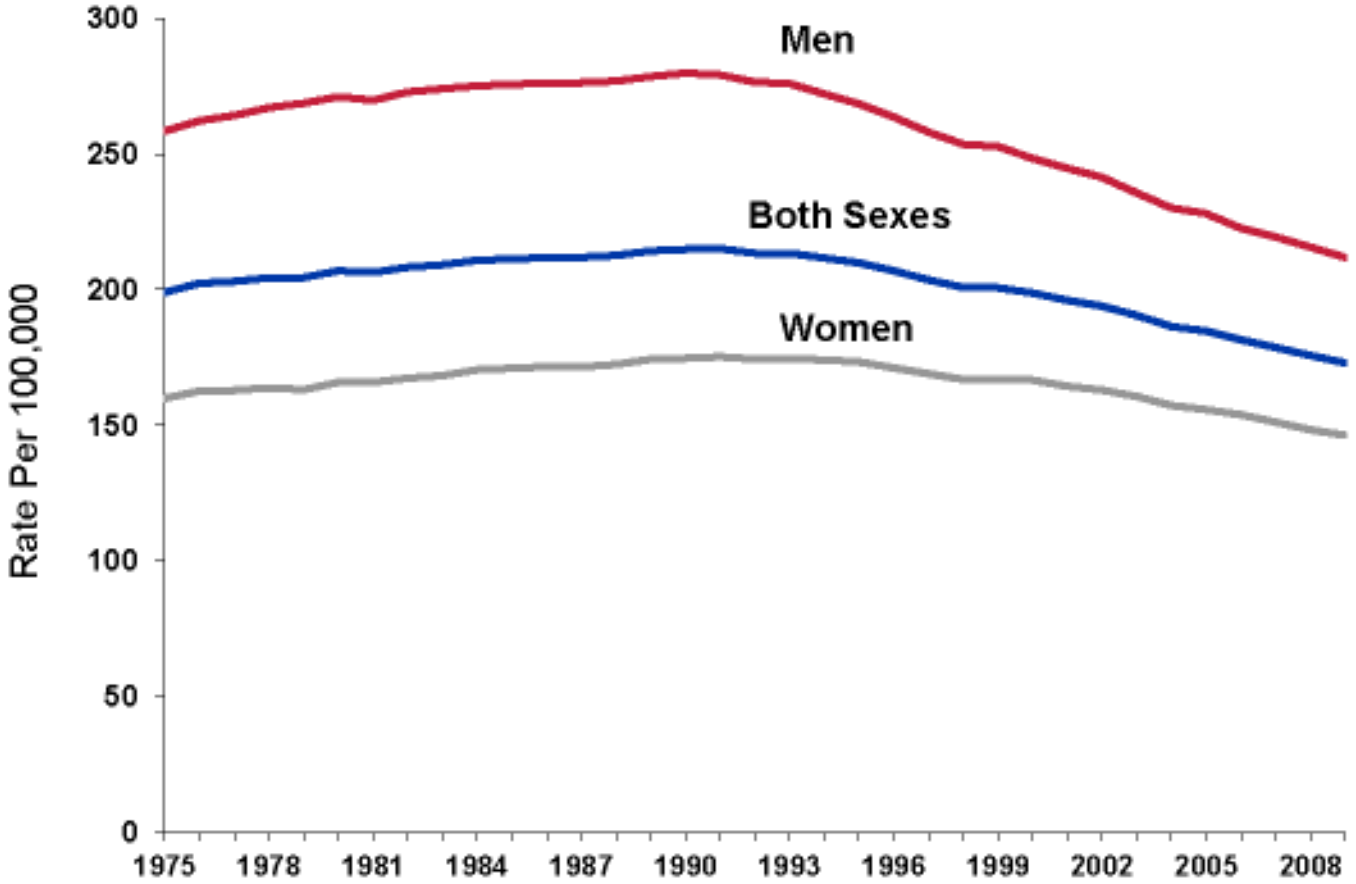
Source: The World Bank (2014). "Data: Population ages 65 and above (% of total)." Retrieved 17 September, 2014, from http://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS.

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

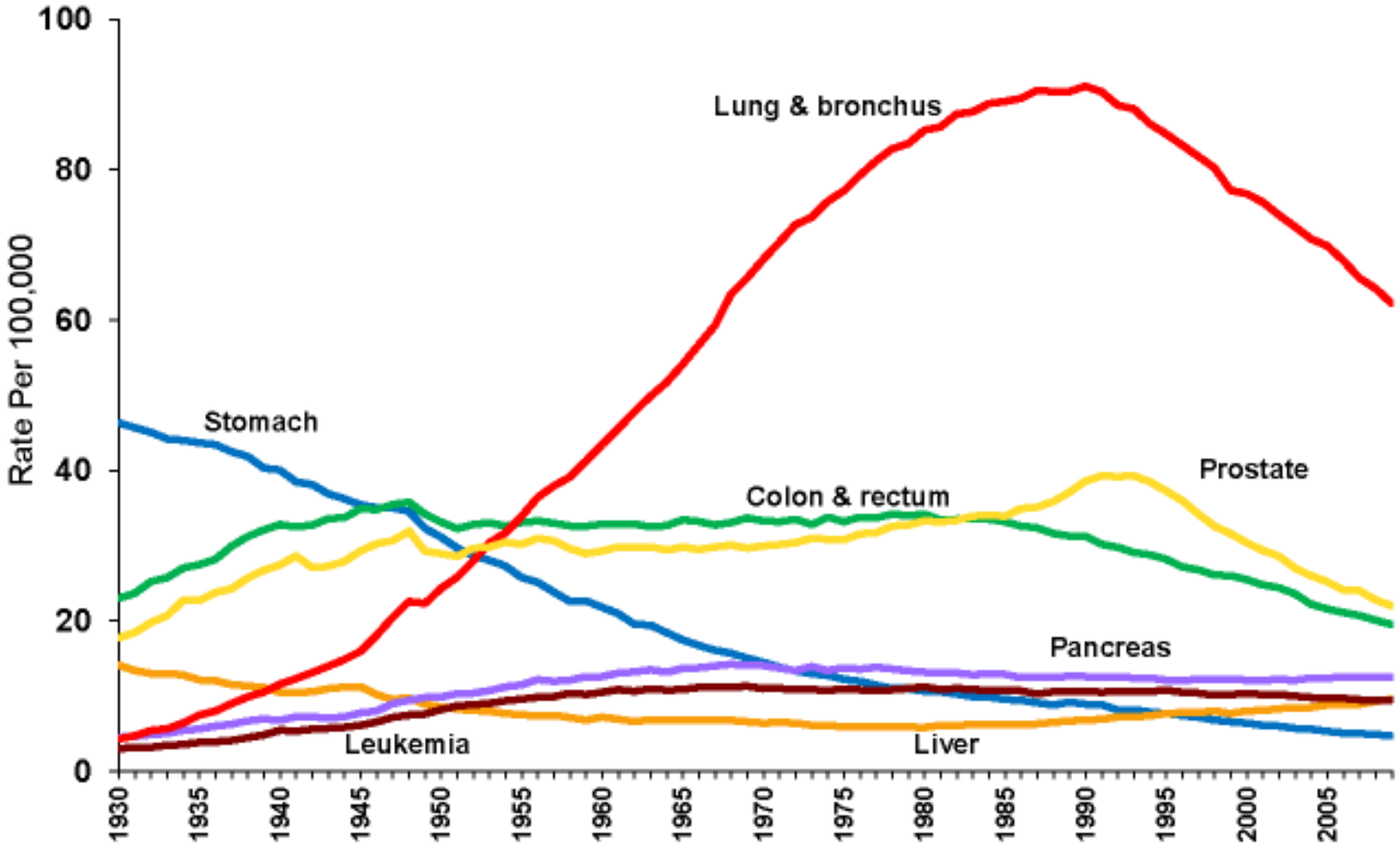


Cancer Death Rates* by Sex, US, 1975-2009



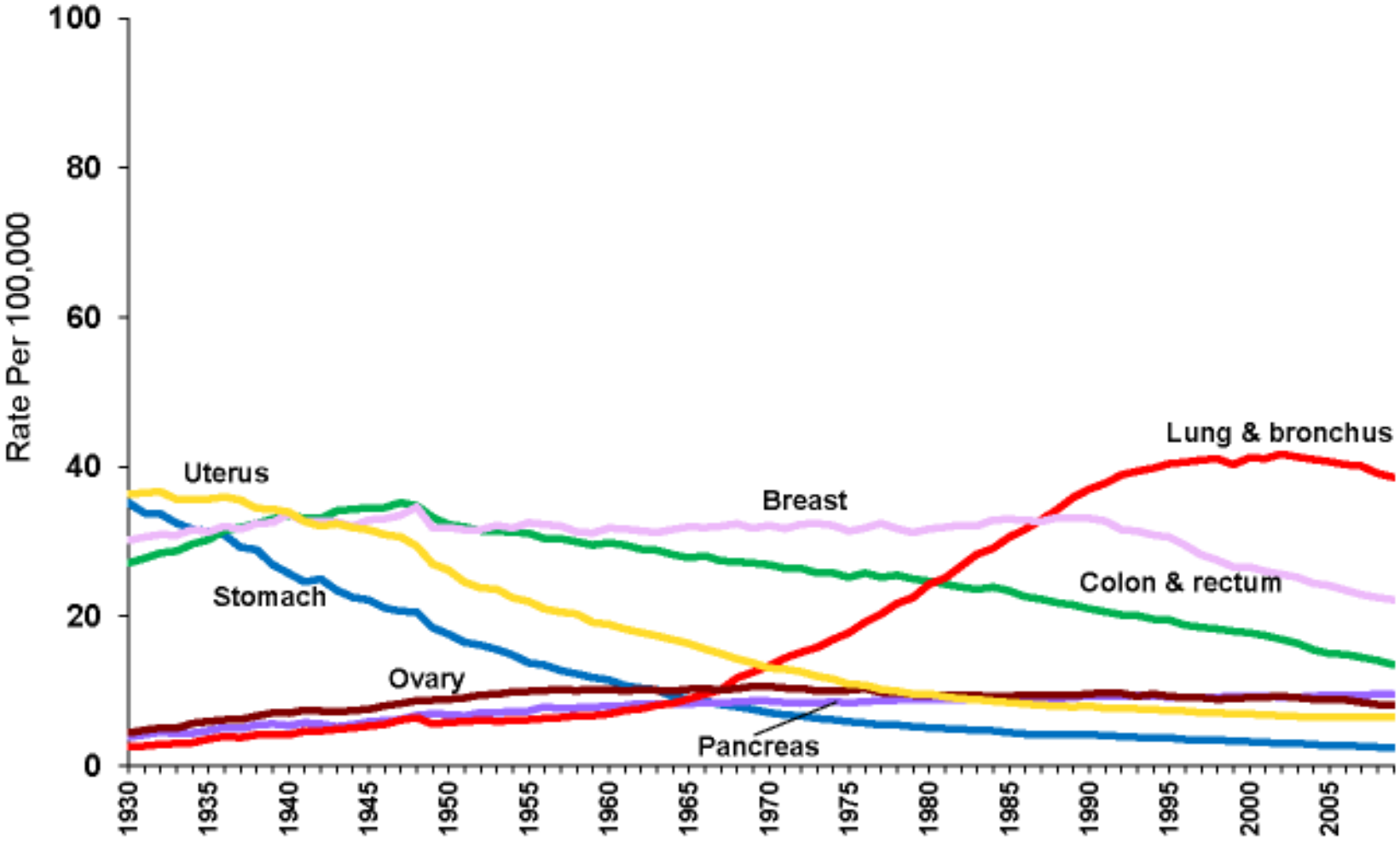
*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1975-2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

Cancer Death Rates* Among Men, US,1930-2009



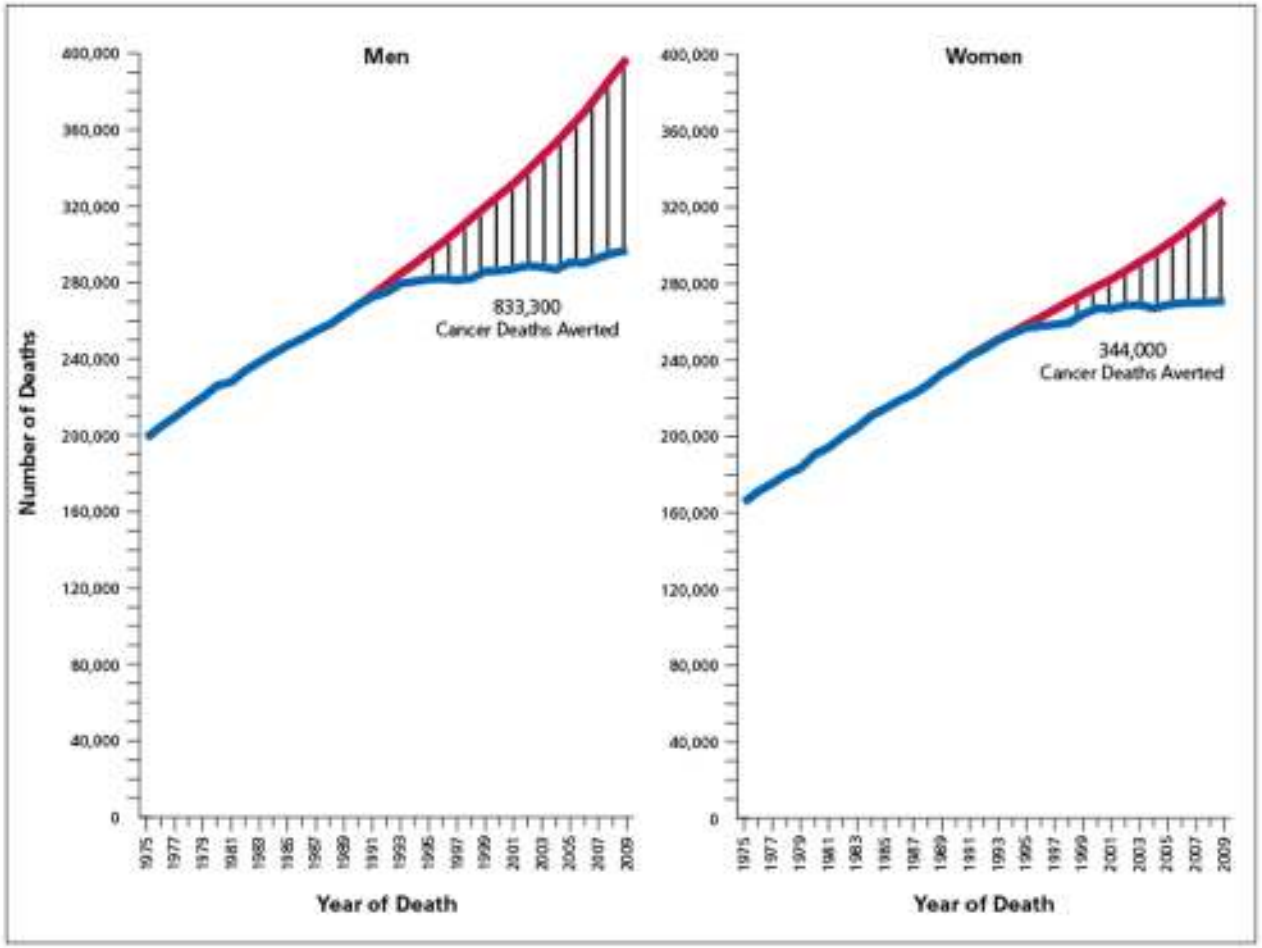
*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2009, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention.

Cancer Death Rates* Among Women, US,1930-2009



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2009, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention.

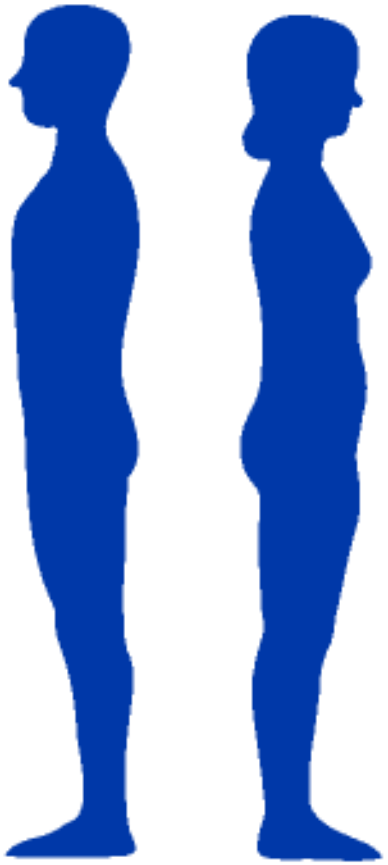
Total Number of Cancer Deaths Averted from 1991 to 2009 in Men and 1992 to 2009 in Women



The blue line represents the actual number of cancer deaths recorded in each year, and the red line represents the number of cancer deaths that would have been expected if cancer death rates had remained at their peak.

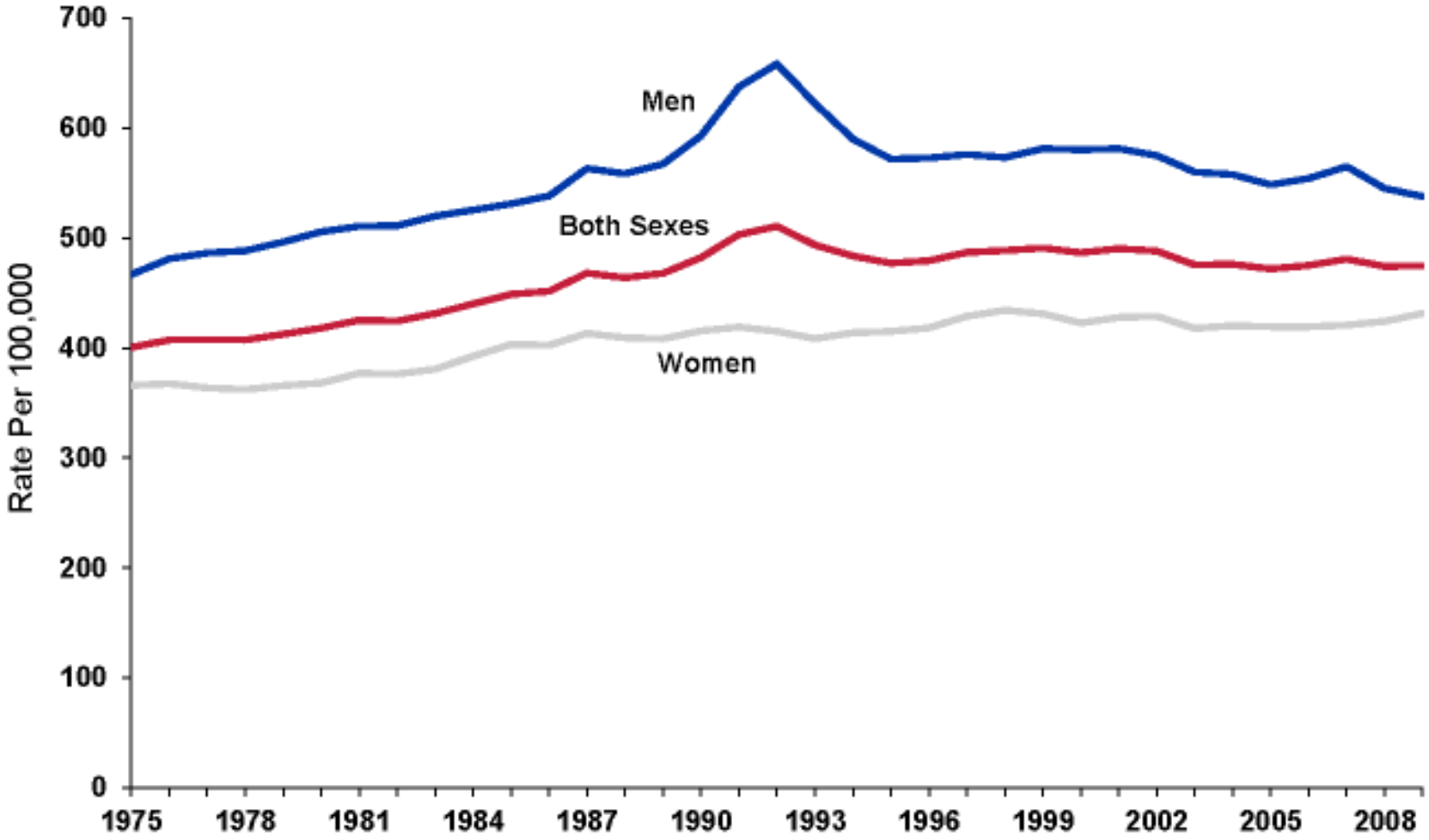
Estimated New Cancer Cases* in the US in 2013

Men 854,790		Women 805,500	
Prostate	28%	29%	Breast
Lung & bronchus	14%	14%	Lung & bronchus
Colon & rectum	9%	9%	Colon & rectum
Urinary bladder	6%	6%	Uterine corpus
Melanoma of skin	5%	6%	Thyroid
Kidney & renal pelvis	5%	4%	Non-Hodgkin lymphoma
Non-Hodgkin lymphoma	4%	4%	Melanoma of skin
Oral cavity	3%	3%	Kidney & renal pelvis
Leukemia	3%	3%	Pancreas
Pancreas	3%	3%	Ovary
All Other Sites	20%	19%	All Other Sites



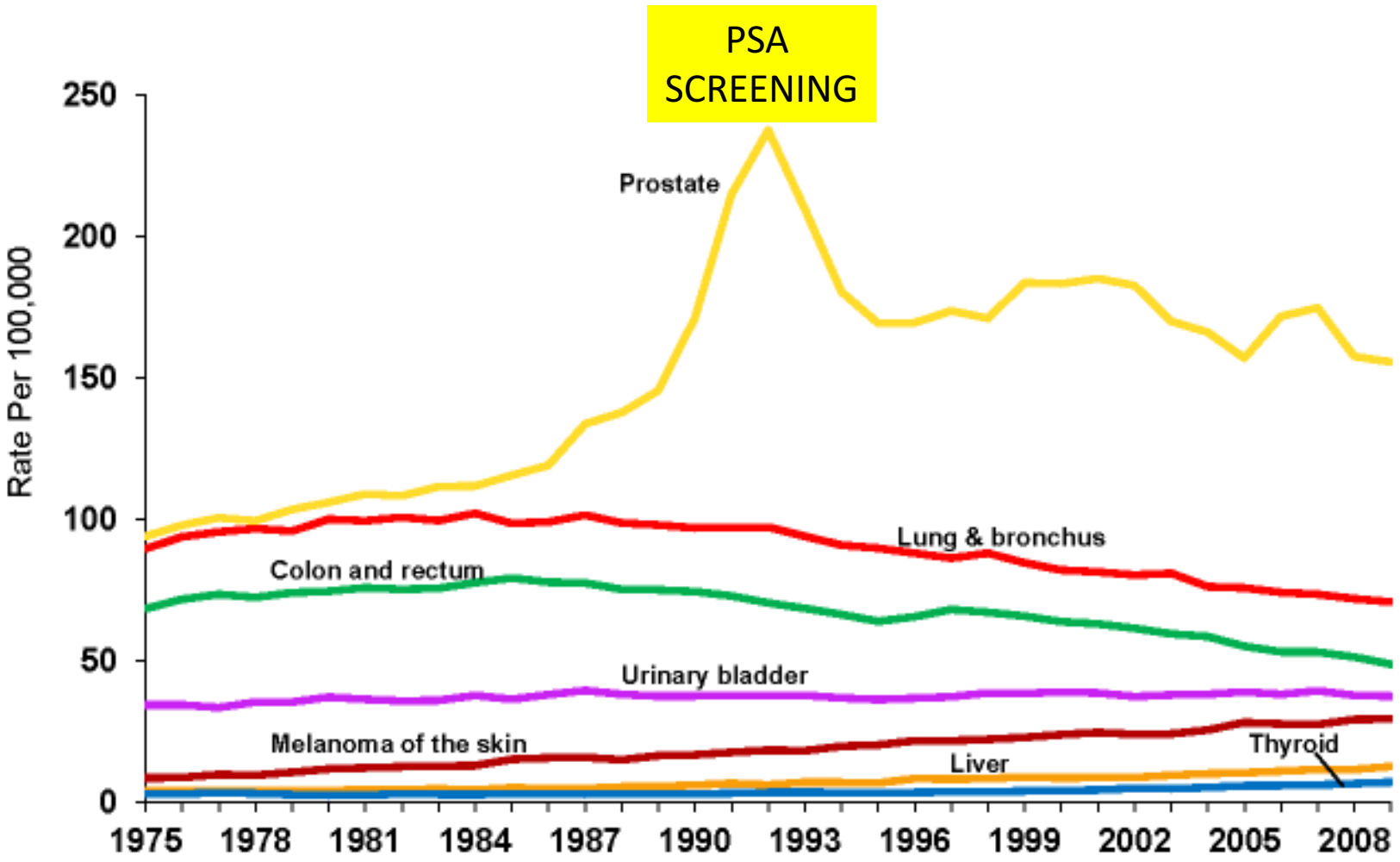
*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Cancer Incidence Rates* by Sex, US, 1975-2009



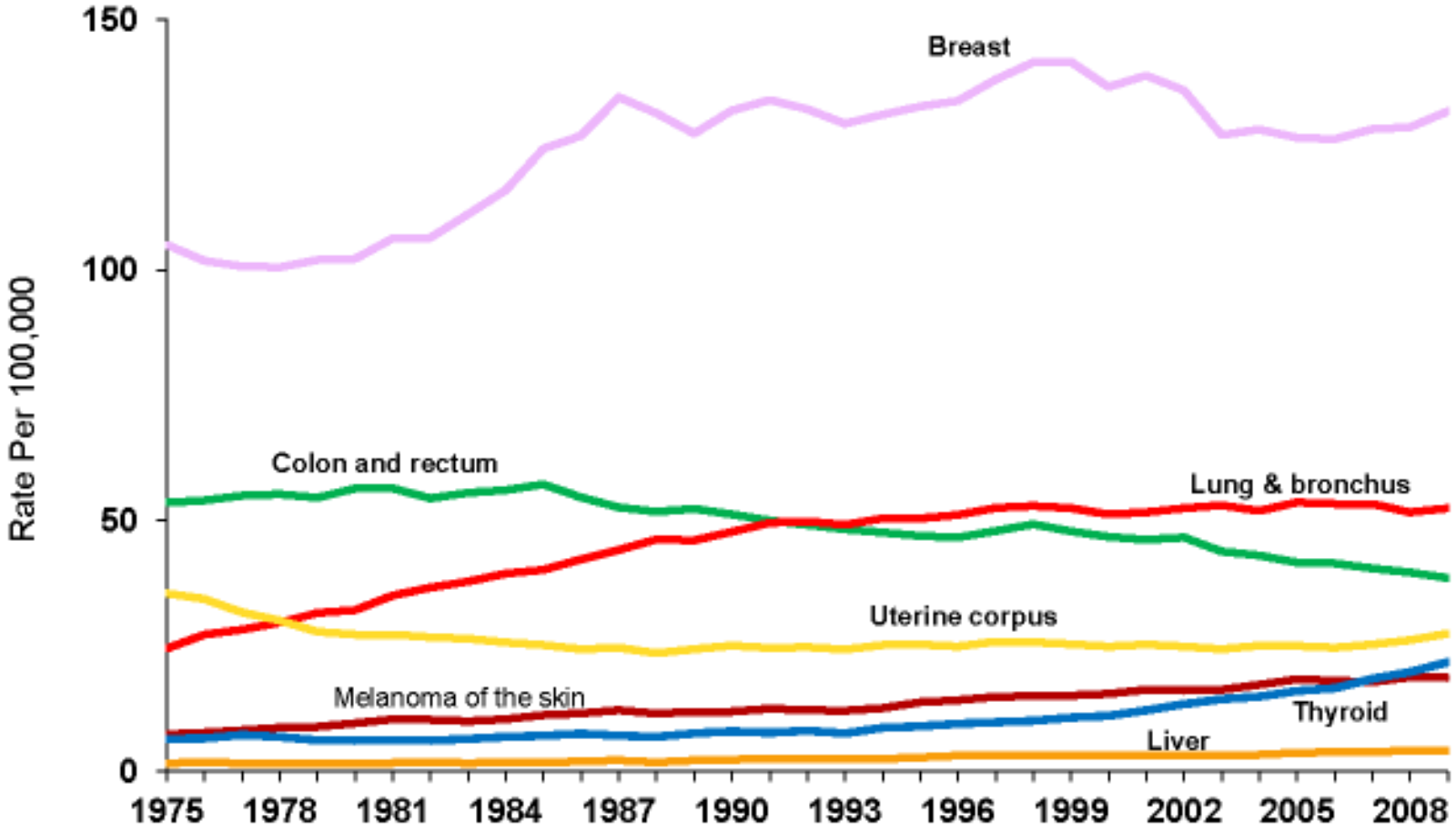
*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database: SEER Incidence Delay-adjusted Rates, 9 Registries, 1975-2009, National Cancer Institute, 2012.

Cancer Incidence Rates* Among Men, US, 1975-2009



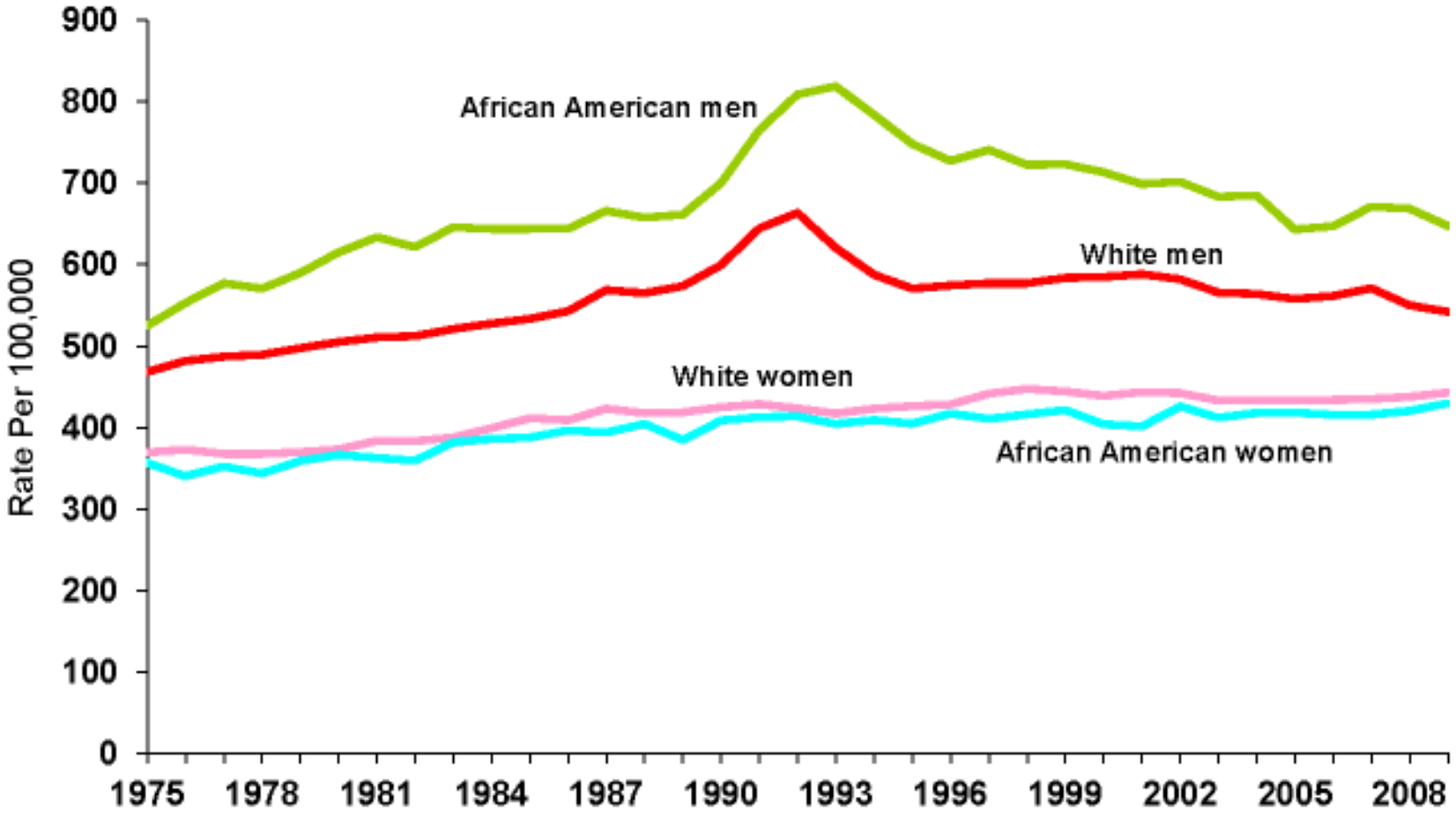
*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database: SEER Incidence Delay-adjusted Rates, 9 Registries, 1975-2009, National Cancer Institute, 2012.

Cancer Incidence Rates* Among Women, US, 1975-2009



*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database: SEER Incidence Delay-adjusted Rates, 9 Registries, 1975-2009, National Cancer Institute, 2012.

Cancer Incidence Rates* by Sex and Race, US,1975-2009



*Age-adjusted to the 2000 US standard population.
Source: Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database: SEER Incidence Delay-adjusted Rates, 9 Registries, 1975-2009, National Cancer Institute, 2012.

The Lifetime Probability of Developing Cancer for Men, 2007-2009*

Site	Risk
All sites†	1 in 2
Prostate	1 in 6
Lung and bronchus	1 in 13
Colon and rectum	1 in 19
Urinary bladder‡	1 in 26
Melanoma§	1 in 35
Non-Hodgkin lymphoma	1 in 43
Kidney	1 in 49
Leukemia	1 in 63
Oral Cavity	1 in 66
Stomach	1 in 92

* For those free of cancer at beginning of age interval.

† All sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.

‡ Includes invasive and in situ cancer cases

§ Statistic for white men.

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.6.1 Statistical Research and Applications Branch, National Cancer Institute, 2012.

The Lifetime Probability of Developing Cancer for Women, 2007-2009*

Site	Risk
All sites†	1 in 3
Breast	1 in 8
Lung & bronchus	1 in 16
Colon & rectum	1 in 21
Uterine corpus	1 in 38
Non-Hodgkin lymphoma	1 in 52
Urinary bladder‡	1 in 87
Melanoma §	1 in 54
Ovary	1 in 72
Pancreas	1 in 69
Uterine cervix	1 in 147

* For those free of cancer at beginning of age interval.
† All sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.
‡ Includes invasive and in situ cancer cases
§ Statistic for white women.
Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.6.1 Statistical Research and Applications Branch, National Cancer Institute, 2012.

Five-year Relative Cancer Survival Rates (%) by Race, 2002-2008

Site	White	African American	Absolute Difference
All Sites	66	58	8
Breast (female)	90	78	12
Colon	64	56	8
Esophagus	18	11	7
Leukemia	55	48	7
Non-Hodgkin lymphoma	69	61	8
Oral cavity	63	42	21
Prostate	100	96	4
Rectum	67	59	8
Urinary bladder	78	64	14
Uterine cervix	69	59	10
Uterine corpus*	84	60	24

5-year relative survival rates based on patients diagnosed from 2002 to 2008, all followed through 2009.
*Includes uterus, NOS (not otherwise specified).
Source: *SEER Cancer Statistics Review 1975-2009 (*SEER 18 registries), National Cancer Institute, 2012.

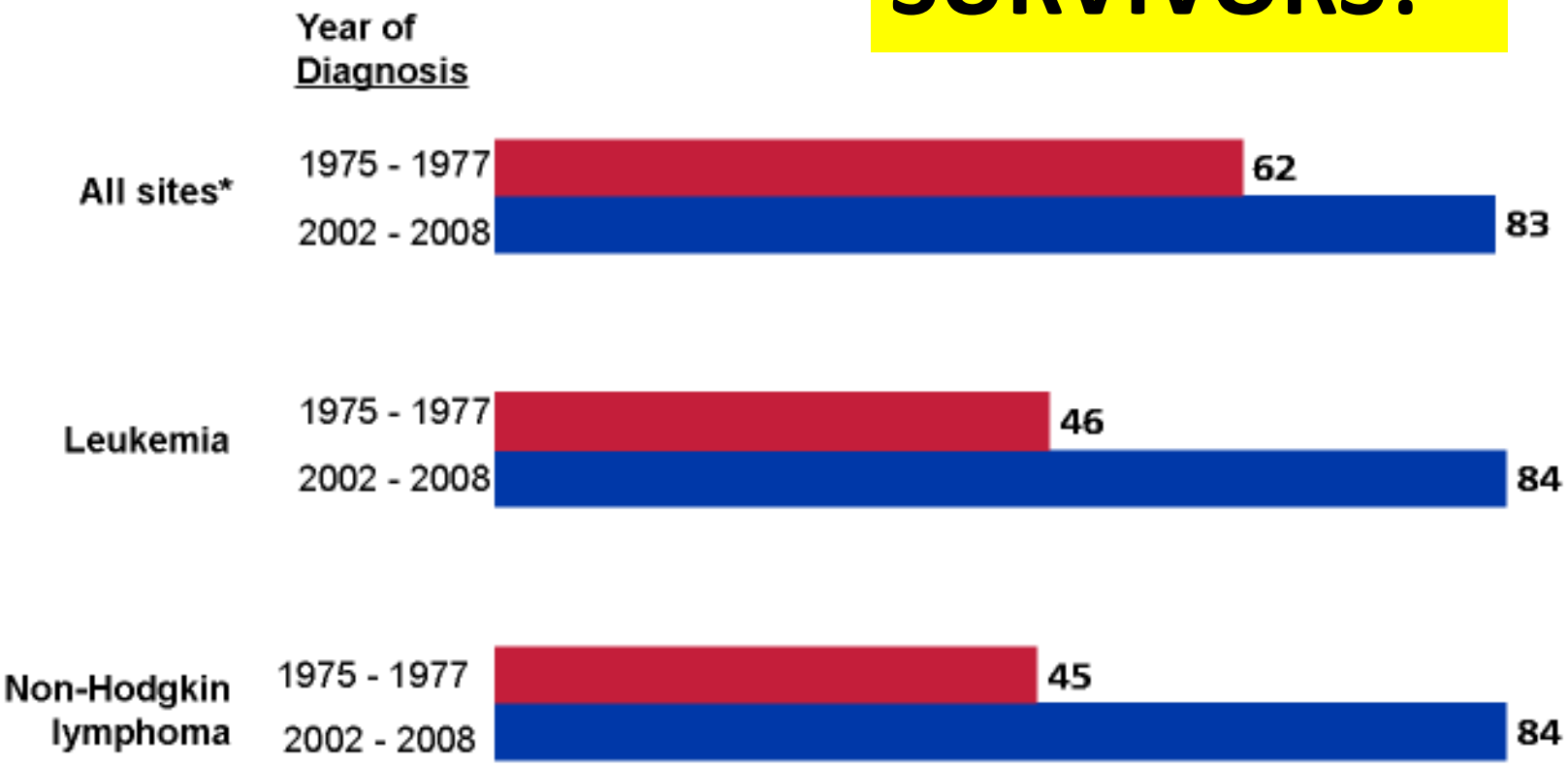
Trends in Five-year Relative Cancer Survival Rates (%), 1975-2008

Site	1975-1977	1987-1989	2002-2008
All sites	49	56	68
Breast (female)	75	84	90
Colon	51	61	65
Leukemia	34	43	58
Lung & bronchus	12	13	17
Melanoma	82	88	93
Non-Hodgkin lymphoma	47	51	71
Ovary	36	38	43
Pancreas	2	4	6
Prostate	68	83	100
Rectum	48	58	68
Urinary bladder	73	79	80

5-year relative survival rates based on patients diagnosed from 2002 to 2008, all followed through 2009.
Source: *SEER Cancer Statistics Review 1975-2009 (*SEER 9 registries), National Cancer Institute, 2012.

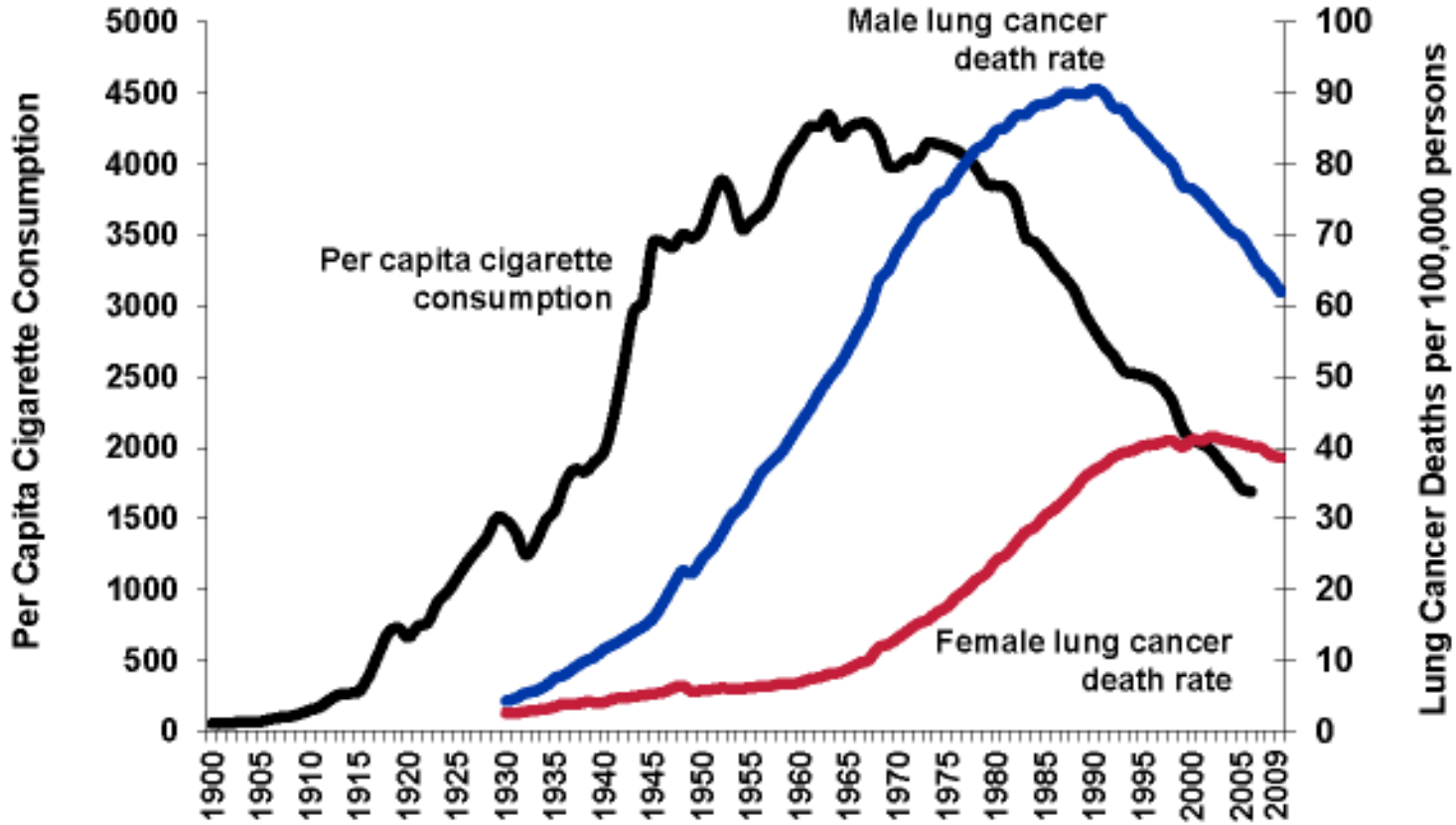
Trends in 5-year Relative Survival Rates for Childhood Cancer, Ages 0-19 yrs,1975-2008

SURVIVORS!



Based on follow up of patients through 2009.
*Excludes benign brain tumors.
Source: *SEER Cancer Statistics Review 1975-2009*, National Cancer Institute, 2012.

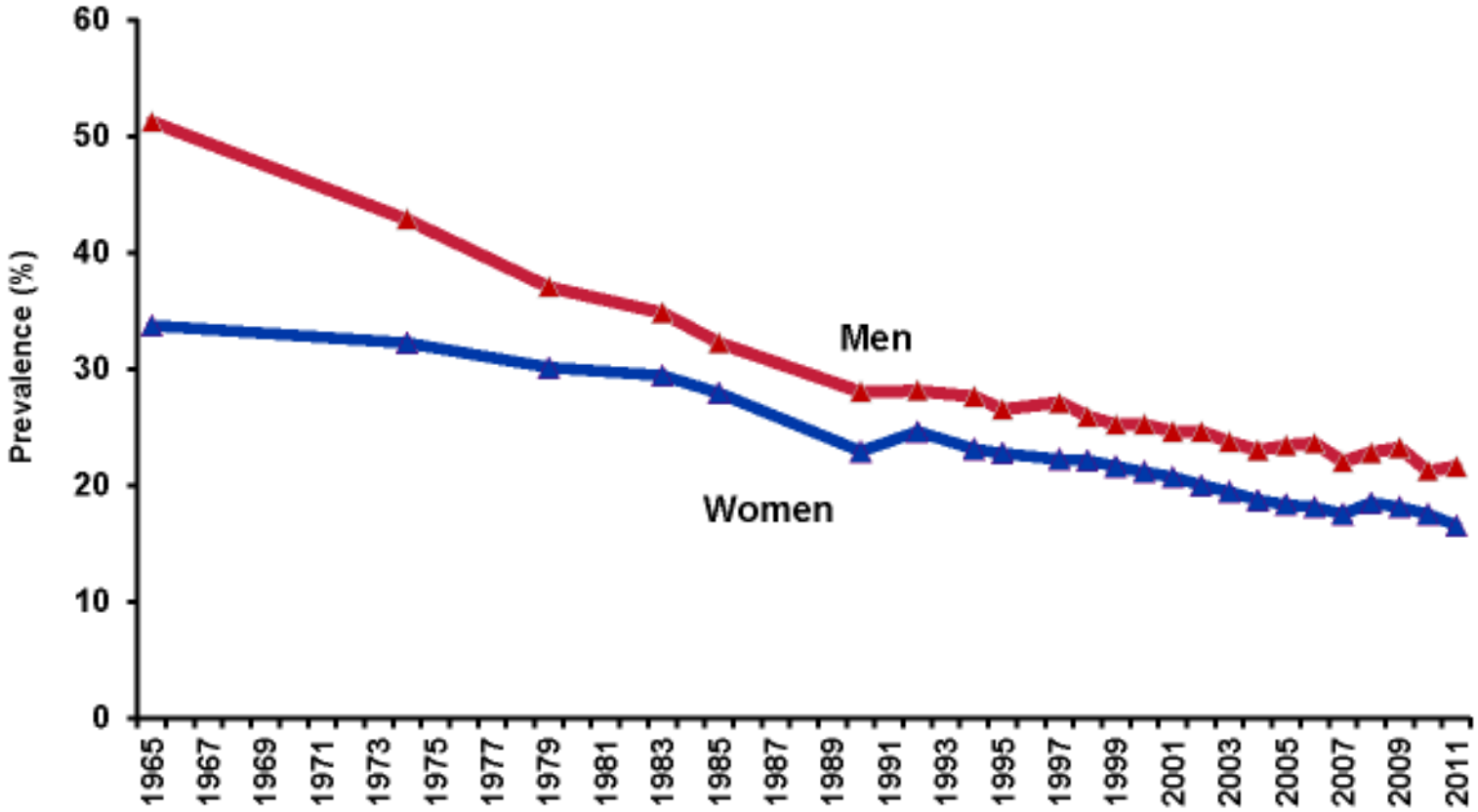
Trends in Tobacco Use and Lung Cancer Death Rates* in the US



*Age-adjusted to 2000 US standard population.

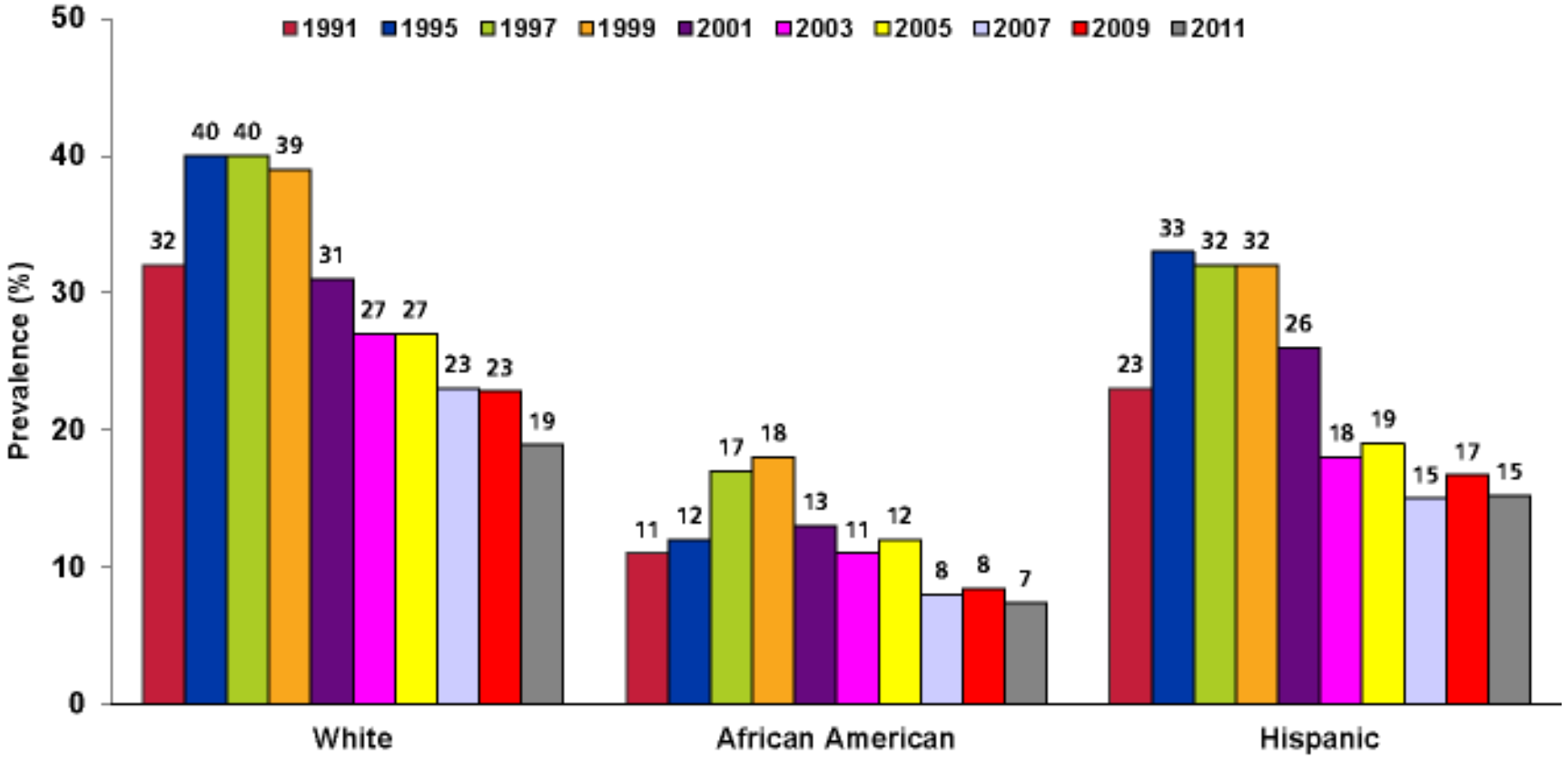
Source: Death rates: US Mortality Data, 1960-2009, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention. Cigarette consumption: US Department of Agriculture, 1900-2007.

Trends in Cigarette Smoking, Adults 18 and Older, US, 1965-2011



Redesign of survey in 1997 may affect trends. Estimates are age adjusted to the 2000 US standard population.
Source: National Health Interview Survey, National Center for Health Statistics, Centers for Disease Control and Prevention, 2012.

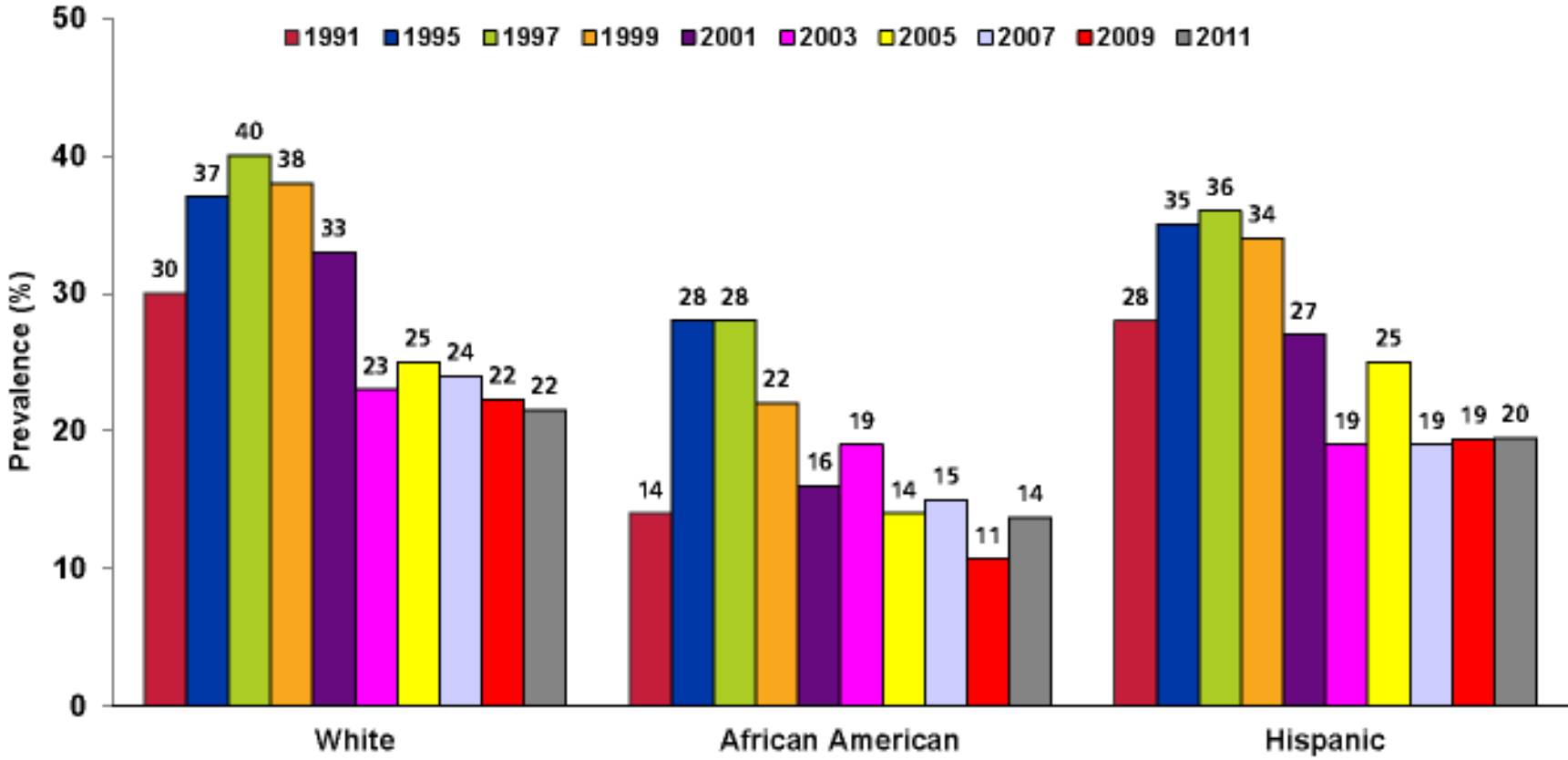
Trends in Cigarette Smoking* among Female High School Students, US, 1991-2011



*Smoked cigarettes on one or more of the 30 days preceding the survey. Whites and African Americans are non-Hispanic.

Source: Youth Risk Behavior Surveillance System, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 2012.

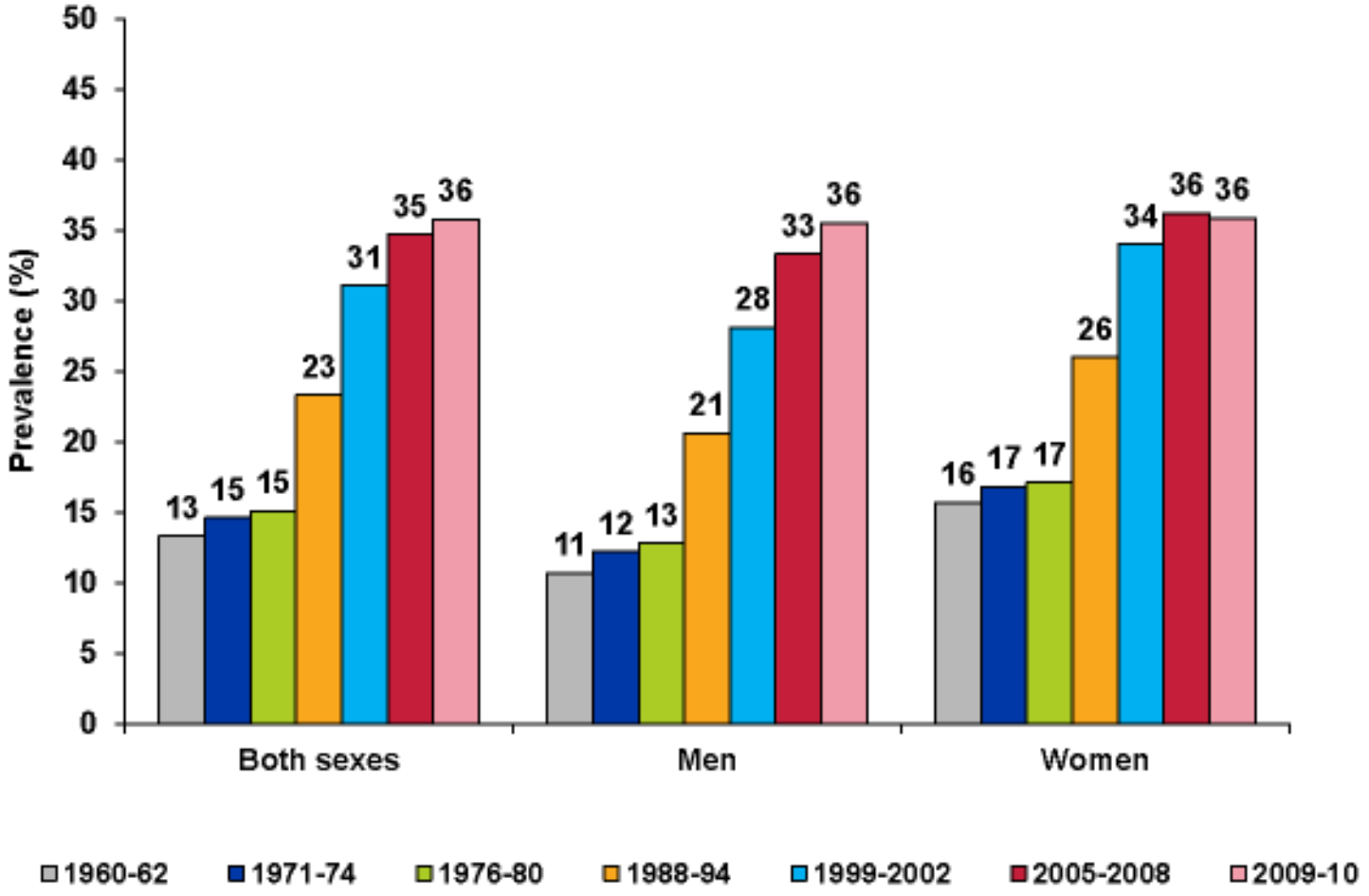
Trends in Cigarette Smoking* among Male High School Students, US, 1991-2011



*Smoked cigarettes on one or more of the 30 days preceding the survey. Whites and African Americans are non-Hispanic.

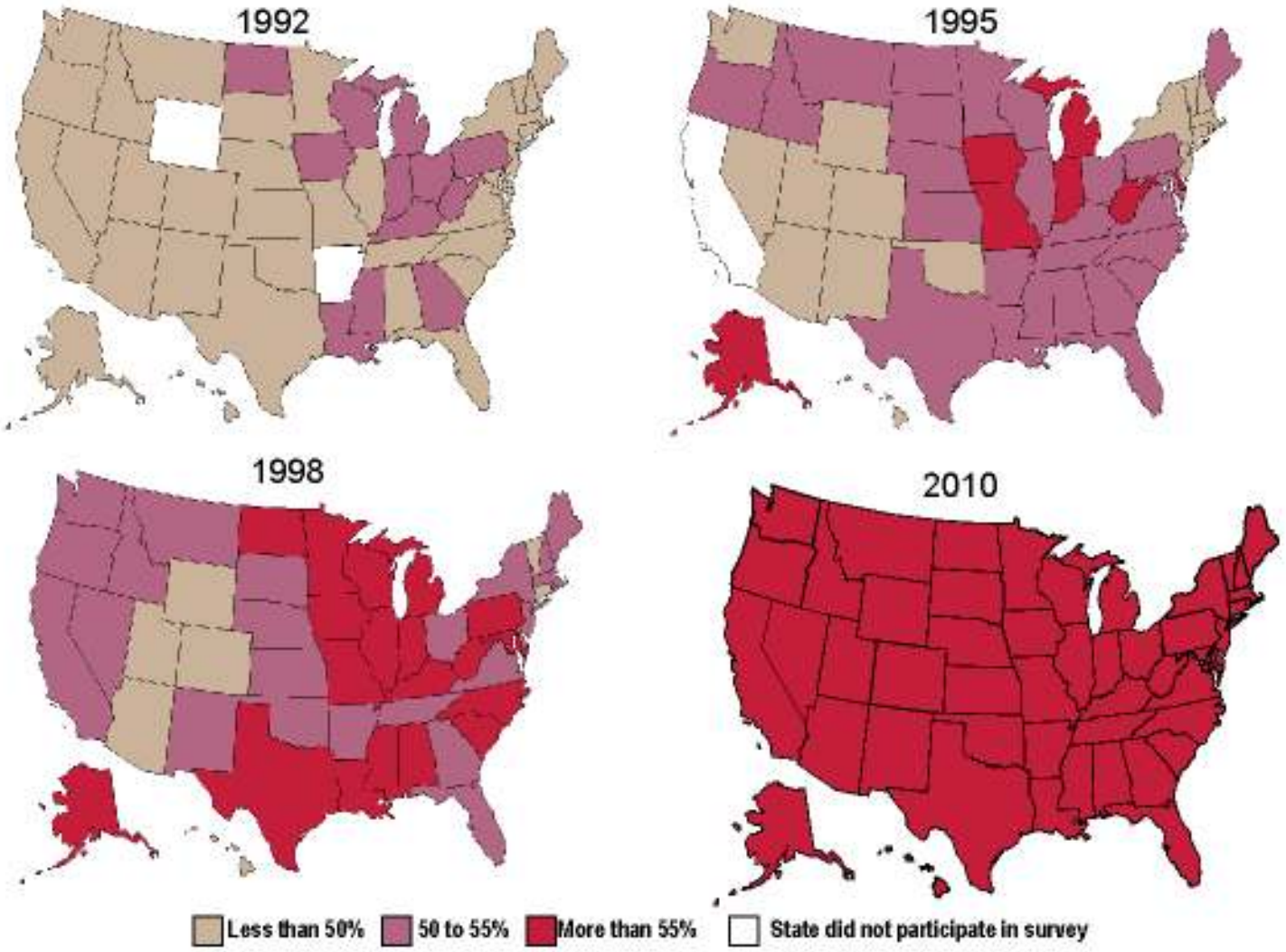
Source: Youth Risk Behavior Surveillance System, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 2012.

Trends in Obesity* Prevalence, Adults Aged 20 to 74, US, 1960-2010



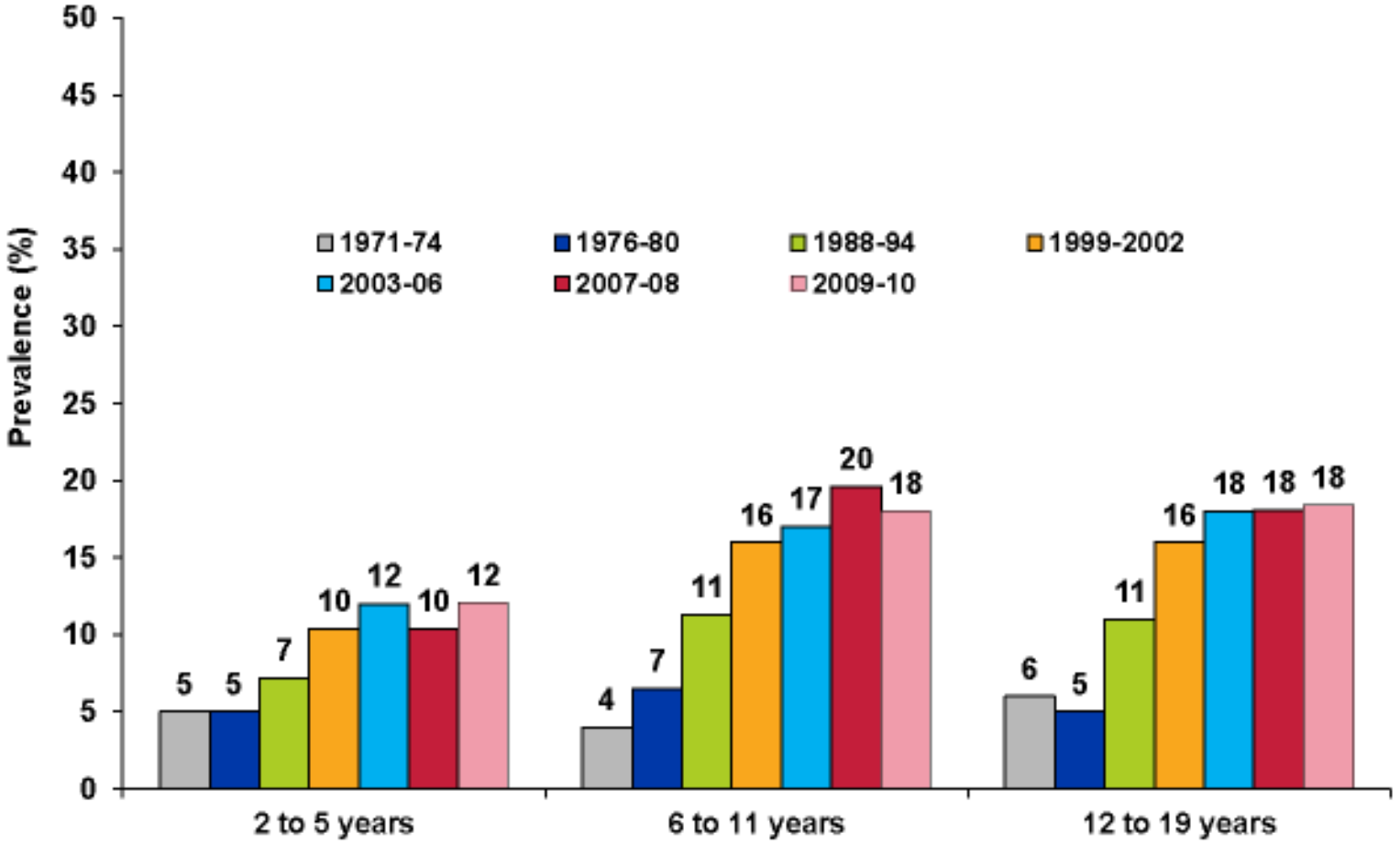
*Obesity=body mass index ≥ 30 kg/m^2; estimates are age adjusted to the 2000 US standard population.
Source: National Health and Nutrition Examination Survey, National Center for Health Statistics, Centers for Disease Control and Prevention.

Trends in Overweight* Prevalence (%), Adults 18 and Older, US, 1992-2010



*Body mass index ≥ 25.0 kg/m². Source: Behavioral Risk Factor Surveillance System, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention.

Trends in Obesity* Prevalence among Children, US, 1971-2010



*Body mass index ≥ the sex-and age-specific 95th percentile cutoff points from CDC Growth Charts.
Source: National Health and Nutrition Examination Survey, 1971-1974, 1976-1980, 1988-1994, 1999-2002, National Center for Health Statistics, Centers for Disease Control and Prevention. 2003-06: Ogden , et al. JAMA 2008. 2007-08: Ogden, et al. JAMA 2010. 2009-10: Ogden, et al. NCHS data brief, no 82. National Center for Health Statistics 2012.

American Cancer Society®

Breast Cancer Screening Guidelines

- Annual mammograms beginning at age 40

2014 - SWITZERLAND ABOLISHED SCREENING MAMMOGRAPHY PROGRAM

- Clinical breast exam:
  - Ages 20-39, as part of a periodic health exam at least every 3 years
  - Ages 40+, prior to mammogram as part of a periodic health exam annually.

- Breast self-exam:
  - Optional; beginning in their early 20s, women should be told about the benefits and limitations of breast-self examination. Women should know how their breasts normally feel and report any breast changes promptly to their health care providers.

Cervical Cancer Screening Guidelines

- Cervical cancer screening should begin at age 21.
- Preferred screening test/s and frequency vary by age:

Age	Frequency	Test
21-29	Every 3 yrs	Pap test*
30-65†	Every 5 yrs	HPV & Pap tests

*Conventional or liquid-based test.
†Every 3 years with the Pap test alone is acceptable.

- Women should stop screening:
  1. At age 66 with adequate negative prior screening
     - ≥ 3 consecutive negative Pap tests within 10 yrs, most recent within 5 yrs **OR**
     - ≥ 2 consecutive negative HPV and Pap tests within 10 yrs, most recent within 5 yrs
  2. After hysterectomy

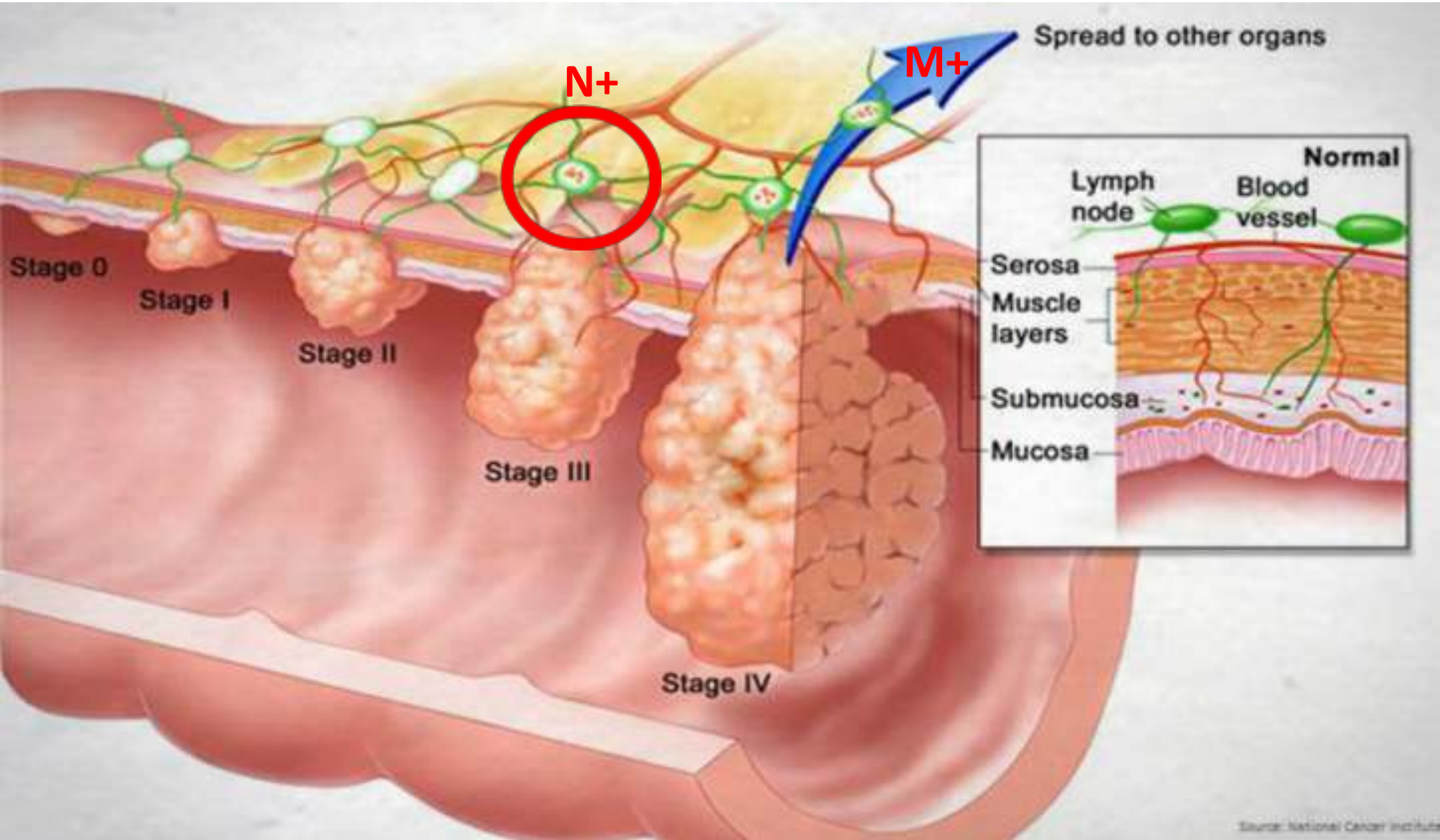
Colorectal Cancer Screening Guidelines*

Beginning at age 50, men and women should follow one of the following examination schedules:

Test	Time interval
Fecal occult blood test	Annual
Flexible sigmoidoscopy	5 yrs
Double contrast barium enema	5 yrs
Colonoscopy	10 yrs
CT Colonography	5 yrs

*For people at average risk; individuals at higher risk should talk with a doctor about a different testing schedule.

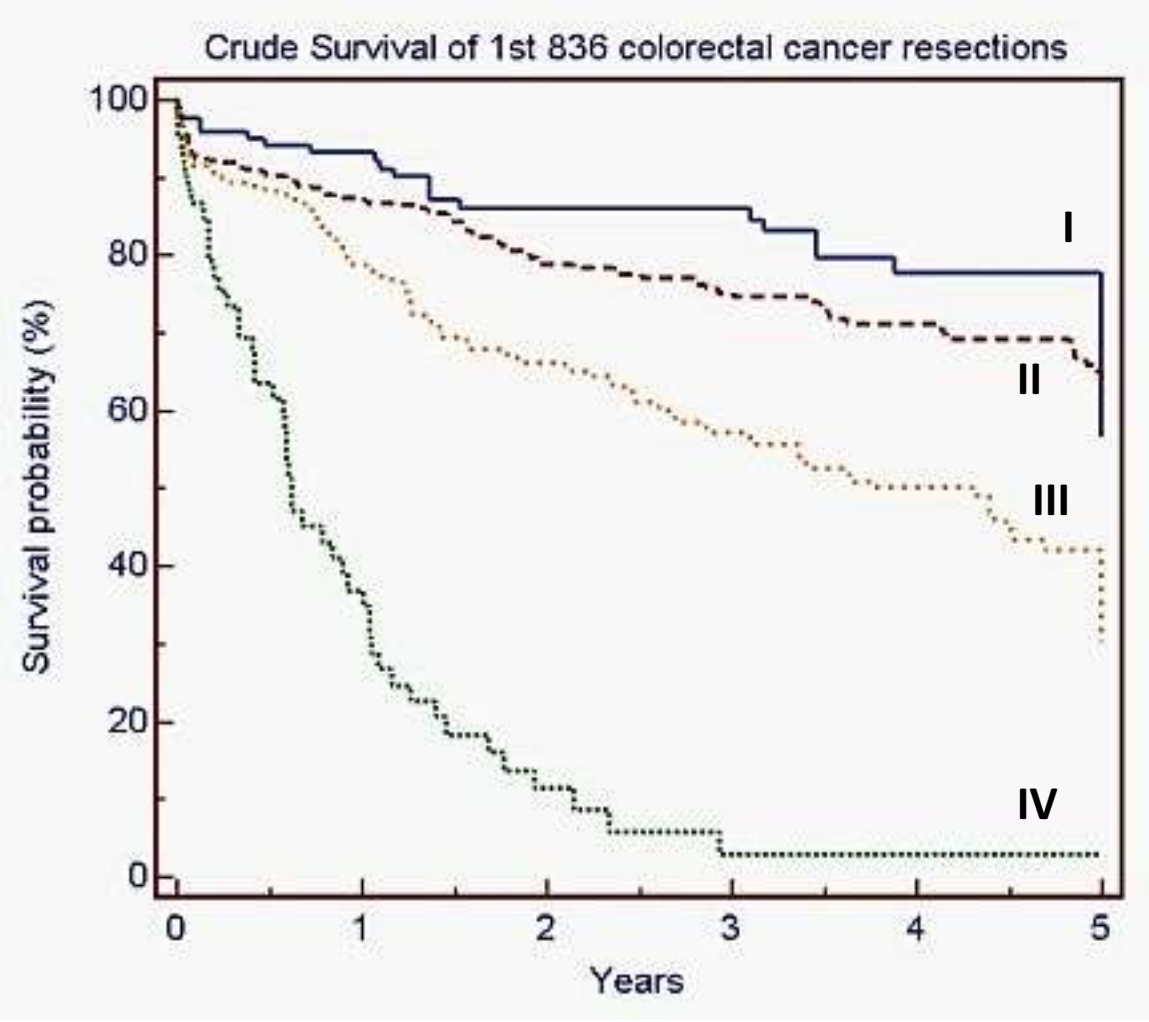
CANCER STAGING



CANCER STAGING - TNM

- T – TUMOR
- N – NODES (LYMPH)
- M – METASTASES

PROGNOSIS IS DIRECTLY ASSOCIATED WITH STAGE



STAGE	5-YEAR SURVIVAL
0	100%
I	85-100%
II	50-80%
III	30-60%
IV	<5%

STAGING vs PROGNOSIS

- STAGE I T1 N-
  - very good prognosis – surgery is usually enough
- STAGE II T2-4 N-
  - good prognosis, surgery +/- adjuvant treatment
- STAGE III N+
  - sugery + adjuvant treatment

RADICAL APPROACH

- STAGE IV M+
  - cure is extremely rare – basically palliative systemic treatment

RADICAL APPROACH

- GOAL - CURE
- AGGRESSIVE TREATMENT
  - \+ SURGERY
  - \+ ADUVANT TREATMENT

    SYSTEMIC TREATMENT
    - chemotherapy
    - endocrine therapy
    - targeted therapy

      RADIOTHERAPY

PALLIATIVE APPROACH
CHRONIC DISEASE=CHRONIC TREATMENT

- GOALS
  - IMPROVED SURVIVAL
  - IMPROVED/MAINTAINED QUALITY OF LIFE

- BASIS– CHRONIC SYSTEMIC THERAPY
  - SKILFULL AND SMART TREATMENT
  - AGRESSIVE DISEASE = AGGRESSIVE TREATMENT
  - FAST DISEASE = FAST TREATMENT