Multi-Disciplinary Attack on Prostate Cancer: Report from the Sidney Kimmel Comprehensive Cancer Center (SKCCC)

William G. Nelson, M.D., Ph.D.
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University School of Medic**ine**

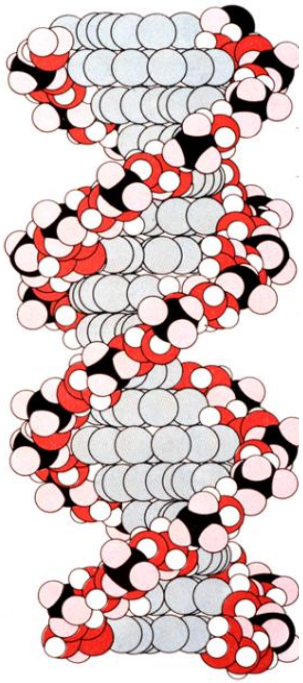
- Clues to the Etiology of Prostate Cancer
- Cancer Genome Defects and Prostatic Carcinogenesis
- Delivering Prostate Cancer Solutions to the Community: New Approaches to Screening, Diagnosis, Detection, and Treatment

Etiologies of the World's Leading Cancers*

Cancer Site	Cases	Infection	Inflammation	Exposure
Lung/Bronchus	1,608,000		Probably	Smoking
Breast	1,383,000		Maybe	Diet, Sex Steroids
Colon/Rectum	1,233,000		Definitely	Diet
Stomach	989,000	*H. pylori*	Definitely	Diet
Prostate	913,000		Definitely	Diet, Sex Steroids
Liver	748,000	Hepatitis viruses	Definitely	Aflatoxin B_1
Uterine Cervix	529,000	HPVs	Probably	Smoking
Esophagus	482,000		Maybe	Smoking, Diet
Bladder	386,000	*S. haematobium*	Probably	Smoking
All Sites (Excluding Skin)	**12,677,000**	**Often**	**Almost Always**	**Almost Always**

*Ferlay J *et al.* Int J Cancer *127:* 2893-917 (2008); data from GLOBOCAN 2008, World Health Organization International Agency for Research on Cancer (IARC)

Inheritance and Prostate Cancer



Twin Studies- Disease Concordance with Gene Sharing*

Swedish twins:19.2% monozygotic vs. 4.3% dizygotic
US twins: 27.1% monozygotic vs. 7.1% dizogitic

➡ 40-50% contribution of inheritance

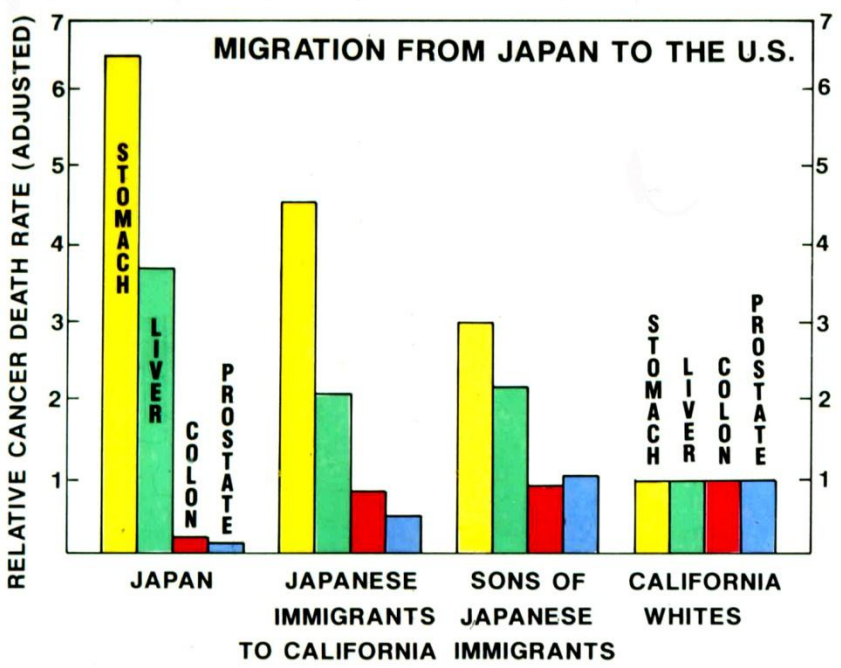
Segregation Analyses of Familial Clusters**

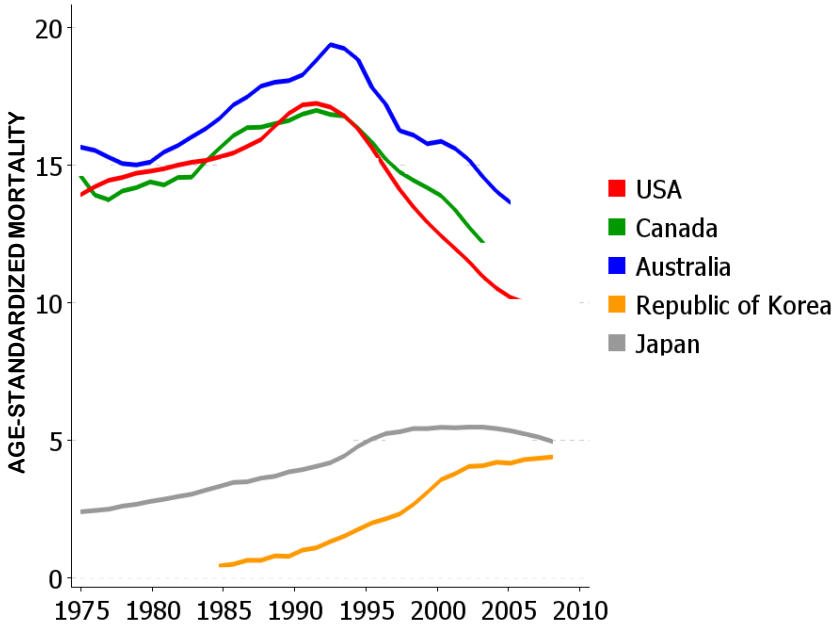
Some familial prostate cancer clusters with early age at disease onset explained by rare autosomal dominant or X-linked genes

➡ no more than 9% of all cases

*Gronberg H *et al.* J Urol *152:* 1484-9 (1994); Page WF *et al.* Prostate *33:* 240-5 (1997)
**Carter BS *et al.* Proc Natl Acad Sci USA *89:* 3367-71 (1992); Xu J *et al.* Nat Genet *20:* 175-9 (1998); Ewing CM *et al.* N Engl J Med *366:* 141-9 (2012); Bambury RM Gallagher DJ BJU Int E-pub (2012)

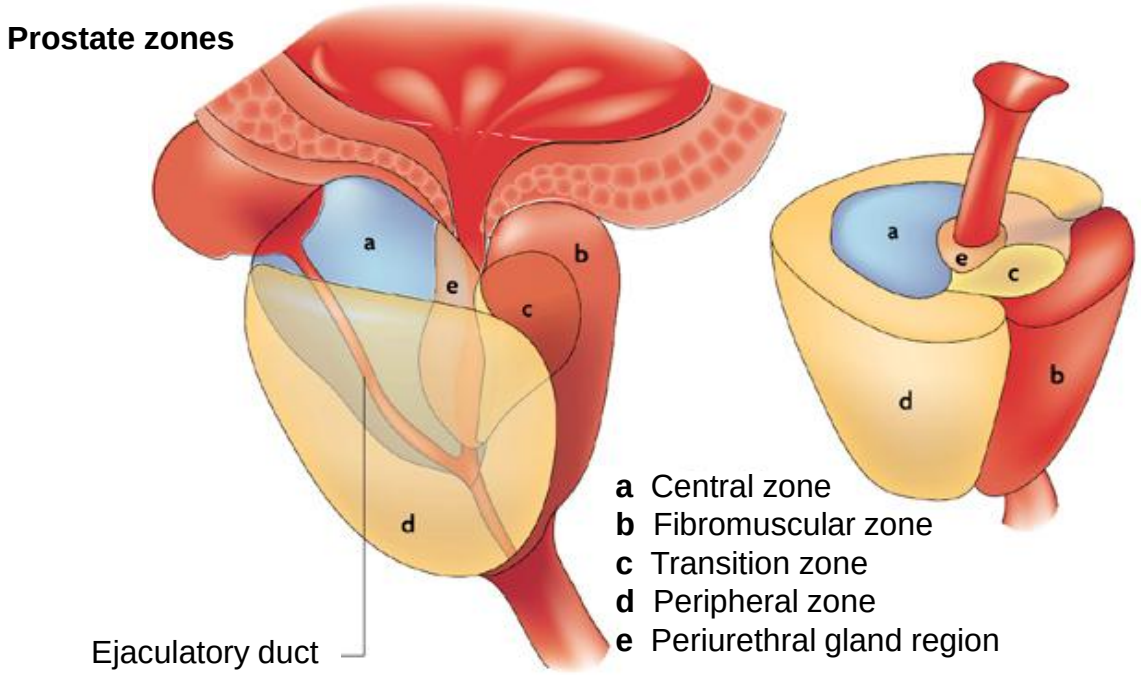
Ecological Epidemiology: Migrants from Low Prostate Cancer Regions of the World Adopt Higher Prostate Cancer Risks*; Prostate Cancer is on the Rise in Low Risk Countries**





*see Kolonel LN *et al.* Nat Rev Cancer *4:* 519-527 (2004)
**www.who.int/gho

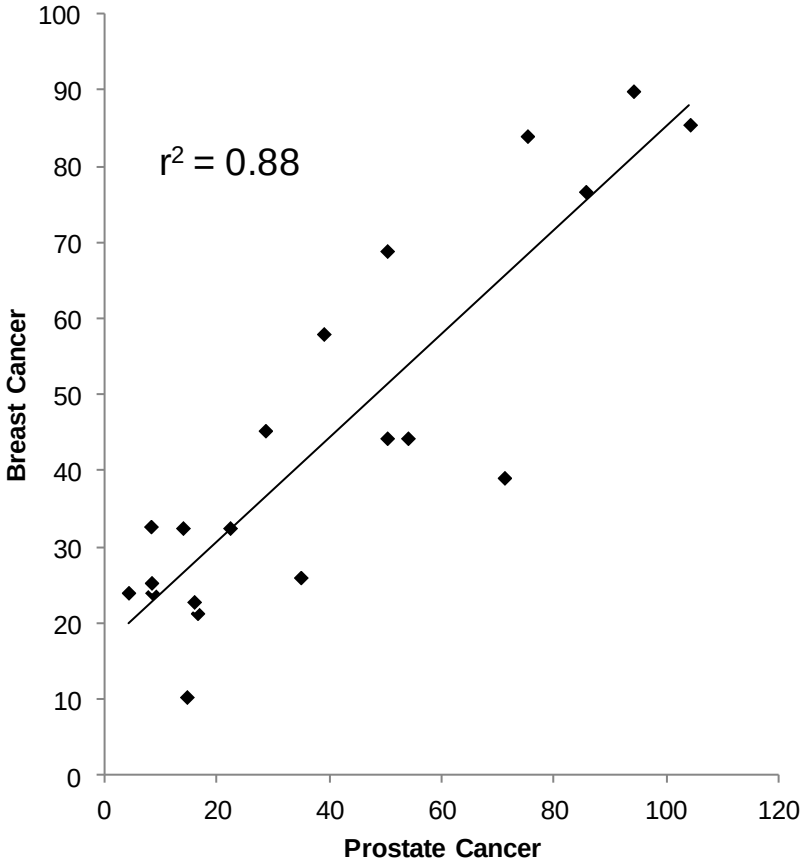
Zonal Distributions of Prostate Diseases*

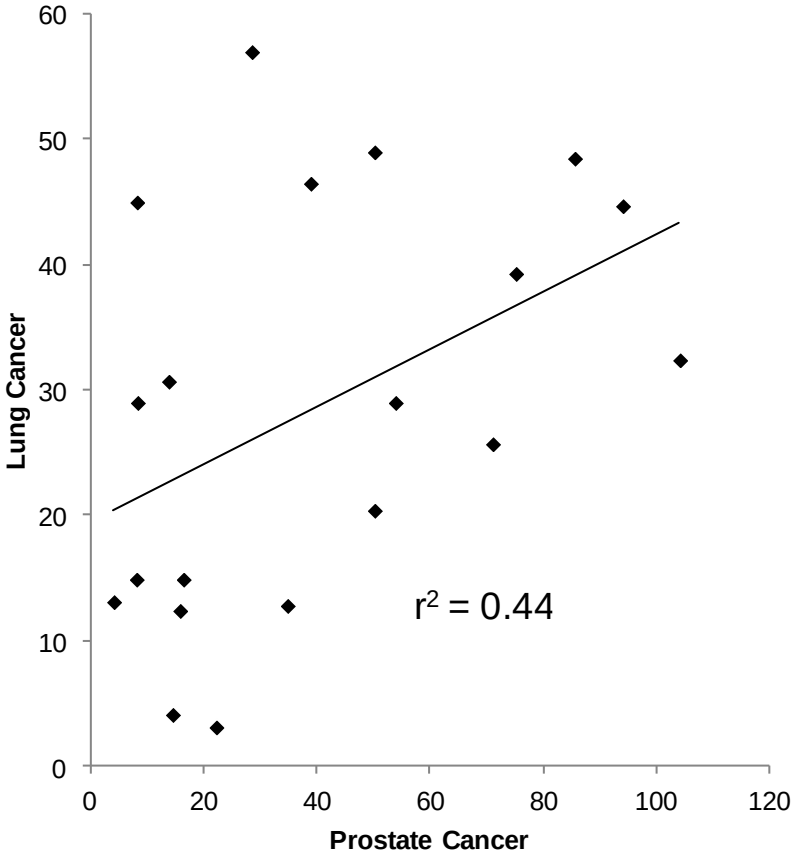


	Prostate zones		
	Peripheral	Transition	Central
Benign Prostatic Hyperplasia/Hypertrophy	None	High	Low
Prostatic Intraepithelial Neoplasia (PIN)	High	Medium	Low
Prostate Cancer	High	Medium	None

*De Marzo A *et al.* Nat Rev Cancer *7:* 256-269 (2007)

Correlation between Breast and Prostate Cancer Throughout Different Regions of the World*





Age-Standardized Incidence Rates Per 100,000

*Jemal A *et al*. CA Cancer J Clin *61:* 69-90 (2011)

Elucidation of Disease Pathogenesis at Autopsy

Gr. *Autopsia* "to see for oneself"
from αυτος (*autos* "oneself") and όψις (*opsis* "eye“)

Giovanni Battista Morgagni

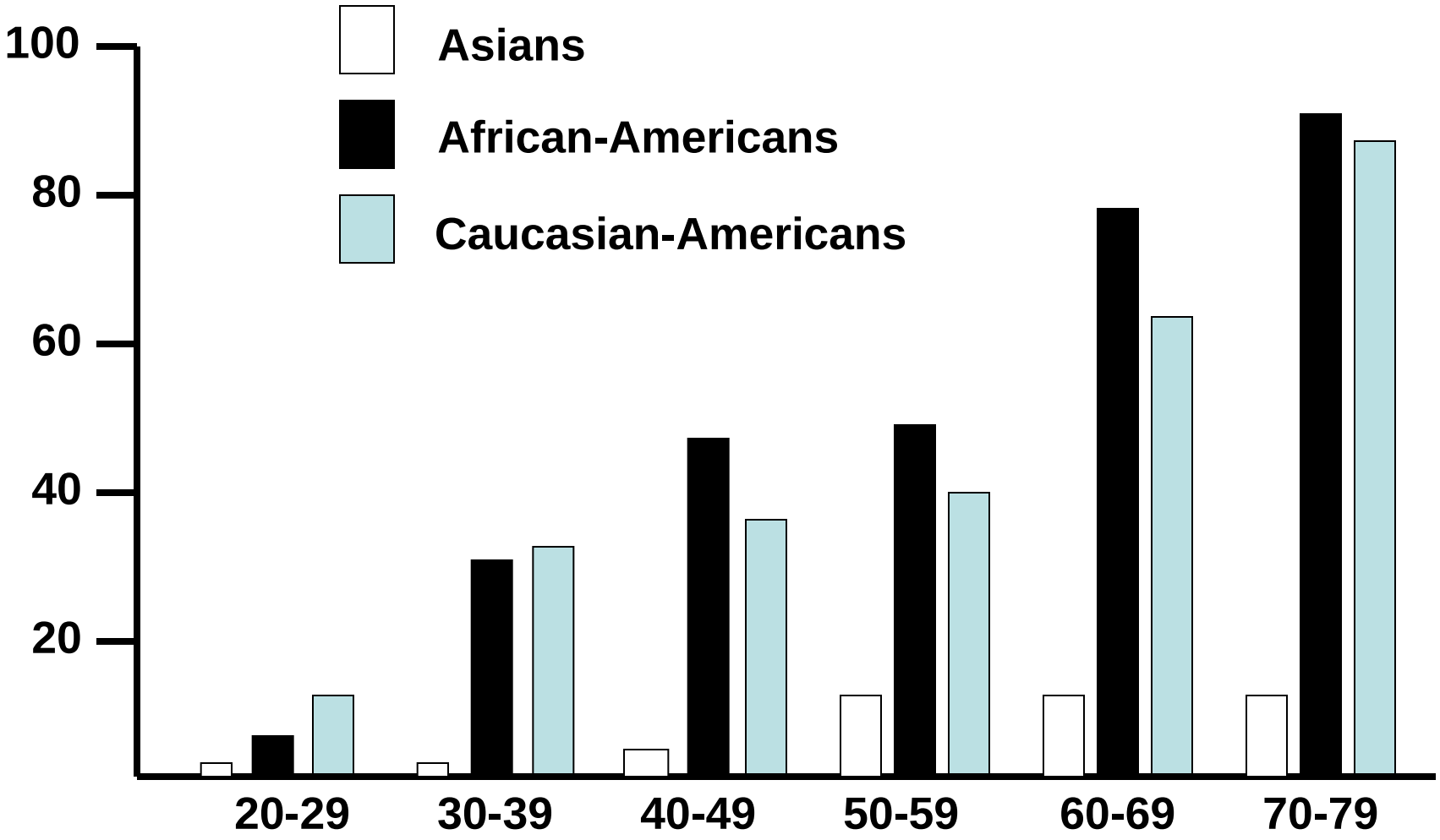
1682-1771

De Sedibus et Causis Morborum per Anatomen Indagatis

The Anatomy Lesson of Dr. Nicolaes Tulp

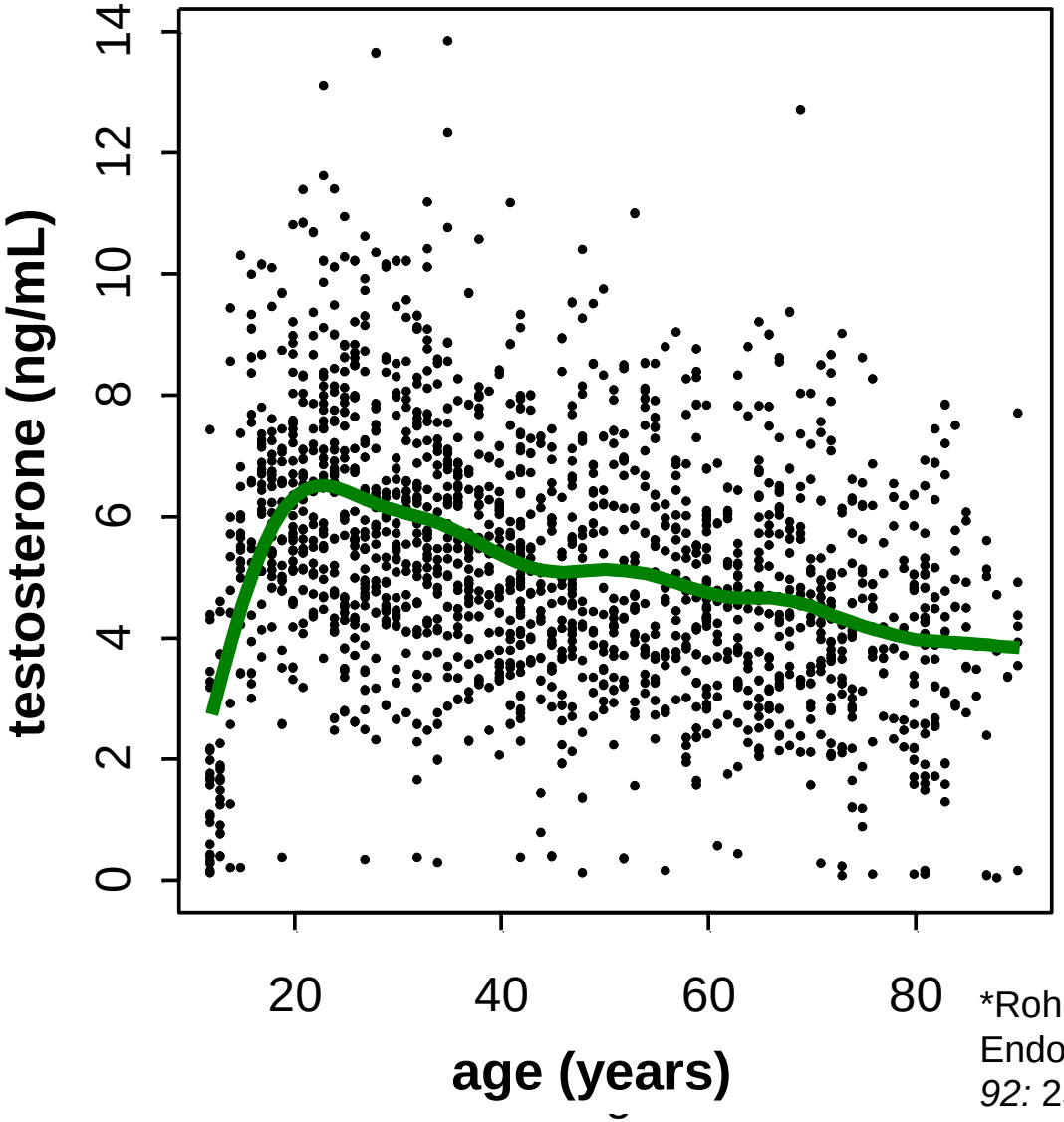
Rembrandt Harmenszoon van Rijn
1632

Prevalence of Prostate Cancer at Autopsy*



*Sakr WA *et al.* In Vivo *8:* 439-43, (1984); Gu FL *et al.* Urology *44:* 688-91 (1994); Lee YS and Shanmugaratnam K Singapore Med J *13:* 1321-6 (1972); Miller GJ *et al.* J Urol *151:* A204 (1994)

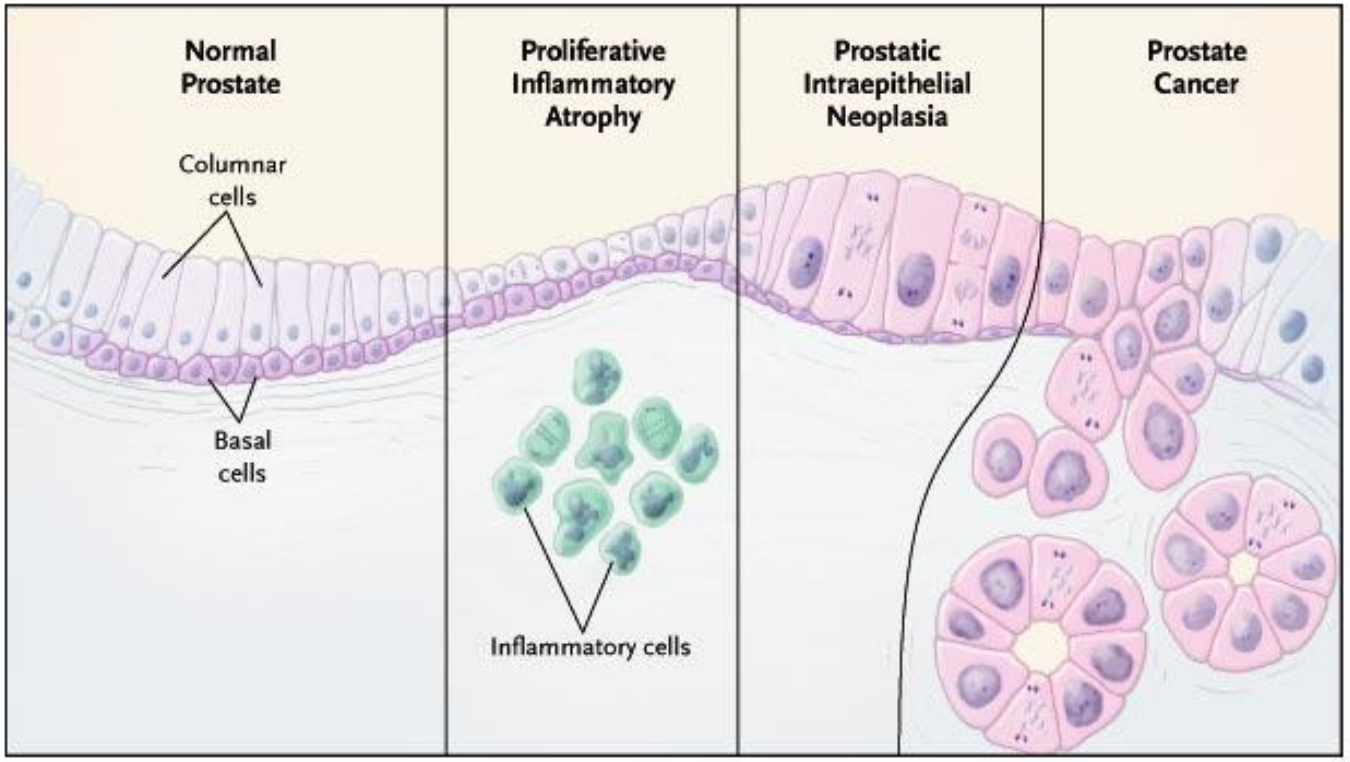
Change in Serum Testosterone with Age (n = 1,575 men in NHANES III)*



Elizabeth A. Platz

*Rohrman S *et al.* J Clin Endocrinol & Metabol *92:* 2519-25 (2007)

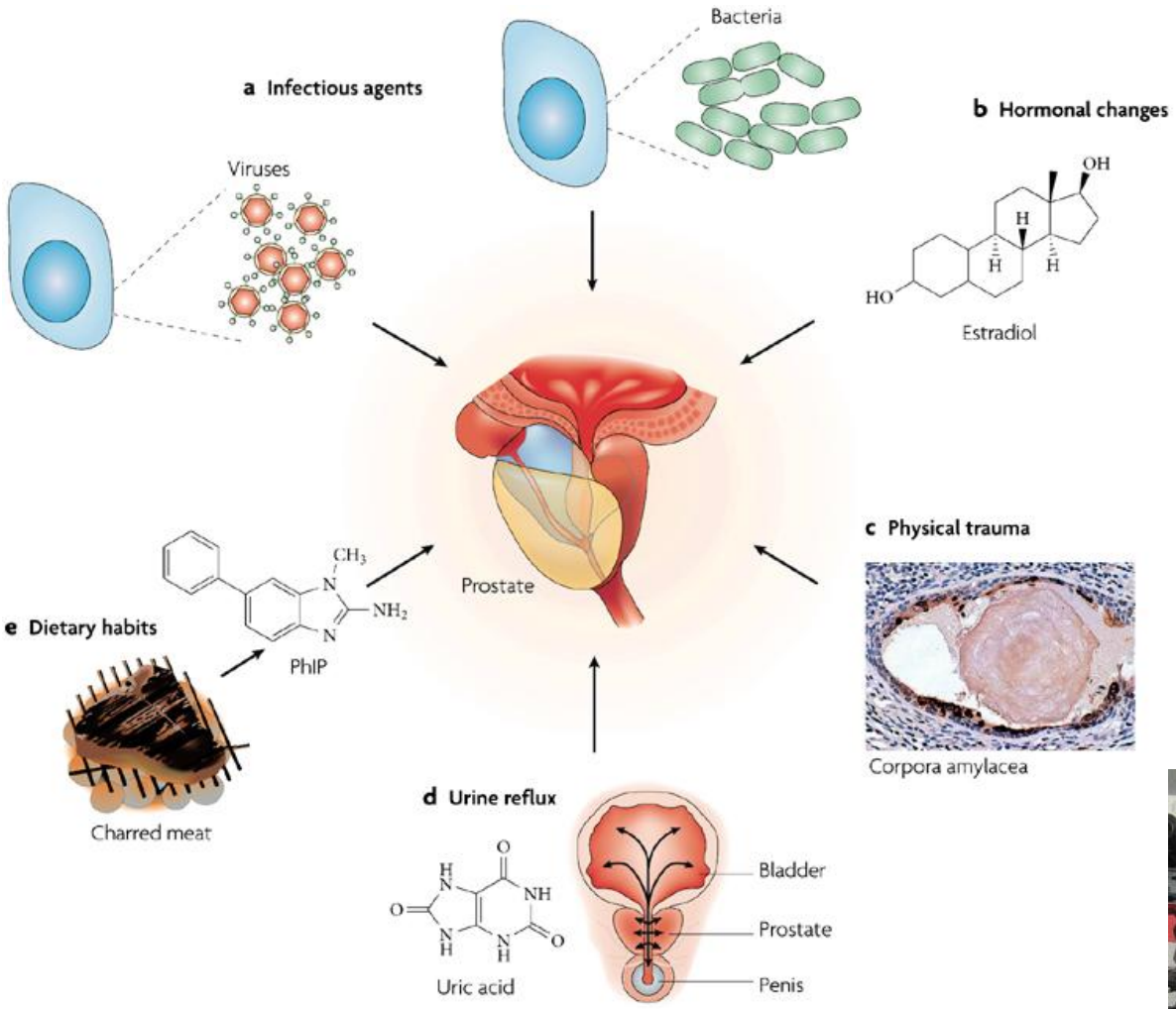
Histological Progression from Normal Prostate Epithelium to Prostate Cancer*



*De Marzo AM *et al.* Am J Pathol *155:* 1985-92 (1999);
Nelson WG *et al.* New Engl J Med *349:* 366-81 (2003)

Angelo M. De Marzo

Diverse Cell and Tissue Damaging Stresses Trigger Proliferative Inflammatory Atrophy in the Prostate*



*De Marzo A *et al.* Nat Rev Cancer *7:* 256-269 (2007)

Angelo M. De Marzo

Can Prostate Tissue Damage Explain Geographic Variation in Prostatic Carcinogenesis?*

Focal atrophy lesions in US Caucasian men versus Asian men**

Amount of Epithelial Atrophy by Type or Location (% of Slide Area)	Caucasian (n = 43)	Asian (n = 56)	p-Value
Any Atrophy	13.90	5.75	<0.0001
Peripheral Zone Atrophy	13.31	4.69	<0.0001
Transition Zone Atrophy	0.17	0.39	0.0625
Simple Atrophy	11.67	4.44	<0.0001
Simple Atrophy with Signs of Epithelial Injury	9.00	2.17	<0.0001
Simple Atrophy with Atypia	4.97	0.83	0.0003
Atrophy with Acute Inflammation	0.1580	0.1601	0.9820
Atrophy with Chronic Inflammation	1.252	0.475	0.0037

**Age-adjusted

*Johsu CE, Magi-Galluzzi C *et al.* (2012)

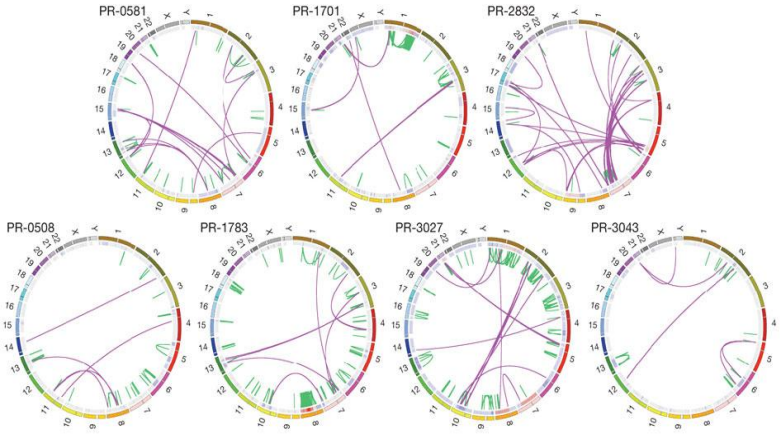
Corinne Johsu

Cristina Magi-Galluzzi

Somatic Alterations in Genomic DNA from Prostate Cancers*†

Genetic Changes

- 3,866 base mutations (range 3,192–5,865)
- 20 non-silent coding sequence mutations (range 13-43)
- 108 rearrangements (range 43-213)

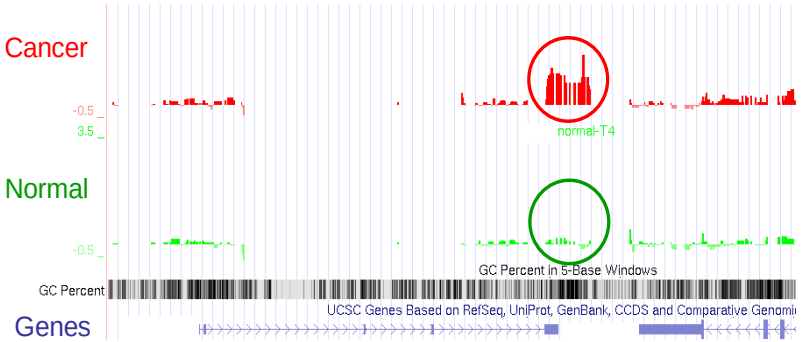


*Berger MF *et al.* Nature *470:* 214-20 (2011)

Levi Garroway

Epigenetic Changes

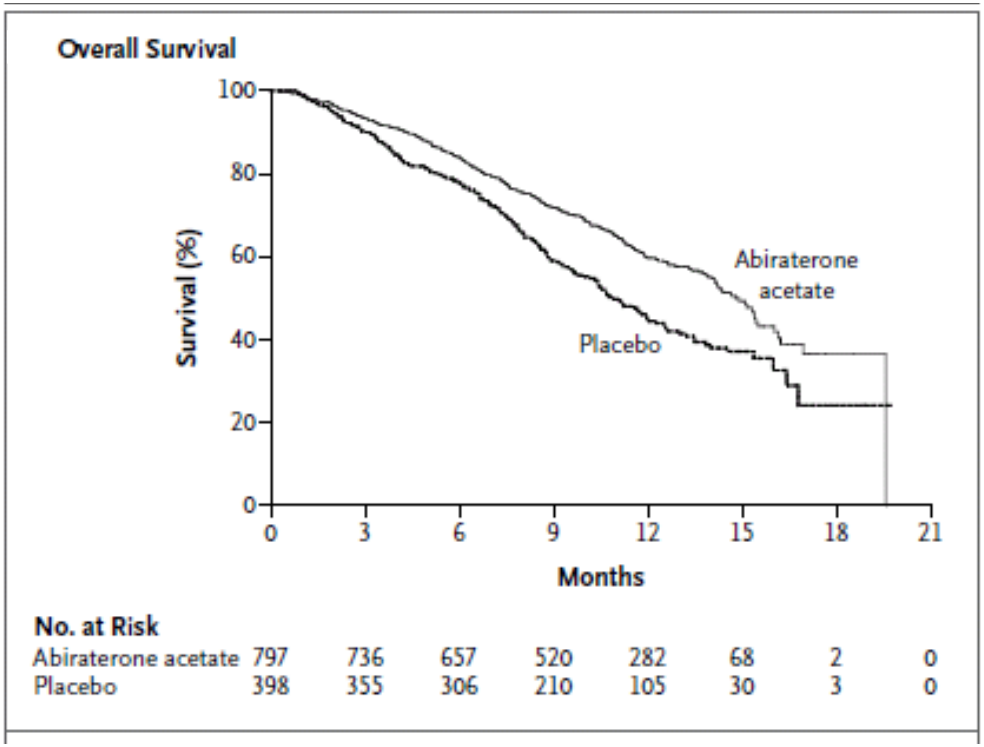
- 5408 hypermethylation regions
  - 73% near genes (5', 3', or intron-exon junctions)
  - 27% conserved intergenic sites



†Yegnasubramanian S *et al.* BMC Genomics *12:* 213 (2011)

Srinivasan Yegnasubramanian

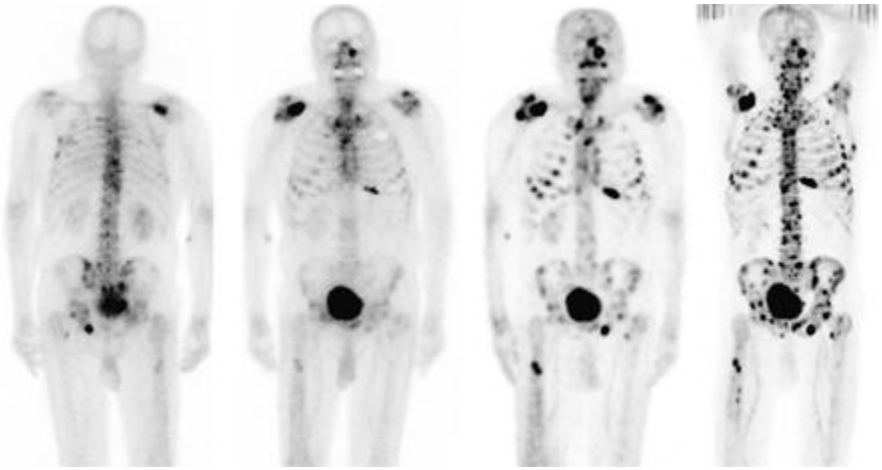
Abiraterone Acetate Improves Overall Survival for Men with Metastatic Prostate Cancer*



*De Bono JS *et al.* New Engl J Med *364:* 1995-2005 (2011)

Current Imaging Technologies Underestimate Extent of Disease in Men with Metastatic Prostate Cancer; New Imaging Agents Poised to Solve this Problem*

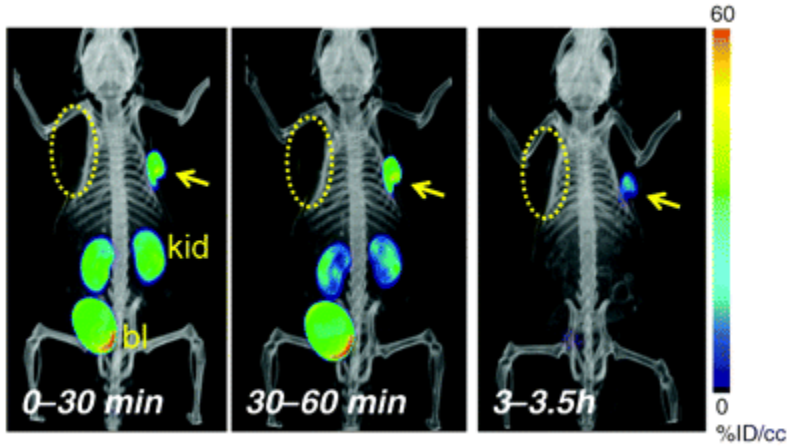
Homo sapiens



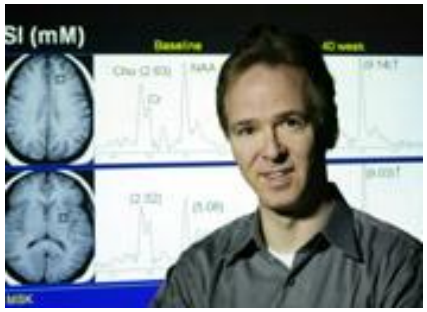
^{99m}Tc-MDP bone scan

^{18}F-fluoride PET image

Mus musculus



2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid, [^{18}F]DCFPyL



Martin G. Pomper

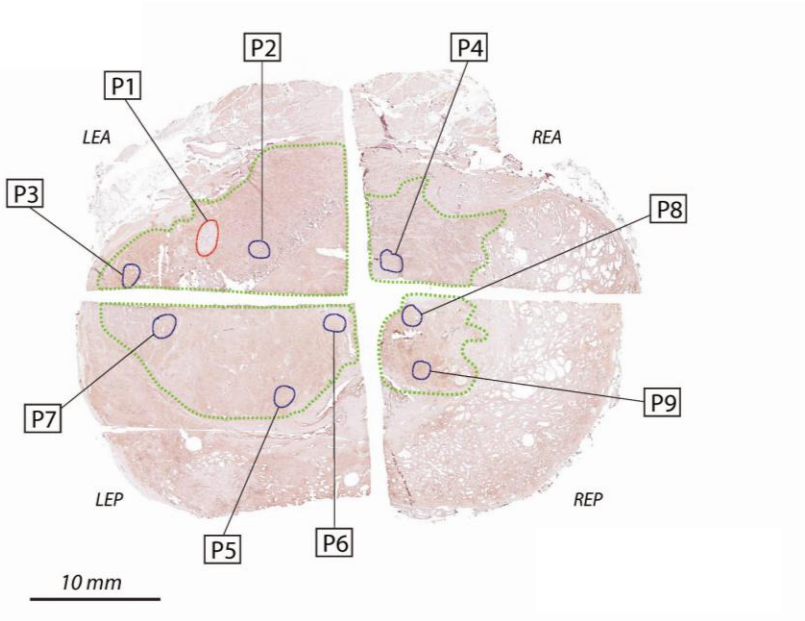
*Even-Sapir E *et al.* J Nucl Med *47:* 287-97 (2006); Chen Y *et al*. Clin Cancer Res *17*: 7645-53 (2011)

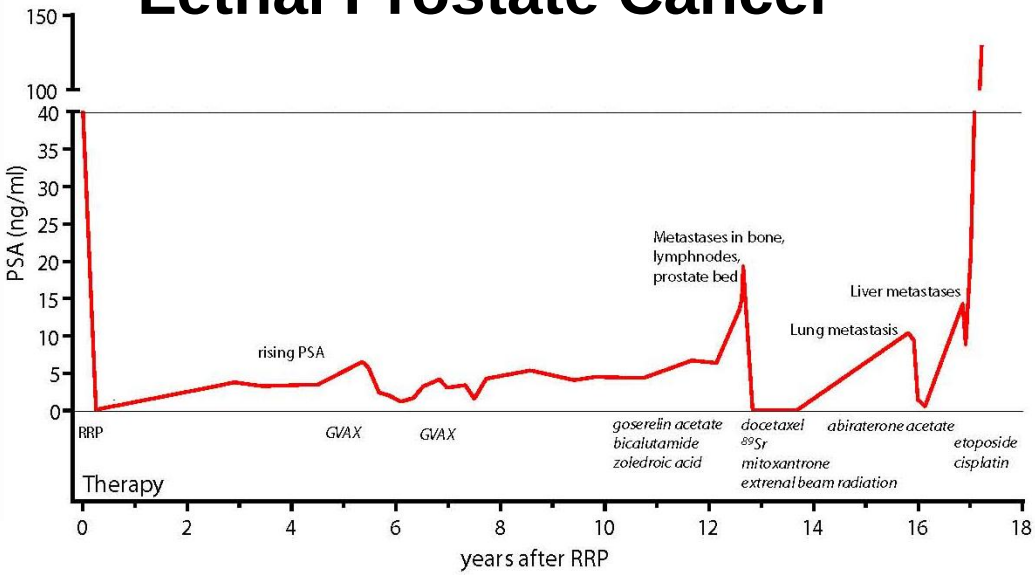
Improving Prostate Cancer Health at a Population Scale: Taking Advantage of in the Johns Hopkins Health System

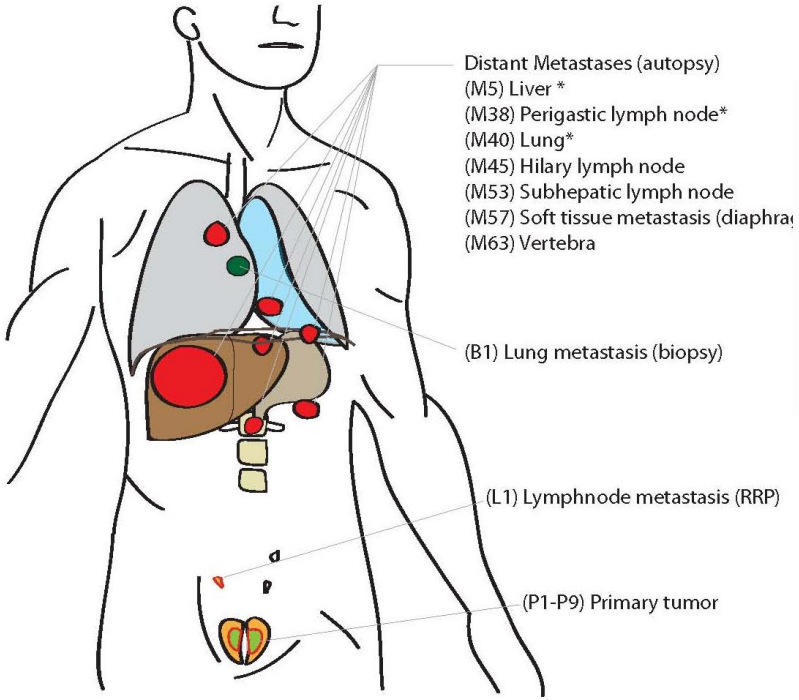
Organization (Characteristics)	Population Size
Johns Hopkins Community Physicians (Primary Care Provider Network)	>260,000
Johns Hopkins Priority Partners (Medicaid Health Maintenance Organization)	>185,000
Johns Hopkins Employee Health Program (Health Insurance Plan)	>50,000
Johns Hopkins US Family Health Plan (Provider to US Government and Military Employees and Families)	Enrolling

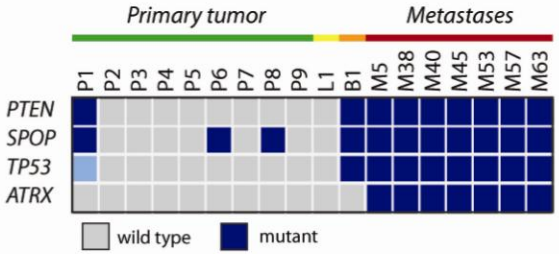
Cancer Prevention and Control Program members already working with these entities to establish cancer screening guidelines and improve screening performance- first project focuses on reducing over-screening for prostate cancer among elderly men

A Molecular Description of Lethal Prostate Cancer









Haffner MC, Yegnasubramanian S *et al.* (2012)

Michael C. Haffner