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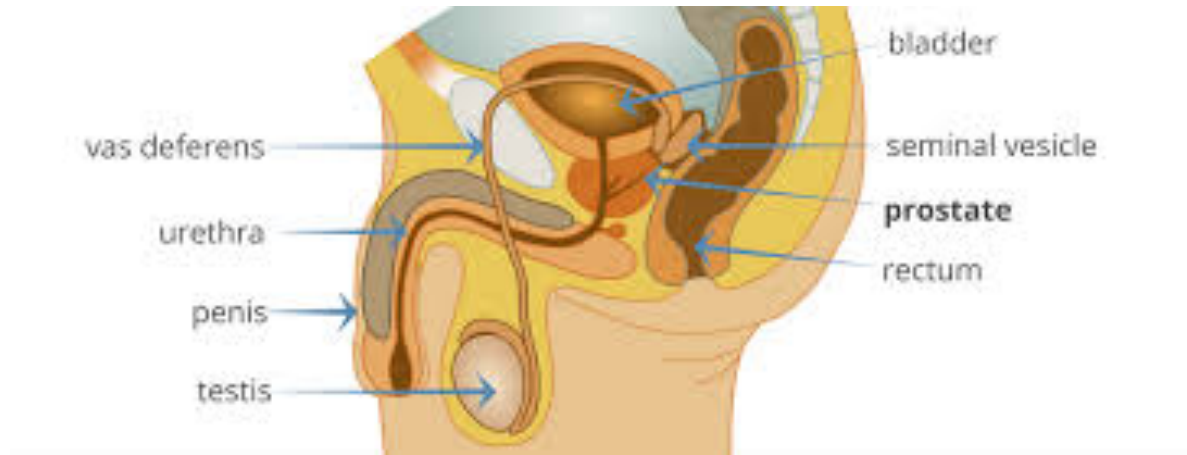
Diet and prostate cancer; overcoming research challenges

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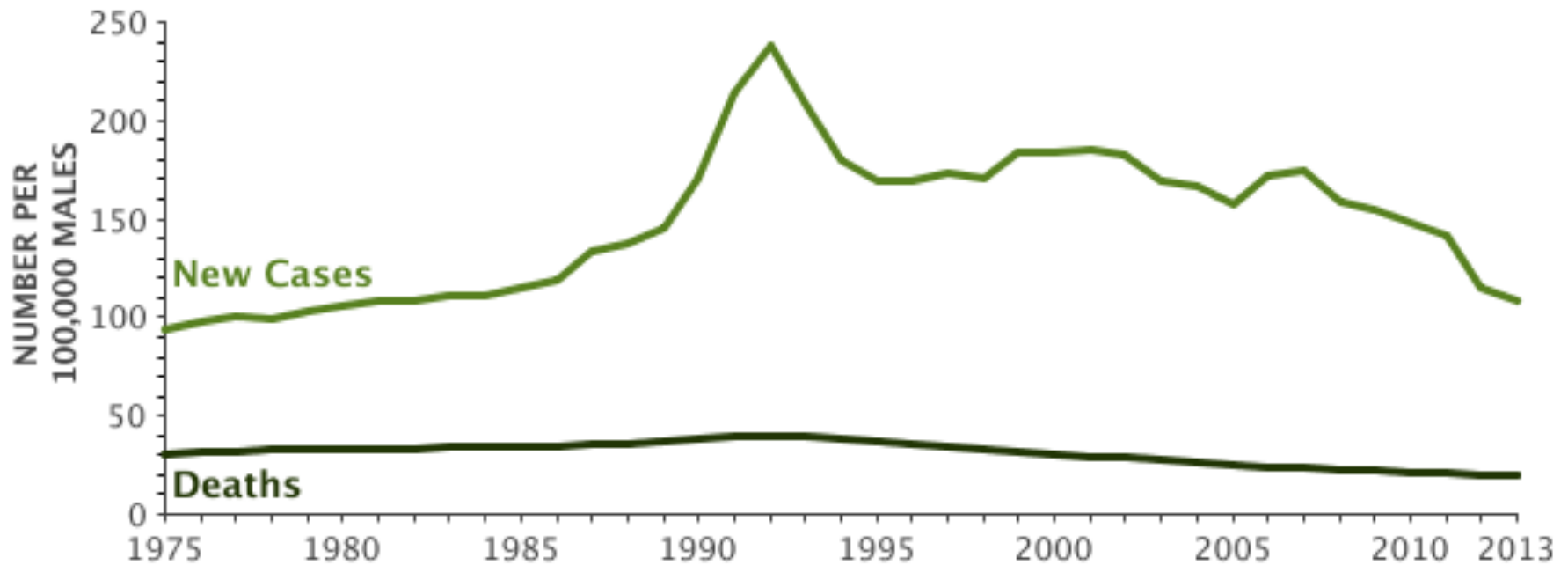
Introducing the prostate



- Walnut-sized gland at the base of the bladder
- Secretes fluid that bathes sperm to form semen
 - PSA: prostate-specific antigen

Prostate cancer: the stats

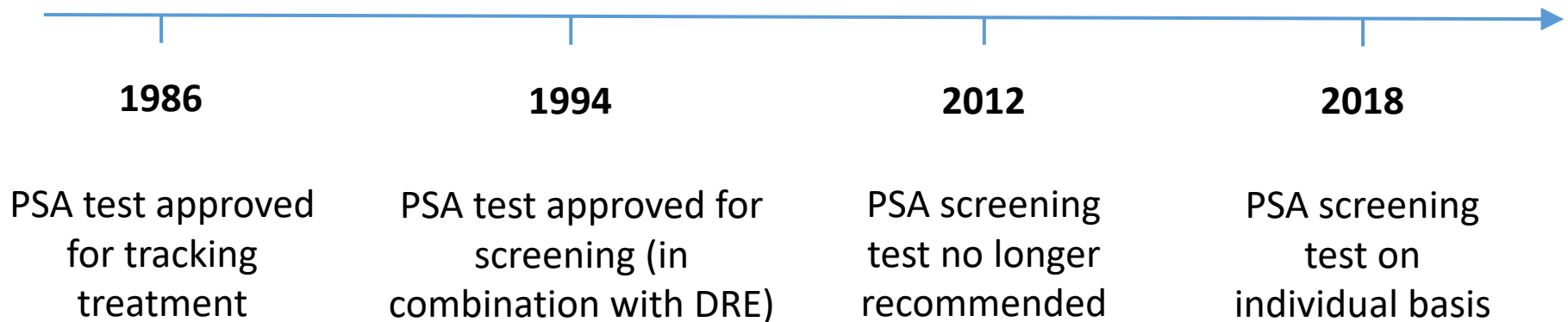
- Most commonly diagnosed male cancer in the US (1 in 8 men)
- Second most common cause of male cancer deaths in the US (1 in 40 men)



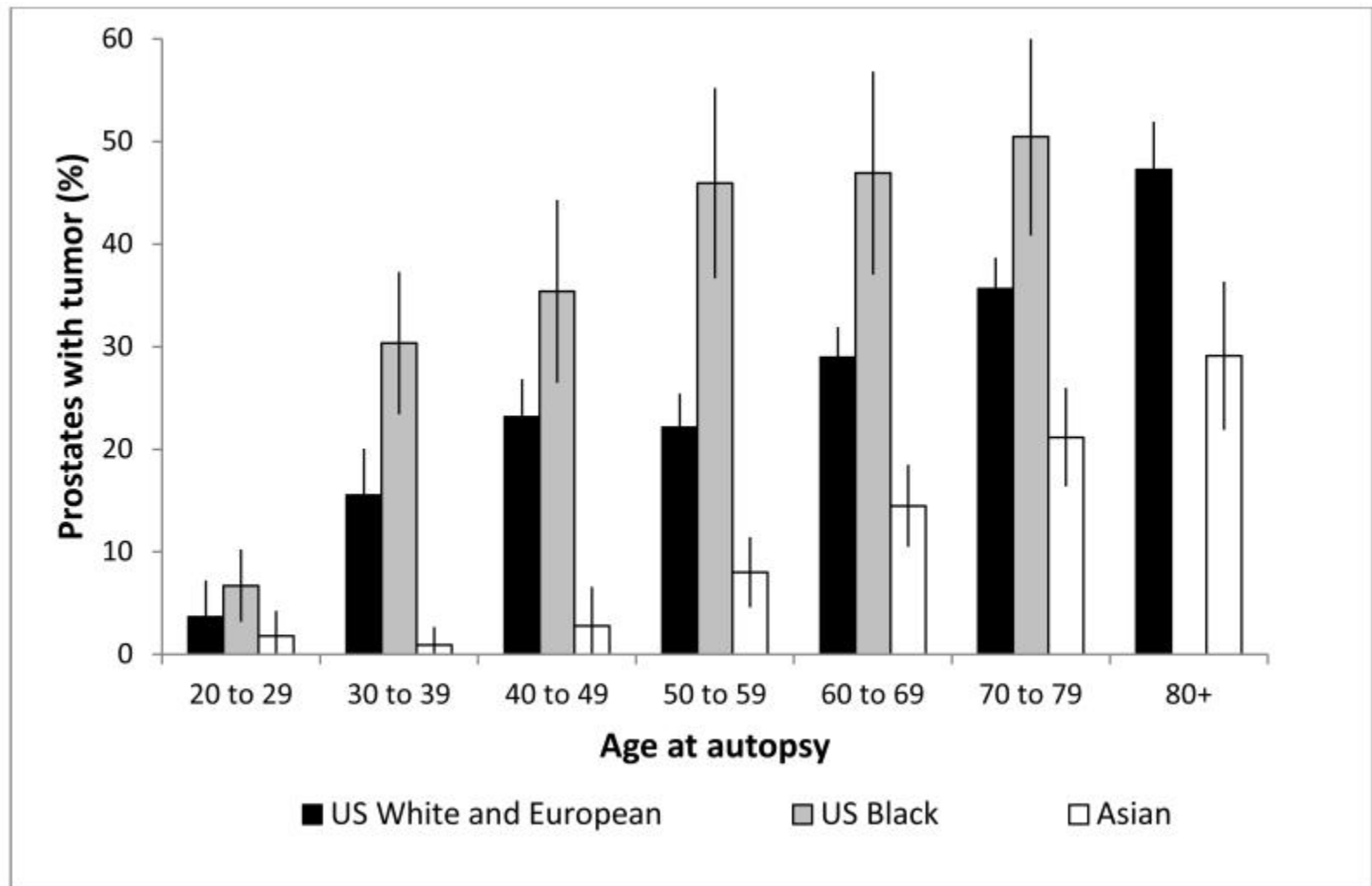
SEER 9 Incidence and Mortality 1975-2013, all races, Rates are age-adjusted

Prostate cancer screening

- PSA: prostate-specific antigen, secreted by the prostate into semen, leaks into blood
- Causes of elevated blood PSA
 - Prostate cancer
 - Prostate inflammation
 - Benign Prostatic Hyperplasia (BPH)



Autopsy studies find prostate cancer in men that died of other causes



Purpose of screening

- To diagnose cancer earlier thus maximizing chances of a cure
- PSA screening shifted the average age for prostate cancer diagnosis ~one decade earlier
- But, we cannot distinguish prostate cancers that men die WITH from prostate cancers that men die FROM

Take home message #1

- Need to identify risk factors for aggressive/lethal prostate cancer, not all prostate cancer





Established risk factors for prostate cancer

Table 1. Summary of evidence for selected risk factors of total prostate cancer

Risk factor	Strength of evidence
<i>Increased risk</i>	
Older age	Strong
African descent	Strong
Family history	Strong
Genetic risk loci	Strong
Taller height	Probable

Pernar et al. 2018

- None modifiable!

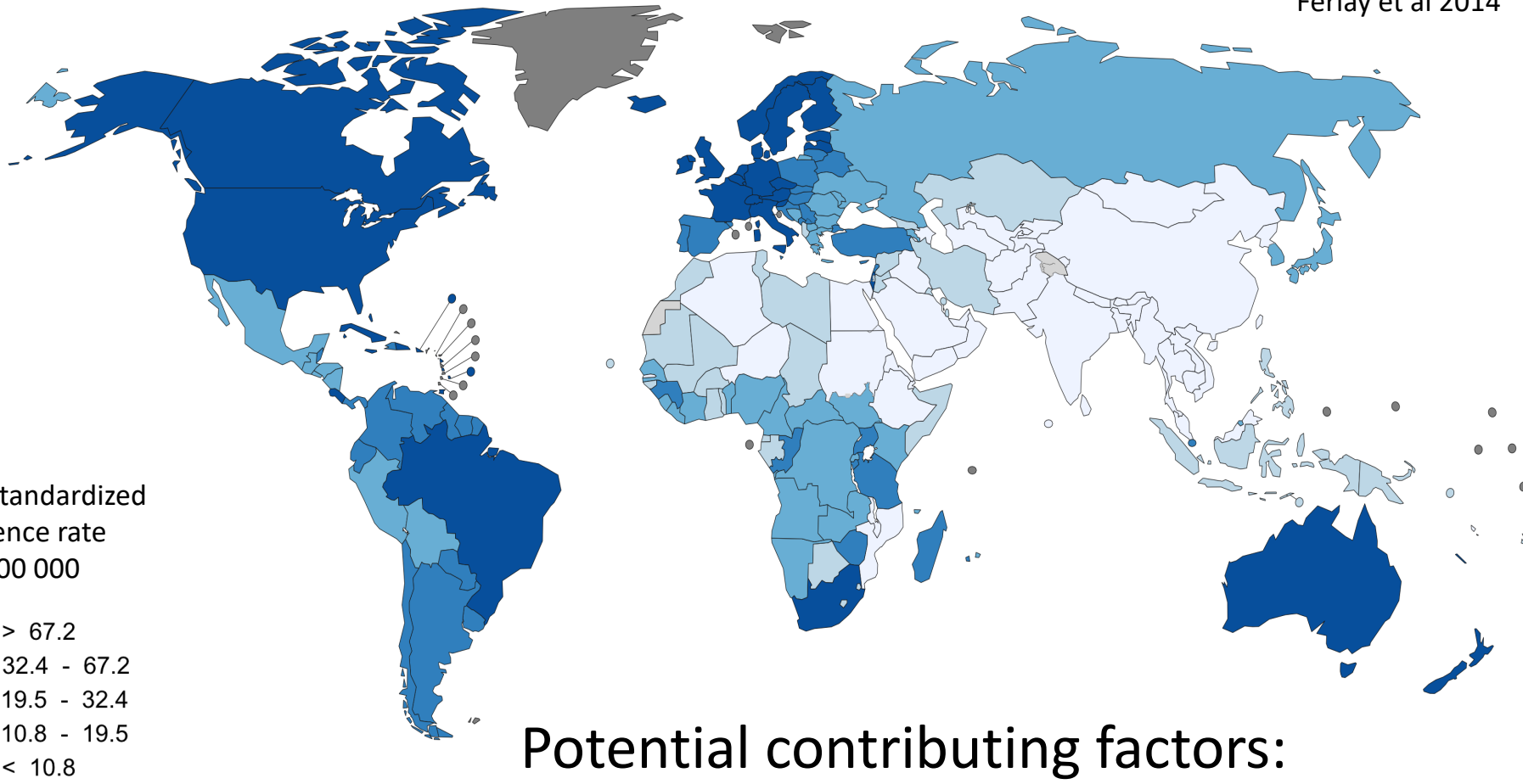
 World Cancer Research Fund International		 CUP Continuous Update Project Analysing research on cancer prevention and survival
DIET, NUTRITION, PHYSICAL ACTIVITY AND PROSTATE CANCER		
EVIDENCE	DECREASES RISK	INCREASES RISK
Convincing		
Probable		Body fatness (advanced prostate cancer) ^{1,2} Adult attained height ³
Substantial effect on risk unlikely	Beta-carotene ^{4,5}	

2014 update; www.aicr.org

Unmet need: Modifiable risk factors for prostate cancer

Substantial global variation

GLOBOCAN 2012
Ferlay et al 2014



Potential contributing factors:

- Screening rates
- Lifestyle factors (including diet)

Barriers to identifying dietary risk factors

1. Heterogeneity of prostate cancer



2. Variation between individuals in response to diet

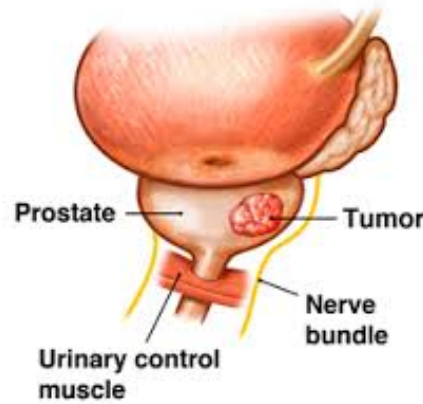
Barriers to identifying dietary risk factors

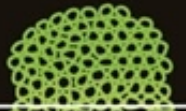




1. **Heterogeneity of prostate cancer**



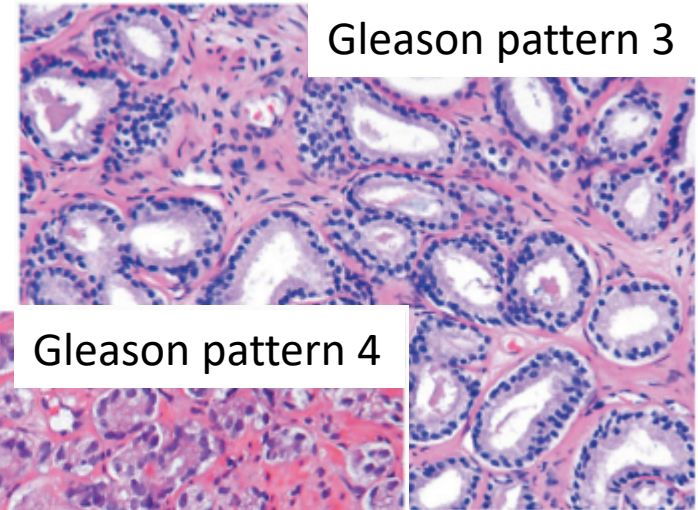
2. Variation between individuals in response to diet

Prostate cancer: Not one disease

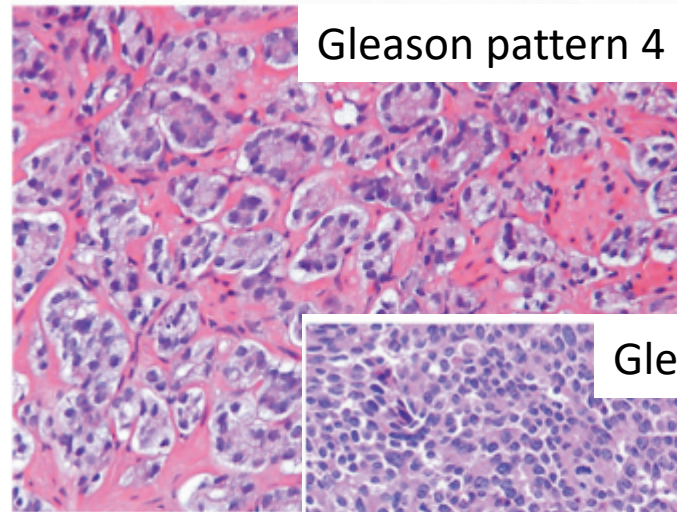


1		Nearly normal cells
2		Some abnormal cells loosely packed
3		Many abnormal cells
4		Very few normal cells left
5		Completely abnormal cells

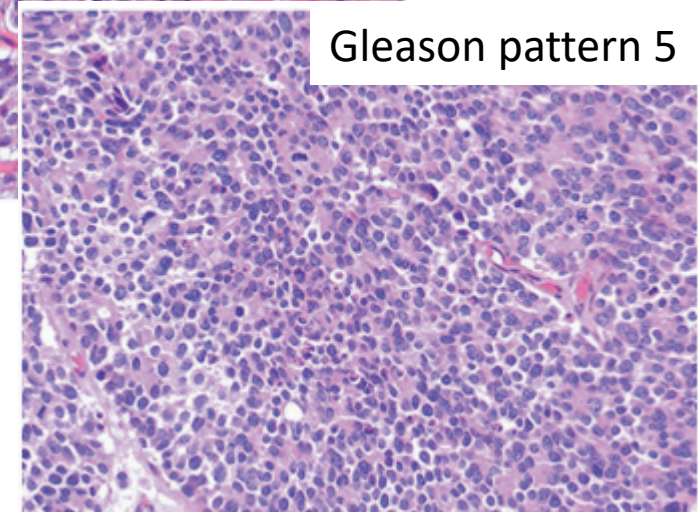
Pathologist classification



Gleason pattern 3



Gleason pattern 4



Gleason pattern 5

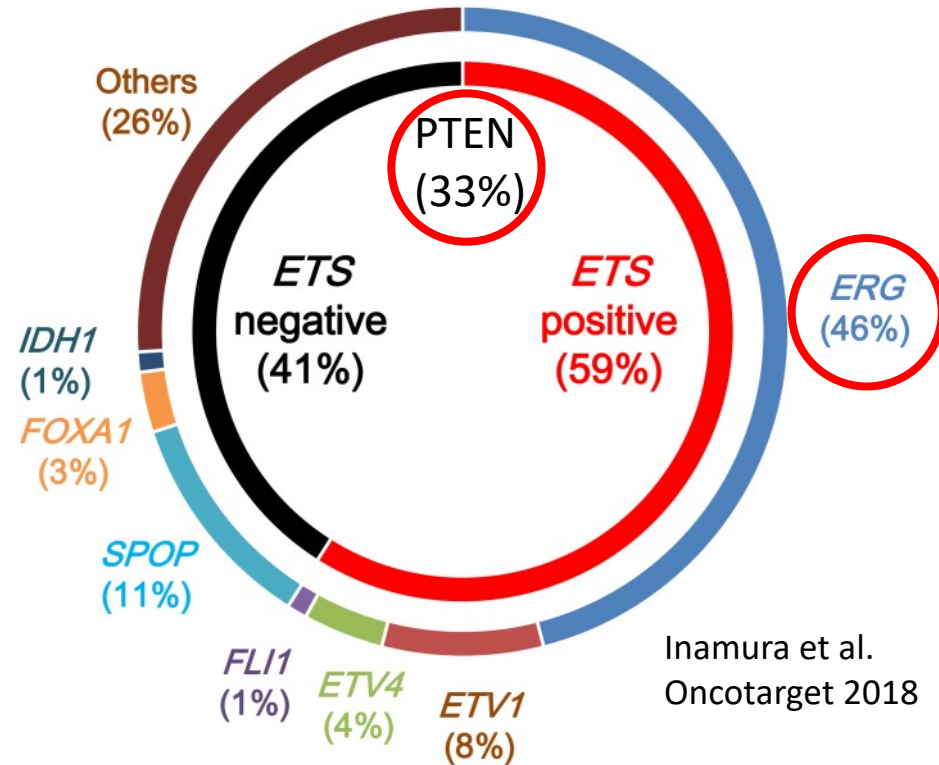
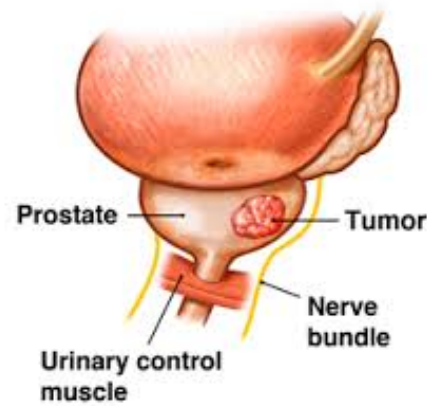
Risk factors vary by type of prostate cancer

<u>Risk factor</u>	<u>Total prostate cancer</u>
Obesity	-
Physical activity	-
Statin use	-
Smoking	-
Coffee	-
Tomato	-

↑ increased risk

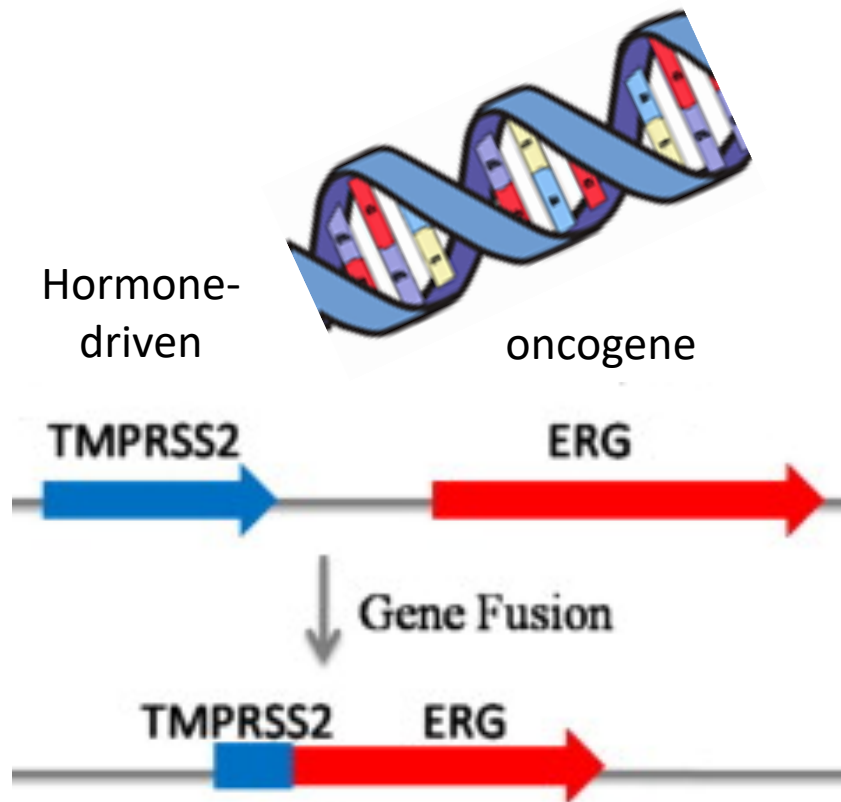
↓ reduced risk

Prostate cancer: Not one disease



Molecular classification

ERG



~50% of all
prostate cancers

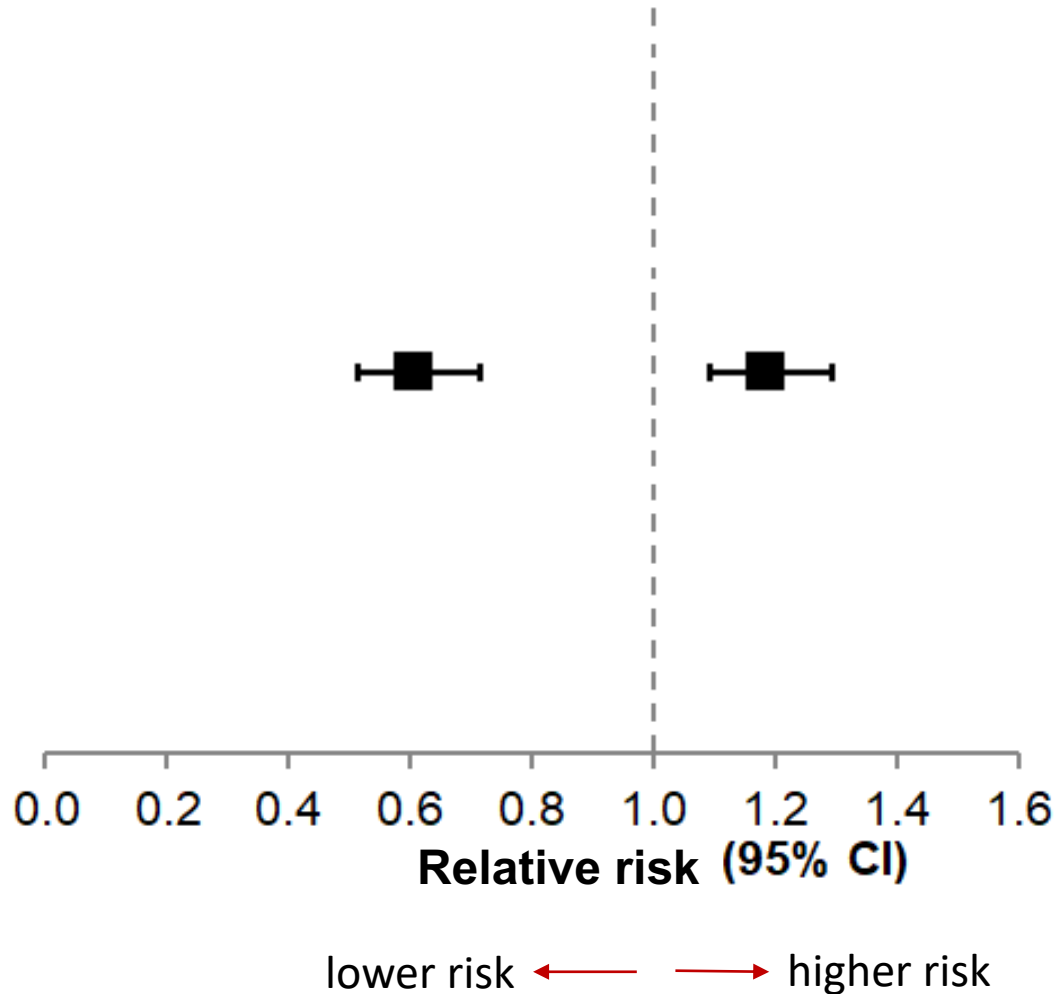
PTEN

The diagram shows a DNA double helix with a red scissors icon indicating a deletion. Below the helix, a long sequence of nucleotide bases is listed, representing the PTEN gene sequence.

```
tgtgtgtgtgctagcacaccatcggctatatactcggctcgctactactacgagctacgatcatct  
agctacgtataaattctcgtcgtactctcgtacgatctactataccgctccctatagatgaa  
aatcgatcgatcgactacgactagcatcgactctctctcttctgctcgatcaacgctctctct  
cgagatctacaaatcgatcgatcgactcgcatcgatcgactacgacgacgacgacgacgacgac  
taaatcgcgcgctctctcagctacgaaaacgctctgagctagctgacgacgacgacgacgacgac  
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gccgatcgactagcgtcgtcgtcgtcgtcgtcgtcgtcgtcgtcgtcgtcgtcgtcgtcgtcgtcgtcgtcgtc  
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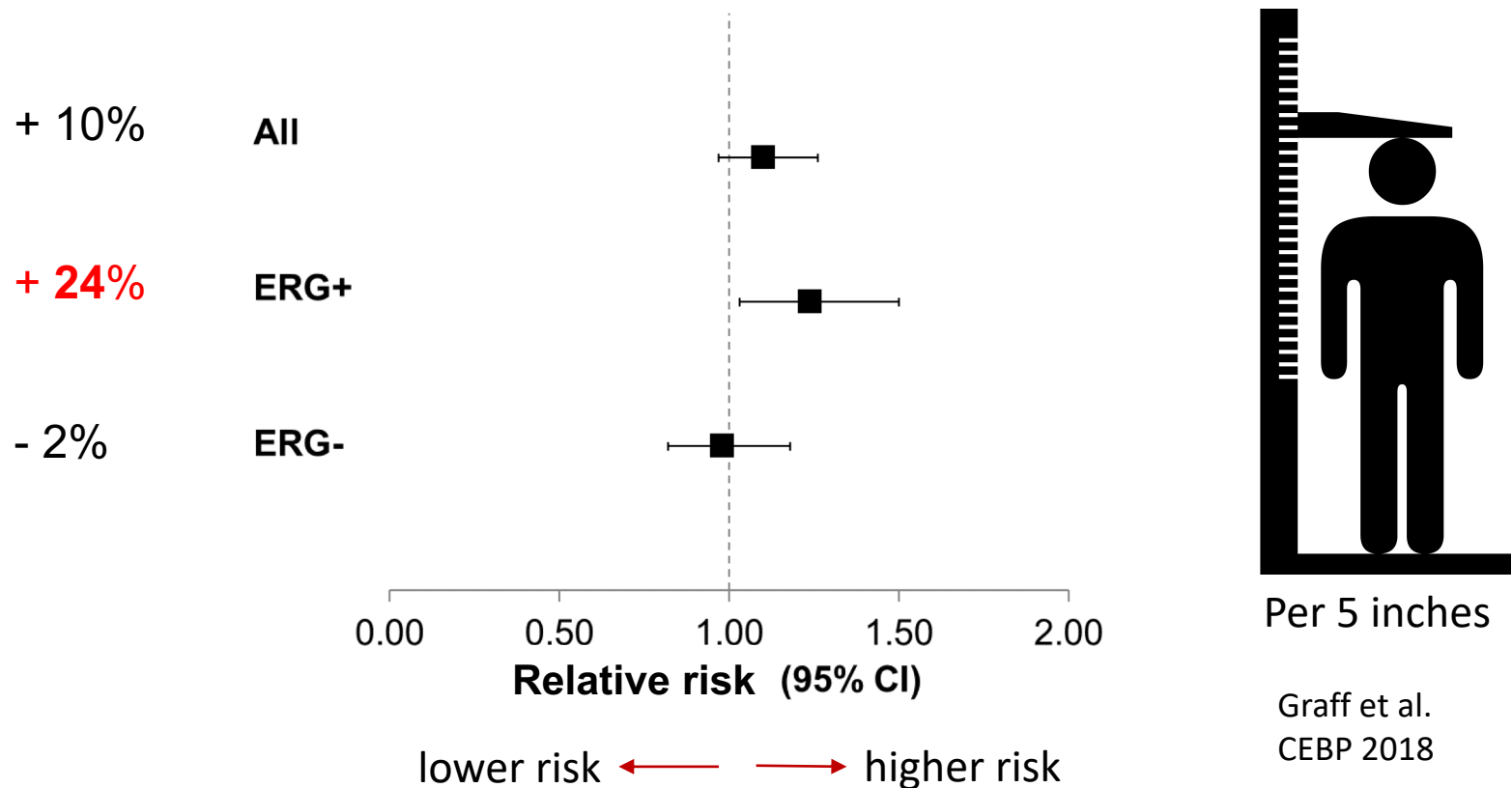
~33% of all
prostate cancers

Interpreting results



Height and prostate cancer

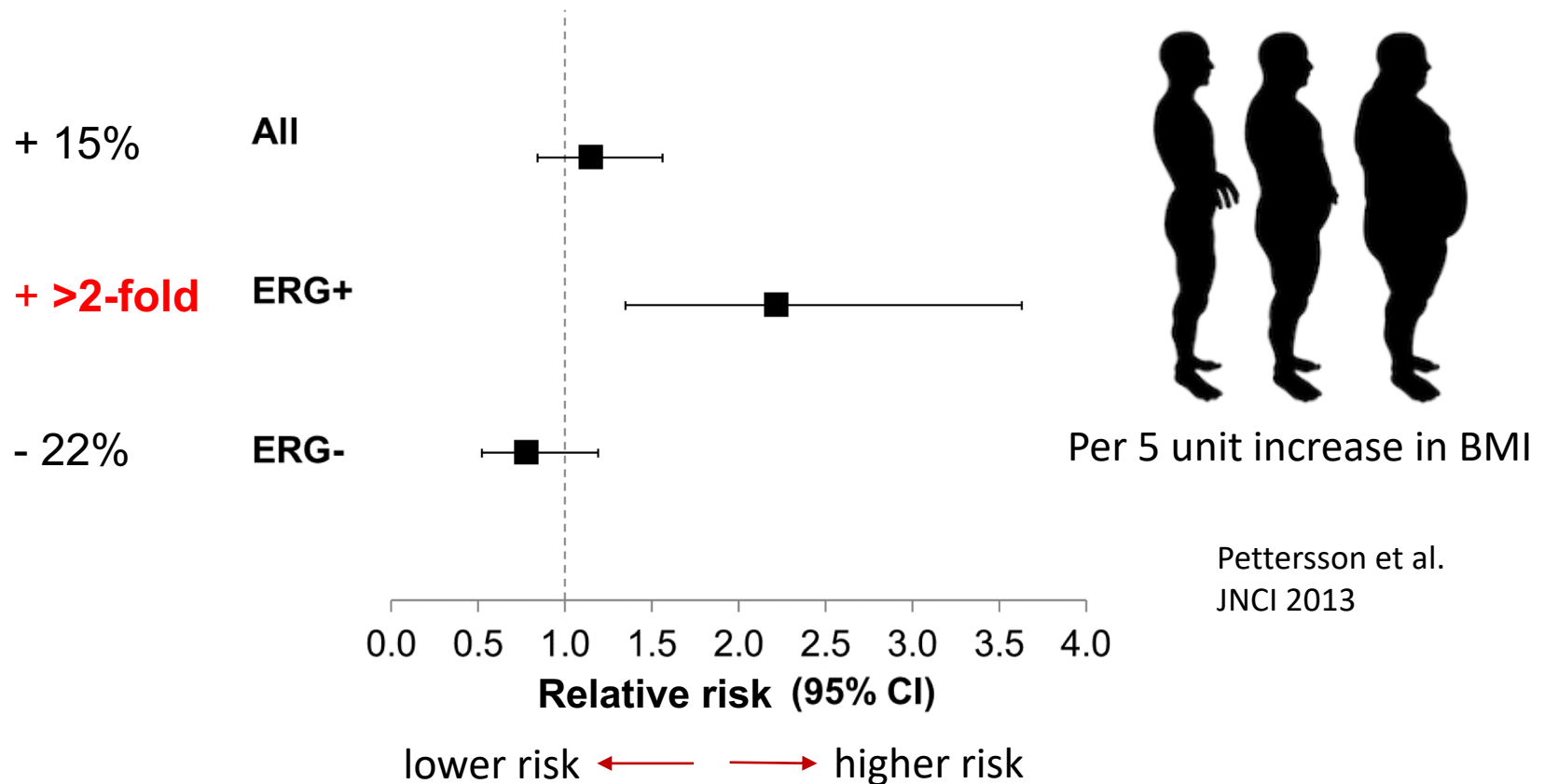
- Taller height associated with higher risk of prostate cancer



- Potential mechanisms: higher levels of growth hormones

Obesity and prostate cancer

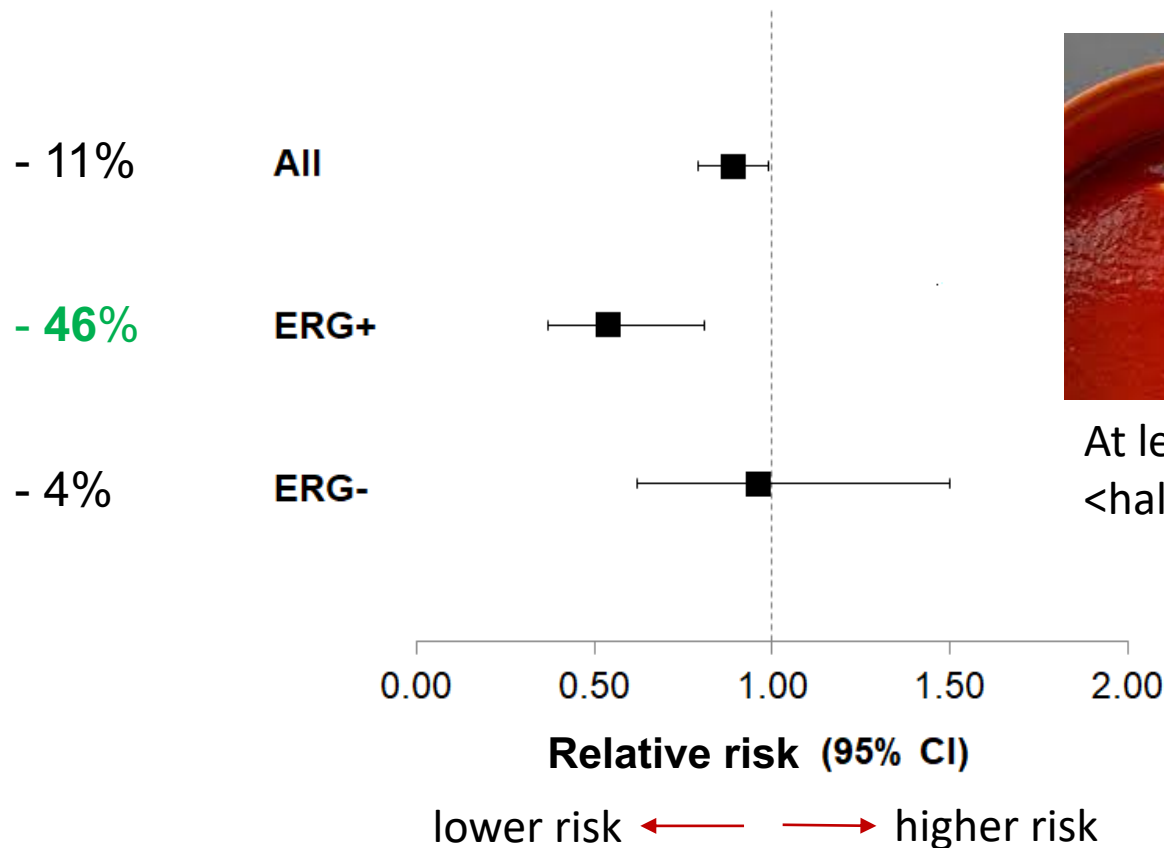
- Obesity associated with higher risk of lethal prostate cancer



- Potential mechanisms: altered levels of sex hormones, chronic inflammation

Lycopene and prostate cancer

- Tomato sauce associated with lower risk of prostate cancer



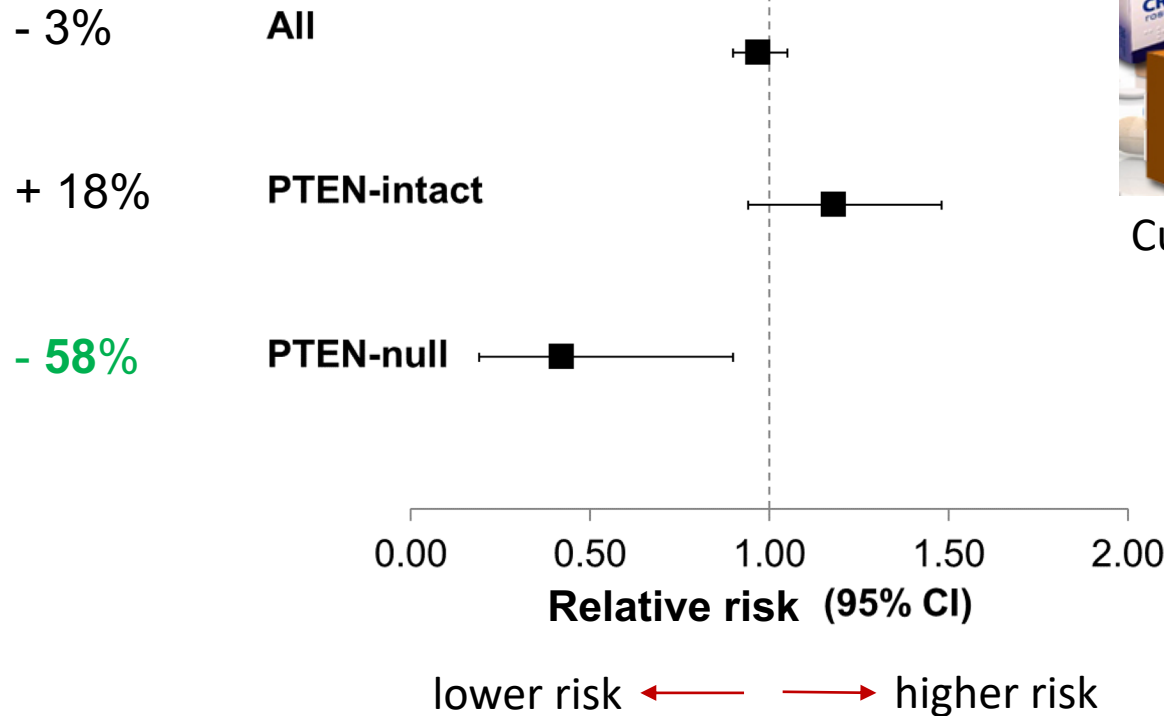
At least 1 cup per week vs.
<half cup per month

Graff et al.
Am J Clin Nutr 2016

- Potential mechanisms: antioxidant properties

Statins and prostate cancer

- Statin use associated with lower risk of advanced/lethal prostate cancer

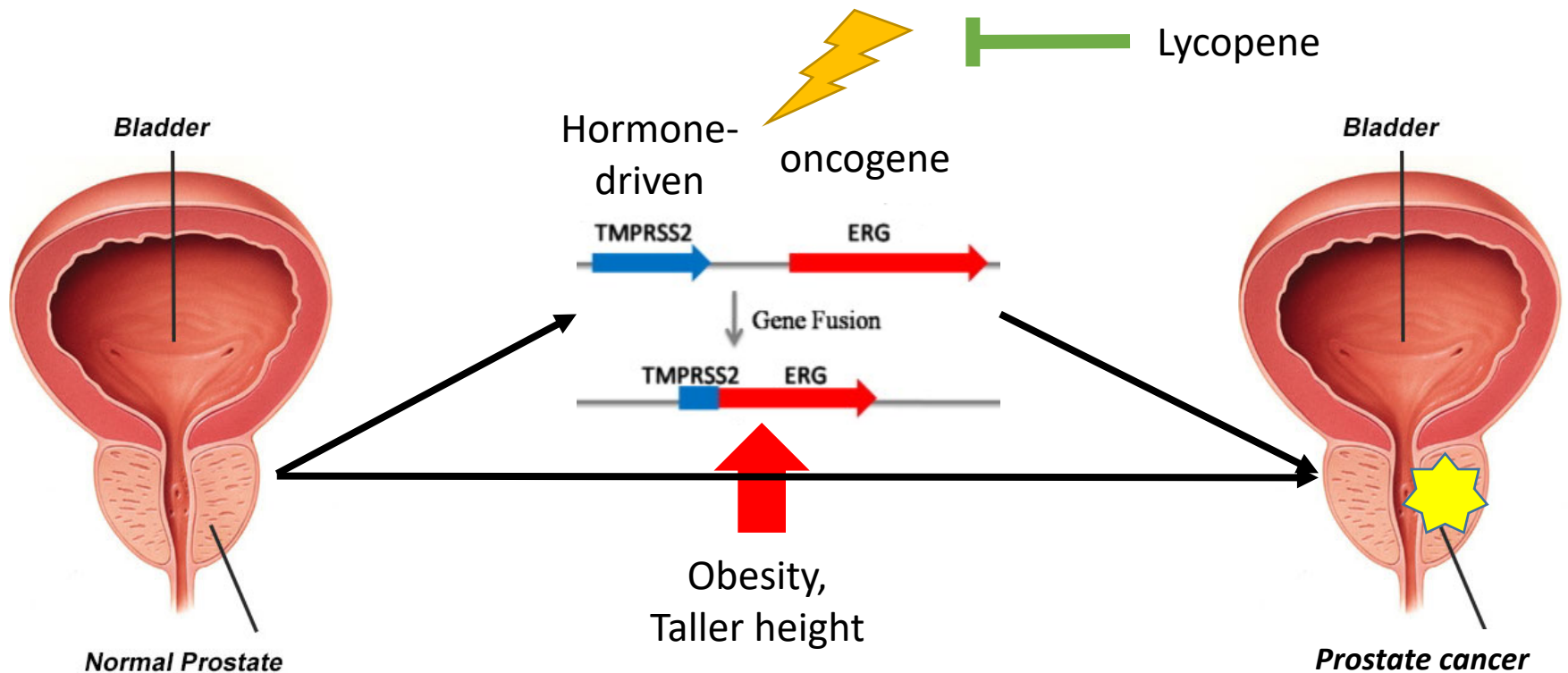


Current vs. past/never statin users

Allott et al.
In preparation

- Potential mechanisms: reducing levels of blood cholesterol

Risk factors for prostate cancer

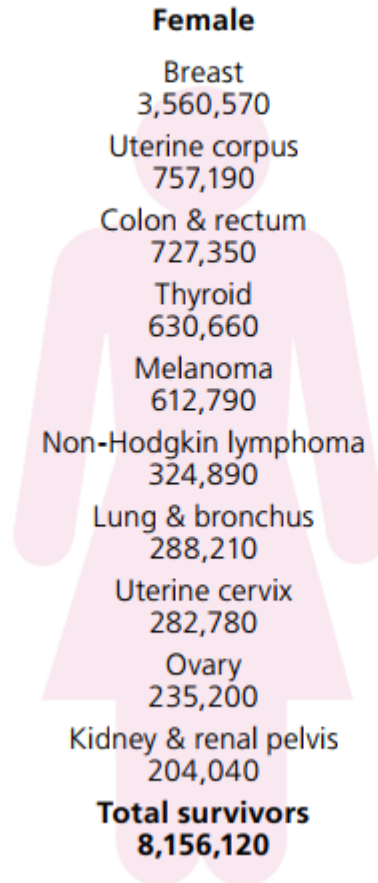
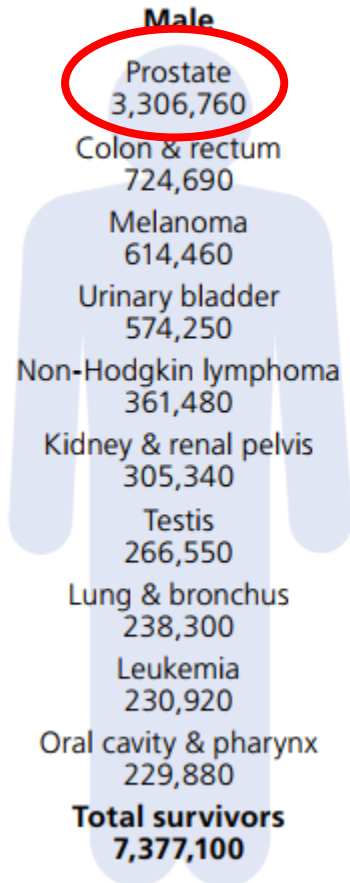


Take home message #2

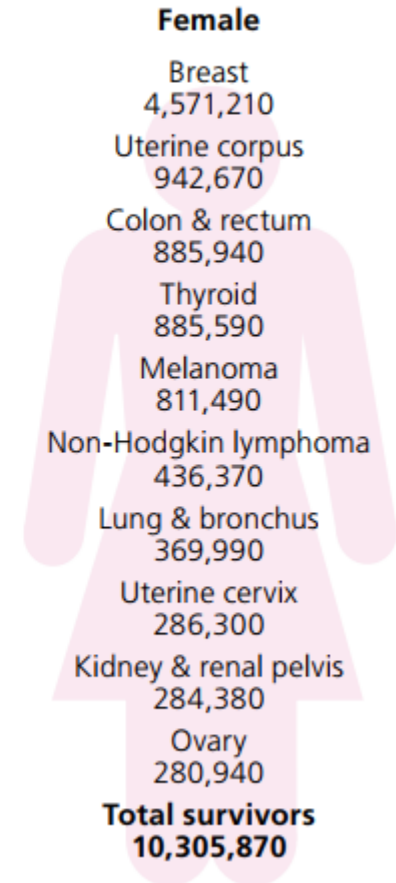
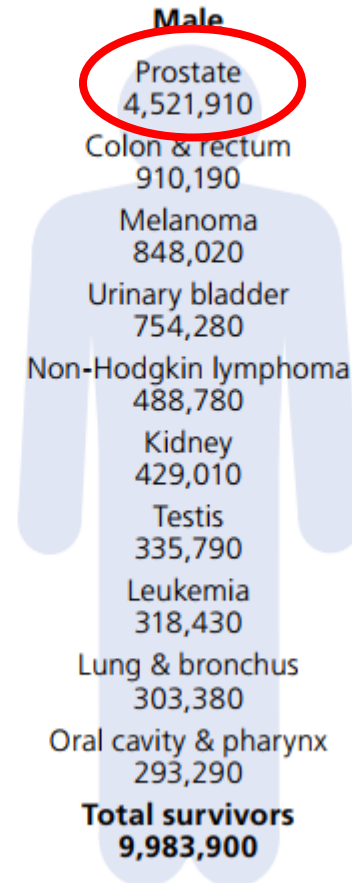
- Understanding tumor biology uncovers prostate cancer risk factors

Can we translate these findings to men with prostate cancer?

As of January 1, 2016



As of January 1, 2026



American Cancer Society

- US prostate cancer survivors to exceed 4.5 million in the next decade

Barriers to identifying dietary risk factors

1. Heterogeneity of prostate cancer



2. **Variation between individuals in response to diet**

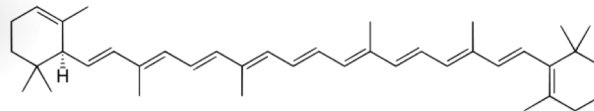
Lycopene and prostate cancer

		XRCC1 rs25487 AA/AG	XRCC1 rs25487 GG
<u>Lycopene intake</u>			
Low	(< 567 µg/d)	0	0
Medium	(~ 1448 µg/d)	-3%	-41%
High	(>1773 µg/d)	-18%	-79%
Genotype frequency		0.43	0.57

Goodman M et al., Nutrition and Cancer 2006



Good lycopene sources:
tomato (sauce, soup, ketchup), watermelon, guava



Charred meat and prostate cancer

	PTSG2 rs20417 CC/CG	PTSG2 rs20417 GG
<u>Meat carcinogen levels</u>		
Low	0	0
Medium	+40%	+30%
High	+10%	+60%
Genotype frequency	0.38	0.62

Joshi A et al., Carcinogenesis 2012



Sources of meat carcinogens:
Well done meat, meat cooked at high temps

Calcium and prostate cancer

	VDR rs11568820 AA/AG	VDR rs11568820 GG (poor calcium absorption)
<u>Calcium intake</u>		
High (>680 mg/day)	0	0
Low (≤680 mg/day)	-30%	-82%
Genotype frequency	0.40	0.60

Rowland G et al., J Bone Miner Res 2012



Sources of calcium:
Milk, cheese, yogurt, spinach, kale, collards

Take home message #3

- Understanding genetic differences between individuals identifies those who could benefit from dietary changes

Summary

- **Unmet need:** Modifiable risk factors for prostate cancer
- **Challenge:** Complex tumor biology & intra-individual genetic differences
- **Solution:** Incorporate molecular & genetic data into studies of diet and prostate cancer
- **Pay off:** Precision prevention of prostate cancer

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