Familial risk and inherited genetics in prostate cancer

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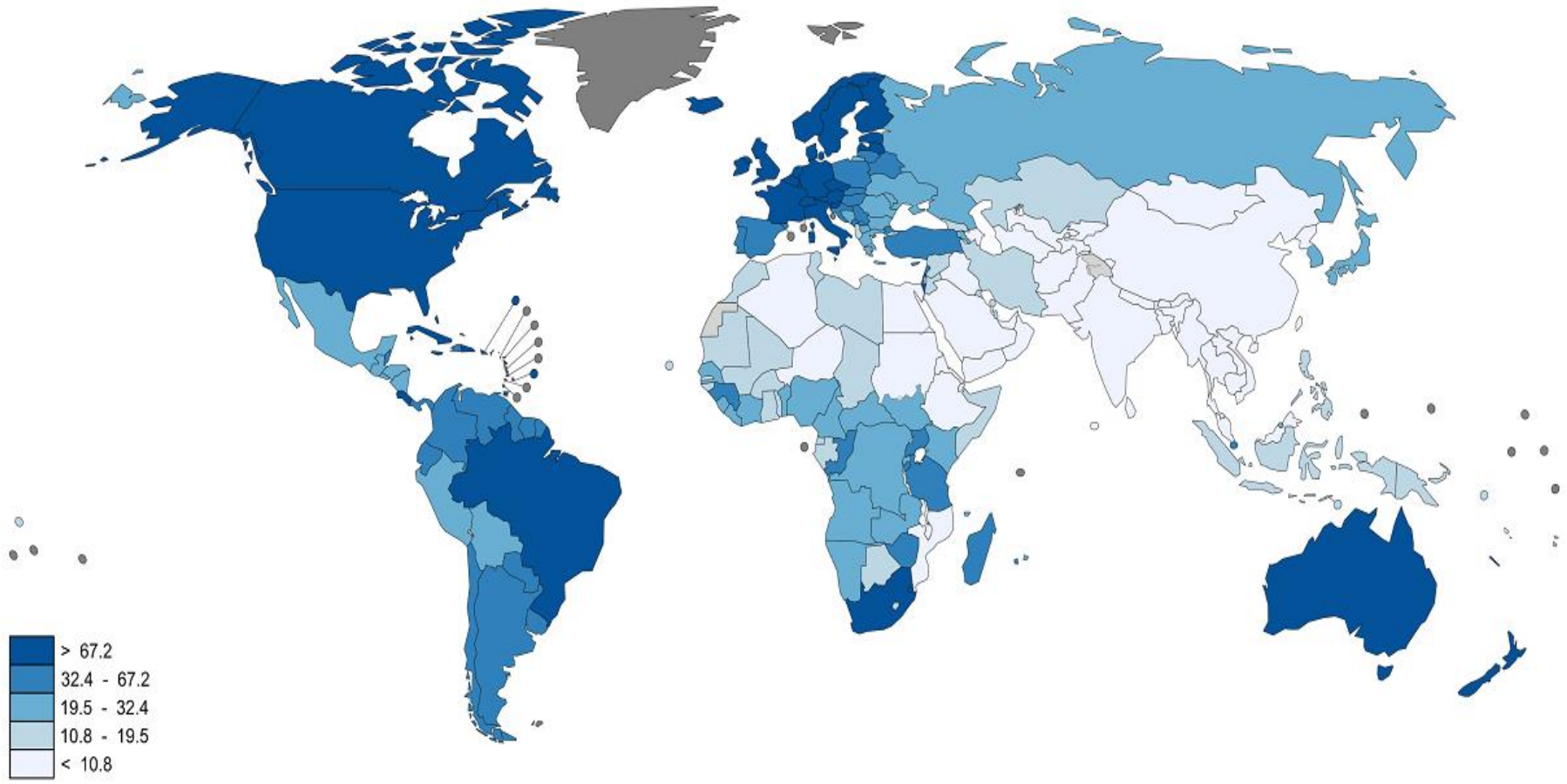
Geographic differences in prostate cancer incidence

→ 1.6 million incident prostate cancers in 2015

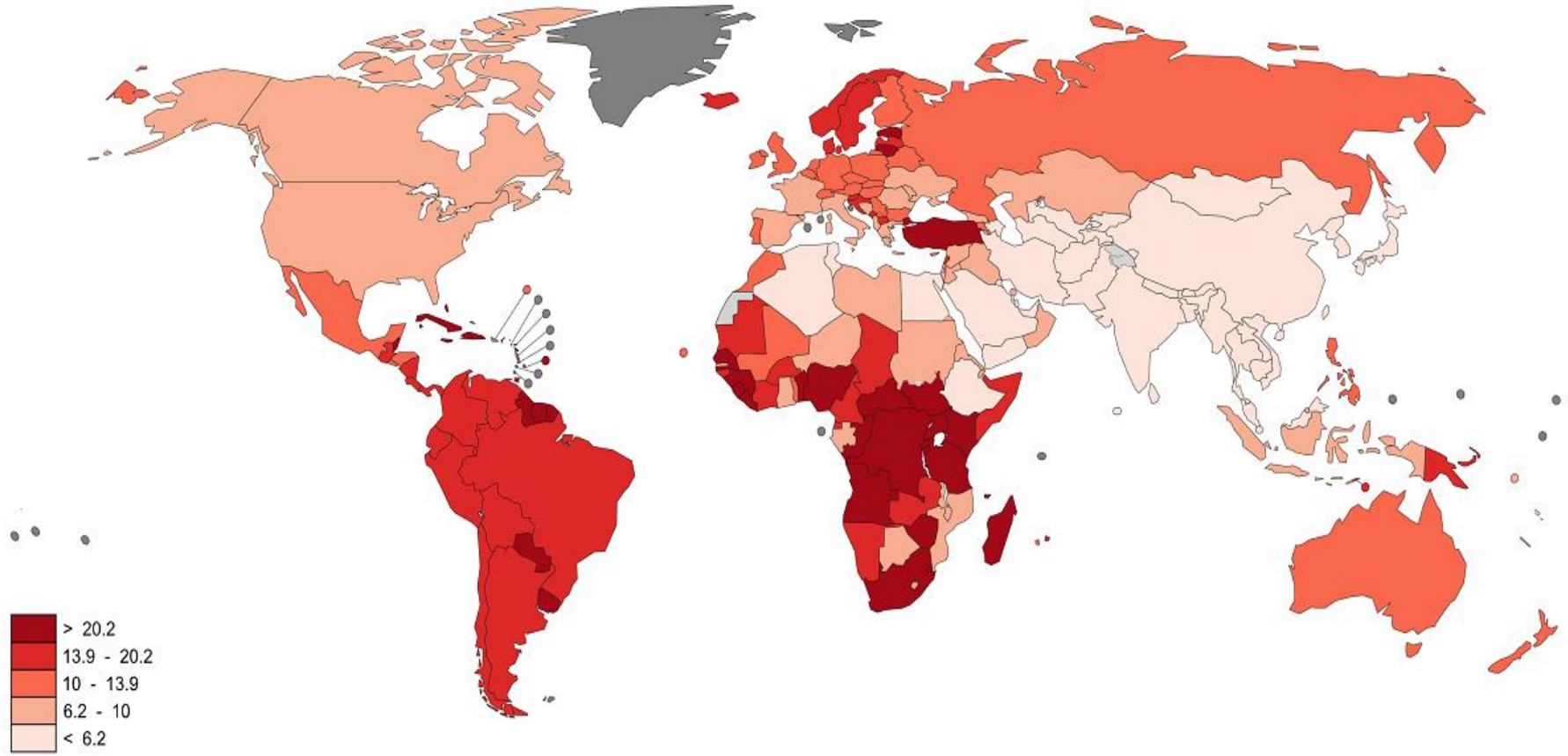
→ Leading causes of cancer incidence in 103 countries

→ 400,000 cases per year in Latin America: highest rates in French Guyana and Brazil

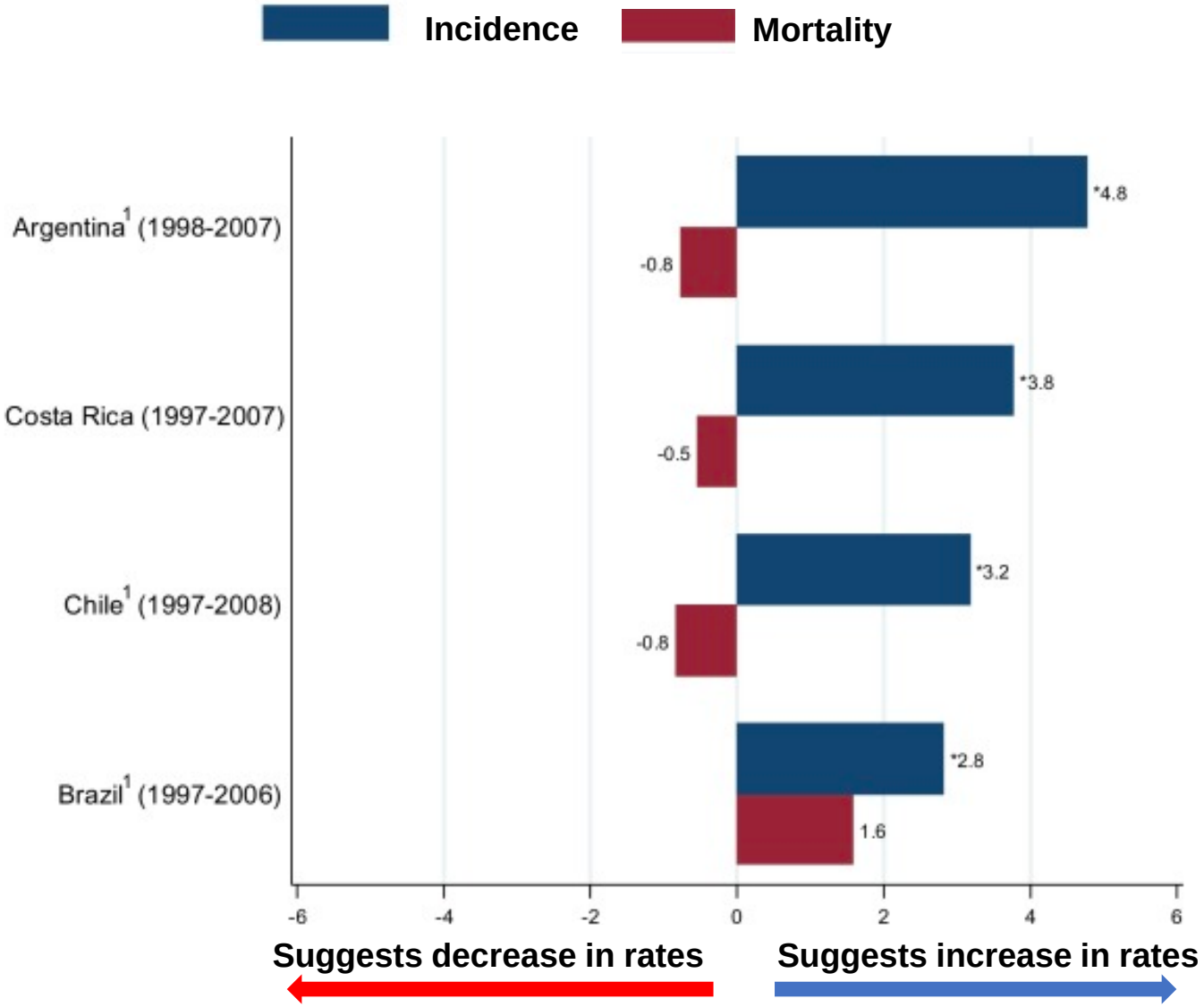


Geographic differences in prostate cancer mortality

- → 366,000 deaths from prostate cancer globally in 2015
- → Leading cause of cancer death in 29 countries (4th globally)
- → 65,000 men die of prostate cancer each year in Latin America



Trends in prostate cancer incidence and mortality over time



Risk factors for total prostate cancer

Risk factor	Direction of association	Strength of evidence
Older age	↑↑	Strong
African descent	↑↑	Strong
Family history	↑↑	Strong
Genetic risk loci	↑↑	Strong
Taller height	↑↑	Probable

Original Investigation

Familial Risk and Heritability of Cancer Among Twins in Nordic Countries

JAMA. 2016;315(1):68-76. doi:10.1001/jama.2015.17703

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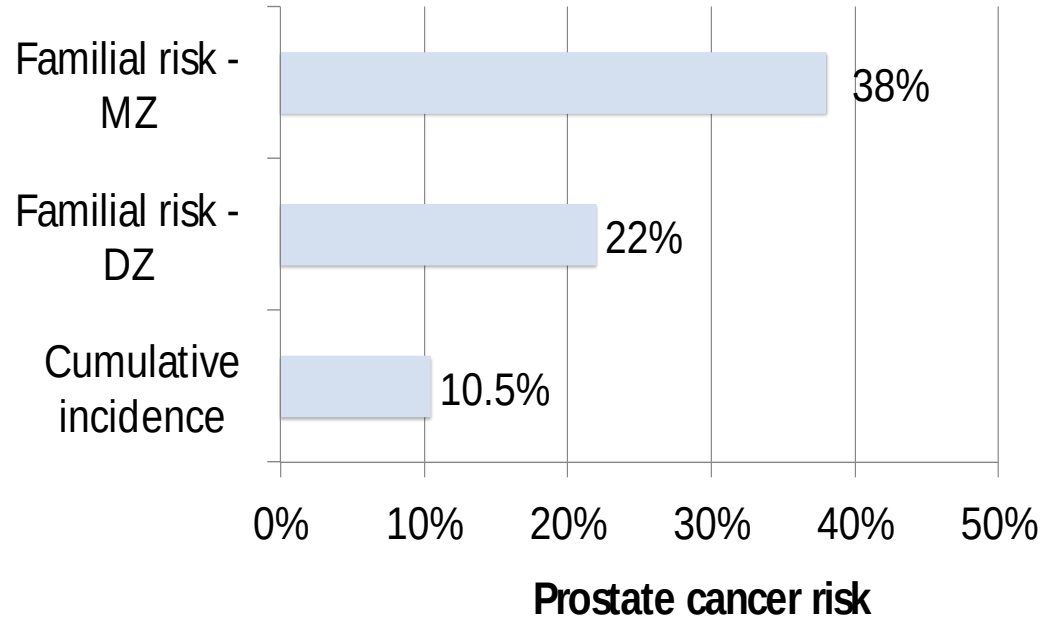
	Denmark	Finland	Norway	Sweden
Birth cohorts	1870–1999	1887–1957	1896–1979	1886–1999
N male twins	53076	12154	12318	65919
N MZ/DZ pairs	6092/11132	1792/4222	2392/3026	8438/11731
End of Follow-up	12/31/2009	12/31/2009	12/31/2008	12/31/2009
N MZ/DZ pairs uncensored at follow-up	1300/2456	388/819	231/298	1632/2843
Cancer registration since	1943	1953	1953	1958
N prostate cancer cases	821	547	356	2385

Familial risk and heritability in NorTwinCan cohort

	MZ Concordant	MZ Discordant	DZ Concordant	DZ Discordant
N twin pairs	197	807	148	1719

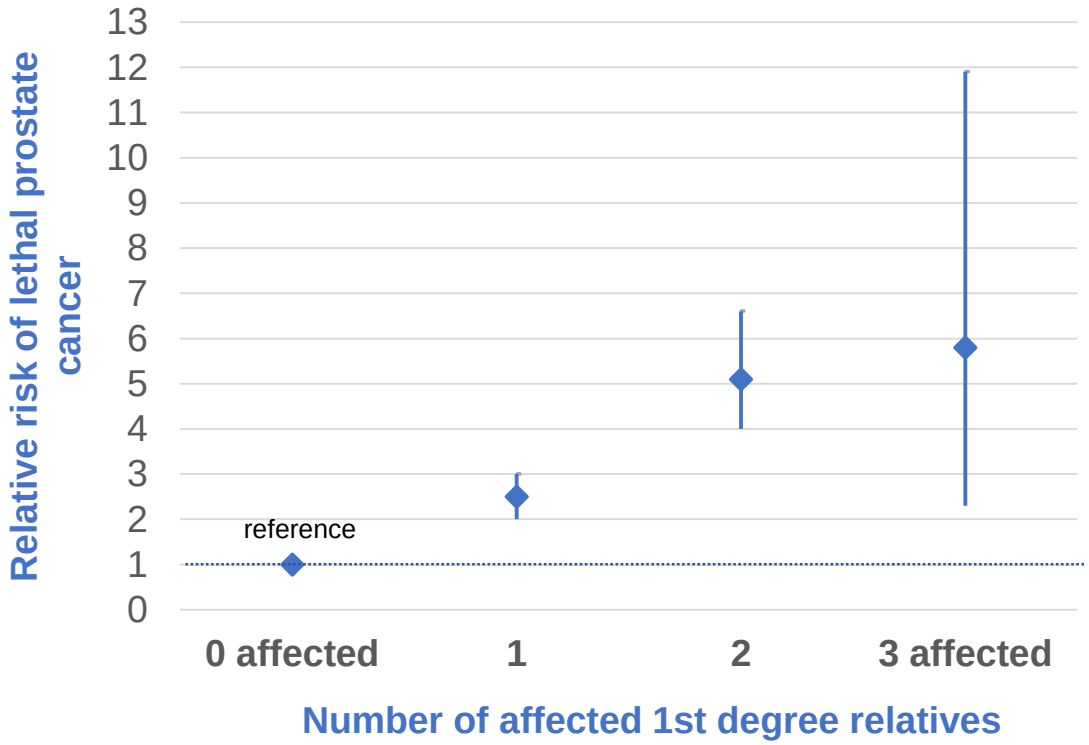
Cumulative and familial risk of prostate cancer



Heritability of prostate cancer = 58%

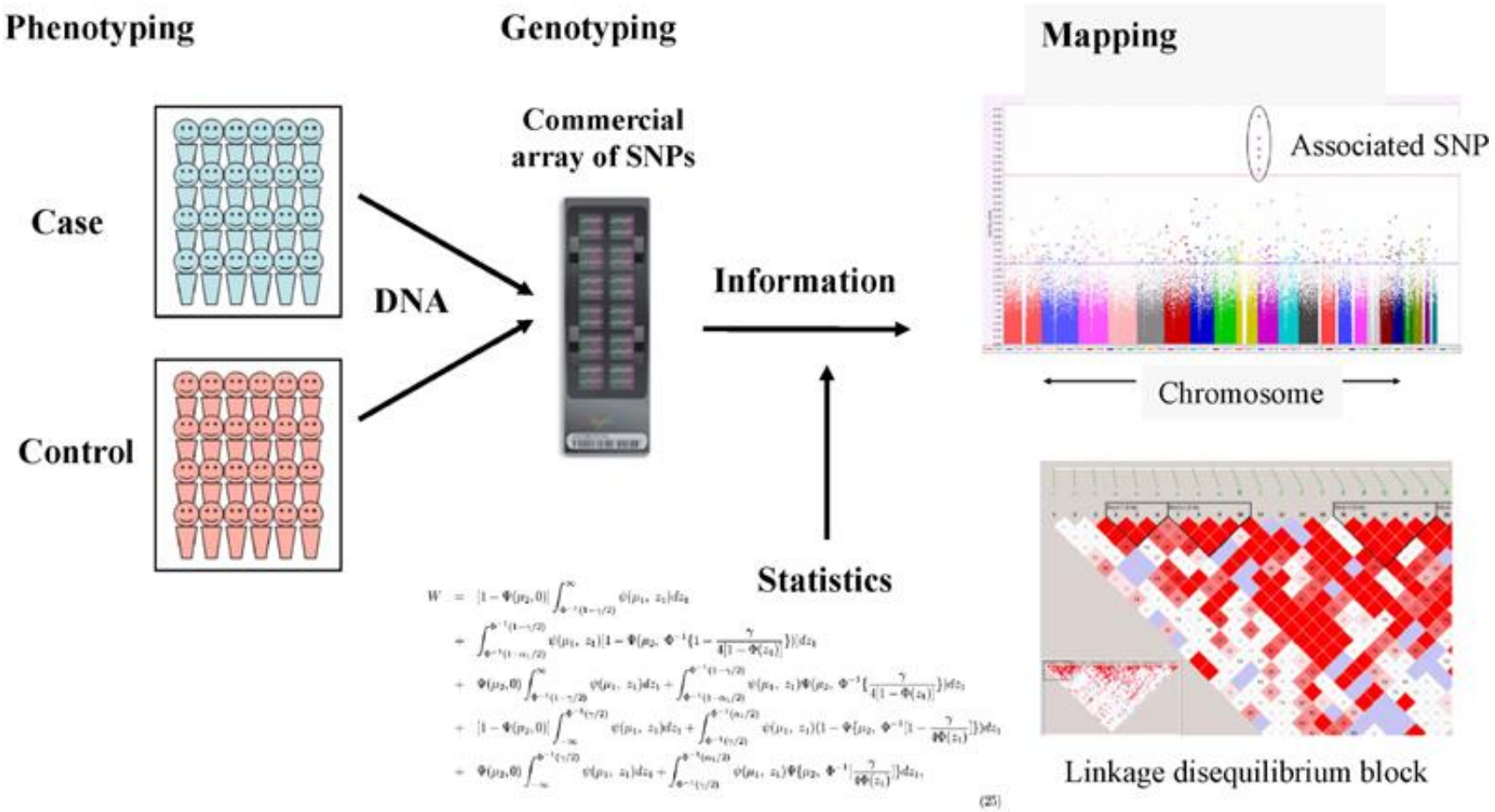
Family history and risk of lethal prostate cancer

Family history lethal prostate cancer	N	N prostate cancers	N lethal prostate cancer
Yes	196,243	8,559	2,045
No	489,060	10,833	1,999

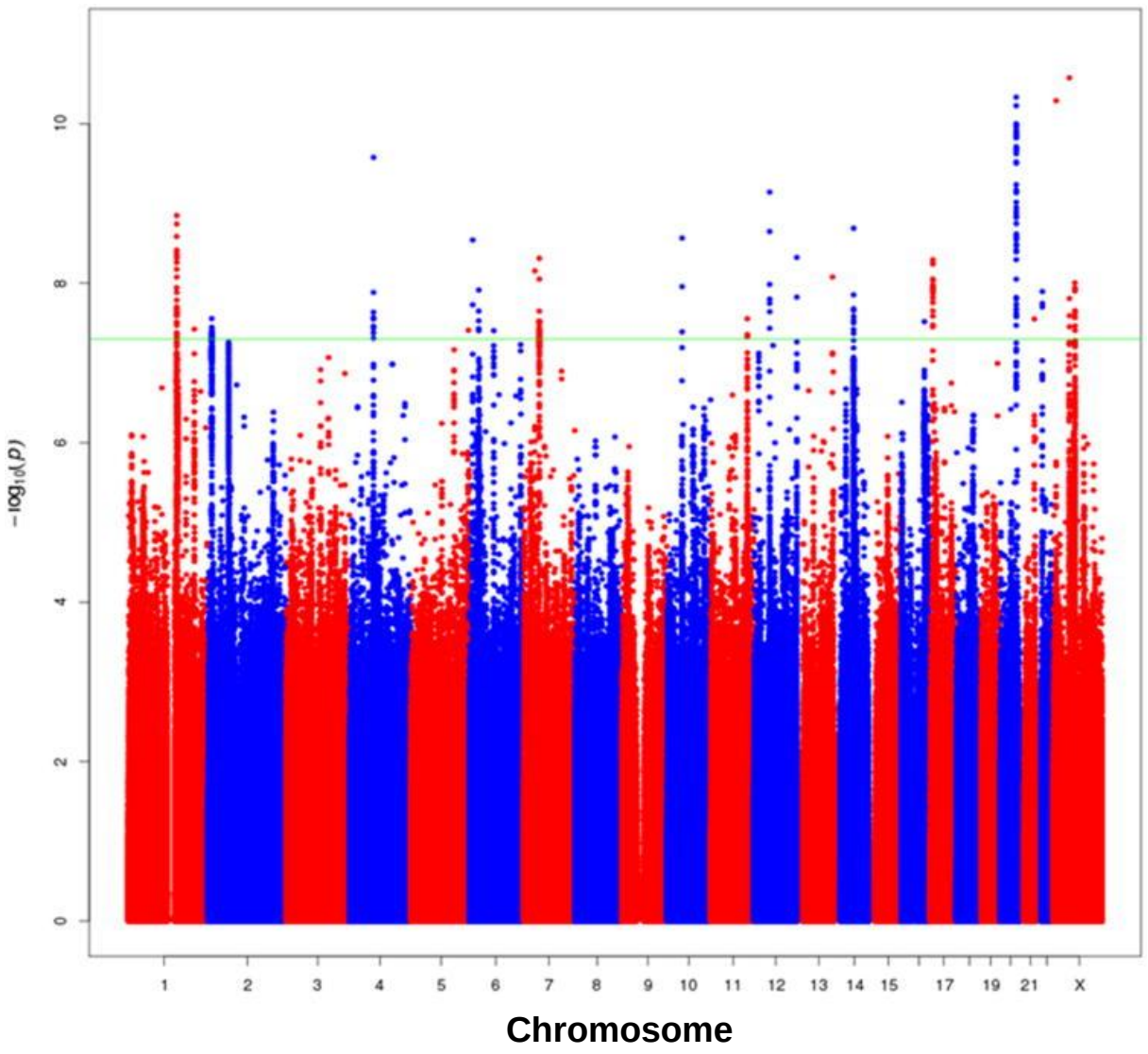


Albright et al, 2017

What is a Genome Wide Association Study (GWAS)



Common genetic risk SNPs and prostate cancer risk



>180 validated inherited prostate cancer risk Single Nucleotide Polymorphisms (SNPs)

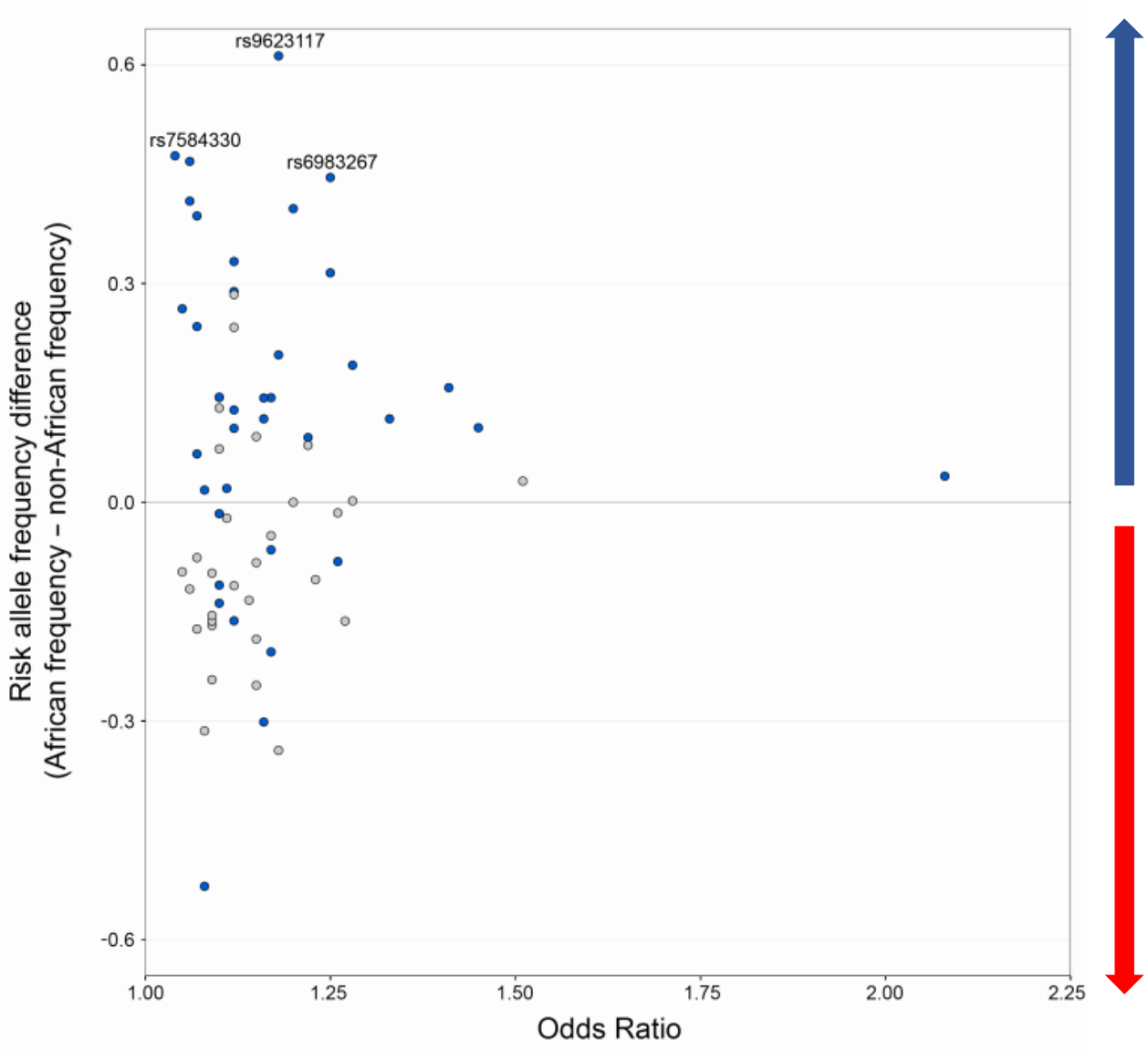
Explain one-third of heritability of prostate cancer

Unique genetic risk loci by race/ethnicity

Most SNPs equally associated with aggressive and indolent prostate cancer

Hoffman et al, Cancer Discov 2015
Al Olaama et al, Nat Genet 2014
Shui et al, Eur Urology 2014

Differences in prostate cancer SNPs by ancestry

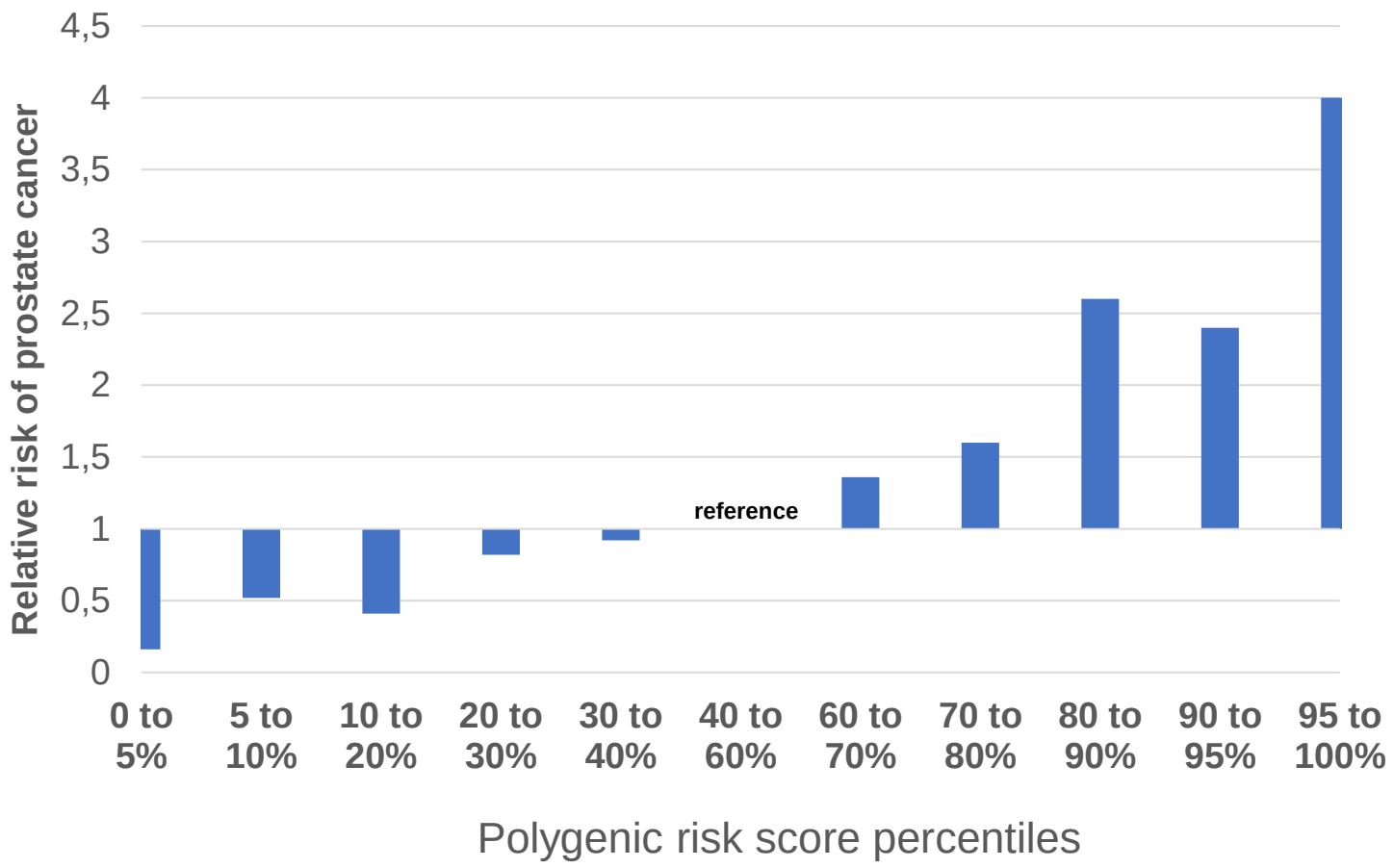


More common in African populations

Less common in African populations

For associations of SNPs and prostate cancer

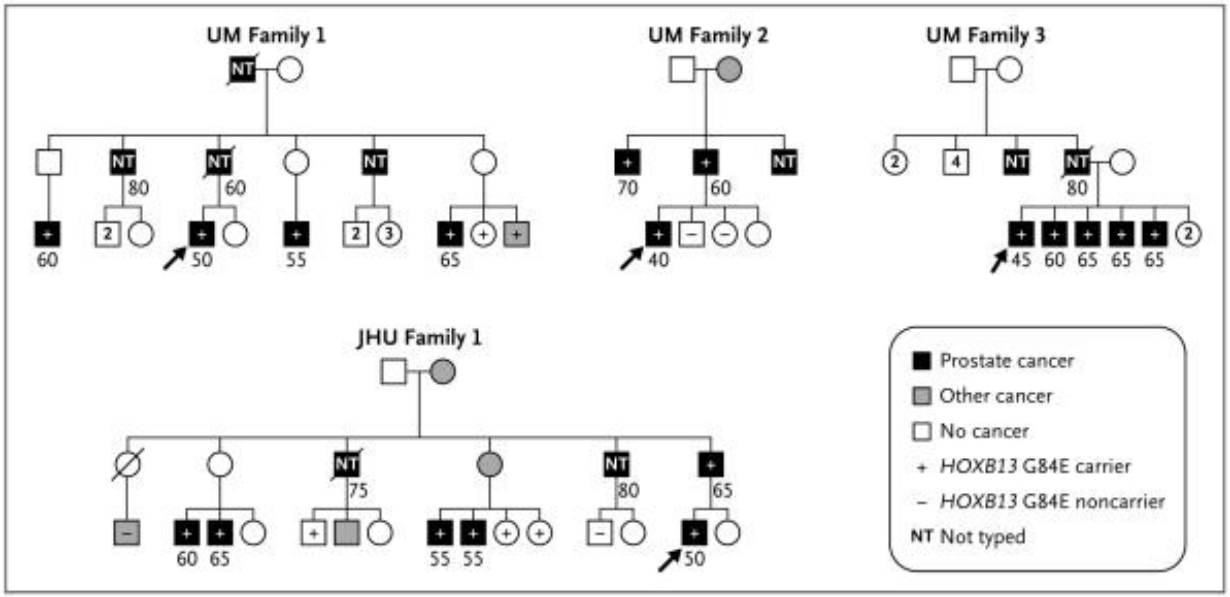
Polygenic risk score and risk of prostate cancer



Szulkin et al, Prostate 2015

Rare genetic variants and prostate cancer risk: *HOXB13*

Screened 200 genes in 17q21-22 region: identified G84E in *HOXB13*



<u>In unselected patients, prevalence of mutation</u>:

0.1% in controls

1.4% in prostate cancer cases

3.1% in early onset, familial prostate cancer

Identified other rare variants in *HOXB13*

<u>Not</u> differentially associated with high-grade or cancer mortality

Ewing et al, NEJM 2012
Kote-Jarai Z, Ann Oncol 2015

Inherited DNA repair mutations in metastatic prostate cancer

<u>Inherited</u> DNA repair alterations in 692 men with metastatic prostate cancer and compared to localized disease

Gene Mutation	% in metastatic cases	% in localized cancers	Relative risk
ATM	2%	0.25%	6.3 (3.2-11.3)
BRCA1	0.9%	0.2%	3.9 (1.4-8.5)
BRCA2	5.3%	0.3%	18.6 (13.2-25.3)
CHEK2	1.9%	0.6%	3.1 (1.5-5.6)
Any inherited mutation in DDR	12%	4.6%	

Prevalence of mutations did not differ by age or family history

Pritchard, 2016 NEJM

Consensus Panel: Role of genetic testing for inherited prostate cancer risk

Gene	Cancer Syndrome	Evidence for association with prostate cancer risk	Screening
BRCA1	Hereditary breast and ovarian cancer	A	*At age 45*
BRCA2	Hereditary breast and ovarian cancer	A	At age 45
DNA Mismatch Repair Genes	Lynch syndrome	B	
HOXB13	Hereditary prostate cancer	A	
TP53	Li Fraumeni Syndrome	D	
ATM		C	
CHEK2		C	

*Grade of evidence for PCA is summarized as follows: (A) High-grade evidence: At least one prospectively designed study or three or more large validation studies or three or more descriptive studies; (B) Moderate-grade evidence: two cohort or case-control studies; (C) Emerging data: increasing data in support of association to PCA, but not yet moderate-grade evidence; (D) Low/insufficient: limited data or not studied in the context of PCA.

Giri, 2018 JCO

Consensus Panel: Role of genetic testing for inherited prostate cancer risk

Strong consensus of the Panel:

- To refer for genetic counseling men with early-onset cancer in patient or 1st degree relative with cancer mortality
- To test *HOXB13* for suspected hereditary prostate cancer
- To test *BRCA1/2* for suspected hereditary breast and ovarian cancer
- To factor *BRCA2* into early-stage management discussion, with stronger consensus in high-risk/advanced and metastatic setting.

Moderate consensus of the Panel:

- To test all men with metastatic CRPC, regardless of family history, with stronger agreement to test *BRCA1/2*
- To test *ATM* to inform prognosis and targeted therapy.

Giri, 2018 JCO

Summary

- Prostate cancer is a major cause of morbidity and mortality globally
- Inherited genetic factors underlie a substantial proportion of variability in prostate cancer incidence
  - Common SNPs explain one-third of heritability
  - Rare SNPs explain a small proportion of risk
  - “Missing heritability”
- Genetic variation may explain part of the ethnic disparity in prostate cancer
- Family history may useful in guiding screening recommendations for cancer risk and mortality
- Emerging role of DNA repair mutations in lethal prostate cancer
- Need for consensus around guidelines for genetic testing in prostate cancer