NON-MODIFIABLE RISK FACTORS

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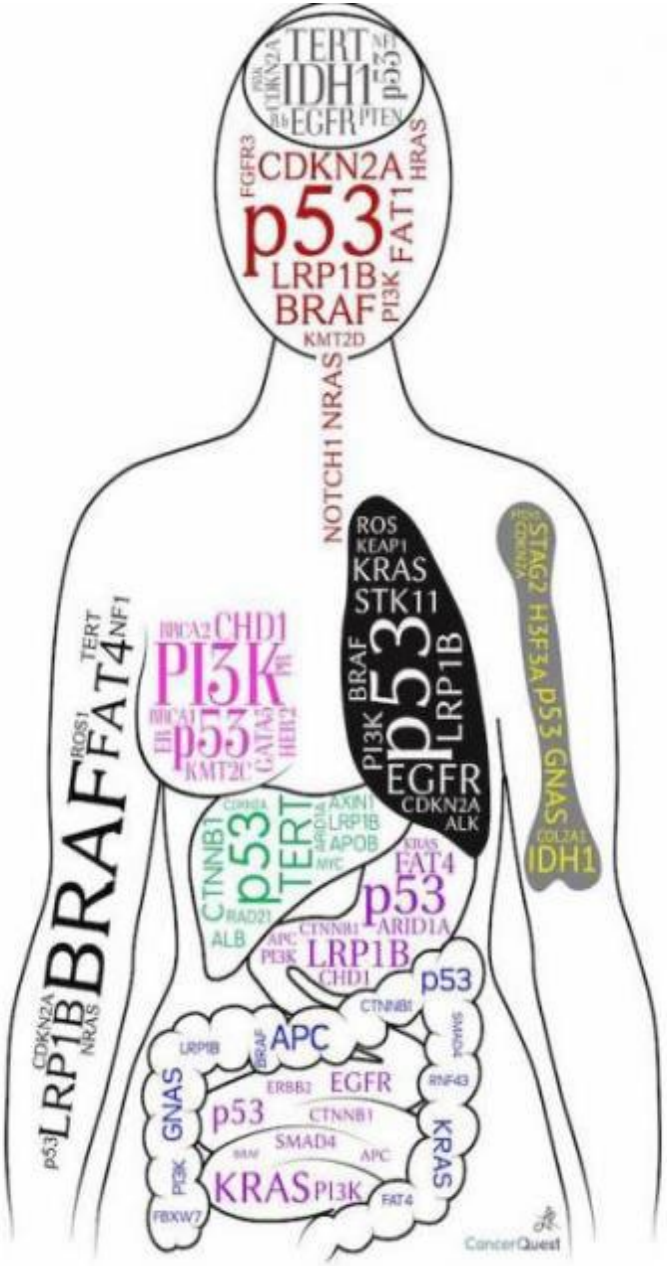
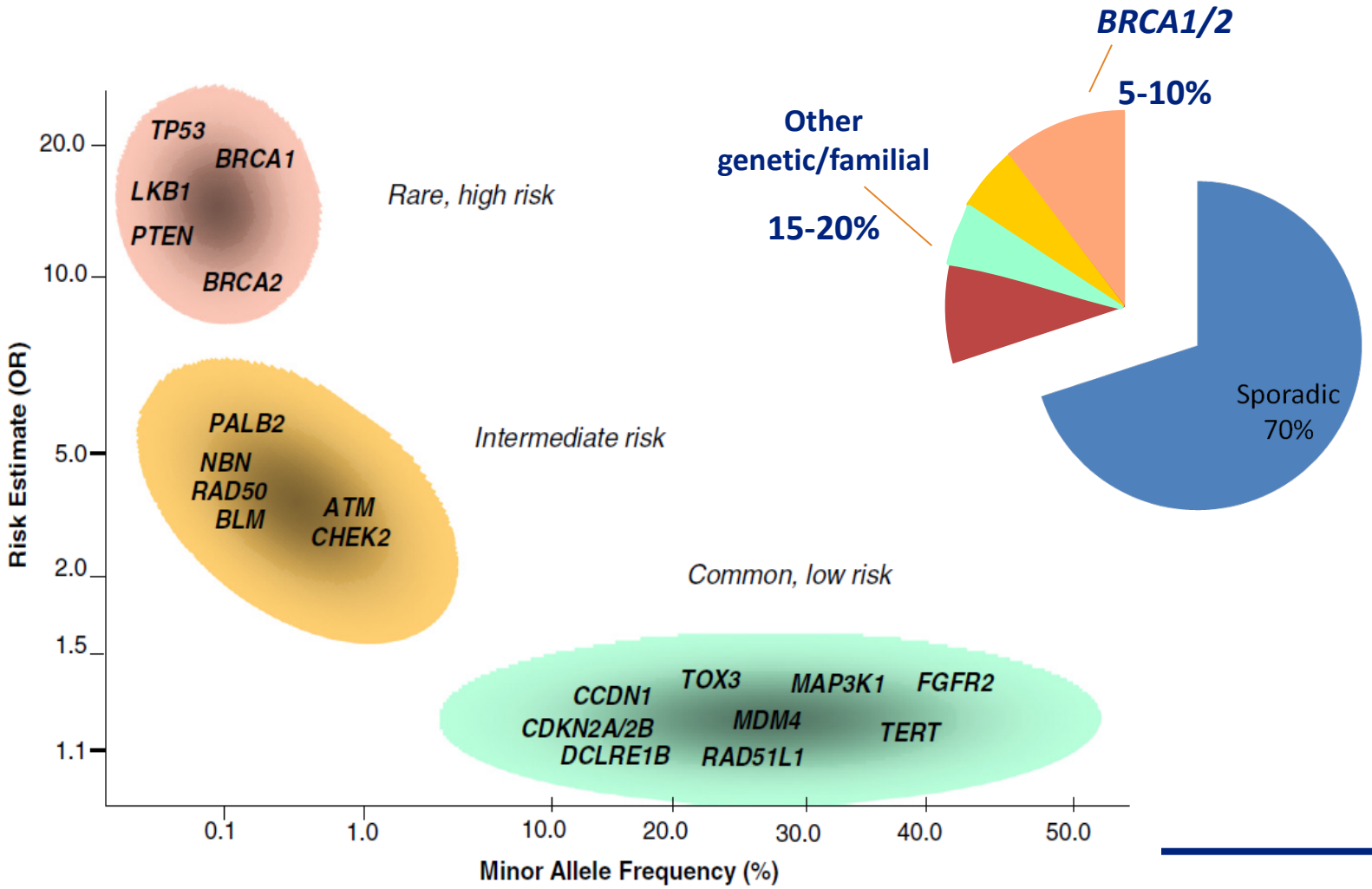
Cancer Genes

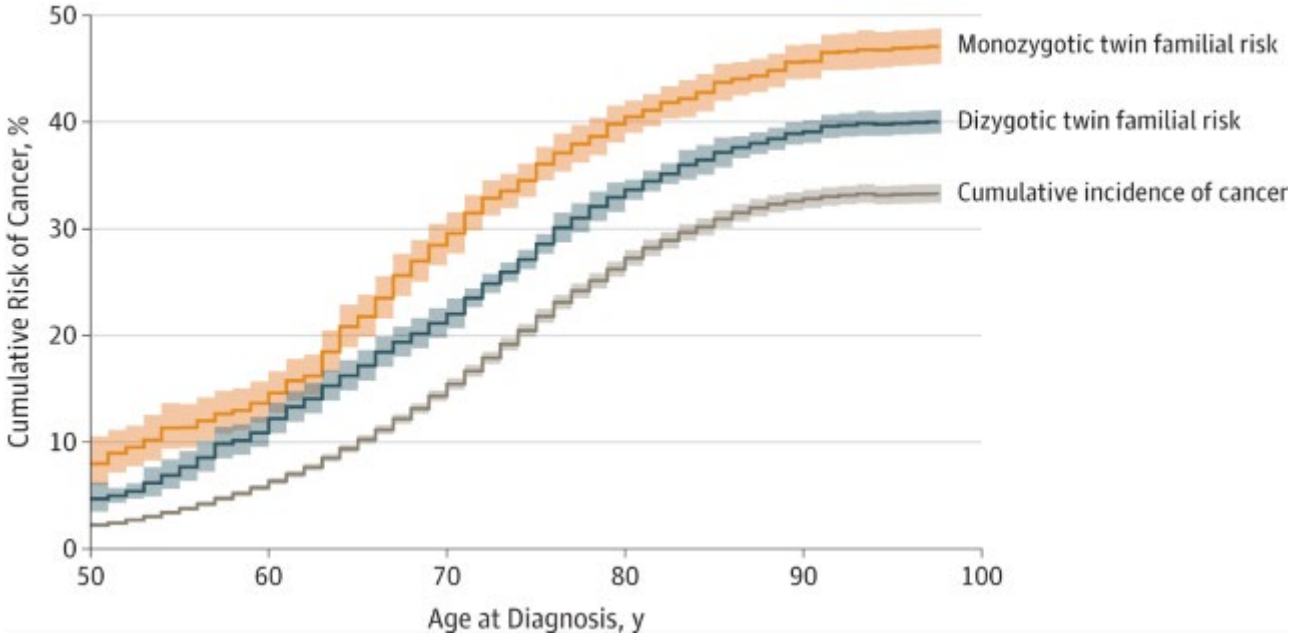


The Case of Breast Cancer: Penetrance vs Prevalence – the false dichotomy between GXE



Bogdanova N et al. Hereditary Cancer in Clinical Practice, 2013

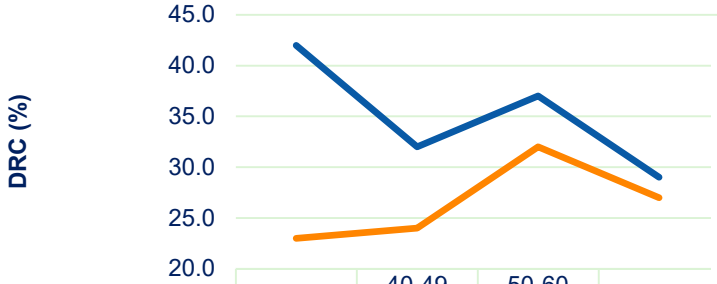
More than just the germline genetics



	Familial Risk, % (95% CI)	
	Monozygotic Twins	**Dizygotic Twins**
Overall cancer	45.9 (44.1-47.7)	37.1 (35.7-38.4)
Breast cancer	28.1 (23.9-32.8)	19.9 (17.0-23.2)

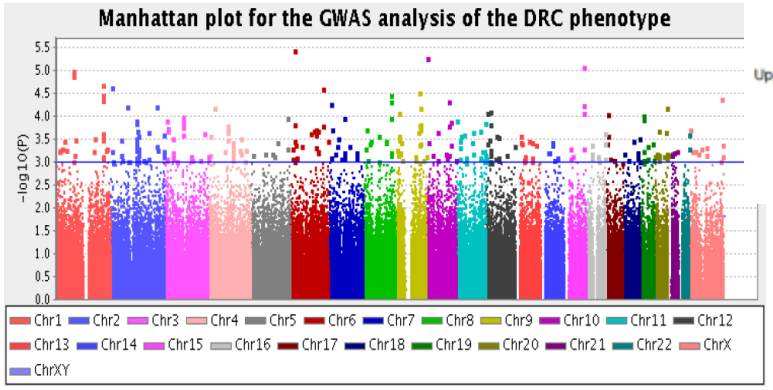
Mucci LA et al. JAMA, 2016

DNA Repair Phenotype Capacity and Cancer Risk

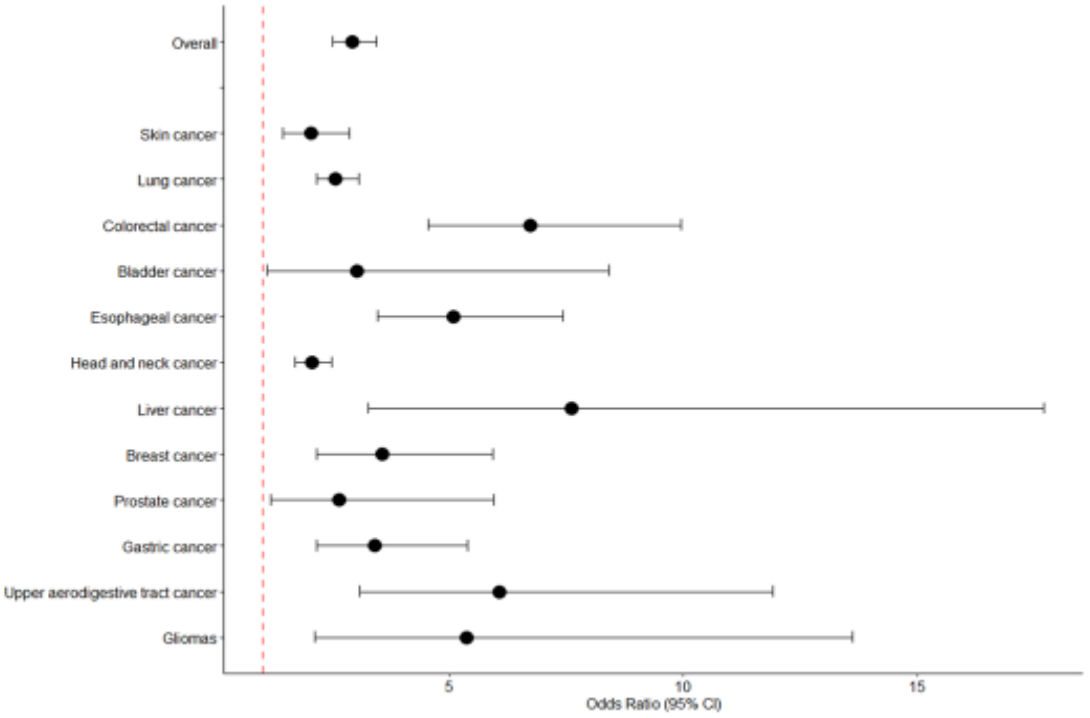


	<40 yrs	40-49 yrs	50-60 yrs	>60 yrs
Case DRC	23.0	24.0	32.0	27.0
Controls DRC	42.0	32.0	37.0	29.0

Genotype ≠ Phenotype



Wang et al, Cancer Res 2013



DNA repair phenotype and cancer risk: a systematic review and meta-analysis of 55 case-control studies

Wu HC et al Scientific Report 2022 Mar 1;12(1):3405. ***PMID:*** *35233009*

Machella N, et al, Carcinogenesis, 2008
Kennedy DO, et al, J Natl Cancer Inst, 2005
Wu et al, CCC 2013

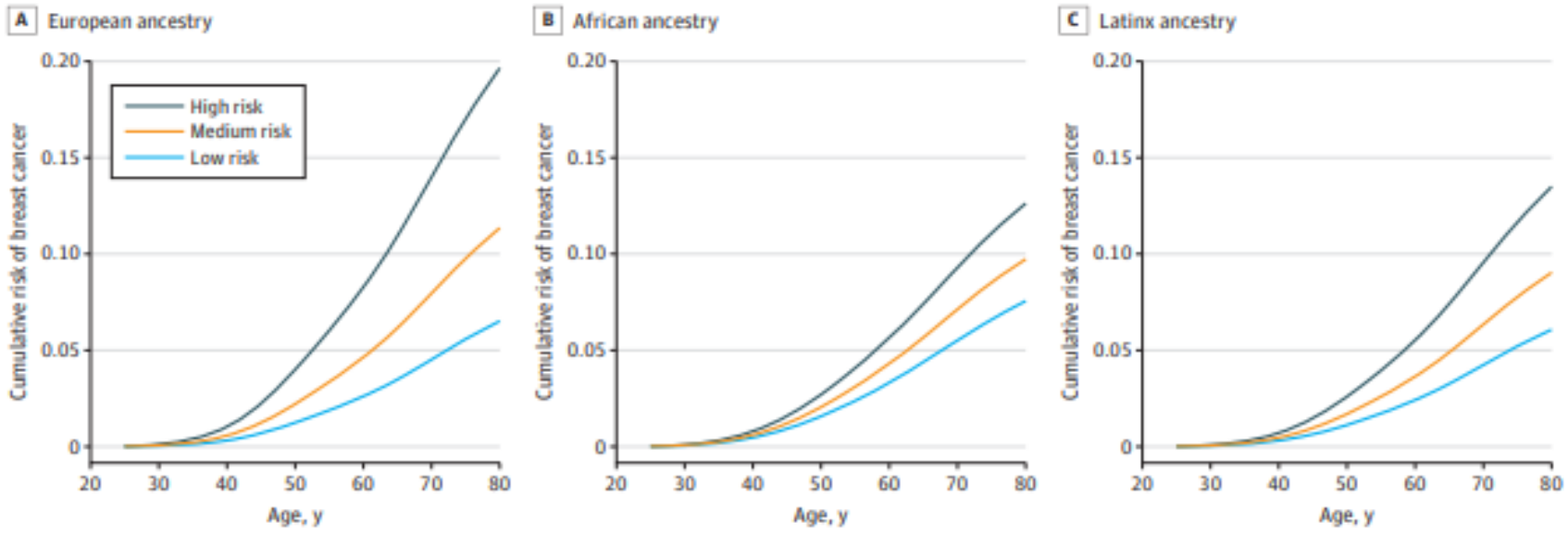
Promise of Genomics and Phenotypic Assays for Cancer Risk Reduction

1) *Risk stratification (for primary and secondary cancers) and screening*

2) *Etiology*

Polygenic Risk Score for Cancer Risk Prediction

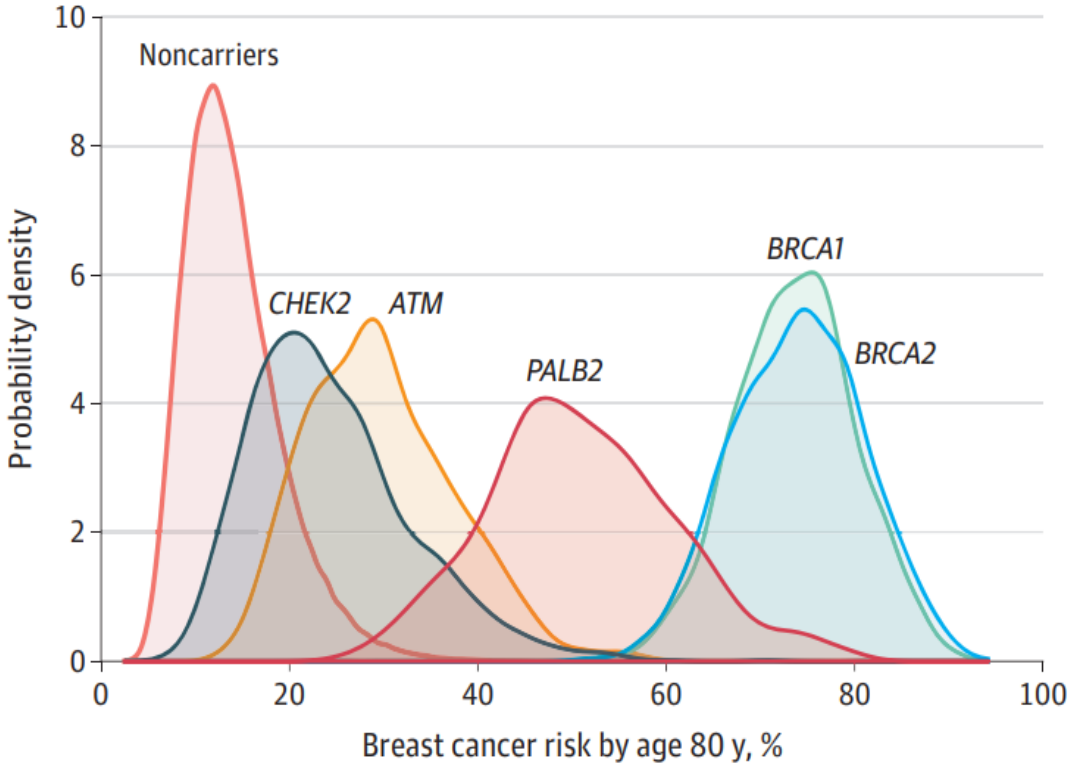
Figure 3. Cumulative Risk of Breast Cancer From Birth Estimated Using UKBB Polygenic Risk Score Model in Women With European, African, and Latinx Ancestry



JAMA Network Open. 2021;4(8):e2119084. doi:10.1001/jamanetworkopen.2021.19084

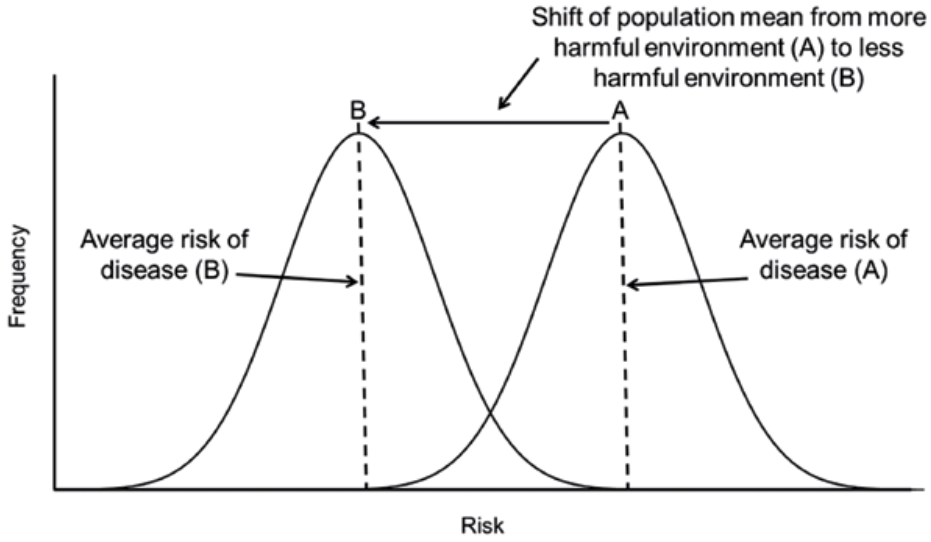
Polygenic Risk Score for Risk Stratification

Figure. Modification of Lifetime Breast Cancer Risk for Pathogenic Variant Carriers and Noncarriers by an 86-Single-Nucleotide Variant Score



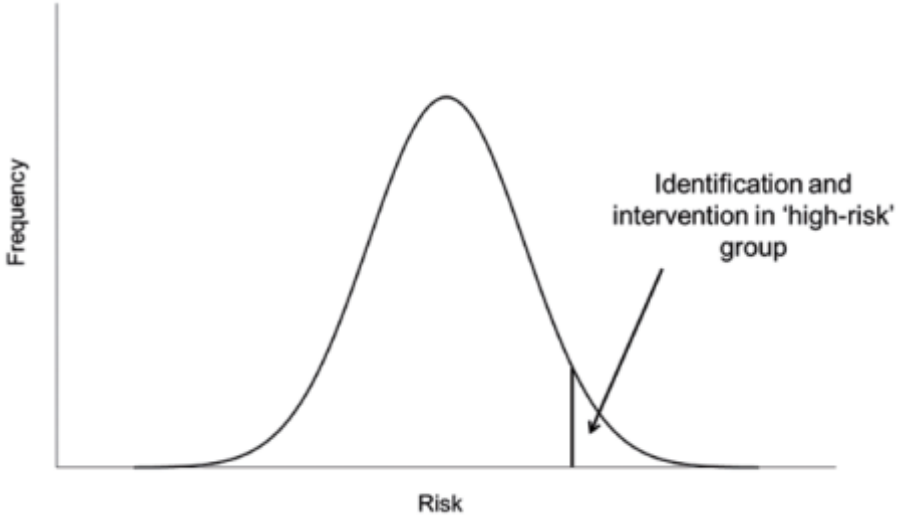
Gallagher S, Hughes E, Wagner S, et al. Association of a Polygenic Risk Score With Breast Cancer Among Women Carriers of High- and Moderate-Risk Breast Cancer Genes. JAMA Netw Open. 2020;3(7):e208501. doi:10.1001/jamanetworkopen.2020.8501
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2767768

Population-wide approaches for prevention



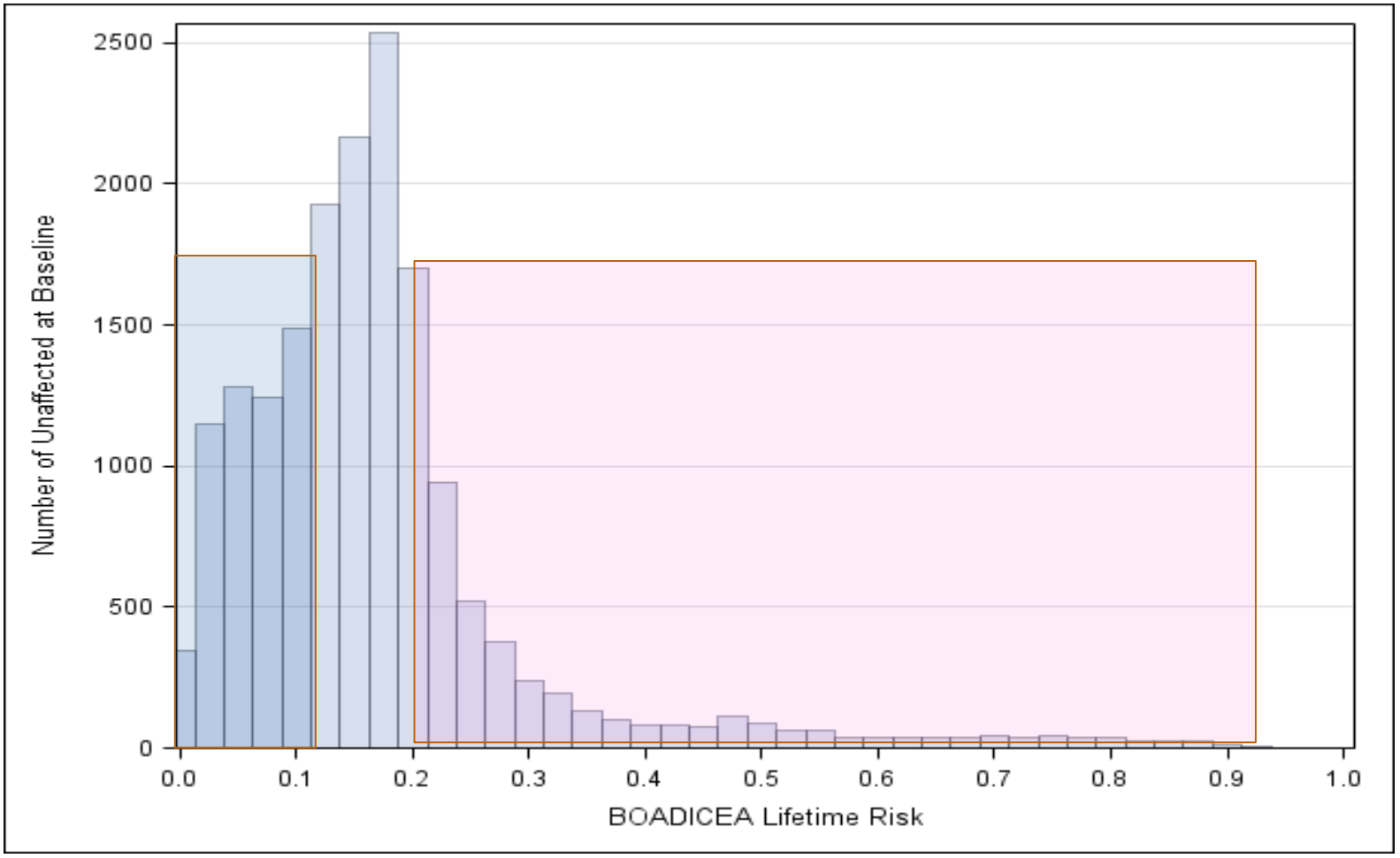
Population-based

Vs. Non-population based approaches for discovery



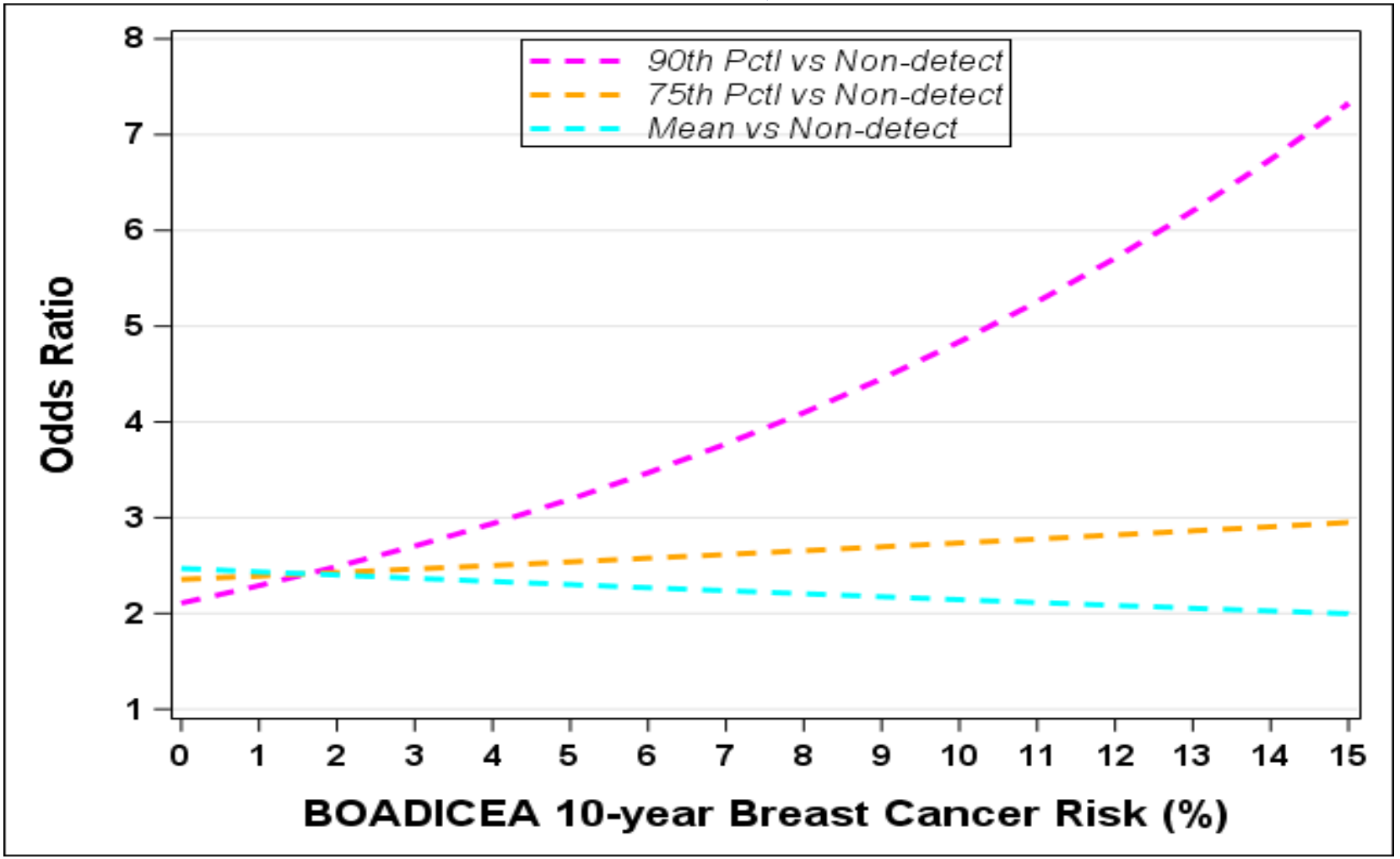
High-risk

Potential of Enriched Cohorts for Etiology



Prospective Family Study Cohort (PROF-SC)

Example of GXE: Increase in breast cancer risk from PAH by absolute risk of breast cancer, New York site of BCFR



Shen J et al., British Journal of Cancer 2017

Summary

1) Cancer genes are critical even for those individuals without a family history

2) Cancer genes essential for risk stratification

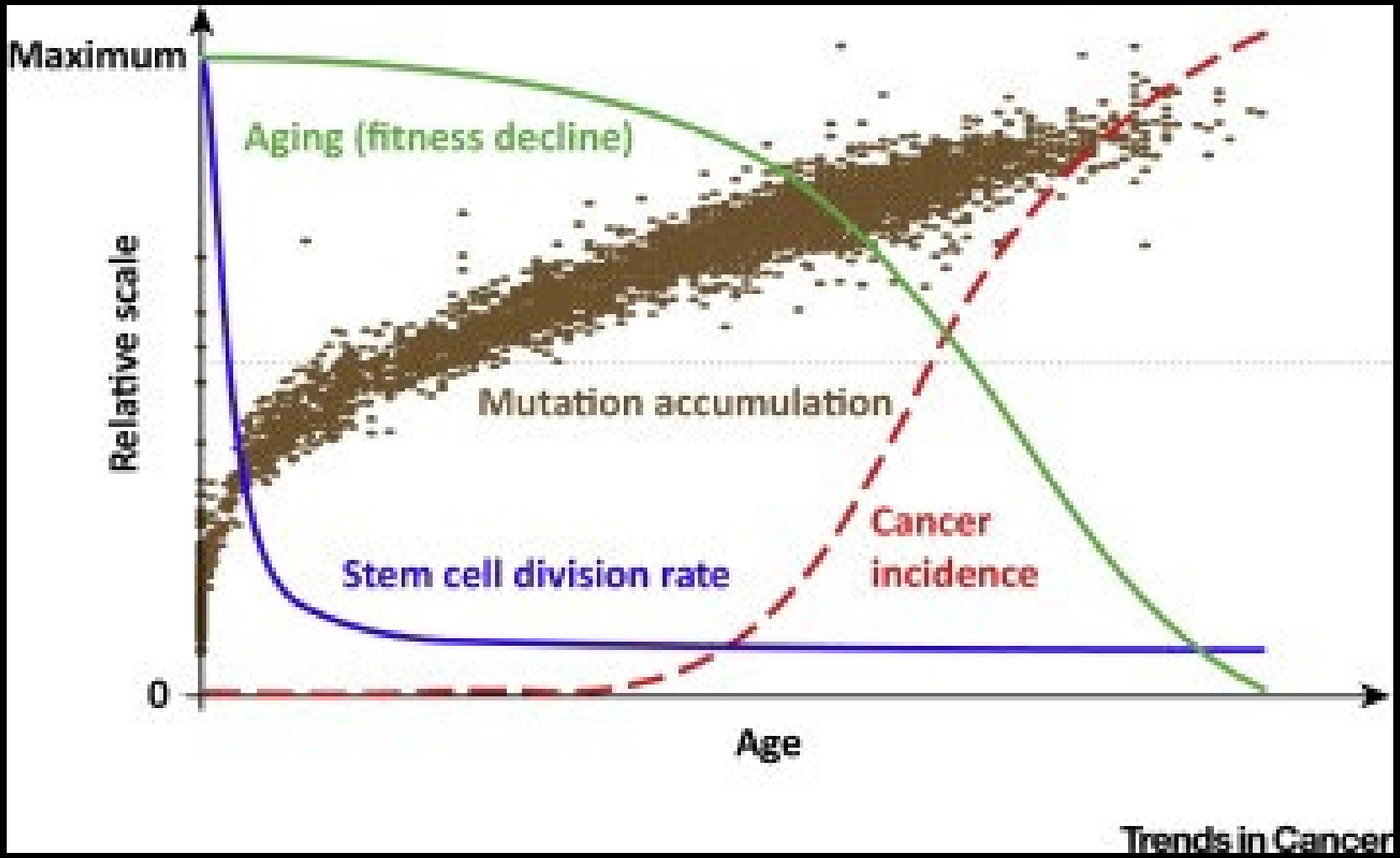
3) Characterizing risk based on underlying susceptibility can also be very helpful for identifying cancer risk factors for common exposures

AND as cancer genes can be altered across life

CANCER RISK REDUCTION NEEDS TO BEGIN EARLIER

Roughly half of all mutations and epigenetic changes occur before full body maturation

Figure 1



The Evolution of Lifespan and Age-Dependent Cancer Risk *Andrii I. Rozhok, James DeGregori* *Trends in Cancer* Volume 2, Issue 10, Pages 552-560 (October 2016) DOI: 10.1016/j.trecan.2016.09.004