Overview of Gene-Environment Interactions in Breast Cancer

Mia M. Gaudet, Ph.D.
Scientific Director, Epidemiology Research

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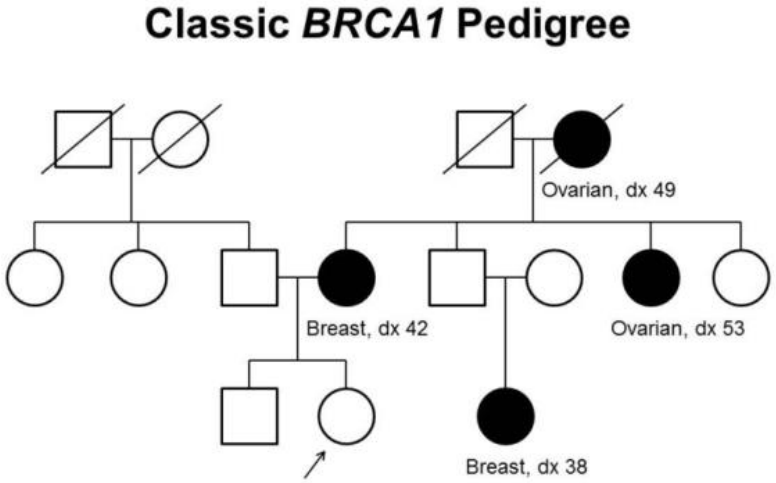
Genetic variation plays an important role in breast cancer etiology



Familial aggregation of cancer observations

Comparison of monozygotic & dizygotic twins

- 31% of breast cancer variability in the population due to interindividual
- 20% lifetime probability of breast cancer if dizygotic twin diagnosed

Family history as a risk factor for most cancers

- Any first-degree family members with breast cancer: RR=2
- Relative risk increases with number of family members, number with early onset disease
- Yet, only 5-10% of cases have a family history

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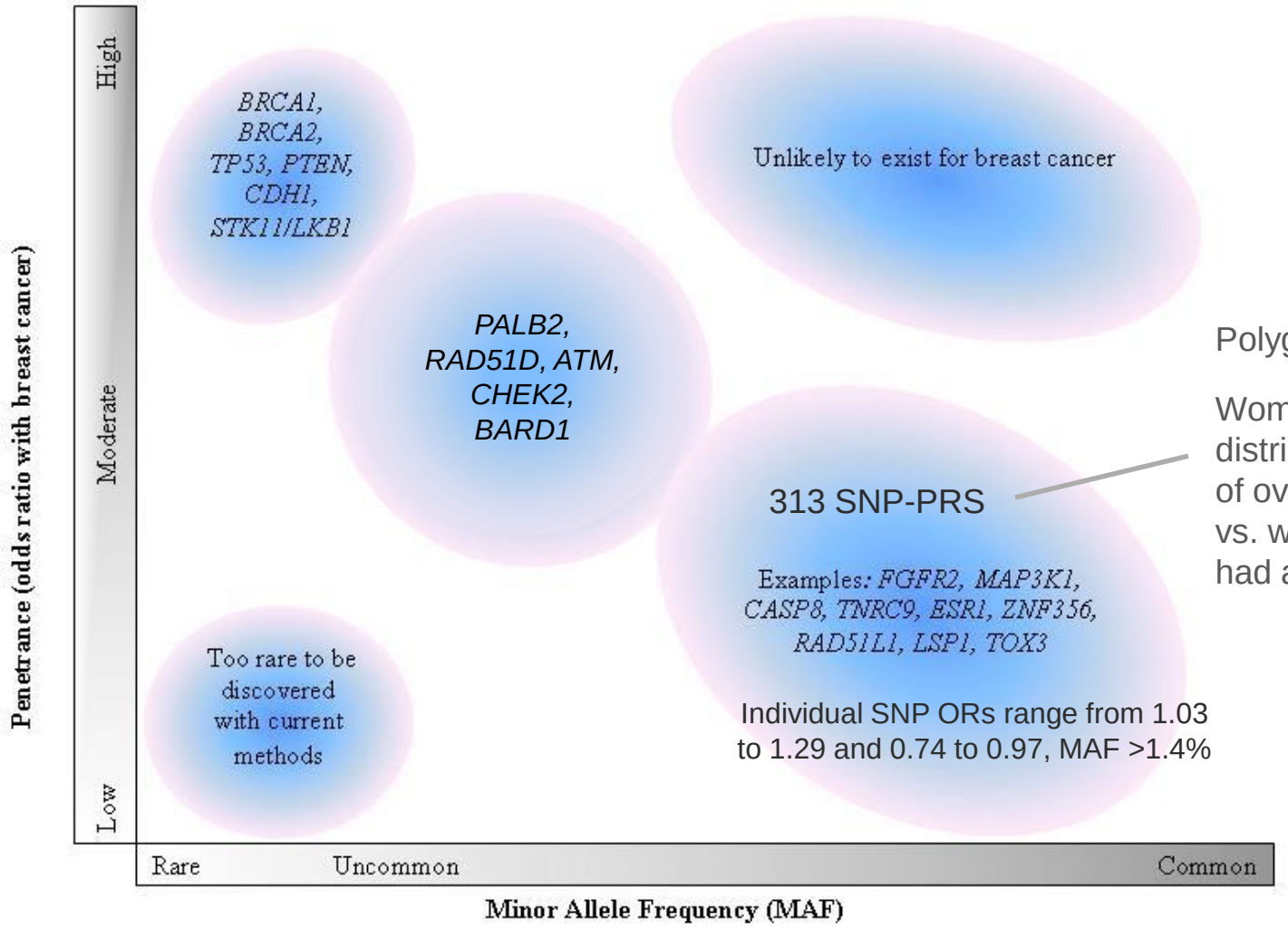
Broca, Traite des tumeurs, 1866; Moller, CEBP2016; Mucci, JAMA 2016; Beral, Lancet, 2001

Rare, high penetrant mutations thru more common, less penetrant variants associated with breast cancer risk



Individual SNP ORs range from 1.03 to 1.29 and 0.74 to 0.97, MAF >1.4%

Polygenetic risk score (PRS):

Women at the top centile of the distribution have a 33% lifetime risk of overall breast cancer by age 80 vs. women in the lowest centile who had a 2% lifetime risk

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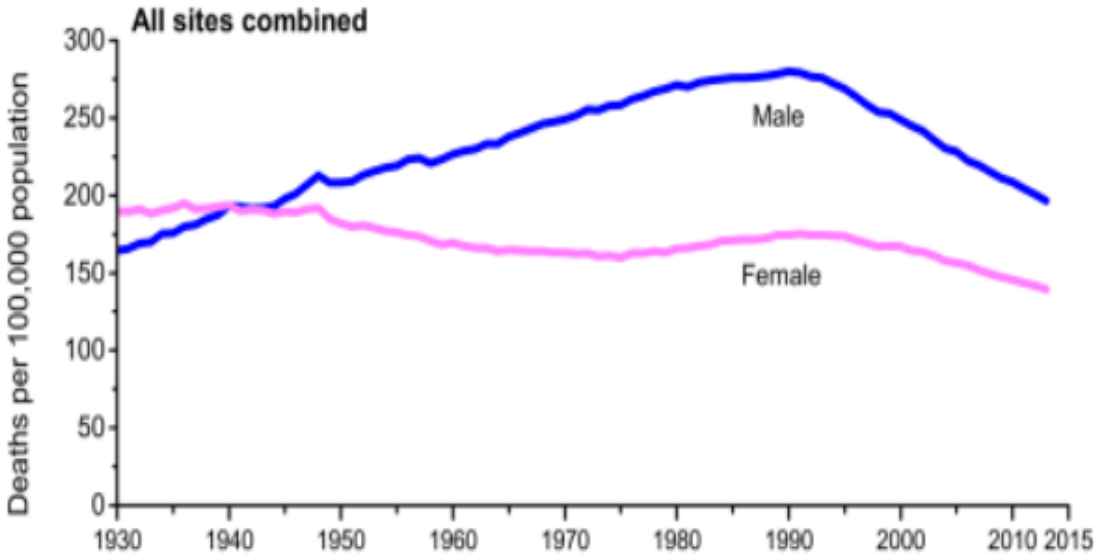
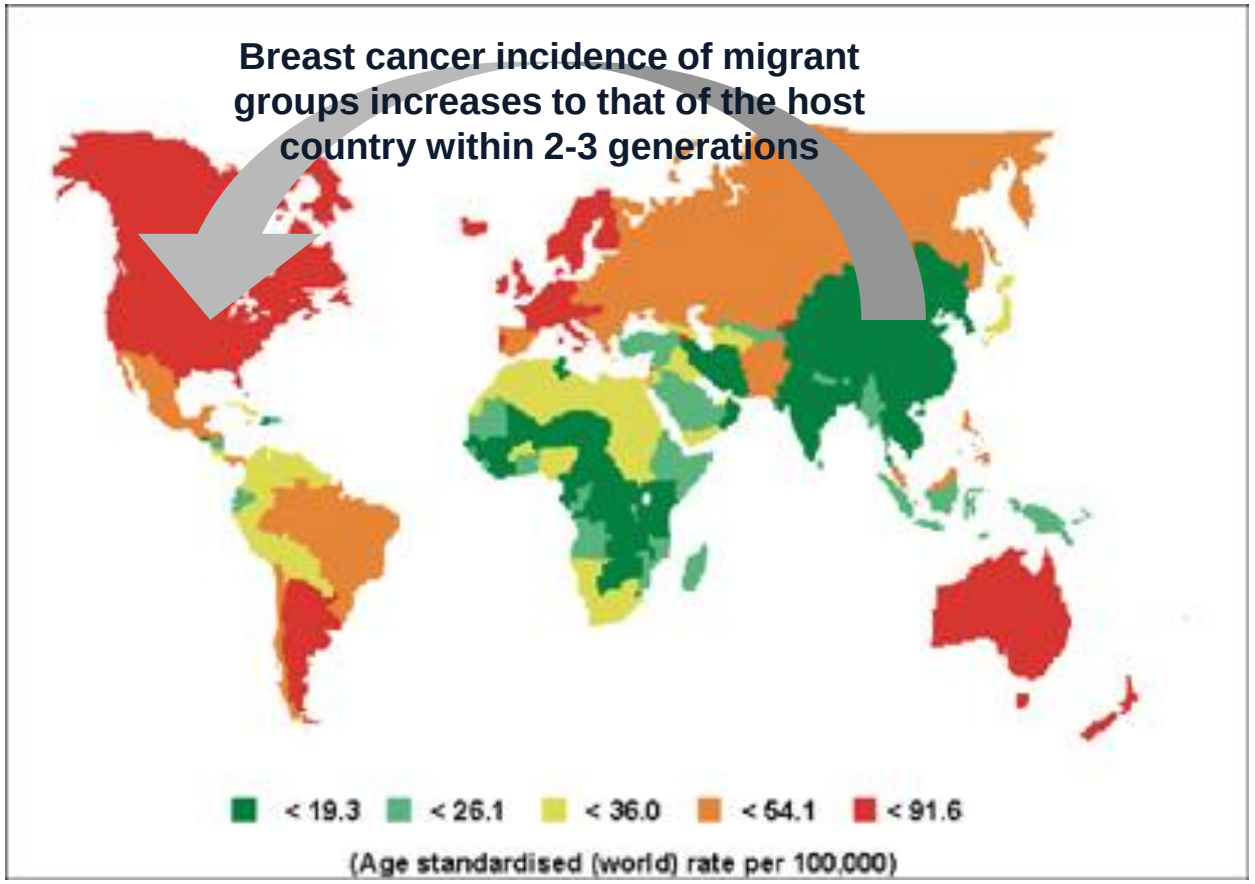
Adapted from Manolio, *Nature,* 2009; Michaildou, Nature 2017; Robson, NEJM 2007; Garber 2005; Updated based on Easton, 1995; Ford, 1998; Hopper, 1999; Antoniou, 2003, 2005b, 2008a,b; Chen, 2006; Begg, 2008; Milne, 2008; Brohet, 2014; Gabai-Kapara, 2014; ; Couch, JAMA Oncology, 2017; Mavaddat, Am J Hum Genet, 2019

Variation of breast cancer incidence over time, country, and migrants demonstrate role of environment





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"Siegel R. Ca Cancer J Clin, 2018; Doll and Peto, JNCI, 1981

Common risk factors for sporadic breast cancer

	Risk Factor	Magnitude of Risk
Biological Factors	High breast tissue density	↑↑↑
	Early menarche (<12 years)	↑
	Late menopause (>55 years)	↑
	No full-term pregnancies	↑
	Tall height (5’9” or taller)	↑
	Never breastfed a child	↑
Modifiable, Lifestyle/ Environmental Factors	Obesity (postmenopausal women)	↑
	Current or long-term use of postmenopausal hormones	↑
	Alcohol consumption	↑
	Cigarette smoking	↑
	Physical inactivity	↑

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Breast cancer differs by ER status

Feature	ER+	ER-
Proportion of cases	2/3	1/3
Diagnosed stage	Early	Late
Age distribution	Older	Younger
Higher relative risk by race	Caucasian	African-American
Treatment Responsiveness	Selective estrogen receptor modulator	Chemotherapy
5-year prognosis	Good	Poor
Risk factors	Nulliparity, delayed childbirth, postmenopausal obesity	Parity, low veggie intake

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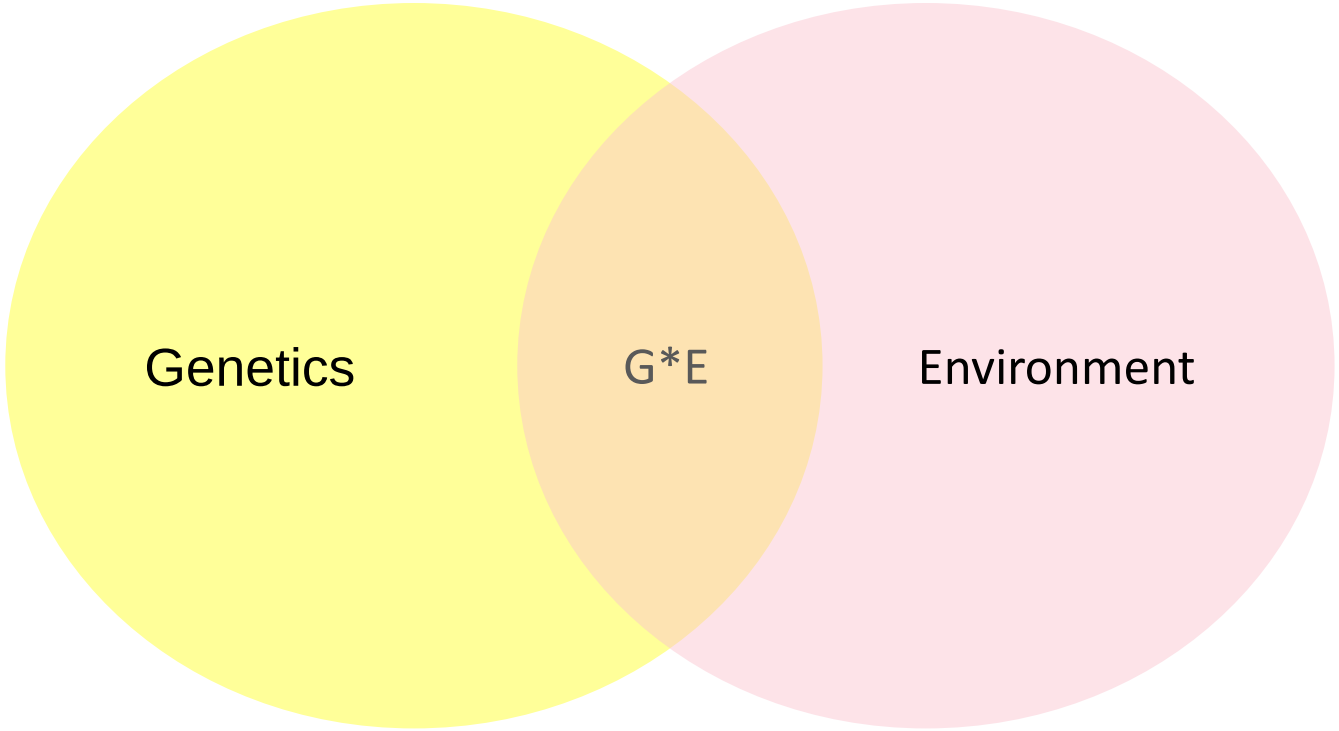
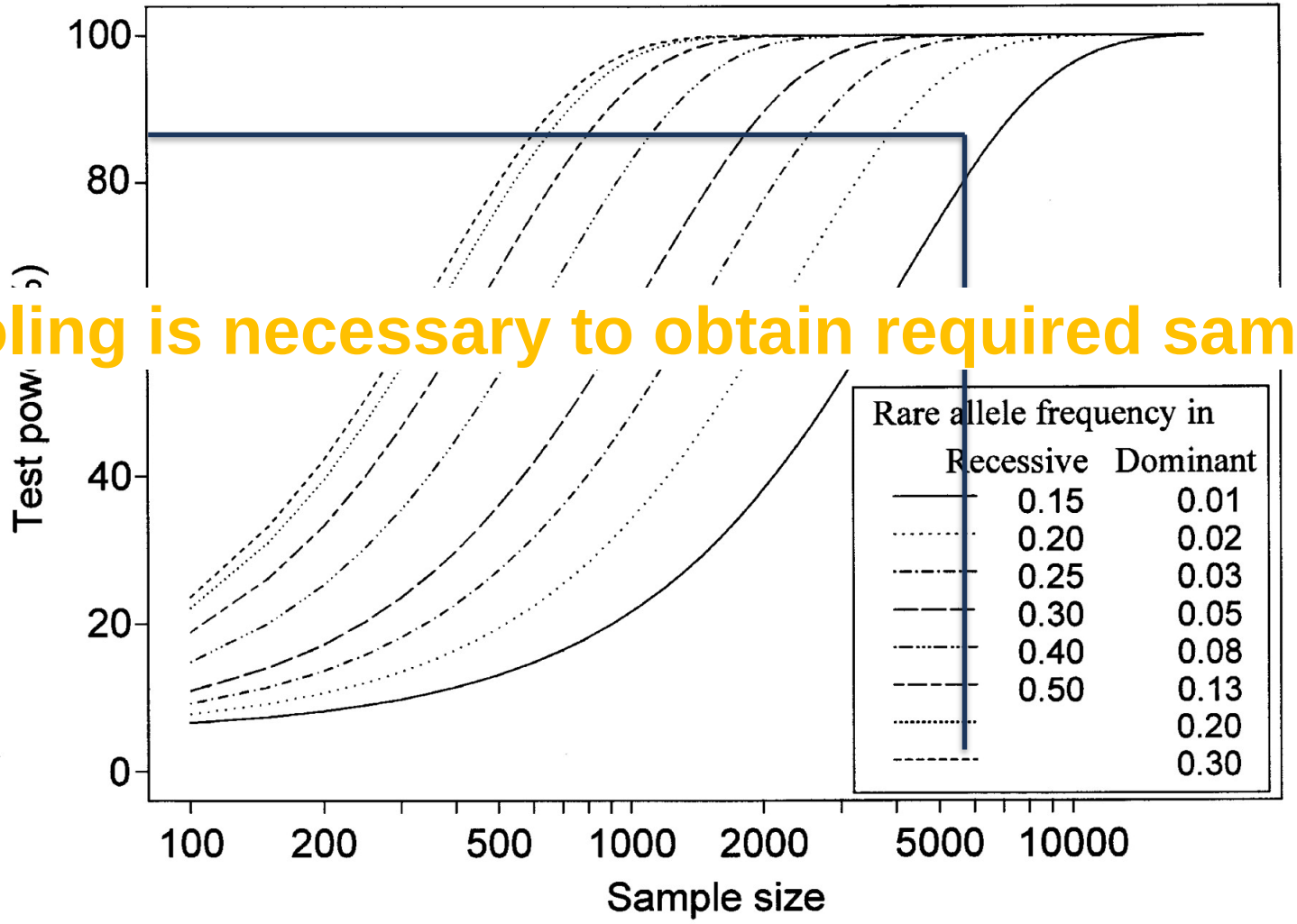
Anderson, CEBP, 2006; Waks, JAMA; Gaudet, Cancer Res 2018

Role of gene-environment (G*E) interactions in breast cancer is unclear



G*E results provide insight into biological mechanisms underlying breast cancer, allow distinction of women at high risk from women at lower risk, and improve the accuracy of risk prediction models.

G*E analyses have high sample size requirements, assuming α=0.05



Pooling is necessary to obtain required sample size!

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Pooling trade-off: quantity vs. specificity and quality

Case-control studies vs. cohort studies

- Concerns about recall bias, timing of exposure relative to disease

Exposures harmonized to lowest common denominator

- e.g., HRT ever/ never use vs. timing and duration

Harmonization across different types of questions

- e.g., definition of unexposed

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Functional variants*E reveal few interactions, but may inform experimental studies

Study population: 26,968 cases and 31,605 controls from 21 studies in the Breast Cancer Association Consortium (BCAC)

Genetics: 55 potentially causal variants as well as 15 newly identified SNP alleles

Environment: age at menarche, oral contraceptive (OC) use, parity, age at first full-term pregnancy (FTP), number of FTPs, breastfeeding, use of menopausal hormone therapy (MHT), body mass index (BMI), adult height, smoking and alcohol consumption

Breast cancer: overall and by ER status

Breast cancer subtype	SNP/risk factor	OR_{int} (95% CI)	ABF
Overall	CFLAR-rs7558475/ current smoking	0.77 (0.67-0.88)	0.007
ER-	5q14-rs7707921/ alcohol	1.36 (1.16-1.59)	0.005
ER-	3p21-rs6796502/ age at menarche	1.26 (1.12-1.43)	0.010
ER-	8q23-rs13267382/ age at first birth	0.89 (0.83-0.95)	0.016

Barrdahl, *Int J Cancer* 2017

PRS*E reveal minimal departures from multiplicative model

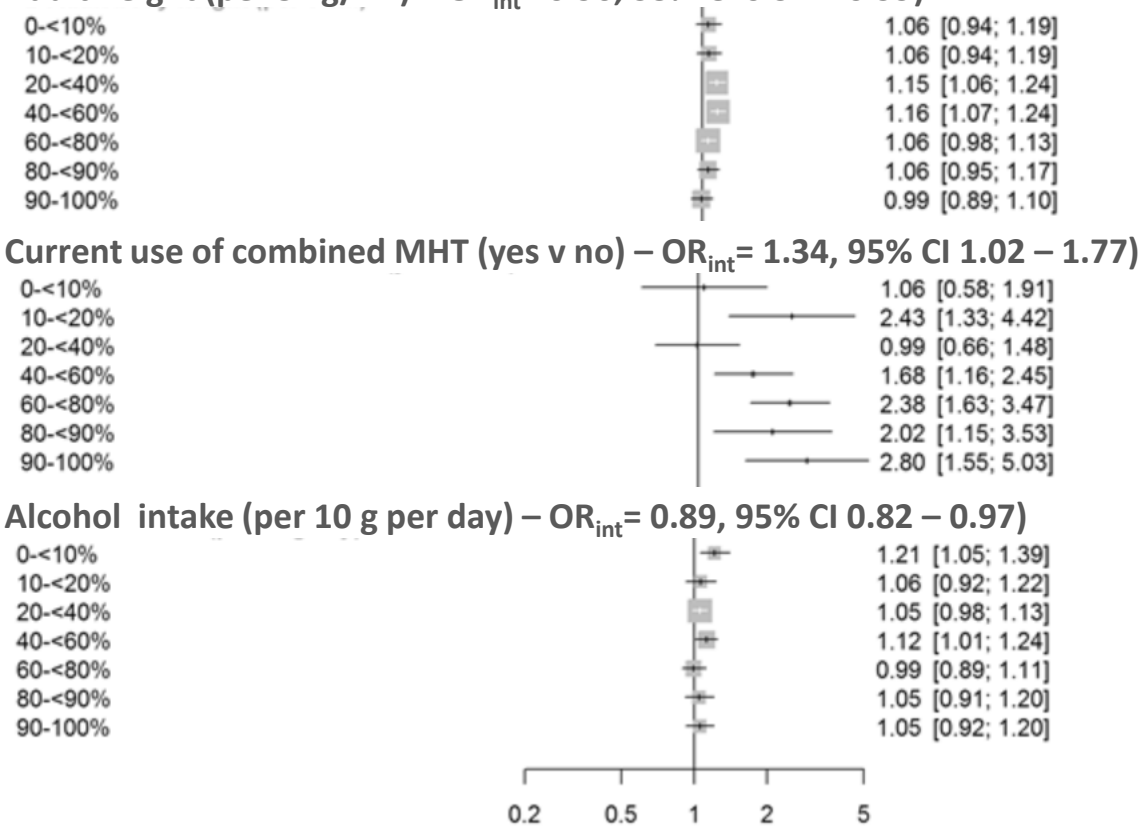
Study population: 3,453 – 23,104 cases and similar controls, depending on E, from 20 studies in BCAC

Genetics: 77-SNP PRS

Environment: reproductive history, alcohol consumption, menopausal hormone therapy (MHT), height and body mass index (BMI)

Breast cancer: overall and by ER status

Odds ratios and 95% confidence intervals for breast cancer risk factors by percentiles of PRS specific for ER-positive breast cancer



Rudolph A, *Int J Epidemiol*, 2018

SNP*E in largest, most comprehensive study to date, yet still no evidence for departures

Study population: 72,285 cases and 80,354 controls from 46 studies in BCAC

Genetics: 205 SNPs

Environment: age at menarche, ever parous, number of full-term pregnancies, age at first full-term pregnancy; ever breastfed, duration of breastfeeding, ever use of oral contraceptives, adult body mass index, adult height, lifetime alcohol consumption, current smoking, and current use of combined estrogen-progesterone menopausal hormonal therapy and current use of estrogen-only therapy for postmenopausal women

Breast cancer: overall and by ER status

Breast cancer subtype	SNP/risk factor	OR_{int} (95% CI)	ABF
Overall	IGFBP5-rs4442975/ current EPT use	0.85 (0.78-0.93)	0.003
ER+	IGFBP5-rs4442975/ current EPT use	0.85 (0.78-0.93)	0.009
ER-	HSPA4-rs6596100/ No. full-term pregn.	0.91 (0.85-0.96)	0.029
ER-	HSPA4-rs6596100/ age at first birth	1.12 (1.05-1.19)	0.012

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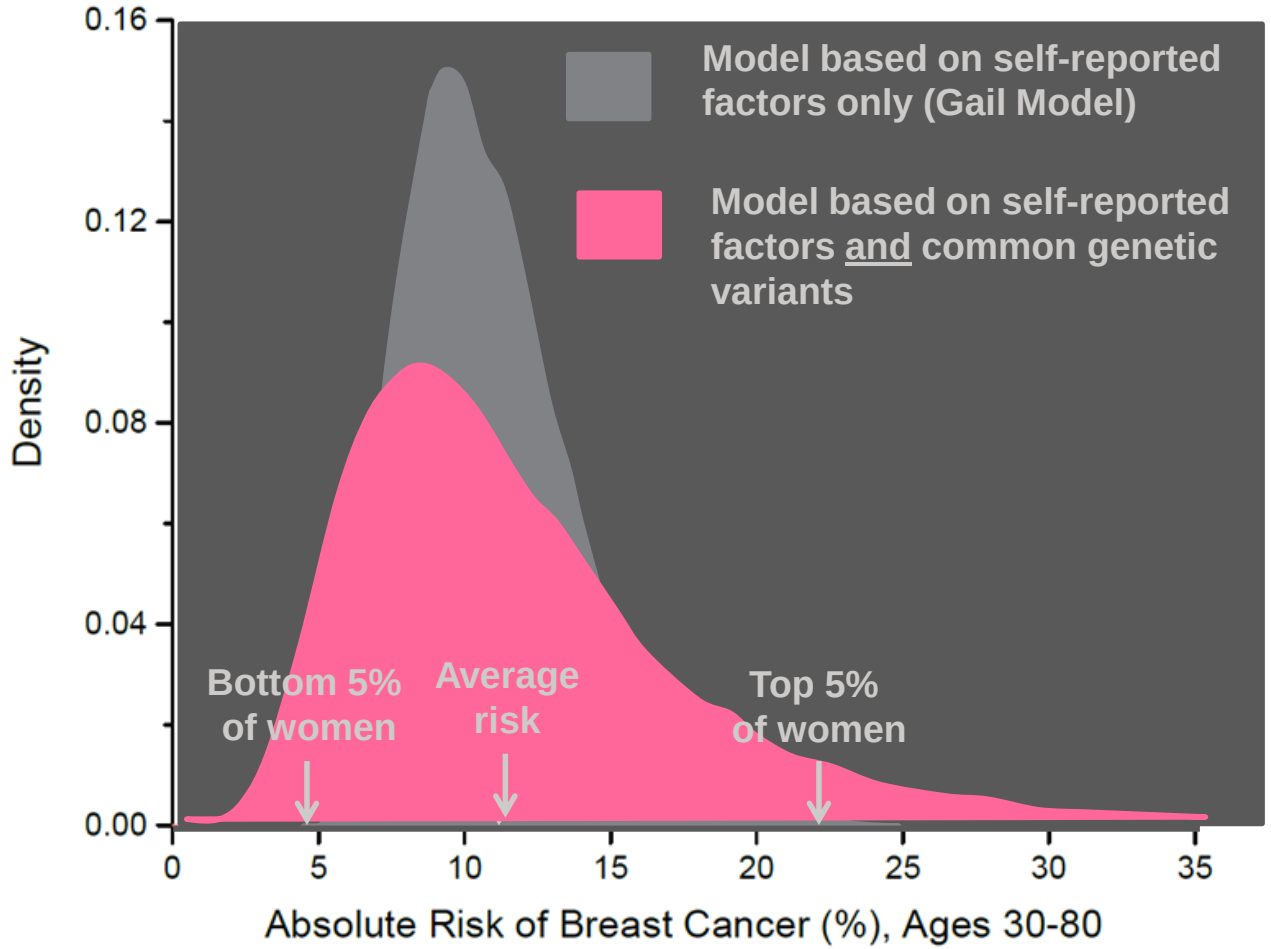
Kapoor, *Int J Epidemiol* 2019

Improved discrimination with inclusion of environmental factors AND common genetic variants

Analysis of ~17,000 breast cancer cases and ~20,000 controls from 8 cohorts

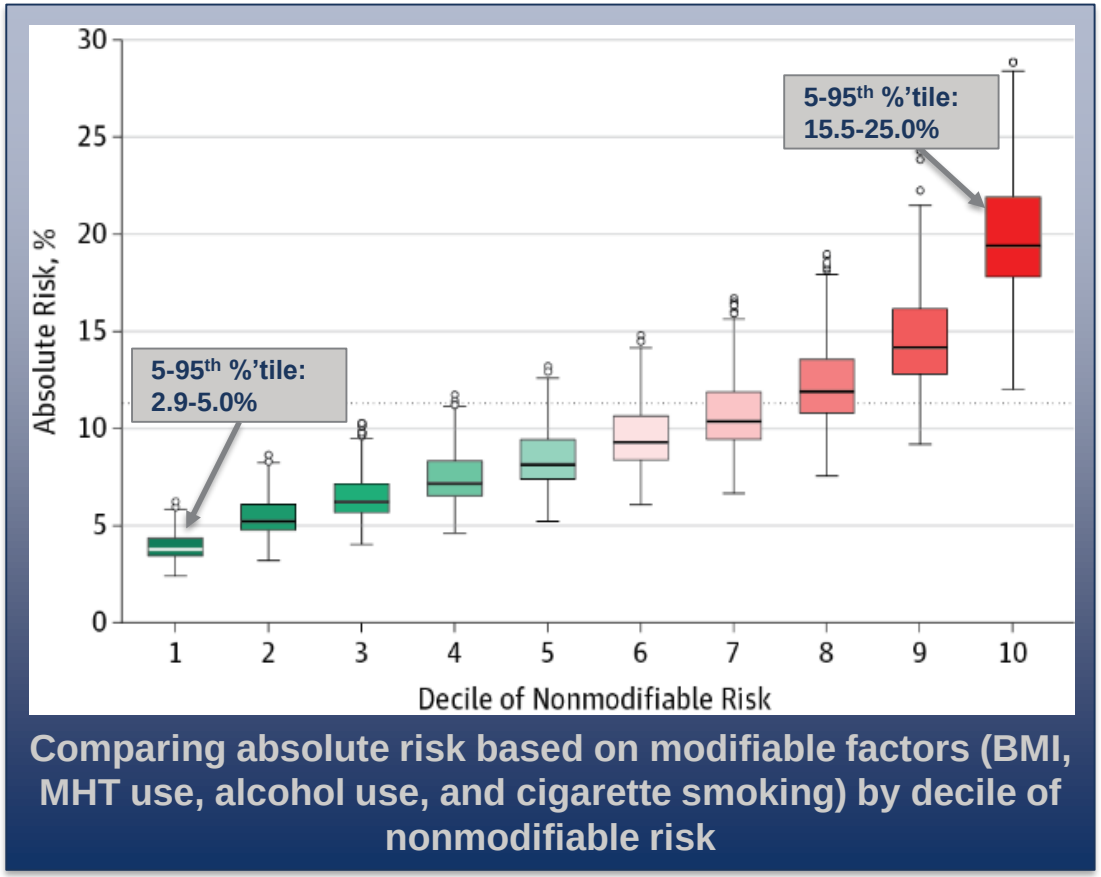


Maas et al, *Lancet Oncology*, 2017

Absolute lifetime risk associated with environmental factors stratified by deciles of genetic risk

28.9% of all breast cancer cases could be prevented if all women had lowest decile of BMI, did not use menopausal hormones, did not drink alcohol, and did not smoke cigarettes

Future work needs to stratify by ER status



Comparing absolute risk based on modifiable factors (BMI, MHT use, alcohol use, and cigarette smoking) by decile of nonmodifiable risk

Maas et al, *Lancet Oncology*, 2017

Influences on sample size requirements to identify G*E interactions

Incomplete identification of all causal genetic variants associated with breast cancer

Error in exposure measurement and less investment in advancements

Insufficient variation in exposures

Differences in environmental and genetic associations by ER status and beyond

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