

# Assessment of Breast Cancer Risk with Genetic Polymorphisms

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# Outline

- Joint effects of common genetic variants?
- Joint effects of common and rare genetic variants?
- How do genetic and lifestyle/hormonal factors interact?
- Implications for breast cancer risk stratification?
- Available breast cancer risk prediction tools?
- BOADICEA updates: rare and common variants

# Individual SNP associations

- Each SNP: 0, 1, 2 risk alleles
- Odds Ratio estimates per risk allele: 1.02-1.30
- Minor allele frequencies:  $>0.01$
  
- Individual SNP predictive ability poor
- SNPs combine multiplicatively on risk scale

# Combined SNP associations

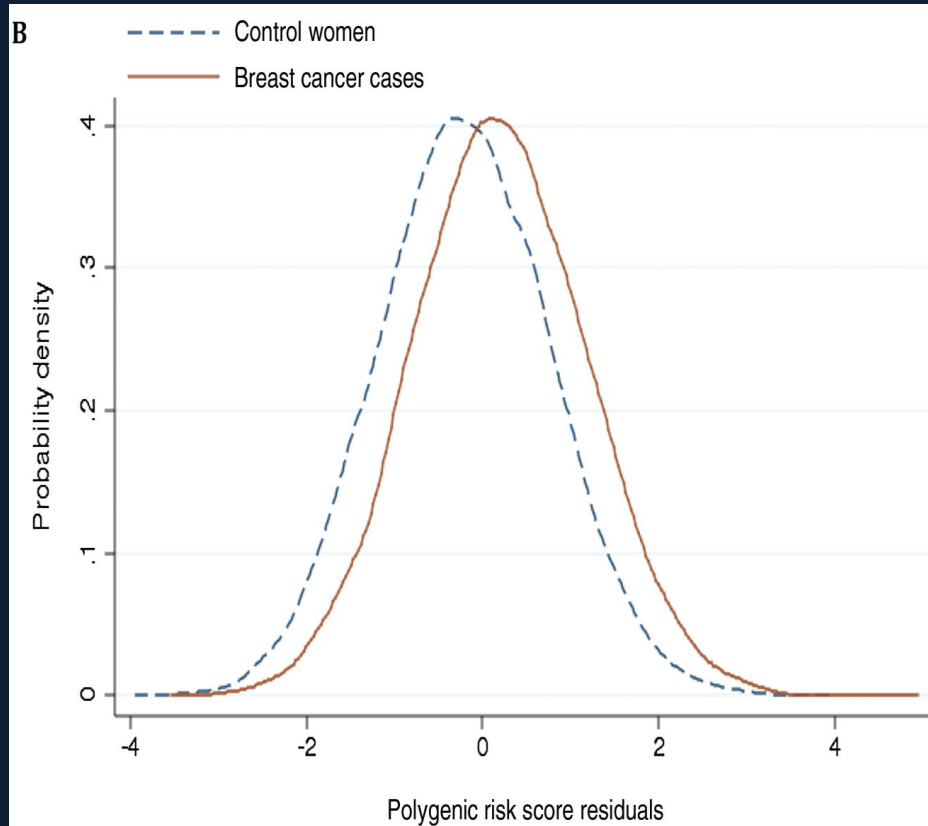
- Polygenic Risk Scores (PRS)

$$\text{PRS} = \beta_1 X_1 + \beta_2 X_2 \dots + \beta_n X_n$$

Log(Odds Ratio) estimate

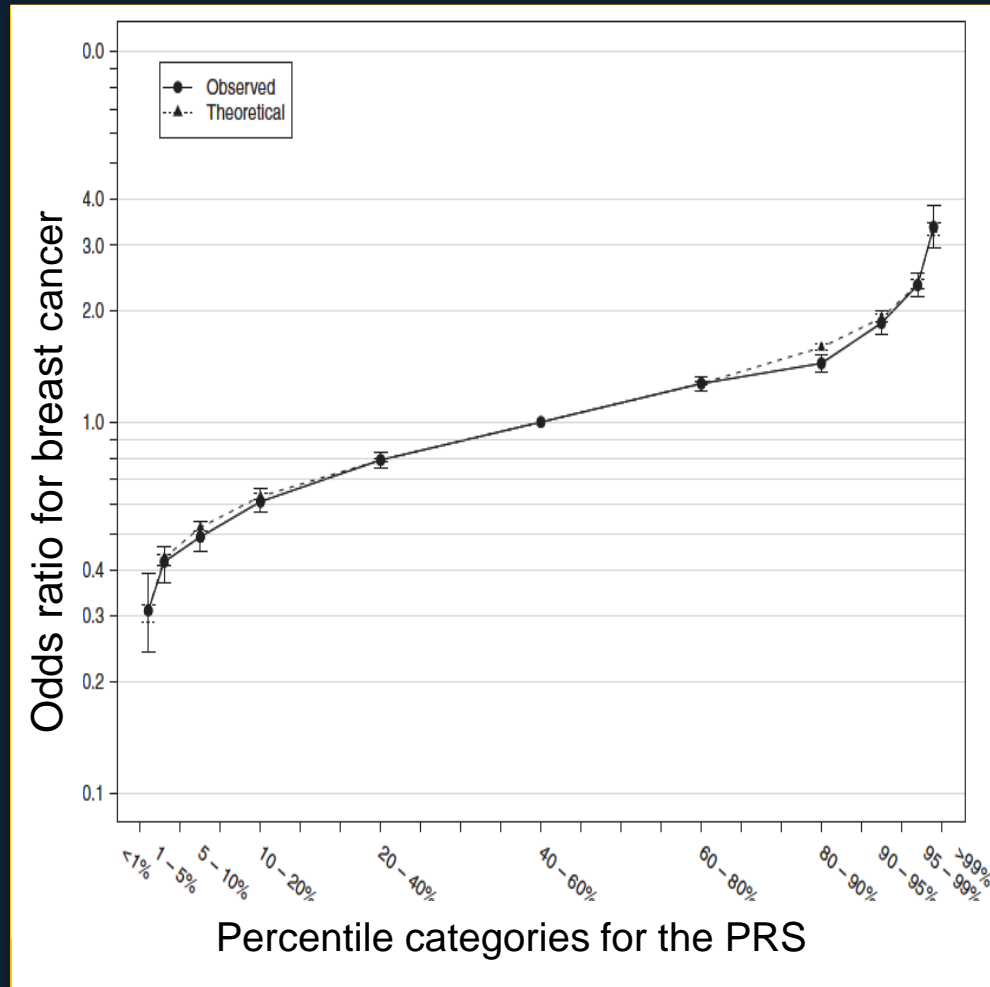
Number of risk alleles  
at each SNP

# 77- SNP Polygenic Risk Score



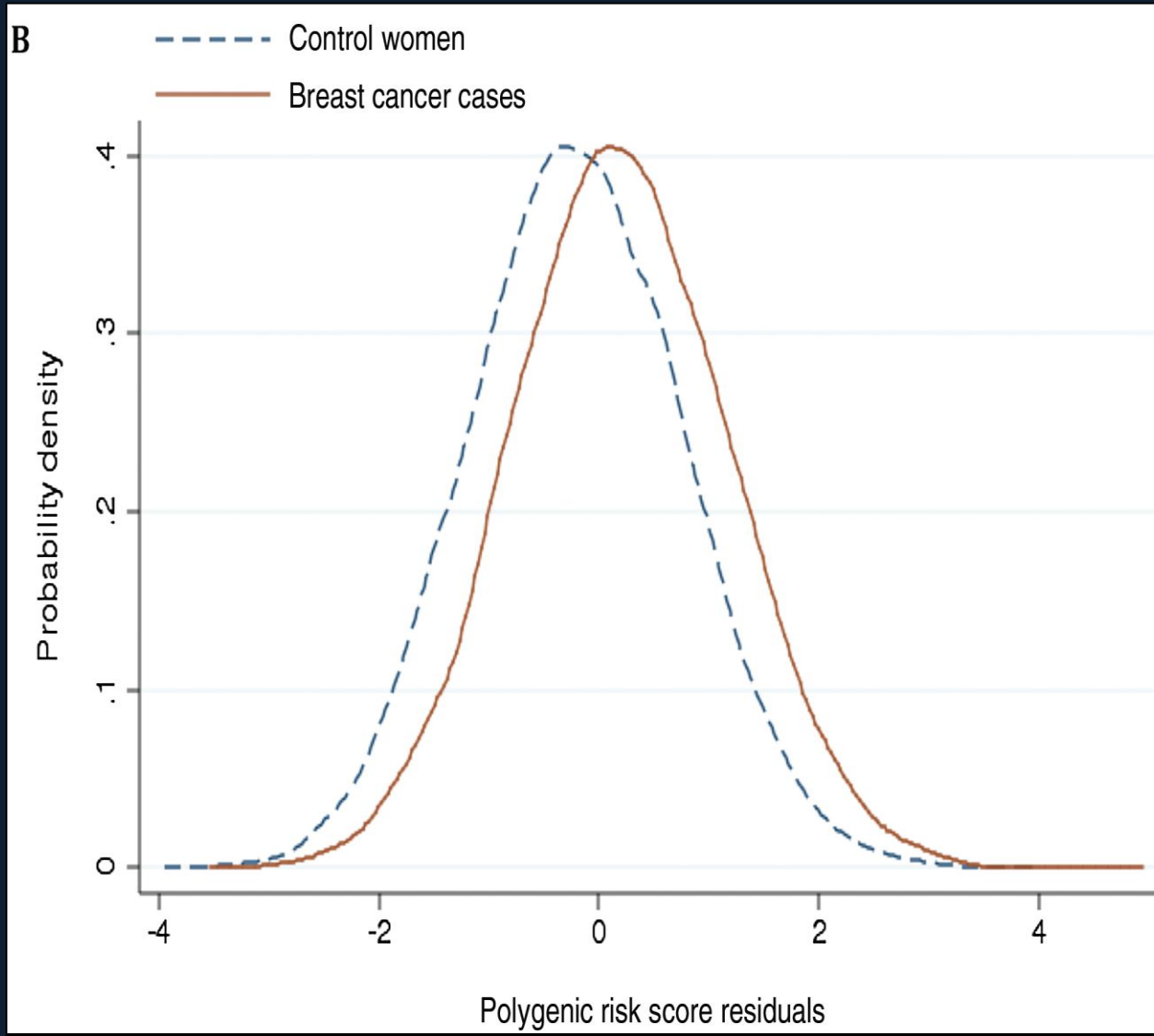
- Breast Cancer Association Consortium (BCAC)
- 33,673 breast cancer cases and 33,381 control women
- PRS normally distributed in both cases and controls
- Mean PRS (cases)=0.69  
Mean PRS (controls)=0.49

# Empirical PRS Odds Ratios VS predicted under multiplicative model



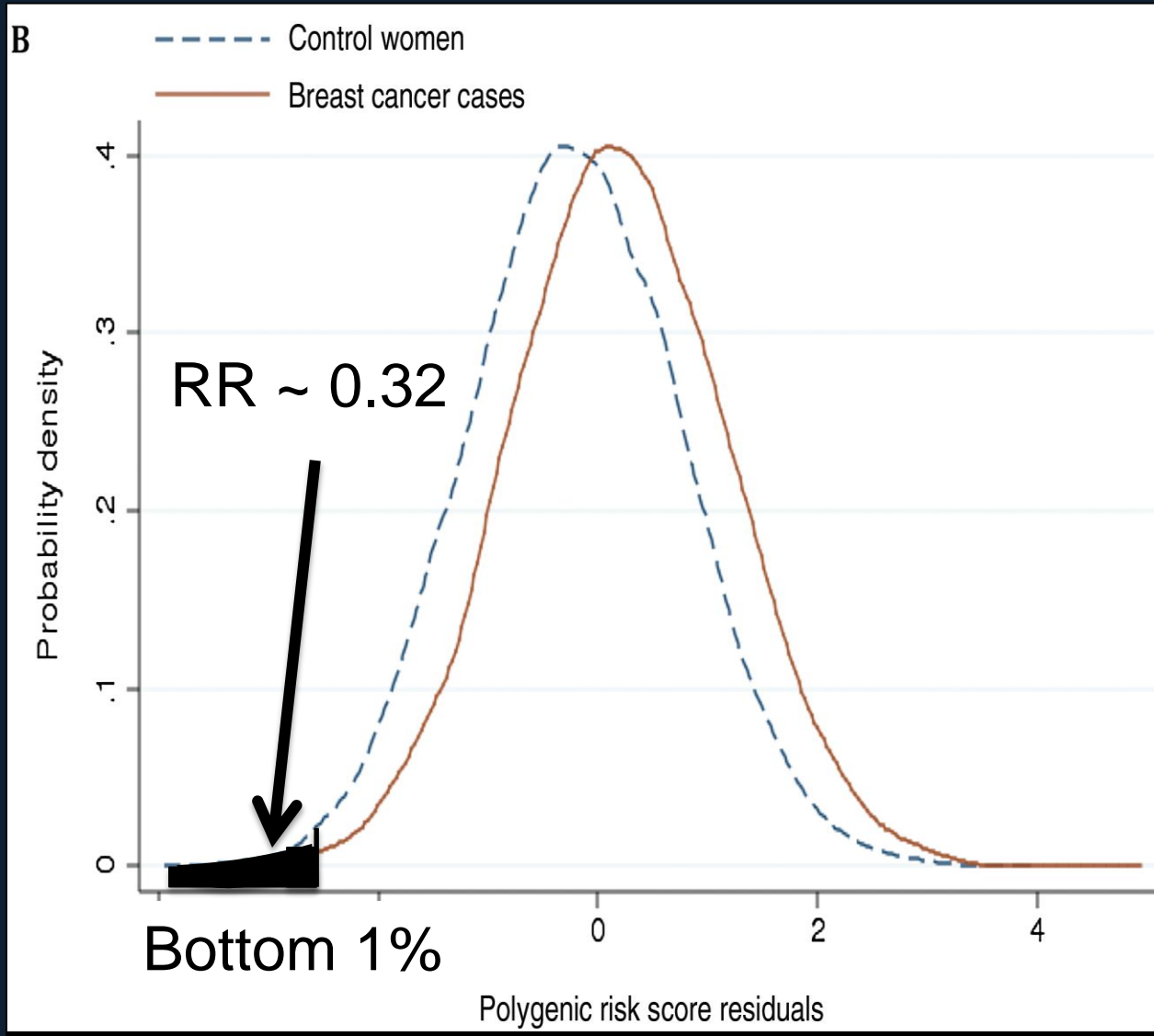
Mavaddat et al JNCI 2015

# 77-SNP PRS and risk stratification

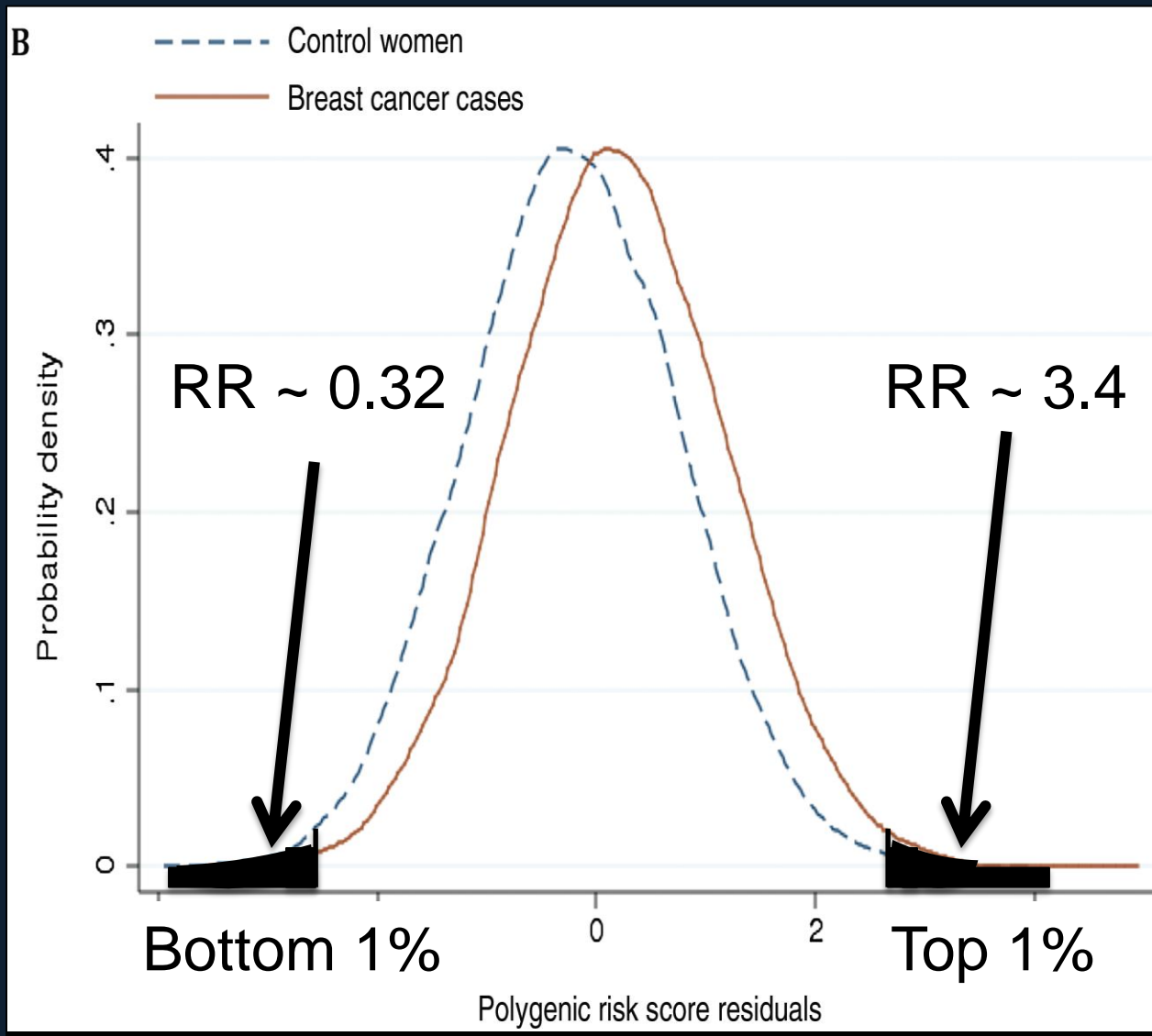




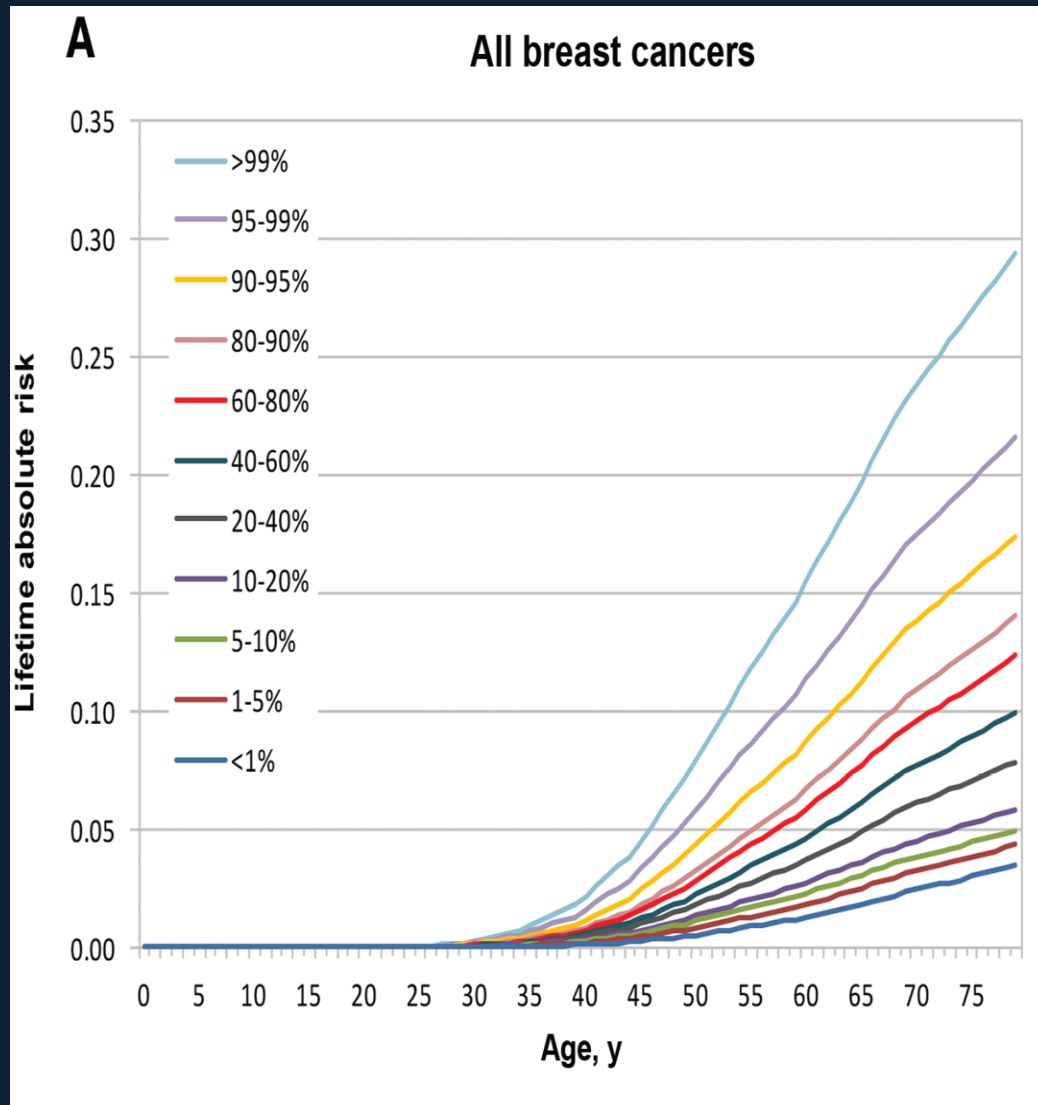
# 77-SNP PRS and risk stratification



# 77-SNP PRS and risk stratification



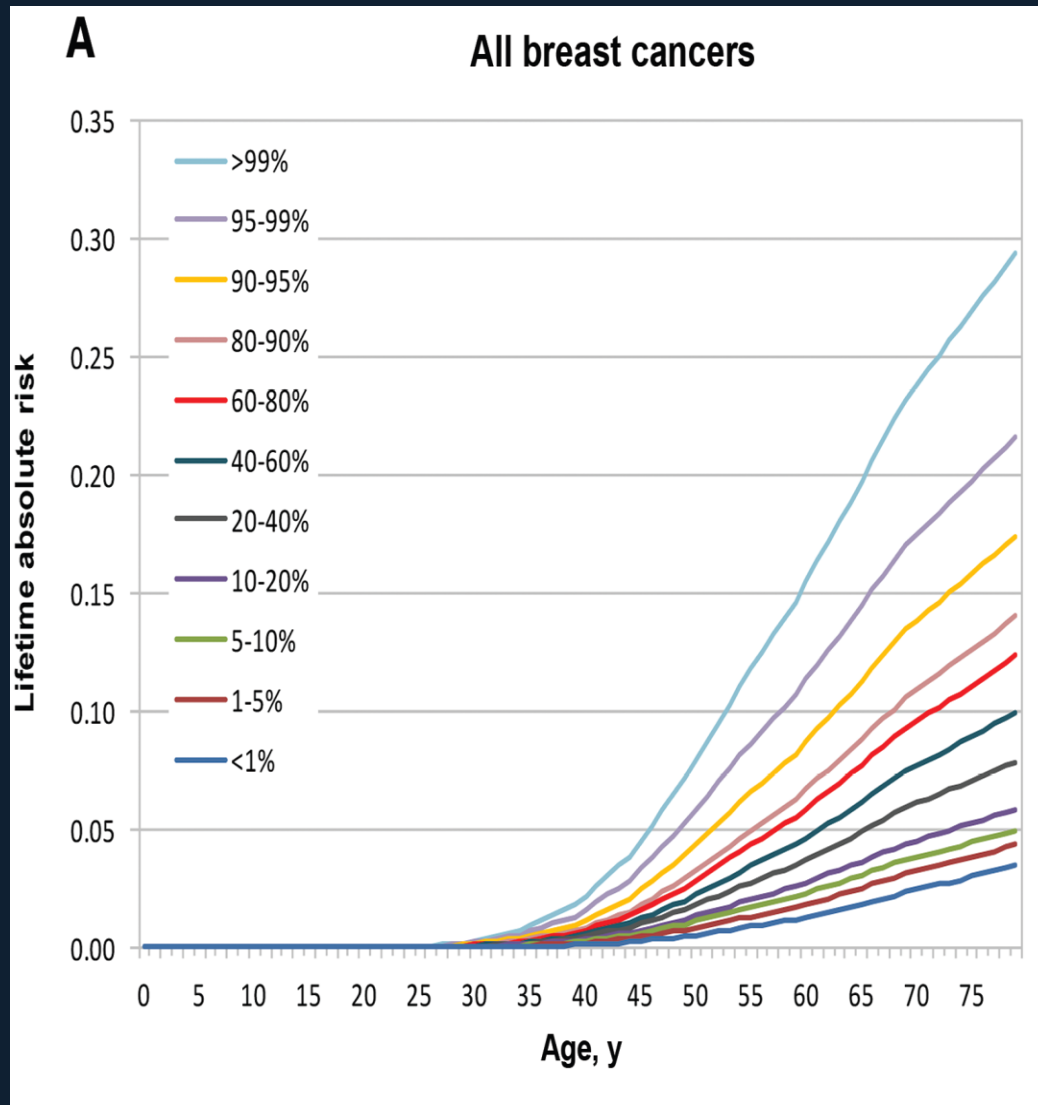
# PRS and lifetime breast cancer risk



← 3.5%

Mavaddat et al JNCI 2015

# PRS and lifetime breast cancer risk

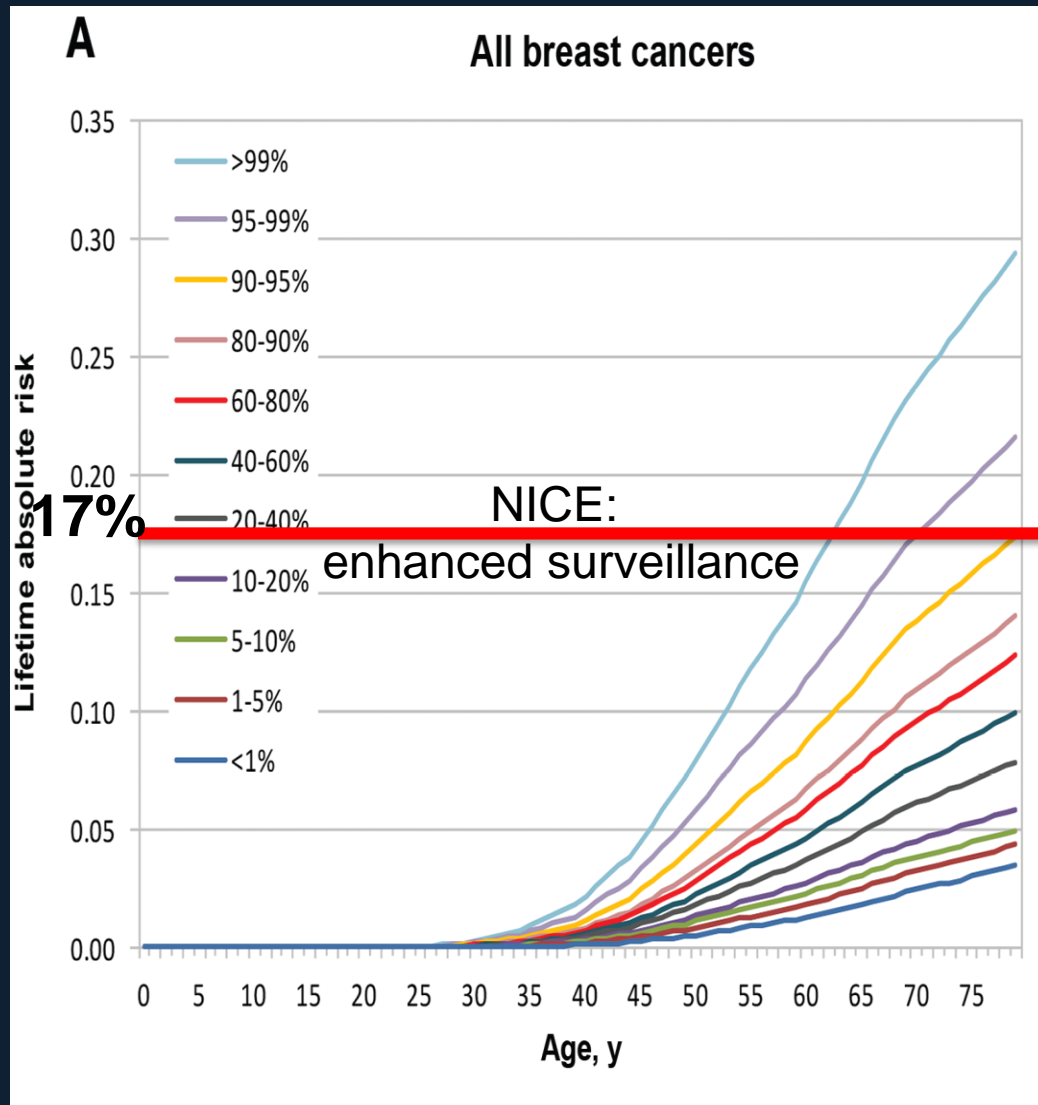


← 29%

← 3.5%

Mavaddat et al JNCI 2015

# PRS: implications for clinical management



- 8% of all UK women
- 17% of all breast cancer cases

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# Consortium of Investigators of Modifiers of *BRCA1/2*

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## CIMBA – Consortium of Investigators of Modifiers of BRCA1/2

Centre for Cancer Genetic Epidemiology

Home | Eligibility | CIMBA Groups | Projects | Publications | Meetings | Links | Members Pages

You are here: CCGE Consortia / CIMBA - Consortium of Investigators of Modifiers of BRCA1/2 / CIMBA Groups

### CIMBA Groups

The map below shows the country locations of the current participating CIMBA study groups. Please zoom in for more detail. New groups are always welcome to join provided they can meet the minimum eligibility requirements.

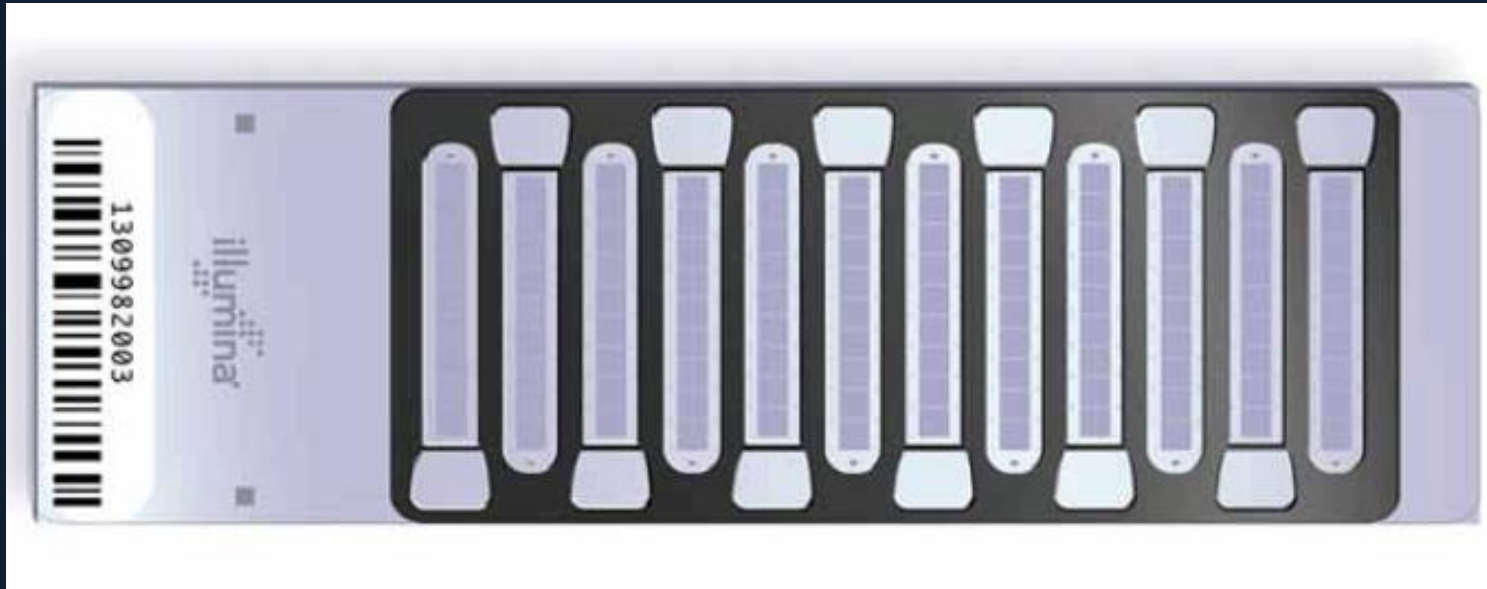


The map displays the global distribution of CIMBA study groups. Pins are color-coded by region: red for Europe, yellow for North America, purple for Asia, blue for Africa, and green for Australia. The map includes labels for major countries and oceans, and is powered by MapPress with data from 2016.

- >70 groups from Europe, North America, Australia, Asia, Africa and South America
- >55,000 *BRCA1*, *BRCA2* mutation carriers

# iCOGS, OncoArray high-density custom arrays

Characterising cancer loci



>35,000 *BRCA1* and *BRCA2* samples genotyped



# CIMBA: OncoArray results

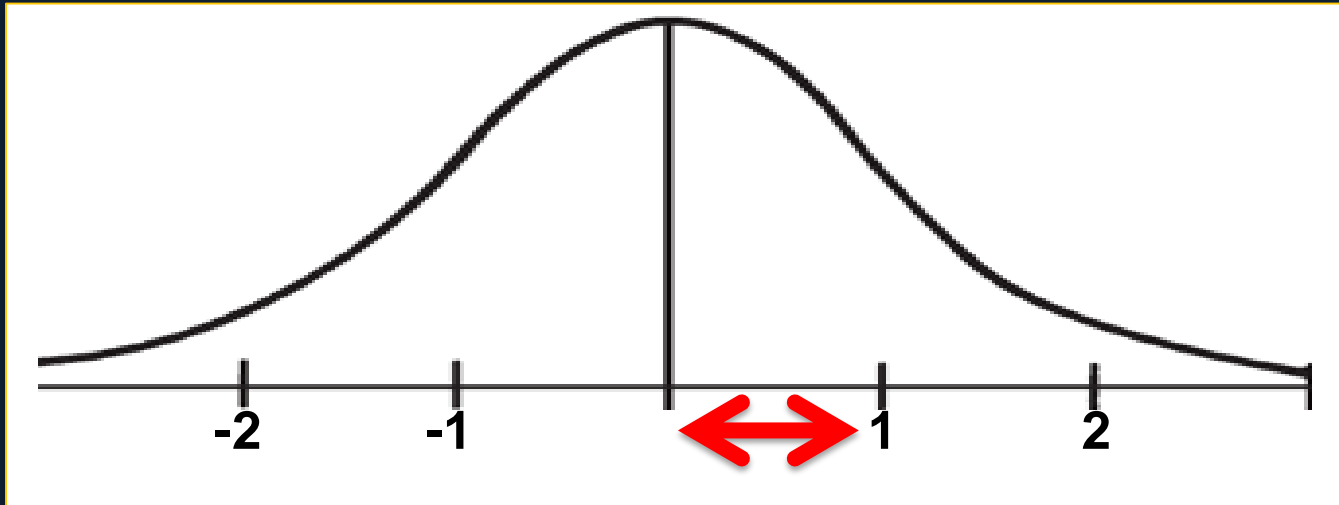
- 10 new *BRCA1* breast cancer susceptibility loci (Milne et al, Nat Genet, In press)
  - 39 modifiers of BC risk for *BRCA1* carriers
  - 37 modifiers of BC risk for *BRCA2* carriers
- 3 new ovarian cancer susceptibility loci
  - 19 modifiers of OC risk for *BRCA1/2* carriers (Phelan et al, Nat Genet, 2017)

# Risk modifying loci – patterns of association

- Most SNPs associated with risk in the population also modify risk for carriers
- *BRCA1* BC modifiers: Primarily associated with ER-negative

# Polygenic Risk Scores: *BRCA1* – Breast Cancer

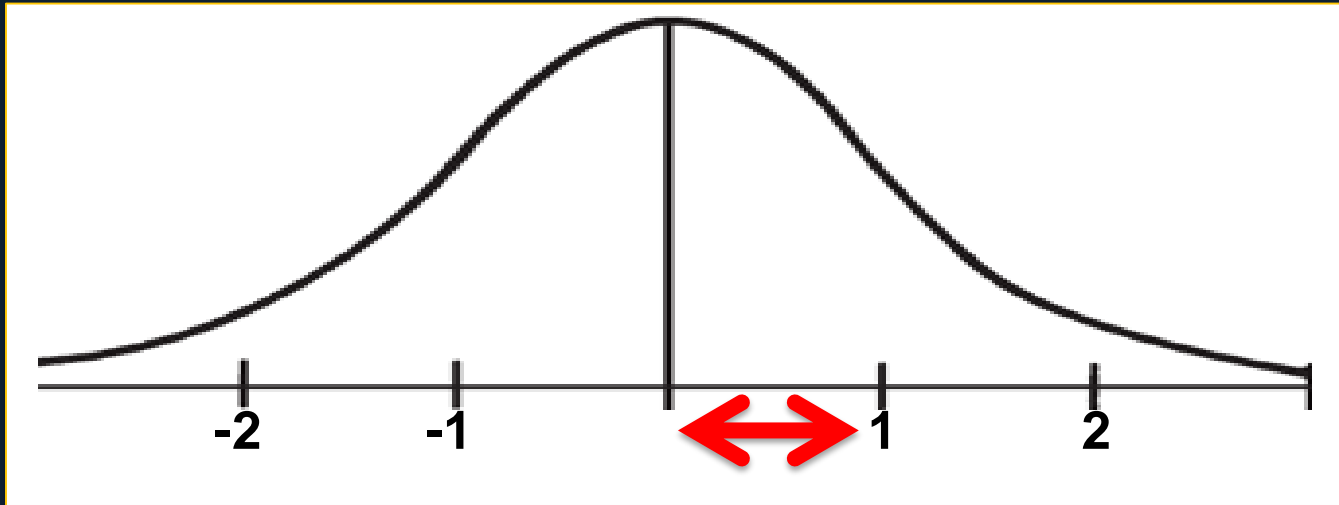
*BRCA1* sample: 7,797 affected vs 7,455 unaffected



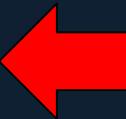
PRS type	HR	P-value
Overall breast cancer (88 SNPs)	1.14	$2 \times 10^{-18}$
ER-positive (87 SNPs)	1.11	$3 \times 10^{-13}$
ER-negative (53 SNPs)	1.27	$7 \times 10^{-53}$

# Polygenic Risk Scores: *BRCA1* – Breast Cancer

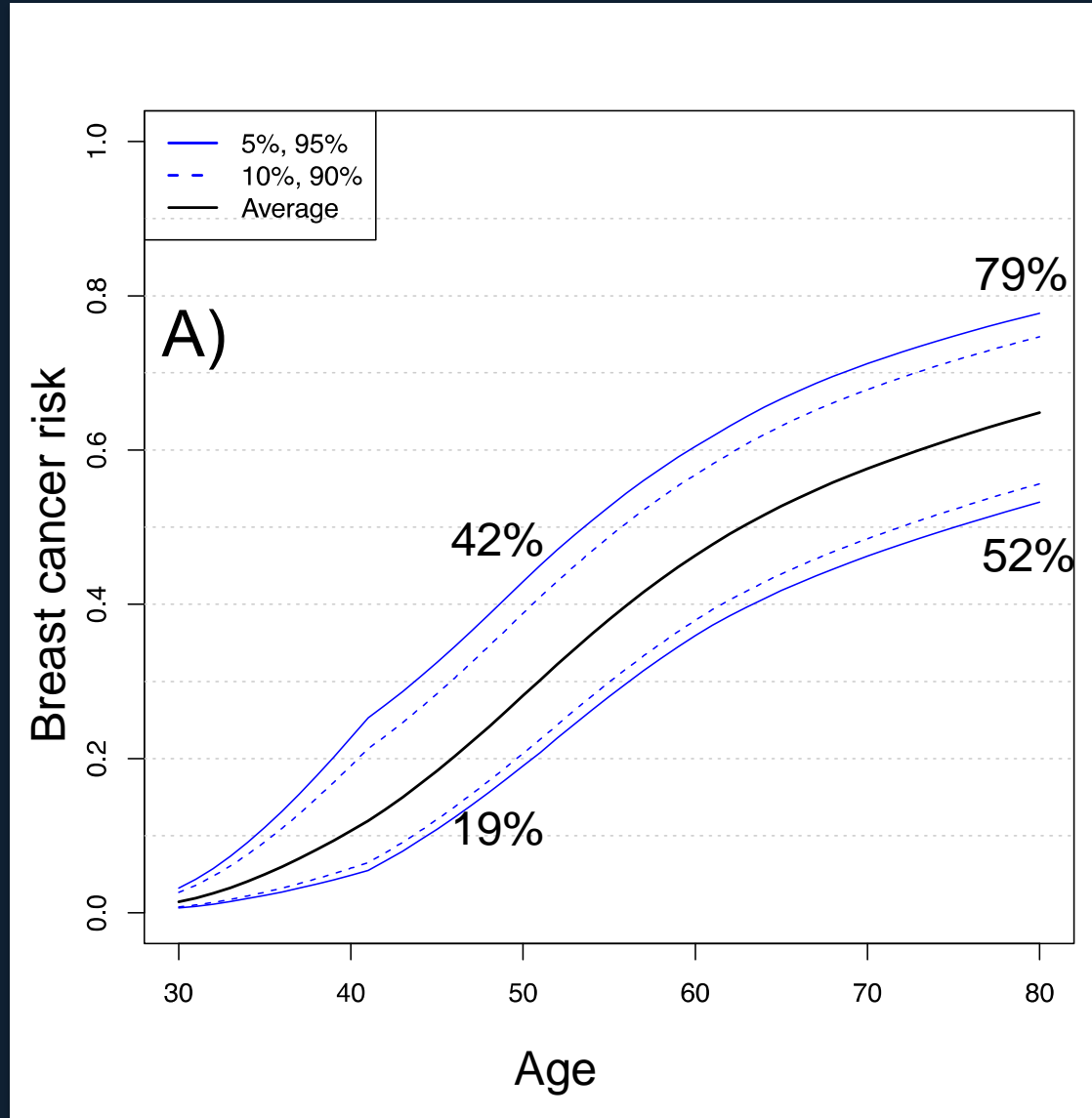
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# BRCA1 mutation carriers: Breast cancer risk by PRS



# PRS and breast cancer risk associations in CHEK2\*1100delC carriers

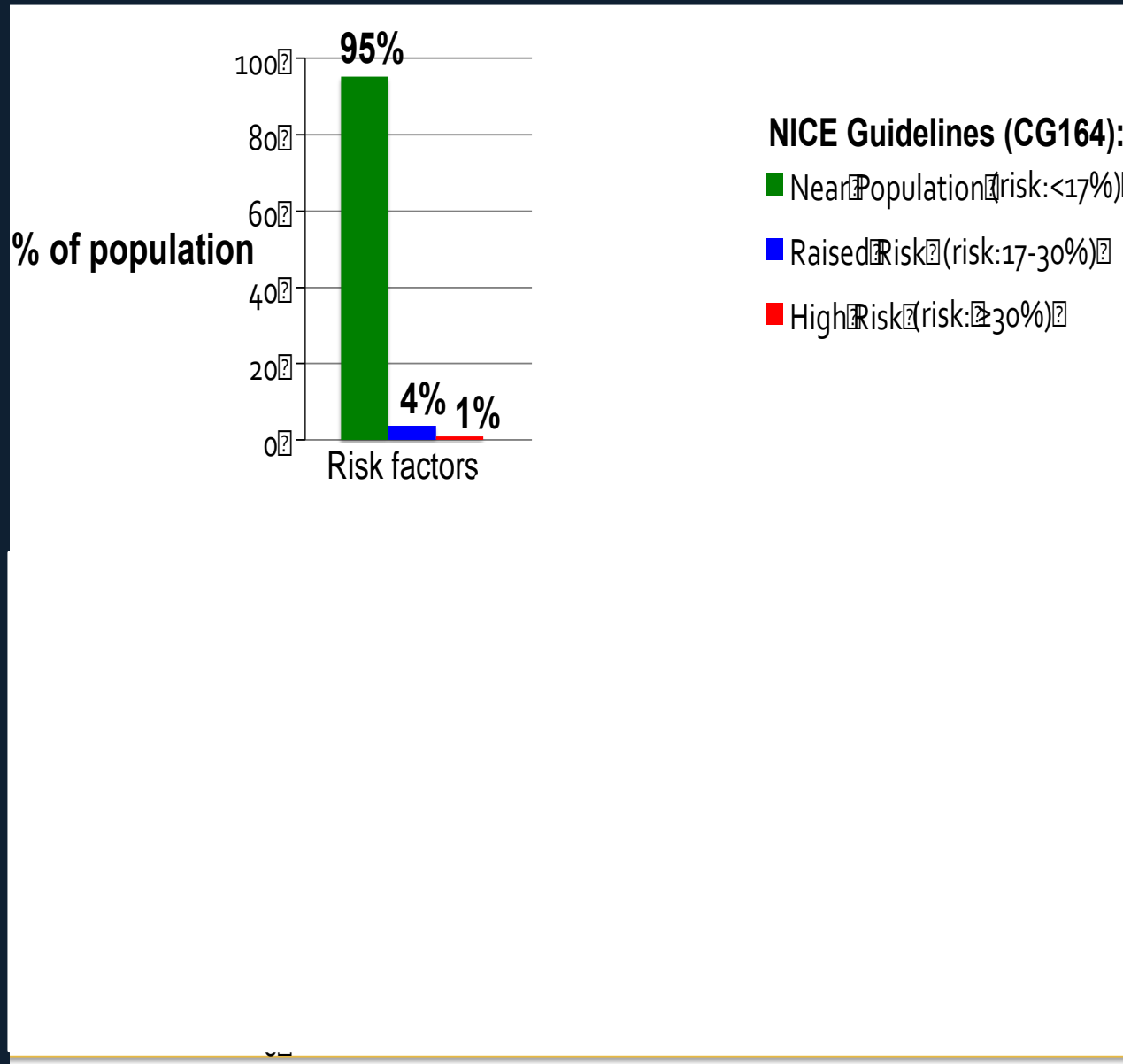
	Noncarriers		CHEK2*1100delC carriers	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
PRS <sup>a</sup>	1.58 (1.55–1.62)	<1.0E-10	1.59 (1.21–2.09) <sup>b</sup>	0.0008
Percentile of PRS, %				
<20	0.52 (0.48–0.56)	<1.0E-10	0.52 (0.16–1.74)	0.29
20–40	0.78 (0.72–0.84)	2E-11	0.72 (0.28–1.88)	0.51
40–60	Referent		Referent	
60–80	1.25 (1.16–1.34)	8E-10	0.93 (0.39–2.25)	0.88
>80	1.92 (1.80–2.06)	<1.0E-10	2.03 (0.86–4.78)	0.11

# Combined effects of genetic, lifestyle/hormonal factors

- Studies of PRS x Lifestyle/hormonal factors ongoing
- SNP x Lifestyle/hormonal factors
  - **Multiplicative model plausible**

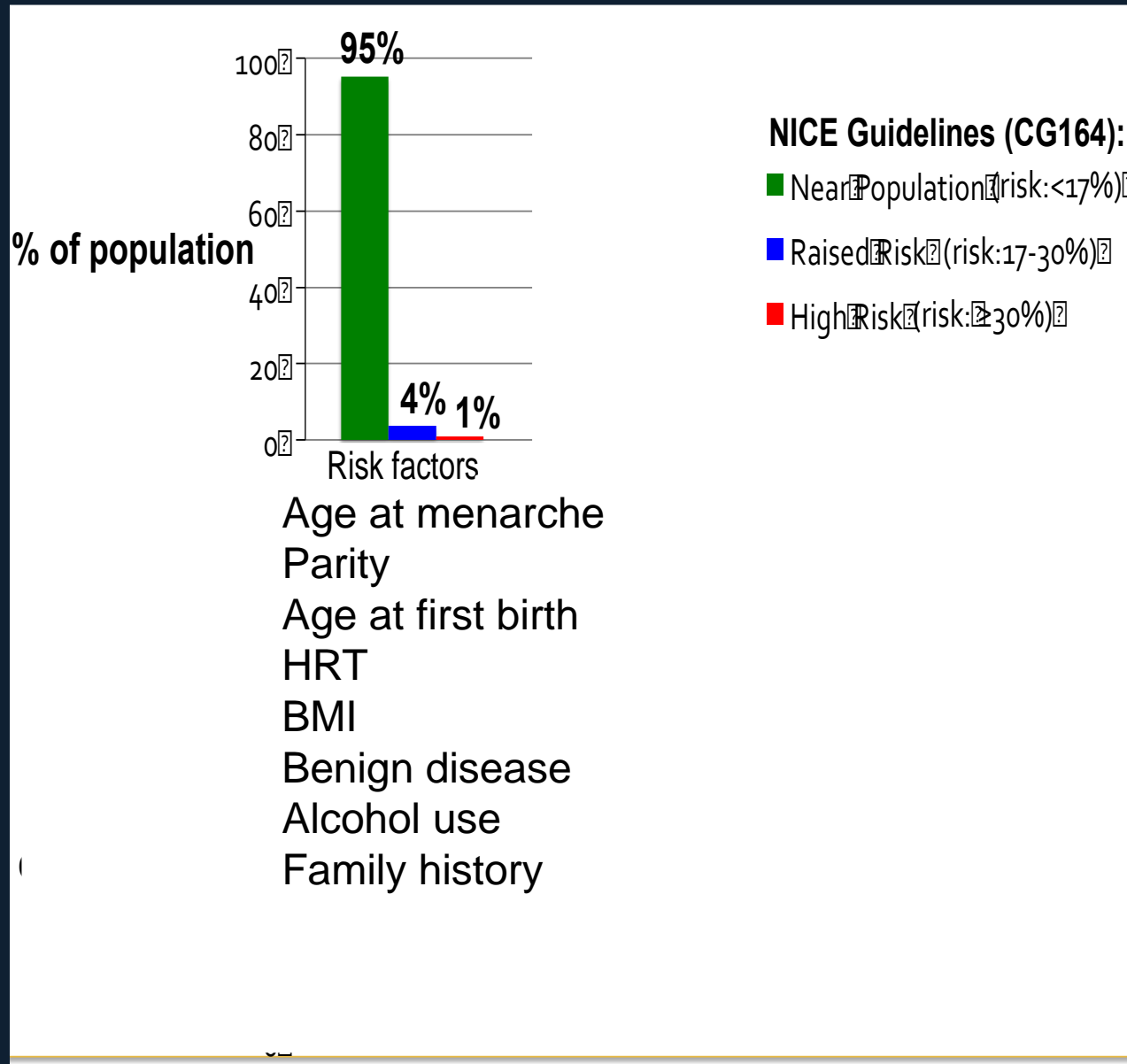
Nickels et al Plos Genet (2013); Campa et al , JNCI 2011; Rudolph et al BCR 2015; Rudolph et al IJC (2015); Vachon et al JNCI (2015); Maas et al JAMA Oncol (2016)

# Potential for transformative risk stratification

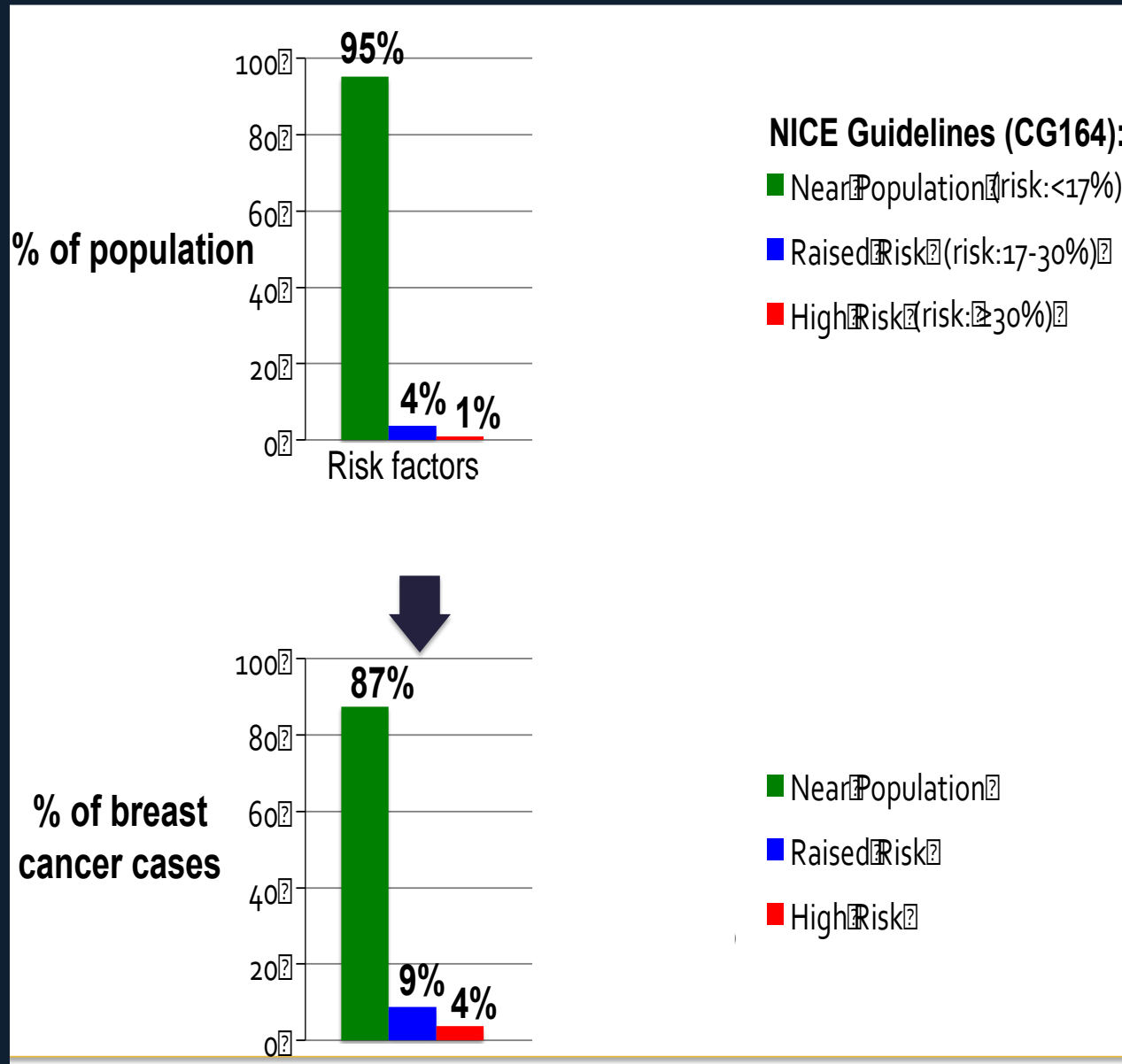




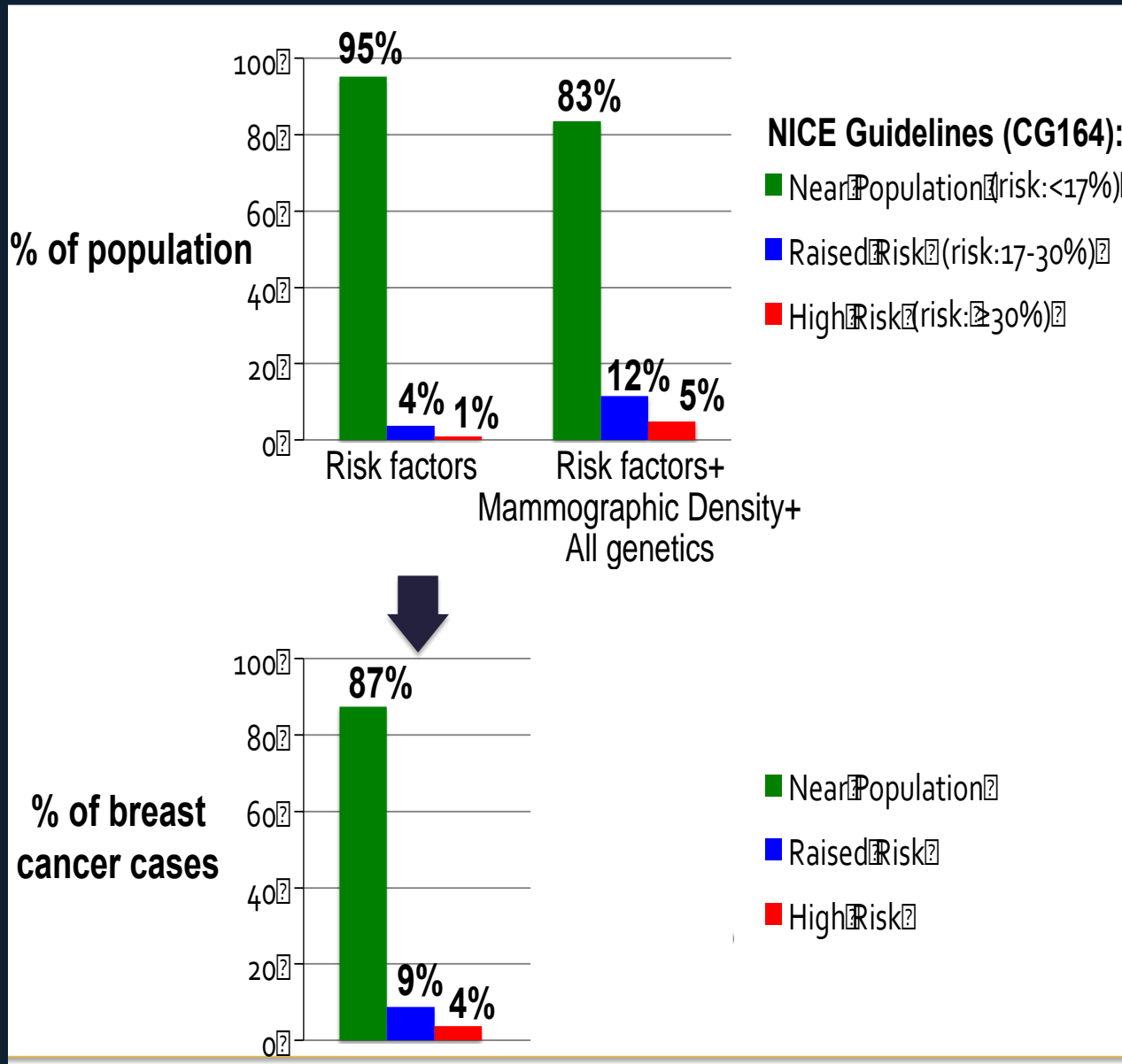
# Potential for transformative risk stratification



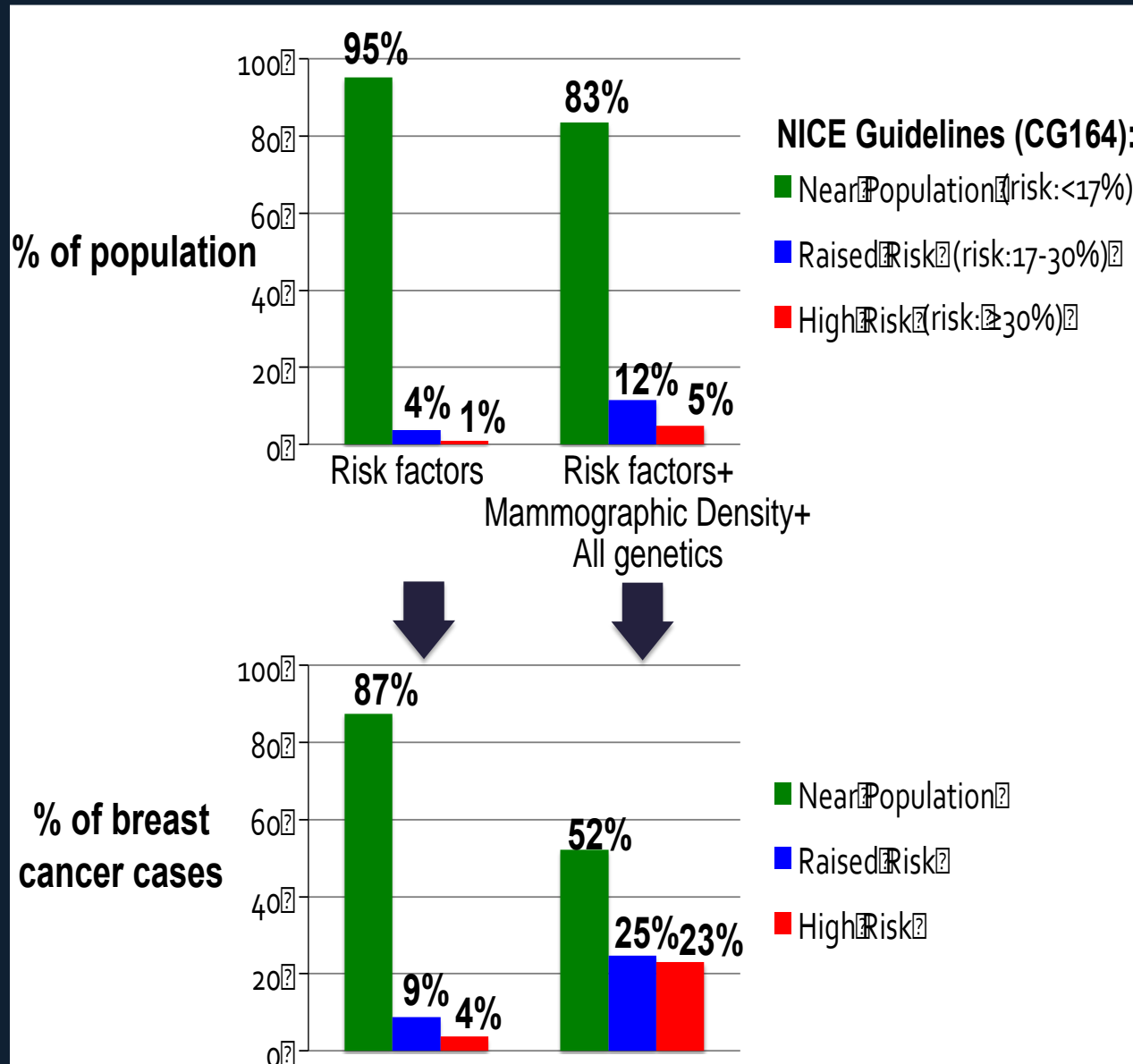
# Potential for transformative risk stratification



# Potential for transformative risk stratification



# Potential for transformative risk stratification



# Breast cancer risk assessment tools

**TABLE 2. Breast Cancer Risk Assessment Tools Used in Clinical Practice: Components and Assumptions**

Factor*	Gail	Claus	BRCAPRO	IBIS	BOADICEA
Family history	YES (descriptive)	YES	YES	YES	YES
<i>BRCA1</i> , <i>BRCA2</i> mutations	NO	NO	YES	YES	YES
Common low-risk alleles	NO	NO	NO	NO	NO
Intermediate-high risk mutations ( <i>CHEK2</i> , <i>PALB2</i> , <i>ATM</i> , etc.)	NO	NO	NO	NO	YES**
Residual non- <i>BRCA1/2</i> familial aggregation	NO	NO	NO	YES; dominant 3rd gene	YES; polygenic
<i>BRCA1/2</i> breast cancer pathology associations	NO	NO	YES <sup>†</sup>	NO	YES
<i>BRCA1/2</i> risk modification by family history	NO	NO	NO	NO	YES
Variants of uncertain significance	NO	NO	NO	NO	NO
Predicting estrogen receptor (ER)-specific risks	NO	NO	NO	NO	NO
Mammographic density	NO	NO	NO	NO	NO
Hormonal, lifestyle, and reproductive risk factors	YES	NO	NO	YES; assumes same effect on <i>BRCA1/2</i>	NO
Other cancers (nonbreast or ovarian cancer)	NO	NO	YES	NO	YES
Predicting second cancer risks (contralateral breast, ovarian cancer)	NO	NO	NO	NO	YES

Kurian, Antoniou & Domchek, 2016 ASCO Educational handbook

# Genetic variants in existing breast cancer risk tools

- *BRCA1, BRCA2* mutations
  - BRCAPRO, IBIS, BOADICEA
- Common genetic variants – SNPs
  - No tool incorporating SNPs & risk factors available for clinical use
  - Improved performance of existing algorithms (e.g. IBIS, BOADICEA, Gail) Dite et al (2015); Brentnall et al (2014); Darabi et al (2012)
  - Consistency in modeling joint genetic & lifestyle/hormonal factors required
  - **BPC3 model** (Maas et al 2016)
- Truncating variants in moderate/high risk genes (*PALB2, CHEK2, ATM*)
  - BOADICEA Lee et al Genet Med (2016)

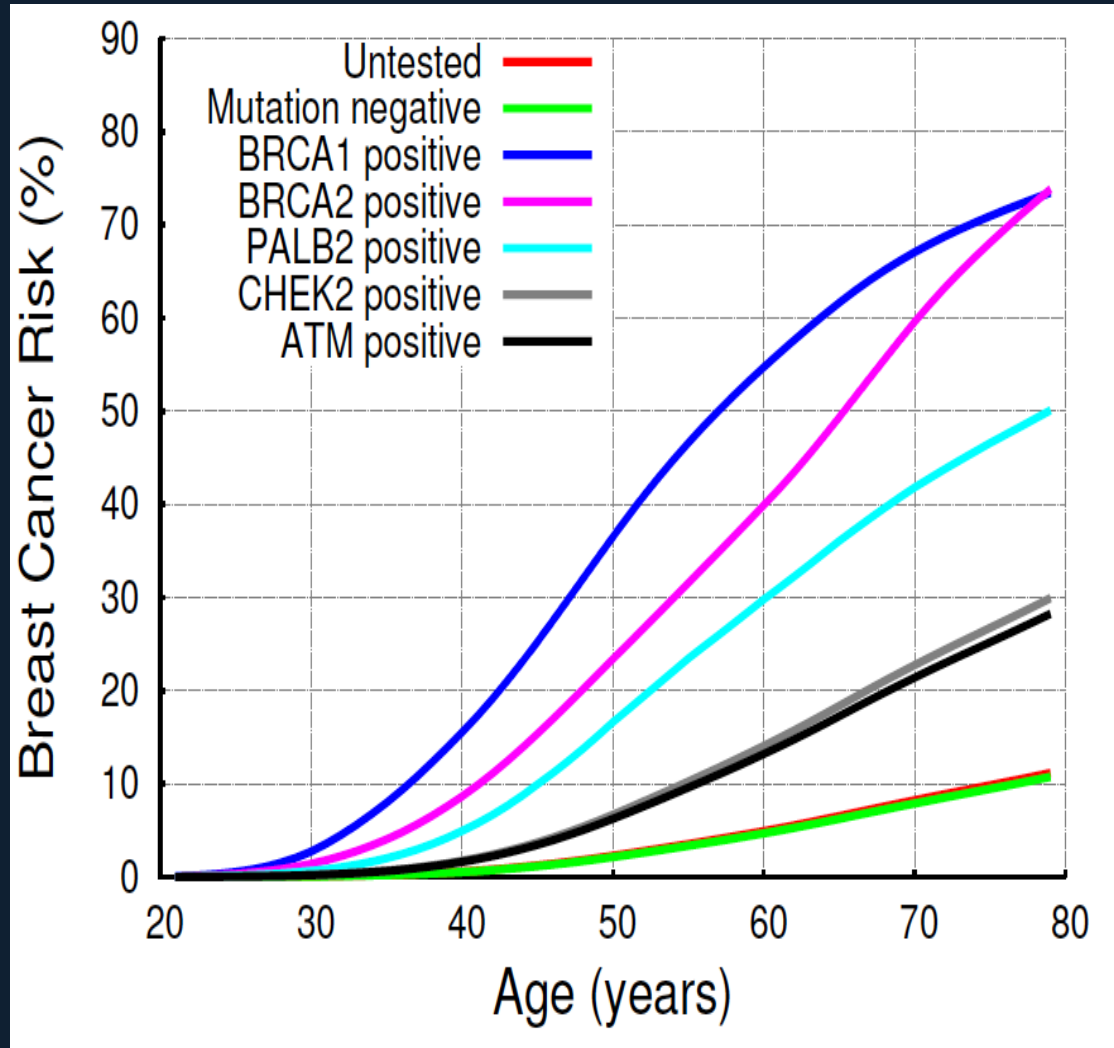
# BOADICEA

<http://ccge.medschl.cam.ac.uk/boadicea/>

The screenshot displays the BOADICEA web application interface. It features a consultation form with sections for clinical history, personal details, breast cancer, contralateral BC, ovarian cancer, prostate cancer, pancreatic cancer, and genetic testing. The form includes input fields for age, sex, and genetic test results, along with radio buttons for selection. A pedigree chart is shown, illustrating family history with individuals affected by breast cancer (indicated by black symbols) and unaffected individuals (white symbols). A graph titled 'Breast Cancer Risk Baseline Risk' plots 'Breast Cancer Risk (percent)' on the y-axis (0 to 25) against 'Age (years)' on the x-axis (40 to 80). Two lines represent risk: a red line for 'Breast Cancer Risk' and a green line for 'Baseline Risk'. The red line shows a steeper increase in risk over time compared to the green line. The interface also includes a 'Logout' button and a 'Reset' button.

- *BRCA1*, *BRCA2*, polygenic (unobserved genetic effects)
- Family history breast, ovarian prostate, pancreatic cancer
- Tumour characteristics - ER/PR/HER2/Cytokeratin markers
- Population, ethnicity, year of birth

# *BRCA1, BRCA2, PALB2, ATM* and *CHEK2* average breast cancer risks in BOADICEA

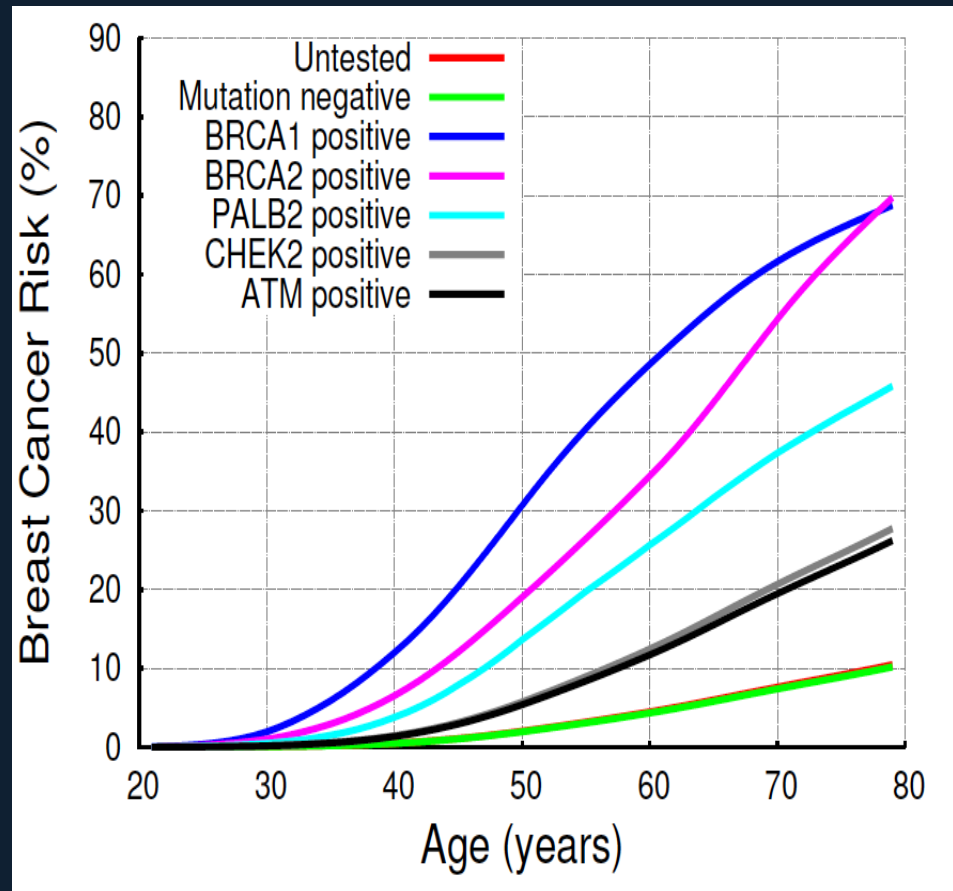


Lee et al, Genet Med (2016)

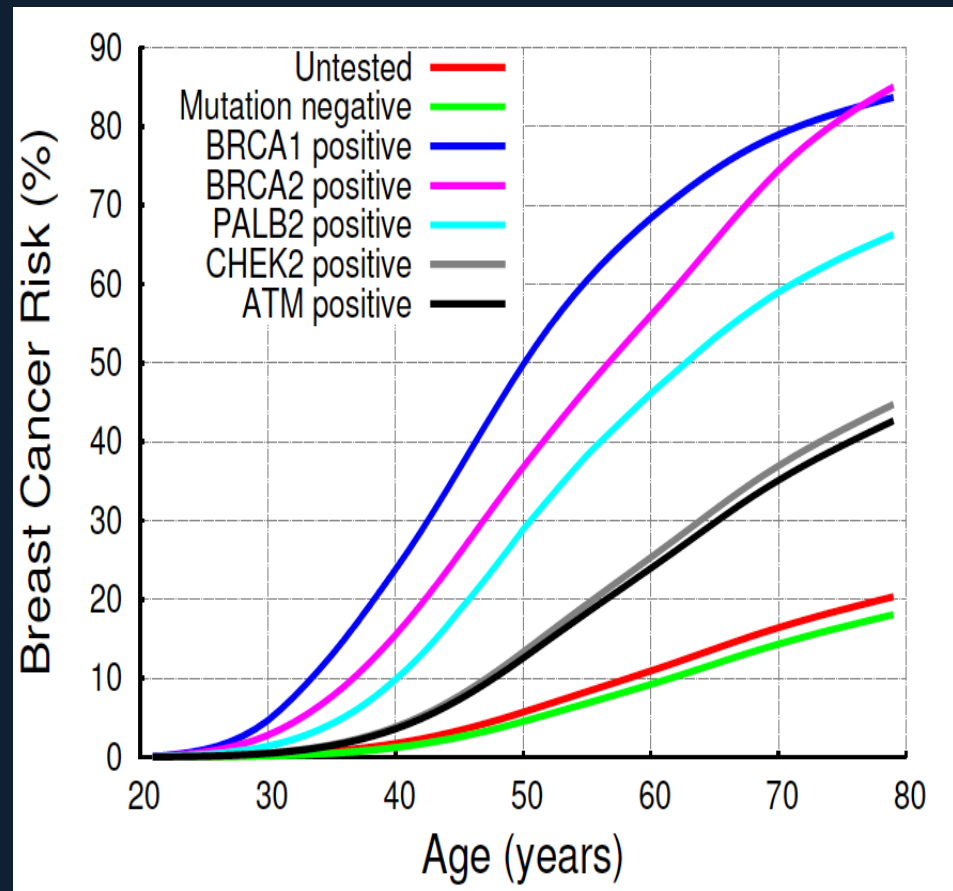


# Risks are family history specific

No affected relatives



Mother with BC at age 40



# BOADICEA: Beta v.4

<https://pluto.srl.cam.ac.uk/cgi-bin/bd4/v4beta14/bd.cgi>

BOADICEA Model Parameters

Use the menus below to change BOADICEA model parameters...

**Warning: computed risks are critically dependent on these settings**

Mutation frequencies: UK  
BRCA1: 6.394d-4  
BRCA2: 0.00102  
PALB2: 0.001  
ATM: 0.0019  
CHEK2: 0.0026

Mutation search sensitivities: Default  
BRCA1: 0.7  
BRCA2: 0.8  
PALB2: 0.8  
ATM: 0.8  
CHEK2: 0.8

Cancer incidence rates: UK

Output data display format: Percent

Update Model

---

BOADICEA

Computed results for the Target: Alice(1)

Genetic Status	Mutation Carrier Probabilities (Percent)	Age	Breast Can
BRCA1	0.4	41	0.3
BRCA2	0.8	42	0.5
PALB2	0.5	43	0.9
ATM	0.7	44	1.2
CHEK2	1.1	45	1.6
No Mutation	96.5	50	4.0
		55	6.7
		60	9.5
		65	12.5
		70	15.3
		75	17.6
		80	19.7

Model Parameters	
Target Family Member	Alice(1)
Mutation Frequencies: UK	Mutation Search Sensitivities: Default
BRCA1: 6.394d-4	BRCA1: 0.7
BRCA2: 0.00102	BRCA2: 0.8
PALB2: 0.001	PALB2: 0.8
ATM: 0.0019	ATM: 0.8
CHEK2: 0.0026	CHEK2: 0.8
Cancer Incidence Rates	UK

Logout Reset Go Back Graph Breast Cancer Risks Graph Ovarian Cancer Risks Reformat Generate Report

Edit details

Update details of this individual...

Clinical history Breast cancer pathology Genetic testing

BRCA1 Genetic test type:  Untested  Mutation search  Direct gene test  
Genetic test result:  Untested  Positive  Negative

BRCA2 Genetic test type:  Untested  Mutation search  Direct gene test  
Genetic test result:  Untested  Positive  Negative

PALB2 Genetic test type:  Untested  Mutation search  Direct gene test  
Genetic test result:  Untested  Positive  Negative

ATM Genetic test type:  Untested  Mutation search  Direct gene test  
Genetic test result:  Untested  Positive  Negative

CHEK2 Genetic test type:  Untested  Mutation search  Direct gene test  
Genetic test result:  Untested  Positive  Negative

# Conclusions

- PRS stratifies breast cancer risk in women with and without a family history of breast cancer, *BRCA1/2* mutations
- High levels of stratification can be achieved by combining all genetic and lifestyle/environmental factors
- Levels of risk stratification informative for targeted screening and prevention strategies
- Novel models (e.g. BOADICEA) available that can be used to counsel women undergoing gene-panel testing
- Risk prediction models and tools required based on valid assumptions about the joint risk factor effects
- Risk model validation required in large prospective cohorts

# Acknowledgments

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Roger Milne

*OCAC*

Cathy Phelan

*IBCCS*

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C. Apicella

