Heritability, OPERA and ICE FALCON:
thoughts on causation, and causes of variation in (some aspect of a) disease

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Heritability: what it isn't

Heritability is *not* the proportion disease due to genes

Many (mis)interpret it this way

Tomlinson et al. A genome-wide association study identifies colorectal cancer susceptibility loci on chromosomes 10p14 and 8q23.3. *Nat Genet* 2008;40:623-30.

Characteristic of a population in fixed environment

Crude measure of the impact of genes on variation, not on cause *per se*

Heritability of a continuous trait

In 1918, Ronald Fisher defined heritability
– for a measured continuously distributed trait –
as the proportion of variance explained by genetic factors

He showed the genetic component of variance is transmitted to future generations

Thereby related Mendelian inheritance of qualities to genetic variance of quantities

Fisher RA. The correlation between relatives on the supposition of Mendelian inheritance.

Trans Roy Soc Edinb 1918;52:399-433.

Hotch-potch of a denominator

Fisher showed that it was the *absolute* genetic variance, not a percentage, that was important

Fisher referred to the total variance as a "hotch-potch of a denominator"

He admonished that:

"loose phrases about the "percentage of causation", which obscure the essential distinction between the individual and the population, should be carefully avoided"

Fisher RA. Limits to intensive production in animals. *Brit Agric Bull* 1951;4:217-218.

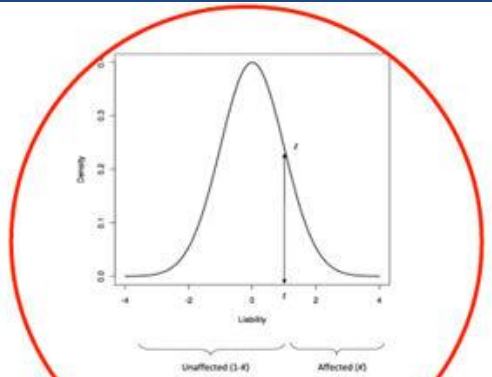
Heritability of an unmeasured trait

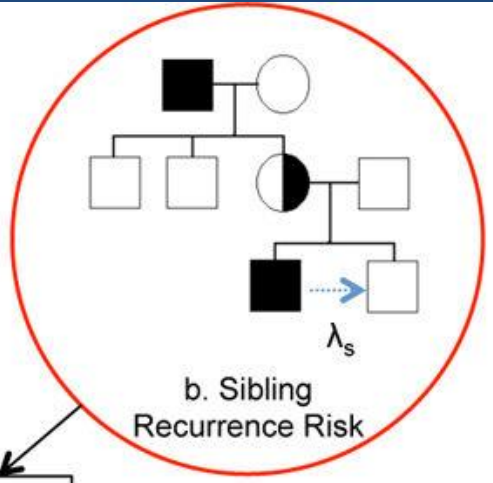
Heritability for binary traits (disease) is problematic

Can apply the continuous trait approach but the estimates are typically small and it is not used.

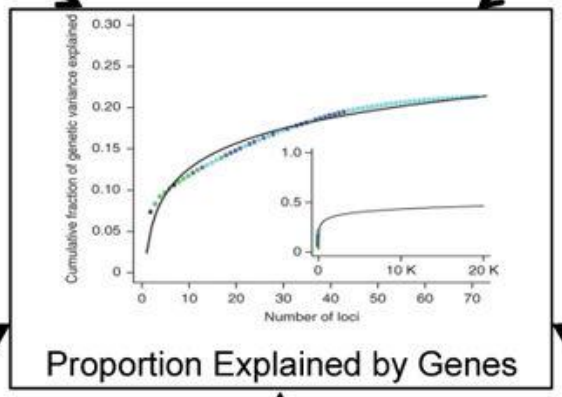
Prevailing paradigm is to assume an underlying latent (i.e. unmeasured) 'liability' scale representing risk, make untestable distribution & modelling assumptions, and make inference as if this was a measured continuous variable

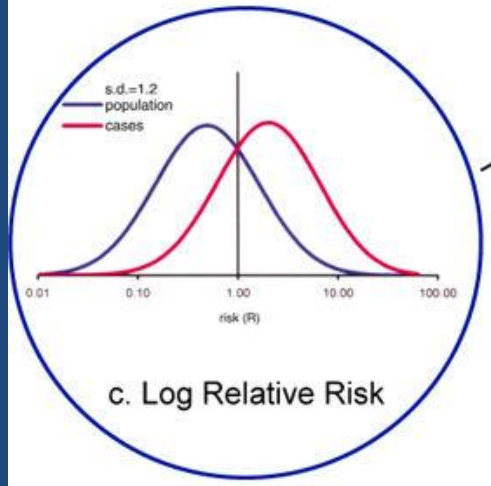
Often incorrectly implied or assumed that 'heritability of liability' is the 'heritability of disease'

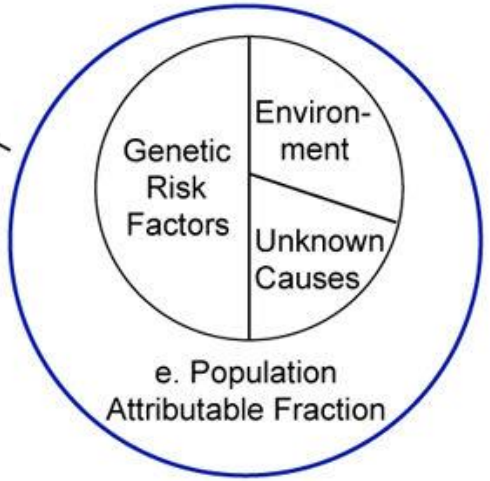


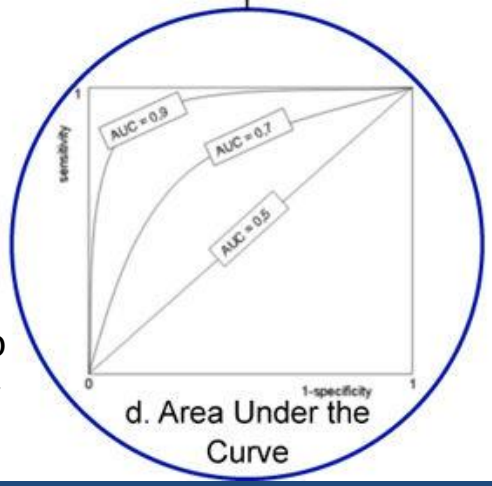


Genetics



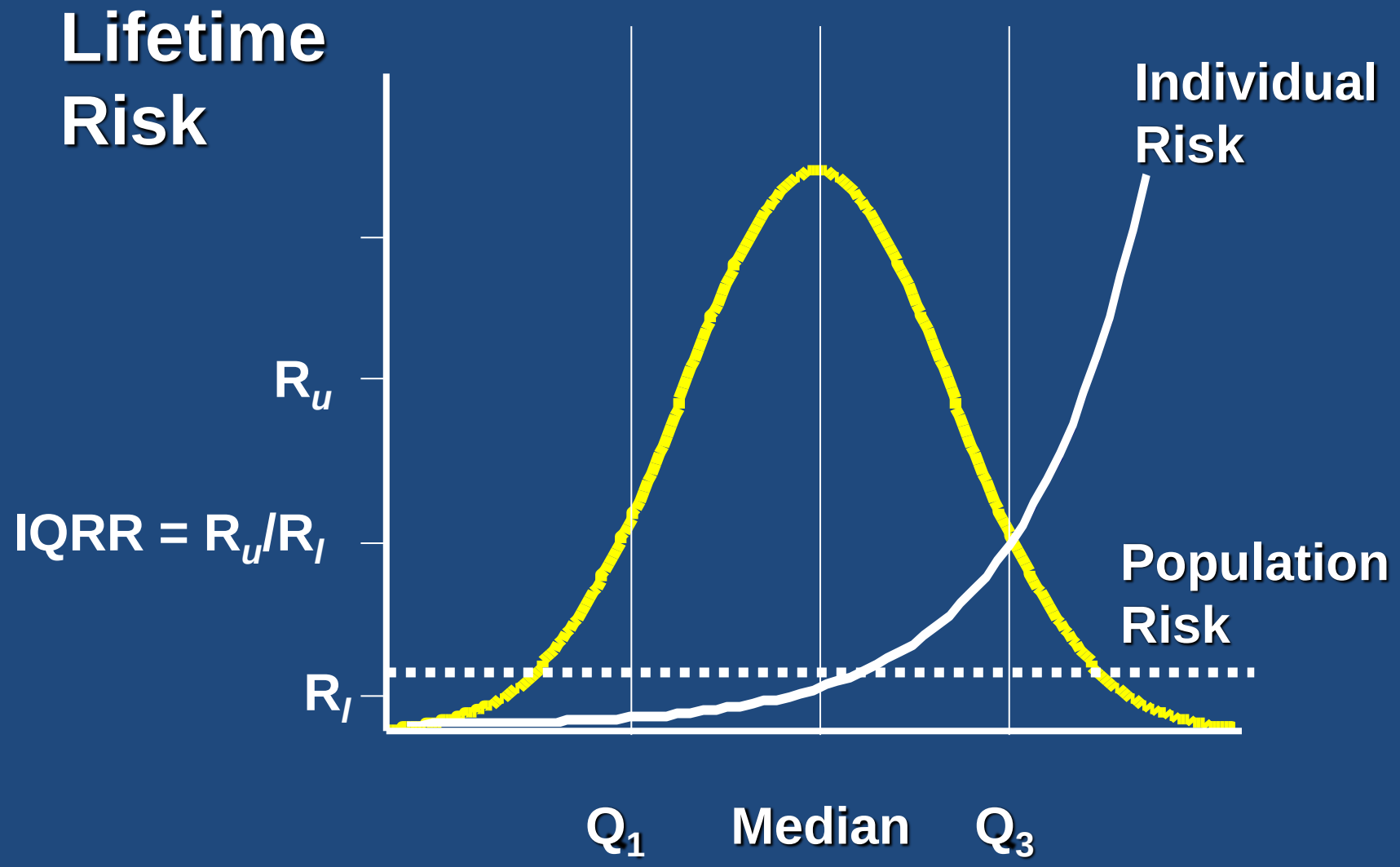






Epidemiology

Witte, Visscher & Wray. The contribution of genetic variants to disease depends on the ruler. *Nat Rev Gene*t. 2014;15:765-76.



Familial Risk Profile

Familial Risk implies Familial Correlations in Risk Factors

IQRR = risk ratio between upper and lower quartile of Familial Risk Profile (FRP)

r = correlation between relatives in FRP

OR = odds ratio for disease in relatives

Hopper & Carlin. Familial aggregation of a disease consequent upon correlation between relatives in a risk factor measured on a continuous scale. *Am J Epidemiol* 1992; 136: 1138-1147

Aalen. Modelling the influence of risk factors on familial aggregation of disease. *Biometrics* 1991; 47: 933-945

Odds Ratio (OR) for Disease in Relatives of Affected

IQRR	r = correlation in relatives				
	0.2	0.4	0.6	0.8	1.0
1.5	1.01	1.01	1.02	1.02	1.03
2	1.02	1.03	1.05	1.06	1.08
3	1.04	1.08	1.12	1.16	1.21
5	1.08	1.17	1.27	1.38	1.49
10	1.17	1.37	1.61	1.88	2.20
20	1.30	1.67	2.15	2.76	3.53
100	1.66	2.71	4.29	6.70	10.4

Variation in risk due to familial factors

For any familial risk (increased risk for relatives of an affected) there are an infinite set of possibilities for:
(i) correlation between relatives in underlying risk; and
(ii) gradient in underlying risk across the population

A given increase in risk for MZ co-twin of an affected twin is consistent with 100% heritability and one gradient of risk, or any heritability < 100% and a corresponding (smaller) gradient of risk

Non-genetic factors can also explain familial risk!

… unmeasured non-familial factors?

All depends on the variation in risk explained by non-familial factors, which could vary across populations and time, and be more than just what is known to date for measured 'environmental' factors

Denominator is not so much a "hotch-potch", it is simply unknowable!

Why ‘all-or-nothing’ liability assumption?

All-or-nothing assumption of the liability model - risk is 100% for those above a given threshold - is arbitrary

There are no degrees of freedom to test this assumption!

Hardly a basis for a scientific theory

What if another liability assumption?

Different scenarios give different correlations in liability

e.g. prevalence = 10% and OR_{MZ} = 5

Proportion above threshold at risk	Correlation in liability
100%	0.5
50%	0.3
25%	0.1

Heritability estimates depend greatly on the assumed liability model

Conclusion

Estimates of the "heritability of *liability*" rely on distributional and other untested assumptions and are not statistically robust

Not a sound scientific construct

Estimates of the "heritability of a disease" are virtually meaningless

It suggests "proportion of disease due to genes"

This not correct, no matter what model is assumed

Comparing risk factors gradients measured on different scales using Odds PER Adjusted standard deviation

(OPERA)

Inspired by Mammographic Density

- (P)MD is “second to BRCA1/2” … but is it?
- Binary versus continuous
- (P)MD is not the risk factor, it is (P)MD for age and BMI
- OPERA is a unifying concept …

1. How can the 'strengths' of risk factors, in sense of how well they discriminate cases from controls, be compared when measured on different scales (continuous, binary, and integer)?

2. Risk estimates take into account other fitted and design-related factors

- That is how risk gradients are interpreted
- So should the presentation of risk gradients

Odds PER Adjusted standard deviation (OPERA)

- For risk factor X_0, derive best fitting relationship between mean of X_0 and all other covariates fitted in the model or adjusted for by design

$(X_1, X_2, \ldots, X_n)$

OPERA presents risk association for X_0

in terms of change in risk per

standard deviation of X_0 ***adjusted for*** $X_1, X_2, \ldots, X_n$,

rather than standard deviation of X_0 itself.

Binary Risk Factors

- For binary factor with prevalence p,

$$s = [p(1-p)]^{0.5}$$

- $A = 1/s$ is the number of standard deviations between the two outcomes

- Risk increases RR-fold over A standard deviations

$$\text{OPERA} = \exp[\ln(RR)/A] = RR^{s}$$

Sex/gender

- Binary (0 = male, 1 = female); $p = 0.5$
- Assume $RR = 100$, say
- Standard deviation $s = [p(1-p)]^{0.5} = 0.5$ (i.e. $A = 2$)

- **OPERA = exp [ln(100)/2)] = $100^{0.5}$ = 10**

- Change from 0 to 1 is $A = 2$ standard deviations
- Odds increase by 100 over two standard deviations
- So increases 10-fold over one standard deviation

Family history: binary

- Binary variable: having an affected first-degree relative (0 = no, 1 = yes)
- Assume $p = 0.1$, say
- $RR = 2$ for having such a family history
- Standard deviation is $s = 0.3$ and $RR = 2$
- **OPERA = $2^{0.3} = 1.23$**

BRCA1 and *BRCA2*

- Probability of being a mutation carrier in either gene ~1 in 600, though as high as 1 in 40 for e.g. Ashkenazi Jewish women
- RR ~ 10-fold, though higher for *BRCA1* carriers at a young age; e.g. 30-fold at age 30
- *p* = 1/600: R*R* = 10 (30) then **OPERA = 1.10 (1.15)**
- *p* = 1/40: *RR* = 10 (30) then **OPERA = 1.43 (1.70)**

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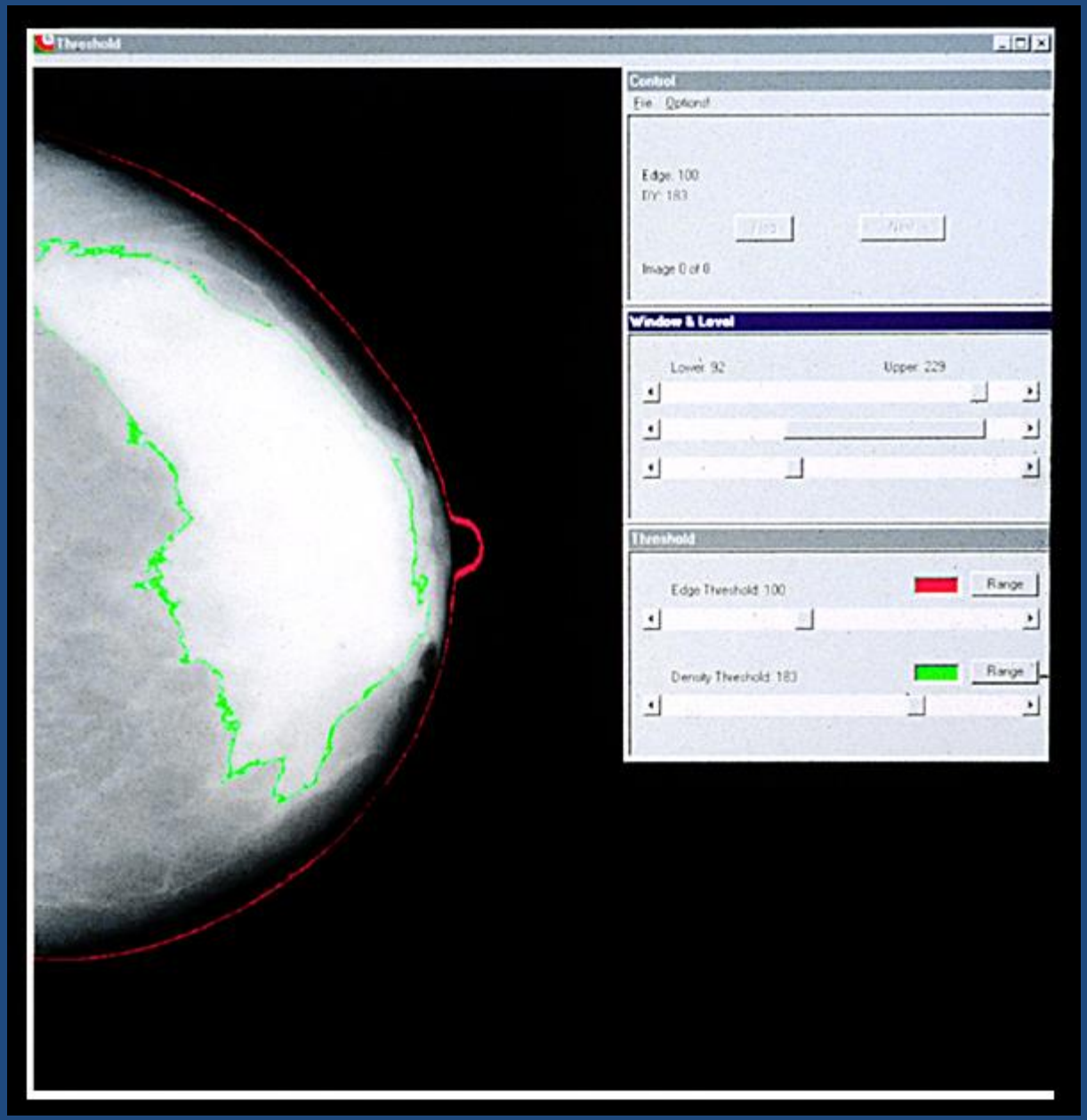
All familial factors

- Multitude of familial factors explain 2-fold increased risk for having affected 1^0 relative
- Under a multiplicative polygenic model, interquartile risk ratio ~20-fold
- Mean upper quartile of normal distribution is 1.27 SD
- 20-fold increased risk across 2.54 standard deviations: IQRR = $OPERA^{2.54}$
- **OPERA = 3.25**

Number of births

- Approximate Poisson distribution, mean *m*
- Standard deviation, *s*, is approximately $m^{1/2}$
- Suppose *m* = 2; each child *x* = 7% reduction in risk
- Risk decreases *RR* = (1+*x*)-fold over $A = 1/(2^{1/2})$
- **OPERA = exp [ln(1+*x*)/A] = 1.10**
- *Maybe less after adjusting for age*
- Note: although protective, *OPERA* >1 (see definition)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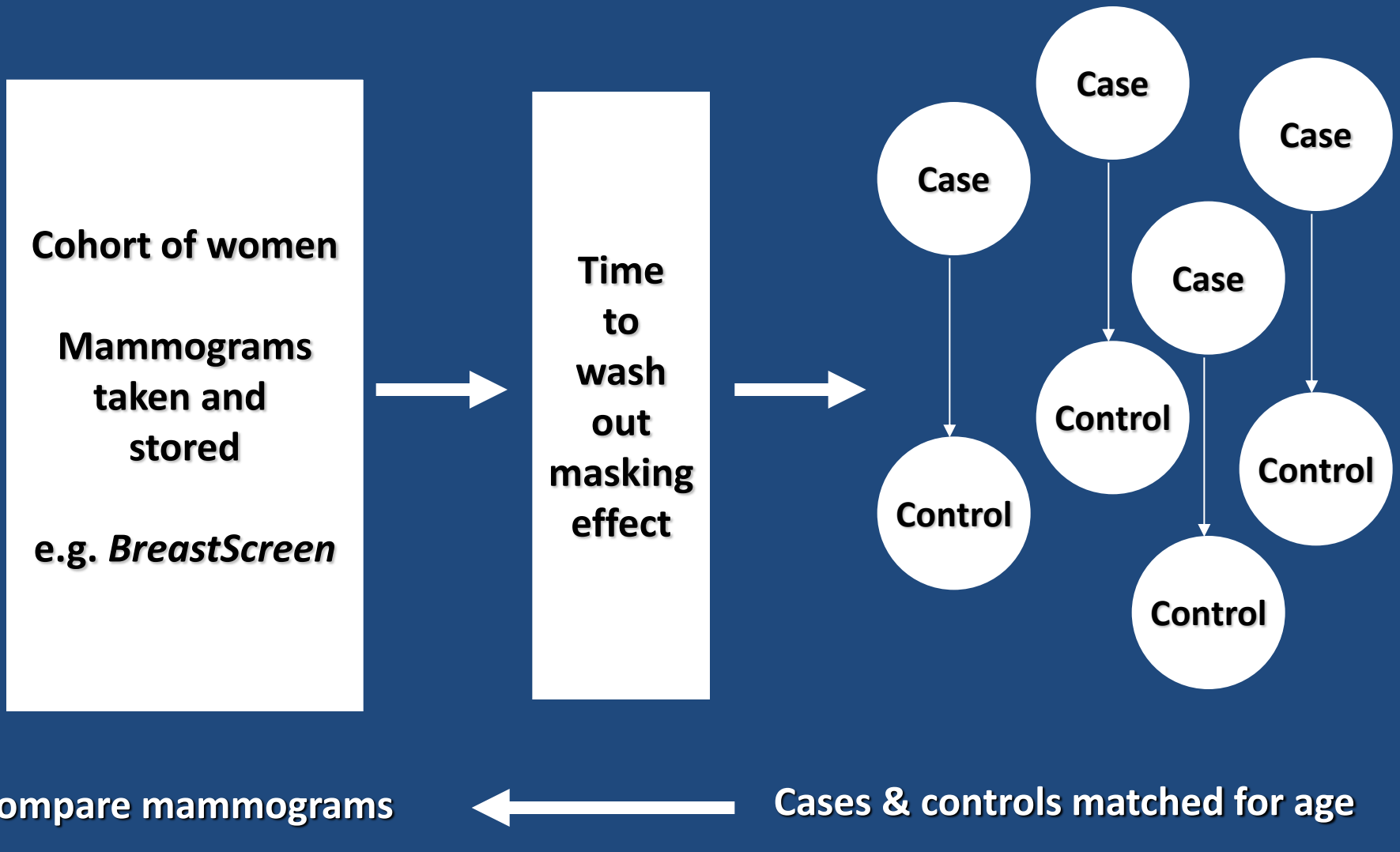
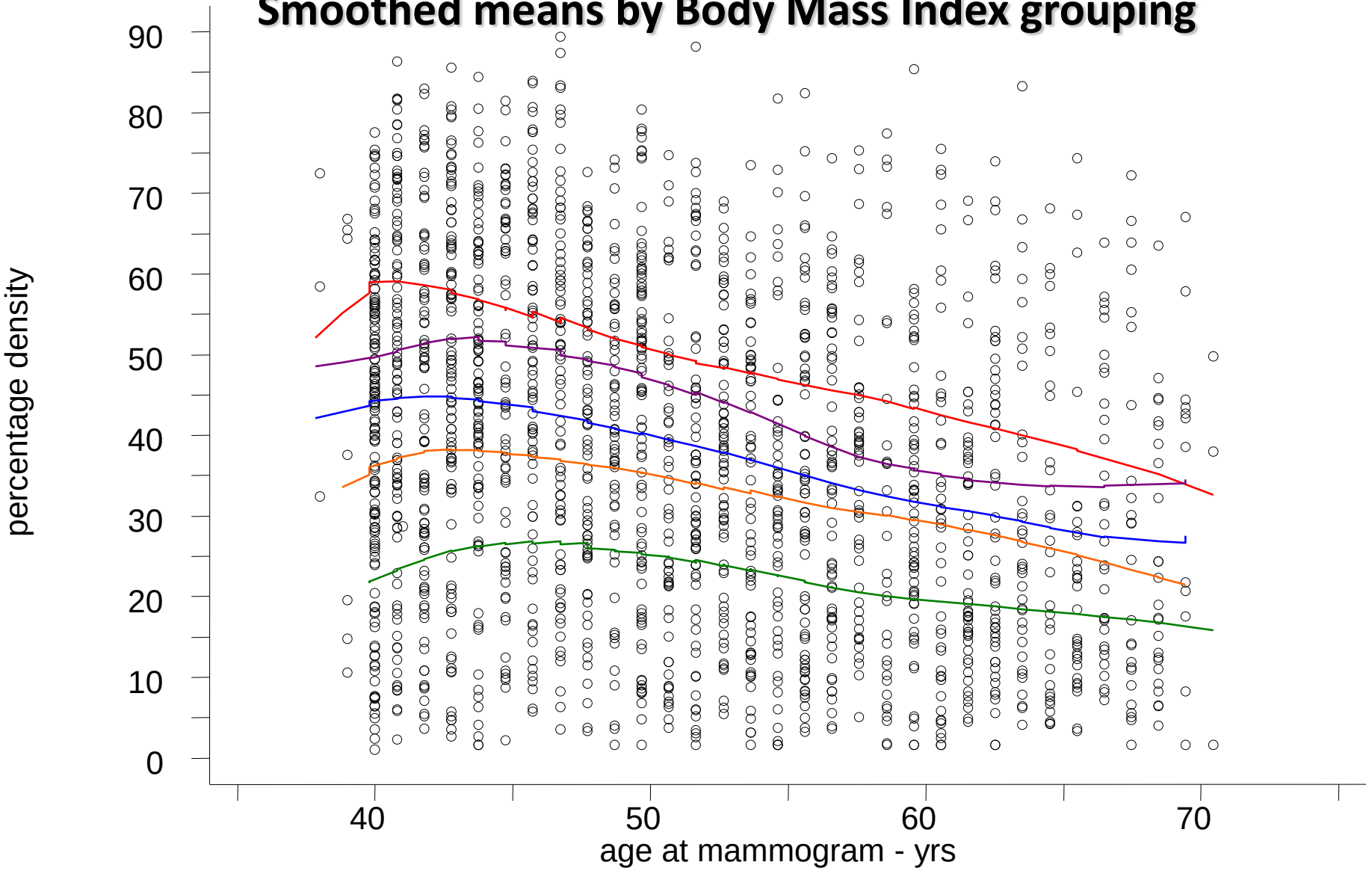
Prospective nested case-control studies in screening cohorts

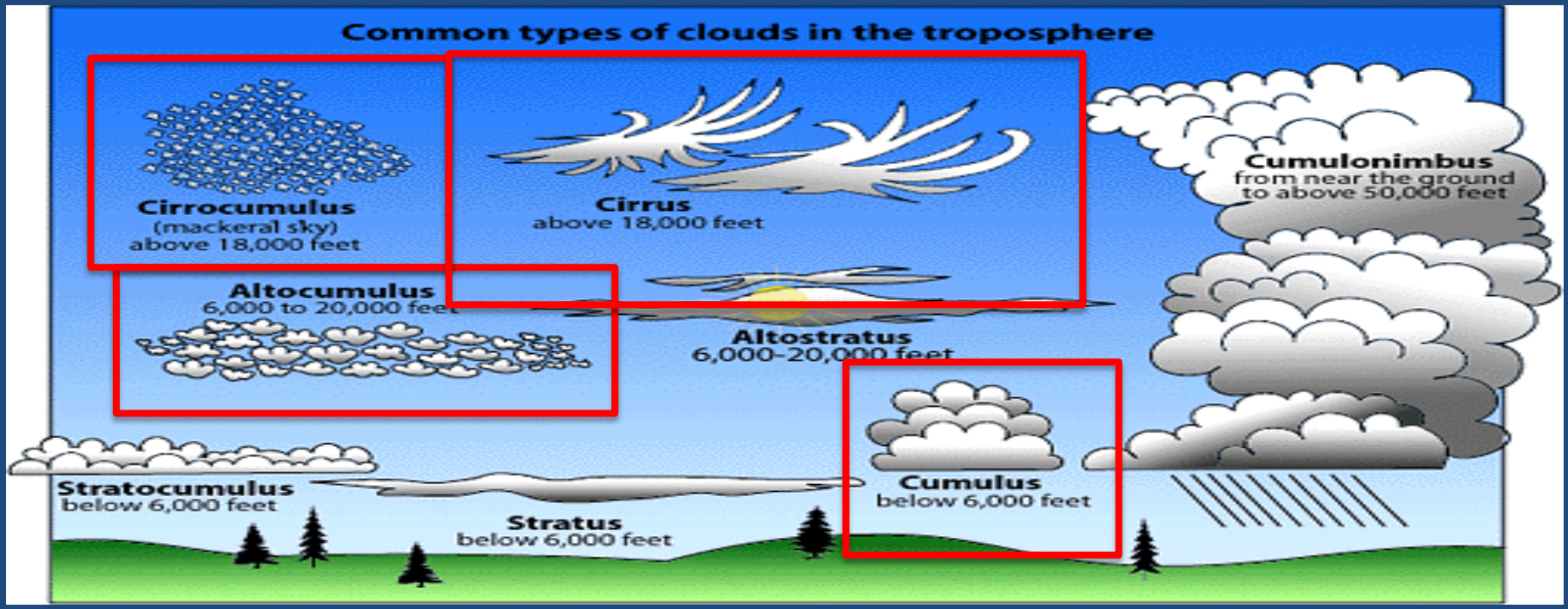


Smoothed means by Body Mass Index grouping



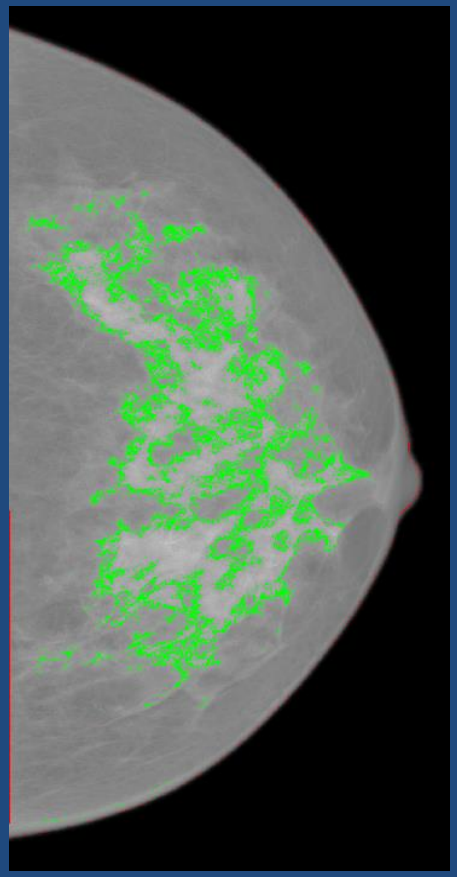
< 21.47	21.48 - 23.29	23.30 - 25.20	25.21 - 28.50	>= 28.51

Mammographic density measures by CUMULUS

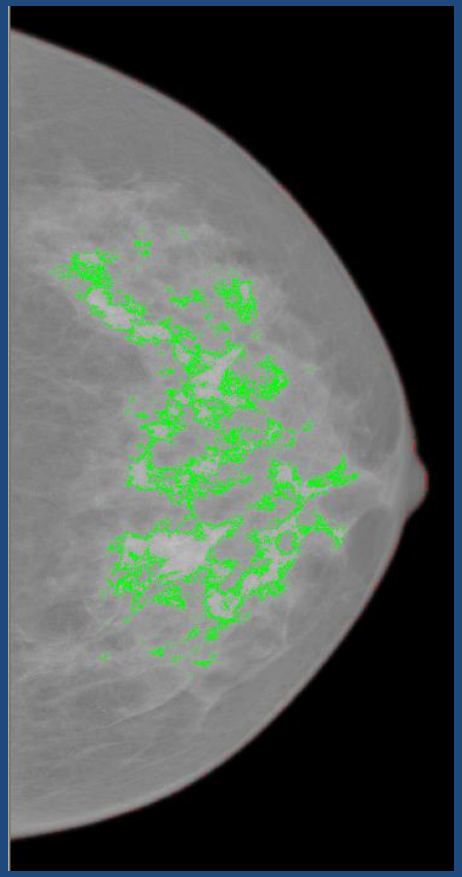


- CUMULUS (Byng, Boyd, Yaffe): standard method, select white or bright non-fat tissue
- ALTOCUMULUS (Nguyen): select mammographic density at higher threshold (brighter area)
- CIRROCUMULUS (Nguyen): select mammographic density at higher threshold (brightest area)

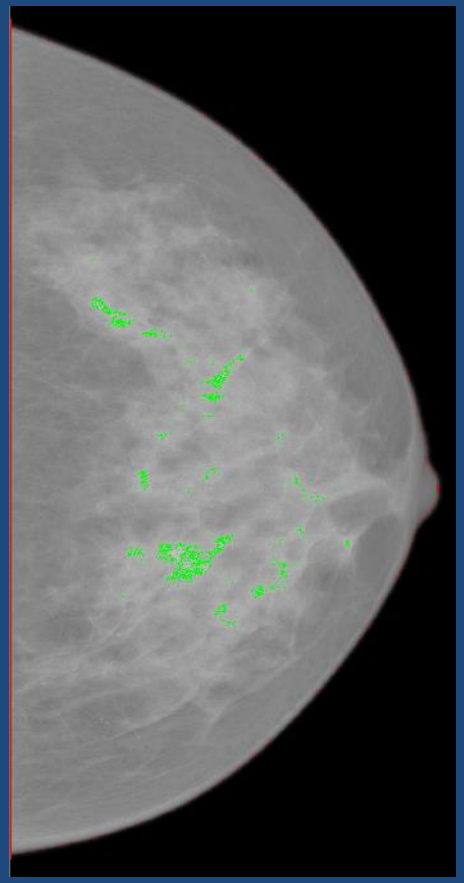
Mammographic density measures by CUMULUS



Cumulus:
Dense Area =331,976 pixels
Percent Density =26.77%



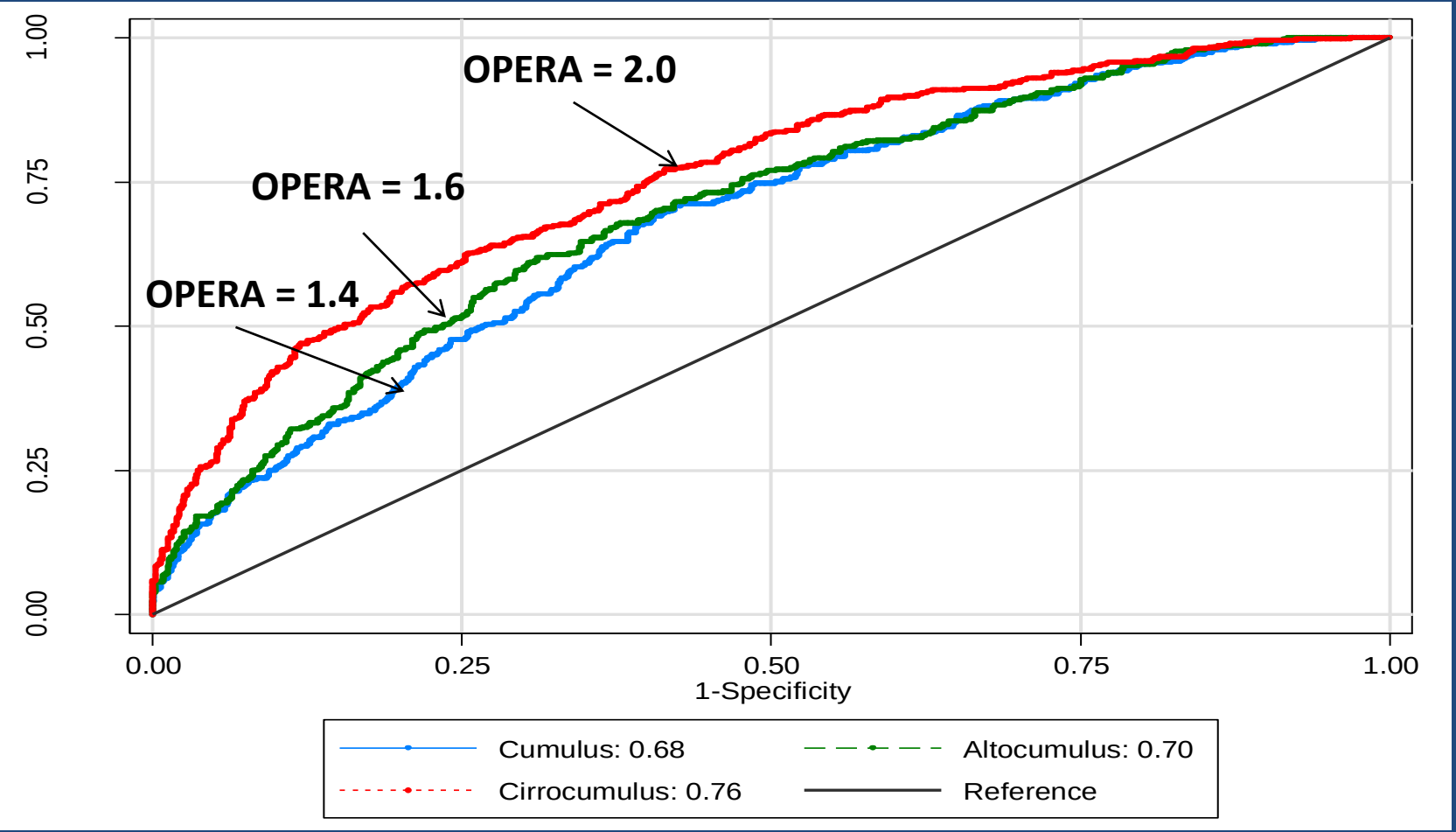
Altocumulus:
Dense Area =123,041 pixels
Percent Density =9.92%
Correlation with Cumulus =**0.8**



Cirrocumulus:
Dense Area =12,986 pixels
Percent Density = 1.05%
Correlation with Cumulus =**0.6**

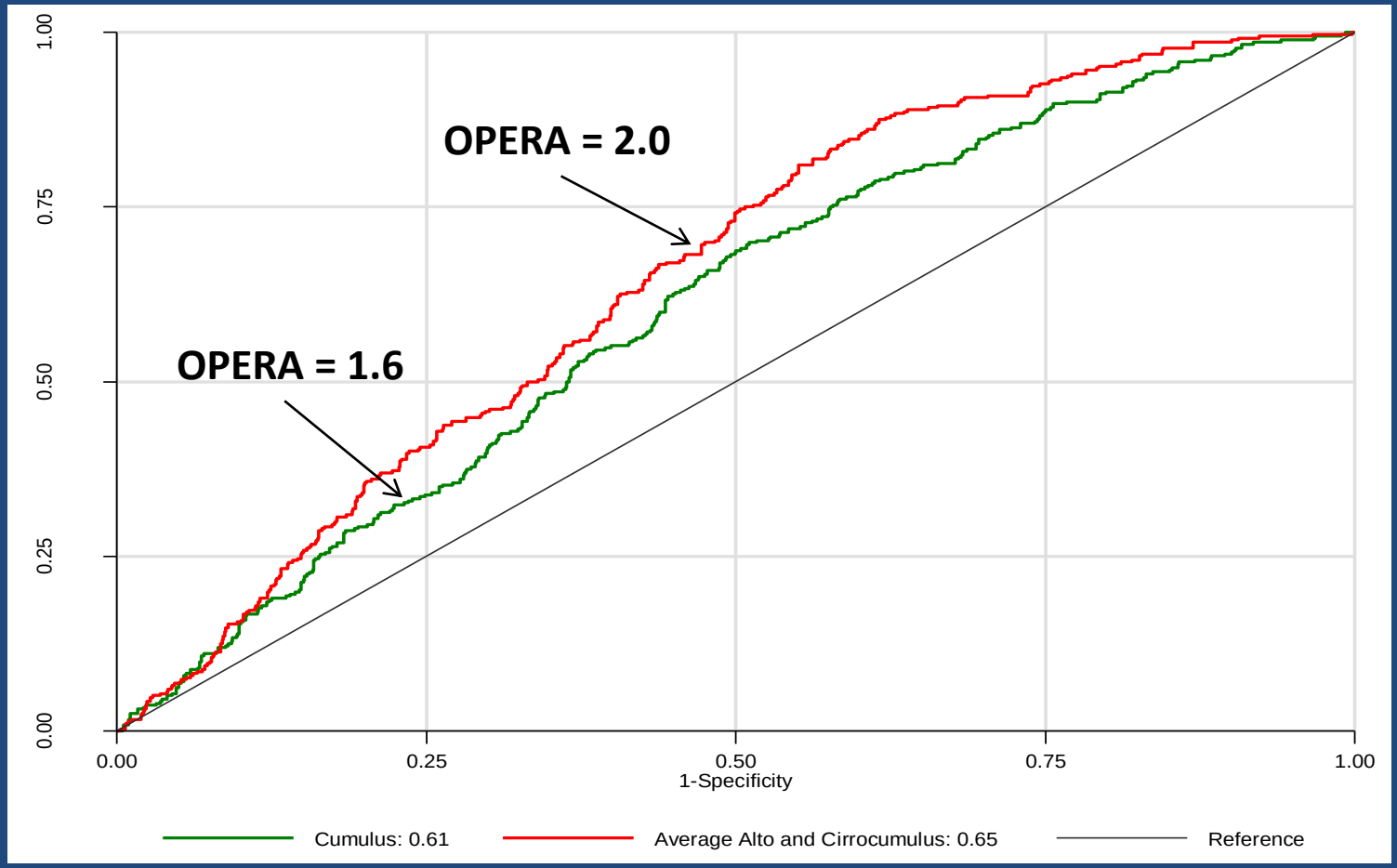
Preliminary results (Korean women 2010 - 2013)

Area Under ROC Curve values to access the discriminatory performance adjusted Dense Area of *Cumulus* (blue), *Altocumulus* (green) and *Cirrocumulus* (red)



Preliminary results (ABCFR – AMDTSS - BCNA)

Area Under ROC Curve values to access the discriminatory performance adjusted Dense Area of *Cumulus* (green) and Average of Alto- and *Cirrocumulus* (red)



Mammographic Density

- Mammographic density - white or bright areas on a mammogram – adjusted for age and BMI
- Observations show that the *OPERA* ~ 1.40
- Novel approaches to extracting more information on risk from mammograms, are proving to be even better risk predictors
- **OPERA as high as 2.0**
- These are not as familial (e.g. r_{MZ} = 0.2 cf. 0.6)

Epi-Genome Wide Methylation in Blood

- Measured from peripheral blood using Illumina Infinium Human Methylation 450 BeadChip array and Melbourne Collaborative Cohort Study

Severi et al. *Breast Cancer Res Treat*. 2014;148:665-73.

- **OPERA ~ 1.4**

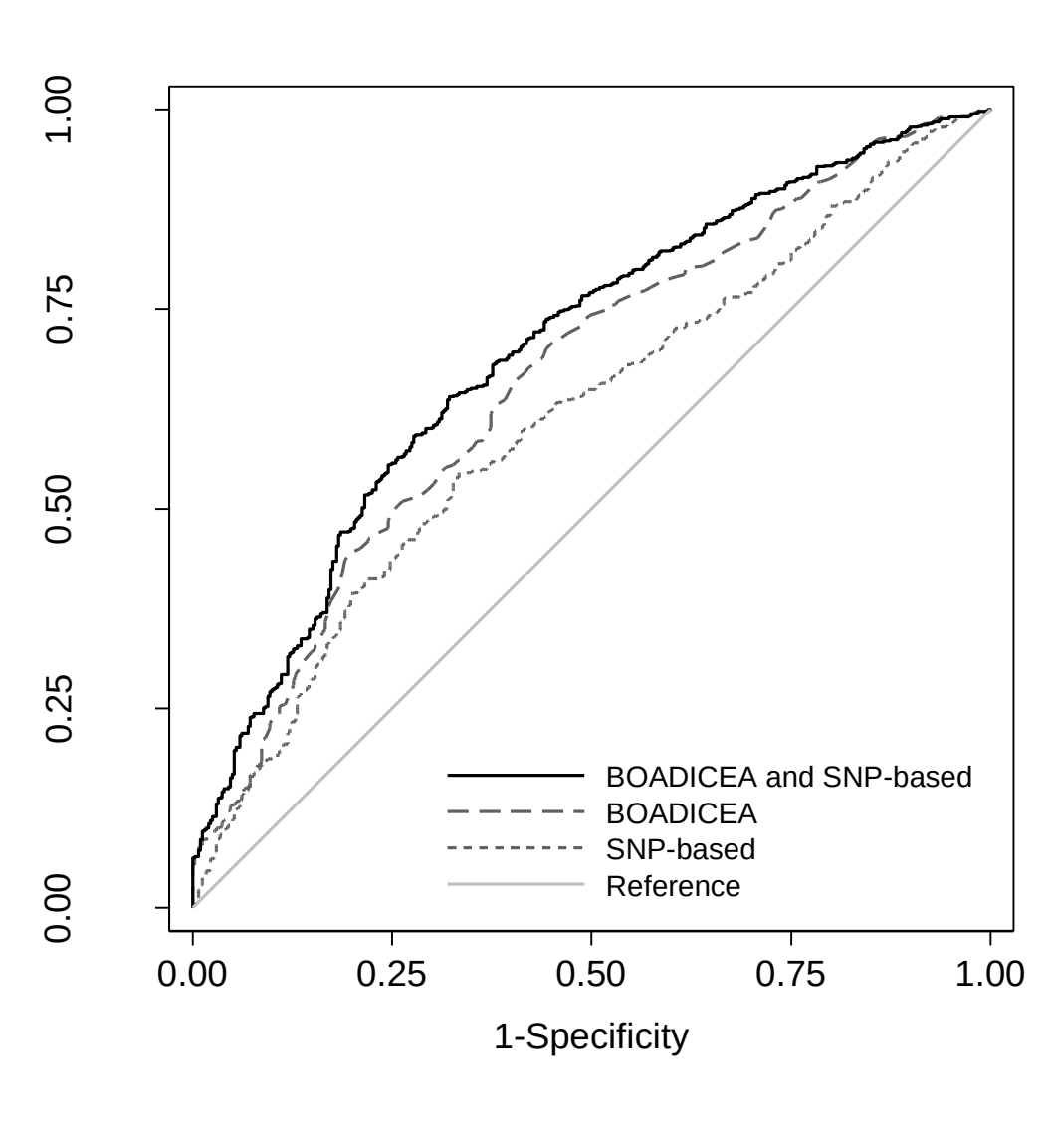
- Familial associations from twins and sisters:

  r_{MZ} and r_{DZ} = 0.4 (SE 0.1); r_{sib} = 0.0 (SE = 0.05)

Single Nucleotide Polymorphisms (SNPs)

- Common genetic markers
- SNPs associated with risk are being found
- Currently 77 independent common genetic markers known to predict breast cancer risk explain ~14% of familial aggregation
- OPERA = 1.56 overall; 1.6 for ER+ve and 1.4 for ER-ve disease, reflecting sampling

BOADICEA and SNP score adjusted for age



Breast Cancer before age 50 years: Australian Breast Cancer Family Registry

Log Risk Score*	OPERA (95% CI)	AUC
SNP score	1.46 (1.29-1.64)	0.61
BOADICEA	1.80 (1.57-2.07)	0.66
BOADICEA & SNP	**1.96 (1.71-2.24)**	0.70
BRCAPRO	1.75 (1.52-2.02)	0.65
BRCAPRO & SNP	1.89 (1.66-2.16)	0.69

* Age-adjusted

OPERA scores for breast cancer

Risk factor	OPERA	Comment
Gender	10	
Age	?	Depends on ages
All familial causes	>3	Known and unknown
Mammographic density	**1.4-2.0**	**Likely to increase**
Family history models	**1.8**	**Multi-generations**
Known polygenic markers	**1.6**	**Likely to increase**
Global methylation	**1.4**	**Not highly familial**
Known gene mutations	1.2-1.7	Depends on age/ethnicity
Family history	1.2	First-degree only; yes/no
Number of child births	1.1	Depends on family size

How do OPERAs increase when combing variables?

- OPERAs are independent, but for combined scores they do not multiply
- Instead, the log OPERAs increase like the hypotenuse of a right-angled triangle
- If $OPERA_1 = 1.5$ (ln 1.5 = 0.4) and $OPERA_2 = 1.5$, $OPERA_{12} = 1.8$ ($= e^{0.6}$)
- As predictors get better, it gets harder to improve (in terms of AUC, OPERA, etc.)

Putting risk gradients into perspective across diseases, populations and settings

- Risk gradients can be compared across
  - diseases
  - sub-sets of a disease (e.g. based on age at onset or sub-type)
  - populations and different environmental settings
- For any risk factor, rank the diseases to which it predisposes
- How changes in a risk factor impact on multiple diseases - for which disease(s) an intervention might have most impact
- Take into account benefits per disease (some might be negative) to see the overall impact of the intervention

Summary

- OPERA estimates are independent, by definition

  (Of course, depend on sample and population)

- Compare predictive strengths of risk factors across:
  - diseases
  - populations, etc.

- OPERA principle also applies to hazard ratio (HR) estimates from cohort studies