CanPath
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Pre-diagnostic serum metabolomics and breast cancer risk

LY TRINH
SCHOOL OF POPULATION AND PUBLIC HEALTH, UNIVERSITY OF BRITISH COLUMBIA
BC CENTRE FOR CANCER RESEARCH

CANPATH TRAINEE RESEARCH WEBINAR
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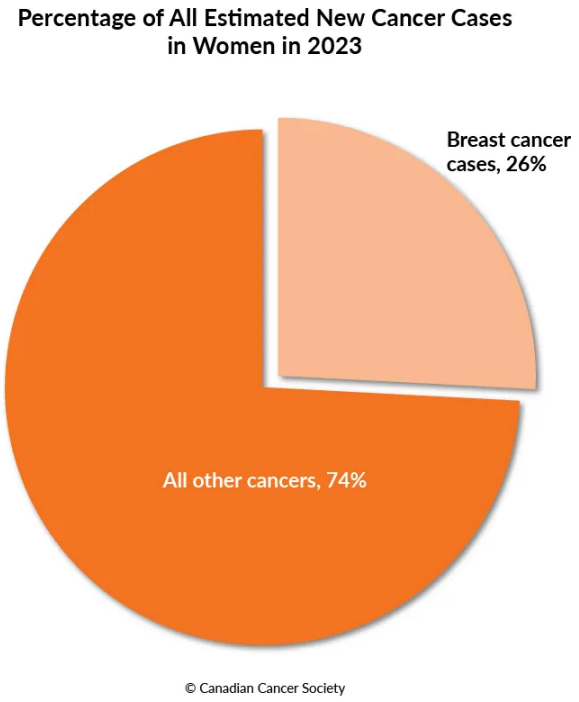
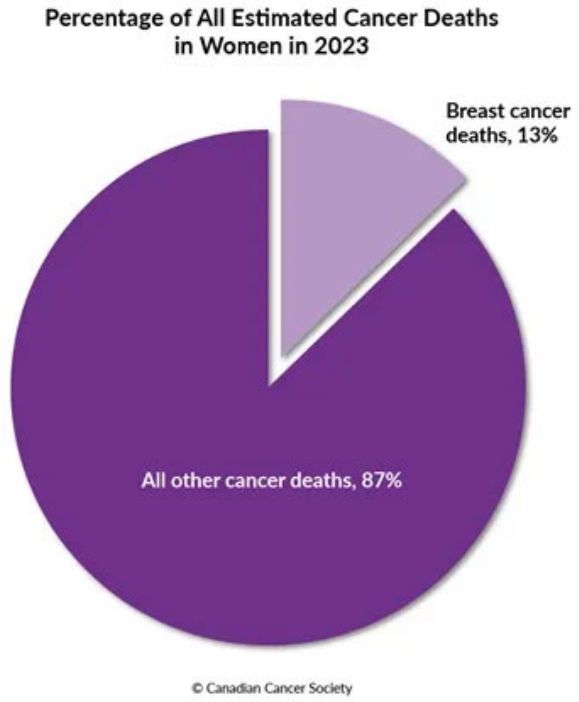
Introduction
Breast cancer epidemiology

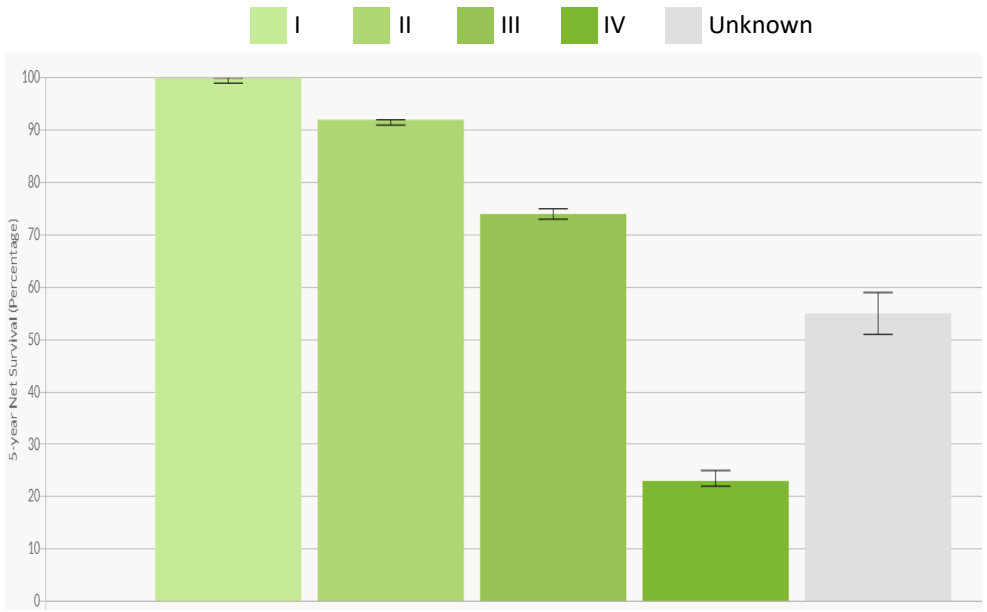




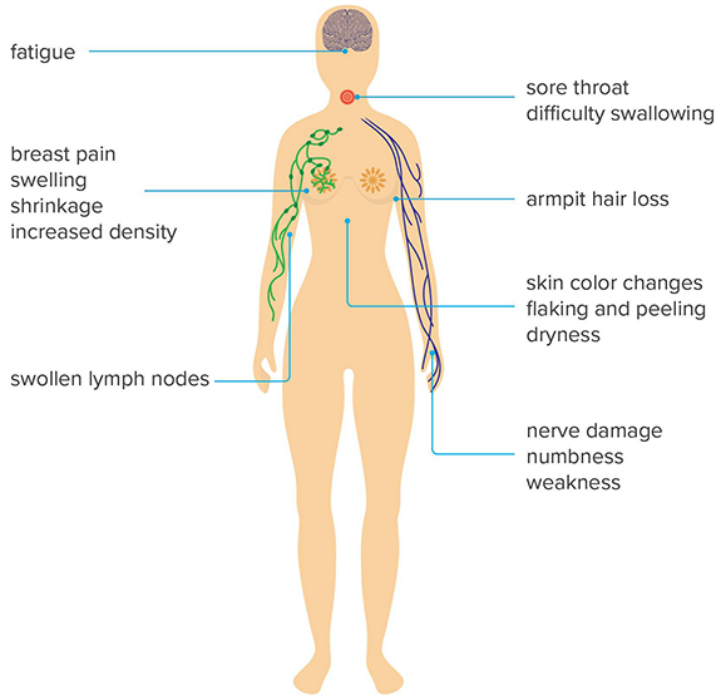
Source: cancer.ca

Introduction
Breast cancer epidemiology

Five-year stage-specific breast cancer survival, ages 15-99, Canada (excluding Quebec)
2010-2017 period



Source: cancerstats.ca

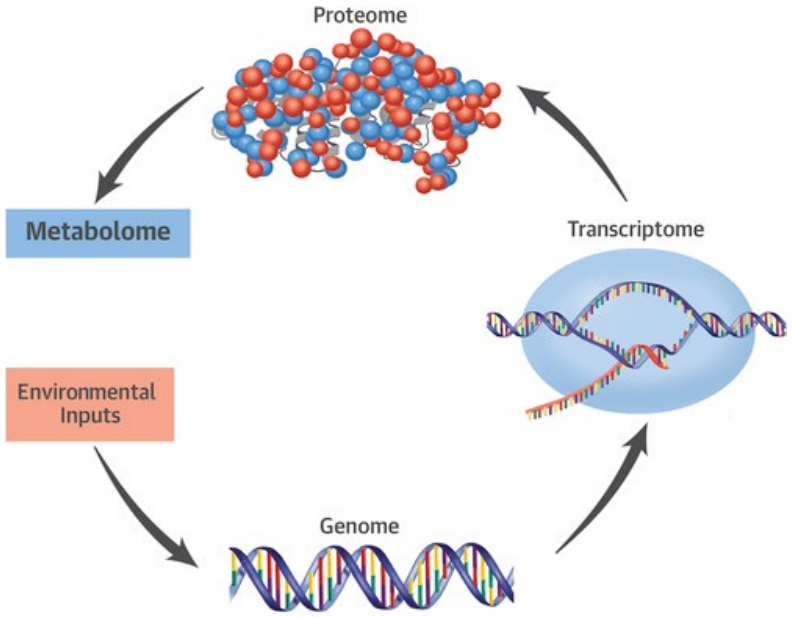


Source: ohcare.com

- Breast cancer survival remains poor for later stages, and survivors face long-term adverse effects
- Identifying patients at elevated risk allows for targeted intervention and enhanced screening

Introduction
Metabolomics

- Metabolomics is the study of low-molecular-weight molecules (i.e., metabolites) in biological samples
- Metabolites provide a functional readout of genes and environment
- Pre-diagnostic samples are key for risk prediction



Source: Ussher et al (2016), JACC.

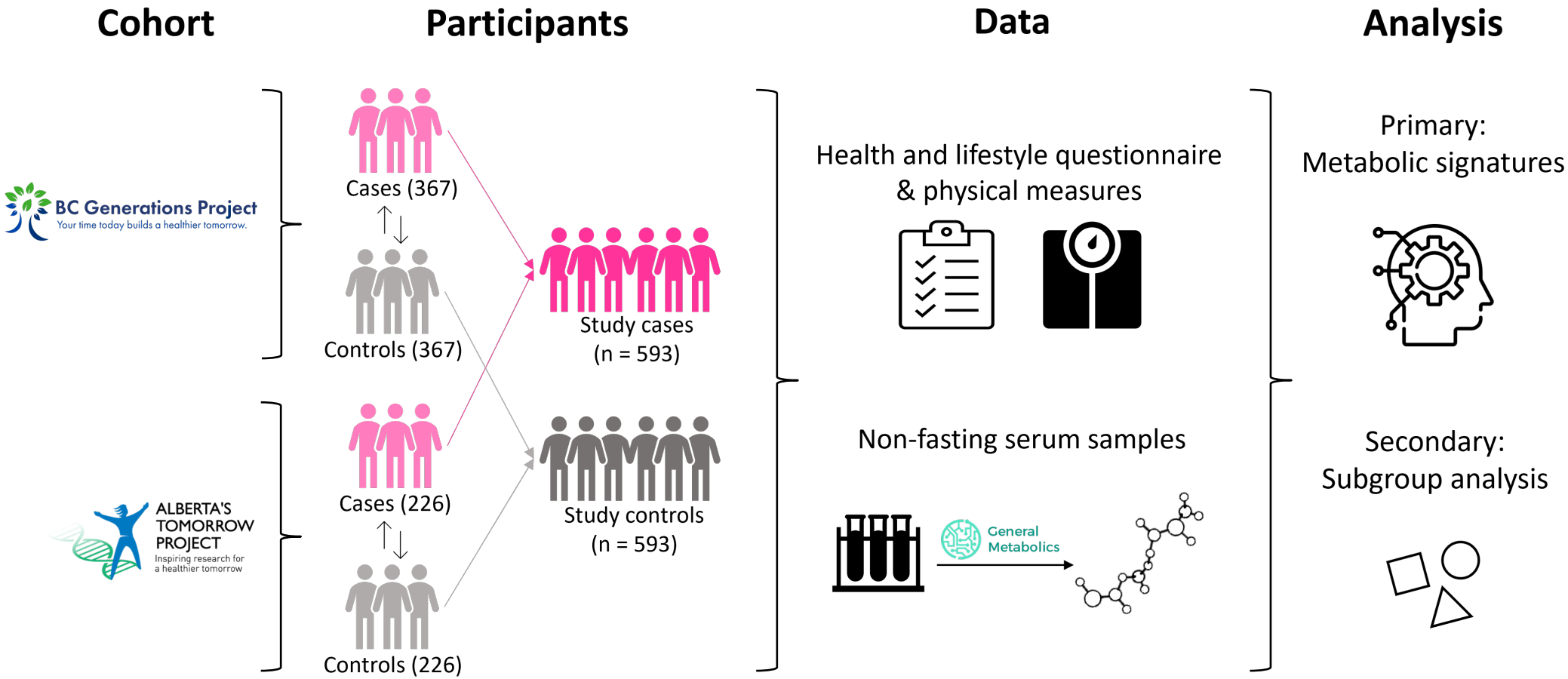
Introduction

Study objectives

- Determine metabolomic signatures associated with breast cancer risk
- Utilize metabolites to predict breast cancer risk

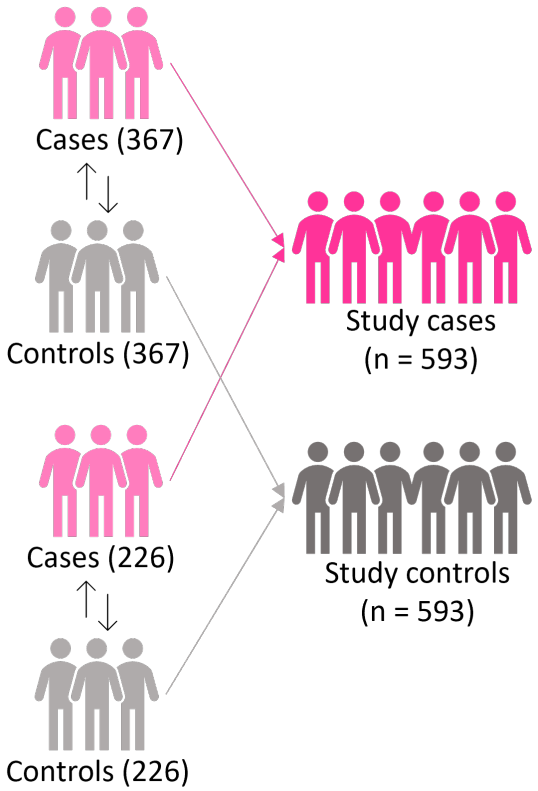
Methods

Study design



Methods

Participants



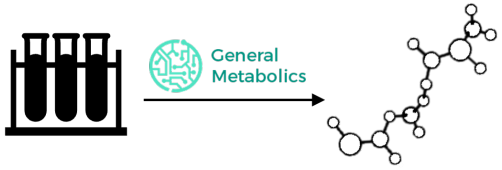
- Cancer-free at baseline
- Diagnosis ascertained through cancer registries
- 1:1 case-control matching
  - Cohort
  - Age at blood collection
  - Year of blood collection (+/-2 years)
  - Baseline menopause status

Methods

Data

Health and lifestyle questionnaire & physical measures

Non-fasting serum samples



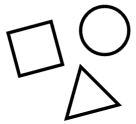
- Baseline questionnaire and measurements
  - Demographics
  - Family and reproductive history
  - Lifestyle behaviors
- Untargeted metabolomics
  - Blood samples collected at baseline
  - Quadrupole time-of-flight mass spectrometry (Q-TOF-MS) by General Metabolics (Boston, MA)
  - Compound annotations based on HMDB, ChEBI, and KEGG

Methods

Analysis

Primary:
Metabolic signatures

Secondary:
Subgroup analysis

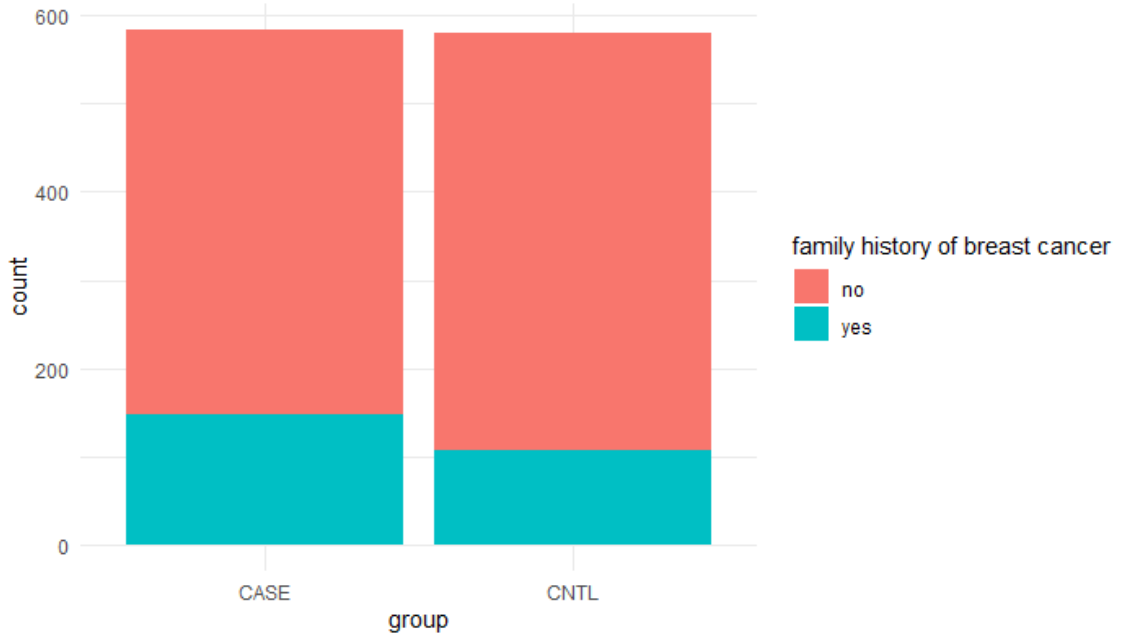


- Assess breast cancer risk associated with each metabolite, adjusting for matching factors and confounding
- Breast cancer risk prediction using metabolomics data (ongoing)
- Subgroup analyses for postmenopausal (72%), ductal carcinoma (75%), and hormone receptor-positive cases (78%) (ongoing)

Results

Study characteristics

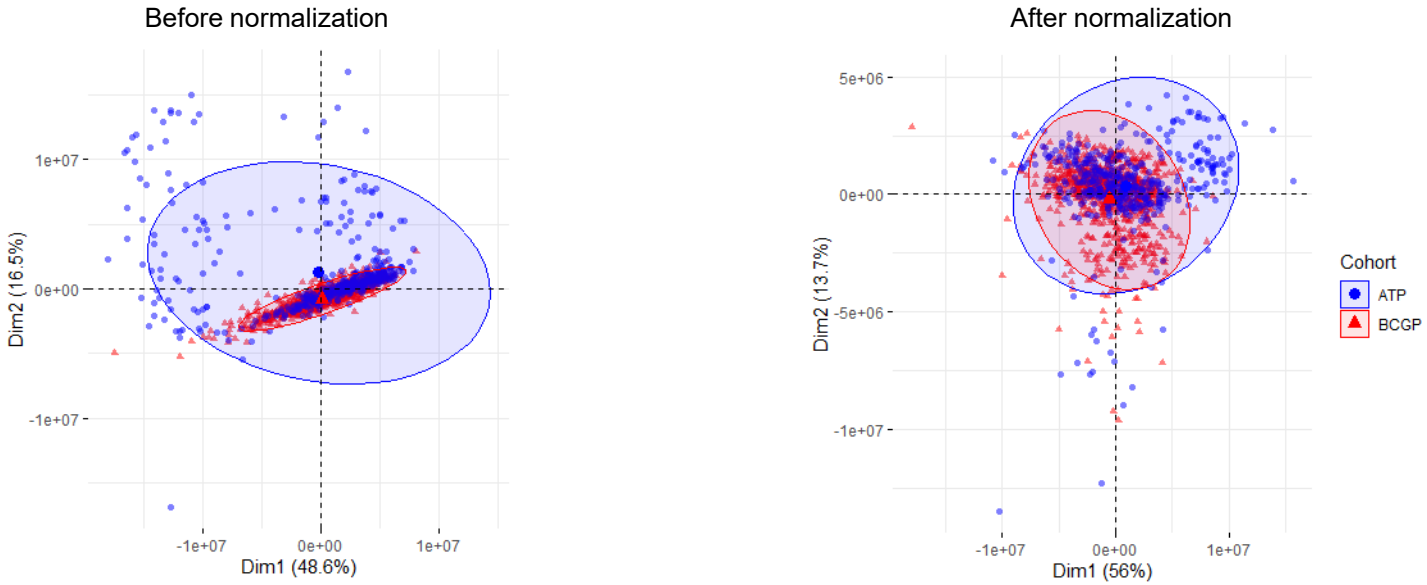
- Cases are more likely to have first-degree relatives with breast cancer
- Most health and lifestyle characteristics are similar between study groups



Results

Metabolomics profiling

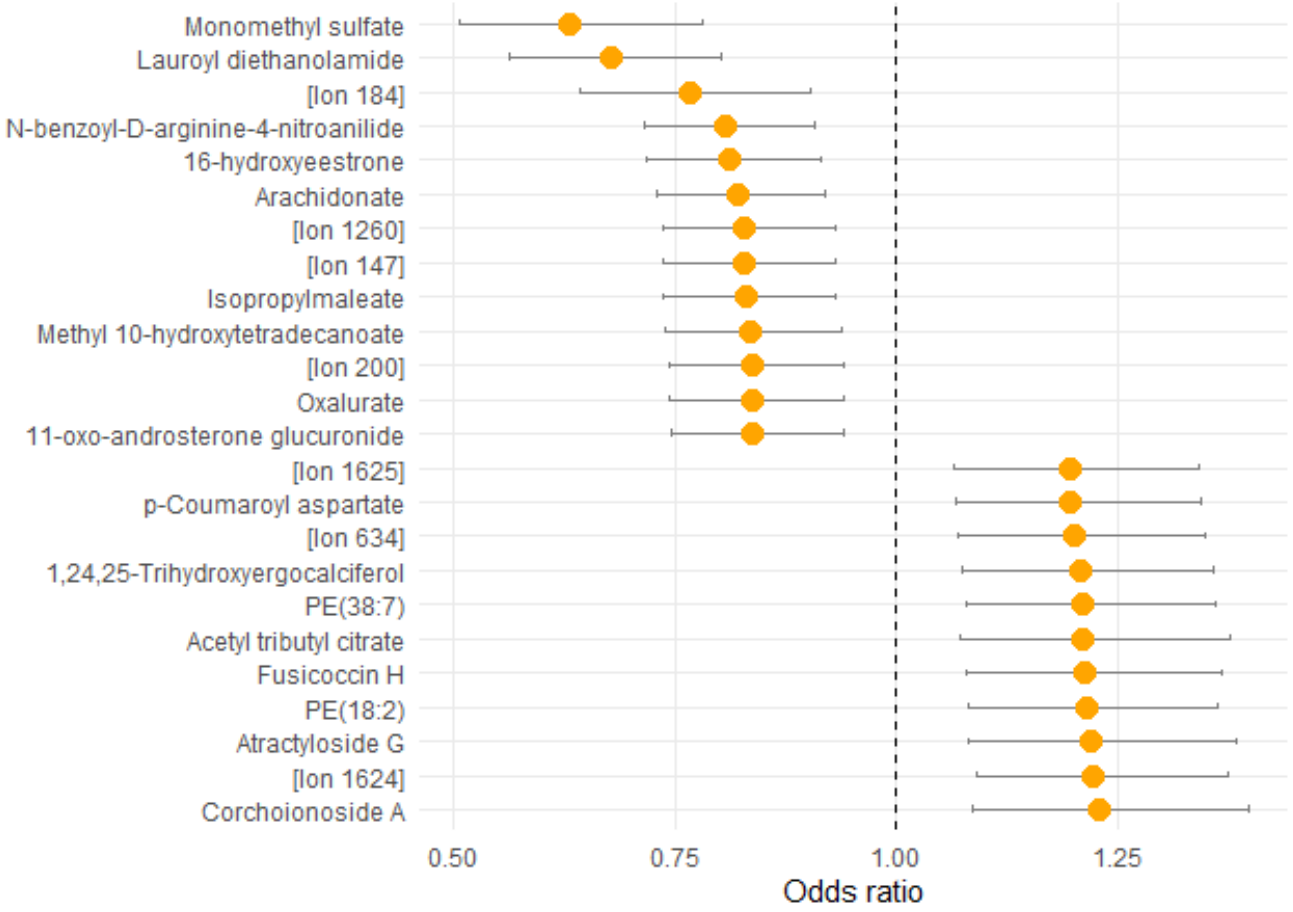
- 854 metabolites were detected in ≥ 50% of study samples
- 87% compounds have multiple possible annotations
- Cohort effect present, required normalization



PCA of metabolite grouping patterns before and after normalization

Results

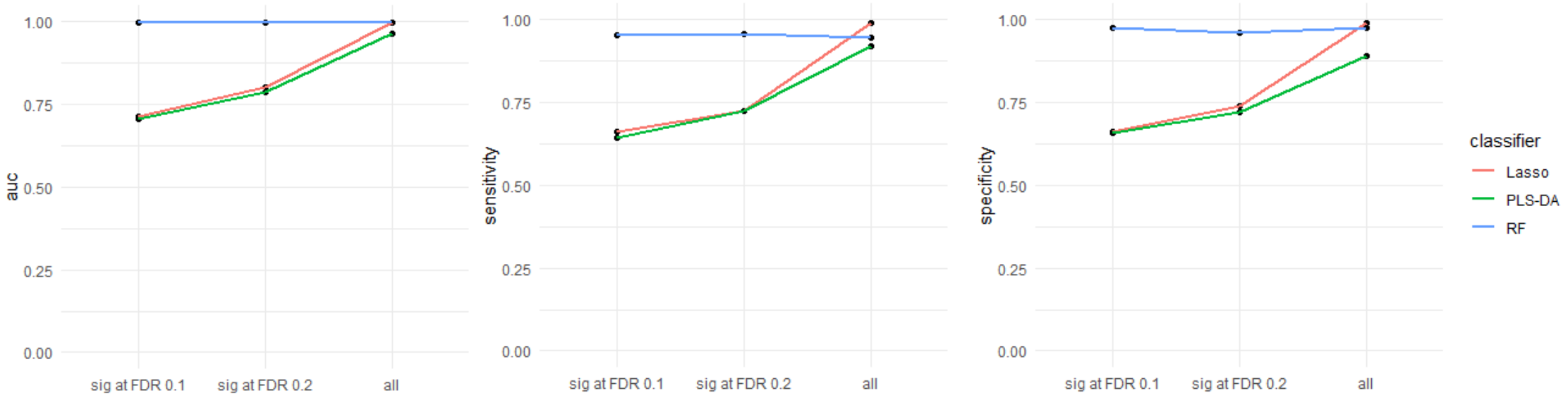
Metabolic associations with breast cancer



- Significant associations were found for 24 metabolites
  - 13 associated with lower risk
  - 11 associated with higher risk

Results

Risk prediction (preliminary)



Cross-validated AUC, sensitivity, and specificity, for breast cancer predictions using significant metabolites after correction for multiple testing at FDR = 0.1 and 0.2, and all metabolites.

AUC on 10% holdout test set:

$Lasso_{(all)}$: 0.575 $PLS\text{-}Da_{(all)}$: 0.576 $RF_{(0.1)}$: 0.517

Results

Subgroup analyses (preliminary)

- Differential expressions of metabolites were mostly consistent in full and subgroup analyses
- Associations were observed for new metabolites, but with high variation due to reduced sample size

	Metabolite	Full	Postmenopausal	Ductal	ER+/PR+
1	Monomethyl sulfate	0.63 (0.51-0.78)	0.57 (0.44-0.75)	0.65 (0.50-0.83)	-
2	Lauroyl diethanolamide	0.67 (0.56-0.80)	0.61 (0.49-0.76)	0.65 (0.51-0.81)	0.72 (0.58-0.88)
3	[Ion 184]	0.77 (0.64-0.90)	0.68 (0.54-0.84)	-	0.67 (0.53-0.85)
4	N-Benzoyl-D-arginine-4-nitroanilide	0.81 (0.72-0.91)	0.80 (0.69-0.92)	-	0.75 (0.63-0.89)
5	[ion 724]	0.81 (0.72-0.92)	0.75 (0.64-0.88)	0.79 (0.68-0.91)	-
6	Arachidonate	0.82 (0.73-0.92)	0.77 (0.66-0.88)	-	-
7	[Ion 147]	0.83 (0.74-0.93)	-	0.81 (0.71-0.93)	-
8	Isopropylmaleate	0.83 (0.74-0.94)	0.77 (0.67-0.89)	-	-
9	Methyl 10-hydroxytetradecanoate	0.83 (0.74-0.94)	-	0.81 (0.71-0.93)	-
10	[Ion 200]	0.84 (0.74-0.94)	-	0.78 (0.68-0.90)	-
11	[Ion 123]	0.84 (0.74-0.94)	0.8 (0.69-0.93)	-	-
12	11-Oxo-androsterone glucuronide	0.84 (0.75-0.94)	-	-	0.76 (0.65-0.89)
13	p-Coumaroyl aspartate	1.20 (1.07-1.34)	1.23 (1.08-1.41)	1.26 (1.10-1.44)	-
14	[Ion 1282]	1.21 (1.08-1.36)	-	1.35 (1.18-1.56)	-
15	Phophatidylethanolamine(38:7)	1.21 (1.08-1.36)	-	1.33 (1.16-1.52)	-
16	Fusicoccin H	1.21 (1.08-1.37)	-	1.29 (1.13-1.49)	-
17	PE(18:2)	1.21 (1.08-1.36)	1.23 (1.08-1.42)	-	-
18	[Ion 1624]	1.22 (1.09-1.37)	-	1.34 (1.18-1.54)	-

Discussion

Next steps & future directions

Next steps

- Literature review to assess biological significance of metabolites identified in regression analysis
- Predictive modeling for subgroups

Future directions

- Larger-scale studies with diverse participant samples
- Incorporate other methods for breast cancer prediction

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