

Otago Spotlight Series Cancer Research

Genomic health for personalised cancer care and prevention

Logan Walker, PhD

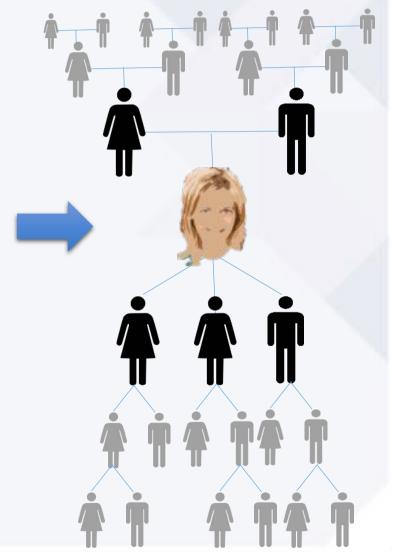
Mackenzie Cancer Research Group

University of Otago Christchurch



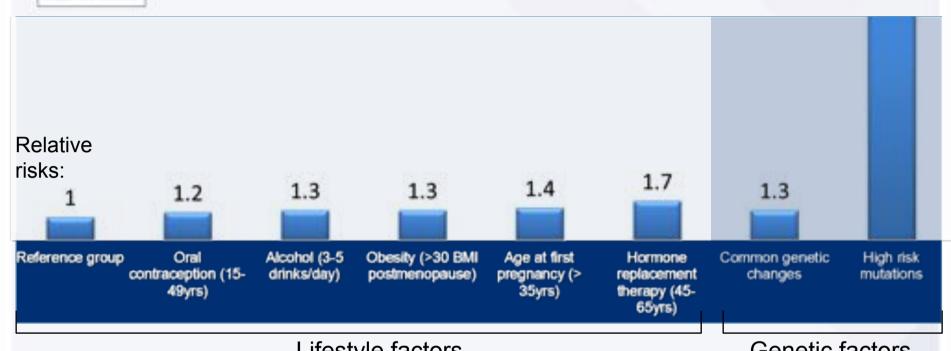
Who are most vulnerable to breast cancer?







Breast cancer risk factors



Lifestyle factors

Genetic factors

Breast cancer is not caused by

- wearing underwire bras
- implants
- deodorants/antiperspirants
- mammograms
- caffeine
- microwaves
- cell phones



Breast cancer statistics in NZ

Population statistics

~3000 women develop breast cancer in NZ each year



How many affected women carry a high-risk mutation?

Genetic screening statistics

300-350 women undergo genetic testing each year





<20% tests positive

~5-10% tests unclear



Future of genetic screening



Whole gene sequencing

Gene panel screening

Greater number of individuals screened

Greater number of reported unclassified variants

BRCA Challenge Project

Standardise data collection, variant interpretation and clinical genetic databases



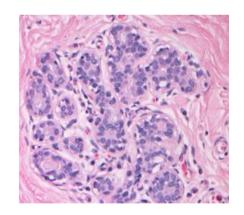
Classifying genetic variants

Reported variant

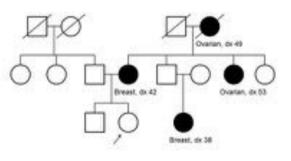
ENIGMA

(Evidence-based Network for the Interpretation of Germline Mutant Alleles)

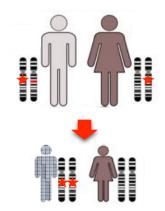
Multifactorial analysis



Tumour type



Family history and segregation



Co-occurrence



Molecular biology

otago.ac.nz/cancer-research

Not pathogenic or pathogenic



The Angelina Jolie effect

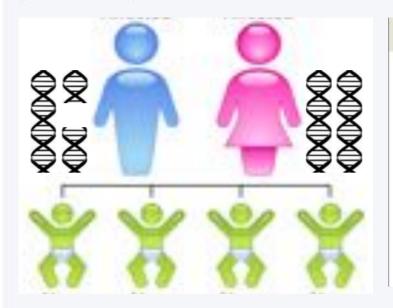


 "My doctors estimated that I had an 87 percent risk of breast cancer and a 50 percent risk of ovarian cancer, although the risk is different in the case of each woman."

 Why do BRCA1 and BRCA2 mutation carriers vary in risk?



Genetic modifiers of risk



genetics

A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population

Gerniline BRCA1 mutalions predispose in breast cancer. To identify genetic modifiers of this risk, we performed a proone wide association study in 1,193 individuals with ERCAF mutations who were diagnosed with invasing breast capter under over age 35. We took forward % SNPs for replication in another BBC 4.5 cambon, CL97.4 Individuals with broad cancer

2.500 BRCA1 carriers using the Blumina Infinium 600K array. which included 620,901 SNPs blutation carriers were selected on the basis of an inmastre breast cancer diagnosis at under 40 years of age (n = 1,250) or the absence of breast cancer when 35 years of age or age 40 and 1,190 ERCAT carriers without breast cancer diagnosis older (n = 1,25t). After quality control exclusions, 2,345 carriers (3,190 unaffected and 1,190 affected) from 16 centers in 11 different countries and \$55,650 \$00% were available for

Genetic data from 2500 BRCA1 mutation carriers

Genome-wide association study

$$\begin{split} L &= \prod_{i=1}^{m} P(g_{i}|y_{i}(t_{i})) = \prod_{i=1}^{m} \frac{P(g_{i})P(y_{i}(t_{i})|g_{i})}{P(y_{i}(t_{i}))} \\ &= \prod_{i=1}^{m} \frac{P(g_{i})P(y_{i}(t_{i})|g_{i})}{\sum_{k} P(g_{i} = k)P(y_{i}(t_{i})|g_{i} = k)} \\ &= \prod_{i=1}^{m} \frac{\tau_{g_{i}} \exp[-\Lambda_{0}(t_{i}) \exp(\beta g_{i}) + O_{i}\beta g_{i}]}{\sum_{k} \tau_{k} \exp[-\Lambda_{0}(t_{i}) \exp(\beta k) + O_{i}\beta k]} \end{split}$$

$$U = \frac{\partial \log L}{\partial \beta} \Big|_{\beta=0}$$
$$= \sum_{i=1}^{m} (g_i - \bar{g})[O_i - \Lambda_0(t_i)]$$

New findings:

Breast Cancer GeneX **Ovarian Cancer** GeneY



>20,000 BRCA1 mutation carriers (CIMBA Consortium)

LETTERS



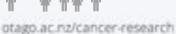
Genomic medicine 21st Century Health Care

Utilise international resources

Unpack genetic data

Reduce the impact of disease







Acknowledgements

University of Otago Christchurch

John Pearson
Vanessa Lattimore
Arthur Morley-Bunker
George Wiggins
Mackenzie Cancer Research Group
Cancer Society Tissue Bank

Canterbury District Health Board

Bridget Robinson Anne Smith

Canterbury Health Laboratories

Gavin Harris
Martin Whitehead

Genetic Health Service NZ

Caroline Lintott Jan Sullivan

Otago Genomics and Bioinformatics Facility / NZ Genomics Ltd

QIMR Berghofer (Australia)

Mandy Spurdle Michael Parsons Louise Marquart

ENIGMA consortium

>100 research scientists/clinicians from >20 countries

CIMBA consortium

>100 research scientists/clinicians from >30 countries

kConFab (Peter MacCallum Cancer Centre)

Heather Thorne Eveline Niedermayr







