Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

With well characterised bio-bank samples, the secret of aggressive prostate cancer is unlocked.

On behalf of the kConFab consortium: www.kconfab.org

kConFab history

Established in 1997, we are a biobank (cohort) with linked data, to facilitate breast, ovarian prostate & pancreatic cancer genetic research.

We obtain signed consent from participants at very high risk of breast and ovarian cancer via the 32 Family Cancer Clinics in Australia and New Zealand – *BRCA1/2, PALB2, ATM, p53*.

From all family members (females and males over 18 years, affected & unaffected) we collect germline mutation test reports, *medical/treatment*, lifestyle information and biological material such as tissue (normal and cancer) removed at surgery and blood. *Routine annual follow up.*

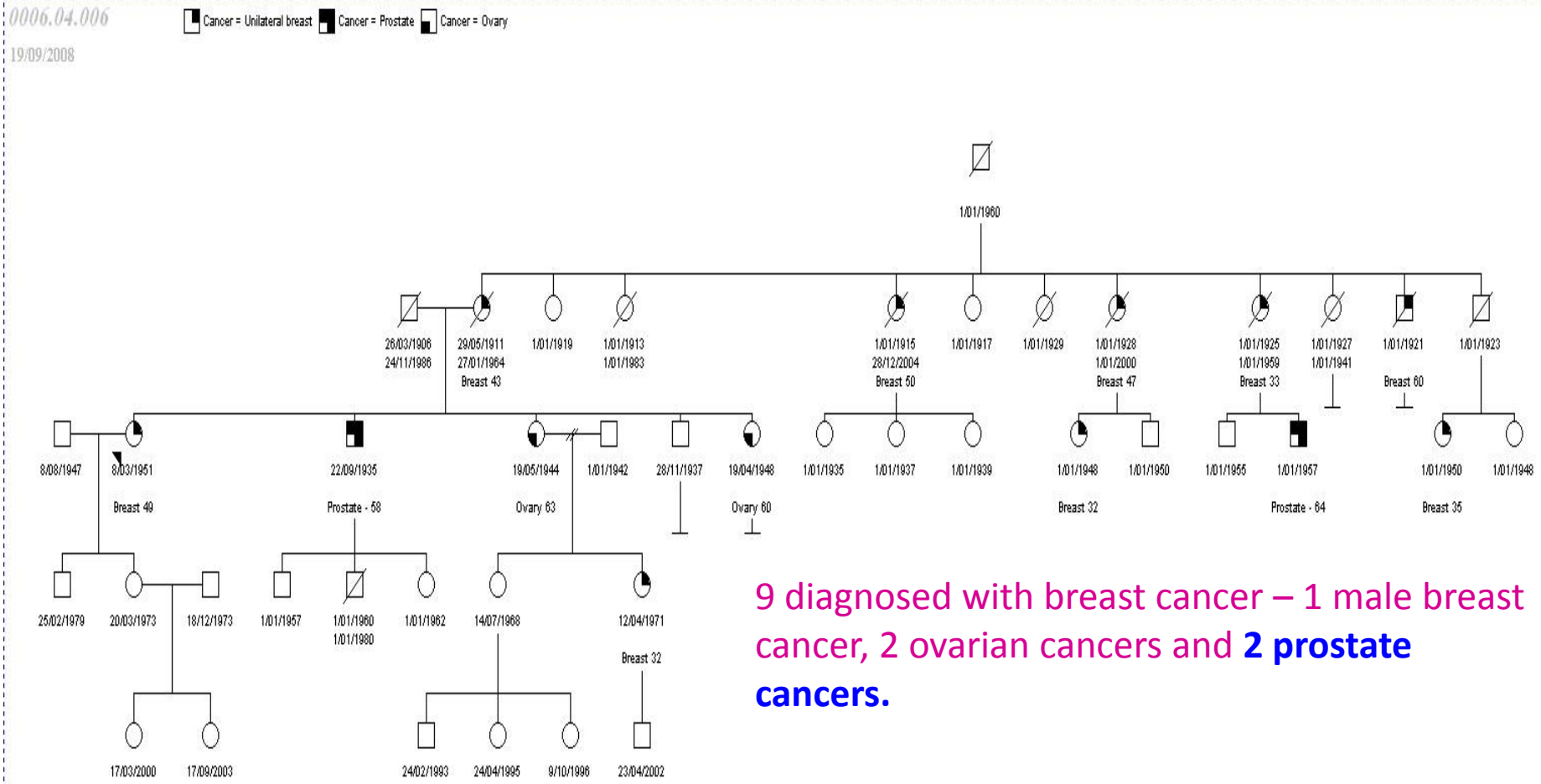
We verify all cancers diagnosed reported in a family, preferably with a pathology report.

On average 10 bloods and 5.2 cases of breast cancer/family – ideal for segregation studies to determine if a variant tracks with disease.

The biobank supplies to 162 projects world wide (1/3 active 15 hears) & 340 high ranking publications

The work - publications span basic biology, genetics – gene discovery, lifestyle factors, psychosocial and research for new treatment options based on a patients genetic profile.

A typical kConFab Family



9 diagnosed with breast cancer – 1 male breast cancer, 2 ovarian cancers and **2 prostate cancers.**

Was there a genetic factor causing so many prostate cancers in multi-case breast cancer families?

Was its occurrence expected ? as prostate cancer (PC) is also a common cancer.
Or
Was the genetic fault that was causing breast cancer, *BRCA1* or *BRCA2*, also causing the prostate cancer in these family members?

The association between a *BRCA1* or *BRCA2* mutation and prostate cancer through genetic analysis is of paramount importance in further understanding the risk of prostate cancer to men within these families and their treatment response, esp. in the era of personalised medicine.

By 2009, 1,423 families had been recruited to kConFab.

147 men diagnosed with PC and with a known pathogenic *BRCA* germline mutation status.

- 36 *BRCA2* mutation carriers had FFPE tissue/blood available and comprehensive treatment details. The majority of these men (79%) were classified as *High Risk* using the *D'Amico risk stratification:*
  Stage > T2c or
  Gleason score ≥ 8 or
  PSA level > 20 ng/mL
- 11 *BRCA1* mutation carriers were eliminated from further analysis due to small numbers.

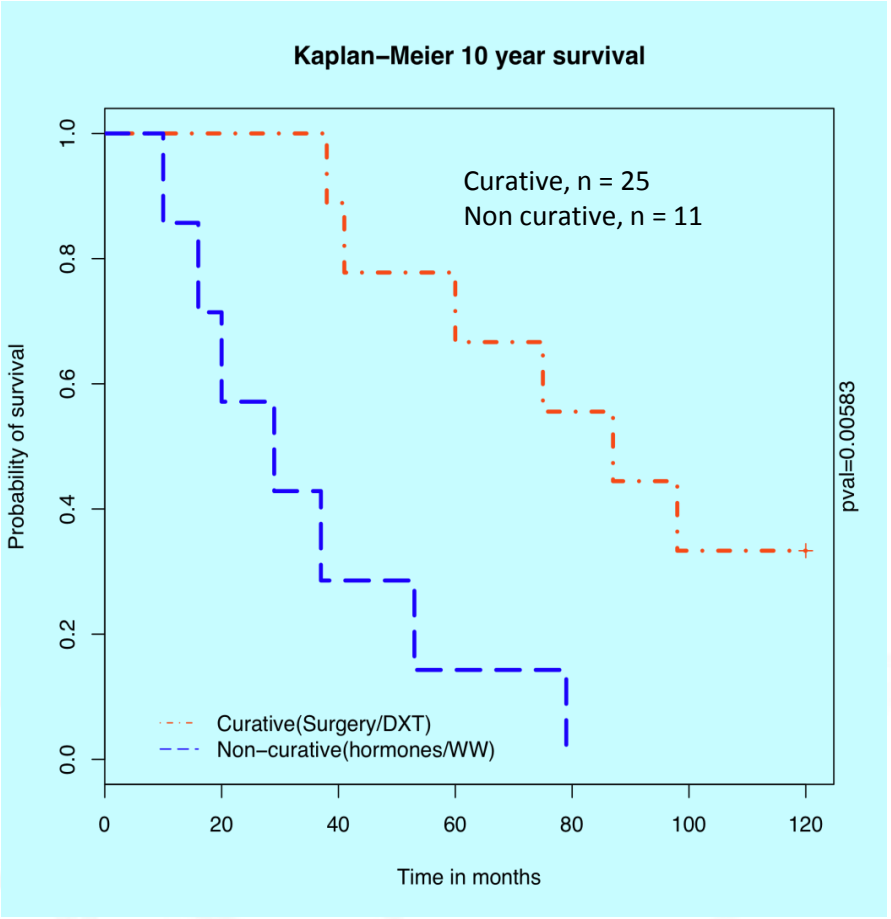
Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Study 1.

***36 BRCA2* carriers treatment outcomes:**

70% (5 yrs) ; 30% (10yrs) were deceased.

This is in contrast to *High Risk* men in general population: 94% at 5 yrs ; 80% alive at 10 yrs



Amongst our cohort:

a) 79% of *BRCA2* mutation carriers had *High Risk* disease at diagnosis

b) 23/36 *BRCA2* mutation carriers died with a mean survival of 3.5 years

c) A BRCA2 mutation status was a significant predictor of overall survival (HR= 3.175) and of prostate cancer related survival (HR=4.968).

d) Age adjusted serum PSA readings prior to diagnosis were elevated in 90% of men

From the review of treatment outcomes, a *BRCA2* mutation is associated with aggressive prostate cancer with poor survival.

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Families.

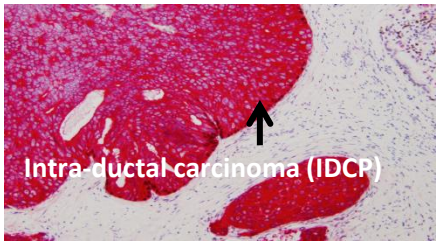
Decreased Prostate Cancer-Specific Survival of Men with BRCA2 Mutations from Multiple Breast Cancer. Heather Thorne et al. Cancer Prev Res; 4(7); 1002–10. 2011 AACR.

Study 2. Establishment of Primary PDX of *BRCA2* mutation carrier tumour specimens. Why are these tumours so aggressive?.

Collect and dissect fresh prostate tumour tissue n= 11 patients

4mm3 sized pieces grown under kidney capsule

8 weeks



Collect and analyze grafts. Xenografts faithfully retain the H&E pathology and *BRCA2* genetic alterations of original patient tumour . n = 100% take

Know what you grow as there are different prostate cancer pathologies: adenocarcinoma (is common) and can differentiate to Intra Ductal Carcinoma–Prostate (IDC-P) vs. ductal. Neuroendocrine is another pathology type

Importantly, the pathology in our *BRCA2* PDX was both *adenocarcinoma* with a large, over represented component of *IDC-P*. Due to the H&E and genomic QA, we were confident that PDX model retains the pathologies of patient *BRCA*-mutation carrier tumours.

IDC-P is historically considered a premalignant lesion and associated with:

- High-grade disease
- Large tumour volume
- Poor clinical outcomes
- Significantly, not routinely reported by pathologists

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Retrospective study using kConFab prostate cancer patients H&Es to determine frequency of IDC-P in *BRCA2*-carriers vs. sporadic PC cases

Archived H&E slides were reviewed by our uropathologist.

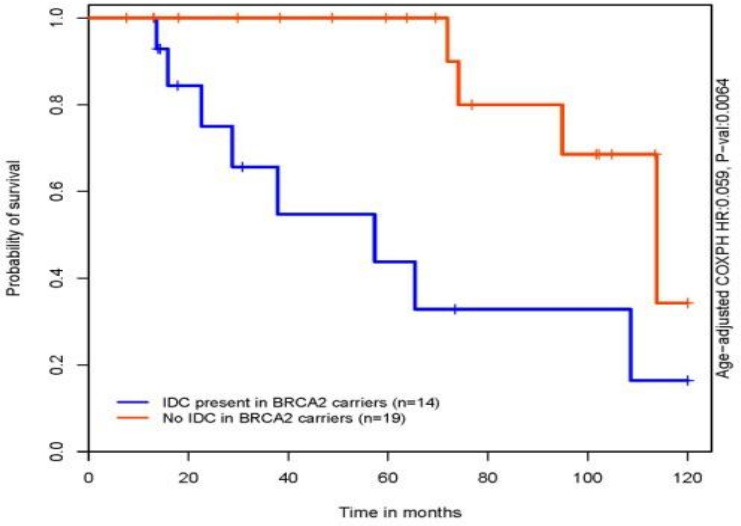
	Sporadic	BRCA2 carriers
n	32	33
IDC-P present	3 (9%)	14 (42%)

P = 0.004

Importantly, not one clinical pathology report detailed the IDC-P morphology

Within the *BRCA2* carrier group:

- 42% of *BRCA2* carriers had IDCP, 58% did not.
- Multivariate analysis revealed that in *BRCA2* patients with IDCP they had poor outcome in terms of time to survival.



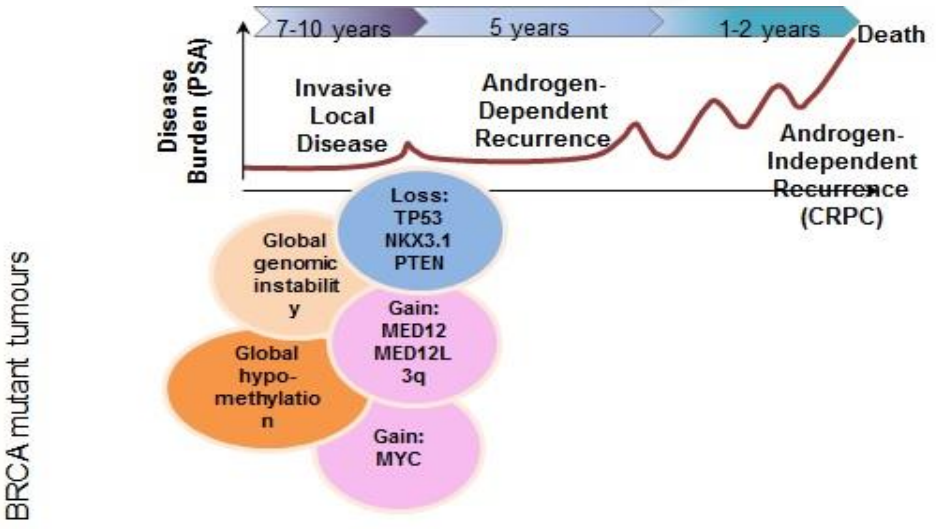
Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Risbridger et al, 2015, European Urology

Study 3. In addition to a germline *BRCA2* mutations are there other driver mutations in prostate cancers?

Generated mutational profiles of *BRCA2* carriers vs. 200 sporadic cases (Uni of Toronto).

- We used whole-genome sequencing (WGS), along with genotyping and methylation arrays, to fully characterize localized PCa
- Localized *BRCA2* carrier tumours show elevated genomic instability and a mutational profile that more closely resembles mCRPC than localized sporadic PCa.
- *BRCA2* carriers PCa is defined by unique copy number gains and hypomethylation events. These include alterations in pathways associated with negative prognosis, including the *MED12L*/*MED12* axis, which are frequently dysregulated in mCRPC
- **IDC-P and adenocarcinoma are clonally-related but distinct lesions**



Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories. [Nat Commun.](#) *2017 Jan 9;8:13671.*

Conclusions:

Data and biospecimens from a small but well annotated patient cohort complements but is different to large scale studies such as the ICGC. A well characterised patient profile that includes germ-line mutation test results, pathology, all treatments, their outcomes and annual follow up has identified a sub-set men who are at for *high risk* prostate cancer.

Thorough QA at each step has identified important clinical features and the pathways involved in aggressive Pca that has a poor outcome.

Clinical impact:

- In many international centres now ask their Uropathologist to note the presence or absence of IDCP. This request has been approved at a recent international pathology consensus meeting.
- Alter standard care of BRCA 2 patients – immediate, multi-modal therapy, not active surveillance.

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Acknowledgements

Prostate Cancer Research Group, Monash University, Melbourne

Ashlee Clark

Stuart Ellem

Luc Furic

KoheiHashimoto

Mitchell Lawrence

Daisuke Obinata

Melissa Papargiris

Gail Risbridger

ReneaTaylor

Jenna Van Gramberg

Hong Wang

AniaSlinwinski(kConFab)

Pathologists

David Clouston

Tim Nottle

Sam Norden

Collaborators

Rob Bristow (University of Toronto)

Paul Boutros (University of Toronto)

Michael Fraser (University of Toronto)

Urologists

Damien Bolton

Mark Frydenberg

Nathan Lawrentschuk

Declan Murphy

Daniel Moon

kConFab

Executive committee & membership

National Breast Cancer Foundation

National Health & Medical Research Foundation

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia