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McGILL FAMILY MEDICINE REFRESHER COURSE WORKSHOP

Screening and prevention strategies for BRCA mutation carriers

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December 2, 2020

Hôpital général juif
Jewish General Hospital

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No disclosures

Hôpital général juif
Jewish General Hospital

CASE ONE

MRS. W

Mrs. W is a 40 year old patient from South Africa whose mother had high grade ER- breast cancer at 42 years. Because of this, she began annual mammographic screening in her 30's. More recently, however, she finds out her mother's youngest sister, her maternal aunt, was diagnosed with stage III ovarian cancer at 53. She asks if she should undergo ovarian cancer screening as well?

You explain to her that:

a) Yes, she should undergo CA-125 levels annually

b) Yes, she should undergo a TVUS annually

c) No, unfortunately there are no effective screening methods for detecting ovarian cancer early

d) She should seek genetic counselling given her family history of breast and ovarian cancer

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Version 2.2021 — November 20, 2020

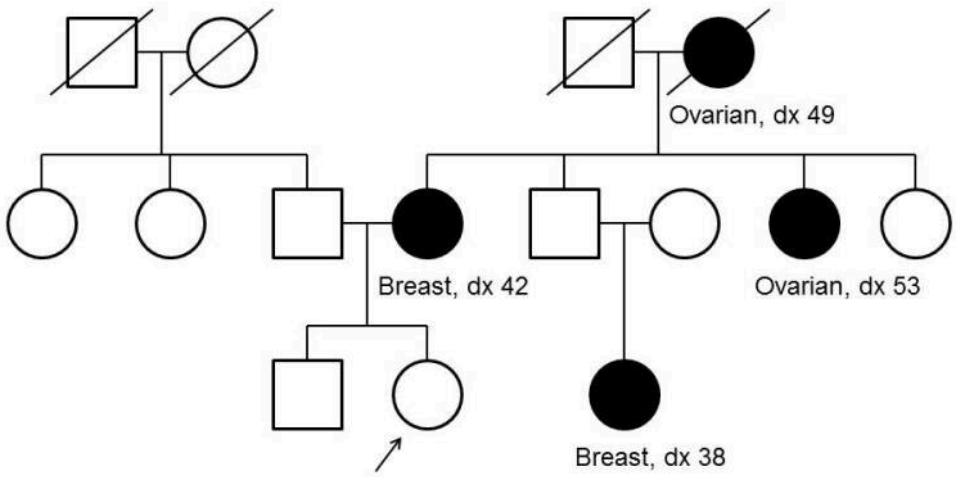
NCCN GUIDELINES

GENETIC TESTING REFERRAL BASED ON FAMILY HISTORY

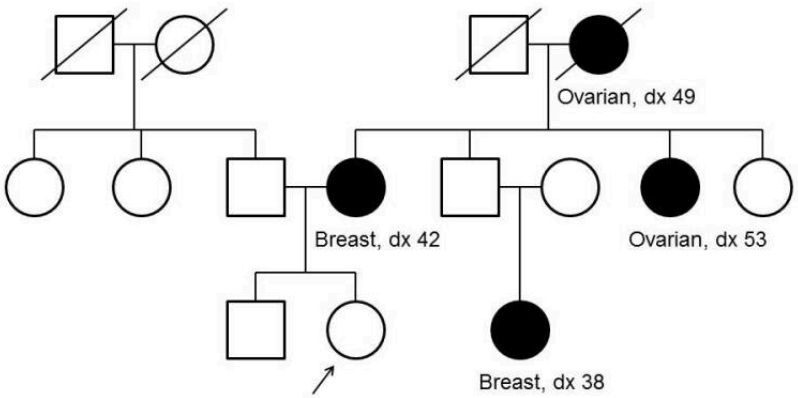
- Patients with a blood relative with a known gene mutation

- Patients with 1st or 2nd degree blood relatives* that have been:
  - Diagnosed with very early onset breast cancer (<45 years)
  - Diagnosed with breast cancer between 46-50 years but have close another relative with breast, ovarian, pancreatic or prostate cancer at any age
  - Bilateral breast cancer, or more than 3 diagnoses of breast cancer
  - Triple negative breast cancer <60 years
  - Male breast cancer
  - Any of the above + Ashkenazi Jewish ancestry

- A greater than 2.5-5% probability of a BRCA1/2 variant based on hereditary risk models (Tyrer-Cuzick, BRCAPro, CanRisk)

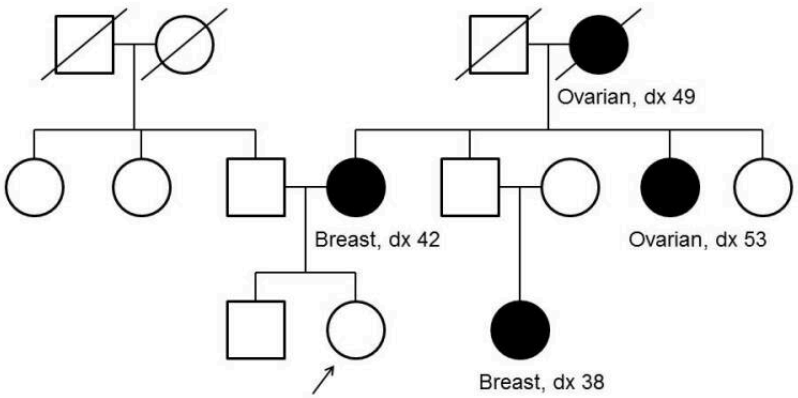


The genetic counseling session reveals a clustering of cases of breast and ovarian cancer on Ms. W's maternal side of the family in her mother, maternal grandmother, aunt and cousin. The genetic counsellor discusses the possibility of a hereditary breast ovarian cancer (HBOC) syndrome.



Who is the most ideal person to undergo genetic testing first?

a) Your patient, Ms. W
b) Your patient's mother
c) Your patient's father



Who is the most ideal person to undergo genetic testing first?

a) Your patient, Ms. W

b) Your patient's mother

c) Your patient's father

Because Ms. W's mother is in South Africa and does not have access to testing, she is offered genetic testing herself. A blood (or saliva sample) is taken. One month later, she is informed that she is a carrier of a pathogenic variant in the *BRCA1* gene (1832del5 mutation).

BRCA1 GENE MUTATION

- Chromosome 17
- Autosomal dominant transmission (50% likelihood children will also be carriers)
- BRCA1 protein involved in homologous recombination/DNA repair
  - Inheriting a mutated copy of the gene from either parent creates genomic instability
  - Mutations accumulate in cells
    - Higher lifetime risk of breast (72%) or ovarian cancer (44%) by age 80

BRCA1 GENE MUTATION

- Breast cancers tend to be aggressive, triple-negative subtypes
- Ovarian cancers tend to be high grade serous fallopian tube/ovarian/primary peritoneal cancers
- Cancers tend to be 8-10 years earlier in onset than BRCA2 patients
  - Breast cancer incidence increases rapidly between 30-40 years
  - Earlier oophorectomy recommended; between 35-40 years or after child-bearing is complete

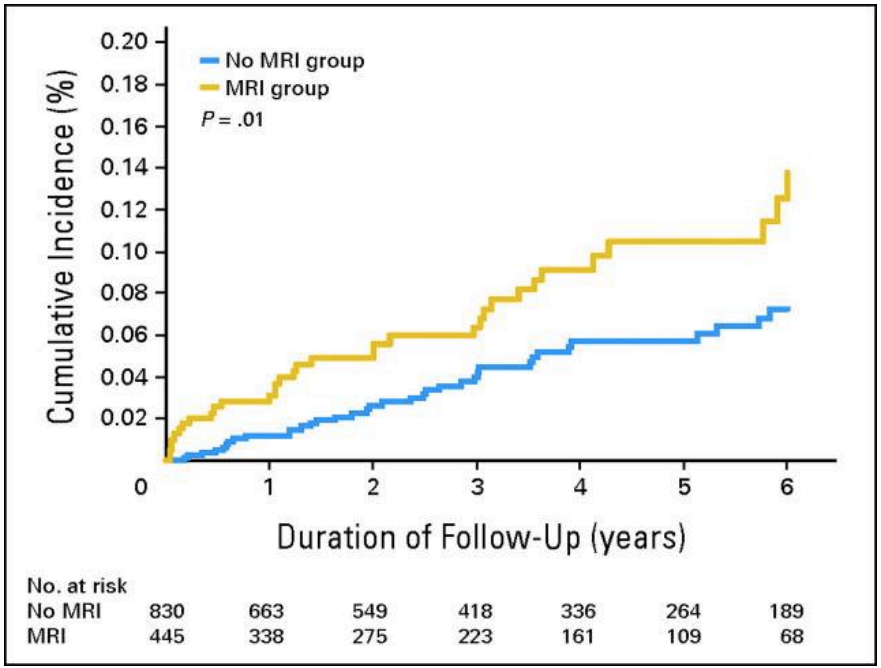
BRCA1
CHROMOSOME 17

BREAST & OVARIAN CANCER SCREENING

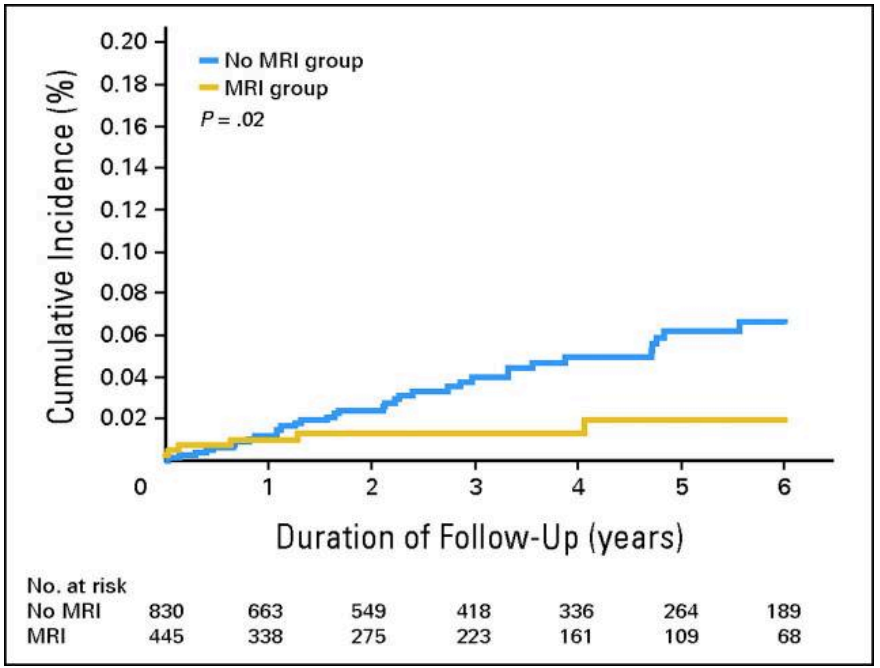
	1 Bilateral Breast MRI	2 Screening Mammogram	3 Transvaginal Ultrasound (TVUS)	4 Serum CA-125
Age of onset	25 years	30 years	30--35 years	30-35 years
Frequency	Annual	Annual	Annual	q4months
Sensitivity	77-94%	19-50% (must be combined with MRI)	When combined: 95% per UK FOCSS study	
Level of Evidence	●●●●●	●●●●○	●●○○○	●●○○○

BRCA1/2 SCREENING

MRI HELPS DETECT CANCER AT EARLIER STAGES



Cumulative incidence of stages 0 to I breast cancer in magnetic resonance imaging (MRI) group (yellow) vs. MG alone group (blue)



Cumulative incidence of stages II to IV breast cancer in magnetic resonance imaging (MRI) group (yellow) vs. MG alone group (blue)

Warner et al. JCO 2011

United Kingdom Familial Ovarian Cancer Screen Study (2017)

- Multi-institutional prospective study including 4348 women of familial and genetic risk
- 20% were genetic mutation carriers
- CA-125 every 4 months, TVUS annually
- ROCA (risk of ovarian cancer) calculated based on CA-125 results, rate of change, and age-specific OC incidence estimates and used to triage more expedited TVUS + CA-125

Conclusions:

At a median follow up of 4.8 years, 19 cancers diagnosed (13 screen detected)

Half of the detected ovarian or FTCs were early stage ("significant stage shift")

No clear impact on survival

Rosenthal et al. JCO 2017

BRCA1/2 SCREENING

SOGC RECOMMENDATIONS (2018)

RECOMMENDATIONS

3 There is currently insufficient data to support ovarian/tubal/peritoneal cancer screening.

4 Risk-reducing surgery according to established guidelines (Table 3) is the most effective way to reduce the risk of ovarian cancer in women with a hereditary predisposition or risk (strong, low).

BREAST & OVARIAN CANCER SCREENING

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Level of Evidence	●●●●●	●●●●○	●●○○○	●●○○○

CASE TWO

MS. M

Ten years later, Mrs. W's daughter accompanies her to clinic. Her mother has undergone risk reducing ovarian and breast surgeries and is doing well without cancer. She asks about when her daughter should get tested for BRCA1. She is currently 18 years old.

CASE TWO

MS. M

You advise them that genetic testing of family members (cascade testing or predictive genetic testing):

a) Usually occurs at 18 years of age, so you will send a genetics consult now

b) Usually occurs at 21 years of age

c) Usually occurs at 25 years of age

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c) Usually occurs at 25 years of age

- Genetic testing of family members usually recommended at or just before 25 years of age when MRI screening is typically initiated
  - In cases of very early onset BC, may be offered earlier
- Testing offered to both daughters (screening and prevention) and sons (family planning +/- prostate cancer screening)

CASE TWO

MS. M

Knowing that she has a 50% risk of being a BRCA1 carrier, Ms. M asks about timeline of screening and prevention recommendations…

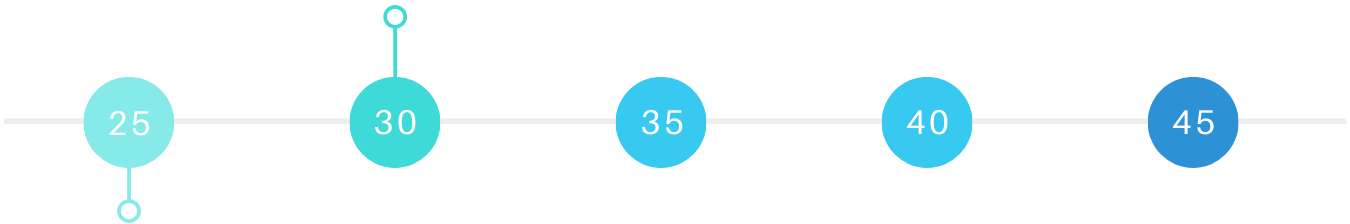
25 30 35 40 45

ANNUAL BREAST MRI

Begin yearly screening with bilateral breast MRI at 25 years old. You will need a blood test to check your kidney function several weeks before each MRI. An IV will also be used during the imaging procedure. Screening MRIs typically take about 30 minutes.

ANNUAL MAMMOGRAM

In addition to MRI, at 30 years old yearly mammograms are recommended. These will typically be planned 6 months before or after your last MRI, so that you have breast screening twice per year.



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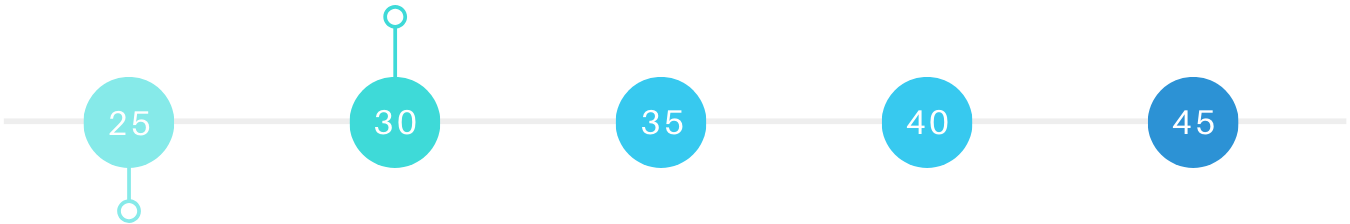

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BILATERAL PROPHYLACTIC MASTECTOMY

Can be considered at any time. Factors that might influence this decision are the age of onset of breast cancers within your family, family planning with plans to breastfeed, and the desire to prevent breast cancer or avoid treatments associated with a breast cancer diagnosis. After preventive surgery, you will no longer require breast screening with mammograms and MRIs.

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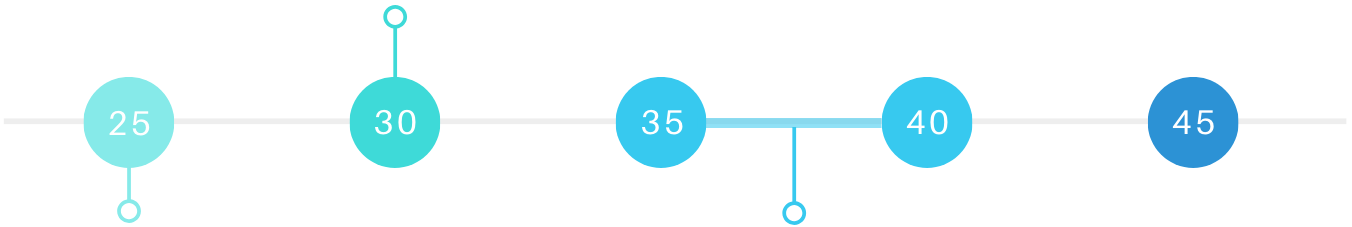

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FOR BRCA1 CARRIERS

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FOR BRCA2 CARRIERS

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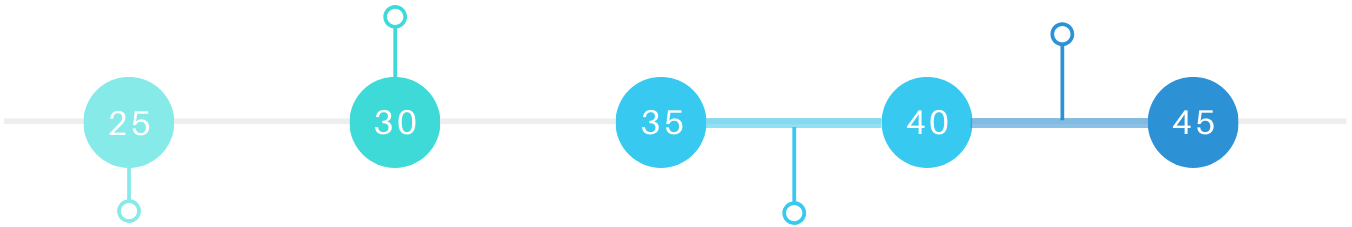

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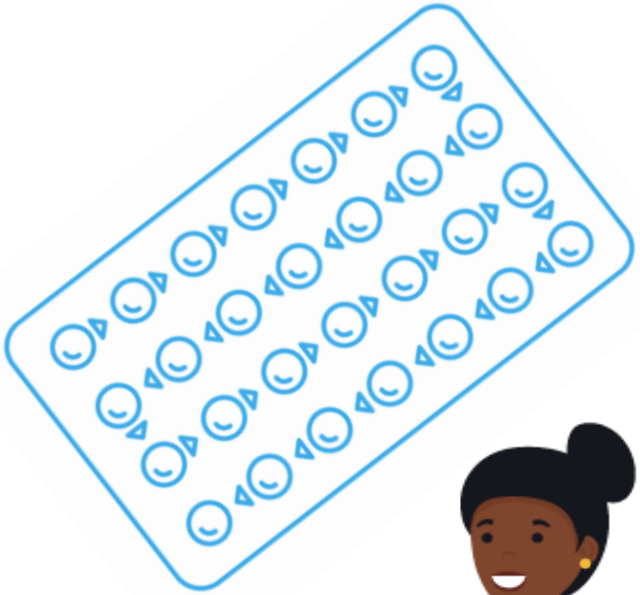
CASE TWO

MS. M

At 25, Ms. M finds out that she is a BRCA1 carrier. She asks about the oral contraceptive pill. She is currently taking Lolo to regulate her heavy cycles and is worried about breast cancer risk with OCPs.



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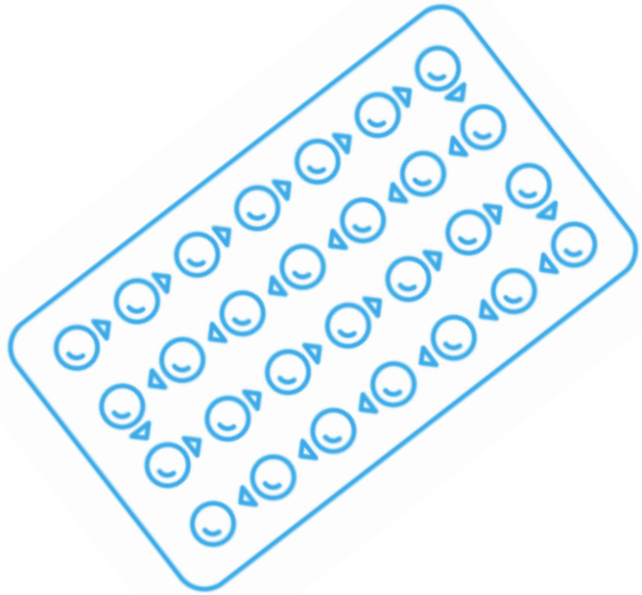
MS. M

You tell her that:

a) Combined OCPs are felt to be safe in BRCA carriers and will reduce her risk of ovarian cancer

b) Combined OCPs should be stopped in BRCA carriers given the increased risk of breast cancer



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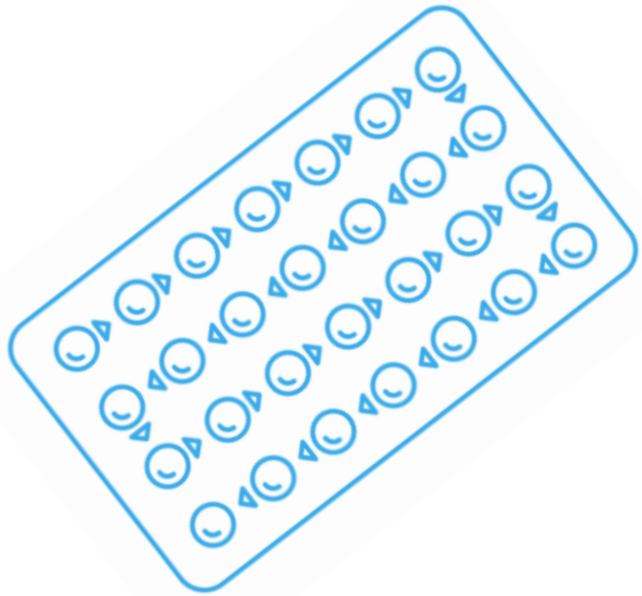
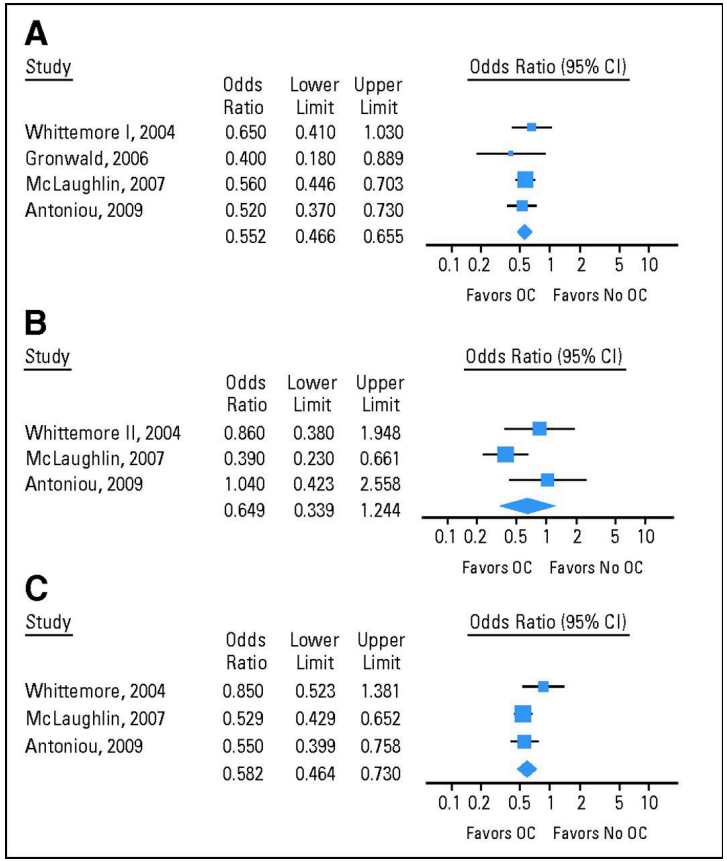


BRCA1/2 MANAGEMENT

OCPs + OVARIAN CANCER RISK



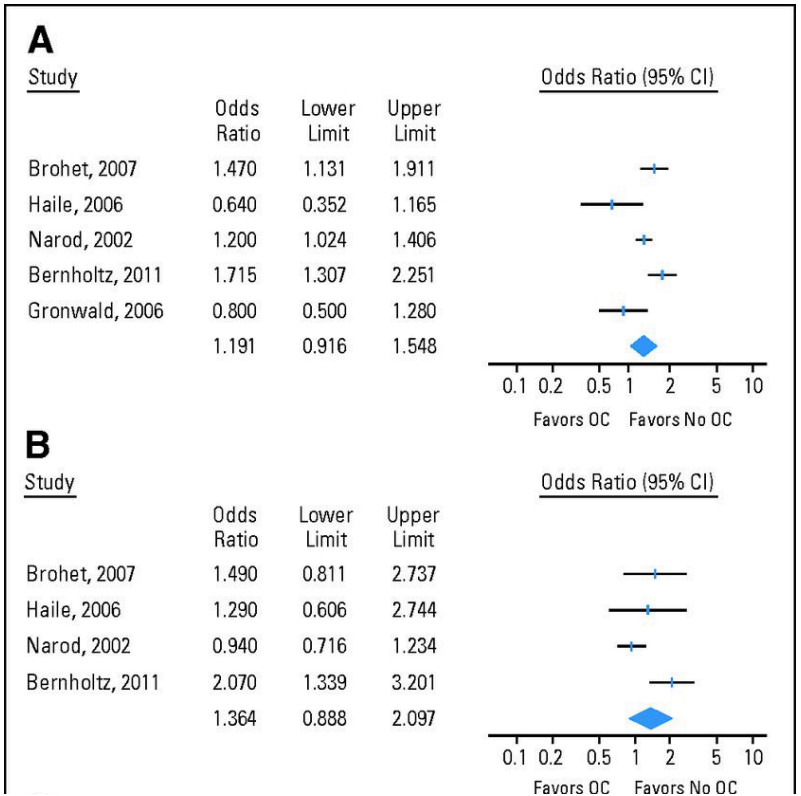
"Our results suggest that OC use reduces the risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers, similar to what has been observed consistently in the general population."

(Approximate 40% risk reduction)

Moorman et al. JCO 2013

"Our meta-analysis did not suggest a significantly increased risk of breast cancer among BRCA1/2 mutation carriers"

(a) *BRCA1* (OR 1.19, 95% CI 0.92-1.55)
(b) *BRCA2* (OR 1.21, 95% CI 0.93-1.58)



Moorman et al. JCO 2013

CASE THREE

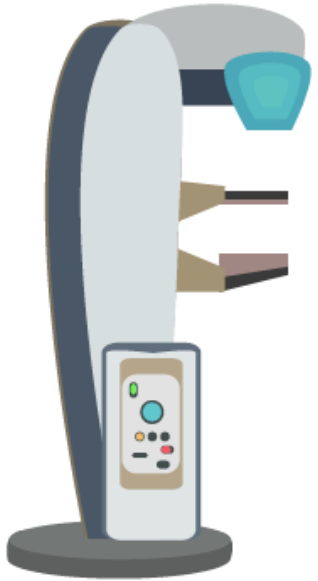
MS. S

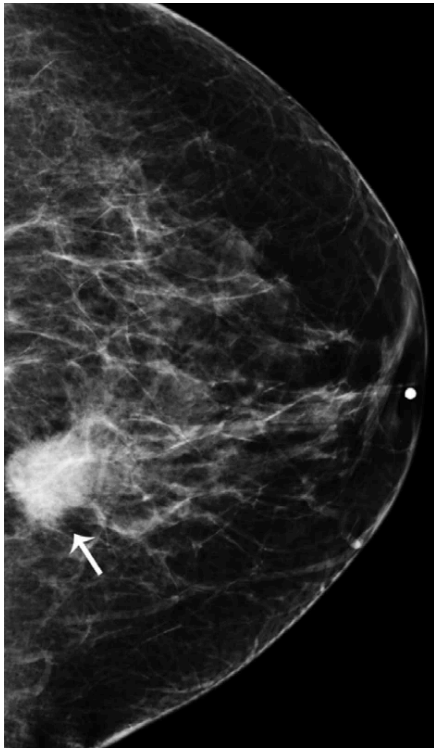
Ms. S is a 54 year old French Canadian female with a history of stage I right breast cancer at 41 years old treated with breast conserving therapy (lumpectomy and radiation) followed by 5 years of endocrine therapy.

CASE THREE

MS. S

She returns to you because her annual screening mammogram has diagnosed a contralateral left breast mass, with investigations demonstrating an early-stage ER+HER2- invasive breast cancer.





CASE THREE

MS. S

Ms. S is referred to genetic testing given her history of bilateral breast cancer and early onset disease. In addition to asking about breast and ovarian cancer, what other cancers are associated with a BRCA2 pathogenic variant?

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MS. S

In addition to asking about breast and ovarian cancer, what other cancers are associated with the BRCA2 gene?

a) Diffuse gastric
b) Prostate and pancreatic
c) Thyroid and renal
d) Colon and endometrial

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CASE THREE

COUNSELING SESSION

You find out that Ms. S's older brother had prostate cancer in his early 50's. Her younger brother is unaffected. Their father died of pancreatic cancer.

They are both tested and found to have a BRCA2 gene mutation.

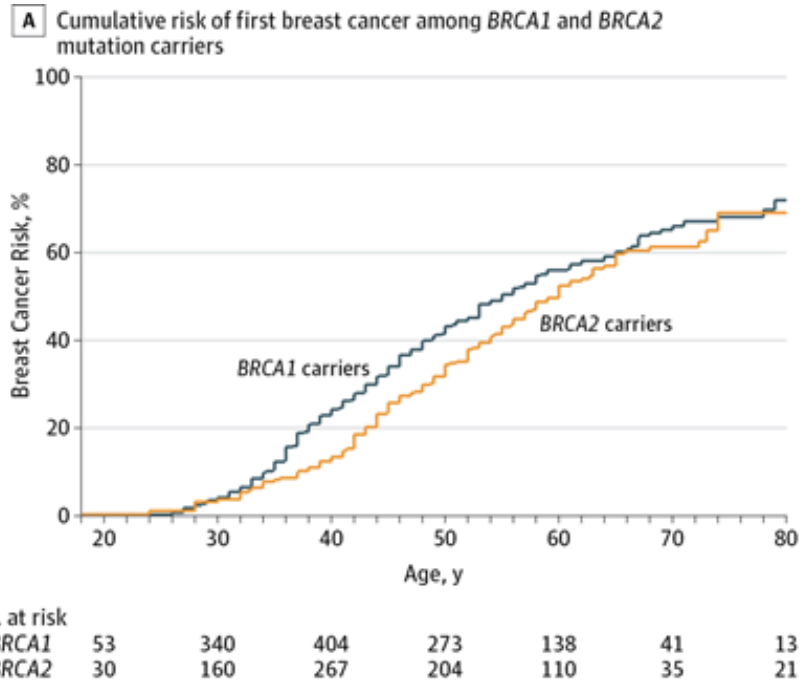
BRCA2 GENE MUTATION

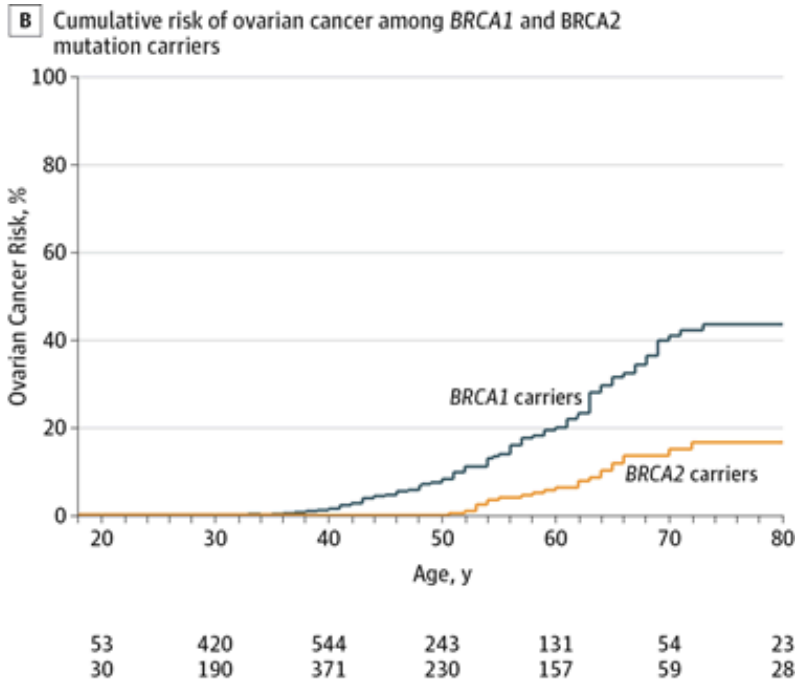
- Chromosome 13
- AD transmission (50% likelihood children will also be carriers)
- BRCA2 protein involved in homologous recombination/DNA repair
  - BRCA2 PV creates genomic instability = mutations accumulate in cells
    - Higher lifetime risk of breast (61%) and ovarian cancer (17%) by age 80
    - Also associated with pancreatic cancer, melanoma, and prostate cancer in males

BRCA2
CHROMOSOME 13

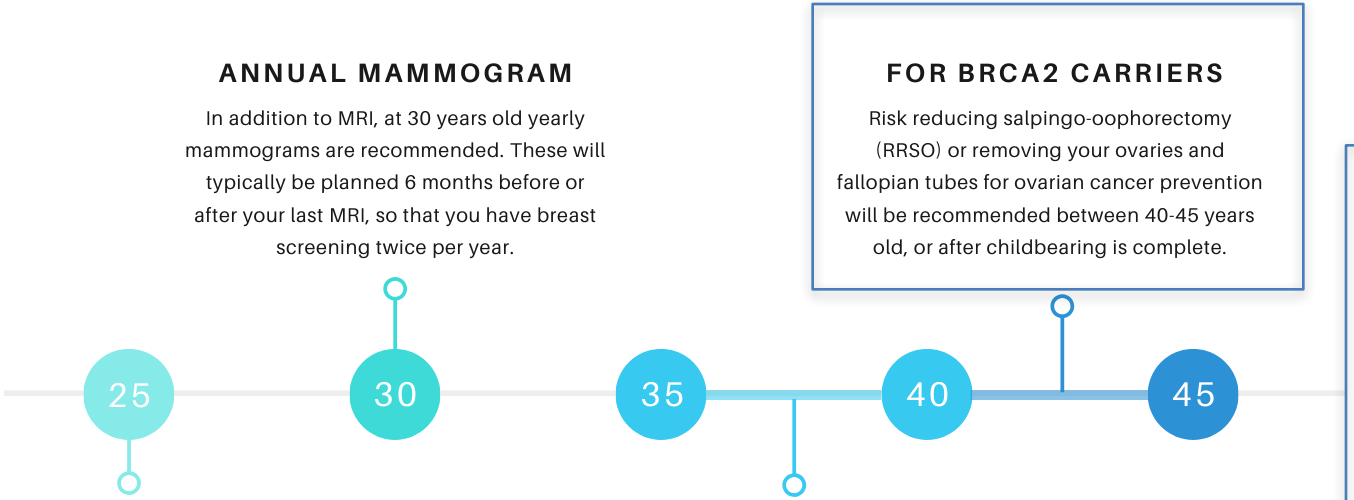
INCIDENCE

EFFECT OF BRCA MUTATION ON AGE OF ONSET





Kuchenbaecker et al. JAMA 2017



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BILATERAL PROPHYLACTIC MASTECTOMY

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CASE THREE

COUNSELING SESSION

Ms. S proceeds with bilateral nipple sparing mastectomies with implant based reconstruction. She receives adjuvant chemotherapy and is started on Letrozole.

After completing her breast cancer treatment, she meets with a gynecologist to sign consent for risk-reducing laparoscopic salpingo-oophorectomy (RRSO).

CASE THREE

BRCA2 POSITIVE MALES

Ms. S has one son aged 22 years old. He is interested in undergoing genetic testing in the future. If he tests positive for the BRCA2 gene mutation, what screening would be recommended?

SCREENING

BRCA2 POSITIVE MALES

1) **Prostate (21% lifetime risk)**
   - Onset typically before 65 years
   - Higher prostate-cancer specific mortality
   - Baseline PSA at 40 years, repeat testing annually
2) **Pancreatic (7% lifetime risk)**
   - Annual CE MRI/MRCP endoscopic ultrasound under clinical screening protocol*
3) **Breast (6-13% lifetime risk)**
   - Annual clinical breast exam starting at 35 years
   - Consideration for mammogram starting at 50

REFERRAL

CONSULTATION

High Risk Evaluation

RISK ASSESSMENT
TYRER-CUZICK V8,
BOADICEA

GENETICS

- Pre-test Counselling and Testing
- Post-test Counseling
- Cascade Testing for Family members

ALLIED HEALTH PARTNERS

- Bariatrics for Weight Loss Surgery (BMI >40)
- Nutrition workshop (BMI 30-40)
- Smoking Cessation Program
- GI for CRC/ Pancreatic Screening
- Gynecology for Ovarian Cancer Risk
- Dermatology for Melanoma Screening

BREAST SCREENING

- Mammo-graphic Screening
- Whole breast US or Screening MRI
- Bone health BMD/DEXA

PREVENTION

- SERMs/AI
- Bilateral Prophylactic Mastectomy
- RRS/ RRSO

FOLLOW UP

Hôpital général juif
Jewish General Hospital
Centre du cancer Segal Cancer Centre

McGILL HIGH RISK BREAST CLINIC

For women at increased breast cancer risk, individualized risk assessment, referral for screening, genetic testing, and improved access to risk reducing strategies that include lifestyle, pharmacologic, and surgical interventions can markedly decrease the incidence of malignancy.

Stroll Cancer Prevention Centre
E740 | 3755 Ch. de la Cote Ste Catherine
Montreal, QC, Canada
www.mcgill.ca/cancerprevention

McGill

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Questions?

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