BRCA at FMF
Gynecologic Risk Reduction

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Disclosures

- I am currently enrolling patients in trials run by Merck, AstraZeneca, Pfizer, Clovis and CCTG
- Speaker for CANO, hosted by AstraZeneca

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Objectives

- Understand the gynecologic risks associated with BRCA 1 and BRCA 2 germline mutations
- Understand an approach to risk management strategies in BRCA carriers
- Appreciate the nuances and impact of decision making in BRCA carriers

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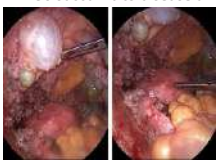
Ovarian Cancer

- Over 2600 Canadian women are diagnosed ovarian cancer every year
- 1750 succumb to disease annually



- Second most common gynecologic malignancy
- Most lethal gynecologic malignancy, and the 5th ranking cause of cancer death for women

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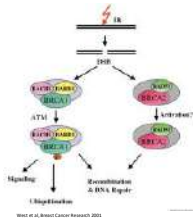
BRCA Gene

- Repair of DNA double-strand (dsDNA) breaks via the homologous recombination (HR) pathway
- Functional *BRCA* proteins regulate cell growth and prevent abnormal cell division that might otherwise lead to tumour development



West et al, Breast Cancer Research 2001

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Case Discussion

- Alice is a 24y/o G0P0 in your practice. You knew her mother was being treated for ovarian cancer, and she was just diagnosed as a carrier for a BRCA1 mutation.
  - Should she get tested?
  - Should she get regular ultrasounds? Ca125?
  - What about surgery?
  - What about raising a family?
  - Is there anything she can do to reduce her risk?

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Ovarian Cancer

	BRCA 1		BRCA 2	
Antoniou	40%	30-60%	18%	5-20%
Chen	59%		16%	
Rebbeck	12%		5%	
Mavaddat	35%		11%	

Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117-1130.
Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007;25:1329-1333
Rebbeck TR, Mitra N, Wan F, et al. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. Jama 2015;313:1347-1361.
Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst 2013;105:812-822.

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Ovarian Cancer

RRs of Breast and Ovarian Cancer in Mutation Carriers

	RR[a] (95% CI) OF CANCERFOR CARRIERS OF MUTATIONS IN			
	BRCA1		*BRCA2*	
AGE GROUP	BreastCancer	OvarianCancer	BreastCancer	OvarianCancer
20–29 years	17 (4.2–71)	1.0	19 (4.5–81)	1.0
30–39 years	33 (23–49)	49 (21–111)	16 (9.3–29)	1.0
40–49 years	32 (24–43)	68 (42–111)	9.9 (6.1–16)	6.3 (1.4–28)
50–59 years	18 (11–30)	31 (14–66)	12 (7.4–19)	19 (9.0–41)
60–69 years	14 (6.3–31)	50 (22–114)	11 (6.3–20)	8.4 (2.2–32)

Chen et al

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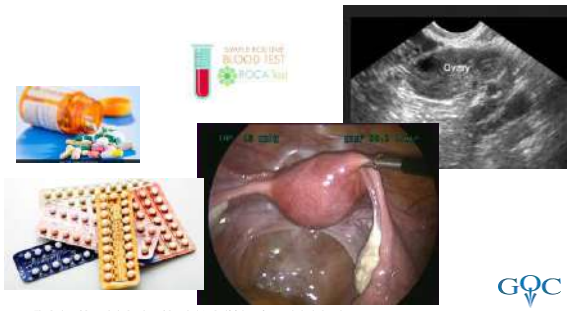

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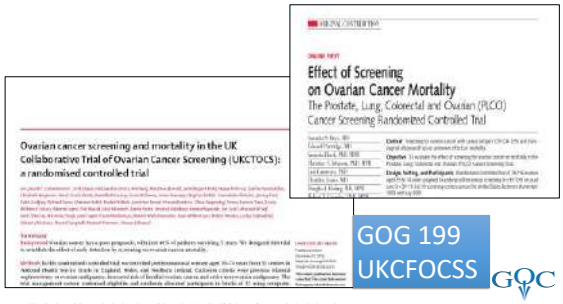

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UKCTOCS

Intervention	Number of patients	Deaths	False positives
MMS	50 624	148	2
USS	50 623	154	10
No screening	101 299	347	0

The Lancet Vol 387 March 5, 2016

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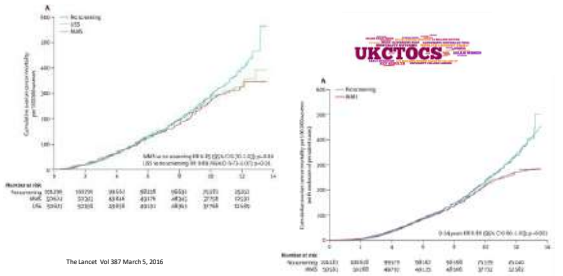

The Lancet Vol 387 March 5, 2016

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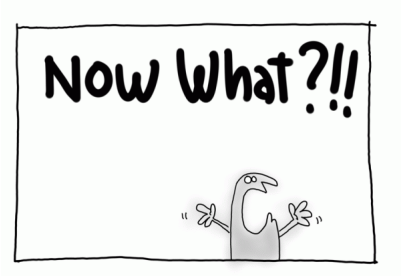
Other Trials

- PLCO
- GOG 199
- UKFOCSS



Chemoprevention

- Meta-analysis of OCP use in BRCA carriers
  - 2855 breast cancer cases
  - 1503 ovarian cancer cases
  - **RR 0.50 (0.33-0.75)**
  - 36% reduction in ovarian cancer with each additional 10 years of use
  - Breast cancer 1.13 (0.88-1.45)*

Eur Jour Cancer 2010;46:2275-2284

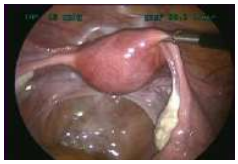
Chemoprevention

- ASA and NSAID use
  - Mostly small volume studies
  - Pooled analysis of 12 case control studies showed a 10% decrease in risk, most pronounced in low dose daily users
  - Included 758 829 women who at study enrollment self-reported analgesic use, among whom 3514 developed ovarian cancer
  - Ongoing OV25

Ovarian Cancer consortium, International Journal of Cancer Research Feb 2019

RRSO

- Risk reducing salpingo-oophorectomy
- **Associated with a 70% reduction in all cause mortality**
  - BRCA 1 HR 0.30 (0.24-0.38 p<0.001)
  - BRCA 2 HR 0.33 (0.22-0.50 p<0.001)



Journal of Clinical Oncology 2014 May 20;32(15):1547-53. Finch A

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Benefits of surgery

Risk Reduction	
Ovarian cancer	90%
Breast cancer	50%
Breast cancer mortality	50%
All cause mortality	70%

Domchek *et al*, JAMA 2010;304(9):967-75
Kauff *et al*, JCNI 2009;101(2):80-7

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RRSO recommended for all BRCA carriers

National Comprehensive Cancer Network
Royal College of Obstetricians & Gynaecologists
ESMO
SGO Society of Gynecologic Oncology
GOC THE SOCIETY OF GYNECOLOGIC ONCOLOGY OF CANADA

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Practically speaking

- BRCA 1 or BRCA 2
- Breast cancer recovery
- Prophylactic mastectomy/recovery
- Personal considerations
  - Family planning
  - Family experience

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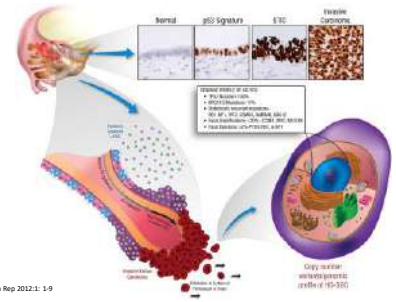
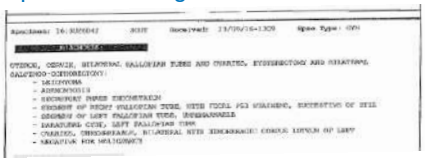
Considerations

- SEE-FIM protocol
- Unexpected findings in the OR
  - Surgical consent
- Role for hysterectomy



Cur Obs Gyn Rep 2012:1: 1-9

Intraoperative findings



Incidental occult findings in 3-7%

- BRCA1 4.6%
- BRCA2 3.5%
- Non-carriers 0.5%

J Clin Onc 32, 35;2014

Role for hysterectomy

OR time
Complication rates
Recovery time
Risk of laparotomy

Simplifies HRT
Serous endometrial cancer
Tamoxifen associated endometrial cancer

Other considerations

- Salpingectomy alone
- No BRCA diagnosis but strong family history

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PARP inhibitors

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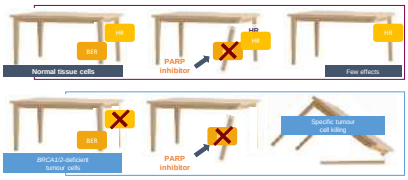
PARP Inhibition and Tumour Selective Synthetic Lethality



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Case Discussion

- Alice decided to get tested. She carries the same mutation as her mother
- No role for screening with ultrasound or bloodwork
- Decided to start an oral contraceptive
- Is in a stable relationship. Not ready to have children yet, but is going to discuss the plan with her partner. Plan for risk reducing surgery after age 35

Summary

- No reliable screening for ovarian cancer
  - In BRCA patients OR non-BRCA patients
- Consider oral contraceptives in most BRCA carriers as a risk reduction strategy prior to surgery
- Removing the fallopian tubes and ovaries is the most important thing….but it's not as easy as removing the tubes and ovaries
- PARP inhibitors are exciting
- These ladies need a lot of help and guidance, and family physicians are uniquely situated to help!

QUESTIONS?