

Ovarian Cancer Genetics

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• I serve on the Genetic Counseling Advisory Board for Invitae Laboratories.



Ovarian Cancer

Risk Factors

Non-Genetic

- Age
- Nulliparity (never being pregnant)
- Family history of ovarian cancer

Genetic

- BRCA1 or BRCA2 carrier
- Lynch syndrome (HNPCC)
- Other single gene mutations (rare)



Ovarian Cancer Risk in General Population

1 out of 72 women will develop ovarian cancer in their lifetime (1.4%)





Ovarian Cancer Risks









Causes of Hereditary Susceptibility to Ovarian Cancer



WalshT et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci 2011;108:18032–7.



Clues for a Hereditary Cancer Syndrome

- Early age of diagnosis
 - Typically diagnosed under the age of 60
- Multiple primary cancers in one individual
 - Such as ovarian cancer and breast cancer
- Individual with ovarian cancer and family history of ovarian and/or breast cancer typically diagnosed under the age of 50
- Multiple generations affected with cancer
- Rare cancers (i.e. male breast cancer)
- Ashkenazi Jewish ancestry









AGCTGTTCAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCA What are these "genes"?

- Tumor suppressor genes
- Carried by both men and women
- Two copies of every gene in our body (~25,000)

What does a mutation mean?

AGCTGTTCAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAA

- One copy of gene can no longer perform normal function of "tumor suppressing"
- Increased risk of cancer









Genes BRCA1 and BRCA2 MLH1, MSH2, MSH2, PMS2, EPCAM BRIA Ovarian Cancer Risk 20-40% 10-15% 10 Other Cancer Risks Female/Male Breast (50-60%, up to 6%) Prostate (15%) Melanoma (5%) Pancreatic Colon (up to 70%) Uterine (40-60%) Gastric (up to 13%) Urinary Tract (up to 7%) Pancreatic (up to 6%) Second		Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	Lynch Syndrome	Other/Moderate Risk Genes for Ovarian Cancer		
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Ovarian Cancer Risk Reduction

HBOC and Lynch Syndrome

- Birth control pills
 - 5 years of use: 27% reduction
 - 15 years of use: 60% reduction
- First full-term pregnancy < age 25; number of pregnancies
- Breast-feeding
- Bilateral tubal ligation/hysterectomy
- Prophylactic oophorectomy
 - Risk of primary peritoneal cancer remains



Ovarian Cancer Risk Reduction

BRIP1, RAD51C, RAD51D

- Ovarian cancer
 - Approximately 15% lifetime risk of ovarian cancer
- Currently no established guidelines
 - Recommend risk reducing oophorectomy following natural menopause
- Other cancer risks?
 - TBD



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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Primary Fallopian Tube Malignancies in *BRCA*-Positive Women Undergoing Surgery for Ovarian Cancer Risk Reduction

Michael J. Callahan, Christopher P. Crum, Fabiola Medeiros, David W. Kindelberger, Julia A. Elvin, Judy E. Garber, Colleen M. Feltmate, Ross S. Berkowitz, and Michael G. Muto

> Human Reproduction Update, Vol.17, No.1 pp. 55–67, 2011 Advanced Access publication on July 15, 2010 doi:10.1093/humupd/dmq030

human reproduction update

Tubal ligation and the risk of ovarian cancer: review and meta-analysis

D. Cibula ^{1,*}, M. Widschwendter², O. Májek³, and L. Dusek³



Prophylactic Salpingectomy with Delayed Oophorectomy

- Recent studies have suggested majority of ovarian cancer begins in fallopian tubes in women with *BRCA1/2* mutations (~80%)
- **<u>RESEARCH</u>** currently ongoing to evaluate for removal of fallopian tubes first
 - Delays surgical menopause while *hopefully* reducing ovarian cancer risk
 - Remove ovaries few years later
- NOT STANDARD OF CARE, only being performed on research basis at this point



- Sequencing Analysis
 - Reads through each letter one by one
 - Picks up approximately 95% of mutations in BRCA1/2









AGCTGTTCAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGT TCAAGTCAGTCACTGCAGTCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTTCAAAA ATGTCAGTCACTGCAGTCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTTCAAGTCA GTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAATTGCACCGTGACAGTCACGT GACT

- Deletion/Duplication Analysis
 - Looks for large amounts of letters that are missing or added
 - Picks up approximately 5% of mutations in *BRCA1* or *BRCA2*



What if I already had negative *BRCA1* and *BRCA2* testing? Are there other genes related to ovarian cancer?

- Gene panels...
 - Includes more than one gene related to specific indication such as ovarian cancer
 - High risk genes: Lynch syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM)
 - Moderate risk genes: BRIP1, RAD51C, RAD51D
 - And many more...
- Changing yearly, even monthly



Genetic Testing

- Multi-Gene Panel vs Single Gene Testing
 - Multiple cases of cancer within a family
 - Isolated case of ovarian cancer diagnosed at any age
 - Identified familial mutation
- Genetic Testing Results:
 - No Mutation Found
 - Pathogenic
 - Variant of uncertain significance (VUS) inconclusive



All of my genetic testing was negative, now what?

- Management based on personal and family history of cancer
- First degree female relatives (daughters, sisters, mothers):
 - Consider ovarian cancer screening as part of a *research protocol*
 - Northwestern Ovarian Cancer Detection and Prevention Program
 - Trans-vaginal ultrasound and CA-125 level
- Consult with physicians/genetic counselors periodically for updated genetic testing and recommendations



Benefits of Genetic Testing

- Provide an explanation for your personal or family history of cancer
- Evaluate your risk of developing future cancers
- Make informed medical decisions, including treatment, surveillance, and preventive options
- Potential use of other chemotherapy options
 - PARP inhibitors for *BRCA1/2* individuals
- Qualify you for participation in clinical trials or research studies
- Identify other at-risk relatives for whom genetic testing is recommended
- Always changing and evolving periodically check-in with genetics



Drawbacks to Genetic Testing

- Will results make a difference in my care?
- May be inconclusive
- Risk for developing cancer not always established
- What interventions are available?
- Psychosocial implications



Tumor DNA Testing

- Uses next generation sequencing (many, many genes)
- Testing performed to look for DNA mutations *within* cancer cells/tumor only
 - Different from genetic testing (testing we just reviewed)
- Typically performed to look for treatment targets or response to treatment
- Incidentally can find a genetic mutation that you were born with (inherited mutation)
- "New-er" so work in progress and rapidly evolving... (stay tuned)













Sporadic Cancer Χ xX Х \rightarrow \rightarrow Х \rightarrow хΧ Normal Cell Accumulate changes or mutations over Tumor time Development Hereditary Cancer Predisposed Cell ХХ Х X X Χ ХХ Х Tumor

Accumulate changes or mutations over time

Development











- Genetic Information Nondiscrimination Act (GINA) passed in 2008
- Family planning options
- Openness or willingness to communicate with family members
 - Family letter
- Psychosocial Implications
- Patient advocacy groups



Family Letter Example

Dear family:

I am writing this letter to inform you that I recently had genetic testing and was diagnosed with a condition called hereditary breast and ovarian cancer syndrome (HBOC) which affects families. This letter contains information about HBOC, how it might affect you, and how to find out if you have this condition also.

People who have HBOC have increased cancer risks. Specifically women have increased risks for breast cancer and ovarian cancer, and men have increased risks for prostate cancer and male breast cancer. It is recommended that anyone with HBOC have increased screening for these cancers which helps detect cancers earlier when they are more easily treated, and in some cases, prevent them altogether.

Hereditary breast and ovarian cancer syndrome is caused by a mutation in a gene that can be inherited in families. The specific mutation identified in me was in the **BRCA*** gene (***). Genetic testing is available for you to see if you carry this same mutation. You can take this letter to your doctor, or contact the genetics team at Northwestern Cancer Genetics to discuss this further and find out how to get tested in your area. You can also find a genetic counselor near you by going to the following website: <u>www.nsgc.org</u> and using the "Find a Genetic Counselor" tool.

If you or your doctors have additional questions, the Northwestern Cancer Genetics team would be happy to discuss this further. You can reach a member of the Cancer Genetics Team at 312-472-0518 or 312-472-0523.

Sincerely,



Find a Genetic Counselor Near you

http://www.aboutgeneticcounselors.com/



Search Tips:							
The "First Name" and "Last Nam If you do not return any results v Students interested in contactin	ne" fields should only be u within your zip code, try se Ig a genetic counselor abo	sed if you kno earching just b out the profes:	w the name of t y state. sion should cheo	he genetic counse ck the "Student Co	elor you are looki ontact Welcome"	ng to contact. box.	
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Thank You

Email: <u>Brittany.DeGreef@nm.org</u> Scheduling: (312) 695-0320

