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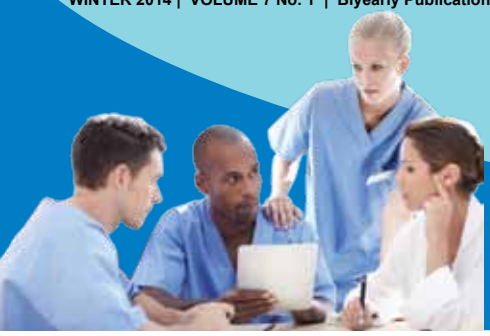

The Laboratorian SM

Era of new diagnostic approaches: *BRCA1* and *BRCA2* genes

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INTRODUCTION

Actress Angelina Jolie raised global awareness of breast cancer and genetic testing on May 2013, when she revealed her decision to have a double mastectomy after genetic testing showed she was at a high risk for developing breast and ovarian cancer. The so-called "Angelina Jolie effect" induced a marked increase in genetic testing at treatment centers across the country, according to the National Society of Genetic Counselors.

Breast cancer is the second most common newly diagnosed cancer and second leading cause of cancer death among women in the United States. In 2013, an estimated 232,340 new cases of invasive breast cancer were expected to be diagnosed among US women, as well as an estimated 64,640 additional cases of *in situ* breast cancer, according to the National Cancer Institute (1). About 7 out of 100 women (or 7%) will get breast cancer by age 70; about 1 out of 100 women (or 1%) will get ovarian cancer by age 70 (2).

*Of all Americans, **one million** of us carry a BRCA1 mutation!*

Epidemiologic studies have clearly established the role of family history as an important risk factor for breast and ovarian cancer. For women who have mutations in their *BRCA1* and/or *BRCA2* genes, the risk for early breast cancer and ovarian cancer is greatly increased: their life time risk can reach up to 65%–80% for breast cancer and 45%-56% for ovarian cancer by the age of 70 (3). Of all Americans, one million of us carry a *BRCA1* mutation!

*BRCA*1 and *BRCA*2

Almost 25 years ago, the first quantitative evidence that breast cancer segregated as an autosomal dominant trait was reported [4]. In the early 1990s, a susceptibility gene *BRCA1* for breast cancer was mapped by genetic linkage to the long arm of chromosome 17, and the second gene, *BRCA2*, was localized to chromosome 13 [5]. *BRCA1* and *BRCA2* are human genes that produce tumor suppressor proteins. These proteins help repair damaged DNA and, therefore, play a role in ensuring the stability of the cell's genetic material.
Hundreds of unique mutations have been identified in both the *BRCA1* and *BRCA2* genes. The overall prevalence of disease-related mutations in the *BRCA1* and *BRCA2* genes has been estimated as 1 in 300 and 1 in 800, respectively (6). Mutations of *BRCA1* and *BRCA2* can be highly penetrant, meaning a high percentage of individuals who have the disease-causing mutation will manifest clinical symptoms and presentation of the disorder. Estimates of penetrance of *BRCA* mutations range from a 41% to 90% lifetime risk for breast cancer (7). Currently the next-generation DNA-sequencing (NGS) technologies provide exquisite sensitivity and resolution for detection of *BRCA* mutations in clinical practice for screening and treatment purposes (8).

Cancer Risk Associated to *BRCA* Mutations

Female breast and ovarian cancers are clearly the dominant cancers associated with *BRCA1* and *BRCA2* genes mutations. About 55%-65% of women with *BRCA1* mutation and around 50% of women with *BRCA2* mutation will develop breast cancer by age 70 years (2). In addition, approximately 39% of women with *BRCA1* mutation and 11%-17% of women with *BRCA2* mutation will develop ovarian cancer by age 70 years (9, 10). Together, *BRCA1* and *BRCA2* mutations account for about 20% to 25% of hereditary breast cancers, about 5%-10% of all breast cancers, and around 15% of ovarian cancers overall (1). Mutations in *BRCA1* and *BRCA2* appear to be responsible for disease in 45% of families with multiple cases of breast cancer only and in up to 90% of families with both breast and ovarian cancer (11).

Breast cancers associated with *BRCA1* and *BRCA2* mutations tend to develop at younger ages than sporadic breast cancers. Ovarian cancer arising in women with *BRCA1* and *BRCA2* mutations is more likely to be invasive serous adenocarcinoma (12, 13), and the mean tumor doubling time is two-times less compared with the time in non-carriers (14). It is important to note that other characteristics of a particular woman like her family or reproductive history can make an individual risk higher or lower than the average risks. However, none of these other factors is as strong as the effect of carrying a harmful *BRCA1* or *BRCA2* mutation (1).

Specific inherited mutations in *BRCA1* and *BRCA2* have been associated with increased risks of several additional types of cancer (Table 1). Harmful *BRCA1* mutations may increase a woman's risk of developing fallopian tube cancer, peritoneal cancer (15), and men's risk of breast cancer and prostate cancer (16-19). Men and women with *BRCA1* or *BRCA2* mutations may be at increased risk of pancreatic cancer and melanoma (20, 21).

Table 1. Spectrum of Cancers in *BRCA1* and *BRCA2* Mutation Carriers (1)

Cancer Sites	*BRCA1* Mutation Carrier		*BRCA2* Mutation Carrier	
	Strength of Evidence	Magnitude of Absolute Risk	Strength of Evidence	Magnitude of Absolute Risk
Breast (female)	+++	High	+++	High
Ovary, fallopian tube, peritoneum	+++	High	+++	Moderate
Breast (male)	+	Undefined	+++	Low
Pancreas	++	Very Low	+++	Low
Prostate	+	Undefined	+++	High

+++ Multiple studies demonstrated association and are relatively consistent. ++ Multiple studies and the predominance of the evidence are positive. + May be an association, predominantly single studies; smaller limited studies and/or inconsistent but weighted toward positive.

BRCA and Fertility

Women in general, and particularly women with cancer, face many challenges when considering fertility preservation. Impairment of *BRCA1* related DNA repair leads to ovarian aging in mice and humans (22), and is also associated with altered sperm production in mutant mice (23). Recent work has suggested that women with *BRCA* mutations may experience an early onset of menopause (24, 25) and to be at risk of occult primary ovarian insufficiency (26, 27). A trend toward shorter mean reproductive life spans and decreases of ovarian reserve may be related to *BRCA* genes involvement in repair and maintenance of chromosome telomerase integrity, which is important during reproduction.

Women with *BRCA1* and *BRCA2* mutations did not find an adverse effect of fertility treatment on the risk for developing breast cancer (27). The possibility of transmitting a mutation to a child may pose a concern to families affected by a history of breast or ovarian cancer. Pre-implantation genetic diagnosis (PGD) can be a reproductive option for *BRCA* mutation carriers, especially for those who require *in vitro* fertilization due to fertility problems (28).

WHAT'S INSIDE

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The last decade brought many options for women with cancer considering fertility preservation. *BRCA* mutation carriers may be more susceptible to chemotherapy-induced ovarian reserve loss because mutation carriers may have a lower ovarian reserve and because deficient DNA repair may also make oocytes more susceptible to DNA-damaging agents. Different ovarian tissue preservation methods may be a promising alternative to ovarian stimulation in patients with *BRCA* mutations before the risk for ovarian cancer increases with age or before chemotherapy (27).

DIAGNOSTIC AND MANAGEMENT STRATEGY

People with *BRCA* mutations can take effective steps to prevent cancer or lower their chances of dying from cancer if it does develop. Mutation carriers are counseled on different risk reducing strategies, e.g. more frequent screening or prophylactic surgery.

Cancer Screening in Risk Groups

Women screening

Most experts agree that mutation testing of individuals should be performed when the person's family and personal history suggests the possible presence of a harmful mutation in *BRCA1* or *BRCA2* genes (1, 29). (Table 2).

Table 2. Recommendations for *BRCA* screening according to the National Cancer Institute (1).

Family history characteristics associated with an increased likelihood of carrying *BRCA* mutations include the following:
• Multiple cases of breast cancer. • Both breast and ovarian cancer. • One or more breast cancers in male family members. • Ashkenazi Jewish background.
Personal characteristics associated with an increased likelihood of a *BRCA1* and/or *BRCA2* mutation include the following:
• Breast cancer diagnosed at an early age. • Ovarian cancer. • Bilateral breast cancer. • A history of both breast and ovarian cancer. • Breast cancer diagnosed in a male at any age. • Triple-negative breast cancer diagnosed in women younger than 50 years. • Ashkenazi Jewish background.
For women who are not of Ashkenazi Jewish descent, genetic testing is recommended if:
• Two first-degree relatives diagnosed with breast cancer, with one of them before age 51. • Three or more first- or second-degree relatives diagnosed with breast cancer. • A combination of first- and second-degree relatives diagnosed with breast cancer or ovarian cancer. • A first-degree relative diagnosed with cancer in both breasts. • A first- or second-degree relative diagnosed with breast and ovarian cancer; • A male relative diagnosed with breast cancer.
For women of Ashkenazi Jewish descent, who are more likely to carry a specific *BRCA2* mutation passed from generation to generation, genetic testing is recommended if:
• A first-degree relative diagnosed with breast or ovarian cancer. • Two second-degree relatives on the same side of the family diagnosed with breast or ovarian cancer.

In the general population, strong evidence suggests that regular mammography screening of women leads to a 17% to 30% reduction in breast cancer mortality (30). Intensive breast cancer screening in *BRCA* mutation carriers consisting of an annual MRI, mammography, and clinical breast examination can reach a sensitivity of more than 90% in finding early stage breast cancer in mutation carriers (31, 32). The National Comprehensive Cancer Network (NCCN) currently recommends for *BRCA1* and *BRCA2* mutation carriers annual mammography and MRI screening beginning at age 25 years or individualized based on the earliest age of cancer onset in their family (29). It was suggested that the most cost-effective screening strategy in *BRCA1* and *BRCA2* mutation carriers may be an annual MRI beginning at age 25 years, with alternating MRI and digital mammography (so that each test is done annually but screening occurs every 6 months) beginning at age 30 years (33).

Certain observations have also led to the concern that *BRCA* mutation carriers may be more prone to radiation-induced breast cancer than women without mutations. A large, international, case-control study described an increased risk of breast cancer among women who were exposed to chest x-rays, with risk being highest in women aged 40 years and younger, born after 1949, and exposed to x-rays only before age 20 years (34).

Men screening

Clinical guidelines to manage male carriers with *BRCA* mutations are based on consensus statements and expert opinions (29, 35). *BRCA2* mutations have been associated with a 2- and 6-fold increase in the risk of prostate cancer, more aggressive and more rapid progressive disease phenotype (Gleason score ≥8), higher histologic grade, and poor prognosis (18, 36-38). Cause-specific survival outcome was significantly poorer in *BRCA* mutation carriers compared with non-carriers (median survival 8.6 years *vs.* 15.7 years) (39). The presence of a germline *BRCA2* mutation is an independent prognostic factor for survival in prostate cancer (38). Screening guidelines for prostate cancer include PSA screening and digital rectal exam on an annual basis starting at age 50 years. Information on *BRCA* mutation status in men may inform optimal clinical strategies. Recent findings suggest that PSA screening may be of potential utility in men with *BRCA* mutations (40, 41).

Screening for male breast cancer in *BRCA* mutation carriers as suggested by the NCCN clinical practice guidelines (29) includes breast self-exam training and education, clinical breast exam every 6 to 12 months, and consideration of a baseline mammogram.

Risk-Reducing Surgery

The actual timing of radical surgical treatment decisions depend on the presence of *BRCA1* and *BRCA2* mutations, and many personal circumstances such as previous cancer, marital status, previous or planned pregnancies, and psychological acceptance of definitive surgical procedure.

In the general population, both subcutaneous mastectomy and simple (total) mastectomy have been used for prophylaxis of breast cancer in *BRCA1* and *BRCA2* mutation carriers. Prophylactic risk-reducing mastectomy (RRM) strongly reduces the breast cancer risk, with about 90% at the age of 70 when conducted at the age of 38 years (42, 43).

Removal of both ovaries has been associated with a total reduction in ovarian cancer risk and a reduction in breast cancer risk of up to 75%, depending on parity, weight, and age at time of artificial menopause. As of 2007, counseling has moved toward specific advice to have risk-reducing salpingho-oophorectomy (RRSO) around the age of 40, because ovarian screening did not appear to be effective in reducing ovarian cancer death (44, 45). In addition to the reduction in incidence of both breast and ovarian cancer, RRSO is associated with a reduction in all-cause mortality, breast cancer–specific mortality, and ovarian cancer–specific mortality (46).

CONCLUSION

Genetic testing for *BRCA1* and *BRCA2* mutations has been available to the public since 1996. During the last 20 years, new research findings open up a window of opportunity to optimize a risk assessment, prevention, diagnostic and treatment of breast, ovarian and prostate cancer in *BRCA* mutation carriers. Next-generation genome sequencing technology and genetic testing is a major advancement towards our ultimate goal of cancer prevention and treatment. Information on *BRCA* mutation status may guide optimal screening and treatment management of high risk populations in the future. Researchers at the Moffitt Cancer Center have found that when breast cancer patients are offered pre-test genetic counseling before definitive breast cancer surgery, patients exhibited decreases in distress and improvements in informed decision making [47].

Additional efforts are needed to encourage appropriate counseling and genetic testing for all patients at high risk of hereditary cancer, particularly among general internists, family physicians and obstetrician-gynecologists. A study published in *Cancer*, a peer-reviewed journal of the American Cancer Society, indicated that for high-risk women, less than half of the physicians reported that they would recommend referral for genetic counseling or testing, consistent with all guidelines (47). The benefits of genetic testing include the ability to make medical and lifestyle decisions based on genetic background. The ability to make a proactive decision regarding risk-reducing surgery, preventive chemotherapy or fertility preservation for high risk population emphasizes the importance of genetic counseling in current clinical practice.

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e-Quiz

1. **True of False**. By the age of 70, 7/100 women (7%) will get breast cancer and 1/100 (1%) will get ovarian cancer.

2. **Match the risk on the right with the family history on the left for the following statement:** Mutations in *BRCA1* and *BRCA2* appear to be responsible for:

History:	**Occurrence:**
	10%
Families with multiple cases of breast cancer only	90%
Families with both breast and ovarian cancer	75%
	45%

3. Of all Americans, _____ may carry a *BRCA1* mutation.

   a. One hundred
   b. One thousand
   c. One hundred thousand
   d. One million

4. **True of False**. Currently the next-generation DNA-sequencing (NGS) technologies provide exquisite sensitivity and resolution for detection of *BRCA* mutations in clinical practice for screening and treatment purposes.

5. The benefits of genetic testing includes the ability to:

   a. Make medical and lifestyle decisions based on genetic background.
   b. Make a proactive decision regarding risk-reducing surgical treatment.
   c. Make a proactive decision regarding preventive chemotherapy for high risk populations.
   d. Make a proactive decisions regarding fertility preservation for high risk populations.
   e. All of the above

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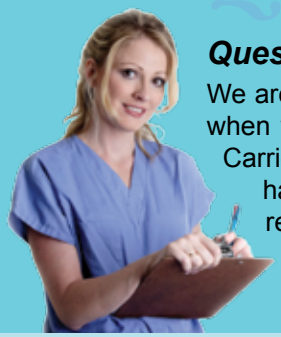

Question:

We are sometimes contacted by your laboratory when we order Test 1201 Cystic Fibrosis Gene Carrier Screening by Bio-Plex Analysis. We have been told that results cannot be released until we provide the patient's ethnicity. Why?

Answer:

Cystic Fibrosis (CF) has an autosomal recessive inheritable pattern whereby people may be carriers of the disease, having inherited a defective gene but not exhibiting symptoms. It is estimated that one in every thirty-one Americans are carriers. Carrier status occurs more frequently in some ethnic populations that in others. For example, Ashkenazi Jewish and Caucasians of European descent have a higher carrier risk rate than Asian Americans.

Incidence and Carrier Risk for Cystic Fibrosis Based on Race or Ethnicity (1).		
Ashkenazi Jewish	1/24	1/3,300
European Caucasian	1/25	1/3,300
Hispanic American	1/58	1/8,000 – 9,000
African American	1/61	1/15,300
Asian American	1/94	1/32,100

Information about your ethnic dissent is used to calculate the chance that you could still be a Cystic Fibrosis carrier even if the results of your screening test are normal and none of the mutations in the CF Core Panel are detected. This information is requested on the test requisition form. If this information is not provided up front on the test requisition form that is submitted with the patient specimen, we will contact the office of the ordering physician. Results may be finalized once this information is obtained.

1. Committee Opinion Number 486, April 2011, Replacing No. 325, December 2005. The American College of Obstetricians and Gynecologists. Obstetrics & Gynecology, Vol. 117, No. 4, April 2011.

If you have a question you would like addressed in future issues, please email your question(s) to QAQ&A@mdlab.com

Recent Publications

Femeris Women's Health Research Center™ Peer-Reviewed Papers:

1. **Balashov SV, Mordechai E, Adelson ME, Sobel JD, Gygax SE.** 2013. Multiplex qPCR assay for the identification and quantification of major vaginal lactobacilli. *DMID, In Press.*

2. **Balashov SV, Mordechai E, Adelson ME, Gygax SE.** 2013. Identification, Quantification, and Subtyping of *Gardnerella vaginalis* in Noncultured Clinical Vaginal Samples by qPCR. *J Med Microbiol, In Press.*

3. **Steier Z, Vermitsky JP, Chadwick S, Gygax SE, Edlind TD**. 2013. Flucytosine and antagonism of azole activity versus *C. glabrata*. *Antimicrob Agents and Chemother*, **57**(11):5543-7.

Abstracts:

1. **Chadwick SG, Schuyler JA, Balashov S, Adelson ME, Mordechai E, and Gygax SE.** Disruption of *Gardnerella vaginalis* Biofilms with Clindamycin and Metronidazole. 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 10-13, 2013, Denver, Colorado.

Institute of Metabolic Disorders™ Peer-Reviewed Papers:

1. **Yang M, Liu W, Pellicane C, Sahyoun C, Joseph BK, Gallo-Ebert C, Donigan M, Pandya D, Giordano C, Bata A, Nickels JT Jr.** 2013. Identification of miR-185 as a regulator of de novo cholesterol biosynthesis and low-density lipoprotein uptake. *J Lipid Res. In Press*

2. **Gallo-Ebert C, Donigan M, Liu HY, Pascual F, Manners M, Pandya D, Swanson R, Gallagher D, Chen W, Carman GM, Nickels JT Jr.** 2013. The Yeast Anaerobic Response Element AR1b Regulates Aerobic Antifungal Drug-dependent Sterol Gene Expression. *J Biol Chem.* **288**(49):35466-77.

3. **Gallo-Ebert C, Donigan M, Stroke IL, Swanson RN, Manners MT, Francisco J, Toner G, Gallagher D, Huang CY, Gygax SE, Webb M, Nickels JT Jr.** 2014. Novel antifungal drug discovery based on targeting pathways regulating the fungus-conserved upc2 transcription factor. *Antimicrob Agents Chemother.* **58**(1):258-66.

HUMIGEN, the Institute for Genetic Immunology Peer-Reviewed Papers:

1. **Swider A, Siegel R, Eskdale J, and Gallagher G.** 2014. Regulation of IFN-λ1 expression in human colon epithelial cells. *Cytokine*, **65:**17-23.

Venenum Biodesign Abstracts:

1. **Stein, P.** Simple and Complex Science and Technology. Rutgers University, November 21, 2013.

Kim J, Oktay K. 2013. Baseline E2 levels are higher in *BRCA2* mutation carriers: a potential target for prevention? *Cancer Causes Control* **24**:421–426.

BRCA gene mutations and elevated serum estradiol (E2) are well-known risk factors for breast cancer. The aim of this study was to investigate the association between *BRCA* gene mutations and serum E2 level. The baseline (menstrual cycle day 2–3) E2 levels were measured in 96 women with breast cancer who underwent *BRCA* testing. The mean age, parity, and menarche age did not differ between women with and without *BRCA1/2* mutations. Basal serum E2 level was significantly higher in women with *BRCA2* mutations compared to women with *BRCA1* mutations or without *BRCA* mutations (71.7±41.6 vs. 45.5±20.7 vs. 38.5±12.6 pg/ml in *BRCA2* mutation carriers, *BRCA1* mutation carriers, and non-carriers, respectively; p=0.03). Women with *BRCA2* mutations had 3.1 times as great risk for high basal E2 level as women without *BRCA* mutations. *BRCA* mutation carriers with high serum E2 level were significantly younger than the carriers with low serum E2 level (31.4±3.1 vs. 34.7±4.9 years; p=0.04). The authors suggest that the association between high basal serum E2 levels and *BRCA2* mutations may have a role in the pathogenesis of *BRCA2*-mutation-related breast cancer.

Weghofer A, Tea MK, Barad DH, Kim A, Singer CF, Wagner K, Gleicher N. 2012. *BRCA1/2* Mutations appear embryo-lethal unless rescued by low ($CGG_{n<26}$) FMR1 sub-genotypes: explanation for the "*BRCA* paradox"? *Plos One* **7**(9):1-7. e44753.

The fragile X mental retardation 1 (*FMR1*) gene, located on the long arm of the X chromosome contains a repetitive DNA segment, the CGG_n trinucleotide. The gene has historically been investigated due to associated neuro-psychiatric risks at so-called premutation range CGG expansions and at full mutation range, the so-called fragile X syndrome. In women, the premutation range genotype of *FMR1* has been associated with increased risk of premature ovarian failure. *BRCA1/2* mutations and recently described constitutional *FMR1* genotypes have, independently, been associated with prematurely diminished ovarian reserve. The distribution of constitutional *FMR1* genotypes, normal, heterozygous and homozygous, and of their respective sub-genotypes (high/low), was investigated in 99 *BRCA1/2* mutation-positive women and 410 female controls. In contrast to controls, *BRCA1/2* carriers demonstrated almost complete absence of all constitutional *FMR1* genotypes except for sub-genotypes with low ($CGG_{n<26}$) alleles. Cross tabulation between *BRCA1/2*-positive patients and controls confirmed significant group membership, related to *FMR1* distribution (P<0.0001). These results offer as most likely explanation the conclusion that *BRCA1/2* mutations are embryo-lethal, unless rescued by low ($CGG_{n<26}$) *FMR1* sub-genotypes, present in approximately one quarter of all women. Women with low *FMR1* sub-genotypes, therefore, should reflect increased *BRCA1/2*-associated cancer risks, while the remaining approximately 75 percent should face almost no such risks. This study also suggests that previously reported risk towards prematurely diminished ovarian reserve in association with *BRCA* mutations is *FMR1*-mediated, and offers a possible explanation for the so-called "*BRCA* paradox" by raising the possibility that the widely perceived *BRCA1/2*-associated tumor risk is actually *FMR1*-mediated.

Tea MK, Weghofer A, Wagner K, Singer CF. 2013. Association of *BRCA1/2* mutations with FMR1 genotypes: effects on menarcheal and menopausal age. *Maturitas* **75**: 148– 151.

Female *BRCA-1* and *BRCA-2* mutations are significantly associated with risk of developing breast and ovarian cancers. *BRCA-1* mutations have also been associated with occult primary ovarian insufficiency, as have different mutations of the *FMR1* gene. *FMR1* genotype and sub-genotype distribution was compared in 99 *BRCA1/2* positive women and in 182 healthy women without history of familial breast and ovarian cancer. Women with *BRCA1/2* mutations showed significantly different *FMR1* genotype and subgenotype distributions when compared with the healthy group (p<0.001). Only 6.1% of *BRCA*-positive women showed normal *FMR1* genotypes, the majority of all *BRCA*-positive women (78.8%) showed heterozygous genotypes (74.0% in *BRCA-1* and 83.7% in *BRCA-2* women, respectively). In addition, *BRCA1/2* mutation carriers indicated a trend toward shorter reproductive lifespan. This data confirmed the previously reported highly skewed distribution of *FMR1* genotypes and sub-genotypes toward a high preponderance of low *FMR1* alleles in *BRCA1/2* mutations carriers. *BRCA-1* mutations were associated with an earlier onset of menopause compared to *BRCA-2*, although the distribution of the het-norm/low genotype was similar in both groups. There may be other factors beside the genotype that has an influence on menarche and especially menopause age in *BRCA* mutation carriers.

Titus S, Li F, Stobezki R, Akula K, Unsal E, Jeong K, Dickler M, Robson M, Moy F, Goswami S, Oktay K. 2013. Impairment of *BRCA1*-Related DNA Double-Strand Break Repair Leads to Ovarian Aging in Mice and Humans. *Fertility* **5** (172): 172ra21.

The underlying mechanism behind age-induced wastage of the human ovarian follicle reserve is unknown. It was identified impaired ataxia-telangiectasia mutated (*ATM*)–mediated DNA double-strand break (DSB) repair as a cause of aging in mouse and human oocytes. DSBs accumulate in primordial follicles with age. In parallel, expression of key DNA DSB repair genes *BRCA1, MRE11, Rad51*, and *ATM*, but not *BRCA2*, declines in single mouse and human oocytes. In *BRCA1*-deficient mice, reproductive capacity was impaired, primordial follicle counts were lower, and DSBs were increased in remaining follicles with age relative to wildtype mice. Furthermore, oocyte-specific knockdown of *BRCA1, MRE11, Rad51*, and *ATM* expression increased DSBs and reduced survival, whereas *BRCA1* overexpression enhanced both parameters. Likewise, ovarian reserve was impaired in young women with germline *BRCA1* mutations compared to controls as determined by serum concentrations of anti-Müllerian hormone. These data implicate DNA DSB repair efficiency as an important determinant of oocyte aging in women.

Mocci E, Milne RL, Mendez-Villamil EY, Hopper JL, John EM, Andrulis IL, Chung WK, Daly M, Buys SS, Malats N, Goldgar DE. 2013. Risk of Pancreatic Cancer in Breast Cancer Families from the Breast Cancer Family Registry. *Cancer Epidemiol Biomarkers Prev* **22**(5): 803-11.

Increased risk of pancreatic cancer has been reported in breast cancer families carrying *BRCA1* and *BRCA2* mutations; however, pancreatic cancer risk in mutation-negative (*BRCAX*) families has not been explored to date. The aim of this study was to estimate pancreatic cancer risk in high-risk breast cancer families according to the *BRCA* mutation status. A retrospective cohort analysis was applied to estimate standardized incidence ratios (SIR) for pancreatic cancer. A total of 5,799 families with ≥1 breast cancer case tested for mutations in *BRCA1* and/or *BRCA2* were eligible. Families were divided into four classes: *BRCA1* mutations positive (class 1); *BRCA2* mutations positive (class 2); *BRCAX* with ≥2 breast cancer diagnosed before age 50 (class 3), and the remaining *BRCAX* families (class 4). *BRCA1* mutation carriers were at increased risk of pancreatic cancer (SIR = 4.11; 95% CI, 2.94–5.76) as were *BRCA2* mutation carriers (SIR = 5.79; 95% CI, 4.28–7.84). *BRCAX* family members were also at increased pancreatic cancer risk, which did not appear to vary by number of members with early-onset breast cancer (SIR = 1.31; 95% CI, 1.06–1.63 for class 3 and SIR = 1.30; 95% CI, 1.13–1.49 for class 4). Germline mutations in *BRCA1* and *BRCA2* are associated with an increased risk of pancreatic cancer. Given its high mortality, pancreatic cancer should be included in risk assessment in familial breast cancer counseling.

Trivers KF, Baldwin LM, Miller JW, Matthews B, Andrilla HA, Lishner DM, Goff BA. 2011. Reported referral for genetic counseling or *BRCA1/2* testing among United States physicians. *Cancer* **117**(23): 5334-43.

Genetic counseling and testing is recommended for women at high but not average risk of ovarian cancer. National estimates of physician adherence to genetic counseling and testing recommendations are lacking. Using a vignette-based study, authors surveyed 3200 United States family physicians, general internists, and obstetrician/gynecologists and received 1878 (62%) responses. For average-risk women, 71% of physicians self-reported adhering to recommendations against genetic counseling or testing. In multivariable modeling, predictors of adherence against referral/testing included black versus white race (RR, 1.16; 95% CI, 1.03-1.31), Medicaid versus private insurance (RR, 1.15; 95% CI, 1.02-1.29), and rural versus urban location. Among high-risk women, 41% of physicians self-reported adhering to recommendations to refer for genetic counseling or testing. Predictors of adherence for referral/testing were younger patient age (35 vs 51 years; RR, 1.78; 95% CI, 1.41-2.24), physician sex (female vs male; RR, 1.30; 95% CI, 1.07-1.64), and obstetrician/gynecologist versus family medicine specialty (RR, 1.64; 95% CI, 1.31-2.05). Physicians reported that they would refer many average-risk women and would not refer many high-risk women for genetic counseling/testing. Efforts are needed to encourage appropriate counseling and genetic testing for women at high risk of hereditary breast and ovarian cancer, particularly among male physicians, family physicians, and general internists.

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