Treatment and fertility issues for women with BRCA germline mutation

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Overview

Fertility and reproductive lifespan
The impact of reproductive life on breast and ovarian cancer risk
Screening recommendations during pregnancy and lactation
Reproductive lifespan?

Hypothesis:
Because DNA repair mechanisms are impaired in patients with BRCA 1/2 mutations, oocytes are more prone to DNA damage and thereby experience accelerated follicular depletion
> more likely to experience occult ovarian insufficiency
> higher incidence of infertility and early menopause
Potential health impacts of ovarian aging

Hartge 2009 *Nature Genetics*
Earlier age at natural menopause?

Yes

**Purpose:** To determine if BRCA 1/2 carriers have an earlier age at menopause than non-carriers

**Method:** Cross-sectional study

Caucasian BRCA 1/2 carriers (n=382) identified within the UCSF Breast Cancer Risk Program Registry

Compared to non-clinic-based Caucasian women (n=765)

Questionnaire including medical and surgical history, menstrual history, detailed history and timing of cancer diagnosis and treatment history of oral contraceptive use, recent weight change, age and smoking history

Lin et al 2013 *Cancer*
Median age at natural menopause in BRCA 1/2 carriers was significantly earlier than the unaffected sample (49 vs 53 years, p< 0.001)

HR 3.98 (95% CI 2.87-5.53) after adjusting for smoking, parity and contraceptive use

Iatrogenic menopause
56% in BRCA carriers
16% in control group

Figure 3.
Kaplan-Meier estimates of age at natural menopause in Northern California Caucasians, comparing BRCA1/2 carriers to SWAN cross-sectional screened sample, excluding medical and surgical menopause. (Secondary Analysis)
No significant difference was observed in the median age at natural menopause between the BRCA 1 (n=238) and BRCA 2 (n=144) carriers (50 vs 49 years).
Earlier age at natural menopause?

no

**Purpose:**

To determine if BRCA 1/2 carriers have an earlier age at menopause than non-carriers

**Method:**

Longitudinal cohort study between August 1997 and October 2011

BRCA 1/2 carriers (n=819) compared to female blood relatives that were tested BRCA-negative (n=1021)

Questionnaire every 3 years after cohort entry

Collins et al 2013 *JCO*
Overall only 19% (n=344) reached natural menopause (median age 51y)
37.8% (n=696) censored at iatrogenic menopause or participation in chemoprevention trial
42.8% (n=788) were censored at last follow up (still premenopausal)

Adjusted HR 1.03 (95% CI 0.75-1.40) for BRCA 1
Adjusted HR 1.01 (95% CI 0.71-1.42) for BRCA 2
Comparison between both studies

Methodological differences: Cross-sectional versus longitudinal

Collins et al used internal control for genetic factors by using blood relatives as control group – but 42% still menopausal at the end of study

> update of results is needed
Anti Mullarian Hormone

Purpose:

Methods:

Cross sectional study of 693 women
Age 25-45y
Both ovaries in situ, not pregnant or breastfeeding, no cancer in prior history

BRCA1 carriers had average 25% (95%CI 5%-41%; P=0.02) lower AMH concentrations than non-carriers

No difference for BRCA 2 carriers (p=0.94)
Fertility

Purpose: is fertility reduced in BRCA 1/2 mutation carriers?
Method: Matched case-control study
2,254 BRCA carriers and 764 noncarrier female blood relative controls, tested negative
- Parity
- Age at first birth
- Age at last birth
- Use of fertility medication

Pal et al 2010 Fertil steril
No difference in fertility problems.

No difference in mean parity between carriers (1.9) and noncarriers (1.9)
Table 1. Sample Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BRCA1 (n = 445)</th>
<th>BRCA2 (n = 374)</th>
<th>Total (N = 1,840)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carriers</td>
<td>Noncarriers</td>
<td>Carriers</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Median year of birth</td>
<td>1963</td>
<td>50%</td>
<td>1959</td>
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<tr>
<td>Median age at menarche, years</td>
<td>13</td>
<td></td>
<td>13</td>
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<tr>
<td>Cigarette smoker*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ever</td>
<td>221</td>
<td>50%</td>
<td>256</td>
</tr>
<tr>
<td>Never</td>
<td>224</td>
<td>50%</td>
<td>303</td>
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<tr>
<td>Alcohol drinker*</td>
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<tr>
<td>Ever</td>
<td>313</td>
<td>70%</td>
<td>396</td>
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<tr>
<td>Never</td>
<td>132</td>
<td>30%</td>
<td>163</td>
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<td>OCP use</td>
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<tr>
<td>Ever</td>
<td>405</td>
<td>91%</td>
<td>500</td>
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<tr>
<td>Never</td>
<td>40</td>
<td>9%</td>
<td>59</td>
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<tr>
<td>Parity</td>
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<tr>
<td>Nulliparous</td>
<td>103</td>
<td>23%</td>
<td>131</td>
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<tr>
<td>Parous</td>
<td>342</td>
<td>77%</td>
<td>428</td>
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<tr>
<td>Age at first birth, years</td>
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<tr>
<td>14-19</td>
<td>36</td>
<td>11%</td>
<td>55</td>
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<tr>
<td>20-24</td>
<td>119</td>
<td>35%</td>
<td>134</td>
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<td>25-29</td>
<td>117</td>
<td>34%</td>
<td>142</td>
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<td>30-34</td>
<td>51</td>
<td>15%</td>
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<td>35-45</td>
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<td>21</td>
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<td>Median</td>
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<td>Infertility treatment</td>
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<tr>
<td>Ever</td>
<td>24</td>
<td>5%</td>
<td>32</td>
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<tr>
<td>Never</td>
<td>421</td>
<td>95%</td>
<td>527</td>
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<tr>
<td>Median body mass index, kg/m²</td>
<td>24</td>
<td></td>
<td>25</td>
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</tbody>
</table>

Abbreviation: OCP, oral contraceptive pill.
*Regular cigarette smoking: at least one per day for 3 months or longer.
1Regular alcohol use: any alcohol at least once per week for 6 months or longer.
Its a boy/girl!
But with or without BRCA 1/2 gene mutation??
Preimplantation genetic diagnosis

In vitro fertilization
Genetic testing of a single cell from a eight-cell embryo
Transfer only unaffected embryo’s

What about the boys with BRCA 1/2 mutation?
PGD in practice?

Personal considerations for the decision to utilize PGD may include individual ethical beliefs, value systems, cultural and religious beliefs and social and economic factors.

¹Survey of BRCA carriers:
   50-75% of respondents felt that PGD was an acceptable option for high-risk individuals
   Only 14-33% would consider PGD for themselves

²Survey in high-risk men: 80% unaware of PGD, after being informed 34% would consider the option

¹Menon et al 2007 Human Reproduction
²Quinn et al 2010 Human Reproduction
The impact of reproductive life on cancer risk
Factors influencing the risk of breast cancer

N=2522 – evaluation of characteristics of reproductive life

**Protective factors** in BRCA mutation carriers:

- At least one full-term pregnancy (HR 0.27; 95% CI 0.12-0.58)
- Breastfeeding <1y (HR 0.24; 95% CI 0.09-0.66)
  - >1y (HR 0.25; 95% CI 0.08-0.82)
- Late age at menopause (HR 0.10; 95% CI 0.01-0.82)

Toss et al 2017 Oncotarget
Factors Influencing Ovulation and the Risk of Ovarian Cancer

Purpose:
The role of the lifetime number of ovulatory cycles in the context of BRCA-associated ovarian cancer

Methods:
Matched case-control study
72 participating centers in 20 countries
N= 1329 cases
N= 5267 controls
Questionnaire

Kotsopoulos et al 2015 *Int J Cancer*
Results:

45% risk reduction of developing ovarian cancer among women in the lowest vs. highest quartile of ovulatory cycles (OR=0.55; 95% CI 0.41-0.75, p=0.0001).

Breastfeeding for more than 12 months was associated with a 38% (95% CI 0.48-0.79) and 50% (95% CI 0.29-0.84) risk reduction among BRCA1 and BRCA2 mutation carriers, respectively.

For oral contraceptive use, maximum benefit was seen with five or more years of use among BRCA1 mutation carriers (OR=0.50; 95% CI 0.40-0.63) and three or more years for BRCA2 mutation carriers (OR=0.42; 95% CI 0.22-0.83).

A later age at menopause was associated with an increased risk in women with a BRCA1 mutation (OR trend=1.18; 95% CI 1.03-1.35; p=0.02).
Take home message

Important role of breastfeeding and oral contraceptive use for the primary prevention of ovarian cancer among women carrying BRCA mutations.