Surgical risk reducing strategies in hereditary breast and ovarian cancer

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Plan

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2. Risk reducing surgery
   a. prophylactic bilateral mastectomy (PBM)
      • psychological effects
   b. prophylactic bilateral salpingo-oophorectomy (PBSO)
      • prevention of BC
      • prevention of OC
      • prevention of mortality
      • psychological effects
      • HRT
3. Guidelines
4. Conclusion
1. Introduction

- Hereditary breast (BC) and ovarian cancer (OC) syndrome is an inherited cancer-susceptibility syndrome characterized by:
  - multiple family members with BC, OC or both
  - BC and OC in one person
  - early age onset of BC (<40y)
1. Introduction

- The majority of patients with hereditary BC and OC have mutations BRCA 1 or BRCA 2
  - autosomal dominant pattern of inheritance
  - 60%-70% of hereditary BC
  - the majority of autosomal-dominant inherited OC
- Other genes when mutated → predisposition to BC or OC (LFS, Lynch,..)
- Hereditary BC and OC without an identified genetic cause
1. Introduction

<table>
<thead>
<tr>
<th></th>
<th>BRCA 1</th>
<th>BRCA 2</th>
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</thead>
<tbody>
<tr>
<td><strong>Breast Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average cumulative risk by 80y of age</td>
<td>67%</td>
<td>13%</td>
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<tr>
<td></td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Starts at 30, median 43</td>
<td>starts at 30, median 41</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td>80-90% triple negative</td>
<td>65-80% ER + 16% triple negative</td>
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<tr>
<td><strong>Ovarian Cancer</strong></td>
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<tr>
<td>Average cumulative risk by 80y of age</td>
<td>45%</td>
<td>1-2%</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td></td>
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<tr>
<td><strong>Age</strong></td>
<td>Starts mid-30’s, median mid-40’s</td>
<td>Starts age 50, median 63</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td>High grade serous</td>
<td>High grade serous</td>
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</tbody>
</table>
1. Introduction

- Different tools are used to estimate BC risk
  - the Gail model
  - the Claus model
  - the IBIS model
  - the BRCAPRO model
  - (tools for predicting OC risk are more limited)
- Genetic counselors use:
  1. likelihood models to estimate the probability of carrying a germline mutation
  2. NCCN qualitative criteria to identify appropriate candidates
- Women tested positive or at high risk may benefit from screening and prevention strategies to reduce their risk
1. Introduction

• Risk-reducing strategies
  • Clinical surveillance
    • self breast examination
    • clinical breast examination
  • Imagery
    • mammography
    • MRI
    • trans-vaginal ultrasound scanning + CA 125
  • Chemoprevention
  • Prophylactic surgery

→ involves a trade-off between life expectancy & quality of life
2. Risk reducing surgery

a. Prophylactic bilateral mastectomy (PBM)

b. Prophylactic bilateral salpingo-oophorectomy (PBSO)

→ aim: reducing the risk of cancer development and mortality

• When?
  • depends on the risk of cancer associated with specific mutations
  • the prognosis of the tumour
  • anxiety relief
  • potential impact on women's self-image and on their sexual and reproductive function
a. Prophylactic bilateral mastectomy

- No RCT on the potential impact of BM on the survival
- Evidence comes from retrospective and prospective studies:
  - 6 studies: ↓ 90% in the risk of BC among women underwent PBM\(^1-6\)
  - 1 small study: doesn’t show a significant reduction in the risk of BC after PBM\(^7\)
  - 1 study: based on hypothetical mathematical models: a 30-year-old BRCA1/2 positive woman extends her survival by 3.4 years (2.7-3.7 years) when doing PBM\(^8\)
a. Prophylactic bilateral mastectomy

• Which procedure?
  • Simple or total mastectomy:
    • classic mastectomy
  • Skin-sparing mastectomy:
    • only the nipple and areola are removed
    • then the breast tissue through the small opening is removed
  • Nipple-sparing mastectomy:
    • all of the breast tissue is removed
    • the nipple and areola are left
  • +/- immediate breast reconstruction (90%)
a. Prophylactic bilateral mastectomy

- Psychological effects
  - In a large study (572 women) on the psychological effects after BPM\(^9\)
    - 74% reduction in anxiety about BC
    - 86% favorable or unchanged level of stress
    - 70% satisfied with their decision
  - A prospective 1-year follow-up study of 98 women\(^{10}\)
    - The most common psychological side effects, difficulties
      - *body appearance*
      - *feelings of femininity*
      - *sexual relationships*
  - Mutation carriers opting for PM:
    - often in their 30\(^{\text{ies}}\)
    - often have young children
    - greater awareness of the genetic nature of cancer in the family
b. Prophylactic bilateral salpingo-oophorectomy

- Risk reducing salpingo oophorectomy for prevention of OC in BRCA
  - 7 efficiency studies\(^6,11-16\)
  - 1 meta analysis\(^17\)
    - significant risk reduction of OC \(\approx 80\%\)

- High grade serous cancers are probably originating in the fallopian tubes
  - bilateral salpingectomy with delayed oophorectomy may be an option
    - (for premenopausal women who want to delay surgical menopause)
  - date regarding efficiency are lacking
b. Prophylactic bilateral salpingo-oophorectomy

- Risk reducing salpingo oophorectomy for prevention of BC in BRCA
  - 6 observational studies
    - 5 showed ↓ of 50% of the risk when it was performed before menopause $^6,12,14,18,19$
    - 1 , in 2015 (dutch analysis of a nationwide cohort) of over 800 women with a BRCA mutation did not found any effect of BSO on the risk of BC $^{20}$

More cautious when counseling patients about a protective effect of BSO on BC risk
b. Prophylactic bilateral salpingo-oophorectomy

- Risk reducing salpingo oophorectomy on *mortality* in BRCA
  - 2 prospective cohorts that include unaffected BRCA carriers \(^6,16\)
    - decreased risk of BC and OC
      - *decreased rates of BC and OC* – *specific mortality*
      - *decreased of all-cause mortality*
b. Prophylactic bilateral salpingo-oophorectomy

- Psychological effects
  - reduced cancer related worry in 80% of BRCA carriers
  - 95% satisfaction with their decision

- Surgical procedure
  - laparoscopy
    - methodical survey of the abdomen (diaphragm, liver, omentum, bowel,..) and the pelvis
    - peritoneal washing
    - all ovarian tissue (resection of the entire adhesion with the ovary)
b. Prophylactic bilateral salpingo-oophorectomy

- Hormone replacement therapy
  - young women who undergo BSO experience side effects due to surgically induced menopause
  - 2 prospective cohort study of BRCA mutation carriers who underwent BSO and receive HRT\(^{21,22}\)
    - HRT did not negate the beneficial effect of BSO on breast cancer risk
    - but data are limited and lacking
      - on type of HRT
      - on duration of use
      - short follow up

First line: non-hormonal approaches

HRT is a reasonable option for carriers from the time of BSO until about age 50
b. Prophylactic bilateral salpingo-oophorectomy

- General population
  - theory: most OC have a tubal origin
  - propose to do a opportunistic salpingectomies when hysterectomy for benign conditions
  - not yet any scientific evidence to justify a universal recommandation
3. Guidelines NCCN
### 3. Guidelines

<table>
<thead>
<tr>
<th>BRCA 1</th>
<th>BRCA2</th>
<th>no mutation detected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast Cancer</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Surveillance</strong></td>
<td>• at 18y: breast awareness</td>
<td>• at 18y: breast awareness</td>
</tr>
<tr>
<td></td>
<td>• 25y: clinical examination every 6-12 mo</td>
<td>• 25y: clinical examination every 6-12 mo</td>
</tr>
<tr>
<td></td>
<td>• 25-29y: annual MRI</td>
<td>• 25-29y: annual MRI</td>
</tr>
<tr>
<td></td>
<td>• 30-75y: annual mammography and MRI</td>
<td>• 30-75y: annual mammography and MRI</td>
</tr>
<tr>
<td><strong>Bilateral mastectomy</strong></td>
<td>higher priority than surveillance</td>
<td>option for women who prefer surgery than surveillance or chemoprevention</td>
</tr>
<tr>
<td><strong>Ovarian Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Surveillance</strong></td>
<td>not recommended in routine screening: transvaginal US + CA125 (except in women who delay surgery and start at 30-35y every 6-12 mo)</td>
<td>not recommended in routine screening: transvaginal US + CA125 (except in women who delay surgery and start at 30-35y)</td>
</tr>
<tr>
<td><strong>salpingo-oophorectomy</strong></td>
<td>recommended by age 35-40y and upon completion of child bearing</td>
<td>recommended by age 45-50y</td>
</tr>
</tbody>
</table>
3. Guidelines

- Salpingectomy alone is not the standard and is discouraged outside a clinical trial

- Hysterectomy?
  - not for cancer prevention
  - for simplifying later hormonal therapy (Tamoxifene and oestrogen)
  - no national guidelines that recommend routine hysterectomy in BRCA mutation carriers
4. Conclusion

- Women from families with hereditary BC and OC syndrome face substantial risk of BC and OC
- Cancer risk assessment and genetic counseling is highly recommended when genetic testing is offered
- Discussion of management options
  - surveillance
  - medication
  - surgery
    - BSO is the most effective option for hereditary predisposition to OC
    - PBM should be proposed for BRCA but can also be discussed on a case-by-case basis based on personal preference, given that effective screening is available
4. Conclusion

- Decisions are complex, extensive counselling should be offered to all women who consider prophylactic surgery, including:
  - a detailed explanation of the cancer risk and various age at diagnosis
  - complications associated with surgery
  - aesthetic outcome
  - quality of life issues
  - and potential life expectancy gain

- Physical and psycho-sexual effects → emotional support
4. Conclusion

- Currently, no RCT about the potential benefits or harms of prophylactic surgery
  - evidence is derived from retrospective and short follow-up prospective studies
  - randomization is unethical, given the available evidence
- Large studies (10 y follow-up) have consistently shown the efficiency of PBM
- Longer follow-up is needed in studies of the efficiency and side effects of PBSO
  - questions remain about the reduction in BC risk from PBSO among premenopausal women
  - data to evaluate the effect of salpingectomy alone with delayed oophorectomy are needed
References


References


Merci – Dank u

Respect Innovatie Engagement Solidarité Qualité

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