بنام خداوند جان و خرد

Management of young patients with BRCA-mutated early breast cancer

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Questions:

1. High risk individuals? genetic assessment & screening programs?
2. Bilateral **prophylactic mastectomy** in BRCA carriers
3. Outcome of **BCS and MST** in BRCA mutation affected patients
4. **Contralateral prophylactic mastectomy** in BRCA positive breast cancer patients
5. Management of **non-carriers** in family with positive test
6. Risk-reducing **salpingo-oophorectomy**

Introduction

- In 10% of breast cancers: a pathogenic germline variant.
- **Mutations** with an increased risk of breast cancer:

  - most common (**50%**) : **BRCA1** and **BRCA2**

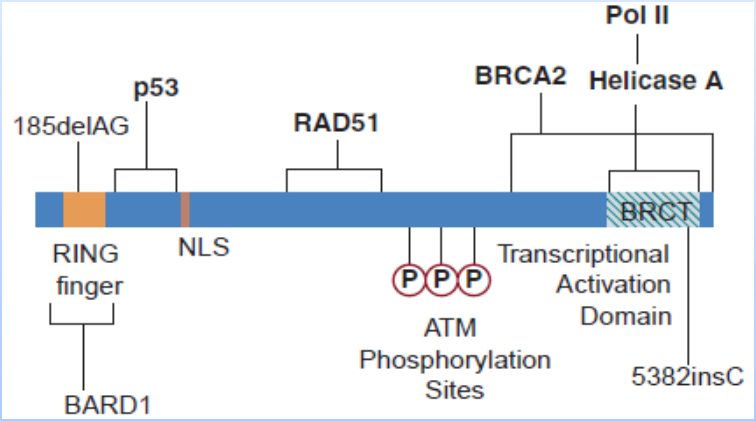
    (AD, with hundreds of highly penetrant mutations)

  - less common: TP53, PALB2, ATM and CHEK2 mutations.

- BRCA1:

discovered in 1994

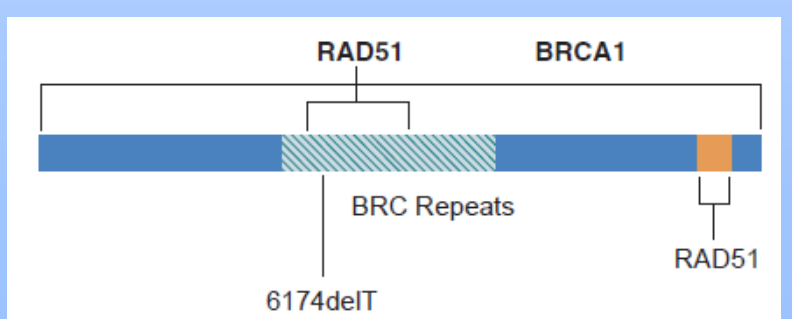
on chromosome 17q (17q21)



- BRCA2:

discovered in 1995

on chromosome 13q (13q12-13)



BRCA1 or BRCA2 mutation:

- Elevated risk of breast (7 times) and ovarian cancer (25 times).
- increased risk of pancreatic, prostate, and male breast cancer.

Breast cancer associated with **BRCA1** mutation:

- more likely to be hormone receptor negative & higher grade
- more lymphocytic infiltration, more continuous pushing margins
- more frequently have medullary or atypical medullary features

Breast cancer associated with **BRCA2** mutation:

- May be associated with poorer survival.
- Association with other cancer: prostate, melanoma, pancreas.

	BRCA1	BRCA2	Sporadic
The average age of onset	44	47	64
Lifetime risk for breast cancer	65%	55%	8%

High risk individuals

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Breast and/or Ovarian Cancer Genetic Assessment

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CRITERIA FOR FURTHER GENETIC RISK EVALUATION[a]

- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene within the family, including such variants found on research testing[b]
- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene found on tumor testing (See BR/OV-A 3 of 3)
- An individual diagnosed at any age with any of the following:
  - Ovarian cancer[c]
  - Pancreatic cancer
  - Metastatic prostate cancer[d]
  - Breast cancer or high-grade (Gleason score ≥7) prostate cancer and of Ashkenazi Jewish ancestry
- An individual with a breast cancer diagnosis meeting any of the following:
  - Breast cancer diagnosed age ≤50 y
  - Triple-negative (ER-, PR-, HER2-) breast cancer diagnosed age ≤60 y
  - Two breast cancer primaries[e]
  - Breast cancer at any age, and
    - ≥1 close blood relative[f] with:
      - breast cancer age ≤50 y; or
      - invasive ovarian cancer[c]; or
      - male breast cancer; or
      - pancreatic cancer; or
      - high-grade (Gleason score ≥7) or metastatic prostate cancer[d]
    - ≥2 close blood relatives[f] with breast cancer at any age
- An individual who does not meet the above criteria but has a first- or second-degree relative with any of the following:[g]
  - Breast cancer ≤45 y
  - Ovarian cancer[c]
  - Male breast cancer
  - Pancreatic cancer
  - Metastatic prostate cancer[d]
  - ≥2 breast cancer primaries in a single individual
  - ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 y
- An individual with a personal and/or family history on the same side of the family of three or more of the following (especially if diagnosed age ≤50 y; can include multiple primary cancers in same individual):[g]
  - breast cancer, sarcoma, adrenocortical carcinoma, brain tumor, leukemia (see LIFR-1),
  - colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations,[h] macrocephaly, or hamartomatous polyps of gastrointestinal (GI) tract (see COWD-1),
  - lobular breast cancer, diffuse gastric cancer (see CDH1 guidelines, GENE-2),
  - breast cancer, gastrointestinal cancer or hamartomatous polyps, ovarian sex chord tumors, pancreatic cancer, testicular sertoli cell tumors, or childhood skin pigmentation (see STK11 guidelines, GENE-4)

→ Consider referral to cancer genetics professional[i] → See Assessment (BR/OV-2)

Genetic Assessments

ASBS Recommendations: (February 14, 2019)

- Breast surgeons, genetic counselors:**education, counseling, recommendation**
- **Genetic testing** (BRCA1/BRCA2 and PALB2) should be **offered to each patient with breast cancer** (newly diagnosed or with a personal history).
- Patients who had genetic testing previously specially prior to 2014 (without pathogenic variant) may **benefit from updated testing**.

  *may not have included testing for PALB2 and large genomic rearrangements in BRCA1 or BRCA2.
- **Genetic testing should be made available to patients who meet NCCN guidelines**(preferably multi-gene panel)

Impact of genetic testing on treatment

St. Gallen/Vienna 2017:

Panelists believed that BRCA 1-2 mutations impact decisions on:

- Breast surgery yes 88.5%, no 8%
- Systemic therapies yes 73.1%, no 23.1%
- Prophylactic interventions yes 94.1%, no 4%

ASBS:

- **BRCA1** pathogenic variant benefit from **PARP inhibitors** in their adjuvant therapy regimen.
- **Radiation** is relatively contraindicated in patients with **TP53** pathogenic variants (Li-Fraumeni Syndrome).

Screening
in
high risk individuals

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
BRCA-Related Breast and/or Ovarian Cancer Syndrome

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BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

WOMEN

- Breast awareness[1] starting at age 18 y.
- Clinical breast exam, every 6–12 mo,[2] starting at age 25 y.
- Breast screening[3,4]
  - Age 25–29 y, annual breast MRI[5] screening with contrast[6] (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
  - Age 30–75 y, annual mammogram with consideration of tomosynthesis and breast MRI[5] screening with contrast.
  - Age >75 y, management should be considered on an individual basis.
  - For women with a *BRCA* pathogenic/likely pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram and breast MRI should continue as described above.
- Discuss option of risk-reducing mastectomy
  - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
- Recommend risk-reducing salpingo-oophorectomy (RRSO),[7] typically between 35 and 40 y, and upon completion of child bearing. Because ovarian cancer onset in patients with *BRCA2* pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with *BRCA1* pathogenic/likely pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 y in patients with *BRCA2* pathogenic/likely pathogenic variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery. See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer - Principles of Surgery.
  - Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone replacement therapy, and related medical issues.
  - Salpingectomy alone is not the standard of care for risk reduction, although clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy likely reduces the risk of developing breast cancer but the magnitude is uncertain and may be gene-specific.
- Limited data suggest that there may be a slightly increased risk of serous uterine cancer among women with a *BRCA1* pathogenic/likely pathogenic variant. The clinical significance of these findings is unclear. Further evaluation of the risk of serous uterine cancer in the *BRCA* population needs to be undertaken. The provider and patient should discuss the risks and benefits of concurrent hysterectomy at the time of RRSO for women with a *BRCA1* pathogenic/likely pathogenic variant prior to surgery.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.
- For those patients who have not elected RRSO, transvaginal ultrasound combined with serum CA-125 for ovarian cancer screening, although of uncertain benefit, may be considered at the clinician's discretion starting at age 30–35 y.
- Consider risk reduction agents as options for breast and ovarian cancer, including discussing risks and benefits (See Discussion for details). (See NCCN Guidelines for Breast Cancer Risk Reduction).
- Consider investigational imaging and screening studies, when available (eg, novel imaging technologies, more frequent screening intervals) in the context of a clinical trial.

Footnotes on next page

Screening recommendations for BRCA1/2 mutation carriers (by NCCN and ACS)

	Starting age
Breast cancer screening in **women**	
Monthly breast self-exam	18
Semiannual clinical breast exam	25
Annual MRI	25
Alternating annual MG with annual MRI	30
Individual base	>75
Breast cancer screening in **men**	
Annual clinical breast exam	35
Annual mammograms	40

Breast cancer risk reduction

- **lifestyle modifications**

Breastfeeding, regular exercise, maintaining healthy body weight and limiting alcohol consumption, avoiding of hormone replacement therapy.

- **Screening:**

- **Clinical breast examination** q 6–12 months (from 25 yrs or 10 years before the youngest breast cancer in family
- **Breast-awareness** (any changes in breast or axilla)
- **Annual MRI** (most sensitive screening tool) from the age of 25
- **Annual MG** from the age of 30

* when MRI is not available : **US** <30 yrs, US & MG > 30yrs.

- **risk-reducing agents**

-Use of tamoxifen may be considered (LOE is weak)

- **risk-reducing surgery** (Bilat risk-reducing mastectomy- RRM)

Include: Total mastectomy, SSM, NSM

- Most effective method, reduces risk by ~90%.

*Routine SLNB is not indicated (possibility of occult breast cancer <5%)

Screening following risk-reducing surgery

Following MST & SSM:

- There is no currently recommended surveillance schedule after RRS.

Following NSM :

- Continued screening with annual breast MRI or ultrasound may be considered (due to tissue behind NAC).

Bilateral prophylactic mastectomy in BRCA carriers without breast cancer

- For **healthy** BRCA1/2 mutation **carriers:**

  Risk-reducing bilateral mastectomy (RRM) can decrease the risk of breast cancer by up to 95% (ref 9) (ref 11: 95–98%)(97% ref 12)

Before RRM:

- Information on the different possibilities of breast reconstruction (sensory loss of skin and areolae)
- Residual risk of primary breast carcinoma

1 year after RRM:

- MR tomography (MRT) for assess residual parenchyma. If case of no residue annual US is sufficient for aftercare.

Overall survival benefit of RRM in BRCA carriers?

Results of an analysis studies on RRM (39 studies- 2010) with a total of 7,384 women after bilateral prophylactic mastectomy(ref 11):

- Reduction in **incidence of breast cancer**
- Reduction in **breast cancer-specific mortality**,
- Reduction of **stress** and **fear** levels after RRM
- Highly **satisfaction** with the **cosmetic** results

- **Re-surgery** is necessary in up to 49% of the patients

Survival benefit

In a study on 593 mutation carriers - 105 underwent RRM (Ref 12):

- The 10-year **OS**: **89% in RRM** - 71% observing group.
- The survival advantage remained after matching for oophorectomy, gene, grade and stage.

Impact of BSO

Risk-reducing **bilateral salpingo-oophorectomy(RRSO)** in premenopausal women **reduces** the risk of (Ref 9 & ASBS):

- Ovarian cancer 80–90%
- Breast cancer (BRCA2?) 50%

- Screening before RRSO, q6m from age of 30:
  trans-vaginal ultrasound, serum **CA125.**
- Risk-reducing surgery(BSO) at age 35–40
  The most effective(removal of ovaries and fallopian tubes)

Mastectomy or BCS
in
affected BRCA-carriers?

In comparison of BCS+RTx with mastectomy:

Meta-analysis (6 cohort studies, 4 case-control studies) of 526 BRCA carriers and 2,320 control patients showed:

- **No** significant increase of the local recurrence risk
- **No** difference in overall survival

Another 2 studies (893 patients) with median F/U 4.5 & 3.4 yrs:

- **No** significant increase in true recurrences
- Ipsilateral **affected lymph nodes** are a negative predictor for IBR (Ref 11)

ASBS:

- **Breast conservation** is equivalent to **mastectomy** in survival outcome.

Contralateral prophylactic mastectomy In BRCA positive breast cancer patients

Risk of developing a contralateral breast cancer (CBC)

In **sporadic** breast cancer:

- Annual risk of contralateral breast cancer is 0.5-1% (20% at 20)

  (ASBS: 0.1 to 0.6 %)

In **BRCA mutated** breast cancer, **overall risk** of contralateral disease :

- At 10 years: 31% (<40 years)
- At 25 years: 63% (<40 years)
- At 10 years: 8% (**>50 years**)

- CHEK2, p53, PALB2, ATM, and NBN: **insufficient evidence** to support an increased CBC risk for these mutations.
- **Mantle radiation** for Hodgkin lymphoma: may be at increased risk for CBC (few data).

Impact of risk reducing MST

Retrospective study by Metcalfe: after a median follow-up of 14.3 years on women with BRCA mutated breast cancer (Ref 12):

- **Overall survival**: - RRM group 88% - Surveillance group 66%

- Prediction:
  - Of 100 women **bilateral RRM** 87 would be alive at 20 years
  - Of 100 women **unilateral MST** 66 would be alive at 20 years

- Systemic **adjuvant therapy** and **adnexectomy** were associated with a reduction of the risk of CBR by 50%.

Study in Netherlands on 583 patients with **BRCA-mutant breast cancer** between 1980 and 2011 - median F/U of 11.4 years (Ref 11-12):

- **Contralateral cancer**:
  - In contralateral RRM group (42%) 4 patients (2%),
  - In surveillance group (58%), 64 patients (19%).
- The **mortality**:
  - In RRM group 74%
  - In surveillance group 86%.
- **Survival benefit** was especially seen in:
  - young patients (<40 years),
  - breast cancer with a grade 1/2 and/or no Triple negative phenotype,

Mastectomy in BRCA mutant breast cancer increased probability of being alive at age 80 (Ref 7):

- - CPM at age 25: 8.7% benefit (from 42.7 to 51.3%).
- - CPM at age 50: 2.8% benefit (from 42.7 to 45.5%).

- RRM : 48% reduction in death from breast cancer.

- If the primary disease has a **poor prognosis**, the woman should be advised against bilateral mastectomy.

Impact of age & family history on CBC risk

- Annual risks of CBC are highest in:

  - patients younger than 30 years

  - patients with multiple affected 1st & 2nd degree relatives.

Impact of hormone receptor status on CBC risk

In the overview analysis, the risk of CBC was:

- 0.4 % per year for **ER–positive** patients
- 0.5 % per year for **ER–negative** patients.

- **Tamoxifen**: 50–70% **reduction** in the risk of **contralateral** breast cancer in BRCA1/2 carriers

- There was no effect of tamoxifen on **ER–negative** breast cancers (ref 9).

CPM & reconstruction complications

- **CPM** is never an emergency and is **never mandatory**.
- CPM **double the complication** rate compared to unilateral MST.
- Complications: **40–64 %** (equally on affected and prophylactic sides).
- Local complications from the mastectomy and reconstruction:

  - tissue/skin flap necrosis, infection, bleeding, implant loss, flap loss, unanticipated revisions.

Oncologic Risks of CPM

- Surgical complications may **delay the onset of adjuvant therapy**.
- CPM may **negatively affect oncologic outcomes** for patients who were never destined to develop a CBC.

Conclusion

Indications of CPM

CPM **should be considered** for:

- Documented **BRCA1/2 carrier**.
- **Strong family history** without **genetic testing**. (>25 % lifetime risk)
- History of **mantle chest radiation** before age 30 years.

CPM **can be considered** for:

- Gene carrier of **non-BRCA** (e.g., CHEK-2, PALB2, p53, CDH1).
- **Strong family history**, BRCA negative, **no** known BRCA family member.

CPM **may be considered** for:

- To **limit** contralateral breast **surveillance** (dense breasts, failed surveillance, recall fatigue).
- To improve reconstructed breast **symmetry**.
- To manage extreme **anxiety** (better managed by psychological support).

CPM should be discouraged

- **Average-risk woman** with unilateral breast cancer.
- Women with advanced index cancer (e.g., **inflammatory** breast cancer, **T4** or **N3** disease, **stage IV** disease).
- Women at **high risk for surgical complications**
- Woman tested **BRCA negative with a family of BRCA positive** carriers.
- **Male** breast cancer, including BRCA carriers.

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Thank You