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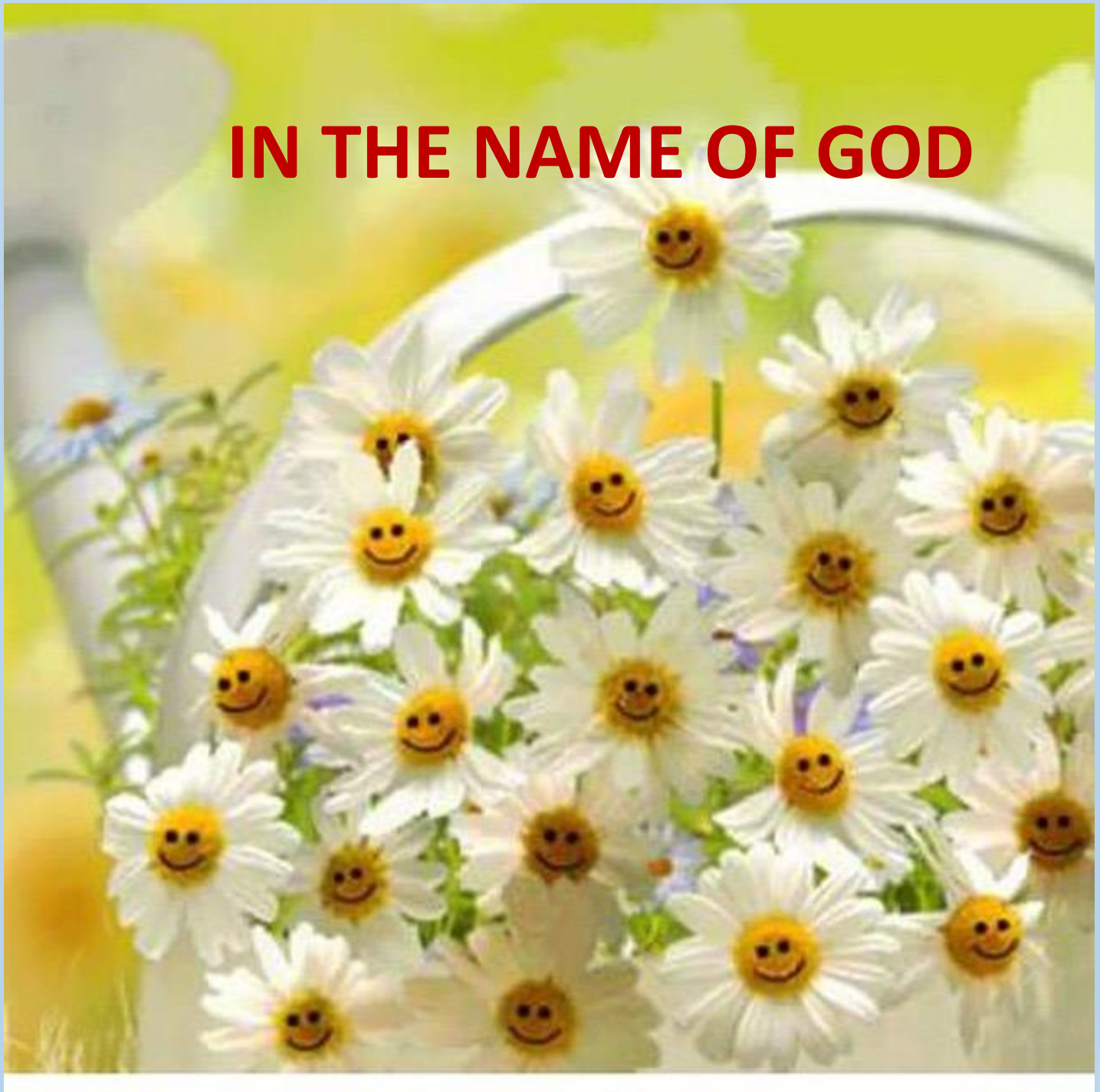
IN THE NAME OF GOD

# Prophylactic mastectomy

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- **Prophylactic mastectomy is defined as the removal of the breast in the absence of malignant disease. Prophylactic mastectomies may be performed in**
- **women considered at high risk of developing breast cancer, either due to a family history, presence of a BRCA1, BRCA2, or PALB2 gene mutation,**
- **the presence of lesions associated with an increased cancer risk.**

- Breast cancer is the most frequently diagnosed malignancy in women in the United States of America (USA). With an incidence of 127.5 new cases per 100,000 women per year, approximately 12.8% of women overall will be diagnosed with breast cancer during their lifetime.
- Surgical treatment options for primary breast cancer include lumpectomy, which is called breast conservation therapy if combined with radiation, and mastectomy.
- If the patient has no contraindication to breast conservation therapy, ultimately patients decide if breast conservation or mastectomy is preferred, given the absence of survival difference between the two options.
- While some will choose to undergo unilateral mastectomy for treatment of the primary tumor, others will also undergo contralateral prophylactic mastectomy (CPM) which is sometimes referred to as contralateral risk-reducing mastectomy, is removal of the unaffected breast, often performed to prevent contralateral breast cancer
- In women with breast cancer, the average risk of contralateral breast cancer is around 0.4% per year with a cumulative incidence of 1.9% after five years

- **Deleterious BRCA mutations**
  - High lifetime risk of breast cancer (~55-70% BRCA1, ~45-70% BRCA2)
  - Increased risk of ovarian cancer (~40-45% BRCA1, ~10-15% BRCA2)
  - BRCA2 also associated with male breast cancer, prostate, pancreatic
- **Screening:**
  - **Women**
  - Annual clinical breast exam starting at age 25
  - Annual screening with MRI age 24-29; mammo +/- MRI age 30+
  - **Men**
  - Annual clinical breast exam starting at age 35
  - Consider annual mammo at age 50 or 10 years before youngest family member diagnosed with male BC
  - Prostate cancer screening starting at age 40 for BRCA2
- **Discuss risk-reducing surgery:**
  - Bilateral mastectomy
  - Bilateral salpingo-oophorectomy (after completion of childbearing or between ages

# Who may consider prophylactic mastectomy to reduce breast cancer risk?

- **Bilateral prophylactic mastectomy may be considered medically necessary when ONE or more of the following risk factors are present:**
- **Those with a strong family history of breast cancer**
- **Individual has tested positive for BRCA1, BRCA2, or PALB2 gene mutations; or**
- **High-risk histology: Atypical ductal or lobular hyperplasia, or lobular carcinoma in situ confirmed on biopsy; or**
- **Li-Fraumeni syndrome or Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome; or**
- **Individuals who received radiation therapy to the thoracic region before the age of 30.**
- **Individuals with lobular carcinoma in situ (LCIS) plus a family history of breast cancer.**

- Mastectomy of the contralateral breast may be considered medically necessary when ONE or more of the following situations exists:
- For risk reduction in individuals at high risk for a contralateral breast cancer as stated above; or
- For individuals in whom subsequent surveillance of the contralateral breast would be difficult such as for:
  - Dense breast tissue as shown clinically or mammographically; or
  - Diffuse and/or indeterminate calcifications; or
- For improved symmetry in individuals undergoing mastectomy with reconstruction for the index cancer who:
  - Have a large and/or ptotic contralateral breast; or
  - Disproportionately sized contralateral breast.
- Prophylactic mastectomy for any other reason is considered not medically necessary.

# How much does prophylactic mastectomy reduce the risk of breast cancer?

- **Prophylactic mastectomy can reduce the chances of developing breast cancer in women at high risk of the disease:**
- **For women with the *BRCA1* or *BRCA2* mutation, prophylactic mastectomy reduces the risk of developing breast cancer by 90 to 95 percent.**
- **For women who have already had breast cancer and also have a family history of the disease, prophylactic mastectomy can reduce the risk of developing cancer in the other breast by 90 to 95 percent.**
- **However, studies indicate that prophylactic mastectomy of the unaffected breast (contralateral prophylactic mastectomy) has little or no effect on overall survival for women who have had breast cancer in one breast and do not have genetic mutations or hereditary risk factors.**
- **Having a prophylactic mastectomy doesn't guarantee that you'll never develop breast cancer because all of your breast tissue can't be removed during the surgery. Sometimes breast tissue can be found in your chest, armpit or skin, above your collarbone, or on the upper part of your abdominal wall.**
- **It is impossible for a surgeon to remove all of this breast tissue. Although the chances are slim, breast tissue remaining in your body can still develop breast cancer.**

# With whom should women at high risk discuss their options?

- **Deciding what to do with the knowledge that you are at high risk of breast cancer is a complex and time-consuming process. It's best if you can work with a team of health professionals that includes a genetic counselor to get a complete evaluation of your risk and take the time to understand all of your options.**
- **Many breast centers are staffed with breast-health specialists, genetic counselors, breast surgeons and reconstructive surgeons who can collaborate with you.**
- **Second opinions are strongly recommended for women considering prophylactic mastectomy.**
- **Making the decision whether to have prophylactic mastectomy is not urgent. Give yourself time to weigh all the pros and cons. You may want to discuss your concerns and feelings with a breast-health specialist and a psychologist.**

# What are the risks?

- **As with any surgery, prophylactic mastectomy has potential complications, including:**
- **Bleeding**
- **Infection**
- **Pain**
- **Anxiety or disappointment about changes to your appearance**
- **Complications arising from breast reconstruction**
- **The need for multiple operations**

# Are there other options for reducing the risk of breast cancer?

- **If you're at high risk of breast cancer and you decide against prophylactic mastectomy, you have other options for early detection and risk reduction.**
- **Medications**
- **Tamoxifen for premenopausal or postmenopausal women**
- **Raloxifene (Evista), for postmenopausal women**
- **Exemestane (Aromasin), for postmenopausal women**
- **Anastrozole (Arimidex), for postmenopausal women**
- **Although these medications can reduce the risk of invasive breast cancer by about 50 percent, they carry a risk of side effects. Discuss the risks and benefits of these medications with your doctor, and together you can decide whether medication is right for you.**

# Other options

- **Breast cancer screening. Women who have a high risk of developing breast cancer and do not want to have their breasts surgically removed can have annual breast cancer screening with MRI, generally initiated by age 25 years, and annual screening mammography (sometimes along with tomosynthesis) initiated by age 30 years, with MRI and mammography staggered every 6 months thereafter.**
- **Surgery to remove the ovaries (prophylactic oophorectomy). This procedure can reduce the risk of both breast and ovarian cancers. In women at high risk of breast cancer, prophylactic oophorectomy may reduce that risk by up to 50 percent if the procedure is done before age 50, when women are premenopausal.**
- **Healthy lifestyle. Maintaining a healthy weight, exercising most days of the week, limiting alcohol use and avoiding hormone therapy during menopause may reduce the risk of breast cancer.**
- **Eating a healthy diet might decrease your risk of some types of cancer, as well as diabetes, heart disease and stroke.**

# Contralateral Prophylactic Mastectomy (CPM)

# Rates and Trends

- **Between 2004 and 2012 in the USA the proportion of women undergoing CPM showed a nearly three-fold increase in all age groups, with the largest increase in women under the age of 40.7,38,39 .**
- **The proportion of patients choosing CPM has an inverse relationship with age, ranging from 2.4% in patients 70 years or older to 29.3% in patients between 20 and 29 years old.**
- **Other factors associated with undergoing CPM include having lobular (compared to ductal) tumor histology, ER+/PR + cancer, Noninvasive histology, Caucasian race, and having private insurance.**
- **Patients with stage III breast cancer???**

- **Patients may want CPM to reduce risk of contralateral breast cancer and mortality.**
- **Patients do not always have the tools available to make a well-informed decision.**

**SO**

- **Patient and surgeon's shared decision-making could optimize the use of CPM.**

- Studies indicate a large gap between patient preferences for radical risk reduction with CPM and the current approaches recommended by important guidelines
- The current guidelines by the NCCN and the ASBrS state that CPM should be considered in patients at high risk of contralateral breast cancer, such as patients with a BRCA1/2 mutation or a strong family history.
- 31% of all women undergoing CPM have a BRCA1/2 mutation or a strong family history

**Good decision-making requires the best available evidence about CPM combined with well-considered patient preferences.**

**The identified patient rationales include the following:**

**-Will CPM reduce mortality risk?**

**•Will CPM reduce the risk of contralateral breast cancer?**

**•Can I avoid future screening with CPM?**

**•Will I have better breast symmetry after CPM?**

# Risk of contralateral breast cancer

- **Annual risk of contralateral breast cancer in the general breast cancer patient population to be 0.5–0.75%.**
- **However, many of the population-based studies from which these estimate were derived were conducted decades ago.**
- **Only a few articles with recent data are published. One recent population-based study found a 5-year cumulative contralateral breast cancer incidence of 1.9%, a 10-year cumulative incidence of 4.6%, and a 20-year cumulative incidence of 10.5%**

- The contralateral breast cancer risk is 1.3–1.9 times higher than the risk of primary breast cancer in the general population.
- However, for most patients with primary breast cancer the risk of distant metastases exceeds the risk of developing contralateral breast cancer. 10–12% of women treated for primary breast cancer developed distant recurrence during a mean follow-up of just over 5 years.
- The overall rate of first distant metastasis is 1.94% per year, and receipt of CPM has not been shown to improve distant metastases-free survival

- **Carrying a BRCA1 or BRCA2 mutation is the strongest known predictor for contralateral breast cancer risk in patients with a history of breast cancer.**
- **The annual risk of contralateral breast cancer in these mutation carriers is 2–3%, with a 5-year cumulative risk of contralateral breast cancer of 13% in BRCA1 and 8% in BRCA2 mutation carriers. At 10-years, the cumulative risk is 40% and 26%, respectively.**
- **A very strong family history, classified as two or more first degree relatives with breast or ovarian cancer, also puts women at high risk of contralateral breast cancer. Having any first-degree relative with breast cancer doubles the risk of contralateral breast cancer in mutation negative women.**

- Other factors that increase the risk of contralateral breast cancer to a smaller extent include
- younger age at primary breast cancer diagnosis,
- lobular histology,
- higher grade and size of the tumor,
- ER/PR negative primary breast cancer,
- higher breast density,
- and/or a high Body Mass Index (BMI) at primary breast cancer diagnosis;
- a combination of these characteristics may be associated with an even further increase in risk.

## Risk of contralateral breast cancer

- Patients with breast cancer: annual risk 0.4%.
- 1.3–1.9 times the risk of first breast cancer in general population.
- Strongest risk factor: BRCA1/2 mutation.
- Annual risk 2–3%.
- Other risk factors: family history, younger age, certain tumor characteristics.

## CPM rates and trends

- Nearly threefold increase in CPM uptake 2004–2012
- All age groups
- Breast cancer stage I–III.
- Specially younger women, non-Hispanic whites, privately insured.
- Patients with low risk of contralateral breast cancer contribute to upward trend.

## Surgeons' influence on patient decisions

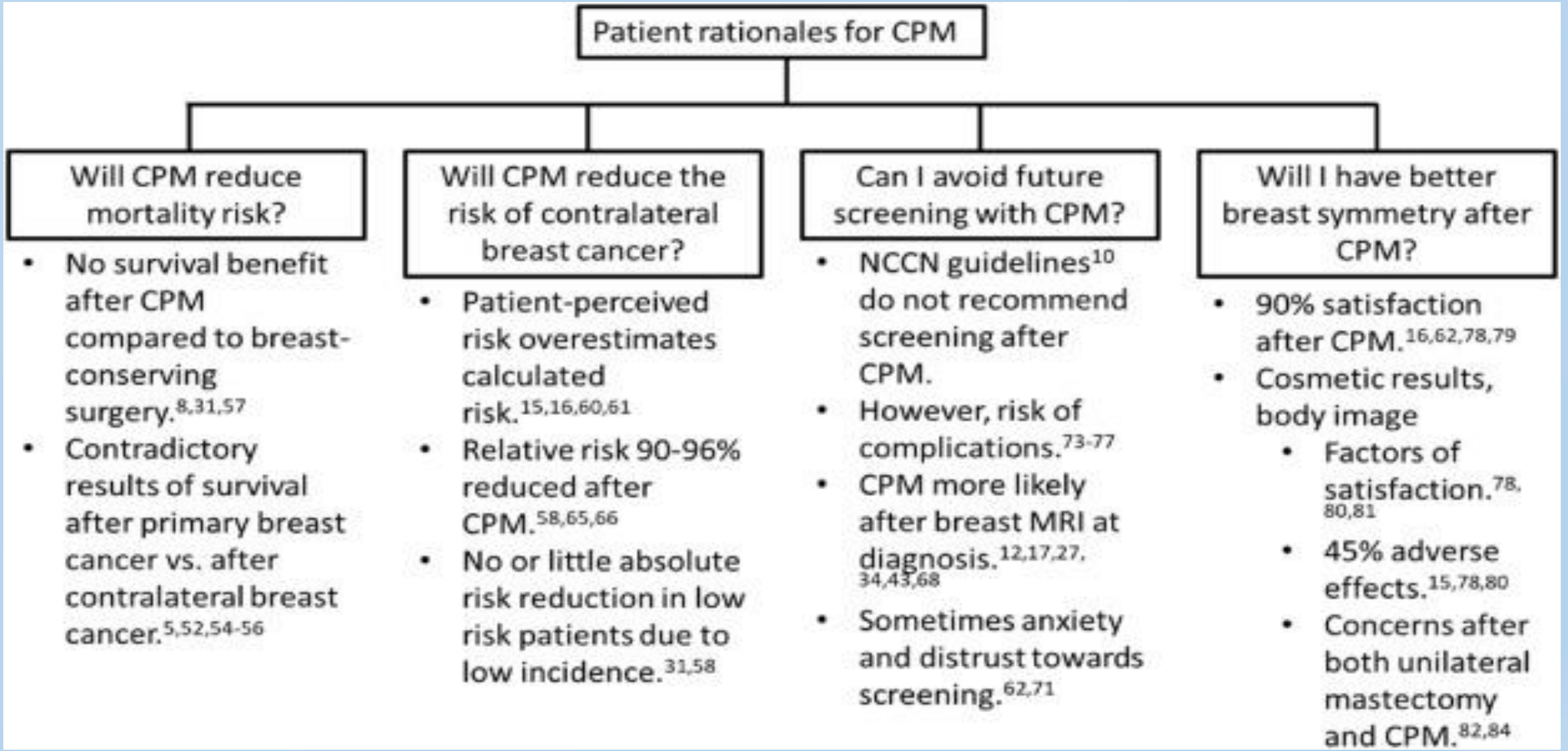
- Surgeon's opinion may have a large influence.
- Surgeons' knowledge vary widely.
- Wide variation between surgeons in recommendations and approaches to the discussion with the patient.

- **Will CPM reduce mortality risk?**
- **One of the main rationales reported for undergoing CPM is improving survival**
- **Several large cohort studies found no significant improvement in breast cancer-specific and overall survival in CPM compared to breast-conserving surgery.**

- **Will CPM reduce the risk of contralateral breast cancer?**
- **Concern about contralateral breast cancer is another reason that patients with breast cancer undergo. Misconceptions about contralateral breast cancer and CPM benefit may contribute to these decisions, since patient-perceived risk of contralateral breast cancer consistently overestimates actual calculated risk.**
- **In a recent study breast cancer patients without a BRCA mutation perceived their 10-year risk of contralateral breast cancer to be 22%, nearly four times the actual 10-year risk. On the other hand, a study using in-depth interviews with 45 patients found that patients knew of their low risk of contralateral breast cancer, but they still wanted CPM.**

- **Can I avoid future screening with CPM?**
- **Two studies using interviews, found that anxiety towards mammograms and no trust in screening to detect future cancers were reasons why patients chose CPM. Also, patients who choose CPM believe that it has more benefits than harms**
- **Current NCCN guidelines do not recommend routine breast imaging after CPM, but do recommend history and physical examination at least annually.**

- **Will I have better breast symmetry after CPM?**
- **A desire for breast symmetry is also a common reason to choose CPM, usually secondary to avoiding the risk of a contralateral breast cancer.**
- **Despite the lack of demonstrated clinical advantage and the risk of complications, studies show that most women are happy with their choice to undergo CPM. Approximately 90% of women are satisfied about CPM and would choose it again,**
- **Factors influencing satisfaction with the surgery include peace of mind, satisfaction with the cosmetic results, body image, risk reduction, and the feeling to be 'prevailing over cancer.**
- **Despite high satisfaction in those studies, 45% or more patients report adverse effects on aspects such as body image, cosmetic results, and sexuality.**


Patient rationales for CPM
Will CPM reduce mortality risk?
No survival benefit after CPM compared to breast-conserving surgery.[8,31,57]
Contradictory results of survival after primary breast cancer vs. after contralateral breast cancer.[5,52,54-56]
Will CPM reduce the risk of contralateral breast cancer?
Patient-perceived risk overestimates calculated risk.[15,16,60,61]
Relative risk 90-96% reduced after CPM.[58,65,66]
No or little absolute risk reduction in low risk patients due to low incidence.[31,58]
Can I avoid future screening with CPM?
NCCN guidelines[10] do not recommend screening after CPM.
However, risk of complications.[73-77]
CPM more likely after breast MRI at diagnosis.[12,17,27,34,43,68]
Sometimes anxiety and distrust towards screening.[62,71]
Will I have better breast symmetry after CPM?
90% satisfaction after CPM.[16,62,78,79]
Cosmetic results, body image
Factors of satisfaction.[78,80,81]
45% adverse effects.[15,78,80]
Concerns after both unilateral mastectomy and CPM.[82,84]

# Surgeons' influence on patient decisions.

- **The surgeon's opinion may largely influence the patient's decision whether to undergo CPM.**
- **In one study, when surgeons recommended against CPM, only 6.1% of the patients underwent the procedure compared to 57.5% of those whose surgeons did not recommend against it.**
- **In a large study based on surveys, only 55% of breast surgeons had high knowledge regarding contralateral breast cancer, and low knowledge was significantly associated with favoring CPM.**
- **Despite the higher risk of distant metastasis, surgeons were more likely to recommend CPM to patients with stage III disease compared to stage I.**

# Guidelines

## NCCN (USA)

- CPM only recommended in high-risk situations, including BRCA1/2.
- Gail model used to identify non-mutation carriers at high risk.

- Options for risk reduction should be discussed in a shared decision-making environment.
- Patient counseling and informed discussion are important.

## ASBrS (USA)

- CPM only recommended in high-risk situations, including BRCA1/2 and a strong family history.

- Options for risk reduction should be discussed in a shared decision-making environment
- Patient counseling and informed discussion are important.
- Surgeons should make a direct recommendation for or against CPM to each patient.

## Manchester Guidelines (UK)

- Five step process of pre-operative assessment and counseling:

1. Reasons and clinical history
2. Calculating CBC risk
3. Giving the patient time for the decision
4. Multi-disciplinary team discussion
5. Patient decision and consent form

- **Discussion**
- **CPM rates have risen steadily over the last two decades in all patients of all age groups and breast cancer stages, but most notably in women under the age of 40.**
- **Although the NCCN and ASBrS guidelines recommend CPM only in high contralateral breast cancer risk patients such as BRCA1/2 carriers and those with a strong family history, the increase of CPM in women without genetic predispositions is mainly responsible for the overall increased uptake of CPM.**
- **Data suggest that women without a BRCA1/2 mutation or a family history may be at risk for being over treated with CPM.**

- **The main reasons are to reduce risk of mortality and contralateral breast cancer. Based on the presented evidence, a patient should be discouraged to undergo CPM if her main drive is to reduce the risk of mortality.**

- **Patients who choose CPM believe that the benefits are greater than the harms. Studies also identify breast symmetry as a reason for patients to choose CPM. The surgeon's opinion plays a major role in patients' choice for CPM.**
- **Satisfaction after CPM is very high (around 90%), although adverse effects related to body image, cosmetic results, and sexuality are also common.**

- **Despite high patient satisfaction, professional societies are concerned that the benefits of CPM in low-risk patients do not outweigh the risks.**
- **CPM does not impact mortality and has only a very small impact on the chance of developing a contralateral cancer.**
- **If a patient really wants to avoid screening or take away all worry about future breast cancer, CPM might be a good option for that patient despite the risks.**

## Recommendations

**While action to disrupt the rise of CPM rates is warranted, patient preference should be the major factor in the decision whether to perform CPM.**
**Clinicians have an ethical role to facilitate good decision making based on the best available evidence and well-considered patient preferences.**

**Surgeons need to make sure that patients understand the impact of CPM on the chance of dying of breast cancer, the chance of experiencing another cancer diagnosis and treatment, the chance of avoiding screening, and the chance to gain breast symmetry.**
**We recommend that breast surgeons have a conversation about the option of CPM and patient preferences with every patient considering any type of mastectomy.**

# • Psychosocial effects

- **Body image, femininity —**
- **Adverse changes in body image including diminished feelings of femininity, sexuality and sexual satisfaction, and self-esteem can occur following a CPM.**
- **The personal satisfaction following a CPM is reportedly high. For example, a survey of 583 patients found that the majority (83 percent) of women were satisfied with the CPM 10 years after the operation, while 8 percent were neutral and 9 percent were dissatisfied.**
- **Quality of life — Quality-of-life-related measures for women undergoing a CPM were comparable to women in the general population.**
- **In a prospective study of 60 women with breast cancer who had also undergone a CPM, most patients had a satisfactory health-related quality of life two years after the operation, with no difference in anxiety or depression**

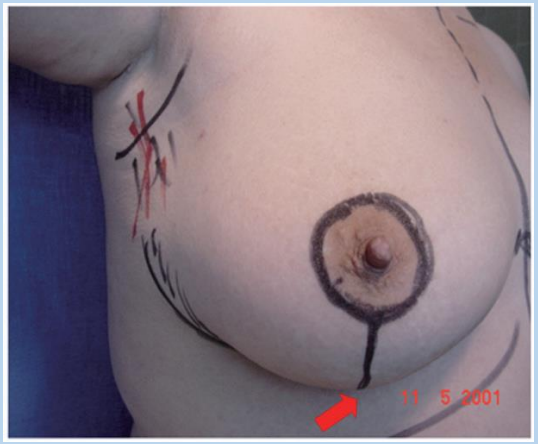
# Operations for Removal of Healthy Breasts

- **Three operations are used to remove healthy breasts for women with a high risk of developing breast cancer.**
- **Simple (total) mastectomy refers to removal of the nipple-areolar complex, breast tissue, and most of the overlying skin.**
- **Skin-sparing mastectomy refers to removal of the nipple-areolar area and breast tissue while preserving most of the overlying skin.**
- **Nipple-sparing (subcutaneous) mastectomy refers to removal of only the breast tissue, sparing both the nipple-areolar area complex and skin over the breast.**

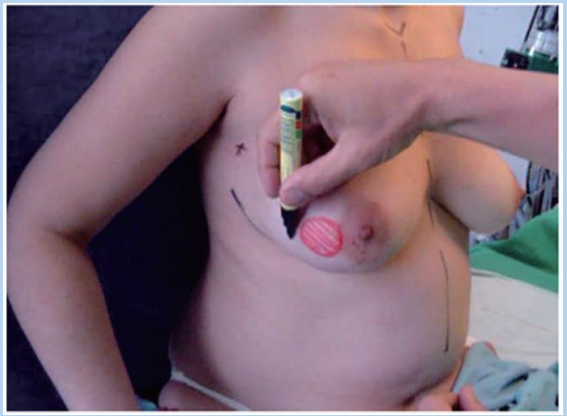
# Risks of Surgery for Breast Cancer Prevention

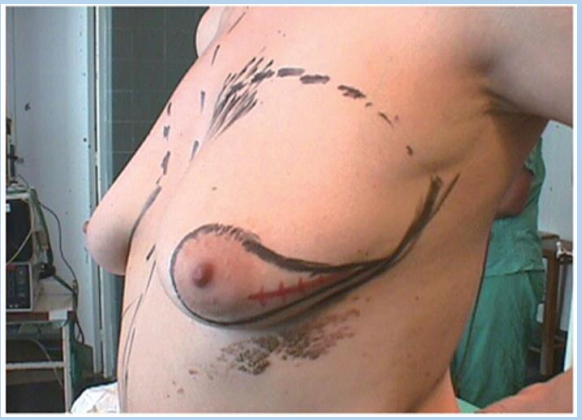
- **The risks of these operations include wound problems, infections, bleeding, and occasional need for additional surgery to treat unexpected complications.**
- **Also, some women may develop emotional difficulties, abnormal sensations on their chest wall, or problems with body image and sexual relationships after these operations.**
- **Women who are at high risk of developing breast cancer should discuss all options with their doctor before making the decision to have their breasts surgically removed.**

# Skin Sparing Mastectomy

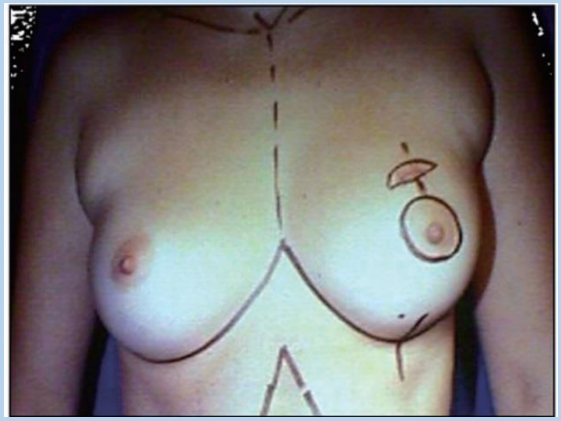



Type I
Periareolar

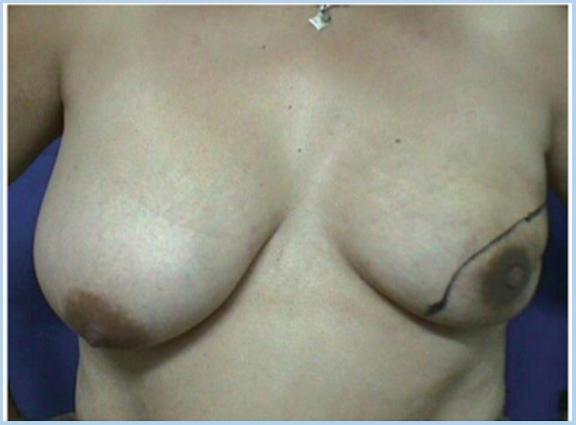




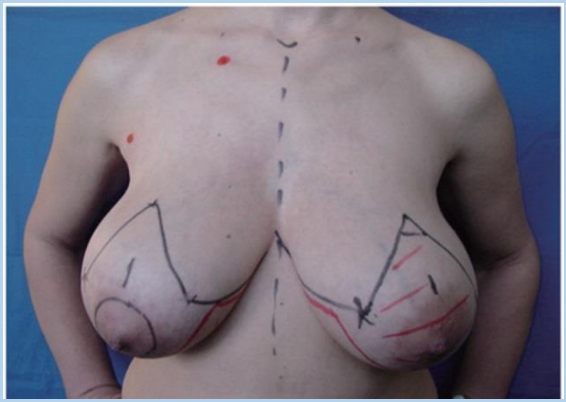
Type II
Periareolar with medial or lateral extension and resection of previous scar



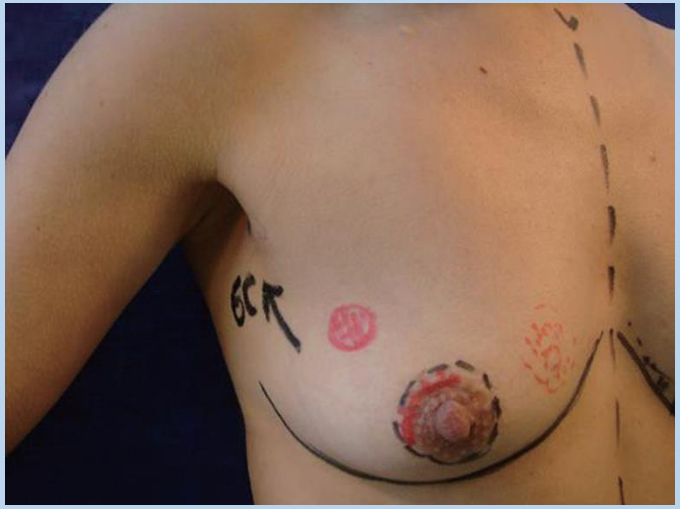
Type III
Periareolar. Previous scar resection
with another incision

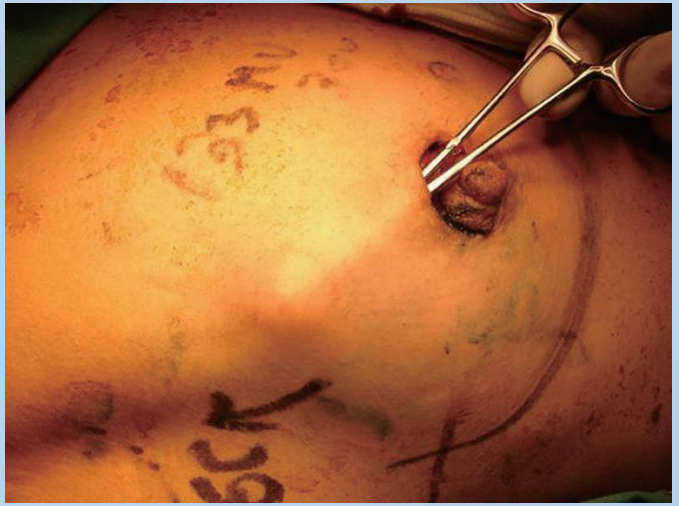


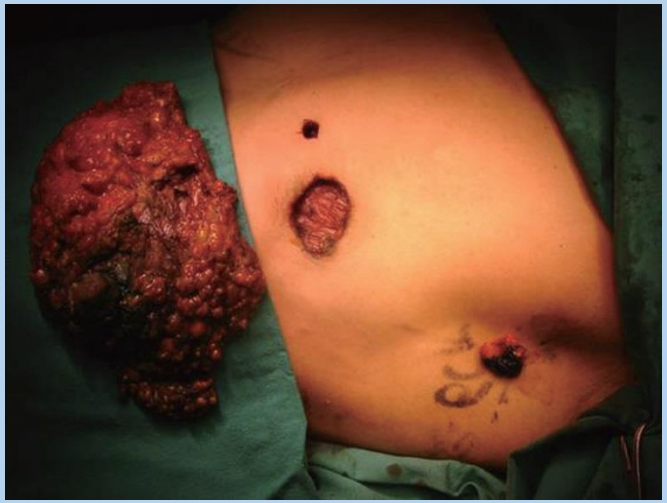
Type IV
Elliptical. Ptotic and hypertrophic breast

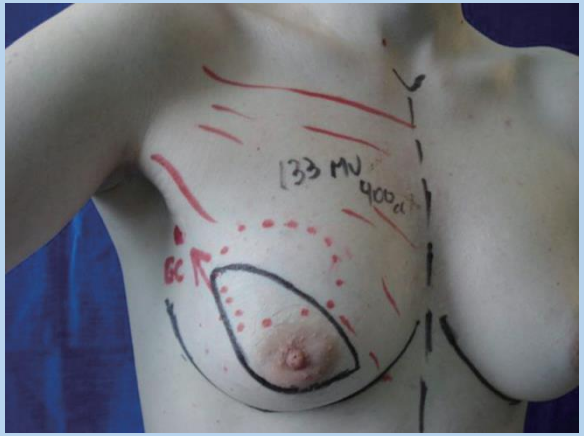


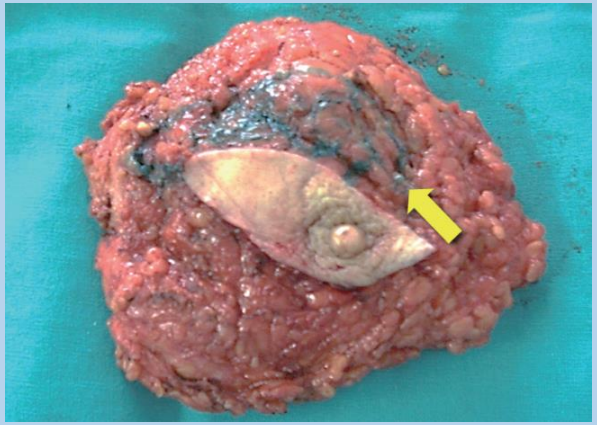
Type IV
Incision inverted “T”

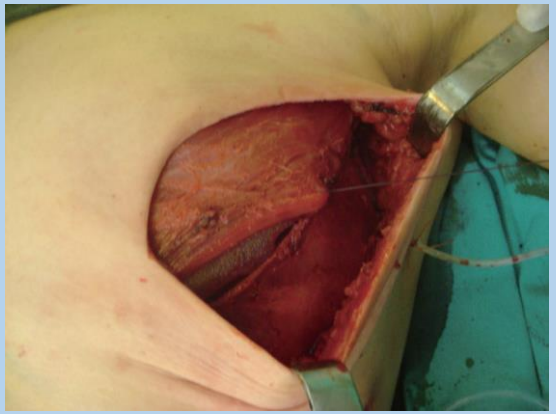


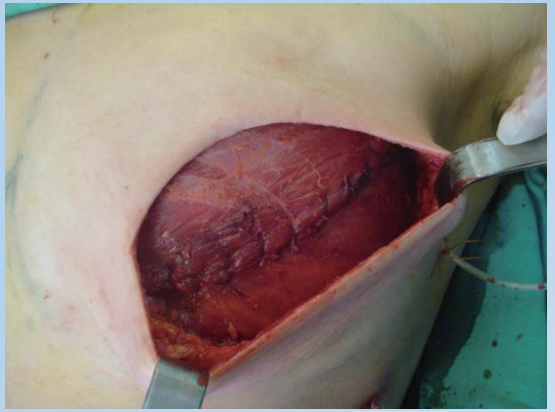


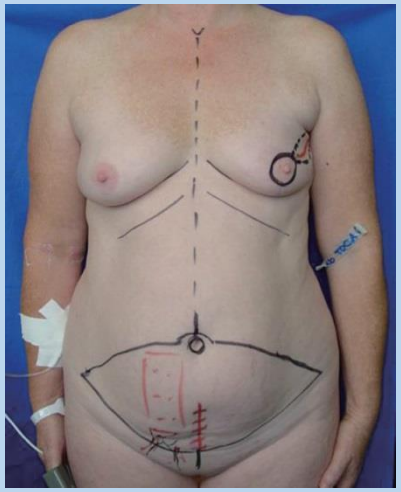


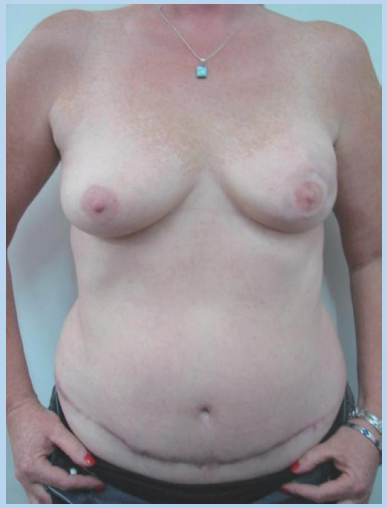


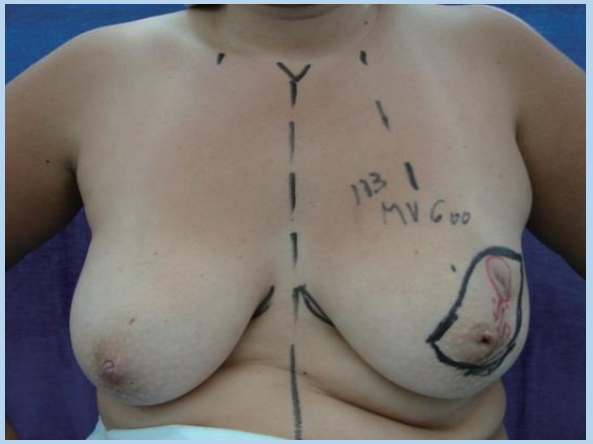


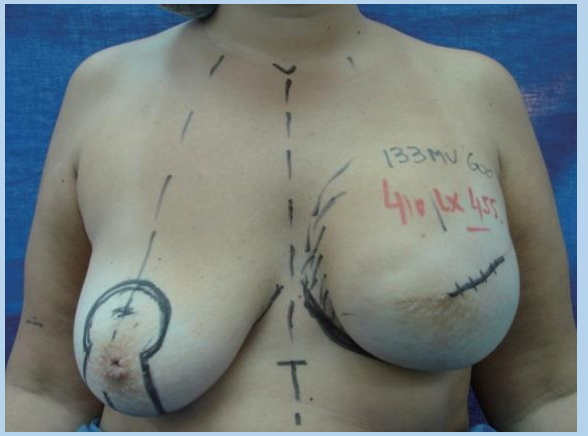


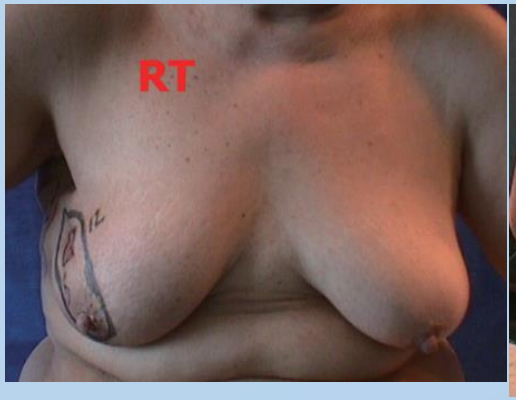








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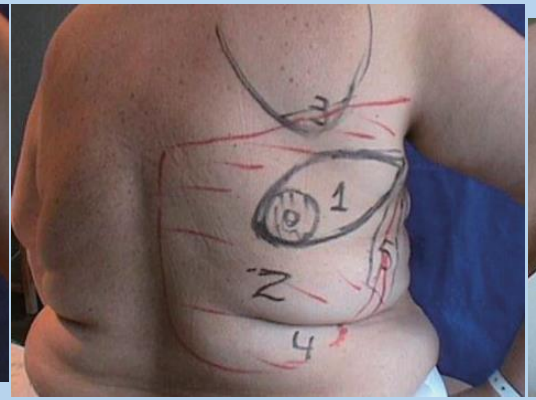
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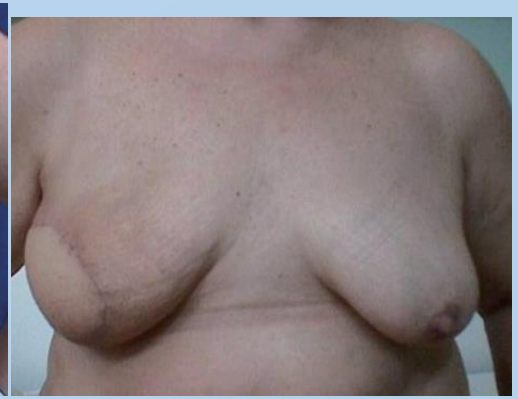
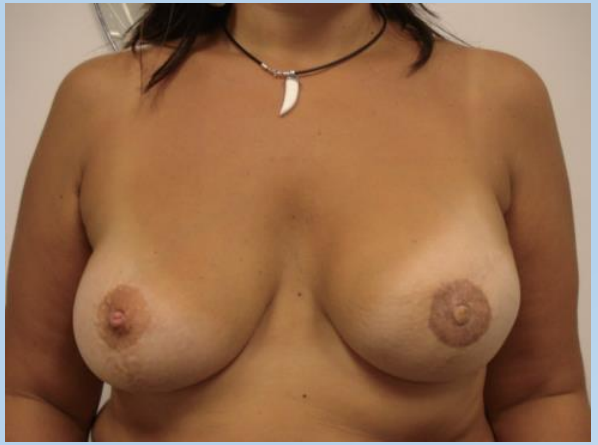
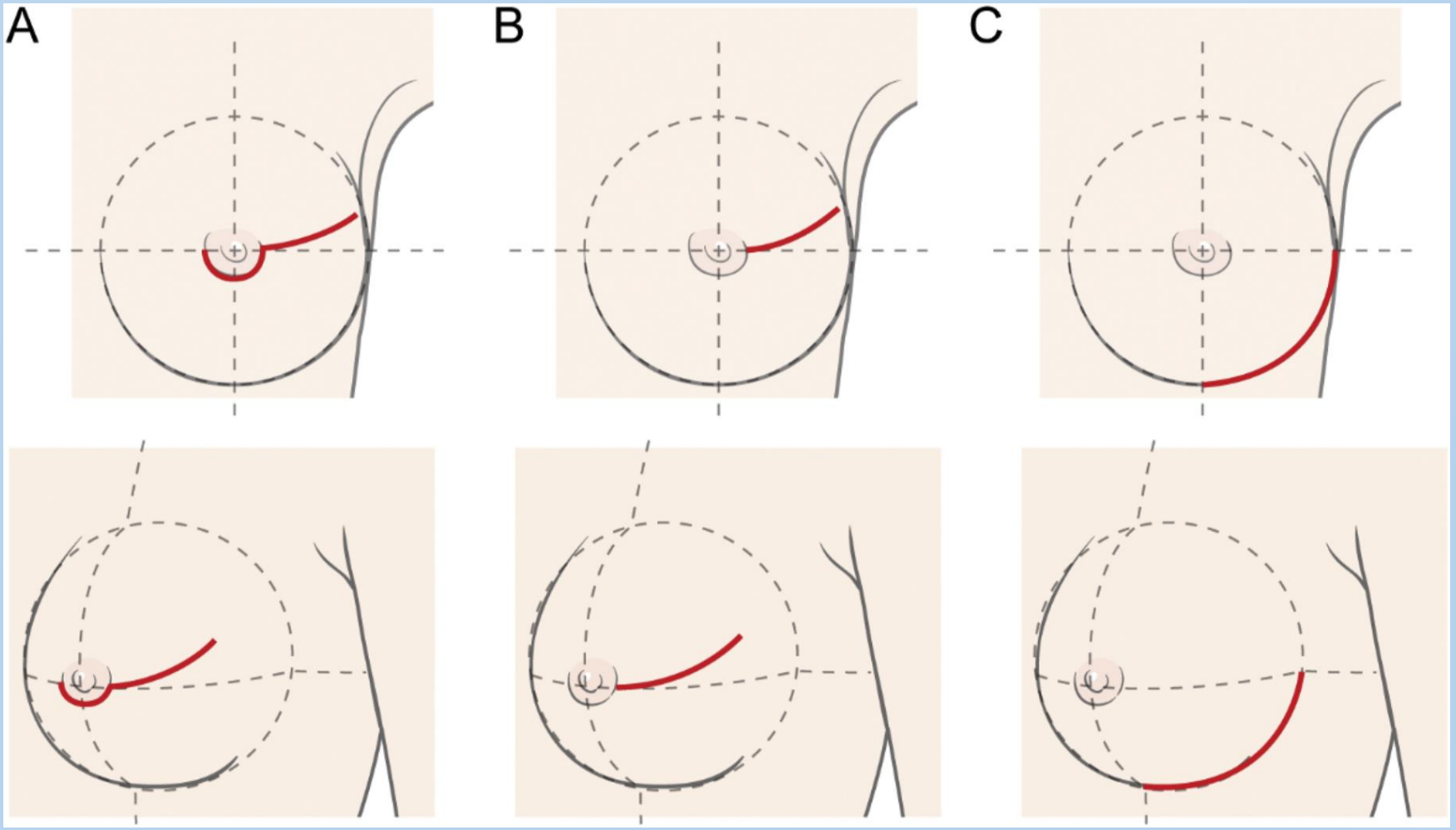
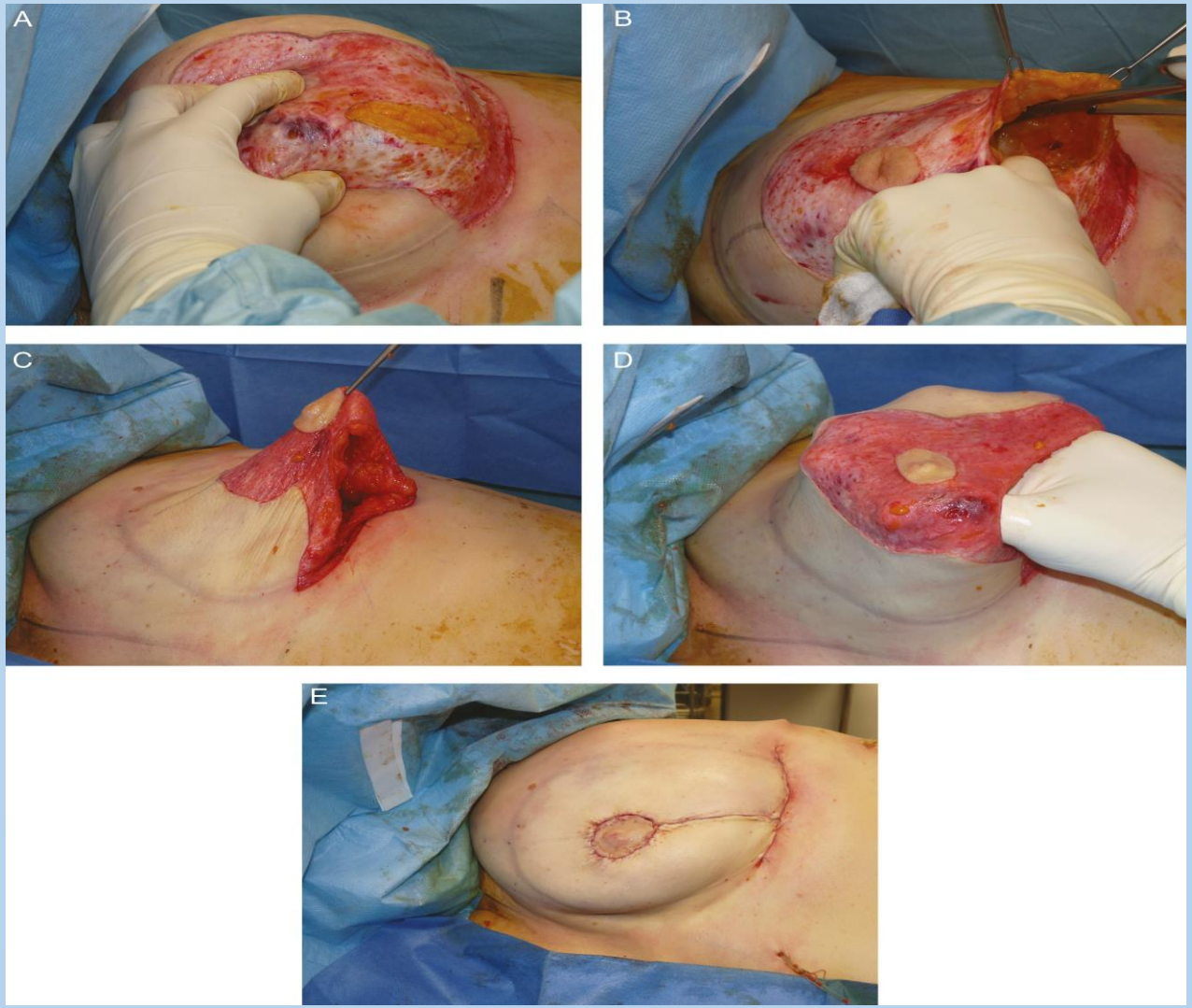


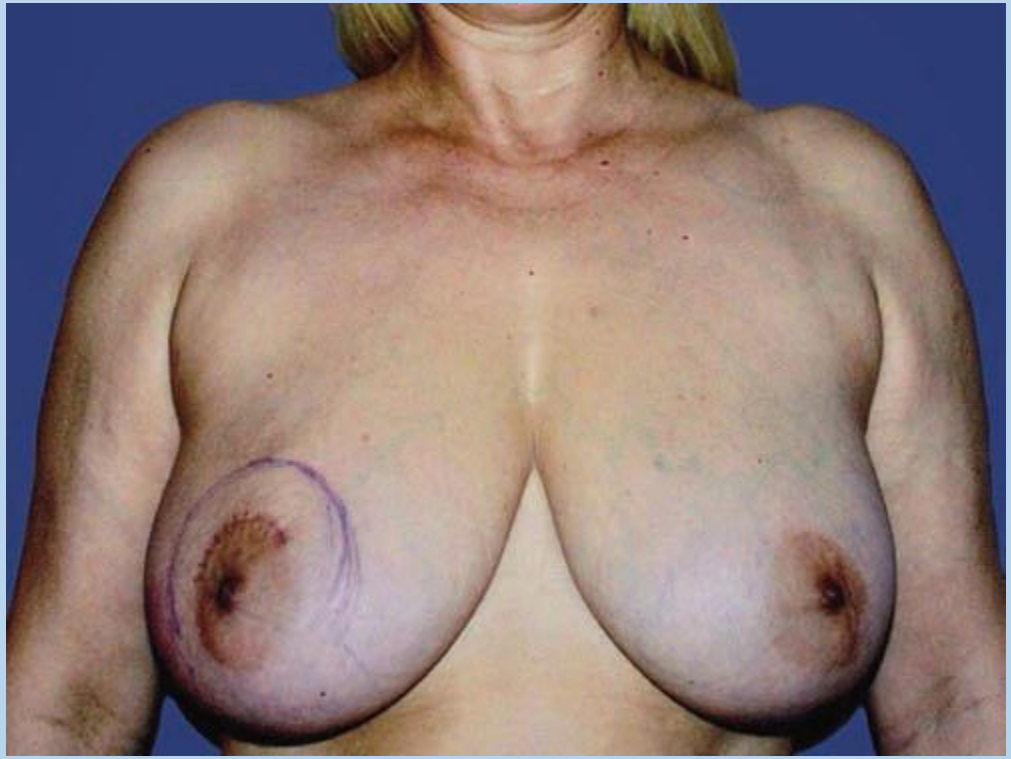


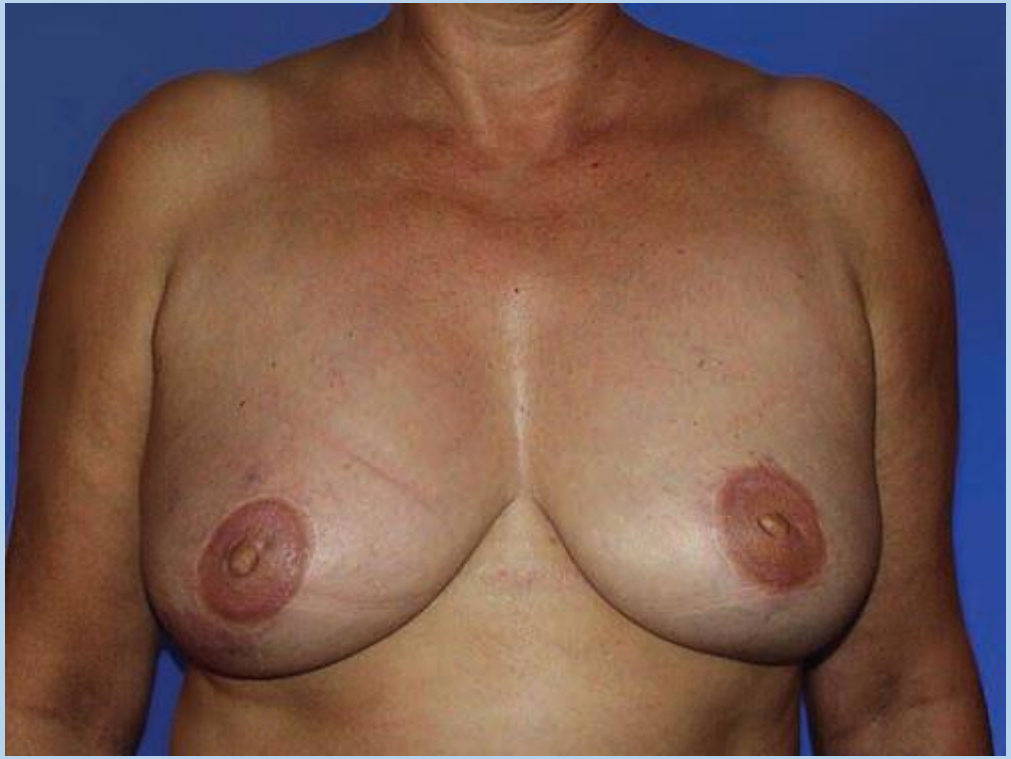
# Nipple Sparing Mastectomy



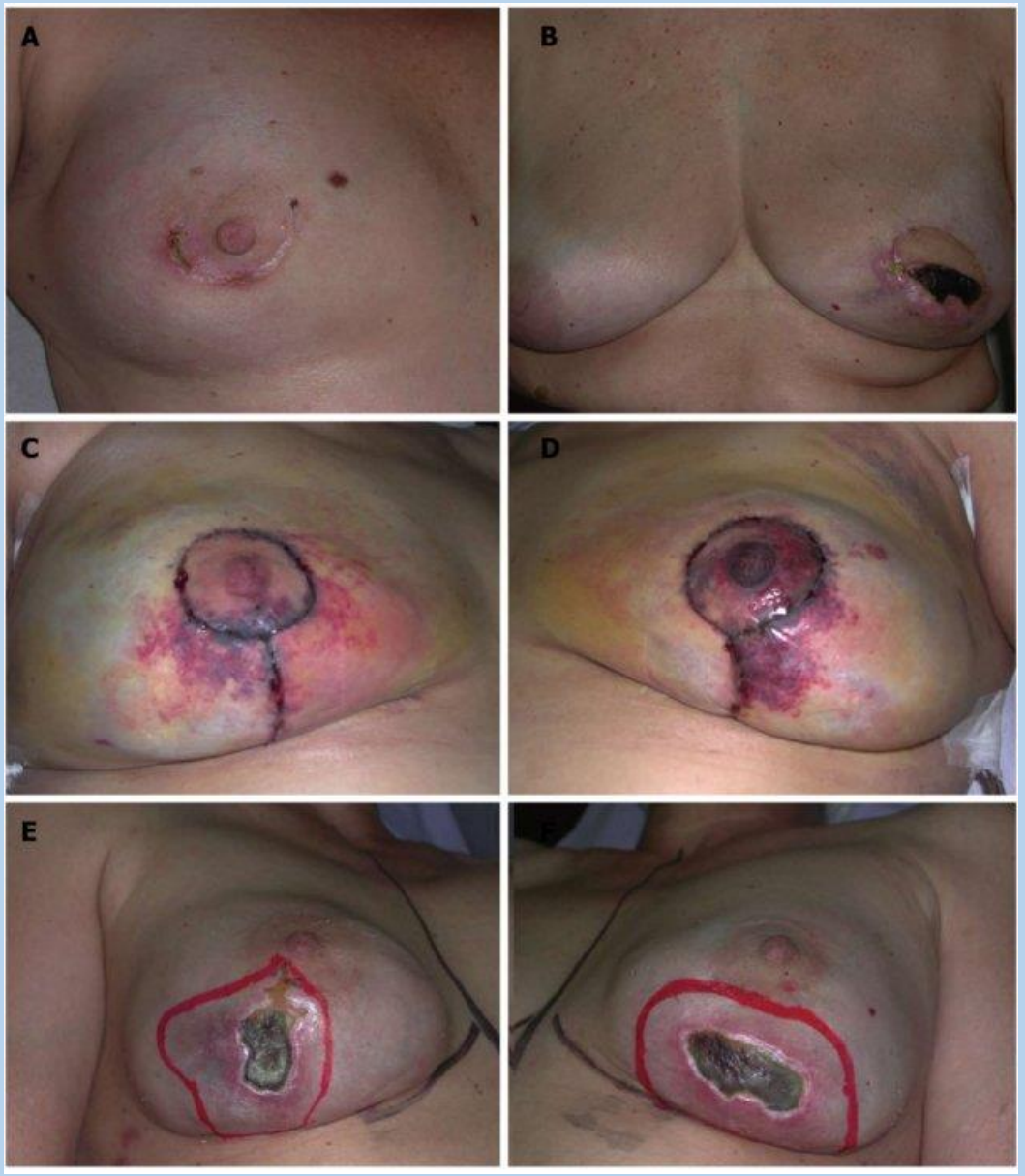
# Skin-reducing mastectomy (SRM) with nipple-areola complex (NAC) preservation utilizing a Wise pattern

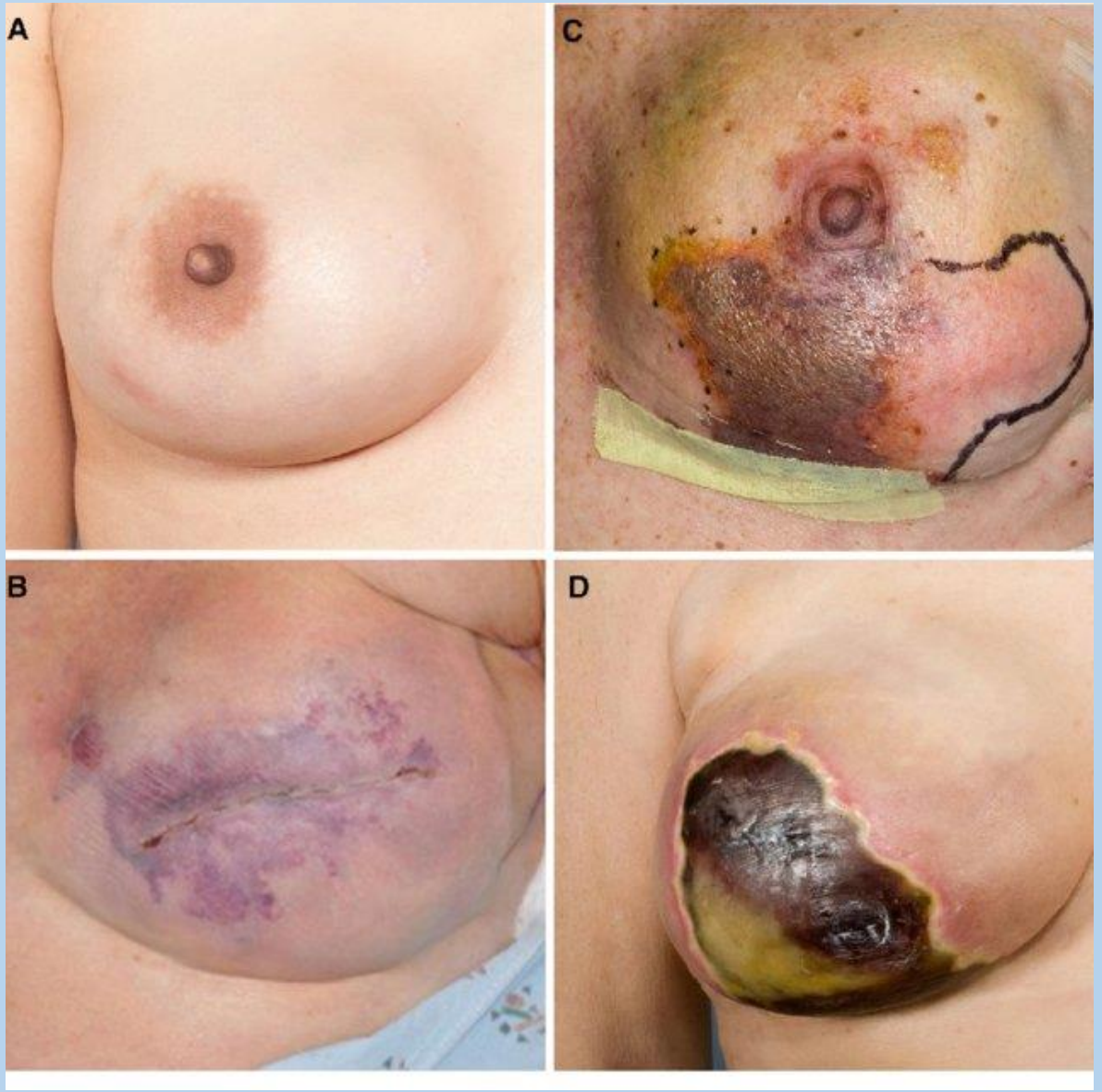


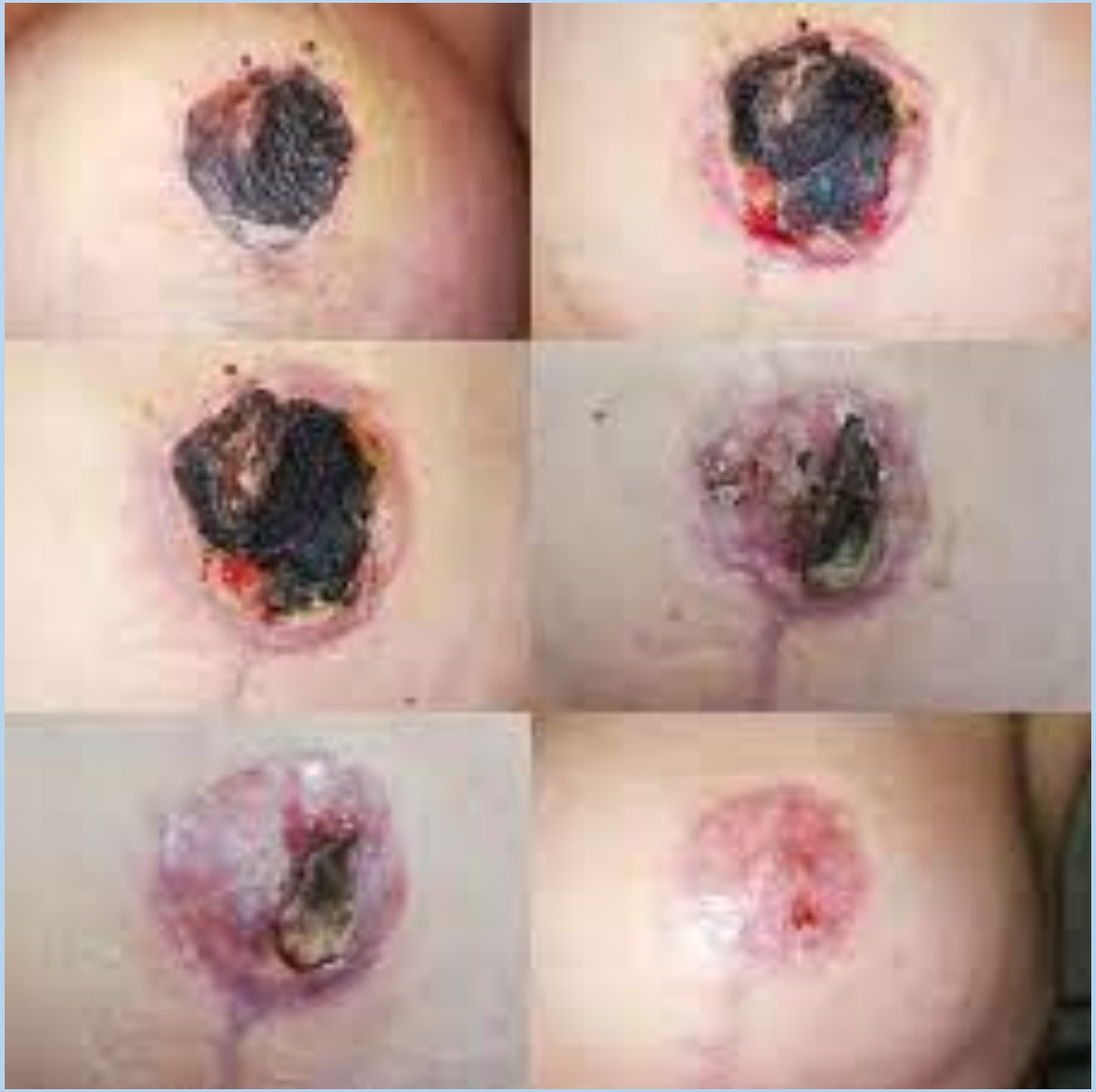


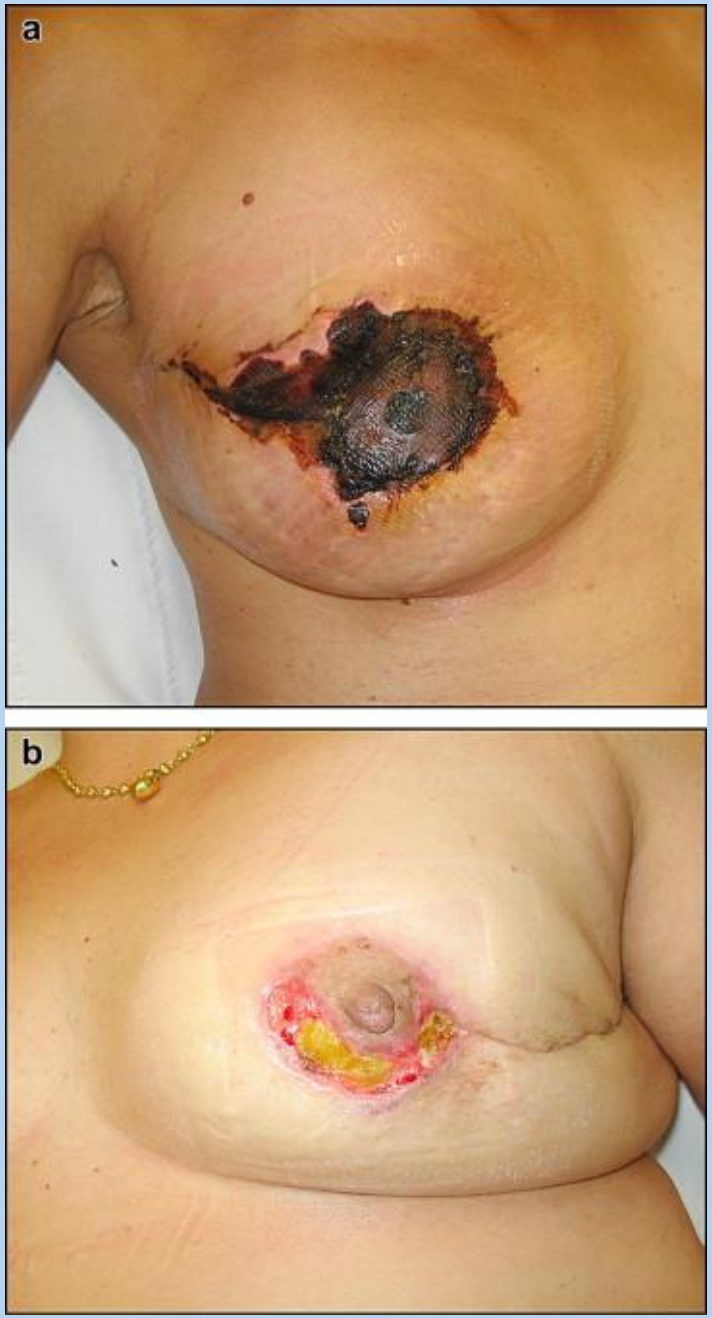


# Complications




A
C
B
D




a
b

# THANKS FOR YOUR ATTENTION

# اسلاید های دکتر کیوان مجیدزاده

# risk reducing mastectomy could be considered

| Gene | Breast Cancer Risk | Ovarian Cancer Risk |
|---|---|---|
| BRCA1 | **Evidence for increased risk:** very strong (with predisposition to TNBC) **Absolute risk:** >60% | **Evidence for increased risk:** very strong **Absolute risk:** 39-58% |
| BRCA2 | **Evidence for increased risk:** very strong (with predisposition to ER+) **Absolute risk:** >60% | **Evidence for increased risk:** very strong **Absolute risk:** 13-29% |
| PALB2 | **Evidence for increased risk:** strong **Absolute risk:** 41-60% | **Evidence for increased risk:** strong **Absolute risk:** 3-5% |
| PTEN | **Evidence for increased risk:** strong **Absolute risk:** 40-60% | **Evidence for increased risk:** None |
| TP53 | **Evidence for increased risk:** strong **Absolute risk:** >60% | **Evidence for increased risk:** None |

# Strong Risk without sufficient evidence for Risk Reducing Mastectomy

| Gene | Breast Cancer Risk | Ovarian Cancer Risk |
|---|---|---|
| ATM | **Evidence for increased risk:** strong<br>**Absolute risk:** 15-40% | **Evidence for increased risk:** strong<br>**Absolute risk:** <3% |
| CDH1 | **Evidence for increased risk:** strong (with predisposition to Lobular disease)<br>**Absolute risk:** 41-60% | **Evidence for increased risk:** None |
| CHEK2 | **Evidence for increased risk:** strong (with predisposition to ER+)<br>**Absolute risk:** 15-40% | **Evidence for increased risk:** None |
| NF1 | **Evidence for increased risk:** strong<br>**Absolute risk:** 15-40% | **Evidence for increased risk:** None |
| STK11 | **Evidence for increased risk:** strong<br>**Absolute risk:** 40-60% | **Evidence for increased risk:** strong<br>**Absolute risk:** >10% |

# Limited risk without sufficient evidence for risk reducing mastectomy

| Gene | Breast Cancer Risk | Ovarian Cancer Risk |
|---|---|---|
| BARD1 | **Evidence for increased risk:** Limited but stronger in TNBC<br>**Absolute risk:** insufficient data to define | **Evidence for increased risk:** None |
| BRIP1 | **Evidence for increased risk:** Limited but stronger in TNBC<br>**Absolute risk:** insufficient data to define | **Evidence for increased risk:** strong<br>**Absolute risk:** >10% |
| NBN | **Evidence for increased risk:** Limited<br>**Absolute risk:** insufficient data to define | **Evidence for increased risk:** Limited<br>**Absolute risk:** insufficient |
| RAD51C | **Evidence for increased risk:** Limited but stronger in TNBC<br>**Absolute risk:** 15-40% | **Evidence for increased risk:** strong<br>**Absolute risk:** >10% |
| RAD51D | **Evidence for increased risk:** Limited but stronger in TNBC<br>**Absolute risk:** 15-40% | **Evidence for increased risk:** strong<br>**Absolute risk:** >10% |

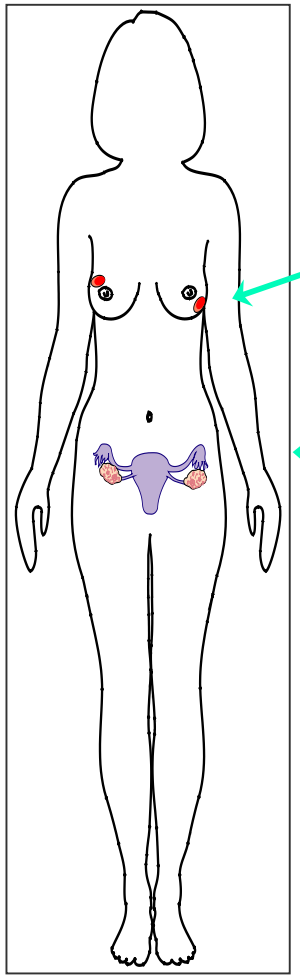
# Limited risk without sufficient evidence for risk reducing mastectomy

| Gene | Breast Cancer Risk | Ovarian Cancer Risk |
|---|---|---|
| MSH2, MLH1, MSH6, PMS2, EPCAM | **MLH1,MSH2, MSH6, PMS2, EPCAM**<br>**Evidence for increased risk:** Limited<br>**Absolute risk:** <15% | **MLH1, MSH2, MSH6**<br>**Evidence for increased risk:** strong<br>**Absolute risk:** >10 %<br>**PMS2**<br>**Evidence for increased risk:** Limited<br>**Absolute risk:** <3%<br>**EPCAM**<br>**Evidence for increased risk:** Limited<br>**Absolute risk:** <10 % |

انجام ماستکتومی پیشگیرانه در فردی که سابقه فامیلی بسیار قوی دارد ولی هنوز تست نشده است چگونه است؟

# HBOC Syndrome

# BRCA-Associated Lifetime Risks

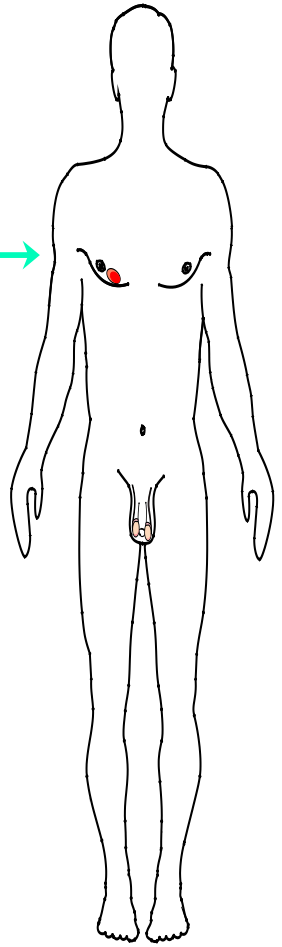


Breast cancer ~ (41- 90%)

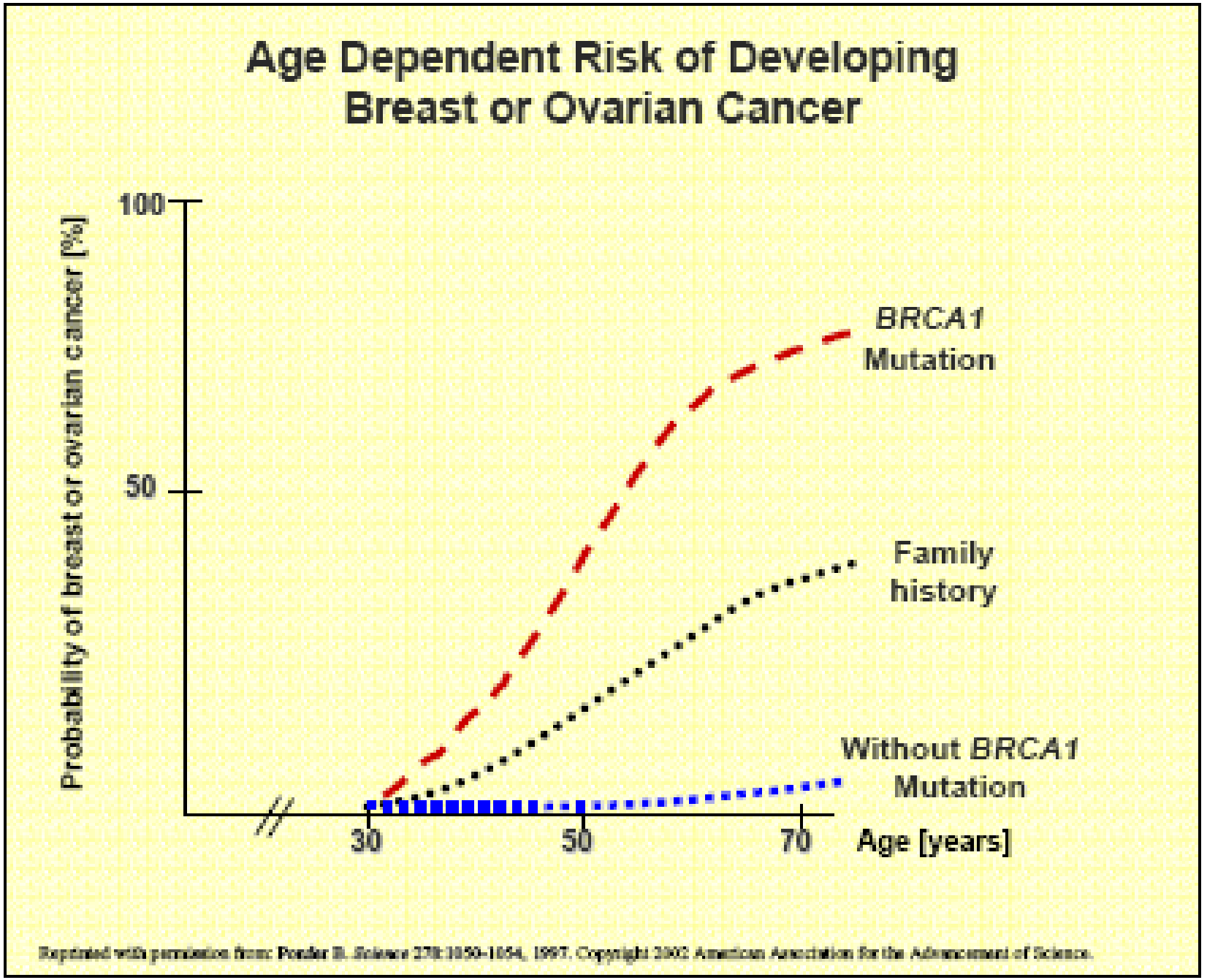
Second primary breast cancer ~8-50%

Ovarian cancer: ~ (8 – 62%)

Male breast cancer: 7-8%



Motamed Cancer Institute


Age Dependent Risk of Developing Breast or Ovarian Cancer
Probability of breast or ovarian cancer [%]
100
50
BRCA1 Mutation
Family history
Without BRCA1 Mutation
30
50
70
Age [years]
Reprinted with permission from: Ponder B. Science 278:1050-1054, 1997. Copyright 2002 American Association for the Advancement of Science.

# BRCA related Breast Cancer Syndrome

- Survival: inconsistent evidence for poor survival for BC among carriers
  - recent Meta-analysis including 60 studies and 105220 patients with BC
    - BRCA1 carriers had the worse OS compared to non carriers
    - BRCA2 carriers had worse breast cancer-specific survival compared to non-carriers though OS was not different
    - Among Triple Negative BC brca1/2 carriers associated with better OS.

- Genetic Anticipation:
  - Age of disease onset may become lower over time

# Contralateral BC risk among BRCA carriers until 10 years after the first BC

**BRCA1**: 11% - 50%

**BRCA2**: 8% - 30%

# Cancer Spectrum in BRCA Mutations

- Breast Cancer
- Ovary Cancer
  - Better survival, most favorable for BRCA2 carriers
  - BRCA2 carriers: higher response rates to primary chemotherapy
  - Histology:
    - more likely serous & high grade
    - endometrioid & clear cell also have been reported
    - Non mucinous versus mucinous (which is seen more likely in Li-Fraumeni)
    - Non epithelial carcinomas are NOT associated with BRCA1/2
      - Sex cord tumors: Peutz Jeghers
      - Sertoli-Leidig: Peutz Jeghers & DICER1
- Prostate Cancer
  - esp. Gleason Score>8, Nodal involvement, distant met.
  - Decreased Survival
- Pancreatic Cancer

# Cancer Spectrum in BRCA Mutations

- Serous Uterine Cancer: BRCA1/2 (part of which may be related to TAM)
- Colorectal Cancer: Just BRCA1 (OR:1.4) NOT BRCA2
- Leukemia: BRCA2 carriers
- Ocular Melanoma: BRCA2 Carriers
- Cutanous Melanoma: BRCA2: Inconsistence conclusions

Familial Cancer
https://doi.org/10.1007/s10689-021-00242-4

ORIGINAL ARTICLE

# A comprehensive reference for *BRCA1/2* genes pathogenic variants in Iran: published, unpublished and novel

Keivan Majidzadeh-A[1] · Shiva Zarinfam[1] · Nasrin Abdoli[1] · Fatemeh Yadegari[1] · Rezvan Esmaeili[1] · Leila Farahmand[2] · Azin Teimourzadeh[1] · Mahdieh Taghizadeh[3] · Mansoor Salehi[4] · Mohamad Zamani[1]

Received: 12 May 2020 / Accepted: 4 March 2021

Human Mutation
Variation, Informatics, and Disease
OFFICIAL JOURNAL HGV HUMAN GENOME VARIATION SOCIETY
DATA ARTICLE

# The spectrum of *BRCA1* and *BRCA2* pathogenic sequence variants in Middle Eastern, North African, and South European countries

Yael Laitman, Tara M. Friebel, Drakoulis Yannoukakos, Florentia Fostira, Irene Konstantopoulou, Gisella Figlioli, Bernardo Bonanni, Siranoush Manoukian, Monica Zuradelli, Carlo Tondini, Barbara Pasini, Paolo Peterlongo, Dijana Plaseska-Karanfilska, Milena Jakimovska, **Keivan Majidzadeh**, Shiva Zarinfam, Maria A. Loizidou, Andreas Hadjisavvas, Kyriaki Michailidou, Kyriacos Kyriacou, Doron M. Behar, Rinat Bernstein Molho, Patricia Ganz, Paul James, Michael T. Parsons, Aminah Sallam, Olufunmilayo I. Olopade, Arun Seth, Georgia Chenevix - Trench, Goska Leslie, Lesley McGuffog, Makia J Marafie, Andre Megarbane, Fahd Al-Mulla, Timothy R. Rebbeck, Eitan Friedman

JAMA Oncol. 2020 Aug 1;6(8):1218-1230. doi: 10.1001/jamaoncol.2020.2134.

# Characterization of the Cancer Spectrum in Men With Germline BRCA1 and BRCA2 Pathogenic Variants: Results From the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)

Valentina Silvestri [1], Goska Leslie [2], Daniel R Barnes [2], CIMBA Group; Bjarni A Agnarsson [3 4], Kristiina Aittomäki [5], Elisa Alducci [6], Irene L Andrulis [7 8], Rosa B Barkardottir [3 9], Alicia Barroso [10], Daniel Barrowdale [2], Javier Benitez [11 12], Bernardo Bonanni [13], Ake Borg [14], Saundra S Buys [15], Trinidad Caldés [16], Maria A Caligo [17], Carlo Capalbo [1], Ian Campbell [18], Wendy K Chung [19], Kathleen B M Claes [20], Sarah V Colonna [15], Laura Cortesi [21], Fergus J Couch [22], Miguel de la Hoya [16], Orland Diez [23 24], Yuan Chun Ding [25], Susan Domchek [26], Douglas F Easton [2 27], Bent Ejlertsen [28], Christoph Engel [29], D Gareth Evans [30], Lidia Feliubadalò [31], Lenka Foretova [32], Florentia Fostira [33], Lajos Géczi [34], Anne-Marie Gerdes [35], Gord Glendon [7], Andrew K Godwin [36], David E Goldgar [37], Eric Hahnen [38 39], Frans B L Hogervorst [40], John L Hopper [41], Peter J Hulick [42 43], Claudine Isaacs [44], Angel Izquierdo [45], Paul A James [18 46], Ramunas Janavicius [47], Uffe Birk Jensen [48], Esther M John [49], Vijai Joseph [50], Irene Konstantopoulou [33], Allison W Kurian [49], Ava Kwong [51 52 53], Elisabetta Landucci [54], Fabienne Lesueur [55 56 57], Jennifer T Loud [58], Eva Machackova [32], Phuong L Mai [59], Keivan Majidzadeh-A [60], Siranoush Manoukian [61],

# HBOC Testing Criteria

- **Personal HX:**

➢ **1** known deleterious mutation in the family

➢ **1** Epithelial Ovary/ Fallopian tube/ primary peritoneal/ pancreas/ prostate cancers at any age

➢ **1** Male Br. Ca. at any age

➢ **1** Triple Negative Br. Ca. <60

➢ **1** Br. Ca. diagnosed Age < 45

➢ **1** Exocrine Pancreatic Cancer at any age

➢ **1** Prostate Cancer (Metastatic, Intraductal/cribriform histology, high risk group) at any age

➢ **1** Her2 Neg. Metastatic BC ( To aid PARP inhibitor decision making)

➢ **2** BC 1 BC< 50 and 1 BC at any age

➢ **2** Cancers 1 BC <50 and 1 (ovary, Prostate, Pancreas)

➢ **3** or >, Br. Ca. or Prostate and Pancreatic Ca. at any age

➢ Positive above criteria & Limited previous testing (single gene or absent del/dupl analysis)

- **Family HX:** with the above mentioned criteria in
  - 1st degree relatives (Prostate & Pancreas) &
  - 1st and 2nd degree relatives (Other CAs)
- **probability models** (Tyrer Cuzic, BRCA Pro, CanRisk):
  - An affected or unaffected individual not meeting the above criteria with >5% Probability

Motamed Cancer Institute

# Cowden Syndrome

# Cowden Syndrome (PTEN gene)

- Rare
- Many benign growths called *Hamartomas* (Skin,Mouth, GI tract, Thyroid,breast, Uterus, Soft tissues, brain)
- Increased Risk of Cancer (Melanoma, Breast, Thyroid, Endometrium, Kidnney, colon, Rectum)
- Macrocephaly
- Blood Vessel Problems
- Autism spectrum Disorders
- Learning & Developmental delays

**Major criteria:**

- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas[aa]
- Macrocephaly (megalocephaly) (ie, ≥97%, 58 cm in adult women, 60 cm in adult men)[bb]
- Macular pigmentation of glans penis
- Mucocutaneous lesions[cc]
  - One biopsy-proven trichilemmoma
  - Multiple palmoplantar keratoses
  - Multifocal or extensive oral mucosal papillomatosis
  - Multiple cutaneous facial papules (often verrucous)

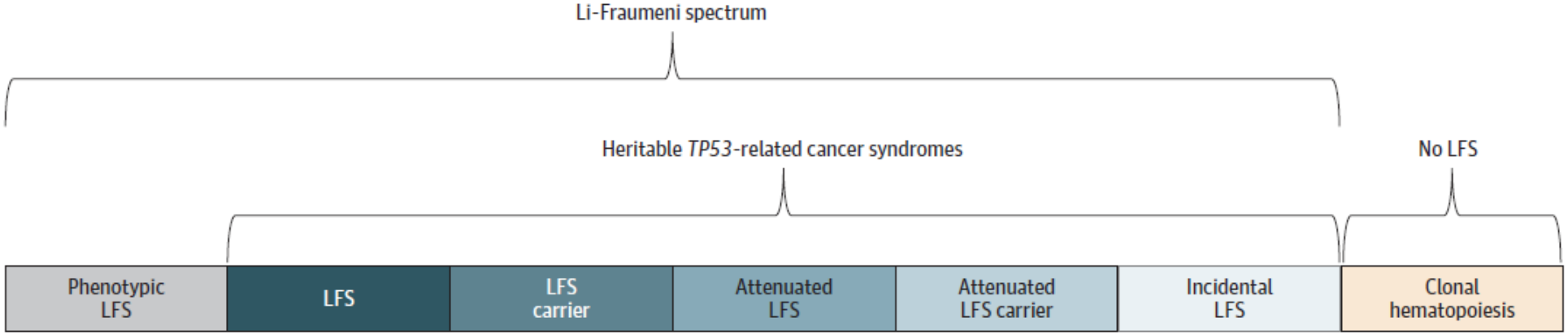
**Minor criteria:**[dd]

- Autism spectrum disorder
- Colon cancer
- ≥3 esophageal glycogenic acanthoses
- Lipomas
- Intellectual disability (ie, IQ ≤75)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (eg, adenoma, nodule[s], goiter)
- Renal cell carcinoma
- Single GI hamartoma or ganglioneuroma
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

# Li- Fraumeni Syndrome

# Li Fraumeni Syn. Tumor Spectrum
# ABS

- A Adrenocortical
- B
  - Breast
  - Brain
  - Bone (Osteosarcoma)
- S Soft Tissue Sarcoma




| | |
|---|---|
| **Phenotypic LFS** | No P/LP germline (or germline mosaic) *TP53* variant + no other genetic explanation + meeting classic LFS criteria or category A Chompret criteria |
| **LFS** | P/LP germline (or germline mosaic) *TP53* variant + meeting LFS testing criteria and/or any cancer before age 18 y |
| **LFS carrier** | P/LP germline *TP53* variant + no (history of) cancer + LFS in family |
| **Attenuated LFS** | P/LP germline (or germline mosaic) *TP53* variant + (history of) cancer but not meeting LFS testing criteria + no cancer before age 18 y |
| **Attenuated LFS carrier** | P/LP germline *TP53* variant + no (history of) cancer + attenuated LFS in family |
| **Incidental LFS** | P/LP germline (or germline mosaic) *TP53* variant + no (history of) cancer + no LFS or attenuated LFS in family |

**LFS genetic testing criteria (Chompret criteria)**

**Category A**

- Proband with a core tumor before age 46 y and ≥1 first- or second-degree relative with a core tumor (except a breast cancer if proband had breast cancer) before age 56 y
- ≥2 Tumors (not multiple breast cancers), including 2 core tumors, the first of which occurred before age 46 y

**Category B**

- Adrenocortical carcinoma
- Choroid plexus carcinoma
- Anaplastic rhabdomyosarcoma
- Breast cancer before age 31 y
- Osteosarcoma
- Childhood hypodiploid acute lymphoblastic leukemia
- Sonic hedgehog-medulloblastoma

**Core tumors** Breast cancer, soft tissue sarcoma, osteosarcoma, brain tumor, adrenocortical carcinoma

**Classic LFS criteria**

A person with a sarcoma diagnosed before age 45 y
+ First-degree relative with any cancer before age 45 y
+ First- or second-degree relative with any cancer diagnosed before age of 45 y or a sarcoma at any age

# TP53 Li-Fraumeni Mutation

- P53 gene: **Chromosome 17**
- •Tumor suppressor gene with a vital role in cell cycle and inducing apoptosis when cell damage is beyond repair
- • Can see **more aggressive disease and worse overall survival**
- • Associated with **poor response** to chemotherapy, radiotherapy and hormonal therapy
- Contraindication of Radiotherapy & X-Ray Imaging

# Common Features of High penetrance Breast and ovarian cancer susceptibility genes and syndromes

- Arise from germline mutations not within sex-linked genes
- Can be inherited from either parents
- High penetrance mutations
- Early age onset
- Autosomal dominant inheritance Pattern
- So 50% chance of inheriting the mutation to offsprings
- multiple cases in the family
- Bilateral Breast Cancer

# Multi Gene Testing
# Next generation Sequencing

- Allows sequencing of multiple genes simultaneously
- can detect pathogenic variant not found in single Gene testing
- Most useful when more than one Gene can explain and inherited cancer syndrome
- for those who tested negative for one particular syndrome but whose personal and family history is suggestive of an inherited susceptibility
- A management plan based on genetic test results should only be developed for clinically actionable variants

# اسلاید های دکتر کامران آقاخانی

# چند سوال؟

- چرا از ما شکایت میشود؟
- راهکارهای پیشگیری از شکایت کدام است؟
- زمانی که بین قانون و اخلاق ، تناقض وجود داشته باشد ....
- میزان اراده طرفین در خصوص ادامه ارتباط بین پزشک و بیمار چقدر است؟
- در خصوص درخواستهای غیر علمی بیمار از طبیب ، وظیفه پزشک چیست؟
- رازداری پزشکی و حق بیمارنسبت به اطلاع از بیماری خود و یا حفظ راز وی نسبت به اطرافیان !
- رضایت و برائت در امر درمان

## عوامل موثر در طرح شکایت بیماران از پزشکان:

۱- عوامل رفتاری

۲- آگاهی ندادن به بیمار و اطرافیان او درباره عوارض احتمالی و خطرات غیر قابل پیش بینی

۳- مسائل مالی و هزینه درمان

---

۴- عامل رشته تخصصی

۵- دخالت و تحریک سایر همکاران

۶- نگرفتن شرح حال کامل و عدم تکمیل دقیق پرونده قبل از اقدامات درمانی

۷- قصور در مراقبتهای بعد از عمل جراحی

۸- انتخاب بیمار

۹- عدم مطالعه کافی و نداشتن اطلاعات کافی از تازه های پزشکی

۱۰- مجهز نبودن مراکز درمانی به وسایل و لوازم ضروری پزشکی

۱۱- نقص در مدیریت و عدم استفاده صحیح از نیروی انسانی و لوازم وتجهیزات

۱۲- بی توجهی به مسائل فرهنگی ، سنن و آداب قبیله ای و اعتقادی

# قانون مجازات سال ۱۳۹۲

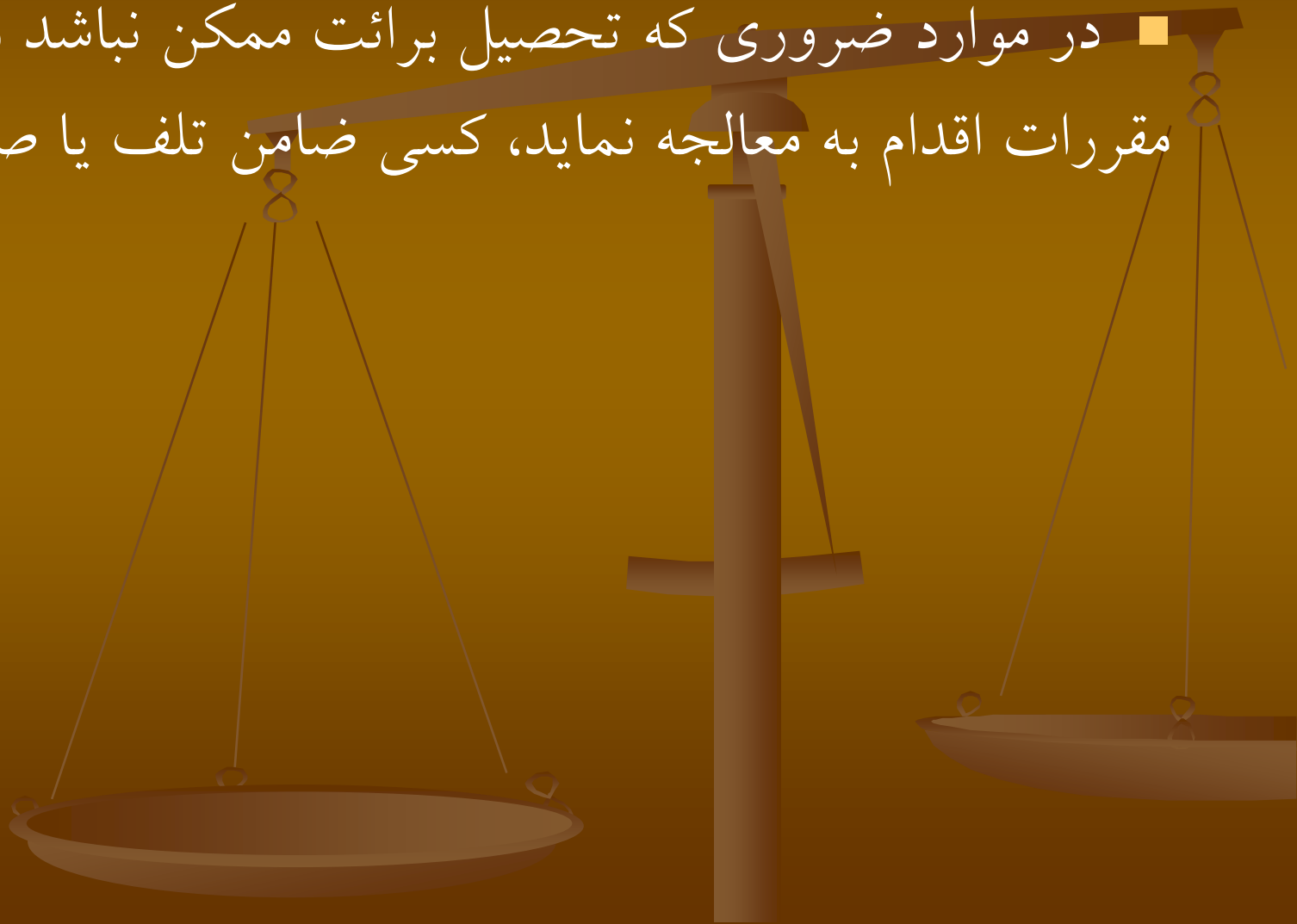
- **ماده ۴۹۵**- هرگاه پزشک در معالجاتی که انجام می‌دهد موجب تلف یا صدمه بدنی گردد، ضامن دیه است مگر آنکه عمل او مطابق مقررات پزشکی و موازین فنی باشد یا این که قبل از معالجه برائت گرفته باشد و مرتکب تقصیری هم نشود و چنانچه أخذ برائت از مریض به‌دلیل نابالغ یا مجنون بودن او، معتبر نباشد و یا تحصیل برائت از او به‌دلیل بیهوشی و مانند آن ممکن نگردد، برائت از ولی مریض تحصیل می‌شود.
- تبصره ۱– در صورت عدم قصور یا تقصیر پزشک در علم و عمل برای وی ضمان وجود ندارد هرچند برائت أخذ نکرده باشد.
- تبصره ۲– ولیّ بیمار اعم از ولی خاص است مانند پدر و ولی عام که مقام رهبری است. در موارد فقدان یا عدم دسترسی به ولی خاص، رئیس قوه قضائیه با استیذان از مقام رهبری و تفویض اختیار به دادستانهای مربوطه به اعطای برائت به طبیب اقدام می‌نماید

## ماده ۴۹۶-

- پزشک در معالجاتی که دستور انجام آن را به مریض یا پرستار و مانند آن صادر می‌نماید، درصورت تلف یا صدمه بدنی ضامن است مگر آنکه مطابق ماده(۴۹۵) این قانون عمل نماید.
- تبصره۱ – در موارد مزبور، هرگاه مریض یا پرستار بداند که دستور اشتباه است و موجب صدمه و تلف می‌شود و با وجود این به دستور عمل کند، پزشک ضامن نیست بلکه صدمه و خسارت مستند به خود مریض یا پرستار است.
- تبصره۲ – در قطع عضو یا جراحات ایجاد شده در معالجات پزشکی طبق ماده(۴۹۵) این قانون عمل می‌شود

# ماده ۴۹۷-

- در موارد ضروری که تحصیل برائت ممکن نباشد و پزشک برای نجات مریض، طبق مقررات اقدام به معالجه نماید، کسی ضامن تلف یا صدمات وارده نیست.



# ـ ماده ۶۴۸ قانون مجازات اسلامی:

- "اطبا، جراحان و ماماها و دارو فروشان (داروسازان) و کلیه کسانی که به مناسبت شغل و یا حرفه ، محرم اسرارمی شوند، هرگاه در غیر از موارد قانونی اسرار مردم را افشا کنند به سه ماه و یک روز تا یک سال حبس و یا به یک میلیون و پانصد هزار تا شش میلیون ریال جزای نقدی محکوم می شوند

- ماده ٤ آیین نامه انتظامی ـ شاغلان حرفه‌های پزشکی و وابسته حق افشای اسرار و نوع بیماری بیمار، مگر
به موجب قانون را ندارند.

# ماده ۱۸ آیین نامه انتظامی

- ـ پزشک معالج مسؤول ادامه درمان بیمار خود در حد توانایی و تخصص به استثنای موارد ضروری است، مگر اینکه بیمار یا بستگان او مایل‌نباشند.
تبصره ـ موارد اورژانس از این ماده مستثنی است.

# ماده ۳ آیین نامه انتظامی

- ـ شاغلان حرفه‌های پزشکی و وابسته باید طبق ***موازین علمی***، شرعی و قانونی و نظامات دولتی صنفی و حرفه‌ای انجام وظیفه کرده و از هرگونه سهل انگاری در انجام وظایف قانونی به پرهیزند.