

# The Role of Risk-Reduction Mastectomy and Oophorectomy

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# Prophylactic Mastectomy

- **Definitions:**
- **In prophylactic surgery, healthy breast or ovarian tissue is removed**
- **Bilateral prophylactic mastectomy (BPM)**
- **Contralateral prophylactic mastectomy (CPM)**
- **Bilateral salpingo-oophorectomy (BSO)**

# Objectives

- Investigate whether PM reduces incidence and mortality in women who have never had breast cancer, and...
- In women who have a history of breast cancer in one breast
- Examine the quality of life, satisfaction, or other assessments of emotional or social function of women who undergo PM
- Examine the usefulness of prophylactic oophorectomy

# Prophylactic Mastectomy

- **Pennisi et al (1989)**
  - **1500 women, aesthetic reasons**
  - **41% family history**
  - **6 (0.4%) subsequent breast cancer**
  - **Faults: low risk, 30% loss to FU, pathology**

# Prophylactic Mastectomy Efficacy

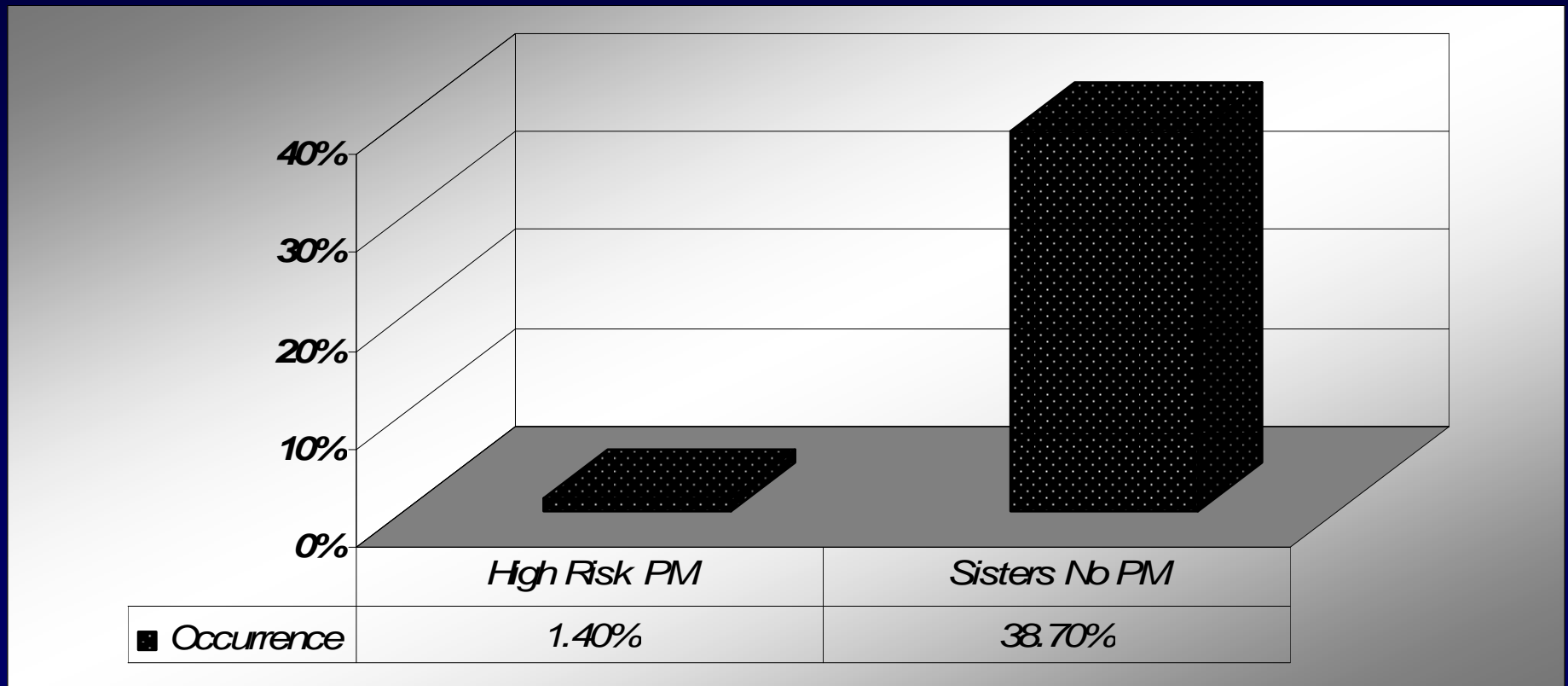
- **Hartmann, et al (1999)**
  - **Mayo clinic, 639 w with family history operated 1960-1993**
  - **425 moderate risk, 214 high risk**
  - **Compared to expected rates + sisters**
  - **Median FU 14y**

# Prophylactic Mastectomy

- Predicted 37.4 events
- Moderate-risk group: observed 4
- Risk reduction: 89.5%
- High-risk group: 3
- Risk reduction: 94%
- Risk reduction for death from BC: 80%

# The Effect of PM on Breast Cancer Development

- Subset analysis of 214 high-risk subjects compared to 403 sisters.



# Prophylactic Mastectomy

- 2001 (NEJM) Dutch study
- 139 BRCA1/2 carriers
- 76 elected prophylactic mastectomy
- 63 careful FU
- Median FU 3y
- 0 cases with prophylactic mastectomy
- 8 cases in controls

# Prophylactic Mastectomy

- **100% risk reduction!!**
- **Note: 4/8 breast cancers were node-positive!**
- **7/8 were ER-negative.**

# Prevention and Observation of Surgical End Points (PROSE) Study

- A large prospective cohort study
- 483 women with high-risk BRCA mutation
  - 105 w with PM vs 384 w no PM
  - -6 years follow-up
- a 90% reduction,
  - Subset with PM and PO had a 95% reduction

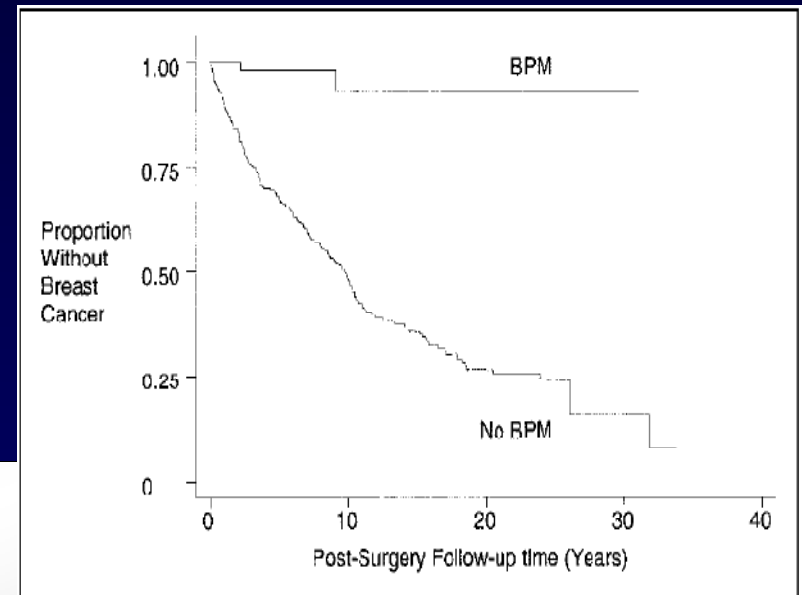
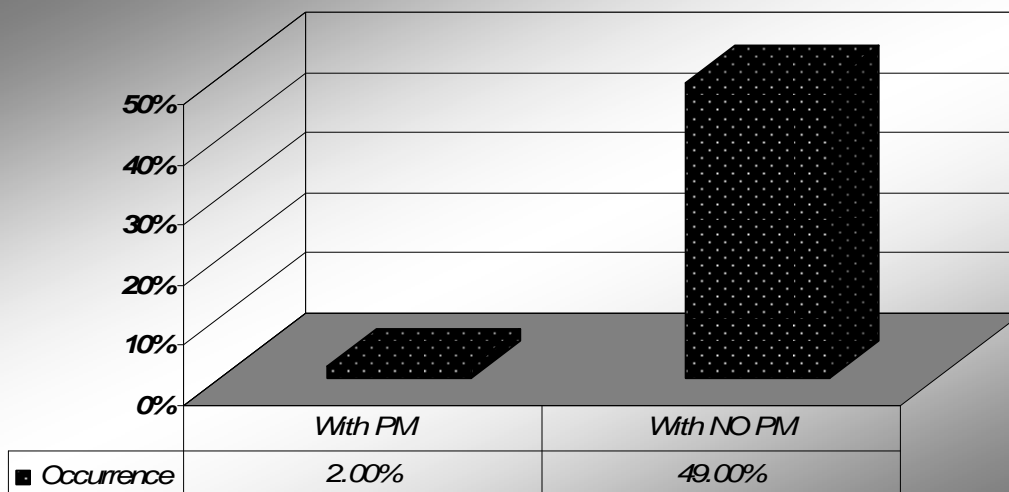


Fig 1. Time to breast cancer diagnosis in female *BRCA1* mutation carriers with and without bilateral prophylactic mastectomy (BPM).



Rebbeck, TR, et al. *J Clin Oncol.* 2004;22(6):1055-1062.

Samuel JC, et al. *Breast Dis.* 2005-2006;23:31-35.

# Association of Risk-Reducing Surgery in *BRCA1* or *BRCA2* Mutation Carriers With Cancer Risk and Mortality

- **22 centers in Europe & USA (PROSE)**
  - **Prospective cohort of 2482 w**
  - **All *BRCA1* or *BRCA2* mutation carriers**
  - **Breast and ovarian cancer risk**
  - **Cancer-specific and overall mortality**

# Association of Risk-Reducing Surgery in *BRCA1* or *BRCA2* Mutation Carriers With Cancer Risk and Mortality

- Median follow-up 3.65y
- No breast cancers in 247 w with BPM
- 7% in w with follow-up only
- Effect on BC mortality not yet determined

# Contralateral Prophylactic Mastectomy

- Risk for cont lat breast ca 0.5-1%/y
- Harris et al (1978) 35% in 16y with positive family history
- BRCA1/2 20-30% in 5y
- Peralta (2000) 64 w vs 182 controls
- 3 incidental breast cancers
- FU 7y

# Prophylactic Contralateral Mastectomy

- CPM group, 0 events; Control, 36
- DFS @ 15y, CPM: 55%; Control: 28%
- Overall survival: CPM 64%; Control: 48% (NS)

# Contralateral Prophylactic Mastectomy

- **McDonnell et al (2001) (Mayo Clinic)**
  - **745 w (388 pre- & 357 post-menopausal) who had CPM**
  - **Breast cancer + fam history**
  - **FU 10y 8 cancers**
  - **6 in premen (expected 106, reduction 94%)**
  - **2 in post (expected 50, reduction 96%)**

# Contralateral Prophylactic Mastectomy

- **Surveillance, Epidemiology & End Results (SEER) database:**
  - **107,106 w underwent mastectomy for cancer between 1998 and 2003**
  - **8902 also had CPM**
  - **Univariate analysis: CPM pts had improved disease-free survival**
  - **Especially in young, stage 1-2 women**

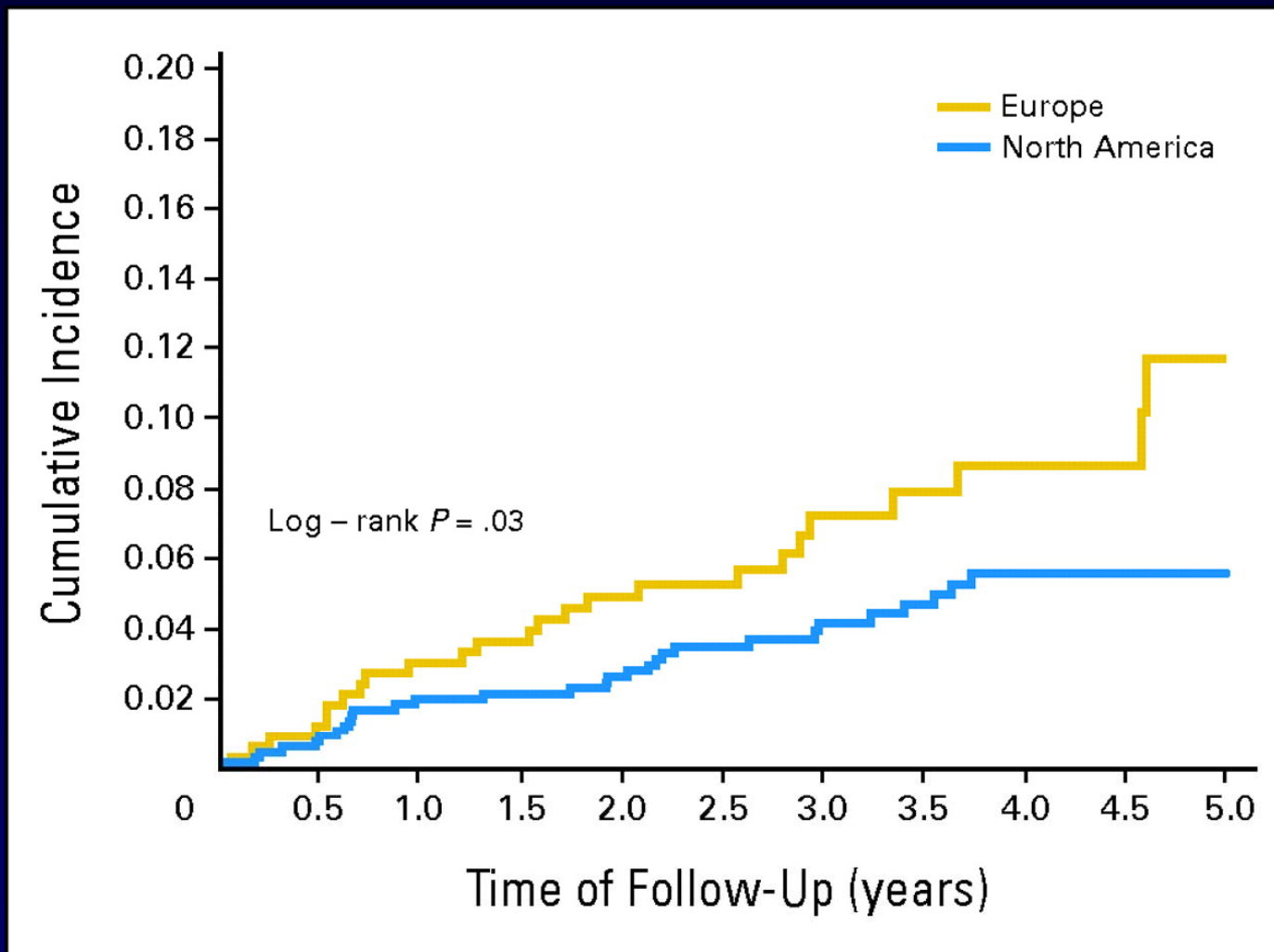
# Contralateral Prophylactic Mastectomy

- 385 pts from Mayo clinic, stage 1-2
  - Compared to 385 matched pts
  - Median follow-up 17.3y
  - CBC 2 vs 31 (95% risk reduction)
  - Death 128 vs 162
  - 10y survival 83% and 74%

# Contralateral Prophylactic Mastectomy

- The hereditary breast cancer clinical study group
  - 927 BRCA+ w with unilateral cancer
  - 253 (27.3%) underwent CPM
  - Norway 0%; USA 49.3%
  - USA CPM women were younger 39 vs 43, and had more BSO

# Cumulative Incidence of Contralateral Breast Cancer



# Increase Use of CPM

- Breast cancer database – 1391 pts
- 2000 - 2008
- CPM increased from 0% to 20%
- Factors associated with CPM: younger age, significant family history, genetic testing, BRCA, MRI
- Tumor factors: LN-positive, triple-negative

# Does Contralateral Prophylactic Mastectomy (CPM) Improve Survival?

- The risk of contralateral disease vs risk of mortality from primary metastasis?
  - Babiera, 1997: CPM 5-year survival 89% vs control 90% survival
  - Overall survival CPM 64%, No CPM 48%.  $P = 0.28$
  - CPM does not translate into survival advantage
- The risk of systemic disease far exceeds the risk of new contralateral breast cancer

# Prophylactic Mastectomy: Utilization

- 216 w (about ½ BRCA1/2 carriers) were offered prophylactic mastectomy
- 1m, 36% considered
- 1y 3% operated
- 14 (9%) eventually operated

# Prophylactic Mastectomy

- Dutch study (Lancet, 2000), women who came for genetic counseling<sup>1</sup>
  - 51% opted for prophylactic mastectomy
- Sloan-Kettering (2002), 194w BRCA+<sup>2</sup>
  - 20 (8.6%) had PM before counseling
  - 29 (14.9%) after
- Evans et al (2001) Manchester; 11% of high-risk women agreed to surgery<sup>3</sup>

# Prophylactic Mastectomy: Complications

- **Mayo Clinic (2000)**
  - **592 w, post-PM + implants**
  - **52% reoperation at 14y FU**
  - **502 w post contralateral PM**
  - **38% reoperations**
  - **Indications: complications 10%**
  - **Implant-related (rupture, leakage, capsula) 50% - 60%**
  - **Node excision 10%**
  - **Aesthetic 15-23%**

# Prophylactic Mastectomy: Psychosocial Issues

- **Frost (2000) long-term satisfaction 572 w**
  - **74% decreased concern for breast cancer**
  - **Majority: no change in stability, stress, self-esteem, sexual function, femininity**
  - **36% reduced satisfaction with appearance**
  - **Note: doctors' advice!**

# Prophylactic Mastectomy: Psychosocial Issues

- **Karolinska Institute data:**
  - **90 women with BPM**
  - **Decreased anxiety over time**
  - **No difference in depression, health**
  - **48% less sexually attractive, dissatisfaction with scars, less sexual pleasure at 1 year**

# Prophylactic Oophorectomy

- Several cohort studies provide evidence that PO reduces the risk of breast ca
- Meta-analysis:
  - 10 studies, all pts BRCA +
  - Risk reduction for breast cancer 50%
  - BRCA1=BRCA2
  - Risk reduction for ovarian cancer 80%

# Association of Risk-Reducing Surgery in *BRCA1* or *BRCA2* Mutation Carriers With Cancer Risk and Mortality

- 22 centers in Europe & USA (PROSE)
  - Prospective cohort of 2482 w
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# PROSE (cont)

- Reduction of ovarian cancer 1% vs 6%
- For breast cancer: BRCA1: 14% vs 20% (37%)
- BRCA2: 7% vs 23% (64%)
- Lower all risk mortality (3% vs 10%)
- Lower breast ca-specific m (2% vs 6%)
- Ovarian ca-specific m (0.4% vs 3%)
- Advantage if performed before age 50

# Primary Prevention: Prophylactic Oophorectomy

- **Several weaknesses**
- **No RCTs**
- **Not sufficient data regarding disease-specific survival/mortality**
- **Also, PO results in a decreased risk of ovarian ca, but an increased risk of endometrial ca**
- **Effect on fertility and quality of life**
  - **Induces early menopause and associated side effects (vaginal dryness, dyspareunia)**
- **Women considering PO encouraged to complete childbearing at early age**

# Limitations of Current Studies

- **No RCTs**
  - **Difficult since women would be reluctant to randomize regarding their decision**
  - **Justifying randomization of women to control group is problematic**
  - **Long follow-up period**
  - **All participants in the studies are self-selected**

Samuel JC, *Breast Disease*, 2005, 2006.

Lostumbo L, et al. *Cochrane Database Syst Rev*. 2004;18(4):CD002748.

# Limitations of Current studies

- **BRCA1 vs BRCA2**
- **Variability in cancer risk 50% - 80%**
- **Prevalence of cancer in the pts' families**
- **Other risk factors: exercise, diet, etc**
- **Stratification for BSO, menopause, HRT**
- **Disease vs mortality**

Samuel JC, *Breast Disease*, 2005, 2006.

Lostumbo L, et al. *Cochrane Database Syst Rev*. 2004;18(4):CD002748.

# **Risk-Reduction Surgery Conclusions**

- **Many women overestimate their risk**
- **Good prognosis for early breast cancer**
- **Data is sparse, but it seems that risk-reduction rates are very high**
- **The higher the risk, the younger the women, operation is more effective**
- **Consider alternatives**

# **Risk-Reduction Surgery Conclusions**

- **Because of the invasive & irreversible nature of prophylactic surgery, knowledge of its efficacy and the extent of risk-reduction is crucial**
- **The procedures do not completely eradicate cancer risk because, often, not all tissue at risk is removed**

# Thank You, Enjoy Tel-Aviv

