TINTERRI CORRADO BREAST UNIT MILAN
BRCA MUTATION PATIENTS: WHAT SURGERY?

NEGRAR (VERONA) 13.10.2015

CORRADO TINTERRI
BREAST UNIT
HUMANITAS CANCER CENTER
ROZZANO-MILAN
Breast cancer: genetic testing soars after Angelina Jolie's double mastectomy

After Jolie, women less shy to investigate mastectomies
Great media impact that sometimes dominates the scientific aspects
The Jolie effect: Number of women asking about mastectomies quadruples since actress revealed she had her breasts removed to reduce cancer risk

By SOPHIE BORKHURST

Published: 11:45 IST, 31 December 2013 | Updated: 13:03 IST, 31 December 2013

Breast cancer charities have reported a four-fold surge in women enquiring about having their breasts removed since Angelina Jolie announced she had the operation to lessen her risk of developing the disease.

Figures from Cancer Research UK show the numbers of calls to its helpline have increased four-fold while there has been a similar rise in visits to its website.

The actress revealed she'd had a double mastectomy in May after learning she carried a faulty gene that gave her an 87 per cent chance of developing breast cancer.

Miss Jolie, 37, said she'd made the decision for the sake of her eight children having witnessed her own mother Marcheline Bertrand lose a
The Panel recommend that women with breast cancer who are less than or equal 35 yrs or premenopausal or CARRIER of a KNOW BRCA1\2 mutation consider additional risk reduction strategy. Following appropriate risk assessment and counselling, this process should involves multidisciplinary consultation prior the surgery.
Recommendations for the management of early breast cancer in women with an identified BRCA1 or BRCA2 gene mutation or at high risk of a gene mutation

FEBRUARY 2014 | Incorporates published evidence to August 2013

A CLINICAL PRACTICE GUIDELINE DEVELOPED BY CANCER AUSTRALIA

RECOMMENDATIONS – SURGERY
Surgical management on the ipsilateral side for women diagnosed with breast cancer with a BRCA1/2 mutation

Offer a choice of either breast conserving treatment (breast conserving surgery and radiotherapy) or mastectomy to women diagnosed with breast cancer with a BRCA1/2 mutation as both are effective in terms of survival.

- If women diagnosed with breast cancer with a BRCA1/2 mutation are considering a contralateral risk-reducing mastectomy (at the time of the cancer diagnosis or in the future) inform them that therapeutic ipsilateral mastectomy may be preferable to breast conserving treatment.

- Inform women diagnosed with breast cancer with a BRCA1/2 mutation that there is an increased risk of ipsilateral breast cancer after breast conserving treatment compared to mastectomy, but this is reduced by adjuvant chemotherapy. *(see practice points B and F).*
STATEMENTS OF EVIDENCE
SURGICAL RISK-REDUCING STRATEGIES

CONTRALATERAL RISK-REDUCING MASTECTOMY

Survival outcomes

It is unclear whether contralateral risk-reducing mastectomy (compared to no contralateral risk-reducing mastectomy) improves overall survival or breast cancer-specific survival in women with breast cancer and a BRCA1/2 mutation.

Contralateral breast cancer

Contralateral risk-reducing mastectomy (compared to no contralateral risk-reducing mastectomy) substantially decreases (by more than 90%) the risk of contralateral breast cancer, particularly in younger women (less than 50 years) with breast cancer with a BRCA1/2 mutation.
The survival advantage remained after matching for oophorectomy, gene, grade and stage: HR 0.37 (0.17–0.80, p = 0.008) CRRM appeared to act independently of RRBSO.

CRRM appears to confer a survival advantage. If this finding is confirmed in a larger series it should form part of the counselling procedure at diagnosis of the primary tumour. The indication for CRRM in women who have had RRBSO also requires further research.
We examined the efficacy of CRRM on overall survival in mutation carriers with a history of PBC. From a Dutch multicentre cohort, we selected 583 BRCA-associated PBC patients, being diagnosed between 1980 and 2011.

Survival benefit was especially seen in young PBC patients (<40 years), in patients having a PBC with differentiation grade 1/2 and/or no triple-negative phenotype, and in patients not treated with adjuvant chemotherapy.
...and those who harbor a deleterious mutation in BRCA1 or BRCA2 are frequently considered to be at highest risk of local failure, leading to speculation that more-aggressive surgical treatment is warranted in these patients.

For those at inherited risk, a more-aggressive surgical approach may be preferable, however; patient age, ER status, stage of the index lesion, and individual patient preferences should all be considered in the surgical decision-making process.
BREAST PROPHYLACTIC SURGERY

- Most effective if implemented before the age of 40
- Functional and aesthetic irreversible changes

Inevitable conditioning of the psycho-physical aspects of the women with undeniable implications of the life’s relationship
Literature more and more consistent,

**BUT**

- Fragmented and uneven casistics
- No randomized trials
- Small number of patients
- Limited follow-up
- Different surgery
- Different indications (≠ USA/Europa)
- Different reimbursement (USA insurance – Italia/EuropaDRG)
Limitations of Current Studies

- No RCTs
- Difficult since women be reluctant to randomize regarding their decision
- Justifying randomization of women to control group is problematic.
- Long follow up period
- Difficulty blinding participants and investigators
Main points: First, a risky condition is not a disease and prevention does not improve well-being. The benefits are only statistical and make sense at the population level. Secondly, the cause of the risk is a genetic factor and some might argue about genetic ‘exceptionalism’. Thirdly, there is no organ as connected to femininity, sensuality, sexuality, adulthood and motherhood as the breast. Lastly, making tough and complex choices requires assistance from ethics.
Hereditary breast cancer: clinical features and risk reduction strategies

A. Paradiso¹ & S. Formenti²

¹Scientific Direction, National Cancer Center, Istituto Tumori ‘Giovanni Paolo II’, Bari, Italy; ²Department of Radiation Oncology and NYU Cancer Institute, New York University School of Medicine, New York, USA

Prophylactic bilateral mastectomy has resulted in up to 97% risk reduction of CBC [7, 26, 27]. Interestingly, the pattern of utilization of bilateral mastectomy differs widely between countries, reflecting providers’ biases in interpreting the evidence, communicating it and offering treatment options. It also reflects the diversity of the value systems affecting medical decision and health care delivery in differing countries [28].

In conclusion, the management of BRCA mutation carriers is evolving: it reflects the available evidence as well as the bias of different ethical value systems and structural characteristics of the different health care systems operating worldwide.
RISK REDUCING SURGERY

- WHY?
- FOR WHOM?
- WHAT SURGERY?
- HOW?
- TIMING?
- WHICH UPTAKE?
- WHERE?
Efficacy of Bilateral Prophylactic Mastectomy in Women with a Family History of Breast Cancer


The New England Journal of Medicine

Volume 339

Number 3

March 14, 1999

ABSTRACT

Background: Options for women at high risk for breast cancer include surveillance, chemoprevention, and prophylactic mastectomy. The data on the outcomes for these classes and prophylactic mastectomy are limited.

Methods: We conducted a retrospective study of all women with a family history of breast cancer who underwent bilateral prophylactic mastectomy at the Mayo Clinic between 1960 and 1993. The women were divided into two groups—high-risk and moderate-risk—on the basis of family history. A control study of the incidence of breast cancer and the published data were used to predict the number of cases that were expected to occur in each group.

Results: We identified 172 women with a family history of breast cancer who underwent bilateral prophylactic mastectomy. Of these, 114 were high-risk and 58 were moderate-risk. Of the high-risk group, 2.5% developed breast cancer, compared with 7% of the moderate-risk group. In the control group, 11% of the high-risk group and 30% of the moderate-risk group were expected to develop breast cancer. The difference in the incidence of breast cancer between the high-risk and moderate-risk groups was statistically significant (p < 0.001).

Conclusion: Prophylactic bilateral mastectomy, used as a primary or secondary intervention, is an option for the prevention of breast cancer. This study provides evidence that prophylactic mastectomy is effective in reducing the incidence of breast cancer in women with a family history of breast cancer.

Breast Cancer After Bilateral Prophylactic Mastectomy

E. Neale K. Kershaw, M.D., Ph.D., and L. Jan Van Der Waal, M.D., Ph.D.

The New England Journal of Medicine

Volume 350

Number 16

July 19, 2004

ABSTRACT

Background: Women with a BRCA1 or BRCA2 mutation have an increased risk of breast and ovarian cancer and generally choose to undergo prophylactic bilateral mastectomy to reduce their risk of breast cancer. We evaluated the efficacy of this procedure.

Methods: We conducted a prospective study of 108 women with a pathogenic BRCA1 or BRCA2 mutation who were enrolled in a breast cancer surveillance program at the Rotterdam Family Cancer Clinic. All of the women underwent bilateral mammography and ultrasonography at baseline and annually thereafter. The results were compared with the findings of the surveillance program.

Results: The incidence of breast cancer was 6% in the 5 years before surgery and 3% in the 5 years after surgery. The difference was statistically significant (p = 0.008). The mammographic and ultrasonographic findings were similar in the two groups. The median number of breast lumps was 1 in the 5 years before surgery and 0 in the 5 years after surgery. The difference was statistically significant (p = 0.001).

Conclusion: Prophylactic bilateral mastectomy is effective in reducing the incidence of breast cancer in women with a BRCA1 or BRCA2 mutation.
Conclusions: In healthy BRCA1/2 mutation carriers, BRRM when compared with surveillance reduces BC risk substantially, **while longer follow-up is warranted to confirm survival benefits.**
A total of 691 female BRCA1/2 mutation carriers were identified in the Genetic Medicine database from BRCA families ascertained between February 1980 and December 2011. This cohort included 346 BRCA1 carriers and 345 BRCA2 carriers.
Risk Reducing Surgery Vs Observation

![Graph showing survival probability over time from ascertainment to death for No Surgery and Any Surgery groups. The graph indicates a decrease in survival probability with time.]
Risk Reducing Surgery by Age
Risk Reducing Surgery Vs Intensively Screened
Their analysis included four prospective studies and estimated a 93% reduction in breast cancer risk.

The fact that only 4 of 627 women undergoing risk-reducing mastectomy had a diagnosis of breast cancer could be encouraging, but the median follow-up period for all the included studies was only about 4 years.
they found that in patients who underwent BRRM plus RRSO the benefit was confirmed (HR 0.11; p = 0.03) but was slightly lower than the one recorded in patients receiving BRRM without RRSO (HR 0.06; p = 0.005).

it was not possible to delineate a correct standardization by age

they only analyzed studies of a prospective nature because randomized studies have not been published in this setting, probably because they are ethically unacceptable.
clinical practice guidelines

**BRCA in breast cancer: ESMO Clinical Practice Guidelines**

J. Balmaña¹, O. Díez²,³, I. T. Rubio⁴ & F. Cardoso⁵,⁶

On behalf of the ESMO Guidelines Working Group*

¹Medical Oncology Department, Breast Cancer Center; ²Oncogenetics Laboratory, University Hospital Vall d’Hebron, Barcelona, Spain; ³Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; ⁴Breast Cancer Surgical Unit, Breast Cancer Center, University Hospital Vall d’Hebron, Barcelona, Spain; ⁵European School of Oncology, Milan, Italy; ⁶Breast Cancer Unit, Champelmsud Clinical Center, Liege, Belgium.

... BUT....

**prophylactic bilateral mastectomy**

This is the most effective strategy available for risk reduction of breast cancer in mutation carriers [III, B]. Studies have shown a risk reduction of at least 90% with PBM. In two prospective studies published to date, no breast cancers were diagnosed in the risk-reducing mastectomy group compared with 7–13% breast cancers in women under surveillance with a mean follow-up of 3 years. However, survival benefits have not been demonstrated with risk reduction breast surgery.
Recent reports suggest that as many as 80% of women submitted to prophylactic mastectomy resulting from limited risk assessment and counseling are not BRCA carriers or carry an inordinate risk for these mutations.
Position Statement on Prophylactic Mastectomy

Potential Indications for Bilateral Prophylactic Mastectomies
(In Patients without a Cancer Diagnosis)

1. A known mutation of BRCA 1 or BRCA2 or other strongly predisposing breast cancer susceptibility genes.
2. A family history of breast cancer in multiple first-degree relatives and/or multiple successive generations of family members with breast and/or ovarian cancer (family cancer syndrome). Additionally, a family history of multiple family members with bilateral and/or pre-menopausal and/or male breast cancer may be associated with a familial breast cancer syndrome. Genetic counseling should be strongly considered, although prophylactic surgery is appropriate in women with a family history consistent with genetic predisposition and no demonstrable genetic mutation.
3. High-risk histology: Atypical ductal or lobular hyperplasia, or lobular carcinoma in situ confirmed on biopsy. These changes are especially significant if present in a patient with a strong family history of breast cancer.
The NCCN Breast Cancer Risk Reduction Panel supports the use of RRM for carefully selected women at high risk for breast cancer who desire this intervention (e.g., women with a BRCA1/2, TP53, PTEN, CDH1, or STK11 mutation or, possibly, women with a history of LCIS). Although the consensus of the NCCN Breast Cancer Risk Reduction Panel is that consideration of RRM is an option for a woman with LCIS without additional risk factors, it is not a recommended approach for most of these women. There are no data regarding RRM in women with prior mantle radiation exposure. The value of RRM in women with deleterious mutations in other genes associated with a high risk for breast cancer (based on large epidemiologic studies) in the absence of a compelling family history of breast cancer is unknown.
«Il network che promuove il rispetto dei requisiti europei, la multidisciplinarietà e il controllo di qualità nella cura del tumore della mammella»

www.senonetwork.it
WHAT RISK REDUCING SURGERY?
WHAT SURGERY?

- TOTAL MASTECTOMY (without reconstruction !!!!)
Nipple-Sparing Mastectomy

IT’S REALLY SAFETY?
NIPPLE SPARING MASTECTOMY

POSSIBLE LOCATION OF GLANDULAR RESIDUAL

- “BREAST TAIL” AND SUPERIOR AREA
- RETROAREOLAR AND BELOW THE NIPPLE
- INFRAMAMMARY FOLD
Conclusions. The probability of nipple involvement by premalignant or malignant lesions in the NAC of BRCA mutation carriers is low at time of prophylactic mastectomy, but higher (10%) in women undergoing therapeutic mastectomy. NSM may be appropriate and oncologically safe for selected women with BRCA mutations.
WHAT SURGERY?

Nipple-Sparing Mastectomy for Breast Cancer and Risk-Reducing Surgery: The Memorial Sloan-Kettering Cancer Center Experience

Paulo de Alcantara Filho, MD¹, Deborah Capko, MD¹, John Mitchel Barry, MD¹, Monica Morrow, MD¹, Andrea Pusic, MD², and Virgilio S. Sacchini, MD¹

¹Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY; ²Plastic and Reconstruction Service, Memorial Sloan-Kettering Cancer Center, New York, NY

ABSTRACT
Background. Nipple-sparing mastectomy (NSM) has been gathering increased recognition as an alternative to more traditional mastectomy approaches. Initially, questions concerning its oncologic safety limited the use of NSM. Nevertheless, mounting evidence supporting the practice of NSM for both prophylactic and oncologic purposes is leading to its more widespread use and broadened indications.
Methods. Using a prospectively maintained database, we reviewed our experience of 353 NSM procedures performed from 2004 to 2018.

Conclusions. The trends demonstrate the increasing acceptance of NSM as a prophylactic procedure as well as for therapeutic purposes. Although NSM is not standard, our experience supports the selective use of NSM in both prophylactic and malignant settings.

V. S. Sacchini, MD
e-mail: sacchini@mskcc.org

The surgical management of breast cancer has evolved over the past several decades from the radical mastectomy...
There have been no randomized trials comparing the effectiveness of different surgical techniques.
The possibility of finding an occult synchronous invasive tumor during a prophylactic mastectomy is quite low at ~5%.
At this time, there is insufficient evidence to recommend routine sentinel node biopsy for patients undergoing prophylactic mastectomy.
Little is known about how these individuals in fact make these decisions - particularly, what stresses they face in making these decisions, and what roles, if any, health care providers and others may play.

These issues are important since many women who might benefit from prophylactic surgery do not undergo it.
Review Article

Clinical Considerations of BRCA1- and BRCA2-Mutation Carriers: A Review

O. Bougie and J. I. Weberpals

1 The Department of Obstetrics, Gynaecology, and Newborn Care, The Ottawa Hospital, Ottawa, ON, Canada K1H 8L6
2 Centre for Cancer Therapeutics, Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, ON, Canada K1H 8L6
3 The Division of Gynecologic Oncology, The Ottawa Hospital, Ottawa, ON, Canada K1H 8L6

Correspondence should be addressed to J.I. Weberpals, jweberpals@ottawahospital.on.ca

Received 2 April 2011; Accepted 16 June 2011

The most effective single intervention for BRCA1-mutation carriers was a BSO at age 40, yielding a 15% absolute survival gain. For BRCA2-mutation carriers, the most effective single intervention was a prophylactic mastectomy, yielding a 7% survival gain if performed at age 40. The combination of prophylactic mastectomy and BSO at the age of 40 improved survival more than any single intervention, yielding a 24% and 11% survival gain for BRCA1- and BRCA2-mutation carriers, respectively.

When choosing a surveillance option, patients must be cautioned that premalignant and malignant changes can occur in spite of normal radiological investigations. When
Bilateral risk-reducing mastectomy

- Bilateral risk-reducing mastectomy is appropriate only for a small proportion of women who are from high-risk families and should be managed by a multidisciplinary team.
REQUIREMENTS FOR MANAGEMENT OF BRCA MUTATED WOMEN

- Multidisciplinary Dedicated Team
- Time!
Breast Unit Humanitas: flow chart high risk patients

Breast Surgery

Genetic Counselling

Breast Clinic Review

Psychological Assessment

MDT meeting

Accepted for RRM

Declined breast reconstruction

Combined Breast Surgery and Reconstruction Clinic

RRM by breast surgeon

Joint operation: RRM by breast surgeon; Immediate reconstruction by reconstructive surgeon
Breast Unit Humanitas Cancer Center: 2009-2014

Nipple Sparing Mastectomy: total number 273

- 90% of cases were therapeutic mastectomy
- 10% of cases were prophylactic mastectomy
Breast Unit Humanitas Cancer Center: 2009-2014

Mutation BRCA1/2: 17 patients

- Bilateral Prophylactic Mastectomy (9 patients)
- Monolateral Prophylactic Mastectomy, controlateral Breast cancer (8 patients)

The other 10 patients had monolateral prophylactic mastectomy without genetic test or with negative genetic test, but all of them had history of breast cancer.
Malattie ad andamento degenerativo di particolare rilevanza sociale,
con specifico riguardo al tumore della mammella, alle malattie reumatiche croniche ed alla sindrome HIV. Documento conclusivo
con cd di testi allegato
Codice sito: 4.10/2014/71

Al Ministero della Salute
- Gabinetto
gab@postacert.sanita.it
Ufficio legislativo
segr.legislativo@sanita.it
- Direzione generale della programmazione sanitaria
dgprog@postacert.sanita.it

Al Ministero dell’Economia e delle Finanze
- Gabinetto
configabmef@pec.mef.gov.it
- Dipartimento della Ragioneria Generale dello Stato - Coordinamento delle attività dell’Ufficio del Ragioniere generale dello Stato
rgs.ragioneregenerale.coordinamento@pec.mef.gov.it

Al Presidente della Conferenza delle Regioni e delle Province autonome
c/o CINSEDO
conferenza@pec.regioni.it

All’Assessore della Regione Veneto
Coordinatore Commissione salute
protoccolo.generale@pec.regione.veneto.it
statoregioni@pecveneto.it

Oggetto: Intesa sul documento recante “Linee di indirizzo sulle modalità organizzative ed assistenziali della rete dei centri di senologia”

Si trasmette, per il seguito di competenza, l’atto dell’intesa sancita dalla Conferenza Stato-Regioni, nella seduta del 18 dicembre 2014.
...must provide specific training and pathway for the prevention and diagnosis for women with genetic risk or high risk family.

...must provide specific clinic for risk-reduction options with all the specialists (onco-genetist, breast and plastic surgeon, psycho-oncologist, nursing, gynecologist, radiologist)
Breast Cancer Genes Found
• BRCA1 (for Breast Cancer gene 1) was described in 1990 on chromosome 17, isolated in 1994
• BRCA2 was isolated on chromosome 13 in late 1994
• BRCA3?

In summary, NSM is one risk-management option for BRCA gene mutation carriers but it should only be provided within a Breast Unit. Complications, reoperation, and potentially negative impacts on psychosocial and physical functioning require careful preoperative counseling and individualized, patient-driven decisions.

If life gives you lemons, a simple operation can give you melons.