Surgical Prevention

10

Paolo Veronesi and Nickolas Peradze

The surgical strategies available today for breast cancer prevention are prophylactic bilateral or unilateral mastectomy and prophylactic bilateral salpingo-oophorectomy.

Mastectomy is intended to remove breast tissue and therefore to remove the very substance of cancer growth, while oophorectomy eliminates the major part of the body's source of estrogen, with the additional benefit of decreasing ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers.

Overall mastectomy rates have increased over the past decades [1–3]. In part, this is due to the introduction of new imaging modalities capable of detecting additional breast lesions, which in turn require more extensive surgery. It is also due to the growing patient choice for preventive surgery as a reflection of the increased awareness of genetic breast cancer, increased genetic testing, and increased knowledge of improvements in mastectomy and reconstruction techniques, together with anxiety and overestimation of the risk of developing breast cancer.

Several studies have demonstrated that the risk as perceived by patients of developing breast cancer is much higher than the objective risk, given the fact that those patients who are the most well informed and involved in decision-making are more likely to choose mastectomy [4, 5].

Mastectomy, especially bilateral, is an extended and elective surgery and may have unfavorable effects in terms of complications and associated costs as well as in terms of body image and sexual function. Therefore a better understanding of its indications, use, and outcomes is crucial to improve cancer care [6–9].

In general, prophylactic mastectomy may occur in two populations of patients: those already affected by unilateral breast cancer who undergo contralateral mastectomy for the prevention of cancer development in the contralateral breast and those without breast cancer, but at high risk, and therefore undergo bilateral risk-reducing mastectomy.

In 2007 Giuliano et al. stated the potential indications for prophylactic mastectomies. In this statement, the indications for prophylactic mastectomies include BRCA mutations or other susceptibility genes, strong family history without genetic mutation, histologic risk factors, difficult surveillance, and reconstructive issues (symmetry/balance) [10].

10.1 Contralateral Prophylactic Mastectomy

Various studies have evaluated trends, implications, and outcomes of contralateral prophylactic mastectomy (CPM).

The Surveillance, Epidemiology, and End Results Program (SEER) from 1998 to 2003 in the USA confirmed increased rates of CPM by 150% [11]. Similar trends were observed in other studies [12–15].

The categories of patient who may benefit from CPM may be varying.

Despite limited evidence in survival improvement after CPM published in 2010 in a large Cochrane analysis [16], several studies which were subsequently published showed minimal benefit in overall survival [17–19].

Yao et al. examined the effect of CPM on survival on 219,983 mastectomy patients using the National Cancer Data Base (the largest study so far to examine survival with CPM). Adjusted hazard ratio (HR) was 0.88 (95% CI 0.83–0.93; $p < 0.001$), and an absolute 5-year benefit of 2% was observed. Differential effect of CPM by stage and age was observed with HR = 0.88 (95% CI 0.82–0.94; $p < 0.001$) in women younger than 70 with stage I/II, and HR = 0.95 (95% CI 0.88–1.04; $p = 0.28$) in women with stage III or older than age 69 with absolute 5-year benefit of 1.3%. This improvement in survival could be attributed to the category of high-risk patients (family history and/or BRCA mutation carriers), who have higher risks of contralateral cancers and therefore may benefit from a CPM. Finally, the authors were unable to establish a cause-and-effect relationship between CPM

P. Veronesi (✉)
Division of Breast Surgery, European Institute of Oncology, University of Milan, 20141 Milan, Italy
e-mail: paolo.veronesi@ieo.it

N. Peradze
Division of Breast Surgery, European Institute of Oncology, 20141 Milan, Italy

U. Veronesi et al. (eds.), *Breast Cancer*, DOI 10.1007/978-3-319-48848-6_10

and survival, due to the lack of data regarding family history, BRCA carrier status, hormonal receptor, and HER2 status [20].

In large meta-analysis performed by Fayanju et al., the authors concluded that patients without known high risk (familial/genetic) should not be advised to undergo CPM [21].

In the recent study conducted by Basu et al. [22], the authors developed a series of guidelines to aid clinicians dealing with requests for, and management of, CPM. These included several steps for the process of preoperative assessment and counseling before CPM can be given and may be summarized as follows:

- Taking a history
- Calculating the risk of contralateral breast cancer
- Cooling-off period whenever possible
- Multidisciplinary team (MDT) discussion
- Patient consent

Therefore breast cancer patients should be provided with precise and accurate information on the risk of contralateral breast cancer and on the risks and benefits of CPM.

10.2 Bilateral Prophylactic Mastectomy

As outlined earlier, indications for bilateral prophylactic mastectomies include BRCA1/BRCA2 mutation or other susceptibility genes, strong family history without genetic mutations, and histologic risk factors.

Large prospective analyses report the average cumulative risks for breast cancer by the age of 70 years for BRCA1 carriers of 60% (95% confidence interval [CI] = 44–75%) and 83% (95% CI = 69–94%) for contralateral breast cancer. For BRCA2 carriers, the corresponding risks are 55% (95% CI = 41–70%) and 62% (95% CI = 44–79.5%) for contralateral breast cancer [23, 24].

Retrospective analyses of the results of the study conducted by Hartmann et al. demonstrated risk reduction of about 90% for BRCA1 and BRCA2 mutation carriers after bilateral prophylactic mastectomy (BPM) [25, 26].

In the study conducted by Heemskerk-Gerritsen et al., authors evaluated breast cancer incidence, all-cause mortality, and breast cancer specific mortality in healthy BRCA1 and BRCA2 mutation carriers undergoing bilateral prophylactic mastectomy. These were compared with a surveillance group. No incidence of breast cancer cases was observed during 1379 person-years of observation after BPM. 10-year overall survival was 99% for the BRRM and 96% for the surveillance groups, respectively. The authors concluded that BPM substantially reduces breast cancer occurrence in healthy BRCA1/BRCA2 mutation carriers. However, longer follow-up and larger sample size are needed to confirm statistical significance [27].

Interesting results were presented by the study of Skytte et al., which included 307 women with a pathogenic BRCA1 or BRCA2 mutation, of whom 96 underwent bilateral risk-reducing mastectomy. None of the study participants had a previous history of breast or ovarian cancer or had undergone risk-reducing bilateral salpingo-oophorectomy prior to the time of BRCA testing. The annual incidence of post-mastectomy breast cancer was 0.8% compared with 1.7% in the non-operated group [28].

A more recent meta-analysis performed by De Felice et al. reported risk reduction of developing breast cancer in BRCA1 and BRCA2 mutation carriers after risk-reduction mastectomy by 93% [29].

The risk of breast cancer after mastectomy could be presumably explained by a tumor developing in left-over breast tissue. However this hypothesis is debatable. In fact in the study of Skytte et al., women who developed breast cancer after mastectomy had undergone a simple mastectomy including removal of the nipple–areola complex.

Today the most popular prophylactic mastectomy technique is the so-called conservative mastectomy or nipple-sparing mastectomy/skin-sparing mastectomy or subcutaneous mastectomy with immediate reconstruction. This surgical technique has been shown to be feasible and safe, with outstanding cosmetic results, and allows preservation of the woman's body image [30–33].

This was also supported by a recent review by van Verschuer et al. in which the authors stated that the incidence of primary breast cancers after prophylactic mastectomy is very low after total mastectomy as well as after conservative mastectomy [34]. It is suggested to surgeons that they minimize risk by paying particular attention to ensure that all glandular tissue is dissected, especially in the axillary tail, chest wall, and nipple–areola complex.

Recently Toesca et al. reported the first experience of robotic prophylactic nipple-sparing mastectomy. This seemed to improve outcomes of mastectomy from a cosmetic and patient satisfaction point of view [35].

NCCN guidelines support the use of risk-reducing mastectomies for selected patients at high risk who desire this intervention. Nevertheless histologic factors such as ADH, LCIS are associated with an increased risk of breast cancer, surgical risk reduction is not recommended in most of these patients [36].

There is a lack of data concerning the utility of sentinel lymph node biopsy (SLNB) during risk-reducing surgery. It is recommended that MRI assessment be performed prior to risk-reducing surgery as some patients may be at risk of occult breast cancer, having strong family history or mammographic density, and the use of SLNB should be decided on a case-by-case basis [37].

10.3 Bilateral Prophylactic Salpingo-Oophorectomy

Several studies have reported a breast cancer risk reduction of approximately 50% after risk-reducing salpingo-oophorectomy in BRCA1/BRCA2 mutation carriers [26, 38–43].

Heemskerk-Gerritsen et al. revised the association between risk-reducing salpingo-oophorectomy (RRSO) and breast cancer risk in BRCA1/BRCA2 mutation carriers, proposing a different analytical approach in order to mini-

mize potential biases as much as possible compared with previous studies. Applying the requirement of no history of cancer at the date of DNA diagnosis and the inclusion of person-time preceding risk-reducing salpingo-oophorectomy, the authors found no evidence for first breast cancer risk. Nonetheless, cumulative breast cancer risk curves suggest a slightly protective effect of risk-reducing salpingo-oophorectomy on breast cancer risk when performed at premenopausal age [44].

BRCA1 tumors have been more frequently found to be steroid hormone receptor-negative, rather than BRCA2 tumors [45, 46]. Therefore, the BC risk-reducing effect of RRSO may be expected more in BRCA2 mutation carriers.

In the most recent review conducted, Hartmann et al. summarized and presented current guidelines and statements on indications for preventive surgical procedures [47] (See table provided by Hartmann et al., NEJM).

In conclusion, risk-reducing surgery provides considerable benefits in terms of cancer prevention. Although, being an extended surgery, risk-reducing procedures may be associated with complications and adverse physical and psychosexual effects. Patient education plays an important role in avoiding the overestimation of breast cancer risk. Efforts should be made to provide information regarding sexuality, body image, reconstruction techniques, fertility, and the likelihood of familial predisposition.

The decision to undergo preventive surgical procedures is complex and patients require careful assessment in a multidisciplinary setting comprising clinicians, psychologists, and geneticists.

Box 1. Overview of Key Positions Regarding Risk-Reducing Surgery in Women with Hereditary Breast and Ovarian Cancer Syndrome.

The following position statements pertain to women without prior breast or ovarian cancer. These statements acknowledge that bilateral risk-reducing mastectomy and salpingo-oophorectomy have potential adverse effects, and multidisciplinary consultations before surgery are recommended to ensure informed decision making by the patient.

Bilateral Mastectomy

NCCN (National Comprehensive Cancer Network; www.nccn.org): "Risk-reducing mastectomy . . . provides a high degree of protection against breast cancer in women with a *BRCA1/2* mutation." Discuss risk-reducing mastectomy on a case-by-case basis, with a review of the potential adverse effects of the procedure. Risk-reducing mastectomy is also an option for patients with the Li–Fraumeni syndrome and the Cowden syndrome. Consensus recommendations are not provided for carriers of mutations in other genes.[34]

USPSTF (U.S. Preventive Services Task Force): "Among high-risk women and mutation carriers, risk-reducing mastectomy [as compared with no surgery] decreased breast cancer by 85 to 100% and breast-cancer mortality by 81 to 100%."[35]

Society of Surgical Oncology: Indications for bilateral prophylactic mastectomy include mutations in *BRCA1*, *BRCA2*, or other strongly predisposing breast-cancer susceptibility genes or, in the absence of data on mutations, a hereditary breast-cancer syndrome.[36]

NICE (National Institute for Health and Care Excellence; United Kingdom): "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 . . . . Bilateral mastectomy should be raised as a risk-reducing strategy option with all women at high risk."[37]

Additional international guidelines have been summarized by Easton et al.[10]

Comments on the procedure: No mastectomy can remove all breast tissue, which is widely distributed on the chest wall. Several mastectomy approaches have been used for prophylaxis. A total (simple) mastectomy removes more than 95% of breast tissue, including the overlying skin and nipple–areolar complex. In a classic subcutaneous mastectomy, the skin and nipple–areolar complex are preserved, and varying amounts of glandular tissue may be left below the areola. The use of this procedure for prophylaxis has been criticized because of the possible retention of excess at-risk tissue in the skin flaps and below the areola. Most surgical oncologists recommend a skin-sparing mastectomy for prophylaxis; this preserves the natural skin of the breast. A recent technique called "nipple-sparing" or "total skin-sparing" mastectomy also preserves the overlying skin of the nipple–areola complex. The underlying glandular tissue at risk is removed, and immediate reconstruction is performed. Cosmesis is enhanced by preserving the nipple skin.[38,39] More than 90% of women who undergo bilateral risk-reducing mastectomy elect immediate breast reconstruction, usually with implants. Complications may be immediate or delayed. In a prospective cohort of 112 consecutive women who underwent risk-reducing mastectomy followed by immediate breast reconstruction and were followed for 2.8 years, 10% had bleeding, 9% infection, and 14% capsular contracture. A total of 33% of women required reoperation.[40]

Bilateral Salpingo-Oophorectomy

NCCN: "Recommend risk-reducing salpingo-oophorectomy (ideally in consultation with a gynecologic oncologist) typically between 35 and 40 years, and upon completion of child bearing."[34]

USPSTF: "Risk-reducing salpingo-oophorectomy decreased breast cancer incidence by 37 to 100%, ovarian cancer by 69 to 100%, and all-cause mortality by 55 to 100%."[35]

Society of Gynecologic Oncology: "The most proven method for the prevention of ovarian cancer in women who carry a deleterious *BRCA1* or *BRCA2* mutation is risk-reducing salpingo-oophorectomy. Prospective studies have reported a 70% to 85% reduction in ovarian cancer . . . risk-reducing salpingo-oophorectomy between the ages of 35 and 40 years is recommended for risk reduction in women at increased genetic risk of ovarian cancer. The age [at which risk-reducing salpingo-oophorectomy is performed] may also be individualized according to the earliest age of onset in the family and personal choices."[41]

Comments on the procedure: The procedure, usually performed laparoscopically, should include visual assessment of the abdomen and pelvis, a pelvic washing, and total bilateral salpingo-oophorectomy, including ligation of the ovarian artery and vein approximately 2 cm proximal to the ovary and tube to ensure removal of all tissue. Because of the possibility of occult cancer, including serous tubal in situ carcinoma, meticulous processing of the surgical specimen is necessary according to the SEE-FIM protocol (protocol for sectioning and extensively examining the fimbriated end).[41-43]

Salpingectomy Alone

NCCN: "Salpingectomy [alone] is not the standard of care and is discouraged outside a clinical trial. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer."[34]

Society of Gynecologic Oncology: "Salpingectomy can be considered at the completion of childbearing in women at increased genetic risk of ovarian cancer who do not agree to salpingo-oophorectomy. However, this is not a substitute for oophorectomy, which should still be performed as soon as the woman is willing to accept menopause, preferably by the age of 40 years."[41]

New England Journal of Medicine, 2016, by Hartmann et al.

References

1. Tuttle TM, Habermann EB, Grund EH et al (2007) Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol 25:5203–5209
2. Kurian AW, Lichtensztajn DY, Keegan TH et al (2014) Use of and mortality after bilateral mastectomy compared with other surgical treatments for breast cancer in California, 1998–2011. JAMA 312(9):902–914
3. Yao K, Stewart AK, Winchester DJ et al (2010) Trends in contralateral prophylactic mastectomy for unilateral cancer: a report from the National Cancer Data Base, 1998–2007. Ann Surg Oncol 17:2554–2562
4. Fehniger J, Livaudais-Toman J, Karliner L et al (2014) Perceived versus objective breast cancer risk in diverse women. J Womens Health (Larchmt) 23(5):420–427
5. Banegas MP, Püschel K, Martínez-Gutiérrez J et al (2012) Perceived and objective breast cancer risk assessment in Chilean women living in an underserved area. Cancer Epidemiol Biomark Prev 21(10):1716–1721
6. Barton MB, West CN, Liu IL et al (2005) Complications following bilateral prophylactic mastectomy. J Natl Cancer Inst Monogr 35:61–66
7. Miller ME, Czechura T, Martz B et al (2013) Operative risks associated with contralateral prophylactic mastectomy. Ann Surg Oncol 20(13):4113–4120
8. Bresser PJ, Seynaeve C, Van Gool AR et al (2006) Satisfaction with prophylactic mastectomy and breast reconstruction in genetically predisposed women. Plast Reconstr Surg 117(6):1675–1684
9. Frost MH, Schaid DJ, Sellers TA et al (2000) Long-term satisfaction and psychological and social function following bilateral prophylactic mastectomy. JAMA 284(3):319–324
10. Guiliano AE, Boolbol S, Degnim A et al (2007) Society of surgical oncology: position statement on prophylactic mastectomy. Ann Surg Oncol 14:2425–2427
11. Tuttle TM, Jarosek S, Habermann E et al (2009) Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. J Clin Oncol 27:1362–1367
12. McLaughlin CC, Lillquist PP, Edge SB et al (2009) Surveillance of prophylactic mastectomy: trends in use from 1995 through 2005. Cancer 115:5404–5412
13. Sorbero ME, Dick AW, Burke Beckjord E et al (2009) Diagnostic breast magnetic resonance imaging and contralateral prophylactic mastectomy. Ann Surg Oncol 16:1597–1605
14. Jones NB, Wilson J, Kotur L et al (2009) Contralateral prophylactic mastectomy for unilateral breast cancer: an increasing trend at a single institution. Ann Surg Oncol 16:2691–2696
15. King TA, Sakr R, Patil S et al (2011) Clinical management factors contribute to the decision for contralateral prophylactic mastectomy. J Clin Oncol 29:2158–2164
16. Lostumbo L, Carbine NE, Wallace J (2010) Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev. doi:10.1002/14651858.CD002748
17. Bedrosian I, Hu CY, Chang GJ et al (2010) Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. J Natl Cancer Inst 102:1–9
18. Boughey J, Hoskin TL, Degnim AC et al (2010) Contralateral prophylactic mastectomy is associated with a survival advantage in high risk women with a personal history of breast cancer. Ann Surg Oncol 17:2702–2709
19. Basu NN, Barr L, Ross GL et al (2015) Contralateral risk-reducing mastectomy: review of risk factors and risk-reducing strategies. Int J Surg Oncol 2015:901046
20. Yao K, Winchester DJ, Czechura T et al (2013) Contralateral prophylactic mastectomy and survival: report from the National Cancer Data Base, 1998–2002. Breast Cancer Res Treat 142(3): 465–476
21. Fayanju OM, Stoll CR, Fowler S et al (2014) Contralateral prophylactic mastectomy after unilateral breast cancer: a systematic review and meta-analysis. Ann Surg 260(6):1000–1010
22. Basu NN, Ross GL, Evans DG et al (2015) The Manchester guidelines for contralateral risk-reducing mastectomy. World J Surg Oncol 13:237
23. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E et al (2013) Cancer risks for BRCA1 and BRCA2 mutation carriers: results from a prospective analysis of EMBRACE. J Natl Cancer Inst 105(11):812–822
24. Chen S, Parmigiani G (2007) Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 25:1329–1333
25. Hartmann LC, Sellers TA, Schaid DJ et al (2001) Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst 93:1633–1637
26. Domchek SM, Friebel TM, Singer CF et al (2010) Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 304(9):967–975
27. Heemskerk-Gerritsen BA, Menke-Pluijmers MB, Jager A et al (2013) Substantial breast cancer risk reduction and potential survival benefit after bilateral mastectomy when compared with surveillance in healthy BRCA1 and BRCA2 mutation carriers: a prospective analysis. Ann Oncol 24(8):2029–2035
28. Skytte AB, Crüger D, Gerster M et al (2011) Breast cancer after bilateral risk-reducing mastectomy. Clin Genet 79:431–437
29. De Felice F, Marchetti C, Musella A et al (2015) Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis. Ann Surg Oncol 22(9):2876–2880
30. Petit JY, Veronesi U, Orecchia R et al (2009) Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five years experience at the European institute of oncology of Milan (EIO). Breast Cancer Res Treat 117:333–338
31. Petit JY, Veronesi U, Lohsiriwat V et al (2011) Nipple-sparing mastectomy—is it worth the risk? Nat Rev Clin Oncol 8:742–747
32. Petit JY, Veronesi U, Orecchia R et al (2012) Risk factors associated with recurrence after nipple-sparing mastectomy for invasive and intraepithelial neoplasia. Ann Oncol 23:2053–2058
33. Manning AT, Sacchini VS (2016) Conservative mastectomies for breast cancer and risk-reducing surgery: the memorial Sloan Kettering cancer center experience. Gland Surg 5(1):55–62
34. Van Verschuer VM, Maijers MC, van Deurzen CH et al (2015) Oncological safety of prophylactic breast surgery: skin-sparing and nipple-sparing versus total mastectomy. Gland Surg 4(6):467–475
35. Toesca A, Peradze N, Galimberti V et al (2015) Robotic nipple-sparing mastectomy and immediate breast reconstruction with implant: first report of surgical technique. Ann Surg 7. [Epub ahead of print]
36. Breast cancer risk reduction, NCCN guidelines Version 1.2016
37. Nagaraja V, Edirimanne S, Eslick GD (2016) Is sentinel lymph node biopsy necessary in patients undergoing prophylactic mastectomy? A systematic review and meta-analysis. Breast J. doi:10.1111/tbj.12549. [Epub ahead of print]
38. Rebbeck TR, Levin AM, Eisen A et al (1999) Breast cancer risk after bilateral prophylacticoophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst 91(17):1475–1479
39. Rebbeck TR, Lynch HT, Neuhausen SL et al (2002) Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 346(21):1616–1622
40. Eisen A, Lubinski J, Klijn J et al (2005) Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol 23:7491–7496
41. Kramer JL, Velazquez IA, Chen BSE et al (2005) Prophylactic oophorectomy reduces breast cancer penetrance during prospec-

tive, long-term follow-up of BRCA1 mutation carriers. J Clin Oncol 23(34):8629–8635
42. Domchek SM, Friebel TM, Neuhausen SL et al (2006) Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol 7(3):223–229
43. Kauff ND, Domchek SM, Friebel TM et al (2008) Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol 26(8):1331–1337
44. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ et al (2015) Hereditary Breast and Ovarian Cancer Research Group Netherlands. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. J Natl Cancer Inst 107(5):djv033
45. Loman N, Johannsson O, Bendahl PO et al (1998) Steroid receptors in hereditary breast carcinomas associated with BRCA1 or BRCA2 mutations or unknown susceptibility genes. Cancer 83(2): 310–319
46. Honrado E, Benítez J, Palacios J et al (2006) Histopathology of BRCA1- and BRCA2-associated breast cancer. Crit Rev Oncol Hematol 59(1):27–39
47. Hartmann LC, Lindor NM (2016) The role of risk-reducing surgery in hereditary breast and ovarian cancer. N Engl J Med 374(5):454–468