Indications for Contralateral Prophylactic Mastectomy

A Consensus Statement Using Modified Delphi Methodology

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Objective: To reach a consensus about contralateral prophylactic mastectomy in unilateral breast cancer.

Summary Background Data: There has been a substantial increase in the number of North American women with unilateral breast cancer undergoing a therapeutic mastectomy and a contralateral prophylactic mastectomy (CPM) either simultaneously or sequentially. The purpose of this project was to create a nationally endorsed consensus statement for CPM in women with unilateral breast cancer using modified Delphi consensus methodology.

Methods: A nationally representative expert panel of 19 general surgeons, 2 plastic surgeons, 2 medical oncologists, 2 radiation oncologists, and 1 psychologist was invited to participate in the generation of a consensus statement. Thirty-nine statements were created in 5 topic domains: predisposing risk factors for breast cancer, tumor factors, reconstruction/symmetry issues, patient factors, and miscellaneous factors. Panelists were asked to rate statements on a 7-point Likert scale. Two electronic rounds of iterative rating and feedback were anonymously completed, followed by an in-person meeting. Consensus was reached when there was at least 80% agreement.

Results: Our panelists did not recommend for average risk women with unilateral breast cancer. The panel recommended CPM for women with a unilateral breast cancer and previous Mantle field radiation or a BrCa1/2 gene mutation. The panel agreed that CPM could be considered by the surgeon on an individual basis for: women with unilateral breast cancer and a genetic mutation in the CHEK2/PTEN/p53/PALB2/CDH1 gene, and in women who may have significant difficulty achieving symmetry after unilateral mastectomy.

Conclusion: Contralateral prophylactic mastectomy is rarely recommended for women with unilateral breast cancer.

Keywords: breast cancer, consensus statement, contralateral prophylactic mastectomy, national representative panel, prophylactic mastectomy

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In the last decade, there has been a substantial increase in the number of average-risk women with early stage breast cancer undergoing a therapeutic mastectomy and a contralateral prophylactic mastectomy (CPM) either simultaneously or sequentially in North America. The rate of CPM is increasing by 1% yearly[1] especially in younger women with low-risk disease[2–4] and is predominantly patient driven.[5,6] This is despite the fact that the current consensus is that CPM has no survival benefit in the average risk population.[7–9] CPM is also associated with harm, the overall complication rate for women undergoing unilateral mastectomy and CPM is 1.9 times greater than women who underwent unilateral mastectomy alone.[10] These women are at higher risk for chronic pain[11,12] and long-term concerns around body image, sexuality, and cosmesis.[13]

Previous research demonstrated that women predominantly chose CPM in addition to a therapeutic mastectomy because they overestimate their risk of developing a contralateral breast cancer, their risk of a breast cancer recurrence, and their risk of dying from breast cancer.[6,14,15] In focus groups, Canadian and American surgeons recommended that a formal consensus statement regarding CPM be generated.[5]

The National Comprehensive Cancer Network[16] and The American Society of Breast Surgeons[17] have both recently released statements that do not support the use of bilateral mastectomy for unilateral breast cancer in average risk women. The methodology for these statements did include a literature review and expert panel; however, the methodologies are not extensively described. The goal of this project was to create a methodologically rigorous nationally endorsed consensus statement on CPM for women with unilateral breast cancer using modified Delphi consensus methodology. The goal of such a statement would be to support and improve patient-provider discussion and decision-making related to CPM.

METHODS

Overall Approach

In this study, we used a modified Delphi approach to generate consensus about CPM in women with breast cancer. When evidence is contradictory or lacking, a Delphi process offers a way to systematically review and synthesize the evidence with a consensus-based approach to inform clinical decisionmaking.[18] The Delphi method utilizes a panel of experts to assess and rank agreement with statements about the topic of interest in an anonymous fashion. The results of the statement ranking are fed back to the participants in a controlled fashion for a second round and perhaps third round of ranking until consensus is met. Features of the Delphi approach include anonymity (which avoids dominance), iteration (which allows participants to change their opinions in response to feedback from the other participants), and controlled feedback. A modified Delphi approach also includes an in-person meeting of participants to finalize consensus.[18] The definition of consensus is varied and inconsistent[19] however, in the Fink guidelines[20] on consensus methods, at least two-thirds (67%) of participants must agree for consensus to be reached. We used 80% agreement/disagreement to

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signify consensus in this study as the steering committee felt it was important to have strong agreement around this potentially controversial topic.

Ethical approval for this study was obtained from Sunnybrook Health Sciences Centre Research Ethics Board.

Panel Identification, Sampling, and Recruitment

The research team consisted of general surgeons with special expertise in breast cancer (FCW, NJLH, AC, ST, MLQ) as well as experts in Delphi methodology (NB, ARG). The team identified potential panelists from general and plastic surgery, medical and radiation oncology and psychology based on publicly available directories and web sites demonstrating expertise in breast cancer management, and based on their own knowledge of physicians with a practice primarily based in breast cancer. General surgeons are the health care providers who meet the patient first in their breast cancer treatment journey and have the initial discussion with the patient about their surgical treatment including CPM. It was for this reason that the panel was comprised of primarily general surgeons although other appropriate health care providers were included in the panel to provide their views. In a systematic review of the Delphi Method, the median number of panel members was 17 with (Q1–Q3: 11–31) and a range of 3 to 418.[19] In our study, panel size was informed by sampling with the intent to achieve a multidisciplinary representation and to represent community and academic settings from across Canada. As suggested by Fink et al,[20] stakeholder agencies were also represented on the panel including the Canadian Partnership Against Cancer (CPAC), the Canadian Association of General Surgeons (CAGS), the Canadian Society of Surgical Oncology(CSSO), and Cancer Care Ontario (CCO). No patient advocacy groups or survivors were included in this initial panel as the goal of this consensus statement was to assess the clinical implications of CPM and create professional consensus.

Preparation of Materials for the Panel: Systematic Review

The most recent systematic review of quantitative CPM outcomes was published in 2014 and included studies up until 2011.[21] Building on this high-quality systematic review, we searched Medline, Embase, CINAHL, and the Cochrane Library for English-language meta-analyses, systematic reviews, randomized controlled trials, case control studies, or prospective or retrospective cohort studies published from 2012 to 2015 inclusive that examined outcomes in women with unilateral breast cancer undergoing CPM, and extracted data on survival, cause-specific mortality, and incidence of contralateral breast cancer and/or recurrence (appendix 1, http://links.lww.com/SLA/B237). Findings were analyzed using stratified subgroup and bivariate meta-regression analyses for patient age, race, stage, lymph node status, receipt of other therapy, multifocality and multicentricity, ER status, tumor histology. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria guided the rigorous conduct and reporting of the systematic review. Qualitative outcomes (searched from 2004 to 2015) of interest included knowledge, attitudes, beliefs about breast cancer in general and specifically regarding the safety and effectiveness of CPM, views about communication related to CPM, involvement in informed/shared decision-making, and satisfaction with decision for CPM (appendix 2, http://links.lww.com/SLA/B237). The quality of each article was assessed using the Standards for Reporting Qualitative Research: A Synthesis of Recommendations.[22] Thematic analysis was performed. Two major themes were identified: 1) women choose CPM to manage anxiety, decrease risk of recurrence, and improve survival and 2) overall women were satisfied with the decision to undergo CPM but the majority had some dissatisfaction, especially those who underwent reconstruction. Both quantitative and qualitative summaries were completed and distributed to the panel. The data from the qualitative and quantitative analysis will be published separately.

Statement Generation

To create relevant statements for the panel to assess, the research team independently reviewed the information gathered from the quantitative and qualitative systematic reviews to create a list of statements about specific scenarios associated with CPM. The researchers then met to review the statement lists that were then merged to achieve the final list over 2 separate meetings. Five main domains for the creation of statements about CPM were identified: predisposing risk factors for breast cancer, tumor factors, reconstruction and symmetry issues, patient factors, and other miscellaneous factors. In this modified Delphi process, each participant was to rank their agreement, disagreement, or neutrality with the statements.

Delphi Survey

First Round

Two rounds of the Delphi survey were planned. Panel members were electronically sent the results of the updated systematic reviews, a copy of the previous systematic review,[21] and instructions for how to complete the survey. Over a 2-week time period, participants reviewed statements and answered using a 7-point Likert scale their degree of agreement with the statement and a ''not sure'' comment. Panel members also had the ability to suggest additional questions for the next round (Appendix 1, http://links.lww.com/SLA/B237). An email reminder was sent 2 weeks after the initial distribution and nonresponders were contacted by email to promote return of the questionnaire. Anonymized results were then calculated. Answers were grouped into 3 groups: strongly disagree and disagree (1–2 on Likert scale), neutral (3–5), strongly agree or agree (6–7). Eighty percent agreement or disagreement with a statement was considered to have met consensus and those statements that achieved consensus were not redistributed for ranking in the second round of the survey.

Second Round

The summarized results from the first round of the Delphi (percentage of agreement/disagreement with each statement) along with a summary of the comments were then shared with the participants for the second round of the survey. Participants then reanswered each statement that did not meet consensus using the 7-point Likert scale. An email reminder was sent 2 weeks after the initial distribution and nonresponders were contacted by email to promote return of the questionnaire. The results of the second round of the survey were then calculated in the preparation for the in-person consensus conference.

In-person Consensus Conference

The in-person consensus conference was arranged in conjunction with the annual meeting of The Canadian Association of General Surgeons. All the participants in the Delphi survey were invited. The initial part of the conference focused on a discussion about the appropriate wording of statements. All the statements were then reviewed and additional information was presented and discussed in a nonanonymized fashion. Nonanonymized voting was completed after each statement. The consensus conference was audio recorded and a verbatim transcript was created to aid in the writing of the consensus statement.

RESULTS

Participants

Nineteen general surgeons who were experts in breast cancer from across Canada representing academic and community settings were invited, and all accepted the invitation to participate. Three of the general surgeons also represented stakeholder agencies, CCO, Canadian Partnership Against Cancer, and Canadian Association of General Surgeons (Table 1). Two of 4 plastic surgeons specializing in breast reconstruction, both medical oncologists who specialized in breast cancer care (2/2), 2 of 3 radiation oncologists who specialized in breast cancer care, and 1 psychologist who worked extensively with breast cancer patients and their families (1/1) also agreed to participate. Expertise was determined by the publications in the field of breast cancer and/or working at a regional high volume referral center. The panel was comprised of 15 females and 11 males, 22 health professionals working at academic centers, and had representation from 8 of 10 Canadian provinces (Table 1).

Two rounds of the electronic anonymous Delphi survey were completed. On the initial round, 39 statements were reviewed by participants and 9 statements reached consensus. One statement was discarded as it was a repeat of another statement and 2 new statements were suggested by the participants. For the second round of the survey, the 2 new statements and the 29 statements that did not meet consensus in the first round (total 31 statements) were reviewed and 6 of these statements reached consensus (Fig. 1).

For the consensus conference, statements were reorganized into 4 sections to facilitate discussion: predisposing risk factors for breast cancer, tumor factors, breast reconstruction and symmetry, and patient factors. Thirty-nine statements were discussed at the in-person consensus conference. Some of these statements were combined for clarity and all 28 reached consensus (80% agreement). Six statements were omitted and 2 were added (appendix 1, http://links. lww.com/SLA/B237) and (Table 2).

Introductory Preamble

Initial discussions at the consensus conference focused on the goal of CPM and how to word the recommendations. Participants all acknowledged that:

- Apart from BrCa1/2 gene mutation carriers who are diagnosed with a unilateral breast cancer,[23] CPM has not been proven to convey a survival benefit.
- There is a 3% to 5% likelihood of developing a contralateral breast cancer 10 years after initial diagnosis in an average risk woman.[24]
- There is a persistent small risk of a chest wall occurrence (0.5%) even after CPM.[25]
- Benefits from CPM included:
  - A 95% risk reduction in the development of a breast cancer in the contralateral breast.
  - Breast symmetry (with or without reconstruction) in women undergoing mastectomy.
- Concerns regarding CPM included:
  - Double the risk of postoperative infection and bleeding.[10]
  - Long-term chronic pain and body image issues.[11–13]

Wording of statements was extensively discussed and the panel agreed that the term ''not recommended'' implies ''not medically recommended'' and reflects the current medical evidence. In clinical terms, this meant to panelists they would not initiate discussion with patients about CPM.

TABLE 1. Expert Panel Participants

	Name	Medical Specialty	Province of Practice	Hospital Setting	Sex
1	Angel Arnaout	General surgeon	Ontario	Academic	Female
2	Christopher R Baliski	General surgeon	British Columbia	Community	Male
3	Jean Francois Boileau	General surgeon	Quebec	Academic	Male
4	Muriel Brackstone*	General surgeon	Ontario	Academic	Female
5	Christopher Cox	General surgeon	Newfoundland	Academic	Male
6	Kelly Dabbs	General surgeon	Alberta	Academic	Female
7	Jay Engel‡	General surgeon	Ontario	Academic	Male
8	Ralph George	General surgeon	Ontario	Academic	Male
9	Renee Hanrahan R	General surgeon	Ontario	Community	Female
10	Pamela Hebbard	General surgeon	Manitoba	Academic	Female
11	Lucy Helyer	General surgeon	Nova Scotia	Academic	Female
12	Claire Holloway* §	General surgeon	Ontario	Academic	Female
13	David McCready	General surgeon	Ontario	Academic	Male
14	Pamela Meiers	General surgeon	Saskatchewan	Academic	Female
15	Sarkis Meterissian	General surgeon	Quebec	Academic	Male
16	Geoff Porter†	General surgeon	Nova Scotia	Academic	Male
17	Louise Provencher	General surgeon	Quebec	Academic	Female
16	Glen Vajcner	General surgeon	Alberta	Community	Male
19	Rebecca Warburton	General surgeon	British Columbia	Community	Female
20	Claire Temple Oberle	Plastic surgeon	Alberta	Academic	Female
21	Toni Zhong	Plastic surgeon	Ontario	Academic	Female
22	Ivo A. Olivotto∗	Radiation oncology	Alberta	Academic	Male
23	Eileen Rakovitch∗	Radiation oncology	Ontario	Academic	Female
24	Christine Brezden-Masley	Medical oncology	Ontario	Academic	Female
25	Mark Clemons	Medical oncology	Ontario	Academic	Male
26	Karen Fergus	Psychologist	Ontario	Academic	Female

*Did not attend in-person consensus conference.
†Representing Canadian Partnership against Cancer.
‡Representing Canadian Association of Surgical Oncologists.
§Representing Cancer Care Ontario.

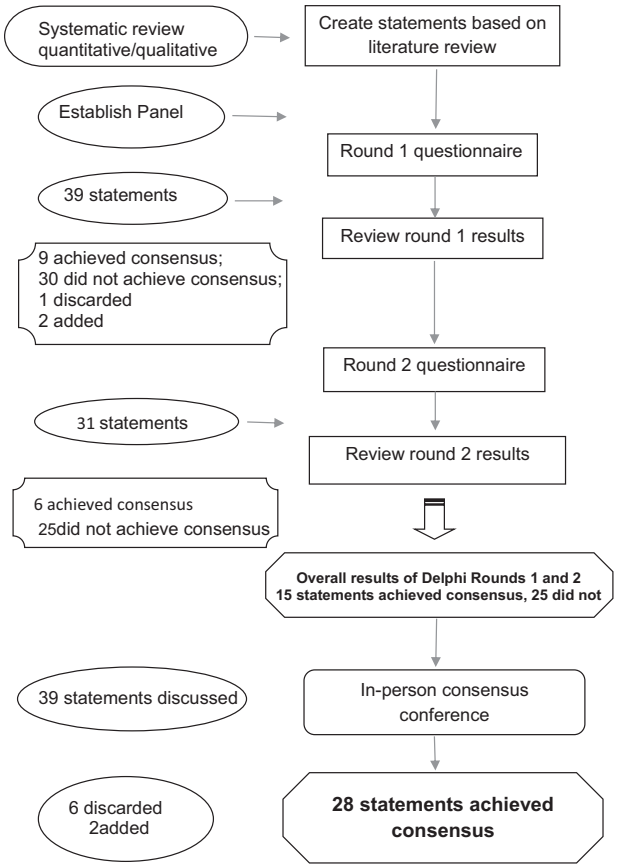

FIGURE 1. Process used to select and achieve consensus for statements about contralateral Prophylactic mastectomy. A number of statements were combined together for clarity, after the in-person consensus conference.

However, all the participants acknowledged that even if CPM was not medically recommended, it could still be performed. If patients initiated discussion about CPM, surgeons supported such discussion and if a well-informed patient fully understood the rationale, risks, and benefit of CPM and still wished to go ahead with the procedure, the surgeon and patient may decide that it is appropriate in that individual patient's particular situation.

Statements That Address Predisposing Factors for Breast Cancer With Regards to CPM

A summary of the consensus statements is found in Table 3.

Age

The panel does not recommend CPM for average risk women with early stage breast cancer regardless of age.

Family History of Breast Cancer But Non-BrCa1/2 Carrier

The panel does not recommend CPM for women with unilateral breast cancer with multiple family members with breast cancer under or over 50 as there is no known survival benefit of CPM for this patient population. The panel created an additional statement; CPM was not recommended for women who had genetic testing and were non-BrCa1/2 gene carriers but had family members who did have genetic testing and did carry the BrCa1/2 gene mutation. In addition, CPM was not recommended for women with a strong family history who declined BrCa1/2 testing as no current evidence was felt to support a survival benefit from CPM for this patient population.

Genetic Mutations (VUS in BrCA1/2, CHEK2, PTEN, p53, PALB2, and CDH1)

Patients with a variant of uncertain significance (VUS) in the BrCa1/2 gene have a change in the expected genetic sequence that has not been observed with any frequency and has not been classed as nonpathogenic.[26] The Evidence Based Network for Interpretation of Germline Mutant Alleles (ENIGMA) clinical working group states that most VUS variants are unlikely to be pathogenic but it is possible that some might be and therefore recommends assessing the patient's family history to inform clinical decision-making.[26] The panel felt that no evidence exists for a survival benefit for women with VUS in the BrCA1/2 gene with or without a strong family history. Consequently, CPM is not recommended in this cohort of patients.

Other pathogenic gene mutations were discussed. The panel acknowledged there is no evidence of survival benefit for CPM in women with gene mutations inCHEK2, PTEN, p53, PALB2, and CDH1. There is some evidence describing the likelihood of developing a contralateral breast cancer in the setting of some of these mutations.

Current evidence was reviewed which included: for women who have a mutation in CHEK2 1100delC, the 20-year cumulative incidence of developing a breast cancer is 25% to 30% (HR 3.52).[27] Additional research suggests that the 10-year risk of a contralateral breast cancer is 28.9% in this patient cohort.[28] With a Palb2 mutation, the cumulative risk of breast cancer by age 70 is estimated to be 47.5% and in a patient with a CDH1 mutation, there is a 52% cumulative risk of breast cancer by age 75.[29] No data exists on the contralateral breast cancer risk for Palb2 and CDH1 mutation carriers.

For women with a p53 mutation (Li-Fraumeni), the cumulative risk of breast cancer is 49% at age 60; however, the risk of a contralateral breast cancer and the role of CPM in improving long-term survival are uncertain, especially in light of the overall increased risk of other malignancies.[29] Similarly, for women with a PTEN mutation (Cowden syndrome), although there is a 25% to 50% increase in the lifetime risk of breast cancer, it is unclear if CPM would improve survival in light of the overall risk of malignancy.[29]

In light of limited evidence with respect to incidence of contralateral breast cancer and its effect on survival, the panel agreed that CPM may be considered on an individual basis for women with unilateral breast cancer and a genetic mutation in the CHEK2/ PTEN/ p53/ PALB2/CDH1 gene. Further research was suggested in this area.

Mantle Field Radiation

Supradiaphragmatic radiotherapy or mantle field radiation and combination chemotherapy have brought substantial improvements in survival for patients with Hodgkin lymphoma.[30] Second malignancies, a result of lifesaving but toxic treatments, are unfortunately the leading cause of death in long-term Hodgkin lymphoma patients and breast cancer is the most commonly diagnosed.[31] The long-term risk of breast cancer is dependent on multiple treatment factors including: age at radiation (age 10–24 yrs has the highest risk of breast cancer development), use and dose of alkylating chemotherapy and pelvic radiation (both induce the protective effect of menopause), and supra-diaphragmatic radiation that excludes axillary radiation.[30,32] Swerdlow et al[32] calculated the overall risk of

TABLE 2. Results of Deliberations

Statement	Consensus (>80%) Reached		
	Round 1 (Percentage Agreement)	Round 2 (Percentage Agreement)	In Person Conference
CPM should not be recommended to women with early stage unilateral breast cancer	92.3%		
CPM should be discouraged for average risk women with unilateral breast cancer		84.6%	
CPM should not be recommended to women with early stage breast cancer if they have a strong family history of multiple family members with breast cancer under 50 (Non BrCA 1–2)			>80%
CPM should not be recommended to women with early stage breast cancer if they have a strong family history of multiple family members with breast cancer over 50 (Non BrCA 1–2)			>80%
CPM should not be recommended if BrCA1–2 testing shows a variant of uncertain significance and there is a strong family history of multiple family members with breast cancer			>80%
CPM should not be recommended if BrCA1–2 testing shows a variant of uncertain significance and there is no strong family history			>80%
CPM should not be recommended if a woman has a >25% lifetime risk of breast cancer but is a non BrCA1–2 carrier			Discarded
CPM should not be recommended if a woman has a strong family history but refuses BrCA 1–2 testing			>80%
CPM is recommended if a woman has a history of mantle radiation under the age of 30			>80%
CPM should not be recommended if a woman is a carrier of a non-BRCA gene mutation (eg, CHEK-2, PALB2, p53, CDH1)			>80%
CPM should not be recommended to women with early stage breast cancer if they are <60 yrs of age	88.5%		
CPM should not be recommended to women with early stage breast cancer if they are <50 yrs of age	84%		
CPM should not be recommended to women with early stage breast cancer if they are <40 yrs of age			>80%
CPM should not be recommended to women with early stage breast cancer if they are <30 yrs of age		80.8%	
CPM should not be recommended if the patient's breast cancer is ER/PR negative		96.2%	
CPM should not be recommended if the patient's breast cancer is Her2neu positive	84.6%		
CPM should not be recommended if the patient's breast cancer is ER, PR, and Her2neu negative (triple negative)		88.5%	
CPM should not be recommended if the patient has a lobular breast cancer			>80%
CPM should not be recommended if the patient has a locally advanced unilateral breast cancer (LABC: > 5 cm (T3), extensive palpable nodes (N2, N3), chest wall and/or skin involvement)	92.3%		
CPM should not be recommended if the patient has unilateral multifocal or multicentric disease	80.8%		
CPM should not be recommended if the patient has high grade breast cancer	88.5%		
CPM should not be recommended if the initial cancer was only identified on MRI imaging and there is concern for occult new contralateral breast cancer			>80%
CPM should not be recommended to women in whom breast symmetry may be a major issue after unilateral mastectomy			Combined statement on reconstruction >80%
CPM should not be recommended if the patient is having immediate breast reconstruction			
CPM should not be recommended if the patient is having delayed breast reconstruction		84.6%	
CPM should not be recommended if the patient is having autologous abdominal tissue reconstruction (ex. DIEP /TRAM)			
CPM should not be recommended if the patient is having an implant based reconstruction			
CPM should not be offered if the patient expresses significant concern around breast symmetry			
CPM should not be offered to women with early stage breast cancer if they ask about it			Discarded
CPM should not be offered to women with early stage breast cancer if they request it			Discarded
CPM should not be offered if the patient expresses significant anxiety about developing a new contralateral breast cancer			Combined statement on patient support >80%
CPM should not be offered if the patient expresses significant anxiety around breast cancer related death			

TABLE 2. (*Continued*)

Statement	Consensus (>80%) Reached		
	Round 1 (Percentage Agreement)	Round 2 (Percentage Agreement)	In Person Conference
CPM should not be offered if the patient expresses significant anxiety around breast cancer distant metastases	80.8%		
CPM should not be offered if the patient expresses significant anxiety around ongoing breast cancer surveillance			
CPM should not be offered if the patient's nonmedical sources of information (eg, family, friends, internet) strongly advocate for CPM	80.8%		
CPM should not be offered if the patient visits my office several times to discuss CPM			Discarded
CPM should not be offered if it is recommended by a non-general surgical (plastic surgery, medical oncology, radiation oncology, family physician)			>80%
CPM should be recommended if the patient is planning to have or has had a prophylactic oophorectomy	Discarded		
CPM should be recommended if the patient has a contralateral indeterminate or benign breast imaging finding		84.6%	
New statement added after round 1: CPM should be recommended if a woman is a carrier of a non-BRCA gene mutation that is also associated with an increased risk of breast cancer (eg, CHEK-2, PALB2, p53, CDH1)			Discarded
New statement added after round 1: Discussion about CPM should be discouraged at the time of therapeutic mastectomy			Discarded
New statement added at consensus conference: CPM is not recommended for women with early stage breast cancer if they are BrCa1/2 gene negative but a family member is a BrCa1/2 mutation carrier			>80%
New statement added at consensus conference: CPM is recommended in a woman with a unilateral breast cancer and a mutation in the BrCa1/2 gene			>80%

breast cancer for women of England and Wales who had received mantle field radiation that was 20.2% at 40 years posttreatment.[32] However, depending on the previously mentioned risk factors, the maximum risk could be as high as 36%. In other studies, the bilateral breast cancer rate was 12.8% (5.5% synchronous and 7.8% metachronous).[33] In the Elkin et al[31] study, the rate of bilaterality at diagnosis was 6% and the actuarial rate of metachronous contralateral breast cancer was 18% at 5 years.

The panel discussed and concluded that because of the high rate of contralateral breast cancer, CPM in a woman diagnosed with a unilateral early stage breast cancer who had mantle field radiation is recommended. Further research was recommended to determine if a survival benefit is derived from a bilateral mastectomy in women with a unilateral breast cancer who had received mantle field radiation.

Statements That Address Tumor Factors With Regards to CPM

The panel agreed that tumor factors including receptor status, unifocality or multifocality, grade, stage of breast cancer or a contralateral indeterminate or benign breast finding identified by mammogram or MRI should not affect the decision for CPM.

Lobular Breast Cancer and CPM

Discussions regarding lobular breast cancer were undertaken by the panel and it was acknowledged that limited data exists with respect to the likelihood of bilateral invasive lobular cancer. One study[34] described a 17.3% rate of bilaterality of invasive lobular cancers which 8% were metachronous and 9.3% were synchronous at a median 3 years postdiagnosis.[33] The panel reached consensus that unilateral invasive lobular cancer alone was not an indication for CPM as there is no data with regards to survival benefit and no modern data on incidence of contralateral cancer.

Statements That Address Breast Reconstruction and Symmetry With Regards to CPM

The panel agreed that reconstruction type (implant or tissue-based) or timing of reconstruction (immediate or delayed) should not be the driving force for CPM in women with a unilateral breast cancer. Patients should be informed; however, that autologous breast reconstruction using abdominal wall tissue can only be completed once. CPM (with or without reconstruction) was not recommended as the only way of attaining symmetry and it was identified that symmetry may be attained by oncoplastic lumpectomy, mastopexy, or breast reduction.

Statements That Address Patient Factors With Regards to CPM

Research has demonstrated that women overestimate their risk of developing a contralateral breast cancer, developing distant metastases and dying from breast cancer.[5,15] Because of the belief that they are at high risk of recurrence, developing distant metastases and dying from breast cancer, women look to control their cancer outcomes and request CPM,[5] the panel did not recommend that CPM be used as a method of coping with anxiety and fear regarding breast cancer recurrence and death. Patients should have appropriate access to emotional and psychological supportive care services to help cope with anxiety. Most importantly, patients should receive appropriate information and recommendations, possibly supplemented by decision-aides, about the benefits and drawbacks of CPM.

DISCUSSION

The impetus for this modified Delphi consensus statement was the rising rate of CPM in average-risk women with unilateral breast cancer in the context of no consistent survival benefit. After careful review of both the quantitative and qualitative literature, our panel

TABLE 3. Summary of Recommendations for CPM

CPM is not Recommended	Contralateral Prophylactic Mastectomy (CPM) is not recommended for average risk women with early stage unilateral breast cancer regardless of age*
	CPM is not recommended to women with early stage unilateral breast cancer if they are <60 years of age*
	CPM is not recommended to women with early stage unilateral breast cancer if they are < 50 yrs of age*
	CPM is not recommended to women with early stage unilateral breast cancer if they are < 40 yrs of age
	CPM is not recommended to women with early stage unilateral breast cancer if they are < 30 yrs of age*
	CPM is not recommended for women with early stage breast cancer if they have a strong family history of multiple family members with breast cancer under 50 (NonBrCa 1/2)
	CPM is not recommended for women with early stage breast cancer if they have a strong family history of multiple family members with breast cancer over 50 (NonBrCa 1/2)
	CPM is not recommended for women with early stage breast cancer if they are BrCa1/2 gene negative, but a family member is BrCa1/2 mutation carrier
	CPM is not recommended if BRCA1–2 testing shows a variant of uncertain significance (VUS) and there is a strong family history of multiple family members with breast cancer
	CPM is not recommended if BRCA1–2 testing shows a variant of uncertain significance (VUS) and there is no strong family history
	CPM is not recommended for women with a strong family history of breast cancer who is declining BrCa1/2 mutation testing
	CPM is not recommended if the patient's breast cancer is ER/PR negative*
	CPM is not recommended if the patient's breast cancer is ER, PR and Her2neu negative (triple negative)*
	CPM is not recommended if the patient's breast cancer is Her2neu positive*
	CPM is not recommended if the patient has a locally advanced unilateral breast cancer (LABC: > 5 cm (T3), extensive palpable nodes (N2,N3), chest wall and/or skin involvement)*
	CPM is not recommended if the patient has unilateral multifocal or multicentric disease*
	CPM is not recommended if the patient has high grade breast cancer*
	CPM is not recommended if the patient has a contralateral indeterminate or benign breast imaging finding
	CPM is not recommended if the patient has a lobular breast cancer
	CPM is not recommended if the initial cancer was only identified on MRI imaging
	CPM is not recommended based on timing (immediate or delayed) or type (implant or tissue-based) of reconstruction†
	CPM is not recommended based solely on patient anxiety around developing a contralateral breast cancer, distant metastases, breast cancer related death, and/or ongoing breast surveillance *
	CPM is not recommended even if the patient's nonmedical sources of information strongly advocate for CPM*
CPM is recommended	CPM is recommended in women who had Mantle field radiation with a unilateral breast cancer
	CPM is recommended in women with a mutation in the BrCa1/2 gene with a unilateral breast cancer
CPM can be considered	There is insufficient evidence to recommend for or against CPM and therefore CPM may be considered on an individual basis for women with early stage breast cancer and a genetic mutation in CHEK2/ PTEN/ p53/ PALB2/CDH1 genes
	CPM (with or without reconstruction) is not recommended, but may be considered, in a woman in whom breast symmetry may be a major issue after unilateral mastectomy (with or without reconstruction

*Met consensus in either first or second round of the Delphi survey (prior to in-person meeting).
†Part of this statement met consensus in first or second round of Delphi survey (statement was reworded at in-person meeting).

identified 2 scenarios where CPM is medically recommended and therefore, discussion of CPM should be initiated by the surgeon:

1. CPM is recommended in women with a unilateral breast cancer with a BrCa1/2 gene mutation who is having a therapeutic mastectomy.
2. CPM is recommended in women with a unilateral breast cancer who had Mantle field radiation who is having a therapeutic mastectomy.

The panel identified 2 scenarios where the literature is inconclusive and therefore, discussion of CPM could be initiated by the surgeon on a case-by-case basis when a woman was having a therapeutic mastectomy:

1. Discussion of CPM could be initiated by the surgeon in women with a unilateral breast cancer and a genetic mutation in CHEK2/ PTEN/ P53/ PALB2/CDH1.
2. Discussion of CPM could be initiated by the surgeon in women in whom breast symmetry may be a major issue after unilateral mastectomy (with or without reconstruction). However, symmetry should not be the driving factor for CPM.

Importantly, all the participants acknowledged that even if CPM was not medically recommended, it could still be performed. Surgeons supported discussion with patients if they initiated discussion about CPM and if a well-informed patient fully understood the rationale, risks, and benefit of CPM, and still wished to have a CPM, the surgeon and patient may decide that it is appropriate.

This work is timely and is reflected in the support received from health care providers, stakeholder agencies as well as the recent statements by the American Society of Breast Surgeons[35] and the American Choosing Wisely Campaign.[36] The Choosing Wisely campaign focuses on identifying unnecessary care that does not provide value or benefit to patients, and that can potentially cause harm and waste resources.[37,38] The campaign highlights harms that can arise from unnecessary care, such as adverse drug reactions from needless medication, radiation exposure from unwarranted diagnostic imaging, or complications from procedures that do not provide benefit.[38] Similarly, in this consensus statement, our panel reviewed potential harms from CPM, including a doubling of risk for wound and postoperative complications, longer hospital stays, higher reoperation and transfusion rates, and potential long-term body image issues and pain.[10,13,39] As such, there is support from the panelists to decrease the number of CPMs being performed. There are mixed responses from patients about the Choosing Wisely Campaign. Primary care patients are receptive to the idea of judicious medication use, and limiting annual ECGs and investigations for low back

pain, but are not open to foregoing screening tests (prostate cancer, osteoporosis, colonoscopy).[40,41] Decisions about screening are driven by a complex interplay of attitudes, social norms, patient self-efficacy, and emotional comfort.[41] We have observed similar decision-making patterns for women choosing CPM, as we know that CPM is predominantly a patient-driven phenomenon.[5] Hence, this consensus statement is the first step in a process to engage patients around decision making about CPM, within a larger ongoing effort to promote evidence based, and value-driven medical care.

Our panel discussed areas for future research:

1. To investigate if there is a survival benefit associated with CPM for a woman with a unilateral breast cancer who had Mantle field radiation.
2. To investigate if there is a survival benefit associated with CPM for women who have a >25% lifetime risk of developing a breast cancer (as determined prior to her diagnosis of breast cancer by the International Breast Intervention Study tool or the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm tool) and are diagnosed with a unilateral breast cancer.
3. To investigate if there is a survival benefit associated with CPM for women with a unilateral breast cancer and a genetic mutation in CHEK2/ PTEN/p53/ PALB2/CDH1 genes.
4. To investigate if there is a survival benefit associated with CPM for women diagnosed with a unilateral invasive lobular cancer.
5. To investigate if there is a survival benefit associated with CPM for young women < 50 diagnosed with a unilateral breast cancer.

The strengths of this work include the qualitative and quantitative systematic review (to be published independently), and the modified Delphi approach that ensures a rigorous approach to attaining consensus in an arena where the literature may be imperfect. Our participants were representative breast cancer experts in their fields and all panelists completed the 2 electronic surveys. One possible criticism is that no breast cancer survivors or patient advocates were invited to participate. However, the goal of this consensus statement was to assess the clinical implications of CPM and create professional consensus. In the future, we will be engaging with patient advocacy groups to discuss and disseminate the consensus statement.

In summary, this methodologically rigorous statement is an important first step in providing education for health care providers, patients, and families about the medical indications for CPM in women choosing a therapeutic mastectomy. Further work is needed to ensure that this statement is readily accessible to patients, stakeholder agencies, patient advocacy groups, and health care providers.

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