RISK REDUCTION AND SURVEILLANCE STRATEGIES FOR INDIVIDUALS AT HIGH GENETIC RISK FOR BREAST AND OVARIAN CANCER

Effective Date: April, 2011

The recommendations contained in this guideline are a consensus of the Alberta Provincial Breast Tumour Team and represent a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Mutation of the BRCA1 and BRCA2 genes, two types of tumour suppressor genes, has been associated with an increased risk of hereditary breast and ovarian cancer. The mutation of these genes is autosomal dominant. From a meta-analysis of mutation penetrance studies, mean cumulative breast cancer risk at age 70 for BRCA1 mutation carriers is 57% (95% CI, 47% - 66%) and for BRCA2 mutation carriers is 49% (95% CI, 40% - 57%). [1] Mean cumulative ovarian cancer risk by age 70 for BRCA1 mutation carriers is 40% (95% CI, 35% - 46%) and for BRCA2 mutation carriers is 18% (95% CI, 13% - 23%). [1] Breast cancer risk may be similar in the setting of a strong family history where there are inconclusive genetic testing results. [2,3,4] There is growing evidence for a number of risk reduction and surveillance strategies applicable to the high genetic risk population.

GUIDELINE QUESTION

What breast and ovarian cancer risk reduction and surveillance options should be offered to individuals with high genetic risk?

DEVELOPMENT AND REVISION HISTORY

A multidisciplinary panel from the Alberta Health Services, Calgary High Risk Breast and Ovarian Cancer Interest Group was convened in early 2007 to undertake a guideline adaptation process. The panel included representation from medical genetics (medical geneticist and counselors), breast surgery, gynecology, radiology, medical oncology, psychology and nursing. All panel members were asked to disclose information on potential conflicts of interest prior to initiation of the first meeting (none disclosed).

The current update of this guideline was commissioned by the CancerControl Alberta, Alberta Provincial Breast Tumour Team. This guideline was reviewed and endorsed by the Alberta Provincial Breast Tumour Team and academic Medical Genetics Departments affiliated with the University of Calgary and the University of Alberta. Members of the tumour teams include medical oncologists, radiation oncologists, surgeons, gynecologic oncologists, pathologists, nurses, and pharmacists. Contributing members of academic Medical Genetics Departments include medical geneticists and genetic counselors. Evidence used to update the guideline was selected and reviewed by a working group comprised of a medical oncologist, a breast surgeon, and Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

This guideline was originally developed in December 2007. This guideline was revised in April 2011

SEARCH STRATEGY

The original guideline was developed using evidence from existing guidelines, which was gathered by searching PubMed and clinical practice guideline organizations' websites (e.g. the National Comprehensive Cancer Network, Cancer Care Ontario, National Institute for Health and Clinical Excellence, etc.) for relevant practice guidelines. Practice guidelines were considered if they met the following criteria: (1) published, updated or available in draft form (in the English language) from January 2006 through February 2007; (2) pertained to the care of individuals with high genetic risk for breast plus/minus ovarian cancer; (3) had recommendations with clear links to the supporting literature; and (4)

had notation of where expert opinion was employed. Specific guidelines pertaining to the use of breast screening with MRI were also sought.
The most relevant comprehensive guidelines selected for full review were from the National Hereditary Cancer Task Group (NHCTF), [5] the National Institute for Health and Clinical Excellence (NICE), [6] and the National Comprehensive Cancer Network (NCCN). [7] The most relevant specific guidelines pertaining to the use of breast screening with MRI, were from Cancer Care Ontario (CCO) [8] and the American Cancer Society (ACS). [9]

Panel members first met March 21, 2007. The selected guidelines were reviewed and recommendations were adopted or adapted for local use. Consensus was defined as two-thirds quorum but minority opinions and reasons were recorded, as necessary. The adapted guideline was written by the panel chair and reviewed by all panel members.

The guideline was updated using evidence identified by searching the Ovid Medline, EMBASE, Cochrane Database of Systematic Reviews, National Guidelines Clearinghouse, and relevant conference websites (all 2007 through September 27, 2010) for new or recently updated clinical practice guidelines, systematic reviews, clinical trials, abstracts, and other relevant evidence deemed eligible to inform the topic. Reference lists of related papers and recent review articles were also scanned for additional citations. Search terms included 'hereditary breast and ovarian cancer' or 'breast and ovarian cancer syndrome' with a limit of English language.

The current search identified a total of 41 citations: seven new or updated guidelines, four systematic reviews, two meta-analyses, and 28 original articles.

TARGET POPULATION

Individuals who meet one of the following criteria: (1) are found to carry a deleterious mutation in BRCA1 or BRCA2, (2) have not undergone genetic testing but have a first degree relative with a deleterious mutation in BRCA1 or BRCA2, or (3) are assessed to be at high risk for hereditary breast/ovarian cancer as per a formal consultation with a medical geneticist or after assessment at a high risk clinic (i.e. an individual with a projected lifetime breast cancer risk of at least 20– 25% based on family history models).

RECOMMENDATIONS

Breast Cancer Risk Reduction and Surveillance

1. Surgery: Prophylactic Bilateral Mastectomy

- Benefits and risks of prophylactic bilateral mastectomy should be raised for BRCA1 and BRCA2 mutation carriers but can also be discussed on a case-by-case basis for other women in the target population.
- The possibility of an incidental breast cancer being diagnosed, and breast reconstruction options should be discussed in advance.
- Prophylactic bilateral mastectomy should be performed by a breast surgeon. Preservation of the nipple and areola could be considered; however the patient should be informed that there is currently little evidence on this topic and that there is a slightly increased risk of breast cancer (versus complete removal of nipple and areola) and possible loss of sensation and ischemia.

- Excised tissue should be examined by a pathologist who is aware of the individual's high genetic risk status, and who is experienced in breast cancer pathology.
- Mammography and MRI should not be part of routine surveillance practice after bilateral mastectomy or reconstruction.

Prior to, or in the absence of, bilateral prophylactic mastectomy, surveillance and other risk reduction options can be considered.

2. Recommended Screening for Those with Intact Breasts

- Both mammography and magnetic resonance imaging (MRI) should be offered on an annual basis from age 25-30 years to age 65-69 years.
  - Individuals should be informed of the potential for false negative results (leading to a breast cancer diagnosis between screening rounds) and false positive results (leading to recall imaging studies and possibly unnecessary biopsies) associated with this approach.
  - In addition, individuals and their physicians should be aware that MRI should be requested at least six months prior to the desired screening date.
- Where available, MRI should be performed at a centre with a dedicated breast coil and experienced breast radiologists. Full recommendations for the use of MRI in patients with breast cancer were developed by Alberta Health Services, Cancer Care in 2010. [10]
- For annual breast screening, the addition of ultrasound to mammogram could replace MRI, where MRI is not available or not feasible for the patient (e.g. claustrophobia, pacemakers, electronic/magnetic/mechanical implants, magnetic clips, etc.); however, MRI has higher sensitivity for breast screening.
- In women 70 years and older, the decision to continue mammography should depend on life expectancy and preference.
- Clinical breast exam should be offered at 6-month intervals starting at age 25 years.
- Pregnant and lactating women should be offered clinical breast exam every 6 months. Mammography and MRI can resume post partum.
- Male BRCA1 and BRCA2 mutation carriers should be offered a clinical breast exam every 12 months. Surveillance imaging studies are not recommended.
- Individuals who wish to pursue breast self-examination, should be counseled about the potential benefits and limitations, and should be offered information on technique.

3. Other Risk Reduction Strategies

- Chemoprevention: The potential benefit and risks associated with preventive tamoxifen can be discussed. This discussion should be led by a physician who is well-informed on the potential benefits and risks associated with tamoxifen. Of note, tamoxifen has only been found to reduce the risk of hormone sensitive cancers. As 80% of BRCA1 cancers are estrogen receptor negative, the expected benefit would be less for this population.

- Bilateral oophorectomy: The benefit (e.g. 53-68% risk reduction) of prophylactic bilateral oophorectomy on breast cancer risk if performed in the premenopausal period should be raised for BRCA1 and BRCA2 mutation carriers but can also be discussed on a case-by-case basis for other women in the target population. The full recommendation on prophylactic bilateral oophorectomy follows in the next section (*Ovarian Cancer Risk Reduction and Surveillance*).

Ovarian Cancer Risk Reduction and Surveillance

1. Surgery: Prophylactic Bilateral Salpingo-Oophorectomy

- The benefits and risks of prophylactic bilateral salpingo-oophorectomy plus/minus hysterectomy should be raised for BRCA1 and BRCA2 mutation carriers but can also be discussed on a case-by-case basis for other women in the target population.
  - The issue of premature menopause and the possibility of an incidental ovarian or fallopian tube cancer being diagnosed should be discussed in advance.
  - Prophylactic bilateral salpingo-oophorectomy plus/minus hysterectomy should be performed by a gynecologist. Laparoscopy should be undertaken if possible. Surgery should be directed towards complete removal of both ovaries and fallopian tubes. Peritoneal surfaces should be inspected and fluid collected for cytological analysis.
  - Excised tissue should be examined by a pathologist who is aware of the individual's high genetic risk status and who is experienced in ovarian cancer pathology. A protocol for the pathological evaluation of tissue specimens can be found in the appendix.
  - In most instances, this procedure can be delayed until age 35-40 years.

- Hormone replacement therapy can be considered in premenopausal women undergoing prophylactic oophorectomy.
  - It should be used for as short a duration as possible and not beyond the average age for natural menopause.
  - Estrogen only is preferred but should only be prescribed in the setting of hysterectomy. A gynecologist should be available for consultation.
  - If an individual has had a prior breast cancer diagnosis, hormone replacement therapy is generally not recommended, and should not be considered without assessment by a multidisciplinary team.

2. Other Risk Reduction Strategies

- Oral contraceptives: Premenopausal individuals currently using, or contemplating the use of, oral contraceptive pills should be counseled on the probable protective effect against ovarian cancer but uncertainty surrounding increased breast cancer risk. Oral contraceptive pills should not be prescribed solely for the purpose of ovarian cancer risk reduction.

- Ovarian cancer surveillance: screening for ovarian cancer is controversial and generally not recommended. Individuals should be counseled on the limitations of the currently available surveillance methods and the symptoms/signs of ovarian cancer. A gynecologist with expertise in the high-risk field should be available for consultation.

Summary

Table 1 summarizes the expected relative risk reduction associated with each of the various strategies outlined in this guideline. [11,12] In addition, screening and surgical risk reduction strategies may offer survival benefit for BRCA1 and BRCA2 mutation carriers. Kurian, et al. (2009) have estimated that the baseline (i.e. no intervention) survival rate for BRCA1 mutation carriers is 53% by age 70 and that prophylactic oophorectomy at age 40 provides an absolute survival gain of 15%; for BRCA 2 mutation carriers the baseline survival rate is 71% by age 70 and prophylactic mastectomy at age 40 provides a 7% survival gain. Together, prophylactic mastectomy and prophylactic oophorectomy provides a survival gain of 24% for BRCA1 and 11% for BRCA2 carriers. Screening alone provided absolute survival gains of 6% and 4%, respectively, for BRCA1 and BRCA2 carriers. [13] In contrast, data is not yet available to support survival benefit for any risk reduction strategy (screening, surgical prophylaxis or tamoxifen) amongst other high risk groups.

Table 1. Risk reductions associated with surgical and medical strategies (Source: Kurian, et al. 2009 [13]).

Recommended Strategy	Risk Reduction (%)
Breast Cancer	
Prophylactic mastectomy	90-95
Prophylactic bilateral oophorectomy	53-68
Tamoxifen for 5 years	50 *
Ovarian Cancer	
Prophylactic bilateral oophorectomy	85-95

* of hormone sensitive cancers

DISCUSSION

Target Population

The National Hereditary Cancer Task Group (NHCTF) guidelines target known BRCA1 or BRCA2 mutation carriers with the caveat that recommendations could serve as a guide, on a case by case basis, in situations where a mutation is not found. [5] Recommendations from the National Institute of Health and Clinical Excellence (NICE) pertain to individuals at risk of familial breast cancer and vary according to risk level with high risk referring to individuals with a known BRCA1, BRCA2 or TP53 mutation or a risk of carrying a BRCA1, BRCA2 or TP53 mutation of at least 20% or a 10-year risk of breast cancer between ages 40 and 49 years greater than 8% or a lifetime risk of breast cancer at least 30% based on family history models. [6] The National Cancer Clinical Network (NCCN) recommendations are directed at individuals who carry a BRCA1 or BRCA2 mutation or who have not been tested but are from a family where a BRCA1 or BRCA2 mutation has been identified or who are assessed to be at high risk for carrying a BRCA1 or BRCA2 mutation but have not been tested. [7] The target population for this guideline is in accordance with the NHCTF, NICE and NCCN but also has strived to ensure inclusion of all women potentially eligible for screening breast MRI as per the primary published studies. The benchmark has been adopted from the ACS which includes women with a predicted lifetime risk of breast cancer of at least 20-25% according to family history models. This can include women from BRCA-untested families or BRCA-negative. There is mounting observational evidence for high breast cancer amongst women who

have a strong family of breast cancer where the proband has tested negative for a BRCA1 or BRCA2 mutation. [2-4]

Breast Cancer Risk Reduction and Surveillance

Prophylactic bilateral mastectomy, as an option for individuals with BRCA1 and BRCA2 mutations, is supported by the NHCTF, NICE, and NCCN guidelines. [5-7] The NHCTF suggests that there is fair evidence to support the clinical preventive action. [5] Observational studies consistently show a reduction in breast cancer risk by at least 90%. [5,12] Preservation of the nipple and areola could be considered; however the patient should be informed that there is currently little evidence on this topic and that there may be a slightly increased risk of breast cancer (versus complete removal of nipple and areola) and possible loss of sensation and ischemia. [14-16] Patients best suited for preservation of the nipple and areola include those candidates who will likely have minimal reconstructive complications (e.g. young women who are not obese, who are nonsmokers, who have not undergone previous irradiation, who do not have collagen vascular disease, and who do not have multiple breast incisions, particularly surrounding the nipple and areola). [14]

Prior to, or in the absence of, bilateral prophylactic mastectomy, the NHCTF, NICE, CCO and ACS guidelines recommend mammography and MRI in women with high genetic risk. [5,6,8,9] The NCCN suggests that MRI can be considered as an adjunct to mammography and clinical breast exam. [6] The rationale for combination surveillance is as follows. Randomized studies of mammography versus no screening in the general population, downstages breast cancer and decreases mortality by 20-30%. [17,18] Randomized studies of mammography plus/minus, or in comparison to, MRI have not been done; however, prospective observational studies of mammography versus MRI in women with high genetic risk, reveal much higher sensitivity estimates for MRI relative to mammography.[19,20] Furthermore, these studies, in comparison to mammography only studies, appear to detect smaller and more node-negative breast cancers. [19] It is anticipated (but currently unknown) that surveillance MRI further reduces mortality. The CCO conducted a meta-analysis of twelve mammography plus MRI observational studies. [21-35] A summary of the sensitivity and specificity for each modality is provided below (Table 2).

Table 2. Sensitivity and specificity of MRI and mammography as screening modalities in women at high risk of hereditary breast cancer (Source: Warner, et al. 2007 [8]).

	MRI (%, 95% CI)	***Mammography (%, 95% CI)***	***MRI + Mammography (%)***
Sensitivity	80.1, 73.3-85.8	36.8, 29.6-44.5	87.4
Specificity	93.0, 92.5-93.6	97.5, 97.1-97.8	94.2
Diagnostic odds ratio	77.34, 29.12-205.41	32.00, 14.63-69.99	NR

Abbreviations: MRI, magnetic resonance imaging; CI, confidence interval; NR, not reported

The NHCTF, NICE and CCO recommend mammography and MRI commence at age 30 years. [5,6,8] The NCCN suggests commencing at age 25 years [7] and the ACS does not clearly address the lower age limit issue. The NHCTF and CCO recommend continuing MRI until the age 69 years; [5,8] whereas, NICE recommends continuing MRI until age 50 years. [6] NCCN guidelines state that an upper age limit for breast screening has not been established but that severe, co-morbid conditions limiting life expectancy do need consideration. [7] The ACS does not clearly address the upper age limit issue. Taken together, the panel felt that the current recommendation with respect to age range should reflect the inclusion criteria of the

six key mammography plus MRI observational studies. [21,22,32,36-38] Four of the six studies included women at least age 25 years, including the largest of the studies. Only the UK study capped the upper age limit as young as 49 years. The Canadian study included women up to age 65 years and the largest study included women up to age 70 years. Moreover, sub-group analysis in the Canadian study revealed that the sensitivity of MRI relative to mammography was higher in women at least age 50 years compared with in women under age 50 years. Breast screening in the general population is routinely recommended only until the age of 69. The prospective observational studies of mammography and MRI employed these modalities concurrently. It has been postulated, that staggering these tests might lower the interval breast cancer rate; however the is currently no evidence to support one approach over the other.

The NICE guideline recommends that when mammography is being utilized in women under the age of 50, digital mammography be performed. [6] It is unknown if this approach would increase the sensitivity of combination mammography and MRI in any age group. However, as mammography may be more sensitive for detecting DCIS relative to MRI in centres gaining experience with MRI, the panel felt that any maneuver to potentially improve detection of DCIS in women with dense breasts is defensible. The recommendation that, in women 70 years and older, the decision to continue mammography should depend on life expectancy and preference was adopted from the NHCTF. [5] NICE states that individualized strategies for mammography should be developed for women at high genetic risk who are at least age 50 years. [6] The NCCN states that an upper age limit for breast screening has not been established but that severe, co-morbid conditions limiting life expectancy need consideration. [7]

The recommendation that MRI should be performed at a centre with a dedicated breast coil and experienced breast radiologists was adapted from the NHCTF guideline, which was similar in sentiment to the NICE guideline: *MRI of both breasts should be performed to high quality standards ensuring both high temporal and spatial resolution, dynamic sequences are recommended post contrast, studies should be double-read where possible, and MRI with accompanying mammography data should be collected for audit purposes.* [6]

Routine surveillance using ultrasound was not recommended by any of the guidelines reviewed; however, ultrasound can be used in problem-solving mammography or MRI-detected abnormalities.

The NHCTF and the NCCN recommend that clinical breast exam at six-month intervals be part of an overall surveillance strategy. [5,7] NICE does not address this issue. Again it has only been postulated that staggering screening tests might lower the interval breast cancer rate. The NHCTF's leading statement on breast self-examination is that it is not recommended as a routine approach to surveillance for breast cancer. [5] The NCCN recommends encouraging periodic breast self-exam; [7] however, NICE does not address this issue. As such, the panel was divided as to whether to adopt the NHCTF approach or the NCCN approach; the recommendation is therefore neutral and reflects the NHCTF's second statement on breast self-examination.

For pregnant women, the NHCTR recommends that clinical breast exam should be offered every three months, not during lactation, but resuming to every three months after weaning and that mammography and MRI should not be used for surveillance during pregnancy or lactation. [5] This issue was not clearly addressed in the other guidelines. The panel felt that every three months was not a feasible schedule for pregnant women and recommends that pregnant women be offered clinical breast exam every six months with mammography and MRI resuming postpartum.

For men, the NHCTF also recommended that male BRCA1 and BRCA2 mutation carriers should be offered a clinical breast exam every six to twelve months. [5] The NCCN recommends, based on expert opinion, clinical breast exam every six months, periodic breast self-examination, and a baseline mammogram with annual surveillance mammography if gynecomastia or fibroglandular breast density is identified. [7] The NICE guideline does not address this issue. The panel felt that every twelve months was a more reasonable schedule for men and recommends that men be offered clinical breast exam every twelve months with no annual mammography.

Regarding prophylactic bilateral oophorectomy, observational studies consistently show a reduction in breast cancer risk by at least 50%. [5,12] One observational study has shown a significant reduction in breast cancer specific mortality. [12] More recently, a multicenter cohort study demonstrated a reduction in breast cancer risk. [39] Among women with BRCA1 or BRCA2 mutations, those who underwent risk reducing salpingo-oophorectomy had a lower risk of first diagnosis of breast cancer in BRCA1 mutation carriers (20% vs. 14%; hazard ratio 0.63; 95% CI, 0.41-0.96) and BRCA2 mutation carriers (23% vs. 7%; hazard ratio 0.36; 95% CI, 0.16-0.82). Moreover, compared with women who did not undergo risk-reducing salpingo-oophorectomy, undergoing salpingo-oophorectomy was associated with lower breast cancer–specific mortality (6% vs. 2%; hazard ratio 0.44; 95% CI, 0.26-0.76).

The NHCTF suggests that, in the absence of prophylactic oophorectomy performed during the premenopausal period, the potential benefit and risks associated with preventive tamoxifen can be discussed. [5] However, there was insufficient evidence to make a recommendation for or against the administration of tamoxifen and other factors may influence decision-making. [5] The stance taken by the NCCN is similar. [7] The rationale is that although observational studies reveal that tamoxifen reduces the risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers who have had a diagnosis of hormone-receptor positive breast cancer by at least 50%, [40,41] evidence is not available for primary prevention in this population. In very small sub-groups of BRCA1 and BRCA2 mutation carriers from the NSABP-P1 prevention trial, no benefit was observed. [5,12,42] This finding was inconsistent with the overall finding that tamoxifen significantly reduced the risk breast cancer by 50% in women with increased risk of multifactorial etiology. Preventive tamoxifen is not addressed by NICE with the rationale that it is not licensed for this indication in any population with elevated breast cancer risk. The panel concurred with the overall stance of the NHCTF and the NCCN. Tamoxifen is contraindicated during pregnancy and should be delayed until child-bearing is complete in the setting of risk reduction.

Ovarian Cancer Risk Reduction and Surveillance

The NHCTF, NICE and NCCN guidelines, [5-7] as well as the Society of Gynecologic Oncologists Clinical Practice Committee [43] all recommend raising the option of prophylactic bilateral salpingo-oophorectomy in individuals with BRCA1 and BRCA2 mutations. Observational studies consistently show a reduction in ovarian cancer risk by 85-95%. [5,12,44,45] A significant reduction in ovarian cancer specific mortality has also been demonstrated. [44] More recently, a multicenter cohort study [38] among women with BRCA1 or BRCA2 mutations demonstrated that risk reducing salpingo-oophorectomy resulted in a lower risk of ovarian cancer: 6% vs. 1% in those with prior breast cancer (hazard ratio 0.14; 95% CI, 0.04-0.59) and 6% vs. 2% in those without prior breast cancer (hazard ratio 0.28; 95% CI, 0.12-0.69). Risk reducing salpingo-oophorectomy was also associated with lower ovarian cancer–specific mortality (3% vs. 0.4%; hazard ratio 0.21; 95% CI, 0.06-0.80).

Hysterectomy may be an additional consideration for the following reasons: excess of fallopian tube carcinomas – hysterectomy allows for complete removal of such tissue; possible excess of endometrial and cervical carcinomas in BRCA1 and BRCA2 mutation carriers; [46,47] preference for estrogen only hormone replacement therapy for managing postmenopausal sequelae with minimization of increased breast cancer risk; and finally, tamoxifen use and desire to eliminate endometrial cancer risk. [12]

On the issue of oral contraceptive pills, the standpoints of the NHCTF and NICE are similar: premenopausal women currently using or contemplating the use of oral contraceptive pills should be counseled on the probable protective effect against ovarian cancer but the uncertainty surrounding increased breast cancer risk and oral contraceptive pills should not be prescribed solely for the purpose of ovarian cancer risk reduction. [5,6] The issue is not addressed by the NCCN.

The panel recommends that prior to, or in the absence of, prophylactic bilateral oophorectomy, ovarian cancer surveillance is controversial and generally not recommended and that individuals should be counseled on the limitations of the currently available surveillance methods and the symptoms/signs of ovarian cancer. This recommendation takes into account the discrepancy in the literature and variation in local clinical practice (i.e. some institutions still include some ovarian cancer screening). The Society of Gynecologic Oncologists Clinical Practice Committee [43] recommends against CA-125 screening. The NHCTF guideline states that ovarian cancer surveillance is not routinely recommended; however, the guideline discussion points out evidence for lack of benefit and risk of harm. [5] This is in contrast to the NCCN guideline which suggests that in the absence of prophylactic oophorectomy, concurrent transvaginal ultrasound and CA-125 can be performed every six months starting at age 35 years or five to ten years earlier than the earliest age of first diagnosis of ovarian cancer in the family, and preferably day 1-10 of the menstrual cycle in premenopausal women. [7] The NICE guideline does not address this issue. The panel also opted to place an emphasis on consultation with a gynecologist with expertise in the high risk field.

The standpoints of the NHCTF, NICE and the NCCN on hormone replacement therapy are similar: hormone replacement therapy can be considered in premenopausal women undergoing prophylactic oophorectomy. It should be used for as short a duration as possible and not beyond the average age for natural menopause. [5-7] There is observational data showing that the benefit of prophylactic oophorectomy in the premenopausal period on breast cancer risk in BRCA1 and BRCA2 mutation carriers is not affected by short-term hormone replacement therapy. [5] Observational data in the general population shows lesser elevation of breast cancer risk in those exposed to estrogen only versus estrogen plus progesterone hormone replacement therapy. [5]

GLOSSARY OF ABBREVIATIONS

Acronym	Description
ACS	American Cancer Society
CCO	Cancer Care Ontario
CI	confidence interval
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Clinical Excellence
NHCTF	National Hereditary Cancer Task Group

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2013. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Breast Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Breast Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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APPENDIX

Protocol for the examination of specimens from patients with a history of BRCA
(courtesy of Dr. Carol Ewanowich, Royal Alexandra Hospital, Edmonton, Alberta)

Whether submitted as a salpingo-oophorectomy specimen or in conjunction with a hys-BSO, a detailed pathologic examination of the fallopian tube and ovary will be undertaken by the SEE-FIM protocol (Sectioning and Extensively Examining the FIMbriated End) as follows:

Each salpingo-oophorectomy is submitted in toto for examination. The fimbriated end of the fallopian tube is transected as a 2 cm long segment to include the tubal fimbria and infundibulum. This segment is then longitudinally sectioned – this may entail 3 to 4 longitudinal cuts, the goal being to maximize the surface area of the tubal epithelium for histologic examination. The remainder of the fallopian tube comprising isthmus and ampulla is sectioned transversely at 2 to 3 mm intervals. The ovary, with supporting soft tissue, is similarly sectioned at 2 to 3 mm intervals perpendicular to the long axis (breadloaf) and also submitted in toto.

Source: Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. Am J Surg Pathol. 2006 Feb;30(2):230-6.