

Clinical Management Recommendations for Surveillance and Risk-Reduction Strategies for Hereditary Breast and Ovarian Cancer Among Individuals Carrying a Deleterious BRCA1 or BRCA2 Mutation

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Abstract

Background: In Canada, there are wide variations in services for patients at risk for hereditary breast and ovarian cancer (HBOC), and clinical interventions and recommendations differ between regions and/or provinces. National strategies for the clinical management of HBOC exist in the United Kingdom, France, and Australia, and clinical programs in Canada would benefit from similar national recommendations and a consistent approach to clinical management. The National Hereditary Cancer Task Force developed recommendations to address the clinical management of patients at high risk of HBOC and related cancers. These recommendations are based on current practice in high-risk cancer clinics that provide care for individuals with known BRCA1 or BRCA2 mutations.

Methods: Canadian consensus recommendations were generated by the National Hereditary Cancer Task Force and compared mainly with two recently published guidance documents on the clinical management of women with increased risk of HBOC, one from the United Kingdom and the other from France. After review of these documents and the associated supporting scientific evidence, the Canadian consensus recommendations were modified and rated using predefined criteria.

Key Words: Breast cancer, ovarian cancer, genetics, clinical practice recommendations, BRCA1, BRCA2

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Conclusions: These recommendations pertain to (1) surveillance options including breast self-examination, clinical breast examination, breast surveillance by imaging, ovarian cancer surveillance, and surveillance for men; (2) risk-reduction strategies including prophylactic mastectomy, prophylactic salpingo-oophorectomy, and pharmacoprevention; and (3) the use of exogenous hormones. Regular updates should occur as new evidence becomes available.

Résumé

Contexte : Au Canada, les services offerts aux patientes courant des risques de connaître un cancer du sein et de l'ovaire héréditaire (CSOH) varient grandement; de plus, les interventions et les recommandations cliniques varient d'une région et/ou d'une province à l'autre. Le Royaume-Uni, la France et l'Australie comptent tous une stratégie nationale visant la prise en charge clinique du CSOH; les programmes cliniques canadiens tireraient profit de la mise sur pied de recommandations nationales similaires et d'une approche uniforme en matière de prise en charge clinique. Le *National Hereditary Cancer Task Force* a élaboré des recommandations traitant de la prise en charge clinique des patientes qui courent un risque élevé de connaître un CSOH et des cancers connexes. Ces recommandations sont fondées sur la pratique actuellement en cours, en ce qui concerne les patientes qui présentent des mutations connues du BRCA1 ou du BRCA2, au sein de cliniques vouées aux personnes courant des risques élevés de cancer.

Méthodes : Des recommandations de consensus canadiennes ont été rédigées par le *National Hereditary Cancer Task Force* et comparées principalement à deux documents d'orientation

récemment publiés sur la prise en charge clinique des femmes qui courent un risque accru de CSOH (l'une provenant du Royaume-Uni et l'autre, de France). À la suite de l'analyse de ces documents et des données scientifiques justificatives connexes, les recommandations de consensus canadiennes ont été modifiées et évaluées au moyen de critères prédéfinis.

Conclusions : Ces recommandations portent sur (1) les options de surveillance, y compris l'auto-examen des seins, l'examen clinique des seins, la surveillance mammaire par imagerie, la surveillance du cancer de l'ovaire et la surveillance visant les hommes; (2) les stratégies de réduction des risques, y compris la mastectomie prophylactique, la salpingo-ovariectomie prophylactique et la pharmacoprévention; et (3) le recours à des hormones exogènes. Ces recommandations devraient être mises à jour régulièrement, au fur et à mesure de la publication de nouveaux résultats.

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INTRODUCTION

Background to This Document

Advances in human genetics are becoming increasingly relevant in medicine. The identification of genes responsible for specific hereditary cancer susceptibility syndromes provides an important opportunity to review how new genetics knowledge can be used to improve clinical services and patient outcomes. The detection of an inherited BRCA1 or BRCA2 mutation allows for the development of a personalized program of surveillance and risk reduction strategies that may extend the lives of those found to carry the mutations, while freeing those who do not from having to consider drastic surgical options. The Canadian Strategy for Cancer Control has noted that policies addressing the prevention, detection, diagnosis, treatment, and cure of breast cancer are far from consistent across the provinces and communities.¹ The situation is similar with respect to services and resources available to patients and families at risk for hereditary breast and ovarian cancer (HBOC). The National Hereditary Cancer Task Force was charged with developing and preparing recommendations to address the clinical management of patients at high risk of HBOC. These recommendations are based on current practice in high-risk cancer genetics clinics that provide care for individuals with known BRCA1 or BRCA2 mutations. The goal of these clinical management recommendations is to promote consistency in clinical management and services and to foster clinical practice based on best scientific evidence, where it is available. The specific aims are to

- reduce mortality from breast and ovarian cancer;
- promote quality of life and reduce morbidity;
- assist individuals at risk who would benefit from surveillance and/or risk reduction;
- help physicians in decision making;
- minimize adverse emotional and psychological consequences;

- address the needs of previously affected individuals and those so far unaffected.

Scope of the Recommendations

These clinical management recommendations are concerned primarily with surveillance and risk-reduction strategies for HBOC in women at high risk for breast and ovarian cancer because they are known to be carriers of a deleterious BRCA1 or BRCA2 mutation. When a mutation is not found in a high-risk woman, these recommendations could serve as a guide; however, situations should be addressed on a case-by-case basis. A later section in this review addresses the specific issues for men with known BRCA1 or BRCA2 mutations who may face an increased risk of developing one or more specific cancers. Although most high-risk patients are managed in specialty clinics, these recommendations are also relevant to primary care providers in understanding the recommended management for their patients.

Statement of Intent

These recommendations are not intended to serve as a standard of medical care. Standards of care are based on all clinical data available for an individual case and are subject to modification with advancements in scientific knowledge and technology. These parameters of practice are recommendations only. Adherence to them will not ensure a successful outcome in every case, and they should not be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. After discussing options with the patient, the physician will ultimately decide on a particular procedure or treatment plan based on the basis of available diagnostic and treatment choices. Significant departures from these recommendations should be documented in the patient's chart.

METHODS

Over a period of two years, The National Hereditary Cancer Task Force (experts from across Canada representing numerous clinical disciplines, see Appendix 1) generated consensus recommendations that were then scrutinized in light of two published evidence-based guidance documents from the United Kingdom (UK)² and France³ on the clinical management of patients at increased risk of HBOC. Several other guidelines were excluded from the comparison exercise because they were not developed using a systematic review of the literature. Details of the development process are provided in Appendix 2. Quality of evidence and recommendations were ranked in accordance with the Canadian Task Force on Preventive Health Care (Table),^{4,5} following extensive appraisal and discussion. The recommendations cover the areas of clinical management

Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care^{4,5}

Quality of Evidence Assessment*	Classification of Recommendations†
I: Evidence obtained from at least one properly randomized controlled trial.	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on the Periodic Preventive Health Exam Care.⁴

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Preventive Health Exam Care.⁴

considered by the National Hereditary Cancer Task Force as most relevant to patient care. The classification (A, B, C, D, E, or I) assigned to each recommendation represents the Task Force's consensus interpretation of the *strength of evidence* underpinning that recommendation, using the grades for *evidence quality* indicated in Table (I, II-1, II-2, II-3, III). The final assembly of evidence was completed by the Editorial Group in the summer of 2006. In many clinical areas, evidence was not available or was unclear. The absence of evidence does not imply that statements based on expert opinion are invalid but reflect the limited state of published research knowledge at that time. Given the rapid progress in this area, periodic reviews and updates should occur on a regular basis as new evidence becomes available.

RECOMMENDATIONS

Early Detection of Cancer in Women

Methods of surveillance for breast cancer in women include breast self-examination (BSE), clinical breast examination (CBE), and imaging (mammography, magnetic resonance imaging (MRI), and ultrasound).

Breast Cancer Surveillance by Breast Examination

Breast self-examination

There have been no trials of BSE in high-risk populations of women with known BRCA1 or BRCA2 mutations,

although this surveillance method is considered potentially helpful when combined with other measures. In the general population, meta-analyses of randomized controlled trials indicate that BSE does not effectively reduce mortality from breast cancer, and it is associated with higher rates of biopsies in experimental groups.⁶⁻⁸ Nevertheless, a proportion of breast cancers in high risk women are detected by women themselves.⁹ Promotion of this modality may result in false reassurance or create anxiety, particularly in subgroups of women who either tend to avoid or over-use BSE. Health care professionals should be aware of these possible adverse effects and counsel women that there is no evidence that this method is effective.

Clinical breast examination

In the general population, CBE has not been proven to be beneficial, and may in some instances cause harm.¹⁰ Non-controlled studies suggest that, when used as a surveillance method, CBE detects few cancers that are not detected by imaging.¹¹ CBE has recently been shown to have a low sensitivity (9%) but a high specificity (99.3%).¹² However, some clinicians and researchers consider it a reasonable intervention if it is performed by an experienced clinician attuned to the patient's high-risk status and in conjunction with other surveillance measures. CBE may be an important complementary measure for women who choose to perform BSE.

Recommendation for Breast Cancer Surveillance by Breast Examination

	Class
1 BSE is not recommended as a routine approach to surveillance for breast cancer.	E
2 Women who wish to use BSE as a primary surveillance option should be counselled about its benefits and limitations so that they have realistic expectations. If they continue using this approach, they should be offered information on the technique. CBE should be offered at six-month intervals.	I
3 Regular CBE is not recommended as a sole cancer surveillance modality. It should be performed as part of an individualized surveillance program that includes imaging appropriate to the patient's age, breast density, and preferences.	I
4 Occasionally, breast cancer surveillance is indicated in a woman under age 30 (e.g., if there is a history of breast cancer under age 30 in the family). In this setting, CBE should be combined with MRI.	I
5 After prophylactic mastectomy, regular clinical examination of the chest wall, reconstructed breast, or breast implant is recommended.	I
6 Surveillance of pregnant women should consist of CBE every three months with ultrasound for any questionable findings and mammography plus ultrasound for any suspicious findings.	I
7 For women who choose not to breast-feed, CBE should resume six months after delivery. Otherwise, it may be resumed three months after weaning.	I

Surveillance by Imaging: Mammography, Magnetic Resonance Imaging, Ultrasound

The three types of surveillance by imaging are mammography, magnetic resonance imaging (MRI), and ultrasound. Their roles are complementary for women at average risk. In the general population, meta-analysis suggests mammographic surveillance reduces mortality from breast cancer in women aged 50 and over, limited evidence of benefit in 40- to 49-year-old women, and no evidence of benefit in women under 40.¹³ Specific evidence does not exist for

high-risk women with known BRCA1 or BRCA2 mutations; therefore they cannot be directly compared with the general population. Mammographic surveillance is the most widely used surveillance modality for high-risk women across Canada, despite concerns about its false negative rate in this population.^{14–23} Recent descriptive studies have shown an elevated incidence of interval cancers in women with known BRCA1 or BRCA2 mutations, suggesting that annual mammography alone may not be an adequate surveillance strategy for women in this high risk group.²⁴ Its sensitivity is influenced by patient age, breast density, and the characteristics of tumours associated with BRCA1 or BRCA2 mutations, which may render them more difficult to detect by mammography than those in the general population.²⁵ There is also concern about exposing young women to increased radiation risk in the absence of clear benefits.^{26–28}

There are no definitive randomized controlled trials to clarify whether ultrasound and/or MRI are effective surveillance modalities for carriers of BRCA1 or BRCA2 mutations. However, evidence is currently accumulating through a randomized controlled trial²⁹ and several prospective studies^{12,30–34} that MRI is more sensitive than mammography or ultrasound and that a combination of techniques has even higher sensitivity. Uncontrolled studies suggest ultrasound may increase the detection of small cancers when combined with mammography,¹¹ particularly in women with high breast density² for which mammography is less sensitive.^{23,35–37} Given the state of current evidence, MRI and ultrasound should be considered as secondary evaluation or diagnostic tools only, although MRI may be increasingly used in the future in high-risk patients as a first line surveillance technique. More data are required to clarify whether the improvements in sensitivity (detection of cases) that might be achieved through combined use of ultrasound and/or MRI with mammography are associated with improvements or reductions in specificity (false positive rates) in women with known BRCA1 or BRCA2 mutations.

When imaging is used, there is an argument that it should be offered as part of multidisciplinary team care, in order to allow the option of proceeding immediately to biopsy should a lesion be detected.

Recommendation for Breast Cancer Surveillance by Imaging

	Class
1 In general, no imaging modality should be used in isolation, particularly in younger women and/or those with dense breast tissue. See exception, recommendation No.2 below.	I
2 Mammography is not recommended for screening women under 30 years of age because of concerns relating to a potential radiation risk. MRI should be used if imaging is considered clinically indicated.	I
3 For women aged between 30 and 69 years, mammography should be done annually and complemented by MRI where it is available.	B
4 In women 70 years and over, the decision to continue screening by imaging depends on the woman's health, life expectancy, and preference.	I
5 All women should be counselled regarding the current evidence relating to different imaging modalities and should receive written information on their benefits, radiation risks, and the potential psychological impact of false positive or false negative findings.	I
6 After mammography, a woman and her physician should be informed of her breast density score, as this may influence other surveillance and treatment options.	I
7 Routine imaging is not recommended for women who have undergone bilateral prophylactic mastectomies and/or breast reconstruction.	I
8 Mammography and MRI are not recommended for screening during pregnancy or lactation.	I
9 Where possible, imaging should ideally be delivered by an experienced team of radiologists with experience in all three imaging modalities. The imaging centre should be accredited by the Canadian Association of Radiologists.	I

Ovarian Cancer Surveillance

Current methods for ovarian cancer surveillance include pelvic examination, measurement of serum cancer antigen 125 (CA125), and ultrasound (transvaginal and/or pelvic).^{6,31,38-46} Evidence from randomized controlled trials and prospective non-randomized studies does not support the routine use of any of these surveillance methods in the general population^{47,48} and there is no evidence to support their efficacy in high-risk groups.^{6,31,38-40} The high rates of false negative results associated with these tests may provide inappropriate reassurance and possible harm. Similarly, high rates of false positive findings may lead to unnecessary investigations and surgeries, and create excessive anxiety.⁴⁹ In the face of apparent powerlessness to detect ovarian cancer at an earlier stage, some women may experience high levels of anxiety and depression. New genetic marker-based approaches including those derived from proteomics are considered promising but remain to be validated for routine clinical use.^{41,47,50}

Recommendation for Ovarian Cancer Surveillance

	Class
1 With currently available technologies, ovarian cancer surveillance is not routinely recommended.	E
2 Women should be counselled on the limitations of current surveillance methods.	I
3 Recognition of ovarian cancer symptoms should be emphasized for both the patient and the clinician.	I
4 If, despite counselling, a woman strongly prefers surveillance, it should be performed every 6 to 12 months and should be accompanied by clear advice on the importance of acting on suspicion of symptoms.	I
5 If a woman strongly prefers surveillance by ultrasound, it should be scheduled to take place immediately following menses in premenopausal women.	I
6 Individualized psychosocial support should be made available to all women whether or not they opt for surveillance.	I

Risk Reduction Surgery in Women

Prophylactic Mastectomy

Consistent evidence from observational studies suggests that prophylactic mastectomy reduces the risk of breast cancer in women with known BRCA1 or BRCA2

mutations.⁵¹⁻⁶⁵ In general, the reduction of anxiety in women who choose mastectomy creates positive outcomes,^{62,66-69} particularly when this is accompanied by active participation in decision-making on the part of the patient.^{56,57,62,70} Comprehensive psychological assessment, genetic counselling, and discussion that includes an individualized breast cancer risk assessment offered at the beginning of the process appear to be associated with lower levels of post-surgical regret.^{60,62,71-77}

Although it is suggested that discussing the procedure with others who have already undergone it is beneficial for some women's decision-making, professionally led support groups are viewed as more appropriate. Women should be provided with information on potential sexual and psychosocial consequences,^{57,58,62,66,71,73,74,76,77} and it is suggested that some women benefit from seeing postoperative clinical photographs.

There have been no trials comparing the relative effectiveness of different surgical techniques. However, as the goal is to ensure that the least possible residual breast tissue remains, nipple/areola-sparing surgery is not considered appropriate^{51,53,54,63,65,68,78-80} and consideration should be given to removing the axillary and subclavian extensions of the breast tissue. When breast prostheses are planned, the pectoral fascia should not be removed in order to reduce the risk of prosthetic rejection.^{51,55,65,68,79,80} Because of the possibility of detecting an occult cancer at the time of prophylactic surgery, resected breast tissue should be subjected to careful histological examination.⁷⁹

Recommendation for Prophylactic Mastectomy

	Class
1 The potential benefits of prophylactic mastectomy as a risk-reduction strategy should be raised with all women with known BRCA1 or BRCA2 mutations.	B
2 Women considering prophylactic mastectomy should be managed by a multidisciplinary team that includes at least a geneticist/genetic counsellor, a breast surgeon, and a plastic surgeon.	I
3 Written and oral information should be provided.	I
4 Surgery should be scheduled after the patient has had adequate time for reflection on the issues to make an informed decision.	I
5 Patients should have access to a full range of ancillary supportive care services.	I

6 The surgical technique should aim for maximum removal of breast tissue, including removal of nipple and areola, and possibly also the axillary and subclavian extensions.	I
7 In women who are considering breast prostheses, pectoral fascia should not be removed in order to reduce the risk of prosthesis rejection.	I
8 The possibility that histologically evident breast cancer may be diagnosed as a result of the surgical procedure should be discussed with the patient in advance.	I
9 The excised breast tissue should be examined for presence of cancer by a pathologist experienced in breast pathology who is aware of the high-risk status of the patient.	I
10 Breast reconstruction options should be discussed with the patient in advance.	I

Prophylactic Bilateral Salpingo-Oophorectomy

Prophylactic bilateral salpingo-oophorectomy (BSO) appears to be associated with a reduction of 85% to 95% in the risk of ovarian and fallopian tube cancers in women with known BRCA1 or BRCA2 mutations.^{30,44,57,58,61,63,81-86} If performed in the premenopausal period, this intervention may also decrease the risk of developing breast cancer by 50% or more,⁸¹⁻⁸³ even in women taking short-term hormone replacement therapy (HRT) after their prophylactic BSO.^{87,88} For women with the BRCA1 mutation, a reduction in breast cancer risk after BSO occurs despite the estrogen receptor-negative status of most BRCA1-associated breast tumors.^{87,89}

There are issues beyond cancer risk reduction that must be considered before making a decision on prophylactic BSO. Patients need to be aware that their quality of life may be affected by a sudden premature menopause that can create psychological distress (for example, body image alterations, feeling "older," mood and sleep disturbances, decreased libido)⁹⁰⁻⁹³ and physical distress (such as hot flashes, vaginal dryness, and potentially long-term health issues).^{81,90,94} There is controversy surrounding the use of HRT^{83,95,96} (see section on exogenous hormones). Patients should be informed about available non-hormonal options to alleviate or minimize the symptoms associated with the onset of premature menopause.

There is a lack of evidence regarding the timing of risk-reduction surgery, although the risk of ovarian cancer is

low before the age of 35 years, and many women are still considering child-bearing at 40 and above.^{81–83} Evidence suggests that, provided they have appropriate psychosocial support, most women who undergo surgery are pleased with their decision because it lowers their anxiety about developing ovarian cancer.^{90–94}

Particular attention should be paid to surgical technique and pathology examination to ensure complete removal of the ovaries and fallopian tubes.^{84,97–99} A number of studies have reported the existence of occult epithelial cancers at the time of surgery,^{100–103} detected by careful inspection of the peritoneum, evaluation of peritoneal washings by cytology, and/or pathological examination of excised tissue. Cancers of the fallopian tube are considered part of the clinical syndrome.¹⁰⁴ The issue of carrying out a hysterectomy at the same time deserves special consideration: although it is not routinely recommended in the absence of separate clinical indications, it may be favoured in women who would strongly consider taking an estrogen-only HRT regimen. Indeed, data from the Women's Health Initiative (WHI) study has recently suggested that the use of combined estrogen-progesterone regimen is associated with a higher risk of breast cancer in the general population.¹⁰⁵ Similarly, a simultaneous hysterectomy may be favoured in women taking tamoxifen for a previously diagnosed breast cancer or for breast cancer pharmacoprevention in order to reduce the risk of endometrial carcinoma. Whenever possible, the BSO should be performed laparoscopically as it is considered a minimally invasive surgical approach. It should be recognized that the surgical morbidity of the combined hysterectomy and BSO is higher than with BSO alone; in some cases, hysterectomy necessitates a laparotomy instead of a laparoscopic approach.

Recommendation for Prophylactic Bilateral Salpingo-Oophorectomy

	Class
1 The potential benefits of prophylactic BSO as a risk-reduction strategy should be raised with all women at high risk.	B
2 Surgery should be directed towards complete removal of both ovaries and fallopian tubes.	B
3 Laparoscopy is the procedure of choice whenever possible. Peritoneal surfaces should be inspected and fluid collected for cytological analysis.	B
4 The ovarian and fallopian tube tissue specimens should be examined in their entirety for presence of cancer by a pathologist experienced in ovarian cancer pathology who is aware of the high-risk status of the patient.	B

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| 5 | Women considering BSO should be counselled about age-specific risks of ovarian and breast cancer and also about dealing with menopausal symptoms. They should be managed by a multidisciplinary team that includes at least a geneticist/genetic counsellor and gynaecologist. | I |
| 6 | Written and oral information should be provided. | I |
| 7 | In women facing premature menopause, issues relating to HRT and alternatives should be discussed explicitly before surgical intervention. Ongoing medical care addressing health issues related to premature menopause should be available (e.g., regular bone density measurements and assessment of cardiovascular risk factors). | I |
| 8 | Patients should have access to the full range of ancillary supportive care services. | I |
| 9 | Hysterectomy is not routinely recommended unless there are separate clinical indications. It should be considered if women plan to take HRT after the BSO or if they are on tamoxifen therapy. | I |
| 10 | The possibility that histologically evident epithelial cancer may be detected as a result of the surgical procedure should be discussed in advance. | I |

Pharmacoprevention

Potential pharmacoprevention agents include the selective estrogen receptor modulators (SERMs, e.g., tamoxifen and raloxifene) and the aromatase inhibitors. Although these agents are not approved for use in Canada for pharmacoprevention, national guidelines produced in 2001 recommend counselling women at high risk of breast cancer (as determined by the Gail model¹⁰⁶) about the risk and benefits of pharmacoprevention with tamoxifen.¹⁰⁷ Indeed, recent evidence suggests that in these women, five years of therapy with tamoxifen reduces the risk of breast cancer by about 40%.¹⁰⁸ More evidence of the protective effect of tamoxifen among women with a known BRCA1 or BRCA2 mutation is needed, as a small subset analysis showed no effect.¹⁰⁹ However, the benefit of tamoxifen for women with a BRCA1 or BRCA2 mutation has been demonstrated in other indications: it reduced the risk of death in women who received it for adjuvant therapy¹¹⁰ and reduced the risk of contralateral breast cancer in women with a prior history of breast cancer.^{111–113} The optimum length of tamoxifen

therapy for prevention is unknown, although existing data recommend five years, which is the same duration that has been shown to be the best in adjuvant therapy trials.¹¹⁴

Among women at high-risk of breast cancer (according to the Gail model¹⁰⁵), early results of the STAR trial indicate that five years of tamoxifen or raloxifene prophylaxis are similarly protective against invasive breast cancer but that tamoxifen is more effective than raloxifene in reducing the risk of non-invasive breast cancer.¹¹⁵ However, raloxifene demonstrates a toxicity profile superior to that of tamoxifen.¹¹⁶ Women with a known BRCA1 or BRCA2 mutation were eligible to participate in the STAR trial, but efficacy and safety data for this subset of patients are not yet available. Further, only 20% of participants had two or more first-degree relatives with breast cancer, and all were postmenopausal; thus the ability to generalize these results to women with a known BRCA1 or BRCA2 mutation carriers may be limited.

Studies in the United States and United Kingdom suggest that it is challenging to make a decision about pharmacoprevention, especially for premenopausal women experiencing psychological distress. Referral to ancillary supportive services would be appropriate, and effective interventions are required to assist decision-making.^{116,117}

Recommendation for Pharmacoprevention

	Class
1 Women who wish to consider pharmacoprevention should be offered individualized care that includes a full discussion of the potential benefits and possible adverse effects. Women should be directed to support services that will help with decisions on care. When it is available, women should be offered pharmacoprevention as part of a registered clinical trial.	I

Exogenous Hormones

Hormone Replacement Therapy for the Management of Menopausal Symptoms and Effects

Among unaffected women with a known BRCA1 or BRCA2 mutation who have undergone prophylactic BSO, HRT may be considered for the management of menopausal symptoms. Consistent with the Women's Health Initiative (WHI) study,¹⁰⁵ recent studies show an association between the use of a combination of estrogen and progesterone for longer than five years and an increased incidence of breast cancer in the general population.^{95,118-128} In

women with known BRCA1 or BRCA2 mutations, the increased risk is probable though not proven. However, estrogen alone did not increase the risk of breast cancer in the WHI study.¹⁰⁵ Prospective cohort evidence of women with a BRCA1 mutation⁸³ as well as a recent decision analysis model in women with known BRCA1 and BRCA2 mutations⁹⁶ suggests that HRT use after BSO is not associated with significant changes in life expectancy and may in fact extend survival in some women. HRT use in women with a prior history of breast cancer should be carefully discussed with their medical oncologists.

Recommendation for Hormone Replacement Therapy

	Class
1 Women considering HRT should be counselled regarding its risks and benefits.	B
2 Where used, HRT should be used for as short a duration as possible and no later than the natural age of menopause (e.g., 50 years) and, if possible, should consist of estrogen only (see section on prophylactic BSO).	B
3 In women who require therapy for the management of menopausal symptoms, non-hormonal modalities should be considered first.	I
4 HRT should be considered only for the management of severe and persistent menopausal symptoms that fail to respond adequately to non-hormonal interventions.	I
5 HRT should be prescribed only after a thorough discussion and evaluation with a knowledgeable health care practitioner as part of a multidisciplinary team.	I

Oral Contraceptives

Oral contraceptives (OCs) and pregnancy have been shown to be protective against ovarian cancer in the general population.¹²⁹ There is limited and inconsistent evidence that they may also exert these effects in women with known BRCA1 or BRCA2 mutations, especially among those with a BRCA1 mutation.¹³⁰⁻¹³³ Observational studies suggest an increased risk of early onset breast cancer in women with known BRCA1 or BRCA2 mutations,¹³⁴ especially among those with a BRCA1 mutation who first used OCs before 1975, used them before age 30, or used them for five or more years.¹³⁵ There is equivocal evidence that OC use is

associated with an increased risk of breast cancer in the general population when there is a family history of breast cancer.^{136–139} There is limited evidence of a possible protective effect from tubal ligation in women with a BRCA1 mutation.¹³⁰

Recommendation for Oral Contraceptive Use

	Class
1 Women of childbearing age in the general population should be advised about the protective effects of pregnancy and breastfeeding on the risk of ovarian cancer.	B
2 Women under 35 years of age seeking advice on OCs should be counselled regarding the current state of evidence regarding the benefits and risks for women with a known BRCA1 or BRCA2 mutation. In general, the advice regarding oral contraceptives for women of this age should be the same as for the general population of that age.	B
3 Women aged 35 years or over seeking advice on OCs should be counselled regarding the current uncertainty surrounding their use, including a full discussion of potential benefits and harms.	I
4 OC use in women with a prior history of breast cancer should be carefully discussed with their medical oncologists.	I
5 Women considering tubal ligation should be counselled regarding the current state of evidence regarding its potential benefits and risks for those with a known BRCA1 or BRCA2 mutations.	I

Early Detection of Cancer in Men

Prostate Cancer

Men with known BRCA1 or BRCA2 mutations are at increased risk of prostate cancer. Potential surveillance modalities for prostate cancer include prostate specific antigen (PSA) and digital rectal examination (DRE). At this time, there is insufficient evidence either in favour of or against PSA testing or DRE for prostate cancer surveillance in men with known BRCA1 or BRCA2 mutations.¹⁴⁰

Recommendation for the Early Detection of Prostate Cancer

		Class
1	Patients should be counselled regarding the current state of evidence to support or reject PSA and DRE surveillance.	B
2	Men should be advised about the importance of early recognition of symptoms of prostate cancer.	I
3	If a man strongly prefers surveillance, he should be offered both PSA and DRE. The potential psychosocial and clinical impact of false positive and negative results should be clearly communicated and appropriate services put in place. The importance of acting promptly on possible symptoms of prostate cancer should be emphasized.	I
4	Patients should have access to the full range of ancillary supportive care services.	I

Breast Cancer in Men

Men with known BRCA1 or BRCA2 mutations are at increased risk of breast cancer. Surveillance methods for men include BSE and CBE. Currently, there is insufficient evidence on their efficacy to make clear recommendations.¹⁴⁰

Recommendation for the Early Detection of Breast Cancer in Men

		Class
1	Patients should be counselled about their increased risk of breast cancer.	I
2	BSE is not recommended as a routine approach to surveillance for breast cancer in men.	I
3	CBE, performed every 12 months by an experienced clinician, should be considered as a surveillance modality. It should be started upon detection of the mutation or when the patient is at least 10 years younger than the age of the earliest diagnosis of breast cancer in the family.	I
4	Routine mammography surveillance is not recommended.	I
5	Bilateral mammography is recommended as a diagnostic modality in men in whom there is clinical suspicion of abnormality.	I

- 6 Men with known BRCA1 or BRCA2 mutations should have access to gender-specific information and psychosocial care about issues of breast cancer risk. I

- the patient's stage of life (e.g., plans for pregnancy that may influence choice of surveillance and timing for risk-reduction surgery);
- individual physiological or clinical factors (e.g., large fibrocystic breasts may be difficult to evaluate with CBE, and therefore use of other tools would be more appropriate);
- previous risk reduction strategies (e.g., a prior BSO may reduce risk of breast cancer, and thus influence choice between surveillance and prophylactic surgery; type of HRT post-BSO may be influenced by the presence or absence of breast tissue or uterus);
- psychological factors; and
- choices between strategies will be individual to each patient.

CONCLUSION

From the review of the guidelines and of the literature, and in consultation with experts in the field, a number of challenges emerged. First there are some general principles that need to be addressed, implementation challenges to overcome, and further research to be undertaken.

General Principles

The process of making decisions about surveillance and risk-reduction decisions should take into account the unique needs of each high-risk patient. Decisions should reflect the patient's individual values and preferences and be adaptable to local resources, particularly where current evidence is limited. As in any clinical domain, surveillance and risk-reduction decisions require a full discussion of the known and potential benefits and risks, complemented by accurate and appropriate written information. The complexity of the information on risks and benefits suggests that the inclusion of a geneticist, genetic counsellor, or genetic nurse in the clinical team may facilitate effective, informed decision-making. Estimates of age-specific detection rates, specific to the surveillance technique being considered, are important components of the overall information being provided to patients.

Concerns exist about the possible adverse psychological effects associated with breast and ovarian cancer surveillance; therefore, support is important for patients and their families. This has implications for the provision of additional support services, such as appropriate mental health professionals.

Clinical management strategies (including risk reduction and surveillance) should take into consideration the following factors:

- the patient's projected lifespan (especially if the patient has had cancer);

Implementation of Recommendations

Many barriers may stand in the way of the successful implementation of these recommendations. Those who wish to promote the use of these recommendations among their colleagues or in their organization should consider the resources and educational and organizational issues required to support their full implementation. Reviews of the effectiveness of various strategies for implementing evidence in practice may be found at the Effective Practice and Organization Care Group of the Cochrane Collaboration (<http://www.epoc.uottawa.ca/>).

Future Research Needs

There is a pressing need for further rigorous research to strengthen the evidence underlying the recommendations, particularly well-designed studies including randomized controlled trials to confirm the findings of various studies. In addition, an evaluation of these recommendations should be performed to assess their utilization and usefulness.

APPENDIX 1. THE NATIONAL HEREDITARY CANCER TASK FORCE

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Affiliations reflect the period during which individuals participated and may no longer be accurate.

APPENDIX 2. DEVELOPMENT OF THE RECOMMENDATIONS

Introduction

In order to develop these recommendations, the Interdisciplinary Health Research International Team on Breast Cancer susceptibility (InHeRIT BRCA_s), in collaboration with the Canadian Association of Provincial Cancer Agencies (CAPCA) and Health Canada, established the National Hereditary Task Force in March 2002. The Task Force initiated the development of consensus recommendations addressing education, counselling, and clinical management issues for HBOC.

The recommendations are based on current practice in high-risk cancer clinics providing care for individuals with known BRCA1 or BRCA2 mutations or with a strong family history of breast or ovarian cancer.

Recommendation development process

The recommendations were developed through multidisciplinary process to reflect diverse professional disciplines, clinical practice areas, and geographic locations (Appendix 1). A first consultation was held in November 2002 in Quebec City with national and international experts, including health providers, researchers, and representatives from consumer groups and governmental agencies. During this meeting, a first draft of the recommendations was developed using a formal consensus process involving key stakeholders.

We decided that an efficient way to ensure that the Canadian recommendations reflect the most up to date evidence is to scrutinize each recommendation with reference to two published guidance documents on the clinical management of patients at increased risk of HBOC. The first was produced in the UK by the National Institute for Clinical Excellence² and the second in France by an ad hoc committee, led by Dr François Eisinger, for the Ministère de la Santé.³ Several guidelines were excluded from the comparison exercise because they were not developed using a systematic review of the literature or were published several years ago. The Editorial Group of the National Hereditary Task Force then carried out a comparative review of existing evidence-based guidelines, supplemented by an extensive literature search. Tables were drawn up to allow direct comparison of the Canadian consensus recommendations with the evidence-based guideline documents.^{2,3}

These tabulated comparisons were sent for clinical expert review (Appendix 1). This group was asked specifically to review and evaluate the Canadian recommendations in comparison with the guidelines from the UK² and France.³ The reviewers were asked to appraise the Canadian recommendation content and the references supplied, to note any

missing information, and to assess their applicability and utility to the Canadian situation. They were also asked to suggest topics for consideration for any future updated version.

The Editorial Group of the National Hereditary Cancer Task Force was then asked to review the comments of the clinical experts, specifically assessing whether they had reached consensus on the proposed recommendations and/or whether there were conflicting views that needed to be reconciled. A final Task Force workshop was held in Ottawa in September 2004 to review all recommendations and address any outstanding areas of uncertainty or disagreement. Thereafter the editorial group continued to revise and adapt the recommendations in light of new scientific developments.

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