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Clinical Practice Guidelines - Breast Disease Site

Guideline Title:	Chemoprevention of Breast Cancer in High Risk Patients	**Date:**	**(O):**	May 31, 2011
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Tumor Group:	Breast Disease Site Group	**Page:**		1 of 6
Issuing Authority:	Dr. Kara Laing Clinical Chief, Cancer Care Program	**Date Signed:**		May 23, 2012
Adapted From:	Alberta Health Services "risk reduction and surveillance strategies for individuals at high genetic risk for breast and ovarian cancer" guideline, April 2011.			

Introduction:

Patients, deemed to be at high risk for the development of breast cancer, are currently referred to medical oncology by their surgeon, family physician or by medical genetics. Management of these women at increased risk should be a comprehensive approach including a quantitative risk assessment, counseling appropriate to the individual's risk, the opportunity for genetic testing where appropriate, and a specific plan of medical surveillance and possible pharmaceutical intervention. A risk assessment is carried out using a tool such as the Gail model (1,2), which takes into account the patient's own personal medical history, reproductive history, and history of breast cancer among first degree relatives, to help define the individual's own personal risk. A person determined to have a ≥ 1.66% five year risk of breast cancer is considered high risk according to the Gail model.

The patient may be a genetic carrier of known mutations, such as BRCA1 and BRCA2 (3-5), as well as E-Cadherin gene mutations (6-11) and have already undergone genetic testing or are from families, with well-documented, pedigrees of known genetic carriers. There are also other patients who meet the criteria for high risk status, but may not have had genetic testing, or may not carry these particular mutations. Once the risk assessment is completed, the oncologist will determine whether the risk warrants intervention and if so, will offer the patient chemoprevention either in the form of selective estrogen receptor modulators (SERMs) or aromatase inhibitors.

The potential benefit of using the SERMs, tamoxifen and raloxifene, for chemoprevention would be primarily to help reduce the risk of developing breast cancer in the high risk population. Also, these drugs may have favorable effects on blood lipids and bone density. The potential risks, though relatively small, include development of endometrial cancers, thromboembolic events and cataract formation, while unpleasant side effects such as a notable increase in hot flashes are known to influence quality of life. Exemestane, an aromatase inhibitor, can also significantly reduce invasive breast cancers in postmenopausal women who are at moderate increased risk,

and is associated with no serious side effects and only minimal changes in health-related quality of life (12).
The oncologist will determine if the patient may be a candidate for breast MRI screening, and whether follow-up is required at the cancer center or can be carried out by their referring or family physician.

Question:

What is the optimal chemoprevention management offered to high risk patients?

Target Population:

Patients who meet the high risk criteria for the development of breast cancer.

Supporting Evidence:

The current standard of treatment offered to high risk patients would be tamoxifen 20mg/daily taken orally, for five consecutive years, as per the National Surgical Breast and Bowel Project (NSABP) P-1 clinical trial (13,14). Other tamoxifen prevention trials have also been reported in the past, such as the Royal Marsden Hospital study (15,16), the Italian Tamoxifen Prevention study (8,9), and the first International Breast Cancer Intervention study (IBIS-1) (17,18), but the NSABP P-1 has historically been recognized as the landmark trial proving tamoxifen to be an effective chemopreventative agent. The conclusion reached from this trial suggests that tamoxifen reduces the risk of invasive breast cancer by 49% compared to placebo. The Early Breast Cancer Trialists' meta-analysis confirmed that the risk of contralateral primary breast cancer is substantially reduced by 5 years of tamoxifen therapy in women with first breast cancers that are estrogen receptor-positive or have an unknown estrogen receptor status (19).

An alternative to tamoxifen for postmenopausal women is raloxifene 60mg/daily, taken orally, for five consecutive years, as per the STAR trial (Study of Tamoxifen and Raloxifene) (20,21). This trial concluded that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer. Also, findings suggest that though the risk of thromboembolic events and cataracts exist with both SERMs, the risk appears to be less for raloxifene. However, raloxifene did not reduce the risk of developing ductal carcinoma insitu (DCIS) in the STAR trial. Both of these drugs have received FDA approval for use in chemoprevention of breast cancer.

Another alternative for postmenopausal patients is exemestane 25mg/daily, taken orally, for five consecutive years as per the recently published NCIC CTG MAP.3 clinical trial (12). In this large chemoprevention trial, 4560 women were randomly assigned to exemestane or placebo. At a median follow-up of 35 months, there was a 65% relative reduction in the annual incidence of invasive breast cancer in the exemestane arm compared to the placebo arm. No significant differences were noted between the two arms in terms of skeletal fractures, cardiovascular events, other cancers, or treatment-related deaths.

The consultation with the medical oncologist will also include a thorough discussion with the patient of the known side effects of tamoxifen, raloxifene, or exemestane to allow the patient to make a fully informed treatment decision.

Recommendations:

All premenopausal patients ≥ 35 years of age and postmenopausal patients who are deemed high risk for the development of breast cancer, and with no contraindications, should be offered tamoxifen 20mg/daily taken orally, for five consecutive years. Raloxifene 60mg/daily taken orally, for five consecutive years is an option for postmenopausal patients only. Exemestane 25mg/daily taken orally, for five consecutive years is also an option for postmenopausal patients only.

Search Strategy:

Literature searches were conducted in Pubmed, CINAHL, and the Cochrane Library, using keywords “breast” AND “neoplasms” AND “selective estrogen modulators” AND “primary prevention” OR “risk reduction” AND “tamoxifen” AND/OR “raloxifene”. Guideline searches were also carried out on the websites of the world’s most highly respected cancer organizations and agencies. All selected literature articles and source guidelines were in English and dated after the year 2000 (unless the selection was an earlier landmark study) up to the March 2011. The inclusion/exclusion process consisted of selecting guidelines from reputable cancer organizations with preference given to those from Canadian sources where possible. Twelve source guidelines were identified but only five were chosen to be reviewed due to currency of content (22-33).

The five identified source guidelines (29-33) were put through the ADAPTE process (34) with an AGREE II assessment (35), and the Alberta Health Services (AHS) “risk reduction and surveillance strategies for individuals at high genetic risk for breast and ovarian cancer” guideline was chosen to be adapted for use in our guideline (32). The AHS guideline was selected as the optimal choice due to its applicability, quality and currency of content.

There has been much debate but no consensus on the ‘grading of evidence’ in Canada. Presently, Canadian experts in the field of guideline development are involved in an ongoing in-depth analysis of the functionality of grading. Until such time as a report is released of their findings, and a consensus reached on whether to assign a grade of recommendation to a guideline, this group has decided to forgo the use of grading.

No competing or conflicts of interest were declared.

Disclaimer:

These guidelines are a statement of consensus of the Breast Disease Site Group regarding their views of currently accepted approaches to diagnosis and treatment. Any clinician seeking to apply or consult the guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

Contact Information:

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