CURRENT ONCOLOGY
A Canadian Cancer Research Journal

Supplemental Materials for:

Recommendations on breast cancer screening and prevention in the context of implementing risk stratification: impending changes to current policies

J. Gagnon, E. Lévesque, the Clinical Advisory Committee on Breast Cancer Screening and Prevention (F. Borduas, J. Chiquette, C. Diorio, N. Duchesne, M. Dumais, L. Eloy, W. Foulkes, N. Gervais, L. Lalonde, B. L'Espérance, S. Meterissian, L. Provencher, J. Richard, C. Savard, I. Trop, N. Wong), B.M. Knoppers, and J. Simard

Curr Oncol. **2016 Dec;23(6):e615-e625**

Supplementary material: Background literature supporting the recommendations.

1. Risk assessment

1.1 Referral to a breast clinic for risk assessment

₪ Previous history of atypical ductal hyperplasia

Evidence from the literature:

Women who have been diagnosed with atypical ductal hyperplasia have a relative risk of 3.7 to 5.3 for developing breast cancer. [1,2,3,4,5,6]

Diagnosis of atypical ductal hyperplasia in one breast equally increases ipsilateral and contralateral risk of developing a breast cancer.[3] In one U.S. study, only 56% of the cancer cases developed after a diagnosis of atypical ductal hyperplasia were ipsilateral. The relative risk of developing breast cancer with a history of atypical hyperplasia was 4.38. [7]

According to some authors, women with a history of atypical ductal hyperplasia of the breast should be evaluated in a specialized breast clinic to determine monitoring and risk reduction strategies. [2,5,8,9,10]

Studies suggest that a family history of breast cancer could contribute to an increased risk of developing breast cancer in women with a personal history of atypical ductal hyperplasia, which supports the referral of these women to a specialized breast clinic to determine the appropriate risk level. 3,[11] The relative risk could be as high as 5.37. [12]

₪ Previous history of lobular neoplasia

Context:

The term lobular neoplasia used in this document includes lobular carcinoma *in situ* and atypical lobular hyperplasia.

Evidence from the literature:

Women with a history of lobular neoplasia have a relative risk of 2.1- 6.8 of developing breast cancer. [5,6,7,11,13]

The annual risk of breast cancer after lobular neoplasia is approximately 1%,[14,15,16] and the lifetime risk of breast cancer in women with a history of lobular neoplasia in the breast is estimated to be 10-20%. [3,6,17]

₪ Prior history of columnar cell change with atypia

Evidence from the literature:

The association between breast cancer and columnar cell lesions, with or without atypia and diagnosed from breast biopsies, is controversial. Some studies suggest that when these lesions are found through biopsy, there is no increased risk of finding a cancer during surgery. However, other studies suggest the opposite. Some studies only include a small number of women, and/or have certain experimental design flaws. In addition, very few studies examined columnar cell lesions without atypia.

In one study, no invasive breast cancer was detected during pathological examinations of surgically removed specimens with columnar cell lesions. However, few women participated in the study, and it did not specify whether non-invasive cancer was found. [18]

One study suggests that columnar cell lesions detected during biopsy can indicate increased risk of breast cancer, but this increase is not independent of other proliferative changes in the breast. [19]

Several studies showed underestimation rates in surgery to the extent of 6 to 19% for atypical columnar cell lesions. [20,21,22,23,24]

One study (n=20 women) showed that 10% of columnar cell lesions found in the biopsy were underestimated in surgery. This article did not differentiate between lesions with or without atypia.[25]

One study suggested the presence of columnar cell lesions was associated with breast density, which is a breast cancer risk factor in itself. Half of the lesions (20/40) were not atypical. Two cases of cancer were observed during surgery, and only in atypical lesions (10%, 2/20).[26]

₪ Prior history of thoracic radiation therapy before age 30

Evidence from the literature:

Women who have been exposed to a strong dose of ionizing radiation (radiotherapy or survivors of atomic bombs or nuclear accidents) have a higher risk of developing breast cancer. [27,28,29,30,31]

The risk is highest when the exposure to radiation occurred during puberty, between ages 10 and 14, but high risk is observed in women who were exposed to these doses up until age 30. [32]

In women of all ages (including women over 30) diagnosed with Hodgkin's disease, breast cancer carried the strongest excess risk observed of any cancer, with a relative risk of approximately 1.5, [33,34,35] although higher risks were reported in other studies (4.1 to 5.6). [36,37,38,39]

Breast cancer is one of the major secondary conditions among women who received radiotherapy before age 30 for Hodgkin's lymphoma and long-term follow-ups. [35,37,38]

The risk of breast cancer associated with thoracic radiotherapy is even higher in women who received mantle field radiation,[40] or who did not receive chemotherapy for their lymphoma. [41]

One study identified different risks of breast cancer over a 30-year period according to the age of exposure, the dose of radiation and the use of alkylating agents. Table 1 summarizes the risks identified in this study.[42]

Table 1: Risk of breast cancer following mediastinal radiotherapy based on radiation dose and the use of alkylating agents

Age at diagnosis	Mediastinal radiotherapy (Gy)	Absolute risk of breast cancer over 30 years of follow-up (%)	
		Alkylating agents used	Alkylating agents not used
15	0	0.8	1.7
	20-<40	4.1	8.5
	≥40	5.0	10.3
20	0	1.6	3.4
	20-<40	7.9	16.0
	≥40	9.5	19.1
25	0	2.6	5.5
	20-<40	12.5	24.6
	≥40	15.0	29.0
30	0	4.0	8.2
	20-<40	18.1	34.1
	≥40	21.6	39.6

Recommendations from organizations:

For women who received thoracic radiation between ages 10 and 30, NCCN recommends annual mammograms and MRI screening 8 to 10 years after treatment, but not before age 25. [43]

For women who received thoratic radiotherapy before age 30, Cancer Care Ontario offers annual mammograms and MRIs starting at age 30 but at least 8 years after the radiotherapy. [44]

The American Cancer Society recommends annual MRI screening to women who have received thoracic radiotherapy between ages 10 and 30, without a specific starting age. [45]

₪ Previous history of a biopsy with benign results

Evidence from the literature:

The National Institutes of Health (NIH) Breast Cancer Risk Assessment tool includes the medical history of breast biopsies. Women who have a history of breast biopsies could be at a higher risk for breast cancer since they have the characteristic higher breast tissue activity and breast changes that lead to biopsies. [46]

Studies have shown that a history of breast biopsies with benign results is associated with a relative risk of 1.4 to 1.87 of developing breast cancer.[1,47,48]

₪ Prior history of proliferative lesions without atypia

Context:

By "proliferative lesions without atypia", we mean usual intraductal hyperplasia, intraductal papilloma, sclerosing adenosis, radial scars and simple fibroadenomas.

Evidence from the literature:

Data suggests that proliferative breast lesions without atypia are breast lesions that will either evolve slowly into breast cancer or not at all. [2,3,8,10,49,50,51]

One American study showed a relative risk of 1.51 of developing breast cancer among women who have a history of proliferative lesions without atypia, compared to women with a history of non-proliferative lesions. [12]

₪ Prior history of a non-proliferative lesion without atypia

Context:

In this context, "non-proliferative lesion without atypia," is understood as: simple cysts, papillary apocrine changes, epithelial-related calcifications and moderate hyperplasia of the usual type.

Evidence from the literature:

Non-proliferative lesions constitute a heterogeneous group of lesions without any particular clinical significance. [52,53,54]

Columnar cell change without atypia

Refer to the section above on columnar cell change with atypia.

1.2 Referral to a genetics service

Context:

In addition to breast cancer risk, the BOADICEA risk calculation tool assesses the risk of carrying a mutation in the BRCA1/BRCA2 genes. The percentage is often calculated in a genetics clinic to determine eligibility for a genetic analysis that will either confirm or disconfirm the presence of a mutation in the BRCA1/BRCA2 genes. However, this percentage is not currently used as a criterion for referral to a genetics service in Quebec or elsewhere.

The criteria for **referral** to a genetics service are different from the **eligibility** criteria for genetic analysis.

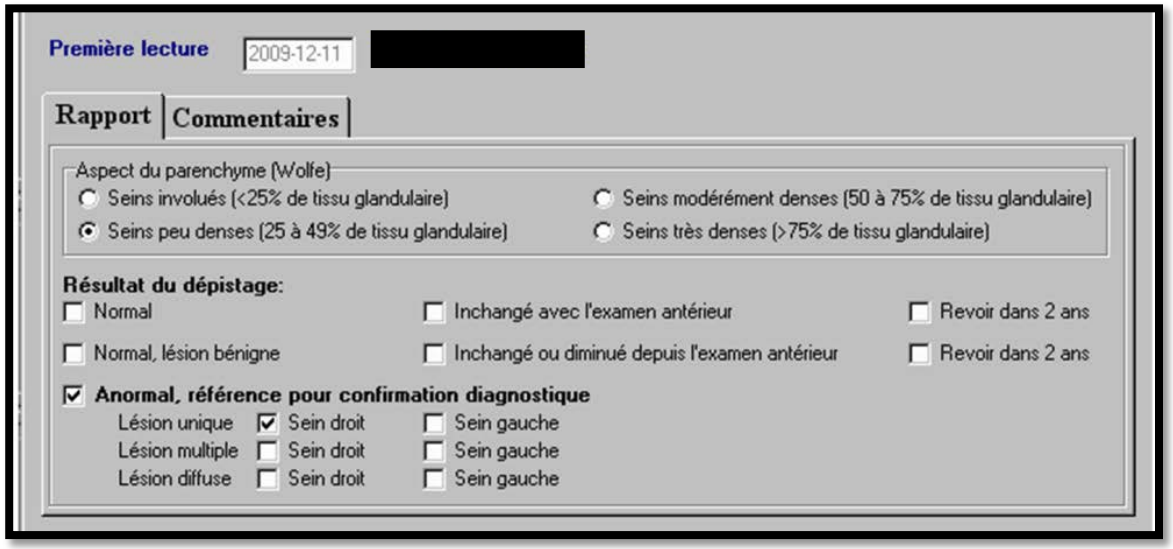
Recommendations from organizations: A 10% threshold is generally accepted as a criterion designating eligibility for genetic testing for mutations of the BRCA1/BRCA2 genes in an individual who has developed breast or ovarian cancer.[55,56,57,58]

2. Breast density

Context:

Presently, breast density is visually estimated for all mammographic screening done within the Quebec Breast Cancer Screening Program (see figure 1).

Figure 1: Data entry for the radiographic report in the PQDCS (in French)



Approximately 27% of Quebec women between the ages of 40 and 49 reported undergoing mammographic screening in the last two years (i.e., outside of the Quebec Breast Cancer Screening Program).[59]

The BOADICEA risk calculation tool will soon include breast density as a factor for calculating individual risk. It will be possible to calculate the risk with or without breast density, but the calculation will be more precise if density is included.

Evidence from the literature:

In the literature, breast density is often divided as indicated in table 2.

Table 2: Categorization of breast density and number of women in each category

BI-RADS category 4th edition	**BI-RADS category** 5th edition	**Percentage of dense tissue (%)**	**Categorization according to the PQDCS**	**Women ages 40-49 in each category** [60]	**Women ages 50-59 in each category** [60]	**Women ages 60-69 in each category** [60]
1	a	0-25%	Mostly fatty breasts	3%	6%	12%
2	b	26-50%	Slightly dense breasts	23%	37%	43%
3	c	51-75%	Moderately dense breasts	57%	41%	41%
4	d	76-100%	Extremely dense breasts	17%	8%	4%

Breast density is strongly linked to breast cancer risk. A meta-analysis using data from women ages 40 to 49 showed a relative risk of breast cancer of 0.46, 1.62 and 2.04 for women with a breast density in categories a, c and d respectively, compared to women with category b breast density.[48]

Breast density also affects the mammographic sensitivity and the risk of developing an interval cancer. One study (see below table) showed a more elevated risk of interval cancer for women who have more than 75% dense tissue, compared to women with less than 10% dense tissue. The effect was also noted in women who have between 50-74% dense tissue. Since the increased risk of interval cancer was primarily within the first year after the mammogram, the authors concluded that the cancer was likely hidden by the dense tissue visualized in the mammogram. Table 3 shows the relative risk of cancer detection during a mammogram, less than 12 months after a negative result and over 12 months after a negative result. [61]

Table 3: Breast density and breast cancer risk depending on the detection method

	Relative risk (95% Confidence intervals)			
Breast density	All detection methods	Detection by screening	Detection < 12 months after a negative screening	Detection ≥ 12 months after a negative screening
<10%	1.0	1.0	1.0	1.0
10 to <25%	1.8 (1.4-2.2)	1.6 (1.2-2.2)	2.1 (0.9-5.2)	2.0 (1.2-3.4)
25 to <50%	2.1 (1.6-2.6)	1.8 (1.3-2.4)	3.6 (1.5-8.7)	2.6 (1.5-4.6)
50 to <75%	2.4 (1.8-3.3)	2.0 (1.3-2.9)	5.6 (2.1-15.3)	3.1 (1.6-6.2)
≥ 75%	4.7 (3.0-7.4)	3.5 (2.0-6.2)	17.8 (4.8-65.9)	5.7 (2.1-15.5)

Another study also showed an increased relative risk of cancer being detected in the time between two screenings, rather than during screening, when density increases. Compared to women who have categories a and b breast density, the relative risk was 3.02 for women in category c and 6.14 for women in category d. [62]

Breast density generally decreases with age. [63]

Recommendations from organizations:

The Canadian Association of Radiologists recommends the use of the American College of Radiology BI-RADS classification system for writing mammographic screening reports. The BI-RADS system should include breast composition in the report (density categories a, b, c, d). [64,65]

The California Breast Density Law provides that a woman must be informed via written report if their mammogram detects heterogeneously dense breasts (category c) or extremely dense breasts (category d). [66] There are currently 19 states with similar laws in the United States. [67]

The Ontario Breast Screening Program automatically invites women with over 75% dense tissue to annual screening by mammogram, instead of screening every two years. Breast density is reassessed every year.[68]

3. Screening

3.1 Women near population risk

Context:

The PQDCS offers screening by mammography to women. For more information, visit the PQDCS website at: www.msss.gouv.qc.ca/sujets/santepub/pqdcs/index.php?home.

3.2 Women at intermediate risk

₪ Mammography

Evidence from the literature:

Using a simulation model, one study concluded women ages 40-49 with twice the average breast cancer risk (around 3% over 10 years for a 40 year-old woman) have a risk-benefit ratio similar to women ages 50 to 74 among the general population with mammographic screening every two years. [69]

Recommendations from organizations:

NICE recommends offering annual mammograms to women ages 40 to 49 who are at moderate risk (between 17% and 30% for life, according to their definition, or a risk of 3% to 8% between ages 40 and 49). These recommendations were established using cost-effectiveness analyses. [55]

The National Breast and Ovarian Cancer Centre offers annual mammograms to women ages 40 and older at moderate risk, if they have a first degree relative diagnosed with breast cancer before age 50. A woman is considered at moderate risk if her calculated risk of breast cancer up until age 75 is between 12.5% and 25%. [70] The reason for this recommendation is not specified.

₪ High breast density

Evidence from the literature:

One study (see table 3 above) showed a higher risk of interval cancer among women with more than 75% dense tissue, compared to women with less than 10% dense tissue. This effect was also present for women who have between 50-74% dense tissue. Since the risk increase in interval cancer was primarily within the first year following the last screening, the authors concluded that the increase was likely due to dense tissue masking the cancer during the mammogram. The above table shows the relative risk of having a cancer detected via mammography, less than 12 months after a negative mammography screening, and more than 12 months after a negative screening. [61]

Another study also showed an increase in the relative risk of the cancer being detected in the interval between two screenings, rather than during a screening, when density increases. Compared to women whose breast density is in categories a and b, the relative risk was 3.02 for women in category c and 6.14 for women in category d. [62]

Recommendations from organizations:

The Ontario Breast Screening Program automatically offers women with over 75% dense tissue annual mammography screening, instead of once every two years. Breast density is reassessed with each mammogram, until the density drops below 75%. [68]

₪ Ultrasound

Evidence from the literature:

One study assessed the effect of combining screening ultrasound with mammography in a group of 2,809 women with an elevated breast cancer risk. [71] Table 4 summarizes the evidence obtained in terms of sensitivity and specificity.

Table 4: Sensitivity and specificity of mammography and ultrasound screening, alone and combined

Screening method	Sensitivity	Specificity
Mammography	52.0%	91.3%
Ultrasound	45.3%	89.9%
Mammography and ultrasound	76.0%	84.1%

One study evaluated the effect of combining a screening ultrasound with mammography for women who have an elevated breast cancer risk and dense breasts (density >50%). The additional ultrasound identified 3.7 cancer cases per 1,000 screenings. Ultrasound increased sensitivity (76% versus 52% with mammography alone), but reduced specificity (84% versus 91%) and the positive predictive value (16% versus 38%). [72]

One retrospective study found a similar sensitivity when ultrasound screening was combined with mammography among women with category c-d density compared to women who have category a-b density and mammography screening. [73]

A research team performed ultrasound screening on 22,131 women with negative mammograms. The ultrasound screening detected 1.85/1,000 additional breast cancer cases (a total of 41, of which 37 were invasive). No significant difference was observed between women with category a-b density compared with category c-d density. [74]

No randomized trial studying ultrasound screening and its potential to reduce mortality has been conducted.

₪ Age when screening ceases

Recommendations from organizations:

NICE recommends that mammography screening continue until age 73 for women at both population and intermediate risk. [55]

3.3 Women at high risk

₪ Mammograms

Recommendations from organizations:

NICE recommends performing annual mammograms on women with high risk (over 30%) between ages 40 and 59 and to consider annual mammograms between ages 30 and 39. These recommendations were established using cost-effectiveness analyses. [55]

Cancer Care Ontario offers annual mammograms to women with high risk (over 25% lifetime risk) between ages 30 and 69. This recommendation is based on a review of evidence. [44]

The National Breast and Ovarian Cancer Centre suggests that screening include annual mammograms for women with high risk (over 25% lifetime risk). [70]

The NCCN recommends annual mammograms for women ages 30 and older and for whom family history puts them at greater than 20% risk. This recommendation is based on a review of evidence with expert consensus. [75]

₪ Magnetic Resonance Imaging (MRI)

Evidence from the literature:

The Ontario Breast Cancer Screening Program published preliminary findings from screening of 2,359 women enrolled in the program up until now. Of the 35 cancer cases detected, none were detected by mammography alone, 23 were detected by MRI alone, and 12 were detected using both screening methods.[76]

Table 5: Sensitivity and specificity of mammography and MRI, alone and combined, in a high-risk population.

Screening method	Sensitivity	Specificity
Mammography	36.8%	97.1%
MRI	80.1%	97.0%
Mammography and MRI	87.4%	94.2%

Table adapted from the Program in evidence-based care and Cancer Care Ontario.[77]

Recommendations from organizations:

The American Cancer Society recommends annual MRI screening starting at ages 25-30 for women with a breast cancer risk of over 20-25%, calculated according to models based on family history. This conclusion is based on a review of studies for this population, revealing an increase in the number of cancer cases detected when MRI screening is combined with mammography. [45]

The NCCN recommends considering annual MRI for women whose risk is over 20%, calculated with risk assessment models using family history. This recommendation is based on an expert consensus with a review of evidence showing that MRI increases the number of detected cancer cases among women with high risk. [75]

Cancer Care Ontario offers annual MRI screening to women from 30 to 69 years of age whose risk of breast cancer is over 25%. This recommendation is based on a review of evidence showing that MRI increases the number of detected cancer cases among women at an elevated risk. [44]

NICE recommends annual MRI screening among women with an elevated breast cancer risk (>30%) only if they are also at greater than 30% risk for carrying a BRCA1/2 or TP53 gene mutation. The organization also recommends starting MRI screening at age 30 and mammography screening at age 40, but mammography screening can be considered starting at age 30. These recommendations were established using cost-effectiveness analyses. [55]

₪ Ultrasound

Context:

No randomized trial conducted on ultrasound screening has been reported and there is no conclusive evidence demonstrating that this technology reduces mortality.

Evidence from the literature:

One retrospective study found a similar sensitivity when ultrasound screening is used in combination with mammography among women with a category c-d density compared to women with a category a-b density and mammography screening. [73]

A research team performed ultrasound screening on 22,131 women with negative mammograms. The ultrasound screening detected 1.85/1,000 additional breast cancer cases (a total of 41, of which 37 were invasive). No significant difference was observed between women with category a-b density when compared with category c-d density. [74]

Recommendations from organizations:

The American College of Radiology recommends ultrasound screening for women who are eligible for MRI but who cannot tolerate it. [78]

NICE states that ultrasound screening is possible for women who are eligible for MRI but for whom it is contraindicated. [55]

Cancer Care Ontario offers ultrasound screening to women for whom MRI is contraindicated. [79]

₪ Age when screening ceases

Recommendations from organizations:

Cancer Care Ontario provides annual MRI and annual mammography until age 69 for women with elevated risk. Screening then consists of mammograms every two years up until age 74. [44]

NICE offers MRI to eligible women until age 49. To continue MRI screening after age 50, NICE requires the mammography results show dense breast tissue. Mammography screening continues until age 73 in accordance with the United Kingdom's public screening program. [55]

The NCCN and the American Cancer Society do not suggest an age when MRI or mammography screening should cease. [45,75]

3.4 Tomosynthesis

Context:

Tomosynthesis is a digital mammography technique that produces multiple images of the entire breast from different angles while reducing the effect of overlapping tissue. Unlike digital mammography, where each image is created from a single exposure to x-rays, tomosynthesis images are reconstructed from a series of low-dose exposures when the x-ray tube moves in arcs or linearly above the breast. A conventional mammogram and tomosynthesis can be conducted during the same test on the same scanner. [80]

In Quebec, few clinics and hospitals are equipped with tomosynthesis scanners at present.

The clinical use of tomosynthesis has been approved by Health Canada and the FDA (U.S. Food and Drug Administration). [64]

Evidence from the literature:

The goal of the Oslo Tomosynthesis Screening Trial is to compare digital mammography alone to being combined with tomosynthesis for women ages 50 to 69. A 27% increase in the number of cancer cases detected was observed in the group scanned using tomosynthesis, as well as a 15% reduction in false-positives. There was a 40% increase in the detection of invasive cancers. [81]

The Oslo Tomosynthesis Screening Trial also aimed to compare the efficiency of combining tomosynthesis with conventional mammography, versus tomosynthesis and the synthetic 2D image obtained using tomosynthesis. There was no difference in terms of the rates of cancer detection and false-positives. Using a synthetic 2D image along with tomosynthesis, instead of mammography, would reduce the radiation dose by around 45% without compromising performance.[82]

One retrospective study found no increase in breast cancer detection using tomosynthesis combined with mammography (versus mammography alone), but found that tomosynthesis significantly reduced the recall rate among women with dense breasts and among younger women. Table 6 shows the results of this study regarding recall rates.[83]

Table 6: Recall rates for tomosynthesis in combination with mammography, and digital mammography alone

	Recall Rates (%)				
Parameter	Tomosynthesis plus mammography	Digital mammography alone	P value	Percent reduction of recall rate (95% confidence interval)	Number of tomosynthesis + mammography examinations needed to prevent one recall
Overall	8.4	12.0	<0.01	29.7 (19.1, 36.5)	28.0
Breast density					
Mostly fatty	5.0	7.2	0.12	30.0 (-7.8, 54.5)	46.3
Slightly dense	7.9	10.6	<0.01	25.0 (12.5, 35.7)	37.9
Moderately dense	10.2	16.7	<0.01	39.4 (29.1, 48.2)	15.2
Extremely dense	6.7	15.6	<0.01	57.3 (29.2, 74.2)	11.2
Age					
< 40 years	11.0	25.0	<0.01	55.8 (25.7, 73.7)	7.2
40-49 years	10.4	16.3	<0.01	35.8 (24.2, 45.7)	17.2
50-59 years	7.6	10.6	<0.01	28.0 (12.7, 44.6)	33.7
60-69 years	7.4	10.7	0.01	30.3 (12.3, 44.6)	31.0
≥ 70 years	6.7	7.9	0.38	15.4 (-21.3, 41.0)	82.6

Recommendations from organizations:

The INESSS concluded in an information note on Digital Breast Tomosynthesis (DBT) that "DBT is a promising technological advance that has moved beyond the technological development stage and is about to move beyond the investigational phase. However, there is still not sufficient standardization from an operational standpoint for it to be included in a population-based screening program." [84]

3.5 Clinical breast exam

Context:

There is currently no consensus in the literature regarding the role of the clinical breast exam in screening.

Evidence from the literature:

A review of the literature reveals that clinical breast exam sensitivity varies between 40 and 69%, specificity between 88 and 99%, and positive predictive value between 4% and 50%. [85]

One study compared women who were screened with mammography alone to women screened with mammography and the clinical breast exam. This study was conducted with the general population of women following the Ontario screening program, among women without a history of breast cancer, breast implants or acute symptoms. The results show that adding the clinical breast exam only allows for the detection of 0.4 additional cases of cancer per 1,000 women in screening, compared to mammography alone, and increases false-positives by 2.2%. The study does not provide analysis for other levels of breast cancer risk. [86]

The CNBSS-2 study is the only one to have compared the clinical breast exam alone versus mammography plus the clinical exam. This study did not show a difference in mortality between women who underwent screening using mammography and the clinical breast exam, compared to women screened with the clinical exam alone. [87]

One study conducted in a routine clinical setting shows that some 5% of cancers detected in screening were detected by the clinical breast exam while the mammography screening was negative. [88]

In a population of women at high risk, where a total of 165 cases of breast cancer had been diagnosed, the clinical breast exam contributed to 30% of the diagnoses, and detected 9 cancer cases that were invisible to mammography screening. [89]

Recommendations from organizations:

The Canadian Task Force on Preventive Health Care recommends against performing clinical breast exams in breast cancer screening for women ages 40-74 with average risk. [90]

The recommendations for adult periodic medical evaluation from the Collège des Médecins du Québec states that the clinical breast exam can provide additional information, but is no longer officially recommended for screening. [91]

Cancer Care Manitoba recommends against performing the clinical breast exam in routine screenings. [92]

According to the U.S. Preventive Services Task Force, there is insufficient evidence to recommend clinical breast exams for breast cancer screening. [93,94]

NICE recommends against routine clinical breast exams in its general guideline for breast cancer and in its guideline for family breast cancer and for asymptomatic women. [55,95]

The NCCN recommends that women with a risk of breast cancer comparable to the general population and who are between the ages of 25 to 39 receive a clinical breast exam every 1 to 3 years, then annually starting at age 40. The NCCN also recommends that women ages 35 and over with a $\geq$1.7% risk of breast cancer over 5 years, receive a clinical breast exam every 6 to 12 months. For women with a >20% lifetime risk, clinical breast exams should be performed every 6 to 12 months starting at age 30. Finally, women with a strong suspicion of a genetic predisposition (according to the Claus, BRCAPRO, BOADICEA or Tyrer-Cuzick models) should receive clinical breast exams every 6 to 12 months starting at age 25. In addition, the NCCN recommends that women ages 35 and over with a history of lobular neoplasia receive a clinical breast exam every 6 to 12 months. [75]

The ACOG recommends the clinical breast exam annually for women ages 40 and over, and once every 1 to 3 years for women ages 20 to 39. [96]

The BC Cancer Agency recommends an annual clinical breast exam for women ages 20 and up.[97]

The World Health Organization does not recommend the clinical breast exam in screening. [98]

According to the Memorial Sloan-Kettering Cancer Centre, women with an average risk of breast cancer should get annual clinical breast exams starting at age 25. For women with a first-degree relative diagnosed with breast cancer, the clinical breast exam should be performed every 3 to 6 months, and 10 years before the age when the cancer appeared in the relative. For women with a history of lobular neoplasia or atypical hyperplasia, a clinical breast exam should be performed every 3 to 6 months after diagnosis.[99]

3.6 Women with breast implants

Context:

The information discussed in this section regards women with cosmetic breast implants for breast augmentation. It does not concern women who received breast implants following a mastectomy (to prevent or following breast cancer).

Evidence from the literature:

One systematic review and meta-analysis had revised several studies on breast cancer detection and the survival of women with breast implants. The results would suggest diagnosis at a more advanced stage for women with breast implants than for women without implants. They also revealed a higher mortality linked to breast cancer in women with implants than in women without them. However, the number of studies revised was low and several of them were found to contain significant biases. [100]

Studies done on augmented patients with palpable breast cancer showed that screening mammography sensitivity was reduced (41.4-66.3%) and that the number of false-negatives was increased. [101,102,103]

One literature review concludes that mammography could potentially be useful in screening women with breast augmentation, but that its usefulness remains controversial. [104] Only one study looked at the efficiency of ultrasound compared to mammography. It was a retrospective study done in Taiwan that showed highly increased sensitivity (87.5% vs. 25%) of the ultrasound compared to mammography among women with breast implants. This study was based on low numbers of participating women. [105]

Recommendations from organizations:

The First International Breast (Implant) Conference recommended that screening for women with breast augmentation be done with mammography. [106]

4. Prevention

4.1 Habits and lifestyle choices

₪ Alcohol

Evidence from the literature:

The Canadian Centre on Substance Abuse conducted a literature review and summarized evidence concerning the increase in the relative risk of death from breast cancer per level of alcohol consumption, as illustrated in table 7. [107]

Table 7: Percentage of breast cancer risk increase according to the daily consumption of alcohol

Proportion of all deaths, 2002-2005	Percentage of breast cancer risk increase Daily amount of alcohol consumption				
	1 glass	**2 glasses**	**3 to 4 glasses**	**5 to 6 glasses**	**Over 6 glasses**
1 out of 45	13%	27%	52%	93%	193%

It should be noted that the increase in breast cancer risk linked to alcohol consumption follows a dose-response curve, and consequently, any level of consumption can potentially increase the risk of breast cancer.[108]

Recommendations from organizations:

In 2011, the Canadian Centre on Substance Abuse conducted a review of conclusive evidence on alcohol consumption and established guidelines for low-risk consumption (not directly pertaining to breast cancer risk). The group recommended that adult women limit consumption to 0 to 2 glasses of alcohol a day, with a maximum of 10 glasses of alcohol a week. [107] This recommendation was adopted by the Collège des médecins du Québec and Éduc'alcool.[109]

NICE recommends informing women with a family history of breast cancer that alcohol consumption can slightly increase their risk. [55]

The NCCN recommends limiting alcohol consumption to less than one glass a day. [43]

₪ Tobacco

Evidence from the literature:

The Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk concluded that evidence demonstrates a causal relationship between active tobacco smoking and breast cancer (pre- and post-menopause). The panel also found that evidence showed a causal relationship between second-hand smoke and breast cancer among young women, mainly premenopausal women who have never smoked. However, this evidence is insufficient to make a statement on the link between second-hand smoke and the occurrence of breast cancer among post-menopausal women. [110]

Recommendations from organizations:

NICE recommends advising women not to smoke. [55]

₪ Weight

Evidence from the literature:

Obesity (BMI ≥30), overweight, (BMI from 25 to 29.9) and weight gain at an adult age are associated with increased risk of breast cancer after menopause. However, obesity appears to be linked to reduced risk of breast cancer before menopause. [111,112,113,114,115,116,117]

Recommendations from organizations:

The NCCN recommends weight management. [43]

NICE recommends informing women of the probable risk increase of breast cancer linked to being overweight after menopause. [55]

₪ Physical Activity

Evidence from the literature:

Several studies have shown a reduced risk of breast cancer in women who are physically active. [118,119,120,121,122] A review of different studies had estimated a 25% reduction in breast cancer risk among physically active women compared to that of sedentary women. [123]

Recommendations from organizations:

The Canadian Society for Exercise Physiology recommends doing at least 150 minutes of moderate to vigorous intensity physical activity a week. Examples of moderate physical activity include cycling and fast-paced walking. [124] The Public Health Agency of Canada supported the development of these guidelines and uses them in their recommendations. [125]

Health Canada (in Canada's Health Food Guide) recommends 150 minutes or more of moderate to intense physical activity a week. [126]

The World Cancer Research Fund / American Institute for Cancer Research recommends 30 minutes of moderate physical activity a day (equal to a fast-paced walk). [127]

The NCCN recommends physical exercise in the *Guideline* on reducing the risk of breast cancer. [43]

NICE recommends informing women of the potential benefits of physical exercise on their risk of breast cancer. [55]

₪ Diet

Evidence from the literature:

One study showed an overall postmenopausal breast cancer risk reduction of 60% in women who adhere to 5 out of the 6 recommendations of the World Cancer Research Fund / American Institute for Cancer Research, compared to those who adhere to none. The recommendations studied looked at weight, physical activity, high calorie food, plant-based food, red and processed meats, and alcohol. [128]

Recommendations from organizations:

Canada's Food Guide recommends that women between the ages of 18 and 50 eat 7 to 8 portions of fruit and vegetables a day (one portion is equal to about a ½ cup of fresh, frozen or canned fruit or vegetables). The Food Guide also recommends that half of all grain intake should be from whole grains. Furthermore, it is also advised to eat meat substitutes regularly, to eat at least two portions of fish a week and to choose lean meats or substitutes prepared with little fat and salt. [129]

The American Cancer Society recommends opting for a diet that helps achieve and maintain a healthy weight level, limiting consumption of red or processed meats, eating at least 2 ½ cups of fruit and vegetables a day, and choosing whole grains over refined ones. [130]

The World Cancer Research Fund and the American Institute for Cancer Research recommends avoiding high calorie foods and sugary drinks, eating mostly plant-based food, limiting consumption of red or processed meats and limiting salt intake. [131]

₪ Breastfeeding

Evidence from the literature:

Breastfeeding is associated with reduced breast cancer according to results from several studies. They also observed the magnitude of this risk reduction depended on the length of breastfeeding. [132,133,134,135] One combined analysis of 47 studies estimated a 4.3% reduction in breast cancer risk per 12 months of breastfeeding. [136]

Recommendations from organizations:

NICE recommends that women be advised to breastfeed if possible as it is likely to reduce their risk of breast cancer, and because breastfeeding is recommended in general. [55]

₪ Breast Awareness

General information:

Some organizations have developed tools for women, to explain how to be aware of changes in their breasts. For example, they suggest noting any change in texture, and pay attention to discharge or redness, etc. [137,138,139]

After some studies demonstrated that breast self-examinations do not reduce mortality, the concept of "breast awareness" arose and has been included in some recommendations.

Evidence from the literature:

Two studies, conducted in Russia and in Shanghai, demonstrate that breast self-examinations do not impact overall mortality or breast cancer mortality. [140,141] According to a Cochrane review that looks mainly at these two studies, breast self-examination has no benefits, but women should be encouraged to be aware of changes in their breasts. [142]

Recommendations from organizations:

Cancer Care Manitoba recommends encouraging women to know their breasts. [92]

The NCCN recommends all women be aware of their breasts ("*breast awareness"*). [75]

The ACOG recommends encouraging women to be aware of their breasts.[143]

According to the BC Cancer Agency, breast self-examination may be suggested to women so that they can detect any changes early on. All the same, the BC Cancer Agency recognizes that there is no evidence that breast self-examination improves survival. [97]

The Quebec Breast Cancer Screening Program's website states "**it is still crucial that each woman observe her breasts**". [139]

4.2 Pharmacoprevention

General information:

The use of tamoxifen and raloxifene in breast cancer primary prevention is not approved by Health Canada. [144,145.146] Their use is however approved in the United States.[147,148,149]

Studies on raloxifene only examined its effects in postmenopausal women.

Evidence from the literature:

Evidence on tamoxifen:

Table 8: Effectiveness of tamoxifen. Data adapted from NCCN. [43]

Rate of invasive breast cancer in the National Surgical Adjuvant Breast and Bowel Project's (NSABP) clinical trial for breast cancer prevention		
Patient characteristics	**Risk ratio (tamoxifen vs. placebo)**	**95% Confidence interval**
All women	0.51	0.39-0.66
≤ 49 years old	0.56	0.37-0.85
Ages 50 to 59	0.49	0.29-0.81
≥ 60 years old	0.45	0.27-0.74
History of lobular carcinoma *in situ*	0.44	0.16-1.06
History of atypical hyperplasia	0.14	0.03-0.47
Rate of non-invasive breast cancer in the NSABP clinical trial for breast cancer prevention		
Patient characteristics	**Risk ratio (tamoxifen vs. placebo)**	**95% Confidence interval**
All women	0.50	0.33-0.77

Table 9: Toxicity of tamoxifen. Data adapted from the NCCN. [43]

Toxicity among women enrolled in the NSABP clinical trial for breast cancer prevention				
Toxicity	Annual rate per 1,000 patients			
	Placebo	Tamoxifen	Relative risk (tamoxifen vs. placebo)	95% Confidence interval for the relative risk
Invasive endometrial cancer				
≤ 49 years	1.09	1.32	1.21	0.41-3.60
≥ 50 years	0.76	3.05	4.01	1.70-10.90
Deep vein thrombosis				
≤ 49 years	0.78	1.08	1.39	0.51-3.99
≥ 50 years	0.88	1.51	1.71	0.85-3.58
Stroke				
≤ 49 years	0.39	0.30	0.76	0.11-4.49
≥ 50 years	1.26	2.20	1.75	0.98-3.20
Pulmonary embolism				
≤ 49 years	0.10	0.20	2.03	0.11-119.62
≥ 50 years	0.31	1.00	3.19	1.12-11.15
Bone fracture				
≤ 49 years	2.24	1.98	0.88	0.46-1.68
≥ 50 years	7.27	5.76	0.79	0.60-1.05
Ischemic heart disease	2.37	2.73	1.15	0.81-1.64
Development of cataracts	21.72	24.82	1.14	1.01-1.29
Development of cataracts and cataract surgery performed	3.00	4.72	1.57	1.16-2.14

Evidence comparing tamoxifen and raloxifene:

Table 10: Comparison of the effectiveness of tamoxifen and raloxifene. Data adapted from the NCCN. [43]

Rate of invasive breast cancer in the NSABP Study of Tamoxifen and Raloxifene (STAR) – median follow-up of 81 months		
Patient characteristics	**Risk ratio (raloxifene vs. tamoxifen)**	**95% Confidence interval**
All women	1.24	1.05-1.47
≤ 49 years	1.53	0.64-3.80
Ages 50-59	1.23	0.97-1.57
≥ 60 years	1.22	0.95-1.58
History of lobular carcinoma *in situ*	1.13	0.76-1.69
History of atypical hyperplasia	1.48	1.06-2.09
Rate of non-invasive breast cancer in the NSABP Study of Tamoxifen and Raloxifene (STAR) – median follow-up of 81 months		
Patient characteristics	**Risk ratio (raloxifene vs. tamoxifen)**	**95% Confidence interval**
All women	1.22	0.95-1.59

Table 11: Comparison of the toxicity of tamoxifen and raloxifene. Data adapted from the NCCN. [43]

Toxicity among women enrolled in the NSABP Study of Tamoxifen and Raloxifene (STAR) – median follow-up of 81 months				
Toxicity	Annual rate per 1,000 patients			
	Tamoxifen	Raloxifene	Risk ratio (raloxifene vs. tamoxifen)	95% Confidence interval for the risk ratio
Invasive endometrial cancer	2.25	1.23	0.55	0.36-0.83
Endometrial hyperplasia	4.40	0.84	0.19	0.12-0.29
Hysterectomy during follow-up	12.08	5.41	0.45	0.37-0.54
Thromboembolic event	3.30	2.47	0.75	0.60-0.93
- Deep vein thrombosis	1.93	1.38	0.55	0.54-0.95
- Pulmonary embolism	1.36	1.09	0.27	0.57-1.11
Development of cataracts	14.58	11.69	0.80	0.72-0.89
Development of cataracts and cataract surgery performed	11.18	8.85	0.79	0.70-0.90

Table 12 illustrates the net benefit index, which is the number of potentially fatal events predicted over 5 years without chemoprevention, minus the number of potentially fatal events predicted over 5 years with chemoprevention.[150]

Table 12: Risks and benefits of tamoxifen and raloxifene, among white, non-Hispanic women, with uterus.

Risk of invasive breast cancer over 5 years (%)	Tamoxifen *v.* placebo (with uterus)			Raloxifene *v.* placebo (with uterus)		
	Ages 50-59	Ages 60-69	Ages 70-79	Ages 50-59	Ages 60-69	Ages 70-79
1.5	-133	-310	-325	21	-11	-15
2.0	-105	-283	-298	43	11	7
2.5	-78	-255	-271	65	33	29
3.0	-51	-228	-244	86	55	51
3.5	-25	-202	-217	108	76	71
4.0	3	-175	-190	128	97	93
4.5	29	-148	-164	150	119	115
5.0	56	-121	-137	172	140	136
5.5	83	-95	-111	193	161	157
6.0	109	-69	-84	214	183	179
6.5	135	-42	-58	236	204	199
7.0	162	-15	-32	256	225	221

Strong evidence that the benefits outweigh the risks

Moderate evidence that the benefits outweigh the risks

The benefits do not outweigh the risks

Table 13 illustrates the net benefit index, which is the number of potentially fatal events predicted over 5 years without chemoprevention, minus the number of potentially fatal events predicted over 5 years with chemoprevention. [150]

Table 13: Risks and benefits of tamoxifen and raloxifene, among white, non-Hispanic women, without uterus.

Risk of invasive breast cancer over 5 years (%)	Tamoxifen *v.* placebo (without uterus)			Raloxifene *v.* placebo (without uterus)		
	Ages 50-59	Ages 60-69	Ages 70-79	Ages 50-59	Ages 60-69	Ages 70-79
1.5	3	-53	-93	27	2	-4
2.0	31	-26	-66	49	23	18
2.5	57	2	-39	71	45	40
3.0	84	29	-12	92	67	62
3.5	111	56	15	114	88	82
4.0	138	83	42	134	109	104
4.5	164	109	69	156	131	126
5.0	191	136	96	178	152	147
5.5	218	163	121	199	173	168
6.0	244	189	148	220	195	190
6.5	270	215	175	242	216	210
7.0	297	242	201	2622	237	232

Strong evidence that the benefits outweigh the risks

Moderate evidence that the benefits outweigh the risks

The benefits do not outweigh the risks

Recommendations from organizations:

The ASCO recommends that tamoxifen be discussed as an option among women at "increased risk" of breast cancer and at ≥35 years of age (a woman is considered at an "increased risk" if her risk of breast cancer over 5 years is ≥1.66% or if she was diagnosed with lobular carcinoma *in situ*).

The use of raloxifene is also endorsed among menopausal women. The recommended treatments are over a period of 5 years.[151]

The NCCN recommends chemoprevention as an option for premenopausal and postmenopausal women ≥35 years old, and who are at an increased risk of breast cancer (≥1.7% over 5 years OR diagnosed with lobular carcinoma *in situ*). Tamoxifen is recommended for both premenopausal and postmenopausal women, while raloxifene is recommended for postmenopausal women. [43]

The U.S. Preventive Services Task Force recommends that clinicians engage in a shared medical decision with women ≥35 years old at an increased risk of breast cancer, concerning chemoprevention, if appropriate. The exact definition of what is considered as an increased risk has not been specified. The recommendation endorses tamoxifen and raloxifene medication.[152]

NICE recommends offering chemoprevention among women at an elevated breast cancer risk (≥30% lifetime risk) and considering chemoprevention among women at moderate risk of breast cancer (17-30% lifetime risk), except if there is a personal history or a potentially increased risk of thromboembolism or endometrial cancer. The target medications are tamoxifen among premenopausal women, and tamoxifen or raloxifene among postmenopausal women. No minimum age is recommended for chemoprevention. [55]

4.3 Preventive surgery

Evidence from the literature:

Conclusive evidence shows a reduction in breast cancer risk of at least 90% following a preventive bilateral mastectomy among women with a family history of breast cancer or a mutation of the BRCA1/2 genes. [153,154,155,156] There is, however, no evidence that shows the effect of mastectomy on life expectancy.

Recommendations from organizations:

NICE recommends that preventive mastectomy be discussed with all women at high risk for breast cancer (which represents a >30% lifetime risk for NICE). NICE meanwhile specifies that a mastectomy is only appropriate among a small proportion of women who belong to high-risk families. [55]

The NCCN recommends that preventive mastectomy generally only be considered for women with a BRCA1/2 mutation, or with another strongly predisposing mutation, significant family history, or possibly women who have been diagnosed with lobular carcinoma *in situ* (LCIS) or who have had thoracic radiotherapy before the age of 30. [43]

The National Breast and Ovarian Cancer Centre recommends discussing risk reduction strategies, which could include preventive mastectomy with women at an elevated risk (risk between 25% and 50%). [70]

From Saint-Paul-de-Vence, the recommendations mention discussing prophylactic surgery in cases where the risk of breast cancer is over 30%.[157]

---

[1] Clemons M, Goss P. Estrogen and the risk of breast cancer. *N Eng J Med*. 2001;344:276-285.

[2] Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Eng J Med*. 1985;312:146-151.

[3] Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. *N Eng J Med*. 2005;353:229-237.

[4] Courtillot C, Plu-Bureau G, Binart N, et al. Benign breast diseases. *J Mammary Gland Biol Neoplasia*. 2005;10:325-335.

[5] Page DL, Dupont WD, Rogers LW, Landenberger M. Intraductal carcinoma of the breast: follow-up after biopsy only. *Cancer*. 1982;49:751-758.

[6] Degnim AC, Visscher DW, Berman HK, et al. Stratification of breast cancer risk in women with atypia: a Mayo cohort study. *J Clin Oncol*. 2007;25:2671-2677.

[7] Collins LC, Baer HJ, Tamimi RM, Connolly JL, Colditz GA, Schnitt SJ. Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia: results from the Nurses' Health Study. *Cancer*. 2007;109:180-187.

[8] London SJ, Connolly JL, Schnitt SJ, Colditz GA. A prospective study of benign breast disease and the risk of breast cancer. *JAMA*. 1992;267:941-944.

[9] Page DL, Dupont WD. Anatomic markers of human premalignancy and risk of breast cancer. *Cancer*. 1990;66:1326-1235.

[10] Dupont WD, Page DL, Parl FF, et al. Long-term risk of breast cancer in women with fibroadenoma. *N Eng J Med*. 1994;331:10-15.

[11] Page DL, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast. A long-term follow-up study. *Cancer*. 1985;55:2698-2708.

[12] Collins LC, Baer HJ, Tamimi RM, Connolly JL, Colditz GA, Schnitt SJ. The influence of family history on breast cancer risk in women with biopsy-confirmed benign breast disease: results from the Nurses' Health Study. *Cancer*. 2006;107:1240-1247.

[13] Page DL, Dupont WD, Rogers LW. Ductal involvement by cells of atypical lobular hyperplasia in the breast: a long-term follow-up study of cancer risk. *Hum Pathol*. 1988;19:201-207.

[14] Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst*. 2005;16:1652-1662.

[15] Page DL, Kidd TE Jr, Dupont WD, Simpson JF, Rogers LW. Lobular neoplasia of the breast: Higher risk for subsequent invasive cancer predicted by more extensive disease. *Hum Pathol*. 1991;22:1232-1239.

[16] Fisher ER, Land SR, Fisher B, Mamounas E, Gilarski L, Wolmark N. Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project; twelve-year observations concerning lobular carcinoma in situ. *Cancer*. 2004;100:238-244.

[17] Arpino G, Laucirica R, Elledge RM. Premalignant and in situ breast disease: biology and clinical implications. *Ann Intern Med*. 2005;143:446-457.

[18] Catteau X, Simon P, Noel JC. Predictors of invasive breast cancer in mammographically detected microcalcification in patients with a core biopsy diagnosis of flat epithelial atypia, atypical ductal hyperplasia or ductal carcinoma in situ and recommendations for a selective approach to sentinel lymph node biopsy. *Pathol Res Pract*. 2012;208:217-220.

[19] Aroner SA, Collins LC, Schnitt SJ, Connolly JL, Colditz GA, Tamimi RM. Columnar cell lesions and subsequent breast cancer risk: a nested case-control study. *Breast Cancer Res*. 2010;12:R61.

[20] Ceugnart L, Doualliez V, Chauvet MP, et al. Pure flat epithelial atypia: is there a place for routine surgery? *Diagn Interv Imaging*. 2013;94:861-869.

[21] Rajan S, Sharma N, Dall BJ, Shaaban AM. What is the significance of flat epithelial atypia and what are the management implications? *J Clin Pathol*. 2011;64:1001-1004.

[22] Peres A, Barranger E, Becette V, Boudinet A, Guinebretiere JM, Cherel P. Rates of upgrade to malignancy for 271 cases of flat epithelial atypia (FEA) diagnosed by breast core biopsy. *Breast Cancer Res Treat*. 2012;133:659-666.

[23] Khoumais NA, Scaranelo AM, Moshonov H, et al. Incidence of breast cancer in patients with pure flat epithelial atypia diagnosed at core-needle biopsy of the breast. *Ann Surg Oncol*. 2013;20:133-138.

[24] Biggar MA, Kerr KM, Erzetich LM, Bennett IC. Columnar cell change with atypia (flat epithelial atypia) on breast core biopsy-outcomes following open excision. *Breast J*. 2012;18:578-581.

[25] Polom K, Murawa D, Murawa P. Flat epithelial atypia diagnosed on core needle biopsy-Clinical challenge. Rep Pract Oncol Radiother. 2012;17:93-96.

[26] Turashvili G, McKinney S, Martin L, et al. Columnar cell lesions, mammographic density and breast cancer risk. *Breast Cancer Res Treat*. 2009;115:561-571.

[27] Henderson TO, Amsterdam A, Bhatia S, Hudson MM, Meadows AT, Neglia JP, et al. Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. *Ann Intern Med*. 2010;152(7):444-55; W144-54.

[28] Kenney LB, Yasui Y, Inskip PD, et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Intern Med*. 2004;141:590-597.

[29] Guibout C, Adjadj E, Rubino C, et al. Malignant breast tumors after radiotherapy for a first cancer during childhood. *J Clin Oncol*. 2005;23:197-204.

[30] Pukkala E, Kesminiene A, Poliakov S, et al. Breast cancer in Belarus and Ukraine after the Chernobyl accident. *Int J Cancer*. 2006;119:651-658.

[31] Ostroumova E, Preston DL, Ron E, et al. Breast cancer incidence following low-dose rate environmental exposure: Techa River Cohort, 1956-2004. *Br J Cancer*. 2008;99:1940-1945.

[32] John EM, Kelsey JL. Radiation and other environmental exposures and breast cancer. *Epidemiol Rev*. 1993;15:157-162.

[33] Swerdlow AJ, Douglas AJ, Hudson GV, Hudson BV, Bennett MH, MacLennan KA. Risk of second primary cancers after Hodgkin's disease by type of treatment: analysis of 2846 patients in the British National Lymphoma Investigation. *BMJ*. 1992;304:1137-1143.

[34] Tucker MA, Coleman CN, Cox RS, Varghese A, Rosenberg SA. Risk of second cancers after treatment for Hodgkin's disease.*N Eng J Med*. 1988;318:76-81.

[35] van Leeuwen FE, Klokman WJ, Hagenbeek A, et al. Second cancer risk following Hodgkin's disease: a 20-year follow-up study. *J Clin Oncol*. 1994;12:312-325.

[36] Mauch PM, Kalish LA, Marcus KC, et al. Second malignancies after treatment for laparotomy staged IA-IIIB Hodgkin's disease: long-term analysis of risk factors and outcome. *Blood*. 1996;87:3625-3632.

[37] Wolden SL, Hancock SL, Carlson RW, Goffinet DR, Jeffrey SS, Hoppe RT. Management of breast cancer after Hodgkin's disease. *J Clin Oncol*. 2000;18:765-772.

[38] Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst*. 1993;85:25-31.

[39] De Bruin ML, Sparidans J, van't Veer MB, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. *J Clin Oncol*. 2009;27:4239-4246.

[40] Basu SK, Schwartz C, Fisher SG, et al. Unilateral and bilateral breast cancer in women surviving pediatric Hodgkin's disease. *Int J Radiat Oncol Biol Phys*. 2008;72:34-40.

[41] Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA*. 2003;290:465-475.

[42] Travis LB, Hill D, Dores GM, et al. Cumulative breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst*. 2005; 97:1428-1437.

[43] National Comprehensive Cancer Network. Breast Cancer Risk Reduction (Version 1.2014). 2014. Available from: www.nccn.org/. Accessedon August 21, 2014.

[44] Cancer Care Ontario. Lignes directrices pour le dépistage du cancer du sein, du col de l'utérus et colorectal. Available from: https://www.cancercare.on.ca/cms/one.aspx?portalId=1377&pageId=9514. Accessed on may 19th, 2015.

[45] Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. 2007;57:75-89.

[46] National Cancer Institute. Breast Cancer Risk Assessment Tool. Available from: www.cancer.gov/bcrisktool/. Accessed February 3, 2014.

[47] Pfeiffer RM, Park Y, Kreimer AR, et al. Risk prediction for breast, endometrial, and ovarian cancer in white women aged 50 y or older: derivation and validation from population-based cohort studies. *PLoS medicine*. 2013;10. DOI: 10.1371/journal.pmed.1001492.

[48] Nelson HD, Zakher B, Cantor A, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. *Ann Intern Med*. 2012;156:635-648.

[49] Manfrin E, Remo A, Falsirollo F, Reghellin D, Bonetti F. Risk of neoplastic transformation in asymptomatic radial scar. Analysis of 117 cases. *Breast Cancer Res Treat*. 2008;107:371-377.

[50] Guray M, Sahin AA. Benign breast diseases: classification, diagnosis, and management. *Oncologist*. 2006;11:435-449.

[51] Wang J, Costantino JP, Tan-Chiu E, Wickerham DL, Paik S, Wolmark N. Lower-category benign breast disease and the risk of invasive breast cancer. *J Natl Cancer Inst*. 2004;96:616-620.

[52] Schnitt SJ. Benign breast disease and breast cancer risk: Morphology and beyond. *Am J Surg Pathol*. 2003; 27:836-841.

[53] Love SM, Gelman RS, Silen W. Sounding Board. Fibrocystic disease of the breast – an nondisease? *N Engl J Med*. 1982;14:1010-1014.

[54] Schnitt SJ, Collins LC. Pathology of benign breast disorders. In: Harris JR, ed. *Breast diseases*. 4th ed. Philadelphia, PA: Lippincott; 2010.

[55] National Institute for Health and Care Excellence. NICE clinical guideline 164. 2013. Available from: guidance.nice.org.uk/cg164. Accessed May 22, 2015.

[56] Balmaña J, Díez O, Rubio IT, Cardoso F. BRCA in breast cancer: ESMO clinical practice guidelines. *Ann Oncol*. 2011; 22:vi31-vi34.

[57] Ontario Ministry of Health and Long-term Care. Mount Sinai Hospital. Criteria for breast and colon cancer screening. Available from: www.mountsinai.on.ca/care/pathology/laboratory-forms-and-requisitions/laboratory-forms-and-requisitions?searchterm=laboratory. Accessed May 22, 2015.

[58] Gadzicki D, Evans DG, Harris H, et al. Genetic testing for familial/hereditary breast cancer – comparison of guidelines and recommendations from the UK, France, the Netherlands and Germany. *J Community Genet*. 2011; 2:53-69.

[59] Canadian Partnership against Cancer. Breast Cancer Control in Canada: A System Performance Special Focus Report, Available from: http://www.partnershipagainstcancer.ca/new-report-provides-valuable-information-on-breast-cancer-control-across-canada/. Accessed May 22, 2015.

[60] Checka CM, Chun JE, Schnabel FR, Lee J, Toth H. The relationship of mammographic density and age: Implications for breast cancer screening. *AJR*. 2012;198:W292-W295.

[61] Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med*. 2007;356:227-236.

[62] Mandelson MT, Oestreicher N, Porter PL, et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Nal Cancer Inst*. 2000;92:1081-1087.

[63] Lokate M, Stellato RK, Veldhuis WB, Peeters PHM, van Gils CH. Age-related changes in mammographic density and breast cancer risk. *Am J Epidemiol*. 2013; 178: 101-109.

[64] Canadian Association of Radiologists. CAR Practice Guidelines for Breast Imaging and Intervention. Available from: www.car.ca. Accessed May 22, 2015.

[65] D'Orsi CJ, Bassett LW, Berg WA, et al. BI-RADS: Mammography, 5th edition in: D'Orsi CJ, Mendelson EB, Ikeda DM, et al: Breast Imaging Reporting and Data System: ACR BI-RADS – Breast Imaging Atlas, Reston, VA, American College of Radiology, 2013.

[66] Bill text SB-1538. California Legislative information website. 2012. Available from: leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201120120SB1538. Access May 22, 2015.

[67] Are you dense advocacy. 2014. Available from: areyoudenseadvocacy.org/worxcms_published/news_page170.shtml. Accessed August 27, 2014.

[68] Ontario Breast Screening Program. Information for healthcare providers. 2013. Available from: www.cancercare.on.ca/cms/one.aspx?portalId=1377&pageId=9514. Accessed May 22, 2015.

[69] Van Ravesteyn NT, Miglioretti DL, Stout NK, et al. Tipping the balance of benefits and harms to favor screening mammography starting at age 40 years. *Ann Intern Med*. 2012; 156:609-617.

[70] National Breast and Ovarian Cancer Centre. Advice about familial aspects of breast cancer and epithelial ovarian cancer. 2010. Available from: www.nbocc.org.au. Accessed May 22, 2015.

[71] Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. *JAMA*. 2012;307:1394-1404.

[72] Berg WA, Zhang Z, Lehrer D, et al. Detection of Breast Cancer With Addition of Annual Screening Ultrasound or a Single Screening MRI to Mammography in Women With Elevated Breast Cancer Risk. *JAMA*. 2012;307:1394-1404.

[73] Corsetti V, Houssami N, Ghirardi M, et al. Evidence of the effect of adjunct ultrasound screening in women with mammography-negative dense breasts: Interval breast cancers at 1 year follow-up. *Eur J Cancer*. 2011;47:1021-1026.

[74] Girardi V, Tonegutti M, Ciatto S, Bonetti F. Breast ultrasound in 22,131 asymptomatic women with negative mammography. *The Breast*. 2013; 22:806-809.

[75] National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis (Version 1.2014). Available from: www.nccn.org. Accessed August 28, 2014.

[76] Chiarelli AM, Prummel MV, Muradali D, et al. Effectiveness of screening with annual magnetic resonance imaging and mammography: Results of the initial creen from the Ontario high risk breast screening program. *J Clin Oncol*. 2014;32:2224-2230.

[77] Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Magnetic resonance imaging screening of women at high risk for breast cancer. Toronto (ON): Cancer Care Ontario; 2012 Aug 31. Program in Evidence-based Care Evidence-based Guideline No.: 15-11 Version 2.

[78] Mainiero MB, Lourenco A, Mahoney MC, et al. ACR Appropriateness criteria breast cancer screening. *Am Coll Radiol*. 2013;10:11-14.

[79] Cancer Care Ontario. Information for Healthcare Providers. 2013. Available from: https://www.cancercare.on.ca/pcs/screening/breastscreening/healthcare_provider_information/. Accessed May 22, 2015.

[80] Rafferty EA, Park JM, Philpotts LE, et al. Assessing radiologist performance using combined digital mammography and breast tomosynthesis compared with digital mammography alone: results of a multicenter, multireader trial. *Radiology*. 2013;266:104-113.

[81] Skaane P, Bandos AI, Gullien R, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. *Radiology*. 2013;267:47-56.

[82] Skaane P, Bandos AI, Eben EB, et al. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: Comparison with digital breast tomosynthesis with full-field digital mammographic images. *Radiology*.2014;271:655-663.

[83] Haas BM, Kalra V, Geisel J, Raghu M, Durand M, Philpotts LE. Comparison of tomosynthesis plus digital mammography and digital mammography alone for breast cancer screening. *Radiology*. 2013; 269: 694-700.

[84] Institut national d'excellence en santé et en services sociaux (INESSS). *La tomosynthèse mammaire numérique.* Note informative rédigée par François Pierre Dussault. Montréal, Qc: INESSS; 2014. 56 p.

[85] Barton MB, Harris R, Fletcher SW. The rational clinical examination. Does this patient have breast cancer? The screening clinical breast examination: should it be done? How? *JAMA*. 1999;282:1270-1280.

[86] Chiarelli AM, Majpruz V, Brown P, Theriault M, Shumak R, Mai V. The contribution of clinical breast examination to the accuracy of breast screening. *J Natl Cancer Inst*. 2009;101:1236-1243.

[87] Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomized screening trial. *BMJ*. 2014;348:g366.

[88] Bobo JK, Lee NC, Thames SF. Findings from 752,081 clinical breast examinations reported to a national screening program from 1995 through 1998. *J Natl Cancer Inst*. 2000;92:971-976

[89] Maurice A, Evans DG, Affen J, Greenhalgh R, Duffy SW, Howell A. Surveillance of women at increased risk of breast cancer using mammography and clinical breast examination: further evidence of benefit. *Int J Cancer*. 2012;131:417-425.

[90] Canadian Task Force on Prevendive Health care. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. *CMAJ*. 2011;183:1991-2001.

[91] Collège des Médecins du Québec. L'évaluation médicale périodique de l'adulte – Recommandations adaptées à la pratique médicale au Québec. 2014. Available from: www.cmq.org/fr/MedecinsMembres/Ateliers/ExamenMedicalPeriodique.aspx. Access May 22, 2015.

[92] Cancer Care Manitoba. Guidelines for breast, cervical and colorectal cancer screening. Available from: www.cancercare.mb.ca/home/prevention_and_screening/professional_screening/. Accessed May 22, 2015.

[93] US Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2009;151:716-726.

[94] Nelson HD, Tyne K, Naik A, et al. Screening for Breast Cancer: Systematic Evidence Review Update for the US Preventive Services Task Force. U.S. Preventive Services Task Force Evidence Synthesis. Rockville (MD); 2009.

[95] National Institute for Health Care Excellence. Improving outcomes in breast cancer. 2002. Available from: guidance.nice.org.uk/CSGBC/Guidance/pdf/English. Accessed May 22, 2015.

[96] American College of Obstetricians and Gynecologists. Practice Bulletin #122: Breast Cancer Screening. *Obstet Gynecol*. 2011;118:372-382.

[97] BC Cancer Agency. Cancer Management Guidelines: Screening/Early detection. 2009. Available from: www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Breast/ScreeningEarlyDetection.htm. Accessed May 22, 2015.

[98] World Health Organization. Screening for Breast Cancer. Available from: www.who.int/cancer/detection/breastcancer/en/index.html. Accessed May 22, 2015.

[99] Memorial Sloan-Kettering Cancer Centre. Breast cancer screening guidelines. Available from: www.mskcc.org/cancer-care/adult/breast/screening-guidelines-breast. Accessed May 22, 2015.

[100] Lavigne E, Holowaty EL, Pan SY, et al. Breast cancer detection and survival among women with cosmetic breast implants: systematic review and meta-analysis of observational studies. *BMJ*. 2013;346.

[101] Skinner KA, Silberman H, Dougherty W, et al. Breast cancer after augmentation mammoplasty. *Ann Surg Oncol*. 2001;8:138-144.

[102] Handel N, Silverstein MJ. Breast cancer diagnosis and prognosis in augmented women. *Plast Reconstr Surg*. 2006;118:587-593.

[103] Miglioretti DL, Rutter CM, Geller BM, et al. Effect of breast augmentation on the accuracy of mammography and cancer characteristics. *JAMA*. 2004;291:442-450.

[104] Uematsu T. Screening and diagnosis of breast cancer in augmented women. *Breast cancer*. 2008;15:159-164.

[105] Hou MF, Ou-Yang F, Chuang CH, et al. Comparison between sonography and mammography for breast cancer diagnosis in oriental women after augmentation mammoplasty. *Ann Plast Surg*. 2002;49:120-126.

[106] Stöblen F, Rezai M, Kümmel S. Imaging in patients with breast implants—results of the First International Breast (Implant) Conference 2009. *Insights Imaging*. 2010; 1:93-97.

[107] Butt P, Beirness D, Gliksman F, Paradis C, Stockwell T. Alcohol and Health in Canada : A Summary of Evidence and Guidelines for Low-Risk Drinking, Ottawa (Ontario), Canadian Centre on Substance Abuse, 2011.

[108] Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA*. 2011;306:1884-1890.

[109] Collège des Médecins du Québec and Éduc'alcool. Low-risk Drinking Guidelines. A guide for physicians and health professionals. Available from: http://educalcool.qc.ca/en/publications/. Accessed May 22, 2015.

[110] Collishaw NE (Chair), Boyd NF, Cantor KP, Hammond SK, Johnson KC, Millar J, Miller AB, Miller M, Palmer JR, Salmon AG, Turcotte F. *Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk*. Toronto, Canada: Ontario Tobacco Research Unit, OTRU Special Report Series, April 2009.

[111] Van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol*. 2000;152:514-527.

[112] Lahmann PH, Hoffmann K, Allen N, et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). *Int J Cancer*. 2004;111:762-771.

[113] Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. *JAMA*. 2006;296:193-201.

[114] Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control*. 2002;13:741-751.

[115] Feigelson HS, Jonas CR, Teras LR, Thun MJ, Calle EE. Weight gain, body mass index, hormone replacement therapy, and postmenopausal breast cancer in a large prospective study. *Cancer Epidemiol Biomarkers Prev*. 2004;13:220-224.

[116] Ahn J, Schatzkin A, Lacey JV Jr, et al. Adiposity, adult weight change, and postmenopausal breast cancer risk. *Arch Intern Med*. 2007;167:2091-2102.

[117] Alsaker MD, Janszky I, Opdahl S, Vatten LJ, Romundstad PR. Weight change in adulthood and risk of postmenopausal breast cancer: the HUNT study of Norway. *Br J Cancer*. 2013; 109:1310-1317.

[118] Maruti SS, Willett WC, Feskanich D, Rosner B, Colditz GA. A prospective study of age-specific physical activity and premenopausal breast cancer. *J Natl Cancer Inst*. 2008;100:728-737.

[119] McTiernan A, Kooperberg C, White E, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. *JAMA*. 2003;290:1331-1336.

[120] Patel AV, Callel EE, Bernstein L, Wu AH, Thun MJ. Recreational physical activity and risk of postmenopausal breast cancer in a large cohort of US women. *Cancer Causes Control*. 2003;14:519-529.

[121] Bardia A, Hartmann LC, Vachon CM, et al. Recreational physical activity and risk of postmenopausal breast cancer based on hormone receptor status. *Arch Intern Med*. 2006;166:2478-2483.

[122] Kobayashi LC, Janssen I, Richardson H, Lai AS, Spinelli JJ, Aronson KJ. Moderate-to-vigorous intensity physical activity across the life course and risk of pre- and post-menopausal breast cancer. *Breast Cancer Res Treat*. 2013; 139:851-861.

[123] Lynch BM, Neilson HK, Friedenreich CM. Physical activity and breast cancer prevention. *Recent Results Cancer Res*. 2011;186:13-42.

[124] CSEP/SCPE. Canadian Physical Activity Guidelines for Adults 18- to 64 years. 2011. Available atfrom: http://csep.ca/English. Accessed verified on May 22, 2015.

[125] Public Health Agency of Canada. Physical Activity Guidelines. Available from: http://www.phac-aspc.gc.ca/hp-ps/hl-mvs/pa-ap/03paap-eng.php. Accessed May 22, 2015.

[126] Health Canada. Physical Activity. Available from: http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/basics-base/activit-eng.php. Accessed May 22, 2015.

[127] World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2007

[128] Hastert TA, Beresford SAA, Patterson RE, Kristal AR, White E. Adherence to WCRF/AICR cancer prevention recommendations and risk of postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2013;22:1498-1508.

[129] Health Canada. Eating Well with Canada's Food Guide. Available from: http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index-eng.php. Accessed May 22, 2015.

[130] Kushi LH, Doyle C, McCullough M, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention. *CA Cancer J Clin*. 2012;62:30-67.

[131] Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: A global perspective. *Proc Nutr Soc*. 2008;67:253-256.

[132] Stuebe AM, Willett WC, Xue F, Michels KB. Lactation and incidence of premenopausal breast cancer: a longitudinal study. *Arch Intern Med*. 2009;169:1364-1371.

[133] Zheng T, Holford TR, Mayne ST, et al. Lactation and breast cancer risk: a case-control study in Connecticut. *Br J Cancer*. 2001;84:1472-1476.

[134] Tryggvadóttir L, Tulinius H, Eyfjord JE, Sigurvinsson T. Breastfeeding and reduced risk of breast cancer in an Icelandic cohort study. *Am J Epidemiol*. 2001;154:37-42.

[135] Jernström H, Lubinski J, Lynch HT, et al. Breast-feeding and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst*. 2004;96:1094-1098.

[136] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet*. 2002;360:187-195.

[137] Programme québécois de dépistage du cancer du sein - Région de la Capitale-Nationale.. Être attentive à ses seins. 2014. Available atfrom: www.depistagesein.ca/etre-attentive-a-ses-seins/. Accessed verified on August 28, 2014May 22, 2015.

[138] Quebec Breast Cancer Foundation. Breast observation. Available from: breastsobservation.org. Accessed May 22, 2015.

[139] Programme québécois de dépistage du cancer du sein. Auto-examen des seins. Available atfrom: www.pqdcs.qc.ca/Programme/Depistage/AES. Accessed verified on August 28, 2014May 22, 2015.

[140] Semiglazov VF, Manikhas AG, Moiseenko VM, et al. Results of a prospective randomized investigation [Russia (St.Petersburg)/WHO] to evaluate the significance of self-examination for the early detection of breast cancer. Voprosy onkologii. 2003;49:434-441.

[141] Thomas DB, Gao DL, Ray RM, Wang WW, Allison CJ, Chen FL, et al. Randomized trial of breast self-examination in Shanghai: final results. *J Natl Cancer Inst*. 2002;94:1445-1457.

[142] Kösters JP, Gøtzsche PC. Regular self-examination or clinical examination for early detection of breast cancer. *Cochrane Database of Systematics Reviews* 2003, Issue 2. Art. No.: CD003373. DOI: 10.1002/14651858.CD003373.

[143] American College of Obstetricians and Gynecologists. Practice Bulletin #122: Breast Cancer Screening. *Obstet Gynecol*. 2011;118:372-382.

[144] Health Canada. Important Safety Information Regarding Tamoxifen and Incidence of Uterine Malignancies, Stroke and Pulmonary Embolism. 2002. Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2002/14724a-eng.php. Accessed May 22, 2015.

[145] Health Canada. APO RALOXIFENE Product information. Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/language-langage.do?lang=eng&url=t.search.recherche. Accessed August 28, 2014.

[146] Pfizer Canada Inc. Aromasin product monograph. 2012. Available from: http://www.pfizer.ca/aromasin-product-monograph. Accessed May 22, 2015.

[147] Soltamox [Package insert]. Savient Pharmaceuticals, Inc., East Brunswick, NJ; October 2005. Available from: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. Accessed August 28, 2014.

[148] Evista. Evista prescribing information. Available from: www.lilly.com/products/human/Pages/From-Our-History.aspx. Accessed May 22, 2015.

[149] FDA. Aromasin (exemestane) prescribing information. Available from: www.fda.gov/Safety/MedWatch/SafetyInformation/ucm250607.htm. Accessed May 22, 2015.

[150] Freedman AN, Yu B, Gail MH, et al. Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. *J Clin Oncol*. 2011;29:2327-2333

[151] Visvanathan K, Hurley P, Bantug E, et al. Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology practice guideline. *J Clin Oncol*. 2013;23:2942-2962.

[152] Moyer V. Medications for risk reduction of primary breast cancer in women: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2013; 159:698-708.

[153] Hartmann LC, Schaid DJ, Woods JE, et al. Efficacity of bitateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med*. 1999;340:77-84.

[154] Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacity of bilateral mastectomy in BRCA1 and BRCA2 gene mutation carriers. *J Natl Cancer Inst*. 2001; 93: 1633-1637.

[155] Meijers-Heijboer H, van Geel B, van Putten WLJ, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2001; 345: 159-164.

[156] Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: The Prose study group. *J Clin Oncol*. 2004; 22:1055-1062

[157] Cohen M, Jacquemier J, Maestro C, Pujol P, Saada E. Femmes à risque. *Oncologie*. 2011; 13:618-644.