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THE EVOLVING APPROACH TO BREAST CANCER SCREENING AND TREATMENT IN CANADA: IMPLICATIONS FOR PRIMARY CARE PROVIDERS

Introduction

Nearly 30,000 Canadians are diagnosed with breast cancer annually, and while its mortality has decreased by over 55% since the 1970s due to modernized screening technologies and advances in systemic therapy, 5,500 Canadians are estimated to die of the disease every year.[1,2] Primary care providers are critical through all steps of a patient's breast cancer journey, from facilitating routine screening, to identifying breast cancer risk factors, ensuring expedient referrals, and recognizing acute or chronic treatment toxicities and their impact on overall physical and psychological health.

Breast Cancer Risk Factors

While prevention remains a pillar of cancer care, many breast cancer risk factors are unmodifiable, with female gender and age representing the greatest risks. Inherited breast cancer risk, including family history or a known high-risk gene mutation and ductal or lobular carcinoma *in situ*, are less common non-modifiable risks. The total cumulative exposure, either endogenous or exogenous, to ovarian hormones is also associated with an elevated breast cancer risk. As such, early menarche, late menopause, nulliparity or older age at first pregnancy, absence of breastfeeding, oral contraceptives, and hormone replacement therapy all affect risk. Further, history of thoracic radiation, body mass index (BMI) ≥30, and even light alcohol consumption, defined as less than one standard drink per day, are known to increase the risk of breast cancer.[3-5] While recognition of breast cancer risk factors is prudent, of the aforementioned determinants, only a strong family history, *in situ* carcinoma, chest wall irradiation, and a known mutation in high-risk genes such as breast cancer gene (*BRCA*)1, *BRCA2*, and *PALB2*, lead to modified screening recommendations across Canadian jurisdictions.

Updates to Breast Cancer Screening Guidelines and Implementation of Novel Imaging Modalities

For over a decade, the Canadian Task Force on Preventative Health Care (CTFPC) has been consistent in their stance that among individuals with an average risk of breast cancer, those aged 50 to 74 years should be systematically offered a screening mammography every

2–3 years. While the CTFPC recommends against routine screening for those aged 40–49, this stance has long been subject to debate. The CTFPC's position recognizes that routine mammography in this age group has a probable benefit for breast cancer mortality, with screening of this population estimated to prevent 0.27 deaths from breast cancer per 1,000 screens. However, the CTFPC suggests that this mortality benefit is perceived to be outweighed by the burden of false positive results.[4]

Critics note limitations of the randomized control trials that serve as the foundation of the CTFPC's position, including relatively small patient sample sizes and long inter-mammographic intervals, and point instead to observational studies of modern screening protocols that demonstrate a relative reduction in breast cancer mortality of up to 40%.[5,6] Further, a 2023 review of national breast cancer survival data found that women diagnosed with breast cancer in their 40s had a 10-year net-survival that was 1.9% higher in Canadian jurisdictions that offered organized screening programs for those aged 40–49 (84.8%) compared to those lacking such programs for this demographic (82.9%), with provincial screening rates significantly correlating with 10-year net-survival.[7] This debate is further highlighted by the recent inclusion of individuals aged 40–49 in the US Preventive Services Task Force's biennial mammographic screening recommendations.[8]

Although the directionalities of the CTFPC's recommendations have remained unchanged since 2011, there has been greater emphasis on patient values and individual risk-benefit discussion. The 2024 draft guidelines highlight that breast cancer screening is a personal choice, and all individuals aged 40–74 years should be provided with information on the potential benefits and harms of screening, with mammography offered every 2 to 3 years if desired. As summarized in **Table 1**, the application of the CTFPC's recommendations varies between Canadian jurisdictions. In line with the breadth of emerging evidence demonstrating survival benefits with early screening, within the last year, five Canadian jurisdictions have committed to reducing the age of eligibility for screening mammography self-referral to age 40 years. In the current screening landscape, Manitoba and Québec are the only Canadian jurisdictions with organized screening programs that have not extended eligibility to those under the age of 50 years.

With the advent of more sensitive imaging technologies, certain populations may benefit from supplemental breast cancer screening. Breast density refers to the proportion of fibroglandular tissue relative to fat in the breast and is divided from least (A) to most (D) dense using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS).[9] Breast density is subjectively assessed on mammography and can change over time. Categories C and D are regarded as dense, with sensitivity of traditional mammography falling to as low as 50% in these cases.[10] In addition, increased breast density is associated with higher breast cancer risk, with the risk being 1.2 times higher in those with heterogeneously dense breasts (BI-RADS C), and 2.1 times higher in those with extremely dense breasts (BI-RADS D), relative to those with average breast density.[11] In this cohort, ultrasound, contrast-enhanced mammography (CEM), and/or magnetic resonance imaging (MRI) can be used as supplemental imaging and improve the sensitivity of screening by up to 21%, with CEM nearing the sensitivity of breast MRI at a fraction of the cost.[12,13] Nevertheless, while awaiting compelling survival data, recommendations for and access to supplemental imaging in patients with dense breasts vary across jurisdictions.

While the age of screening onset and recommended supplemental screening modalities continue to evolve, it is critical that primary care providers in Canada evaluate a patient's breast cancer risk at no later than 30 years of age,[14] discuss the benefits and harms associated with mammographic screening with all patients at average risk of breast cancer aged 40–74 years, and facilitate access to mammography for those who make an individualized decision to pursue screening.

Considerations in Breast Cancer Referral

In many urban centers, there is automatic integration of a patient into local multidisciplinary breast cancer treatment infrastructure at the time of diagnosis. In jurisdictions that lack such systems, it is critical that primary care providers recognize patients with early-stage disease who may benefit from a medical oncology consultation prior to surgical intervention.

While surgical resection is the foundation of treatment in early-stage breast cancer, pre-operative systemic therapy, also known as neoadjuvant therapy (NAT), is employed in select circumstances. NAT may render inoperable cancers operable or facilitate breast-conserving surgery, while offering prognostic information based on both clinical and pathologic response.[15] Recently, patients with stage II and III triple-negative breast cancer (TNBC) have been demonstrated to benefit from neoadjuvant chemoimmunotherapy and, as such, patients with a primary tumour measuring >2 cm or with nodal involvement should be referred to medical oncology in parallel to the surgical referral.[16] Similarly, neoadjuvant anti-HER2 therapy is utilized in patients with HER2-positive tumours measuring >2 cm or with nodal involvement, warranting presurgical medical oncology assessment.[17] In the case of hormone (estrogen) receptor-positive HER2-negative cancer, NAT is most often employed to downstage disease and facilitate surgical intervention in select cases. Thus, referral

Jurisdiction	Ages 40–44	Ages 45–49	Ages 50–74	Ages 75+
British Columbia	Available every 2 years	Available every 2 years	Recommended every 2 years	Available every 2 years
Alberta	Not recommended, available every year (referral required)	Recommended every 2 years	Recommended every 2 years	Available every 2 years (referral required)
Saskatchewan	Available (referral required)[1]	Available (referral required)[1]	Recommended every 2 years	Available every 2 years
Manitoba	Not recommended, available (referral required)	Not recommended, available (referral required)	Recommended every 2 years	Available every 2 years
Ontario	Available (referral required)[2]	Available (referral required)[2]	Recommended every 2 years	Available every 2 years (referral required)
Québec	Not recommended, available every 2 years (referral required)	Not recommended, available every 2 years (referral required)	Recommended every 2 years	Available every 2 years (referral required)
Newfoundland and Labrador	Recommended every 2 years	Recommended every 2 years	Recommended every 2 years	Available every 2 years
Nova Scotia	Recommended every year	Recommended every year	Recommended every 2 years	Available every 2 years
New Brunswick	Recommended every 1–2 years	Recommended every 1–2 years	Recommended every 2–3 years	Available every 2 years (referral required)
Prince Edward Island	Available every year	Available every year	Recommended every 2 years	Available every 2 years (referral required)
Yukon Territory	Available every year	Available every year	Recommended every 2–3 years	Available every 2 years
Northwest Territories	Not recommended, available every 2 years (referral required)	Recommended every 2 years	Recommended every 2 years	Available every 2 years
Nunavut[3]	Available every year	Available every year	Available every year	Available every year

Table 1. Varying Canadian breast cancer screening recommendations by jurisdiction; *courtesy of Greydon Arthur, MD, Charlotte J. Yong-Hing, MD, FRCPC, and Nathalie LeVasseur, MD, FRCPC.*

Self-referral available unless otherwise indicated.

[1]Beginning January 2025, individuals living in Saskatchewan can self-refer for screening mammography starting at age 40.

[2]Beginning October 2024, individuals living in Ontario can self-refer for screening mammography starting at age 40.

[3]Nunavut currently has no organized breast cancer screening program.

often originates from surgeons at the time of surgical candidacy assessment.

Beyond facilitating early medical oncology referral, primary care providers play a critical role in assessing a patient's familial risk and, in certain circumstances, helping patients navigate hereditary breast cancer testing. As a patient's longitudinal, often multigenerational provider, primary care physicians may have unique insight into a patient's family history and can help identify individuals at potential risk of genetic cancer predisposition. While there are subtle interprovincial differences in hereditary breast cancer testing eligibility criteria, the following should prompt consideration of referral for genetic testing:

Patient History

- Age at diagnosis
  - *Breast cancer at a young age (typically below ages 35–45 years)*
- Multiple primary breast cancers
  - *Often with one diagnosed before age 50*
- Disease pathology
  - *TNBC at age ≤60*
- Ancestry
  - *Ashkenazi Jewish heritage*
- Male breast cancer
- Ovarian cancer

Family History

- Family history of cancers affecting close relatives with any of the aforementioned characteristics
  - *Close relatives are defined as first- or second-degree relatives.*
- Multiple affected family members
  - *2–3 close relatives with breast cancer*
- Known mutations
  - *Family member with BRCA1, BRCA2, or other high-risk gene mutations*
- Multiple different malignancies
  - *Breast and ovarian cancer in close relatives*

Facilitating patient access to NAT in early-stage disease and recognizing patient and family history suggestive of possible hereditary breast cancer predisposition ensures opportunities for early intervention, screening intensification, and genetic counselling are not missed.

Evolving Treatment Modalities, Implications for Follow-up and Monitoring

The breast cancer therapeutic landscape is rapidly expanding, with recognition of the utility of immunotherapy in this setting and an ever-growing selection of targeted agents. While the diversification of this therapeutic arsenal has led to improved disease-specific outcomes and more favourable toxicity profiles, these novel agents often confer unique toxicities that merit discussion.

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block immune-inhibitory signalling in the tumour microenvironment. This blockade can enhance the native immune system's ability to recognize cancer antigens as foreign and induce T cell-mediated cytotoxicity. The ICI pembrolizumab has established an increasingly prominent role in the realm of breast cancer treatment over the last five years. Pembrolizumab was first approved by Health Canada in 2021 for use in combination with chemotherapy in the treatment of unresectable or metastatic TNBC in patients whose tumours express the immune checkpoint protein programmed cell death ligand 1 (PD-L1).[18] Health Canada expanded approval of pembrolizumab in 2022 to include use in combination with chemotherapy in the NAT setting, followed by adjuvant pembrolizumab monotherapy in patients with high-risk early-stage TNBC, irrespective of PD-L1 status.[16]

As ICIs block inhibitory immune signalling in an indiscriminate fashion, many of the toxicities associated with immunotherapy result from iatrogenic autoimmunity, termed immune-related adverse events (irAEs). In the clinical trials cited above, irAEs of any grade were reported in up to 26.5% of patients, manifesting most commonly as thyroid dysfunction (hypothyroidism 15.8%, hyperthyroidism 4.3%), pneumonitis (2.5%), and colitis (1.8%), though irAEs can affect any non-immune privileged tissue and, in rare circumstances, can be fatal if left unrecognized.[16,18] To identify these toxicities, one must first recognize that while many occur within 3 months of ICI initiation, irAEs can present at any point during treatment and delayed-onset irAEs may arise many months after treatment completion.[19] Once identified, despite variability in symptomatology and impacted tissue, treatment generally consists of some combination of ICI discontinuation, steroid-based therapy, hormone replacement in the case of some autoimmune endocrinopathies, and rarely, intensive immunosuppression.[20] Patients presenting to primary care with new unexplained symptoms or flare of existing autoimmune disease should be carefully considered for possible irAEs and warrant prompt discussion with the patient's medical oncologist.

Drug Class and Mechanism of Action	Approved Agent(s)	Approved Indication(s)	Toxicities of Interest
CDK4/6 inhibitors – Block proliferative cell cycle signalling	Palbociclib, ribociclib, abemaciclib	**1)** First-line treatment (or following progression on endocrine therapy) of HR^+, $HER2^-$ locally advanced or metastatic breast cancer in combination with an aromatase inhibitor (palbociclib, ribociclib, abemaciclib) **2)** Adjuvant therapy in early, node-positive HR^+, $HER2^-$ breast cancer with high disease recurrence risk (abemaciclib)	• Pancytopenia and risk of febrile neutropenia (<1% with all listed agents) • Nausea/vomiting and diarrhea (abemaciclib) • QT prolongation and associated risk of arrhythmia, including Torsades (ribociclib)
Immune checkpoint inhibitors – Block immunosuppressive signalling in tumour microenvironment	Pembrolizumab, atezolizumab	**1)** First-line treatment of locally advanced or metastatic TNBC in combination with chemotherapy (pembrolizumab) **2)** Neoadjuvant/adjuvant therapy for >T2N0 TNBC in combination with chemotherapy (pembrolizumab)	• Cutaneous: rash (often eczematous), rare risk of severe cutaneous a diverse reactions • Gastrointestinal: colitis, hepatitis • Endocrine: hyper/hypothyroidism, hypophysitis, diabetes mellitus (risk of DKA), adrenal insufficiency • Respiratory: pneumonitis • Renal: nephritis (AIN, glomerulonephritis) • Cardiac: autoimmune myocarditis • Neurologic: NMJ disorders, aseptic meningitis, peripheral neuropathy
Antibody-drug conjugates – Deliver cytotoxic payload to a tumour using antibodies	Trastuzumab deruxtecan, trastuzumab emtansine, sacituzumab govitecan	**1)** Treatment of $HER2^+$ metastatic breast cancer with prior exposure to trastuzumab and taxane (trastuzumab emtansine) **2)** Treatment of $HER2^+$ metastatic breast cancer with prior exposure to dual anti-HER2 therapy or HER2-low disease with at least 1 prior line of chemotherapy (trastuzumab deruxtecan) **3)** $2^{nd}/3^{rd}$ line treatment of metastatic TNBC or HR^+ $HER2^-$ breast cancer after 2–4 lines of prior chemotherapy (sacituzumab govitecan)	• Reversible myocardial dysfunction with reduction in LVEF (trastuzumab-based antibody-drug conjugates) • Pneumonitis (trastuzumab deruxtecan) • Neutropenia • Nausea/vomiting and diarrhea
PARP inhibitors – Prevent repair of DNA double-strand breaks in BRCA-deficient cancers	Olaparib	**1)** Adjuvant treatment for $HER2^-$ breast cancer treated with neoadjuvant or adjuvant chemotherapy in patients with germline BRCA1/2 mutation **2)** Treatment of metastatic breast cancer in patients with germline BRCA1/2 mutation	• Secondary neoplasms (myelodysplastic syndrome, acute myeloid leukemia; <1%) • Pneumonitis (<1%)
Anti-HER2 tyrosine kinase inhibitors – block growth signalling originating from the HER2 receptor	Tucatinib, lapatinib, neratinib (non-specific inhibitor)	**1)** Treatment of locally advanced or metastatic $HER2^+$ breast cancer, in combination with trastuzumab and capecitabine (tucatinib) **2)** Treatment of HR^+, $HER2^+$ metastatic breast cancer not suitable for trastuzumab, in combination with aromatase inhibitor (lapatinib) **3)** Extended adjuvant treatment of HR^+, $HER2^+$ breast cancer after completing trastuzumab-based regimen, used in combination with aromatase inhibitor (neratinib)	• Hepatotoxicity • Hand-foot syndrome • Reversible myocardial dysfunction with reduction in LVEF • QT prolongation and associated risk of arrhythmia, including Torsades • Diarrhea
PI3K/AKT inhibitors – block PI3K growth and proliferation pathway	Alpelisib, Capivasertib	**1)** Second-line treatment of HR^+, $HER2^-$, PI3K-mutated (alpelisib) or PTEN, PI3K, AKT-mutated (capivasertib) advanced or metastatic breast cancer	• Severe hyperglycemia and risk of DKA and HHS • Rash • Mucositis, diarrhea

Table 2. Indications for novel therapeutic agents approved by Health Canada since 2015 for the treatment of breast cancer and unique toxicities relevant in the primary care setting: *courtesy of Greydon Arthur, MD, Charlotte J. Yong-Hing, MD, FRCPC, and Nathalie LeVasseur, MD, FRCPC.*

Abbreviations: AIN: acute interstitial nephritis, **AKT:** protein kinase B, **BRCA:** breast cancer gene, **CDK:** cyclin-dependent kinase, **DKA:** diabetic ketoacidosis, **HER2:** human epidermal growth factor receptor 2, **HHS:** hyperosmolar hyperglycemic syndrome, **HR:** hormone receptor, **LVEF:** left ventricular ejection fraction, **NMJ:** neuromuscular junction, **PARP:** poly(ADP-ribose) polymerase, **PI3K:** phosphoinositide 3-kinase, **PTEN:** phosphatase and tensin homolo, **TNBC:** triple-negative breast cancer

Emerging treatments in breast cancer extend beyond immunotherapy and vary substantially in their mechanisms of action and molecular targets, offering exciting new therapeutic opportunities. Trastuzumab is an antibody that targets the cell surface marker HER2 that is expressed on 1 in 5 breast cancers. While this technology has been approved and widely utilized in Canada for some time, the ability of such antibodies to target breast cancer surface proteins has recently been leveraged to deliver a cytotoxic payload directly to the tumour, joining a class of drugs known as antibody-drug conjugates (ADCs). To date, three such ADCs have been approved for the treatment of metastatic breast cancer: trastuzumab-deruxtecan, trastuzumab-emtansine, and sacituzumab-govitecan. Beyond antibody-based therapies, several small molecule inhibitors have recently received Health Canada approval. These agents often either target common mechanisms of cell proliferation and survival, as in the case of cyclin-dependent kinase (CDK)4/6 inhibitors, or target-specific genetic susceptibilities unique to an individual patient's disease, as with olaparib in BRCA-mutated breast cancer.

As highlighted in **Table 2**, many of these novel agents are associated with unique, clinically relevant toxicities. In the primary care setting, an awareness of said toxicities is prudent to facilitate prompt treatment reassessment with medical oncology and, if required, further expert referral.

Take Home Message for Primary Care Providers

The current landscape of oncologic care is dependent on well-connected, multidisciplinary teams, with primary care providers being critical members of this infrastructure, from screening to survivorship and occasionally palliation. Together, as a patient's longitudinal care provider, primary care physicians are uniquely positioned to help patients contextualize their breast cancer among multi morbidities, share insights into the prognosis of competing comorbidities, and leverage preexisting knowledge of a patient's values and motivations to guide discussion of a patient's goals of care.

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