Demystifying Breast Cancer

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Faculty/Presenter Disclosure

- **Faculty**: Anna Wilkinson

- **Relationships with financial sponsors:**
  - Ontario College of Family Physicians Speaker Honoraria (ASA)
  - Osler Clinic Day- speaker honoraria
  - CPAC- travel to one day meeting in Toronto
  - CFPC- travel to MIG meetings
  - CFPC Grant for Breast Cancer Survivorship Tool
Learning Objectives

• Describe screening guidelines and the diagnostic workup for breast cancer

• List and discuss potential adjuvant therapies for breast cancer, including surgery, chemotherapy, targeted therapy, radiotherapy, and endocrine therapy

• Identify appropriate survivorship care for breast cancer patients
Objectives

1) Screening
2) Diagnosis
3) Treatment
4) Survivorship Care
1) Screening
Recommendations on screening for breast cancer in women aged 40–74 years who are not at increased risk for breast cancer

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Breast cancer mortality rates among Canadian women have declined from 41.7 per 100 000 in 1988 to an estimated 23.2 per 100 000 in 2017, while age-standardized incidence has remained relatively stable, at around 130 per 100 000 since 2004.1 Declining mortality with stable incidence

KEY POINTS
- Low-certainty evidence indicates that screening for breast cancer with mammography results in a modest reduction in breast cancer mortality for women aged 40 to 74 years. The

https://canadiantaskforce.ca/guidelines/published-guidelines/breast-cancer-update/
2018 CTPHC Guidelines:

- **Age 40-49**
  - No screening recommended
  - *Conditional recommendation; low certainty evidence*
    - NNS (Number needed to screen to prevent one death): 1724

https://canadiantaskforce.ca/tools-resources/breast-cancer-update/1000-person-tool-age-40-49/
2018 CTPHC Guidelines:

- Age 50-74
  - Mammography every 2 to 3 years
  - *Conditional recommendation; very low certainty evidence*
    - NNS 50-59: 1333
    - NNS 60-69: 1087
    - NNS 70-74: 645
  - the decision to undergo screening is conditional on the relative value a woman places on possible benefits and harms from screening.

https://canadiantaskforce.ca/guidelines/published-guidelines/breast-cancer-update/
Other Screening Modalities

- **No Role for:**
  - **Strong recommendation; no evidence**
    - MRI
    - Tomosynthesis
    - Ultrasound
  - **Conditional recommendation; no evidence**
    - Clinical breast examination
  - **Conditional recommendation; low-certainty evidence**
    - Breast self-examination
Mortality benefit of screening

- Studies used in 2018 CTFPHC guidelines to derive mortality benefit began between 1963 and 1991
- Significant advances in technology/treatment since this time
- Earlier diagnosis = less treatment- morbidity impact?
- CTFPHC mortality benefit 15%-21%; other studies suggest ~40%

Improvement in Mammography Quality between 1980 and 1995

Courtesy: Dr. Roberta Jong, Dr. Martin Yaffe, Univ. Toronto

Overdiagnosis

- Diagnosis of a cancer that would not cause a problem in a person’s lifetime
- Estimates of overdiagnosis vary widely from 0-57% (validity)
  - Canadian Task force states is ~50%
  - Other RCT’s state ~10%

Age of Initiation

- 1 in 5 breast cancers diagnosed are women in their 40’s
- 33% of lives lost to breast cancer occur in women in 40s
- There is no abrupt change at age 50
- Earlier initiation of screening in US, UK, Sweden

Coldman et al, Pan Canadian study, *J Natl Cancer Inst* 2014
Tabar L, et al. *Cancer*, Nov. 2018
Breast Density

- Dense (C) or extremely dense (D) breast tissue increases risk of developing breast cancer (odds ratio ~4.0)
- Dense breast tissue limits cancer detection with mammography
- Woman with dense breast are at increased risk of developing interval cancers

Breast Density-Supplemental Screening?

- Consider yearly mammogram to decrease interval cancers
- Calculate risk:
  - IBIS calculator: https://ibis.ikonopedia.com/
  - Intermediate Risk: 15-20% Lifetime risk
    - consider supplemental US
  - High Risk: >=20-25% Lifetime risk
    - may be eligible for MRI screening - refer to high risk program

2) Diagnosis
Presenting symptoms

- Not all breast cancers present as “lumps”
- Palpable breast mass
- Nipple discharge without mass
  - Concerning if: persistent, reproducible, spontaneous, unilateral, serous/serosanguinuous or sanguineous
- Asymmetric thickening or nodularity
- Skin changes
- Axillary mass
  - Can be associated with an occult breast cancer
- Breast pain
  - Up to 6.7% will be dx breast cancer
Work-up

• Mammogram
  • Screening
    • 2 views each breast
  • Diagnostic
    • Additional views, magnification

• Ultrasound
  • Does not detect microcalcifications
  • Good for cysts
  • Often first investigation in woman <30

• MRI
  • Suspicion of inflammatory breast cancer- skin changes with negative biopsy
  • Suspicious nipple discharge when mammo or u/s non-diagnostic
BI-RADS

• Breast Imaging-Reporting and Data System
• A quality assurance tool used to categorise findings and provide recommendations for follow up

<table>
<thead>
<tr>
<th>BI-RADS 1 (negative)</th>
<th>• Resume routine screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI-RADS 2 (benign)</td>
<td></td>
</tr>
<tr>
<td>BI-RADS 3 (probably benign)</td>
<td>• Diagnostic mammogram @ 6 months and q6-12 months for 1-2 years</td>
</tr>
<tr>
<td>BI-RADS 4 (suspicious)</td>
<td></td>
</tr>
<tr>
<td>BI-RADS 5 (highly suspicious of malignancy)</td>
<td>• Biopsy Required</td>
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</table>
Biopsy

- Fine Needle Aspiration (FNA)
  - Small bore needle
  - Less invasive
  - Less tissue

- Core
  - Multiple cores of tissue
  - More accurate than FNA
  - More tissue

- Excisional
  - Removal of entire breast mass in OR
  - Usually needle/wire localization prior

- Skin biopsy
  - If changes with skin or nipple
Don’t be fooled….

- **Inflammatory Breast Cancer**
  - Rare aggressive form of breast cancer
  - Dermal edema (peau d’orange) and breast erythema
- **Paget's**
  - Neoplastic cells in areola or nipple
  - Presents as eczema of nipple, bleeding, ulcer or itching
  - Occult on mammogram, requires skin biopsy

[Image of breast with redness and swelling]
[Image of nipple with eczema-like condition]

http://www.aboutcancer.com/paget.htm
Sampling Error

• If clinical/imaging/biopsy results discordant consider:
  • re-biopsy or
  • close observation clinically or
  • close observation with imaging
3) Treatment
Breast Cancer Pathology

- **Cell type**
- **Grade**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
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<tbody>
<tr>
<td>Well differentiated</td>
<td></td>
<td>Poorly differentiated</td>
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- **ER/PR**
  - Estrogen receptor status
  - Progesterone receptor status

- **HER2**
  - human epidermal growth factor receptor 2, a transmembrane tyrosine kinase receptor
  - \( \text{HER2} + \) breast cancers have a gene amplification or HER2 protein overexpression = uncontrolled cell growth
  - HER2 can be targeted by Trastuzumab
Staging

Stage 0
- LCIS/DCIS

Stage 1-2
- Operable- Adjuvant Therapy
  - Tumour <5cm, up to 3 nodes

Stage 3
- Non-operable- Neoadjuvant Therapy
  - Tumour >5cm or >4 nodes

Stage 4
- Metastatic

No staging investigations required for Stage 0, 1 or 2 breast cancer in absence of clinical symptoms and normal LFT’s, ALP

LCIS= Lobular Carcinoma in Situ
DCIS= Ductal Carcinoma in Situ
Overview of Treatment

- Surgery
- Chemotherapy (4-6 months)
- Trastuzumab (1 year)
- Radiation Therapy (3-5 wks)
- Bisphosphonates (2-3 years)
- Endocrine Therapy (5-10 years)

HER2+ 
ER/PR+

Aug 31, 2018
Surgery

• Lumpectomy vs Mastectomy?

• **Lumpectomy**
  • For tumours <5cm
  • Margins must be negative
  • Must able able to receive XRT post

• **Mastectomy**
  • Equivalent to lumpectomy + radiation
  • If underlying genetic mutation
Axillary staging

- Sentinel Node vs Axillary dissection?
  - No nodes clinically = **sentinel node**
    - Further nodal resection if sentinel node positive
    - Decreased arm/shoulder pain, lymphedema
  - Clinically positive nodes = **axillary dissection**
    - Pathologic confirmation with FNA/core biopsy
    - At least 10 nodes should be examined

Who Gets Chemotherapy?

Based on careful review of treatment benefit/toxicity, patient comorbidities and preference. Generally:

**No chemotherapy**
- Tumour <0.5cm and no node involvement
- Tumour >0.5cm, no node involvement with favourable prognostic factors
  - Her2-
  - ER/PR+
  - Low grade
- Genomic Profiling: low-intermediate risk

**Chemotherapy**
- Positive lymph nodes
- Tumour >0.5cm, no node involvement but unfavourable prognostic factors
  - HER2 +
  - ER/PR-
  - High grade
- Genomic Profiling: high risk
Genomic Profiling: Personalized Therapy

- 21 gene assay (OncotypeDx): “Recurrence Score”
- No benefit for chemotherapy for low/intermediate risk breast cancer
- Up to 70% of women with early stage, favourable disease (ER/PR+, HER2-, No Nodes) don’t need chemo
- Shows treatment benefit primarily from endocrine therapy
- Compliance!

Neoadjuvant Chemotherapy

- Chemotherapy given for large (>5 cm) or high risk (N2 or N3) tumours preoperatively, especially “triple negative”

- Benefits
  - Inoperable tumours become operable
  - Time for genetic testing prior to surgery
  - Facilitates breast conservation
  - Pathological response gives prognostic information
Chemotherapy Regimes

- Within 8 (up to 12) weeks from surgery
- Choice of chemotherapy regime depends on comorbidities, known toxicities

- **AC+T**
  - Adriamycin/Cyclophosphamide q 2-3 wks x 4 + Taxane q2-3wks x 4 or weekly x 12
  - or
- **FEC/Docetaxol**
  - 5-FU/Epirubicin/Cyclophosphamide q3wks x 3 + Taxotere q3wks x3
  - or
- **TC**
  - Taxotere/Cyclophosphamide q3 wks x 4

- Adriamycin + Epirubicin= Anthracyclines
Anthracycline Cardiotoxicity

- Months to > 20 years after treatment
- Additive with cardiotoxicity from other therapies (XRT/trastuzumab)
- Incidence ~2%
- Decreased EF or CHF
- Low threshold for investigation of dyspnea

Prevention
- Aggressively address CV risk factors
- Consider ace-inhibitor or ARB for tx of hypertension

Management
- As per heart failure guidelines

Adriamycin + Epirubicin = Anthracyclines
Trastuzumab

- Trastuzumab (Herceptin)
  - monoclonal antibody for extracellular domain of HER2 receptor
- For patients who are HER2+
- Q3wks x 1 yr, given concomitantly with non-anthracycline chemotherapy
- 48% reduction in risk of recurrence
- 39% reduced risk of death
- Adverse Effects
  - decreased EF

Radiation Therapy

- Lumpectomy
  - Whole breast: 50 Gy in 25 # (5 weeks) or 40 Gy in 15 # (2-3 weeks)
  + If high risk (Age <50, high grade, positive margins) may also get:
    - Boost to tumour bed: 10-16 Gy in 4-8#
    - Regional nodes (infra/supraclavicular, axillary, internal mammary): 50 Gy in 25#

- Mastectomy
  - If high risk (Large tumour (>5cm), LN+, positive margins)
    - Chest wall: 50 Gy in 25#
    - Nodes: 50 Gy in 25#

- If age >70 and Stage 1, can potentially forego XRT
Bisphosphonates

- Intermediate/high risk cancers, postmenopausal
- Zoledronic acid q6mon x 2-3 yrs.
- Significantly decreases in bone recurrence (RR 0.86) and breast cancer mortality (RR 0.85)
- Avoid invasive dental procedures where possible

https://www.cmaj.ca/content/172/13/1684
Endocrine Therapy

- For ER/PR + disease
- Tamoxifen
- Aromatase Inhibitors
  - Letrozole
  - Anastrozole
  - Exemestane
- GnRH agonists
- Fulvestrant
Mechanism of Action of Endocrine Therapy

- Testosterone (peripheral tissues)
- Estradiol
- Ovaries
- Pituitary
- GnRH Agonist
- Breast Tumour Cell
- Cell Replication

Aromatase Inhibitors
Tamoxifen
Fulvestrant
Tamoxifen

- Selective Estrogen Receptor Modulator (SERM)
- Can be used in both pre and post menopausal women
- Efficacy
  - Reduces recurrence by 39%
  - Reduces 10 yr mortality by 31%
- Side Effects
  - VTE
  - Endometrial cancer (risk 3.1%)
  - Vaginal dryness and hot flashes
- Caution with SSRI’s: Fluoxetine and Paroxetine decrease efficacy of Tamoxifen

Aromatase Inhibitors

- Post menopausal women only
- Efficacy
  - 10 yr mortality decreased by an additional 10% (in addition to 31% from tamoxifen)
- Side Effects
  - Hyperlipidemia
  - Osteoporosis
  - Arthralgias and myalgias
  - Vaginal dryness and hot flashes
- Compliance ~70%


Menopausal Status- Why does it matter?

- Aromatase Inhibitors (AI) block peripheral conversion of androgens to estrogen
- In premenopausal women with functioning ovaries, decreased circulating estrogen with AI’s will cause ovaries to be stimulated to make more estrogen
- Estrogen levels are therefore higher than without treatment
Endocrine Therapy Options

- **Premenopausal**
  - Tamoxifen
  - Ovarian Suppression (GnRH agonist/Ablation/Oophorectomy) + tamoxifen
  - Ovarian Suppression (GnRH agonist/Ablation/Oophorectomy) + AI

- **Post Menopausal**
  - Tamoxifen
  - Tamoxifen followed by AI
  - AI

- **Duration**
  - At least 5 yrs
  - If node positive/high risk continue to 7 yrs
  - No survival benefit beyond 7 yrs, but prevents new breast cancers up to 10 yrs
Adjuvant Treatment- What’s in the Pipeline???

- **Immunotherapy**
  - Role in triple negative breast cancer? Studies ongoing

- **CDK4/6 Inhibitors**
  - Used in conjunction with endocrine therapy
  - “molecular brakes”-stop or slow cell division
    - Palbociclib
    - Ribociclib
    - Abemaciclib
  - 3.5% improvement in disease free survival rate.
  - $$

4) Survivorship Care
Survivorship Care - 4 stages

Breast Cancer

STEP 1
Care Knowledge and Co-ordination

STEP 2
Cancer Surveillance

STEP 3
Management of Long term Treatment side Effects

STEP 4
Health Promotion

Survivorship Tool
STEP 2  Cancer Surveillance: Cancer Recurrence

Common Sites of Disease Recurrence: local, lung, liver, bone, brain

Always consider the possibility of a new primary cancer and the need for biopsy in addition to referral.

New neurological symptoms
- Headache
- Seizures
- Nausea and vomiting
- New weakness/paresthesia

Further Steps
- MRI (if available) or CT head with contrast
- Refer to radiation/medical oncology and/or neurosurgery

New breast/axillary symptoms
- Dimpling of the skin
- Discharge from the nipple
- New palpable breast mass
- New palpable lymph node
- New lymphedema

Further Steps
- Mammogram, ultrasound
- Refer to breast surgeon and/or breast diagnostic centre
- Refer to medical oncology

New respiratory symptoms
- Coughing
- Hemoptysis
- Shortness of breath

Further Steps
- Chest X-ray, CT thorax
- Refer to medical oncology

New abdominal symptoms
- Nausea and vomiting
- New somatic and visceral pain
- Abdominal distension
- Jaundice

Further Steps
- Consider LFTs, ultrasound, or CT abdomen/pelvis
- Refer to medical oncology

New bone pain
- Acute or progressive bone pain

Further Steps
- Consider X-ray, bone scan, or CT/MRI axial skeleton
- Refer to medical oncology/radiation oncology
<table>
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<tr>
<th>Year 1</th>
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<th>Year 4</th>
<th>Year 5</th>
<th>And beyond</th>
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<td>Medical history and physical exam every six months (III)</td>
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<td>Medical history and physical exam every six months (III)</td>
<td>Breast self-exam monthly (III)</td>
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<td>Diagnostic mammogram one year from pre-treatment mammogram and not less than six months after radiation treatment (II)</td>
<td>Diagnostic mammogram (II)</td>
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<td>Diagnostic mammogram yearly (II)</td>
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<td>Screen for distress, depression, and anxiety (I)</td>
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<td>BMD every two years (III)</td>
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<td>• Lipid levels yearly (III)</td>
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* LFTs = liver function tests
† BMD = bone mineral density
‡ AI = aromatase inhibitor

Levels of evidence are indicated in parentheses where applicable. For an explanation of evidence levels please see: https://tinyurl.com/Leve1sofevidence5.
**STEP 4** Health Promotion

**Weight management** 3,25,30,31
Breast cancer survivors who have BMIs higher than 30 are at an increased risk of disease recurrence and the development of new primary malignancies. Primary care physicians should encourage:
- Healthy dietary habits (III)
- Physical activity (III)
- Weight loss (III)

**Physical activity** 5,10,31
Physical activity is recommended for all breast cancer survivors. Evidence shows that survivors who participate in daily physical activity have a decreased risk of death, less fatigue, less pain, lower rates of depression, and a better quality of life. Primary care physicians should:
- Recommend returning to daily activities as soon as possible after the initial diagnosis (II)
- Recommend 150 minutes of moderate exercise per day or 75 minutes of high-intensity exercise weekly (I)
- Recommend twice-a-week strength training (I)

**Nutrition** 5
Although there is no scientific evidence demonstrating that nutrition alone can prevent cancer recurrence, primary care providers should emphasize the importance of a diet that has a positive impact on cardiovascular health. This includes:
- A diet rich in fruit, legumes, and whole grains and low in saturated fat (I)
- Limited amounts of processed meat and red meat (I)
- Vitamin and iron supplementation only if deficiencies are demonstrated (III)
- Daily intakes of calcium (1,200 mg/day) and vitamin D (800 IU/day)

**Smoking cessation** 3,8
Breast cancer survivors who stop smoking have significantly lower all-cause mortality (II). Primary care physicians should therefore:
- Encourage smoking cessation (I)
- Offer smoking cessation resources and support (I)

Concerning marijuana, there is no evidence addressing its use and health implications in breast cancer survivors.

**Reduction of Alcohol Intake**
Cancer survivors who have a greater alcohol intake have an increased rate of cancer recurrence. Breast cancer survivors should limit their consumption to no more than three or four standard drinks (14 g of alcohol/drink) a week.

**Preventative health** 3,33
A Canadian study demonstrated that 65% of eligible breast cancer survivors were not screened for colorectal cancer and 40% were not screened for cervical cancer over a four-year follow-up period. Primary care physicians should continue recommended routine screening during and after cancer treatment.
Questions?
Bisphosphonates can be used in the adjuvant treatment of breast cancer.

a) True
b) False
Anthracycline cardiotoxicity can manifest more than 20 yrs post treatment.

a) True

b) False
Aromatase Inhibitors can be used in:

a) Premenopausal women with functioning ovaries
b) Postmenopausal women
c) Premenopausal women with suppressed ovarian function
d) B + D
e) All of the above
Follow up care for breast cancer patients should include the following:

a) Mammography
b) Breast MRI
c) Bone Scan
d) LFT’s
e) All of the above
Who should be referred to Genetics?

- Breast cancer diagnosis at age < 50 (especially < 35)
- Triple-negative breast cancer age < 60
- Ovarian cancer at any age
- Bilateral breast cancer
- Breast and ovarian cancer in the same woman or family
- Multiple breast cancers on same side of family (paternal or maternal)
- Male breast cancer
- Ashkenazi Jewish ethnicity
Fertility Preservation

• Childbearing after treatment of invasive breast cancer does not increase rates of recurrence
• There is no increased risk of birth defects/serious illnesses after treatment for breast cancer
• Treatment for breast cancer may impair fertility
• Consider discussing fertility with newly diagnosed patients and referring to fertility specialist before treatment starts
Menopausal Status

- Use LH, FSH, estradiol to determine menopausal status
- Amenorrhea post chemo not reliable especially if on tamoxifen


Investigations not routinely indicated

- Breast MRI
- Blood work
  - CBC, LFT, tumour markers
- Imaging
  - CXR, CT, Bone scan
- Cardiac markers, ECHO