

What's New in Breast Cancer?

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Breast cancer is the most common malignancy affecting women in Canada, accounting for almost a third of all cancer diagnoses and the second highest mortality rate after lung cancer. Most women have no identified risk factors apart from aging. The incidence rate of this disease continues to rise while the mortality rate has been falling slightly (Figures 1a and 1b). This result is likely due to a combination of factors, including detection of disease at earlier stages due to screening mammography and improvements in treatment.

Advances in knowledge related to the diagnosis and treatment of breast cancer continue on many fronts, including;

- gene profiling,
- imaging procedures,
- endocrine modulators,
- biologic agents,
- dose dense or intense chemotherapy regimens,
- limited surgery, particularly sentinel node biopsy, and
- newer radiotherapy techniques.

Janet's Case

Janet, 58, is post-menopausal and has never had mammograms. She found a lump in the superior hemisphere of the left breast. She is otherwise well. Her family history is negative for any cancers.



An exam reveals a 2 cm mobile lump at the 12 o'clock position in the left breast. There are no other abnormalities. The patient's mammograms show a spiculated lesion corresponding to the palpable abnormality. A core biopsy was positive for an intermediate grade, estrogen receptor/progesterone receptor (ER/PR) positive, and her2neu negative breast cancer.

What are her treatment options?

Surgery would be the initial treatment normally offered to this patient. The breast could be treated with mastectomy or breast-conserving surgery (BCS), followed by adjuvant whole breast radiotherapy. Both treatments have been shown to provide equivalent local control.^{1,2} Formal axillary node dissection (AND) remains the standard recommended treatment, as lymph node status is the most important prognostic factor for recurrence and survival.

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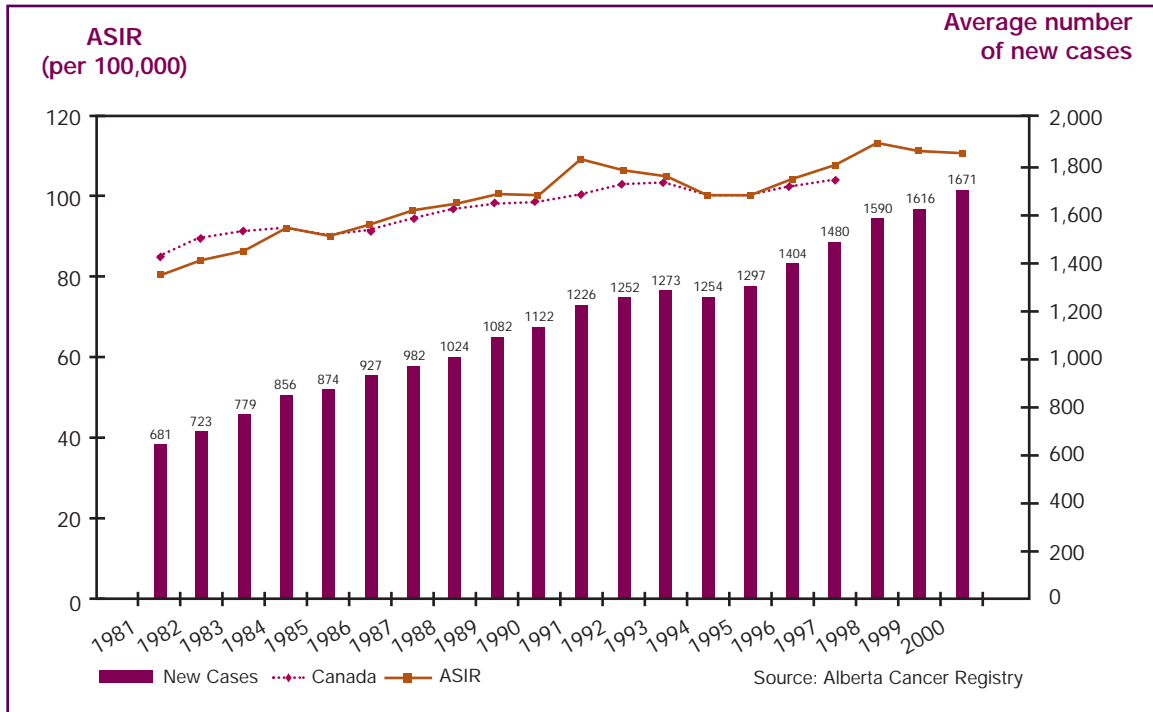


Figure 1a. Age-standardized incidence rates (ASIR) and new cases for invasive breast cancer, females, Alberta (1981-2000) using 3-year averages.

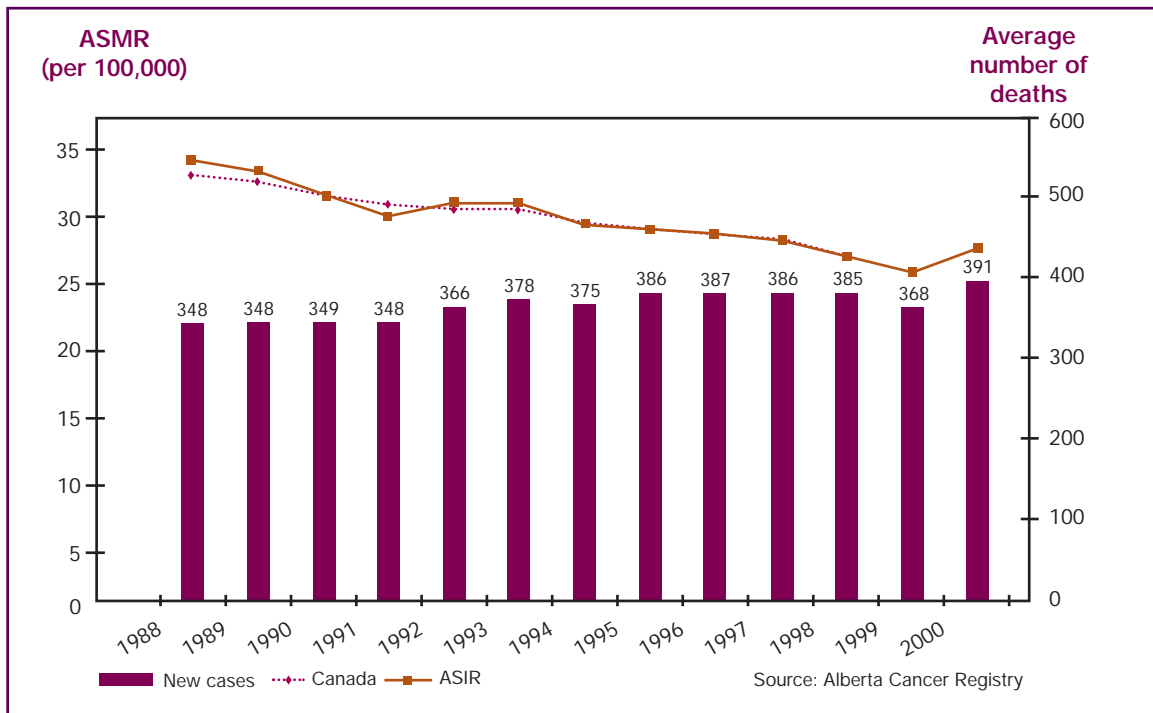


Figure 1b. Age-standardized mortality rates (ASMR) and deaths for invasive breast cancer, females, Alberta (1988-2000) using 3-year averages.

In this case, the patient opted to undergo BCS plus AND. Pathology showed a 1.8 cm, grade-2 tumour, which was excised with clear margins, and 2/11 lymph nodes were positive for metastatic disease (Stage IIA).

After the initial treatment, and without further therapy, her risk of recurrence is approximately 50% at 5 years.³ Adjuvant chemotherapy would be recommended for this patient, which would consist of an anthracycline-based regimen. This therapy would decrease her risk of recurrence to approximately 30%. Adjuvant radiotherapy would also be recommended to reduce the risk of local relapse from about 35% to 8% at 10 years.

Controversy exists regarding the extent of the radiotherapy field. Whole breast radiotherapy is standard, but the benefit from radiotherapy to the regional lymph nodes is currently being assessed. Previously published data has shown a survival benefit for post-mastectomy radiotherapy to the chest wall and regional nodes. More extensive radiotherapy increased survival by 10% at 10 years.⁴

However, due to changes in surgery (BCS vs. mastectomy) and changes in chemotherapy since those trials were published, it is not clear whether this benefit will still be apparent. Adjuvant hormonal therapy, usually tamoxifen, would be recommended to further decrease the systemic relapse risk.⁵

What advancements might change her outcome?

Imaging

Mammography is not new, but there are still women who, for a variety of reasons, do not go for screening. This is troublesome considering that screening women between the ages of 50 and 69 has been shown to decrease mortality by about 30%. Since survival is improved when the disease is found earlier, screening programs continue to target women in this age group. Digital mammography may increase positive prediction value.

Breast magnetic resonance imaging (MRI) is not generally used for screening, but in women who are at high-risk for developing breast cancer or whose mammogram does not show the palpable abnormality (this occurs in 10-15% of mammograms), it can be very helpful.⁶ This is especially true in young patients, where breast density limits the sensitivity of mammograms. MRI will help define whether a lesion is truly solitary, and therefore suitable for BCS, or whether there is multicentric disease, in which case a mastectomy would be the preferred treatment.



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Sentinel node biopsy

Lymphatic mapping with sentinel node biopsy, first developed in the management of melanoma, has more recently been applied to breast cancer. While the specificity is excellent (95%), the sensitivity can be low as the procedure is operator-dependent and takes considerable practice to ensure high sensitivity. Several studies have shown that this procedure is a safe and accurate method of evaluating the axilla in patients with small breast cancers and a clinically negative axilla.⁷

Although this procedure is not yet the standard of care in North America, studies currently in progress may soon make sentinel node biopsy standard procedure. Limiting the axillary dissection to the sentinel node only, is reported to be associated with lower morbidity rates than a full AND. If the sentinel node is positive, formal axillary dissection is recommended.

Gene expression profiling

Defining recurrence risk and mortality risk for a patient with breast cancer is based on population results from many different studies. Sophisticated computer programs, such as "Adjuvant!" are helpful for estimating the prognosis of an individual patient based on recognized prognostic factors, such as age, stage, tumour grade, and hormone receptor status. Tissue microarrays, which can systematically assess thousands of genes at the same time (gene-expression profiling), may provide an individualized molecular portrait

of a tumour.⁸ This information could be an important new prognostic as well as predictive marker. Recent work in this area is very exciting but at this time, must still be considered investigational.

Chemotherapy regimens

Over the past 30 years, numerous chemotherapy drugs, singly or in combination, have been evaluated in the treatment of breast cancer. At present, high-dose epirubicin regimens or a taxane-based treatment have demonstrated the best outcomes with very good toxicity profiles. Different combinations of

drugs and altered dosing schedules will continue to generate new data, some of which already look promising in terms of further decreasing recurrence risks and improving survival.

Endocrine therapies

Tamoxifen has been the mainstay of hormonal therapy for three decades. It can be used in both pre- and post-menopausal women. Long term data has shown an 11% absolute survival benefit at 10 years in node-positive patients and 5.5% in node-negative women who took adjuvant tamoxifen for five years.³ The third generation aromatase inhibitors (letrozole and anastrozole) and aromatase inactivator (exemestane) are emerging as important new hormonal therapies, but can only be used in post-menopausal patients (Figure 2). Compared to tamoxifen, anastrozole has been shown to improve disease-free

Screening for women between 50 and 69 has been shown to decrease mortality by about 30%.

survival by 2%, but overall survival figures are still pending.⁹

One point of concern with the aromatase inhibitors is the effect on bone, with an increased risk of fracture and joint and muscle symptoms as compared to tamoxifen.

Recent data on improved disease-free survival with letrozole, after five years of tamoxifen, has generated significant discussion and will prompt further trials.¹⁰

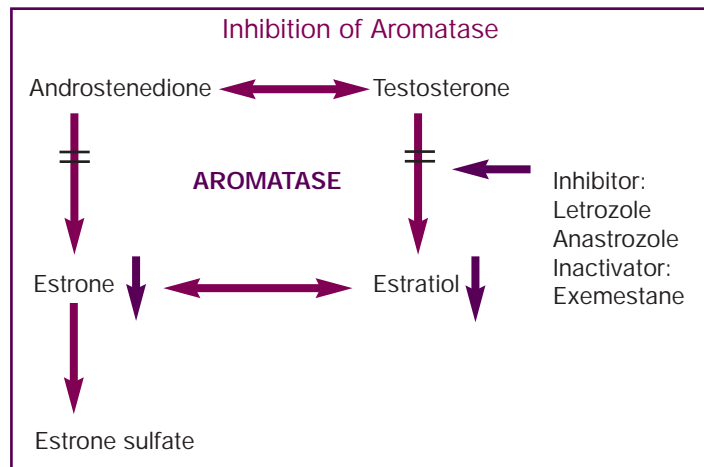


Figure 2. Aromatase inhibitor.

Biologic agents

Her2/neu is an epidermal growth-factor receptor which is involved with intracellular signaling and leads to cellular proliferation. About 30% of women with breast cancer overexpress this receptor, which is associated with a worse prognosis.¹¹ Trastuzumab is a monoclonal antibody which binds to the her2/neu receptor, causing regression of her2-overexpressing breast cancer cells. When used in conjunction with chemotherapy, particularly with anthracyclines or taxanes, herceptin has been shown to improve disease-free survival in the metastatic setting. Many new agents, which bind to a variety of different receptors, are under investigation.

Partial breast radiotherapy

While whole breast radiotherapy has been the standard for many years, it is recognized that most of the morbidity resulting from treatment has been related to the treatment of normal breasts. Work is being done to evaluate partial breast radiotherapy as an alternative.¹² This treatment has the advantage of a short delivery time, a sig-



Take-home message

Patients, 50-69, with no obvious risk factors, such as a family history of breast cancer, need to be encouraged to attend routine screening mammography.

In the future for patients diagnosed with breast cancer:

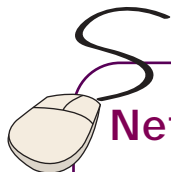
- Molecular information may soon be available to help individualize treatment.
- Systemic therapy could include a diverse array of targeted biologic therapy.
- Hormonal therapies may be used sequentially.
- Radiation treatment may be limited to partial breast irradiation.

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nificant advantage over traditional 3.5- to 5-week treatments. Studies are now being done to evaluate this new approach. [CME](#)

Suggested Readings

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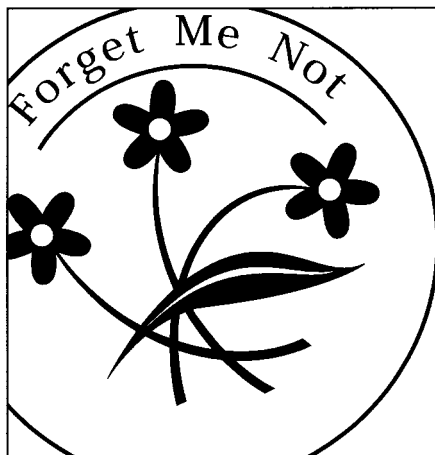
Net Reading

Adjuvant!
www.adjuvantsite.com

www.stacommunications.com



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* Canadian Study of Health and Aging