Factors affecting breast cancer outcomes

Can we do better?

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ABSTRACT

There are reasons to be optimistic about breast cancer outcomes. Significant investment in research and the availability of a range of effective diagnostic and therapeutic approaches are enabling steady improvements. However, access to treatment advances is uneven between and even within countries. As well, improvements in mortality are occurring in a context of rising incidence, especially in less developed countries. This review looks at the evolution of breast cancer incidence and mortality over time, comparing different provinces within Canada and considering global trends, in order to identify factors that contribute to mortality and incidence. Our aim is to encourage the spread of best practices in cancer care and to articulate possible strategies for the prevention of breast cancer.

Keywords: Breast cancer outcomes; age-standardised breast cancer incidence, age-standardised breast cancer mortality; socio-economic status and breast cancer outcomes, organization of cancer care and breast cancer outcomes, screening mammography, adjuvant therapy.

Encouraging news on breast cancer outcomes, dominated by steadily declining age-standardized mortality rates (ASMR) in the Western world,1-4 has been tempered recently by even more dramatic changes in the underdeveloped world, where the incidence of breast cancer, particularly in urban regions, is rapidly rising.4-6 Age-standardized incidence rates (ASIR) for breast cancer recently recorded in urban Asia show increases of 200% to 300% over levels seen before these areas were “westernized.” This trend is evident in data from urban regions in Japan, Taiwan, Hong Kong, Singapore and, more recently, China.7-9 Similar trends are seen in Asian immigrants to western countries.10

Westernization, a term encompassing the combination of urbanization, industrialization and economic affluence of less-developed countries,11 unquestionably contributes to increased breast cancer rates. The features of westernization offer unique insight into lifestyle-related breast carcinogenesis, both in urban regions of the less developed world and in western countries. While there is evidence that lifestyle factors are associated with increased human breast cancer rates, no single risk factor has, as yet, clearly emerged as dominant. Thus, as outlined in this review, research into different aspects of the western lifestyle is of rising public health importance, as deeper understanding of the etiologic factors of breast carcinogenesis may lead to more rapid progress in the identification and implementation of preventive interventions.12

Outcomes are also affected by access to optimum cancer care, such as screening and early treatment, and our research into breast cancer mortality over time in different Canadian provinces provides compelling data. The recently presented13 comparative data from British Columbia and the Atlantic provinces traces the impact on outcomes of organizational aspects of cancer care: specifically, securing optimum and timely delivery of guideline-driven interventions uniformly across the whole population of a province.14,15 This review examines some of the differences we identified.

VARIATIONS WITHIN CANADA

In general, variations in socioeconomic status, population heterogeneity related to generous long-term immigration policy, and sheer geographic distances are responsible for the diversity seen in many aspects of Canadian life. Greater affluence in the western provinces, evident historically since the 1950s, is also likely related to differences in organizational aspects of medical care, including cancer care and funding, between provinces. At one end of the spectrum is British Columbia (BC), which has had a centralized Cancer Agency since the 1930s, and a higher provincial cancer budget than elsewhere in Canada. This has historically facilitated a more uniform, broad-spectrum distribution of cancer care than seen in the rest of Canada.

On the other side of the continent is Atlantic Canada, with 4 provinces (Newfoundland & Labrador, Nova Scotia, Prince Edward Island and New Brunswick) known for a
more rural lifestyle related to fishery, forestry and agriculture. In general, the Atlantic provinces have had less urbanization and industrialization, and less affluence when compared to BC. For decades, less cancer funding was available in the Atlantic provinces, and there was substantially less uniformity in key organizational aspects of cancer care, especially those that would secure province-wide delivery of adjuvant breast cancer therapy and the provision of screening mammography in rural regions. These were introduced in the Atlantic provinces many years later than in BC.

One of the key organizational aspects of cancer in BC was the formation in the 1970s of tumour groups, charged with coordinating guideline policies. These enabled new diagnostic interventions and/or therapeutic policies to be incorporated into guidelines as research evolved; this occurred more rapidly than in other provinces, and much more rapidly than in Atlantic Canada. The other feature of cancer care in BC was the formation, through the 1960s and 1970s, of a comprehensive community oncology program permitting these guideline-driven care policies to be spread across all BC communities almost simultaneously with their implementation in the academic institutions of the BC Cancer Institute. This organizational structure was already in place when two pivotal breast cancer interventions — adjuvant therapies and screening mammography — were introduced, and meant that these would spread much more rapidly through BC that in the rest of Canada. This difference allows us today to observe the impact these interventions have on breast cancer incidence and mortality.

**BREAST CANCER INCIDENCE IN BC AND ATLANTIC CANADA**

Historically, breast cancer ASIRs were substantially lower in the Atlantic provinces than in BC; in 1970 the Atlantic provinces had an ASIR of 60/100,000 compared to 75/100,000 in BC (Table 1). While the difference is seemingly small, it represents hundreds, if not thousands, of breast cancer diagnoses each year. These early differences are thought to be related to lower affluence in the Atlantic provinces up until the 1980s, that was accompanied by more work-related exercise and a less sedentary lifestyle typical of rural life for the female population, and a diet based more on fish and grains, and less on “meats and sweets.”

Interpreting breast cancer incidence trends later on, in the 1990s and 2000s, is more complex, as it requires taking into account both the introduction of adjuvant therapies and screening mammography programs (first in BC and later in the Atlantic provinces), and changes in the patterns of affluence across Canada. These show a trend toward increased affluence generally in the 1990s and 2000s, and more specifically a jump in socioeconomic status in the Atlantic provinces.

**How would these changes influence breast cancer outcomes?**

Screening mammography in BC began gradually in the early 1980s, growing into an official provincial program by 1988. The province saw a 25% increase in age-standardized breast cancer incidence between the mid- and late 1980s, due primarily to more diagnoses of lower stage invasive (and subclinical) cancers related to screening mammography. This increase was short-lived and, after the mid-1990s, BC’s age-standardized breast cancer incidence rates declined back to the levels seen in the 1970s (Table 1). The Atlantic provinces saw a much higher increase in incidence — over 40% — which became evident in the early 1980s and persisted until the late 1990s (Table 1). Incidence increases between 1980 and 1990 are likely a reflection of the rising affluence seen in Atlantic Canada after 1980, and are also possibly due to improved capture of new incidence data by evolving cancer registries in those provinces. The persistent increase throughout the 1990s, however, is most likely related, as in BC and other western jurisdictions, to the introduction of screening mammography in the Atlantic provinces in those years, as well as to ongoing socioeconomic improvements. Both factors are likely responsible for the steady increase in breast cancer incidence that persisted until the late 1990s. As seen in Table 1, from the late 1990s on, the Atlantic provinces also start showing a steady ASIR decline, albeit at a later time, and to a lesser degree than seen in BC.

**BREAST CANCER MORTALITY IN BC AND ATLANTIC CANADA**

Breast cancer mortality in Canada, as elsewhere in the western world, is determined both by access to the best breast cancer care and by incidence rates. Interventions with confirmed curative capabilities, such as screening mammography, anthracycline and taxane regimens in the adjuvant setting, locoregional radiation for node-positive cases, and adjuvant tamoxifen for premenopausal cohorts, were all incorporated into BC guidelines years, if not decades, earlier than in other parts of Canada.

The earlier province-wide implementation of these policies is most likely responsible for superior mortality outcome data, with an earlier and more substantial mortality decline evident in BC than in the rest of Canada.

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**Table 1. Age-standardized incidence rates (ASIRs) in British Columbia (BC), the Atlantic provinces (AP) and Canada, 1970 to 2010**

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<thead>
<tr>
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<th>1970s</th>
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<tbody>
<tr>
<td><strong>BC</strong></td>
<td>75</td>
<td>75</td>
<td>90*</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td><strong>AP</strong></td>
<td>60</td>
<td>60</td>
<td>75</td>
<td>85*</td>
<td>75</td>
</tr>
<tr>
<td><strong>Canada</strong></td>
<td>65</td>
<td>68</td>
<td>75</td>
<td>83*</td>
<td>78</td>
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</tbody>
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**ASIRs relative to 1970 (in %)**

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<th>1970s</th>
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<tr>
<td><strong>BC</strong></td>
<td>100</td>
<td>100</td>
<td>125*</td>
<td>110</td>
<td>100</td>
</tr>
<tr>
<td><strong>AP</strong></td>
<td>100</td>
<td>100</td>
<td>120</td>
<td>140*</td>
<td>120</td>
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<tr>
<td><strong>Canada</strong></td>
<td>100</td>
<td>110</td>
<td>120</td>
<td>135*</td>
<td>122</td>
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* Highest level (peak incidence) before incidence decline observed
** Data obtained in collaboration with the Public Health Agency of Canada from the Canadian Cancer Registry database or Statistics Canada, with the consent of the Provincial and Territorial Cancer Registries. Manuscript, in preparation.
By 1990, age-standardized mortality rates (ASMRs) in BC were already 10% lower than 1950 levels, while in the Atlantic provinces, the ASMRs were 40% higher (Table 2). A definitive mortality decline was eventually also seen in the Atlantic provinces, but came some 10 years later. By 2007, ASMRs in the Atlantic provinces were 25% lower than the 1950 levels, compared to the 45% decline in mortality rates seen in BC (Table 2).

CRUDE NUMBERS AS A MARKER OF RISING BREAST CANCER BURDEN

Despite improvements in cancer care and declining age-standardized incidence and mortality rates in most parts of Canada, the harsh reality remains that the absolute number of new breast cancers diagnosed annually is growing. While in 1974, there were 8,500 new breast cancers diagnosed in Canada, by 2007 the number had reached close to 25,000 — nearly a 300% increase! Breast cancer deaths are also substantially more numerous, with crude numbers rising from 2,700 in 1970 to 5,000 in 2007 — almost a 200% increase.

Population growth has been cited as the main reason for such a rapid increase in crude numbers, and age standardization would adjust for population growth as it permits comparison of cancer rates within each 5-year age group. However, the rise of breast cancer events is out of proportion with the substantially more modest 40% population growth between the 1970s and 2010s.

It must be emphasized that while age-standardized rates are essential for comparison of trends among various regions, the crude numbers of annual new cancers remain important, as these are the patient volumes that oncology professionals need to see on a daily basis in Canadian cancer centers. These are the numbers responsible for rising cancer budgets, and taxpayers need to be aware of them.

PREVENTION

While contemporary western interventions are undoubtedly associated with substantially reduced mortality from established breast cancers, they do not contribute — with the exception of hormonal therapies used in adjuvant1 and preventive settings20,21 — to the suppression of new incident breast cancer cases. In light of the steady and substantial increase in crude new breast cancers diagnosed each year in Canada, a focus on prevention is essential.

Recent data indicate that preventive measures directed against some elements of the western diet,16,22,23 in addition to interventions such as increasing exercise24 and reducing alcohol consumption,25 can yield substantial all-cause mortality benefits, including a reduction in breast cancer risk. Other preventive measures that may be useful for identified high-risk women include medical interventions such as selective estrogen receptor modulators (SERMs — i.e. tamoxifen or raloxifene)21 or aromatase inhibitors. Both classes of hormonal interventions have been shown to reduce rates of new breast cancers significantly.20,21,26 More recently, preclinical and clinical studies indicate that anti-inflammatory approaches using cyclooxygenase-2 (COX-2) inhibitors with aspirin and or other anti-inflammatory agents27,28 could have great potential as preventive interventions, with a favourable cost/benefit ratio in high-risk populations.

The implementation of preventive strategies is important worldwide, as new annual incident cases and breast cancer deaths are rising rapidly in all regions of both the western and less-developed world. Changes in reproductive factors such as age at first pregnancy, parity and lactation, while of primary importance to breast carcinogenicity, are driven by strong social factors and are thus not candidates for easy modification. However, targeted counselling focused on all prevention factors, including reproduction, starting from a young age, may have significant effects. Breast cancer prevention counselling of women at high risk has recently been initiated in certain largely academic settings in North America, and may become required through federal health policy, accompanied by additional funding.

SUMMARY

In this review, we show that the breast cancer burden is rising rapidly both in urban parts of the underdeveloped world and in the West, even though age-standardized incidence and mortality rates are improving. There are several take-home messages for Canadian oncologists.

First, uneven access to cancer care between Canadian regions during the 1970s and 1980s sends strong signals regarding breast cancer outcomes: uneven delivery of optimum breast cancer care in parts of Canada resulted in large numbers of potentially avoidable breast cancer deaths.14,15 The “proof of principle” for a positive association between improved cancer care and improved breast cancer outcomes is seen in the evolving “equivalence” in cancer care delivery in most parts of Canada reached by the 2000s, matched by an evening out of both incidence and mortality differences between provinces.

Second, western lifestyles are associated...
with increased population breast carcinogenesis, as seen mostly in data from urban regions of Asia, but likely also reflected in our analysis of BC and the Atlantic provinces. Therefore, these data are relevant to both the developing urban regions of the less developed world and to the West. While epidemiologic research needs to intensify in order to tease out more accurately the contribution of individual causative factors associated with breast carcinogenesis, systematic preventive measures targeting factors with a stronger evidence base (Table 3) should be initiated now, and assertively. These may include a wide range of counselling regarding diet and exercise, as well as reproductive planning, and importantly, systematic delivery of preventive medical interventions for population cohorts at high risk for breast cancer (Table 3).

The consistent, substantial rise of new breast cancers, both in urban centres in the developing world and in western countries such as Canada, should be considered a global medical emergency. If appropriate guideline-driven preventive measures are not started systematically in the near future, the numbers of newly diagnosed breast cancers and related breast cancer deaths will continue to grow.

References:

TABLE 3. Factors implicated in breast carcinogenesisa

- Greater weight, height and body mass index
- Sedentary habits and less exercise
- Diet
- Greater alcohol consumption
- More female employment, often shiftwork
- Reproductive factors that increase cumulative endogenous estrogen exposures over the lifespan:
  - Older age at first pregnancy
  - Nulliparity & lower birth rates
  - Reduced rates of breastfeeding
  - Earlier menarche and later menopause