CANCER PREVENTION IN CANADA

The Sooner the Better

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The objective of this report is to show that prevention is the single most cost-effective initiative Canada could successfully escalate quickly in the fight against breast (and other) cancers. The report will provide an updated review of the research on breast cancer prevention and reveal its current potential impact for breast cancer risk reduction. The scientific community has already been made aware of these data through the normal scientific channels, albeit not all clinicians are aware. So now it is imperative that the information be presented to all the medical community and the other stakeholders - the Canadian public and administrative and medical policy decision makers.

The research shows that if individual lifestyle factors and the identified preventive medical interventions were applied consistently to high risk women, then hormone receptor positive breast cancer could be prevented in 20-50 per cent of cases. The result would be several thousand fewer breast cancers each year in Canada. This report will summarize the data and identify some of the challenges that delay implementing these interventions.

Background

Breast Cancer mortality has decreased by approximately 25-30 per cent in most parts of the western world over the last two decades, with variations across Canada depending on local services.[1,2]

The main factors known to impact breast cancer mortality include:

1 Widespread public education about breast cancer leading to earlier diagnosis particularly by using screening mammography.
2 Evidence-based therapy i.e., effective surgery, adjuvant chemotherapy, hormonal therapy, radiotherapy and post-recurrence therapy.

Breast cancer incidence rates have stabilized since the mid 1990s and slowly decreased since the late 1990s. This has been attributed, according to some reports, to the reduced use of hormonal replacement therapy (HRT) based on the U.S. Women's Health Initiative group (WHI) publication of adverse HRT effects.[3] However, breast cancer incidence rates had already stabilized in the mid-1990s, and thus other reasons ought to be considered.

Some aspects of breast cancer prevention, common to cardiovascular and breast cancer pathogenesis and related to lifestyle, have been increasingly practised by small cohorts of mostly urban-located western populations – such as weight reduction and diet focused on vegetables, fruit and exercise. In addition, across the western world there has been increased use of anti-cholesterol and anti-inflammatory interventions,[4] which may also beneficially affect breast cancer risk rates.

Despite the decreasing mortality rates for breast cancer over the last decade, more than 22,000 women are still diagnosed each year in Canada and of these, close to 20 per cent will die, with absolute numbers of breast cancer deaths increasing annually (from 4,335 in 1986 to 5,066 in 2007).[5] The ongoing breast cancer morbidity and the anguish of those affected remain one of the largest public health concerns of the female population.

Practical Aspects of Cancer Prevention

Of all breast cancer cases diagnosed in Canada annually, less than five per cent are associated with the expression of identified mutations in the two known genes: the BRCA-1/BRCA-2. Carriers of these genes have a 60–80 per cent lifelong chance of developing breast cancer and a 40–60 per cent lifelong risk for ovarian cancer, particularly those with the BRCA-2 mutations.[6,7]

These patients and their families are now part of the genetic counselling programs in most cancer institutions across the country, involving professional counsellors, with emphasis on two important steps.

1 Preventive surgery in the form of bilateral mastectomy and/or bilateral oophorectomy.
2 Medical interventions with tamoxifen and raloxifene.

However, the remaining breast cancers, although still likely having some genetic component other than BRCA-1/BRCA-2,

cannot be identified by a single genetic test before diagnosis and thus are not sought out by organized initiatives aimed at prevention. There is evidence that a large sector of this population of women would benefit from the lifestyle and medical interventions described in this review.

To implement population-based breast cancer prevention as part of the accepted clinical guideline programs across Canada will, however, require infrastructure changes and initiatives, including the formation and funding of dedicated breast cancer prevention clinics, ideally associated with, or under the auspices of existing cancer facilities. Currently, only a few U.S. based cancer centres provide prevention counselling by oncologists to non BRCA-1/BRCA-2 women, and there are currently no dedicated breast cancer counselling centres in Canada for the purpose of breast cancer prevention. Due to expected population health gains and related long-term societal cost savings as described below, this should be a high priority.

At least three steps are required:

1 identify which breast cancer risk reduction interventions are evidence-based and most cost-effective;
2 identify women at higher risk using quantitative prediction tools[8] and preferentially counsel this group;
3 finalize the cancer prevention logistics: identify who should do the counselling, who should fund it and consciously expand the focus from diagnosis and treatment of established disease to include prevention.

The results are in… An ounce of prevention equals thousands of pounds of cure

Risk Factors and Risk-reducing Interventions

Risk measure, named as relative risk (RR) or hazard rates (HR), is a statistical term that compares events with or without a given risk factor or intervention. If risk is unaltered, RR=1.0; if risk increases, for example by 20 per cent, it is expressed as RR=1.2; if risk is reduced by 20 per cent, RR=0.8.

Current literature indicates that the impact of some of the risk-reducing interventions could be profound, with ranges of 20–50 per cent fewer new hormone receptor positive breast cancers annually, (i.e., RR=0.5–0.8) depending on the individual intervention. These data permit estimates that if risk-reduction interventions are practiced with a higher level of compliance, several thousand new breast cancer cases in Canada could be avoided annually. What are these individual risk factors and possible interventions?

1. Excess weight and obesity

The current western diet (based on high carbohydrates, animal fat with high cholesterol and too few vegetables and fruits), associated with obesity and higher body mass index (BMI), has a well-established link to higher breast cancer rates, particularly if associated with a sedentary lifestyle.[1-3] High breast densities on mammogram and or higher serum estrogen hormonal levels are probably markers of these metabolic phenomena. Obesity, with adipose tissue as a source of carcinogenic molecular growth factors, has been described as increasingly relevant in the recent literature.[9]

The impact of long-term dietary and weight-reducing interventions on breast cancer risk is not precisely known, as no long-term validated intervention studies have been done for breast cancer. The proposed prevention clinics aimed at high risk populations will have potential to study the impact of these interventions. In addition, new data are accumulating on the adverse effects of obesity after a breast cancer diagnosis,[10] showing potential for improving survival rates through life style initiatives, in women already diagnosed with breast cancer.

What about interventions leading to obesity reduction, with dieting and exercise and or more targeted interventions? Old literature did not support a substantial influence of dietary manipulation on either breast cancer rates or breast cancer outcomes after the diagnosis. However, more recent studies come to a different conclusion. George et al.[11] showed, in 670 women with breast cancer, that patients consuming better-quality diets (as defined by higher Healthy Eating Index-2005 scores) had a 60 per cent reduced risk of death from any cause when compared to ordinary diet, (HR=0.40, 95 per cent CI: 0.17, 0.94) and an 88 per cent reduced risk of death from breast cancer (HR=0.12, 95 per cent CI: 0.02, 0.99)

2. Exercise

Recent evidence associates regular aerobic exercise with reduced breast cancer incidence rates and improved survival in women with diagnosed breast cancer.[12-14] In 2008, Irwin et al.[15] reported that when compared with inactive women, the multivariate hazard ratios (HRs) showed a 31 per cent reduction of total deaths for women who are physically active in the year before diagnosis – meaning approximately two to three hours per week of brisk walking. (HR=0.69, 95

per cent CI 0.45 to 1.06; P=.045.) In patients who exercised two years after diagnosis, even larger benefits were seen, with a 67 per cent reduction of deaths (HR=0.33, 95 per cent CI, 0.15 to 0.73; P=.046).

The estimates for risk reduction depend on the quality of the study, the duration of follow-up and the intensity of exercise, but fall in the range of 20-30 per cent (RR=0.7-0.8) or more with prolonged exercise. On the basis of 20-30 per cent risk reduction, comparing 1,000 women who do not exercise with 1,000 women who do, the sedentary group would produce 100 cases of breast cancer while the exercising group would produce 80 or less. Thus, a large number of the annual 22,000+ new breast cancers in Canada could be avoided through lifestyle changes that incorporate regular exercise, simultaneously reducing cardiovascular risk.

3. Alcohol

There is rising evidence for an association of increased breast cancer risk with alcohol intake,[16,17,18] with some data indicating dose dependence: the more alcohol, the higher breast cancer incidence. More than six drinks per week would increase the risk by 30-90 per cent compared to less than one to two drinks per week (RR=1.3–1.9). The mechanism is likely related to metabolic changes leading to increased breast tissue estrogen effect, which is considered carcinogenic.[17]

4. Medical interventions with breast cancer prevention agents

i. Tamoxifen. At least four randomized trials have documented a 40–50 per cent risk reduction of estrogen positive invasive and in situ breast cancer rates by tamoxifen (RR=0.5-0.6) given to women at high risk of breast cancer High risk was determined by the Gail model, based on first degree family history at a young age, or abnormal pathology (atypia lobular carcinoma in situ, etc.).[19] Prolonged adverse publicity associating tamoxifen with uterine cancer and increased thromboembolism (clotting), cited in the early years when they were identified but not rated accurately, has negatively affected its use in prevention. More recent updates of tamoxifen net-effect in patients with established breast cancer clarify the picture.

- Incidence rather than mortality from uterine cancer is increased (i.e., more uterine cancers are diagnosed on tamoxifen, but because of early diagnosis most are cured), with reduced breast cancer mortality leading to a much larger net gain: reduction of overall mortality.[20]
- Thromboembolism rates are similar to those on birth control pills and or hormone replacement therapy, so the rates are not disproportionately increased with tamoxifen.
- Updated data from the original NSABP P-1 prevention trial show minimal risk of uterine cancer or thromboembolism among younger women, under age 55, while the benefit of breast cancer risk reduction of 40–50 per cent is significant.[21]
- Most recently, Noah-Vanhoucke et al.[22] provided one of the most comprehensive cost-benefit analysis of tamoxifen. Their meta-analysis of four randomized trials indicated that tamoxifen chemoprophylaxis, for postmenopausal women under age 55, is cost-effective in reducing breast cancer incidence and improving life expectancy.

Thus, tamoxifen for breast cancer prevention in young women, under age 55, at high risk of developing future breast cancer, is generally much safer than many other medical interventions and is currently substantially underutilized.[20]

ii. Raloxifene (Evista). In a recently completed randomized trial of tamoxifen against raloxifene in a high risk population of postmenopausal women (the STAR trial), raloxifene produced similar risk reduction to that of tamoxifen, while being associated with significantly lower uterine cancer and thromboembolism.[21,23]

Therefore, the 2010-2011 St. Gallen's-based consensus conference on breast cancer prevention[24] recommends tamoxifen for premenopausal women and raloxifene for postmenopausal women at high risk, indicating that "Because of its proven effectiveness and well understood side-effect profile, tamoxifen is presently deemed to be the preventive agent of choice in most high-risk women, especially in premenopausal women or those with atypical hyperplasia or lobular carcinoma in situ."

iii. Lasofoxifene. The newest agent, lasofoxifene is a modified SERM, with more cholesterol-reduction and less uterine cancer rates than tamoxifen.[25,26] Furthermore, lasofoxifene was associated with significantly reduced risk of bone fractures, a very significant (more than 80 per cent) reduction in ER-positive invasive breast cancers and more than 30 per cent reduction in coronary heart disease and strokes. In addition, there was a reduction of more than 30 per cent in coronary heart disease and strokes. Thus, in postmenopausal women with osteoporosis, lasofoxifene presents a favourable prevention profile. Longer follow-up is required to confirm these promising results. The agent is not yet available in Canada for clinical use.

iv. Bisphosphonates are a class of medications approved in North America and Europe for prevention of bone loss. These drugs have been recently shown to prevent bone fractures not only in cases with advanced metastatic breast cancer (where their use in Canada has been approved), but also to reduce rates of metastases in hormone sensitive breast cancer cases treated with hormonal therapies in the adjuvant setting, just after the primary surgery, to prevent recurrences.[27]

Recent analysis of one of the largest breast cancer epidemiology studies has shown a strong association of oral bisphosphonates taken by women without breast cancer, with a significant reduction of primary breast cancer in the range of 32 per cent (RR=0.68; 95 per cent CI, 0.52 to 0.88; $P < .01$).[28]

v. COX 2 inhibitors such as aspirin,[29-31] celecoxib (Celebrex)[31-35] and many non-steroidal anti-inflammatory agents, have been known to reduce carcinogenesis in animal studies. Recent human studies in colon cancer and more recently breast cancer confirm almost a 40–50 per cent reduction of new cancers in subjects with regular use of aspirin – a strong anti-inflammatory and a Cox2 inhibitor – compared to non-aspirin users.[29-31,36,39] There is promising potential of celecoxib or ibuprofen as examples of a more powerful Cox2 inhibitor. Confirmation of their cost-benefit impact is needed in future studies.[36-39]

Interpretation of Prevention Studies

These estimates are relevant to the prevention issues under discussion: if all prevention initiatives were put into practice today, with high adherence by high risk Canadian women, several thousand breast cancers could be prevented in Canada annually.

Conversely, if prevention is not practiced, and the present status quo is perpetuated, Canadians will be confronted with several thousand additional breast cancers each year.

Thus, delays in incorporating appropriate interventions into guidelines result in higher rates of death in our population, compared to the decreasing rates if optimum prevention interventions were adopted today.

Low Profile of Breast Cancer Prevention in North America

There are several reasons why prevention of breast cancer is not systematically practiced.

First, no medical specialty in Canada has a mandate for practising prevention at the present time simply because none is claiming this practice as their main domain. Oncologists within cancer institutions accept cases only after biopsy-confirmation of cancer.

Surgeons, even those specialized in breast cancer, do not deal with cancer cases unless a surgical procedure is contemplated. Even then, most lack the knowledge base and the time required to counsel high risk women. Family physicians also lack the specialized background required. They refer cancer patients to oncology centres only when a cancer diagnosis is imminent and or biopsy-proven.

Second, no provincial funding is available for the sustained operation of cancer prevention counselling services. Such a clinical infrastructure would require dedicated oncologists, non-specialty physicians, nurses, social workers, physiotherapists, and nutritionists.

Additional skills would be required in risk assessment and selection of cases for the counselling clinics. Educational resources are required to introduce, reinforce, and monitor recommendations for lifestyle change. Dedicated activity would involve prescription of the appropriate preventive agents and monitoring of their use. These activities are analogous to those involved in operating well-established and funded cancer clinics.

One of the most important steps in planning a targeted prevention practice is to narrow down as much as possible the at-risk population, so that costly preventive initiatives will be focused on those who need them most.

The risk of getting breast cancer can be assessed by a refined new generation of risk assessment tools—most of them expanding on the original Gail risk model,[44,45] taking into consideration, besides the family history and pathology, also weight, body mass index, exercise and alcohol intake. Attempts are underway to integrate these established risk factors prospectively with screening mammography criteria such as high breast density.

These risk models define a quantitative risk prediction of an individual woman to develop breast cancer and if the risk exceeds a certain level, the woman would be a candidate for a prevention trial or ideally, for prevention initiatives once incorporated into guidelines.

Summary

Data increasingly indicate that breast cancer prevention initiatives should be at the forefront of action. Today, however, despite these data, obesity rates are on the rise, particularly among young teenage girls and generally among women with low socio-economic or aboriginal background. This in turn is related to higher rates of sedentary lifestyle associated with lower exercise in the western population as a whole.

The data forecast a very promising impact of obesity reduction on breast cancer rates, through a combination of diet and exercise. A similar effect is apparent on general health outcomes, including profound cardiovascular and stress-relief benefits, with an associated high cost-benefit to the health system. Professional counselling to promote exercise and sensible diet, in a dedicated prevention clinic, deserves priority attention from health planners and administrators.

Both tamoxifen and raloxifene are substantially underutilized for breast cancer prevention, mostly due to the biased perception of their side effects, despite randomized trials showing Level 1 evidence for their large scale benefit in breast cancer. The tamoxifen/raloxifene underutilization is made worse by these drugs not being approved and funded for prevention in Canada, where only Quebec funds their use for breast cancer prevention. In contrast, in the U.S., insurance companies fund these agents for prevention if indicated by an oncologist.

In Canada, in general, we lack dedicated prevention facilities and systematically organized cancer prevention programs. One of the first such programs in Canada, proposed by the University of British Columbia, is the Breast Cancer Prevention Clinic to open in Vancouver in the late Spring of 2011.

Conclusion

The main objective of this report is to alert Canadians to the issues of cancer prevention using breast cancer as an example and to document the huge potential for avoiding a large number of breast cancers if all evidence-based prevention initiatives were systematically applied to high risk women. While prevention interventions with medication are clearly indicated due to their documented impact and cost-benefit, the advantages of aggressive weight and diet control, with escalating exercise, are undeniable for both breast cancer and cardiovascular disease. Furthermore, large societal cost saving for Canadian taxpayers will follow, as in the long-term millions more would be spent to cure a developed breast cancer than to prevent it today.

It is the intention of this report to provide compelling support for the development of dedicated breast cancer prevention clinics supervised by trained oncologists, staffed with the related counselling team of nurses, dietitians, physiotherapists and social workers. Truly, an ounce of prevention is worth many pounds of cure. The sooner the better.

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