Breast Cancer: Recent Progress

By Dr. Ivo A. Olivotto

Breast cancer is the commonest malignancy affecting Canadian women. One in ten women will develop breast cancer sometime in her life. Nearly 15,000 new cases will be diagnosed and over 5,000 women will die of breast cancer in Canada in 1992. These statistics are frightening. There are three ways to reduce morbidity and mortality from breast cancer; prevention, screening and better treatment. This article will review progress which has been made in the past ten years in all three areas.

Prevention of Breast Cancer

Female sex and advancing age are the most important risk factors for the development of breast cancer. A positive family history, early age at which the menstrual periods start, a late age of menopause, a prior breast cancer or previous biopsy showing atypical proliferation of the cells in the milk ducts also increase the likelihood of breast cancer. None of these factors can be changed by individual behavior modification. What is a woman to do?

Diet is almost certainly important. Unfortunately, the data relating any one dietary factor to risk is conflicting. Excess total calories, animal fat, total fat content and lack of green and orange vegetables in the diet have been implicated but no direct causal relationship with any particular diet has been proven sufficiently to be able to give specific dietary recommendations with confidence. Prudence would dictate that a balanced diet with fewer calories, less total fat and more 'roughage' may reduce premature death from cardiovascular disease and may also reduce the risk of developing breast, colon and possibly other cancers. Studies assessing behavior and diet modification are in the planning phase.

While the lifestyle question is under investigation, a new study is exploring whether the drug tamoxifen can prevent the development of breast cancer in women at high risk for developing the disease. It is known that the growth of some breast cancers is simulated by the female hormone estrogen. Tamoxifen is a complex molecule with estrogen blocking as well as weak estrogen agonist functions. Tamoxifen has been used successfully to treat women with invasive breast cancer for nearly twenty years. Recent evidence (E.B.C.T.C.G.(I) 1992, Nayfield, 1992) has demonstrated that women who take tamoxifen for two to five years after surgery for one breast cancer have a 35-40% lower chance of developing a second breast cancer when compared to women who do not take tamoxifen. This observation has lead to the hypothesis that tamoxifen might also be employed in healthy women, at risk of developing breast cancer, as a prevention strategy.

To test this hypothesis a clinical trial was launched April 29, 1992 cooperatively in over 200 cancer centres in Canada and the United States. The plan is to enrol 16,000 healthy, volunteer participants by April, 1994. Women will be randomly assigned to take tamoxifen or placebo (a tablet of no medicinal value) for five years. Table 1 outlines examples of the sorts of women deemed to have a high enough risk of developing breast cancer to be eligible for study participation. Women with a prior diagnosis of cancer, deep venous thrombosis or those planning to become pregnant are not eligible.

Table 1
Entry Criteria
Breast Cancer Prevention Study

1. Any woman > age 60.
2. Any woman ≥ age 35 with Lobular Carcinoma In-Situ (LCIS).
3. Women age 35-59 with combinations of risk factors (for example):
   - i. age 35+: one or more first degree relatives with breast cancer and two benign breast biopsies.
   - ii. age 40+: two or more first degree relatives with breast cancer or two benign breast biopsies.
   - iii. age 45+: one or more first degree relatives with breast cancer.
   - iv. age 55+: one or more relatives or first live birth at age 30 or older.

The reason to not just start using tamoxifen to prevent breast cancer in high risk women is uncertainty regarding the relative risks and benefits of this drug. Tamoxifen is usually well tolerated but by blocking estrogen actions, it can sometimes cause hot flushes, vaginal dryness and discharge which at times can be quite disabling. A small increased risk of developing blood clots and pulmonary embolism has been observed and for post menopausal women, the weak estrogen agonist action of tamoxifen may stimulate the endometrium to develop neoplasia in a similar fashion as can estrogen replacement therapy.

A carefully designed study is necessary to evaluate tamoxifen's safety and effectiveness in preventing breast cancer before advising healthy women to start taking this medication. Further information about study participation can be obtained by calling your regional contact number in Table 2.

Table 2
Contact Numbers for the
Breast Cancer Prevention Trial

B.C. and Yukon	1-604-822-7997
Ontario	1-800-263-6750
Quebec	1-800-361-4212
Other provinces	1-416-387-1153

Screening and Early Diagnosis

Breast cancer takes years to develop from the first malignant cell in the milk duct to a mass which can be felt by a woman in her breast. A woman's chance of survival is directly related to the extent of disease at diagnosis. For example, while less than 5% of women with disease in distant organs at diagnosis are alive at five years, approximately 50% of women with involved axillary lymph glands are alive at five years and in excess of 95% of women with mammographically detected cancers, less than 1 cm. in diameter, are alive at ten years. (Figure 1) The goal of screening is to detect cancers when they are small and curable with local treatment alone. Many different technologies have been evaluated in breast screening but only breast self-examination, professional physical examination and mammography are routinely supported.

Breast self-examination (BSE) is a method for a woman to take charge of her health care. It is recommended that women learn how to perform BSE and 'check that they are healthy' once a month. Teaching is best done in one-on-one sessions rather than from pamphlets. Canadian Cancer Society volunteers and nurse practitioners conduct BSE teaching sessions and one's family physician should be familiar with the technique. Perhaps the greatest importance of regular BSE is that a woman will be aware of her own body health and be confident to report new changes to her physician for evaluation.

Multiple international studies have demonstrated a consistent reduction of approximately 30% in breast cancer related mortality for women ≥ 50 years old who have regular screening with mammography and physical examination. The data is less convincing for women < 50. Contrary to leaked media reports, there is no evidence that mammography under age 50 is harmful (Allison, 1992). Results of studies in the 40-49 year old age group vary from showing no benefit to a 30% reduction in mortality which was shown in the longest running randomized breast screening study. Results from a study conducted across Canada do not show a reduced mortality from screening women age < 50.

The Screening Mammography Program of B.C. (SMPBC) was established in July, 1988. The SMPBC was the first, universal access, publicly-funded screening mammography program in North America. Among first time attenders, 4.8 women of every 1000 screened are found to have a previously unsuspected cancer

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(Figure 1). Many of these cancers are much more curable than if they had been diagnosed only when the woman or her physician were able to feel a lump. There is a realistic expectation that this early detection will translate into a net decrease in premature death from breast cancer. Currently, the SMPBC recommends that women have a yearly mammogram and physical examination of the breasts starting at age 40. Programs in other provinces recommend screening with mammography begin at age 50. Women who are pregnant or lactating, have current breast complaints, a previous breast cancer or breast prosthesis in place require special views of the breast and should be referred to private, diagnostic centres for mammograms. In British Columbia women over 40 can refer themselves or be referred by their physician to an SMPBC centre. By the end of 1993, SMPBC screening centres will be open in Burnaby, Kelowna, Kitimat, Nanaimo, Prince George, Prince Rupert, Terrace, Surrey, Vancouver and Victoria. Two mobile vans serve the interior of the province from Kamloops and Nelson.

Treatment Advances: 1992

Two substantial advances in the management of invasive breast cancer have occurred in the last 10-15 years. The first is that lumpectomy followed by radiation therapy has been proven to provide equivalent local control and survival as does total mastectomy thereby giving a woman an option to save her breast (Olivotto et al, 1991). The second is proof that chemotherapy and/or tamoxifen given immediately following primary therapy increases the chance of survival five and ten years later. (E.B.C.T.C.BG. (I & II), 1992)

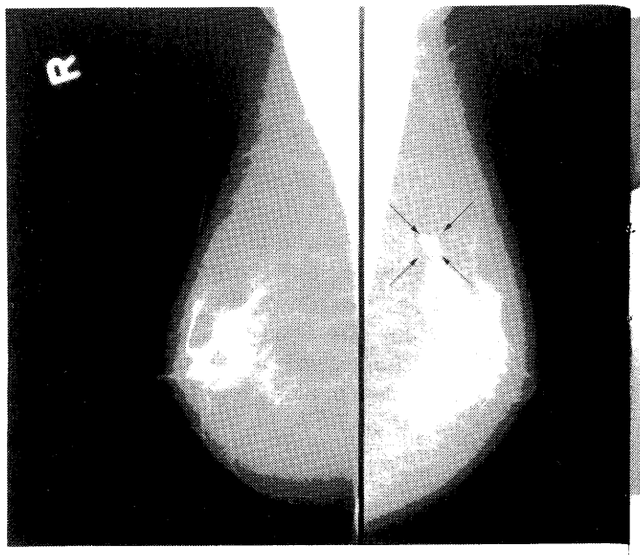
The Approach To Breast Conservation

Before 1980, very few breast conserving operations were performed in Canada. Today, breast conservation is accepted standard therapy for primary cancers < 5 cm. diameter with or without palpable mobile lymph glands at diagnosis. In certain circumstances however, mastectomy may still be selected. If there are multiple primary tumours or if complete surgical removal cannot be achieved, an unacceptably high rate of recurrent disease in the breast occurs. These women are best served by mastectomy. Even if it appears that complete removal has been achieved surgically, 40% of women relapse in the same site unless radiation therapy is routinely delivered post-operatively. The radiation therapy takes 4-5 weeks of daily treatments at a cancer clinic. Refusal of, or inability to tolerate radiation therapy (i.e. patients with lupus erythematosus or scleroderma get excessive fibrosis) or an inability to attend for the daily treatment visits (i.e. elderly or frail individuals) mandate mastectomy as the most appropriate treatment. Beyond these relatively uncommon circumstances, it becomes a question of whether the surgeon can adequately remove the primary tumour while retaining sufficient normal breast tissue to have a good cosmetic symmetry when compared to the contralateral side. This depends upon the size and location of the tumour within a breast of a specific size and shape. Attention to the technical details can result in an excellent cosmetic appearance, figure 2, while achieving local control and survival equivalent to total mastectomy.

It is important to avoid excessive resection of normal breast tissue, to place incisions carefully, achieve hemostasis and to close with a subcuticular technique which avoids ridges, puckering and breast distortion. (Figure 3)

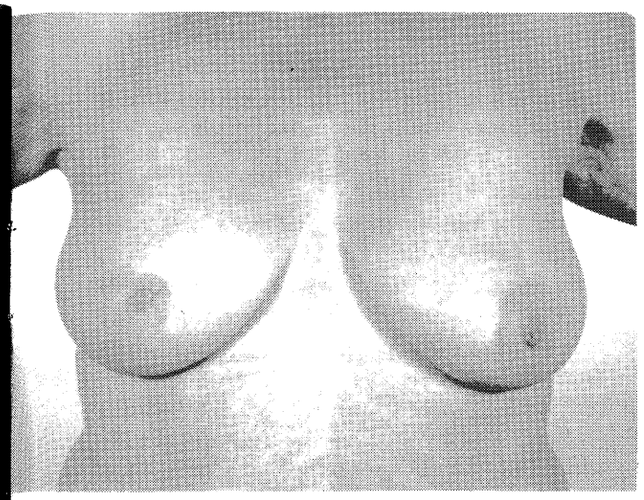
While breast conservation has been shown to be equivalent to mastectomy in terms of survival, it is not necessarily better treatment. The important principle is that women today should be informed of the possibility of breast conservation and be given sufficient

Figure 1



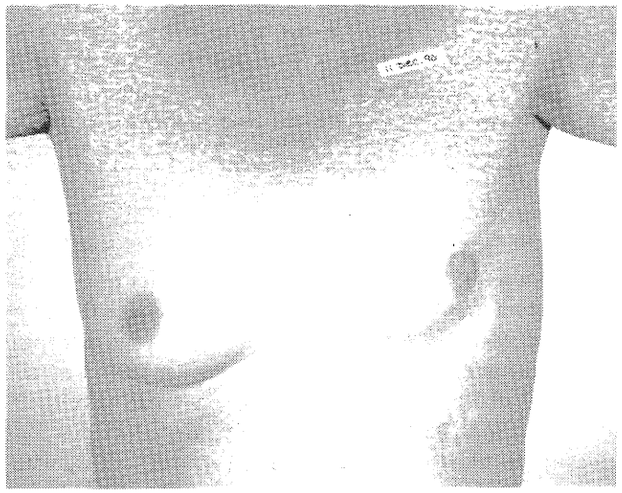
6 mm diameter, non-palpable, invasive ductal carcinoma detected by screening mammography. (reproduced with permission, Canadian Journal of C.M.E.)

Figure 2



Excellent cosmetic outcome three years after treatment of carcinoma of the right breast with tumorectomy, axillary dissection and radiation therapy.

Figure 3



Poor cosmetic outcome three years after treatment of carcinoma of the left breast due to excessive resection of breast tissue and an incontinuity dissection of the primary site and axilla. Separate incisions avoid the retraction of the nipple due to scar contracture. (reproduced with permission, Canadian Journal of C.M.E.)

information and respect to participate in the decision about how their breast tumour will be managed.

Adjuvant Systemic Therapy

Adjuvant therapy is treatment added to the primary, curative treatment to reduce the risk of recurrence from presumed residual microscopic disease. In the context of breast cancer after the initial surgery (mastectomy or lumpectomy and axilliary dissection) even though no apparent disease can be found on physical examination, blood tests or x-rays, a substantial proportion of women will have the cancer recur and eventually die of disease. In most cases this is due to microscopic disease which has spread throughout the body but remains undetectable at the time of diagnosis. Tamoxifen (an anti-estrogen) and various chemotherapy combinations (drugs capable of killing dividing cancer cells) when given immediately after the primary surgery have been shown to significantly reduce the chance of recurrence and death from breast cancer. (E.B.C.T.C.G. (I-II), 1992).

Response to treatment is determined by age (menopausal status) and certain tumour characteristics. Younger women (< 50) have been shown to derive most benefit from chemotherapy with a small additional gain in some individuals by adding tamoxifen or stopping ovarian function. For older women (> 65-70) tamoxifen achieves a similar benefit and the very small additional gain from adding the toxicity of chemotherapy is not usually justified. In the intermediate age range (50-65) the therapy resulting in an optimal balance between benefit and toxicity is related to the hormonal responsiveness of the tumour. Chemical or immunofluorescent measurements can be made at diagnosis to determine the estrogen receptor (ER) content of the tumour cells. Women with ER+ tumours enjoy significant improvements in survival with minimal toxicity when given tamoxifen for two to five years after surgery. A small additional gain may be realized by adding chemotherapy but at the cost of added toxicity. In contrast to what was formerly believed, women with ER- tumours do benefit from tamoxifen but to a smaller degree than those with ER+ tumours. Today, fit women in the 50-65 age group with ER- tumours are often offered chemotherapy followed by tamoxifen.

Much current research is focused on trying to select which women have such a low risk of recurring that the toxicity of adding chemotherapy and/or tamoxifen are not justified. Today we define the 'lowest' risk

group to be those women with solitary primary tumours, < 2 cm in diameter with no invasion of the lymphatics or blood vessels in the breast and no spread to the lymph glands found in the axillary dissection. These 'lowest risk' women are treated with local therapy (mastectomy or lumpectomy plus radiation therapy) alone and are not offered chemotherapy or tamoxifen.

Summary

Much remains to be learned about this commonest malignancy in women. However, in the past 10-15 years substantial progress has been made in defining optimal treatment for individual women and in recognizing the importance of the patient's input into medical decision making. Women today can save their breast in most circumstances if they elect that approach and can expect a better chance of survival with the judicious use of adjuvant tamoxifen and/or chemotherapy. For the majority of women, early detection has been shown to reduce the chances of dying of breast cancer. Screening mammography, together with physical examination, although available to women over 40, is strongly encouraged for women over 50 on an annual basis. With respect to prevention, the first ever intervention study is now underway across North America assessing the efficacy and safety of tamoxifen in preventing the development of breast cancer among healthy, high risk women. Future research will hopefully identify those dietary and lifestyle factors which we can modify to reduce the relentless rise in numbers of cases of breast cancer seen in our population.

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"Reflections on Adelaide" Planning for a World Conference

By Joan Donald, ORNAC Past President

"Those far away places with strange sounding names
Far away over the sea
Those far away places I've been dreaming about
Are calling, calling me."

As we edge closer to 1993, our thoughts start drifting toward the next World Conference and the lure of far away places. The World Conference from **September 6 - 10, 1993, is to be held in Adelaide, Australia.**

Having had the privilege of being a member of the International Planning Committee (IPC), I thought it might be interesting to share with you my experience of attending the IPC meeting in Adelaide in May, 1992.

After more than thirty hours of travel time, I was glad to see the lights of Sydney gleaming out into the harbour as our plane landed. Once on the ground, the crew came through the aisles of the plane with sprays which are required by the Department of Agriculture. Although it is reported to be non-toxic, one wonders how effective it can be as an insecticide if it is non-toxic. Once inside the terminal, there were numerous signs warning of a $50,000 fine if any undeclared edible food products and/or plants were brought into the country. Fellow passengers were frantically checking for leftover snacks and making sure they were listed. One thing I learned the hard way, was that all entrants to Australia must have a visa, in addition to a valid passport. Unfortunately, I had not been told of this and after one full hour with a very exasperated but nice gentleman, I was issued a temporary visa and allowed to proceed. Another three hours of travel and I landed in Adelaide, Australia.

Adelaide is a beautiful city surrounded by a one mile circle of green space. It was fall there and very pleasant, by my standards, even though the leaves were changed and had fallen from the trees. The people were very polite, gracious and hospitable - now if I could only understand them!

One of the first lessons learned was that there is no tipping in Australia. What a great thing to learn. In addition, the prices on items are exactly what is paid - no addition of PST, GST or taxes of any kind. On Sunday, May 15, 1992, we gathered bright and early at the Convention Center for our IPC meeting.

Representatives from Australia, Canada, Germany, Japan, United Kingdom and the United States of America were present. Countries represented by corresponding members were Argentina, Finland, Germany, Greece, Italy and Mexico. Everyone was made to feel so welcome and we compared travel notes over our first tea and coffee of the day. A recap of the last World Conference held in Vancouver, B.C. lead to some suggestions for change and improvements. The remainder of the morning was spent in brainstorming and sharing of ideas, concerns, topics and items for presentation. Amazingly, we all came with pieces of paper that had almost identical issues listed on them. It very quickly became evident that our theme would evolve with a world wide mutually shared vision.

Following lunch and a stroll outside for some fresh air, we then went on a conducted tour of the Convention Center. What an incredible facility! Whole meeting rooms became transformed before our very eyes as bleachers suddenly recessed into the ceiling and walls moved here and there. The exhibit hall is such that the huge transport vehicles can be driven right into the hall and on site.

Well, back to work and before the afternoon was over we had agreed on our theme of "Strategies for Strength". The topics for presentation were chosen and the next day we expanded on these topics, devel-