Management of women at increased risk for breast cancer: preliminary results from a new program

Education

Éducation

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Abstract

Objective: To examine the characteristics of malignant tumours that develop in women undergoing surveillance for increased risk for breast cancer and to identify presentation patterns in order to determine the respective roles of mammography, clinical breast examination (CBE) and breast self-examination (BSE).

Setting: Breast Diagnostic Clinic and Familial Breast Cancer Clinic at Toronto–Sunnybrook Regional Cancer Centre.

Participants: A total of 1044 women evaluated for breast cancer risk from Oct. 1, 1990, to Dec. 31, 1996, of whom 381 were categorized as being at high risk, 204 as being at moderate risk, 401 as being at slightly increased risk and 58 as being at no appreciably increased risk.

Program components: Comprehensive review and discussion of risk factors, clinical assessment, surveillance recommendations that include mammography, CBE and BSE, genetics consultation (Familial Breast Cancer Clinic) and psychosocial support. Data are captured prospectively, updated at each visit and audited every 3 to 6 months.

Program outcomes: During the study period breast cancer was diagnosed in 24 patients, 12 in the high-risk group, 4 in the moderate-risk group and 8 in the group at slightly increased risk. The mean age at diagnosis was 47 (range 32 to 82) years. Ten cases of cancer were diagnosed during surveillance (incident cancer), 5 in women under age 50. The mean length of time from initial assessment to diagnosis was 28.6 (range 12 to 51) months. Of the 24 women, 17 reported a family history of breast cancer. The mean age at diagnosis in this cohort was 45.5 years, and the diagnosis was made under age 50 in 10 patients (59%). The mean earliest age at which breast cancer was diagnosed in a family member was 42.5 years.

Conclusions: These preliminary results suggest that surveillance of women at increased risk for breast cancer may be useful in detecting disease at an early stage. The regular performance of mammography, CBE and BSE appears necessary to achieve these results.

Résumé

Objectif : Examiner les caractéristiques des tumeurs malignes qui font leur apparition chez les femmes suivies parce qu'elles présentent un risque accru de cancer du sein et définir les tendances de l'apparition de ces tumeurs afin de déterminer les rôles respectifs de la mammographie, de l'examen clinique des seins et de l'autoexamen des seins.

Contexte : Clinique de diagnostic du cancer du sein et clinique familiale de dépistage du cancer du sein au Centre régional d'oncologie Toronto–Sunnybrook.

Participantes : Au total, on a évalué le risque de cancer du sein chez 1044 femmes entre le 1er oct. 1990 et le 31 déc. 1996 : 381 d'entre elles ont été classées comme étant à risque élevé, 204, à risque moyen, 401, à risque légèrement plus élevé; 58 ne présentaient aucun risque accru de façon appréciable.

Éléments du programme : Examen détaillé et discussion des facteurs de risque, évaluation clinique, recommandations relatives au suivi comportant la mammographie, l'examen clinique des seins, l'autoexamen des seins, une consultation

génétique (clinique familiale de dépistage du cancer du sein) et appui psychosocial. Les données sont saisies de façon prospective, mises à jour à chaque consultation et vérifiées aux 3 à 6 mois.

Résultats du programme : Au cours de la période d'étude, on a diagnostiqué un cancer du sein chez 24 patientes, dont 12 du groupe à risque élevé, 4 du groupe à risque moyen et 8 du groupe à risque légèrement accru. L'âge moyen au diagnostic était de 47 ans (de 32 à 82). On a diagnostiqué 10 cas de cancer au cours du suivi (cancer nouveau), dont 5 chez des femmes de moins de 50 ans. Il s'est écoulé en moyenne 28,6 (12 à 51) mois entre l'évaluation initiale et le diagnostic. Sur les 24 femmes, 17 ont signalé des antécédents familiaux de cancer du sein. Cette cohorte avait en moyenne 45,5 ans au moment du diagnostic qui a été posé chez les patientes de moins de 50 ans dans 10 cas (59 %). L'âge moyen le plus jeune auquel on a diagnostiqué un cancer du sein chez un membre de la famille était de 42,5 ans.

Conclusions : Ces résultats préliminaires indiquent que le suivi des femmes à risque accru de cancer du sein peut aider à repérer la maladie à un stade précoce. Il semble nécessaire de procéder régulièrement à des mammographies, à des examens cliniques des seins et à l'autoexamen des seins pour parvenir à ces résultats.

Physicians increasingly encounter women, often young women, who are or perceive themselves to be at increased risk for breast cancer. The value of preventive activities among these women is unknown. In this report we suggest an approach to stratify women at increased risk and describe the early results of a surveillance program based on the experience of the Breast Diagnostic Clinic and the Familial Breast Cancer Clinic at the Toronto-Sunnybrook Regional Cancer Centre from Oct. 1, 1990, to Dec. 31, 1996.

Background

Organized population-based screening for breast cancer targeting women aged 50 years or more exists in most provinces. Such programs have been established as a result of recognition that age and sex are the 2 most important risk factors for breast cancer. Randomized controlled trials suggest that such screening results in a 30% reduction in rates of death from breast cancer.[1,2]

The role of population-based screening for women aged 40 to 49 years remains controversial, although evidence of benefit strengthens with time. Nonetheless, it is unlikely that population-based screening for this age group will be widely encouraged or supported in the near future.[3–5]

For women under age 40 years, data on the usefulness of mammography are limited, as this age group has not been recruited to randomized controlled trials. Although screening mammography is not commonly done in women under 40 years, mammography is reported to visualize 65% of malignant tumours in women in this age group.[6] When breast cancer occurs in younger women the initial abnormal finding is most often a palpable mass identified by the patient (in 68% of cases) or by her physician (in 27%); few cases (2%) present with a mammographic abnormality.[6,7]

This does not mean that women with specific risk factors (i.e., factors suggesting that their risk significantly exceeds that of the general population) would not benefit from early detection strategies. It is recognized that women at increased risk may need to be managed differently; however, there is no consensus as to how this should be done. Epidemiologic models are still regarded as poor, and further work to better manage this group is needed.[8] With advances in molecular genetics it will be possible to identify subsets of women who are genetically predisposed to disease and who may see bilateral prophylactic mastectomy as the only "safe" alternative.[9–15]

The role of mammography, clinical breast examination (CBE) and breast self-examination (BSE) among these women needs to be defined. Dershaw, Yahalom and Petrek[16] found that, among women at increased risk because of previous exposure to high-dose radiation, 38% of tumours presented as mammographic abnormalities. This finding suggests that mammography has an important role.

The value of systematic CBE has been demonstrated by the Canadian National Breast Screening Study.[17–19] As well, the Ontario Breast Screening Program has incorporated CBE in its screening strategy for women aged 50 years or more. Reports from that program indicate that the median diameter of 42 tumours that presented as a palpable abnormality only (with a normal mammogram) was 1.6 cm,[20] which supports the usefulness of CBE in the diagnosis of early-stage disease. This evidence is strengthened by reports that frequent CBE results in greater detection of breast cancer when it is node-negative.[21]

Regular BSE appears at least to have potential to result in greater detection of primary tumours when they are smaller and node-negative.[22] However, the quality of BSE performance is difficult to measure, and proficient BSE often requires high personal motivation and reinforcement by physicians and nurses. In spite of these limitations, evidence from the Mama Program in Finland indicates a reduction in rates of death from breast cancer associated with regular BSE.[23]

Given these findings, the management recommendations for women at increased risk at our centre include mammography, CBE and regular BSE to maximize early detection.

Several different methods of ascertaining risk have been proposed. Most models are useful to assess risk for the general population and are not directly applicable to individuals. Models that attempt to use epidemiologic principles for individual risk prediction may tend to underestimate risk for those genetically predisposed, and different approaches may result in substantially different risk estimates.[24–27] Inherited cancer accounts for 5% to 10% of all breast cancer; for these cases, genetic models may be accurate, but pedigree analysis is complex and knowledge about penetrance imprecise.

To be useful in the clinical setting, any approach must involve consideration of both risk and management recommendations. We adopted a practical approach by considering women at high, moderate or slightly increased risk. For the high-risk group all factors listed are estimated to have a relative risk of more than 4. For those at moderate risk the factors are estimated to have a relative risk of 2 to 4, and for those at slightly increased risk all the factors are estimated to have a relative risk of less than 2. This approach allows effective rationalization and use of resources.[15,28]

Program objectives

- To provide clinically useful information to assist in the identification and management of women at increased risk for breast cancer.
- To examine the characteristics of tumours that develop in women undergoing surveillance for increased risk for breast cancer, including age, stage of disease, histologic features and time to diagnosis.
- To examine presentation patterns of breast cancer, specifically the initial mode of detection, so as to determine the respective roles of mammography, CBE and BSE.
- When there is a family history of breast cancer, to relate age at diagnosis of cancer to the earliest age at detection of breast cancer in the family to assist in understanding patterns of disease within families and to better target early detection efforts.

Methods

The patients in this report were seen in the Breast Diagnostic Clinic (Oct. 1, 1990, to Dec. 31, 1996) or the Familial Breast Cancer Clinic (Sept. 1, 1995, to Dec. 31, 1996). All patients were referred specifically for risk evaluation or had risk evaluation carried out as an integral part of the consultation. When patients are referred to one of these clinics, the following information is obtained at the initial visit: basic demographic information, reason for referral, relevant medical history and an initial inventory (Table 1). BSE is taught or reinforced by a dedicated nurse supported by a videotape. A systematic CBE is performed by the clinic physician, and a review of imaging studies is arranged. In addition to these steps, patients seen in the Familial Breast Cancer Clinic also have pedigree analysis, complete a questionnaire to determine their baseline psychologic profile and receive genetic counselling; a small subset are invited to participate in genetic research projects.

Clinic staffing is multidisciplinary. The basic team includes general physicians with expertise in breast disease, a breast surgeon and dedicated nurses. This clinical team is supported by consultants with expertise in radiology, pathology and psychology. The Familial Breast Cancer Clinic also includes a clinical geneticist, a genetic counsellor and a medical oncologist.

Table 1: Initial inventory obtained in the evaluation of women at increased risk for breast cancer

History
Atypical epithelial hyperplasia (breast)
Lobular carcinoma in situ
Other types of cancer
Benign breast disease
Exposure to high-dose radiation (where possible, age at exposure and estimated dose are obtained)
Family history
All known cancer in first- and second-degree family relatives, including age at diagnosis, history of unilateral or bilateral breast cancer and menopausal status (updated at each visit)
Reproductive history
Age at menarche
Menopausal status (updated at each visit)
Age at first live birth
Use of oral contraceptives (no. of years)
Use of hormone replacement therapy (updated at each visit)
Duration of breast-feeding (cumulative)
Use of diethylstilbestrol during pregnancy
Other
High alcohol intake (> 4 oz [112 mL] daily)
Obesity (height, weight)
Racial origin (white, black, Asian, other)
Number of previous mammographic examinations and age at first examination
Breast self-examination (BSE) experience (practised, taught or reinforced)

Prospective data collected in both clinics are entered into a database under close supervision of a biostatistician.

Assessing risk

Breast cancer risk is ascertained by applying the criteria outlined in Table 2. Women are categorized according to the highest risk factor present. Women are considered at high risk if 1 or more factors are estimated to increase their relative risk more than fourfold, at moderate risk if 1 or more factors are estimated to increase their relative risk two- to fourfold, and at slightly increased risk if 1 or more factors are estimated to increase their relative risk less than twofold.

Follow-up recommendations

Surveillance recommended for all patients includes monthly BSE. In addition, for those at high risk, mammography is recommended annually and CBE every 6 months. For women at moderate risk, annual mammography and CBE are recommended. Mammography is started 10 years before the earliest age at which breast cancer was detected in the family, 5 to 10 years after exposure to high-dose radiation, or immediately after diagnosis of atypical hyperplasia or lobular carcinoma in situ. Mammography is not done in women under age 30 or in pregnant or lactating women. For women at slightly increased risk, annual mammography and CBE are advised after age 40 (Table 2).

Women found to be at no increased risk for breast cancer are referred to the provincial screening program if they are 50 years or more. If under 50, they are offered the option of participating in annual surveillance, including mammography, when they reach the age of 40. Those not participating in surveillance are discharged to be monitored within the general care in the community.

Data collection and clinic management

At each follow-up visit cancer status is recorded. Tumours detected during surveillance (incident tumours) are

Table 2: Risk ascertainment criteria and surveillance recommendations

Risk category	Risk ascertainment criteria	Surveillance recommendations
High	Family history of breast cancer in 2 or more first-degree relatives Family history of breast or ovarian cancer that suggests inherited disease (collection of first- and second-degree relatives) Bilateral or premenopausal (< 45 years) breast cancer in 1 first-degree relative Atypical hyperplasia Lobular carcinoma in situ	Surveillance is started at age 40 or 10 years before the earliest age at which cancer was detected in the family (whichever comes first) or at the time of diagnosis of atypical hyperplasia or lobular carcinoma in situ. Surveillance includes: • mammography* — annually • clinical breast examination (CBE) — every 6 months • BSE — monthly
Moderate	Family history in which a number of breast cancer cases exist but the pattern is less likely to be hereditary, and in which high-risk criteria are lacking Exposure to high-dose radiation (estimated > 100 cGy) in those under age 30 (e.g., for treatment of Hodgkin disease)†	Surveillance is started at age 40 or 10 years before the earliest age at which cancer was detected in the family, or 5 to 10 years after exposure to high-dose radiation. Surveillance includes: • mammography* — annually • CBE — annually • BSE — monthly
Slightly increased	Family history limited to 1 relative with postmenopausal disease Early menarche (< 12 years), late menopause (> 55 years), late age at first live birth (> 30), nulligravid, use of hormone replacement therapy Benign breast disease High alcohol intake (> 4 oz [112 mL] daily)	Surveillance is started at age 40 and includes: • mammography* — annually • CBE — annually • BSE — monthly

*Not done in women under age 30 or in those who are pregnant or lactating.
†Patients exposed early in adolescence may have a higher risk of cancer.

defined as those diagnosed more than 10 weeks after initial assessment, given that it may take 4 to 6 weeks for a full evaluation. Furthermore, all cases diagnosed 10 weeks to 6 months from initial assessment are reviewed to ensure that neither a mammographic nor a clinical abnormality was present at initial assessment.

On follow-up visits risk factors are updated, CBE is performed and BSE status is recorded. Mammography is done according to the schedule outlined in the previous section. Data are updated at each visit, and auditing occurs every 3 to 6 months.

Patients who fail to keep appointments for follow-up or mammography are called and offered rebooking. Women in whom cancer is diagnosed are followed in another setting in the cancer centre. Patients are considered lost to follow-up if they are not seen for 2 years. When appropriate, patients may be discharged to be followed outside the centre.

Results

A total of 1044 patients were seen from Oct. 1, 1990, to Dec. 31, 1996, for risk evaluation. Of the 1044, 894 were seen in the Breast Diagnostic Clinic and 150 in the Familial Breast Cancer Clinic. Most (75%) were referred by physicians; the remainder were self-referred or referred by other health care providers. The mean age of the patients seen in the Breast Diagnostic Clinic was 42.7 (standard deviation [SD] 10.9) years and in the Familial Breast Cancer Clinic 39.5 (SD 10.8) years.

The average length of follow-up for the total population was 21.9 (SD 21) months (Breast Diagnostic Clinic 23.9 [SD 21.3] months, Familial Breast Cancer Clinic 5.1 [SD 5.8] months).

Of the 1044 women 381 (36%) were categorized as being at high risk, 204 (20%) at moderate risk, 401 (38%) at slightly increased risk and 58 (6%) at no increased risk.

Overall, 98 patients were discharged, in 17 cases because the woman was found not to be at increased risk, and in 81 cases because it was felt by the patient and by us that follow-up in the community was more appropriate. A total of 131 women (12%) were lost to follow-up. Those lost to follow-up represented women from all risk groups (24% were from the high-risk group, 10% from the moderate-risk group, 56% from the group at slightly increased risk and 10% from the group at no increased risk that initially chose to be followed) and from all age groups, including those under 30 and over 49.

A total of 24 tumours were detected in the 986 patients at increased risk (Table 3). The mean age at diagnosis was 47 (range 32 to 82) years. Of the 24 tumours 13 were diagnosed at initial assessment, 10 developed during surveillance, and 1 was diagnosed in a patient who was categorized at the age of 34 as being at slightly increased risk and was advised to return at age 40; cancer was diagnosed at age 39.

For the 10 cases of cancer diagnosed during surveillance, the mean length of time from the initial visit to diagnosis was 28.6 (range 12 to 51) months (Table 4). Five cases occurred in women under age 50. Seven of these cases involved invasive tumours, which were all 1.5 cm or less in diameter and node-negative. Ductal carcinoma in situ was diagnosed in 3 cases; axillary node dissection was not done in these patients. Four tumours were detected on mammography, 2 on CBE and 4 on BSE. As expected, all cases of ductal carcinoma in situ were detected on mammography. Two cases of lobular carcinoma in situ and 1 phylloides tumour were diagnosed in patients during surveillance (Table 4); all 3 patients had a family history of breast cancer.

Of the 13 tumours diagnosed on initial assessment 6 were in situ, 3 were stage I, and 4 were stage II or greater.

Of the 24 patients 17 reported a family history of breast cancer. The mean age at diagnosis in this cohort was 45.5 (SD 8.7) years, and the diagnosis was made under age 50 in 10 patients (59%) (Table 5). The mean earliest age at which breast cancer was diagnosed in a family member was 42.5 (SD 13.8) years.

Discussion

Even with the small number of tumours detected, these preliminary results are consistent with the assumption that the incidence of cancer increases with patients' risk, as defined in this article. This is an indication that the criteria used to categorize risk in the clinic setting are

Table 3: Number of patients in whom cancer was diagnosed and time of diagnosis among 986 women at increased risk for breast cancer

Risk category	No. (and %) of patients	Time of diagnosis; no of patients: At initial visit	Time of diagnosis; no of patients: During surveillance
High (n = 381)	12 (3.1)	7	5
Moderate (n = 204)	4 (2.0)	2	2
Slightly increased (n = 401)	8* (2.0)	4	3

*In 1 case, cancer was diagnosed in a 39-year-old woman who was to return for screening at age 40.

appropriate to identify women for whom early detection strategies may be applied.

For women at high or moderate risk with a family history of breast cancer the mean age at diagnosis was 45.2 years. Hence, to achieve early diagnosis in this group, younger women need to be targeted.

Stage of disease (tumour size and nodal status) and tumour grade at diagnosis are practical measures for predicting outcome and making decisions in the treatment setting. These measures are currently the only practical guide and represent the best available evidence to guide us in predicting the value of disease detection in those at increased risk. In our population to date, tumours detected during surveillance have been diagnosed at either stage 0 (in situ) or stage I, both known to be associated with a 10-year survival rate of at least 80%.[29] Although long-term follow-up of survival data is required, these preliminary results are encouraging.

The current view of lobular carcinoma in situ is that it is a marker for disease that may subsequently develop in either breast. Patients in our population with a previous diagnosis of lobular carcinoma in situ are entered into the high-risk program. Those in whom disease develops during surveillance continue to be followed. To understand patterns of emerging disease in our cohort we have included lobular carcinoma in situ and phylloides tumour under other relevant conditions.

Of the 3 methods used in early detection of breast cancer, mammography is accepted as the most effective in established screening programs. Nevertheless, some tumours are not visible with this imaging technique. In our population mammography was particularly effective in demonstrating ductal carcinoma in situ but was the initial abnormal finding in only 1 of the 7 invasive tumours. However, both CBE and BSE were capable of identifying the other tumours at an early stage. Two of the 10 tumours diagnosed during surveillance were detected through regular, systematic CBE. Our results further suggest that regular practice of BSE has a critical role, as it enables women to note any progressive change in their breasts. The three methods are complementary, and all three appear to be required to achieve early detection of disease. Reliance solely on mammography is a concern, given the current findings.

Our centre offers dedicated radiologic and pathologic expertise, with multidisciplinary rounds providing a forum for discussion of difficult cases. It will be important for our results to be compared with the experience of

Table 4: Clinical and pathologic characteristics of the 10 tumours diagnosed during surveillance and of 3 other relevant conditions found during surveillance

Risk category; patient's age at diagnosis, yr	Pathologic description	Time to diagnosis, mo	Nodal status	Tumour size, cm	Grade	Mode of diagnosis
TUMOURS						
High (n = 5)						
54	Infiltrating ductal carcinoma (IDC)	27	Negative	1.5	Intermediate	CBE
81	Infiltrating lobular carcinoma (ILC)	29	Negative	1.0	Intermediate	CBE
49*	Ductal carcinoma in situ (DCIS)	51	NA	NA	Low	Mammography
52*	IDC	44	Negative	1.0	Intermediate	BSE
42*	IDC	13	Negative	1.5	High	BSE
Moderate (n = 2)						
41*	IDC	20	Negative	1.5	High	BSE
50*	IDC	45	Negative	1.0	Not stated	BSE
Slightly increased (n = 3)						
41	DCIS	12	NA	NA	High	Mammography
52	DCIS	31	NA	NA	Low	Mammography
48	Tubular carcinoma	14	Negative	1.5	Low	Mammography
OTHER RELEVANT CONDITIONS						
High (n = 2)						
44*	Lobular carcinoma in situ (LCIS)	24	NA	NA	NA	CBE
21*	Phylloides tumour	24	NA	NA	NA	CBE
Moderate (n = 1)						
39*	LCIS	14	NA	NA	NA	BSE

*Patients with a family history of breast cancer.

other institutions, where the teams may be differently constructed.

The identification of some women genetically predisposed to disease is now possible. Women who carry *BRCA1* or *BRCA2* mutations face a very high risk for breast cancer, and options for them include bilateral mastectomy and oophorectomy.[10] The latter is considered more acceptable, whereas bilateral prophylactic mastectomy with or without reconstruction is a radical procedure. There is no guarantee of effectiveness, and 5 to 10 years after the procedure, women may regret such a decision, given advances in diagnosis and therapy. Confidence in the capability to diagnose disease early is an important factor in discussion of alternatives.

The best age to begin breast cancer surveillance in women at increased risk is unknown. For women with a family history of breast cancer the optimal age to start mammography is unclear, but 10 years before the earliest age at which the disease was diagnosed in the family appears to be a reasonable time. Our decision to start surveillance early was influenced by 2 clinical observations. First, in some families affected with cancer, the disease appears earlier in subsequent generations. Second, radiation-induced tumours are usually diagnosed 10 or more years after exposure. Our position is a practical approach that can be used in the clinical setting. It should be modified as knowledge increases.

Randomized controlled trials provide the best evidence to assess benefit of any program. Before any such trial is attempted in women at increased risk for breast cancer, a feasibility study should be done to establish whether women or their physicians would accept random allocation to a control group. Furthermore, definition of a control group may be difficult, as the usual care in the community varies. These important issues are beyond the scope of this paper.

Conclusion

Our early results suggest that surveillance of women at increased risk for breast cancer may be useful in detecting the disease at an early stage. However, to achieve these results, the regular performance of all 3 methods of detection (mammography, CBE and BSE) is important. Long-term follow-up is necessary to confirm these encouraging preliminary results.

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Table 5: Age at diagnosis and earliest age at diagnosis of family members for patients who had a family history of breast cancer

Risk category; age at diagnosis, yr	Earliest age at diagnosis of family members, yr	Affected family member(s)*
High (n = 10)		
49	35	Sister, aunt (M)
52	42	Mother, aunt (M), aunt (M), aunt (M)
39	38	Sister, mother
34	40	Mother, aunt (M), grandmother (M)
54	40	Mother, aunt (M), grandmother (M)
46	30	Mother
55	40	Mother
40	47	Mother, aunt (M), aunt (M)
38	35	Mother, aunt (M)
42	38	Sister, sister, mother
Moderate (n = 4)		
50	50	Aunt (M), aunt (M), aunt (M), cousin (M)
31†	55	Mother
41	42	Aunt (P), aunt (P), aunt (P), grandmother (P)
62	50	Mother, aunt (M)
Slightly increased (n = 3)		
36	41	Aunt (P)
52	60	Aunt (P)
53	70	Grandmother

*M = maternal, P = paternal.
†Exposure to radiation before 30 years of age for treatment of Hodgkin disease and family history.

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