Clinical practice guidelines for the care and treatment of breast cancer: 9. Follow-up after treatment for breast cancer (2005 update)

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*The steering committee is part of Health Canada's Canadian Breast Cancer Initiative. (A list of members appears on page 17.)

The patient guide, containing questions and answers for women on follow-up care, has also been updated and is available at www.cmaj.ca/cgi/content/full/158/3/DC1.

Abstract

Objective: To provide information and recommendations to patients and their physicians regarding follow-up strategies and topics relevant to follow-up after treatment for breast cancer.

Evidence: Systematic review of the English-language literature retrieved from MEDLINE (1991 to January 2004). A nonsystematic review of the literature was continued through January 2005.

Recommendations:

- All patients with breast cancer should have regular follow-up surveillance.
- The frequency of visits should be adjusted according to individual patient's needs.
- All visits should include a medical history. For women who are taking tamoxifen, it is important to ask about vaginal bleeding. Physical examination should include breasts, regional lymph nodes, chest wall, lungs and abdomen. The arms should be examined for lymphedema. Annual visits should include mammographic examination.
- Routine laboratory and radiographic investigations should not be carried out for the purpose of detecting distant metastases.
- Patients should be encouraged to report new, persistent symptoms promptly, without waiting for the next scheduled appointment.
- If a woman wishes to carry out breast self-examination, it is reasonable to teach her the proper procedure.
- Psychosocial support should be encouraged and facilitated.
- Participation in clinical trials should be encouraged and facilitated.
- The responsibility for follow-up should be formally allocated to a single physician.
- Communication between all members of the team must be ensured to avoid duplication of visits and tests.

Cognitive functioning

- There may be an effect of chemotherapy on cognitive functioning, which may be sustained. However, there is no correlation between subjective complaints of cognitive impairment and objective measures.
- Prospective longitudinal controlled studies should be encouraged.

Fatigue

- Fatigue may affect approximately one-quarter to one-third of breast cancer survivors. Patients should be asked about symptoms of fatigue.
- Physiologic causes of fatigue should be investigated and ruled out. Depression and pain are potentially treatable underlying factors.
- Prospective longitudinal controlled studies should be encouraged.

Weight management

- Weight management should be discussed with all breast cancer survivors.
- Overweight patients should be encouraged to participate in evidence-based weight-management programs.

Osteoporosis

- Patients who are postmenopausal, or are premenopausal with risk factors for osteoporosis, or are taking aromatase inhibitors should undergo a screening bone mineral density test.
- Patients should be counselled on exercise and on adequate intake of calcium and vitamin D.
- Osteoporosis treatment should include a bisphosphonate.

Sexual functioning

- Sexual functioning should be discussed with women at follow-up visits.

Pregnancy

- Women considering pregnancy following a diagnosis of breast cancer should be informed of the limited data on the effect of pregnancy on outcomes such as breast cancer recurrence and survival. Most of the studies have been retrospective case series or case–control studies with small numbers of patients. Nevertheless, there is currently no evidence that subsequent pregnancy adversely affects survival.

Validation: The original guideline was updated by a writing committee, which then submitted it for review, revision and approval by the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. The current update has been peer reviewed.

Sponsor: The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer was convened by Health Canada.

Completion Date: March 2005.

This guideline updates the previously published guideline on follow-up after treatment for breast cancer.[1] The evidence on the goals of follow-up and the components of the follow-up program are updated. As well, special topics of concern to breast cancer survivors, such as cognitive functioning, fatigue, weight management, osteoporosis, sexual functioning and pregnancy, are discussed. These topics were not included in the original 1998 version of the guideline. The topics of hormone replacement therapy (see guideline 14) and lymphedema (see guideline 11) are presented elsewhere.

Methods

The evidence reviewed for this document was obtained through a systematic review of the English-language literature retrieved from MEDLINE (1991 to January 2004). Search terms included "breast neoplasms," "follow-up," "randomized controlled trials," "meta analysis," "quality of life," "fatigue," "weight gain," "osteoporosis," "sexuality" and "pregnancy." A nonsystematic review of the literature and monitoring of major conferences on breast cancer were continued through January 2005.

The quality of the evidence on which conclusions are based is categorized into 5 levels.[2] The iterative process used to develop this guideline is described elsewhere.[3] A writing committee updated the original guideline and submitted it to the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer for further review, revision and approval.

Recommendations (including evidence and rationale)

- **All patients with breast cancer should have regular follow-up surveillance.**

Goals of follow-up

Regular follow-up surveillance should aim to achieve 4 principal objectives:

1. To provide patients with support and counselling

Breast cancer survivors can experience a variety of physical and psychological symptoms during their follow-up. Certain types of early symptoms, such as soft-tissue swelling, hematomas, seromas of the breast area, and numbness or stiffness of the upper arm, are attributable to surgery. Later symptoms may be due to surgery (e.g., postmastectomy syndrome: see 2001 update of guideline 10 for the management of chronic pain after mastectomy); to irradiation (e.g., erythema, swelling, tenderness and skin edema: see 2003 update of guideline 6); to lymphedema (see guideline 11); or to menopausal symptoms associated with tamoxifen and induced by ovarian ablation or chemotherapy (see guideline 14).

Psychosocial problems are most pronounced during the first year after breast cancer diagnosis,[4,5] whereas long-term psychosocial adjustment is generally excellent.[6] Ganz and colleagues reported the results of a longitudinal cohort study involving 817 breast cancer survivors who were disease free.[6] At an average of 6.3 years after diagnosis, physical well-being and emotional well-being were excellent, and the modest clinically nonsignificant changes in the physical domains of health-related quality of life (HRQL)

were consistent with an aging population. The subgroup of women who had received systemic adjuvant therapy, however, had a decline in several aspects of physical functioning. This suggests that systemic therapy can be associated with long-term effects on quality of life. There were no differences in HRQL according to the type of primary breast cancer surgery, which is consistent with findings from other studies.[7] A negative impact was found on work life and career in the study by Ganz and colleagues,[6] which was also shown in a Canadian study.[8] Ganz and associates also conducted a retrospective survey of the quality of life of 577 young (< 50 years of age at the time of diagnosis) breast cancer survivors.[9] The patients were surveyed approximately 6 years after diagnosis. Overall, quality of life was good but was decreased in women less than 35 years of age, particularly those who underwent early menopause. Ganz and colleagues also reported the results of a survey of the quality of life of 691 women aged 65 years or more who were interviewed 3 and 15 months after breast cancer surgery.[10] Quality of life decreased initially but improved over time. For women taking tamoxifen, extrapolation from a randomized trial of tamoxifen versus placebo for primary prevention of breast cancer suggests that tamoxifen does not increase the risk of depression (level I evidence).[11]

It is through follow-up visits that physical and psychological issues can be discussed, and treatment and reassurance provided, as required.

2. To detect potentially curable conditions such as local recurrence of cancer in the breast following breast-conserving surgery and new cancers in the opposite breast

In patients treated with breast-conserving surgery (BCS) and radiotherapy, local recurrence may develop in the same breast. The rate of local recurrence at 20 years of follow-up has been reported to be between 8.8% [12] and 14.3%.[13] Local recurrence in the breast can often be detected earlier by mammographic examination[14] than by physical examination and is potentially curable by mastectomy.[15] Thus, after BCS, regular examination is recommended with the aim of detecting local recurrences early. However, recurrence in the breast early (i.e., within 1 or 2 years after surgery) is often an indicator of aggressive disease and systemic metastases.[16,17] A local recurrence in the chest wall after mastectomy, however, often has the same prognostic significance as a distant metastasis, and its early detection and treatment are unlikely to influence survival.[15]

It is estimated that women who have had breast cancer are at 2 to 6 times greater risk of a new primary cancer in the contralateral breast than are women who have not had breast cancer.[18] The absolute risk is between 0.5% and 1.0% per year.[19] In one series, which involved breast cancer patients who subsequently had contralateral breast cancer, no difference in survival was detected between patients with unilateral versus bilateral cancers.[20] In the case of bilateral breast cancer, prognosis is determined by whichever breast tumour has the worst prognosis. For early stage breast cancer, early detection of a contralateral breast cancer may be beneficial. There is no direct proof, however, that early detection will improve survival in these patients.

Regular mammographic screening of healthy populations results in earlier detection of breast cancer and reduced rates of death from breast cancer among women over 50 years of age.[21] Therefore, by extrapolation, regular clinical and mammographic examinations of breast cancer patients after treatment constitute, in effect, screening of a high-risk population, and these measures could result in improved survival. However, any

such benefit is likely to be small because of the small number of second cancers involved and the competing mortality related to the first cancer.

Nevertheless, early detection is facilitated when clinical and mammographic examinations have been carried out to establish a "baseline" after the inflammatory changes resulting from surgery and radiotherapy have subsided.

3. To provide care for patients in whom metastatic disease develops

Several observational studies,[22–24] 2 randomized controlled trials[25,26] and 1 simulation study[27] have shown that early detection of distant metastases does not improve survival (level I evidence). Symptoms often develop between visits, and physicians rarely detect abnormalities in asymptomatic patients.[22] However, early treatment of metastases can sometimes influence morbidity; thus, with this objective in mind, patients should be encouraged to report new symptoms promptly.

4. To monitor outcome

Cancer specialists recognize that monitoring patient outcomes, such as survival, morbidity and quality of life, is an important aspect of determining the effectiveness of treatment.[28] In order to compare treatment outcomes with national and international standards, such information must be collected systematically, completely and in a format that allows for regular analysis.

The follow-up program

- **The frequency of visits should be adjusted according to individual patient's needs.**

There is no compelling evidence to support any particular frequency of visits. In a British study, women were randomly allocated either to a follow-up schedule of visits every 3 months in year 1, every 4 months in year 2 and every 6 months in years 3 to 5 or to a schedule of 1 visit every 1 or 2 years. No benefit was detected from the more frequent visits, and patients in both groups expressed a preference for reducing rather than increasing the number of follow-up visits (level II evidence).[29] In another British study, patients were randomly allocated to receive standard clinic follow-up versus no routine follow-up. Patients in the latter group received written information on signs and symptoms of recurrence with instructions to make telephone contact with a nurse if they experienced any problems.[30] Although no differences were found in either HRQL or patient satisfaction outcomes, the study was conducted for 1 year only and no clinical outcomes were reported (level II evidence).

The frequency of visits requires a balancing of the probable health benefits against the inconvenience, stress and costs of frequent visits and the number of false-positive test results they may generate. Although follow-up visits can reassure patients, they can also cause anxiety and remind women of their disease without ever being able to provide complete reassurance that they are cured.[31,32] In a report presented at the Bari Consensus Conference, Boccardo and colleagues suggested 4 visits per year for 2 years, 2 visits per year for the next 3 years and annual visits thereafter.[33] The American Society of

Clinical Oncology recommends visits every 3 to 6 months for the first 3 years, every 6 to 12 months for the next 2 years, then annually.[34] In general, follow-up should be tailored to the individual needs of the patient.

- **All visits should include a medical history. For women who are taking tamoxifen, it is important to ask about vaginal bleeding. Physical examination should include breasts, regional lymph nodes, chest wall, lungs and abdomen. The arms should be examined for lymphedema. Annual visits should include mammographic examination.**

Treatment with tamoxifen causes a small increase in the risk of endometrial cancer (level I evidence).[35,36] The annual risk is approximately 2 per 1000 women and is higher among those over 50 years of age than among younger women. Most women taking tamoxifen in whom endometrial cancer develops will have vaginal bleeding.[37] Thus, it is important to ask about vaginal bleeding during the history-taking.[34] When such bleeding is present without an obvious cause, endometrial biopsy should be carried out. Screening with either transvaginal ultrasonography or endometrial sampling is not warranted because of the high false-positive rates and the low yield of clinically important results.[38,39]

Physical and mammographic examinations are complementary: findings on mammographic examination may be normal even when a palpable cancer is present, and nonpalpable cancers may be detected by mammographic examination.[40–42] Although a systematic review of the literature demonstrated that the benefits of annual mammograms are based only on case series and observational studies,[43] annual mammograms are widely recommended in conjunction with regular physical examination.

- **Routine laboratory and radiographic investigations should not be carried out for the purpose of detecting distant metastases.**

In the absence of evidence that early treatment of metastatic disease will prolong life, one should avoid the inconvenience and expense of carrying out routine tests to detect it. In one trial, 655 patients who were randomly assigned to receive intensive surveillance consisting of physician visits, bone scanning, liver echographic examination, chest radiography and laboratory tests had an almost identical 6-year survival and HRQL to that of a control group of 665 women who received only tests that were clinically indicated (level I evidence).[25] Both groups had annual mammographic examination of the contralateral breast. In another randomized trial of similar size and duration, chest radiographs and bone scans obtained every 6 months had no influence on mortality at 5 years.[26] These results have been reaffirmed in a recent meta-analysis of these studies.[44] Except for mammographic examination,[43] scientific evidence does not support the routine use of any other instrumental or laboratory test, including biologic markers.[33,34,45–47]

- **Patients should be encouraged to report new, persistent symptoms promptly, without waiting for the next scheduled appointment.**

Patients should understand clearly that the presence of persistent symptoms, such as bone pain, cough, breast lumps, mastectomy scar changes, fatigue and anorexia, should be reported without waiting for a scheduled visit.

- **If a woman wishes to carry out breast self-examination, it is reasonable to teach her the proper procedure.**

Breast self-examination is not recommended as a screening manoeuvre for women without breast cancer.[48] For women with breast cancer, evidence is lacking that breast self-examination can improve survival. In a follow-up study involving 1004 women newly diagnosed with breast cancer, the cancers found by those who practised self-examination were smaller and associated with fewer involved axillary lymph nodes.[49] Thus, it is theoretically possible that earlier diagnosis may improve survival.

- **Psychosocial support should be encouraged and facilitated.**

Psychosocial support has been defined as information, advice or tangible aid provided through contact with a social network that has beneficial effects for the recipient.[50] Support can be given to patients by other breast cancer survivors.[51] Randomized controlled trials evaluating the effect of different forms of psychosocial interventions on psychosocial outcomes of breast cancer survivors have had conflicting results: some found a positive effect on some psychosocial domains,[52–55] whereas others found no effect.[56]

The effect of psychosocial interventions on survival is also uncertain. Although an early trial by Spiegel and colleagues showed longer survival among 86 patients with metastatic breast cancer randomly allocated to receive a psychosocial supportive intervention than among patients in the control group,[57] a recent Canadian trial found no difference in survival between 235 women with metastatic breast cancer randomly assigned to a psychosocial support intervention and those in the control group (level I evidence).[58]

The results of these studies are difficult to interpret because of the many different patient groups, interventions and outcomes being studied. Nevertheless, in a review of the evidence, Fallowfield recommended that psychological interventions be placed "firmly on the list of requirements for good cancer care."[59] Thus, psychosocial support, whether provided by health care workers, family, friends or organized support groups, should be facilitated and encouraged.

- **Participation in clinical trials should be encouraged and facilitated.**

Improvement in the care of future patients with breast cancer depends on the participation of sufficient numbers of patients in clinical trials. Therefore, physicians treating patients with breast cancer should be aware of currently available trials, and patients should be given the opportunity to participate in them.

- **The responsibility for follow-up should be formally allocated to a single physician.**

Although early follow-up visits are normally carried out by the specialist who has been responsible for treatment (the surgeon, the medical oncologist or the radiation oncologist), the responsibility for long-term follow-up care is frequently not defined. In an Italian study, one-third of 284 women complained of difficulties in follow-up owing to lack of cooperation and integration of follow-up procedures among specialists.[60]

The individuals or organizations that are the most appropriate for carrying out follow-up may differ according to the circumstances. In a British study, follow-up in a general practice was found to be acceptable to both patients and general practitioners.[31] In this study, involving 296 women randomly allocated to receive follow-up care either in the hospital or in general practice, there was no significant difference between the 2 groups in time to confirmation of recurrence or in scores for social functioning, mental health or general health perception (level II evidence).[61] In Canada, continuing care is often carried out by specialists. In a study in southwestern Ontario, family physicians were involved in the care of only 17.5% of 183 women with stage I breast cancer.[62] In another Canadian trial, 968 women with early stage breast cancer who had completed their primary treatment (e.g., chemotherapy or radiotherapy) were randomly allocated to receive follow-up by either their own family physician or an oncologist at a cancer centre.[63] At a median follow-up of 3.5 years, there was no difference between the 2 groups in the primary outcome of serious clinical events (3.3% in the family physician group and 3.7% in the cancer centre group; 0.4% difference; 95% confidence interval [CI] –2.02% to 2.83%).

In a paper presented at the Bari Consensus Conference, the authors concluded that, after long periods of care by their various oncologists, women may feel abandoned when discharged from their cancer clinic. They concluded that patients wanted a "team" of health care professionals to be accessible, when necessary, for their care and treatment.[51] Researchers in the United Kingdom have reached the same conclusions.[64] Thus, when family physicians assume responsibility for follow-up, contact should be maintained with the treating specialists. When responsibility is transferred, irrespective of who is responsible for the follow-up surveillance, the patient must take part in the decision and be kept fully informed of the follow-up plans from the beginning to avoid any feelings of abandonment.

- **Communication between all members of the team must be ensured to avoid duplication of visits and tests.**

Not all of the health care professionals who have taken part in the diagnosis and management of a woman's breast cancer will necessarily wish to be kept informed of the patient's progress during follow-up. However, for those who do, clear arrangements for the transfer of follow-up information will make for improved care and avoid unnecessary repetition of tests.[34]

Special issues

Cognitive functioning

- **There may be an effect of chemotherapy on cognitive functioning, which may be sustained. However, there is no correlation between subjective complaints of cognitive impairment and objective measures.**

- **Prospective longitudinal controlled studies should be encouraged.**

Breast cancer survivors often complain of memory problems, a phenomenon that has been called "chemobrain" or "chemofog."[65] Phillips and Bernhard recently reviewed the literature on the effect of adjuvant chemotherapy on cognitive functioning in breast cancer survivors.[65] They identified 4 cross-sectional studies that measured cognitive impairment in breast cancer survivors.[66–70] All 4 studies found some degree of cognitive impairment.

Schagen and associates[66] demonstrated significantly more cognitive impairment in patients who received standard-dose chemotherapy than in control subjects (odds ratio [OR] 6.4, 95% CI 1.5 to 27.6; $p = 0.013$) at 2 years after therapy. In this study, there was no correlation between subjective reports of cognitive impairment and results of objective neuropsychological testing.

Van Dam and colleagues compared cognitive functioning in 34 patients who had received a high-dose chemotherapy regimen, 36 patients who had received a standard-dose regimen and 34 control patients who had received no chemotherapy; the average time since completion of chemotherapy was 2 years.[67] Patients who received the high-dose chemotherapy had a risk of cognitive impairment 8.2 times higher (95% CI 1.8 to 37.7; $p = 0.006$) than that of the control subjects and 3.5 times higher (95% CI 1.0 to 12.8; $p = 0.056$) than that of patients who received the standard-dose regimen. These results were not related to anxiety, depression or fatigue. There was no correlation between subjective reports of cognitive functioning and results of objective neuropsychological testing. A follow-up report of this study at 4 years after therapy showed an improvement in cognitive functioning in both chemotherapy groups in terms of self-reported problems and neuropsychological test results.[70]

Brezden and colleagues[68] found that 31 patients receiving chemotherapy at the time of the study had worse cognitive functioning than either control subjects or 40 patients who had completed chemotherapy 2 years previously. These differences, however, were not statistically significant.

Ahles and colleagues[69] studied cognitive functioning in 35 patients 10 years after they completed standard-dose chemotherapy and found that it was significantly worse than that of breast cancer patients who had received local therapy only.

In a recent study by Tchen and colleagues, 110 women receiving adjuvant chemotherapy for breast cancer were matched with a disease-free control group not receiving chemotherapy.[71] There was a higher incidence of moderate or severe cognitive impairment in the treatment group than in the control group (16% v. 4%; $p = 0.008$). In addition, chemotherapy patients experienced more fatigue, more menopausal symptoms and worse quality of life.

Although these studies point to an effect of chemotherapy on cognitive functioning, given the limited strength of the evidence, it is premature to recommend routine neuropsychological testing or interventions. All of the studies had methodological problems, such as lack of baseline data to assess cognitive functioning before treatment, small samples, and inability to control for hormonal factors and tamoxifen use. Furthermore, the evidence is conflicting as to whether the duration of the effect is short term or long term. As well, 2 of the studies found no correlation between subjective complaints and objective measures of cognitive functioning. Physicians should assess and treat patients with emotional distress, which may be the underlying cause of subjective complaints of impaired cognitive functioning. Prospective longitudinal controlled studies are needed in order to better understand the relation between chemotherapy and cognitive impairment.

Fatigue

- **Fatigue may affect approximately one-quarter to one-third of breast cancer survivors. Patients should be asked about symptoms of fatigue.**
- **Physiologic causes of fatigue should be investigated and ruled out. Depression and pain are potentially treatable underlying factors.**
- **Prospective longitudinal controlled studies should be encouraged.**

Fatigue is experienced by most breast cancer patients during treatment.[72,73] However, the prevalence of fatigue at 1 year after treatment has been estimated to be between 17%[74] and 38%.[72,75]

The causes of fatigue after breast cancer treatment have not been determined. The potential relation between fatigue and initial treatment has been investigated. Three studies found fatigue to be unrelated to the type of treatment received, the use of tamoxifen or the time since treatment.[72,75,76] In one case–control study involving 61 disease-free patients between 3 and 36 months after treatment, Broeckel and colleagues[73] found that, compared with control subjects, breast cancer survivors had more severe fatigue ($p < 0.01$) and more current fatigue ($p < 0.05$). However, they included only patients who had received chemotherapy, which makes it impossible to determine whether it was the chemotherapy or other aspects of the cancer treatment and diagnosis that were the underlying factors. Bower and associates[72] surveyed 1957 disease-free breast cancer survivors between 1 and 5 years after the initial breast cancer diagnosis. Women who received radiotherapy or chemotherapy or both reported higher levels of fatigue at 1 year after diagnosis than those who did not receive such therapy ($p = 0.02$); after 1 year the difference in fatigue scores associated with treatment was no longer statistically significant. Woo and colleagues[77] found higher fatigue scores among women who received combination treatment (i.e., chemotherapy plus radiotherapy) than among those receiving other forms of treatment. However, the very poor response rate of 15% suggests that this was a biased sample. Furthermore, women were surveyed within only 18 months after treatment.

Multivariate analysis in the study by Bower and associates[72] found that the most important predictors of fatigue were depression (OR 1.13; $p = 0.0001$) and pain (OR 0.97; $p = 0.0001$). The type of treatment received (radiation, OR 1.23, $p = 0.19$; chemotherapy, OR 1.29, $p = 0.18$; radiation plus chemotherapy, OR 1.23, $p = 0.25$) was

not associated with fatigue in the multivariate analysis. Bower and associates also found that breast cancer survivors reported slightly higher levels of energy than age-matched women in the general population ($p = 0.009$). In another study, Okuyama and colleagues found that depression was an important predictor of fatigue.[76]

Fatigue is experienced by many breast cancer survivors. Based on current evidence, the mechanism of fatigue and the relation between fatigue and primary treatment modality remain unclear. Fatigue in breast cancer survivors should be approached by first investigating and ruling out known physiologic causes. In addition, physicians should assess and treat patients with depression or pain, which may be underlying causes of fatigue. Prospective longitudinal controlled studies are needed to better understand the prevalence and cause of fatigue in breast cancer survivors.

Weight management

- **Weight management should be discussed with all breast cancer survivors.**
- **Overweight patients should be encouraged to participate in evidence-based weight-management programs.**

Weight gain is a common problem for breast cancer survivors.[78,79] It has been associated with receipt of adjuvant chemotherapy[78,80] but not with tamoxifen therapy (level I evidence).[37] Weight gain has a negative impact on HRQL[81] and weight-related illnesses.[78,82] There is a growing body of knowledge that shows an association between obesity at diagnosis or weight gain after diagnosis and breast cancer outcomes such as recurrence and survival.[82]

Chlebowski and colleagues[82] conducted a systematic review of the relation between obesity at diagnosis and breast cancer outcomes. They identified observational studies only and did not perform a meta-analysis. Of 34 studies identified, 26 (involving a total of 29 460 patients) showed a statistically significant association between obesity (measured in various ways) and breast cancer recurrence or survival; 8 studies (involving a total of 3727 patients) found no such associations. In an earlier report of a meta-analysis, a hazard ratio for the effect of increased body weight on breast cancer recurrence at 5 years was 1.78 (95% CI 1.50 to 2.11), and the effect on death at 10 years was 1.36 (95% CI 1.19 to 1.55).[83]

The National Surgical Adjuvant Breast and Bowel Project (NSABP) recently examined the relation between obesity and outcomes in 3385 patients with node-negative breast cancer enrolled in the NSABP B-14 trial that compared tamoxifen therapy with placebo.[84] Breast cancer recurrence among obese women was the same as that among underweight and normal-weight women (level I evidence). All-cause mortality was higher among obese women than among normal-weight women, but breast cancer mortality was not increased among obese women.

In a recent analysis involving 5204 women in the Nurses' Health Study, weight before diagnosis and weight gain after diagnosis were associated with increased breast cancer recurrence and breast cancer mortality among women who never smoked compared with past and current smokers.[85,86]

Clinical practice guidelines on weight management for the general population have been published.[87] However, the direct application of these interventions to breast cancer survivors remains to be determined. Three randomized controlled trials are

evaluating the impact of dietary interventions on weight control and breast cancer prognosis.[88–90] In a recent survey 41% of patients reported making positive dietary changes in the 12 months after diagnosis, which suggests that breast cancer survivors are receptive to initiating dietary change.[81]

Research suggests that weight gain is more likely among patients who have received adjuvant chemotherapy than among patients who did not receive chemotherapy.[78] The weight gain appears to be due to a decrease in physical activity rather than an increase in energy intake, and it is associated with a change in body composition involving an increase in body fat relative to lean body mass.[78] Although these changes are consistent with the onset of menopause, in a prospective cohort study involving 535 patients followed for 1 year, Goodwin and associates found that chemotherapy and menopause were independent predictors of weight gain (all $p \leq 0.05$).[79] They also found that tamoxifen therapy did not predict weight gain among patients followed for 1 year after diagnosis.[79] Similarly, in a prospective cohort study involving 200 breast cancer patients who did not receive chemotherapy, there was no difference in weight gain up to 5 years after diagnosis between those who received tamoxifen and those who did not (mean gain 1.2 kg; 95% CI for the difference –1.8 to 1.2; $p = 0.66$).[91] In a randomized controlled trial involving women at high risk of breast cancer, tamoxifen therapy was not associated with weight gain compared with placebo (level I evidence).[37] Although this is strong evidence against the impact of tamoxifen on weight gain, it should be noted that the study involved women at high risk of breast cancer rather than breast cancer survivors.

There is an increasing body of evidence showing a positive association between obesity at diagnosis or weight gain after diagnosis and breast cancer outcomes, although at this time there is no definitive evidence that losing weight after diagnosis influences breast cancer outcomes. However, given the positive effect of weight management on other important comorbid conditions that can affect breast cancer survivors,[87] a discussion with patients about weight management and effective weight-management measures is recommended.

Osteoporosis

- **Patients who are postmenopausal, or are premenopausal with risk factors for osteoporosis, or are taking aromatase inhibitors should undergo a screening bone mineral density test.**

- **Patients should be counselled on exercise and on adequate intake of calcium and vitamin D.**

- **Osteoporosis treatment should include a bisphosphonate.**

Women with a history of breast cancer may be at increased risk of osteoporosis owing to premature ovarian failure resulting from chemotherapy.[92–95] In addition, preliminary results of trials of aromatase inhibitors as adjuvant treatment for breast cancer in postmenopausal women suggest increased rates of fractures and osteoporosis with the use of these agents.[96–100]

Current Canadian guidelines from the Osteoporosis Society of Canada recommend that healthy postmenopausal women with no risk factors for osteoporosis other than age undergo a screening bone mineral density test with dual-energy x-ray absorbtiometry after age 65.[101] Women with risk factors for osteoporosis may be screened at an earlier age.[101] Aromatase inhibitor therapy and premature ovarian failure are considered major risk factors for osteoporosis.[102] Hence, these guidelines can be extrapolated to women with a history of breast cancer. Women given aromatase inhibitors should have a baseline bone mineral density test and be monitored closely for the development of osteoporosis. There is no clear evidence regarding the frequency of bone mineral density monitoring in these patients. In such situations, clinicians should refer to published guidelines for the treatment and monitoring of osteoporosis in women with other high-risk factors.

The American Society of Clinical Oncology guideline on bisphosphonates commented on bone health in women with a history of breast cancer.[102] The guideline recommends that women with breast cancer at high risk of osteoporosis (e.g., age > 65 years, family history of osteoporosis or premature menopause because of treatment) should undergo a screening bone mineral density test and, depending on the results, be given bisphosphonate treatment. As is done for healthy women, follow-up surveillance for women with breast cancer should include timely bone mineral density tests and bisphosphonate treatment if the density is falling.[92,101]

A number of randomized controlled trials involving healthy women have demonstrated the efficacy of bisphosphonates in the treatment of osteoporosis.[103–106] Canadian osteoporosis guidelines recommend bisphosphonates as first-line agents for the treatment of osteoporosis.[101] For women with breast cancer, bisphosphonates such as clodronate and risedronate have been investigated for the prevention of skeletal metastases.[92,107,108] Bone mineral density was a secondary outcome in these studies. There was significantly less decrease in bone mineral density associated with the bisphosphonate therapy than with placebo among women with early breast cancer.[92,107,108] Similarly, studies support bisphosphonate therapy for the treatment or prevention of aromatase-inhibitor–induced bone loss.[109,110] Women should also be counselled regarding the importance of bone health and adequate intake of calcium and vitamin D through diet or supplementation and exercise.[101] A number of recent studies have evaluated the effectiveness of bisphosphonates for the prevention of skeletal metastases, and the results are conflicting.[111–116] Hence, it is premature to make recommendations regarding the use of bisphosphonates for such prevention.

Intranasal calcitonin therapy has been approved for use in the general population for the treatment of osteoporosis and has been shown to reduce pain associated with acute vertebral fractures (level I evidence).[101] However, no studies of calcitonin specifically involving women with breast cancer have been reported.

Tamoxifen, by virtue of its proestrogenic effects, preserves bone mineral density in postmenopausal women. However, its use has been associated with loss of bone mineral density in premenopausal women.[117] Raloxifene, like tamoxifen, is a selective estrogen-receptor modulator with proestrogenic effects on bone metabolism. Although raloxifene and bisphosphonates are considered first-line therapies in the prevention and treatment of postmenopausal osteoporosis[101] (level I evidence), there are few data on the safety of raloxifene in women with a history of breast cancer.[118] Therefore, raloxifene is not recommended for use in women with a history of breast cancer. This recommendation

is based on the fact that the drug is similar to tamoxifen, and 10 years of tamoxifen use has been associated with increased breast cancer recurrence compared with 5 years of tamoxifen use.[119,120] Also, laboratory studies show that raloxifene may stimulate tamoxifen-dependent cells.[121]

Although estrogen replacement therapy reduces the loss of bone mineral density associated with menopause, its use is contraindicated in women with a history of breast cancer because of concerns of precipitating breast cancer recurrence.[122] Recently, a clinical trial that randomly allocated women with a history of breast cancer to receive either hormone replacement therapy or none was stopped because of an increased risk of a new breast cancer.[123]

Sexual functioning

- **Sexual functioning should be discussed with women at follow-up visits.**

Decreased sexual desire, decreased frequency of intercourse, dyspareunia and difficulties with orgasm have been commonly reported in women with breast cancer.[124–126] However, in most studies, sexual functioning of breast cancer survivors appears to be similar to that of healthy, age-matched women.[124,127,128] The highest incidence of sexual dysfunction among women treated for breast cancer has been reported among those who received chemotherapy.[125,126] Except for giving rise to more vasomotor symptoms, treatment with tamoxifen, compared with no systemic treatment, has no effect on sexual functioning.[125,126,129] Ganz and colleagues investigated predictors for sexual interest, dysfunction and satisfaction using a multivariate regression analysis in a cohort of breast cancer survivors.[130] Significant predictors of sexual interest included having a new partner since the diagnosis of breast cancer (more sexual interest; $p \leq 0.05$), having a better mental health score (more sexual interest; $p \leq 0.01$) and having a poorer body image score (less sexual interest; $p \leq 0.001$). Predictors of sexual dysfunction were vaginal dryness (more sexual dysfunction; $p \leq 0.001$), past chemotherapy use (more sexual dysfunction; $p \leq 0.05$) and having a new partner since diagnosis (less sexual dysfunction; $p \leq 0$ .05). Quality of the partnered relationship (better relationship score associated with greater sexual satisfaction; $p \leq 0.001$) and sexual problems in the partner (less sexual satisfaction; $p \leq 0.001$) were significant predictors of sexual satisfaction.

A number of studies have shown that, although the type of surgery may have an impact on body image, sexual functioning is not adversely affected.[131–133] A meta-analysis of studies of psychosocial consequences of surgery for breast cancer showed modest effects for the impact of the type of surgery on sexual functioning.[134]

Ganz and colleagues tested the efficacy of an intervention program consisting of a comprehensive menopausal assessment that was offered to 76 perimenopausal or postmenopausal women with a history of breast cancer.[135] The intervention was delivered by a trained nurse-practitioner and focused on symptom assessment, education, counselling and specific pharmacologic and behavioural interventions as appropriate. Sexual functioning was significantly improved in the group receiving the intervention compared with the usual-care group ($p = 0.04$; level I evidence).

Many of the studies investigating sexual functioning of breast cancer survivors were retrospective or used qualitative methodology. There is a need for prospective

collection of data, particularly from randomized trials involving women receiving chemotherapy with long-term follow-up.

Sexual functioning should be discussed with women in follow-up visits. Interventions to decrease menopausal symptoms (especially vaginal dryness) should be discussed and may aid in improving sexual functioning.[136] Recommendations for the treatment of menopausal symptoms have been made in an evidence-based guideline published previously (see guideline 14).

Pregnancy

- **Women considering pregnancy following a diagnosis of breast cancer should be informed of the limited data on the effect of pregnancy on outcomes such as breast cancer recurrence and survival. Most of the studies have been retrospective case series or case–control studies with small numbers of patients. Nevertheless, there is currently no evidence that subsequent pregnancy adversely affects survival.**

Because many women of child-bearing age are diagnosed with breast cancer, issues of subsequent pregnancy become important. The high levels of estrogen associated with pregnancy have raised concerns about stimulating dormant micrometastases in breast cancer survivors. A number of case series and case–control studies evaluating survival following pregnancy after breast cancer diagnosis have been published.[137–151] Most studies have shown that subsequent pregnancy in breast cancer survivors does not adversely affect survival.[137,138,140,143,144,149–151] However, these studies involved small numbers of patients and were retrospective in nature, which makes them susceptible to significant biases. Also, most of the studies lacked an appropriately matched control group or involved highly selected patients. No prospective studies have been reported, and a randomized controlled trial is clearly not feasible.

Decisions about pregnancy should be discussed between the patient and her physician. The decision should balance the unknown effect of pregnancy on breast cancer outcomes against the concern of declining fertility with increasing age. In addition, pregnancy within 5 years after the diagnosis of breast cancer will probably necessitate the early discontinuation of adjuvant endocrine therapy, which would result in a decreased benefit. There does not appear to be an increase in congenital defects in infants of women who have been treated with chemotherapy before pregnancy.[138,141,152]

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References

1. Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer. A Canadian consensus document. 9. Follow-up after treatment for breast cancer. *CMAJ* 1998;158(3 Suppl):S65-70.
2. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1989;95(Suppl):2S-4S.
3. Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer. A Canadian consensus document. Introduction. *CMAJ* 1998;158(3 Suppl):S1-2.
4. Ganz PA, Coscarelli A, Fred C, Kahn B, Polinsky ML, Petersen L. Breast cancer survivors: psychosocial concerns and quality of life. *Breast Cancer Res Treat* 1996;38:183-99.
5. Ganz PA, Kwan L, Stanton AL, Krupnick JL, Rowland JH, Meyerowitz BE, et al. Quality of life at the end of primary treatment of breast cancer: first results from the Moving Beyond Cancer randomized trial. *J Natl Cancer Inst* 2004;96:376-87.
6. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term disease-free survivors of breast cancer: a follow-up study. *J Natl Cancer Inst* 2002;94:39-49.
7. Janni W, Rjosk D, Dimpfl TH, Haertl K, Strobl B, Hepp F, et al. Quality of life influenced by primary surgical treatment for stage I–III breast cancer — long-term follow-up of a matched-pair analysis. *Ann Surg Oncol* 2001;8:542-8.
8. Stewart DE, Cheung AM, Duff S, Wong F, McQuestion M, Cheng T, et al. Long-term breast cancer survivors: confidentiality, disclosure, effects on work and insurance. *Psychooncology* 2001;10:259-63.
9. Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast cancer in younger women: reproductive and late health effects of treatment. *J Clin Oncol* 2003;21:4184-93.
10. Ganz PA, Guadagnoli E, Landrum MB, Lash TL, Rakowski W, Silliman RA. Breast cancer in older women: quality of life and psychosocial adjustment in the 15 months after diagnosis. *J Clin Oncol* 2003;21:4027-33.
11. Day R, Ganz PA, Costantino JP. Tamoxifen and depression: more evidence from the National Surgical Adjuvant Breast and Bowel Project's breast cancer prevention (P-1) randomized study. *J Natl Cancer Inst* 2001;93:1615-23.
12. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227-32.
13. Fisher B, Anderson S, Bryant J, Margolese R, Deutsch M, Fisher E, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233-41.
14. Orel SG, Troupin RH, Patterson EA, Fowble BL. Breast cancer recurrence after lumpectomy and irradiation: role of mammography in detection. *Radiology* 1992;183:201-6.

15. Kennedy MJ, Abeloff MD. Management of locally recurrent breast cancer. *Cancer* 1993;71:2395-2409.
16. Whelan T, Clark R, Roberts R, Levine M, Foster G. Ipsilateral breast tumor recurrence postlumpectomy is predictive of subsequent mortality: results from a randomized trial. *Int J Radiat Oncol Biol Phys* 1994;30(1):11-6.
17. Fisher B, Anderson S, Fisher ER, Redmond C, Wickerham DL, Wolmark N, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. *Lancet* 1991;338:327-31.
18. Chen Y, Thompson W, Semenciw R, Mao Y. Epidemiology of contralateral breast cancer. *Cancer Epidemiol Biomarkers Prev* 1999;8:855-61.
19. Iglehart JD. Prophylactic mastectomy. In: Harris JR, Lippman ME, Morrow M, Oxborne CK, editors. *Diseases of the breast.* 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 259-64.
20. Heron DE, Komarnichky LT, Hyslop T, Schwartz GF, Masfield CM. Bilateral breast carcinoma: risk factors and outcomes for patients with synchronous and metachronous disease. *Cancer* 2000;88:2739-50.
21. Smith RA, Orsi CJ. Screening for breast cancer. In: Harris JR, Lippman ME, Morrow M, Oxborne CD, editors. *Diseases of the breast.* 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 101-21.
22. Schapira D, Urban N. A minimalist policy for breast cancer surveillance. *JAMA* 1991;265:380-2.
23. Churn M, Kelly V. Outpatient follow-up after treatment for early breast cancer: updated results after 5 years. *Clin Oncol (R Coll Radiol)* 2001;13:187-94.
24. Te Boekhorst DS, Peer NG, van der Sluis RF, Wobbes T, Ruers TJ. Periodic follow-up after breast cancer and the effect on survival. *Eur J Surg* 2001;167:490-6.
25. The GIVIO Investigators. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. *JAMA* 1994;271:1587-92.
26. Roselli Del Turco M, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. *JAMA* 1994;271:1593-7.
27. Jacobs HJ, van Dijck JA, de Kleijn EM, Kiemeney LA, Verbeek AL. Routine follow-up examinations in breast cancer patients have minimal impact on life expectancy: a simulation study. *Ann Oncol* 2001;12:1107-13.
28. Grunfeld E, Mant D, Vessey MP, Yudkin P. Evaluating primary care follow-up of breast cancer: methods and preliminary results of three studies. *Ann Oncol* 1995;6(Suppl 2):47-52.
29. Gulliford T, Opomu M, Wilson E, Hanham I, Epstein R. Popularity of less frequent follow up for breast cancer in randomised study: initial findings from the hotline study. *BMJ* 1997;314:174-7.
30. Brown L, Payne S, Royle G. Patient initiated follow up of breast cancer. *Psycho-oncology* 2002;11:346-55.
31. Loprinzi CL. It is now the age to define the appropriate follow-up of primary breast cancer patients [editorial]. *J Clin Oncol* 1994;12:881-3.
32. Dewar J. Follow-up in breast cancer: a suitable case for reappraisal [editorial]. *BMJ* 1995;310:685-6.
33. Boccardo F, Bruzzi P, Cionini L, Confalonieri C, Fossati R, Gion M, et al. Appropriateness of the use of clinical and radiologic examinations and laboratory tests in the follow-up of surgically-treated breast cancer patients. Results of the Working Group on the Clinical Aspects of Follow-up. *Ann Oncol* 1995;6(Suppl 2):S57-59.
34. Smith TJ, Davidson NE, Schapira DV, Grunfeld E, Muss HB, Vogel III VG, et al for the American Society of Clinical Oncology Breast Cancer Surveillance Expert Panel. American Society of Clinical Oncology 1998 update of recommended breast cancer surveillance guidelines. *J Clin Oncol* 1999;17:1080-2.
35. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst* 1994;86:527-37.

36. Rutqvist LE, Johansson H, Signomklao T, Johansson U, Fornander T, Wilking N. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group. *J Natl Cancer Inst* 1995;87:645-51.
37. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;90:1371-88.
38. Barakat RR, Gilewski TA, Almadrones L, Saigo PE, Venkatraman E, Hudis C, et al. Effect of adjuvant tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy. *J Clin Oncol* 2000;18:3459-63.
39. Gerber B, Krause A, Muller H, Reimer T, Kelz T, Makovitzky J, et al. Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. *J Clin Oncol* 2000;18:3464-70.
40. Mellink WA, Holland R, Hendriks JH, Peeters PH, Rutgers EJ, van Daal WA. The contribution of routine follow-up mammography to an early detection of asynchronous contralateral breast cancer. *Cancer* 1991;67:1844-8.
41. Hassell PR, Olivotto IA, Mueller HA, Kingston GW, Basco VE. Early breast cancer: detection of recurrence after conservative surgery and radiation therapy. *Radiology* 1990;176:731-5.
42. Stomper PC, Recht A, Berenberg AL, Jochelson MS, Harris JR. Mammographic detection of recurrent cancer in the irradiated breast. *Am J Roentgenol* 1987;148:39-43.
43. Grunfeld E, Noorani H, McGahan L, Paszat L, Coyle D, van Walraven C, et al. Surveillance mammography after treatment of primary breast cancer: a systematic review. *The Breast* 2002;11:228-35.
44. Rojas MP, Telaro E, Russo A, Moschetti I, Coe L, Fossati R, et al. Follow-up strategies for women treated for early breast cancer [Cochrane review]. In: The Cochrane Library; Issue 1, 2005. Oxford: Update Software.
45. Dewar J. Follow up in breast cancer: a suitable case for reappraisal. *BMJ* 1995;310:685-6.
46. American Society of Clinical Oncology. Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. *J Clin Oncol* 1996;14:2843-77.
47. Wagman LD, Sanders RD, Terz JJ, Beatty JD, Kokal WA, Riihimaki DU. The value of symptom directed evaluation in the surveillance for recurrence of carcinoma of the breast. *Surg Gynecol Obstet* 1991;172:191-6.
48. Baxter N; Canadian Task Force on Preventive Health Care. Preventive health care, 2001 update: Should women be routinely taught breast self-examination to screen for breast cancer? *CMAJ* 2001;164(13):1837-46.
49. Foster RS Jr, Constanza MC. Breast self-examination practices and breast cancer survival. *Cancer* 1984;53:999-1005.
50. Gottlieb BH, Selby PM. Social support and mental health: a review of the literature. *Ottawa: Health and Welfare Canada*; 1989.
51. The patient's point of view. Results of the Working Group on Socio-Psychological Implications of Follow-up. *Ann Oncol* 1995;6(Suppl 2):S65-8.
52. McArdle JM, George WD, McArdle CS, Smith DC, Moodie AR, Hughson AV, et al. Psychological support for patients undergoing breast cancer surgery: a randomised study. *BMJ* 1996;312:813-6.
53. Allen SM, Shah AC, Nezu AM, Nezu CM, Ciambrone D, Hogan J, et al. A problem-solving approach to stress reduction among younger women with breast carcinoma. A randomized controlled trial. *Cancer* 2002;94:3089-100.
54. Fukui S, Koike M, Ooba A, Uchitomi Y. The effect of a psychosocial group intervention on loneliness and social support for Japanese women with primary breast cancer. *Oncol Nurs Forum* 2003;30:823-30.
55. Taylor KL, Lamdan RM, Siegel JE, Shelby R, Moran-Klimi K, Hrywna M. Psychological adjustment among African American breast cancer patients: one-year follow-up results of a randomized psychoeducational group intervention. *Health Psychol* 2003;22:316-23.

56. Heiney SP, McWayne J, Hurley TG, Lamb LS Jr, Bryant LH, Butler W, et al. Efficacy of therapeutic group by telephone for women with breast cancer. *Cancer Nurs* 2003;26:439-47.
57. Spiegel D, Bloom JR, Kraemer HC, Gottheil E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989;2:888-91.
58. Goodwin PJ, Leszcz M, Ennis M, Koopmans J, Vincent L, Guther H, et al. The effect of group psychosocial support on survival in metastatic breast cancer. *N Engl J Med* 2001;345:1719-26.
59. Fallowfield L. Psychosocial interventions in cancer. *BMJ* 1995;311:1316-7.
60. Paradiso A, Nitti P, Frezza P, Scorpiglione N; G.S.Bio.Ca.M. A survey in Puglia: the attitudes and opinions of specialists, general physicians and patients on follow-up practice. *Ann Oncol* 1995;6(Suppl 2):S53-6.
61. Grunfeld E, Mant D, Yudkin P, Adewuyi-Dalton R, Cole D, Stewart J, et al. Routine follow up of breast cancer in primary care: randomised trial. *BMJ* 1996;313:665-9.
62. Worster A, Wood ML, McWhinney IR, Bass MJ. Who provides follow-up care for patients with early breast cancer? *Can Fam Physician* 1995;41:1314-20.
63. Grunfeld E, Levine M, Julian J, Pritchard K, Coyle D, Mirsky D, et al. A randomized controlled trial (RCT) of routine follow-up for early stage breast cancer: a comparison of primary care versus specialist care [abstract]. *Proc Am Soc Clin Oncol* 2004;23:43.
64. Adewuyi-Dalton R, Ziebland S, Grunfeld E, Hall A. Patients' views of routine hospital follow-up: a qualitative study of women with breast cancer in remission. *Psychooncology* 1998;7:436-9.
65. Phillips KA, Bernhard J. Adjuvant breast cancer treatment and cognitive function: current knowledge and research directions. *J Natl Cancer Inst* 2003;95:190-7.
66. Schagen SB, van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer* 1999;85:640-50.
67. Van Dam FS, Schagen SB, Muller MJ, Boogerd W, vd Wall E, Droogleever Fortuyn ME. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. *J Natl Cancer Inst* 1998;90:210-8.
68. Brezden CB, Phillips KA, Abdolell M, Bunston T, Tannock IF. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol* 2000;18:2695-701.
69. Ahles TA, Saykin AJ, Furstenberg CT, Cole B, Mott LA, Skalla K, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol* 2002;20:485-93.
70. Schagen SB, Muller MJ, Boogerd W, Rosenbrand RM, van Rhijn D, Rodenhuis S, et al. Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. *Ann Oncol* 2002;13:1387-97.
71. Tchen N, Juffs HG, Downie FP, Yi Q-L, Hu H, Chemerynsky I, et al. Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2003;21:4175-83.
72. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J Clin Oncol* 2000;18:743-53.
73. Broeckel JA, Jacobson PB, Horton J, Balducci L, Lyman GH. Characteristics and correlates of fatigue after adjuvant therapy for breast cancer. *J Clin Oncol* 1998;16:1689-96.
74. Cella D, Davis K, Breitbart W, Curt G; Fatigue Coalition. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol* 2001;19:3385-91.
75. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients: a cross-sectional study. *Ann Oncol* 2002;13:589-98.
76. Okuyama T, Akechi T, Kugaya A, Okamura H, Imoto S, Nakano T, et al. Factors correlated with fatigue in disease-free breast cancer patients: application of the Cancer Fatigue Scale. *Support Care Cancer* 2000;8:215-22.
77. Woo B, Dibble SL, Piper BF, Keating SB, Weiss MC. Differences in fatigue by treatment methods in women with breast cancer. *Oncol Nurs Forum* 1998;25:915-20.

78. Demark-Wahnefried W, Peterson BL, Winer EP, Marks L, Aziz N, Marcom PK, et al. Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol* 2001;19:2381-9.
79. Goodwin PJ, Ennis M, Pritchard KI, McCready D, Koo J, Sidlofsky S, et al. Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. *J Clin Oncol* 1999;17:120-9.
80. Rock CL, Flatt SW, Newman V, Caan BJ, Haan MN, Stefanick ML, et al. Factors associated with weight gain in women after diagnosis of breast cancer. *J Am Diet Assoc* 1999;99:1212-21.
81. Maunsell E, Drolet M, Brisson J, Robert J, Deschenes L. Dietary change after breast cancer: extent, predictors, and relation with psychological distress. *J Clin Oncol* 2002;20:1017-25.
82. Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. *J Clin Oncol* 2002;20:1128-43.
83. Goodwin PJ, Esplen MJ, Wincour J, Butler K, Pritchard KI. Development of a weight management program in women with newly diagnosed locoregional breast cancer. In: Bitzer J, Stauber M, editors. *Psychosomatic obstetrics and gynecology*. Bologna, Italy: Monduzzi Editore, International Proceedings Division; 1995. p. 491-6.
84. Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamouonas EP. Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. *J Natl Cancer Inst* 2003;95:1467-76.
85. Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain and survival after breast cancer diagnosis. *J Clin Oncol* 2005;23(7):1370-8.
86. Chlebowski RT. Obesity and early-stage breast cancer [editorial]. *J Clin Oncol* 2005;23(7):1345-7.
87. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults —– the evidence report. *Obes Res* 1998;6:51S-209S.
88. Chlebowski RT, Rose D, Buzzard IM, Blackburn GL, Insull W Jr, Grosvenor M, et al. Adjuvant dietary fat intake reduction in postmenopausal breast cancer patient management. The Women's Intervention Nutrition Study (WINS). *Breast Cancer Res Treat* 1992;20:73-84.
89. Pierce JP, Faerber S, Wright FA, Rock CL, Newman V, Flatt SW, et al. A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. *Control Clin Trials* 2002;23:728-56.
90. Ritenbaugh C, Patterson RE, Chlebowski RT, Caan B, Fels-Tinker L, Howard B, et al. The Women's Health Initiative Dietary Modification trial: overview and baseline characteristics of participants. *Ann Epidemiol* 2003;13:S87-97.
91. Kumar NB, Allen K, Cantor A, Cox CE, Greenberg H, Shah S, et al. Weight gain associated with adjuvant tamoxifen therapy in stage I and II breast cancer: Fact or artifact? *Breast Cancer Res Treat* 1997;44:135-43.
92. Saarto T, Blomqvist C, Valimaki M, Makela P, Sarna S, Elomaa I. Chemical castration induced by adjuvant cyclophosphamide, methotrexate, and fluorouracil chemotherapy causes rapid bone loss that is reduced by clodronate: a randomized study in premenopausal breast cancer patients. *J Clin Oncol* 1997;15:1341-7.
93. Headley JA, Theriault RL, LeBlanc AD, Vassilopoulou-Sellin R, Hortobagyi GN. Pilot study of bone mineral density in breast cancer patients treated with adjuvant chemotherapy. *Cancer Invest* 1998;16:6-11.
94. Twiss JJ, Waltman N, Ott CD, Gross GJ, Lindsey AM, Moore TE. Bone mineral density in postmenopausal breast cancer survivors. *J Am Acad Nurse Pract* 2001;13:276-84.
95. Kanis JA, McCloskey EV, Powles T, Paterson AH, Ashley S, Spector T. A high incidence of vertebral fracture in women with breast cancer. *Br J Cancer* 1999;79:1179-81.
96. The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;359:2131-9.
97. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003;349:1793-802.

98. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004;350:1081-92.
99. ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365:60-2.
100. Perez EA, Josse RG, Pritchard KI, Ingle JN, Martino S, Findlay BP, et al. Effect of letrozole versus placebo on bone mineral density in women completing ≥ 5 years (yrs) of adjuvant tamoxifen: NCIC CTG MA.17b [abstract]. *Breast Cancer Res Treat* 2004;88(Suppl 1):S36.
101. Brown JP, Josse RG, for the Scientific Advisory Council of the Osteoporosis Society of Canada. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *CMAJ* 2002;167(10 Suppl):S1-34.
102. Hillner BE, Ingle JN, Chlebowski RT, Gralow J, Yee GC, Janjan NA, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 2003;21:4042-57.
103. Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women postmenopausal osteoporosis. *N Engl J Med* 1990;322:1265-71.
104. Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, Jackson RD, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990;323:73-9.
105. Pols HA, Felsenberg D, Hanley DA, Stepan J, Munoz-Torres M, Wilkin TJ, et al. Multinational placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT Study. Foxamax International Trial Study Group. *Osteoporos Int* 1999;9:461-8.
106. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial (FIT) Research Group. *J Clin Endocrinol Metab* 2000;85:4118-24.
107. Delmas PD, Balena R, Confravreux E, Hardouin C, Hardy P, Bremond A. Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double-blind, placebo-controlled study. *J Clin Oncol* 1997;15:955-62.
108. Powles TJ, McCloskey E, Paterson AH, Ashley S, Tidy VA, Nevantaus A, et al. Oral clodronate and reduction in loss of bone mineral density in women with operable primary breast cancer. *J Natl Cancer Inst* 1998;90:704-8.
109. Gnant M, Jakesz R, Mlineritsch B, Luschin-Ebengreuth G, Schmid M, Menzel C, et al. Zoledronic acid effectively counteracts cancer treatment induced bone loss (CTIBL) in premenopausal breast cancer patients receiving adjuvant endocrine treatment with goserelin plus anastrozole versus goserelin plus tamoxifen - bone density subprotocol results of a randomized multicenter trial (ABCSG-12) [abstract]. *Breast Cancer Res Treat* 2004;88(Suppl 1):S8-9.
110. Brufsky A, Harker G, Beck T, Carroll R, Tan-Chiu E, Seidler C, et al. Zoledronic acid (ZA) for prevention of cancer treatment-induced bone loss (CTIBL) in postmenopausal women (PMW) with early breast cancer (Bca) receiving adjuvant Letrozole (Let): Preliminary results of the Z-FAST trial [abstract 1114]. San Antonio Breast Cancer Symposium;2004 December 8-11;San Antonio.
111. Powles T, Paterson S, Kanis JA, McCloskey E, Ashley S, Tidy A, et al. Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. *J Clin Oncol* 2002;20:3219-24.
112. Powles T, Paterson A, McCloskey E, Kurkilahti M, Kanis J. Oral clodronate for adjuvant treatment of operable breast cancer: results of a randomized, double-blind, placebo-controlled multicenter trial [abstract]. *Proc Am Soc Clin Oncol* 2004;23:9.
113. Saarto T, Blomqvist C, Virkkunen P, Elomaa I. Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. *J Clin Oncol* 2001;19:10-7.

114. Saarto T, Vehmanen L, Blomqvist C, Elomaa I. Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients [abstract]. *Proc Am Soc Clin Oncol* 2004;23:8.

115. Diel IJ, Solomayer E, Gollan C, Schutz F, Bastert G. Bisphosphonates in the reduction of metastases in breast cancer: results of the extended follow-up of the first study population [abstract]. *Proc Am Soc Clin Oncol* 2000;19:82a.

116. Jaschke A, Bastert G, Solomayer EF, Costa S, Schuetz F, Diel IJ. Adjuvant clodronate treatment improves the overall survival of primary breast cancer patients with micrometastases to bone marrow — a longtime follow-up. *Proc Am Soc Clin Oncol* 2004;23:9.

117. Powles TJ, Hickish T, Kanis TA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. *J Clin Oncol* 1996;14:78-84.

118. Pritchard KI, Levine M, Walley B; Ad Hoc Raloxifene in Breast Cancer Group. Raloxifene: handle with care [letter]. *CMAJ* 2001;165(2):151,153.

119. Fisher B, Dignam J, Bryant J, DeCillis A, Wickerham DL Wolmark N, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst* 1996;88:1529-42.

120. Stewart HJ, Forrest AP, Everington D, McDonald CC, Dewar JJ, Hawkins RA, et al. Randomized comparison of 5 years of adjuvant tamoxifen with continuous therapy for operable breast cancer. The Scottish Cancer Trials Breast Group. *Br J Cancer* 1996;74:297-99.

121. O'Regan RM, Gajdos C, Dardes R, de los Reyes A, Bentrem DJ, Jordan VC. Effect of raloxifene after tamoxifen on breast and endometrial cancer growth [abstract]. P*roc Am Soc Clin Oncol* 2001;20:25a.

122. Pritchard KI, Khan H, Levine M; Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 14. The role of hormone replacement therapy in women with a previous diagnosis of breast cancer. *CMAJ* 2002;166(8):1017-22.

123. Holmberg L, Anderson H, for the HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer — Is it safe?), a randomised comparison: trial stopped. *Lancet* 2004;363:453-5.

124. Meyerowitz BE, Desmond KA, Rowland JH, Wyatt GE, Ganz PA. Sexuality following breast cancer. *J Sex Marital Therapy* 1999;25:237-50.

125. Berglund G, Nystedt M, Bolund C, Sjoden P, Rutquist L. Effect of endocrine treatment on sexuality in premenopausal breast cancer patients: a prospective randomized study. *J Clin Oncol* 2001;19:2788-96.

126. Mourits MJ, Bockerman I, de Vries EG, van der Zee AG, ten Hoor KA, van der Graf WT, et al. Tamoxifen effects on subjective and psychosocial well-being, in a randomised breast cancer study comparing high-dose and standard-dose chemotherapy. *Br J Cancer* 2002;86:1546-50.

127. Joly F, Espie M, Marty M, Heron JF, Henry-Amar M. Long-term quality of life in premenopausal women with node-negative localized breast cancer treated with or without adjuvant chemotherapy. *Br J Cancer* 2000;83:577-82.

128. Ganz PA, Rowland JH, Desmond K, Meyerowitz BE, Wyatt GE. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. *J Clin Oncol* 1998;16:501-14.

129. Mortimer JE, Boucher L, Baty J, Knapp DL, Ryan E, Rowland JH. Effect of tamoxifen on sexual functioning in patients with breast cancer. *J Clin Oncol* 1999;17:1488-92.

130. Ganz PA, Desmond KA, Belin TR, Meyerowitz BE, Rowland JH. Predictors of sexual health in women after a breast cancer diagnosis. *J Clin Oncol* 1999;17:2371-80.

131. Wapnir IL, Cody RP, Greco RS. Subtle differences in quality of life after breast cancer surgery. *Ann Surg Oncol* 1999;6:359-66.

132. Rowland JH, Desmond KA, Meyerowitz BE, Belin TR, Wyatt GE, Ganz PA. Role of breast reconstructive surgery in physical and emotional outcomes among breast cancer survivors. *J Natl Cancer Inst* 2000;90:1422-9.
133. Dorval M, Maunsell E, Deschênes L, Brisson J. Type of mastectomy and quality of life for long term breast carcinoma survivors. *Cancer* 1998;83:2130-8.
134. Moyer A. Psychosocial outcomes of breast-conserving surgery versus mastectomy: a meta-analytic review. *Health Psychol* 1997;16:284-98.
135. Ganz PA, Greendale GA, Petersen L, Zibecchi L, Kahn B, Belin TR. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *J Natl Cancer Inst* 2000;92:1054-64.
136. Hordern A. Intimacy and sexuality for the woman with breast cancer. *Cancer Nurs* 2000;23:230-6.
137. Cooper DR, Butterfield J. Pregnancy subsequent to mastectomy for cancer of the breast. *Ann Surg* 1970;171:429-33.
138. Ribeiro G, Jones DA, Jones M. Carcinoma of the breast associated with pregnancy. *Br J Surg* 1986;73:607-9.
139. Ariel IM, Kempner R. The prognosis of patients who become pregnant after mastectomy for breast cancer. *Int Surg* 1989;74:185-7.
140. Lethaby AE, O'Neill MA, Mason BH, Holdaway IM, Harvey VJ. Overall survival from breast cancer in women pregnant or lactating at or after diagnosis. *Int J Cancer* 1996;67:751-5.
141. Malamos NA, Stathopoulos GP, Keramopoulos A, Papadiamantis J, Vassilaros S. Pregnancy and offspring after the appearance of breast cancer. *Oncology* 1996;53:471-5.
142. Nugent P, O'Connell TX. Breast cancer and pregnancy. *Arch Surg* 1985;120:1221-4.
143. Kroman N, Jensen MB, Melbye M, Wohlfahrt J, Mouridsen HT. Should women be advised against pregnancy after breast-cancer treatment? *Lancet* 1997;350:319-22.
144. Sankila R, Heinavaara S, Hakulinen T. Survival of breast cancer patients after subsequent term pregnancy: "healthy mother effect." *Am J Obstet Gynecol* 1994;170:818-23.
145. Sutton R, Buzdar AU, Hortobagyi GN. Pregnancy and offspring after adjuvant chemotherapy in breast cancer patients. *Cancer* 1990;65:847-50.
146. Velentgas P, Daling JR, Malone KE, Weiss NS, Williams MA, Self SG, et al. Pregnancy after breast carcinoma. Outcomes and influence on mortality. *Cancer* 1999;85:2424-32.
147. Von Schoultz E, Johansson H, Wilking N, Rutqvist LE. Influence of prior and subsequent pregnancy on breast cancer prognosis. *J Clin Oncol* 1995;13:430-4.
148. Mignot L, Morvan F, Sarrazin D. Breast cancer and subsequent pregnancy. *Proc Am Soc Clin Oncol* 1986;5:57
149. Gelber S, Coates AS, Goldhirsch A, Castiglione-Gertsch M, Marini G, Lindtner J, et al. Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer. *J Clin Oncol* 2001;19:1671-5.
150. Upponi SS, Ahmad F, Whitaker IS, Purushotham AD. Pregnancy after breast cancer. *Eur J Cancer* 2003;39:736-41.
151. Mueller BA, Simon MS, Deapen D, Kamineni A, Malone KE, Daling JR. Childbearing and survival after breast carcinoma in young women. *Cancer* 2003;98:1131-40.
152. Sutton R, Buzdar AU, Hortobagyi GN. Pregnancy and offspring after adjuvant chemotherapy. *Cancer* 1990;65:847-50.