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Medical, Psychosocial, and Health-Related Quality of Life Issues in Breast Cancer Survivors

Julie Lemieux, Louise J. Bordeleau, and Pamela J. Goodwin

Women with breast cancer account for the largest group of female cancer survivors. It is estimated that there are currently 10.5 million cancer survivors in the United States; 40% of the female survivors are breast cancer survivors.[1] The growing number of breast cancer survivors reflects increasing incidence of the disease, diagnosis at earlier stages when outcome is better, and widespread adoption of effective adjuvant treatment.

Methodologic Issues in Survivorship Research

The Office of Cancer Survivorship of the National Cancer Institute (U.S.) defines a survivor as follows: "An individual is considered a cancer survivor from the time of cancer diagnosis, through the balance of his or her life. Family members, friends and caregivers are also impacted by the survivorship experience and are therefore included in this definition."[1] This is a very broad definition; most survivorship research in breast cancer focuses on the experience of individuals with cancer after they have completed their primary therapy, usually while they are free of recurrent disease. Some studies have focused on women who are 1, 3, 5, or more years postdiagnosis. In breast cancer, where long-term survival is becoming increasingly common, this variable definition may account for some of the inconsistencies in the literature. In this chapter, we have not adopted a single definition of survivorship but have tried to relate results to the definition used in each study.

Definition, recruitment, and identification of study populations are among the most challenging aspects of breast cancer survivorship research. Ideally, if the objective is to examine long-term outcomes, an inception cohort identified at a uniform time early in the course of the disease should be assembled (e.g., women with locoregional breast cancer in the immediate postoperative period, before adjuvant therapy). Prospective recruitment of a sample such as this is costly and time consuming. An alternative approach involves the use of administrative databases (including tumor registries) that retrospectively identify women diagnosed years earlier; however, careful attention must be paid to refusers and nonresponders, who may differ in important ways from responders. Investigators often conducted cross-sectional surveys of breast cancer patients attending follow-up clinics, or in a community. The populations thus assembled may not be representative of all breast cancer survivors, particularly when response rates are low, or well women have been discharged from follow-up clinics. Convenience samples, drawn from breast cancer advocacy groups or other sources, were recruited in some studies. This approach may lead to systematic overestimation or underestimation of the long-term impact of breast cancer and its treatment, because participation of women in these groups may be related to their survivorship experience.

Inclusion of a control population without cancer should be considered in breast cancer survivorship research. This condition allows the effects of aging and comorbid conditions to be differentiated from those of prior breast cancer and its treatment, important for many of the medical concerns of breast cancer survivors (e.g., menopause, osteoporosis, heart disease). Although inclusion of a noncancer control group is often desirable, it increases costs and complexity of research. Instead, investigators may opt to use measurement instruments for which population-based norms are available, comparing the results obtained in the breast cancer survivors with published results in age-matched controls.

Breast cancer survivorship studies often examine a broad variety of attributes: medical status, psychosocial issues, health-related quality of life (HRQOL), and sexuality, for

example. Some of these attributes are readily measurable (e.g., bone density after chemotherapy-induced early menopause) while others are not (e.g., the social impact of breast cancer diagnosis). It is important that measurement instruments be valid and reliable and that they measure key areas of interest. A wide variety of standardized, validated instruments are available to measure many of the important psychosocial issues and health-related quality of life (HRQOL) in breast cancer survivors. When valid instruments are not available for key attributes, such as body image postmastectomy, investigators may need to develop new instruments and validate these instruments during the course of the research. In selecting questionnaires, investigators should avoid overburdening respondents.

It is likely that not all salient issues in breast cancer survivors have been identified. Recent evidence that cognitive dysfunction may occur in women receiving adjuvant chemotherapy is a prime example. Investigators should be aware of new and ongoing research and be prepared to examine newly emerging concepts.

Statistical analysis should include the use of appropriate statistical tests, with adjustment for the effects of age because it could be an important confounder. The use of baseline information, which allows evaluation of change over time, can provide valuable insights into the breast cancer survivorship process. As noted previously, comparison of study data with population-based norms also provides insight into the impact of aging versus the impact of prior breast cancer diagnosis.

In the remainder of this chapter, we review the survivorship literature in breast cancer, first as it relates to medical status and then as it relates to psychosocial status and HRQOL. This separation is somewhat artificial; there is overlap between the sections. Because most studies are observational, grading of evidence regarding efficacy of interventions is usually not possible.

Medical Status

Arm Symptoms/Upper Body Function

Treatment for breast cancer can be associated with a number of localized physical sequelae including arm edema (AE), impaired shoulder mobility, pain, neurologic deficits, and reduced upper body function. The literature assessing arm symptoms and limitations is summarized in Table 11.1.

There are three approaches to arm measurement: (1) circumference at various points (with bony landmarks as references), (2) volumetric measurements using limb submersion in water, and (3) skin and soft tissue tonometry.[2] Tape-measured circumference (10 cm above and below the olecranon or the lateral epicondyle) has been the traditional method but can be imprecise. Volumetric measurements are more accurate but have limited availability. Tonometry is not used clinically.

The occurrence of, and risk factors for, AE have been reviewed by Erickson et al.[3] The reported incidence of AE has ranged from 0% after partial or total mastectomy with sentinel node biopsy to 56% after modified radical mastectomy (MRM) or breast-conserving surgery (BCS) with both axillary lymph node dissection (ALND) and axillary radiation therapy (XRT).[4,5] Werner et al.[6] reported that the median time to development of AE in patients treated with BCS, ALND (almost one-third had level 3 ALND), and breast XRT (with or without axillary XRT) was 14 months (range, 2–92 months); 97% of those who developed AE did so by 4 years.

The association between the extent of breast surgery and AE is less clear. Tasmuth et al. reported AE to be significantly more frequent in a prospective cohort study of 93 women treated with MRM versus BCS; however, women undergoing MRM had axillary XRT (also associated with AE) more commonly than those undergoing BCS.[7] Paci et al.[8] reported the odds ratio of chronic AE to be slightly, but not significantly, higher after MRM [odds ratio (OR), 1.62; 95% confidence interval (CI), 0.91–2.88] than after BCS (XRT was not examined). In a randomized trial comparing MRM to BCS with XRT to the breast and internal mammary and supraclavicular nodes, Gerber et al. reported the rate of AE did not differ between the two groups; however, axillary XRT (given if the dissection was inadequate or there was extracapsular extension) was not considered in the analysis.[5]

The risk of AE increases with the extent of axillary dissection. Yeoh et al.[9] reported frequency of AE to be 25% with no axillary surgery, 50% after axillary sampling, and 84% after ALND. The risk of AE was higher with an increasing number of axillary lymph nodes resected (more than 15 nodes[10]; more than 40 nodes[11]) in two studies. Schrenk et al. reported AE did not occur in a small cohort of patients undergoing sentinel lymph node dissection.[4] In a prospective randomized trial of sector resection and ALND with or without breast XRT, young age [relative risk (RR), 0.93 per year of increasing age; 95% CI, 0.91–0.97) and number of lymph nodes resected (RR, 1.11 per lymph node resected; 95% CI, 1.05–1.18) were significantly associated with any arm symptoms (not necessarily AE).[12]

Axillary XRT has been associated with AE. Senofsky et al., in a cohort of 264 patients treated with total ALND, found AE to occur in 6% of those not treated with XRT, 14.7% of those receiving XRT to the breast only, and 29.6% of those receiving XRT to the breast and regional nodes.[13] Furthermore, Keramopoulos et al. reported AE to be significantly more frequent when XRT was delayed (6 months postoperatively) than when it was given immediately postoperatively (4% versus 27%).[11]

The combination of XRT and ALND further increases the risk of AE. Kissin et al.[14] reported AE in 8.3% of women treated with breast surgery and axillary XRT, 9.1% undergoing axillary sampling and XRT, and 7.4% undergoing ALND only (7.4%). However, AE occurred in 38.3% of women undergoing both ALND and axillary XRT. In a randomized trial comparing ALND to axillary sampling, a significant increase in arm volume was experienced in 14 (12 of whom received axillary XRT) of 47 (29.8%) patients treated with ALND.[15] None of the 48 patients undergoing axillary sampling experienced AE (regardless of XRT).

The occurrence of other reduced upper body function, pain, neurologic deficits, and restricted shoulder mobility has also been evaluated. In a prospective cohort study, decline in upper body function was substantially higher during the first year after MRM or BCS with or without XRT than in the subsequent 4 years.[16] Cardiopulmonary comorbidity significantly increased the risk of decline in upper body function at 5 months (OR, 2.8; 95% CI, 1.3–5.7). Cardiopulmonary

TABLE 11.1. Arm symptoms in treatment for breast cancer.

Reference	*Primary objective(s)*	*Study population and follow-up (years)*	*Number of patients*	*Type of local treatment*	*Instruments*	*Response rate*	*Results and conclusions*
Kissin et al. 1986[14]	Compare the incidence of AE by subjective and objective methods; identify independent risk for late AE; compare the incidence of AE after different treatments	Cohort (clinic) diagnosed at least 1 year prior	200 patients	BCS or MRM with no axillary surgery, sampling or ALND	• Subjective: graded as no difference, moderate AE, or severe AE (patient + observer) • Objective: (1) arm circumference measured 15 cm above and 10 cm below the lateral epicondyle, (2) volume measured by water immersion		Objective AE more frequent (25.5%) than subjective AE (14%). Subjective AE was significantly more common after ALND with XRT (38.3%), axillary XRT alone (8.3%), axillary sampling with XRT (9.1%), and ALND alone (7.4%).
Yeoh et al. 1986[9]	Assess the complications following surgery and postoperative XRT	Cohort assessed median F/U of 1.7–3.24 years	187 patients	Surgical management of the axilla: none, sampling, or ALND with three different XRT dose fractionation	• Physical exam: (1) arm circumference measured 7.5 cm above the olecranon process, (2) shoulder movement and degree of restriction		Complication rates similar with three different XRT schedules. AE ± restriction of shoulder movements were different at 30 months with no surgery (25%), sampling (50%), and ALND (84%).
Borup Christensen et al. 1989[15]	Compare the sequelae of ALND vs. axillary sampling ± XRT	Prospective randomized trial with assessment at 14 days, 3, 6, and 12 months postoperative	100 patients	BCS or MRM ± XRT, randomization to ALND vs. axillary sampling	• Physical exam: (1) arm volume (measured by water displacement and corrected for changes in body weight), (2) shoulder mobility using 360 scale • Questionnaire re: arm swelling, shoulder mobility, and loss of sensibility.		AE (≥10% volume increase) in 14 pts (all with ALND), 12 received XRT. Impairment of shoulder mobility was more frequent after axillary XRT ($P = 0.07$).

Satariano et al. 1990[138]	Assess physical functioning	Case control (3 and 12 months post diagnosis) (Metropolitan Detroit Cancer Surveillance System)	571 cases (breast cancer) 647 controls (no breast cancer)	Not mentioned	• Structured interview with items from (1) Massachusetts Health Care Panel Study, (2) Framingham Disability Study, and (3) the National Institute on Aging EPESE	Cases: 81.1% 3 months, 95.1% 12 months Controls: 83.3% 3 months, 90.9% 12 months	At 3 months, cases age 55–74 had greater difficulty completing tasks requiring upper body strength. At 12 months, upper body strength remained diminished in cases aged 65–74, more so than cases aged 55–64.
Senofsky G.M. et al. 1991[13]	Assess the effects of TAL	Prospective cohort, median follow-up of 41 months	264 patients	BSC or MRM + TAL ± XRT	• Medical records review • Clinical examination: AE graded I–IV (method of measurement not stated).		AE in 9.4% of patients. Breast and nodal XRT significantly associated with AE. Breast edema associated with XRT.
Segerstrom et al. 1991[18]	Study the natural history of pain and functional impairment after surgery and XRT	Prospective cohort assessed at 1–23 months and 1 week–24 months after exam 1	100 patients	MRM + ALND + high-dose XRT (±XRT to axilla)	• Questionnaire • Physical exam: (1) arm edema (water displacement method), (2) ROM (inspection)	93 patients (93%)	AE observed in 43% of patients; AE disappeared in 8 patients at follow-up (all had slight to moderate edema). Stiffness and edema good predictors of subjective functional impairment.
Werner et al. 1991[6]	Assess predictors of AE	Cohort of patients receiving XRT, median F/U of 37 months	282 patients	BCS + ALND (30.5% had level I, II, and III dissected) + XRT	• Arm circumference measured 13 cm above and 10 cm below the olecranon on both arms		Transient AE in 7.4%, chronic arm edema in 12.1%. Persistent AE at 5 years in 16%. Body mass index strongly associated with AE.
Sneeuw et al. 1992[139]	Assess the cosmetic and functional outcomes of BCS and relationship to psychosocial functioning	Cohort, mean 4 years (2–11 years)	160 patients eligible	BCS + XRT; most patients had ALND	• In-home interview: GHQ, QOL • Physical exam	76 (47.5%) patients	High levels of psychologic distress, disturbance of body image, and decreased sexual functioning ~25%. Patient ratings of overall cosmesis and AE significantly associated with body image.
Gerber et al. 1992[5]	To compare pain, motion, and edema after MRM vs. BCS with ALND and XRT	Prospective randomized trial, annual evaluation	247 patients	MRM vs. BCS + XRT with ALND	• Physical exam: (1) functional ROM (goniometry), (2) chest wall tenderness, (3) arm circumference at ulnar styloid, olecranon, and 35 cm proximal to the ulnar styloid, (4) cosmetic outcome	165 patients (66.8%) had pre-op and post-op ROM, 131 (53%) patients had pre-op and 1 yr post-op arm circumference	Greater chest wall tenderness post-XRT. Slower recovery of pre-operative ROM post MRM. No difference in arm circumference.

(*continued*)

TABLE 11.1. Arm symptoms in treatment for breast cancer. (*continued*)

Reference	*Primary objective(s)*	*Study population and follow-up (years)*	*Number of patients*	*Type of local treatment*	*Instruments*	*Response rate*	*Results and conclusions*
Lin et al. 1993[19]	Assess impact of ALND	Retrospective review	283 patients	BCS or MRM + ALND	• Chart review • Physical examination 1 year: arm circumference, ROM, numbness, and pain.		Arm swelling (≥2 cm) in 16% of women, ≥15 degrees of restriction in 17%, numbness in the distribution of the intercostals brachial nerve in 78%, and numbness and pain in 22%.
Keramopoulos et al. 1993[11]	Assess arm morbidity following treatment	Clinic population over a 6-month window	104 patients	BCS or MRM with ALND	• Interview • Physical examination: arm circumference measured at 15 cm above and 10 cm below the lateral epicondyles in both hands.		Late AE (>3 months postsurgery) occurred in 17%; more frequent when XRT <6 months postoperative or >40 LN resected. Limb pain was more frequent >60 years old or after MRM.
Kiel et al. 1996[10]	Incidence of AE after BCS and XRT	Cohort q 6 mo for up to 3 years	402 women	BCS + XRT (±AND)	• Physical examination: arm circumference measured 15 cm above and 10 cm below the olecranon process.	183 included in the study	Axillary dissection (>15 LN) and age (>55 years) are predictors of AE.
Paci et al. 1996[8]	Assess long-term sequelae of breast cancer surgery	Cohort of 5-year survivors	346 survivors	BCS or MRM	• Interview • Physical exam: arm circumference measured at six points	238 women (68.8%)	30.2% had a chronic lymphedema and 18.9% a shoulder deficit. Chronic lymphedema greater after MRM vs. BCS. Early lymphedema more frequent after BCS.
Tasmuth et al. 1996[7]	Assess physical symptoms and anxiety/depression	Prospective cohort day—1, 1 month, 6 months, and 1 year after surgery	105 women	MRM vs. BCS with ALND ± XRT	• Interview • Neurologic examination • Grip strength • Arm circumference • STAI + 2 additional questions re depression	93 women (89%)	Incidence of chronic posttreatment pain higher after BCS vs. MRM. Phantom sensations in 25%. Psychologic morbidity highest before surgery and decreased with time.

Liljegren et al. 1997[12]	Assess arm morbidity after sector resection and ALND ± XRT	Prospective randomized trial 3, 12, 24, and 36 months after surgery	381 women	Sector resection and ALND ± XRT	• Arm circumference 10 cm above and below the elbow on both arms • Subjective arm symptoms (graded as none, moderate, or severe)	Arm circumference: 273 pts at 3–12 mo., 270 pts at 13–36 mo., <50 pts at >36 mo. Arm symptoms: 368 pts at 3–12 mo., 335 pts at 13–36 mo., 115 pts >36 mo.	Extent of surgical procedure and young age are determinants of arm morbidity. Arm symptoms are most common during the first year.
Silliman et al. 1999[17]	To identify risk factors for decline in upper body function	Cross-sectional observational study 3–5 months postoperative	300 women	BCS or MRM ± XRT	• Review of medical records • Telephone interview	213 women (71%)	Extent and type of primary therapy and cardiopulmonary comorbidity associated with a decline in upper body function.
Schrenk et al. 2000[4]	Assess postoperative morbidity of the operated arm	Prospective cohort 15–17 months F/U	35 women	BCS or MRM ± XRT with ALND or SN dissection	• Physical exam: arm circumference (15 cm above and 10 cm below the lateral epicondyle), numbness, mobility, strength, stiffness • Interview	35 patients (100%)	SN associated with negligible morbidity compared with ALND.
Lash et al. 2000[16]	Assess the effect of patient characteristics and therapy on self-reported upper-body function and discomfort	Prospective cohort 5 and 21 months postoperative	388 invited, 303 interviewed	MRM or BCS ± XRT	• Review of medical records • Computer-assisted telephone interviews		Cardiopulmonary comorbidity associated with decline at 5-month interview (OR 2.8, 95% CI 1.3–5.7). ALND associated with axillary numbness, pain.
Lash et al. 2002[140]	Characterize the incidence and predictors of upper body function decline and recovery	Cohort for 5 years	303 women	BCS ± XRT or MRM	• Review of medical records • Telephone interviews • SF-36	82 met case definition for upper-body function decline. 32 met the definition for recovery.	The incidence of decline in the first year was substantially higher than in the subsequent 4 years. Women with less than a high school education had an increased risk of decline (HR 2.3). Recovery was higher for women followed by breast cancer specialist.

BCS, breast-conserving surgery; XRT, radiation therapy; HR, hazard ratio; OR, odds ratio; ALND, axillary lymph node dissection; SN, sentinel node dissection; AE, arm edema; F/U, follow-up; TAL, total axillary lymphadenectomy; EPESE, Established Populations for the Epidemiological Study of the Elderly; GHQ, General Health Questionnaire; STAI, State Trait Anxiety Inventory; SF-36, Medical Outcomes Study Short Form—36 Items.

morbidity was an independent predictor of upper body function decline ($P = 0.006$) in a second study[17]; mastectomy and XRT were also associated with significant declines in upper body function. Women treated with an ALND were more likely to report numbness or pain in the axilla (OR, 6.4; 95% CI, 0.2–33).[16]

In a prospective cohort study, Segerstrom et al.[18] reported 35 of 93 (37.6%) patients had restricted shoulder range of motion during the first 2 years after surgery; this increased to 49.5% up to 2 years later. Paci et al.[8] reported that 18.9% of patients experienced shoulder deficit as assessed by physical examination performed 5 or more years after diagnosis. Lin et al.[19] reported 15° or greater loss of ROM in 17% of the patients and 30° or more loss in 4% at 1 or more years after ALND. In contrast, Gerber et al.[5] found no significant loss in functional ROM (assessed using goniometry) 1 year postoperatively; however, patients undergoing MRM reached their preoperative ROM more slowly than those undergoing BCS.[5] Pain and chest wall tenderness have been reported following breast surgery.[5,7,11] Pain was more frequent after BCS in one study[7] and after mastectomy in another.[11]

Arm symptoms have been associated with psychologic, social, sexual, and functional morbidity.[20] In two case-control studies, women experiencing AE after treatment for breast cancer showed greater psychologic morbidity and greater impact of illness measured using the Psychosocial Adjustment to Illness Scale (PAIS), effects that remained stable over a 6-month period, even if AE was being treated.[21,22] Maunsell et al. also reported the proportion of women experiencing psychological distress as measured by the Psychiatric Symptom Index (PSI) increased significantly with an increased number of problems in the affected arm.[23]

In summary, significant physical and functional sequelae in the arm and upper body may occur as a result of local therapy, especially ALND and axillary XRT. Prospective, population-based studies that include an assessment of patient demographics, risk factors, stage, and treatment coupled with outcome evaluation that involves standardized, blinded assessment of arm symptoms and function preoperatively and during long-term follow-up would expand available information; intervention research to identify effective management approaches is urgently needed.

Menopause

Women with breast cancer may experience early menopause as a result of their treatment. They report a higher frequency of menopausal symptoms than women in the general population.[24] The high frequency of menopausal symptoms in breast cancer survivors is caused by several factors[25]: (1) age at diagnosis (frequently over 50 years), (2) abrupt discontinuation of hormone replacement therapy (HRT) at the time of breast cancer diagnosis, (3) induction of premature menopause by therapy (i.e., chemotherapy and ovarian ablation), and (4) induction of estrogen deficiency symptoms by therapy (e.g., tamoxifen and aromatase inhibitors) (Table 11.2). Chemotherapy is frequently associated with either temporary or permanent amenorrhea. The incidence of amenorrhea is related to the type of chemotherapy regimen, the cumulative dose (particularly cyclophosphamide), and the age of the patient.[26,27] Surgically induced menopause and premature menopause have been associated with more severe symptoms than natural menopause.[28,29] The health consequences of menopause can be divided into four categories: vasomotor symptoms, genitourinary signs and symptoms, skeletal effects, and cardiovascular effects.[30] In a survey of 190 breast cancer survivors, the most common symptoms experienced were hot flashes (65%), night sweats (44%), vaginal dryness (44%), difficulty sleeping (44%), depression (44%), and dyspareunia (26%).[31] Hot flashes (HF) are more frequent, severe, distressing, and of greater duration in breast cancer survivors compared with controls without breast cancer.[32]

Before 2002, HRT was frequently prescribed to healthy women for the control of menopausal symptoms and primary prevention of disease (i.e., cardiovascular disease and osteoporosis). In 2002, the Women's Health Initiative (WHI), a large randomized trial of HRT versus placebo in healthy women, was stopped early because overall health risks of combined estrogen plus progesterone exceeded benefits at an average 5.2-year follow-up.[33] Risks of coronary heart disease, stroke, pulmonary embolism, and invasive breast cancer were increased, whereas risks of colon cancer and hip fracture were minimally decreased. Results for estrogen alone versus placebo did not show an increased risk for breast cancer.[33a]

The use of HRT in breast cancer survivors has been controversial.[34,35] Four case series,[36–39] three case-control studies,[40–43] and one cohort study[44] failed to identify an increased risk in women who chose to take HRT; two additional studies reported a lower risk of recurrence and death when HRT was used.[42,43] The studies are susceptible to selection bias, particularly in view of the reluctance of many breast cancer survivors to accept HRT.[45,46] One randomized clinical trial of HRT in 434 breast cancer survivors was recently stopped for safety reasons because of an unacceptably high risk of breast cancer events [hazard ratio (HR), 3.5; 95% CI, 1.5–8.1] in women receiving HRT.[47] Women on HRT were advised to discontinue the treatment. Current guidelines[34,48] that recommend postmenopausal breast cancer survivors be encouraged to consider alternatives to HRT but state that minimal HRT use may be considered in a well-informed patient with severe symptoms will likely be modified in view of these results, with a greater focus on recommending nonhormonal approaches to symptom management.

Vasomotor symptoms are the most common complaint of perimenopausal and postmenopausal women. More than 60% of postmenopausal women experience hot flashes, and one-third of those find them nearly intolerable.[49] HRT relieves HF in 80% to 90% of women who initiate treatment.[50–52]

Progestational agents (e.g., megestrol acetate, medroxyprogesterone acetate, and depo-Provera) decrease HF by 85%.[53–57] Herbal remedies, including soy products and black cohosh, have been reported to minimally decrease HF or have no effect. Vitamin E (800 IU/day) minimally decreases HF (i.e., one fewer HF/day). Clonidine is modestly active in reducing hot flashes. Selective serotonin reuptake inhibitors (SSRIs) such as venlafaxine and paroxetine have also been shown to significantly reduce HF. Possible interactions between SSRIs and selective estrogen receptor modulators (SERMS) are being evaluated. Gabapentin (widely used in neurologic disorders) has been recently reported to reduce HF scores.[58] Most of these trials have evaluated the short-term effect (e.g., 4–12 weeks); long-term effects have not been addressed.

Severe symptoms of urogenital atrophy occur in nearly half of postmenopausal women surviving breast cancer.

Lubricants and moisturizers have been shown to be helpful but do not completely relieve symptoms. Very low dose vaginal estrogen creams can reverse atrophy but systemic absorption of estrogen may occur. Newer methods of estrogen delivery include a ring device (Estring; Pfizer, New York, NY). This device provides almost complete relief of symptoms and minimal systemic absorption[48]; however, recent evidence that lipid levels may be altered[59] raises concerns about its use.

One randomized trial[60] evaluated the use of a comprehensive menopause assessment program in breast cancer survivors; the intervention (which did not involve use of estrogen but permitted megestrol acetate and nonhormonal agents such as clonidine) reduced menopausal symptoms and improved sexual functioning when compared with a control arm.

Bone loss occurs at a rate of 1% to 5% per year and is greatest during the first 5 years after natural menopause.[61] Chemotherapy-induced ovarian failure causes more rapid and significant bone loss.[62] Tamoxifen in premenopausal, but not postmenopausal, women and aromatase inhibitors have also been associated with increased bone loss. Bone density should be monitored in survivors.[63] Preventive measures such as proper intake of vitamin D and calcium, regular exercise, and counseling about the relationship between cigarette smoking, alcohol, and bone loss should be initiated in all patients. Pharmacologic approaches currently recommended for survivors include (1) bisphosphonates (alendronate, risedronate), (2) SERMs (raloxifene), and (3) calcitonin.

The risk of coronary heart disease increases with increasing age.[64,65] HRT in the primary and secondary prevention of coronary heart disease has not been shown to reduce cardiac events in four large randomized clinical trials.[33,66,67] Management of known risk factors and encouragement of lifestyle modification are warranted.[68]

Pregnancy

Limited data exist on the effect of pregnancy on breast cancer outcome. Based on the experience at major institutions[68–71] and population-based registries,[68,72,73] women who become pregnant after a diagnosis of breast cancer appear to have similar breast cancer outcomes to those who do not. Selection biases may be responsible for these results. Prior chemotherapy does not appear to have teratogenic effects in future pregnancies[74,75]; however, local breast cancer treatment (i.e., surgery and XRT) may affect the ability to lactate after BCS.[68,76,77] Breast cancer and pregnancy have been recently reviewed.[78,79]

Fatigue

Fatigue is often experienced during, and shortly after, cancer treatment. The level of fatigue in a large survey of breast cancer survivors (1–5 years after initial diagnosis) was comparable with that of age-matched controls using the RAND-36 questionnaire.[80,81] However, severe and persistent fatigue was experienced in a subgroup of survivors and was related to depression and pain. In a second smaller cohort study, fatigue (measured using a number of fatigue questionnaires including the RAND-36) was more common in breast cancer survivors than in age-matched controls.[81,82]

Second Malignancies

Second malignancies (e.g., angiosarcoma, sarcoma, and skin cancer) at the site of previous local treatment for breast cancer occur in less than 1% of survivors (see Chapter 17).[68]

Cardiac Toxicity

The most common form of anthracycline-induced cardiotoxicity is chronic cardiomyopathy.[83] The risk of cardiomyopathy is principally dependent on the cumulative anthracycline dose and may occur years after therapy.[84] Prospective monitoring of signs and symptoms of congestive heart failure (CHF) revealed a 9% risk of CHF after 450 mg/m^2 doxorubicin and 25% after 500 mg/m^2 [85]; this risk may be higher when doxorubicin is used in combination with paclitaxel.[86] Prospective cardiac monitoring using MUGA scans has been included in more recent clinical trials of breast cancer treatment including anthracyclines, taxanes, and herceptin. Based on a recent randomized trial,[87] cardiotoxicity is particularly pronounced when herceptin is combined with either adriamycin or epirubicin plus cyclophosphamide (any cardiotoxicity = 27%, grade 3–4 cardiotoxicity = 10%). Bradycardia has been reported with the use of paclitaxel alone.

Surveillance

Evidence-based surveillance strategies for breast cancer survivors have been established.[63] There are sufficient data to recommend monthly breast self-examination, annual mammography of the preserved and contralateral breast, as well as a careful history and physical examination every 3 to 6 months for 3 years, then every 6 to 12 months for 2 years, then annually. Data are not sufficient to recommend routine radiologic investigations or blood work (including tumor markers). Primary care of breast cancer survivors has also been reviewed.[68] Grunfeld et al.[88] conducted a large randomized trial of specialist versus general practitioner care in Great Britain; patients were more satisfied with care provided by the latter, with no differences in medical outcomes being observed, although only a small number of medical events were reported.

Psychosocial Status and HRQOL

Breast cancer is a stressful event that can perturb psychologic equilibrium and reduce HRQOL in the short-term[89–92]; recent survivorship research has evaluated long-term sequelae. Early studies involved mainly small convenience samples (maximum, 61 survivors), descriptive designs, and interview-based measurements.[93–97] Key results of these studies include observations that the majority of survivors are fairly to very satisfied with their lives 8 years after diagnosis despite thoughts of recurrence reported by 50%[93]; that survivors have a positive perception of life and attach less importance to trivial stressors even though fear of recurrence is a major concern[94]; and that the majority of survivors thrive despite experiencing problems related to breast cancer and its treatment.[95] Several ongoing issues were identified in a focus group of 10-year survivors: integration of disease into current life, change in relationship with others, restructuring life perspective, and unresolved issues.[96]

TABLE 11.2. Menopause in breast cancer survivors.

Reference	*Primary objective(s)*	*Study population and follow-up (years)*	*Number of patients*	*Instruments*	*Response rate*	*Results and conclusions*
Guidozzi et al. 1999[141]	Determine whether ERT adversely affects outcome of survivors	Prospective descriptive study of women 8–91 months postdiagnosis treated with oral continuous opposed ERT observed for 24–44 months	24	• History and physical exam 3×/year • Mammogram yearly. • BSE taught to the patient. • Appointment with surgeon annually.		No recurrences.
Brewster et al. 1999[142]	Evaluate the outcome of patients who elected ERT	Convenience sample treated with oral continuous ERT for at least 3 months starting 41 months (range 0–401 months) postdiagnosis; median F/U 30 months	145	• Routine surveillance by an oncologist	145/168	13 recurrences (9%).
Vassilopoulou-Sellin et al. 1999[44]	Determine whether ERT alters the development of new or recurrent breast cancer	Prospective randomized study of ERT, cohort of nonparticipants	319	• Monitor clinical outcome for new or recurrent cancer	319/331	ERT does not seem to increase events. Events during follow-up: 20/280 in controls vs. 1/39 in ERT group.
Ganz et al. 1999[45]	Assess willingness to undergo HRT in survivors	Sample of survivors from a previous survey an average of 3.1 years postdiagnosis	39	• Interview • Standardized health-related instruments including the RAND Health Survey • Decision analysis interview.		Older survivors are reluctant to take estrogen. Increased willingness to consider therapy if multiple symptoms coexisted and the risk of recurrence was small.
Ganz et al. 2000[60]	Assess the efficacy of a comprehensive menopausal assessment (CMA) intervention program in achieving relief of symptoms, improvement in QOL, and sexual functioning in survivors	Randomized controlled design of postmenopausal breast cancer survivors (8 months to 5 years after diagnosis)	72	• Menopausal symptom scale score adapted from the Breast Cancer Prevention Trial Symptom Checklist • Vitality Scale from the RAND Health Survey 1.0 • Sexual Summary Scale from the Cancer Rehabilitation Evaluation System.	72/197	A clinical assessment and intervention program for menopausal symptom management is feasible and acceptable to patients, leading to reduction in symptoms and improvement in sexual functioning.
Peters et al. 2001[143]	Define the prevalence of ERT usage, identify risks	Cohort of survivors (ER+ in 74%), median disease-free 46.7 months (range, 0–448 months), followed for ≥60 months, treated with ERT	56	• Review of medical records Routine surveillance by an oncologist including history and physical examinations every 3–6 months, annual mammograms and CXR, and evaluation of liver chemistries at each visit.	56/607 interviewed	Use of ERT was not associated with increased events.

O'Meara et al. 2001[43]	Evaluate the impact of HRT on recurrence and mortality	Record-based study of women 35–74 years identified in the SEER records (1977–1994) (1 user matched to 4 nonusers) (48% of users/59% of nonusers ER+)	2,755	Data obtained from: • The Cancer Surveillance System • Group Health Cooperative pharmacy • Medical records		Lower risks of recurrence and mortality observed with HRT.
Harris et al. 2002[24]	Assess the burden of menopausal symptoms, HRT use, and alternative treatments in recent survivors	Population-based, case-control study of survivors (8–11 months postdiagnosis) and age-matched controls	183	• Standardized telephone questionnaire • F/U 10-minute telephone questionnaire on HRT and menopause	93% cases, 95% controls	Cases more likely to experience menopausal symptoms, less likely to use HRT, more likely to use alternative therapies (soy, vitamin E, and herbal remedies).
Durna et al. 2002[144]	Compare the QOL of survivors who received HRT and those who did not	Nonrandomized qualitative study of women from a cancer registry. QOL was compared for 3 groups based on the time since diagnosis: <4 years, 4–8 years and >8 years	123	Questionnaires including: • Demographic data • QOL Breast Cancer version Questionnaire • QOL Self Evaluation Questionnaire	123/190 (64.8%)	No significant difference between users and nonusers. Near-normal QOL after a 4-year adjustment period.
Carpenter et al. 2002[32]	Compare the HF symptom experience and related outcomes between survivors and healthy women	Descriptive, cross-sectional, comparative study of survivors (mean of 39 months postdiagnosis) and age-matched healthy female volunteers	69 survivors/ 63 age-matched	Questionnaires: • Demographic and disease/ treatment information • Gynecologic and reproductive history form • Hot flash questionnaire and diary • POMS-SF • PANAS • HFRDIS	69/207 survivors	Hot flashes are a significant problem for survivors. Survivors with severe hot flashes reported significantly greater mood disturbance, higher negative affect, more interference with daily activities (sleep, concentration, and sexuality), and decreased QOL.
Biglia et al. 2003[46]	Determine the prevalence of menopausal symptoms, explore attitudes toward HRT or other treatments and the willingness to take estrogen	Convenience sample (early breast cancer) Mean F/U not stated	250	• 35-item questionnaire formulated for this study	Not stated	Survivors are interested in treatments that may improve their QOL, but fear of HRT persists among survivors and their doctors.
Holmberg 2004[47]	To examine impact of HRT on events in survivors	RCT of HRT vs. no therapy in survivors	434	• Clinical examination, mammography	345 had ≥1 follow-up	RCT stopped early because of excess events in survivors treated with HRT (relative hazard 3.5, 95% CI 1.5–8.1).

HRT, hormone replacement therapy; ERT, estrogen replacement therapy; RCT, randomized clinical trial; F/U, follow-up; POMS-SF, Profile of Mood States-Short Form; PANAS, Positive and Negative Affect Scale; HFRDIS, Hot Flash-Related Daily Interference Scale; BSE, breast self-examination; QOL, quality of life.

Second-generation studies used stronger designs, more standardized measurement approaches, and larger sample sizes. They were more often population based and/or used control groups of women without breast cancer. They frequently used generic instruments (applicable to healthy and medically ill individuals) for which normative data are available. One generic instrument that has been widely used in survivorship research is the Medical Outcomes Study Short Form—36 (MOS SF-36), a reliable and valid measure of HRQOL. It has 36 items rated on a 5-point Likert scale. There are eight subscales grouped in two composite scales: Physical Component Summary (PCS) and Mental Component Summary (MCS). Cancer-specific instruments, which measure attributes that are specific or unique to cancer patients, were also used in a large number of studies. Due to their nature, normative data for the general population are not available for these instruments. Nonetheless, they provide data that can be used to describe groups of survivors, evaluate change in their status over time, or compare different groups of survivors. Specific examples of these instruments are discussed.

Psychologic Status and Overall HRQOL

Many studies have examined psychosocial status and HRQOL in breast cancer survivors as a single group. Results of these studies are reviewed first, followed by a discussion of the status of defined subgroups of survivors.

Several cross-sectional, case-control, and cohort studies using the MOS SF-36 have reported scores on the Mental Component Summary scale or one of its subscales in breast cancer survivors 2 to 8 years postdiagnosis to be comparable with, or better than, scores obtained from either the general population or individuals with other chronic illnesses[80,98–102] (Table 11.3). Dorval et al.[103] used the Psychiatric Symptom Index (PSI), another generic instrument that measures the presence and intensity of four psychologic dimensions (depression, anxiety, cognitive impairment, and irritability) in a case-control study; no difference was found between 8-year survivors and controls randomly matched for age and residence. Studies using the generic measure of mood, the Profile of Mood States (POMS), reported women with breast cancer who were 2 years postdiagnosis to have scores comparable to published norms[80] or to a control group.[104] Taken together, these observations using generic instruments provide little evidence of impaired long-term HRQOL or psychologic status in breast cancer survivors compared to the general population.

A cancer-specific instrument, the QOL Cancer Survivors Tool (QOL-CS), yielded psychologic subscale scores that were worse than those for the social, spiritual well-being, and physical subscales 5.7 years postdiagnosis.[105] The inclusion of specific questions related to fear of recurrence of the cancer, which are not explicitly evaluated in generic questionnaires, and the specific population studied (members of the National Coalition for Cancer Survivorship) may have contributed to this result. Mosconi et al.[102] used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30), a multidimensional cancer-specific questionnaire, to study Italian breast and colon cancer survivors. Overall HRQOL was reported to be good, and scores for emotional functioning did not differ between the two groups of survivors.

Physical Functioning

Earlier, we discussed specific physical symptoms in breast cancer survivors. The MOS SF-36 has been employed to measure general physical functioning. Physical functioning scores in survivors have been reported to be similar to,[102] or better than, published norms for individuals with other chronic illnesses[80,106] or the general population.[106] However, some studies[98,99,101] reported physical functioning scores in survivors that were lower than norms for the general population. A modest decline in physical functioning over time (mean, 6.3 years) has been reported by Ganz et al.[99]; the magnitude of the decline was small and was thought to be related to aging. Dow et al.[105] studied members of the National Coalition for Cancer Survivorship, a group that may not be representative of all cancer survivors. Overall physical well-being scores were good compared with other domains (e.g. psychologic); however, problems with components of physical well-being (i.e., pain, energy) were identified.

Thus, evaluation of general physical functioning in breast cancer survivors has yielded inconsistent results in comparison with published norms for the general population. However, differences from general population norms are small and may be due to effects of age.

Sexual Functioning

Breast cancer diagnosis and treatment can adversely affect sexuality. Surgical treatment of the primary tumor can affect body image, while systemic therapy can cause premature menopause or vaginal dryness. Measurement of the impact of breast cancer and its treatment on sexual functioning is challenging because few instruments specifically address this aspect of HRQOL. These measurement challenges may be compounded by a reporting bias if survivors are reluctant to respond to questions about sexual functioning. The use of specific questionnaires (e.g., the Sexual Activity Questionnaire, SAQ) in recent studies permits a more detailed assessment than is possible using more general multidimensional questionnaires.

Matthews et al.[98] administered the Satisfaction with Life Domains Scale for Cancer (SLDS-C) to breast cancer survivors (American Cancer Society Reach to Recovery volunteers) a mean of 8.6 years postdiagnosis. Scores for sexual functioning were worse than for other aspects of functioning. Dow et al.[105] also reported that satisfaction with sex life was the worst of all domains on the Functional Assessment of Cancer Therapy—General (FACT-G) in 294 survivors taking part in a peer-support group 5.7 years postdiagnosis. In contrast, Kurtz et al.[107] reported 5- to 10-year breast cancer survivors had high levels of sexual satisfaction on the Long Term Quality of Life Instrument.

Ganz et al.[99,106] used questionnaires that specifically address sexual functioning in two recent studies. In a cross-sectional study of 864 women,[106] use of the Watts Sexual Functioning Questionnaire identified modest increases in sexual dysfunction with aging but use of the Cancer

TABLE 11.3. Psychosocial status and health-related quality of life (HRQOL) overall associations in breast cancer survivors.

Reference	*Primary objective(s)*	*Study population and follow-up (years)*	*Number of subjects*	*Instrument(s)*	*Response rate*	*Results and conclusions*
Vinokur et al. 1989[120]	To assess the effect of age, time since diagnosis and disease severity	Case-control (population-based screening program) 53% > 5 years	178 survivors 176 controls	• HSC • PM • SE • ICO • PQOL • PREF • SC • Others	91%	Comparable QOL (physical, mental, health, and emotional well-being) in survivors and controls. Severity and recency of diagnosis were independent predictors of adverse effects on mental and physical well-being in survivors. Younger survivors with recent diagnosis have psychosocial concerns. Older with recent diagnosis have physical concerns.
Ellman et al. 1995[145]	To measure anxiety and depression	Case-control (screening clinic registry) 13 years	331 survivors 584 controls	• HADS	76% (survivors) 75% (controls)	Significantly more cases of depression and anxiety in controls. Time since diagnosis did not affect depression or anxiety except for the first anniversary.
Kurtz et al. 1995[107]	To explore six aspects of QOL	Hospital based tumor registry >5 years	191	• LTQL • CARES	55%	Best scores on psychologic domain and sexual satisfaction. Good psychologic state highly correlated with low somatic concerns and sexual satisfaction. Middle-aged: more positive philosophical/spiritual outlook.
Ganz et al. 1996[80]	To describe psychosocial concerns and QOL among survivors	Participants in rehabilitation RCT 2–3 years	139 (12 had recurrence)	• FLIC • CARES • SF-36 • POMS	77%	FLIC-POMS: no difference at 2–3 years versus 1 year. CARES: decline in global QOL, sexual and marital functioning at 3 vs. 1 year. Sexual functioning difficulties persisted from diagnosis to 3 years. Arms symptoms persist. Maximum recovery in QOL 1 year after treatment.
Dow et al. 1996[105]	To describe QOL in survivors including positive and negative outcomes	Convenience sample (mailed questionnaire to national coalition for cancer survivorship-peer support) 5.7 years	294 BCS (56 had recurrence)	• QOL-CS • FACT-G	56%	Fatigue, aches, sleep problems, fear of recurrence, family distress, sex life problems persisted over time. Physical QOL better than emotional/social QOL.
Saleeba et al. 1996[146]	To compare emotional status of survivors to screening population	Case-control (MDACC, screening clinic) >5 years	Survivors = 52 Control = 88	• BDI • STAI	Not stated	Mean depression score higher in survivors (within normal range). Survivors seek more frequent counseling (29% vs. 16%).
Weitzner et al. 1997[147]	To compare mood and QOL of survivors to screening population	Case-control, clinic samples >5 years	Survivors = 60 Controls = 93	• BDI • STAI • FPQLI	Not stated	No difference between cases and controls. Worse mood score correlated with lower QOL in survivors.
Lee 1997[148]	To examine social support, type of surgery, geographic location, and QOL	Convenience sample (Reach for Recovery volunteers) 14.1 years	100	• FPQLI	88%	QOL not associated with number of support persons, mental status, time from surgery, or type of surgery.
Ganz et al. 1998[106]	To describe survivorship in relation to age, menopausal status, treatment	Cross-sectional (random selection from two large metropolitan areas; tumor registry, clinics, hospitals) 3.1 years	864	• SF-36 • CES-D • DAS • CARES • WSFQ • Others	39%	Survivors had more frequent physical symptoms. Worse sexual functioning in survivors with chemo, menopause. and age <50, but no difference in sexual satisfaction and marital/partner adjustment. Unpartnered women have concerns about dating. Body image worse with MT.

(*continued*)

TABLE 11.3. Psychosocial status and health-related quality of life (HRQOL) overall associations in breast cancer survivors. (*continued*)

Reference	*Primary objective(s)*	*Study population and follow-up (years)*	*Number of subjects*	*Instrument(s)*	*Response rate*	*Results and conclusions*
Ganz et al. 1998[100]	To describe QOL related to adjuvant treatment	Cross-sectional (mailed survey, tumor registry, clinics, hospitals) 2.7–3.1 years	1,098	• SF36 • CES-D • CARES • LLS • Others	35%	No difference in mental-psychologic (SF-36, CES-D) and global QOL according to treatment. Physical and sexual: worse functioning in adjuvant therapy. Small adverse impact of adjuvant treatment on physical functioning but no impact on overall QOL.
Dorval et al. 1998[103]	To compare QOL in 8-year survivors	Survivors cohort assembled from seven hospitals, random digit dialing age-matched control, random digit dialing age-matched control 8.8 years	124 survivors (26 had new events) 427 controls	• PSI • LWMAT • MOS SSS • Others	96% (survivors) 61% (controls)	No difference in QOL. Arm problems and sexual satisfaction worse in survivors.
Dorval et al. 1999[108]	To examine marital breakdown	Survivors cohort assembled from seven hospitals 3 months–8 years	366	• SLES • LWMA • Others	89%–95%	Marital breakdown similar in survivors and controls. Marital satisfaction: predictor of marital breakdown in both groups.
Joly et al. 2000[135]	To evaluate long-term QOL in relation to chemo	Inception cohort (from a RCT on chemo) 9.6 years	119	• EORTC QLQ-C30 • Others	68%	No difference in functioning scales, body image, sex life, breast symptoms, social or professional life; trend for poorer cognitive functioning in CMF.
Montazeri et al. 2001[149]	To assess QOL at two time points	Members of the three support groups 1–5 years (54%)	56	• HADS	100%	29% and 14% scored above "case" cutpoint for anxiety and depression at baseline; significant improvement at 1 year.
Holzner et al. 2001[136]	To evaluate the effect of time on QOL	Convenience sample (outpatient)	87	• EORTC QLQ-C30 • FACT-B	Not stated	Worse emotional, cognitive, sexual functioning, global QOL >5 years vs. 2–5 years posttreatment. Better global QOL, social, emotional functioning >5 years vs. 1–2 years post Rx. Highest QOL in the period between 2–5 year post Rx.
Matthews et al. 2002[98]	To compare health status, life satisfaction, and QOL	Convenience sample (peer support-volunteers) 8.6 years	586	• SF-36 • SLDS-C	63%	Survivors reported higher emotional well-being, social functioning, and vitality but lower physical functioning compared to population-based norms. Worse sexual satisfaction, body image, physical strength for survivors. Younger women had better physical functioning but lower emotional well-being and vitality.
Tomich et al. 2002[101]	To compare QOL and psychologic well-being in BCS and controls	Survivors from RCT of peer and education groups; neighborhood controls >5.5 years	BCS = 164 Control = 164	• WAS • SWBS • FACI • SF-36 • PANAS	61%	Overall HRQOL similar in survivors and controls; no-intervention survivors had worse physical functioning. Poor QOL associated with beliefs of lasting harmful effect of treatment, low level of personal control, lack of sense of purpose in life.

Kessler et al. 2002[137]	To assess HRQOL	Convenience sample (ACS Reach for Recovery program) Mean 3.5 years (<0.1 to >10 years)	148 (23 had metastasis)	• PANAS • QOLM (Selby and Boyd) • Others	71%	QOL improved with increasing time from diagnosis and less extensive disease. More positive and less negative affect associated with better QOL.
Mosconi et al. 2002[102]	To assess long-term HRQOL of survivors	Survivors in a RCT of F/U testing (colon cancer survivors also studied) 8.3 years	433	• SF-36 • EORTC QLQ-C30	52%	Long-term survivors have HRQOL comparable to age/sex-matched norms. HRQOL lower with comorbidities or chemo. Physical functioning lower in breast vs. colon survivors.
Cimprich et al. 2002[121]	To assess age, duration of survival, and QOL	Tumor registry of Midwestern comprehensive cancer center 11.5 years	105	• QOL-CS	54%	Lower QOL on physical domain in older survivors. Lower QOL on social domain in younger survivors. Best QOL (overall and physical) in middle-aged survivors.
Ganz et al. 2002[99]	To evaluate long-term survivorship	5- to 10-year F/U of earlier cohort (population-based tumor registries, clinics, and hospitals) 6.3 years.	817 (*54 had recurrence and were excluded)	• SF-36 • LLS • CES-D$ • PANAS • RDAS • SAQ • CARES • MOS-SSS • Others	61%	Excellent physical and emotional well-being (minimal declines reflected expected age-related changes). No change in sexual interest but sexual activities declined. Stable energy level and social functioning. Some symptoms improved; others worsened. Survivors not receiving chemo had better overall QOL, physical functioning, less sexual discomfort.
Ganz et al. 2003[122]	To evaluate QOL and reproductive health in younger survivors	Cohort (two hospitals tumor registries) 5.9 years	577	• SF-36 • LLS • CES-D • PANAS • SAQ • Others	56%	High level of physical functioning. Youngest: Decrement in vitality, lowest score in social and emotional functioning, more depressive symptomatology, lower positive affect, and more negative affect. Amenorrhea frequent in women age ≥40 and associated with poorer health perception.
Ganz et al. 2003[123]	To examine HRQOL in older survivors	Cohort (identified through pathology reports, tumor registries) 3–5, 6–8, and 15–17 months	691	• PF10 • MHI-5 • CARES-SF-36 • MOS-SSS • Others	43%	Physical and mental health score decreased significantly at 15 months (SF-36). Improvement at 15 months in CARES.

Response rate: as stated in the paper or if not, the percentage of eligible patients who completed the study.

*, Valid and reliable instruments.

QOL, quality of life; BC, breast cancer; F/U, follow-up; Rx, treatment; ACS, American Cancer Society; HSC, Hopkins Symptom Checklist*; PM, positive morale, based from Bradburn's positive affect scale; SE, self-esteem: based on Rosenberg's scale of self esteem; ICO, internal control orientation, based on Rotter's scale; PQOL, perceived QOL, based on scale developed by Andrews and Withey; PREF, perceived role and emotional functioning; SC, social contacts, from Berkman's Social Network Index; HADS, Hospital Anxiety and Depression Scale*; LTQL, long-term quality of life*; CARES, Cancer Rehabilitation Evaluation System*; FLIC, Functional Living Index–Cancer*; SF-36, RAND or MOS Short-Form-36*; POMS, Profile of Mood States*; QOL-CS, Quality of Life–Cancer Survivors*; FACT, Functional Assessment of Cancer Therapy*; BDI, Beck Depression Inventory*; STAI, State-Trait Anxiety Inventory*; FPQLI, Ferrans and Powers Quality of Life Index*; CES-D, Center of Epidemiologic Studies–Depression Scale*; DAS, Dyadic Adjustment Scale*; WSFQ, Watts Sexual Function Questionnaire*; PSI, Psychiatric Symptom Index*; LWMAT, Locke–Wallace Marital Adjustment Test*; MOS SSS, MOS Social Support Survey*; SLES, Stressful Life Event Scale*; EORTC-QLQ C-30, European Organization for Research and Treatment of Cancer–Quality of Life Questionnaire C-30*; SLDS-C, Satisfaction with Life Domains Scales for Cancer; WAS, Words Assumption Scale; SWBS, Spiritual Well-Being Scale of FACI (Functional Assessment of Chronic Illness therapy); PANAS, Positive and Negative Affect Schedule*; QOLM, WOL Measurement, Selby and Boyd*; RDAS, Revised Dyadic Adjustment Scale*; SAQ, Sexual Activity Questionnaire*; LLS, Ladder of Life scale*; PF-10, 10-item functioning scale from SF-36; MHI-5, Mental Health Inventory, from the SF-36.

Rehabilitation Evaluation System (CARES) identified no impairment in sexual satisfaction. Sexual functioning was significantly worse in those who received chemotherapy (but not tamoxifen), particularly in women who were menopausal (either naturally or secondary to treatment) and in women under 50 years of age. Using the SAQ in their cohort study of 763 long-term breast cancer survivors, this group also reported sexual discomfort to be greatest in women who received chemotherapy but identified no differences in sexual pleasure or sexual habits.[99] In summary, sexual functioning appears to be adversely impacted in breast cancer survivors, particularly in younger women who receive adjuvant chemotherapy.

Social Functioning and Marital Status

Studies evaluating social functioning in breast cancer survivors have usually shown little evidence of impairment. The social functioning subscale of the MOS SF-36 has yielded similar scores in breast cancer survivors and in the general population in the majority of studies.[80,98–102] Use of the EORTC QLQ-C30 has also demonstrated high level of social functioning in breast cancer survivors.[102] Use of the MOS Social Support Measure also showed no difference between breast cancer patients with a control population[99,103] and no change according to time elapsed since diagnosis.[99]

In a cohort of 763 survivors, there was no significant change in marital status over 5 years of follow-up.[99] In another cohort followed for 8 years, no difference in divorce or separation rates at 12 months, 18 months, and 8 years after diagnosis was identified in survivors compared to age-/residence-matched women.[108] In survivors, low marital satisfaction at 3 months predicted future marital difficulties (16.7% divorced at 1 year versus 2.1% in those with high marital satisfaction; $P = 0.02$). Women not in a partnered relationship expressed concerns about dating, telling about cancer, and fear of initiating sexual relationship.[80,106]

Finally, in their follow-up of 817 long-term breast cancer survivors, Ganz et al. reported more than two-thirds had stable household income and 20% had increased income (versus 12% who had decreased income) since diagnosis.[99] Eighty percent reported no change in employment status; a minority moved from full- to part-time work or retired. Marital status did not change. In a separate study, this group reported that 90% of survivors had health insurance 2 or 3 years postdiagnosis, although some had their premiums increased or had switched to a spouse's plan.[80] Most (65%) were working or doing volunteer work.

Thus, there is little evidence that social or marital functioning or employment is adversely affected in survivors. Specific concerns about dating have been reported, especially in young, unpartnered women.

Cognitive Functioning

In 1995, Wieneke and Dienst[109] published the first report of cognitive dysfunction in women with breast cancer (Table 11.4). To date, four reports have evaluated cognitive functioning during and within the first 2 years postchemotherapy using a battery of neuropsychologic tests[109–111] or the High Sensitivity Cognitive Screen,[104] a valid reliable instrument that predicts overall qualitative results of formal neuropsychologic testing. All four studies identified significantly lower cognitive functioning in women receiving adjuvant chemotherapy (with or without anthracyclines) compared with those not receiving chemotherapy or to a control group without breast cancer. Cognitive dysfunction was more prevalent in women who received high-dose chemotherapy in one study.[111] Interestingly, there appears to be little correlation between cognitive functioning as assessed by the test battery and self-reported by the patient.[110,111]

Studies evaluating cognitive dysfunction beyond 2 years have yielded conflicting results. Schagen et al.[112] reported improvement in performance in all chemotherapy groups between 2 and 4 years posttreatment. Ahles et al.[113] reported patients who had been diagnosed at least 5 years earlier had greater cognitive impairment on a battery of neuropsychologic tests and were more likely to report memory problems on the Squire Memory Self-Rating Questionnaire if they had received adjuvant chemotherapy.

Cognitive dysfunction in women receiving adjuvant chemotherapy is an emerging area of interest in survivorship research. Future research should identify risk factors for this complication and evaluate potential interventions to minimize its impact.

Spirituality

Spirituality is often poorly addressed in multidimensional questionnaires. Based on the holistic Ferrell[114] model of QOL in breast cancer survivors (physical, psychologic, social, spiritual), Wyatt et al. developed the Long-Term Quality of Life (LTQL) instrument, which includes a philosophical/spiritual view dimension.[115] Kurtz et al.,[107] using this instrument in long-term (more than 5 years) survivors, reported a positive spiritual outlook to be associated with good health habits and an increased likelihood of being supportive of others. In their cohort of long-term survivors (6.3 years), Ganz et al.[99] reported a positive impact of breast cancer on religious beliefs and activities, an effect that tended to be more pronounced in young survivors. Dow et al.[105] used the QOL-CS to evaluate spiritual well-being in members of the National Coalition for Cancer Survivorship. Although fears about future cancer and uncertainty about the future were identified as important concerns, beneficial spiritual outcomes including hopefulness and having a purpose in life as well as positive and spiritual change were also reported. Further research is needed to confirm these early observations, using population-based controls as a comparison group.

Diet and Complementary and Alternative Medicine

Maunsell et al.[116] evaluated diet during the first year after breast cancer diagnosis in a group of 250 women who were surveyed with a standardized interview about diet changes. Forty-one percent of women reported a change in their diet; these changes were positive (i.e., healthy) in over 90%. Women under 50 years and those who were more distressed

TABLE 11.4. QOL and cognitive dysfunction in breast cancer survivors.

Reference	*Primary objective(s)*	*Study population and follow-up (years)*	*Number of subjects*	*Instruments*	*Response rate*	*Results and conclusions*
Wieneke et al. 1995[109]	To evaluate cognitive functioning after adjuvant chemo	Convenience sample (clinic) 6.6 months post chemo	28	• Neuropsychologic tests	84%	Cognitive deficit related to tests norms (adjusted for age, education, gender) in 5 of 7 domains assessed. 75% had moderate impairment on at least 1 test. Level of impairment unrelated to depression, type of chemo, time since treatment; positively related to the length of chemo.
van Dam et al. 1998[111]	To assess the prevalence of cognitive deficit after adjuvant chemo	RCT of high-dose vs. standard dose chemo Control group were BCS who did not received chemo 2 years	34 high dose 36 standard dose 34 no chemo	• Neuropsychologic tests • Semistructured interview for self-reported cognitive functioning • EORTC QLQ-C30 • HSCL-25	84%–85% (chemo treated) 68% (controls)	Lower global QOL and higher score on depression subscale with high dose. Cognitive impairment: 32% high dose, 17% standard dose, 9% no chemo ($P = 0.043$).
Schagen et al. 1999[110]	To assess neuropsychologic functioning following CMF vs. no chemo	Consecutive series 2 years	39 chemo 34 control	• Neuropsychologic test • Semistructured interview • EORTC QLQ-C30 • HSCL-25	78% (chemo) 68% (control)	Higher IQ at baseline in CMF group. Neuropsychologic tests: 28% of patients in chemo cognitively impaired vs. 12% in control. Self-reported problems: in chemo group, more problems with concentration and memory. No relation between reported complaints and neuropsychologic testing. Chemo: lower QOL (physical, cognitive), greater depression.
Brezden et al. 2000[104]	To assess cognitive function in chemo vs. control patients	Convenience sample (two academic hospitals) 2.1 years for the group post chemo	Chemo: 31 Postchemo: 40 Controls: 36	• HSCS • POMS	Not stated	More patients with cognitive impairment during or after chemo vs. controls. No difference in mood status in the three groups.
Schagen et al. 2002[112]	To assess long-term neuropsychologic sequelae following chemo	Follow-up of earlier cohort[120,121] 4 years	103	• Neuropsychologic tests • EORTC QLQ-C30 • HSCL	84%–96%	Improvement in performance in all chemo group (FEC, high-dose, CMF) and a slight deterioration in controls. Cognitive dysfunction following adjuvant chemo may be transient.
Ahles et al. 2002[113]	To compare neuropsychologic functioning of long-term survivors	Tumor registry 9.7 years for BC	BC = 70 Lymphoma = 58	• Neuropsychologic tests • SMSRQ • CES-D • STAI • FSI	75%	Neuropsychologic test and SMSRQ: chemo group score lower than local therapy group (adjusted for age and education). No other differences.

Response rate: as stated in the paper or if not, the percentage of eligible patients who completed the study.

*, Valid and reliable instruments.

CMF, cyclophosphamide, methotrexate, 5-fluouracil; Chemo, chemotherapy; RCT, randomized controlled trial; FEC, 5-fluouracil, epirubicin, cyclophosphamide; BC, breast cancer; neuropsychologic tests, a battery of tests were used; Cf., see reference for more details; EORTC-QLQC-30, European Organization for Research and Treatment of Cancer–Quality of Life Questionnaire C-30*; HSCL, Hopkins Symptom Checklist-25; HSCS, High Sensitivity Cognitive Screen*; POMS, Profile of Mood States*; SMSRQ, Squire Memory Self-Rating Questionnaire; CES-D, Center for Epidemiological Study-Depression*; STAI, State-Trait Anxiety Inventory*; FSI, Fatigue Symptom Inventory*.

at diagnosis were most likely to change their diets (P = 0.0001).

Burstein et al.[117] evaluated complementary and alternative medicine (CAM) use during the first 12 months after breast cancer diagnosis. Twenty-eight percent of 480 women began an alternative therapy after diagnosis; these women tended to be younger and more educated. Ganz et al.[99] reported vitamins and herbal preparations were used by 86.6% and 49.3% of breast cancer survivors, respectively. More than half (60.7%) altered diet or used dietary supplements. Few women were using psychosocial or counseling therapies (13%) or attending a cancer support group (5.5%). More than one-third reported enhanced physical activity postdiagnosis. Lee et al.[118] conducted telephone interviews in 379 women (black, Chinese, Latino, white) 3 to 6 years after breast cancer diagnosis. At least one alternative therapy was used by 48.3%. Most common approaches therapies were dietary change (26.6%), herbal/homeopathic medication (13.5%), psychologic or spiritual healing (30.1%), and physical approaches such as yoga or acupuncture (14.2%). Therapies were used for brief periods, usually for 3 to 6 months. Women who used alternative therapies were younger and more educated.

Thus, more than one-third of breast cancer survivors use at least one kind of alternative therapy. Nonpharmacologic supplements appear to be most commonly used. Further research is needed to evaluate duration of use and changes over time in use of CAMS, comparing survivors to healthy controls.

Psychosocial Status and HRQOL in Defined Subgroups

Consideration of breast cancer survivors as a group may mask important differences in subgroups and over time. In this section we summarize research examining subgroups defined by age, ethnicity, and treatment (surgery, adjuvant therapy) and according to time elapsed since diagnosis.

Age at Diagnosis

Age at diagnosis appears to be an important determinant of the survivorship experience. This may be due, in part, to treatment: women who receive chemotherapy, many of whom are younger, experience greater long-term physical and sexual sequelae (see following discussion); psychosocial effects of mastectomy may also differ with age, especially in the short term.[119] However, Ganz et al.[106] reported poorer sexual functioning in younger survivors who became menopausal, regardless of whether they received chemotherapy. Vinokur et al.[120] compared survivors (50% of whom were followed more than 5 years) to controls participating in a breast cancer screening program; younger survivors had more problems in psychosocial adjustment while older survivors had more physical difficulties. Cimprich et al.[121] reported similar findings in 105 survivors using the QOL-CS. Women over 65 at diagnosis had worse scores in the physical domain while those diagnosed before 44 years of age had poorer scores in the social domain. Women diagnosed between 45 and 65 years of age had the best overall HRQOL. Two pivotal studies examining survivorship issues in younger[122] and older women[123] have been reported recently. In the first of these, a cohort of 577 patients diagnosed at age 50 or younger was assembled for the Cancer and Menopause Study a mean of 5.9 years postdiagnosis.[122] Most had received adjuvant chemotherapy. Physical functioning was good. The youngest women reported poor mental health, less vitality, and poorer social and emotional functioning (MOS SF36). In the second study, 691 women aged 65 years of age or more at diagnosis were evaluated 3, 6, and 15 months after surgery.[123] Physical and mental functioning (MOS SF-36) showed significant declines during the year of follow-up. Declines in the former were associated with greater comorbidity and receipt of adjuvant chemotherapy. In contrast, the CARES Psychosocial Summary and Medical Interaction Scales showed significant improvement over time. Social support was lowest in women over 75 years. The discrepant results obtained with the MOS SF-36 Mental Health Inventory and the CARES Psychosocial Summary Scale were explored: the former appeared to be influenced to a greater extent by declines in physical functioning and the latter appeared to reflect adaptation and adjustment to cancer-specific concerns. In summary, younger age is associated with lower mental and emotional well-being. Older women experience more physical problems, partly the result of aging.

Ethnicity

The impact of ethnicity on survivorship has been poorly studied. Ashing-Giwa et al.[124] investigated HRQOL in white and African-American survivors. Response rate among African-Americans was significantly lower than among whites (44% versus 65%). The former were more often single, had a lower income, and lower HRQOL. Multivariate analyses revealed that 45% of the variance in HRQOL was accounted for by general health perception, life stress, partnership status, and income; ethnicity was not a significant contributor. The authors concluded that African-American and white breast cancer survivors report favorable overall QOL; differences are secondary to life burden and socioeconomic factors but not to ethnicity per se.

Primary Surgical Procedure

The primary surgical procedure performed also appears to impact survivorship (Table 11.5). Maunsell et al.[119] reported that psychologic distress (measured using the PSI) at 3 months was worse in women undergoing BCS; this difference was not present at 18 months. Age modified this effect; the greater psychologic distress at 3 months was not present in women under 40 years. Follow-up 8 years after diagnosis found that psychologic distress declined over time and was similar to that in the general population.[125] Ganz et al.,[126] using a battery of general questionnaires, reported few differences in HRQOL with respect to type of surgery; however, women undergoing mastectomy had more problems with clothing and body image than those undergoing BCS. Mosconi et al.[102] found none of the EORTC QLQ C-30 domains to be affected by the type of surgery. Janni et al.[127] studied 76 pairs of patients who had undergone either a mastectomy or BCS a mean of 3.8 years earlier; women undergoing mastectomy were significantly less satisfied with their cosmetic result and change in appearance and were twice as likely to be stressed by their physical appearance secondary to the surgery. No

TABLE 11.5. Survivorship and surgery in breast cancer survivors.

Reference	*Primary objective(s)*	*Study population and follow-up (in years)*	*Number of subjects*	*Instruments*	*Response rate*	*Results and conclusions*
Schain et al. 1983[130]	To compare QOL after MRM vs. BCS	RCT of MRM vs. BCS 11.3 months	38	• Others	97%	No difference in psychosocial outcomes, except greater concerns about seeing oneself naked in MRM. 69% of BCS vs. 28% of MT had limited arm motion.
Meyer et al. 1989[131]	To compare long-term psychosocial and sexual adaptation after MRM vs. BCS	Convenience sample (one center) 5 years	58	• Interview	68%	No differences in psychiatric state, marital adjustment, fear of recurrence. BCS preserves female identity and acceptance of body image.
Maunsell et al. 1989[119]	To describe psychologic distress after MRM vs. BCS	Cohort (consecutive cases from seven hospitals) 3 and 18 months	227 at 3 months and 205 at 18 months	• PSI • LES (modified) • DSI • Others	97%	At 3 months, greater psychologic distress (PSI) in BCS vs. MRM but no difference at 18 months. Age modified the relation: BCS was protective for women <40 years of age.
Ganz et al. 1992[126]	To evaluate QOL and psychologic adjustment after MRM vs. BCS	RCT testing (two rehabilitation programs) 1 year	109	• FLIC • CARES • Karnofsky (PS) • POMS • GAIS	44%	No difference in mood disturbance, QOL, performance status, global adjustment. MRM associated with more difficulties with clothing and body image.
Mock 1993[150]	To compare body image with MRM, MRM + delayed R, MRM + immediate R, BCS	Clinical sample from four hospitals 14 months	257	• BIS • TSCS • BIVAS	57%	Body image was more positive after BCS (when measured by BIVAS but not by BIS). No difference in self-concept.
Omne-Pontén et al. 1994[128]	To assess psychosocial adjustment after MRM vs. BCS	Consecutive clinic patients 6 years	66	• Interview • Others	80% (of the first study)	No impact of the surgery on psychosocial adjustment.
Dorval et al. 1998[125]	To assess psychosocial adjustment after MRM vs. BCS	Cohort (seven hospitals) 3 months, 18 months, 8 years	235 at 3 months 211 at 18 months 124 at 8 years	• PSI • MOS-SSS • LES • LWMAT	97% 3 months 97% 18 months 96% 8 years	At 8 years no difference in QOL. BCS protected women against distress if they were <50 years of age at diagnosis (short and long term).
Curran et al. 1998[129]	To describe QOL after MRM vs. BCS	Sample from EORTC trial 10801 2 years	278	• Newly constructed questionnaire	14%–64% (between different countries)	BCS gives a better body image with no increase in fear of recurrence. Cosmetic results: patient rating superior to the surgeon.
Rowland et al. 2000[133]	To evaluate women's adaptation to different types of surgery	Two cohorts (from two large metropolitan areas) 2.7 and 3.2 years	1,957	• SF-36 • MOS SSS • CES-D • RDAS • WSFQ • CARES	54%	Fewer problems with body image and sexual attractiveness after BCS vs. MRM ± R. MT + R: report more negative impacts on sex life. MRM ± R vs. BCS: more physical symptom and discomfort at the surgical site. No difference in emotional, social, role function (CES-D, SF-36).
Janni et al. 2001[127]	To compare impact of BCS vs. MRM	Convenience sample (one hospital) 3.8 years	152 pairmatched patients	• EORTC QLQ C-30 • Other	Not stated	No difference for QOL between the two groups. MRM women had less satisfaction with cosmetic results, appearance, and were more emotionally distressed by these issues.
Nissen et al. 2001[134]	To compare QOL after BCS, MRM, MRM ± R	RCT of effect of advanced practice nursing 2 years	198	• MUIS • POMS • FACT-B	94%	BCS vs. MRM: no difference in well-being. More mood disturbance and poorer well-being in MRM + R vs. MRM alone.

Response rate: reported by the author or calculated as the percentage of eligible patients who completed the study.

*, Valid and reliable instruments.

MRM, modified radical mastectomy; BCS, breast-conserving surgery; R, reconstruction; PSI, Psychiatric Symptom Index*; LES, Life Events Schedule*; DSI, Diagnostic Interview Schedule*; FLIC, Functional Living Index–Cancer*; CARES, Cancer Rehabilitation Evaluation System*; POMS, Profile of Mood States*; GAIS, Global Adjustment to Illness Scale*; SBAS, Social Behaviour Assessment Schedule*; BIS, Body Image Scale*; TSCS, Tennessee Self-Concept Scale*; BIVAS, Body Image Visual Analogue Scale; MOS-SSS, MOS Social Support Survey*; LES, Life Experience Survey*; LWMAT, Locke–Wallace Marital Adjustment Test* ; SF-36, RAND or MOS Short-Form-36*; CES-D, Center of Epidemiologic Studies–Depression Scale*; RDAS, Revised Dyadic Adjustment Scale*; WSFQ, Watts Sexual Function Questionnaire*; EORTC-QLQ C-30, European Organization for Research and Treatment of Cancer–Quality of Life Questionnaire C-30*; MUIS, Mishel Uncertainty in Illness Scale*; FACT, Functional Assessment of Cancer Therapy*.

differences were seen in EORTC QLQ-C30 scores. Psychosocial adjustment measured using the Social Adjustment Scale was similar in the mastectomy and BCS treatment groups; however, women undergoing mastectomy felt mutilated and less attractive.[128] A companion study to EORTC trial 10801 comparing mastectomy to BCS and radiotherapy surveyed 278 patients 2 years after treatment.[129] Body image and satisfaction with treatment were better in the BCS. There was no difference in fear of recurrence. Patients considered their cosmetic results to be more acceptable than the surgeon did at several time points. Other studies have reported beneficial effects of BCS on body image.[130,131] In summary, BCS leads to enhanced body image and, in younger women (less than 40), it may protect against psychologic distress. No differences in depression were identified in one study of spouses of women undergoing mastectomy or BCS.[132]

Breast Reconstruction

Breast reconstruction is offered to reduce the adverse impact of mastectomy. Rowland et al.[133] studied a cohort of 1,957 long-term (1 to 5 years) survivors in Los Angeles and Washington. Women undergoing mastectomy had more physical symptoms related to the surgery regardless of whether they had reconstruction. No differences in overall HRQOL or worry about cancer returning were identified in women undergoing BCS, mastectomy alone, or mastectomy with reconstruction. Body image and feelings of sexual attractiveness were significantly better after BCS compared with mastectomy with or without reconstruction. Women who had reconstruction were younger and better educated than those in the other two groups. They also expressed greater concern that their cancer had a negative impact on their sex life. Nissen et al.[134] reported that women who had a mastectomy with reconstruction had greater mood disturbance and poorer well-being 18 months after surgery compared with those who did not undergo reconstruction.

Adjuvant Therapy

There is growing evidence that adjuvant therapy adversely affects survivors' HRQOL. In a cross-sectional survey, Ganz et al.[100] reported global HRQOL (measured using the Ladder of Life and the MOS SF-36) to be similar 1 to 5 years postdiagnosis in women who received chemotherapy and/or tamoxifen compared with those who received no adjuvant therapy. However, physical and sexual functioning were worse in women receiving adjuvant therapy. A mean of 6.3 years postdiagnosis, the no-adjuvant treatment group reported more favorable scores for global HRQOL (Ladder of Life) and most domains of the MOS SF-36 than those who received adjuvant therapy.[99] There were no differences in emotional functioning (MOS SF-36, Center for Epidemiology Study—Depression). The sexual discomfort scale (SAQ) and sexual functioning (CARES) were significantly worse in women who received adjuvant chemotherapy compared to those who received either tamoxifen or no therapy. Mosconi et al.[102] reported slightly better HRQOL (EORTC QLQ-C30) in women treated with tamoxifen versus those who received either chemotherapy or no adjuvant therapy. In contrast, participants of an adjuvant trial of chemotherapy versus no treatment who were 9.6 years postdiagnosis reported no differences in sexual functioning/enjoyment according to treatment arm.[135] Small sample size (119 patients) and the long interval after diagnosis may account for these results. In summary, the majority of studies have identified long-term adverse effects of adjuvant therapy, notably chemotherapy.

Time Elapsed Since Diagnosis

The status of survivors also varies according to time elapsed since diagnosis. Ganz et al.[99] re-evaluated a cross-sectional sample of survivors who had been recruited 1 to 5 years postdiagnosis when they were a mean of 6.3 (minimum, 5) years postdiagnosis. Small decreases in physical functioning, role functioning-physical, bodily pain, and general health (MOS SF-36) over time were thought to be related to aging. Sexual activity with a partner declined significantly and specific symptoms persisted, especially in women receiving chemotherapy. In an earlier cohort study, Ganz et al.[80] compared HRQOL measured using the POMS and Functional Living Index for Cancer at 2 and 3 years after surgery to that between 1 month and 1 year after surgery. Most scores improved between 1 month and 1 year,[126] but there was no subsequent improvement. This might reflect ongoing rehabilitation problems, as most CARES scores worsened between 1 and 3 years postdiagnosis. Holzner et al.[136] evaluated 87 breast cancer survivors using two cancer-specific questionnaires. Women who were more than 5 years postdiagnosis had significantly worse global QOL, role functioning, sexual functioning, and enjoyment than those 1 to 2 or 2 to 5 years postdiagnosis. However, women more than 5 years postdiagnosis were slightly older than those 1 to 2 and 2 to 5 years postdiagnosis (55.1 years old versus 52.9 and 52.5 years old, respectively). Women 2 to 5 years postdiagnosis had less impairment in emotional and social functioning than those diagnosed earlier or later. In contrast, Kessler et al.,[137] studying a convenience sample of 148 breast cancer survivors 0.3 to 19 years postdiagnosis, reported that overall QOL and life satisfaction were high and that greater time since diagnosis and lesser extent of disease were associated with improved global QOL. Thus, HRQOL and most aspects of physical and psychosocial functioning improve during the first few years after breast cancer diagnosis. However, specific treatment-related problems and symptoms persist long term, and there is some evidence of HRQOL decline 2 to 5 years after diagnosis, possibly related to aging.

Conclusions

Long-term survivors have a high level of functioning and good HRQOL, often comparable to that of the general population. However, many survivors experience physical symptoms (notably arm symptoms and early menopause) and reduced sexual functioning related to their diagnosis and treatment. Young women, those receiving chemotherapy, and those with comorbidity may be at greatest risk. Younger women experience greater psychologic distress. Cognitive dysfunction has recently been identified in women receiving adjuvant chemotherapy. BCS leads to enhanced body image; however, reconstruction does not add a major benefit in terms of QOL. Quality of survivorship in different ethnic groups has been inadequately investigated.

A considerable body of observational research has been conducted in breast cancer survivors. Although there are knowledge gaps that should be addressed in further observational research, there is also a need for research to develop and evaluate interventions that will reduce the adverse impact of breast cancer diagnosis and treatment which has been identified in research to date. Primary areas for intervention research include psychologic distress and sexual dysfunction in younger women; cognitive dysfunction, sexual dysfunction, and fatigue in women receiving chemotherapy; and body image in women undergoing mastectomy with or without reconstruction.

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