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Quality of Life in Long-Term, Disease-Free Survivors of Breast Cancer: a Follow-up Study FREE

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Abstract

Background: Women with breast cancer are the largest group of female survivors of cancer. There is limited information about the long-term quality of life (QOL) in disease-free breast cancer survivors. *Methods:* Letters of invitation were mailed to 1336 breast cancer survivors who had participated in an earlier survey and now were between 5 and 10 years after their initial diagnosis. The 914 respondents interested in participating were then sent a survey booklet that assessed a broad range of QOL and survivorship concerns. All P values were two-sided. *Results:* A total of 817 women completed the follow-up survey (61% response rate), and the 763 disease-free survivors in that group, who had been diagnosed an average of 6.3 years earlier, are the focus of this article. Physical well-being and emotional well-being were excellent; the minimal changes between the baseline and follow-up assessments reflected expected age-related changes. Energy level and social functioning were unchanged. Hot flashes, night sweats, vaginal discharge, and breast sensitivity were less frequent. Symptoms of vaginal dryness and urinary incontinence were increased. Sexual activity with a partner declined statistically significantly between the two assessments (from 65% to 55%, P = .001). Survivors with no past systemic adjuvant therapy had a better QOL than those who had received systemic adjuvant therapy (chemotherapy, tamoxifen, or both together) (physical functioning, P = .003; physical role function, P = .02; bodily pain, P = .01; social functioning, P = .02; and general health, P = .03). In a multivariate analysis, past chemotherapy was a

statistically significant predictor of a poorer current QOL (*P* = .003). *Conclusions:* Long-term, disease-free breast cancer survivors reported high levels of functioning and QOL many years after primary treatment. However, past systemic adjuvant treatment was associated with poorer functioning on several dimensions of QOL. This information may be useful to patients and physicians who are engaging in discussion of the risks and benefits of systemic adjuvant therapy.

Topic: emotion , follow-up , personal satisfaction , survivors , tamoxifen , diagnosis , quality of life , breast cancer , adjuvant therapy , physical function

Issue Section: Article

Women with a history of breast cancer are the largest group of female cancer survivors and account for about 41% of the total (*1*). Earlier stage at diagnosis and the use of systemic adjuvant therapy have improved the likelihood of long-term, disease-free survivorship (*2,3*). A number of studies (*4–9*) have examined recovery after breast cancer during the first year after diagnosis and shortly beyond. Few studies have examined the quality-of-life (QOL) outcomes in women who remain disease free for an extended period of time (*10*). As part of a larger program of research, we performed a longitudinal, follow-up assessment of QOL outcomes in breast cancer survivors who were initially evaluated between 1 and 5 years after diagnosis and who were free of disease at the time of initial assessment (*11–15*). Reports from the initial assessment focused on health-related QOL and sexual functioning (*11,13,16,17*), the impact of surgery and systemic adjuvant therapy on QOL outcomes (*12,14*), and the correlates of fatigue in breast cancer survivors (*15*).

This article describes our attempt to resurvey those members of the initial cohort who were more than 5 years after their initial diagnosis. The follow-up survey included many measures used in the initial study to facilitate examination of change over time. New measures were added to capture potentially important concerns of survivors in the areas of spirituality and personal growth (*10*), and these will be reported in a separate publication.

In this article, we will 1) describe the feasibility of follow-up of long-term breast cancer survivors; 2) examine changes over time in QOL, symptoms, marital functioning, and social support, focusing on women who remained disease free; 3) examine the late effects of different types of systemic adjuvant therapy on QOL outcomes; 4) examine other aspects of health and well-being; and 5) examine the predictors of QOL. The findings from this observational cohort study, while primarily descriptive and hypothesis generating, have implications for treatment decision making and future research on the late QOL effects of breast cancer treatment (*18*)

Subjects and Methods

Study Design and Subject Recruitment

We conducted a longitudinal, follow-up assessment of women who were previously recruited for an earlier study of breast cancer survivors in Los Angeles, CA, and Washington, DC (two waves of recruitment over the period September 1994 through June 1997). The initial study eligibility criteria required that women had had a diagnosis of stage I or II breast cancer between 1 and 5 years earlier, that they be disease free, and that they be on no current cancer therapy other than tamoxifen. Details of the original study design and recruitment procedures are published elsewhere (11,12). The initial consent form signed by all of the subjects included a statement of willingness to be contacted about future studies, thus allowing us to approach them for the follow-up. The institutional review boards at the University of California, Los Angeles, and at Georgetown University School of Medicine, Washington, DC, approved this study. Some women from the initial cross-sectional assessment (n = 433) had been selected for a randomized psychosocial intervention trial and had received a follow-up questionnaire as part of the intervention study. This follow-up facilitated ongoing contact with a small sample of the total cohort. Furthermore, all of the participants were mailed a summary of findings from the research after analyses from the original study; these mailings occurred in September 1997 and February 1998. As a result of these mailings, we learned that some of the study participants had moved without a forwarding address, had died, or were no longer interested in participating. These women were not recontacted. Data for this study were collected during calendar year 1998, with eligibility for this study being a breast cancer diagnosis date in 1993 or earlier. Therefore, we excluded all subjects from the original cohorts whose fifth anniversary of diagnosis occurred in 1999 or later.

Instruments

Health-related QOL was assessed with two generic measures, the RAND SF-36 (also known as the MOS SF-36) (19,20) and the Ladder of Life Scale (21). The SF-36 contains eight individual scales that are part of the three general areas of health-related QOL (19,20). The scales are Physical Functioning, Role Function—Physical, Bodily Pain, Social Functioning, Mental Health, Role Function—Emotional, Vitality, and General Health (19). Each scale is scored from 0 to 100, with 100 being the most favorable score. General population norms are available for the SF-36 (22). The General Health Scale of the SF-36 is often used as a global rating of health status, with some evidence that it more frequently tracks with specific health problems, physical functioning, and health behaviors and less strongly tracks with aspects of mental health (23,24). The SF-36 can also be scored as two summary scales—one for

physical health and a second for mental health (24). The data for these summary scales are presented as T–scores, with a normal healthy population mean score set at 50 and a score of 60 or 40 representing 1 standard deviation (SD) above or below the mean, respectively. These scales are called the SF–36 Physical (PCS) and Mental (MCS) Component Summary scales.

The participants' overall QOL was measured with a single-item measure, the "Ladder of Life" (21). On this measure, respondents provide a subjective rating of their own QOL at the present time. Ratings are made on a 10-point scale ranging from "Best Possible Life" to "Worst Possible Life." This scale is widely used in epidemiologic and population studies and provides a global rating of life satisfaction (25). In previous studies with cancer patients, global rating scales of this type have been statistically significantly associated with both the physical and psychosocial dimensions of QOL, thus making them good summary measures of QOL (26).

Social support was measured by a short form of the MOS Social Support Measure (27). The full measure contains 19 items and is scored from 0 to 100, with higher scores indicating better social support. In consultation with the instrument's author (Sherbourne CD: personal communication), we shortened the instrument to a 12-item scale, which was scored similarly to the longer version.

Depression and affect were measured with two instruments. The Center for Epidemiological Studies—Depression Scale (CES-D) (28) is a 20-item self-report scale developed for the general population to measure depressive symptoms during the past week. Normative data are available from community-based samples (29,30). The instrument has excellent reliability and validity, including use with multiethnic samples (28). Responses to the CES-D are rated on a 4-point scale, and the instrument total score ranges from a minimum score of 0 to a maximum score of 60. Higher scores on the CES-D indicate a greater risk of depression, with scores greater than or equal to 16 indicating the possibility of an increased risk of clinical depression (28). The CES-D has been used in recent studies of healthy women participating in large clinical trials (31,32). In addition, we used the Positive and Negative Affect Schedule (PANAS) (33). The PANAS is an adjective checklist on which individuals use a 5-point Likert-type scale to rate the degree to which they have experienced 20 mood states over a 4-week interval. Published data support the reliability and validity of the PANAS (33), and this instrument is preferable to other measures of mood states both because it is brief and easy to administer and because it yields both Positive Affect and Negative Affect Subscale scores.

The Revised Dyadic Adjustment Scale (RDAS) (34) was used to measure the quality of the woman's partnered relationship. This 14-item self-report scale is a shortened version of the Dyadic Adjustment Scale (35). Scores range from 0 to 69, with a mean value of 48.0 (SD = 9.0). The Sexual Activity Questionnaire (SAQ) (36) was used to measure sexual functioning. The SAQ is a reliable and valid scale that was developed

for the British tamoxifen prevention trial for use with healthy women at risk for breast cancer (37). The SAQ has three scales: pleasure, discomfort, and habit (frequency of activities). Higher scores indicate poorer sexual functioning. We also used the Cancer Rehabilitation Evaluation System (CARES) Subscales for body image and sexual interest (26,38) that were used in our earlier studies with these survivors (11,12,17). For these two subscales, higher scores indicate more frequent or severe problems.

In addition to these standardized measures, we obtained follow-up information on symptoms by using an abbreviated list of symptoms from the Breast Cancer Prevention Trial (BCPT) symptom checklist (31). We also collected information on use of various alternative therapies. We developed a new scale for this study to examine the perceived impact of breast cancer on 16 areas of various life plans and activities that were considered to be relevant to long-term survivors (such as education, diet, work, financial situation, exercise, and spirituality). Response categories for this set of questions were "negative," "positive," or "no impact." In this second survey, we also updated relevant medical and demographic information (e.g., recurrence of breast cancer, change in marital status, work, and income).

Procedures

We mailed letters of invitation during each month of 1998 to survivors who had reached their fifth or higher anniversary since diagnosis during that month. We included a response form and a postage-paid return envelope with the mailing. We mailed a second letter of invitation to those who did not respond within 2 weeks. Respondents indicating an interest in participating were mailed the study questionnaire with a postage-paid return envelope and consent form. Subjects who did not return a questionnaire within 2 weeks of its being mailed received a reminder telephone call. We reviewed all of the questionnaires for completeness and contacted participants to obtain missing data. All of the participants returning the questionnaires received a thank-you letter.

Statistical Considerations

Student's *t* and chi-square tests were used to explore potential differences between participants and nonparticipants in the follow-up study. Among participants, we distinguished among those who remained free of disease during the study and those who did not. We analyzed an array of QOL outcomes in the disease-free participants, with the use of chi-square tests to assess whether the distribution of a categorical measure of cancer impact varied across groups defined by age at diagnosis and with the use of analysis of covariance (ANACOVA) controlling for age at diagnosis on continuously scaled outcomes. In addition to the unweighted analyses of respondents, we studied the impact of the propensity of subjects to participate by

carrying out weighted analyses, where first we modeled the probability of participating, using as predictors the baseline background characteristics (*see* Table 1) and then attaching additional weight to respondents to represent disease-free nonrespondents within five weighted cells defined by propensity score *(39)*. Weighted analyses were done with Stata procedures (e.g., "reg" for regressions and ANACOVAs, "svytab" for cross-tabulations, and "svymean" for Student's *t* tests) by use of the "pweight" option to account for these propensity weights. Weighted analyses were performed for all data presented in Fig. 2, Tables 2–4, and selected other analyses.

McNemar's tests were used to compare categorical measures between baseline and follow-up. For continuous outcomes measured at both baseline and follow-up, both the raw follow-up score and the change between baseline and follow-up were studied. The sensitivity of the ANACOVA findings was explored both by including several additional baseline covariates in a multiple regression framework and by transforming each outcome, summarizing change between baseline and follow-up into a 7-point Likert-type scale to dampen the impact of potential extreme outlying change scores. For example, the six cut points (−25, −15, −5, 5, 15, and 25) were used to assign follow-up minus baseline differences in the SF-36 Physical Functioning Scale into seven categories.

Multiple regression analysis was used to investigate predictors of two measures of QOL: the SF-36 General Health Scale and the Ladder of Life Scale. The main effects of chemotherapy and any tamoxifen treatment were supplemented by an interaction term to explore possible nonadditivity of effects.

Since this was planned as a descriptive study, no formal adjustments were made for multiple comparisons. However, although .05 was used as the level of statistical significance, caution should be used in interpretation of findings of *P*>.01. All *P* values were two-sided.

Results

Subjects and Recruitment Results

From among the 1957 survivors in the parent study, we mailed recruitment letters to the 1336 women who met the study eligibility of being 5 years post-diagnosis. Responses were received from 80% (n = 1063). Of the respondents, 86% (n = 914) were interested in participating and 7% were not interested. Five percent of the mailings (n = 58) were returned as undeliverable, and in 1% of the cases (n = 12), the woman had died (Fig. 1). Among the nonresponders (273 of 1336), there were undoubtedly also breast cancer survivors who had moved or died, although the majority were probably those who were not interested in participating.

Questionnaire booklets were mailed to the 914 interested respondents. Among those respondents, 89% (n = 817) completed and returned the booklets. Two percent re-

fused explicitly to complete the booklet; 8% simply failed to return the booklet despite reminder calls. Overall, 817 of 1336, or 61% of survivors initially contacted, returned questionnaires. Baseline demographic and medical characteristics of the 817 women who participated in the follow-up study and the 519 individuals who did not respond are shown in Table 1. Participants in the follow-up study were better educated, were more likely to be white, and had better scores on the CES-D and on some of the SF-36 scores at baseline. There were no statistically significant differences in type of surgery or in receipt of systemic adjuvant therapy.

Survivors With Recurrent Breast Cancer

Among the 817 women who completed a follow-up survey, 54 (6.6 %) reported experiencing a recurrence of breast cancer either in the breast (n = 32) or in a distant metastatic site (n = 22). We mention them briefly for completeness, since the focus of this article is on disease-free survivors. The women with recurrent cancer were similar in age to the total sample (mean, 55.9 years) and were first surveyed an average of 3.6 years after diagnosis (range, 1.3−5.3 years), with the follow-up survey an average of 6.5 years after diagnosis (range, 5.0−8.6 years). The average time between the two surveys was 2.9 years. Between the two assessment times, there were statistically significant declines in SF-36 scores for physical functioning (decline = 8.6 points; P = .01), general health (decline = 13.4 points; $P < .001$), and social functioning (decline = 8.6 points; P = .01). These declines represent a change of from 0.3 to 0.5 SD on these scales, which are clinically significant changes. No significant declines were noted in other SF-36 scores. CES-D scores were not statistically significantly different between the initial and follow-up assessments, consistent with the lack of decline in the SF-36 emotional well-being score.

QOL Over Time in Long-Term, Disease-Free Survivors

The remaining analyses examine results from the 763 disease-free survivors. The follow-up survey was completed an average of 6.3 years after diagnosis (range, 5.0−9.5 years). The baseline demographic characteristics of the disease-free survivors (data not shown) are essentially the same as those of the full sample of 817 respondents described in Table 1. Some changes in personal circumstances occurred between baseline and follow-up. More than two thirds of the survivors reported that their household income had remained stable over the follow-up period, but significantly more (P = .001) reported increased rather than decreased income (20% increased as opposed to 12% decreased). Nearly 80% of the survivors reported no change in employment status, but significantly more (P = .004) of those changing status were working less at follow-up, with the biggest shifts associated with retirement or moving from full-time to part-time employment. Marital status did not change significantly.

Scores on the SF–36 between baseline and follow-up are shown in Fig. 2. The following scores declined, indicating slightly poorer functioning: physical functioning, role function—physical, bodily pain, and general health. These declines were statistically significant due to the large sample size, but they represent less than a 0.1 SD change in score and are clinically not significant. Furthermore, they reflect expected age-related changes in these domains. There was no statistically significant interval change in the Vitality or Social Functioning Scales. The SF–36 Mental Health Scale improved significantly and was consistent with the decrease in the CES–D score that was also statistically significant. Both of these findings are not clinically significant and reflect modest expected improvements in emotional well-being associated with aging of the cohort.

The mean score for the SF–36 MCS was 52.1, which is slightly above the population norm for healthy women (24). The SF–36 PCS was 48.0, which is slightly below the population norm for healthy women (24). There was a small but statistically significant decrease in the RDAS, suggesting a poorer partner relationship, and there was no change in the MOS social support score. The Ladder of Life Scale was measured only at baseline in the second cohort of survivors. When we examined the ladder score in this subset (n = 349) of patients with both a baseline value and a follow-up value for that measure, we found a slight increase, from 7.66 at baseline to 7.82 at follow-up (P = .044). Weighted analyses accounting for propensity to participate yielded identical qualitative conclusions about statistical significance for all of these analyses.

Interval changes in physical symptoms and sexual functioning were also noted. Statistically significant declines were reported in the frequency of hot flashes (P = .001), night sweats (P = .001), vaginal discharge (P = .010), and breast sensitivity (P = .001). The frequency of other symptoms, however, increased significantly: bladder problems with laughing or crying (P = .003) and at other times (P = .007), vaginal dryness (P = .013), weight gain (P = .006), forgetfulness (P = .001), difficulty concentrating (P = .047), and being easily distracted (P = .014). There was also a statistically significant decline in the frequency of sexual activity over the interval of follow-up, with 65% being sexually active at baseline versus 55% at follow-up (P = .001). There was no change in the frequency of pain with intercourse, and there was no change in sexual interest as measured by the CARES Sexual Interest Subscale. Assessment of body image was unchanged.

Impact of Previous Systemic Adjuvant Treatment on Long-Term QOL

In a previous report from the baseline evaluation of some of these survivors (12), we had described the QOL outcomes according to the type of systemic adjuvant therapy that the survivors had received. We now update those findings in this long-term

follow-up sample. The sample size within each treatment group was as follows: no systemic adjuvant therapy (n = 190), tamoxifen treatment alone (n = 251), chemotherapy alone (n = 111), and tamoxifen treatment and chemotherapy (n = 209). Since these groups differed by mean age at diagnosis (i.e., the tamoxifen-alone group was the oldest, and the chemotherapy-alone group was the youngest), we adjusted all of the subsequent analyses for age at diagnosis, as described in the "Statistical Considerations" section. Follow-up survey results by treatment status are presented in Table 2. Global QOL, measured by the Ladder of Life Scale, was statistically significantly better (P = .005) in women who received no systemic adjuvant therapy. For the SF-36 scores, women who received no adjuvant therapy had statistically significantly better physical functioning (P = .003) and better physical role functioning (P = .02), although the latter was not quite statistically significant in the weighted analysis. Similar patterns emerged for bodily pain (P = .01), social functioning (P = .02), and general health (P = .03), whereas there was no difference among treatment groups for mental health, emotional role functioning, or vitality. (None of these observations was changed by the weighted analysis.) These results differ from our previous findings in a similar analysis with the baseline data (12), where only the SF-36 Physical Functioning Scale was better in the no-treatment group. Scores on the CES-D and PANAS support the lack of difference in emotional well-being by treatment status. Sexual discomfort as measured by the SAQ was significantly worse among the women who had received chemotherapy in the past, in comparison to those who had received either tamoxifen or no therapy ($P<.001$). These latter findings are consistent with our earlier observations in the baseline survey (11,12,17).

We performed several additional exploratory analyses to examine why, at follow-up assessment, there were poorer scores on several SF-36 scales in those who had received systemic adjuvant therapy. First, we examined the *baseline data* in this sample of 763 survivors to determine if their initial SF-36 scores differed by treatment status. There were no statistically significant differences by treatment status for the baseline SF-36 scales at the .05 level, although there were some differences at the .10 level. Where the Physical Functioning Scale score had been reported to be statistically significantly poorer with systemic adjuvant therapy at baseline in our larger sample (n = 1096) reported earlier (12), it was not statistically significant (P = .07) in this smaller sample of 763. We next examined the *change scores* between the baseline and follow-up assessments in the 763 women. The change in the Physical Functioning Scale yielded P = .10 in the ANACOVA, both for the raw change score and for the version transformed to a Likert-type scale to assess sensitivity, while the SF-36 PCS yielded P = .09 for the raw change score and P = .024 for the version transformed to a Likert-type scale. Crude inspection of the mean age-adjusted baseline SF-36 scores by treatment status revealed that, while women who had received no treatment remained stable on all SF-36 scales between baseline and follow-up, there were declines in several SF-36 physical health scales among the women who had received systemic adjuvant therapy (data not shown).

Other Aspects of Health and Well-being in Long-Term Survivors

Using a new scale developed for this study, we queried the survivors about their perceptions about the impact of cancer on a range of life plans and activities. Responses are presented by age at diagnosis in Table 3. Older survivors (≥60 years old at diagnosis) consistently indicated less impact than those who were younger. In almost all areas measured, the greater impact in the younger survivors was in both directions, both positive and negative. Areas where the experience of cancer had the most positive impact for all survivors were in diet, exercise activities, and religious beliefs. The greatest negative impacts came in love life for all survivors and in work life or career and financial situation for the younger survivors. Overall, 70% or more of the survivors indicated no impact in the areas of educational plans, family plans, living arrangements, financial situation, and the ability to care/provide for children or the ability to be caregiver to others. None of these findings were affected by the weighted analyses.

Our survey also asked about current use of a wide range of complementary and alternative therapies, ranging from psychotherapy/counseling interventions to use of vitamins, herbs, diets/diet supplements, and traditional/folk remedies. Most frequently reported was use of some form of vitamins (86.6%), followed by use of diets or diet supplements (60.7%) and herbal preparations (49.3%). More than half of the sample used multivitamins (62.1%), calcium (61.3%), and vitamin E (52.2%). The most commonly endorsed dietary practices were following a low-fat (48.4%), low-calorie (20.4%), or low-salt (18.6%) diet. Herbal preparations most commonly used were *Echinacea* (used by 21.9%), gingko biloba (20.1%), garlic (17.6%), ginseng (10.7%), St. John's Wort (9.8%), and herbal tea used as a remedy (9.8%). Among the 49% of women using herbal remedies, 38% used just one, 36% used two or three, and 26% used four or more.

To explore whether the use of herbal remedies was associated with psychologic and physical functioning, we examined scores from the SF-36 PCS and MCS, the CES-D Scale, the SF-36 Mental Health Scale, and the PANAS. Use of garlic, gingko biloba, or herbal tea was not associated with any of the QOL measures. However, *Echinacea* users reported slightly lower emotional health scores than nonusers (SF-36 MCS: 50.6 versus 52.5 [$P =.022$]; the SF-36 mental health: 75.5 versus 78.7 [$P = .018$]). Ginseng users also had lower SF-36 MCS (48.9 versus 52.5 [$P = .001$]), lower SF-36 mental health scores (74.2 versus 78.5 [$P = .019$]), and higher PANAS negative affect (18.0 versus 16.1 [$P = .006$]). The greatest differences were found between users and nonusers of St. John's Wort. Five measures of emotional distress were significantly different, with users reporting more difficulties: SF-36 MCS (46.9 versus 52.7 [$P = .0001$]), CES-D (12.5 versus 8.3 [$P = .001$]), SF-36 mental health (71.2 versus 78.8 [$P = .001$]), PANAS positive affect (32.3 versus 35.1 [$P = .002$]), and PANAS negative affect (18.8 versus 16.0 [$P = .001$]). Notably, use of these herbal remedies was not statistically significantly associated with physical functioning.

Fewer than 13% of the women were currently using psychosocial or counseling therapies, while many more said that they had used them in the past. Only 6.2% of the women were currently in individual therapy, with fewer than 1% in either couples therapy or family therapy. Only 5.5% were currently active in cancer support groups, although 30.3% said that they had used them in the past. Meditation was currently being used by 12.1% of the survivors, with others using several other stress-reducing activities, such as breathing exercises (10.9%), yoga (6.8%), or other relaxation strategies (12.5%). Use of massage was reported by 11.4% of the respondents, with low current usage of acupressure (2.5%) and acupuncture (2.2%).

Predictors of QOL in Long-Term, Disease-Free Breast Cancer Survivors

In our previous research with breast cancer patients during the first year after diagnosis (6,8,40), we found that medical variables (e.g., type of surgery, stage, and type of adjuvant therapy) were not predictors of QOL; rather, age and measures of current physical and emotional well-being were the most statistically significant predictors in various analyses. In this study sample, we chose to investigate possible predictors for two measures of QOL that were assessed at follow-up: the SF-36 General Health Scale and the Ladder of Life Scale. Predictors used in our models fell into three groups: 1) demographic measures (age, ethnicity, education, income, and partnership status), 2) treatment (time since diagnosis, type of surgery, chemotherapy, tamoxifen treatment, and a chemotherapy–tamoxifen treatment interaction term), and 3) particular aspects of QOL and health status (number of health conditions, social support, emotional well-being, and physical functioning). We hypothesized that treatment-related variables would not be strongly associated with the dependent variables but needed to be controlled for, while self-rated dimensions of well-being (physical, emotional, and social) would contribute statistically significantly to subjective assessments of QOL.

The results of the two regression models are shown in Table 4. Each model identified statistically significant predictors, only some of which were shared. The model R^2 was .38 (P<.001) for the General Health Scale and the model R^2 was .39 (P<.001) for the Ladder of Life Scale, suggesting that the selected predictors accounted for a substantial amount of the variance in each dependent variable. For general health, the statistically significant variables in the model were age at follow-up (P = .02), number of medical conditions (negatively associated, P<.001), social support (P = .02), the SF-36 mental health score (P<.001), and the SF-36 physical functioning score (P<.001). None of the findings in this model were changed in the weighted regression analysis. For the Ladder of Life Scale, the statistically significant predictors in the model were social support (P<.001), having had chemotherapy (negatively associated, P = .003), SF-36 mental health (P<.001), having an income under $45 000 (negatively associated, P = .003), and being of black ethnicity (P = .05). Only the black ethnicity variable became statistically nonsignificant in the weighted regression analyses. Only

two predictors appear in both models—social support and mental health—suggesting that each dependent variable assesses distinct, but not wholly independent, global concepts of QOL. (Overlap of statistically significant predictors between the two models is also consistent with our finding a Pearson correlation of .40 [$P<.0001$] between these two QOL measures.) Time since diagnosis, education, and marital status did not influence ratings of QOL in these survivors, which is consistent with some of our previous observations (6,8,40). The statistically significant negative association of past chemotherapy with current QOL in these long-term survivors is a new finding. Other medical treatments had no statistically significant independent effect on QOL.

Discussion

This article describes one of the largest prospective studies of breast cancer survivors reported in the literature to date. In this follow-up study, we present the results of a comprehensive assessment of QOL in a sample of 817 women surviving an average of 6.3 years after diagnosis (range, 5.0–9.5 years). The majority of the respondents (n = 763) remained free of disease, and their responses are the main focus of this article. The strengths of the study are the large sample size, the longitudinal design, and the use of standardized measures of QOL, mood, and well-being. The limitations of the study include the representation of women from only two urban locations and an overall response rate of only 61%, which may have biased the results. Our weighted analyses to account for nonrespondents, however, showed few, if any, changes in our findings. Importantly, this article provides new information about the QOL of long-term, disease-free breast cancer survivors that can be used by health care providers and the survivors themselves.

In this study, we have also demonstrated the feasibility of conducting follow-up research with long-term breast cancer survivors. Although the demands of this study were not extraordinary (completion of a 42-page questionnaire booklet at home), some women may have chosen not to complete the questionnaire because they were too busy or did not want to be reminded about their past experience with breast cancer. Some recruitment problems arose because the longitudinal follow-up study was not a part of the initial research study and was added on later. If we had planned the follow-up study from the beginning, we would have maintained regular contact with the survivors and obtained alternative contact information. Such follow-up might have eliminated some of our nonresponses in the early part of the recruitment.

We observed considerable stability in the ratings of health-related QOL in the disease-free survivors on the standardized measures. The declines that were observed in physical functioning, role function—physical, bodily pain, and general health are modest and what one would expect in an aging population observed over time (41,42). Social support scores were stable, although the quality of the partnered

relationship declined slightly. In contrast, emotional well–being and depressive

symptoms improved over the two assessments, which is likely related to improved mental health with aging (41,42). Many symptoms that had been frequent at the baseline assessment were now less commonly reported, including hot flashes, night sweats, vaginal discharge, and breast sensitivity. Cessation of tamoxifen after 5 years of treatment, increasing time since menopause, and resolution of changes associated with irradiation of the breast are likely to explain these findings. Nevertheless, a number of symptoms were reported more frequently, including urinary incontinence, vaginal dryness, cognitive complaints, and weight gain. Fewer women reported being sexually active with a partner at the second assessment, but there was no change in sexual interest or in the frequency of reporting pain with intercourse between the two assessments. The increased symptoms and sexual problems reported in these survivors are associated with aging in normal healthy women (31,32,42).

We also examined the impact of systemic adjuvant therapy to determine whether there were any late effects of treatment beyond what we had described previously (12). We observed statistically significant differences among the treatment groups for global QOL, general health, physical functioning, and social functioning, with all comparisons showing the most favorable scores in women who did not receive any systemic adjuvant therapy (Table 2). In particular, the differences in the SF–36 physical functioning scale and the SF–36 PCS are substantial and clinically meaningful. However, there were no statistically significant differences among the treatment groups in emotional well–being or depression, as measured by multiple instruments, or in the quality of the partnered relationship, body image, sexual interest, or vitality. As has been shown in our previous studies (11,17), women who received chemotherapy as part of their adjuvant treatment scored more poorly with regard to sexual comfort (lubrication and pain with intercourse), even many years after completion of chemotherapy.

The differences in scores for some of the QOL scales are substantial (see Table 2). For the SF–36 PCS, women who received systemic adjuvant therapy in the past were roughly 0.3 SD below the mean of the general population and of the reference sample of breast cancer survivors who received no therapy. We cannot infer from this finding that previous systemic adjuvant therapy was causal in leading to the current health status in these long–term survivors, but these findings suggest that there may be late health–related QOL effects from treatment that do not appear until many years later. The four treatment groups were otherwise similar, with the exception of age, which was controlled for in the analysis. This possible change over time is further supported by the fact that we observed a difference in only one aspect of physical functioning at baseline, when patients were first assessed between 1 and 5 years after breast cancer diagnosis (12). Longer term follow–up has supported this early finding and has identified other late effects of systemic adjuvant therapy. The women in this study were treated at a time when therapies for patients with stage I or II disease were

similar, although chemotherapy was not combined with tamoxifen treatment in premenopausal patients or in patients with stage I disease of any menopausal status as frequently as is currently the practice. Women who did not receive systemic treatment most likely had small tumors with favorable histology, or they may have refused treatment. Given that the prognosis for the untreated women might have been better, it is interesting that we saw no differences in any of the assessments of emotional well-being; instead we only saw differences in areas related to physical functioning. Our observations related to changes in physical functioning that worsened over time in women who received systemic adjuvant therapy are provocative and warrant confirmation in future studies that are specifically designed to evaluate this question.

In our exploration of the perceived impact of cancer on life plans and activities, we confirm the findings from other studies (43,44) suggesting that the psychosocial impact of a breast cancer diagnosis is greater in younger women than in older women. The areas of greatest positive impact were in diet, exercise, religious beliefs, and other activities related to spirituality. Although we do not know to what extent women engaged in wellness and stress-management activities before their cancer diagnosis, a substantial number reported doing so now, years after their diagnosis. This was reflected in their health-related activities and active use of a variety of complementary and alternative strategies, including the use of vitamins, low-fat diets, and various herbal remedies. We also explored the relationship between the use of herbal remedies and measures of psychologic distress in this sample. It is interesting that several preparations were statistically significantly associated with poorer scores on standardized measures of emotional well-being, depression, and mood, as reported by others (45). Most disturbing were the statistically significantly poorer scores for women using St. John's Wort, an herbal remedy purported to relieve symptoms of depression. These women were clearly self-medicating for subjective symptoms, which may have been undetected and untreated by the traditional medical care system. This scenario suggests that clinicians should be more alert to the problem of ongoing depressive symptoms in their patients and that taking a careful history of complementary therapy use might provide the first clue to unaddressed psychosocial concerns, even many years after the diagnosis of cancer.

Finally, our examination of the predictors of health-related QOL confirmed our previous observations among breast cancer patients evaluated earlier in the post-treatment period—that the type of surgery does not affect long-term QOL (4,7,8,11). However, one of our predictive models (the Ladder of Life) suggests that adjuvant chemotherapy may be contributing to poorer long-term QOL. This information, along with our demonstration of a decline in several aspects of physical functioning among survivors who received any type of systemic adjuvant therapy, should be taken into account when assisting patients who are making decisions about systemic adjuvant therapy. In particular, this information may be relevant for women with

very small tumors (≤1 cm) with other very favorable characteristics, for whom only minimal gains in absolute disease-free or overall survival are expected from adjuvant chemotherapy (46−48). Although several computerized models have been developed to facilitate the discussion of the survival benefits of adjuvant therapy (49,50), these new decision aids do not include discussion of the short-term and later effects of adjuvant treatment on QOL (18).

In conclusion, long-term, disease-free survivors of breast cancer have an excellent QOL, many years after their breast cancer diagnosis. There are modest age-related changes in functioning over time, and troublesome symptoms associated with the menopause or tamoxifen decline statistically significantly; however, the adverse effects of systemic adjuvant therapy on physical health status appeared to persist and worsen when evaluated 5−10 years after diagnosis. This information may need to be taken into consideration by clinicians helping women to make informed decisions about the choice of systemic adjuvant therapy shortly after diagnosis (49,50) and may also be important for those providing primary care to breast cancer survivors long after the initial diagnosis and treatment (51). The quality of the social support received by survivors also seems to be an important predictor of better health-related QOL. Consequently, psychosocial interventions aimed at increasing social support beyond the acute phase of treatment may have a vital role in the ongoing care of breast cancer survivors.

Table 1.

Demographic, medical, and quality-of-life characteristics at the time of the initial survey; comparison of those who did and did not participate in the follow-up survey

Characteristic	Participants (n = 817)	Nonparticipants (n = 519)	P*
Mean age, y	55.6	56.5	.17
Mean time since diagnosis, y	3.4	3.3	.05
Ethnicity			
White	83.5%	73.6%	.001
Black	8.9%	16.8%	
Other	7.6%	9.6%	
Relationship status			
Married/committed	70.1%	65.9%	.06
Divorced/separated	14.5%	15.2%	

Characteristic	Participants (n = 817)	Nonparticipants (n = 519)	P*
Widowed	9.9%	9.6%	
Single	5.5%	9.3%	
Educational level			
≤High school	13.5%	19.9%	.001
Some college	34.9%	38.2%	
College graduate	15.5%	14.5%	
Postgraduate	36.1%	27.6%	
Surgery			
Lumpectomy	52.6%	54.7%	.64
Mastectomy	28.5%	28.3%	
Mastectomy with reconstruction	18.9%	17.0%	
Had chemotherapy	42.2%	42.4%	.94
Was receiving tamoxifen	48.4%	47.1%	.86
RAND SF-36 scores†			
Physical functioning	81.4	78.1	.01
Role function—physical	76.8	74.3	.20
Mental health	76.4	74.0	.01
Role function—emotional	78.8	75.9	.15
Bodily pain	78.6	77.0	.17
Vitality	61.1	58.5	.03
General health	74.0	70.1	.001
Social functioning	86.9	84.4	.03
SF-36 MCS‡	50.8	49.7	.06
SF-36 PCS§	49.6	48.5	.05
CES-D ‖ mean	10.16	11.28	.04

Characteristic	Participants (n = 817)	Nonparticipants (n = 519)	P*

*P values are from t tests for continuous measures (age, time since diagnosis, RAND SF-36 scores, and CES-D) and from chi-square tests for categorical measures (ethnicity, relationship status, educational level, surgery, had chemotherapy, and was receiving tamoxifen). All tests are two-sided.

†The RAND SF-36 (19,20) has eight scales that describe separate components of functioning and well-being. A higher score represents better functioning.

‡The SF-36 MCS (24) is a summary scale for mental health from the SF-36. The median population score is 50; a higher score represents better functioning.

§The SF-36 PCS (24) is a summary scale for physical health from the SF-36. The median population score is 50; a higher score represents better functioning.

||The CES-D (28–30) is the Center for Epidemiological Studies—Depression Scale. A higher score indicates more depressive symptoms.

Table 2.

Least-squares mean values of quality-of-life scales by adjuvant treatment, adjusted for age at diagnosis

Variable (reference Nos.)	Tamoxifen alone (n = 251)	Chemotherapy alone (n = 111)	Tamoxifen and chemotherapy (n = 209)	Neither treatment (n = 190)	P*
SF-36†: physical functioning (19,20)	77.4	76.7	78.8	84.2	.003
SF-36: role function, physical (19,20)	70.3	72.7	72.7	80.5	.02
SF-36: role function, emotional (19,20)	77.1	81.8	83.0	84.2	.15
SF-36: bodily pain (19,20)	73.7	74.5	77.1	80.9	.01
SF-36: vitality (19,20)	60.8	58.0	59.9	63.8	.11
SF-36: general health (19,20)	71.0	69.6	70.9	75.5	.03
	85.6	85.4	89.5	90.4	.02

Variable (reference Nos.)	Tamoxifen alone (n = 251)	Chemotherapy alone (n = 111)	Tamoxifen and chemotherapy (n = 209)	Neither treatment (n = 190)	P*
SF-36: social functioning (19,20)					
SF-36: mental health (19,20)	77.1	76.5	78.8	79.2	.32
SF-36 PCS Scale‡ (24)	47.1	46.9	47.5	50.3	.001
SF-36 MCS Scale§ (24)	51.5	51.5	52.7	52.5	.44
Step on Ladder of Life Scale (21)	8.0	7.4	7.9	8.0	.005
CES-D‖ Scale (28–30)	9.0	9.9	8.4	7.8	.14
PANAS¶ positive affect (33)	34.8	34.2	34.7	35.3	.64
PANAS negative affect (33)	16.2	16.7	16.5	16.0	.79
14-item revised dyadic adjustment (34)	49.8	46.6	49.2	49.0	.07
CARES# Body Image Scale (26)	1.1	0.9	1.0	0.9	.33
CARES Sexual Interest Scale (26)	0.9	0.8	1.0	0.8	.26
SAQ** Pleasure Scale (36)	12.8	12.0	12.3	13.7	.08
SAQ Discomfort Scale (36)	0.7	1.2	1.2	0.8	<.001

Variable (reference Nos.)	Tamoxifen alone (n = 251)	Chemotherapy alone (n = 111)	Tamoxifen and chemotherapy (n = 209)	Neither treatment (n = 190)	P*
SAQ Habit Scale (36)	1.9	2.1	2.0	1.9	.42

*Two-sided P values from analysis of covariance after adjustment for age at diagnosis. P value is for the comparison between women who received any form of adjuvant therapy and those who received no adjuvant therapy.

†The RAND SF-36 (19,20) has eight scales that describe separate components of functioning and well-being. A higher score represents better functioning.

‡The SF-36 PCS (24) is a summary scale for physical health from the SF-36. The median population score is 50; a higher score represents better functioning.

§The SF-36 MCS (24) is a summary scale for mental health from the SF-36. The median population score is 50; a higher score represents better functioning.

‖The CES-D (28–30) is the Center for Epidemiological Studies—Depression Scale. A higher score indicates more depressive symptoms.

¶The Positive and Negative Affect Schedule [PANAS; (33)] is an adjective checklist on which individuals use a 5-point Likert-type scale to rate the degree to which they have experienced 20 mood states over a specified time interval.

The Cancer Rehabilitation Evaluation System (CARES) subscales (26,38) measure body image and sexual interest. Higher scores indicate more frequent or severe problems.

**The Sexual Activity Questionnaire [SAQ (36)] was used to measure sexual functioning. The SAQ has three scales: pleasure, discomfort, and habit (frequency of activities). Higher scores indicate poorer sexual functioning.

Table 3.

Impact of cancer on disease-free survivors (n = 763) by age at diagnosis

	Impact			
	Negative, %	None, %	Positive, %	P*
Educational plans				
<50 y	5.6	79.4	15.0	.001
50–59 y	3.1	84.0	12.9	
≥60 y	6.2	91.2	2.6	
Work life or career				

*P values are from chi-square tests and are two-sided.

Article Navigation	Impact			
	Negative, %	None, %	Positive, %	*P**
<50 y	15.0	52.9	32.1	.001
50–59 y	14.2	67.1	18.9	
≥60 y	8.8	86.5	4.7	
Diet				
<50 y	10.0	30.0	60.0	.001
50–59 y	10.3	29.0	60.7	
≥60 y	4.6	47.2	48.2	
Family plans				
<50 y	10.1	71.6	18.3	.001
50–59 y	7.1	80.9	12.0	
≥60 y	7.7	87.1	5.2	
Social life				
<50 y	6.8	57.4	35.8	.001
50–59 y	8.4	63.6	28.0	
≥60 y	5.1	78.5	16.4	
Living arrangements				
<50 y	2.9	88.2	8.8	.15
50–59 y	4.0	88.4	7.6	
≥60 y	3.6	93.3	3.1	
Financial situation				
<50 y	19.4	73.8	6.9	.001
50–59 y	17.5	73.5	9.0	
≥60 y	8.8	88.6	2.6	
Exercise activities				

*P values are from chi-square tests and are two-sided.

Article Navigation	Impact			
	Negative, %	**None, %**	**Positive, %**	**P***
<50 y	11.2	38.1	50.7	.002
50–59 y	11.2	41.7	47.1	
≥60 y	7.7	56.1	36.2	
Love life				
<50 y	33.1	46.8	20.1	.001
50–59 y	28.0	58.2	13.8	
≥60 y	16.1	76.7	7.3	
Religious beliefs				
<50 y	4.4	47.2	48.4	.08
50–59 y	2.7	54.7	42.6	
≥60 y	2.1	58.5	39.5	
Religious activities				
<50 y	4.7	64.6	30.7	.27
50–59 y	3.1	71.3	25.6	
≥60 y	3.1	72.8	24.1	
Other activities related to spirituality				
<50 y	2.7	59.3	38.1	.002
50–59 y	3.1	60.4	36.4	
≥60 y	3.1	75.4	21.5	
Retirement plans				
<50 y	11.9	62.3	25.8	.001
50–59 y	9.7	60.2	30.1	
≥60 y	7.7	83.5	8.8	
	Negative, %	**None, %**	**Positive, %**	**P***

*P values are from chi-square tests and are two-sided.

	Impact			
	Negative, %	None, %	Positive, %	*P**
Ability to care/provide for children				
<50 y	9.7	78.8	11.5	.001
50–59 y	5.0	86.4	8.6	
≥60 y	4.2	92.2	3.7	
Ability to be caregiver to others				
<50 y	9.1	65.8	25.1	.001
50–59 y	8.5	65.2	26.3	
≥60 y	6.7	82.4	10.9	
Other changes				
<50 y	4.3	87.5	8.2	.39
50–59 y	5.0	88.6	6.4	
≥60 y	7.1	89.3	3.6	

*P values are from chi-square tests and are two-sided.

Table 4.

Predictors of two linear regression models for quality of life: General Health Scale and Ladder of Life Scale*

	Dependent variable					
	General Health Scale			Ladder of Life Scale		
	Model-adjusted R^2 (*P* value†) .... .38 (<.001)			Model-adjusted R^2 (*P* value) .... .39 (<.001)		
Parameter estimates	Coefficient, β	Standard error	*P*‡	Coefficient, β	Standard error	*P*‡
Intercept	9.74	6.61	.14	2.351	0.529	<.001
Age at follow-up, y	**0.16**	**0.07**	**.02**	0.005	0.006	.35
Ethnicity—black	1.10	2.08	.60	**0.327**	**0.166**	**.05**
Other race/ethnicity	−1.27	2.22	.57	0.040	0.177	.82

Parameter estimates	General Health Scale			Ladder of Life Scale		
Dependent variable						
	Model-adjusted R^2 (P value†) .... .38 (<.001)			Model-adjusted R^2 (P value) .... .39 (<.001)		
	Coefficient, β	Standard error	P‡	Coefficient, β	Standard error	P‡
College graduate	−0.51	1.24	.68	0.025	0.099	.80
Income under $45 000	−0.75	1.57	.63	**−0.374**	**0.125**	**.003**
Income over $75 000	1.08	1.42	.45	0.016	0.114	.89
Married/partnered	−1.83	1.50	.22	0.212	0.120	.08
Time since diagnosis, y	−0.35	0.56	.53	0.032	0.045	.48
Mastectomy	1.04	1.17	.38	−0.035	0.094	.71
Chemotherapy	−1.37	1.87	.47	**−0.443**	**0.150**	**.003**
Ever took tamoxifen	−1.56	1.59	.33	0.063	0.127	.62
Chemotherapy–tamoxifen interaction	0.24	2.38	.92	0.259	0.190	.17
No. of conditions	**−2.12**	**0.47**	**<.001**	0.003	0.038	.94
Social support scale	**0.07**	**0.03**	**.02**	**0.019**	**0.002**	**<.001**
Mental health	**0.40**	**0.04**	**<.001**	**0.043**	**0.003**	**<.001**
Physical functioning	**0.31**	**0.03**	**<.001**	0.003	0.002	.21

*Data presented come from nonweighted multiple linear regression analyses; however, it should be noted that the black ethnicity variable became nonstatistically significant in the weighted analyses because of the lower participation of black women in the follow-up study. The following parameters were measured at follow-up: dependent variables, age, education indicator (comparison group: less than college education), income indicators (comparison group: income $45 000–$75 000), time since diagnosis, married/partnered indicator (comparison group: unpartnered), number of medical conditions, ever took tamoxifen indicator (comparison group: never took tamoxifen), social support scale measured by the MOS social support scale, mental health as measured by the SF-36, and physical functioning as measured by the SF-36. The following parameters were measured at baseline: race/ethnicity indicators (comparison group: white), mastectomy indicator (comparison group:
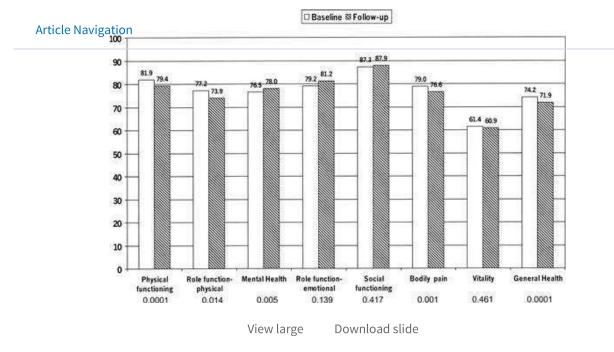
Article Navigation	Dependent variable					
	General Health Scale			**Ladder of Life Scale**		
	Model-adjusted R^2 (*P* value†) .... .38 (<.001)			Model-adjusted R^2 (*P* value) .... .39 (<.001)		
Parameter estimates	**Coefficient, β**	**Standard error**	***P‡***	**Coefficient, β**	**Standard error**	***P‡***

lumpectomy), and chemotherapy indicator (comparison group: did not receive chemotherapy). **Values in bold** indicate statistically significant parameters in each model.

†*P* value from F test for significant overall regression.

‡*P* value from *t* tests of individual parameter estimates.

Fig. 1.

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Recruitment response to mailed invitations and survey questionnaires.

Fig. 2.

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Baseline and follow-up survey scores on the RAND SF-36 Scales *(19,20)* for the 763 women without a recurrence of cancer at the time of the follow-up survey. *P* values for the comparison of baseline and follow-up scores on each scale are listed **below the scale label.**

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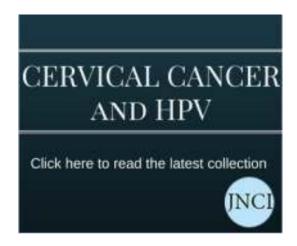Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. *CA Cancer J Clin* 2000;50:7–33.

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