

Quality of Life, Fertility Concerns, and Behavioral Health Outcomes in Younger Breast Cancer Survivors: A Systematic Review

Jessica Howard-Anderson, Patricia A. Ganz, Julienne E. Bower, Annette L. Stanton

Manuscript received May 26, 2011; revised November 29, 2011; accepted December 7, 2011.

Correspondence to: Patricia A. Ganz, MD, Division of Cancer Prevention and Control Research, Jonsson Comprehensive Cancer Center, University of California Los Angeles, 650 Charles Young Dr South, Rm A2-125 CHS, Los Angeles, CA 90095-6900 (e-mail: pganz@mednet.ucla.edu).

Background Breast cancer is the most common cancer in women younger than age 50 years. Cancer treatments in younger women may cause premature menopause, infertility, and negative psychosocial effects. In this systematic review, we examined three key domains of functioning that are particularly relevant for younger breast cancer survivors: health-related quality of life (QOL), menopausal symptoms and fertility concerns, and behavioral health outcomes.

Methods We conducted a literature review using PubMed and secondary sources and examined 840 articles published between January 1990 and July 2010. Inclusion criteria for articles were 1) published in English after 1989; 2) exclusively analyzed female breast cancer survivors aged 50 years or younger or premenopausal at diagnosis, with baseline characteristics and/or quantitative or descriptive analyses for this age group; 3) investigated QOL (health-related QOL including physical functioning and mental health, depression, and anxiety), menopause- or fertility-related concerns, and weight gain or physical activity-related behavioral health outcomes. Data were extracted using a standardized table collecting the purpose, design, population, and results of each study. Extracted data were reviewed for accuracy by two investigators and presented as descriptive tables.

Results A total of 28 articles met the inclusion criteria (15 cross-sectional studies, eight longitudinal studies, and five randomized trials). Regarding data review, no discordance between investigators was noted. Standardized measures of QOL and depressive symptoms identified worse outcomes as being more frequent or severe in breast cancer survivors aged 50 years or younger when compared with the general age-matched population of women without cancer and to older women (aged >50 years) with breast cancer. Concerns about premature menopause, menopausal symptoms, and infertility were common in younger women (aged ≤50 years) and had a role in the level of distress after treatment. Weight gain and physical inactivity were common health outcomes in younger women.

Conclusions Younger women with breast cancer were found to experience distinct psychosocial and menopause-related concerns, weight gain, and physical inactivity. A need for more longitudinal research, including efforts at intervention to manage these symptoms and adverse health outcomes, remains.

J Natl Cancer Inst 2012;104:386–405

Breast cancer is the most common cancer in women, and for those younger than 50 years of age, it is the leading cause of death in the United States (1). However, the survival rate for these younger women with breast cancer has improved continuously over the past two decades, primarily because of the widespread introduction of adjuvant chemotherapy and endocrine therapies (2). Today many younger women can expect long-term survival; however, the quality of their lives may be hampered by premature menopause, infertility, negative psychosocial effects, and risk for recurrence and second episodes of primary breast cancer (3–8). From the perspective of cancer control, younger breast cancer survivors are an

important target population for interventions that focus on physical and psychological symptom relief, cancer prevention, and risk reduction.

To identify potential opportunities for cancer prevention and control interventions in this population, we undertook a systematic review of the literature focused on potentially mutable outcomes. We were particularly interested in the impact of breast cancer on health-related quality of life (QOL) (ie, physical functioning and emotional well-being, depression, and anxiety), unique psychosocial difficulties related to treatment-associated reproductive changes (ie, onset of menopause and its symptoms, concerns about

menopause and fertility), and modifiable behavioral health outcomes (specifically weight gain and lack of physical activity). Although there is no generally accepted definition for “younger women with breast cancer,” we chose to use the chronological age of younger than 51 years (the average age of menopause) and/or premenopausal, to define “younger women” in this review and be as inclusive as possible in capturing the experience of these women who have been diagnosed with breast cancer (note that some researchers consider younger than 40 years as being “young age”). The purpose of this review was to highlight what is currently known, to identify gaps in the research literature, and to specify potential targets for intervention research and improvements in clinical care.

Methods

Search Strategy

In 1993, the National Cancer Institute (NCI) held a conference focused on breast cancer in younger women, described in a published monograph (9). Several articles in the monograph discussed the challenge in defining this population, with the conclusion that “what age defines a ‘younger’ woman is to a large extent arbitrary.” The conference monograph served as a starting point for this review and was followed by a series of literature searches during the months of June and July 2010. Using PubMed, we searched articles published after 1989 using a combination of the following National Library of Medicine’s indexed search terms, known as Medical Subject Headings (MeSH) descriptors: “breast neoplasms” and 1) “age factors” and “quality of life,” 2) “age factors” or “age distribution” and “quality of life,” 3) “age factors” and “survival,” 4) “age factors” and “weight gain,” 5) “age factors” and “exercise,” 6) “premenopause” and “weight gain.” Additional PubMed searches were performed with the phrase “young women” (not a MeSH descriptor), as a substitute for “age factors.” Lastly, PubMed searches were also conducted using the key phrases (not MeSH descriptors) “younger women” or “premenopause” in combination with “breast cancer survivor.” This literature search was supplemented by reviewing relevant citations of the primary studies identified, using the Institute for Scientific Information (ISI) Web of Science to identify studies that had cited many of these primary references, and by using more specific search terms to find any relevant follow-up or closely related studies. We also examined several review articles on this target population that focused on the effects of chemotherapy on relationships, reproductive problems, and QOL (6,10–12).

Inclusion Criteria

We identified 840 titles and abstracts through this search. After eliminating duplicate articles and studies that did not at least broadly pertain to breast cancer survivors, younger age, and one of the three major outcome domains described earlier, 86 articles remained that were more closely reviewed. Although many of these articles were ultimately cited in this review, only 28 articles (4,13–39) met our specific inclusion criteria: 1) published in English between January 1990 and July 2010; 2) exclusively analyzed female breast cancer survivors who were 50 years or younger, or premenopausal at diagnosis, and provided baseline

CONTEXT AND CAVEATS

Prior knowledge

Although younger women diagnosed with breast cancer are surviving longer because of advancement in treatments, the quality of their lives may be affected by premature menopause, infertility, risk of recurrence, and negative psychosocial effects.

Study design

A systematic review of the literature was conducted to examine health-related quality of life (QOL), menopausal symptoms and fertility concerns, and behavioral health outcomes in younger women with breast cancer. Women younger than 51 years (the average age of menopause) and/or premenopausal are defined as “younger” in this review.

Contribution

Standardized measures of QOL and depressive symptoms in the reviewed articles indicated that worse outcomes were more frequent or severe in younger breast cancer survivors compared with the general age-matched population of women without cancer or older women (aged >50 years) with breast cancer. Younger women were more concerned about premature menopause, infertility, and menopause symptoms. Weight gain and physical inactivity were also common initially, but exercise rates increased after treatment.

Implications

QOL is compromised in younger women with breast cancer, and they experience great psychological distress and fertility-related concerns. Interventions to help increase physical activity and decrease weight gain could be beneficial to younger breast cancer survivors.

Limitations

Only specific areas were examined, and it is likely that other important concerns relevant to younger breast cancer survivors have not been addressed. Inclusion of only younger survivors precluded a systematic comparison with older survivors.

From the Editors

characteristics and/or quantitative or descriptive analyses for this group; 3) investigated QOL (health-related QOL including physical functioning and mental health, depression, and anxiety), menopause- or fertility-related symptoms and concerns, or behavioral outcomes (weight gain and lack of physical activity) in young breast cancer survivors. Age 50 years was chosen as the upper age limit of inclusion for reasons mentioned earlier. For the purposes of this review, “breast cancer survivor” refers to any individual who has been diagnosed with breast cancer and is alive without evidence of active or recurrent disease at the time of the analysis. Small pilot or solely qualitative studies were not included.

Our review was guided by a broad conceptual framework (Figure 1) that focused on relevant personal predictors (demographic variables, medical factors, psychosocial variables), the cancer diagnosis and treatment exposures, and their hypothesized relationships to the three key outcome domains (QOL, menopause and fertility, and behavioral outcomes) particularly relevant to younger women with breast cancer. In this review, the section on QOL outcomes focused on assessments of health-related QOL (which includes physical function and mental health score),

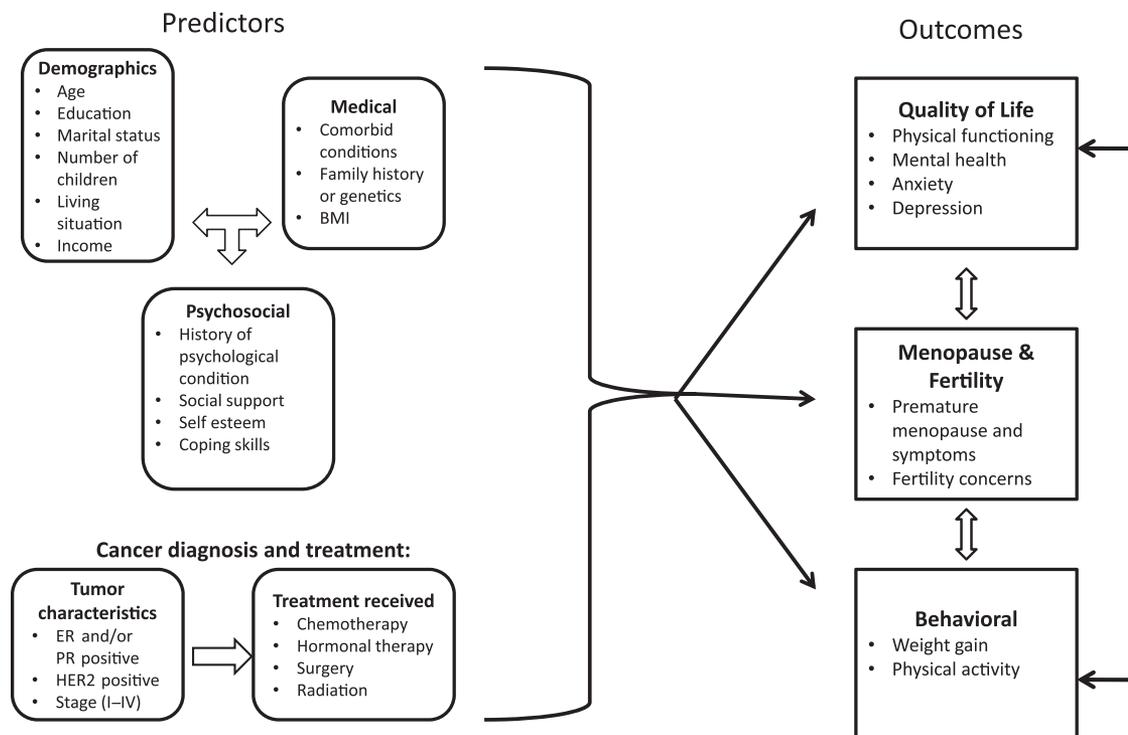


Figure 1. Conceptual framework for understanding predictors and outcomes in breast cancer in younger women. The framework shows how different demographic, medical, and psychosocial characteristics of a patient can combine with different disease and treatment variables to predict unique biological and behavioral outcomes in younger women (age <51 years or premenopausal) with breast cancer. This framework was created based on the authors' previous research and clinical

experience with breast cancer survivors and shaped how this systematic review was performed. **Arrows** in the figure indicate author-hypothesized directions of influence among the predictors, as well as among predictors and outcomes. Living situation refers to who the patient lives with, what type of place they live in (apartment, house, etc.), and if the living situation is stable or transient. BMI = body mass index; ER = estrogen receptor; PR = progesterone receptor.

depressive symptoms, and anxiety. The section on menopause and fertility concerns further elaborated the issues affecting QOL in this domain and included self-reported symptoms related to change in menstrual status (eg, hot flashes, vaginal dryness, breast sensitivity, and sexual dysfunction) and fertility concerns. Because chemotherapy-induced amenorrhea has been widely described (40–45), we did not include studies that were designed primarily to document the incidence or likelihood of chemotherapy-induced menopause or its effects on survival and other purely medical outcomes. We did not include studies that primarily discussed biological endpoints, such as the risk of becoming infertile, safety of future pregnancies, or options for preserving fertility. In examining the behavioral outcomes, we focused on weight gain and lack of physical activity because of their particular relevance in younger women in association with change in menopausal status.

Large Cohort Studies of Target Population

Our search identified eight large cohort studies that focused specifically on younger breast cancer survivors and that led to more than one publication, which are included in this review (4,13,15–25,27,28,36,37,39). We highlighted the features of these cohort studies in Table 1 to provide background information on the cohorts and to facilitate understanding of the domain-specific reporting in the subsequent review tables. Many of these studies focused on the special needs of younger breast cancer patients and were stimulated by the conference and monograph described earlier (9) and were funded by an associated NCI Request for

Applications (RFA: CA/HD-93-033, Rehabilitation And Psychosocial Research In Younger Women With Breast Cancer). These cohort studies include both cross-sectional and longitudinal designs, including several intervention studies in response to the RFA, including Scheier et al. (46,47), Bloom et al. (48), and Allen et al. (39), but these studies were only included if they met the previously specified study criteria for this review.

We identified several clinical and/or therapeutic trials that focused on premenopausal women with breast cancer, some of which included self-reports of physical symptoms, QOL, depression, and anxiety (49–54). We considered inclusion of these studies in this review; however, as they primarily focused on medical treatment outcome differences, we elected to exclude them. A complete list of recent therapeutic trials that include measures of QOL was published by Lemieux et al. (55). We also reviewed a wide range of epidemiological studies assessing risk factors for breast cancer incidence in younger women; however, only one study had relevant outcomes in survivors (24).

Data Extraction Methods and Analysis

The data from the relevant articles were extracted by J. Howard-Anderson and initially recorded in one standardized table that included information on the articles' purpose, design, population, and results. The articles were then separated into descriptive tables based on category (large cohort studies that focused exclusively on younger women with breast cancer, QOL, menopausal and/or fertility concerns, and behavioral health outcomes), and the results

Table 1. Major cohort studies that focused exclusively on younger women (aged <51 years) with breast cancer*

Study†, first author, year (reference)	Purpose (reference)	Type of study and sample size‡ (reference)	Participant characteristics (reference)	Outcomes examined
BCYW: a population-based approach (part I), Bloom, 1998, 2001, 2004 (13,20,21) and Wong-Kim, 2005 (22)§	Identify problem areas in young BCS.	Cross-sectional and longitudinal studies. n = 336 subjects; n = 185 subjects in follow-up study (21).	Identified through RCA of the San Francisco SEER Cancer Registry. Age <51 y at diagnosis. Analyzed 2 mo, 7 mo, or 5 y after diagnosis.	Menopause and fertility concerns: menopause, physical symptoms Psychosocial: depression, anxiety, QOL
BCYW: a population-based approach (part II), Fobair, 2006 (23) and Bloom, 2008 (37)§	Examine sexual functioning and body image shortly after treatment (23). Test psycho-educational intervention (37).	Cross-sectional and RCT. n = 549 subjects (23); n = 404 subjects (37).	Identified by Greater Bay Area Cancer Registry (SEER program) and the California Cancer Registry through RCA. Age <51 y at diagnosis. Analyzed 2–7 mo after diagnosis (23) or 5 y after diagnosis (37). Fobair only analyzed participants in stable relationships.	Menopause and fertility concerns: menopause, physical symptoms Behavioral: weight, PA
Allen, 2002 (39) and Duffy, 2005 (25)§	Evaluate a problem-solving intervention in younger BCS (39) and examine rates of reproductive health counseling in younger women (25).	Cross-sectional and interventional RCT. n = 164 subjects (39); n = 144 subjects (25).	Recruited from hospitals and clinics in New England area. Age <51 y at diagnosis. Analyzed when starting first round of CT (mean 3.7 wks after start). Duffy analyzed only premenopausal women.	Menopause and fertility concerns: menopause, fertility concerns Psychosocial: QOL
CAMS, Ganz, 2003 (4) and Crandall, 2004 (15) and Herman 2005 (36)§	Assess QOL, reproductive health, menopausal status, and weight gain in younger BCS.	Cross-sectional. n = 577 subjects (4); n = 476 subjects (15); n = 441 subjects (36).	Recruited from two hospital cancer registries in Los Angeles. Age <51 y at diagnosis. Analyzed 2–10 y after diagnosis.	Menopause and fertility concerns: menopause, physical symptoms Psychosocial: QOL, depression Behavioral: weight, PA
Avis, 2004, 2005 (18,19)§	Examine medical symptoms, concerns and QOL in young BCS.	Cross-sectional. n = 204 subjects (18); n = 202 (19).	Recruited from Boston and New Hampshire. Age <51 y at diagnosis. Analyzed <42 mo after diagnosis.	Menopause and fertility concerns: menopause, physical symptoms, fertility concerns Psychosocial: QOL Behavioral: weight
Burwell, 2006 (27) and Danhauer, 2009 (28)§	Analyze coping, QOL, and sexual problems in younger BCS.	Longitudinal and RCT (not published). n = 267 subjects (28); n = 209 subjects (27).	Recruited from Boston and New Hampshire. Age <51 y at diagnosis. Analyzed <26 wk after surgery. F/U at 6–8 wk and 6–8 mo later. Burwell examined only sexually active participants.	Menopause and fertility concerns: menopause, physical symptoms Psychosocial: QOL
YSC, Partridge, 2004 (16) and Leining, 2006 (17)§	Assess menopausal symptoms and fertility concerns in very young BCS.	Cross-sectional. n = 657 subjects (16); n = 370 subjects (17).	Recruited from the YSC through email. Age <41 y at diagnosis. Majority analyzed <2 y after diagnosis. Leining required participant to be >1 y after diagnosis.	Menopause and fertility concerns: menopause, physical symptoms, fertility concerns Psychosocial: anxiety
Kendall, 2005 (24)§	Examine effects of physical activity on QOL in young BCS.	Case-control, cross-sectional. n = 371 subjects.	Recruited from USC Cancer Surveillance Program. Age <41 y at diagnosis. Analyzed >10 y after diagnosis. Cases matched on date of birth, race, parity, and neighborhood of residence.	Psychosocial: QOL Behavioral: weight, PA

* All outcomes were included in the systematic review. BCS = breast cancer survivors; BCYW = Breast Cancer in Young Women; CAMS = Cancer and Menopause Study; CT = chemotherapy; F/U = follow-up; PA = physical activity; QOL = quality of life; RCA = rapid case ascertainment; RCT = randomized controlled trial; SEER = Surveillance, Epidemiology, and End Results; YSC = Young Survival Coalition.

† Study name is provided only if applicable.

‡ The number of evaluable subjects is shown.

§ Studies included in the systematic review.

section was tailored to contain only pertinent outcomes and relevant measures. Data extraction and tables were reviewed by P. A. Ganz and discussed with J. Howard-Anderson. J. Howard-Anderson reviewed the tables one more time to ensure accuracy of values presented in the tables.

Results

Summary of Reviewed Articles

A total of 28 articles specifically described the relevant outcomes identified for this review. Cross-sectional studies were the most common (15 studies), followed in frequency by longitudinal or follow-up studies (eight studies), and interventional studies (five studies). Data review by two investigators identified no discordance, and we present the results in three broad non-mutually exclusive tables describing QOL (Table 2), concerns regarding menopausal symptoms and fertility (Table 3), and behavioral outcomes as defined earlier (Table 4).

Large Cohort Studies

To promote understanding of the detailed results, we first describe the purpose and design of eight large cohort studies that focused on younger women with breast cancer from which many of the 28 published articles selected for this review emanated (Table 1). Additionally, many of these studies led to other published articles that were not included in this review because they did not meet the inclusion criteria. As described in Table 1, The Breast Cancer in Young Women (BCYW) Study is one of the earliest cohort studies to investigate breast cancer survivors younger than age 51 years at the time of diagnosis (13,20–23,37,48). The first phase of the study aimed to identify psychosocial problems and symptomatic complaints affecting physical functioning in younger breast cancer survivors, so that effective psychoeducational support group interventions could be designed and tested in a subsequent second phase of the study (48). Five-year follow-up studies were performed on cohorts from both phases to analyze change in QOL and rates of physical activity (21,37). Fobair et al. (23) combined data from both phases of the BCYW Study to examine sexual functioning and body image.

Allen et al. (39) recruited breast cancer survivors younger than age 51 years in a randomized controlled trial for testing a problem-solving psychosocial intervention aimed at improving QOL. Duffy et al. (25) used the baseline data from this randomized trial (39) to examine the rates of reproductive health counseling performed by physicians.

The Cancer and Menopause Study (CAMS) examined a cross-sectional sample of breast cancer survivors younger than 51 years at diagnosis who were surveyed 2–10 years after their diagnosis (4,15,36,57–59). The first phase of this study consisted of a mailed questionnaire (4,15). In the second phase, a subgroup of the women surveyed in the first phase was invited for in-person assessments of anthropometric indices, cholesterol, bone mineral density, and blood pressure (36,57). Additional studies with a subsample of the participants in the second phase focused on cognitive functioning and its relationship to adjuvant therapy exposures (58,59).

In 2004 and 2005, Avis et al. (18,19) aimed to describe and analyze a wide range of concerns regarding menopausal symptoms

and QOL in a cross-sectional sample of breast cancer patients younger than 51 years at diagnosis, surveyed within 3.5 years of diagnosis. Later in 2007, Manuel et al. (60) used this same database and examined the relationship between QOL and coping.

In collaboration with Nancy E. Avis, Danhauer et al. (28) and Burwell et al. (27) performed longitudinal studies with women younger than age 51 years, starting within 6 months of their initial breast cancer surgery. Danhauer et al. (28) examined the relationships between QOL, coping strategies, and social support, whereas Burwell et al. (27) only included sexually active participants and examined sexual difficulties. The participants in both of these studies also took part in a randomized trial in which women received either a booklet or a videotape depicting common reactions to a breast cancer diagnosis; however, we learned that the results of this trial will not be published (S. R. Burwell, personal communication).

Partridge et al. (16) and Leining et al. (17) collaborated with the Young Survival Coalition (YSC), an online international support network for young women with breast cancer, and recruited very young breast cancer survivors (aged <41 years) for a survey study. Partridge et al. (16) investigated attitudes and concerns about fertility, whereas Leining et al. (17) studied the prevalence of menopausal symptoms by including only a subset of participants who had been diagnosed with breast cancer more than a year earlier.

Bernstein et al. have conducted extensive research investigating the different risk factors for breast cancer in a cohort of younger women who were recruited shortly after diagnosis (56,61–67). In collaboration with Leslie Bernstein, Kendall et al. (24) performed a follow-up study on selected younger women who had been diagnosed with breast cancer at least 10 years earlier [participants were first described in the article by Bernstein et al. (56)]. This study (24) assessed changes in physical activity from before to after diagnosis and whether this affected QOL.

QOL and Psychosocial Outcomes

QOL, depression, anxiety, and stress perceptions have been examined in many studies of breast cancer survivors. In studies of women of all ages with breast cancer, younger women typically report responses indicating greater likelihood of clinical depression or greater severity of depressive symptoms (on standardized psychological self-report instruments), a heightened level of stress, and/or worse QOL when compared with older women with breast cancer (68–79). This effect of age was seen when age was used as a continuous variable or as a categorical variable. The definition of “younger women” ranged from younger than 40 years to younger than 55 years old. We identified 14 articles that examined these concerns in samples of younger women with breast cancer (Table 2).

Quality of Life. QOL was the most frequent outcome examined and described in 10 of the 14 identified articles (4,14,19–21, 24,28,29,38,39). Many studies used the 36-Item Short Form (SF-36) developed by the RAND Corporation (Santa Monica, CA) to assess the physical and emotional domains of health-related QOL. The Physical Component Summary (PCS) scores ranged from 46 to 51 and the Mental Component Summary (MCS) scores ranged from 45 to 50 in four articles that reported this measure

Table 2. Quality of life and psychosocial outcomes in younger women (aged <51 years) with breast cancer*

First author, year (reference)	Population and eligibility	Study design	Participant characteristics†	Relevant measures	Outcomes (QOL, depressive symptoms, anxiety)‡
Bloom, 1998 (13)	Cancer registry. BCYW, phase 1. Age <51 y at diagnosis, <7 mo after diagnosis.	Cross-sectional. 50% interviewed <2 mo after diagnosis, 50% interviewed 6–7 mo after diagnosis.	41% subjects were aged <45 y at survey. n = 308 subjects.	CES-D, illness intrusiveness, cancer problem scale, SF-36, Rosenberg's self-esteem.	Depressive symptoms: illness severity, body image, symptom distress, pain, and physical functioning indirectly associated with CES-D score. Illness intrusiveness is a mediator. Illness intrusiveness, physical functioning, worry of future, self-esteem, and emotional support directly associated with CES-D score.
Bloom, 2001 (20)	Cancer registry. BCYW, phase 1 [same as Bloom, 1998 (13)]. Age <51 y at diagnosis, <7 mo after diagnosis.	Cross-sectional. 50% interviewed <2 mo after diagnosis, 50% interviewed 6–7 mo after diagnosis.	Mean age 44 y at survey. 41% subjects had CT. n = 336 subjects.	SF-36, SNI, instrumental support scale, PSS.	QOL: Mean (SD) PCS score was 45.6 (9.2); mean (SD) MCS score was 45.4 (11.7). Emotional support and self-esteem positively associated with MCS score. Palliative coping (use of tobacco and drugs), CT, and symptom distress negatively associated with MCS score. Larger, integrated social networks associated with more emotional and instrumental support. Instrumental support negatively correlated with PCS score.
Wong-Kim, 2005 (22)	Cancer registry. BCYW, phase 1 [same as Bloom, 1998 (13)]. Age <51 y at diagnosis, <7 mo after diagnosis.	Cross-sectional. 50% interviewed <2 mo after diagnosis, 50% interviewed 6–7 mo after diagnosis.	Median age 45 y at survey. n = 331 subjects.	CES-D, Rosenberg's self-esteem, biological symptoms scale.	Depressive symptoms: Mean (SD) CES-D score was 16.18 (4.02). Bodily pain associated with CES-D score. Self-esteem, emotional support, and age negatively associated with CES-D score.
Bloom, 2004 (21)	Cancer registry. 5-y F/U of BCYW (Bloom, 1998 and 2001 (13,20)) Age <51 y at diagnosis, 5 y after diagnosis.	Longitudinal. Compared data to Bloom, 1998 and 2001.	Median age 45 y at survey. 53% had CT. n = 185 subjects.	SF-36, history of chronic conditions, Rosenberg's self-esteem, cancer problem scale.	QOL: All SF-36 scores (except general health subscale) improved (mean physical functioning score: 82.4–87.8, mental health score 72.5–78.0). Improving mental QOL associated with fewer chronic conditions and smaller decrease in emotional support. Improving physical QOL associated with fewer chronic conditions, CT, employment, and having no children at home. Anxiety: 52% "overly stressed, tense, or anxious." 68% had anxiety about the future. Worry about future and intrusiveness of treatment improved since diagnosis.
Sammarco, 2001 (38)	Cancer registry and American Cancer Society. Age <50 y at diagnosis.	Cross-sectional.	Mean age 44 y at diagnosis, analyzed at mean 3.4 y after diagnosis. 68% had CT. n = 101 subjects.	QLI-CV, Mishel uncertainty in illness, social support questionnaire.	QOL: Mean (SD) total QLI-CV score was 21.96 (4.46). QOL associated with increased social support and less uncertainty.
Allen, 2002 (39)	Clinic based. Age <51 y at diagnosis, starting CT.	RCT (problem-solving intervention). Baseline: start of CT. F/U: 4 and 8 mo later. Intervention lasted 12 wk.	Mean age 42 y at baseline. n = 164 subjects.	CARES, MHI-5, SPSI-R.	QOL: Mean (SD) baseline CARES global score: control group, 1.89 (0.5); experimental group, 1.90 (0.54). Mean (SD) MHI-5 score: control group, 64.6 (16); experimental group, 65.2 (17). Mean (SD) MHI-5 score for all subjects improved at 4 mo FwU. No differences between groups at 8 mo for CARES or MHI-5 score. Intervention improved CARES score more at 8 mo F/U in group with average or good problem-solving skills at baseline (assessed by SPSI-R).

(Table continues)

Table 2 (Continued).

First author, year (reference)	Population and eligibility	Study design	Participant characteristics	Relevant measures	Outcomes (QOL, depressive symptoms, anxiety)#
Ganz, 2003 (4)	Cancer registry, CAMS. Age <51 y at diagnosis, 2–10 y after diagnosis.	Cross-sectional. Analyzed by age at diagnosis (25–34, 35–39, 40–44, 45–51 y).	Mean age 50 y at survey, analyzed at a mean 6 y after diagnosis. 62% had CT. n = 577 subjects.	CES-D, SF-36, menstrual status, LOL.	QOL: Mean (SD) PCS score was 50.2 (9.5). Mean (SD) MCS score was 49.4 (10.6). Mean (SD) MCS score in the youngest group (age <35 y) was 44.7 (12.6), and in the oldest group (age 45–51 y) the mean (SD) MCS was 51.2 (9.6). The youngest group MCS score was >0.5 SD below reference MCS score. Vitality, social, emotional, and MCS subscores were lowest in youngest group. Women with menopause transition scored worst: mean (SD) MCS score was 41.9 (14.5). Mean (SD) LOL score was 7.4 (1.9). Depressive symptoms: 25.7% scored ≥ 16 on CES-D. Mean (SD) CES-D score was 11.2 (10.1). CES-D score was higher in youngest age group (for <35 y, mean [SD] score was 13.4 [11.8]; for 45–51 y, mean [SD] score was 10.2 [9.9]).
Casso, 2004 (14)	Clinic based. Age 40–49 y at diagnosis, 5–10 y after diagnosis.	Cross-sectional.	Mean age 44 y at diagnosis, analyzed at a mean 7.3 y after diagnosis. 55% had CT. n = 216 subjects.	CES-D, SF-36, CARES (sf).	QOL: Mean (SD) PCS score was 48.6 (11.5). Mean (SD) MCS score was 46.8 (11.3). Mean (SD) MCS score of the youngest group (45–49 y at survey) was 44.9 (12.5). CARES (sf) global mean 0.6 (SD 0.5). CT, breast symptoms, lower income, and mastectomy associated with lower QOL on ≥ 1 scale (SF-36, CARES, CES-D). Breast symptoms correlated with decreased QOL on all scales. Depressive symptoms: Mean (SD) CES-D score was 11.8 (10.6) for all participants; mean (SD) score for the youngest group (45–49 y at survey) was 13.6 (12.4). Pain associated with depression. Anxiety: 56% reported a fear of recurrence.
Partridge, 2004 (16)	Support group members, YSC. Age <41 y, premenopausal at diagnosis.	Cross-sectional. Web-based survey.	Mean age 33 y at diagnosis, mean age 36 y at survey. 62% were analyzed <2 y after diagnosis. n = 657 subjects.	HADS, Lasry fear of recurrence.	
Kendall, 2005 (24)	Cancer registry. From case-control study [Bernstein, 1994 [56]]. Age <41 y at diagnosis, all white, >10 y after diagnosis.	F/U survey, 10 y later. To examine exercise patterns at age 10, 16 and 25 y, and 2 and 9 y after diagnosis.	Mean age 50 y at survey, analyzed at a mean 13.2 y after diagnosis. 45% had CT. n = 371 subjects.	SF-36.	QOL: Mean (SD) MCS score was 50.0 (9.8). Mean (SD) PCS score was 50.9 (9.8). MCS and PCS scores were similar to the reference scores for 1998 US female population without cancer.
Avis, 2005 (19)	Clinic based. Age <51 y at diagnosis, <3.5 y after diagnosis.	Cross-sectional.	Mean age 42 y at diagnosis, analyzed at a mean 23 mo after diagnosis. 75% had CT. n = 202 subjects.	FACT-B, LOL, CARES, BCPT symptom checklist, ways of coping, preparedness.	QOL: Mean (SD) FACT-B score was 111 (19.11), mean (SD) LOL score was 7.2 (1.78), statistically significantly lower than reference sample of women without cancer. FACT-B score negatively associated with ongoing treatment, vaginal dryness, relationship and body image problems, not working, missing 3 mo of activities, and wishful thinking. Positively associated with employment and cognitive restructuring. LOL score negatively associated with recurrence, no relationship since diagnosis, relationship or sexual functioning problems, not feeling prepared, wishful thinking and not using certain coping strategies.

(Table continues)

Table 2 (Continued).

First author, year (reference)	Population and eligibility	Study design	Participant characteristics	Relevant measures	Outcomes (QOL, depressive symptoms, anxiety)†
Danhauer, 2009 (28)	Clinic based. Age <51 y at diagnosis, 4–26 wk after surgery.	Longitudinal randomized trial (brochure or video). Baseline: <26 wk after surgery. F/U: 6–8 wk and 6–8 mo after intervention.	Mean age 43 y at baseline. 53% had CT. n = 267 subjects.	FACT-B, ways of coping.	QOL: Lower QOL correlated with greater use of social support, keeping feelings to self, and wishful thinking. Better QOL associated with more active coping strategies. QOL improved from baseline to 6–8 mo F/U. (FACT-B mean score was approximately 109 baseline, 111 at 6–8 wk, 116 at 6–8 mo). Positive cognitive restructuring was most frequently used coping strategy.
Gorman, 2010 (30)	Multiclinic, recruited from RCT (subset of WHEL study). Age <41 y at diagnosis, entered WHEL study <4 y after diagnosis.	F/U survey. Compare current recalled reproductive concerns to WHEL study assessments of depression at baseline, 1, 2, 3, 4, 6 y.	Mean age 37 y at diagnosis. Mean 1.5 y after diagnosis at WHEL baseline. Mean 11.9 y after diagnosis at F/U study. 89% had CT. n = 131 subjects.	CES-D (sf), RCS, SF-36, MOS social support.	Depressive symptoms: At baseline of F/U study, mean (SE) CES-D (sf) score was 0.056 (0.01). 18.3% had elevated depressive symptoms (CES-D (sf) \geq 0.06). CES-D (sf) score positively associated with increased reproductive concerns and negatively associated with better physical health and greater social support.
Gorman, 2010 (29)	Multiclinic, recruited from RCT (subset of WHEL study). Age <41 y at diagnosis, premenopausal <4 y after diagnosis.	Nested case-control study, longitudinal. Case subjects had at least one child after WHEL enrollment, and control subjects did not. Baseline: After treatment, <4 y after diagnosis. F/U: every year until pregnancy occurred.	74% subjects were aged <35 y at diagnosis. 95% had CT. n = 81 subjects.	SF-36 (PHSS, MHSS).	QOL: Mean (SE) PHSS score before pregnancy were similar in case subjects (85.49 [2.1]) and control subjects (81.27 [1.5]). Mean (SE) MHSS score was higher in case subjects (81.7 [2.3]) than control subjects (72.46 [1.8]). PHSS score was associated with marriage, lower BMI, and older age. MHSS score was associated with lower BMI.

* BCPT = Breast Cancer Prevention Trial; BCYW = Breast Cancer in Young Women; BMI = body mass index; F/U = follow-up; CARES = Cancer Rehabilitation Evaluation System; CAMS = Cancer and Menopause Study; CES-D = Center of Epidemiological Studies Depression Scale; CT = chemotherapy; FACT-B = Functional Assessment of Cancer Therapy–Breast Cancer; HADS = Hospitalized Anxiety and Depression Scale; LOL = Ladder of Life; MCS = Mental Component Summary Scale of SF-36; MHI-5 = Mental Health Inventory; MHSS = Mental Health Summary Scale of SF-36; MOS = Medical Outcomes Study; PABC = Psychosocial Aspects of Breast Cancer Study Group; PCS = Physical Component Summary Scale of SF-36; PHSS = Physical Health Summary Scale of SF-36; PSS = Perceived Social Support; QLI-CV = Ferrans and Powers QOL Index-Cancer Version; QOL = quality of life; RCT = randomized controlled trial; RSC = Reproductive Concerns Scale; SD = standard deviation; SE = standard error; sf = short form; SF-36 = RAND short form (also known as Medical Outcomes Study); SNI = Berkman–Syme Social Networks Index; SPS-IR = Social Problem Solving Inventory-Revised; WHEL = Women’s Healthy Eating and Living; YSC = Young Survival Coalition.

† The number of evaluable subjects are shown. “At survey” refers to the time when participants’ data was first obtained (via in-person interview, phone interview, mail-in, computer, or other form of questionnaire). This is opposed to “at diagnosis,” which refers to data from the participant when she was first diagnosed.

‡ PCS and MCS are standardized scores, derived from the RAND SF-36 assessment used to measure QOL. The population-based mean is set to a score of 50, with higher scores indicating a better QOL. The CES-D score is from a standardized measurement of depression. A CES-D score of 16 or higher is used to define clinically significant depressive symptoms. Higher scores indicate increased depressive symptoms. The QLI-CV score is another standardized way to measure QOL. Scores can range from 0 to 30, with higher scores indicating a better QOL. The CARES score is from a self-report questionnaire assessing QOL in five subcategories (physical, medical, psychological, sexual, and marital). Scores can range from 0 to 4, with higher scores indicating more problems. The MHI-5 is a standardized assessment used to measure emotional distress, adapted from the SF-36. Scores can range from 0 to 100, with higher scores indicating better emotional health. The LOL score is used to measure global quality of life. The scores range from 1 to 10, where 1 represents the worst QOL and 10 represents the best QOL. The FACT-B score is used to assess QOL based on physical, functional, emotional, and social well-being as well as breast cancer-specific concerns. The scores can range from 0 to 144, with higher scores indicating a greater QOL. MHSS and PHSS scores are both standardized ways to assess QOL, also derived from the RAND SF-36 assessment. Scores can range from 0 to 100, with higher scores indicating a greater QOL.

Table 3. Menopausal symptoms and fertility concerns in younger women (aged >51 years) with breast cancer*

First author, year (reference)	Population and eligibility	Study design	Participant characteristics	Relevant measures	Outcomes (menopause, symptoms, fertility concerns)
Ganz, 2003 (4)	Cancer registry, CAMS. Age <51 y at diagnosis, 2–10 y after diagnosis.	Cross-sectional. Analyzed by age at diagnosis (25–34, 35–39, 40–44, 45–50 y).	Mean age 50 y at survey, analyzed at a mean 6 y after diagnosis. 62% had CT. n = 577 subjects.	BCPT symptom checklist, reproductive history and menopausal status, sexual activity questionnaire.	Menopause: 68% premenopausal before diagnosis, 16% premenopausal at survey. Symptoms: Approximate prevalence: hot flashes (20%–65%), night sweats (20%–50%), less common in younger group. Breast sensitivity (40%–55%), most common in younger group. Vaginal discharge (15%–35%), dyspareunia (22%–32%), vaginal dryness (21%–55%).
Crandall, 2004 (15)	Cancer registry, CAMS [same as Ganz, 2003 (4)]. Age <51 y at diagnosis, 2–10 y after diagnosis.	Cross-sectional. Analyzed by menopausal status at survey.	Mean age 50 y at survey, analyzed at a mean 6 y after diagnosis. 64% had CT. n = 476 subjects.	BCPT symptom checklist, menopausal status.	Menopause: 59% had menopause transition during treatment, had higher prevalence, and severity of hot flashes compared with peri- or postmenopausal women without menopause transition. Symptoms: Prevalence 15%–71% (same data as Ganz, 2003). Hot flashes, pain with intercourse, vaginal dryness, weight gain more common and severe in peri- and postmenopausal women. Postmenopausal women seven times more likely to have vaginal dryness, five times more likely to have pain with intercourse than premenopausal women.
Casso, 2004 (14)	Clinic based. Age 40–49 y at diagnosis, 5–10 y after diagnosis.	Cross-sectional.	Mean age 44 y at diagnosis, analyzed at a mean 7.3 y after diagnosis. 55% had CT. n = 216 subjects.	General health characteristics survey.	Menopause: 83.6% postmenopausal at survey. Symptoms: 37.7% had breast-related symptoms (pain, swelling, numbness, etc).
Partridge, 2004 (16)	Support group members, YSC. Age <41 y, premenopausal at diagnosis.	Cross-sectional. Web-based survey.	Mean age 33 y at diagnosis, mean age 36 y at survey. 62% were analyzed <2 y after diagnosis. n = 657 subjects.	Survey on fertility.	Menopause: 61% had menopause concerns. Influenced treatment decisions in 30%. Fertility concerns: 73% had at least minor concerns about treatment infertility, 39% “very concerned.” Influenced treatment in 29%. 65% would have CT even if ≥50% chance of infertility. 72% discussed fertility with physician. 51% had fertility concerns adequately addressed. Fertility concern associated with desire for more children, prior number of pregnancies, and history of difficulty conceiving.
Leining, 2006 (17)	Support group members, YSC [subset of Partridge 2004 (16)]. Age <41 y, premenopausal, 1 y after diagnosis.	Cross-sectional. Web-based survey.	Mean age 33 y at diagnosis, mean age 36 y at survey. 53% were analyzed <3 y after diagnosis. 89% had CT. n = 370 subjects.	BCPT symptom checklist, menopausal status.	Menopause: 77% were premenopausal at assessment (excludes participants on ovarian suppression). Symptoms: Rated at least “slightly bothersome”: vaginal discharge (54%), breast sensitivity (52%), vaginal dryness (51%), hot flashes (46%), night sweats (46%), dyspareunia (39%). Postmenopausal or women on ovarian suppression most likely to report moderate–severe symptoms. More bothersome symptoms associated with current ovarian suppression, postmenopausal status, anxiety before diagnosis, pregnancy after diagnosis, prior CT, and lower financial status.

(Table continues)

Table 3 (Continued).

First author, year (reference)	Population and eligibility	Study design	Participant characteristics	Relevant measures	Outcomes (menopause, symptoms, fertility concerns)
Avis, 2004 and 2005 (18,19)	Clinic based. Age <51 y at diagnosis, <3.5 y after diagnosis.	Cross-sectional.	Mean age 42 y at diagnosis, analyzed at a mean 23 mo after diagnosis. 75% had CT. n = 204 subjects (18); n = 202 (19).	BCPT symptom checklist, CARES.	Menopause: CT was predictor of early menopause concerns. Symptoms†: Hot flashes (64%), vaginal dryness (49%), pain with intercourse (45%). Percentages higher than age-matched controls. 17% were “very bothered” by hot flashes. Mastectomy, CT, and missing 90 days of work associated with decreased sexual interest and/or sexual dysfunction. Fertility concerns: Concerns of premature menopause and pregnancy were highest rated concerns.
Bloom, 2004 (21)	Cancer registry. 5-y F/U of BCYW (Bloom 1998 and 2001 (13,20)). Age <51 y at diagnosis, 5 y after diagnosis.	Longitudinal. Compared data to Bloom 1998 and 2001.	Median age 45 y at survey. 53% had CT. n = 185 subjects.	Menopausal status, PABC, BCPT symptom checklist cancer problem scale.	Menopause: 75% postmenopausal (88% were treatment induced). Symptoms: Hot flashes (63%), sweats (51%), vaginal dryness (49%), sexual dysfunction: lack of desire (56%), difficulty with arousal (46%).
Fobair, 2006 (23)	Cancer registry. BCYW, phase 1 and 2 (1994–1997) Age <51 y at diagnosis, in partnered relationship, 2–7 mo after diagnosis.	Cross-sectional.	20% of subjects were aged <40 y at survey. 50% were analyzed 5–7 mo after diagnosis. 59% had CT. n = 549 subjects.	Menstrual history, body image problems, SF-36, Rosenberg’s self-esteem, MOS-sexual functioning.	Menopause: 63% irregular or absent menses. 76% of CT group were peri- or postmenopausal, 43% of no CT group. Symptoms: Hot flashes (41%), sweats (41%), vaginal dryness (34% overall; 44% in CT group, 18% in no CT group). Increased sexual problems associated with being married, vaginal dryness, worse mental health, a partner with difficulty understanding feelings, and more body image problems.
Duffy, 2005 (25)	Clinic based. Age <51 y, premenopausal at diagnosis, starting CT.	Cross-sectional. Baseline data of interventional trial (39).	33% of subjects were aged <40 y at diagnosis, analyzed at a mean 3.7 wk after starting CT. n = 144 subjects.	CARES	Menopause: 68% discussed early menopause with physician. Hormonal treatment and early-stage cancer associated with discussing menopause with physician. Having children and seeing ≤4 physicians negatively associated. Fertility concerns: 34% discussed fertility with physician. Having discussion was associated with younger age, less anxiety in medical situations, and more difficulty communicating with medical team.
Thewes, 2005 (26)	Clinic based. Age <41 y at diagnosis, 6–60 mo after diagnosis.	Cross-sectional.	Mean age 35 y at diagnosis, analyzed at a mean 29 mo after diagnosis. 88% had CT. n = 228 subjects.	Survey on fertility and menopause, HADS, Spielberger state anxiety inventory-sf, GCS, FACT-B.	Menopause: More important to receive menopausal info than fertility info during treatment and F/U. 86% discussed menopause with physician. 25% saw menopause specialist. Plans for children, endocrine therapy, and poorer QOL associated with rating menopause information more important. Fertility concerns: More important to receive fertility info than menopause info at diagnosis. 71% discussed fertility with physician. 29% saw fertility specialist. Plans for children, childless at diagnosis, and preferring more info associated with rating fertility information more important.

(Table continues)

Table 3 (Continued).

First author, year (reference)	Population and eligibility	Study design	Participant characteristics†	Relevant measures	Outcomes (menopause, symptoms, fertility concerns)
Burwell, 2006 (27)	Clinic based. Age <51 y at diagnosis, 4–26 wk after surgery, sexually active.	Longitudinal, randomized trial (brochure or video). Baseline: <26 wk after surgery. F/U: 6–8 wk and 6–8 mo after intervention.	Median age 43 y at diagnosis. Baseline survey was done at a median of 11.3 wk after surgery. 56% had CT. n = 209 subjects.	MOS-sexual functioning, FACT-B, menopausal status.	Menopause: 9% became postmenopausal after surgery. 36% were peri- or postmenopausal at baseline. Women with menopause transition and CT had more sexual problems than women that did not enter menopause. Symptoms: MOS sexual problem score was greater after diagnosis. Mean MOS (SD) score before diagnosis was 16.7 (23.9), at F/U surveys mean (SD) score was 35.6 (29.2), 26.1 (27.0), and 27.6 (28.2). Feeling sexually attractive predicted less sexual problems. CT predicted sexual problems at baseline. Negative effects of CT decreased over time. Longitudinal model: physical and social well-being, perceived sexual attractiveness, and radiation inversely correlated with sexual problems over time.
Gorman, 2010 (30)	Multicentric, recruited from RCT (subset of WHEL study). Age <41 y at diagnosis, entered WHEL study < 4 y after diagnosis.	F/U survey. Compare current recalled reproductive concerns to WHEL study assessments of depression at baseline, 1, 2, 3, 4, 6 y.	Mean age 37 y at diagnosis. Mean 1.5 y after diagnosis at WHEL baseline. Mean 11.9 y after diagnosis at F/U study. 89% had CT. n = 131 subjects.	Menopausal status, recalled RCS.	Menopause: 72.5% had treatment-induced amenorrhea/irregular periods. 17% had treatment-related ovarian damage. Fertility concerns: Fertility was factor in treatment decision in 11.5%. 47.3% avoided pregnancy after diagnosis. 48.1% wanted more children before diagnosis, but only 27.5% did after diagnosis.

* The number of evaluable subjects is shown. BCPT = Breast Cancer Prevention Trial; BCYW = Breast Cancer in Young Women; CAMS = Cancer and Menopause Study; CARES = Cancer Rehabilitation Evaluation System; CT = chemotherapy; FACT-B = Functional Assessment of Cancer Therapy–Breast Cancer; F/U = follow-up; GCS = Greene Climacteric Scale; HADS = Hospitalized Anxiety and Depression Scale; MOS = Medical Outcomes Study; PABC = Psychosocial Aspects of Breast Cancer Study; QOL = quality of life; RSC = Reproductive Concerns Scale; SD = standard deviation; sf = short form; SF-36 = RAND short form (also known as Medical Outcomes Study); WHEL = Women's Healthy Eating and Living; YSC = Young Survival Coalition.

† The number of evaluable subjects is shown. "At survey" refers to the time when participants' data was first obtained (via in-person interview, phone interview, mail-in, computer, or other form of questionnaire). This is opposed to "at diagnosis" which refers to data from the participant when she was first diagnosed.

‡ Percentages were taken from Avis, 2004 (18). These values are reported slightly lower in Avis, 2005 (19).

Table 4. Behavioral outcomes in younger women (aged <51 years) with breast cancer*

First author, year (reference)	Population and eligibility	Study design	Participant characteristics†	Relevant measures	Outcomes (weight, PA/energy balance)
Loprinzi, 1996 (31)	Clinic based. Premenopausal, CT planned, before or <2 wk after CT start.	RCT (dietician counseling). Baseline: before or within 2 wk of CT. F/U: 4- to 6-wk intervals and every 3 mo while receiving CT.	Median age 43 y at survey. 48% had CMF. n = 107 subjects.	Weight, hip and waist circumference, diet log, survey on exercise, diet and CT side effects. MMPI.	Weight: 33% ≥ 20% over "ideal weight" at baseline. At 6-mo F/U, median weight gain was 3 kg (range -10 to +15 kg). Intervention was ineffective. Increased weight gain associated with higher BMI at baseline, diet in previous 6 mo, and higher MMPI introversion and obsessive/compulsive score.
Demark-Wahnefried 1997 (32)	Clinic based. Premenopausal, CT planned, 2 wk after surgery.	Longitudinal, pilot. Baseline: 2 wk after surgery. F/U: Middle and end of treatment. Retrospective chart review done >1 y after treatment start.	Mean age 40 y at survey. 50% had AC, four cycles. n = 18 subjects.	Diet log, Stanford Five-City Project, resting metabolic rate, diet-induced thermogenesis, body composition, weight (chart review).	Weight: No change from baseline to end of treatment. 3.8 kg mean gain from treatment end to 1 y F/U (n = 14 subjects). No change in body composition and fat distribution. PA/energy balance: PA and energy intake declined over treatment. Resting metabolic rate declined during treatment, but returned to baseline by end.
Kutyrec, 1999 (33)	Cancer registry. Pre- or perimenopausal, planned CT or radiation before treatment.	Longitudinal comparison (CT vs radiation). Baseline: before adjuvant treatment, after surgery. F/U: end of treatment (12 wk).	Mean age 44 y (CT group), 42 y (radiation group) at survey. 44% had AC. n = 18 subjects.	Body composition, diet log, resting energy expenditure, 3-d records of PA, weight (chart review).	Weight: No change in weight or fat mass. Lean body mass decreased, body fat % increased. On later chart review, four of seven (CT group) subjects gained weight (mean 4.7 kg) and four of six (radiation group) subjects gained weight (mean 4.1 kg). PA/energy balance: No change in PA, total energy expenditure, and energy intake between groups or over time. Resting energy expenditure (per kg of lean body mass) was greater after treatment.
Demark-Wahnefried 2001 (34)	Clinic based. Premenopausal, ≤3 wk after surgery.	Longitudinal comparison (CT vs no CT). Baseline: ≤3 wk after surgery, before adjuvant treatment. F/U: 2, 6, and 12 mo after diagnosis.	Mean age 41 y at survey. 68% had CT (20% CMF). n = 53 subjects.	Diet log, FFC, Stanford Five-City Project, resting energy expenditure, height, weight, body composition.	Weight: At 12 mo after diagnosis, no CT group gained mean 1 kg body weight, -0.1% body fat, 0.1 kg fat mass, and 0.8 kg lean body mass. CT group gained mean 2.1 kg body weight, 2.2% body fat, 2.3 kg fat mass, and -0.4 kg lean body mass. Noted weight gain without increase in muscle mass (sarcopenic obesity). Gain in % body fat and fat mass greater in CT group. PA/energy balance: No difference in energy intake, resting energy expenditure, and PA between groups over time. PA levels dropped in first month of treatment but then steadily increased.
Crandall, 2004 (15)	Cancer registry, CAMS [same as Ganz 2003 (4)]. Age <51 y at diagnosis, 2-10 y after diagnosis.	Cross-sectional. Analyzed by menopausal status at survey.	Mean age 50 y at survey, analyzed at a mean 6 y after diagnosis. 64% had CT. n = 476 subjects.	BCPT symptom checklist, menopausal status.	Weight: 24%, 40%, and 43% of pre-, peri-, and postmenopausal reported being bothered by weight gain. Postmenopausal women with treatment-induced menopause had highest odds of gaining weight (OR = 2.94, P = .01).
Herman, 2005 (36)	Cancer registry, CAMS [same as Ganz 2003(4)]. Age <51 y at diagnosis, 2-10 y after diagnosis.	Cross-sectional. Subgroup completed an additional in-person assessment.	Mean age 43 y at diagnosis, analyzed at a mean 6 y after diagnosis. 66% had CT. n = 441 subjects; n = 289 in-person assessments.	BCPT symptom checklist, menopausal status, SF-36, PEPI-Q, BP, weight, height, waist and hip circumference, fasting lipid panel.	Weight: 43% had BMI ≥25. BMI associated with BMI at diagnosis, nonwhite ethnicity, income <\$75 000, greater time since diagnosis, less PA, and body image negativity. Treatment and menopausal status not associated with obesity. PA/energy balance: 35% performed moderate-heavy work PA, 39% moderate-heavy home PA, and 50% moderate-heavy leisure PA. Increased work, home and leisure activity was associated with higher SF-36 energy and physical functioning scores.

(Table continues)

Table 4 (Continued).

First author, year (reference)	Population and eligibility	Study design	Participant characteristics†	Relevant measures	Outcomes (weight, PA/energy balance)
Ingram, 2004 (35)	Clinic based. Premenopausal, CT planned, surgery within last 3 mo.	Longitudinal. Baseline: before CT. F/U: CT cycles 2, 4, 6, and 1 mo after treatment.	Mean age 44 y at survey. 51% had AC, four cycles. 49% had CMF or CEF, six cycles. n = 76 subjects.	Height, weight, body composition.	Weight: 45% had BMI ≥ 25 (mean = 26). 34.2% gained weight (≥ 2.5 kg); 55.3% maintained stable weight; 10.5 lost weight (≥ 2.5 kg). Mean of 1.4 kg weight gain (0.5 increase in BMI) for all; 5 kg in the gained weight group.
Avis, 2004 and 2005 (18, 19)	Clinic based. Age <51 y at diagnosis, <3.5 y after diagnosis.	Cross-sectional.	Mean age 42 y at diagnosis, analyzed at a mean 23 mo after diagnosis. 75% had CT. n = 204 subjects (18); n = 202 subjects (19).	CARES, symptoms.	Weight: 52% at least "a little bothered" by weight gain. 17% "very bothered" by weight gain.
Kendall, 2005 (24)	Cancer registry. From case-control study [Bernstein, 1994(56)]. Age <41 y at diagnosis, all white, > 10 y after diagnosis.	F/U survey, 10 y later. To examine exercise patterns at age 10, 16, and 25 y, and 2 and 9 y after diagnosis.	Mean age 50 y at survey, analyzed at a mean 13.2 y after diagnosis. 45% had CT. n = 371 subjects.	Calendar of life events, SF-36, comorbidities, treatment history, exercise history.	Weight: 83.2% gained weight from diagnosis to F/U. PA/energy balance: 44% were inactive at 2 and 9 y after diagnosis. Mean of 14.2 MET/wk exercise after diagnosis, increase of 4.5 MET from before diagnosis. Increasing MET/wk associated with increase in PCS, physical functioning, pain and general health sub scale. 28% were non-exercisers before and after diagnosis, 16% stopped exercising after diagnosis, 23% started exercising after diagnosis, and 33% exercised before and after diagnosis. Exercise starters had highest PCS and MCS score. Before to after diagnosis activity change was not associated with age, treatment, comorbidities or weight change.
Leining, 2006 (17)	Support group members, YSC. Age <41 y at diagnosis, premenopausal, >1 y after diagnosis.	Cross-sectional. Web-based survey.	Mean age 33 y at diagnosis, mean age 36 y at survey. 53% were analyzed <3 y after diagnosis. 89% had CT. n = 370 subjects.	BCPT symptom checklist.	Weight: 62% moderately to severely bothered by weight gain. Those who were postmenopausal on tamoxifen or using ovarian suppression were most bothered compared with those still premenopausal.
Fobair, 2006 (23)	Cancer Registry. BCYW, phase 1 and 2 (1994-1997). Age <51 y at diagnosis, in partnered relationship, 2-7 mo after diagnosis.	Cross-sectional.	20% of subjects were aged <40 y at survey. 50% were analyzed 5-7 mo after diagnosis. 59% had CT. n = 549 subjects.	Body image problems, weight gain.	Weight: 38% bothered by weight gain or weight loss. Weight change concern associated with body image problems.

(Table continues)

Table 4 (Continued).

First author, year (reference)	Population and eligibility	Study design	Participant characteristics†	Relevant measures	Outcomes (weight, PA/energy balance)
Bloom, 2008 (37)	Cancer registry. Age <51 y at diagnosis, 5 y after diagnosis.	RCT (socioeducational intervention). Baseline: 5 y after diagnosis. F/U: after intervention, 56 mo.	13% of subjects were aged <40 y at diagnosis. 55% had CT. n = 404 subjects.	Breast cancer survey, PA, breast cancer problems scale, SNI, weight, height.	PA/energy balance: Controls: 77% exercised ≥ 2 d/wk pre-intervention, 79% after intervention. Intervention group: 71% exercised ≥ 2 d/wk pre-intervention, 77% after intervention. Intervention group increased PA more than control group (57% vs. 47%, $P = 0.036$). Increase in PA associated with being in intervention group, large social network, no mastectomy, and exercising ≥ 4 times/wk at baseline.

* AC = doxorubicin, cyclophosphamide; BCPT = Breast Cancer Prevention Trial; BCYW = Breast Cancer in Young Women; BMI = body mass index; BP = blood pressure; CARES = Cancer Rehabilitation Evaluation System; CAMS = Cancer and Menopause Study; CMIF = cyclophosphamide, methotrexate, fluorouracil; CEF = cyclophosphamide, epirubicin, fluorouracil; CT = chemotherapy; FFQ = Food-Frequency Questionnaire; F/U = follow-up; MET = metabolic equivalent of energy expenditure; MMPI = Minnesota Multiphasic Personality Inventory; OR = odds ratio; PA = physical activity; PEPIQ = postmenopausal Estrogens and progesterins intervention physical activity assessment questionnaire; RCT = randomized controlled trial; SF-36 = RAND short form (also known as Medical Outcomes Study); SNI = Berkman-Syme Social Networks Index; YSC = Young Survival Coalition.

† The number of evaluable subjects is shown. "At survey" refers to the time when participants' data was first obtained (via in-person interview, phone interview, mail-in or computer questionnaire). This is opposed to "at diagnosis," which refers to data from the participant when she was first diagnosed.

(4,14,20,24). The MCS mean score of women with breast cancer in all of these four articles was below the national reference MCS mean score of women without cancer [standardized to a score of 50 for all ages and 50.07 for a population-based norm-referenced group aged 45–54 years (80)]. The PCS mean score of women with breast cancer was also below the national reference PCS mean score of women without cancer [standardized to a score of 50 for all ages and 48.95 in women aged 45–54 years (80)] in two of the four articles (14,20) reporting this value. Avis et al. (19) used the Ladder of Life (LOL) scale to assess QOL and found that global QOL scores were statistically significantly ($P < .001$) worse in recently diagnosed young breast cancer survivors than in a control sample of young women without cancer (19).

In several cross-sectional studies (4,14,19,20,38), multivariable regression models were used to examine which participant characteristics (independent variable) were associated with a lower or higher QOL (dependent variable) score. Having medical problems or more physical symptom complaints, such as breast pain, comorbid conditions, sexual dysfunction, or active cancer treatment, was associated with poorer QOL (4,14,19,20). Greater social or emotional support (20,38) was associated with better QOL. Being employed, missing fewer days of work after diagnosis and coping with breast cancer through positive cognitive restructuring was associated with better physical or mental QOL (19). In the few studies that analyzed changes in QOL over time, different aspects of physical and mental QOL improved in young breast cancer survivors (21,28,39). The duration and timing of follow-up assessments in these studies varied, limiting direct comparisons.

Depressive Symptoms. Depressive symptoms (such as depressed mood, guilt, worthlessness, hopelessness, loss of sleep, psychomotor retardation, and appetite disturbance, which are evaluated by standardized clinical assessments of depression) were commonly reported by younger breast cancer survivors (4,13,14,23,30). Four studies reported mean scores using different standardized measures (4,14,22,30). The Center for Epidemiologic Studies Depression Scale (CES-D) score reported by Wong-Kim and Bloom (22) (mean score = 16.8, SD = 4.02) exceeded the cut-point score defining clinically significant depressive symptoms (CES-D score ≥ 16). Mean CES-D scores were lower in samples assessed by Ganz et al. (4) (mean [SD] score = 11.2 [10.1]) and Casso et al. (14) (mean [SD] score = 11.8 [10.6]). However, it should be noted that the youngest age group in both these studies [25–34 years at diagnosis in Ganz et al. (4) and 45–49 years at survey in Casso et al. (14)] reported the highest level of depressive symptoms. Ganz et al. (4) and Gorman et al. (30) reported that 26% and 18% of their participants, respectively, met or exceeded the cut point for clinically significant depressive symptoms [ie, CES-D score ≥ 16 , or CES-D short form (sf) score ≥ 0.06 (4,73)]. Depressive symptoms were less pronounced in a general community sample of white women aged 28–40 years (mean [SD] CES-D score = 9.6 [7.5]), and 17.7% of women exceeded the cut-point score for clinically significant depressive symptoms (CES-D score ≥ 16) (81). Depressive symptoms were also less pronounced in a community sample of women aged 50–96 years (mean [SD] CES-D score = 8.7 [7.2]), with 15% of women at or above the CES-D cut-point score for clinically significant depressive symptoms (81,82).

Several researchers created models to examine independent factors associated with depressive symptoms after diagnosis. Bloom et al. (13) and Wong-Kim and Bloom (22) found that self-esteem and emotional support were both negatively associated with depressive symptoms. The model described by Bloom et al. (13) also included poor physical functioning, and the model described by Wong-Kim et al. (22) identified younger age as an independent variable, which was associated with more depressive symptoms. Of these two studies, one (13) found that illness intrusiveness (defined as disruptions in daily life and activities caused by the illness) and worries about the future were related to greater depressive symptoms. Furthermore, higher levels of illness intrusiveness mediated the relationship between disease severity, body image, symptom distress, and pain on greater symptoms of depression. The other study (22) found that bodily pain was linked to greater depressive symptoms. In another model (30), reproductive concerns were positively associated with more depressive symptoms, whereas better physical health and greater social support were protective.

Anxiety. Symptoms of anxiety and/or stress were examined in two studies. Bloom et al. (21) reported that even 5 years after diagnosis, 52% of women reported that they were generally “overly stressed, tense, or anxious” and 68% had anxiety about the future. Despite these long-term complaints, the patient ratings of cancer intrusiveness and worry about the future showed a statistically significant improvement over 5 years (21). Partridge et al. (16) reported similar findings, in which 56% of the sample reported fear of recurrence.

Symptoms and Concerns Regarding Menopausal Status and Fertility Changes

Adjuvant chemotherapy can induce transient or permanent amenorrhea in premenopausal women (40–45,83), with resultant vasomotor symptoms and distress related to the potential for infertility. Some studies suggest that compared with older women, younger women suffer greater chemotherapy toxicity, with greater difficulty managing the side effects of therapy and maintaining daily routines (7). We identified 12 articles that addressed chemotherapy-induced menopause, physical symptoms related to amenorrhea, and reproductive concerns in younger breast cancer survivors (Table 3). When available in the article, we also reported the percentage of women who became amenorrheic with treatment.

Menopausal Concerns. Several articles documented the percentage (range = 33%–73%) of women who became peri- or postmenopausal after treatment (4,15,17,21,30). Some of these reports were prospective and others retrospective. Additional studies reported on the percentage of women who were peri- or postmenopausal at follow-up (range = 36%–84%) but did not delineate who had transitioned from pre- to postmenopause during the course of breast cancer treatment (14,23,27). The reporting of key variables such as age at diagnosis, type of adjuvant treatment, time since diagnosis, and when menopausal status was assessed were not uniformly described. Leining et al. (17) examined the youngest sample of premenopausal women (mean age of 33

years) and reported the lowest rate (33%) of women developing treatment-associated amenorrhea.

Poorer outcomes were reported in younger women who experienced a menopausal transition than in those who did not become menopausal. Burwell et al. (27) noted that women who entered menopause during, or as a result of, chemotherapy had more sexual problems. Similarly, Crandall et al. (15) found that women with treatment-induced menopause experienced a higher prevalence and severity of hot flashes than women who were peri- or postmenopausal and had not become amenorrheic as a result of cancer treatment.

Younger women are also concerned about entering menopause. In one study, 61% of women who were 40 years or younger at diagnosis reported being concerned about menopause, and 30% said that this concern influenced their treatment decisions (16). According to Duffy et al. (25) and Thewes et al. (26), 68% and 86% of women, respectively, recalled discussing menopause with their doctor, and 25% reported seeing a specialist in menopause management. Women were more likely to rate receiving menopausal information as important if they planned to have children, were treated with endocrine therapy, or had poorer QOL (26).

Symptoms. Vasomotor symptoms associated with the onset of amenorrhea were frequently reported (4,14,15,17–19,21,23,27). High rates of symptoms (>50% in some subgroups of women) were reported for hot flashes (4,15,18,21), sweats (21), breast pain or sensitivity (4,15,17), vaginal dryness (4,15,17), vaginal discharge (17), and lack of sexual desire (21). Many symptoms were specifically related to treatment-associated transitions in menopausal status, rather than age group. Weight gain was also commonly reported, which will be discussed in detail later in the review.

Fertility Concerns. Several studies examined concerns related to fertility and reproductive options (16,18,25,26,30). Overall, receiving information pertaining to fertility and reproductive health was important to younger women, and often younger women did not receive all the information they needed or wanted on these topics. Partridge et al. (16) found that 73% of younger breast cancer survivors had at least minor concerns and 39% had major concerns about treatment-induced infertility. Furthermore, 29% reported that these concerns influenced their treatment decisions. Partridge et al. (16), Duffy et al. (25), and Thewes et al. (26) reported the percentage of women who recalled having a conversation about fertility with their physician, which ranged from 34% to 72%. Partridge et al. (16) found that approximately half the women felt that their fertility concerns were sufficiently addressed.

Being more concerned about fertility was associated with a desire to have more children (16,26), fewer previous pregnancies and a history of problems conceiving (16), having no children at diagnosis (26), and preferring more information (26).

Behavioral Outcomes

This section focuses on weight gain and physical inactivity after breast cancer treatments. We were interested in these two outcomes as they are potentially amenable to behavioral intervention and may prove to be important targets for reducing the risk of breast cancer recurrence, cause-specific mortality, and other

comorbid conditions (84–86). Weight gain is of particular concern in younger women with breast cancer because they tend to gain more weight after diagnosis than older women (87–91), especially in relationship to chemotherapy-induced menopausal transition (92).

The findings from the 13 articles that addressed weight gain, physical activity, or energy balance in younger breast cancer survivors are summarized in Table 4. When available in these articles, along with weight gain, we reported the prevalence of women who were overweight or obese after diagnosis. We also focused on outcomes associated with potentially modifiable behaviors that could minimize weight gain, specifically rates of physical activity, caloric intake, and energy expenditure.

Weight Gain. Obesity or weight gain was frequently described (15,17–19,23,24,31–36). Depending on the study, the percentage of women who either reported gaining weight or being bothered by gaining weight after diagnosis, ranged from 23% to 83% (15,17–19,23,24,35). This wide range in percentage of participants who gained weight, at least in part, results from the marked variation in medical treatments and length of follow-up. For example, both studies by Demark-Wahnefried et al. (32) and Kutynec et al. (33) performed small short-term studies that did not observe weight gain initially but found substantial weight gain when longer follow-up after 1 year of treatment was performed through chart review. This effect could reflect either the length of follow-up or differences in reporting techniques (self-report vs chart review). Additionally, the results from these two studies, as well as from studies by Loprinzi et al. (31) and Ingram et al. (35), cannot be applied broadly to younger women, as they only included participants who had received adjuvant chemotherapy, an independent predictor of weight gain (92). However, a cross-sectional study of long-term young breast cancer survivors did not find an association between ever having chemotherapy and body mass index (BMI) at 2–10 years after diagnosis. Baseline BMI was not measured, precluding evaluation of change (36).

Regarding the amount of weight gained, women reported gaining from 1 to 5 kg on average, depending on the study design, treatment regimens, and definition of weight gain (31–35). Two studies also reported that at least 43% of the participants were overweight (BMI ≥ 25 kg/m²) after diagnosis (35,36). Furthermore, two prospective studies showed that women receiving chemotherapy had a statistically significant increase in their body fat percentage, but not in lean body mass, from diagnosis to 3–12 months after diagnosis (33,34). This pattern of weight gain is known as sarcopenic obesity. Independent variables associated with a greater BMI or a greater change in BMI, weight, or body fat percentage over time were higher baseline weight (31,36), greater time since diagnosis (36), and treatment differences (eg, receiving chemotherapy or other hormonal treatments) (17,34).

Because of the changes in chemotherapy regimens during the last 20 years, especially the decreased use of oral cyclophosphamide administered for 14 days with modification to a single intravenous dose in the commonly used cyclophosphamide, methotrexate, fluorouracil (CMF) regimens, we expected that more recent studies analyzing weight gain would report a lower percentage of women gaining weight or a decrease in the amount of weight

gained. The influence of chemotherapy regimen on weight gain was difficult to tease apart because many studies did not report the type of chemotherapy given and most did not analyze outcomes by differing chemotherapy regimens. One study that did report weight gain by type of chemotherapy found that approximately equal numbers of women gained weight (defined as >5 kg) whether they received doxorubicin (trade name Adriamycin) and cyclophosphamide (AC) therapy for 4 cycles; cyclophosphamide, epirubicin, and fluorouracil (CEF) therapy for 6 cycles; or CMF therapy for 6 cycles (35). Although it appeared that participants who received 6 cycles of chemotherapy gained more weight than those who received 4 cycles of chemotherapy (AC regimen, mean [SD] weight gain = 3.5 [0.8] kg; CEF regimen, mean [SD] weight gain = 6 [3.0] kg; CMF regimen, mean [SD] weight gain = 6.3 [3.1] kg), the number of participants in each group was small, and statistical significance could not be assessed. Whether weight gain is related to particular drugs, length of treatment, or antiemetic premedications used is uncertain. It is notable that women described in the report from Kendall et al. (24), which included participants diagnosed between July 1, 1983, and December 31, 1988, reported the greatest percentage (83%) of women gaining weight. This sample is one of the earliest included this review, and they were more likely to have received CMF adjuvant chemotherapy at that time. In addition, this study had a long follow-up (up to 9 years after diagnosis), which could account for the large percentage of women reporting weight gain; however, there were no controls for comparison to determine whether this weight gain was greater than expected for women of this age group. In the more recently recruited YSC cohort published in 2004 (16), 62% of the cohort reported that they were “moderate to severely bothered” by weight gain, indicating that even with more recent chemotherapy regimens, weight gain is still an important concern for younger women (17).

Physical Activity. Physical activity or factors related to energy expenditure (expressed as kilocalories or kilojoules per day) were examined in six articles (24,32–34,36,37). Physical activity was measured in various ways. The most common technique analyzed metabolic equivalents (METs), which are defined for different types of exercise as a way to standardize the amount of energy expended per person (1 MET = 1 kcal/kg/h), but other techniques such as recording the number of days per week exercised or the “kind” (inactive, light, moderate, heavy) of exercise performed were also used. During treatment, participants had difficulty maintaining their prediagnosis level of physical activity. Throughout treatment, Demark-Wahnefried et al. (32) reported a decline in physical activity, and Kutynec et al. (33) reported no change. A later study by Demark-Wahnefried et al. (34) showed an initial steep drop in physical activity after 1 month of treatment, but this was followed by steadily increasing rates of physical activity up to 1 year after diagnosis. Longer follow-up studies of activity levels in women at least 2 years after diagnosis found moderate rates of physical activity (24,36,37). Herman et al. (36) reported that greater than 50% of women performed “moderate to heavy” leisure time physical activity (as defined by the participant in response to survey), and Bloom et al. (37) reported that greater than 70% of women exercised at least 2 days per week. Kendall et al. (24) reported that greater than half of the participants in their

study were either exercising consistently or increased the level of physical activity level from before to after (mean of 2 and 9 years) diagnosis (24).

Increasing physical activity could be especially helpful in preventing weight gain because overeating does not seem to be the cause of the weight gain observed in younger women. Demark-Wahnefried et al. (34) found that younger women having chemotherapy gained more weight than the control group, but they did not report a greater daily energy intake (kcal/d). Demark-Wahnefried et al. (32) and Kutynec et al. (33) also observed a constant or decreased energy intake in women undergoing chemotherapy treatment. In addition to helping prevent weight gain, two studies revealed that a greater amount of physical activity, or increasing the amount of physical activity, was associated with a better QOL (24,36).

Discussion

In this systematic review of research on younger women (<51 years) with breast cancer, we focused on three categories of outcomes: QOL, psychosocial sequelae of menopause and fertility-related symptoms and concerns, and behavioral outcomes related to weight gain and physical activity. A total of 28 articles that met the inclusion criteria and specifically focused on women who were younger than age 51 years or premenopausal were included in this review. Several tentative conclusions are warranted with regard to young women's standing on the outcomes of interest. The overall QOL appeared somewhat compromised in younger women with breast cancer (with mental as opposed to physical functioning domains of QOL most severely impacted), and anxiety over the future and fear of cancer recurrence are prominent. With regard to psychosocial outcomes, depressive symptoms appeared more common in younger women, and particularly in the youngest age group (eg, < 35 years), compared with the general population of women without cancer in the respective age groups. We noted that 33%–73% of younger women reported undergoing a menopausal transition with treatment, which was associated with bothersome consequences (eg, vasomotor symptoms and sexual problems). Fertility concerns were prominent for women who desired children. With regard to the behavioral outcomes, weight gain was a concern for younger women with breast cancer, and some evidence indicated that weight gain might be a particular problem for young women, although methodological features across studies render definitive conclusions about weight gain difficult. Physical activity, which carries benefits both with regard to weight maintenance and QOL, appeared to diminish during treatment and increase after treatment completion with a majority of survivors engaging in some form of exercise many years after their diagnosis.

Although we examined each outcome of interest separately in this review, our conceptual framework and interpretation of the findings suggest that it may be important to consider the interrelationships among these three domains. Specifically, depression and anxiety may influence physical activity and eating behaviors, leading to weight gain. However, weight gain and physical changes that are biomedically driven by a change in menopausal status may influence a woman's self-image, contributing to psychological distress. These considerations suggest the need to take a more com-

prehensive and integrative perspective when considering the impact of breast cancer and its treatments on younger women.

We hoped to identify studies that would examine how personal predisposing factors (demographics, medical, psychosocial) might interact with breast cancer treatment factors (tumor characteristics, treatment received) to predict these outcomes. Unfortunately, most of the available literature in young breast cancer survivors is cross-sectional, providing largely associations that may or may not be causal, although a handful of longitudinal studies do provide some information about predictors of these major outcomes. Many studies cited in this review also are retrospective and are thus influenced by recall (eg, studies related to fertility concerns). With regard to psychosocial outcomes, findings from one cohort (13,22) revealed that women who report lower emotional support, lower self-esteem, more treatment-related problems (eg, pain, symptom distress), and more cancer-related intrusive thoughts and feelings, also report more depressive symptoms. Treatment-related symptoms, social support, and particular coping strategies also appear associated with more general QOL.

With regard to menopausal symptoms and behavioral outcomes, symptoms associated with reproductive changes are worse among those who have chemotherapy-induced amenorrhea. Management of psychological and menopausal symptoms is crucial for improving a women's general QOL, but in addition, it is important to address these symptoms as ongoing psychological and hormonal problems may lead to poor adherence to adjuvant endocrine therapies in younger women (15,93–96). Failure to adhere to adjuvant endocrine therapy may have important consequences for survival (97). Intervention studies that focus on adherence to therapy should include symptom management strategies, and in parallel, studies that focus on improved symptom management should capture data on medication adherence behavior.

Considering the unique needs of younger women with regard to fertility preservation and decision making in regard to this concern, we found a limited number of studies. All were cross-sectional and retrospective, limiting an accurate picture of what happens in clinical decision making. Although there has been an American Society of Clinical Oncology (ASCO) guideline related to fertility since 2006 (92), the technological advances in fertility preservation may be available only at a limited number of medical centers, and the ability to offer these fertility services to patients in a timely manner remains a challenge (42). Since the end date of our literature search (July 2010), it is heartening to note that several additional studies regarding fertility in younger breast cancer survivors are currently ongoing or have been published (12,98,99).

Menopausal status changes and weight gain seem to be strongly associated with age and chemotherapy exposures. Future research is needed to identify contributors to healthy weight maintenance and physical activity in young women as well as to test interventions that may mitigate these negative health outcomes.

In the treatment of breast cancer, we have begun to match our therapy to the molecular subtypes of breast cancer (eg, luminal A, luminal B, basal). Similarly, it may be appropriate to examine demographic subgroups of breast cancer patients, to refine our psychosocial and cancer control interventions. Certainly, the very old (aged >75 years) and very young (aged <35 years) in our society have differing life expectancies that are relevant when determining

the best course of cancer treatment. Therefore, the context in which breast cancer is diagnosed may influence the pattern of psychosocial consequences, physical symptoms, and behavioral outcomes. Younger women as a demographic constitute approximately 25% of incident breast cancer cases in the United States each year (ie, about 50 000 women aged ≤ 50 years). Cumulatively, these young women, who have a long life expectancy, survive breast cancer with many physical and emotional sequelae, as well as adverse reproductive and behavioral health outcomes. By tailoring adjuvant therapy regimens and giving cytotoxic therapy only to those who may benefit, we can mitigate some of these side effects, but the long life expectancy for these younger women also provides a window of opportunity for cancer prevention and health promotion activities.

This review has a few limitations. Specifically, we selected particular areas to examine, and there are likely other important issues relevant to younger breast cancer survivors that are not addressed in this review. Furthermore, by only selecting studies that solely included women less than age 51 years or premenopausal, we were not able to provide a systematic comparison between younger and older breast cancer survivors. Finally, we did not assess individual articles for risk of bias.

Overall, our findings raise more questions than answers and suggest the need for more dedicated research on this vulnerable population, including longitudinal research examining pretreatment personal characteristics, cancer treatment exposures, and physical and psychological effects during and after treatment, and extending into survivorship. Women younger than age 50 years are heterogeneous with regard to reproductive and fertility needs, as well as developmental life stage. This review and the literature may not provide adequate information for the very young women with breast cancer who are younger than 40 years or even younger than 35 years, or for ethnically diverse women whose numbers will be increasing in coming decades (97). The life disruptions in these very young women may be even more serious, yet their small numbers make it difficult to study them in detail.

It has been nearly 20 years since the NCI convened its conference on younger women with breast cancer. Advances in breast cancer treatment since that time have increased survival time for younger women with breast cancer but at the cost of extended duration and complexity of initial treatments, as well as persistent long-term and late effects beyond those documented in this review (eg, cognitive changes, cardiac toxicity, neuropathy, persistent fatigue, and sleep disturbance). With an increased number of younger women who are long-term survivors, it may be appropriate for another such conference to examine what is known and what needs further investigation to improve the outcomes for this population. Given the long life expectancy of this group of breast cancer survivors, serious consideration should be given to the development and evaluation of interventions that target energy balance, fertility preservation, menopausal symptoms, and management of depression and anxiety. A consensus on the ideal measures for symptoms, QOL, and other health outcomes would be valuable to facilitate future reviews of the literature and potential for meta-analysis. Studies that evaluate interventions to prevent second cancers, as well as implementation and dissemination of interventions that are known to improve QOL and psychological distress

after breast cancer, should be part of the delivery of high-quality survivorship care. In addition, we need more longitudinal research, as well as information on the late effects of commonly used treatments, for example, cardiac late effects. It is anticipated that research that is currently underway will provide additional insights into the concerns of younger women with breast cancer, as well as new strategies to improve their long-term health outcomes.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics, 2010. *CA Cancer J Clin*. 2010;60(5):277–300.
2. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353(17):1784–1792.
3. Ganz PA, Rowland JH, Desmond K, et al. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. *J Clin Oncol*. 1998;16(2):501–514.
4. Ganz PA, Greendale GA, Petersen L, et al. Breast cancer in younger women: reproductive and late health effects of treatment. *J Clin Oncol*. 2003;21(22):4184–4193.
5. Ganz PA. Breast cancer, menopause, and long-term survivorship: critical issues for the 21st century. *Am J Med*. 2005;118(suppl 12B):136–141.
6. Baucom DH, Porter LS, Kirby JS, et al. Psychosocial issues confronting young women with breast cancer. *Breast Dis*. 2005;23:103–113.
7. Mor V, Malin M, Allen S. Age differences in the psychosocial problems encountered by breast cancer patients. *J Natl Cancer Inst Monogr*. 1994; (16):191–197.
8. Mariotto AB, Rowland JH, Ries LAG, et al. Multiple cancer prevalence: a growing challenge in long-term survivorship. *Cancer Epidemiol Biomarkers Prev*. 2007;16(3):566–571.
9. Trimble EL, Abrams JS, Nayfield SG. Breast cancer in younger women. *J Natl Cancer Inst Monogr*. 1994;(16):1–222.
10. Knopf MT. The influence of endocrine effects of adjuvant therapy on quality of life outcomes in younger breast cancer survivors. *Oncologist*. 2006;11(2):96–110.
11. Camp-Sorrrell D. Cancer and its treatment effect on young breast cancer survivors. *Semin Oncol Nurs*. 2009;25(4):251–258.
12. Peate M, Meiser B, Hickey M, Friedlander M. The fertility-related concerns, needs and preferences of younger women with breast cancer: a systematic review. *Breast Cancer Res Treat*. 2009;116(2):215–223.
13. Bloom JR, Stewart SL, Johnston M, Banks P. Intrusiveness of illness and quality of life in young women with breast cancer. *Psychooncology*. 1998; 7(2):89–100.
14. Casso D, Buist DS, Taplin S. Quality of life of 5-10 year breast cancer survivors diagnosed between age 40 and 49. *Health Qual Life Outcomes*. 2004;2:25.
15. Crandall C, Petersen L, Ganz PA, Greendale GA. Association of breast cancer and its therapy with menopause-related symptoms. *Menopause*. 2004;11(5):519–530.
16. Partridge AH, Gelber S, Peppercorn J, et al. Web-based survey of fertility issues in young women with breast cancer. *J Clin Oncol*. 2004;22(20):4174–4183.
17. Leining MG, Gelber S, Rosenberg R, et al. Menopausal-type symptoms in young breast cancer survivors. *Ann Oncol*. 2006;17(12):1777–1782.
18. Avis NE, Crawford S, Manuel J. Psychosocial problems among younger women with breast cancer. *Psychooncology*. 2004;13(5):295–308.
19. Avis NE, Crawford S, Manuel J. Quality of life among younger women with breast cancer. *J Clin Oncol*. 2005;23(15):3322–3330.
20. Bloom JR, Stewart SL, Johnston M, et al. Sources of support and the physical and mental well-being of young women with breast cancer. *Soc Sci Med*. 2001;53(11):1513–1524.
21. Bloom JR, Stewart SL, Chang S, Banks PJ. Then and now: quality of life of young breast cancer survivors. *Psychooncology*. 2004;13(3):147–160.
22. Wong-Kim EC, Bloom JR. Depression experienced by young women newly diagnosed with breast cancer. *Psychooncology*. 2005;14(7):564–573.
23. Fobair P, Stewart SL, Chang S, et al. Body image and sexual problems in young women with breast cancer. *Psychooncology*. 2006;15(7):579–594.

24. Kendall AR, Mahue-Giangreco M, Carpenter CL, et al. Influence of exercise activity on quality of life in long-term breast cancer survivors. *Qual Life Res*. 2005;14(2):361–371.
25. Duffy CM, Allen SM, Clark MA. Discussions regarding reproductive health for young women with breast cancer undergoing chemotherapy. *J Clin Oncol*. 2005;23(4):766–773.
26. Thewes B, Meiser B, Taylor A, et al. Fertility- and menopause-related information needs of younger women with a diagnosis of early breast cancer. *J Clin Oncol*. 2005;23(22):5155–5165.
27. Burwell SR, Case LD, Kaelin C, Avis NE. Sexual problems in younger women after breast cancer surgery. *J Clin Oncol*. 2006;24(18):2815–2821.
28. Danhauer SC, Crawford SL, Farmer DF, Avis NE. A longitudinal investigation of coping strategies and quality of life among younger women with breast cancer. *J Behav Med*. 2009;32(4):371–379.
29. Gorman JR, Roesch SC, Parker BA, et al. Physical and mental health correlates of pregnancy following breast cancer. *Psychooncology*. 2010;19(5):517–524.
30. Gorman JR, Malcarne VL, Roesch SC, et al. Depressive symptoms among young breast cancer survivors: the importance of reproductive concerns. *Breast Cancer Res Treat*. 2010;123(2):477–485.
31. Loprinzi CL, Athmann LM, Kardinal CG, et al. Randomized trial of dietician counseling to try to prevent weight gain associated with breast cancer adjuvant chemotherapy. *Oncology*. 1996;53(3):228–232.
32. Demark-Wahnefried W, Hars V, Conaway MR, et al. Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy. *Am J Clin Nutr*. 1997;65(5):1495–1501.
33. Kutynec CL, McCargar L, Barr SI, Hislop TG. Energy balance in women with breast during adjuvant treatment. *J Am Diet Assoc*. 1999;99(10):1222–1227.
34. Demark-Wahnefried W, Peterson BL, Winer EP, et al. Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol*. 2001;19(9):2381–2389.
35. Ingram C, Brown JK. Patterns of weight and body composition change in premenopausal women with early stage breast cancer: has weight gain been overestimated? *Cancer Nurs*. 2004;27(6):483–490.
36. Herman DR, Ganz PA, Petersen L, Greendale GA. Obesity and cardiovascular risk factors in younger breast cancer survivors: the Cancer and Menopause Study (CAMS). *Breast Cancer Res Treat*. 2005;93(1):13–23.
37. Bloom JR, Stewart SL, D’Onofrio CN, et al. Addressing the needs of young breast cancer survivors at the 5 year milestone: can a short-term, low intensity intervention produce change? *J Cancer Surviv*. 2008;2(3):190–204.
38. Sammarco A. Perceived social support, uncertainty, and quality of life of younger breast cancer survivors. *Cancer Nurs*. 2001;24(3):212–219.
39. Allen SM, Shah AC, Nezu AM, et al. A problem-solving approach to stress reduction among younger women with breast carcinoma—a randomized controlled trial. *Cancer*. 2002;94(12):3089–3100.
40. Goldhirsch A, Gelber RD, Castiglione M. The magnitude of endocrine effects of adjuvant chemotherapy for premenopausal breast cancer patients. The International Breast Cancer Study Group. *Ann Oncol*. 1990;1(3):183–188.
41. Minton SE, Munster PN. Chemotherapy-induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer. *Cancer Control*. 2002;9(6):466–472.
42. Lee S, Kil WJ, Chun M, et al. Chemotherapy-related amenorrhea in premenopausal women with breast cancer. *Menopause*. 2009;16(1):98–103.
43. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *J Clin Oncol*. 1996;14(5):1718–1729.
44. Goodwin PJ, Ennis M, Pritchard KI, et al. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol*. 1999;17(8):2365–2370.
45. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol*. 2006;24(36):5769–5779.
46. Scheier MF, Helgeson VS, Schulz R, et al. Interventions to enhance physical and psychological functioning among younger women who are ending nonhormonal adjuvant treatment for early-stage breast cancer. *J Clin Oncol*. 2005;23(19):4298–4311.
47. Scheier MF, Helgeson VS, Schulz R, et al. Moderators of interventions designed to enhance physical and psychological functioning among younger women with early-stage breast cancer. *J Clin Oncol*. 2007;25(36):5710–5714.
48. Bloom JR, D’Onofrio C, Banks P, et al. A Psycho-educational group intervention for young women with breast cancer: design and process evaluation. *Cancer Res Ther Control*. 1999;8:93–102.
49. Nystedt M, Berglund G, Bolund C, et al. Randomized trial of adjuvant tamoxifen and/or goserelin in premenopausal breast cancer—self-rated physiological effects and symptoms. *Acta Oncologica*. 2000;39(8):959–968.
50. de Haes H, Olschewski M, Kaufmann M, et al. Quality of life in goserelin-treated versus cyclophosphamide + methotrexate + fluorouracil-treated premenopausal and perimenopausal patients with node-positive, early breast cancer: the Zoladex Early Breast Cancer Research Association Trialists Group. *J Clin Oncol*. 2003;21(24):4510–4516.
51. Groenvold M, Fayers P, Petersen M, Mouridsen H. Chemotherapy versus ovarian ablation as adjuvant therapy for breast cancer: impact on health-related quality of life in a randomized trial. *Breast Cancer Res Treat*. 2006;98(3):275–284.
52. Bernhard J, Zahrieh D, Castiglione-Gertsch M, et al. Adjuvant chemotherapy followed by goserelin compared with either modality alone: the impact on amenorrhea, hot flashes, and quality of life in premenopausal patients—the International Breast Cancer Study Group Trial VIII. *J Clin Oncol*. 2007;25(3):263–270.
53. Berglund G, Nystedt M, Bolund C, et al. Effect of endocrine treatment on sexuality in premenopausal breast cancer patients: a prospective randomized study. *J Clin Oncol*. 2001;19(11):2788–2796.
54. Nystedt M, Berglund G, Bolund C, et al. Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: a prospective randomized study. *J Clin Oncol*. 2003;21(9):1836–1844.
55. Lemieux J, Goodwin PJ, Bordeleau LJ, et al. Quality-of-life measurement in randomized clinical trials in breast cancer: an updated systematic review (2001–2009). *J Natl Cancer Inst*. 2011;103(3):178–231.
56. Bernstein L, Henderson BE, Hanisch R, et al. Physical exercise and reduced risk of breast cancer in young women. *J Natl Cancer Inst*. 1994;86(18):1403–1408.
57. Crandall C, Petersen L, Ganz PA, Greendale GA. Bone mineral density and adjuvant therapy in breast cancer survivors. *Breast Cancer Res Treat*. 2004;88(3):257–261.
58. Castellon SA, Ganz PA, Bower JE, et al. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *J Clin Exp Neuropsychol*. 2004;26(7):955–969.
59. Silverman D, Dy C, Castellon S, et al. Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5–10 years after chemotherapy. *Breast Cancer Res Treat*. 2007;103(3):303–311.
60. Manuel JC, Burwell SR, Crawford SL, et al. Younger women’s perceptions of coping with breast cancer. *Cancer Nurs*. 2007;30(2):85–94.
61. Ursin G, Ross RK, Sullivan-Halley J, et al. Use of oral contraceptives and risk of breast cancer in young women. *Breast Cancer Res Treat*. 1998;50(2):175–184.
62. Hill DA, Preston-Martin S, Ross RK, Bernstein L. Medical radiation, family history of cancer, and benign breast disease in relation to breast cancer risk in young women, USA. *Cancer Causes Control*. 2002;13(8):711–718.
63. Enger SM, Bernstein L. Exercise activity, body size and premenopausal breast cancer survival. *Br J Cancer*. 2004;90(11):2138–2141.
64. Ma H, Bernstein L, Ross RK, Ursin G. Hormone-related risk factors for breast cancer in women under age 50 years by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. *Breast Cancer Res*. 2006;8(4):R39.
65. Prescott J, Ma H, Bernstein L, Ursin G. Cigarette smoking is not associated with breast cancer risk in young women. *Cancer Epidemiol Biomarkers Prev*. 2007;16(3):620–622.

66. Ma H, Hill CK, Bernstein L, Ursin G. Low-dose medical radiation exposure and breast cancer risk in women under age 50 years overall and by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. *Breast Cancer Res Treat.* 2008;109(1):77–90.
67. Berstad P, Ma H, Bernstein L, Ursin G. Alcohol intake and breast cancer risk among young women. *Breast Cancer Res Treat.* 2008;108(1):113–120.
68. Wenzel LB, Fairclough DL, Brady MJ, et al. Age-related differences in the quality of life of breast carcinoma patients after treatment. *Cancer.* 1999;86(9):1768–1774.
69. King MT, Kenny P, Shiell A, et al. Quality of life three months and one year after first treatment for early stage breast cancer: influence of treatment and patient characteristics. *Qual Life Res.* 2000;9(7):789–800.
70. Cimprich B, Ronis DL, Martinez-Ramos G. Age at diagnosis and quality of life in breast cancer survivors. *Cancer Pract.* 2002;10(2):85–93.
71. Kroenke CH, Rosner B, Chen WY, et al. Functional impact of breast cancer by age at diagnosis. *J Clin Oncol.* 2004;22(10):1849–1856.
72. Arndt V, Merx H, Sturmer T, et al. Age-specific detriments to quality of life among breast cancer patients one year after diagnosis. *Eur J Cancer.* 2004;40(5):673–680.
73. Kornblith AB, Powell M, Regan MM, et al. Long-term psychosocial adjustment of older vs younger survivors of breast and endometrial cancer. *Psychooncology.* 2007;16(10):895–903.
74. Costanzo ES, Lutgendorf SK, Mattes ML, et al. Adjusting to life after treatment: distress and quality of life following treatment for breast cancer. *Br J Cancer.* 2007;97(12):1625–1631.
75. Hopwood P, Haviland J, Mills J, et al. The impact of age and clinical factors on quality of life in early breast cancer: an analysis of 2208 women recruited to the UK START Trial (Standardisation of Breast Radiotherapy Trial). *Breast.* 2007;16(3):241–251.
76. Harrison SA, Hayes SC, Newman B. Age-related differences in exercise and quality of life among breast cancer survivors. *Med Sci Sports Exerc.* 2010;42(1):67–74.
77. Sammarco A. Quality of life of breast cancer survivors: a comparative study of age cohorts. *Cancer Nursing.* 2009;32(5):247–256.
78. Jones JM, Cheng T, Jackman M, et al. Self-efficacy, perceived preparedness, and psychological distress in women completing primary treatment for breast cancer. *J Psychosoc Oncol.* 2010;28(3):269–290.
79. Hartl K, Schennach R, Muller M, et al. Quality of life, anxiety, and oncological factors: a follow-up study of breast cancer patients. *Psychosomatics.* 2010;51(2):112–123.
80. Ware JE Jr, Kosinski M, Keller SD. *SF-36 Physical and Mental Health Summary Scales: A User's Manual.* Boston, MA: The Health Institute; 1994.
81. Henderson C, Diez Roux AV, Jacobs DR, et al. Neighbourhood characteristics, individual level socioeconomic factors, and depressive symptoms in young adults: the CARDIA study. *J Epidemiol Commun Health.* 2005;59(4):322–328.
82. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging.* 1977;12(12):277–287.
83. Swain SM, Jeong JH, Geyer CE, et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. *N Engl J Med.* 2010;362(22):2053–2065.
84. Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. *J Clin Oncol.* 2002;20(4):1128–1143.
85. Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain, and survival after breast cancer diagnosis. *J Clin Oncol.* 2005;23(7):1370–1378.
86. Holmes MD, Chen WY, Feskanich D, et al. Physical activity and survival after breast cancer diagnosis. *JAMA.* 2005;293(20):2479–2486.
87. Makari-Judson G, Judson CH, Mertens WC. Longitudinal patterns of weight gain after breast cancer diagnosis: observations beyond the first year. *Breast J.* 2007;13(3):258–265.
88. Caan B, Sternfeld B, Gunderson E, et al. Life After Cancer Epidemiology (LACE) study: a cohort of early stage breast cancer survivors (United States). *Cancer Causes Control.* 2005;16(5):545–556.
89. Rock CL, Flatt SW, Newman VA, et al. Factors associated with weight gain in women after diagnosis of breast cancer. *J Am Diet Assoc.* 1999;99(10):1212–1218, 1221.
90. Irwin ML, McTiernan A, Baumgartner RN, et al. Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. *J Clin Oncol.* 2005;23(4):774–782.
91. Gu K, Chen X, Zheng Y, et al. Weight change patterns among breast cancer survivors: results from the Shanghai breast cancer survival study. *Cancer Causes Control.* 2010;21(4):621–629.
92. Goodwin PJ, Ennis M, Pritchard KI, et al. Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. *J Clin Oncol.* 1999;17(1):120–129.
93. Partridge AH, Wang PS, Winer EP, Avorn J. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *J Clin Oncol.* 2003;21(4):602–606.
94. Yoon J, Malin J, Tisnado D, et al. Symptom management after breast cancer treatment: is it influenced by patient characteristics? *Breast Cancer Res Treat.* 2008;108(1):69–77.
95. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. *J Clin Oncol.* 2010;28(27):4120–4128.
96. Hershman D, Shao T, Kushi L, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat.* 2011;126(2):529–537.
97. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol.* 2009;27(17):2758–2765.
98. Kim SS, Klemp J, Fabian C. Breast cancer and fertility preservation. *Fertil Steril.* 2011;95(5):1535–1543.
99. Pagani O, Partridge A, Korde L, et al. Pregnancy after breast cancer: if you wish, ma'am. *Breast Cancer Res Treat.* 2011;129(2):309–317.

Funding

The study was supported by funding from the Breast Cancer Research Foundation (to P.A.G.) and the Jonsson Comprehensive Cancer Center Foundation (to P.A.G.).

Notes

Ms J. Howard-Anderson was supported in part by a summer medical student fellowship (Internal Medicine Chiefs' Fellowship) from the Department of Medicine, David Geffen School of Medicine at the University of California Los Angeles. The authors are solely responsible for the study design, review of literature, collection of data, analysis and interpretation of the data, writing the review, and decision to submit the review for publication.

Affiliations of authors: David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA (JH-A); Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA (PAG); Department of Health Services, School of Public Health, University of California Los Angeles, Los Angeles, CA (PAG); Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA (PAG, JEB, ALS); Department of Psychology, University of California Los Angeles, Los Angeles, CA (JEB, ALS); Cousins Center for Psychoneuroimmunology, Semel Institute, University of California Los Angeles, Los Angeles, CA (PAG, JEB, ALS).