

## Life After Cancer Epidemiology (LACE) Study: A cohort of early stage breast cancer survivors (United States)

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Received 27 August 2004; accepted in revised form 30 December 2004

*Key words:* breast cancer, cancer survivorship, diet, physical activity, weight gain, cohort.

### Abstract

The Life After Cancer Epidemiology (LACE) Study, a cohort of 2321 early stage breast cancer survivors, was established in 2000 to examine how modifiable behavioral risk factors affect quality of life and long-term survival. Women were recruited primarily from the Kaiser Permanente Northern California Cancer Registry (KPNCAL) and the Utah cancer registry (UCR), United States. Baseline data were collected, on average, at two years post-diagnosis through self-administered questionnaires that included information on demographics, medical history, anthropometry, diet, supplements, physical activity and quality of life. The purpose of this paper is to describe the creation and baseline characteristics of the cohort. Forty-six percent of women to whom questionnaires were mailed agreed to participate. The cohort which is 80% white, was diagnosed predominantly with Stage I and II breast cancer (93%), and will have been followed for 5.6 years post-diagnosis, on average, by the end of 2004. Women reported slightly over four daily servings of fruit and vegetables, well below the suggested 5-A-Day national guidelines. Compared to women free of cancer, physical activity patterns were similar, while weight gain, especially in younger women, was higher than is typical. These data suggest that in the early years post-diagnosis, breast cancer survivors exhibit similar patterns to the general population in many health behaviors.

### Introduction

Among women in the United States, breast cancer is the second most common type of cancer, after skin cancer, and is the second leading cause of cancer death [1]. Through most of the 1990s, incidence rates continued to increase [2] while, starting in the mid 1990s, mortality rates have declined. As a result, there is a growing population of breast cancer survivors. The National Alliance of Breast Cancer Organizations estimates that over two million breast cancer survivors are living in the US today [3].

Despite the fact that there are a large number of breast cancer survivors, relatively little is known about

the factors that predict recurrence, survival, and quality of life. Non-modifiable factors that influence these outcomes include diagnostic features and clinical course, such as tumor stage, tumor grade, hormone receptor status, and treatment modality [2, 4–7]. Recurrence and survival rates also vary by demographic characteristics such as age and race [2]. However, even among women with similar presenting diagnoses and treatment, substantial variation exists in long-term survival and late-effects due to treatment. This suggests the possibility that other factors such as genetic and behavioral factors may contribute to differences in rates of recurrence and survival.

The Life After Cancer Epidemiology (LACE) Study, funded by the National Cancer Institute in 1999 specifically to establish a cohort of early stage breast cancer survivors, was designed to examine modifiable lifestyle predictors of recurrence, survival, and quality of life. The cohort has been followed from the early years after diagnosis and will continue to be followed through

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the extended survivorship period. It is one of few such cohorts in existence and a large percentage of its members (82%) are enrolled in an integrated health care delivery system that allows for comprehensive follow-up. The purpose of this paper is to describe the formation of the cohort and its baseline characteristics, and to examine those characteristics in relation to age.

## Materials and methods

### *Cohort recruitment*

Women diagnosed with breast cancer from 1997 to 2000 were recruited primarily from two sampling frames: the Kaiser Permanente Northern California Cancer Registry (KPNCAL) and the Utah cancer registry (UCR). Additionally, lists of women who were screened and eligible for, but declined to participate in, the Women's Healthy Eating and Lifestyle Trial (WHEL), a dietary intervention trial to prevent recurrence of breast cancer, were used as a third, supplemental sampling frame. The study was approved by the Institutional Review Board of the Kaiser Permanente Medical Program of Northern California, the University of Utah and the University of California, San Diego. To be eligible for LACE, women had to be 18–79 years of age at diagnosis, have received a diagnosis of primary breast cancer (Stage I  $\geq$  1 cm, II or IIIA) within 39 months of enrollment, have no other cancers within five years of enrollment, and have completed cancer treatment and be free of any recurrence by self-report. Further verification that women were free of breast cancer recurrence was done by medical chart review at the time a recurrence was self-reported on the semi-annual health status update, or will be done at the end of the five year study period when all medical charts are reviewed for eligibility. Surgical treatment had to be either total mastectomy or breast sparing surgery followed by breast radiation. With either type of surgery, axillary node dissection or sentinel node biopsy must have been performed.

Between January 2000 and April 2002, 5656 women from these sampling frames who were presumed to meet the eligibility criteria were sent a recruitment package that informed them of the study and invited them to join the cohort by completing and returning a series of questionnaires. Of these, 2614 women (46.2%) responded positively. Subsequent review to confirm eligibility resulted in 293 exclusions. The remaining 2321 women constitute the LACE cohort, 82% of whom come from the KP cancer registry, 12% from the Utah cancer registry, and 6% from the WHEL lists.

### *Baseline data collection*

All baseline data were collected through mailed, self-administered questionnaires, a method with established validity [8–11], that considerably reduces expense compared to in-person data collection. To ease participant burden associated with completing a single comprehensive and extensive questionnaire, data were collected on two separate occasions. The first mailing included questions regarding demographics, medical history, including co-morbid conditions and medication use, reproductive history, including hormone use, family history of breast and ovarian cancer, weight history, use of dietary supplements, quality of life and depressive symptoms. The second mailing included questionnaires to assess diet, physical activity, and functional limitations, and instructions for self-measurement of height, weight and waist circumference. The response rate to the second mailing was 88.2% (n = 2048). Details regarding the measurement of major exposures of interest (diet, physical activity, and quality of life) and other covariates are provided below.

### *Diet*

Diet was assessed for the previous 12 months using The Fred Hutchinson Cancer Research Center Food Frequency Questionnaire (FHRCC-FQ), a self-administered, semi-quantitative food frequency questionnaire with over 100 food and beverage items, adapted from the 95 item Health Habits and Lifestyle Questionnaire (HHLQ) developed by Block and colleagues at the National Cancer Institute [12]. The FHRCC-FQ was designed initially for the Women's Health Feasibility Trial and is currently being used in the Women's Health Initiative (WHI) [13]. For each food or beverage, participants marked a category of how frequently they consumed it, and indicated the serving size as small, medium or large. Questionnaires were sent to the FHCRC for nutrient analyses. Questionnaires with extremes of total energy (less than 500 kcal or more than 4000 kcal) were considered unreliable and were excluded.

Although the LACE Dietary Intake Questionnaire included two food items (tofu and soy milk) that are phytoestrogen-rich food sources based on their genistein and daidzein values, assessment of a wider range of soy food products is desirable among breast cancer survivors. To accomplish this, the LACE questionnaire included 14 items (soy yogurt, soy frozen yogurt, soy ice cream, soy cheese, soy hot dogs and cold cuts, other meat substitutes made from soy, tempeh, miso, soybeans, roasted soy nuts, soy sauce, soybean sprouts, alfalfa sprouts, and

protein powder supplements made from soy) selected from the 40-item soy questionnaire developed by Kirk *et al.* [14] based on their contribution to dietary intake of genistein, daidzein or coumestrol [15, 16].

#### *Supplements and herbs*

The questionnaire developed by Patterson *et al.* [17] was adapted to provide information on vitamin, mineral and herb supplement use. Respondents were asked about five general classes of multivitamins (one-a-day types with or without minerals, B-complex, stress and antioxidant mixtures) as well as single vitamin and mineral supplements. For each supplement, the participant indicated whether she had ever taken it since her breast cancer, and if yes, the duration (4-level response ranging from less than 6 months to more than 24 months) and frequency (4-level response ranging from less than one day per week to six to seven days per week). Participants also indicated whether the specific supplement was used during the five years before the breast cancer diagnosis for at least three times per week for a year or more. Respondents were also asked about their use of specific herbal supplements using a list obtained from the WHEL trial which has compiled an extensive database of supplements and herbs taken by breast cancer survivors [18].

#### *Physical activity*

The LACE physical activity questionnaire (PAQ) was modeled loosely after the Arizona Activity Frequency Questionnaire (AAFQ) [19], which, in turn, was developed on the basis of repeated responses to a one-month adaptation of the Minnesota Leisure Time Physical Activity Questionnaire (LTPA), a well-established, widely used and validated physical activity questionnaire [20, 21].

The LACE PAQ is divided into four main domains of activity: occupation (including volunteer work), household tasks and caregiving, recreation, and transportation. Women who did paid or volunteer work were asked to choose one of five categories corresponding to how many hours (ranging from none or less than one to more than six) they usually spent doing each of six general activities (e.g. sitting, standing, walking, carrying heavy loads, etc.). The response categories were then scored from 0 to 4, with hours of sitting reverse scored, summed over all activities and multiplied by the number of days per week a respondent worked. The resulting variable is an ordinal ranking indicative of amount of occupational activity in a typical week.

To assess activity in the remaining three domains, respondents were asked about their participation during the prior year in specific activities grouped into the following areas: household chores (six items), caregiving (five items), and home maintenance and repairs (seven items); sports, exercise, and dance (22 items) and sedentary recreational activities, such as reading or socializing (six items); active and sedentary transportation (four items). For each activity that respondents did at least once a month, they were asked to report the frequency, duration and intensity (low, moderate, vigorous). Standard MET values, from the Compendium of Physical Activities [22] were assigned according to the level of intensity of activity performed [23]. Intensity was then multiplied by duration and frequency and summed over all activities in a given domain. All domain-specific summary scores are expressed as MET-hours per week, except for sedentary behavior that is expressed as hours per week. Since the summary scores tend to be highly skewed, they are often categorized into quartiles or tertiles for analytic purposes.

#### *Quality of life (QoL)*

QoL was assessed with the Functional Assessment of Cancer Therapy (FACT-B) questionnaire, a reliable, valid self-administered questionnaire for measuring domain-specific QoL in women with breast cancer [24]. The instrument consists of a series of statements with 5-level categorical responses that range from not at all to very much. The domains include: (a) physical well-being; (b) social/family well-being; (c) emotional well-being; (d) functional well-being; and (e) additional concerns about appearance and sexual attractiveness, lymphedema, and other breast cancer related concerns. Domain-specific scores are created by summing the values of the categorical responses.

Other covariates included depression, functional limitations, co-morbidities, medications, smoking status, alcohol and caffeine intake, family history and anthropometric measures. The Center for Epidemiologic Studies Depression scale (CES-D), used extensively in epidemiological studies, and having established reliability and validity [25], was used to assess depressive symptoms during the prior week. Thirteen items, taken from those used in the Framingham Disability Study [26] and the Established Populations for Epidemiologic Studies of the Elderly [27] and from the Nagle [28] and Rosow and Breslau [29] scales were used to assess functional limitations. These items have been validated against direct measures of physical performance [30] and cover both upper and lower body functions involving endurance, strength, muscular range of motion or small muscle

dexterity. To obtain height, weight, and waist circumference, women were given specific instructions about how to take and record these measurements (a tape measure was included in their questionnaire packet), an approach that has proven validity [9, 31]. Standardized questions frequently used in epidemiological studies were used to assess the other self-reported covariates (for copies of the questionnaires, contact authors).

In addition to the self-reported questionnaire data, information for confirming eligibility and for describing prognostic factors (tumor size, histology, extension, lymph node involvement and distant metastasis, estrogen and progesterone receptor status, and HER2/Neu status), and treatments (surgical procedures, dates and types of chemotherapy, radiation therapy, and hormonal therapy) were obtained through tumor registry records or from medical chart review.

#### Outcome ascertainment

Cohort members are contacted every six months with a health status update questionnaire that asks about any events occurring in the preceding six months, including recurrences, hospitalizations or other conditions believed to be long-term health consequences or late effects associated with breast cancer treatment. Women who report an event are then called on the telephone to obtain greater detail and request the medical record to verify the outcome. All non-respondents to the health

status questionnaire are called to complete a report by phone. Response rates to the semi-annual health status update have been 91%, 89%, 89%, 87%, 89% and 88% respectively. Computerized mortality files for KPNCAL members are regularly searched for any cohort members whom we fail to contact. Copies of death certificates are obtained on all study subjects who are known to have died, and date of death and cause of death recorded in the study database. Women who report a recurrence are still actively followed for mortality.

#### Data analysis

Results are presented as frequency distributions for ordinal and nominal variables, and as means, standard deviations, medians and interquartile ranges for continuous variables. Differences in frequency distributions of baseline characteristics across levels of age and stage are assessed via the  $\chi^2$  test. Differences in means and medians across age and stage are assessed by analysis of variance and the Kruskal–Wallis test, respectively.

## Results

#### Recruitment

The overall response rate was 46.2% and response rates varied by recruitment source (Table 1). Those recruited from the Kaiser and Utah tumor registries were more likely to respond (49.6% and 58.1% respectively) than

Table 1. Recruitment and reasons for ineligibility

|  | Packet mailed <i>n</i> | Packet received and agreed to participate <i>n</i> (%) <sup>a</sup> | Ineligible or Excluded <i>n</i> (%) <sup>b</sup> | Enrolled <i>n</i> (%) <sup>a</sup> |
|--|------------------------|---|--|------------------------------------|
| <b>Recruitment source</b>  |                        |   |  |                                    |
| Kaiser Permanente Northern California  | 4160                   | 2062 (49.6%)  | 151 (7.3%)                                       | 1911 (45.9%)                       |
| Utah   | 613                    | 356 (58.1%)   | 86 (24.2%)                                       | 270 (44.1%)                        |
| WHEL   | 883                    | 196 (22.2%)   | 56 (28.6%)                                       | 140 (15.9%)                        |
| Total  | 5656                   | 2614 (46.2%)  | 293 (11.2%)                                      | 2321 (41.0%)                       |
| <b>Reasons for ineligibility or exclusion</b>  |                        |   |  |                                    |
|  | <i>n</i> (%)           |   |  |                                    |
| Stage 0, Stage I < 1 cm, Stage IIIB or IV, or ineligible histology                     | 98 (33.5%)             |   |  |                                    |
| Prior breast cancer  | 18 (6.1%)              |   |  |                                    |
| Other cancer within 5 years prior to enrollment  | 30 (10.2%)             |   |  |                                    |
| Non-standard therapy, surgery with positive margins, or still receiving chemotherapy   | 5 (1.7%)               |   |  |                                    |
| More than 39 months from diagnosis to enrollment                                       | 18 (6.1%)              |   |  |                                    |
| Breast cancer recurrence/new primary or woman expired within 3 months after enrollment | 109 (37.2%)            |   |  |                                    |
| Language or other difficulty filling out questionnaire                                 | 7 (2.4%)               |   |  |                                    |
| Incomplete demographic, medical and weight history data                                | 8 (2.7%)               |   |  |                                    |

<sup>a</sup> percentage of packets mailed.

<sup>b</sup> percentage of women who agreed to participate.

those who were recruited from WHEL (22.2%). Since Kaiser participants make up the majority of the cohort (82%), we examined differences in respondents *versus* non-respondents within persons recruited from Kaiser. There were no differences between the two groups with regard to severity of cancer (stage, number of positive nodes) or treatment (chemotherapy, type of surgery). The only significant differences found were that women approached within 15 months of diagnosis were more likely to enroll than those approached later post-diagnosis, and women less than 50 were less likely to enroll than older women.

Of those who responded, eligibility also varied by recruitment source, where those recruited from Kaiser

were less likely to be ineligible (7.3%) than those recruited from either Utah (24.2%) or WHEL (28.6%). The majority of women were ineligible because they had another breast cancer event prior to enrollment (37.2%) or because of stage or histology of the initial tumor (33.5%).

The average time from diagnosis to enrollment was 22.8 months. Eleven percent of the women enrolled within 15 months of diagnosis, 62% enrolled between 15 months and 27 months post-diagnosis and the remaining 38% of the women enrolled between 27 and 39 months post-diagnosis. We examined differences in some demographic (age, BMI) and tumor characteristics (stage, number of positive nodes, ERA status) by time from diagnosis to enrollment and found no significant

Table 2. Characteristics of the LACE Cohort

|                                  | Age group |           |           |           |            | All      | p-Value <sup>a</sup> |
|----------------------------------|-----------|-----------|-----------|-----------|------------|----------|----------------------|
|                                  | <50       | 50 to <60 | 60 to <70 | ≥70       |            |          |                      |
| Total n (%)                      | 440 (19%) | 711 (31%) | 665 (29%) | 505 (22%) | 2321       |          |                      |
| Ethnicity                        |           |           |           |           |            |          |                      |
| White                            | 326 (74%) | 556 (78%) | 537 (81%) | 439 (87%) | 1858 (80%) | 0.002    |                      |
| Black                            | 28 (6%)   | 42 (6%)   | 28 (4%)   | 18 (4%)   | 116 (5%)   |          |                      |
| Hispanic                         | 36 (8%)   | 42 (6%)   | 43 (6%)   | 21 (4%)   | 142 (6%)   |          |                      |
| Asian                            | 19 (4%)   | 24 (3%)   | 22 (3%)   | 12 (2%)   | 77 (3%)    |          |                      |
| Other                            | 31 (7%)   | 46 (6%)   | 34 (5%)   | 14 (3%)   | 125 (5%)   |          |                      |
| Education                        |           |           |           |           |            |          |                      |
| ≤ High school                    | 77 (18%)  | 144 (20%) | 202 (31%) | 206 (41%) | 629 (27%)  | < 0.0001 |                      |
| Some college                     | 163 (37%) | 283 (40%) | 241 (36%) | 178 (35%) | 865 (37%)  |          |                      |
| College grad                     | 200 (45%) | 284 (40%) | 219 (33%) | 118 (24%) | 821 (35%)  |          |                      |
| Marital status                   |           |           |           |           |            |          |                      |
| Married                          | 326 (74%) | 526 (74%) | 464 (70%) | 263 (52%) | 1579 (68%) | < 0.0001 |                      |
| Smoking                          |           |           |           |           |            |          |                      |
| Never                            | 256 (58%) | 394 (55%) | 322 (49%) | 254 (51%) | 1226 (53%) | < 0.0001 |                      |
| Past                             | 136 (31%) | 249 (35%) | 302 (46%) | 229 (45%) | 916 (40%)  |          |                      |
| Current                          | 48 (11%)  | 68 (10%)  | 39 (6%)   | 22 (4%)   | 177 (8%)   |          |                      |
| Multivitamin use <sup>b</sup>    |           |           |           |           |            |          |                      |
| No or < 3 days/week              | 187 (46%) | 276 (41%) | 248 (39%) | 203 (42%) | 914 (42%)  | 0.17     |                      |
| 3+ days/week                     | 216 (54%) | 394 (59%) | 381 (61%) | 278 (58%) | 1269 (58%) |          |                      |
| Family history of breast cancer  | 80 (18%)  | 143 (20%) | 143 (22%) | 109 (22%) | 475 (20%)  | 0.514    |                      |
| Live births                      |           |           |           |           |            |          |                      |
| 0                                | 113 (26%) | 127 (18%) | 88 (13%)  | 49 (10%)  | 377 (16%)  | < 0.0001 |                      |
| 1–2                              | 215 (49%) | 373 (52%) | 237 (36%) | 178 (35%) | 1003 (43%) |          |                      |
| 3–4                              | 99 (23%)  | 163 (23%) | 257 (39%) | 199 (39%) | 718 (31%)  |          |                      |
| 5+                               | 13 (3%)   | 48 (7%)   | 83 (12%)  | 78 (15%)  | 222 (10%)  |          |                      |
| Hysterectomy before diagnosis    | 45 (10%)  | 165 (24%) | 202 (31%) | 189 (39%) | 601 (27%)  | < 0.0001 |                      |
| Oophorectomy before diagnosis    | 23 (5%)   | 98 (14%)  | 110 (17%) | 107 (23%) | 338 (15%)  | < 0.0001 |                      |
| Ever Hormone Replacement Therapy | 61 (14%)  | 438 (63%) | 528 (81%) | 336 (69%) | 1362 (60%) | < 0.0001 |                      |
| Menstruating at diagnosis        | 353 (80%) | 207 (29%) | 14 (2%)   | 2 (< 1%)  | 576 (25%)  | < 0.0001 |                      |
| Menstruating at baseline         | 159 (36%) | 21 (3%)   | 2 (< 1%)  | 1 (< 1%)  | 183 (8%)   | < 0.0001 |                      |

<sup>a</sup>  $\chi^2$  test.

<sup>b</sup> Took a multivitamin with minerals at least 6 months.

Table 3. Age and self-reported treatments by stage

|                         | Stage       |             |             | <i>p</i> -Value <sup>a</sup> |
|-------------------------|-------------|-------------|-------------|------------------------------|
|                         | I           | II          | III A       |                              |
| n (%)                   | 1074 (47%)  | 1161 (50%)  | 69 (3%)     | –                            |
| Age (mean, SD)          | 61.5 (10.7) | 59.2 (11.0) | 56.3 (11.3) | <0.0001                      |
| Surgery                 |             |             |             |                              |
| Lumpectomy              | 671 (63%)   | 488 (42%)   | 9 (13%)     | <0.0001                      |
| Mastectomy              | 402 (37%)   | 676 (58%)   | 60 (87%)    |                              |
| Radiation               | 683 (64%)   | 713 (62%)   | 59 (86%)    | <0.001                       |
| Chemotherapy            | 361 (34%)   | 883 (76%)   | 65 (96%)    | <0.0001                      |
| Tamoxifen               | 788 (76%)   | 888 (78%)   | 53 (80%)    | 0.284                        |
| Raloxifene              | 40 (4%)     | 31 (3%)     | 1 (2%)      | 0.240                        |
| Prophylactic mastectomy | 43 (4%)     | 72 (6%)     | 7 (10%)     | 0.016                        |

<sup>a</sup>  $\chi^2$  test for treatment, *F*-test for age.

differences in any of these characteristics. At the end of the year 2004, the average follow-up time will be 5.6 years post-diagnosis and 3.8 years post-enrollment. Currently, 10.7% of the cohort has experienced either a breast cancer recurrence or new primary (*n* = 194) or unrelated death (*n* = 54).

#### Behavioral, demographic and medical characteristics of cohort

As seen in Table 2, the cohort is predominantly post-menopausal. However, among the 576 women (25% of

the cohort) who were menstruating at the time of diagnosis, the majority of them (68%) had become post-menopausal by the time of enrollment, presumably primarily as the result of breast cancer treatment. The age distribution of the cohort closely mirrors that of all women diagnosed with early stage cancer in the Kaiser Permanente Tumor Registry (KPNCAL) in the year 2000. LACE has a slight over-representation of 50 to 59 year olds (30% in LACE *versus* 23% in the KPNCAL) and a slight under-representation of women over 70 (22% LACE *versus* 33% in KPNCAL). Approximately 80% of the LACE cohort is Caucasian; the percentage of minorities are slightly higher among the youngest age group and slightly lower among the oldest women. College education in the LACE cohort varies by age with 45% of women under 50 having college degrees while only 24% of the women over 70 attained that same level of education. Current smoking rates were low overall (8%) but were higher in younger women than older women while regular multivitamin use (58%) was high overall and did not vary by age.

Younger women were more likely to be diagnosed at later stages and as expected, treatments vary by stage of diagnosis (Table 3). Almost 90% of stage IIIA women had a mastectomy while only 37% of Stage I women chose mastectomy over lumpectomy. Similar rates and variation are seen for adjuvant chemotherapy (96% in Stage IIIA *versus* 34% in Stage I). The use of radiation

Table 4. Daily dietary intake by age

| n<br>Nutrient             | Age group         |                   |                   |                   | <i>p</i> -value <sup>a</sup> |
|---------------------------|-------------------|-------------------|-------------------|-------------------|------------------------------|
|                           | <50               | 50–<60            | 60–<70            | ≥70               |                              |
|                           | 346               | 595               | 572               | 426               |                              |
|                           | Mean (SD)         | Mean (SD)         | Mean (SD)         | Mean (SD)         |                              |
|                           | median            | median            | median            | median            |                              |
|                           | (25th, 75th pctl) | (25th, 75th pctl) | (25th, 75th pctl) | (25th, 75th pctl) |                              |
| Energy (kcal)             | 1458 (578)        | 1425 (559)        | 1356 (508)        | 1336 (512)        | <0.01                        |
|                           | 1402 (1059, 1774) | 1326 (1034, 1719) | 1269 (988, 1648)  | 1255 (963, 1612)  | 0.02                         |
| % Energy as fat           | 35.1 (8.34)       | 34.3 (8.51)       | 33.8 (8.57)       | 35.4 (8.11)       | 0.01                         |
|                           | 35.3 (29.2, 41.0) | 34.3 (28.8, 39.9) | 33.6 (27.6, 39.9) | 35.4 (29.9, 41.1) | 0.09                         |
| % Energy as saturated fat | 12.2 (3.53)       | 11.6 (3.36)       | 11.3 (3.62)       | 12.0 (3.30)       | <0.001                       |
|                           | 12.0 (9.7, 14.3)  | 11.5 (9.3, 13.9)  | 11.1 (8.6, 13.4)  | 11.9 (9.6, 14.3)  | <0.01                        |
| % Energy as protein       | 16.8 (3.33)       | 17.1 (3.46)       | 16.8 (3.15)       | 16.5 (3.57)       | 0.06                         |
|                           | 16.7 (14.5, 18.8) | 16.9 (14.8, 19.3) | 16.6 (14.6, 18.8) | 16.2 (14.1, 18.7) | 0.03                         |
| % Energy as carbohydrate  | 47.3 (9.81)       | 48.0 (10.4)       | 48.6 (10.3)       | 47.8 (9.34)       | 0.30                         |
|                           | 47.0 (40.8, 54.0) | 48.0 (41.3, 54.9) | 48.3 (41.7, 55.3) | 47.9 (41.1, 53.7) | 0.66                         |
| Fiber (gm)                | 15.0 (7.72)       | 15.0 (6.85)       | 15.4 (6.65)       | 14.1 (6.35)       | 0.04                         |
|                           | 13.4 (9.5, 19.0)  | 13.6 (9.8, 19.0)  | 14.3 (10.2, 19.2) | 13.0 (9.4, 17.7)  | 0.09                         |
| Fruit (sv)                | 1.92 (1.50)       | 1.88 (1.31)       | 2.06 (1.38)       | 1.93 (1.26)       | 0.13                         |
|                           | 1.53 (0.79, 2.72) | 1.72 (0.82, 2.72) | 1.83 (1.00, 3.00) | 1.64 (1.00, 2.72) | 0.28                         |
| Vegetables (sv)           | 2.20 (1.52)       | 2.24 (1.44)       | 2.26 (1.37)       | 2.12 (1.24)       | 0.45                         |
|                           | 1.79 (1.09, 3.06) | 1.82 (1.19, 2.93) | 1.99 (1.23, 2.97) | 1.84 (1.19, 2.82) | 0.31                         |

<sup>a</sup> *p*-value associated with *F*-test for difference in means, or non-parametric Kruskal–Wallis test for difference in medians.

Table 5. Domain-specific physical activity by age

| Activity domain       | Age Group    |              |              |              | <i>p</i> -Value <sup>a</sup> |
|-----------------------|--------------|--------------|--------------|--------------|------------------------------|
|                       | <50          | 50 to <60    | 60 to <70    | ≥70          |                              |
| Household/caregiving  |              |              |              |              |                              |
| n                     | 330          | 570          | 555          | 425          |                              |
| Mean (SD)             | 28.3 (15.6)  | 29.4 (15.6)  | 29.2 (15.3)  | 26.7 (14.8)  | 0.027                        |
| Median                | 25.8         | 27.4         | 26.5         | 24.9         | 0.134                        |
| (I-Q range)           | (16.8, 38.8) | (17.5, 38.2) | (18.0, 38.9) | (16.1, 35.5) |                              |
| Sports/exercise/dance |              |              |              |              |                              |
| n                     | 338          | 608          | 576          | 439          |                              |
| Mean (SD)             | 18.5 (19.5)  | 14.8 (17.0)  | 15.5 (17.4)  | 10.9 (12.7)  | <0.0001                      |
| Median                | 11.9         | 8.8          | 9.8          | 6.5          | 0.005                        |
| (I-Q range)           | (3.7, 28.1)  | (1.7, 21.7)  | (2.0, 22.9)  | (0.4, 17.1)  |                              |
| Transportation        |              |              |              |              |                              |
| n                     | 344          | 608          | 574          | 439          |                              |
| Mean (SD)             | 5.6 (8.3)    | 4.9 (7.8)    | 4.3 (7.4)    | 3.7 (8.1)    | <0.0001                      |
| Median                | 4.5          | 4.2          | 1.7          | 0.5          | <0.0001                      |
| (I-Q range)           | (0.4, 5.5)   | (0.0, 5.3)   | (0.0, 5.3)   | (0.0, 4.5)   |                              |
| Sedentary behavior    |              |              |              |              |                              |
| n                     | 338          | 603          | 576          | 436          |                              |
| Mean (SD)             | 15.1 (6.3)   | 16.7 (6.7)   | 17.5 (7.1)   | 18.1 (7.5)   | <0.0001                      |
| Median                | 14.3         | 16.4         | 16.9         | 18.0         | <0.0001                      |
| (I-Q range)           | (10.8, 19.5) | (11.6, 21.1) | (12.5, 22.4) | (13.0, 22.4) |                              |
| Work activity score   |              |              |              |              |                              |
| n                     | 217          | 353          | 136          | 32           |                              |
| Mean (SD)             | 18.5 (15.6)  | 17.2 (13.4)  | 18.6 (13.7)  | 19.6 (13.9)  | 0.506                        |
| Median                | 15.0         | 15.0         | 15.0         | 16.3         | 0.556                        |
| (I-Q range)           | (5.0, 30.0)  | (5.0, 25.0)  | (7.0, 25.0)  | (10.3, 28.7) |                              |

All units are per week. Units for household/caregiving, sports/exercise/dance and transportation are met-h. Units for sedentary behavior are hours.

<sup>a</sup> *p*-Value associated with *F*-test for difference in means, or non-parametric Kruskal–Wallis test for difference in medians.

therapy and tamoxifen did not vary as dramatically by stage and approximately two-thirds to three-fourths of all women in the cohort received both of those treatments. Very few women in this cohort (<4%) were using raloxifene.

As shown in Table 4, the median percentage of energy from fat ranged from 33.6% to 35.4%, similar to that of women in the general population, with at least 25% consuming diets close to 40.0% or more calories from fat. Median fiber intake in the LACE cohort (13.0–14.4 g) was less than half of the recommended 30 g of fiber for a 1600–1800 kcal/day diet. Energy decreased with age, while percentage energy as fat and saturated fat were highest in the youngest and oldest age women. Servings of fruits and vegetables remained relatively stable across all age groups.

The relationship between physical activity and age varied by domain (Table 5). The median level of activity in sports and exercise and transportation decreased significantly with age, while the median time spent in sedentary behavior increased from a low of 2.0 hours a day in those less than 50 to a high of 2.6 hours a day in those 70 and older. The levels of both household/

caregiving and occupational activity were relatively constant across all age groups.

Table 6 describes the distribution of body size and weight gain patterns from pre-diagnosis to one year post-diagnosis by age. Over 20% of the women in each age group were obese (BMI over 30) at the time of diagnosis, and at least 50% in each age group were considered overweight or obese. BMI varied slightly by age with women aged 50–60 having the greatest percentage with a BMI over 30 (32%). The amount of weight change from one year pre-diagnosis to one year post-diagnosis varied by age. The percentage of women reporting stable weight ( $\pm 2$  kg) increased with age. Younger women reported gaining more weight, with 33–36% of women younger than 60 reporting a weight gain of 2–8 kg and 18–20% reporting a gain of greater than 8 kg. In women older than 60 the corresponding percentages were 23–28% and 6–8%.

Co-morbid conditions were extremely prevalent in this population of breast cancer survivors (Table 7) and as expected, rates for most conditions increased significantly with age. An exception to that was depression, which was more prevalent among younger women.

Table 6. Body measurements at enrollment and self-reported weight change patterns by age

|   | <50       | 50 to <60 | 60 to <70 | ≥70       | <i>p</i> -Value <sup>a</sup> |
|---|-----------|-----------|-----------|-----------|------------------------------|
|   | n (%)     | n (%)     | n (%)     | n (%)     |                              |
| Height  |           |           |           |           |                              |
| ≤1.60 m   | 86 (20%)  | 174 (24%) | 167 (25%) | 139 (27%) | 0.004                        |
| >1.60 to <1.67 m  | 183 (42%) | 287 (40%) | 283 (43%) | 229 (45%) |                              |
| ≥1.67 m   | 171 (39%) | 250 (35%) | 215 (32%) | 137 (27%) |                              |
| Body mass index   |           |           |           |           |                              |
| <20   | 22 (6%)   | 22 (4%)   | 19 (3%)   | 14 (3%)   | < 0.001                      |
| 20 to <25   | 144 (42%) | 187 (32%) | 200 (35%) | 140 (33%) |                              |
| 25 to <30   | 102 (30%) | 196 (33%) | 196 (34%) | 166 (39%) |                              |
| 30 to <35   | 48 (14%)  | 99 (17%)  | 106 (18%) | 70 (16%)  |                              |
| 35+   | 29 (8%)   | 88 (15%)  | 55 (10%)  | 39 (9%)   |                              |
| Weight change 1 year pre-diagnosis to 1 year post-diagnosis |           |           |           |           |                              |
| Lost >8 kg  | 17 (4%)   | 45 (6%)   | 50 (8%)   | 39 (8%)   | < 0.0001                     |
| Lost >2–8 kg  | 62 (14%)  | 99 (14%)  | 134 (20%) | 90 (18%)  |                              |
| Stable  | 113 (26%) | 198 (28%) | 233 (35%) | 225 (45%) |                              |
| Gained >2–8 kg  | 156 (36%) | 232 (33%) | 187 (28%) | 112 (23%) |                              |
| Gained >8 kg  | 89 (20%)  | 126 (18%) | 54 (8%)   | 29 (6%)   |                              |

<sup>a</sup>  $\chi^2$  test.

Table 7. Co-morbid conditions and functional limitations by age

| Co-morbid condition                            | <50       | 50 to <60 | 60 to <70 | ≥70       | <i>p</i> -value <sup>a</sup> |
|--|-----------|-----------|-----------|-----------|------------------------------|
|  | n (%)     | n (%)     | n (%)     | n (%)     |                              |
| Arthritis                                      | 70 (16%)  | 202 (29%) | 281 (43%) | 259 (53%) | < 0.0001                     |
| Other cancers                                  | 30 (7%)   | 65 (9%)   | 72 (11%)  | 76 (15%)  | < 0.001                      |
| Cardiovascular disease                         | 28 (6%)   | 55 (8%)   | 81 (12%)  | 110 (23%) | < 0.0001                     |
| Diabetes                                       | 15 (3%)   | 34 (5%)   | 58 (9%)   | 62 (13%)  | < 0.0001                     |
| High cholesterol                               | 52 (12%)  | 151 (22%) | 220 (34%) | 184 (38%) | < 0.0001                     |
| Hypertension                                   | 40 (9%)   | 175 (25%) | 258 (40%) | 257 (52%) | < 0.0001                     |
| Thyroid disorders                              | 60 (14%)  | 126 (18%) | 144 (22%) | 120 (25%) | < 0.0001                     |
| Gall bladder disease                           | 25 (6%)   | 79 (11%)  | 109 (17%) | 90 (19%)  | < 0.0001                     |
| Intestinal polyps                              | 10 (2%)   | 37 (5%)   | 62 (10%)  | 70 (14%)  | < 0.0001                     |
| Irritable bowel syndrome                       | 35 (8%)   | 69 (10%)  | 50 (8%)   | 37 (8%)   | 0.400                        |
| Osteoporosis                                   | 11 (3%)   | 38 (5%)   | 51 (8%)   | 54 (11%)  | < 0.0001                     |
| Depression Symptoms (CES-D ≥16)                | 116 (26%) | 140 (20%) | 117 (18%) | 110 (22%) | 0.005                        |
| Number of co-morbid conditions                 |           |           |           |           |                              |
| 0  | 195 (44%) | 199 (28%) | 77 (12%)  | 39 (8%)   | < 0.0001                     |
| 1  | 132 (30%) | 180 (25%) | 154 (23%) | 69 (14%)  |                              |
| 2  | 69 (16%)  | 158 (22%) | 159 (24%) | 108 (21%) |                              |
| 3  | 30 (7%)   | 77 (11%)  | 118 (18%) | 114 (23%) |                              |
| 4 or more                                      | 14 (3%)   | 97 (14%)  | 157 (24%) | 175 (35%) |                              |
| Number of functional limitations               |           |           |           |           |                              |
| 0  | 325 (74%) | 459 (65%) | 387 (58%) | 230 (46%) | < 0.0001                     |
| 1  | 33 (8%)   | 72 (10%)  | 75 (11%)  | 72 (14%)  |                              |
| 2  | 29 (7%)   | 50 (7%)   | 68 (10%)  | 55 (11%)  |                              |
| 3 or more                                      | 53 (12%)  | 130 (18%) | 132 (20%) | 146 (29%) |                              |
| Limited ability to walk 2–3 blocks             | 21 (5%)   | 60 (8%)   | 53 (8%)   | 92 (18%)  | < 0.0001                     |
| Shoulder limited range of motion (one or both) | 43 (10%)  | 71 (10%)  | 63 (10%)  | 65 (13%)  | 0.236                        |
| Arm lymphedema (one or both)                   |           |           |           |           |                              |
| None   | 220 (50%) | 384 (54%) | 404 (61%) | 326 (65%) | < 0.0001                     |
| A little bit; somewhat                         | 157 (36%) | 229 (32%) | 189 (29%) | 128 (26%) |                              |
| Quite a bit; very much                         | 61 (14%)  | 94 (13%)  | 66 (10%)  | 45 (9%)   |                              |

<sup>a</sup>  $\chi^2$  test.



Arthritis, hypertension and multiple co-morbidities (three or more) were present in 40% or more of women 60 years of age and over. Although the prevalence of arm lymphedema increased by age, there was no similar trend seen for shoulder limited range of motion. Younger women reported significantly fewer functional limitations and almost three-fourths of those under 50 reported none at all.

## Discussion

The findings of this study suggest that breast cancer survivors, for at least the first 1–3 years post-diagnosis, are similar in some important health-related behaviors to the population at large, although there is a tendency for large amounts of weight gain, particularly in younger survivors.

The reported levels of dietary energy and macronutrients in LACE are consistent with those reported in other populations using the same dietary instrument, both in women diagnosed with breast cancer as well as women of similar age who are free of breast cancer. In the women enrolled in the comparison group of the dietary arm of Women's Health Initiative (WHI), for instance, total energy (1521–1587 kcal) and percent calories from fat (36.1–38.9%) were just slightly higher than that reported in LACE [32]. In the HEAL (Healthy Eating, Activity and Lifestyle) study, a population-based, multi-center, multi-ethnic prospective cohort study of 1185 women with early stage breast cancer, reported energy (1369 kcal) and percent of calories from fat (35.5%) were remarkably consistent with the LACE cohort, and other macronutrients in the two cohorts were within 4% of each other [33].

However, the intakes reported in other studies of breast cancer survivors, assessed at approximately the same time post-diagnosis as in the LACE study have been much higher. For example, women in the WINS trial, whose dietary intake was measured by repeated 24 h recalls, reported a range of 1586–1713 kcal [34] and women in the WHEL trial, whose intake was measured by a more extensive food frequency, reported a range of 1900–1954 kcal [35]. The differences in the dietary instruments used in these studies, as well as age distributions of participants, could account for observed differences in reported energy.

Relative to other studies of breast cancer survivors, the LACE cohort reported a relatively low intake of fruit and vegetables. Although the mean intake (4.1 servings) was more than in the HEAL study (3.5) [33], it was lower than the average in either WHEL (6.7 servings) [35] or WINS (5.7–6.0) [34]. However, the

fruit and vegetable intake in LACE was similar to intake reported by women in the general population free of breast cancer. Women in WHI reported 3.8 daily servings [32] while data from the Continuing Study of Food Intakes (CSFII) [36], that utilizes a dietary recall, reported a mean of 4.6 servings for women. Less than 25% of the women in both of these studies reported consuming more than five fruits and vegetables a day, the minimum recommended by the National Cancer Institute.

A direct comparison of the level of physical activity in the LACE cohort with that of the population as a whole is difficult for a number of reasons. Most importantly, the population-based, national surveys, such as NHANES or Behavioral Risk Factor Surveillance System, generally only assess leisure time activity, and even in that one domain, they do not collect as much detailed information as does the LACE questionnaire [23]. As a result, the national surveys usually summarize physical activity in terms of prevalence, such as prevalence of no leisure activity [37] or prevalence of the activity level recommended to achieve health benefits [38, 39].

However, data from several studies with large and generally representative samples suggest that the activity level of the LACE cohort is comparable to or somewhat greater than that of other middle-age and older women who have not experienced cancer. For instance, about 50% of the participants in the Women's Health Initiative who did not develop breast cancer, reported ten or fewer MET-hours per week of physical activity [40], while in the LACE cohort, the median level of sports, exercise, and dance ranged from 12.2 MET h/week in the women under 50 to 6.8 MET h/week in the women over 70. Similarly, in the California Teachers Study, just over a quarter of the women without breast cancer reported more than four hours a week of exercise [41], while in LACE, the upper quartile of the youngest women in the sample reported a frequency and duration of leisure time activity equivalent to about five hours a week or more of a 6 MET activity. The level of household/caregiving activity reported by the LACE cohort, about 60 min a day, assuming an average MET value of 3.5, is also comparable to that reported in other studies, such as the Study of Activity and Fitness Evaluation, in which women reported spending about 83 min a day on household activities [42].

To our knowledge, only one other observational study has reported on physical activity behavior in breast cancer survivors [43]. In that study, the survivors reported the same level of moderate, vigorous and total physical activity as non-cancer controls, although mode of exercise differed in several specific ways, (e.g. the survivors did more yard work and stretching). Two

other studies suggest that cancer survivors might even be more active than the general population. In a population-based survey of cancer patients, 20.8% increased their physical activity in the two years following diagnosis [39], and in a survey of cancer survivors who identified as athletes, exercise was reportedly used during treatment, both to reduce cancer-related fatigue and increase energy [44]. These findings, coupled with the findings of the present study, suggest that physical activity in cancer survivors is at least as high as that of other women, that recreational activity generally decreases with age, as it does in the general population, and that self-reported activity may be as valid a measure in breast cancer survivors as in other population groups.

Excessive weight gain may put breast cancer survivors at risk for future obesity-related morbidity and mortality. Although the magnitude of overweight in the LACE population is similar to rates observed in the general adult female population, the rate of weight gain in these women over a three year period is higher than expected. Women aged 30–55 typically gain 4 lbs over a ten year period. In the LACE cohort, the mean weight gain of 2.89 kg in two years (data not shown) suggests that breast cancer survivors typically gain weight at a much higher rate than women of similar ages in the general population. Several studies have reported on the high incidence of obesity among women diagnosed with breast cancer, and the extensive number of women who gain weight post-diagnosis [45, 46]. Weight gain is generally more prevalent among women who were pre-menopausal at diagnosis and who received adjuvant therapy as part of their treatment [47] and usually ranges from 2.5–6.2 kg [45]. In the WHEL study, 41% of the women gained more than 5% of their body weight from pre-diagnosis to on average two years post diagnosis [48]. In the LACE cohort, weight change findings were similar in women less than 50 (the group most likely to be pre-menopausal at diagnosis) – 56% gained weight, while in women 70 and older, only 29% gained weight. Furthermore, the majority of those who gained weight gained between 2 and 8 kg, similar to the ranges reported above.

Multiple, concurrent health conditions are common in older women. In the National Health Interview Supplement on Aging, 45% of women aged 60–69% and 61% of those aged 70–79 report two or more co-morbid conditions [49], rates substantially less than found in LACE. Additionally, the consequences of those co-morbidities may be greater for women newly diagnosed with breast cancer in whom co-morbidity may elevate the risk of death by as much as 20-fold [50, 51]. The findings from the LACE cohort confirm previous reports that show that the prevalence of most co-morbidities increase with advancing age [50–52]. When compared with a cohort of breast

cancer survivors diagnosed between 1994 and 1998 in the Detroit metropolitan area, where co-morbid conditions were obtained from medical records [51], the LACE cohort reported similar rates for diabetes and irritable bowel syndrome, higher rates of arthritis, thyroid conditions and other cancers, and lower rates of hypertension and heart disease. One potential reason for differing rates of some conditions between the two cohorts may be the difference in ascertainment method.

We report a low level of functional limitations in breast cancer survivors less than 50 years of age and a lower level of these limitations in younger *versus* older survivors. Other studies have reported similar differences by age [53–55]. However, Kroenke *et al.* [56] have demonstrated that when women with breast cancer are compared to women of similar age who are free of breast cancer, young women ( $\leq 40$  years of age) experienced the largest relative declines in functional status, concluding that young women fare worse than middle aged or elderly women after breast cancer diagnosis.

As with any observational study where participation is voluntary/and or only a select group is invited to participate, response bias and selection bias may limit the interpretability of the findings. Although only women who declined participation in WHEL were invited to participate in LACE, all the women we recruited for LACE from WHEL met the WHEL eligibility criteria for enrollment and were similar to those who participated in WHEL with regard to tumor and demographic characteristics. Women who met the eligibility criteria from the Kaiser Permanente Tumor registry were all invited to participate and when we compared those who responded to those who did not, we found that the non-responders had very similar cancer diagnoses to those enrolled, thus it is unlikely that cancer severity limits the generalizability of our findings. We did find some under-representation in our cohort of the youngest age group ( $< 50$ ), which could limit our overall generalizability, however we intend to, whenever possible, report results within age strata.

Since women entered the cohort on average approximately two years post-diagnosis and those who had already recurred were ineligible to participate, it is also likely that there is some survivor bias. This may limit the generalizability of the findings to a group of survivors who are at lower risk for recurrence. However, we believe this bias is minimal since we examined some demographic and tumor characteristics of those who enrolled earlier post-diagnosis compared to those who enrolled later post-diagnosis and there appeared to be no significant differences in severity of disease.

In summary, the LACE cohort is one of the few existing cohorts of early stage breast cancer survivors,

and is similar to the general population of women in terms of demographic characteristics and many health behaviors. They differ from the general population, however, in terms of susceptibility to excessive and rapid weight gain. As follow-up of the LACE cohort continues, attention will be focused on the influence of health behaviors, such as dietary intake and physical activity, on the risk of breast cancer-associated outcomes (quality of life, recurrence, late effects of treatment, mortality) – questions of great interest and relevance to scientists, health care providers, public health professionals, and, most importantly, to the two million breast cancer survivors alive today.

### Acknowledgements

This study was supported by funds from the National Cancer Institute, grant number RO1 CA80027-05 and by the Utah Cancer registry, which is funded by Contract #N01-PC-67000 from the National Cancer Institute, with additional support from the State of Utah Department of Health.

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