

# The Pathways Study: a prospective study of breast cancer survivorship within Kaiser Permanente Northern California

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## Abstract

**Objective** With 2.3 million breast cancer survivors in the US today, identification of modifiable factors associated with breast cancer recurrence and survival is increasingly important. Only recently new studies have been designed to examine the impact of lifestyle factors on prognosis, including Pathways, a prospective study of women with breast cancer in Kaiser Permanente Northern California (KPNC).

**Methods** Pathways aims to examine the effect on recurrence and survival of (1) lifestyle factors such as diet, physical activity, quality of life, and use of alternative

therapies and (2) molecular factors such as genetic polymorphisms involved in metabolism of chemotherapeutic agents. Eligibility includes any woman diagnosed with invasive breast cancer within KPNC, no previous diagnosis of other invasive cancer, age 21 years or older, and ability to speak English, Spanish, Cantonese, or Mandarin. Newly diagnosed patients are identified daily from electronic pathology records and are enrolled within two months of diagnosis. An extensive baseline interview is conducted, blood and saliva samples are collected, and body measurements are taken. Women are followed for lifestyle updates, treatment, and outcomes by self-report and query of KPNC databases.

**Results** Recruitment began in 9 January, 2006, and as of 16 January, 2008, 1,539 women have been enrolled along with collection of 1,323 blood samples (86%) and 1,398 saliva samples (91%).

**Conclusions** The Pathways Study will become a rich resource to examine behavioral and molecular factors and breast cancer prognosis.

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## Introduction

It is estimated that at least 2.3 million breast cancer survivors currently live in the US. [1]. Advances in early detection and in types of therapies and their application have resulted in prolonged survival among women diagnosed with breast cancer. As this population grows, information related to whether lifestyle factors such as diet or physical activity can influence prognosis is of increasing interest.

Despite the large number of breast cancer survivors, surprisingly little is known regarding the effects of lifestyle factors on breast cancer prognosis [2–5]. In contrast, a plethora of publications are available from epidemiologic studies that relate dietary factors to the development of cancer [6]. Investigators interested in studies of breast cancer prognosis have generally ignored the potential role of dietary or other lifestyle factors and have instead focused on studies that examine modifications in adjuvant therapy, such as the National Surgical Adjuvant Breast Program [7, 8], or the identification of molecular or other prognostic indicators, such as hormone receptor status [9] or genetic profiles [10, 11]. Changes in diet, use of supplements, or other lifestyle factors have been considered an afterthought.

Many of the currently available studies on lifestyle factors and breast cancer prognosis suffer from design limitations that substantially limit their ability to address even the most basic questions that confront survivors, their families, and their health care providers. These limitations are due to the fact that many such studies have not been specifically designed to address questions related to prognosis, thus creating a situation in which informed guidance is difficult. This dilemma has been noted in two recent reports by the American Cancer Society (ACS) [12] and the World Cancer Research Fund/American Institute for Cancer Research [6].

Recently, investigators have started to conduct studies related to lifestyle factors and cancer prognosis. The aim of one such study, the Pathways Study, is to examine the effect on recurrence and survival of (1) lifestyle factors such as diet, physical activity, quality of life, and use of complementary and alternative medicine (CAM) and (2) molecular factors such as genetic polymorphisms involved in metabolism of chemotherapeutic agents. In this article, we describe the formation of the Pathways prospective cohort and report baseline demographic and tumor characteristics among the first 1,539 study participants.

## Materials and methods

### Overall study design

The Pathways Study is a prospective cohort study, with recruitment of women from the Kaiser Permanente Northern California (KPNC) patient population as soon after diagnosis of invasive breast cancer as possible. Women are typically enrolled within two months postdiagnosis during an in-person baseline interview. Blood specimens and saliva samples are also collected at baseline to enable investigation of molecular and other factors. Among all participants, follow-up questionnaires are

mailed at six months and 24 months after baseline to assess updates in lifestyle factors while telephone interviews occur every 12 months after baseline to identify breast cancer outcomes. The study was approved by the institutional review board of all collaborating institutions. Written informed consent is obtained from all participating subjects.

### Identification of women eligible for recruitment

Since 9 January, 2006, women diagnosed with invasive breast cancer are being recruited from the KPNC patient population into the Pathways Study. In order to be eligible, women have to be at least 21 years of age at diagnosis and a current KP member, have a recent (usually within two months) diagnosis of invasive breast cancer (all stages), have no previous history of malignant cancer, speak English, Spanish, Cantonese, or Mandarin, and live within a 65-mile radius of a field interviewer.

The study is designed for rapid case ascertainment in order to enroll women prior to start of adjuvant therapy. The KP Laboratory Utilization and Reporting System (LURS) database, which exists in a mainframe environment, is automatically accessed on a daily basis for pathology reports and is the method by which pathologists report their findings to clinicians. This automated process involves scanning all records for any new patients with Systematized Nomenclature of Human and Veterinary Medicine (SNOMED) Topography and Morphology Codes indicating malignant breast cancer. For those records found to be eligible, demographic, pathology, and physician-related data are collected and uploaded to a Structured Query Language (SQL) server to begin the tracking process. This procedure enables the identification of women diagnosed with breast cancer within one day of notification by the pathologist.

Breast cancer diagnosis and patient notification of the incident diagnosis is verified in the KP Clinical Information Presentation System (CIPS). In addition, a passive consent is obtained from the patient's physician of record by an email notification stating our intention to contact his or her patient for study recruitment. If the physician has not objected within one week after notification of intent to contact the patient, recruitment procedures are initiated.

### Recruitment of participants

Recruitment, enrollment, and baseline data collection are conducted by 14 field interviewers (two Spanish-speaking and one Chinese-speaking) based throughout the major geographic regions served by KPNC, including the East Bay, Marin, San Francisco, San Jose, Fremont, Sacramento, and Stockton. Women who are diagnosed with

breast cancer are assigned to interviewers according to geographic location. Interviewers are not expected to travel further than 65 miles from their home. Thus, some women are not eligible for recruitment because of their distance from an interviewer.

Prior to recruitment, and after confirmation of patient notification of her breast cancer diagnosis and passive physician consent, an invitation letter, reply postal card, and brochure describing the study is sent to the potential participant. Concurrently, potential participants are assigned to interviewers based on geographic location as noted above. After two weeks, or if we are notified of interest by the potential participant, the interviewer will contact her by telephone. If the woman agrees to participate, an in-person interview is arranged at a location of convenience for the woman, usually in her home. Interviewers are expected to make no more than ten telephone calls to recruit each potential participant.

All relevant recruitment information is documented through a secure study website, including assignment of participants to interviewers, and information on contacts between the interviewer and the potential participants. Patients are excluded who are contacted more than two months after diagnosis and if they have begun chemotherapy, radiation treatment, or hormone therapy. Interviewers are responsible for recording special needs or disabilities of the participant which might affect future study retention and for completing an evaluation of the overall quality of the interview.

For quality control purposes, yearly re certifications are conducted among all interviewers in which the field staff coordinator reviews the baseline interview protocols and procedures with the interviewer at the study coordinating center and then observes a live baseline interview in the field. Appropriate feedback and corrective action is taken as necessary to ensure standardization of the interview process among all field staff. Furthermore, quality assurance procedures, including review of baseline files by two separate staff members, are conducted at the study coordinating center to provide an additional check of data collection consistency. Participants are called back for clarification if necessary.

#### Baseline and follow-up data collection

During the baseline interview, which averages three hours in length, interviewers first consent the study participants, and then administer detailed questionnaires on diet, exercise, use of CAM, and psychosocial and quality-of-life measures. Anthropometry measures are taken, including arm, waist, and hip measurements. A saliva sample is obtained, and if the interviewer is a certified phlebotomist, a blood sample is also collected. Otherwise, arrangements

are made to draw blood at a KPNC facility for a courtesy research blood draw or at home by an outside vendor (Examination Management Services, Inc. [EMSI], Irving, TX). A \$20 gift certificate is mailed to the participant upon completion of the interview. Completed questionnaires are sent every two weeks to the study coordinating center. Blood samples are shipped to Roswell Park Cancer Institute on the same day as collection.

The baseline data collection consists of interviewer- and self-administered questionnaires. Interviewer-administered questionnaires collect information on demographics, family health history, prenatal exposures, pregnancy health history, developmental history, menstrual history, child health history, history of breast care screening procedures, smoking history, hormone use, medication history, use of vitamins and minerals, and consumption of organic foods. Self-administered questionnaires collect information on diet (food frequency questionnaire [FFQ] and three-day food record), physical activity, CAM use, lymphedema, and psychosocial and quality-of-life measures.

A packet of follow-up materials is mailed to the participant's home at six and 24 months after baseline. Follow-up materials include a primary follow-up questionnaire, FFQ, three-day food record, and a form and tape measure for anthropometric measurements. The primary follow-up questionnaire is similar to the baseline interview in asking for updates on menstrual history, smoking, medication use, vitamin use, organic food consumption, CAM use, physical activity, lymphedema, and psychosocial measures. Interviewer assistance is offered to participants to complete the follow-up packet. Table 1 shows the timeline of data collection in the Pathways Study.

#### Diet

Dietary history is collected using two assessment methods: a 139-item modified version of the Block 2005 FFQ

**Table 1** Timeline of data collection in the Pathways Study

Months since baseline interview <sup>a</sup>	Details of data collection
0	In-person baseline interview
6	Mailed follow-up questionnaires
12	Health status update call
24	Mailed follow-up questionnaires and health status update
36	Health status update call
48	Mailed follow-up questionnaires and health status update

<sup>a</sup> Baseline interview is usually within two months of breast cancer diagnosis

(NutritionQuest, Berkeley, CA) and an undocumented three-day food record (Nutritional Assessment Shared Resource [NASR], Fred Hutchinson Cancer Research Center, Seattle, WA).

For the FFQ, food items were selected by identifying the top population contributors of each nutrient among Whites, African Americans, and Hispanics in the National Health and Nutrition Examination Survey (1999–2002) [13, 14]. The 139 food items and additional questions were selected to be representative of a wide range of dietary factors, as well as to capture foods that are popular in Hispanic and Asian populations. Questionnaires are sent to NutritionQuest for scanning using a nutrient database developed primarily from the USDA Food and Nutrient Database for Dietary Studies [15].

A three-day food record is left with participants to complete over the next two weeks after the baseline interview. They are instructed by the interviewer to record three nonconsecutive days (two weekdays and one weekend day) of all the foods consumed being as descriptive as possible for brand names and preparation methods as well as including nutrition facts labels and recipes. The booklet also contains 12 questions on food-use patterns such as “When you eat bread or rolls, how often do you add butter or margarine?” to collect information typically obtained during review of completed food records. The participants are given a postage-paid return envelope to mail the food record to the study coordinating center. Completed food records are sent to NASR, and trained staff enter information into the Nutrition Data System for Research (NDS-R) software (version 4.04, Food and Nutrient Database 32) [16, 17], using a set of established rules to standardize entry of foods with incomplete information.

### Anthropometry

Body measurements are taken by the field interviewer during the baseline interview and are also requested with the follow-up mailed questionnaire packets. For the mailed data collection, women are instructed to have a family member or friend assist with the measurements; if necessary, an interviewer is available to take the measurements. Waist, hips, and arm lengths and circumferences are measured using a specialized tape measure called the Figure Finder Tape Measure (Novel Health Products, Rockton, IL), which is designed to create a uniform amount of tension (four ounces). The waist is measured one inch above the navel in a horizontal plane while the hips are measured around the maximum extension of the buttocks in a horizontal plane. The measurements of both arms consist of serial circumference measurements at the wrist, elbow, and upper arm as well as the length between the three bounding circumferences. All measurements are

taken twice, with a third measurement obtained if a one centimeter margin of error is exceeded.

### Complementary and alternative medicine (CAM)

The use of CAM is assessed with a modified two-part self-administered questionnaire based on previous studies [18–21]. Part 1 is a checklist asking for ever use of five main modalities: herbal and botanical supplements such as black cohosh, ginseng, and mistletoe (90 items); other natural products such as co-enzyme Q10, DHEA, and melatonin (26 items); special diets such as low-fat, macrobiotic, or vegan (12 items); mind-body healing such as hypnosis, support groups, or yoga (17 items); and body-based, energy-based, and other treatments such as acupuncture, naturopathy, or reiki (23 items). Space is available for women to report use of CAM therapies that are not specified on the questionnaire. Part 2 asks for more detailed information for each CAM supplement, approach, or treatment reported in Part 1, including total length of use, use in the five years before diagnosis and since diagnosis, and frequency, duration, and reason of prediagnosis use. Whether the CAM therapy was used during conventional breast cancer therapy is also determined in follow-up questionnaires.

### Physical activity

Physical activity is assessed in Pathways with a questionnaire developed for another study of breast cancer survivors within KPNC (Life After Cancer Epidemiology Study [LACE] [22]), which was modeled loosely after the Arizona Activity Frequency Questionnaire (AAFQ) [23]. The questionnaire is divided into four main sections: job or work-related activities, activities not related to paid or volunteer work, recreational activities, and transportation. The activities not related to paid or volunteer work are further subdivided into household chores (six items), caregiving (five items), and home maintenance and repairs (seven items). Recreational activities are sub-divided into sports, exercise, and dance (23 items) and sedentary recreational activities, such as reading or socializing (six items). Four items are included under transportation. For each activity that respondents did at least once a month during the past six months, they report the frequency, duration, and intensity. A validation study of the LACE questionnaire is currently underway using accelerometers and physical activity diaries as direct validation criteria and cardiorespiratory fitness and body composition as indirect criteria.

### Psychosocial and quality-of-life measures

A number of instruments are used in Pathways to measure various psychosocial issues important to women with breast

cancer. Seven quality-of-life domains for patients with breast cancer are assessed using the Functional Assessment of Cancer Therapy questionnaire (FACT-B) [24]. The Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane) scale is used to measure neurotoxicity symptoms associated with some taxane agents [25]. In addition, the Center for Epidemiological Studies Depression Scale (CES-D) [26] as well as a 12-question scale developed by Scheier and Carver [27] measure symptoms of depression during the past seven days and dispositional optimism, respectively. Questions were modified from the 1979 National Survey of Black Americans to assess the experience of stress during the past seven days in various areas including health, money, job, family, and crime [28]. In addition, questions on racial discrimination [29], health literacy [30], aspects of doctor-patient communication [31], preference for doctor-patient decision-making [32], global trust in one's doctor [33], and social support [34] are asked. Finally, questions from the KP Breast Cancer Patient Survey are used to measure difficulty taking time off from work to attend medical appointments and keeping medical appointments due to distance or transportation.

#### Outcome ascertainment

##### *Yearly health status update*

Cohort members are contacted every year subsequent to their baseline interview to complete a health status update questionnaire asking about any new breast cancer events since the previous update, including recurrence and new breast cancer diagnosis, new diagnosis of another cancer, and hospitalizations or other conditions believed to be health consequences or late effects associated with breast cancer treatment. If an event is reported, KP electronic medical records are searched for confirmation of the event (see below). The first yearly health status update began in January 2007.

##### *Electronic medical records*

Medical record abstraction from KPNC clinical and administrative electronic databases will be performed on all cohort members. Data of interest include breast tumor characteristics (including but not limited to hormone receptor status, HER-2/Neu expression, tumor size, number of positive nodes, and American Joint Committee on Cancer [AJCC] stage), chemotherapy, radiation therapy, and hormonal therapy regimen and associated adverse events, general medications, laboratory results, co-morbidities, recurrences, and new cancers. Data for pharmacy, laboratory, radiology, hospitalizations, emergency room visits, and other outpatient clinical visits can be obtained from the

following databases: Outpatient Summary Clinical Record (OSCR), Pharmacy Information System (PIMS), Admission Discharge and Transfer (ADT), LURS, Case Management for Medical Oncology with Laboratory and Outcome Tracking (CAMMOLOT), Medical Record Management System—radiology component (MRMS), Transcription Results Reporting System—radiology component (TRRS), and Health Connect (KP's automated medical record system). Services provided by nonKP vendors can be collected from authorized outside medical services (AOMS) and claims, adjudication, and tracking system (CATS).

In addition, the KPNC Cancer Registry (KPNCRR) [35] is accessed to obtain diagnostic tumor characteristic data. Data are collected, coded, and added to the KPNCRR approximately four months postdiagnosis to allow for the completion of treatment. Over 1,600 new cases are processed monthly. The registry covers 19 KPNC medical centers and includes over 322,000 cases of in situ and invasive cancers diagnosed from 1947 to the present. Data in the KPNCRR are also reported to the State of California and Northern California (Bay Area) SEER Registries. Finally, computerized mortality files will be regularly searched for any cohort member whom we fail to contact.

#### Biospecimen collection, processing, and storage

##### *Blood and saliva*

Blood is collected from the participant around the time of the baseline interview. Nonfasting blood is drawn into three 10 ml polystyrene tubes (lavender, green, and red tops) to maximize diversity in blood components available for later analyses (see below). When possible, the blood is drawn prior to initiation of adjuvant therapy to ensure integrity of biomarkers that may be assessed. The blood is shipped cold overnight to Roswell Park Cancer Institute (RPCI) for processing and storage. Protocols for shipment and handling were developed to standardize procedures to prevent variability that could affect sample degradation. In addition, 2 ml of saliva is collected using the Oragene<sup>TM</sup> DNA Self-Collection Kit (DNA Genotek Inc., Ottawa, Ontario, Canada) at the time of the baseline interview as a back-up source of DNA in the event a blood specimen is insufficient or not obtained. The saliva is mixed with preservative immediately after collection, kept at room temperature, and shipped to RPCI within three weeks of collection.

Upon receipt at RPCI, blood samples are processed and divided into multiple aliquots. The lavender top tube is the source of DNA for genotyping; the green top tube is the source of buffy coat, red blood cells (RBCs), and plasma; the red top tube is the source of serum. RBCs can be used for analysis of membrane-bound markers, as well as other factors that are best evaluated in erythrocytes, such as

folate and catalase. Serum and plasma will be used for assessment of a number of circulating markers.

Approximately 4 ml of whole blood from the lavender tube is aliquoted into cryovials and stored at  $-80^{\circ}\text{C}$  for DNA extraction at a later date. RBCs, buffy coat, plasma, and serum are aliquoted into 0.5 ml straws using the MAPI Cryobiosystem (IMV Technologies, Paris, France), slow frozen to  $-80^{\circ}\text{C}$ , and then transferred into long term storage in liquid nitrogen vapor. All aliquots are imprinted with scannable barcodes and user readable characters. Their positions within the freezers, which are locked, temperature monitored, and alarmed, are tracked by a laboratory information management system (LIMS).

The Oragene<sup>TM</sup> saliva samples for future DNA extraction are received at RPCI and stored at room temperature in a locked storage device. The saliva samples are also labeled with scannable barcodes and user readable characters, and their positions within the storage system tracked by a LIMS.

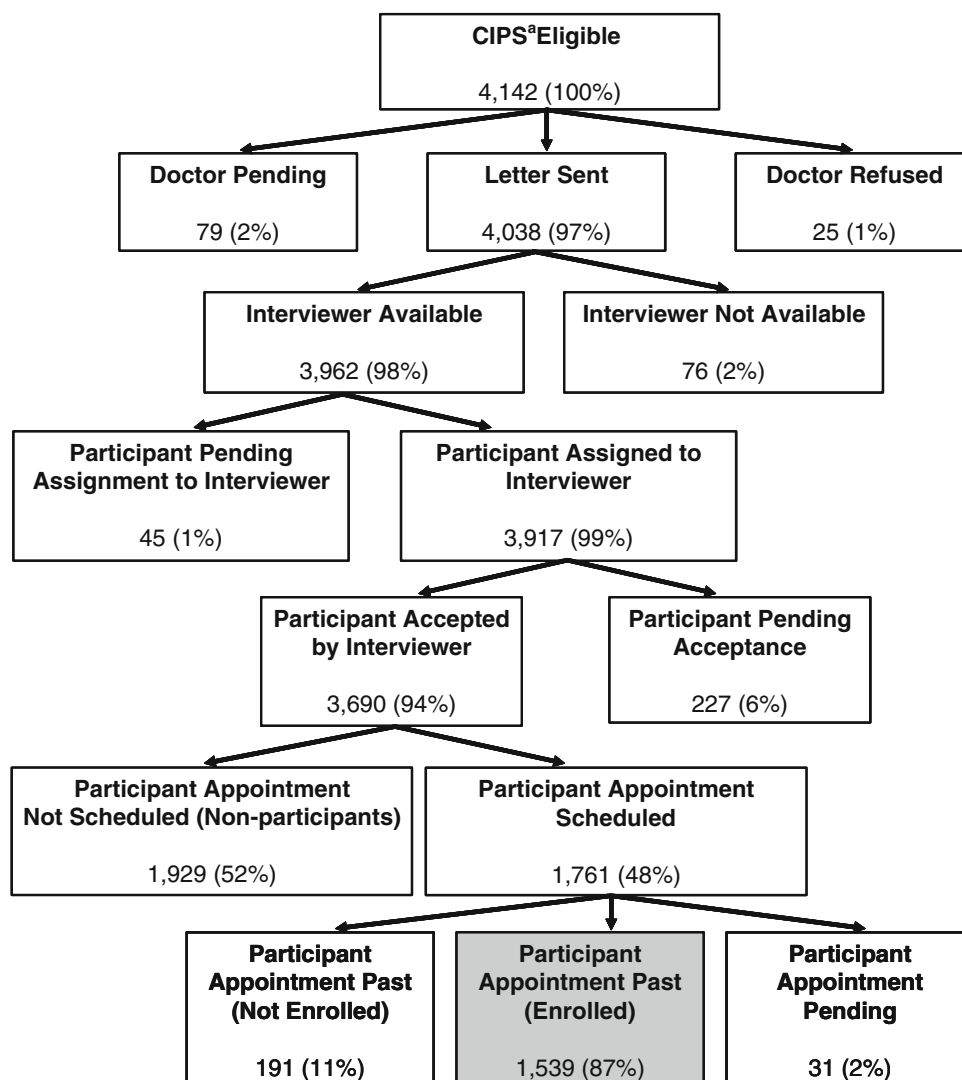
## Results

Data are presented as frequency distributions for ordinal and nominal variables. Differences in frequency distributions of baseline characteristics across enrolled and nonenrolled women were assessed via the Pearson chi-square test.

### Recruitment

Since the beginning of Pathways recruitment in January 2006, 1,539 breast cancer patients have been enrolled (indicated by completion of the baseline interview) as of 16 January, 2008. The mean time from diagnosis (date on which the pathologist reports information in LURS) to enrollment is 1.8 months (minimum = 0.3 months; maximum = 7.2 months). Figure 1 shows the general recruitment scheme into the cohort. Out of 3,690 patients who were available for contact ("Participant Accepted by Interviewer"), 1,761 (48%) had an appointment scheduled, among which 1,539 (87%) were

**Fig. 1** Pathways Study recruitment process, as of 16 January, 2008. <sup>a</sup> Kaiser Permanente Clinical Information Presentation System



enrolled, 191 (11%) were not enrolled, and 31 (2%) have a participant appointment pending. Participation status has been confirmed on 1,783 (92%) out of 1,929 nonparticipants where 957 (54%) refused, 514 (29%) were ineligible, and 312 (17%) were unreachable (Table 2). The majority of the ineligible women (64%) was contacted two months after diagnosis and had already started conventional treatment. The overall Pathways recruitment rate among those who were ultimately found to be eligible and were contacted by the interviewers is 51% (1,539 divided by 4,142 potential participants [sum of 957 refusals, 514 ineligibles, and 1,539 enrolled]). This rate is higher than the 46% rate achieved in another KPNC prospective breast cancer study using only mailed questionnaires which recruited women on average two years postdiagnosis after completion of adjuvant therapy [22].

### Demographic characteristics of cohort

Table 3 presents selected demographic characteristics of the Pathways cohort by age group. In addition, women enrolled in Pathways ( $n = 1,539$ ) are compared to women who were diagnosed with breast cancer over the same time period but not enrolled ( $n = 2,478$ ). The average age

**Table 2** Reasons for nonparticipation in the Pathways Study among women assigned to field interviewers for recruitment, as of 16 January, 2008

Nonparticipants	1,929	(100%)
Bad address, deceased	6	(1%)
To be contacted	140	(7%)
Participation status confirmed	1,783	(92%)
Participation status confirmed	1,783	(100%)
Unreachable	312	(17%)
Refusal	957	(54%)
Ineligible	514	(29%)
Reasons for ineligible <sup>a</sup>	514	(100%)
Elapsed two month eligibility period	328	(64%)
Previous invasive cancer	72	(14%)
Language difficulty	72	(14%)
Dementia	38	(7%)
Not invasive breast cancer	2	(<1%)
Other <sup>b</sup>	2	(<1%)
Overall recruitment rate <sup>c</sup>	51%	

<sup>a</sup> Estimated for 148 potential participants with missing data by applying the distribution of ineligibility status from the remaining 366 potential participants with valid data

<sup>b</sup> Includes one woman who was legally blind and one woman who left the Kaiser Permanente health plan prior to the baseline interview

<sup>c</sup> 1,539 participants were enrolled out of a possible 3,010 potential participants (sum of 957 refusals, 514 ineligibles, and 1,539 enrolled) for an overall recruitment rate of 51%

at diagnosis is 59.5 years (range: 24.6–91.9 years) among the enrolled and 62.1 years (range: 21.0–96.5 years) among the nonenrolled. The women in our study are somewhat younger than the overall breast cancer population, with underrepresentation of women aged 70 years or older. The cohort consists mainly of nonHispanics/Latinas (90%) and is primarily of White (73%) followed by Asian (11%), African American (7%), and American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and Other (9%) racial make-up. The cohort is evenly distributed across levels of body mass index (BMI). Most of the participants are enrolled from the Golden Gate KP service area, which includes San Francisco and Marin counties. In general, the women enrolled in the study are largely representative of the total KPNC incident breast cancer population, with a slight under-representation of women in the Capital (Sacramento region) and Central California Service Areas and slight over-representation of women in the Golden Gate (San Francisco/Marin region) Area. This difference reflects our hiring of field staff in which the first interviewers were hired in Marin County and the last interviewers were hired in the Sacramento and Central California areas. Since we identify newly diagnosed women who do not appear in the KPNCRR for several weeks or months after diagnosis, approximately three-quarters (77%) of the cohort members have cancer registry data currently available.

### Tumor characteristics of cohort

Table 4 shows selected breast-cancer related characteristics from the KPNCRR of the Pathways cohort by age group. Most of the diagnosed breast cancers are of local cancer stage (68%), node-negative (65%), 1 to less than 2 cm in size (38%), and have no metastases (96%). As for tumor hormone receptor status, 84% are ER-positive, 69% are PR-positive, and 73% are HER-2/Neu-negative. More women have undergone chemotherapy (46%) and/or hormone therapy (40%), while fewer have had radiation therapy (34%). More detail on treatment information will be obtained from other data sources as described in the Methods section.

The enrolled women are largely representative of the overall breast cancer population, although a slightly larger proportion of study participants have earlier stage disease compared to women not enrolled in the study. This difference can be noted in the SEER Summary Cancer Stage ( $p < 0.01$ ) and AJCC Stage Group ( $p = 0.04$ ), as well as in the somewhat higher proportion of women who have negative nodal status ( $p < 0.001$ ) and absence of metastases ( $p < 0.01$ ). Slightly higher proportions of women in our study have ER-positive tumors and have undergone conventional therapies.

**Table 3** Demographic characteristics by age at diagnosis in the Pathways Study, as of 16 January, 2008

	<50 years <i>n</i> (%)	50–59 years <i>n</i> (%)	60–69 years <i>n</i> (%)	≥70 years <i>n</i> (%)	Total enrolled <i>n</i> (%)	Total not enrolled <sup>a</sup> <i>n</i> (%)	<i>p</i> -value <sup>b</sup>
<b>Ethnicity</b>							
Hispanic/Latino	68 (20)	40 (9)	31 (7)	21 (7)	160 (10)	238 (10)	<0.001
Not Hispanic/Latino	274 (80)	429 (91)	399 (93)	277 (93)	1,379 (90)	2,201 (89)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	39 (1)	
<b>Race</b>							
AI/Alaska Native	8 (2)	13 (3)	12 (3)	7 (2)	40 (2)	3 (<1)	<0.001
Asian	52 (15)	66 (14)	35 (8)	10 (3)	163 (11)	384 (15)	
Pacific Islander	3 (1)	1 (<1)	2 (<1)	0 (0)	6 (<1)	9 (<1)	
African American	26 (8)	40 (8)	28 (6)	9 (3)	103 (7)	216 (9)	
White	202 (59)	319 (68)	334 (78)	262 (89)	1,117 (73)	1,170 (71)	
Other	51 (15)	30 (6)	19 (4)	10 (3)	110 (7)	57 (2)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	39 (2)	
<b>Body mass index<sup>c</sup></b>							
<25 (kg/m <sup>2</sup> )	121 (36)	129 (28)	106 (25)	95 (32)	451 (29)	724 (29)	0.27
25–29 (kg/m <sup>2</sup> )	104 (30)	118 (25)	138 (32)	83 (28)	443 (29)	770 (31)	
≥30 (kg/m <sup>2</sup> )	96 (28)	173 (37)	150 (35)	97 (32)	516 (34)	766 (31)	
Unknown	21 (6)	49 (10)	36 (8)	23 (8)	129 (8)	218 (9)	
<b>KP service area<sup>d</sup></b>							
Diablo	54 (16)	65 (14)	54 (12)	40 (13)	213 (14)	310 (12)	<0.001
East Bay	49 (14)	84 (18)	71 (16)	33 (11)	237 (15)	381 (15)	
Golden Gate	74 (22)	109 (23)	80 (19)	73 (25)	336 (22)	420 (17)	
Napa/Solano	23 (7)	33 (7)	29 (7)	27 (9)	112 (7)	167 (7)	
Capital	61 (18)	75 (16)	89 (21)	69 (23)	294 (19)	516 (21)	
South Bay	63 (18)	86 (18)	81 (19)	44 (15)	274 (18)	442 (18)	
Central California	18 (5)	17 (4)	26 (6)	12 (4)	73 (5)	242 (10)	
<b>Data available in KPNCCR</b>							
No	76 (22)	98 (21)	103 (24)	74 (25)	351 (23)	570 (23)	<0.89
Yes	266 (73)	371 (79)	327 (76)	224 (75)	1,188 (77)	1,908 (77)	
<b>Total</b>	<b>342</b>	<b>469</b>	<b>430</b>	<b>298</b>	<b>1,539</b>	<b>2,478</b>	

<sup>a</sup> Diagnosed during the same time period as the total number of enrolled participants

<sup>b</sup> From Pearson chi-square test comparing enrollment status by demographic characteristic

<sup>c</sup> Prediagnosis

<sup>d</sup> Diablo Service Area includes Walnut Creek, Martinez, and Antioch; East Bay includes Fremont, Union City, Hayward, Oakland, and Richmond; Golden Gate Service Area includes San Francisco, South San Francisco, San Rafael, and Santa Rosa; Napa/Solano includes Vacaville and Vallejo; Capital Service Area includes Roseville, Sacramento, South Sacramento, and Rancho Cordova; South Bay includes Redwood City, Santa Clara, Santa Teresa, and Gilroy; Central California includes Fresno, Stockton, Modesto, and Manteca

### Questionnaire and biospecimen collection status

As of 16 January, 2008, baseline questionnaire data collection has been completed by approximately 96% of the enrolled participants (1,473 out of 1,539) with the exception of the three-day food record (75%), which is left with the participant to return within three weeks of the baseline interview. The response rates for the six-month follow-up and 12-month health status update are approximately 72% and 91%, respectively. Blood and saliva specimens have been obtained at baseline from 86% (1,323 out of 1,539)

and 91% (1,398 out of 1,539) of the entire cohort, respectively.

### Discussion

The Pathways Study is one of the first prospective cohort studies of lifestyle factors and outcomes among recently diagnosed breast cancer patients. As such, Pathways will provide direct contemporaneous data in the first few months after diagnosis of the impact of lifestyle factors

**Table 4** Kaiser Permanente Northern California Cancer Registry characteristics by age at diagnosis in the Pathways Study, as of 16 January, 2008

	<50 years <i>n</i> (%)	50–59 years <i>n</i> (%)	60–69 years <i>n</i> (%)	≥70 years <i>n</i> (%)	Total enrolled <i>n</i> (%)	Total not enrolled <sup>a</sup> <i>n</i> (%)	<i>p</i> -value <sup>b</sup>
SEER summary cancer stage							<0.01
Local	158 (59)	249 (67)	236 (72)	165 (74)	808 (68)	1,237 (65)	
Regional	105 (40)	113 (31)	82 (25)	56 (25)	356 (30)	590 (31)	
Distant	3 (1)	8 (2)	8 (3)	3 (1)	22 (2)	72 (4)	
Unknown	0 (0)	1 (<1)	1 (<1)	0 (0)	2 (<1)	9 (<1)	
AJCC stage group							0.04
0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	
I	103 (39)	189 (51)	181 (55)	122 (55)	595 (50)	899 (47)	
II	103 (39)	121 (33)	97 (30)	63 (28)	384 (32)	637 (33)	
III	43 (16)	37 (10)	26 (8)	20 (9)	126 (11)	186 (10)	
IV	3 (1)	7 (2)	8 (2)	3 (1)	21 (2)	72 (4)	
Not applicable	0 (0)	0 (0)	2 (<1)	0 (0)	2 (<1)	3 (<1)	
Unknown	14 (5)	17 (4)	13 (4)	16 (7)	60 (5)	110 (6)	
Nodal status							<0.001
Negative	153 (57)	240 (65)	234 (72)	418 (66)	775 (65)	1,139 (60)	
Positive	100 (38)	111 (30)	79 (24)	54 (24)	344 (39)	570 (30)	
Unknown	13 (5)	20 (5)	14 (4)	22 (10)	69 (6)	199 (10)	
Tumor size							0.75
<1 cm	46 (17)	68 (19)	70 (21)	48 (21)	232 (20)	373 (19)	
1–<2 cm	73 (28)	156 (42)	141 (43)	87 (39)	457 (38)	690 (36)	
2–<3 cm	71 (27)	70 (19)	66 (20)	37 (17)	244 (21)	403 (21)	
3–<4 cm	24 (9)	38 (10)	28 (9)	16 (7)	106 (9)	174 (9)	
4–<5 cm	17 (6)	9 (2)	6 (2)	9 (4)	41 (3)	70 (4)	
≥5 cm	24 (9)	12 (3)	10 (3)	16 (7)	62 (5)	120 (6)	
Diffuse	3 (1)	3 (1)	3 (1)	0 (0)	9 (1)	9 (<1)	
Unknown	8 (3)	15 (4)	3 (1)	11 (5)	37 (3)	69 (4)	
Metastases							<0.01
No	255 (96)	360 (97)	308 (94)	214 (96)	1,137 (96)	1,774 (93)	
Yes	3 (1)	7 (2)	8 (2)	3 (1)	21 (2)	72 (4)	
Unknown	8 (3)	4 (1)	11 (4)	7 (3)	30 (2)	62 (3)	
Chemotherapy							0.01
No	70 (26)	170 (46)	203 (62)	192 (86)	635 (53)	1,124 (59)	
Yes	193 (73)	200 (54)	121 (37)	28 (12)	542 (46)	767 (40)	
Unknown	3 (1)	1 (<1)	3 (1)	4 (2)	11 (1)	17 (1)	
Radiation therapy							0.25
No	208 (78)	251 (68)	180 (55)	145 (65)	784 (66)	1,297 (68)	
Yes	58 (22)	120 (32)	147 (54)	79 (35)	404 (34)	611 (32)	
Hormone therapy							0.22
No	171 (64)	220 (59)	149 (46)	105 (47)	645 (54)	1,097 (58)	
Yes	74 (28)	130 (35)	161 (49)	111 (49)	476 (40)	712 (37)	
Unknown	21 (8)	21 (6)	17 (5)	8 (4)	67 (6)	99 (5)	
ER status							0.44
Negative	53 (20)	64 (17)	45 (14)	24 (11)	186 (16)	333 (17)	
Positive	213 (80)	306 (83)	281 (86)	198 (88)	998 (84)	1,564 (82)	
Borderline	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	
Test not done	0 (0)	1 (<1)	1 (<1)	2 (1)	4 (<1)	8 (<1)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	

**Table 4** continued

	<50 years <i>n</i> (%)	50–59 years <i>n</i> (%)	60–69 years <i>n</i> (%)	≥70 years <i>n</i> (%)	Total enrolled <i>n</i> (%)	Total not enrolled <sup>a</sup> <i>n</i> (%)	<i>p</i> -value <sup>b</sup>
PR status							0.91
Negative	78 (29)	121 (33)	96 (29)	60 (27)	355 (30)	585 (31)	
Positive	188 (71)	249 (67)	227 (70)	162 (72)	826 (70)	1,312 (69)	
Borderline	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	
Test not done	0 (0)	1 (<1)	3 (1)	2 (1)	6 (<1)	8 (<1)	
Unknown	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	2 (<1)	
HER-2/Neu status							0.97
Negative	171 (64)	271 (73)	249 (76)	176 (79)	867 (73)	1,402 (74)	
Positive	37 (14)	35 (9)	30 (9)	15 (7)	117 (10)	193 (10)	
Borderline	44 (17)	43 (12)	30 (9)	26 (11)	143 (12)	218 (11)	
Test not done	3 (1)	11 (3)	2 (<1)	3 (1)	19 (1)	37 (2)	
Unknown	11 (4)	11 (3)	16 (5)	4 (2)	42 (4)	58 (3)	
Total	266	371	327	224	1,188	1,908	

<sup>a</sup> Diagnosed during the same time period as the total number of enrolled participants

<sup>b</sup> From Pearson chi-square test comparing enrollment status by cancer registry characteristic

such as diet, physical activity, and use of alternative therapies on breast cancer prognosis. The prepaid, integrated health care setting of KPNC provides an unparalleled resource for epidemiologic studies of this nature, enabling rapid case ascertainment through electronic pathology records, efficient follow-up through member identification databases, and linkage to other clinical databases or paper charts for relevant factors. The final projected cohort size is at least 3,000 women. With recent enrollment rates averaging 70 women per month, we anticipate achieving this projected sample size by the end of the funded study period in June 2010.

Significant strengths of the Pathways Study include being one of the largest prospective cohort studies of breast cancer prognosis, and the only such study to collect longitudinal information about lifestyle factors in the first several months after diagnosis when questions regarding interactions with conventional therapy are best studied. Due to our ability to identify women within days after diagnosis, and our criterion of only enrolling women who are within two months of their diagnosis, survival bias is essentially nonexistent.

The Pathways Study is also the only study that includes women diagnosed at all stages of invasive breast cancer, although the number of enrolled women with advanced disease is relatively small. Other studies of lifestyle factors and breast cancer prognosis have largely avoided enrolling women with advanced stage disease since enrollment of women several months or years after diagnosis may bias women available against those with poorer survival rates. Yet, these women with poorer prognosis may be most interested in exploring options outside of conventional

therapy. In the future, we will be able to investigate interactions of lifestyle and genetic factors on breast cancer prognosis. Furthermore, we have begun to establish a biospecimen resource for future genetic and molecular studies of breast cancer prognosis.

Thus far, the Pathways Study has achieved a participation rate similar to other breast cancer prognosis studies of more limited scope [22, 36, 37]. Our study collects data on a plethora of lifestyle factors during a lengthy baseline interview averaging four hours, which might deter older women or women with more advanced disease from participating. Based on the data presented above comparing our study population to the nonparticipating KPNC breast cancer population, this participation bias is apparent, but minimal. In addition, Pathways is one of the first observational studies to attempt to address past methodologic issues in CAM assessment such as having a population-based sample and capturing past and present CAM use, including reasons for use, and identifying interactions with conventional treatments [38]. Since CAM use varies tremendously among cancer patients and no standardized resource exists outlining all possible exposure combinations, designing a questionnaire to adequately assess this information has been a challenge.

Over the next several years, we will be conducting both descriptive and association analyses. Descriptive analyses include, but are not limited to, the use of CAM at the time of breast cancer diagnosis and during conventional treatment such as chemotherapy; changes in physical activity and diet during the early survival period; and quality of life at the time of breast cancer diagnosis, and during treatment and follow-up. Further descriptive questions will address

interactions of factors such as CAM use, vitamin supplement use, quality of life, and prescription medication use. We will not be able to address immediately the association between lifestyle factors and traditional breast cancer outcomes of recurrence and death since the accumulation of a sufficient number of outcomes in the cohort will take several years, but we will have the ability to examine markers of treatment toxicities as outcomes, which is an emerging research priority in breast cancer prognosis [39–41]. For example, we would like to explore the impact of CAM use and weight change on chemotherapy toxicities, as well as genetic variants in DNA repair and oxidative stress pathways on chemotherapy toxicities. We will eventually begin examining the associations between factors such as diet, physical activity, weight gain, and CAM use and risk of breast cancer recurrence and/or death.

In addition to the knowledge gained from the above analyses, several ancillary studies are being conducted which build upon the Pathways Study. The first study (ACS, RSG-06–209–01-LR) will describe the natural history as well as quantify the direct medical costs of lymphedema, a debilitating condition characterized by irregular swelling of the affected arm that can occur among breast cancer survivors following treatment [42]. The second study (U.S. Department of Defense, BC043120) will examine racial disparities in breast cancer adjuvant therapy by identifying barriers to receipt of optimal treatment among women with nonmetastatic breast cancer; identifying racial differences in the distribution of these barriers; and modeling the effects of these barriers on racial disparities in survival. The third study (National Cancer Institute, R01 CA124924) will address gaps in knowledge about treatment decision-making for the growing older population of women 65 years and older. An index of physiological age, defined as capacity to respond to stressors such as chemotherapy, will be developed and validated, and then used to enhance a web-based clinical decision tool.

Further ancillary studies to the Pathways Study are possible using the KPNC biorepository of tumor specimens that are kept indefinitely. We have conducted a small pilot study in which 200 specimens were retrieved and DNA and RNA was successfully extracted. These specimens can be used to examine genetic and epigenetic modifications of the tumor. Additional studies could also examine molecular factors using the blood biorepository of the Pathways Study.

In summary, the Pathways Study will be one of the largest, ethnically diverse prospective studies to examine the integrated effects of lifestyle factors and molecular markers on breast cancer prognosis. Currently, women with breast cancer engage in many behavioral changes, yet the rationale for these actions is almost nonexistent. In

addition, intriguing evidence shows that molecular characteristics may have profound influences on tumor progression. Whether these factors can influence prognosis is of great interest to these women and their clinicians. The Pathways Study should be able to tease apart these varied changes and to help provide much needed guidance in this understudied area of cancer prognosis research.

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