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Cohort profile: Helping Ourselves, Helping Others - The Young Women's Breast Cancer Study (YWS): A multi-site prospective cohort study to advance the understanding of breast cancer diagnosed in women aged 40 and younger

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Complete List of Authors:	Rosenberg, Shoshana M. ; Dana-Farber Cancer Institute; Weill Cornell Medicine Zheng, Yue; Dana-Farber Cancer Institute Ruddy, Kathryn; Mayo Clinic Poorvu, Philip D.; Dana-Farber Cancer Institute, Medical Oncology Snow, Craig; Dana-Farber Cancer Institute, Medical Oncology Kirkner, Gregory J.; Dana-Farber Cancer Institute, Medical Oncology Meyer, Meghan E.; Dana-Farber Cancer Institute, Medical Oncology Tamimi, Rulla M. ; Weill Cornell Medical College, Schapira, Lidia; Stanford University Peppercorn, Jeffrey; Massachusetts General Hospital Come, Steven; Beth Israel Deaconess Medical Center Borges, Virginia; University of Colorado Denver Warner, Ellen; Sunnybrook Health Sciences Centre, Medical Oncology Gelber, Shari; Dana-Farber Cancer Institute, Medical Oncology Collins, Laura; Beth Israel Deaconess Medical Center, Pathology Winer, Eric P.; Dana-Farber Cancer Institute, Medical Oncology Partridge, Ann; Dana-Farber Cancer Institute, Medical Oncology
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Cohort profile: Helping Ourselves, Helping Others - The Young Women's Breast Cancer Study (YWS): A multi-site prospective cohort study to advance the understanding of breast cancer diagnosed in women aged 40 and younger

Shoshana M. Rosenberg,[1,2,3] Yue Zheng,[4] Kathryn J. Ruddy,[5] Philip D. Poorvu,[2,3] Craig Snow,[2,3] Gregory J. Kirkner,[2,3] Meghan E. Meyer,[2,3] Rulla M. Tamimi,[1] Lidia Schapira,[6] Jeffrey Peppercorn,[7] Steven Come,[8] Virginia F. Borges,[9] Ellen Warner,[10] Shari Gelber,[2,3] Laura C. Collins,[11] Eric P. Winer,[2,3,12] and Ann H. Partridge[2,3]

[1]Population Health Sciences, Weill Cornell Medicine, New York, NY, USA (current affiliation); [2]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [3]Breast Oncology Program, Dana-Farber Brigham Cancer Center, Boston, MA, USA; [4]Data Science, Dana-Farber Cancer Institute, Boston, MA, USA; [5]Medical Oncology, Mayo Clinic, Rochester, MN, USA; [6]Department of Medicine, Division of Medical Oncology, Stanford University, Stanford, CA, USA; [7]Department of Medicine, Division of Medical Oncology, Massachusetts General Hospital, Boston MA, USA; [8]Medical Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA; [9]Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [10]Deparment of Medicine, Division of Medical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [11]Pathology, Beth Israel Deaconess Medical Center, Boston, MA, USA; [12]Yale Cancer Center, New Haven, CT, USA (current affiliation)

Corresponding author:

Ann H. Partridge

Dana-Farber Cancer Institute

450 Brookline Avenue

Boston, MA 02067

Tel: 617-632-3800

Email: ann_partridge@dfci.harvard.edu

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Abstract

Purpose: Compared to older women diagnosed with breast cancer, younger women are more likely to die of breast cancer and more likely to suffer psychosocially in both the short and long-term. The Young Women's Breast Cancer Study (YWS) is a multisite prospective cohort study established to address gaps in our knowledge about this vulnerable and understudied population.

Participants: The YWS enrolled 1,302 women newly diagnosed with stage 0-IV breast cancer at age 40 years or younger at 13 academic and community sites in North America between 2006 and 2016. Longitudinal patient-reported outcome data are complemented by clinical data abstraction and biospecimen collection at multiple time-points.

Findings to Date: Key findings related to fertility include that nearly 40% of participants were interested in pregnancy following diagnosis; of those who reported interest, 10% pursued fertility preservation. Overall, approximately 10% of YWS participants became pregnant in the first 5 years after diagnosis; follow-up is ongoing for pregnancies after 5 years. Studies focused on psychosocial outcomes have characterized quality of life, post-traumatic stress, and fear of recurrence, with findings detailing the factors associated with the substantial psychosocial burden many young women face during and following active treatment. Multiple studies have leveraged YWS biospecimens, including whole exome sequencing of tumor analyses that revealed that select somatic alterations occur at different frequencies in young (age <35) versus older women with luminal A breast cancer, and a study that explored clonal hematopoiesis of indeterminate potential found it to be rare in young survivors.

Future Plans: With a median follow-up of approximately 10 years, the cohort is just maturing for many relevant long-term outcomes and provides outstanding opportunities to further study and build collaborations to address gaps in our knowledge, with the ultimate objective to improve care and outcomes for young women with breast cancer.

Registration: clinicaltrials.gov, NCT01468246

Strengths and Limitations

- The Young Women's Breast Cancer Study (YWS) is the first and one of the largest, multi-site, prospective cohorts of women with young onset breast cancer designed to conduct regular medical record review and collect biospecimens and patient-reported outcomes.
- From 2006-2016, the YWS enrolled 1,302 women diagnosed with breast cancer at age 40 years and younger from 13 North American academic and community sites, with planned follow-up of participants up to at least 20 years post-diagnosis.
- High participant engagement (the average survey completion rate is 86%) has facilitated extended follow-up to investigate a diverse range of survivorship issues and outcomes.
- Medical record review has been completed for 100% of participants through 18 months post-diagnosis and we have collected ≥1 blood sample on 92%, and centrally reviewed primary tumor pathology on 97%, with blocks archived on 84% and tissue microarrays created on 89% of those reviewed.
- While women were recruited via systematic approaches from community and academic sites in North America, participants enrolled in the YWS are predominantly white, non-Hispanic, and highly educated, which may impact generalizability of findings to young breast cancer survivors from more diverse racial, ethnic, and socio-economic backgrounds.

Introduction

Greater than 14,000 women aged 40 years and younger are diagnosed with breast cancer annually in the United States alone, with thousands more worldwide. Far less is known, however, about breast cancer in younger vs. older women. Further, recent population-based data have demonstrated that the incidence of breast cancer is growing in this population.[1,2] Breast cancer is the leading cause of cancer-related deaths in women under 40 years of age, and while improved over time, survival rates for young women with breast cancer remain lower compared to older women.[3,4] The reasons for the poorer outcomes experienced by young women as understood to date are complex and multifactorial. Compared to older women, young women are more likely to present with symptoms and at a more advanced stage, due in part to diagnostic delays and lack of screening in this population.[5,6] Breast cancers arising in young women tend to have more unfavorable pathologic features and aggressive subtypes, including greater proportions with luminal B, HER2-positive, or triple-negative disease.[7,8] Young women are at high risk of non-adherence to risk reducing adjuvant hormonal therapy.[9-11] Compounding their disparate disease outcomes, young breast cancer survivors may be at greater risk of long-term or late morbidity given the aggressive therapy that they usually receive and anticipated long life trajectory in survivorship, although there are limited data in this area.

Of particular significance are the variety of young age-related medical and psychosocial issues that this population faces as a result of their diagnosis and treatment, which contribute to a greater risk of psychosocial distress compared to older patients.[12] These issues include hereditary predisposition and risks of future cancer, sexual dysfunction, infertility, premature menopause, body image concerns, role functioning including parenting, career and schooling disruption and the development of short- and long-term comorbidities. Collectively, these problems may influence treatment decisions, as well as disease and psychosocial outcomes.

Purpose of the Young Women's Breast Cancer Study

Young women are underrepresented in large prospective cohorts as well as in randomized trials evaluating novel therapies and prognostic tools to guide breast cancer treatment decisions.[13-15] Hesitancy to extrapolate data from studies of primarily older populations may result in young women being excluded or delayed in benefits from treatment improvements, or put at risk for overtreatment based solely on young age. Even in large prospective cohort studies and clinical trials inclusive of premenopausal women, as well as in population-based registries, there are rarely enough young women and/or adequate granularity of data to draw meaningful conclusions for this subpopulation. For example, the Nurses' Health Studies have previously reported 374 incident cases age <40 years (vs. 2,533 cases in women age ≥40),[16] the Black Women's Health Study had 529 cases of breast cancer diagnosed at age <45 years documented through 2013 (vs. 1,534 cases in women aged 45 and older),[17] and the Suppression of Ovarian Function Trial had 933 participants age <40 years at diagnosis,[18] with limited details in follow-up for most. The Young Women's Breast Cancer Study (YWS) was designed to address gaps in knowledge regarding breast cancer in younger women, including unanswered questions pertaining to diagnosis and presentation, underlying disease biology, optimal treatment, survivorship, psychosocial issues, and living with metastatic disease. The YWS is the first and one of the largest cohorts of women with young onset breast cancer designed to conduct regular medical record review and collect biospecimens and patient-reported outcomes (PROs) (**Figure 1**). The original study objectives were to 1) enroll a cohort of women age ≤40 years newly diagnosed with breast cancer; 2) characterize the cohort at diagnosis and in follow-up regarding disease and psychosocial outcomes; and 3) archive tumor and blood specimens for future studies.

Cohort Description

Overview

From 2006-2016, the YWS enrolled 1,302 women from 13 North American academic and community sites (**Supplemental Table 1**). There was high accrual of those approached for enrollment

(1302/2186, 60% participate rate). Four patients were determined to be ineligible, and one withdrew consent following enrollment leaving 1,297 women who are followed. Reasons for non-participation are detailed in **Figure 2**. The YWS is approved by the Institutional Review Board at Dana-Farber Harvard Cancer Center (DF/HCC) and other participating sites.

Enrollment procedures

At Massachusetts sites, potentially eligible participants were systematically identified by pathology review or by pathology or clinic list review by a research nurse on a monthly or bi-monthly basis. The Dana-Farber Cancer Institute (DFCI) Survey and Data Management Core then reviewed the medical record to confirm eligibility. At sites outside of Massachusetts, study staff assisted with recruitment via systematic review of patient lists. Eligibility was confirmed prior to inviting. Inclusion criteria included: 1) female; 2) a new diagnosis of stage 0-IV breast cancer 3) age ≤40 years at diagnosis; and 4) ability to understand written and spoken English to the extent necessary to complete the questionnaires. Participants enrolled a median of 4 (range: 0-29) months following diagnosis. Following receipt of written informed consent, participants were mailed a welcome letter, medical record release form, tumor specimen request form, and the baseline survey. Current median follow-up of the cohort is 10 years (range: 0.4-16 years).

Participant characteristics

Table 1 includes a summary of YWS participant age at diagnosis, race, and ethnicity. Baseline survey questions asked participants about their race and ethnicity. For baseline survey non-responders or instances where this information was not reported, race/ethnicity as determined from medical record at screening/enrollment was used. Approximately 14% of YWS participants are from a non-White and/or Hispanic racial/ethnic background. Median age at diagnosis was 36 (range: 17-40) years. Key cancer information including stage, grade, subtype, and BRCA mutation status is detailed in **Table 2**. Recognizing that there have been changes in how we measure social determinants of health since the baseline survey was developed and to make these data more complete, we are sending YWS

participants a supplemental survey including updated questions regarding race, ethnicity, gender, and sexual identity.

Patient and Public Involvement

Since the study's inception, we have invited patient volunteers and patient advocates to review survey content as well as assist with strategies to communicate results to YWS participants and other young patients. We routinely share lay summary results from YWS analyses directly through the DFCI Program for Young Adults with Breast Cancer newsletter as well as intermittent webinars and patient forums. Newsletters and webinars are also archived on the program's public website (https://youngandstrong.dana-farber.org).

YWS Data Collection and Follow-up

Surveys: Participants completed surveys at study baseline (median of 5 months post-diagnosis), 6 months after enrollment, and 1-year post-diagnosis. Participants were then surveyed every 6 months through 3 years, and annually thereafter. Participants enrolled at the Toronto site (N=62) are sent abbreviated ("short-form") surveys that ask for socio-demographics, how their breast cancer presented, fertility and gynecologic information, and cancer endpoints. At the 10-year timepoint, Toronto participants are sent a full survey to complete. A smaller subset of participants (N=29) who enrolled at other sites chose to complete the short-form follow-up annual surveys that only ask about fertility, gynecologic and cancer outcomes. For the initial 7 years of the YWS, all surveys were mailed to main study participants; participants completing short-form surveys were given the option of completing surveys on paper or online via Survey Monkey. Beginning at the 8-year survey time point, participants were offered the option to complete an electronic survey through REDCap. In March 2020, due to COVID restrictions limiting the ability to mail materials, participants with a valid email address (98%) were sent surveys through REDCap. Collectively, these surveys have yielded an unparalleled resource of longitudinal PRO data related to menopausal status, fertility, anxiety, depression, quality of life (QOL), fear of recurrence, treatment side-effects, employment, genetics, and treatment decision-

making (see **Table 3** for domains/timeline for the first 15 years of follow-up). We also periodically invite participant subsets to complete supplemental surveys to investigate salient issues in greater detail.[19-24]

Follow-up to optimize survey response rates: A research coordinator systematically contacts participants who do not complete their surveys with a phone call at 3 weeks after the initial survey is sent out; the survey is re-sent at 6 weeks if the participant has still not completed the survey at that timepoint. Additional calls and/or survey resends are then conducted monthly up to 6 months following the initial send out, as needed. Response rates (surveys received/surveys sent) for the majority of survey time points range from 86%-91%. Response rates for 7 and 10-year surveys are modestly lower (71% for 7-year and 65% for 10-year) due to our attempt to re-engage non-responding participants at those timepoints.

*Medical Records***:** Medical records through the first 18 months following diagnosis are available for 100% of participants. Records are also reviewed at additional timepoints (including at 10 years) to 1) confirm and collect specifics on cancer outcomes (recurrences, new primary breast cancers, other cancers) that are self-reported on surveys; and 2) to update comorbidities including recurrences and new cancers and vital status among participants who do not regularly complete surveys. We have abstracted initial treatment information, including specific chemotherapy regimens started and received, surgery, radiation, genetic testing (panel type and results), and co-morbidities using the Charlson framework[25,26] from the medical record to validate/supplement what patients report on surveys, and to fill in missing data.

Ascertainment of Cancer Outcomes and Vital Status: Recurrences, new primary breast cancers, and new (non-breast) cancers are assessed on each survey. In addition to site(s) of recurrence or new cancer, participants are asked to report the date of the recurrence. Any self-report of a recurrence or new cancer, including site and date (either radiologic or pathologic confirmation) is confirmed by medical record review. Because this process relies on survey responses to ascertain outcomes, for those participants who are no longer responding to surveys we request and review updated medical

records for these patients every 4 years. For participants treated at DFCI, Brigham and Women's Hospital, Massachusetts General Hospital or an affiliate network site, the National Death Index is queried periodically to obtain vital status information. Following the 2018-2019 update, we were able to ascertain oncologic outcomes and vital status for 321 patients who were survey non-responders. As of September 2023, among the entire cohort, we have documented 181 participants with distant metastatic recurrences, 96 participants with locoregional recurrences, 22 participants with new primary breast cancers, and 49 participants with new non-breast primary cancers, and 186 deaths.

Tissue Specimen Collection/Storage: Pathology reports, hematoxylin and eosin (H&E) stained slides, and a representative paraffin block of tumor were requested from the institution where the patient had her surgery; the patient's signed release for the specimens and reports were sent to the pathology department. A YWS study pathologist reviewed each pathology report and an H&E stained section of the tumor block to annotate tumor details.[8,27] Slides from the core needle biopsy were requested as well as from the surgery in neoadjuvant therapy cases. Hormone and HER-2/neu (HER2) receptor expression, and lymph node status, were extracted from the pathology reports. Of 1297 participants followed, 1278 (99%) consented to providing a tumor specimen for review. Primary tumor pathology has been centrally reviewed on 97% of patients (1242/1278), with blocks (N=1120) and cores for the tissue microarray (N=21) from tumor specimens collected on 1141 patients (88%). Currently, there are 1370 specimens from 1242 patients available in the tissue microarray blocks (patients who received neoadjuvant therapy may have more than one block).

*Blood Collection/Storage***:** Blood is collected at three timepoints (two 10mL tubes of whole blood at each timepoint), each with a several month "window" to maximize our ability to collect blood while minimizing burden: baseline (enrollment up to 9 months post-diagnosis); 1-year (9 months-2 years post-diagnosis); and 4-year (3.5 – 5 years post diagnosis). Overall, 94% (1224/1297) of participants consented to blood collection. Of these, there is at least one sample available from 92% of participants, with 73% of participants providing samples at two or more time points (**Supplemental Table 2**).

Women were asked to go to their treating institution or a local laboratory with the materials provided in the blood specimen kit, unless drawn at DFCI where kits are provided on site by staff. Specimens were processed at the DFCI Breast Cancer CORE Blood Repository, where whole blood (4 aliquots/2ml each) and plasma (2 aliquots/2mL each) were isolated and banked for future studies.

Findings to Date

Since its inception, YWS investigations have characterized more fully the experience of breast cancer in young women, creating a platform from which to study molecular and biologic issues, as well as the health and psychosocial repercussions of a breast cancer diagnosis and treatment at a young age. As the YWS has matured, we have expanded our investigations to include collaborations with basic and translational scientists enabling us to address new questions, advancing knowledge of the biology of the disease as well as to improve clinical care and outcomes. In addition, research findings from the YWS have informed international guidelines and clinical practice.[28,29]

Fertility Issues and Pregnancy

In 2014, we published findings from the baseline survey regarding fertility concerns and fertility preservation strategies used.[30] Since then, additional publications from the YWS have described breast cancer diagnosed during pregnancy,[31] pregnancy after breast cancer,[32] treatment-related amenorrhea,[33] fertility concerns and endocrine therapy decision-making,[34] and fertility concerns in germline genetic carriers.[35] Key findings included the observation that nearly 40% of participants were interested in pregnancy after breast cancer; of those interested, 10% pursued fertility preservation strategies.[30] Another study documented that approximately 20% of women become amenorrheic in survivorship after standard chemotherapy, with variability by chemotherapy type and age.[33] A third study evaluated post-diagnosis pregnancies, observing that 10% became pregnant in the first 5 years after breast cancer.[32] Fertility outcomes remain a primary outcome of interest in continued follow-up of the cohort and the rich and detailed fertility and gynecologic data collected at each time point will allow for novel and detailed investigations regarding impact of pregnancy on cancer endpoints, and

menopausal and related comorbidity outcomes. Findings from this work have been referenced in international guidelines[28,29] and informed an international trial that evaluated the safety of pregnancy after breast cancer.[36] We are also participating in an international, multi-site, retrospective cohort study (PI: Dr. Matteo Lambertini, University of Genoa, IT) inclusive of >1400 patients with BRCA+ breast cancer from 30 sites across North America, Europe, Latin America, and Israel, contributing clinical, genetic, and PRO data on 125 YWS participants with BRCA mutations. To date, there have been two major publications reporting analyses of pregnancy outcomes as well as clinical outcomes from this collaboration.[37,38]

Systemic Treatment and Disease Recurrence and Response

In 2017, we conducted a study examining the prognostic value of genomic expression prediction assays in the YWS. Prior research that led to the routine incorporation of such tools into clinical care had included relatively few women <40 years old, resulting in hesitation among providers to use them for young women. We demonstrated that Recurrence Score (RS) was prognostic and appeared to be predictive of chemotherapy benefit or lack thereof in patients with node-negative disease.[39] These data have informed recent guidelines and clinical practice supporting the use of RS in young patients to influence chemotherapy decisions.[28] We subsequently demonstrated the association of RS with pathologic complete response (pCR) after neoadjuvant chemotherapy for hormone receptor-positive disease[40]; results from this study are providing preliminary data for planned correlative work in a pre-operative clinical trial in the Alliance for Clinical Trials in Oncology.

Psychosocial Implications of Breast Cancer in Young Women

A large focus of the YWS has been to study the early psychological and social repercussions of breast cancer in young women to identify areas for tailored support and management strategies. We have characterized sexual functioning and body image issues, the impact of a diagnosis on employment, post-traumatic stress, fear of recurrence, anxiety and depression in women with de novo stage IV disease, as well as the impact of the diagnosis on the partners of YWS participants.[41-48]

Recent studies have found that more extensive surgery and radiation are associated with poorer QOL[21,49] as well as increased arm morbidity.[50] Collectively, our findings indicate that young women experience a substantial psychosocial burden during and following the completion of active treatment, and this burden is associated with certain patient, disease and treatment variables which can be targeted for intervention.

Biological Differences in Breast Cancer by Age

Collaborative efforts have yielded important findings to date including a comparison of whole exome sequencing profiles of the youngest 100 participants (≤35 years at diagnosis) to older women from The Cancer Genome Atlas (TCGA).[51,52] This analysis revealed that somatic alterations in three genes (*PIK3CA, GATA3,* and *ARID1A*) occur at different frequencies in young versus older women with luminal A breast cancer.[52] Additional investigation of these genes could delineate biological susceptibilities for young patients. Several additional studies have used or pooled tissue and/or blood specimens including a genome wide association study characterizing single nucleotide polymorphisms in young patients,[53] a study of RasGAP genes in luminal B tumors,[54] and a study of somatic mutations in patients with metastatic triple negative breast cancer,[55] and the development of a test to identify minimal residual disease in early-stage breast cancer.[51] Most recently, we used novel DNA sequencing methods to evaluate the prevalence and mutation spectrum of clonal hematopoiesis in young women and its association with patient and treatment characteristics and outcomes.[56] Reassuringly, clonal hematopoiesis of indeterminate potential (CHIP) was rare, with a prevalence of <3% among the 878 women in the analytic cohort.[56] The YWS has also provided clinical data detailing cancer outcomes of nulliparous vs. recently parous women, for an analysis supporting the novel pre-clinical finding that weaning-induced liver involution establishes a pro-metastatic microenvironment, a potential explanation for more poor cancer outcomes of recently parous women.[57] Several analyses to understand the biologic underpinnings of early onset breast cancer are underway.

Collaboration

The YWS is uniquely positioned for investigations of age-related tumor and host biology as well as studies evaluating the impact of hereditary predisposition, post-diagnosis pregnancy, premature menopause, psychosocial, lifestyle and care delivery on cancer endpoints and comorbidities. The YWS research team includes medical, surgical, and radiation oncologists, epidemiologists, pathologists, and biostatisticians, and our collaborations have grown to include experts in cancer genomics, biology, tumor microenvironment, and behavioral health. While data are not publicly available, investigators interested in accessing YWS-generated data and/or biospecimens should contact the Principal Investigator (A. Partridge) and submit a request to the DF/HCC breast users committee (https://www.dfhcc.harvard.edu/research/research-programs/clinical-based-programs/breast-cancer/program-resources/dfhcc-breast-users-committee/).

Future Directions

The YWS has proven to be a rich scientific resource that has resulted in impactful research that has advanced our understanding of breast cancer in young women, generated new lines of investigation, and informed clinical guidelines. Breast cancer is the leading cause of cancer-related deaths in young women, and while improved over time, survival rates for young women with breast cancer remain lower compared to older women.[3,4] Thus, identifying risk factors for these poorer outcomes in younger women is critical. With the cohort maturing, we expect the number of recurrent disease events expected to increase by ~50% over the next 5 years and beyond, allowing for further evaluation of predictors of oncologic outcomes, including breast cancer free survival and overall survival. With relatively large numbers of young patients treated with contemporary regimens and well-annotated treatment details, we will be well-positioned to evaluate the impact of post-diagnosis pregnancies on recurrence, new primary cancer, or death, assessment of risk factors for second cancers by breast cancer phenotype and germline pathogenic variant status, as well as risk factors for late recurrences among women diagnosed at a young age. Studies of the role of ctDNA on predicting

late recurrence and exploring tumor and host characteristics that may be conducive to recurrence/disease resistance to therapy in young women (e.g., tumor immune microenvironment differences by recent parity status at diagnosis) have great potential.

As a survivorship cohort, evaluating long-term, late effects of breast cancer treatment and survivorship is a central objective of the YWS. A critical charge of cancer survivorship research is identifying potentially modifiable factors that predict these risks. Young breast cancer survivors may be at high risk of long-term or late morbidity given the aggressive therapy they usually receive and anticipated long life trajectory after the cancer. Additionally, they may have hereditary, behavioral, and comorbidity predispositions to disease. The concerns unique to or accentuated by their stage of life at diagnosis also appear to contribute to the increased risk of psychological distress seen in this age group both at diagnosis and in long-term follow-up.[12] With a median follow-up of 10 years, we are now well-poised to study late and long-term morbidity, including premature menopause (age <45 years), which in non-cancer populations is associated with substantial multimorbidity including increased risk of depression, hyperlipidemia, heart disease, asthma, chronic obstructive pulmonary disease, arthritis and osteoporosis.[58] On each survey, YWS participants are asked about their menstrual status, including date of last menstrual period, reasons for periods stopping, as well as questions about gynecologic procedures providing granular data to inform analyses. Given the current age of the cohort, the next several years are a critical time to conduct in-depth assessment of the menopausal transition among women who remained premenopausal following treatment, including timing, risk factors for premature menopause, and the impact of early menopause on QOL and comorbidities in this population. This data resource will also facilitate investigations ranging from health care utilization assessments, changes in lifestyle factors over time, and trajectories of QOL, to evaluations of the association of specific co-morbidities (e.g., heart disease, diabetes) with premature menopause, weight gain, body composition, metabolic biomarkers, inflammatory mediators, hormone levels, and biomarkers of accelerated aging.

Strengths and Limitations

With a repository of biospecimens, clinical data, and serial PRO collection, the YWS is a robust platform from which to study molecular and biologic issues, as well as the health and psychosocial repercussions of a breast cancer diagnosis and treatment in young women. One of the core strengths of the YWS is high participant engagement, which has facilitated our ability to follow participants for both medical and psychosocial outcomes in extended follow-up. Additionally, we have leveraged the collection of blood specimens at three time points – baseline, 1 year, and 4 years after diagnosis – for novel investigations that are complemented with clinical data that have been systematically abstracted from the medical record. However, as the YWS is an observational cohort study, establishing causality vs. association can be challenging and there is a risk of unmeasured or unaccounted for confounders in analyses. Additionally, while the YWS is a multi-site study that included both academic and community sites, women enrolled in the YWS are predominantly white, non-Hispanic, and highly educated, which may impact generalizability of findings to young breast cancer survivors from more diverse racial, ethnic, and socio-economic backgrounds. Acknowledging this limitation, more recent studies conducted by our team, including intervention trials informed by YWS findings, have focused efforts to improve outreach to patients from historically under-represented racial and ethnic groups.

Data availability statement: Requests to access YWS data/biospecimens should be made to the Principal Investigator, Dr. Ann Partridge (ann_partridge@dfci.harvard.edu).

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Ethics statements: The YWS is approved by the Institutional Review Board at Dana-Farber Harvard Cancer Center (IRB# 06-169) and other participating sites. Participants provided written informed consent at the time of enrollment.

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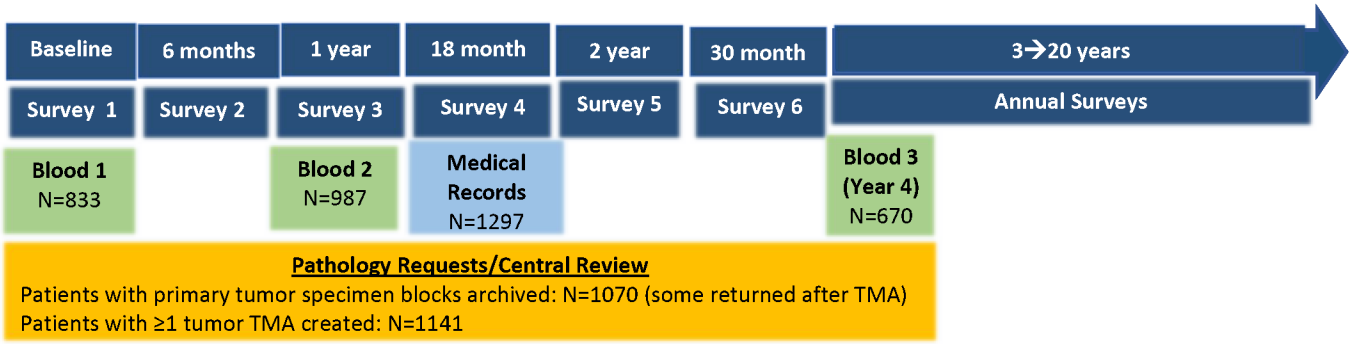
Figures

Figure 1. Overview of YWS data and biospecimen collection



YWS, Young Women's Breast Cancer Study

Figure 2. YWS Study Flow Diagram

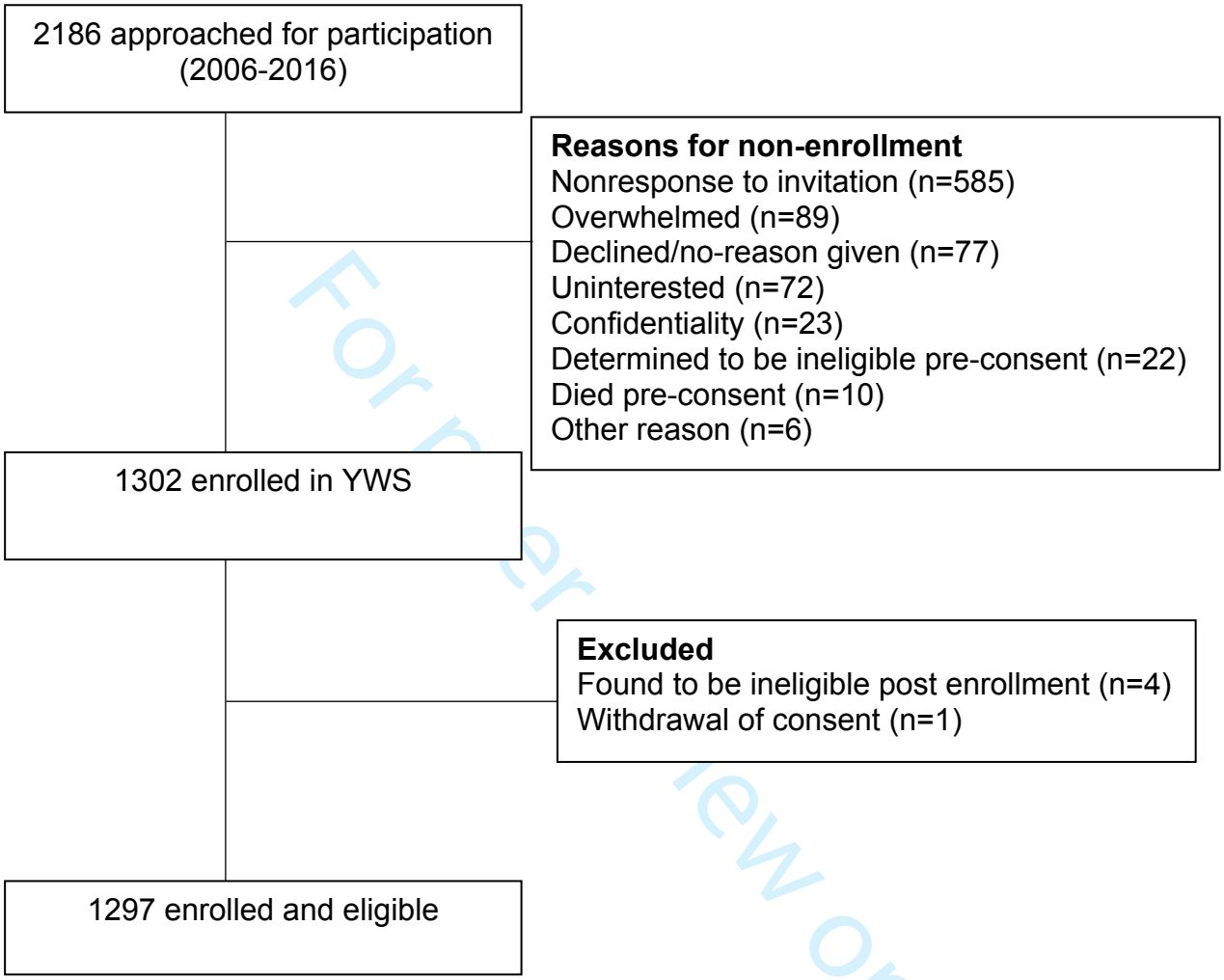


Table 1. Demographic Characteristics

	N (%)
Age at diagnosis	
<25	25 (2)
25-30	139 (11)
31-35	352 (27)
36-40	780 (60)
Race	
American Indian /Alaska Native	6 (<1)
Asian	88 (7)
Native Hawaiian/Other Pacific Islander	0 (0)
Black or African American	48 (4)
White	1101 (85)
More than one race	16 (1)
Unknown or not reported	38 (3)
Ethnicity	
Hispanic	56 (4)
Non-Hispanic	1045 (81)
Unknown or not reported	196 (15)

Table 2. Disease/tumor characteristics and BRCA mutation status (N=1297)

	N (%)
Stage	
0	98 (8)
I	413 (32)
II	525 (41)
III	197 (15)
IV	64 (5)
Bilateral breast cancer	21 (2)
Tumor grade	
1	89 (7)
2	445 (34)
3	752 (58)
Missing/Unknown	11 (0.9)
ER status	
Positive	945 (73)
Negative	351 (27)
Missing/Unknown	1 (<1)
PR status	
Positive	848 (65)
Negative	441 (34)
Missing/Unknown	8 (<1)
HER2 status	
Positive	360 (28)
Negative	880 (68)
Missing/Unknown/Not performed*	57 (4)
Subtype	
Luminal A-like	395 (31)
Luminal B-like	269 (21)
Luminal B/HER2	255 (20)
HER2-enriched (ER-, PR-, HER2+)	105 (8)
Triple negative	210 (16)
Missing/Unknown	63 (5)
BRCA mutation status	
BRCA1+	90 (7)
BRCA2+	54 (4)
Variant of unknown significance	54 (4)
No mutation detected	919 (71)
Not tested or unknown testing status	180 (14)

*Missing/Unknown subtype includes cases of DCIS for which HER2 was not performed

Table 3. Summary of Primary Survey Domains and Schedule, Baseline through Year 15

	Survey Schedule																		
		Month					Year												
	Baseline	6	12	18	24	30	3	4	5	6	7	8	9	10	11	12	13	14	15
Socio-demographics including insurance, finances	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/ Family History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Genetics			X		X		X		X		X			X					
Health-related Activities/Social History	X		X		X		X	X	X	X	X	X	X	X					
Fertility/Gynecologic	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lactation Assessment	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X
Contraception										X		X							
QOL/Anxiety/Depression	X	X	X		X		X	X	X		X			X					X
Coping		X		X															
Fear of Recurrence	X		X		X		X	X	X		X			X					X
Menopausal Symptoms	X	X	X		X		X	X	X		X			X					X
Social Support	X		X		X		X	X	X										
Spirituality Assessment	X						X												
Treatment Decisions		X												X					
Medications List	X		X		X		X	X	X	X	X	X	X	X					X
Tamoxifen Adherence						X													
Healthcare Utilization											X								X

SUPPLEMENTAL MATERIAL

Cohort profile: Helping Ourselves, Helping Others - The Young Women's Breast Cancer Study (YWS): A multi-site prospective cohort study to advance the understanding of breast cancer diagnosed in women aged 40 and younger

Supplemental Tables: 2

Supplemental Table 1. YWS enrollment sites

Site	State/Country	Number Enrolled
Dana-Farber Cancer Institute/Brigham and Women's Hospital[a]	MA	669
Beth Israel Deaconess Medical Center[a]	MA	50
Cape Cod Hospital[b]	MA	19
Faulkner Hospital[a]	MA	47
Lowell General Hospital[b]	MA	11
Massachusetts General Hospital[a]	MA	256
Mayo Clinic[a]	MN	35
Milford Hospital[b]	MA	1
Newton-Wellesley Hospital[b]	MA	30
North Shore Cancer Center (Salem)[b]	MA	21
South Shore Hospital[b]	MA	9
Sunnybrook Health Sciences[a]	Canada	62
University of Colorado Hospital[a]	CO	92

[a]academic sites [b]community sites
YWS, Young Women's Breast Cancer Study; MA, Massachusetts; MN, Minnesota; CO, Colorado

Supplemental Table 2. YWS Blood Specimens Collected

Number of Collections	Patients (N)	Baseline	1 year	4 year
1 Timepoint	N=71			
	N=137			
	N=23			
2 Timepoints	N=247			
	N=44			
	N=132			
3 Timepoints	N=471			
Total/Timepoint		N=833	N=987	N=670

BMJ Open

Cohort profile: Helping Ourselves, Helping Others - The Young Women's Breast Cancer Study (YWS): A multi-site prospective cohort study to advance the understanding of breast cancer diagnosed in women aged 40 and younger

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Cohort profile: Helping Ourselves, Helping Others - The Young Women's Breast Cancer Study (YWS): A multi-site prospective cohort study to advance the understanding of breast cancer diagnosed in women aged 40 and younger

Shoshana M. Rosenberg,[1,2,3] Yue Zheng,[4] Kathryn J. Ruddy,[5] Philip D. Poorvu,[2,3] Craig Snow,[2,3] Gregory J. Kirkner,[2,3] Meghan E. Meyer,[2,3] Rulla M. Tamimi,[1] Lidia Schapira,[6] Jeffrey Peppercorn,[7] Steven Come,[8] Virginia F. Borges,[9] Ellen Warner,[10] Shari Gelber,[2,3] Laura C. Collins,[11] Eric P. Winer,[2,3,12] and Ann H. Partridge[2,3]

[1]Population Health Sciences, Weill Cornell Medicine, New York, NY, USA (current affiliation); [2]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [3]Breast Oncology Program, Dana-Farber Brigham Cancer Center, Boston, MA, USA; [4]Data Science, Dana-Farber Cancer Institute, Boston, MA, USA; [5]Medical Oncology, Mayo Clinic, Rochester, MN, USA; [6]Department of Medicine, Division of Medical Oncology, Stanford University, Stanford, CA, USA; [7]Department of Medicine, Division of Medical Oncology, Massachusetts General Hospital, Boston MA, USA; [8]Medical Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA; [9]Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [10]Deparment of Medicine, Division of Medical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [11]Pathology, Beth Israel Deaconess Medical Center, Boston, MA, USA; [12]Yale Cancer Center, New Haven, CT, USA (current affiliation)

Corresponding author:

Ann H. Partridge

Dana-Farber Cancer Institute

450 Brookline Avenue

Boston, MA 02067

Tel: 617-632-3800

Email: ann_partridge@dfci.harvard.edu

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Abstract

Purpose: Compared to older women diagnosed with breast cancer, younger women are more likely to die of breast cancer and more likely to suffer psychosocially in both the short and long-term. The Young Women's Breast Cancer Study (YWS) is a multisite prospective cohort study established to address gaps in our knowledge about this vulnerable and understudied population.

Participants: The YWS enrolled 1,302 women newly diagnosed with stage 0-IV breast cancer at age 40 years or younger at 13 academic and community sites in North America between 2006 and 2016. Longitudinal patient-reported outcome data are complemented by clinical data abstraction and biospecimen collection at multiple time-points.

Findings to Date: Key findings related to fertility include that nearly 40% of participants were interested in pregnancy following diagnosis; of those who reported interest, 10% pursued fertility preservation. Overall, approximately 10% of YWS participants became pregnant in the first 5 years after diagnosis; follow-up is ongoing for pregnancies after 5 years. Studies focused on psychosocial outcomes have characterized quality of life, post-traumatic stress, and fear of recurrence, with findings detailing the factors associated with the substantial psychosocial burden many young women face during and following active treatment. Multiple studies have leveraged YWS biospecimens, including whole exome sequencing of tumor analyses that revealed that select somatic alterations occur at different frequencies in young (age <35) versus older women with luminal A breast cancer, and a study that explored clonal hematopoiesis of indeterminate potential found it to be rare in young survivors.

Future Plans: With a median follow-up of approximately 10 years, the cohort is just maturing for many relevant long-term outcomes and provides outstanding opportunities to further study and build collaborations to address gaps in our knowledge, with the ultimate objective to improve care and outcomes for young women with breast cancer.

Registration: clinicaltrials.gov, NCT01468246

Strengths and Limitations

- Established in 2006, the Young Women's Breast Cancer Study (YWS) is a multi-site, prospective cohort of women with young onset breast cancer.
- The YWS was designed to conduct regular medical record review and collect biospecimens and serial patient-reported outcomes.
- Eligibility criteria included: 1) female; 2) a new diagnosis of stage 0-IV breast cancer 3) age ≤40 years at diagnosis; and 4) ability to understand written and spoken English.
- Robust follow-up procedures optimize participant engagement and ensure accurate ascertainment of oncologic outcomes and vital status.
- Recruitment was hospital-based and may not be truly representative of the general population, potentially impacting generalizability.

Introduction

Greater than 14,000 women aged 40 years and younger are diagnosed with breast cancer annually in the United States alone, with thousands more worldwide. Far less is known, however, about breast cancer in younger vs. older women. Further, recent population-based data have demonstrated that the incidence of breast cancer is growing in this population.[1 2] Breast cancer is the leading cause of cancer-related deaths in women under 40 years of age, and while improved over time, survival rates for young women with breast cancer remain lower compared to older women.[3 4] The reasons for the poorer outcomes experienced by young women as understood to date are complex and multifactorial. Compared to older women, young women are more likely to present with symptoms and at a more advanced stage, due in part to diagnostic delays and lack of screening in this population.[5 6] Breast cancers arising in young women tend to have more unfavorable pathologic features and aggressive subtypes, including greater proportions with luminal B, HER2-positive, or triple-negative disease.[7 8] Young women are at high risk of non-adherence to risk reducing adjuvant hormonal therapy.[9-11] Compounding their disparate disease outcomes, young breast cancer survivors may be at greater risk of long-term or late morbidity given the aggressive therapy that they usually receive and anticipated long life trajectory in survivorship, although there are limited data in this area.

Of particular significance are the variety of young age-related medical and psychosocial issues that this population faces as a result of their diagnosis and treatment, which contribute to a greater risk of psychosocial distress compared to older patients.[12] These issues include hereditary predisposition and risks of future cancer, sexual dysfunction, infertility, premature menopause, body image concerns, role functioning including parenting, career and schooling disruption and the development of short- and long-term comorbidities. Collectively, these problems may influence treatment decisions, as well as disease and psychosocial outcomes.

Purpose of the Young Women's Breast Cancer Study

Young women are underrepresented in large prospective cohorts as well as in randomized trials evaluating novel therapies and prognostic tools to guide breast cancer treatment decisions.[13-15] Hesitancy to extrapolate data from studies of primarily older populations may result in young women being excluded or delayed in benefits from treatment improvements, or put at risk for overtreatment based solely on young age. Even in large prospective cohort studies and clinical trials inclusive of premenopausal women, as well as in population-based registries, there are rarely enough young women and/or adequate granularity of data to draw meaningful conclusions for this subpopulation. For example, the Nurses' Health Studies have previously reported 374 incident cases age <40 years (vs. 2,533 cases in women age ≥40),[16] the Black Women's Health Study had 529 cases of breast cancer diagnosed at age <45 years documented through 2013 (vs. 1,534 cases in women aged 45 and older),[17] and the Suppression of Ovarian Function Trial had 933 participants age <40 years at diagnosis,[18] with limited details in follow-up for most. The Young Women's Breast Cancer Study (YWS) was designed to address gaps in knowledge regarding breast cancer in younger women, including unanswered questions pertaining to diagnosis and presentation, underlying disease biology, optimal treatment, survivorship, psychosocial issues, and living with metastatic disease. The YWS is the first and one of the largest cohorts of women with young onset breast cancer designed to conduct regular medical record review and collect biospecimens and patient-reported outcomes (PROs) (**Figure 1**). The original study objectives were to 1) enroll a cohort of women age ≤40 years newly diagnosed with breast cancer; 2) characterize the cohort at diagnosis and in follow-up regarding disease and psychosocial outcomes; and 3) archive tumor and blood specimens for future studies.

Cohort Description

Overview

From 2006-2016, the YWS enrolled 1,302 women from 13 North American academic and community sites (**Supplemental Table 1**). There was high accrual of those approached for enrollment

(1302/2186, 60% participate rate). Four patients were determined to be ineligible, and one withdrew consent following enrollment leaving 1,297 women who are followed. Reasons for non-participation are detailed in **Figure 2**. The YWS is approved by the Institutional Review Board at Dana-Farber Harvard Cancer Center (DF/HCC) and other participating sites.

Enrollment procedures

At Massachusetts sites, potentially eligible participants were systematically identified by pathology review or by pathology or clinic list review by a research nurse on a monthly or bi-monthly basis. The Dana-Farber Cancer Institute (DFCI) Survey and Data Management Core then reviewed the medical record to confirm eligibility. At sites outside of Massachusetts, study staff assisted with recruitment via systematic review of patient lists. Eligibility was confirmed prior to inviting. Inclusion criteria included: 1) female; 2) a new diagnosis of stage 0-IV breast cancer 3) age ≤40 years at diagnosis; and 4) ability to understand written and spoken English to the extent necessary to complete the questionnaires. Participants enrolled a median of 4 (range: 0-29) months following diagnosis. Following receipt of written informed consent, participants were mailed a welcome letter, medical record release form, tumor specimen request form, and the baseline survey. Current median follow-up of the cohort is 10 years (range: 0.4-16 years).

Participant characteristics

Table 1 includes a summary of YWS participant age at diagnosis, race, and ethnicity. Baseline survey questions asked participants about their race and ethnicity. For baseline survey non-responders or instances where this information was not reported, race/ethnicity as determined from medical record at screening/enrollment was used. Approximately 14% of YWS participants are from a non-White and/or Hispanic racial/ethnic background. Median age at diagnosis was 36 (range: 17-40) years. Key cancer information including stage, grade, subtype, and BRCA mutation status is detailed in **Table 2**. Recognizing that there have been changes in how we measure social determinants of health since the baseline survey was developed and to make these data more complete, we are sending YWS

participants a supplemental survey including updated questions regarding race, ethnicity, gender, and sexual identity.

Patient and Public Involvement

Since the study's inception, we have invited patient volunteers and patient advocates to review survey content as well as assist with strategies to communicate results to YWS participants and other young patients. We routinely share lay summary results from YWS analyses directly through the DFCI Program for Young Adults with Breast Cancer newsletter as well as intermittent webinars and patient forums. Newsletters and webinars are also archived on the program's public website (https://youngandstrong.dana-farber.org).

YWS Data Collection and Follow-up

Surveys: Participants completed surveys at study baseline (median of 5 months post-diagnosis), 6 months after enrollment, and 1-year post-diagnosis. Participants were then surveyed every 6 months through 3 years, and annually thereafter. Participants enrolled at the Toronto site (N=62) are sent abbreviated ("short-form") surveys that ask for socio-demographics, how their breast cancer presented, fertility and gynecologic information, and cancer endpoints. At the 10-year timepoint, Toronto participants are sent a full survey to complete. A smaller subset of participants (N=29) who enrolled at other sites chose to complete the short-form follow-up annual surveys that only ask about fertility, gynecologic and cancer outcomes. For the initial 7 years of the YWS, all surveys were mailed to main study participants; participants completing short-form surveys were given the option of completing surveys on paper or online via Survey Monkey. Beginning at the 8-year survey time point, participants were offered the option to complete an electronic survey through REDCap. In March 2020, due to COVID restrictions limiting the ability to mail materials, participants with a valid email address (98%) were sent surveys through REDCap. Collectively, these surveys have yielded an unparalleled resource of longitudinal PRO data related to menopausal status, fertility, anxiety, depression, quality of life (QOL), fear of recurrence, treatment side-effects, employment, genetics, and treatment decision-

making (see **Table 3** for domains/timeline for the first 15 years of follow-up). We also periodically invite participant subsets to complete supplemental surveys to investigate salient issues in greater detail.[19-24]

Follow-up to optimize survey response rates: A research coordinator systematically contacts participants who do not complete their surveys with a phone call at 3 weeks after the initial survey is sent out; the survey is re-sent at 6 weeks if the participant has still not completed the survey at that timepoint. Additional calls and/or survey resends are then conducted monthly up to 6 months following the initial send out, as needed. Response rates (surveys received/surveys sent) for the majority of survey time points range from 86%-91%. Response rates for 7 and 10-year surveys are modestly lower (71% for 7-year and 65% for 10-year) due to our attempt to re-engage non-responding participants at those timepoints.

*Medical Records***:** Medical records through the first 18 months following diagnosis are available for 100% of participants. Records are also reviewed at additional timepoints (including at 10 years) to 1) confirm and collect specifics on cancer outcomes (recurrences, new primary breast cancers, other cancers) that are self-reported on surveys; and 2) to update comorbidities including recurrences and new cancers and vital status among participants who do not regularly complete surveys. We have abstracted initial treatment information, including specific chemotherapy regimens started and received, surgery, radiation, genetic testing (panel type and results), and co-morbidities using the Charlson framework[25 26] from the medical record to validate/supplement what patients report on surveys, and to fill in missing data.

Ascertainment of Cancer Outcomes and Vital Status: Recurrences, new primary breast cancers, and new (non-breast) cancers are assessed on each survey. In addition to site(s) of recurrence or new cancer, participants are asked to report the date of the recurrence. Any self-report of a recurrence or new cancer, including site and date (either radiologic or pathologic confirmation) is confirmed by medical record review. Because this process relies on survey responses to ascertain outcomes, for

those participants who are no longer responding to surveys we request and review updated medical records for these patients every 4 years. For participants treated at DFCI, Brigham and Women's Hospital, Massachusetts General Hospital or an affiliate network site, the National Death Index is queried periodically to obtain vital status information. Following the 2018-2019 update, we were able to ascertain oncologic outcomes and vital status for 321 patients who were survey non-responders. As of September 2023, among the entire cohort, we have documented 181 participants with distant metastatic recurrences, 96 participants with locoregional recurrences, 22 participants with new primary breast cancers, and 49 participants with new non-breast primary cancers, and 186 deaths.

Tissue Specimen Collection/Storage: Pathology reports, hematoxylin and eosin (H&E) stained slides, and a representative paraffin block of tumor were requested from the institution where the patient had her surgery; the patient's signed release for the specimens and reports were sent to the pathology department. A YWS study pathologist reviewed each pathology report and an H&E stained section of the tumor block to annotate tumor details.[8 27] Slides from the core needle biopsy were requested as well as from the surgery in neoadjuvant therapy cases. Hormone and HER-2/neu (HER2) receptor expression, and lymph node status, were extracted from the pathology reports. Of 1297 participants followed, 1278 (99%) consented to providing a tumor specimen for review. Primary tumor pathology has been centrally reviewed on 97% of patients (1242/1278), with blocks (N=1120) and cores for the tissue microarray (N=21) from tumor specimens collected on 1141 patients (88%). Currently, there are 1370 specimens from 1242 patients available in the tissue microarray blocks (patients who received neoadjuvant therapy may have more than one block).

Blood Collection/Storage: Blood is collected at three timepoints (two 10mL tubes of whole blood at each timepoint), each with a several month "window" to maximize our ability to collect blood while minimizing burden: baseline (enrollment up to 9 months post-diagnosis); 1-year (9 months-2 years post-diagnosis); and 4-year (3.5 – 5 years post diagnosis). Overall, 94% (1224/1297) of participants consented to blood collection. Of these, there is at least one sample available from 92% of participants,

with 73% of participants providing samples at two or more time points (**Supplemental Table 2**). Women were asked to go to their treating institution or a local laboratory with the materials provided in the blood specimen kit, unless drawn at DFCI where kits are provided on site by staff. Specimens were processed at the DFCI Breast Cancer CORE Blood Repository, where whole blood (4 aliquots/2ml each) and plasma (2 aliquots/2mL each) were isolated and banked for future studies.

Findings to Date

Since its inception, YWS investigations have characterized more fully the experience of breast cancer in young women, creating a platform from which to study molecular and biologic issues, as well as the health and psychosocial repercussions of a breast cancer diagnosis and treatment at a young age. As the YWS has matured, we have expanded our investigations to include collaborations with basic and translational scientists enabling us to address new questions, advancing knowledge of the biology of the disease as well as to improve clinical care and outcomes. In addition, research findings from the YWS have informed international guidelines and clinical practice.[28 29]

Fertility Issues and Pregnancy

In 2014, we published findings from the baseline survey regarding fertility concerns and fertility preservation strategies used.[30] Since then, additional publications from the YWS have described breast cancer diagnosed during pregnancy,[31] pregnancy after breast cancer,[32] treatment-related amenorrhea,[33] fertility concerns and endocrine therapy decision-making,[34] and fertility concerns in germline genetic carriers.[35] Key findings included the observation that nearly 40% of participants were interested in pregnancy after breast cancer; of those interested, 10% pursued fertility preservation strategies.[30] Another study documented that approximately 20% of women become amenorrheic in survivorship after standard chemotherapy, with variability by chemotherapy type and age.[33] A third study evaluated post-diagnosis pregnancies, observing that 10% became pregnant in the first 5 years after breast cancer.[32] Fertility outcomes remain a primary outcome of interest in continued follow-up of the cohort and the rich and detailed fertility and gynecologic data collected at each time point will

allow for novel and detailed investigations regarding impact of pregnancy on cancer endpoints, and menopausal and related comorbidity outcomes. Findings from this work have been referenced in international guidelines[28 29] and informed an international trial that evaluated the safety of pregnancy after breast cancer.[36] We are also participating in an international, multi-site, retrospective cohort study (PI: Dr. Matteo Lambertini, University of Genoa, IT) inclusive of >1400 patients with BRCA+ breast cancer from 30 sites across North America, Europe, Latin America, and Israel, contributing clinical, genetic, and PRO data on 125 YWS participants with BRCA mutations. To date, there have been two major publications reporting analyses of pregnancy outcomes as well as clinical outcomes from this collaboration.[37 38]

Systemic Treatment and Disease Recurrence and Response

In 2017, we conducted a study examining the prognostic value of genomic expression prediction assays in the YWS. Prior research that led to the routine incorporation of such tools into clinical care had included relatively few women <40 years old, resulting in hesitation among providers to use them for young women. We demonstrated that Recurrence Score (RS) was prognostic and appeared to be predictive of chemotherapy benefit or lack thereof in patients with node-negative disease.[39] These data have informed recent guidelines and clinical practice supporting the use of RS in young patients to influence chemotherapy decisions.[28] We subsequently demonstrated the association of RS with pathologic complete response (pCR) after neoadjuvant chemotherapy for hormone receptor-positive disease[40]; results from this study are providing preliminary data for planned correlative work in a pre-operative clinical trial in the Alliance for Clinical Trials in Oncology.

Psychosocial Implications of Breast Cancer in Young Women

A large focus of the YWS has been to study the early psychological and social repercussions of breast cancer in young women to identify areas for tailored support and management strategies. We have characterized sexual functioning and body image issues, the impact of a diagnosis on employment, post-traumatic stress, fear of recurrence, anxiety and depression in women with de novo

stage IV disease, as well as the impact of the diagnosis on the partners of YWS participants.[41-48] Recent studies have found that more extensive surgery and radiation are associated with poorer QOL[21 49] as well as increased arm morbidity.[50] Collectively, our findings indicate that young women experience a substantial psychosocial burden during and following the completion of active treatment, and this burden is associated with certain patient, disease and treatment variables which can be targeted for intervention.

Biological Differences in Breast Cancer by Age

Collaborative efforts have yielded important findings to date including a comparison of whole exome sequencing profiles of the youngest 100 participants (≤35 years at diagnosis) to older women from The Cancer Genome Atlas (TCGA).[51 52] This analysis revealed that somatic alterations in three genes (*PIK3CA, GATA3,* and *ARID1A*) occur at different frequencies in young versus older women with luminal A breast cancer.[52] Additional investigation of these genes could delineate biological susceptibilities for young patients. Several additional studies have used or pooled tissue and/or blood specimens including a genome wide association study characterizing single nucleotide polymorphisms in young patients,[53] a study of RasGAP genes in luminal B tumors,[54] and a study of somatic mutations in patients with metastatic triple negative breast cancer,[55] and the development of a test to identify minimal residual disease in early-stage breast cancer.[51] Most recently, we used novel DNA sequencing methods to evaluate the prevalence and mutation spectrum of clonal hematopoiesis in young women and its association with patient and treatment characteristics and outcomes.[56] Reassuringly, clonal hematopoiesis of indeterminate potential (CHIP) was rare, with a prevalence of <3% among the 878 women in the analytic cohort.[56] The YWS has also provided clinical data detailing cancer outcomes of nulliparous vs. recently parous women, for an analysis supporting the novel pre-clinical finding that weaning-induced liver involution establishes a pro-metastatic microenvironment, a potential explanation for more poor cancer outcomes of recently parous

women.[57] Several analyses to understand the biologic underpinnings of early onset breast cancer are underway.

Collaboration

The YWS is uniquely positioned for investigations of age-related tumor and host biology as well as studies evaluating the impact of hereditary predisposition, post-diagnosis pregnancy, premature menopause, psychosocial, lifestyle and care delivery on cancer endpoints and comorbidities. The YWS research team includes medical, surgical, and radiation oncologists, epidemiologists, pathologists, and biostatisticians, and our collaborations have grown to include experts in cancer genomics, biology, tumor microenvironment, and behavioral health. While data are not publicly available, investigators interested in accessing YWS-generated data and/or biospecimens should contact the Principal Investigator (A. Partridge) and submit a request to the DF/HCC breast users committee (https://www.dfhcc.harvard.edu/research/research-programs/clinical-based-programs/breast-cancer/program-resources/dfhcc-breast-users-committee/).

Future Directions

The YWS has proven to be a rich scientific resource that has resulted in impactful research that has advanced our understanding of breast cancer in young women, generated new lines of investigation, and informed clinical guidelines. Breast cancer is the leading cause of cancer-related deaths in young women, and while improved over time, survival rates for young women with breast cancer remain lower compared to older women.[3 4] Thus, identifying risk factors for these poorer outcomes in younger women is critical. With the cohort maturing, we expect the number of recurrent disease events expected to increase by ~50% over the next 5 years and beyond, allowing for further evaluation of predictors of oncologic outcomes, including breast cancer free survival and overall survival. With relatively large numbers of young patients treated with contemporary regimens and well-annotated treatment details, we will be well-positioned to evaluate the impact of post-diagnosis

pregnancies on recurrence, new primary cancer, or death, assessment of risk factors for second cancers by breast cancer phenotype and germline pathogenic variant status, as well as risk factors for late recurrences among women diagnosed at a young age. Studies of the role of ctDNA on predicting late recurrence and exploring tumor and host characteristics that may be conducive to recurrence/disease resistance to therapy in young women (e.g., tumor immune microenvironment differences by recent parity status at diagnosis) have great potential.

As a survivorship cohort, evaluating long-term, late effects of breast cancer treatment and survivorship is a central objective of the YWS. A critical charge of cancer survivorship research is identifying potentially modifiable factors that predict these risks. Young breast cancer survivors may be at high risk of long-term or late morbidity given the aggressive therapy they usually receive and anticipated long life trajectory after the cancer. Additionally, they may have hereditary, behavioral, and comorbidity predispositions to disease. The concerns unique to or accentuated by their stage of life at diagnosis also appear to contribute to the increased risk of psychological distress seen in this age group both at diagnosis and in long-term follow-up.[12] With a median follow-up of 10 years, we are now well-poised to study late and long-term morbidity, including premature menopause (age <45 years), which in non-cancer populations is associated with substantial multimorbidity including increased risk of depression, hyperlipidemia, heart disease, asthma, chronic obstructive pulmonary disease, arthritis and osteoporosis.[58] On each survey, YWS participants are asked about their menstrual status, including date of last menstrual period, reasons for periods stopping, as well as questions about gynecologic procedures providing granular data to inform analyses. Given the current age of the cohort, the next several years are a critical time to conduct in-depth assessment of the menopausal transition among women who remained premenopausal following treatment, including timing, risk factors for premature menopause, and the impact of early menopause on QOL and comorbidities in this population. This data resource will also facilitate investigations ranging from health care utilization assessments, changes in lifestyle factors over time, and trajectories of QOL, to

evaluations of the association of specific co-morbidities (e.g., heart disease, diabetes) with premature menopause, weight gain, body composition, metabolic biomarkers, inflammatory mediators, hormone levels, and biomarkers of accelerated aging.

Strengths and Limitations

With a repository of biospecimens, clinical data, and serial PRO collection, the YWS is a robust platform from which to study molecular and biologic issues, as well as the health and psychosocial repercussions of a breast cancer diagnosis and treatment in young women. One of the core strengths of the YWS is high participant engagement, which has facilitated our ability to follow participants for both medical and psychosocial outcomes in extended follow-up. Additionally, we have leveraged the collection of blood specimens at three time points – baseline, 1 year, and 4 years after diagnosis – for novel investigations that are complemented with clinical data that have been systematically abstracted from the medical record. However, as the YWS is an observational cohort study, establishing causality vs. association can be challenging and there is a risk of unmeasured or unaccounted for confounders in analyses. As the main objective of the YWS was to establish a survivorship cohort that followed young women diagnosed with breast cancer, women older than 40 and women without a history of cancer were not enrolled; thus, our study is not designed to enable cross-age comparisons or comparisons with non-cancer, age-matched "controls." Additionally, while the YWS is a multi-site study that included both academic and community sites, women enrolled in the YWS are predominantly white, non-Hispanic, and highly educated, which may impact generalizability of findings to young breast cancer survivors from more diverse racial, ethnic, and socio-economic backgrounds. Acknowledging this limitation, more recent studies conducted by our team, including intervention trials informed by YWS findings, have focused efforts to improve outreach to patients from historically under-represented racial and ethnic groups.

Data availability statement: Requests to access YWS data/biospecimens should be made to the Principal Investigator, Dr. Ann Partridge (ann_partridge@dfci.harvard.edu).

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Ethics statements: The YWS is approved by the Institutional Review Board at Dana-Farber Harvard Cancer Center (IRB# 06-169) and other participating sites. Participants provided written informed consent at the time of enrollment.

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Author contributions: AHP, EPW, RMT, and SG conceptualized and developed the cohort and methodology. LCC provided oversight for pathology review. MEM, CS, and GJK have supported data and biospecimen collection and management. SG and YZ have provided statistical support. KJR, LS, JP, SC, VFB, and EW have served as site investigators. AHP, KJR, and PDP provided oversight for medical record/clinical data review. AHP and SMR provide general oversight and management of the study. AHP provided funding for the study. AHP is the guarantor of the study. All authors read and approved the final manuscript.

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Figure Legends

Figure 1. Overview of YWS data and biospecimen collection

YWS, Young Women's Breast Cancer Study

Figure 2. YWS Study Flow Diagram

Table 1. Demographic Characteristics

	N (%)
Age at diagnosis	
<25	25 (2)
25-30	139 (11)
31-35	352 (27)
36-40	780 (60)
Race	
American Indian /Alaska Native	6 (<1)
Asian	88 (7)
Native Hawaiian/Other Pacific Islander	0 (0)
Black or African American	48 (4)
White	1101 (85)
More than one race	16 (1)
Unknown or not reported	38 (3)
Ethnicity	
Hispanic	56 (4)
Non-Hispanic	1045 (81)
Unknown or not reported	196 (15)

Table 2. Disease/tumor characteristics and BRCA mutation status (N=1297)

	N (%)
Stage	
0	98 (8)
I	413 (32)
II	525 (41)
III	197 (15)
IV	64 (5)
Bilateral breast cancer	21 (2)
Tumor grade	
1	89 (7)
2	445 (34)
3	752 (58)
Missing/Unknown	11 (0.9)
ER status	
Positive	945 (73)
Negative	351 (27)
Missing/Unknown	1 (<1)
PR status	
Positive	848 (65)
Negative	441 (34)
Missing/Unknown	8 (<1)
HER2 status	
Positive	360 (28)
Negative	880 (68)
Missing/Unknown/Not performed*	57 (4)
Subtype	
Luminal A-like	395 (31)
Luminal B-like	269 (21)
Luminal B/HER2	255 (20)
HER2-enriched (ER-, PR-, HER2+)	105 (8)
Triple negative	210 (16)
Missing/Unknown	63 (5)
BRCA mutation status	
BRCA1+	90 (7)
BRCA2+	54 (4)
Variant of unknown significance	54 (4)
No mutation detected	919 (71)
Not tested or unknown testing status	180 (14)

*Missing/Unknown subtype includes cases of DCIS for which HER2 was not performed

Table 3. Summary of Primary Survey Domains and Schedule, Baseline through Year 15

	Survey Schedule																		
		Month					Year												
	Baseline	6	12	18	24	30	3	4	5	6	7	8	9	10	11	12	13	14	15
Socio-demographics including insurance, finances	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/ Family History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Genetics			X		X		X		X		X			X					
Health-related Activities/Social History	X		X		X		X	X	X	X	X	X	X	X					
Fertility/Gynecologic	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lactation Assessment	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X
Contraception										X		X							
QOL/Anxiety/Depression	X	X	X		X		X	X	X		X			X					X
Coping		X		X															
Fear of Recurrence	X		X		X		X	X	X		X			X					X
Menopausal Symptoms	X	X	X		X		X	X	X		X			X					X
Social Support	X		X		X		X	X	X										
Spirituality Assessment	X						X												
Treatment Decisions		X												X					
Medications List	X		X		X		X	X	X	X	X	X	X	X					X
Tamoxifen Adherence						X													
Healthcare Utilization											X								X

Figure 1

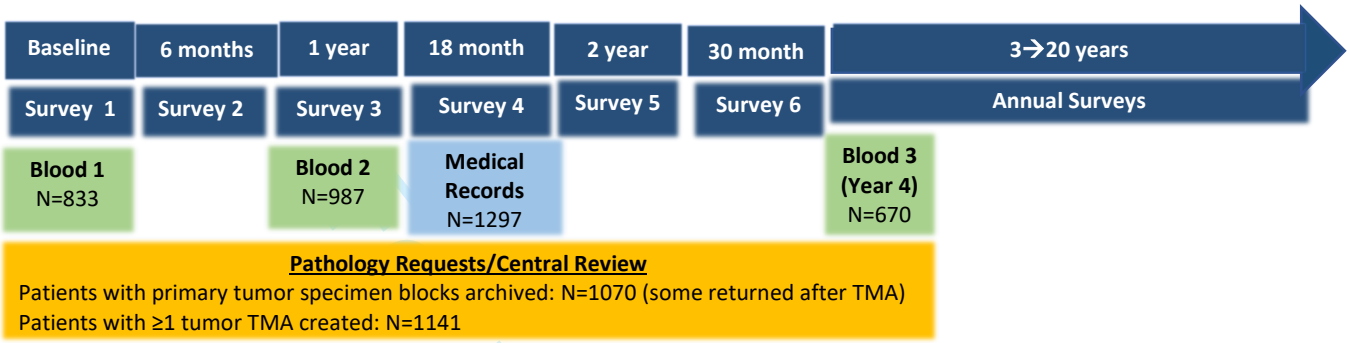
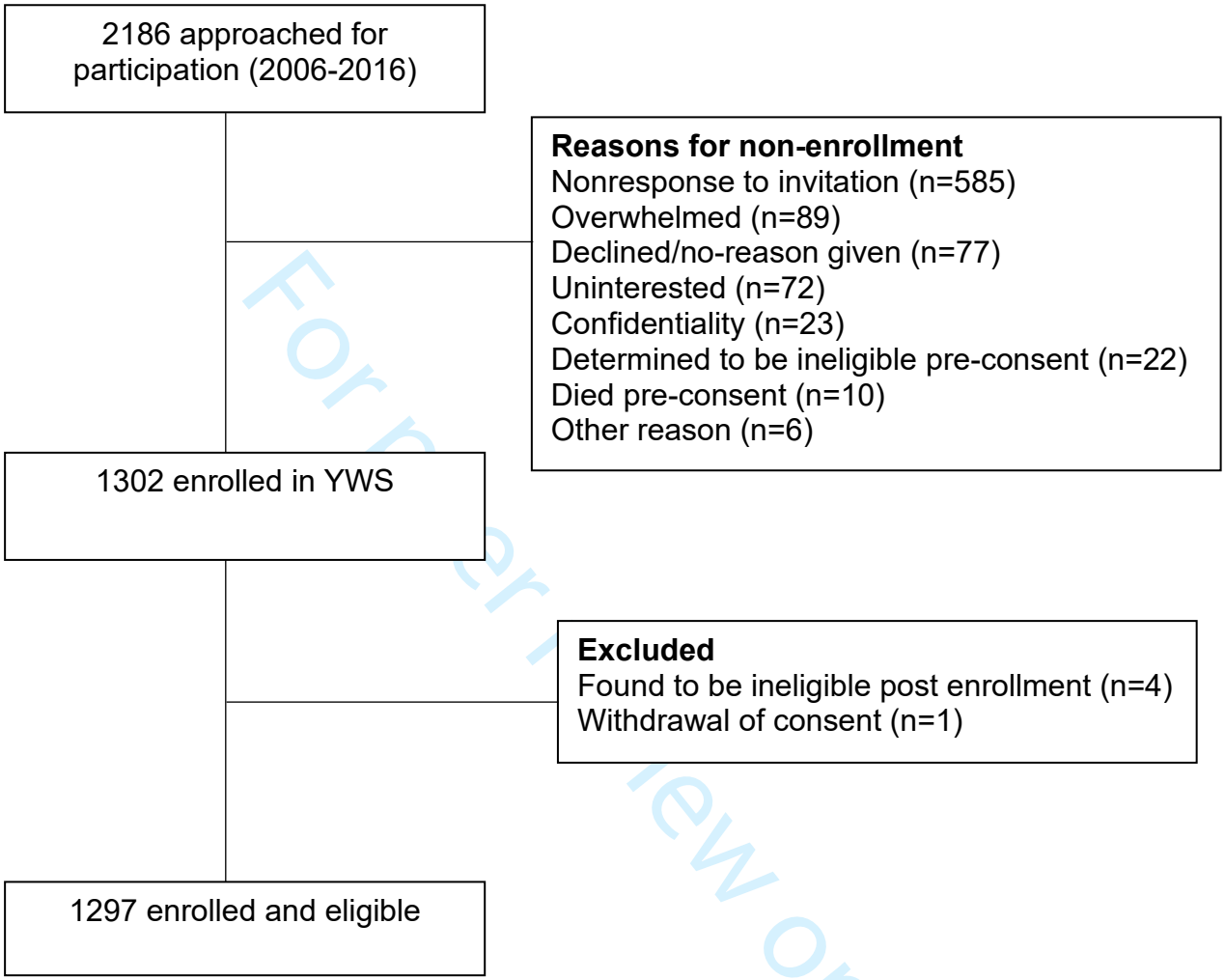


Figure 2.



SUPPLEMENTAL MATERIAL

Cohort profile: Helping Ourselves, Helping Others - The Young Women's Breast Cancer Study (YWS): A multi-site prospective cohort study to advance the understanding of breast cancer diagnosed in women aged 40 and younger

Supplemental Tables: 2

Supplemental Table 1. YWS enrollment sites

Site	State/Country	Number Enrolled
Dana-Farber Cancer Institute/Brigham and Women's Hospital[a]	MA	669
Beth Israel Deaconess Medical Center[a]	MA	50
Cape Cod Hospital[b]	MA	19
Faulkner Hospital[a]	MA	47
Lowell General Hospital[b]	MA	11
Massachusetts General Hospital[a]	MA	256
Mayo Clinic[a]	MN	35
Milford Hospital[b]	MA	1
Newton-Wellesley Hospital[b]	MA	30
North Shore Cancer Center (Salem)[b]	MA	21
South Shore Hospital[b]	MA	9
Sunnybrook Health Sciences[a]	Canada	62
University of Colorado Hospital[a]	CO	92

[a]academic sites [b]community sites
YWS, Young Women's Breast Cancer Study; MA, Massachusetts; MN, Minnesota; CO, Colorado

Supplemental Table 2. YWS Blood Specimens Collected

Number of Collections	Patients (N)	Baseline	1 year	4 year
1 Timepoint	N=71			
	N=137			
	N=23			
2 Timepoints	N=247			
	N=44			
	N=132			
3 Timepoints	N=471			
Total/Timepoint		N=833	N=987	N=670

BMJ Open

Cohort profile: Helping Ourselves, Helping Others - The Young Women's Breast Cancer Study (YWS): A multi-site prospective cohort study to advance the understanding of breast cancer diagnosed in women aged 40 and younger

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Keywords:	ONCOLOGY, Breast tumours < ONCOLOGY, Quality of Life

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Cohort profile: Helping Ourselves, Helping Others - The Young Women's Breast Cancer Study (YWS): A multi-site prospective cohort study to advance the understanding of breast cancer diagnosed in women aged 40 and younger

Shoshana M. Rosenberg,[1,2,3] Yue Zheng,[4] Kathryn J. Ruddy,[5] Philip D. Poorvu,[2,3] Craig Snow,[2,3] Gregory J. Kirkner,[2,3] Meghan E. Meyer,[2,3] Rulla M. Tamimi,[1] Lidia Schapira,[6] Jeffrey Peppercorn,[7] Steven Come,[8] Virginia F. Borges,[9] Ellen Warner,[10] Shari Gelber,[2,3] Laura C. Collins,[11] Eric P. Winer,[2,3,12] and Ann H. Partridge[2,3]

[1]Population Health Sciences, Weill Cornell Medicine, New York, NY, USA (current affiliation); [2]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [3]Breast Oncology Program, Dana-Farber Brigham Cancer Center, Boston, MA, USA; [4]Data Science, Dana-Farber Cancer Institute, Boston, MA, USA; [5]Medical Oncology, Mayo Clinic, Rochester, MN, USA; [6]Department of Medicine, Division of Medical Oncology, Stanford University, Stanford, CA, USA; [7]Department of Medicine, Division of Medical Oncology, Massachusetts General Hospital, Boston MA, USA; [8]Medical Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA; [9]Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [10]Deparment of Medicine, Division of Medical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [11]Pathology, Beth Israel Deaconess Medical Center, Boston, MA, USA; [12]Yale Cancer Center, New Haven, CT, USA (current affiliation)

Corresponding author:

Ann H. Partridge

Dana-Farber Cancer Institute

450 Brookline Avenue

Boston, MA 02067

Tel: 617-632-3800

Email: ann_partridge@dfci.harvard.edu

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Abstract

Purpose: Compared to older women diagnosed with breast cancer, younger women are more likely to die of breast cancer and more likely to suffer psychosocially in both the short and long-term. The Young Women's Breast Cancer Study (YWS) is a multisite prospective cohort study established to address gaps in our knowledge about this vulnerable and understudied population.

Participants: The YWS enrolled 1,302 women newly diagnosed with stage 0-IV breast cancer at age 40 years or younger at 13 academic and community sites in North America between 2006 and 2016. Longitudinal patient-reported outcome data are complemented by clinical data abstraction and biospecimen collection at multiple time-points.

Findings to Date: Key findings related to fertility include that nearly 40% of participants were interested in pregnancy following diagnosis; of those who reported interest, 10% pursued fertility preservation. Overall, approximately 10% of YWS participants became pregnant in the first 5 years after diagnosis; follow-up is ongoing for pregnancies after 5 years. Studies focused on psychosocial outcomes have characterized quality of life, post-traumatic stress, and fear of recurrence, with findings detailing the factors associated with the substantial psychosocial burden many young women face during and following active treatment. Multiple studies have leveraged YWS biospecimens, including whole exome sequencing of tumor analyses that revealed that select somatic alterations occur at different frequencies in young (age <35) versus older women with luminal A breast cancer, and a study that explored clonal hematopoiesis of indeterminate potential found it to be rare in young survivors.

Future Plans: With a median follow-up of approximately 10 years, the cohort is just maturing for many relevant long-term outcomes and provides outstanding opportunities to further study and build collaborations to address gaps in our knowledge, with the ultimate objective to improve care and outcomes for young women with breast cancer.

Registration: clinicaltrials.gov, NCT01468246

Strengths and Limitations

- Established in 2006, the Young Women's Breast Cancer Study (YWS) is a multi-site, prospective cohort of women with young onset breast cancer.
- The YWS was designed to conduct regular medical record review and collect biospecimens and serial patient-reported outcomes.
- Eligibility criteria included: 1) female; 2) a new diagnosis of stage 0-IV breast cancer 3) age ≤40 years at diagnosis; and 4) ability to understand written and spoken English.
- Robust follow-up procedures optimize participant engagement and ensure accurate ascertainment of oncologic outcomes and vital status.
- Recruitment was hospital-based and may not be truly representative of the general population, potentially impacting generalizability.

Introduction

Greater than 14,000 women aged 40 years and younger are diagnosed with breast cancer annually in the United States alone, with thousands more worldwide. Far less is known, however, about breast cancer in younger vs. older women. Further, recent population-based data have demonstrated that the incidence of breast cancer is growing in this population.[1,2] Breast cancer is the leading cause of cancer-related deaths in women under 40 years of age, and while improved over time, survival rates for young women with breast cancer remain lower compared to older women.[3,4] The reasons for the poorer outcomes experienced by young women as understood to date are complex and multifactorial. Compared to older women, young women are more likely to present with symptoms and at a more advanced stage, due in part to diagnostic delays and lack of screening in this population.[5,6] Breast cancers arising in young women tend to have more unfavorable pathologic features and aggressive subtypes, including greater proportions with luminal B, HER2-positive, or triple-negative disease.[7,8] Young women are at high risk of non-adherence to risk reducing adjuvant hormonal therapy.[9-11] Compounding their disparate disease outcomes, young breast cancer survivors may be at greater risk of long-term or late morbidity given the aggressive therapy that they usually receive and anticipated long life trajectory in survivorship, although there are limited data in this area.

Of particular significance are the variety of young age-related medical and psychosocial issues that this population faces as a result of their diagnosis and treatment, which contribute to a greater risk of psychosocial distress compared to older patients.[12] These issues include hereditary predisposition and risks of future cancer, sexual dysfunction, infertility, premature menopause, body image concerns, role functioning including parenting, career and schooling disruption and the development of short- and long-term comorbidities. Collectively, these problems may influence treatment decisions, as well as disease and psychosocial outcomes.

Purpose of the Young Women's Breast Cancer Study

Young women are underrepresented in large prospective cohorts as well as in randomized trials evaluating novel therapies and prognostic tools to guide breast cancer treatment decisions.[13-15] Hesitancy to extrapolate data from studies of primarily older populations may result in young women being excluded or delayed in benefits from treatment improvements, or put at risk for overtreatment based solely on young age. Even in large prospective cohort studies and clinical trials inclusive of premenopausal women, as well as in population-based registries, there are rarely enough young women and/or adequate granularity of data to draw meaningful conclusions for this subpopulation. For example, the Nurses' Health Studies have previously reported 374 incident cases age <40 years (vs. 2,533 cases in women age ≥40),[16] the Black Women's Health Study had 529 cases of breast cancer diagnosed at age <45 years documented through 2013 (vs. 1,534 cases in women aged 45 and older),[17] and the Suppression of Ovarian Function Trial had 933 participants age <40 years at diagnosis,[18] with limited details in follow-up for most. The Young Women's Breast Cancer Study (YWS) was designed to address gaps in knowledge regarding breast cancer in younger women, including unanswered questions pertaining to diagnosis and presentation, underlying disease biology, optimal treatment, survivorship, psychosocial issues, and living with metastatic disease. The YWS is the first and one of the largest cohorts of women with young onset breast cancer designed to conduct regular medical record review and collect biospecimens and patient-reported outcomes (PROs) (**Figure 1**). The original study objectives were to 1) enroll a cohort of women age ≤40 years newly diagnosed with breast cancer; 2) characterize the cohort at diagnosis and in follow-up regarding disease and psychosocial outcomes; and 3) archive tumor and blood specimens for future studies.

Cohort Description

Overview

From 2006-2016, the YWS enrolled 1,302 women from 13 North American academic and community sites (**Supplemental Table 1**). There was high accrual of those approached for enrollment

(1302/2186, 60% participate rate). Four patients were determined to be ineligible, and one withdrew consent following enrollment leaving 1,297 women who are followed. Reasons for non-participation are detailed in **Figure 2**. The YWS is approved by the Institutional Review Board at Dana-Farber Harvard Cancer Center (DF/HCC) and other participating sites.

Enrollment procedures

At Massachusetts sites, potentially eligible participants were systematically identified by pathology review or by pathology or clinic list review by a research nurse on a monthly or bi-monthly basis. The Dana-Farber Cancer Institute (DFCI) Survey and Data Management Core then reviewed the medical record to confirm eligibility. At sites outside of Massachusetts, study staff assisted with recruitment via systematic review of patient lists. Eligibility was confirmed prior to inviting. Inclusion criteria included: 1) female; 2) a new diagnosis of stage 0-IV breast cancer 3) age ≤40 years at diagnosis; and 4) ability to understand written and spoken English to the extent necessary to complete the questionnaires. Participants enrolled a median of 4 (range: 0-29) months following diagnosis. Following receipt of written informed consent, participants were mailed a welcome letter, medical record release form, tumor specimen request form, and the baseline survey. Current median follow-up of the cohort is 10 years (range: 0.4-16 years). Because calculation of follow-up is based on individual patient data, the lower end of this range (e.g., 0.4 years) reflects the follow-up duration of patients who died soon after diagnosis and/or were lost to follow-up early in the study.

Participant characteristics

Table 1 includes a summary of YWS participant age at diagnosis, race, and ethnicity. Baseline survey questions asked participants about their race and ethnicity. For baseline survey non-responders or instances where this information was not reported, race/ethnicity as determined from medical record at screening/enrollment was used. Approximately 14% of YWS participants are from a non-White and/or Hispanic racial/ethnic background. Median age at diagnosis was 36 (range: 17-40) years. Key cancer information including stage, grade, subtype, and BRCA mutation status is detailed in **Table 2**.

Recognizing that there have been changes in how we measure social determinants of health since the baseline survey was developed and to make these data more complete, we are sending YWS participants a supplemental survey including updated questions regarding race, ethnicity, gender, and sexual identity.

Patient and Public Involvement

Since the study's inception, we have invited patient volunteers and patient advocates to review survey content as well as assist with strategies to communicate results to YWS participants and other young patients. We routinely share lay summary results from YWS analyses directly through the DFCI Program for Young Adults with Breast Cancer newsletter as well as intermittent webinars and patient forums. Newsletters and webinars are also archived on the program's public website (https://youngandstrong.dana-farber.org).

YWS Data Collection and Follow-up

Surveys: Participants completed surveys at study baseline (median of 5 months post-diagnosis), 6 months after enrollment, and 1-year post-diagnosis. Participants were then surveyed every 6 months through 3 years, and annually thereafter. Participants enrolled at the Toronto site (N=62) are sent abbreviated ("short-form") surveys that ask for socio-demographics, how their breast cancer presented, fertility and gynecologic information, and cancer endpoints. At the 10-year timepoint, Toronto participants are sent a full survey to complete. A smaller subset of participants (N=29) who enrolled at other sites chose to complete the short-form follow-up annual surveys that only ask about fertility, gynecologic and cancer outcomes. For the initial 7 years of the YWS, all surveys were mailed to main study participants; participants completing short-form surveys were given the option of completing surveys on paper or online via Survey Monkey. Beginning at the 8-year survey time point, participants were offered the option to complete an electronic survey through REDCap. In March 2020, due to COVID restrictions limiting the ability to mail materials, participants with a valid email address (98%) were sent surveys through REDCap. Collectively, these surveys have yielded an unparalleled resource

of longitudinal PRO data related to menopausal status, fertility, anxiety, depression, quality of life (QOL), fear of recurrence, treatment side-effects, employment, genetics, and treatment decision-making (see **Table 3** for domains/timeline for the first 15 years of follow-up). We also periodically invite participant subsets to complete supplemental surveys to investigate salient issues in greater detail.[19-24]

Follow-up to optimize survey response rates: A research coordinator systematically contacts participants who do not complete their surveys with a phone call at 3 weeks after the initial survey is sent out; the survey is re-sent at 6 weeks if the participant has still not completed the survey at that timepoint. Additional calls and/or survey resends are then conducted monthly up to 6 months following the initial send out, as needed. Response rates (surveys received/surveys sent) for the majority of survey time points range from 86%-91%. Response rates for 7 and 10-year surveys are modestly lower (71% for 7-year and 65% for 10-year) due to our attempt to re-engage non-responding participants at those timepoints.

*Medical Records***:** Medical records through the first 18 months following diagnosis are available for 100% of participants. Records are also reviewed at additional timepoints (including at 10 years) to 1) confirm and collect specifics on cancer outcomes (recurrences, new primary breast cancers, other cancers) that are self-reported on surveys; and 2) to update comorbidities including recurrences and new cancers and vital status among participants who do not regularly complete surveys. We have abstracted initial treatment information, including specific chemotherapy regimens started and received, surgery, radiation, genetic testing (panel type and results), and co-morbidities using the Charlson framework[25,26] from the medical record to validate/supplement what patients report on surveys, and to fill in missing data.

Ascertainment of Cancer Outcomes and Vital Status: Recurrences, new primary breast cancers, and new (non-breast) cancers are assessed on each survey. In addition to site(s) of recurrence or new cancer, participants are asked to report the date of the recurrence. Any self-report of a recurrence or

new cancer, including site and date (either radiologic or pathologic confirmation) is confirmed by medical record review. Because this process relies on survey responses to ascertain outcomes, for those participants who are no longer responding to surveys we request and review updated medical records for these patients every 4 years. For participants treated at DFCI, Brigham and Women's Hospital, Massachusetts General Hospital or an affiliate network site, the National Death Index is queried periodically to obtain vital status information. Following the 2018-2019 update, we were able to ascertain oncologic outcomes and vital status for 321 patients who were survey non-responders. As of September 2023, among the entire cohort, we have documented 181 participants with distant metastatic recurrences, 96 participants with locoregional recurrences, 22 participants with new primary breast cancers, and 49 participants with new non-breast primary cancers, and 186 deaths.

Tissue Specimen Collection/Storage: Pathology reports, hematoxylin and eosin (H&E) stained slides, and a representative paraffin block of tumor were requested from the institution where the patient had her surgery; the patient's signed release for the specimens and reports were sent to the pathology department. A YWS study pathologist reviewed each pathology report and an H&E stained section of the tumor block to annotate tumor details.[8,27] Slides from the core needle biopsy were requested as well as from the surgery in neoadjuvant therapy cases. Hormone and HER-2/neu (HER2) receptor expression, and lymph node status, were extracted from the pathology reports. Of 1297 participants followed, 1278 (99%) consented to providing a tumor specimen for review. Primary tumor pathology has been centrally reviewed on 97% of patients (1242/1278), with blocks (N=1120) and cores for the tissue microarray (N=21) from tumor specimens collected on 1141 patients (88%). Currently, there are 1370 specimens from 1242 patients available in the tissue microarray blocks (patients who received neoadjuvant therapy may have more than one block).

*Blood Collection/Storage***:** Blood is collected at three timepoints (two 10mL tubes of whole blood at each timepoint), each with a several month "window" to maximize our ability to collect blood while minimizing burden: baseline (enrollment up to 9 months post-diagnosis); 1-year (9 months-2 years

post-diagnosis); and 4-year (3.5 – 5 years post diagnosis). Overall, 94% (1224/1297) of participants consented to blood collection. Of these, there is at least one sample available from 92% of participants, with 73% of participants providing samples at two or more time points (**Supplemental Table 2**). Women were asked to go to their treating institution or a local laboratory with the materials provided in the blood specimen kit, unless drawn at DFCI where kits are provided on site by staff. Specimens were processed at the DFCI Breast Cancer CORE Blood Repository, where whole blood (4 aliquots/2ml each) and plasma (2 aliquots/2mL each) were isolated and banked for future studies.

Findings to Date

Since its inception, YWS investigations have characterized more fully the experience of breast cancer in young women, creating a platform from which to study molecular and biologic issues, as well as the health and psychosocial repercussions of a breast cancer diagnosis and treatment at a young age. As the YWS has matured, we have expanded our investigations to include collaborations with basic and translational scientists enabling us to address new questions, advancing knowledge of the biology of the disease as well as to improve clinical care and outcomes. In addition, research findings from the YWS have informed international guidelines and clinical practice.[28,29]

Fertility Issues and Pregnancy

In 2014, we published findings from the baseline survey regarding fertility concerns and fertility preservation strategies used.[30] Since then, additional publications from the YWS have described breast cancer diagnosed during pregnancy,[31] pregnancy after breast cancer,[32] treatment-related amenorrhea,[33] fertility concerns and endocrine therapy decision-making,[34] and fertility concerns in germline genetic carriers.[35] Key findings included the observation that nearly 40% of participants were interested in pregnancy after breast cancer; of those interested, 10% pursued fertility preservation strategies.[30] Another study documented that approximately 20% of women become amenorrheic in survivorship after standard chemotherapy, with variability by chemotherapy type and age.[33] A third study evaluated post-diagnosis pregnancies, observing that 10% became pregnant in the first 5 years

after breast cancer.[32] Fertility outcomes remain a primary outcome of interest in continued follow-up of the cohort and the rich and detailed fertility and gynecologic data collected at each time point will allow for novel and detailed investigations regarding impact of pregnancy on cancer endpoints, and menopausal and related comorbidity outcomes. Findings from this work have been referenced in international guidelines[28,29] and informed an international trial that evaluated the safety of pregnancy after breast cancer.[36] We are also participating in an international, multi-site, retrospective cohort study (PI: Dr. Matteo Lambertini, University of Genoa, IT) inclusive of >1400 patients with BRCA+ breast cancer from 30 sites across North America, Europe, Latin America, and Israel, contributing clinical, genetic, and PRO data on 125 YWS participants with BRCA mutations. To date, there have been two major publications reporting analyses of pregnancy outcomes as well as clinical outcomes from this collaboration.[37,38]

Systemic Treatment and Disease Recurrence and Response

In 2017, we conducted a study examining the prognostic value of genomic expression prediction assays in the YWS. Prior research that led to the routine incorporation of such tools into clinical care had included relatively few women <40 years old, resulting in hesitation among providers to use them for young women. We demonstrated that Recurrence Score (RS) was prognostic and appeared to be predictive of chemotherapy benefit or lack thereof in patients with node-negative disease.[39] These data have informed recent guidelines and clinical practice supporting the use of RS in young patients to influence chemotherapy decisions.[28] We subsequently demonstrated the association of RS with pathologic complete response (pCR) after neoadjuvant chemotherapy for hormone receptor-positive disease[40]; results from this study are providing preliminary data for planned correlative work in a pre-operative clinical trial in the Alliance for Clinical Trials in Oncology.

Psychosocial Implications of Breast Cancer in Young Women

A large focus of the YWS has been to study the early psychological and social repercussions of breast cancer in young women to identify areas for tailored support and management strategies. We

have characterized sexual functioning and body image issues, the impact of a diagnosis on employment, post-traumatic stress, fear of recurrence, anxiety and depression in women with de novo stage IV disease, as well as the impact of the diagnosis on the partners of YWS participants.[41-48] Recent studies have found that more extensive surgery and radiation are associated with poorer QOL[21,49] as well as increased arm morbidity.[50] Collectively, our findings indicate that young women experience a substantial psychosocial burden during and following the completion of active treatment, and this burden is associated with certain patient, disease and treatment variables which can be targeted for intervention.

Biological Differences in Breast Cancer by Age

Collaborative efforts have yielded important findings to date including a comparison of whole exome sequencing profiles of the youngest 100 participants (≤35 years at diagnosis) to older women from The Cancer Genome Atlas (TCGA).[51,52] This analysis revealed that somatic alterations in three genes (*PIK3CA, GATA3,* and *ARID1A*) occur at different frequencies in young versus older women with luminal A breast cancer.[52] Additional investigation of these genes could delineate biological susceptibilities for young patients. Several additional studies have used or pooled tissue and/or blood specimens including a genome wide association study characterizing single nucleotide polymorphisms in young patients,[53] a study of RasGAP genes in luminal B tumors,[54] and a study of somatic mutations in patients with metastatic triple negative breast cancer,[55] and the development of a test to identify minimal residual disease in early-stage breast cancer.[51] Most recently, we used novel DNA sequencing methods to evaluate the prevalence and mutation spectrum of clonal hematopoiesis in young women and its association with patient and treatment characteristics and outcomes.[56] Reassuringly, clonal hematopoiesis of indeterminate potential (CHIP) was rare, with a prevalence of <3% among the 878 women in the analytic cohort.[56] The YWS has also provided clinical data detailing cancer outcomes of nulliparous vs. recently parous women, for an analysis supporting the novel pre-clinical finding that weaning-induced liver involution establishes a pro-metastatic

microenvironment, a potential explanation for more poor cancer outcomes of recently parous women.[57] Several analyses to understand the biologic underpinnings of early onset breast cancer are underway.

Collaboration

The YWS is uniquely positioned for investigations of age-related tumor and host biology as well as studies evaluating the impact of hereditary predisposition, post-diagnosis pregnancy, premature menopause, psychosocial, lifestyle and care delivery on cancer endpoints and comorbidities. The YWS research team includes medical, surgical, and radiation oncologists, epidemiologists, pathologists, and biostatisticians, and our collaborations have grown to include experts in cancer genomics, biology, tumor microenvironment, and behavioral health. While data are not publicly available, investigators interested in accessing YWS-generated data and/or biospecimens should contact the Principal Investigator (A. Partridge) and submit a request to the DF/HCC breast users committee (https://www.dfhcc.harvard.edu/research/research-programs/clinical-based-programs/breast-cancer/program-resources/dfhcc-breast-users-committee/).

Future Directions

The YWS has proven to be a rich scientific resource that has resulted in impactful research that has advanced our understanding of breast cancer in young women, generated new lines of investigation, and informed clinical guidelines. Breast cancer is the leading cause of cancer-related deaths in young women, and while improved over time, survival rates for young women with breast cancer remain lower compared to older women.[3,4] Thus, identifying risk factors for these poorer outcomes in younger women is critical. With the cohort maturing, we expect the number of recurrent disease events expected to increase by ~50% over the next 5 years and beyond, allowing for further evaluation of predictors of oncologic outcomes, including breast cancer free survival and overall survival. With relatively large numbers of young patients treated with contemporary regimens and well-

annotated treatment details, we will be well-positioned to evaluate the impact of post-diagnosis pregnancies on recurrence, new primary cancer, or death, assessment of risk factors for second cancers by breast cancer phenotype and germline pathogenic variant status, as well as risk factors for late recurrences among women diagnosed at a young age. Studies of the role of ctDNA on predicting late recurrence and exploring tumor and host characteristics that may be conducive to recurrence/disease resistance to therapy in young women (e.g., tumor immune microenvironment differences by recent parity status at diagnosis) have great potential.

As a survivorship cohort, evaluating long-term, late effects of breast cancer treatment and survivorship is a central objective of the YWS. A critical charge of cancer survivorship research is identifying potentially modifiable factors that predict these risks. Young breast cancer survivors may be at high risk of long-term or late morbidity given the aggressive therapy they usually receive and anticipated long life trajectory after the cancer. Additionally, they may have hereditary, behavioral, and comorbidity predispositions to disease. The concerns unique to or accentuated by their stage of life at diagnosis also appear to contribute to the increased risk of psychological distress seen in this age group both at diagnosis and in long-term follow-up.[12] With a median follow-up of 10 years, we are now well-poised to study late and long-term morbidity, including premature menopause (age <45 years), which in non-cancer populations is associated with substantial multimorbidity including increased risk of depression, hyperlipidemia, heart disease, asthma, chronic obstructive pulmonary disease, arthritis and osteoporosis.[58] On each survey, YWS participants are asked about their menstrual status, including date of last menstrual period, reasons for periods stopping, as well as questions about gynecologic procedures providing granular data to inform analyses. Given the current age of the cohort, the next several years are a critical time to conduct in-depth assessment of the menopausal transition among women who remained premenopausal following treatment, including timing, risk factors for premature menopause, and the impact of early menopause on QOL and comorbidities in this population. This data resource will also facilitate investigations ranging from health

care utilization assessments, changes in lifestyle factors over time, and trajectories of QOL, to evaluations of the association of specific co-morbidities (e.g., heart disease, diabetes) with premature menopause, weight gain, body composition, metabolic biomarkers, inflammatory mediators, hormone levels, and biomarkers of accelerated aging.

Strengths and Limitations

With a repository of biospecimens, clinical data, and serial PRO collection, the YWS is a robust platform from which to study molecular and biologic issues, as well as the health and psychosocial repercussions of a breast cancer diagnosis and treatment in young women. One of the core strengths of the YWS is high participant engagement, which has facilitated our ability to follow participants for both medical and psychosocial outcomes in extended follow-up. Additionally, we have leveraged the collection of blood specimens at three time points – baseline, 1 year, and 4 years after diagnosis – for novel investigations that are complemented with clinical data that have been systematically abstracted from the medical record. However, as the YWS is an observational cohort study, establishing causality vs. association can be challenging and there is a risk of unmeasured or unaccounted for confounders in analyses. As the main objective of the YWS was to establish a survivorship cohort that followed young women diagnosed with breast cancer, women older than 40 and women without a history of cancer were not enrolled; thus, our study is not designed to enable cross-age comparisons or comparisons with non-cancer, age-matched "controls." Additionally, while the YWS is a multi-site study that included both academic and community sites, women enrolled in the YWS are predominantly white, non-Hispanic, and highly educated, which may impact generalizability of findings to young breast cancer survivors from more diverse racial, ethnic, and socio-economic backgrounds. Acknowledging this limitation, more recent studies conducted by our team, including intervention trials informed by YWS findings, have focused efforts to improve outreach to patients from historically under-represented racial and ethnic groups.

Data availability statement: Requests to access YWS data/biospecimens should be made to the Principal Investigator, Dr. Ann Partridge (ann_partridge@dfci.harvard.edu).

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Ethics statements: The YWS is approved by the Institutional Review Board at Dana-Farber Harvard Cancer Center (IRB# 06-169) and other participating sites. Participants provided written informed consent at the time of enrollment.

Competing Interests: SMR reports grant funding from Conquer Cancer/Pfizer. VB reports research funding (paid to institution) from SeaGen, AstraZeneca, Gilead, and Olema; consultation for SeaGen, AstraZeneca, Lilly, Gilead, and Olema; and stock/founder of PEARL Scientific. AHP reports royalties from Wolters Kluwer (paid to self) for authorship of UpToDate. All remaining authors have no disclosures to report.

Author contributions: AHP, EPW, RMT, and SG conceptualized and developed the cohort and methodology. LCC provided oversight for pathology review. MEM, CS, and GJK have supported data and biospecimen collection and management. SG and YZ have provided statistical support. KJR, LS, JP, SC, VFB, and EW have served as site investigators. AHP, KJR, and PDP provided oversight for medical record/clinical data review. AHP and SMR provide general oversight and management of the study. AHP provided funding for the study. AHP is the guarantor of the study. All authors read and approved the final manuscript.

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Figure Legends

Figure 1. Overview of YWS data and biospecimen collection

YWS, Young Women's Breast Cancer Study

Figure 2. YWS Study Flow Diagram

Table 1. Demographic Characteristics

	N (%)
Age at diagnosis	
<25	25 (2)
25-30	139 (11)
31-35	352 (27)
36-40	780 (60)
Race	
American Indian /Alaska Native	6 (<1)
Asian	88 (7)
Native Hawaiian/Other Pacific Islander	0 (0)
Black or African American	48 (4)
White	1101 (85)
More than one race	16 (1)
Unknown or not reported	38 (3)
Ethnicity	
Hispanic	56 (4)
Non-Hispanic	1045 (81)
Unknown or not reported	196 (15)

Table 2. Disease/tumor characteristics and BRCA mutation status (N=1297)

	N (%)
Stage	
0	98 (8)
I	413 (32)
II	525 (41)
III	197 (15)
IV	64 (5)
Bilateral breast cancer	21 (2)
Tumor grade	
1	89 (7)
2	445 (34)
3	752 (58)
Missing/Unknown	11 (0.9)
ER status	
Positive	945 (73)
Negative	351 (27)
Missing/Unknown	1 (<1)
PR status	
Positive	848 (65)
Negative	441 (34)
Missing/Unknown	8 (<1)
HER2 status	
Positive	360 (28)
Negative	880 (68)
Missing/Unknown/Not performed*	57 (4)
Subtype	
Luminal A-like	395 (31)
Luminal B-like	269 (21)
Luminal B/HER2	255 (20)
HER2-enriched (ER-, PR-, HER2+)	105 (8)
Triple negative	210 (16)
Missing/Unknown	63 (5)
BRCA mutation status	
BRCA1+	90 (7)
BRCA2+	54 (4)
Variant of unknown significance	54 (4)
No mutation detected	919 (71)
Not tested or unknown testing status	180 (14)

*Missing/Unknown subtype includes cases of DCIS for which HER2 was not performed

Table 3. Summary of Primary Survey Domains and Schedule, Baseline through Year 15

	Survey Schedule																		
		Month					Year												
	Baseline	6	12	18	24	30	3	4	5	6	7	8	9	10	11	12	13	14	15
Socio-demographics including insurance, finances	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/ Family History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Genetics			X		X		X		X		X			X					
Health-related Activities/Social History	X		X		X		X	X	X	X	X	X	X	X					
Fertility/Gynecologic	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lactation Assessment	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X
Contraception										X		X							
QOL/Anxiety/Depression	X	X	X		X		X	X	X		X			X					X
Coping		X		X															
Fear of Recurrence	X		X		X		X	X	X		X			X					X
Menopausal Symptoms	X	X	X		X		X	X	X		X			X					X
Social Support	X		X		X		X	X	X										
Spirituality Assessment	X						X												
Treatment Decisions		X												X					
Medications List	X		X		X		X	X	X	X	X	X	X	X					X
Tamoxifen Adherence						X													
Healthcare Utilization											X								X

Figure 1

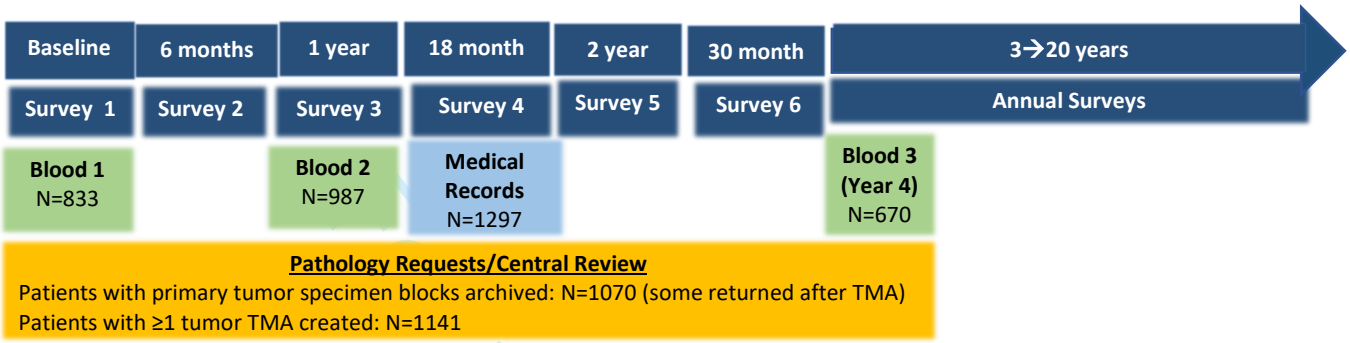
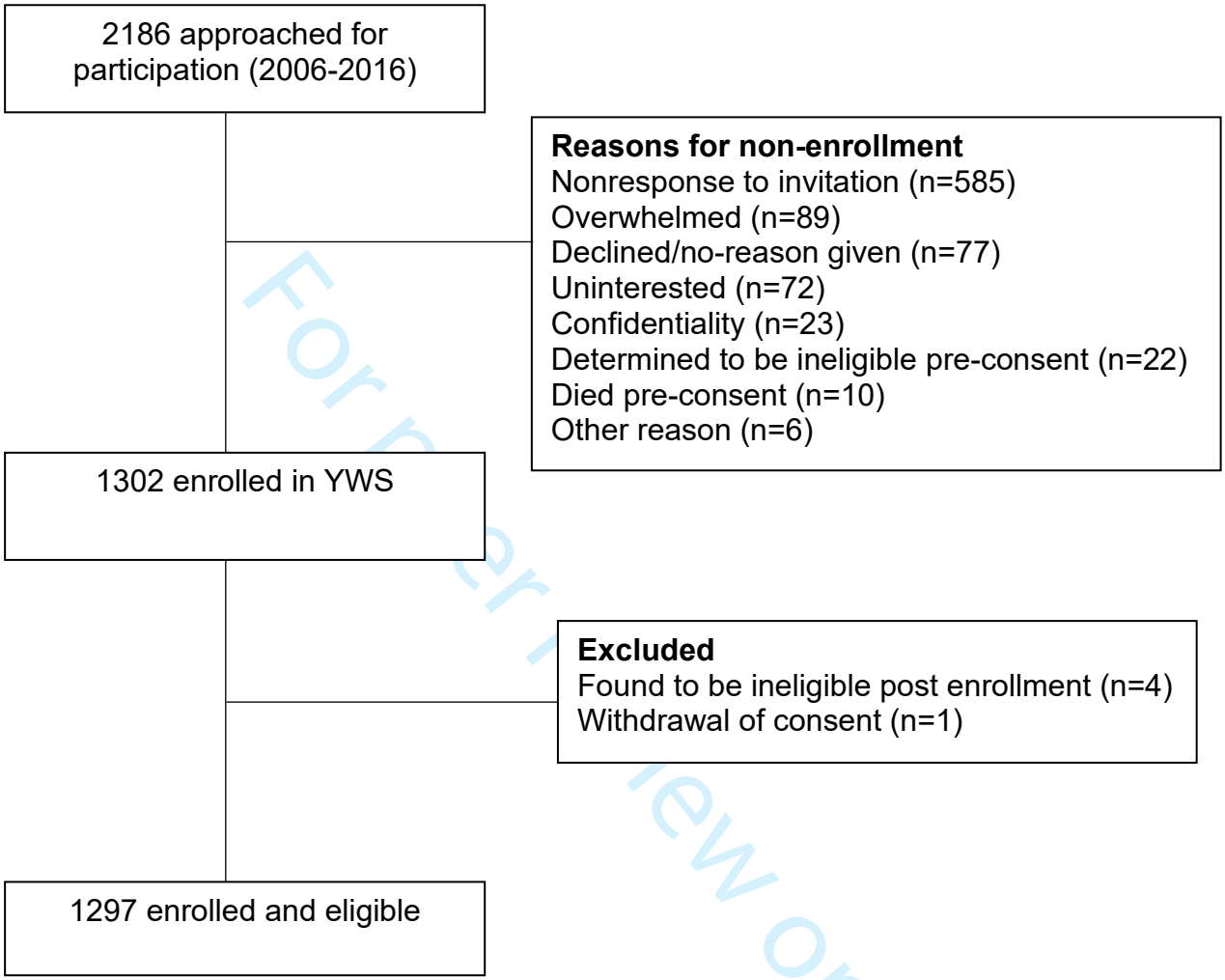


Figure 2.



SUPPLEMENTAL MATERIAL

Cohort profile: Helping Ourselves, Helping Others - The Young Women's Breast Cancer Study (YWS): A multi-site prospective cohort study to advance the understanding of breast cancer diagnosed in women aged 40 and younger

Supplemental Tables: 2

Supplemental Table 1. YWS enrollment sites

Site	State/Country	Number Enrolled
Dana-Farber Cancer Institute/Brigham and Women's Hospital[a]	MA	669
Beth Israel Deaconess Medical Center[a]	MA	50
Cape Cod Hospital[b]	MA	19
Faulkner Hospital[a]	MA	47
Lowell General Hospital[b]	MA	11
Massachusetts General Hospital[a]	MA	256
Mayo Clinic[a]	MN	35
Milford Hospital[b]	MA	1
Newton-Wellesley Hospital[b]	MA	30
North Shore Cancer Center (Salem)[b]	MA	21
South Shore Hospital[b]	MA	9
Sunnybrook Health Sciences[a]	Canada	62
University of Colorado Hospital[a]	CO	92

[a]academic sites [b]community sites
YWS, Young Women's Breast Cancer Study; MA, Massachusetts; MN, Minnesota; CO, Colorado

Supplemental Table 2. YWS Blood Specimens Collected

Number of Collections	Patients (N)	Baseline	1 year	4 year
1 Timepoint	N=71			
	N=137			
	N=23			
2 Timepoints	N=247			
	N=44			
	N=132			
3 Timepoints	N=471			
Total/Timepoint		N=833	N=987	N=670