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Special Article

Breast Cancer in Young Women: Research Priorities. A Report of the Young Survival Coalition Research Think Tank Meeting

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Breast cancer in young women is a significant issue—7% of all female breast cancer is diagnosed in women under 40 years of age. Young women with breast cancer (YWBC) face significant and unique challenges, including a higher likelihood of biologically aggressive disease and metastatic disease at diagnosis, leading to poorer prognosis, more aggressive treatment and long-term treatment-related toxicities, and unique psychosocial concerns. This article summarizes the Young Survival Coalition (YSC) Research Think Tank Meeting, held in Arlington, Virginia, in February 2013, and presents the process that led to YSC's priorities for YWBC research. The meeting's participants focused on six broad categories of investigation in which additional advancements in research on YWBC are crucial: risk factors; treatment; fertility; pregnancy-associated breast cancer; quality of life and survivorship; and metastasis. Several key themes emerged from this meeting. Researchers and advocates felt that a large-scale data registry focused on YWBC is necessary to collect quality information to guide future research for YWBC. This database should include clinical data, genomic profiling of primary tumor and metastatic sites, and an increased focus on fertility and pregnancy following breast cancer treatment. The participants also felt that more must be done to elucidate how and why YWBC develop more aggressive tumors, and to what degree treatment should be modified for young women. The discussions summarized here led to the formulation of YSC's Research Agenda, published in May 2014.

Keywords: breast cancer, chemotherapy, fertility, metastasis, quality of life, survivorship

Breast cancer is widely considered to be a disease associated with aging, but it is also the most common cancer in women under 40 years of age in the United States.[1] Seven percent of all female breast cancer in the United States is diagnosed before the age of 40,[2] and breast cancer is the leading cause of cancer-related death in women 20–39 years old.[3] Compared to older women with breast cancer, young women present more frequently with higher grade and hormone receptor-negative tumors. Young women are often diagnosed with more advanced disease,[4] and the frequency of metastatic disease at diagnosis has increased significantly over the past 30 years in young women in the United States,[5] all contributing to their lower survival rates compared with older women. Studies have also shown a poor long-term outlook for young patients with estrogen receptor (ER)-positive disease.[6] Young women with breast cancer (YWBC) also face distinctive psychosocial issues, including concerns about fertility and child rearing, body image and sexual dysfunction, and the economic impact of disease and treatment.[7–10]

The Young Survival Coalition (YSC) is a patient advocacy organization in the United States focused on highlighting the unique challenges of YWBC. It is a strategic goal of YSC to increase the amount of quality research on YWBC, to define the greatest research needs for YWBC, and to advocate these gaps to clinicians and researchers. YSC hopes that researchers worldwide will use its Research Agenda as a guide in formulating their future research projects and that granting agencies will use it to inform their future funding decisions. In 2001, YSC convened the Medical Research Symposium on Young Women and Breast Cancer, consisting of seven researchers in the New York City area from all of the major

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Table 1. Young Survival Coalition Research Think Tank Participants, By Working Group

Name	*Gender*	*Institution at the time of the meeting*	*Specialty*
Risk factors			
Deb Aruta (Chair)	Female	Advocate	
W. Archie Bleyer, MD[a]	Male	Oregon Health & Science University	Pediatric and young adult medical oncologist
Diana Chingos	Female	Advocate	
Brian J. Czerniecki, MD, PhD	Male	University of Pennsylvania	Surgical oncologist
Jennifer Ivanovich, MS, MBA	Female	Washington University	Genetic counselor
Rebecca H. Johnson, MD	Female	Seattle Children's Hospital	Pediatric and young adult medical oncologist
Irma H. Russo, MD	Female	Fox Chase Cancer Center	Pathologist
Jose Russo, MD[a]	Male	Fox Chase Cancer Center	Pathologist
Nancy Sauers	Female	Advocate	
Medha Sutliff	Female	Advocate	
Treatment			
Kimberly Hagerich (chair)	Female	Advocate	
Leslie Hammersmith	Female	Advocate	
Hannah Klein Connolly	Female	Advocate	
Tracy Leduc	Female	Advocate	
Debra Madden	Female	Advocate	
Ann H. Partridge, MD, MPH (Research Think Tank cochair)[a]	Female	Dana-Farber Cancer Institute	Medical oncologist
Alexander J. Swistel, MD[a]	Male	Weill Cornell Medical Center	Surgical oncologist
Elizabeth Wohl	Female	Advocate	
Fertility			
Anna Cluxton (chair)	Female	Advocate	
Linda Dias	Female	Advocate	
Francesca E. Duncan, PhD	Female	Northwestern University	Female reproductive health researcher
Jacqueline N. Gutmann, MD	Female	Jefferson University Hospital	Reproductive endocrinologist
Kutluk H. Oktay, MD[a]	Male	New York Medical College	Reproductive endocrinologist
Malcolm C. Pike, PhD	Male	Memorial Sloan Kettering Cancer Center	Epidemiologist
Penina Seidman	Female	Advocate	
Kristin Smith	Female	Advocate	
H. Irene Su, MD	Female	University of California, San Diego	Reproductive endocrinologist
Pregnancy-Associated Breast Cancer			
Courtney Preusse (chair)	Female	Advocate	
Carole Baas, PhD	Female	Advocate	
Virginia F. Borges, MD	Female	University of Colorado, Denver	Medical oncologist
Diana Chingos	Female	Advocate	
V.K. Gadi, MD, PhD	Male	University of Washington	Medical oncologist
Susan M. Love, MD[a]	Female	Dr. Susan Love Research Foundation	Surgical oncologist
Irma H. Russo, MD	Female	Fox Chase Cancer Center	Pathologist
Jose Russo, MD[a]	Male	Fox Chase Cancer Center	Pathologist
Julia Tiernan, MD	Female	Advocate	
Melissa A. Troester, PhD	Female	University of North Carolina Lineberger Comprehensive Cancer Center	Epidemiologist
Quality of Life and Survivorship			
Ann Marie Potter (chair)	Female	Advocate	
Shari B. Goldfarb, MD	Female	Memorial Sloan Kettering Cancer Center	Medical oncologist
Julie R. Gralow, MD	Female	University of Washington	Medical oncologist
Sue Ann Mark	Female	Advocate	
Nikki Oliver	Female	Advocate	

(*continued*)

Table 1. (Continued)

Name	*Gender*	*Institution at the time of the meeting*	*Specialty*
Jean Rowe	Female	Advocate	
Jeannine Salamone	Female	Advocate	
Lillie D. Shockney, RN, MAS[a]	Female	Johns Hopkins Breast Center	Breast cancer nurse navigator
Eric P. Winer, MD[a]	Male	Dana-Farber Cancer Institute	Medical oncologist
Metastasis			
Debbie Molis (chair)	Female	Advocate	
Kim Casamassima	Female	Advocate	
Silvia C. Formenti, MD	Female	New York University Langone Medical Center	Radiation oncologist
Stacy Gagas	Female	Advocate	
Generosa Grana, MD	Female	Cooper University Hospital	Medical oncologist
Brunilde M. Gril, PhD	Female	National Cancer Institute	Molecular pharmacologist
Roz Kleban, LCSW[a]	Female	Memorial Sloan Kettering Cancer Center	Oncology social worker and counselor
Larry Norton, MD[a]	Male	Memorial Sloan Kettering Cancer Center	Medical oncologist
Joy Simha (YSC cofounder; Research Think Tank cochair)	Female	Advocate	
Patricia S. Steeg, PhD	Female	National Cancer Institute	Metastasis researcher
Linda T. Vahdat, MD	Female	Weill Cornell Medical Center	Medical oncologist

Note. Some participants were involved in more than one working group.
[a]YSC Medical Advisory Board Member.
YSC, Young Survival Coalition.

cancer disciplines. The resulting white paper set an initial YSC agenda for research involving YWBC.[11]

In 2012, YSC decided to update its research agenda to keep pace with the substantial research progress on YWBC that had taken place over the past decade. In February 2013, YSC convened a panel of experts at a Research Think Tank Meeting aimed at updating and refining priorities for research on YWBC. YSC reviewed its prior research agenda and surveyed the current research landscape. In order to focus the efforts of the meeting participants, YSC leadership identified six broad categories for investigation, each assigned to one working group. These categories represented the areas where YSC believed the biggest research gaps currently existed and which, if answered, could have the most significant impact on young women with breast cancer:

- Risk factors
- Treatment
- Fertility
- Pregnancy-associated breast cancer
- Quality of life and survivorship
- Metastasis

This article summarizes the discussions of the Research Think Tank participants and highlights topics that were proposed to be included in a comprehensive agenda for ongoing research. Selected high priority issues were included in YSC's final Research Agenda, which was made public on May 27, 2014 (www.youngsurvival.org/research-agenda).

Research Think Tank Background

The goal of the Research Think Tank Meeting was to identify timely research questions that had a significant potential to improve quantity and quality of life for YWBC. Prior to the meeting, YSC assembled working groups of healthcare professionals, researchers, and advocates to focus on the six key areas listed above. An experienced survivor research advocate led and coordinated each working group. In order to contain travel expenses, participants were recruited from the United States and Canada.

Participants were selected by YSC staff and its board of directors, who invited medical professionals and researchers with expertise in breast cancer in young women, a stated interest in one or more of the working group topics, and a willingness to work closely with advocates. Some invitees who could not participate recommended colleagues with similar professional interests to participate in their stead. YSC also invited selected members of its Medical Advisory Board. All invited advocates had specific training and/or experience in research, research advocacy, grant review, or participation in research grants, and were willing to collaborate closely with medical professionals and researchers. In creating each of the six working groups, YSC included medical specialists in different disciplines, along with researchers and advocates with interest and expertise in the topic area. The target size for each working group was seven people, although the final number in each group varied from 8 to 11. The full list of Research Think Tank participants by working group can be found in Table 1.

The Research Think Tank process was composed of three phases: information gathering; an in-person meeting; and the development, publication, and dissemination of the Research Agenda. In Phase I (Fall 2012), each working group met online utilizing Basecamp software and by conference calls over a 3-month period to conduct a literature review of their assigned topic and draft a summary for presentation to the full group. The working groups were instructed to summarize the current national and international knowledge gaps pertinent to YWBC and then create a list of high priority research questions for use in future studies. These detailed reports

were distributed to the entire group of Research Think Tank participants in January 2013.

During Phase II (February 2013), the participants attended the two-day in-person Research Think Tank Meeting facilitated by Leapfrog Consulting. This meeting's goal was for the Research Think Tank as a whole to review the summarized literature and refine the suggested research priorities through small and large group discussions. First, each working group presented its literature review and suggested research questions to the full group. YSC then conducted a round-robin exercise during which each participant rotated through breakout rooms for three working groups other than his or her own. One to two representatives of each working group remained in their own working group's breakout room to receive and record individual feedback from others. In each breakout room, the draft research questions were discussed and the participants from other working groups were asked to position each question on a graph to reflect its potential impact on the quantity of life (x-axis) and quality of life (y-axis) for YWBC. Each working group then reconvened, reviewed feedback from the breakout sessions, and defined their working group's three top research priorities. In the concluding session, each working group presented its final recommended research priorities to the entire Research Think Tank. The entire two-day meeting was audio-recorded.

In Phase III (February 2013 to July 2014), YSC analyzed the compiled Research Think Tank Meeting materials in order to create its final research agenda. Members of the YSC staff and its board of directors reviewed the Phase I reports and summary documents, and the audio transcripts and outputs from Phase II. Where clarification or additional information was needed, YSC staff contacted the chairs of the applicable working group. After consulting with the working group chairs to ensure that their working groups' priorities were accurately represented, YSC staff wrote an initial draft of its Research Agenda. YSC circulated multiple drafts of the Research Agenda to all of the Research Think Tank participants for their review and input. YSC made the final decision on the content of the Research Agenda, which was then made public on May 27, 2014 (www.youngsurvival.org/research-agenda). For a variety of reasons, there are some differences between the research priorities recommended at the Phase II Research Think Tank Meeting and the final Research Agenda published by YSC. For example, the work of the fertility and pregnancy-associated breast cancer working groups was combined in the final Research Agenda, a greater number of research priorities were included in the treatment section given the breadth of issues therein, and YSC also reworded or eliminated some priorities as announced at the Phase II Research Think Tank Meeting. However, the participants felt that all priorities highlighted at the Research Think Tank Meeting have merit and warrant presentation. In this article, we recount the discussions and actions at the Phase II Research Think Tank Meeting. This manuscript concludes Phase III of the Research Think Tank process.

Key Issues Highlighted by the Research Think Tank Working Groups

Several common cross-cutting themes emerged during the discussions of the six working groups during Phases I and II. Researchers and advocates proposed two specific modifications in data collection for YWBC. First, they advocated for a large-scale data registry focused on young women with breast cancer that includes clinical data on outcomes and side effect profiles associated with specific treatments, information on specific sites and natural history of metastases, genomic profiling of primary tumor and metastatic sites, and an increased focus on fertility and pregnancy following breast cancer treatment. Second, researchers stressed the need for the collection of clinical trial data by chronological age and not just menopausal status. In addition, clinicians noted that while the paradigm of current treatment suggests that young women receive more aggressive treatment solely based on age, there is scant data regarding whether this practice is warranted and/or beneficial.[12] The key findings and recommendations from each of the six working groups are summarized below.

Risk factors

There are a number of well-defined risk factors for breast cancer, including genetic predisposition, mammographic density, hormonal and reproductive factors, and lifestyle factors. To date, few studies have specifically focused on risk factors for early-onset breast cancer, although data suggest that certain risk factors have a greater or different impact on YWBC compared to older women.[13] Several studies have highlighted that risk factors for triple-negative breast cancer (negative for hormone epidermal growth factor receptor 2 [HER-2], estrogen receptors [ER], and progesterone receptors [PR], which is more common in young women) are different from those for hormone receptor-positive disease.[14–17] Additional research is needed to clarify the risk factors for early-onset breast cancer and to delineate risk factors for aggressive disease and death in YWBC. The latter goal is especially important because YWBC are more likely to manifest aggressive biological subtypes and have a higher and increasing frequency of metastatic disease at diagnosis compared to older women.[5,18–21] Future research should also address whether risk factors vary within subtypes of breast cancer in young women, such as ER-negative versus ER-positive tumors.

While several large studies have identified modifiable risk factors for breast cancer, even studies that include premenopausal women enroll few participants under the age of 40, resulting in a lack of information on lifestyle risk factors for YWBC. For example, obesity is a well-established risk factor for postmenopausal breast cancer,[22] but most evidence suggests that obesity does not increase the risk of breast cancer in premenopausal women.[23] However, recent data indicates that obesity is a risk factor for death from breast cancer[24,25] as well as for advanced disease at presentation[26,27] in young women. In one small study, the combination of obesity, sedentary lifestyle, and high caloric intake predicted early-onset breast cancer,[28] highlighting the potential combined effects of lifestyle factors.

Understanding the relationship between age at which a toxic exposure occurs and subsequent cancer risk is of critical importance,[29] as early life exposures may impact the development of breast cancer.[30] Some examples of exposures that may affect breast cancer risk include chemical exposures (such as bisphenol-A [BPA]),[31–33] secondhand tobacco exposure,[34] and radiation.[35–37] In animal models, the breast is

most susceptible to certain environmental toxins during early development and puberty.[33,38–40]

The interval between menarche and first pregnancy represents a window of particular sensitivity to toxic exposures for breast tissue. Some such exposures are modifiable based on lifestyle choices. Alcohol use and binge drinking, for example, are common in teens and young women in the United States. Alcohol use increases circulating estrogens, stimulates proliferation of mammary epithelial cells, and promotes proliferative benign breast disease (a risk factor for invasive breast cancer). Recent alcohol use increases breast cancer risk in a dose-dependent manner for women of all age groups, and the effect may be greater between menarche and first pregnancy. Further study is needed to examine how the relationship between alcohol use in young women and age of first pregnancy may modify breast cancer risk.[41]

The trend toward later childbearing in developed countries increases the potential for toxic exposures prior to the first pregnancy.[41] Breast cancer incidence increases substantially during the fourth decade of life.[2] Delayed childbearing boosts the likelihood that a woman diagnosed with breast cancer in her 30s and early 40s has given birth within the past 5 years. At least one study suggests that women in this age group are at higher risk of metastases, and therefore poor outcomes.[42]

Future research should include investigation of toxic exposures *in utero* and during early childhood, puberty, and young adulthood. A more detailed understanding of how these exposures affect the normal developing breast is critical to the understanding of YWBC. Retrospective analyses on these topics utilizing existing clinical databases should be prioritized and prospective studies should be initiated.

The role of genetics and epigenetics in early-onset breast cancer was also discussed, with a great divide between those who thought it was a crucial area of research and others who believed it was too broad to study and had already been examined. Ultimately, the Risk Factor Working Group advocated further research on genetic and epigenetic factors in YWBC as a priority, as outlined in YSC's final Research Agenda.

Treatment

Research regarding treatment for young women with breast cancer should focus on two unanswered questions as they relate to quality of life and impact on mortality: (1) determining whether oncologists treat YWBC more aggressively (i.e., with exactly the same disease characteristics, are YWBC more likely than older women to receive chemotherapy or radiation therapy?) and whether this impacts mortality and (2) elucidating whether early-onset breast cancer warrants more aggressive treatment after adjusting for subtype, grade, and stage. For example, studies show that young women are more likely to choose more extensive surgery (i.e., mastectomy vs. lumpectomy or bilateral mastectomy vs. mastectomy).[43–45] However, despite higher local recurrence rates,[46,47] data suggest similar long-term outcomes for young women who undergo breast conservation compared to those who chose more extensive surgery.[48–50] It is therefore important to confirm whether a more aggressive surgical approach is warranted. Data from existing registries could be mined to compare lumpectomy versus mastectomy outcomes, determine whether local recurrence in YWBC[51,52] impacts overall survival, and determine the long-term morbidity and mortality for each surgical option.

The utility of neoadjuvant chemotherapy is a key issue in the treatment of YWBC. Recent data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) and from a German meta-analysis suggest that neoadjuvant chemotherapy is more effective in producing a pathologic complete response in younger women.[53,54] One possible explanation for this finding is that breast tumors in young women have intrinsic biological features different from those currently known to drive treatment response; alternatively, young women may simply have a higher proportion of the more chemoresponsive tumor subtypes. It is likely that there are tumor factors associated with young age that are as yet unidentified. Future research—with careful analysis of age at diagnosis, stage, and disease subtype—is required to determine whether all young women (or just some subsets of YWBC) have more chemosensitive disease or whether there is variation by tumor subtype.

Some research suggests that differences in treatment effects in YWBC compared to older women may relate to the tumor microenvironment. For example, higher mammographic density is a known risk factor for breast cancer,[55] though the mechanism for this association is not clear. One hypothesis of the Treatment Working Group was that density on a mammogram may be a measure of the amount of ''active'' breast tissue, and therefore women with denser breasts have more ''at risk'' tissue. Mammographic density may also impact local and regional recurrence risk.[56] Differences in the tumor microenvironment (including the density of breast tissue) may affect local delivery of chemotherapy, and thus potentially modulate the efficacy of treatment. Research on the relationship between mammographic density and the expression of genes and proteins in breast tissue could provide clues to the pathogenesis of YWBC.

Particularly in YWBC, there is great debate over the ''seed'' versus the ''soil''—that is, is it the breast cancer itself in young women that is aggressive or is it the surrounding microenvironment with greater density, more hormones, etc., that causes the breast cancer to act more aggressively? The tumor microenvironment is a dynamic mix of native immune and stromal cells in close proximity to cancer cells. It may modulate both breast cancer risk and outcome by affecting the likelihood of tumor formation, rate of tumor growth, and potential for metastatic spread, and may account for age-related differences in breast cancer pathogenesis and outcome.[57] More research is needed to resolve the ''seed'' versus ''soil'' debate. If the ''soil'' or microenvironment is implicated, treatments that target the microenvironment may be especially effective in YWBC.

Quality of life and survivorship

YWBC may be at higher risk than older patients for side effects and long-term toxicities of therapy, due to both a longer expected post-treatment life span and to more aggressive therapy.[58] Specific late effects of chemotherapy pertinent to YWBC include premature menopause, cardiotoxicity, pulmonary toxicity, and second malignant neoplasms. Research on long-term sequelae of cancer treatment in YWBC should investigate both the prevalence and impact of these effects, with the goal of clarifying the balance

between appropriately aggressive treatment that improves outcome and overtreatment that adds toxicity without survival benefit. Such information can also be used to inform recommendations for the prevention, screening, and management of late effects. Establishment of clinical registries focused on long-term survivors of early-onset breast cancer will provide critical longitudinal data on late effects of cancer therapy.

The short- and long-term psychosocial effects of a breast cancer diagnosis vary according to stage of life, with apparently greater psychosocial impact in young women.[59] In addition to the potential for depression and anxiety related to fear of recurrence, YWBC face a distinctive pattern of age-related challenges, such as establishing and/or maintaining a career; child rearing; sexuality and body image; socioeconomic concerns; and relationships with partners, friends, and family members.[60] Future research to clarify these unique concerns should focus on describing long-term psychosocial outcomes, implementing age-appropriate psychosocial screening during and after cancer therapy, and designing and validating interventions to prevent and manage negative psychosocial outcomes.

Sex and intimacy are important aspects of quality of life for all breast cancer survivors but can pose particular challenges for YWBC. Women who undergo either temporary or permanent menopause from treatment may experience vaginal dryness and pain with intercourse, which can be more severe in young women due to an abrupt and rapid decrease in estrogen (i.e., from prophylactic oophorectomy, chemotherapy, or hormonal therapy).[61] The use and safety of androgens and estrogens for treatment of sexual dysfunction, even in women with hormone receptor-negative tumors, is not well studied, and should be addressed in future research as a major quality of life concern for YWBC.

The American College of Surgeons' Commission on Cancer, in conjunction with the advocacy community, has recently developed new patient-centered standards (available at: www.facs.org/cancer/coc/programstandards2012.pdf) to better enable cancer patients to become effective partners in their own care. The new standards include a mandate for psychosocial distress screening for all patients by the second visit, and the provision of an individualized survivorship care plan outlining potential long-term toxicities and recommended screening. The Quality of Life and Survivorship Working Group highlighted the particular relevance of survivorship care plans for YWBC. They hypothesized that widespread use of these plans could mitigate the psychosocial challenges noted above. Future research in cancer survivorship should focus on assessing and comparing models of survivorship care in order to maximize the impact for YWBC.

Fertility

For YWBC, the potential for therapy-related premature ovarian failure and the safety of future pregnancies are vitally important.[55] The risk of infertility varies according to chemotherapy regimen, dose, and age at treatment, but current risk estimates are too broad to allow specific counseling for individual patients.[62] Several ongoing cohort studies will provide valuable data on outcomes, including fertility, in YWBC.[6,63,64] Ongoing clinical trials and future cohorts should track rates of infertility by age and treatment regimen and collect data on the safety of fertility preservation and post-therapy pregnancies for mother and child. One factor that complicates the collection of data on fertility after breast cancer is the relatively small number of patients in clinical trials who are diagnosed under the age of 35, leading to large gaps in data on fertility. There is also no standard definition of what constitutes infertility within treatment trials. Often, resumption of menstrual function is presumed to equate with the ability to conceive. This measure is a highly inaccurate surrogate, since women may be fertile before resumption of regular periods or may resume menstrual function but be unable to conceive. There is a need for a standardized and reproducible definition of fertility after cancer treatment.[62] Future studies should also define the most clinically relevant markers of ovarian reserve.

In retrospective analyses, pregnancy following breast cancer does not increase the risk of recurrence and may even have a protective effect.[65–68] However, it is not clear whether the timing of pregnancy affects outcome, particularly for patients who stop hormonal therapy in order to conceive. The current standard of care for premenopausal women with ER-positive breast cancer is 5–10 years of adjuvant tamoxifen.[69,70] For women who are approaching the end of their natural fertility, a 5–10 year delay in attempted conception may preclude a successful pregnancy. Providers often recommend a minimum of 2–3 years of tamoxifen, based on the incrementally greater benefit of tamoxifen in early years of treatment and on the higher risk of recurrence in the first several years after cancer therapy.[62] Research on the timing and safety of stopping hormonal therapy early or interrupting it temporarily will allow more accurate counseling about post-cancer pregnancy for YWBC.

Current literature suggests both that young women are not adequately counseled about their options for future fertility prior to starting cancer treatment and that the majority of YWBC do not seek pregnancy following breast cancer treatment.[64,71,72] Embryo cryopreservation is the most commonly used assisted reproductive technology, but the lack of a defined life partner, lack of insurance coverage for the procedure, and the need to use drugs for ovarian stimulation are all potential barriers to this technique; oocyte cryopreservation has recently been validated as an effective method for fertility preservation in women who have not yet chosen a life partner.[73] Future studies should continue to develop novel assisted reproductive technologies and to test their safety and effectiveness in YWBC.

The Fertility Working Group also recommended several advocacy initiatives as priorities for the near future: to encourage pharmaceutical companies to collect data on the fertility effects of their drugs, including post-marketing surveillance data; to promote fertility preservation counseling by educating surgeons about the importance of referral to a fertility specialist at diagnosis; and for cancer and fertility advocates to promote insurance coverage of fertility preservation prior to beginning cancer treatment, an initiative that was begun several years ago by the LIVESTRONG nonprofit.

Pregnancy-associated breast cancer

In addition to questions of fertility, there are a number of issues surrounding pregnancy-associated breast cancer (PABC) that are pertinent to YWBC. It is estimated that

invasive breast cancer occurs during 1 in 3000 pregnancies.[74,75] Pregnancy causes a transient increase in breast cancer risk followed by a long-term protective effect.[76] Complicating this area of research is the lack of a consistent definition of PABC. Some studies define it as a breast cancer that occurs during pregnancy and up to one year postpartum,[77] while others define it as solely a postpartum diagnosis that can extend 5–10 years after childbirth.[58,59] The Pregnancy-Associated Breast Cancer Working Group emphasized the need for researchers to examine PABC as two distinct and separate subtypes: breast cancer diagnosed during pregnancy and breast cancer diagnosed postpartum. PABC diagnosed during the postpartum period has been found to have worse outcomes, with increasing risk of distant recurrence and death.[42,78] Recent data suggests that a diagnosis of breast cancer up to five or even 10 years after pregnancy may be associated with a poorer prognosis.[42] The Pregnancy-Associated Breast Cancer Working Group discussed research priorities relevant to YWBC that occurs both during and after pregnancy.

PABC has a unique pattern of risk factors and prognostic indicators[78,79] and may affect up to 40,000 young women annually.[78] Future research should examine how known risk factors for breast cancer such as breast-feeding, *BRCA* mutation status, and race/ethnicity impact PABC, and whether specific biomarkers or tumor characteristics define PABC. The biologic basis of PABC remains largely undefined. One compelling hypothesis is that there is a window of susceptibility for hormonal or toxic exposures to confer breast cancer risk. Several candidate windows of susceptibility include early life, puberty/mammary development, pregnancy, lactation and breast involution, and the postpartum period. Future observational studies or interventions that focus on these specific time periods will lead to increased understanding about both PABC and breast cancer biology in general.

Metastasis

YWBC are more likely to present with advanced disease at diagnosis than are older women. One study showed that 20% of women less than 35 years of age presenting with breast cancer had metastatic disease at diagnosis, compared to 3% of older women.[80] However, not all young women with breast cancer will go on to develop metastatic disease. A self-detected breast abnormality is the initial symptom in 80% of women diagnosed at age 40 or younger.[81] While this high percentage likely relates to the fact that women under 40 do not undergo routine screening mammography, it is also possible that young women may more frequently develop rapidly growing tumors that become palpable and attract notice. There is evidence to suggest that breast cancer in young women is a more intrinsically aggressive disease.[2] As with all cancer, research is needed to predict which patients are at highest risk for development of metastatic disease and should receive more aggressive therapy aimed at improving outcome. Conversely, patients at lower risk for disease progression could be potentially spared the toxicity of adjuvant treatment. Future studies should investigate risk factors for advanced disease at diagnosis and for death from breast cancer. Areas of inquiry should include lifestyle patterns, intrinsic risk factors, and studies of the tumor microenvironment. While initial investigations could be retrospective analyses of existing clinical trial data, data collected prospectively would be more meaningful. Traditionally, YWBC comprise only a small fraction of those enrolled on clinical trials; thus, these analyses would likely require pooling of data from multiple trials to provide definitive information. A clinical registry for young women with metastatic breast cancer could look at the tumor subtypes, therapy delivered, pattern of metastatic spread, and length of survival. Associated biospecimens could be used to analyze biological changes in the tumor between initial diagnosis and metastasis.

A clearer understanding of the progression from early stage disease to metastatic disease is an important goal. Emerging data suggest that the progression-free interval may be shorter in young women than in older women, particularly in patients with hormone receptor-negative disease.[82,83] Future studies of both the molecular biology and the microenvironment of breast tumors in young women need to elucidate the mechanisms of tumor metastasis and inform the development of therapies targeting the pathways of progression.

An additional area of interest relevant to YWBC is tumor dormancy. Compared to older patients, patients who are younger at diagnosis have a longer projected lifespan during which they risk distant recurrence. A greater understanding of which tumors stay dormant for many years and why late progression occurs would be aided by a registry of long-term survivors of early-onset breast cancer and could lead to the development of therapies aimed at long-term control of cancer.[84]

The Metastasis Working Group also spent time discussing the promise of anti-tumor vaccines and whether they could be used to prevent breast cancer metastasis. It was recommended that some entity should convene a summit to clarify research priorities and stimulate research collaboration on this topic. In addition, a systematic review of the vaccine literature was suggested. Overall, the Metastasis Working Group believed vaccines to be an important area of future study in metastatic breast cancer.

A significantly understudied topic is the psychosocial effect of a diagnosis of metastatic disease in YWBC, their families, and their support persons. For YWBC, issues related to child rearing, economic burdens, and family relationships are specific examples of psychosocial aspects of metastatic breast cancer that may be particularly challenging. The Metastasis Working Group felt that research aimed at understanding psychosocial needs and developing interventions for this population should be prioritized.

Research Think Tank Meeting Outcomes and Next Steps

The YSC Research Think Tank Meeting successfully convened key stakeholders to review the current body of research in YWBC and to prioritize issues for future research. Several common themes emerged from this work. First, because YWBC—particularly very young women (< 35 years of age)—are underrepresented in current clinical trials, robust data on specific biologic, clinical, and psychosocial aspects of YWBC are currently lacking. Recent data indicates that few young adults with cancer of any type are offered enrollment on clinical trials.[85] Further research is needed to elucidate the reasons for this age group's poor clinical trial participation in order to improve accrual in future studies.[86] An increased awareness of the unique issues faced by YWBC is crucial to improving psychosocial interventions for these

patients and their support persons. For many of the research areas highlighted, it was felt that while retrospective analyses focusing on young women would be helpful, they might provide insufficient information to draw strong conclusions, and that the creation of a targeted prospective registry of YWBC that collected demographic and risk factor information, treatment records, biospecimens, psychosocial data, and long-term outcomes would provide more valuable data on this understudied population.

This summary of the key recommendations of the YSC's Research Think Tank participants defined research priorities specific to YWBC and suggests areas of research inquiry that will improve the quality and quantity of life for YWBC. YSC's hope is that researchers will utilize this information to guide the design of future research projects, and that granting agencies will use it to define funding priorities. While YSC does not fund research studies, it can assist researchers investigating questions on YSC's research agenda and can facilitate collaborations. Many of the priorities outlined here will require large studies, which will be best performed by multinational consortiums of investigators with common goals and consistent definitions of variables of interest that share data and biospecimens.

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