



BRIDGING THE GAPS: CURRENT ISSUES IN MEDICAL RESEARCH ON

YOUNG WOMEN & BREAST CANCER

A BASIS FOR ADVOCACY & ACTION

The following pages outline and summarize a discussion held in 2001 between seven members of the medical and research community – all of whom serve young women diagnosed with breast cancer -- on the state of affairs at that time in breast cancer research for young women.

This White Paper is a snapshot in time – over the past four years, there have been many advances in breast cancer treatment and research. The YSC is planning an educational symposium in 2007 that will again address the issues presented below. The YSC looks forward to our continued collaboration with leading researchers, scientists, and practitioners to map out the landscape of breast cancer research as it relates to young women and answer those questions that remain.

If you have any questions about this White Paper, please contact info@youngsurvival.org.



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1. Introduction

The Young Survival Coalition (YSC) is the only international, nonprofit network of breast cancer survivors and supporters solely dedicated to the critical concerns and issues unique to young women affected by breast cancer. Through action, advocacy, and awareness, the YSC seeks to educate the medical, research, breast cancer, and legislative communities to study breast cancer in women 40 and under. The YSC also serves as a resource for young women affected by the disease.

YSC's core purpose is to improve the quality and quantity of life for young women affected by breast cancer, and our envisioned future is to be the foremost influence on the issues related to breast cancer in women 40 and under.

It is a strategic goal to increase the amount of quality research on young women, and as such, the YSC is working to define the greatest research needs for younger women with breast cancer as a population and to advocate these needs to doctors and researchers.

The YSC-organized **Medical Research Symposium on Young Women and Breast Cancer** was held at the American Cancer Society's Bronx/New York City Division offices in New York City on September 25th, 2001. Leading researchers, scientists, and practitioners representing a varied group of specialties assembled to address the most critical issues regarding the state of knowledge and research on breast cancer within the younger population. Each speaker surveyed the current state of research on this population from the vantage point of his or her respective specialty area: Participants addressed the existing studies, defined the major unanswered research questions, and identified the related research priorities needed to develop more definitive prevention and treatment strategies for young women with or at risk of developing breast cancer.

As the organizer, the YSC compiled the comments provided by each clinical participant and used them to form the foundation of this White Paper. All participants have reviewed their respective sections for content; however, the YSC has exercised editorial rights in summarizing results and defining research priorities based upon our vantage point and position as the global voice of young women with breast cancer. The YSC wishes to thank all participants for volunteering their time and expertise in this effort - the first Symposium to focus on breast cancer in younger women in over ten years.

2. Background: Breast Cancer Today

Breast cancer is the most common cancer in women in the United States and is second only to lung cancer as the leading cause of cancer-related death in this country. In the year 2003, an estimated 211,200 new cases of breast cancer will be diagnosed [1]. Among women of all ages, the lifetime risk of developing breast cancer is 13.4% (1 in 7); the lifetime risk of dying from breast cancer is 3.6% (1 in 28) [2].

Breast cancer remains a serious health concern in the US as well as in other countries. According to the National Cancer Institute [3], the incidence of breast cancer has been rising for the past two decades. Much of the increase in incidence over the past 15 years is attributed to education and screening efforts and initiatives within the general population, which together have resulted in the widespread use of mammographic

screening in women over 40 years of age and the detection of breast cancer at earlier stages. As noted by the NCI, however, screening alone does not seem to explain this increase fully. Incidence in women 40 and under, however, has remained stable.

Data on breast cancer mortality rates over the last several decades vary; some data show a leveling of rates, while others demonstrate decreased rates. According to the American Cancer Society's Cancer Facts & Figures 2003, breast cancer mortality rates in the U.S. declined significantly during 1992-1998.

Progress continues to be made in every area of medicine involved in the prevention, diagnosis, and treatment of breast cancer, and therapeutic strategies involving multidisciplinary treatment approaches that integrate surgery, chemotherapy, and radiation therapy are becoming increasingly available. Furthermore, continued research and advances in the areas of chemoprevention, breast imaging, breast cancer staging, and the genetics of hereditary breast cancer will ultimately benefit all women at risk for or faced with a diagnosis of breast cancer.

3. Early Onset Breast Cancer: Key aspects of breast cancer in women under 40 years of age.

YSC estimates that there are nearly 250,000 women in the United States under the age of 40 currently living with breast cancer.* Although there is cause for optimism regarding advances in the prevention, diagnosis, and treatment of breast cancer among the general population, the situation for young women remains less certain and is complicated by a series of special concerns and questions, coupled with a dearth of population-specific research data.

Among women aged 20 to 39 years, breast cancer is the number one cause of cancer death, accounting for approximately 25% of all cancers deaths for women in this age group [5]. Breast cancers that are diagnosed in younger women are generally more aggressive and result in lower survival rates [3, 4].

Coping with a breast cancer diagnosis, choosing an appropriate treatment strategy, and addressing issues related to the longer-term challenges of breast cancer survivorship all involve obstacles and choices for young women beyond those required of postmenopausal women. Specifically, issues around fertility and childbearing, sexuality and intimacy, the possibility of early menopause following diagnosis and treatment, and issues of long term survival are unique to the younger population of breast cancer patients, many of whom are also coping with more advanced cancers, more aggressive disease, and poorer prognoses.

Differences in the biological characteristics of breast cancer in young women are not fully defined, and debate remains as to the extent of these differences. Such differences may be associated with the increased prevalence of hereditary and genetically predisposed breast cancers among younger women. Furthermore, delayed diagnosis is recognized to be a potential contributing factor for more advanced disease at presentation and poorer long-term prognosis and is an issue of particular importance for young women with or at risk for developing breast cancer.

* Extrapolated from U.S. Census Data.

Research focused on the population of young women at high risk for developing breast cancer and those diagnosed at a young age is absolutely critical if this population is to receive maximum benefit from the advances in prevention, research, and treatment that their postmenopausal counterparts are beginning to receive. Yet most breast cancer studies focus on women over the age of 45, often excluding younger women altogether based on the perception of inadequate numbers in this population.

What follows is intended to provide a closer assessment of the state of current knowledge on breast cancer in young women and a basis for advocacy and action and more research.

3. A. Epidemiological Aspects: Incidence of Early Onset Breast Cancer

Overview presented by: Ruby Senie, PhD, Professor of Clinical Public Health, Mailman School of Public Health, Columbia University, NY, NY

What we know today: Epidemiology

In the United States today, young women between the ages of 30 and 39 have a 1 in 229 (*1 in 251*) probability of developing invasive breast cancer over the next 10 years [4]. For the year 2001 (*2003*), an estimated 192,200 (*211,300*) new cases of invasive breast cancer and 47,100 (*55,700*) new cases of in situ breast cancer were diagnosed in women in the US; an estimated 5% of these cases were diagnosed in women aged 39 or younger, and an estimated 19% (*16.8%*) were in women aged 40 to 49 [6].[†] Data from the NCI-supported SEER (Surveillance, Epidemiology, and End Results) database on incidence of invasive breast cancer over a 25-year period (1973-1998) among African-American and white American women aged 50 and under show an overall lower incidence of invasive breast cancer among young African-American women than among their white counterparts, yet a significantly higher mortality rate among young African-American women diagnosed with invasive breast cancer over the same time period than among their white counterparts. In general, among women aged 50 and under in the US, incidence rates of breast cancer have shown a decline, particularly in the years since 1986; however, from 1990-1998, mortality rates among this same group showed a strong upward trend [7].

Genetically disposed risk of breast cancer

Among the factors recognized as playing a role in breast cancer in young women, family history and genetic factors are considered to be the primary risk factors. A recent population-based study from Sweden [8] looked at genetic influence in breast cancer patients aged 40 and younger at diagnosis. This study found that 48% of patients had a family history of breast and ovarian cancer, while 9% carried a predisposing genetic mutation (7%, BRCA1; 2%, BRCA2). This study also found that younger age at

[†] 2003 statistics in italics.

diagnosis was associated with an increased likelihood of harboring a BRCA1 or BRCA2 mutation. ‡

Endocrine and reproductive factors

Endocrine and reproductive factors also play an important role in influencing breast cancer risk in younger women. Some studies have shown an increased breast cancer risk in women who have used oral contraceptives for more than 10 years; women who are older at the birth of their first child; and, women who are nulliparous. Research also indicates that breast cancer risk is increased for several years after childbirth, which is thought to be due to elevated exposure to hormonal (not just estrogenic) stimulation associated with fetal growth and development during pregnancy. Greater body mass index and obesity also are being investigated as possible associated risk factors. Unfortunately, there is still much to learn about the biologic mechanisms associated with the observed relationships between various aspects of reproduction & breast cancer.

Certain endocrine and reproductive factors appear to play a positive role in decreasing breast cancer risk. The assumed reasons for the protective effect of late menarche, early menopause, and irregular cycles are reduced duration of exposure to the cyclical hormones. Bilateral oophorectomy at young ages removes that exposure, although women are often then prescribed hormone replacement therapy. Some young women with BRCA mutations are removing ovaries, having prophylactic mastectomies, and then taking hormone replacement therapy. Early age at first birth does not appear to lower risk among women younger than 45.

Oral contraceptives (OCs)

Much remains unknown in terms of the role of oral contraceptives in breast cancer in young women. It is possible that OCs may act as initiators or promoters of malignancy. Furthermore, associated risk may vary by age at first use, age at last use, patterns and duration of use, total years of use, and the effect of interruptions for pregnancy. In addition, oral contraceptives have varied in their composition - therefore, earlier studies on available formulations may not have the same risks as currently available OCs.

Large, unbiased studies have been conducted (and some are still underway) to examine the relationship between breast cancer and OC use. Variations in age at use and the composition of OCs make ongoing studies necessary. Many studies have included specific brands and dosages, but correlations are difficult to determine when women have used many different OC brands or have received prescriptions from many different physicians. This variability makes it very difficult to confirm the specific OCs used. Records from HMOs or national data from countries with national health programs (including pharmacy records) provide the most reliable information to confirm self-reported brands. These records, however, are not entirely reliable in terms of describing actual OC use. Large unbiased studies of diverse populations, either cohort or case-control, may be required to address the varied patterns of use.

‡ A recent study at Mount Sinai School of Medicine demonstrated that despite the increased likelihood of BRCA1 & 2 mutations in young breast cancer survivors, young women were rarely referred to genetic counselors.

Recent research suggests that risk associated with OC, HRT use, or even pregnancy, is very likely to differ by genetic status. This includes not just BRCA mutations, but also genes that influence an individual woman's rate of metabolism of hormones. Given this discovery, it may prove difficult to answer these specific risk pattern questions unless we do larger, more expensive research studies.

Pregnancy

There is still much to learn with regard to the effects of pregnancy on mammary tissue and tumor growth rate, as well as the effects of pregnancy, pre-natal, and in utero exposures on breast cancer risk. Many new studies are assessing potential exposure to the female fetus. For example, levels of hormone exposure to the fetus can vary with maternal onset of pre-eclampsia, during twin pregnancies, or DES exposure. Although DES is no longer used, it has been associated with increased vaginal cancer and, potentially, increases in breast cancer among young women. Cohorts of DES-exposed women are still being followed. Other potential indicators of breast cancer risk include weight at birth and in-utero exposure.

Among older women (age>40), pregnancy is associated with long-term risk reduction because it induces differentiation of normal mammary stem cells. However, pregnancy may act as a promoter of previously transformed cells in women at genetic risk. In a 1999 study by Jernstrom et al [9], researchers found that, among carriers of a BRCA mutation, women who had a full pregnancy were significantly more likely to be diagnosed with breast cancer before age 40 than their nulliparous counterparts. Furthermore, it is thought that pregnancy may stimulate initiated cells by inducing increased cell proliferation and an increase in biologic aging of breast tissue.

Recentness of pregnancy also may adversely affect survival due to the influence of the hormonal milieu on tumor growth. Several studies have confirmed that breast cancer may be more aggressive, and therefore more lethal, when diagnosis follows pregnancy by less than 5 years. The hypothesis is that the tumor existed prior to pregnancy, but experienced enhanced development in the hormonal milieu of pregnancy.

Obesity

Although current research into the link between obesity and breast cancer risk suggests the association is confined to post-menopausal women [10, 11], several studies have noted that weight is a factor at all ages. A recent article indicated increased incidence of and increased mortality due to cancers of many sites, including breast. Risk was associated with greater weight at entry to the cohort, and weight cycling also has been shown to have an adverse effect on risk at all ages.

That said, obese younger women often have irregular menstrual cycles which may reduce exposure to endogenous estrogens thus lowering risk. However, obesity at young ages increases risk of heart disease and diabetes, so it is not a very positive means for overall health maintenance. Furthermore, obese younger women may fail to self palpate a breast tumor in their large breasts, thereby delaying detection until older ages when mammography is recommended.

Where we go from here: YSC Defines Priorities for research in Epidemiology

Considering that breast cancer usually presents as a "disease of aging" and occurrence before the age of 40 is relatively rare, greater research is needed to understand the confluence of factors that switch on a breast cancer 20, 30 or even 40 years prior to the typical onset of disease. Studies are needed to elucidate an understanding of the risk factors that may initiate the early onset of disease, including exposures at critical phases of development; particularly those that take place in-utero, early childhood, and puberty.

In general terms, much more research is required into the genetic basis for breast cancer and the best treatment and preventative strategies for genetically predisposed breast cancers. While much progress has been made over the past two decades, this area of breast cancer research is still relatively new. Research on the clinical features, treatment, and prognosis of genetically predisposed breast cancer compared with their non-genetically linked counterparts is necessary to address the immediate needs of young women (indeed, all women) diagnosed with a breast cancer with a genetic mutation. Additional research on future risks and the effectiveness of primary and secondary prevention strategies is also required and is the primary concern of all unaffected women from families in which a history of breast cancer (and other cancers) is present. Research is also needed to identify risk modifiers using serum markers/biomarkers for screening and early diagnosis among women with a genetic mutation, as well as the role of estrogen-metabolizing genes in modifying risk associated with reproductive and hormone-dependent factors. Lastly, as most of our current knowledge of hereditary breast cancer comes from the study of BRCA1- or BRCA2-associated disease, clinical studies addressing the pathology and natural history of breast cancer resulting from germline mutations in other genes is essential [12].

Another critical priority for research is the relationship between environmental factors and the onset and development of disease. There are some young breast cancer patients with BRCA mutations who have no family history of breast cancer; they may in fact be the first diagnosed in their families. Therefore, we recognize that genetic risk may likely be augmented by environmental exposures. The complexity of these environmental exposures poses a significant challenge to researchers, but it is our belief that there is much to gain from having a better understanding of this relationship.

Other areas of future research include: the risk of breast cancer associated with pregnancy, prenatal, and in utero exposures; the risk of breast cancer in relation to other chronic and/or infectious diseases, as well as autoimmune deficiencies; examining the possible contributors to risk and survival associated with biological differences, access to care, and appropriateness of treatment among different ethnic/racial groups; and, assessment of the risk associated with health behaviors and profile factors specifically in young women including BMI, oral contraceptive use, exercise, diet, breast feeding, early detection practices and alternative health practices.

3. B. Pathological Aspects: Is Breast Cancer a More Aggressive Disease in Younger Women?

Overview presented by: Ira Bleiweiss, MD, DABB Professor of Pathology, Medicine, Mount Sinai School of Medicine

What we know today: Pathology

Breast cancer in women under age 40 is often diagnosed at a more advanced stage than among older women for whom annual mammography is routine. Breast cancer in young women is also associated with biologically more aggressive cancers, a greater likelihood of nodal involvement, and higher rates of local and distant recurrence. However, it is unclear whether age is an independent prognostic factor or rather, as is commonly thought to be the case, more often associated with other negative predictive factors such as extensive intraductal component, possible nodal involvement, estrogen-receptor negative tumors, and HER-2/neu over-expression. However, there is little in the literature to address these differences specifically.

In a study published in 2000, Gajdos et al [13] looked at risk factors, clinical presentations, pathological findings, tumor characteristics, extent of disease, treatment, and outcomes in 101 women under age 36 with invasive breast cancer and compared these data with similar data on 631 women aged 36 and older treated during the same period of time. The authors found numerous differences between the two patient groups: young women more often presented with a palpable mass (versus a mammographic finding) than their older counterparts (87% vs. 55%, respectively); the average tumor size was greater in the younger group (2.0cm vs. 1.5cm, respectively); and the younger women presented with more advanced cancers (i.e., more cases involving metastasis to the lymph nodes among the younger women, with a greater number of involved lymph nodes per individual woman compared with numbers in older node-positive women in the study). The authors also reported a higher frequency of features of more aggressive disease in the women under age 36, along with higher rates of local and distant failure in this group despite aggressive treatment (usually mastectomy and chemotherapy). However, even though tumor size and lymph node involvement were associated with distant-disease failure rates, age was not shown to be an independent predictor of outcomes in young breast cancer patients and did not, on its own, indicate a poor prognosis. The authors determined that age was not an independent predictor of outcome.

In a study published in 1999 by VanZee et al [14] from Memorial Sloan-Kettering Cancer Center, the authors looked at the effects of age, postoperative breast irradiation, and other factors on local relapse-free survival after breast-conserving surgery for a series of 157 women with ductal carcinoma in situ treated between 1978 and 1990. The authors reported that older age was significantly associated with lower recurrence rates. No statistically significant correlation was shown between age and any histologic factor examined and, in a multivariate analysis, margin status alone was found to be statistically significant. Yet, in their conclusions, the authors do state that age is one of the factors that should be considered in assessing the risk of local recurrence after breast-conserving surgery for patients with DCIS.

Most recently, a study from Scotland [15] echoed the above findings. Researchers reviewed the histologic and clinical findings of breast carcinomas in 113 women younger than 35. Prognosis as a group remained poor; however, it appeared similar to that of women older than 35 when matched by stage. Thus, age alone seems to be noncontributory.

Pathologic characteristics specific to BRCA1- and BRCA2-mutation-associated carcinomas have not been described; however, most studies report medullary features in the majority of BRCA1-associated lesions. Invasive poorly differentiated duct carcinomas constitute most of the remaining (nonmedullary) cases, and the lesions as a group tend to be negative for estrogen-receptor protein, progesterone-receptor protein, and HER-2/neu oncoprotein overexpression [16-27]. In general, prognosis appears to be similar to that for patients with non-mutation-associated tumors with otherwise identical characteristics. The situation for BRCA2-mutation-associated tumors is far less clear, as the literature contains seemingly contradictory data with some studies reporting low histologic grade [24, 27] and excess tubulo-lobular characteristics [28], and others finding poorly differentiated carcinomas [26, 29]. All of these reports, especially the latter group, suffer from small numbers of cases; thus, further studies, especially of BRCA2 cases, are needed.

The pathologic characteristics of breast carcinomas in specific racial and ethnic groups have been similarly understudied. Although specific genetic abnormalities associated with non-Ashkenazi ethnic groups have yet to be described, such cohorts, especially of younger women, would logically constitute fertile ground for research into other genetic etiologies of breast cancer. For example, the reported pathologic characteristics of breast carcinomas in African-American women have been inconsistent, but show a general trend toward poorly differentiated lesions and an excess of medullary tumors. A recent comprehensive review [30] emphasized that the majority of prior studies suffer from small numbers of cases, lack of central pathologic review, no pathologic review at all, inconsistent application of pathologic criteria, prognostication based purely on tumor grade without consideration of tumor size or other features, or combinations of the above. Thus, further, more carefully planned and controlled studies are necessary, preferably correlating with genetic-testing results and familial pedigrees.

Where we go from here: YSC Defines Priorities for research in Pathology

Varying schools of thought abound regarding whether biological differences in younger women's breast tumors as compared to those of older women exist and, if so, are they responsible for more aggressive disease and higher mortality rates versus the situational component of more frequent delays in diagnosis common in the younger population - for whom screening tools do not readily exist - leading to more advanced cancers upon detection. Closure to this debate may be achieved via meta-analysis of research focused on relationships between delay in diagnoses and survival, as well as additional pathological and genetic profiling studies.

The potential exists to perform detailed biologic analyses using newer tools and techniques, including gene arrays and proteomics, to determine genetic differences in the assessment of early onset breast cancers. Of interest is the answer to whether there are patterns of expression that are unique to this population which might lead to better, more tailored treatments or preventive interventions.

The review of existing and/or development of new tissue banks containing samples of young women's cancerous breast tumors may provide additional clues to potential differences. Well-designed studies documenting pathologic characteristics of BRCA2-mutation-associated carcinomas, as well as those corresponding to yet-to-be-discovered

genes and their mutations, are now required, particularly in less-studied ethnic/racial populations.

3. C. Medical Treatment of Younger Women at Risk and with Breast Cancer

Overview presented by: George Raptis, MD, Head of the Clinical Breast Cancer Program for the Division of Medical Oncology, Mount Sinai School of Medicine, New York, NY.

What we know today: Risk Assessment

Risk assessment for breast cancer in young women continues to pose a number of important challenges. Although there are good models for breast cancer risk assessment currently in use, a model that meets the specific challenges of assessing risk in younger women is not available. Many researchers recognize that the Gail Model, the standard risk-assessment tool available to clinicians to screen for breast cancer, may not be as effective for assessment of women who fall at either end of the age spectrum -- namely, the very young and the elderly. Research on the limitations of this assessment model confirms its more limited efficacy in these populations.[§]

Recently, MacKarem et al [31] compared relative risk of the five cancer factors^{**} used in the Gail model to identify women at increased risk for breast cancer in three equal groups of women, all under age 40 years. The first group comprised women treated for DCIS or invasive cancer; the second, randomly selected women who underwent benign breast biopsy; the third, nurses who responded to the questionnaire. The Gail model failed to differentiate those women diagnosed with cancer as being at higher risk than the two control groups.

Chemoprevention

Chemoprevention refers to cancer prevention through the use of pharmacological agents in a healthy patient to reduce the risk of a particular cancer. All women with significant risk for future breast cancer development are potential candidates for chemoprevention. Tamoxifen, a selective antiestrogen receptor modulator (SERM) that acts as an antiestrogen in breast tissue, is currently the only FDA-approved medication for breast cancer chemoprevention. It was approved largely based on the findings of the NSABP-P1 trial, a randomized, double-blinded trial conducted by the National Surgical Adjuvant Breast and Bowel Project. In this trial, women with a projected risk of breast cancer of greater than 1.66% over a 5-year period received either tamoxifen or a placebo for a period of 5 years. The Gail model (shown to be of limited efficacy in younger women as previously stated) was used to assess the risk. Verified study findings from this trial showed a 50% reduction in invasive disease and initially a 50% reduction of noninvasive disease [32].

[§] Gail Model is also a limited model for varying ethnic populations, particularly African Americans

^{**} I.e., age at menarche, age at first live birth, number of benign breast biopsies, number of first-degree relatives with breast cancer, and history of atypical hyperplasia

Researchers chose age 35 as the lower cutoff for women enrolling in the trial. Age was not a focus of interest (i.e., a biological endpoint) in this study and the decision to use age 35 as the cutoff was done out of statistical considerations (namely, to ensure that a certain number of patients enrolled in the trial would develop breast cancer within a specified time period).

Although the NSABP-P1 study did have applicability to younger women over the age of 35, the applicability for women at increased risk and less than 35 years of age was unclear. Additionally, the P1 trial made no determinations regarding the age at which Tamoxifen chemoprevention therapy should begin, the recommended duration for this therapy, or related quality-of-life measures. The P1 trial also made no determinations as to how Tamoxifen chemoprevention therapy compared with other breast cancer risk-reduction and ovarian risk-reduction strategies. Despite a lack of findings for women under the age of 35, Tamoxifen is often prescribed to them.

The STAR (Study of Tamoxifen and Raloxifene) trial (NSABP-P2), currently under way, is a second important breast cancer chemoprevention trial. Unlike Tamoxifen, which has an associated increased risk of endometrial cancer, Raloxifene has no such associated risk. The purpose of the STAR trial, therefore, is to determine if Raloxifene may be an alternative to Tamoxifen in a chemoprevention role. However, as it is a randomized, double-blinded trial to compare Raloxifene with Tamoxifen in a population of postmenopausal women at increased risk for breast cancer development, premenopausal women are excluded from participating. Unfortunately, because of this exclusion, the implications of the STAR trial's findings for the younger population of high-risk women may also remain unclear.

It is recognized that, in general, breast cancers seen in young women are often more advanced and more aggressive than those seen in older women, and that negative predictors of outcome (such as extensive intraductal component, possible nodal involvement, estrogen-receptor negative tumors, and HER-2/neu over-expression) are seen far more frequently in young women with breast cancer than in their older counterparts.^{††} For this reason, it is commonly thought that young women who are diagnosed with breast cancer have a worse prognosis by virtue of being younger and more likely than their older counterparts to develop metastatic disease. Many of the studies that report on prognosis in younger women have the limitation of having relatively short periods of follow-up, usually involving 5 or 7 years of reporting with a subsequent discontinuation. Due to this short follow-up, long-term disease-free and overall survival in younger women, for whom it is of even greater importance, remains understudied. Substantial additional study is required to better understand this relationship.

Recurrence

Risk of recurrence is an especially important issue for younger women. In a 2000 overview looking at breast cancer recurrence curves over time, researchers reported no leveling off of recurrence [33]. For younger women treated for breast cancer, this finding

^{††} According to the American Cancer Society, when breast cancer is caught in its earliest stages, the 5-year survival rate for young women with breast cancer is 82%, compared with approximately 86% in the older population [1].

carries with it an implication of greater likelihood of recurrence based on the greater number of years of life ahead of them following treatment.

Currently, no long-term disease-free and overall survival data on younger women with breast cancer exist. Given this situation, the question of late recurrences in this population remains a serious concern and a research priority.

Where we go from here: YSC Defines priorities for research in Risk Assessment and Chemoprevention

The comparatively small number of younger women with breast cancer compounds the difficulty of assessing the overall accuracy of the Gail model in this population or of developing a new model better suited to assessment of risk in younger women. Research into the possible role of environmental factors in hereditary and nonhereditary breast cancer will be a necessary part of this effort. An assessment model developed for younger women and women genetically at risk for breast cancer should include evaluation of susceptibility to breast cancer-related environmental stimuli.

Although many of the same questions surrounding chemoprevention apply to younger women as apply to their older counterparts, a set of important additional questions has been identified. As is to be expected, these additional questions reflect the specific period of life and the risk profiles of younger women at high risk for developing breast cancer.

In general, research must address the optimal age for beginning chemopreventive therapy and its optimal duration in younger women. Similarly, study of Tamoxifen's effects on quality of life in young women compared with that in older women must be determined, and questions about the long-term safety ramifications must be considered, particularly given the longer life span of the younger patient.

As young women at high risk for breast cancer are in the midst of their childbearing years, the interplay of chemopreventive therapy and childbearing must be a subject of future research. Likewise, for the many young women at increased risk based on their genetic profile, questions regarding the benefit of Tamoxifen and its long-term effects in BRCA-mutation carriers are paramount.

Future research must also include study of the role of SERMS, aromatase inhibitors, luteinising hormone releasing hormone (LHRH) agonists, and hormone-deprivation therapy.

Absent data on the long-term disease-free and overall survival of younger women with breast cancer, little is known about later life recurrences in this population. As such, research inclusive of a younger patient population must allow for long-term follow-up. An improved understanding of long-term recurrence risk would equip young women with more information for making treatment, reproductive, and other "life" decisions.

More research needs to be done on the role of hormonal therapy in pre-menopausal women. Current research shows that similar outcomes are achieved with Tamoxifen and ovarian ablation in women under age 50 with hormone-positive cancer. However, questions remain as to the best mode of hormonal therapy for young women with

hormone-negative breast cancer. In addition, more studies are needed to look at hormonal therapy in the adjuvant setting, combined with chemotherapy, and in the metastatic cancer setting.

3. D. Diagnostics and Screening Tools for Younger Women

Overview presented by: Miriam Levy, MD and Ulana Suprun, MD, Medical Imaging of Manhattan, New York, NY.

What we know today: Diagnostics and Screening

Risk of breast cancer for younger women is relatively low, with less than 5% of all breast cancers occurring in this group [4]; consequently (in 2001), the issue of screening in younger women-particularly those at high risk of developing breast cancer based on family history or genetic profile-remains virtually unaddressed. Current screening recommendations from the major organizations in the United States that publish standard guidelines provide no specific recommendations for young women. The American Medical Association recommends yearly bilateral mammography starting at age 40, and the American College of Radiology guidelines advise yearly clinical breast examination, again starting at age 40. The American Cancer Society does recommend physical examination of the breasts every 3 years for women aged 20-39; however, these guidelines are wholly inadequate for young women at high risk and, in fact, in the worst scenario, may negatively influence such young women against more rigorous surveillance. Furthermore, breast self-examination, the sole screening method recommended to younger women, has been the subject of some controversy in the general public and mass media in the last several years as the result of a small number of high-profile studies, including a very recent study published in the Journal of the National Cancer Institute that reported no reduction in mortality linked to the practice of breast self-examination in a series of over 200,000 women in China [34].

For these reasons, high-risk young women must be identified and educated on the importance of screening prior to age 40. The rule of thumb on screening for a young woman with a strong family history of breast cancer is to commence screening at an age 10 years younger than the age at which her first-degree relative was diagnosed with breast cancer [35]. If she has several such first-degree relatives, screening should commence at the age many years prior to the age of the relative youngest at time of diagnosis.

Current recommended screening methods available for breast cancer include physical examination (both self-exam and clinical exam by a physician) and analog and digital mammography. The sensitivity of mammography is decreased in younger women, however, because most young, premenopausal women generally have denser breast tissue. In young women at high risk, the addition of sonograms can help in the identification of breast masses. All findings of suspicious masses should be biopsied, which can be performed via mammographic or sonographic guidance.

Other modalities currently under investigation for early detection of breast cancer include magnetic resonance imaging (MRI), scintimammography, positron emission tomography (PET), electrical impedance, and ductal lavage. Table 1 lists the advantages and disadvantages of each of these investigational modalities.

Table 1. Investigational Screening Modalities: Pros & Cons

Modality	Description	Advantages	Disadvantages
MRI	Images internal structures of the body by using electromagnetic qualities of hydrogen atoms in tissues	<p>High sensitivity (approaching 100% in some studies)</p> <p>No radiation exposure for patient</p> <p>Useful in women with dense breasts, implants, and previous surgery</p> <p>Recent development of techniques to perform biopsies</p> <p>Clinical trials in progress for screening use in women at high risk</p>	<p>No defined standard technique for contrast-enhanced MR imaging of the breast</p> <p>Low specificity (benign lesions and normal breast tissue enhance with contrast)</p> <p>Few commercially available MR-guided localization and biopsy systems outside research centers</p> <p>High cost</p>
Scintimammography	Tc-99M sestamibi injection and imaging with a gamma camera	Potential use as an adjunct to mammography and breast sonography in equivocal cases	<p>Low sensitivity and specificity</p> <p>Whole-body radiation exposure</p>
PET	Computerized images (i.e., tomographic scans) of chemical changes in tissue	<p>Whole-body scanning can show metastases</p> <p>Sensitive for tumors >9 mm.</p>	<p>Nonspecific uptake in normal active tissue</p> <p>High cost</p> <p>Limited access</p> <p>No uniform protocols</p>

Electrical impedance	Measures the speed at which electricity travels through the body	Currently under review for use with mammography	Not approved for screening
Ductal lavage	Saline introduced into the milk ducts of the breast via catheterization of the nipple; fluid withdrawn from catheter and analyzed for abnormal cells		Invasive Low specificity and sensitivity Unclear how to proceed upon occasion of positive findings

Mammography

There have been improvements in interpretation of mammographic images. The use of digital mammography with computer-assisted diagnosis marks a major improvement in the efficacy of mammographic imaging. The two big advantages of this new technology are 1) improved detection of microcalcifications (often associated with DCIS) and masses when compared with traditional mammography and 2) fewer retakes required, which results in less radiation exposure for the woman. In the place of the retakes requested in traditional mammography, with digital mammography, the radiologist can simply manipulate the digital image for closer or alternative views.

Mammograms, however, pick up, at best, 75% of early breast cancers in dense breast tissue, 85% in moderately dense tissue, and 95% in breasts that have relatively little dense tissue. To improve these results, radiologists use adjuvant sonography. In a study based on breast images performed from 1998 through 2001 at a private imaging clinic in New York City,^{‡‡} radiologists showed that sonography improves mammographic detection overall by 28.5%. There was a 3% improvement in the detection of DCIS (which most commonly presents as microcalcifications) and a 39.5% improvement in invasive breast cancer detection.

Based on this study, the addition of bilateral whole-breast sonography to mammography in selected patients (namely, women with dense breast tissue and a high-risk profile) increases the detection of nonpalpable invasive breast cancer by 38% and enhances imaging of palpable invasive breast cancer by 41.5%. This last finding is particularly promising for screening and diagnosis of suspicious masses in younger women, in whom such findings are often discounted or immediate treatment delayed in order to "wait and see."

^{‡‡} M. Levy, MD and U.N. Suprun, MD, Medical Imaging of Manhattan, LLC

Where we go from here: YSC Defines priorities for research in Screening and Detection

Current proven screening and diagnostic tools and their current application (i.e., mammogram alone), as well as physician attitudes toward suspicious findings in younger patients, may be factors contributing to underdiagnosis of breast cancers in younger women. Such underdiagnosis can lead to undertreatment and poorer outcomes. Standards of care for screening young women at high risk are needed and should include annual clinical exams, as well as a combination of mammography and sonography.

Given the relative 'rarity' of cases in women 40 and under, screening for the general population of healthy young women may not be epidemiologically warranted or feasible unless the scientific community devises a true method of early detection for all women that can predict presence and biologic behavior of cancer cells and does not discriminate on the basis of age as do our current modalities.

More research is needed to improve breast cancer-diagnostics in younger women. This research must include the investigation of the attitudes of front-line physicians regarding possible biases against offering radiologic workups to younger patients on the basis of these patients being "too young" to be at risk for breast cancer. The published results of this type of study may educate physicians and possibly decrease the incidence of delayed diagnosis in young women. In addition, new cost-effective diagnostic tools to screen younger women that do not involve radiation exposure must be developed. Examples of these include serum or molecular markers. These tools should be measured in clinical trials against the current gold standard option.

Additional studies to address the relative efficacy of mammography, sonography, and MRI in diagnosing breast cancer in young women are also required. Improved understanding of the best format (i.e., the use of two or three methods together) and frequency of screening procedures would assist clinicians in achieving the best treatment for each patient and would therefore contribute to improving outcome.

3. E. Ovarian Function: Premature Menopause and Subsequent Pregnancy after Breast Cancer

Overview presented by: Jeanne Petrek, MD, Director of Surgical Programs, Memorial Sloan-Kettering Cancer Center, New York, NY.

What we know today: Ovarian Functioning

Breast cancer & pregnancy

Breast cancer is the most common cancer in pregnant and postpartum women, occurring in about 1 in 3,000 pregnancies. The average patient in this sub-group is between 32 to 38 years of age [36]. Effective treatment, including surgery and chemotherapy, can be administered during certain periods of pregnancy. The use of radiation therapy during the first and second trimesters of pregnancy is not recommended because of the inability to shield the baby from the radiation. There is, however, no evidence that breast cancer affects fetal development or is passed on to the fetus.

Screening remains an important part of regular health maintenance for pregnant and lactating women. The detection of a lump may be hindered by the natural tenderness and engorgement of the breasts during this time; therefore, pregnant and lactating women should take extra care to practice monthly breast self-examination and to have a clinical breast exam as part of routine pre- and postnatal examinations by their doctor [36].

Pregnancy & outcomes

The issue of pregnancy following breast cancer treatment is of particular relevance to younger women with breast cancer. These women are in their childbearing years at the time of diagnosis and treatment and are also often about to begin, or are in the midst of, building families of their own. Currently, there are no data to suggest a negative effect of pregnancy on breast cancer recurrence. Retrospective studies done in the 1980s [37-41] reported exceptionally good overall survival (at 10 years' follow-up) of women who had pregnancies subsequent to breast cancer. There were limitations to these studies, however, including small sample sizes, the use of large time intervals (of several decades leading to greater variations in treatment, etc.), and nonsystematic patient collection (recall bias) on the part of participating physicians.

In the 90s, some good population-based studies were done that showed that women who became pregnant (and had a live birth) after breast cancer treatment survived at least as well if not better than women who did not [42-45]. However, these studies also had design flaws, among them the "healthy mother effect" [42] whereby some of the women who participated as controls may have already had recurrence (and therefore had made a decision not to become pregnant), while those women who did deliver babies presumably had no known recurrence and may have been more optimistic in general, based on better prognoses among other things.

It is commonly thought that pregnancy subsequent to treatment for breast cancer (particularly when the cancer is hormone receptor-positive) may be risky, because the intensified hormonal milieu associated with pregnancy may potentially cause dormant cancer cells to become reactivated. Many physicians recommend that women wait until they are in their fifth year following treatment and recurrence-free before considering pregnancy, while others recommend waiting only 2 years. In a 1995 study from Sweden, however, researchers reported no evidence that pregnancy during the 5-year period either preceding or following breast cancer treatment altered patients' prognoses. They concluded that the hormonal changes associated with pregnancy seem to have little or no influence on the prognosis of breast cancer. In addition, they found that women with estrogen-receptor-negative breast cancers actually had worse predicted outcomes in all three pregnancy-related scenarios: before, concurrent with, and following breast cancer [43].

Fertility & quality of life

Chemotherapy induces menopause in many young women undergoing breast cancer treatment. For others, while they may continue to menstruate, damage may have been done to their ovaries on a chromosomal level, thereby resulting in loss of fertility. Fertility specialists are often capable of determining the quality of a woman's eggs post-therapy and her likelihood of a successful pregnancy. Fertility treatment for breast cancer survivors is therefore another area of particular concern for younger women. Research is currently under way in a number of centers to reduce damage associated with breast cancer treatment and improve post-treatment fertility options.

Where we go from here: YSC Defined priorities for research in Fertility and Pregnancy

Additional research is required to determine with satisfaction whether subsequent pregnancy following breast cancer treatment is harmful, or potentially beneficial, or possibly the former in certain cases and the latter in others, depending on the disease profile of the individual woman. We need a better understanding of the triggers that cause pregnancy-related and post-partum breast cancer and of the long term/late effects on both the mother's health and survival as well as that of the baby after exposure to cancer therapies in utero.

Fertility following breast cancer treatment also requires careful additional study. Although many women re-establish normal regular menstrual cycles and are fertile post-treatment, subtle changes affecting fertility do occur and must be better understood. To this end, it is critical that menstrual and pregnancy history becomes part of the general patient history obtained from women participating in clinical trials. This is critical for establishing the relationship between pregnancy (subsequent and previous) and breast cancer. Furthermore, charting post-treatment return of fertility, pre and post treatment interventions that women use to become pregnant and health and disease-status following pregnancy (ideally in 5-year increments) will require long-term prospective studies. In order for these to take place, more extensive funding supporting this area of research must be made available and greater interest must be cultivated within the research community.

Although short-term data on premature menopause as the result of breast cancer treatment is currently available, the large number of combination therapies available to

women has hampered determining which therapeutic agents affect fertility and menopausal status and how various therapeutic agents do so. A related issue of great importance is the issue of quality of life for younger women who experience premature menopause.

Appendix 1

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Appendix 2

White Paper Participant Bio Sketches

Ira Bleiweiss

Dr. Bleiweiss is Professor of Pathology and Director, Division of Breast Pathology, Mount Sinai School of Medicine, is a graduate of St. George's University. He completed his residency at Mt. Sinai Medical Center, a fellowship at Mt. Sinai Medical Center in Surgical Pathology, and a fellowship in Pathology at Memorial Sloan-Kettering. Dr. Bleiweiss specializes in breast pathology and is board certified by the American Board of Pathology in Anatomic & Clinical Pathology. He directs the breast-pathology cadre within the CALGB (Cancer and Acute Leukemia Group B), a national cooperative group engaged in clinical trials for patients with breast cancer as well as other forms of malignancy.

Miriam Levy

Dr. Levy founded Medical Imaging of Manhattan in 1989. She received her MD from the Albert Einstein College of Medicine, did her residency in Diagnostic Radiology at the George Washington University Medical Center, is certified by the American Board of Radiology, and completed her fellowship training in imaging at the New York Hospital-Cornell University Medical Center. She spent many years as a Clinical Assistant Professor of Radiology at the Cornell University Medical Center and as an Attending Radiologist at the New York Hospital.

Anne Moore

Dr. Moore is Professor of Clinical Medicine at Weill Medical College of Cornell University and Attending Physician at New York-Presbyterian Hospital. She is a graduate of Smith College, where she was elected to the Society of Sigma Xi. She obtained her MD from Columbia University College of Physicians & Surgeons and did her residency and fellowship training in internal medicine, hematology, and oncology at The New York Hospital and The Rockefeller University. Dr. Moore is active in research, teaching, patient care, and advocacy with a particular interest in the field of breast cancer. She is Chairman of the Breast Cancer Committee at New York Weill Cornell Medical Center of New York-Presbyterian Hospital and immediate past-President of the New York Metropolitan Breast Cancer Group, Inc. She has completed her term as a Director of the American Board of Internal Medicine.

Jeanne Petrek

Dr. Petrek is Director of Surgical Programs, Memorial Sloan-Kettering Cancer Center is a graduate of Case Western Reserve University. She completed her residency at Peter Bent Brigham Hospital and her fellowship at Memorial Sloan-Kettering Cancer Center.

Dr. Petrek's area of clinical expertise is breast disease and she specializes in treating young women. She is currently conducting a study on changes in ovarian function due to breast cancer treatment, with a focus on quality-of-life issues. She has also conducted extensive research on treatment-related lymphedema. Dr. Petrek is board certified in surgery. *(Note: Dr. Petrek passed away in April of 2005)*

George Raptis

Dr. Raptis is Head of the Clinical Breast Cancer Program for the Division of Medical Oncology, Mount Sinai School of Medicine, and is a graduate of Mount Sinai School of Medicine CUNY. He completed his residency at Mount Sinai Medical Center in Medicine and his fellowship at Memorial Sloan-Kettering in Oncology-Hematology. Dr. Raptis specializes in medical oncology and is board certified by the American Board of Internal Medicine in Internal Medicine and Medical Oncology.

Rubie Senie

Dr. Senie is a chronic-disease epidemiologist who has focused her research on breast cancer risk and prognostic factors. She is a Professor of Clinical Public Health at the Mailman School of Public Health at Columbia University. After completing her PhD at Yale University, Department of Epidemiology and Public Health, she directed the Department of Community Medicine of Beth Israel Medical Center and was on faculty of the Department of Community Medicine of Mt. Sinai School of Medicine where she collaborated on several HIV/AIDS studies. She continued these projects after joining the Centers for Disease Control and Prevention in Atlanta, GA. Dr. Senie returned to New York City to direct epidemiologic research with members of the Breast Service of Memorial Sloan-Kettering Cancer Center. Currently her primary focus is on the creation of a resource for genetic and environmental studies of the etiology of breast cancer; the project, The Metropolitan New York Registry of Breast Cancer Families, is one of six international sites contributing to the Cooperative Family Registry for Breast Cancer Studies [CFRBCS].

Ulana Suprun

Dr. Suprun received her MD from Michigan State University College of Medicine and completed her residency in radiology at Sinai Hospital of Detroit where she was Chief Resident. She trained as a fellow in breast radiology at the Henry Ford Hospital in Detroit, and is certified by the American Board of Radiology. She now works with Dr. Miriam Levy at Medical Imaging of Manhattan.