

### Changes in Cognitive Function in Breast Cancer Patients

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Problems with memory, difficulty concentrating, loss of “mental sharpness,” forgetfulness and substantial problems with multi-tasking describe many of the cognitive complaints reported by women treated for breast cancer (1). Research over the past decade has produced evidence to support the subjective reports of changes in cognitive function associated with breast cancer treatment. Three meta-analysis have concluded that chemotherapy negatively affects the following cognitive function domains: executive function, verbal memory, information processing speed, and attention (2,3,4). Adjuvant hormonal therapy, alone or in combination with chemotherapy, has also been associated with impaired verbal memory and processing speed (5,6,7). Limitations related to sample size, methodology, and measurement sensitivity suggest caution in interpretation of this existing

#### Domains of Cognitive Function

- ATTENTION
- CONCENTRATION
- EXECUTIVE FUNCTION
- INFORMATION PROCESSING SPEED
- VERBAL MEMORY
- LANGUAGE
- PSYCHOMOTOR SPEED
- VISUOSPATIAL SKILL
- VISUAL MEMORY
- REACTION TIME
- VERBAL FLUENCY

Figure 1

body of research, yet the conclusions of the meta-analysis and subsequent published studies support further research and the need to identify etiologic mechanisms.

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### Male Breast Carcinoma: The rising incidence and comparison with female breast carcinoma

Thomas Mezzetti, Jr., MD and Fattaneh A. Tavassoli, MD

#### INTRODUCTION

Male breast carcinoma (MBC) is rare, accounting for less than 1% of all breast cancers, but a gradual and steady increase in the incidence rate has been noted. The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) data from 1973 to 1998 shows an increase in the incidence of MBC from 0.86 to 1.08 per 100,000 population - a 26% increase over the 25-year period in the US (1).

Using a novel spatiotemporal model of projection for 2007, 2,030 new MBC cases and 450 deaths from MBC are estimated based on SEER data (2). This compares to 178,480 new female breast cancers (FBC) and 40,460 deaths among women for the same year.

#### ETIOLOGIC FACTORS

The etiology of MBC remains unknown. Factors related to an excess risk include Klinefelter's syndrome, with a 50-fold increased risk,

hormonal imbalances (relative hyperestrogenism and testosterone deficiency) of either endogenous or exogenous nature (testicular disorders, cirrhosis, exogenous estrogens, hormonal therapies for prostatic cancer, obesity, possibly finasteride, etc.), gynecomastia, radiation exposure, and a family history of female or male breast carcinoma. Mutations of either BRCA1 or BRCA2 breast cancer susceptibility genes constitute a major risk factor. Germ-line mutations of the BRCA2 gene are particularly significant and present in 4 to 10% of men with breast cancer. BRCA2-associated cancers tend to present at a younger age and may have a worse prognosis.

#### PRESENTATION

The most common presentation for male breast carcinoma is a painless subareolar mass, nipple retraction and bloody nipple discharge. The tumor may become massive, with direct extension into the nipple. The major differential diagnosis is gynecomastia which affects nearly 30% of healthy men.

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## Editor's Letter

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The Yale Cancer Center Breast Cancer Program continues to grow. This group not only includes specialists from medical, surgical, and radiation oncology, but also pathologists and faculty from the Yale School of Nursing, as is highlighted in this issue.

This issue starts with a fascinating explanation of male breast cancer, in itself a rare but increasingly diagnosed entity. This sheds light on the pathology and similarities and differences between the forms of breast cancer, important building blocks for all breast cancer.

Additionally, we have a wonderful article by a prominent member of the Yale School of Nursing on cognitive changes in breast cancer patients exposed to chemotherapy. This is especially timely because the School of Nursing has recently opened a trial for accrual to better understand this well documented phenomenon.

Finally, there is in depth coverage of a new trial open for accrual at Yale Cancer Center that brings new biologic approaches to the clinic. This trial studies the combined efficacy of an angiogenesis inhibitor (Avastin) with an aromatase inhibitor (Femara) on breast cancer. This will be pathologically as well as biologically studied using a neoadjuvant treatment approach in this trial.

We hope this issue will enlighten and inform all about the continued exciting directions of study in the field of breast cancer. This is our second issue of *Advances for the Breast Program*, and we hope that you find it as interesting and exciting as we do. Feel free to contact me with any suggestions or topics of interests for future issues.

Sincerely,

Dr. Joanne Weidhaas, MD, PhD

## ► CHANGES IN COGNITIVE FUNCTION continued from page 1

### POTENTIAL MECHANISMS FOR COGNITIVE CHANGES

Emerging explanations for changes in cognitive function associated with cancer treatment have been derived from the body of descriptive literature using neuropsychological testing with women treated for breast cancer with chemotherapy, with or without radiation or hormone therapy, preliminary findings from magnetic resonance imaging and position emission tomography, and basic science. Ahles & Saykin (8) propose five potential candidate mechanisms for changes in brain structure and function and cognition: blood-brain barrier integrity, DNA damage, genetic susceptibility, cytokine deregulation, and reduction in estrogen and testosterone levels. These proposed mechanisms provide a foundation to target research to further understand the phenomenon and to begin to develop interventions to minimize the effects of cognitive changes that interfere with everyday life activities for breast cancer survivors.

### LIMITATIONS OF EXISTING RESEARCH

There is a considerable body of research that reports the outcomes of neuropsychological testing in women with breast cancer. We must be cautious, however, in our interpretation of the findings due to methodologic limitations. A significant number of early studies had cross-sectional, retrospective designs; there are a limited number of prospective longitudinal studies; few studies include healthy, age-matched control groups; many have small sample sizes; there is a lack of consensus on classifying cognitive impairment (also referred to as compromise, dysfunction, changes); there are challenges to interpreting pre-treatment data (when available) and the sensitivity of existing neuropsychological

tests is highly debated. Many studies have utilized a battery of neuropsychological tests with multiple tests administered for each cognitive domain (Figure 1, pg 1). These tests are objective measures of cognitive function but their sensitivity to capture the actual experience of patients is unclear. A lack of a correlation between objective neuropsychological measures and subjective cognitive complaints has been consistently reported across studies. This may be related to the subtle nature of perceived cognitive changes or a lack of sensitivity to detect the type of "real world" cognitive changes that women experience with cancer treatment that they describe as significantly interfering with their ability to carry out normal role functions.

### HORMONAL INFLUENCE ON COGNITION IN WOMEN WITH BREAST CANCER

In natural menopause, short-term memory changes during the perimenopause or early postmenopausal period have been consistently reported in clinical practice and lay women's health literature but there is a lack of research evidence to support these subjective reports. In contrast, women who have surgically-induced menopause are reported to experience problems with short-term memory and cognitive functioning following surgery (9). Chemotherapy-induced menopause has similarly been associated with cognitive complaints, specifically forgetfulness, and problems with attention, concentration, and memory. The abrupt change in the hormone level likely contributes to hormonal imbalance that affects cognitive functioning. Women who are on endocrine therapy with selective estrogen receptor modulators or aromatase inhibitors (with or without prior chemotherapy) report very similar cognitive complaints related

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## CLINICAL TRIALS Breast Cancer Program

### BREAST CANCER:

HIC 27735	A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer	Joanne Weidhaas, MD, PhD	(203) 737-2165
HIC 0511000860	A Phase I Study of the mTOR Inhibitor Rapamycin (Rapamune, Sirolimus) in Combination with Abraxane (Paclitaxel protein-bound particles) in Advanced Solid Cancers	Maysa Abu-Khalaf, MD	(203) 785-7564
HIC 0601000957	Phase II Trial of Mammosite Breast Brachytherapy Optimization in the Treatment of Stage 0, I, and II Breast Carcinoma	Joanne Weidhaas, MD, PhD	(203) 737-2165
HIC 0602001073	A Randomized, Phase II Trial of Preoperative Herceptin/Navelbin versus Taxotere/Carboplatin/Herceptin in Early Stage, HER-2 Positive Breast Cancer	Lyndsay Harris, MD	(203) 785-3213
HIC 0605001396	A Phase I/II Study of Rapamycin (Rapamune, Sirolimus) and Trastuzumab (Herceptin) for Patients with HER-2 Receptor Positive Metastatic Breast Cancer	Maysa Abu-Khalaf, MD	(203) 785-7564
HIC 0609001793	Randomized Phase II Study of Preoperative Letrozole (Femara) in Combination with Avastin in Hormone Receptor Positive Breast Cancer	Gina Chung, MD	(203) 737-1569
HSRRC	A Longitudinal Prospective Study of Cognitive Function in Pre-Menopausal Women Diagnosed with Breast Cancer Undergoing Adjuvant Chemotherapy Compared to Pre-menopausal Women with Surgically Induced Menopause	M.Tish Knobf, PhD, RN	(203) 737-2357

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to memory, attention, and concentration. Although the exact mechanisms for cognitive impairment associated with cancer treatment remains unknown, changes in estrogen levels, especially abrupt changes, may provide one explanation for the reported subjective cognitive complaints of women (8).

### RECOMMENDATIONS

Recommendations for future research include the use of longitudinal prospective designs with pre-treatment assessments to continue to explore underlying mechanisms of cognitive changes, determine the most sensitive evaluation measures, include samples of diverse cancer patients and healthy aged matched controls, build consensus on defining cognitive changes and classifying cognitive impairment, and begin to develop interventions (10,11,8).

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## Clinical Trial Review

Gina Chung, MD

### HIC PROTOCOL NUMBER: 0609001793

### A Randomized Phase II Study of Preoperative Letrozole (Femara) in Combination with Avastin in Hormone Receptor Positive Breast Cancer

Angiogenesis plays an important role in the growth and spread of breast cancer and vascular endothelial growth factor (VEGF) is one of the most potent pro-angiogenic mediators. Increased levels of VEGF expression have been found in many human malignancies, sometimes correlated with worse clinical outcomes, and the anti-VEGF monoclonal antibody bevacizumab (Avastin) is effective when combined with chemotherapy in patients with metastatic breast cancer. The estrogen receptor (ER) signaling pathway also plays an important role in breast cancer (as evidenced by the impact of ER modulating agents such as tamoxifen and aromatase inhibitors) and growing evidence suggest cross-talk between this and VEGF-mediated signaling in breast cancer.

Preoperative therapy has long been standard of care for locally advanced/inoperable breast cancer and has recently become an acceptable alternative to adjuvant therapy for women with operable breast cancer. This approach has several advantages including higher rates of breast conservation and assessment of *in vivo* tumor response. The purpose of this study is to evaluate the activity and safety of a combination of an aromatase inhibitor (letrozole) and bevacizumab given preoperatively to postmenopausal patients with hormone sensitive breast cancer. A series of tissue-based, blood-based, and imaging-based studies will also be performed to correlate biomarker findings with clinical endpoints.

Hence all patients will be treated with both drugs for the majority of the treatment period (e.g. 14 weeks). After completion of treatment, definitive surgery (lumpectomy or mastectomy) will be performed at a minimum of 4 weeks from last bevacizumab treatment.

Briefly, eligibility criteria include patients with postmenopausal, ER and/or PR positive, Stage II-III breast adenocarcinoma with adequate end-organ function. The major associated side effects for bevacizumab are hypertension, thromboembolic events, proteinuria, and hemorrhage and for letrozole are hot flashes and arthralgia/myalgias.

In the context of this trial, a series of tissue, blood, and image-based biomarkers will be obtained to evaluate both endocrine and angiogenesis pathways. These data will be compared in matched samples to identify changes that may predict response.

**COMPARISON OF MALE AND FEMALE BREAST CARCINOMAS**

The age adjusted incidence rate of male breast cancer is 16.6 per million compared to a substantially higher incidence of 1557.7 among women (3). The incidence is highest among black men compared to whites and Asian-Pacific Islanders. Black women, in contrast, have lower cancer rates compared to white women. Non-Hispanic whites have higher rates compared to Hispanic whites and Asian-Pacific Islanders have the lowest rates in both male and female populations.

From 1975 to 2001, the total breast carcinoma incidence rates increased by 29% for men and 58% for women; the incidence of intraepithelial (in situ) carcinomas rose by 123% among men and 555% among women (4). Widespread use of screening mammography and public awareness has resulted in earlier detection of female breast cancer. In contrast, advanced stage disease had a downward trend in both genders.

Among men, the mean age at presentation of invasive carcinoma is 65 to 76 years compared to the average age of 57 to 62 years at diagnosis for women. The median age for men with DIN (DCIS) is 62-65 – about 10 years older than that for women.

In our comprehensive morphologic review of over 700 MBCs (5,6), a wide morphologic spectrum was noted. Compared to FBC, papillary carcinomas with invasion are twice as common. Invasive lobular carcinoma, however, is extremely rare in male breast (<1% of MBC vs 5-20% of FBC). About 5-10% of male breast carcinomas are intraepithelial (in situ) and these are mostly low to intermediate grade lesions and predominantly (74%) papillary; high grade DIN, including the comedo type (comedo ductal carcinoma in situ), is extremely rare (6). These morphologic differences are mainly due to the anatomic structure of male breast, where terminal duct-lobular units are absent.

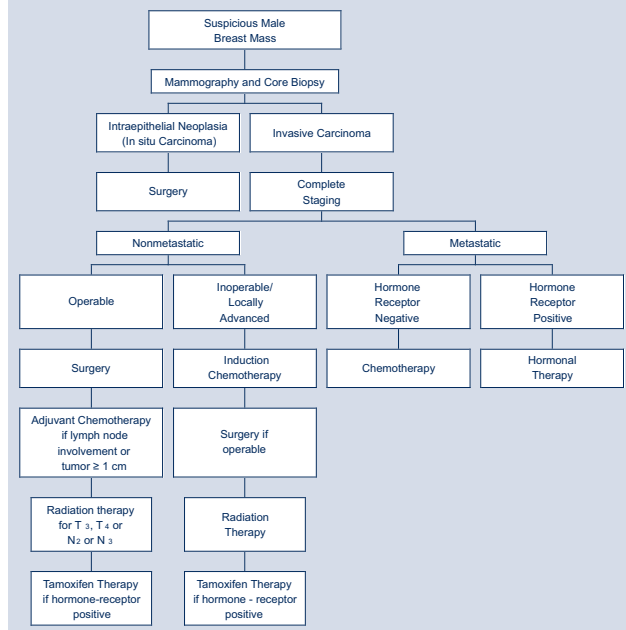
Male breast carcinomas have high rates of ER positivity (90% vs 76% among women) and PR positivity (81% vs 66.7% among women). The HER2-neu oncogene overexpression has ranged from a low of about 5% to as high as 37% in various studies.

**PROGNOSTIC FACTORS AND SURVIVAL**

Tumor size, lymph node status, and extent of spread beyond the breast are important prognostic factors; staging of all male breast carcinomas is absolutely necessary. Negative receptor status and high tumor grade are not independent prognostic factors on multivariate analysis.

Patients with stage I, II, III, and IV disease have a disease-specific survival of 93%, 74%, 44%, and 21% respectively at 10 years. The overall survival at 10 years is 55%, 39%, 21%, and 14% for the stages, respectively.

**TABLE 1 – MANAGEMENT OF MALE BREAST CARCINOMA**



**MANAGEMENT**

Treatment of MBC is based predominantly on protocols used in female breast cancer with minor, if any, gender specific modification (Table 1). Given the high frequency of ER positivity, Tamoxifen therapy is a major consideration, with a response rate of approximately 50% noted in some series; gender specific side effects need further assessment.

**CONCLUSIONS**

The incidence of MBC is increasing. Men are generally diagnosed with higher stage disease at presentation. Stage for stage, the prognosis is similar for male and female breast cancer. A better understanding of male breast carcinoma is desirable for early detection, optimal gender specific therapy, and improved survival.

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A lack of correlation between objective neuro-psychological measures and subjective cognitive complaints has been consistently reported among breast cancer patients.

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