

The Multidisciplinary Scientific Update Meeting on Male Breast Cancer took place on September 4, 2008. Attendance was about 30 individuals. The objectives of the meeting were:

- 1) To form a scientific community of international experts in male breast cancer research; and
- 2) To begin to develop a research program agenda by identifying the most important research questions we need to answer in order to better understand and treat male breast cancer.

Meeting presentations focused on what is currently known about the epidemiology, etiology, genetics, treatment and outcomes of male breast cancer from an international perspective. Summaries of each of the talks, along with the slide presentations, will be posted in the next few weeks on The Breast Cancer Intergroup website. In addition, we plan to publish the meeting proceedings and a position paper in an Oncology journal (the actual journal has not been chosen yet) and hope to follow up the meeting recommendations with an educational session on etiology and treatment of male breast cancer at ASCO.

**The morning sessions were devoted to epidemiology and etiology.** Dr. William Anderson summarized male breast cancer incidence data from SEER and IARC. He noted that there are different age-related natural histories for men and women. Females tend to have bimodal incidence curve with an early onset and a late onset peak. Males lack the early onset peak, as evidenced by a later age at onset and a much higher rate of ER positivity. Dr. Susan Domchek presented on genetic aspects of male breast cancer. The strongest and best described association is with *BRCA2*, although other genetic associations were discussed. She stressed the importance of genetic counseling and testing for men with breast cancer, and also noted that ongoing genome-wide association studies will likely provide further information on the genetic contribution to male breast cancer. Dr. Sharon Giordano presented a concise summary of the literature on risk factors for male breast cancer, including Klinefelter's Syndrome, which is present in 3-7% of male breast cancer cases, radiation exposure, family history, gynecomastia, and hormone levels. She also discussed the influences of age and race on male breast cancer incidence. She also discussed survival and prognostic factors. Dr. Louise Brinton presented new data from the NIH AARP Diet and Health Study Cohort. This study showed increased risks of male breast cancer with family history, obesity, and also found a statistically significant increase in the risk of breast cancer among men with a bone fracture over the age of 45. Dr. Brinton noted her plans to convene a meeting of investigators with cohort or case-control data on male breast cancer in order to form a consortium to validate these findings, and initiate studies investigating associations between serum biomarkers (such as hormone levels) and male breast cancer risk. To conclude the morning discussions, Dr. Giancarlo Pruneri and Dr. Laura van't Veer summarized the current data on histopathologic and molecular characteristics of male breast cancer.

**The afternoon sessions focused on understanding patterns of care with regard to treatment of male breast cancer and on defining a research agenda for moving the**

**field forward.** Dr. Jonas Bergh, who was unable to travel to the meeting but joined by teleconference, presented new data from the Nordic Registries on male breast cancer. Drs. Jo Anne Zujewski and Bruno Cutuli presented data on treatment from the US and Europe. Both presenters noted a wide range of surgical options being used. Comorbid conditions and age were associated with decreased use of chemotherapy. The use of aromatase inhibitors for male breast cancer, for which there is little data, was not uncommon in both the US and internationally. Dr. Katherine Crew presented data on racial differences in treatment for and outcomes of male breast cancer. She noted that black men were more likely to die from breast than white men after controlling for demographic, clinical, and treatment-related factors, and stressed the importance of future studies with larger sample sizes to investigate clinical and biologic factors that may contribute to the racial disparities in male breast cancer. Dr. Zeina Nahleh discussed a SWOG-initiated trial for metastatic male breast cancer, which was open from 9/05 – 1/07 but failed to accrue any patients. Barriers to recruitment to clinical trials for male breast cancer and potential solutions were discussed.

The last two presentations and panel discussions focused on **identifying the major issues that need to be addressed in future research on male breast cancer.** Mr. Guy Jones, a male breast cancer survivor, gave an eloquent presentation of important issues from the advocacy perspective. Dr. Fatima Cardoso presented plans for a multinational research effort, that would include both a retrospective and prospective component, and would focus on collection of demographic and risk factor information, patient and tumor characteristics, treatment information and, most importantly, tumor specimens, in order to better understand the etiology and outcomes of male breast cancer. One eventual goal of this project would be to determine the feasibility of embarking on an international collaborative clinical trial for male breast cancer.

**Major outcomes of the meeting:**

- 1) The attendees of the meeting concluded that while male breast cancer looks like post menopausal hormone receptor positive female breast cancer and patients are being treated according to this understanding, this is just an extrapolation and more data is needed to determine whether and how these treatments work and to truly understand the key differences in the biology of male breast tumors.

**Action Item:** A position paper outlining the proceedings of this meeting would be the first step to increase awareness.

- 2) Meeting attendees agreed that testing **biospecimens** to determine uniqueness of male breast tumors is crucial and will be a challenge. It may be possible with the tissue microarrays in fixed tissue to look at IHC surrogates for molecular subtype, but fresh frozen tissue would be necessary to truly understand the unique biologic aspects of male breast cancer. Issues related to the logistics of sending tissues to a central location for standardized testing were discussed.

**Action Item:** Dr Fatima Cardoso's research initiative, which has recently been funded by the Breast Cancer Research Foundation, will hopefully be able to

address some of these challenges by facilitating the collection and central testing of tumor specimens.

- 3) The prospect of clinical trials in male breast cancer was discussed, although a majority of meeting attendees felt that etiologic questions should be more thoroughly addressed before embarking on a clinical trial. Some issues raised in the discussion included:
- a. Safety versus outcome trial of hormonal therapy-should we be using AIs in men?
  - b. The idea of a registry to collect tamoxifen toxicity information in men, especially for information that can not be found in a chart review.
  - c. The feasibility of establishment of an Orphan Diseases Protocol to cover a number of rare breast cancer subtypes, including male breast cancer, inflammatory breast cancer, breast cancer in pregnant women, etc. This protocol could be reviewed by a Central IRB to reduce the amount of work.
- Action Item:** The NCI to follow up with the Office of Rare Diseases at the NIH to determine if they have funding available

**Challenges:**

- 1) The high expensive of opening a clinical trial for so few eligible patients.
- 2) For data and specimens already collected, older consents do not always have the proper language for researchers to be able to go back and do additional studies or genetic testing on biospecimens.
- 3) Researches will need to go back and either contact patients or get IRB approval to study tissue and blocks for the use of Biospecimens of previously un-identified research. There are blocks and tissue out there, but in the USA it is necessary to have IRB approval of a protocol to use those tissues.
- 4) A prospective trial can not be done in an adjuvant setting because it would require too many patients. It does not seem feasible to do one in neo-adjuvant setting because the female trials in the neo-adjuvant setting do not give discernable results, we only know that it can be done and you can enhance breast conserving.
- 5) A serum bio-markers in a large concerted effort at this point would be too logistically challenging, the focus should be on a centralized collection of TMAs.
  - a. Louise Briton will be trying to do serum estrogen levels and serum estrogen metatbolites, and androgen in a smaller study.
  - b. Serum levels of hormones should be collected in a prospective study
  - c. If TMAs are collected concertedly, then the methods synchronize construction should be uniform
- 6) Advertising and funding

**Suggestions to Address Challenges:**

- 1) Construct a trial that focuses on safety rather than efficacy
- 2) Change the sentiment of the IRBs. Many times IRBs prevent research that patients actually want. This can be done in a position paper.
- 3) Review the differences in international collection and use of bio-specimens

- 4) Establish centers of excellence. This was done with inflammatory breast cancer and it worked well.
  - a. These centers could be supported through the activities of advocates and perhaps, granting mechanisms
  - b. Establish registries at the centers for excellence
- 5) Develop a trans-Atlantic research consortium, much like the one that Fatima Cardoso is working to implement. The beginning goal of this consortium should be to better define very basic aspects of male breast cancer.
- 6) Manage expectations and be realistic about what can be accomplished
- 7) Create a general protocol that allows for tissue collection from all patients who agree to provide tissue and to establish extensive tissue banks, which can be used for future research. In the US, this will require IRB approval
- 8) Use advocates, Internet (Komen, the government, and facingourrisk.org) and Surgeons for advertising registries and prospective clinical trials.
- 9) Inventory biospecimens that are out there and available