

cytochrome P450 2D6, an enzyme known for 30 years to be genetically polymorphic. Endoxifen concentrations associate with CYP2D6 genotype and studies conducted in the prevention, adjuvant and metastatic settings suggest that patients with the CYP2D6 poor metabolizer genotype respond less well to tamoxifen treatment. There is a clear alternative to tamoxifen for these patients: the aromatase inhibitor class of drugs.

Despite the fact that aromatase inhibitors (AIs) appear slightly but definitively superior to tamoxifen as adjuvant therapy in postmenopausal women, the relatively low cost of tamoxifen makes it the only viable oral therapy in many countries, and the AIs are ineffective, monotherapy in premenopausal women. It is possible that the relative benefit of tamoxifen in extensive metabolizers of CYP2D6 may render the drug more effective than AIs in this group of patients. Recent data indicate that patients who are poor metabolizers of tamoxifen drop out of trials and from therapy at a notably lower rate.

A key recent trial (E-2100) demonstrated that the anti-VEGF antibody bevacizumab combined with paclitaxel showed greater reductions in DFS survival than paclitaxel alone, but the combination did not alter overall mortality. We have recently demonstrated that germline genetic variability in the VEGF receptor associated with outcomes in this trial which had a group that experienced overall survival benefits not different from placebo, and a group that survived on average a year longer. It is of note that variants in the same gene are also associated with risk for toxicity from bevacizumab therapy: hypertension.

**Conclusions:** These data suggest that germline genomic variability in candidate genes, but also in pharmacologic and physiologic pathways may be valuable approaches to further refining the targeting of patients with breast cancer to maximize efficacy, but also to reduce toxicity and thus to optimize the overall risk:benefit ratio of therapy for breast cancer.

## 21 Proffered Paper Oral Genetic polymorphism of CYP2D6: a critical factor for early metastatic relapse in patients treated with adjuvant tamoxifen

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Current adjuvant hormonal therapy in postmenopausal women with breast cancer is debatable between upfront aromatase inhibitors and sequential treatment initiated with tamoxifen. We previously reported a retrospective analysis in order to identify risk factors of early systemic relapse among postmenopausal women treated with tamoxifen for an hormone-positive carcinoma in adjuvant setting (Debled, Cancer 2007). A distant recurrence occurred in 5.3% within the first 3 years of tamoxifen. Lymph node involvement and modified SBR grade were identified as independent predictive factors of early recurrence. Exploratory immunohistochemical analyses performed on tumors that subsequently recurred did not reveal any unusual expression of EGFR, HER2, or VEGF-R2 that could have suggested a role in tamoxifen resistance.

As genetic variation in tamoxifen-metabolizing enzymes may be another factor to consider, we examined the frequency of germline cytochrome P450 (CYP)2D6\*4 variant genotype from normal tissue of early relapse patients. Results were compared to frequency of this variant in South-west French healthy people.

**Materials and Methods:** DNA was isolated from paraffin-embedded normal tissue from 22 patients having subsequently relapsed within 3-years adjuvant tamoxifen. After PCR amplification of CYP2D6 gene, the CYP 2D6\*4 polymorphism was detected using restriction enzymes as previously described (Jin, JNCI 2005). Frequency of CYP2D6\*4 variant was simultaneously determined by analysis of DNA from 100 local healthy blood donors.

**Results:** CYP 2D6\*4 heterozygotes were in 14 among 22 relapsed patients (64%) compared to 40 among 100 healthy people. Difference is statistically significant (Chi-2 test, p=0.04). No CYP 2D6\*4 homozygote variant was observed.

**Conclusion:** As CYP 2D6 polymorphism does not appear to increase breast cancer risk, these results confirm a clinical relevant association between genetic variation in tamoxifen-metabolizing enzyme CYP2D6 and early relapse. Analyses of a larger number of relapsed patients are in progress. Results of a cohort of patients treated with adjuvant tamoxifen who did not relapse despite adverse prognostic factors (grade III and N+ >1) will also be available. Individual analysis of CYP2D6 genetic variant may be in the future an important factor to be considered for selection of patients who should receive upfront aromatase inhibitor treatment.

## 22 Proffered Paper Oral Clinical implications of CYP2D6 genotyping on tamoxifen treatment in breast cancer

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**Background:** In October 2006 the FDA recommended an update in the tamoxifen label to reflect the increased risk for breast cancer recurrence in postmenopausal ER-positive patients who are CYP2D6 poor metabolizers. This recommendation however was based on only few studies at that time. More clinical studies addressing the relation between CYP2D6 genotype and tamoxifen efficacy have been performed and published since. An updated analysis of the literature is presented.

**Methods:** Searches were conducted of Medline, Embase, Web of Science, scientific meeting proceedings and manual review of references from eligible publications.

**Results:** 8 eligible studies were evaluated, 7 of which were retrospective analyses and one was published as abstract. One study investigated the effect in metastatic breast cancer in a small partially prospective cohort. Another study investigated the effect on prophylactic tamoxifen use. Five studies were in line with the FDA advice, however 3 studies (including the largest study) showed contradictory results. Possible explanations for the conflicting results are the inability to adjust for possible confounders – especially CYP2D6 inhibitor use – and the comparison of different groups of combined genotypes (\*4/\*4 + \*1/\*4 vs \*1/\*1 or \*4/\*4 vs \*1/\*1 + \*1/\*4). The 3 studies showing no or even an opposite effect were unable to account for some important confounders. Still, confounding bias is expected to be limited because of the influence of Mendelian randomization. Furthermore, mostly only the \*4 allele has been investigated whereas other CYP2D6 variant alleles (e.g. \*5, \*9 and \*41) may also modify the effect.

**Conclusions:** The clinical relevance of CYP2D6 genotyping to tailor tamoxifen therapy has not been fully clarified as present study results are inconsistent. In a small majority of studies an increased risk in poor and intermediate metabolizers is reported. The biological activity of tamoxifen is possibly modified by other factors, some influencing the major metabolite endoxifen (e.g. CYP2D6 inhibitor use). Therefore, at the Leiden University Medical Center, the Netherlands, a prospective study is started to associate complete CYP2D6 genotype by SNP array and endoxifen plasma concentration with breast cancer recurrence and survival, powered to detect a doubled risk of recurrence in poor CYP2D6 metabolizers (n=650).

Wednesday, 16 April 2008

12:30–14:30

## POSTER SESSION

### Advocacy and education

## 23 Poster Informational and supportive needs of women considering extended hormonal adjuvant treatment (ExHAT) – a Canadian survey conducted by SOLARIS (Summit of Opinion Leaders – Advocacy, Research, Information and Support)

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**Background:** The results of NCIC MA-17 led to the need to inform women of the potential benefits of ExHAT with Letrozole (L) following 5 years of adjuvant (adj) tamoxifen (T).

**Method:** In 02/2007, we convened a meeting of 30 key advocates/survivors in Canada (SOLARIS) to discuss this issue. Under the auspices of the Canadian Breast Cancer Network (CBCN), we conducted a 43 question National Survey addressing the informational and supportive needs of women who had completed at least 4 years of adjT. The survey was completed online or by mail through CBCN and Ipsos Reid between 12/04–28/05, 2007.

**Results:** There were 230 respondents (CI:±6.5%)—the vast majority responded through mail/website. Median age was 61.5 years (range

36–84). Most (73%) women had post-secondary education; 70% lived in an urban setting; 38% were menopausal at time of diagnosis and 50% had received prior adjuvant chemotherapy. All women had adjuvant therapy (11% < and 86% >5 years) and 59% were involved in the initial treatment decision to start adjuvant therapy. Following completion of adjuvant therapy, 39% remained 'worried' about cancer recurrence and 35% felt they 'needed additional treatment'. Only 25% of women felt recurrence was 'unlikely'. The majority (66%) were 'satisfied' with the information received from treating physicians at completion of adjuvant therapy, however other sources of information were also consulted by these women, including survivors (59%) and support groups (43%). Post adjuvant therapy, 72% were willing to take ExHAT (78% node+ and 69% node-). Of those unwilling to take ExHAT (24%), the majority felt it was 'unnecessary' or were concerned about side effects. For those who took ExHAT with L (n = 76), treatment duration was assumed to be 5 yrs (39%); <5 yrs (14%), >5 yrs (3%) and undefined (43%).

**Conclusions:** This study addresses gaps in information needs of women completing 5 years of adjuvant therapy. The majority of Canadian women (regardless of nodal status and duration of adjuvant therapy) would take ExHAT. Women need and desire further information about recurrence risk and treatment options. As support groups play a significant role in meeting this need, accurate information sharing through mechanisms such as SOLARIS are warranted. Supported by a research grant to the CBCN by Novartis Canada.

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Poster

**The Pink Lady – Mobilising a community for breast cancer advocacy**

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In August 2007, Breast Cancer Network Australia mobilised the Australian city of Sydney through its stunning *Field of Women LIVE* event. Australians – women and men alike, from across the country – rallied to the call to action with 13,000 standing together in the shape of "The Pink Lady" in pink ponchos and 100 in blue to make a powerful community statement about Australia's annual breast cancer incidence rate.

The display, held in the stadium used for the Sydney Olympics, was orchestrated to occur immediately before a major evening football game of 65,000 spectators and televised live nationally.

The event was an outstanding success from every perspective. Highlights included:

- Strong engagement over several months at the community level
- Significant media activity in the lead-up and on the night
- Unique opportunity to communicate key public health messages
- Attendance and ongoing commitments by major politicians
- Opportunity for the community to express support for the cause through tangible action
- Raising \$650,000 for BCNA's continued work
- Extraordinarily positive feedback from participants

The *Field of Women* display has become an international event, with communities around the world recognising its power as an advocacy tool. Planting of the Pink Lady silhouettes is an annual event in Cyprus and in July 2008 the *Field of Women LIVE* event will rally 10,000 to form the Pink Lady shape in Liverpool, UK.

"The experience will stay with me forever. In memory of my grandmother and mother, for myself and my friends who are now survivors. It was peaceful to be in a place where women all knew how you felt. The emotions and strength of everyone on the field was exhilarating." [Tracey]

"The whole night was totally awesome. Walking onto the stadium was electrifying and full of meaning. I was not alone and I have made it through a tough journey with the support of my loving family and friends. We stood united and I cried with total strangers." [Jenny]

Vision of the Sydney event can be viewed at [www.fieldofwomen.org.au](http://www.fieldofwomen.org.au)

Very moving DVDs from events held in Melbourne (2005) and Sydney are available from Breast Cancer Network Australia

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Poster

**Knowledge, attitudes and behaviour among Cypriot women on breast cancer**

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**Background:** Europa Donna Cyprus in its efforts to increase public awareness commissioned the first survey amongst Cypriot women in order to explore their knowledge, attitude & behaviour regarding breast cancer.

**Method:** A sample of 1000 women over 15 years old was randomly selected by applying the method of Multi-stage Cluster Probability Sampling. The sample population covered both rural and urban areas of Cyprus, the data was collected through personal interviews, based on closed questionnaires at their homes during May–September 2007. The questionnaire consisted of 2 parts: Part A 32 questions focused on perceptions and knowledge of women on breast cancer's issue. Part B 18 questions were designed to target those women in the sample who

were living with breast cancer and volunteered that information to the interviewers.

**Results, Part A:**

- Awareness: Nearly 50% avoid talking about breast cancer, 1 in 4 did not know how to do self examination, 8 in 10 said the prospect of developing breast cancer would frighten them more than having HIV/AIDS or Diabetes, there is positive correlation between the variables Education & Breast Awareness.
- Experience of a relative/friend: 6 in 10 knew someone with breast cancer, 35% said, knowing someone from their familiar environment has prompted them for breast checks.
- National Breast Cancer Screening Program: 58% knew about the program, 78% of those invited to the program responded positively, 22% who were invited and did not go for their appointment did not know getting older was a strong risk factor.
- Europa Donna Cyprus: Half of the participants knew there are around 400 new breast cancer cases a year, 55% was aware of Europa Donna activities.

**Part B:** Out of the 1000, 32 voluntarily disclosed the information of having breast cancer. More specifically, 3 in 10 declared knowledge of the European Resolution on Breast Care, Multidisciplinary Breast Clinics and Clinical Trials.

**Conclusion:** Greater effort is needed for awareness programs to empower women to be informed and active participants in their care, also demand and work effectively towards the implementation of the European guidelines on mammography screening programs, diagnostic procedures/treatment and after care.

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Poster

**Breast cancer – a survey of 2000 Asian women and men to compare their level of knowledge**

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**Background:** Singapore has one of the highest incidence of breast cancer in Asia. A nation-wide breast cancer screening programme was implemented in 2002. However, 21.5% of women still presented with late stage breast cancer. Due to a more conservative attitude, breast cancer is often a taboo topic amongst many Asian cultures. This may lead to incorrect myths and misconception about breast cancer that may result in a delay in treatment. In many Asian households the male relative (father, husband and/or brother) is an important decision maker in health matters.

A survey was conducted to compare the level of knowledge of breast cancer between Asian women and men in terms of screening, symptoms and treatment.

**Material and Methods:** Between January to June 2007, 1000 Asian women and 1000 men in Singapore completed a self-administered questionnaire. One point was given for correct knowledge answer and zero for wrong or "not sure" answer. The maximum knowledge score was 19.

**Results:** The response rate was 100%. The racial distribution follows that of the national demographics. The median score was 12 (women) and 10 (men) ( $p < 0.05$ ) (range 0–19). Overall scores were high for general knowledge but low for risk factors, symptoms, screening and treatment. Older age, race (especially Malays), lower education, lower income, smaller housing and not knowing someone with breast cancer were independent predictors of poor scores. Men tended to score lower than women in most aspects.

Two thirds (60%) of the women compared to 48.2% of men were able to list at least one symptom of breast cancer correctly ( $p < 0.05$ ). Half of the women compared to two-thirds of men thought that a cancerous lump would be painful ( $p < 0.05$ ). Of the women respondents, 63.5% could name a screening centre compared to 42% of men ( $p < 0.05$ ). There were 40.8% of women and 42.6% of men who believed that the arm would be crippled after a mastectomy ( $p < 0.05$ ).

**Conclusion:** The level of breast cancer knowledge in an Asian population is low. Many myths and misconceptions are prevalent. Men compared to women have poorer knowledge. Identifying those with poor knowledge would enable organisation of public education programmes targeted at them. This may help to improve screening rates and hence breast cancer survival.