

a screening modality for women age 50–69, it is out of reach for many socially disadvantaged women in Egypt, and another approach has to be considered for the early detection of breast cancer. The CBST has therefore been designed to evaluate the role of clinical breast examination as a primary screening modality in the context of primary care. It is anticipated that early detection programmes based on primary care, coupled with the provision of adequate treatment for detected cases, could reduce both the morbidity and mortality from breast cancer.

An initial pilot phase of the CBST involving 4116 women has been completed. In that phase a specialised medical centre in Cairo (the Italian Hospital) was selected as the headquarters of the study. An area around the Italian Hospital was geographically defined. The initial target group was the approximately 5000 women age 35–64 living in this area. Maps of the area were obtained, and divided into blocks. Larger scale maps of each of the blocks were made. Trained social workers conducted door to door visits to the houses in the blocks allocated to them, and invited women in the relevant age group to participate in the study. Those 4116 women who agreed to participate were administered an initial enrolment questionnaire, and invited to attend a primary health centre for CBE. Those found abnormal were referred to the Italian Hospital for investigation and treatment. In the second year, cluster randomization was performed and half the women were re-contacted, and invited to attend for screening. In the third year, those not contacted in the second year were visited at home and their health status determined.

The pilot study confirmed that breast screening, using CBE by female doctors detects a high rate of breast cancer; about 8 per 1000 at the first examination and two per thousand among those who attended for re-screening. This suggests that a mortality benefit might be observed if a study with sufficient power proves feasible.

It became apparent, that a substantial segment of women in the community, are resistant to attempts to involve them in the whole process of screening. These women appear to comprise a high risk sub-group, on whom special surveillance and general public education efforts are justified. They have a prevalence of breast cancer at least as high as those who attend, while their delay in attending is probably contributing to advanced disease at diagnosis, completely the reverse of the compliant group. There are indications that as the project proceeded from Phase 1 to 2, there was increasing willingness in the community to participate. This is encouraging and initiation of screening in other districts should be seriously considered.

234

INVITED

#### How does Ukraine cope?

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In Ukraine Breast Cancer (BC) is rated the highest among malignant tumour-related diseases. In Ukraine in 2002 year fall ill with BC 14 579 women. The incidence rates increased more than twice (2.27) within the last 10 years from 22.6 women per 100 000 population in 1986 to 56.4 in 2002. One of the most objective indicators is the rate of deaths within one year of diagnosis. In 2001 14% of women with diagnosed BC have died within one year. According to National Cancer Register in year 2002 only 12% of new cases were identified at stage I and 30.3% of new BC cases are still being identified in the late stages (III and IV).

Due to severe economic conditions of post soviet Ukraine and absence of the consecutive and effective policy in Health Care System reforming medical professionals face great challenges in providing basic primary health care, let alone early detection services and optimal clinical care for women with the disease. Within the last 10 years Screening mammography politics and programs were not developed and implemented. Ukraine has a big lack of the modern equipment. Less than 10% of functioning mammography machines counted in state sector were considered modern.

The treatment of BC is exercised mainly in the Oncological Clinics. The majority of patients receive complex treatment: surgery, radiation, chemotherapy and hormonal therapy. In 2002 specialised treatment was provided for 74.0% of patients with primarily diagnosed BC. Radical mastectomy (removal of the breast and regional lymphatic nodes) outweighs other surgical approaches. The reason lies in the later stages detection. Many surgeons in Ukraine are familiar with conservative surgery but it is often hardly realisable.

The critical situation with BC in Ukraine is further aggravated by the lack of chemotherapeutic medications. Although the State Program "Oncology 2002–2006" has provided near 15.8 million US dollars for the purchase of drugs to treat all cancer patients in Ukraine, but financing has really started in 2003 and not in full. This factor limits the possibility for a majority of women with BC to receive full medical treatment, as they can not afford to pay for the treatment themselves. As a result, BC contributes greatly to the high mortality rate among women in Ukraine.

Last year Europa Donna Ukraine/NGO Women Health and Family Planning created of the national Advocacy network "TOGETHER AGAINST CANCER" which promotes training of knowledgeable and experienced

activists, helps NGOs related to Health Care System, well-known public activists, doctors and women who had BC to initiate women rights advocacy, to launch medical prophylactics programs, to provide modern diagnostics opportunities, treatment, rehabilitation and social support of BC patients. Now this NGOs are successfully working in the field of BC Advocacy, implementation of European guidelines, information – educational programs on early diagnostics of BC, psychological and social support of patients with BC. As the results numerous nation-wide BC awareness and fundraising campaigns have been conducted in Ukraine. Services of psychological and social support of patients with BC were created on the basis of the Oncological Hospital in Kiev and some other cities of Ukraine.

235

INVITED

#### How does South Africa cope?

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South Africa represents a typical middle-income developing country. This results in a dichotomy of breast cancer diagnosis and therapy provision between the 20% of the population that are health insured and the others that have to rely on the state for provision of care. For the health insured there is western standard breast cancer screening and therapy available. The further discussion is limited to the state sector. As is typical for this type of country, translation of medical progress into practice is uneven and has been marked in South Africa's case by stagnation/regression in the past 10 years. Factors are large-scale emigration of health professionals at all levels to other English speaking countries, redistribution of health resources to primary care to the detriment of the tertiary sector, equipment/medicine costs spiraling out of control with the currency devaluation, the challenge of AIDS and a national health care policy motivated by political rather than pragmatic decisionmaking. The result is that despite the commitment to women's and child health, a coherent screening policy, as formulated in 2000 by outside consultants for the National Department of Health, is still not noted on the web-site of the department, even less implemented. Mammography is largely limited to 7 tertiary hospitals, breast cancer treatment has stagnated at the level of 1990. This means, that newer drugs, notably aromatase inhibitors, taxanes, navelbine and trastuzumab are not available. Radiation equipment is outdated and break-downs are frequent. Waiting times for radiation in breast conservation are 4–6 months, for emergencies like spinal cord compression between 1 and 2 weeks. Surgery is usually readily available. On a continental level, Africa presents a mixed picture of emerging, submerging and failed countries. Failed countries will not be able to offer any meaningful breast cancer care. Elsewhere surgery is usually readily available. Progress is only possible if political pressure is exerted to shift priorities from luxuries such as defence to health care. Women empowerment in traditionally male dominated societies of Africa is necessary. Developed countries may play an important role by making aid and trade relationships depending on the political shift described and by a long-term commitment to partner institutions in Africa in breast health training and service.

236

INVITED

#### How does Brazil cope?

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Breast cancer is a public health problem in Brazil. In 2003, more than 40,000 new women will be diagnosed with breast cancer, representing 24% of all malignancies in the female population and being the leading cause of cancer. Considering the global scenario, the incidence of breast cancer in Brazil is average, with 46 new cases per 100,000. More than 9000 women will die from breast cancer during this year. It is the number one cause of cancer death in Brazilian women. Brazil shares with other developing countries a non-age-corrected breast cancer incidence/mortality ratio of 0.39, as opposed to the ratio of 0.33 in the more developed world.

Brazil is a gigantic country with a population of 170,000,000. There is a wide variation in cancer incidence and mortality throughout the different areas. In the southern region, rates are closer to the ones found in North America as opposed to the north, where figures resemble those encountered in Africa.

Life expectancy has been increasing over the last decades in Brazil and, nowadays, a woman lives approximately 69 years. At the same time, a large portion of the population has moved from the rural to the urban areas. These figures may in part explain the increasing incidence and mortality observed throughout the recent decades. In the late seventies, breast cancer mortality was 8/100,000 and in the early 2000 it achieved almost 12/100,000.

A major limitation in terms of breast cancer control in Brazil relates to early detection. Thirty percent of women with breast cancer in Brazil still present with locally advanced breast cancer. There is a large room for

improvement and strategies are being implemented to change this picture. A large national breast cancer project is being planned and soon will incorporate screening mammography after the age of 50.

The increasing costs associated with treatment add to the burden of dealing with breast cancer in Brazil. Currently, breast cancer represents approximately 1/4 of the Government costs with systemic treatment (chemotherapy and hormonal therapy) in cancer.

In summary, breast cancer incidence and mortality are increasing in Brazil. During the next decade, the main challenge will be the development of a coherent strategy for its management based on detection at an earlier stage.

Thursday, 18 March 2004

16:00–17:15

## PROFFERED PAPERS

### Advanced disease

237

ORAL

#### Gene expression profiles of primary breast tumors maintained in lymph node- and distant metastases

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**Background:** Metastases at distant sites are the main cause of death in breast cancer. It is largely unknown whether the characteristics of breast cancer that define the growth rate and therapy response of the primary tumor are alike in the metastases. Furthermore, it is still unclear whether metastases derive from highly metastatic subpopulations of tumor cells within the primary site, or whether they originate from a random fraction of tumor cells. To test this, we compared pairs of human primary breast carcinomas and their lymph node metastases as well as primary breast tumors and their metastases developed years later at distant sites, both by gene-expression profiling.

**Patients and methods:** Surgical specimens of primary breast tumors and their matching lymph node metastasis of 15 patients, and specimens of primary breast carcinomas and their matching distant metastasis from different localizations of eight patients were collected from the frozen tissue bank of our hospital. RNA from these tissues was isolated, DNase treated and cRNA was generated using T7 RNA polymerase. Fluorescently labeled cDNAs were hybridized to an 18k human microarray (Central Microarray Facility, Netherlands Cancer Institute). Intensities of scanned images were quantified, normalized and ratios were calculated and compared to the intensities of a reference pool. Gene clustering and tumor clustering were performed using an unsupervised hierarchical clustering algorithm (Pearson correlation coefficient).

**Results:** We show, by gene-expression profiling, that human primary breast tumors are strikingly similar to their regional lymph node metastases as well as to their distant metastases of the same patient. Unsupervised hierarchical clustering, multidimensional scaling, permutation testing, as well as the comparison of significantly expressed genes within a pair, reveals their genetic similarity.

**Conclusions:** Our results show that the molecular program established in a primary breast carcinoma is not only highly preserved in its regional lymph node metastasis but also in its distant metastasis. These findings suggest that metastatic capability in breast cancer is an inherent feature, and is not based on clonal selections. The results further imply that neo-adjuvant treatment given to patients based on the response expression profiles of their primary breast tumor might also prevent the outgrowth of micrometastases.

238

ORAL

#### The clinical and prognostic implications of isolated supraclavicular fossa recurrence

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**Introduction:** In 2003, AJCC changed the classification of breast supraclavicular fossa (SCF) node metastasis. This is now classified as stage 3C. We have reviewed our experience in the light of these changes.

**Methods:** Review of case notes and database of 8691 patients with a diagnosis of breast cancer and either isolated ipsilateral or contralateral SCF metastasis. All patients had completed treatment for primary breast cancer and had no previous evidence of metastatic disease. Patients

diagnosed with metastatic disease at other sites either at the time of SCF recurrence or within the next three months were excluded.

**Results:** There were 125 cases of ipsilateral (I-L) SCF recurrence (SCFR) and 22 separate cases of contra-lateral (C-L) disease. The median time from primary diagnosis to SCFR was 1.92 yrs for I-L disease and 3.32 years for C-L (p=0.0229). Patients had originally presented with node positive cancer in 79% of cases (I-L 80%, C-L 73%, p=0.58) and locally advanced disease in 9.5% (I-L 8.8%, C-L 13.6%, p=0.75). 57% were primary invasive ductal carcinomas, 3% infiltrating lobular carcinomas and 40% other types. At diagnosis 2.5% were grade 1, 46% grade II and 52% grade III. There was no significant difference in tumour type or grade between I-L and C-L. Treatment for SCF recurrence comprised combinations of chemo and hormonal and radiotherapy. Median time to first relapse after SCF recurrence was 11 months. Sites of first relapse were lung in 16%, pleura 9%, bone 8%, liver 10%, skin 7%, brain 3%, mediastinum in 3%, ascites in 2%, local breast recurrence in 31%, and other mets in 18%. The median time from SCF recurrence to death not significantly different between C-L (1.89 yrs) and I-L (2.63 yrs, p=0.184) recurrence. There were no patients who did not eventually die from their disease (survival = 0%), but 15% were still alive at 5 yrs (3/22 C-L and 19/125 I-L), and 3.4% at 10 years (0/22 C-L and 5/125 I-L). Median survival was 25 months for chemotherapy alone (12.2%), 28.3 months for those treated with combined RT and systemic (hormonal and/or chemotherapy) and 40.6 months for hormonal therapy (21.1%).

**Conclusion:** This is the largest published series of SCF recurrence. It demonstrates that SCF recurrence is associated with subsequent systemic metastases and eventual death in 100% of cases. I-L disease is diagnosed at an earlier stage than C-L, but both have a similarly poor prognosis. SCF recurrence might be better regarded as stage IV disease.

239

ORAL

#### Trastuzumab (Herceptin®) plus docetaxel versus docetaxel alone as first-line treatment of HER2-positive metastatic breast cancer (MBC): results of a randomised multicentre trial

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**Background:** The H0648g trial showed a significant survival benefit for Herceptin (H) plus paclitaxel compared with paclitaxel alone, and as a result the combination is licensed for the treatment of HER2-positive MBC as first-line therapy. Phase II studies have shown that the combination of Herceptin plus docetaxel (HD) is also active in patients with HER2-positive MBC. A large, multicentre randomised trial (M77001) was conducted to compare HD versus docetaxel alone (D) as first-line therapy in HER2-positive MBC.

**Patients and methods:** 188 patients (pts) with HER2-positive MBC and at least one measurable lesion were randomised to either HD or D given as first-line treatment. Two pts in the HD arm received no study treatment and were excluded from analysis. Ninety-five percent of pts had IHC 3+ and/or FISH-positive disease. Herceptin dosing was 4 mg/kg iv (loading) followed by 2 mg/kg weekly until disease progression, and docetaxel 100 mg/m<sup>2</sup> iv q3w × 6 cycles. Patients progressing on D alone were allowed to cross over to receive H. Response was assessed according to WHO criteria and radiologically confirmed by an independent review board. Patient demographics were generally balanced between the arms, although more D than HD pts were hormone-receptor positive (56% v 41%), and more HD than D patients had received adjuvant anthracyclines (64% v 55%).

**Results:** At 12 months after last pt enrolment, efficacy in the HD arm was significantly better than in the D arm: overall response rate 61% v 34% (p=0.0002); median time to progression 10.6 v 5.7 months (mo) (p=0.0001); median duration of response 11.4 v 5.1 mo (p=0.0011). Survival was significantly superior for HD (p=0.0062) (median overall survival 30.5 mo in the HD arm v 22.1 mo in the D arm), despite at least 48% of pts in the D arm crossing over to receive H. Pts who crossed over from D to receive H had a longer estimated median survival (24.5 mo) than those who did not cross over (19.1 mo). Grade 3/4 non-haematological toxicity was similar in the two arms. The incidence of febrile neutropenia was slightly higher in the HD arm (23%) than the D arm (17%) but was generally manageable; two septic deaths occurred in the D arm. Symptomatic heart failure occurred in 2 pts in the HD arm (2%), but both cases were in the