Wednesday, 20 March 2002 **9:00–9.45**

EUROPA DONNA TEACHING LECTURE

Is breast cancer preventable?

16 INVITED

Is breast cancer preventable?

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Breast cancer is certainly not preventable at the same degree as lung cancer is by avoiding cigarette smoking or bladder cancer by avoiding exposure to some specific professional carcinogens. In the fight against breast cancer priority should still be given to early detection and treatment improvement: incidence is still rising in the Western World but mortality is constantly decreasing. However, research should continue in the field of prevention despite the fact that most of the recognized risk factors - mainly age and reproductive factors - are non modifiable. This situation may change in the future when more knowledge will be available on some key biological mechanisms of pregnancy and lactation. It is already known for example that markers like low placental weight, small placenta diameter, increase in blood pressure during pregnancy are associated with a reduced risk of breast cancer both in the mother and the daughter. The whole issue of hormonal balance is crucial and for this reason there is a constant need for investigation and research on the impact of contraceptive pill and Hormone Replacement Therapy (HRT) on the risk of breast cancer. It should also be stressed that in acting on the hormonal balance one should not think only of breast cancer but also of other important aspects like osteoporosis and coronary health disease. Actually these issues are presently being addressed by the so-called chemoprevention trials and in particular by the STAR study in the U.S. confronting Tamoxifen vs Raloxifene as preventive agents for menopausal women.An understanding of the targeted actions of this novel drug group will potentially result in the introduction of new multifunctional medicine with applications as preventive agents or treatments of breast cancer and endometrial cancer, coronary heart disease, and osteoporosis.

From the general point of view of lifestyle a number of possible preventative measures have been suggested including physical exercise, reduction of alcohol intake and diet modifications but none of them is certainly going to play a major role in breast cancer prevention.

From the genetic predisposition point of view the basic statement should be that this is a quite limited issue since only 5 to 10% of breast cancers can be related to an inherited condition. Proposals to prevent familial breast cancer include strict surveillance, chemoprevention and prophylactic mastectomy (also called RRM, risk reduction mastectomy).

Wednesday, 20 March 2002 **11:00–13:00**

KEYNOTE SYMPOSIUM

The prevention of breast cancer

17 INVITED

Biological foundations of breast cancer prevention strategies

M. Pollak. *McGill University, Oncology Department, Montreal*

Individualization of Prevention Strategies: It is frequently assumed that successful breast cancer prevention will follow the discovery of a single prevention method that will reduce the risk of all women. This may be naive; specific risk reduction strategies may have to be offered to individual women based on an understanding of the dominant mechanisms of risk operating in each particular case (analagous to selective rather than universal use of antihypertensives or statins to lower risk of MI). Breast cancer prevention strategies such as increasing exercise or retinoid supplementation that have been reported to show borderline activity in terms of risk reduction in unselected populations may actually be effective at reducing risk, but only in sub-populations that we currently are unable to identify. We will describe genetic polymorphisms that are under investigation as markers that might aid in selection of optimum prevention strategies for individual women. Prevention trials should be designed to allow detailed characterization of subpopulations for whom the intervention is or is not effective.

Implications of Early Life Risk Factors: Higher birth weight has consistently been shown to be positively correlated with breast cancer risk, and understanding of the underlying mechanisms may offer clues to novel prevention strategies. Recent experimental work has provided evidence that factors that favor in-utero growth also increase carcinogen sensitivity in adulthood. One example concerns responsivity to mitogenic stimuli-individuals with high responsivity tend to be larger at birth, but also to have higer levels of cellular turnover in adulthood, and this may predispose to transformation. It is possible that risk/benefit analysis concerning postmenopausal estrogen replacement may yield distinct results according to the presence or absence of concomitant risks that can be assessed prior to menopause.

Hormonal vs. Non-Hormonal Risk Reduction Strategies: Significant clinical trial resources have been devoted to "hormonal" interventions, including SERMs and retinoids. Future work will include not only further investigations of these approaches, but also attempts to improve quantification of effects (if any) of lifestyle factors, including diet, on risk. Clues that aromatase inhibitors and COX2 inhibitors may reduce risk for some women require follow-up.

18 INVITED

Targeting of oestrogen and growth factor signalling pathways in the therapy of breast cancer: Implications for chemoprevention

R.I. Nicholson, I.R. Hutcheson, J.M.W. Gee. *Tenovus Centre for Cancer Research, Welsh School of Pharmacy, Cardiff, UK*

There is an increasing body of evidence demonstrating that growth factor networks are highly interactive with oestrogen receptor (ER) signalling in the control of breast cancer growth and that the mitogenic activities arising from either pathway are unable to operate efficiently in the absence of the other in endocrine responsive cells. This is due to a physical overlapping and common use of their signalling elements, in addition to the ability of oestrogens and growth factors to coregulate the expression of genes involved in proliferation and cell survival. As such, tumour responses to antihormones are likely to be a composite of the ER and growth factor inhibitory activity of these agents. Data will be presented examining the modulation of oestrogen and growth factor networks during endocrine response, and the *in vitro* and clinical evidence that altered epidermal growth factor receptor and c-erbB-2 signalling, maintained in either an ER dependent or independent manner, is critical to antihormonal resistant cell growth. The considerable potential of inhibitors of signal transduction pathways to increase the effectiveness of antihormone therapies will be highlighted, as will the future relevance of the studies to the chemoprevention of breast cancer.

19 INVITED

Chemoprevention: Inside and outside trials

J.F. Forbes. *University of Newcastle, and ANZ BCTG, Newcastle 2298, Australia*

Chemoprevention trials are at the point reached by adjuvant therapy of early breast cancer (BC) in the mid-1970's -the NSABP P1 trial showed that tamoxifen reduces the risk of clinical breast cancer by about 50% in women at increased risk (5 year BC risk of $\geq$1.7%), with short follow-up. This benefit is for women ages 35–49 and 50 years and over, was greater for women with epithelial atypia, and apparently confined to tumours positive for oestrogen receptor (ER+ve). Tamoxifen increased the risk of uterine cancer, and thromboembolic disease, and reduced the risk of osteoporotic fractures (wrist, hip and lumbar spine) in women 50 years and over. Data from 19 women with BRCA1 or 2 mutations suggest the tamoxifen effect is greater in women with BRCA2 mutations rather than BRCA1, although this may be a consequence of BRCA2 related BC being predominantly ER+ve, and BRCA1 related BC predominantly ER-ve. The Gail Model used for P1 did not include bilateral BC, age of BC diagnosis, paternal history or ovarian cancer, and hence excluded proportionately more women at increased genetic risk for BC. The Marsden tamoxifen prevention trial, had proportionately more women at increased genetic risk, and it remains possible that tamoxifen may have a "negative" effect on risk of ER-ve tumours. The large IBIS I (International Breast cancer Intervention Study I) tamoxifen prevention trial remains blinded and may clarify the duration of any tamoxifen effect.

Ovarian ablation in women at increased risk is associated with a reduced BC incidence suggesting that reduction in circulating oestrogen may sup-

press BC growth. Contralateral BC rates were reduced in randomised trials by adjuvant goserelin added to other adjuvant therapies including tamoxifen and by adjuvant anastrozole compared to tamoxifen with short term follow-up. A new international trial, IBIS II, will be launched in 2002 comparing anastrozole to tamoxifen or placebo in postmenopausal women at increased risk. The NSABP STAR trial is comparing tamoxifen with raloxifene. The "RAZOR" pilot trial is investigating the use of goserelin and raloxifene in premenopausal women at very high risk.

Outside of trials, strategies may vary with personal circumstance (age and risks of uterine cancer, thrombosis and osteoporosis) and preferences (attitude to surgery and importance of continued ovarian function. Population strategies however aim to optimise risk-benefit and cost-benefit ratios and are not necessarily relevant to individual women.

20 INVITED

Update on new studies in Europe

J. Cuzick. *Imperial Cancer Research Fund, Mathematics, Statistics & Epidemiology, London WC2A 3PX, UK*

Three European prevention studies using tamoxifen are now maturing and should provide definitive evidence on the role of tamoxifen in prevention in the next few years. New studies are focusing on the value of directly reducing oestrogen levels. The IBIS-II study will randomise 10,000 high risk post-menopausal women between anastrozole, tamoxifen and placebo, and another 4000 women between anastrozole and tamoxifen. The recent ATAC data have shown that anastrozole can reduce recurrence by 27% in receptor positive women compared to tamoxifen and new contralateral tumours have been reduced by 58% compared to tamoxifen, suggesting a 70–80% reduction compared to no treatment. The side effect profile appears to be more favourable, with fewer hot flushes, endometrial cancers, thromboembolic events, and strokes. However, fracture rates are increased.

In premenopausal women, pilot studies with zoladex are being undertaken. The key question here is the most effective 'add-back' agent or agents in terms of bone preservation and menopausal studies. These different pilot studies are exploring the use of raloxifene, tibolone, and bisphosphonates as add-back.

An Italian study – HoT is evaluating the role of low-dose tamoxifen (5 mg/day) in reducing breast cancers associated with HRT.

Wednesday, 20 March 2002 14:45–16:15

SYMPOSIUM

New standards of care in adjuvant endocrine therapy

21 INVITED

The rationale of the new endocrine agents

M. Dowsett. *Royal Marsden Hospital - NHS Trust, Professor of Biochemical Endocrinology, London, United Kingdom*

The rationale for the most widely used medical endocrine therapies is invariably based around the antagonism or withdrawal of oestrogen stimuli to oestrogen receptor and/or progesterone receptor positive breast cancer. The methods of withdrawal differ according to the menopausal status of the patient. In premenopausal women the aim is to block ovarian stimulation using GnRH agonists. There are now GnRH antagonists in late stage development which have the advantage of no initial gonadal stimulation and in contrast to GnRH agonists achieve persistent FSH suppression which may yield more complete ovarian ablation. In postmenopausal women, third generation aromatase inhibitors have been shown to achieve near complete oestrogen deprivation. Cell-line data indicate that increased sensitivity to residual oestrogens occurs after long-term oestrogen deprivation, and there are clinical data consistent with this. This observation suggests that the completeness of oestrogen withdrawal with aromatase inhibitors may be important. Recent data have demonstrated that in post-menopausal women such oestrogen deprivation is more effective than the selective oestrogen receptor modulator (SERM) tamoxifen. This may be due to significant agonist activity of tamoxifen which is more pronounced at low oestrogen levels. Some preclinical and clinical data indicate that the differential effectiveness of oestrogen deprivation and tamoxifen is greater in the presence of HER-2 and/or EGFr. These observations enhance the need for a SERM with no breast agonist activity and provide a rationale for the pure anti-oestrogen ICI 182780 which has a double effect on reducing oestrogen stimulation: antagonism at the level of ER and destabilisation of ER leading to reduced ER levels.

22 INVITED

LHRH agonists

R. Jakesz. *Vienna University, Dept. of Surgery, Vienna, Austria*

Ovarian ablation in the adjuvant treatment of premenopausal patients has shown to improve recurrence-free and overall survival over untreated controls.

In premenopausal women with hormone-responsive tumors, ovarian ablation and CMF chemotherapy produce identical longterm effects with respect to recurrence-free and overall survival.

Patients who develop amenorrhea upon chemotherapy show a significantly better longterm outcome than those retaining their mensis. These results clearly demonstrate that ovarian ablation is an important tool to improve the prognosis of premenopausal patients with hormone-responsive tumors.

LHRH agonists serve to produce reversible ovarian supression and, in premenopausal women with estrogen receptor-positive disease, have resulted in 5-year recurrence-free survival rates that are identical to those achieved with CMF.

A trial conducted by the Austrian Breast and Colorectal Cancer Study Group randomized patients to receive either a combination of LHRH analog (goserelin) and tamoxifen or adjuvant CMF chemotherapy. After a median survival of 5 years, patients undergoing endocrine treatment experienced significantly superior relapse-free survival over those treated with CMF.

In turn, Intergroup Trial 0101 in premenopausal women with hormone receptor-positive tumors allocated patients to either anthracycline-containing chemotherapy alone, to a combination with goserelin, or to a combination with goserelin and tamoxifen. The addition of combined endocrine treatment to chemotherapy yielded significantly superior recurrence-free survival benefits not achieved by the chemotherapy-goserelin combination.

In summary, LHRH analogs are to be considered an important tool in the treatment of premenopausal patients with hormone-responsive breast cancer. Goserelin and CMF are shown to be equally effective modalities. Finally, goserelin-tamoxifen combination treatment is superior to CMF, and this combination added to FAC is significantly more effective than FAC alone.

23 INVITED

Current status of aromatase inhibitors

M. Baum. *The Portland Hospital, Department of Oncology, London, United Kingdom*

Aromatase inhibitors prevent oestrogen biosynthesis in tissues by inhibiting the enzyme aromatase, which catalyses the conversion of adrenal androgens (androstenedione and testosterone) to oestrogens (oestrone and oestradiol). Aromatase activity is present in many tissues, but the main sources of circulating oestrogens are the ovaries in premenopausal women and the adipose tissue in postmenopausal women. Furthermore, unlike most other hormonal pathways, oestrogen concentrations in postmenopausal women are not under feedback control. Aromatase inhibitors can therefore reduce circulating oestrogen concentrations to below the limit of detection.

Aminoglutethimide was the first aromatase inhibitor to be approved for the treatment of breast cancer, but this drug lacked specificity and had troublesome side effects. A new generation of both steroidal and non-steroidal aromatase inhibitors which are highly selective, are well tolerated and have demonstrated clinical effectiveness in the treatment of advanced breast cancer are currently under investigation in the adjuvant setting for postmenopausal women.

The new generation of oral specific aromatase inhibitors, such as Anastrazole, make a very attractive option for adjuvant therapy in ER positive postmenopausal women. In fact the largest and most rapidly recruited trial in the history of the subject (ATAC)involving over 9,000 patients has just been reported.This study compares Anastrozole with Tamoxifen alone or in combination. Other trials making use of alternative aromatase inhibitors,cross over or sequencing with tamoxifen or as perioperative therapy are also in progress.