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

EUROPA DONNA TEACHING LECTURE

# Is breast cancer preventable?

**16** INVITED

### Is breast cancer preventable?

A. Costa[1+2]. [1] *Fondazione Salvatore Maugeri, Division of Breast Surgery, Pavia, Italy;* [2] *European School of Oncology, Milan, Italy*

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-