Friday, 19 March 2004 08:30–09:15

EUROPA DONNA TEACHING LECTURE

Risk factors for breast cancer

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Risk factors for breast cancer

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The large prospective cohort studies published since 1995 confirm beyond a reasonable doubt that postmenopausal women with high plasma sex hormone levels, both androgens and estrogens, have an increased risk of developing breast cancer. The risk associated with postmenopausal overweight is actually explained by an increased production of estrogens in the adipose tissue. Before menopause, epidemiological studies have shown that breast cancer risk is associated with high plasma levels of insulin-like growth factor-1 (IGF-I), with high levels of testosterone, and with luteal insufficiency (i.e. low progesterone levels). Most likely also the other classical risk factors, including high stature, early menarche, and nulliparity, as well as the increased risk during pregnancy and shortly afterward, and during hormonal replacement treatments, depend on the blood levels of hormones and growth factors. A few studies also suggest an association of breast cancer risk with high blood levels of insulin, glucose and triglycerides. These results, together with the demonstration of the protective effect of physical activity, suggest that the dramatic increase of breast cancer observed in the last century in western countries, besides the change in reproductive variables, largely depends on the increasing prevalence of the metabolic syndrome associated with western lifestyle, characterised by high consumption of refined carbohydrates and saturated fats, leading to hyperinsulinemia and reduced insulin sensitivity. Insulin, in fact, stimulates the ovarian synthesis of androgens and inhibits the liver synthesis of sex hormone-binding globulin and IGF-binding proteins 1 and 2, thus increasing the bio-availability of both sex hormones and IGF-I, which co-operate to stimulate breast cell proliferation. Randomised controlled trials have shown that decreasing the consumption of food with high glycaemic and insulinemic index, decreasing animal products, in particular saturated fats, and increasing traditional food based on unrefined grains, various beans and vegetables, may improve insulin sensitivity and decrease the bioavailable fraction of sex hormones and IGF-I. There is increasing evidence that these same risk factors also effect the risk of recurrence in breast cancer patients. Several studies, in fact, showed that overweight, weight gain during chemotherapy, and high plasma levels of insulin and testosterone are associated with a worst prognosis. Studies are ongoing to test whether these same dietary and endocrine/metabolic risk factors effect gene penetrance in women carrying deleterious mutations of BRCA1 or 2.

Friday, 19 March 2004 10:30–12:30

KEYNOTE SYMPOSIUM

High risk women: who are they and what can be done

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EUSOMA guidelines on the management of familial breast cancer risk

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An EC Framework 5 grant, FABRECAN, was obtained to draw up these guidelines, authorised by 35 specialists from 12 European countries, in all disciplines working in this field.

The Guidelines recommend that advice to women with a family history of breast cancer should be given within multidisciplinary family history clinics, the team including surgeon, clinical geneticist, molecular geneticist, pathologist, psychologist and radiologist.

For initial assessment of risk a preliminary questionnaire is recommended with reassurance of those at low risk. Those appearing at risk must be assessed by the clinical geneticist and their risk level explained in absolute terms. The Guidelines recommend which assessment methods should be used.

Women at moderate or high risk should be offered intervention.

There is low grade evidence that mammographic screening is useful in women at moderate risk and this should be offered between the ages of 35 and 50. Neither new screening modalities (eg) MRI, nor hormonal prophylaxis are proven. The recommendations are that these should not be offered outside clinical trials.

There is no clear phenotype of cancers in BRCA1/2 carriers but families with ER positive tumours should have BRCA2 probed first.

Women with recognised BRCA1 and 2 mutations should be offered prophylactic mastectomy (with reconstruction) if they are below the age of 50. Young women diagnosed with breast cancer and with a strong family history should be offered bilateral mastectomy with reconstruction. Otherwise (since 50% of women seeking surgery on family history alone will not have inherited the mutation) every effort should be made to establish mutation status. To ensure that women deciding on prophylactic surgery are making a stable decision they must receive counselling from the psychologist and post-operative support. To ensure the most suitable procedure and the cosmetic outcome of prophylactic surgery, operation must only be carried out by specialist breast surgeons or by plastic surgeons regularly working in association with the breast genetic team.

The Guidelines cover other aspects of the organisation of a Breast Cancer Family History/Genetic service eg. ethics, data recording and audit.

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Endocrine environment and breast cancer risk

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Indirect evidence supports a central role for endogenous hormones and growth factors in breast cancer development. Features of reproductive life like early menarche, late menopause, age at first birth, number of previous biopsies with atypical hyperplasia, increased mammographic density, use of HRT and family history of breast cancer are risk factors included in different individual risk assessment models. Tamoxifen provides a risk reduction in women at-risk for ER positive breast cancer, i.e., those with hormonal and reproductive risk factors, while the benefit in women with family history is unclear. Likewise, the MORE trial has confirmed that lifetime estrogen exposure is related to increased risk and may be reduced by raloxifene intervention. Notably, the magnitude of increased breast cancer risk with oral HRT is enhanced by combined estrogen-progestin regimens relative to estrogen alone, implying that different routes of progestin administration are required to control endometrial cancer risk.

Endogenous estrogens and insulin-like growth factors (IGFs) play an important role in the growth and differentiation of mammary cells and are involved in breast carcinogenesis. Birth weight, partly be mediated by the GH-IGF axis, is positively associated with risk of breast cancer, indicating that prenatal factors are of importance in the etiology of breast cancer. Prospective studies have found positive associations between circulating endogenous sex steroids and subsequent risk for breast cancer in postmenopausal women, while in premenopausal women the major circulating biomarker linked to risk is IGF-I (and/or IGFBP-3). Mammographic percent density, a recently recognized risk factor, has been reported to be positively associated with serum levels of prolactin and sex-hormone binding-globulin, and negatively associated with free estradiol in postmenopausal women and positively associated with plasma IGF-I in premenopausal women. The inter-individual variations in endogenous hormones or growth factor levels may contribute to the differences in breast tissue composition, extent of mammographic density, and breast cancer risk. In postmenopausal women, obesity has been reported to be associated with increased risk for breast cancer, as well as breast cancer recurrence and poor survival among affected women. Recent evidence links the association between increased BMI and increased breast cancer risk among postmenopausal women to increased circulating levels of estrogens, particularly bioavailable estradiol. The association between obesity and breast cancer risk is an important issue in view of the increasing prevalence of obesity in western countries and provides the background for the use of aromatase inhibitors in clinical trials.

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Endocrine prevention of breast cancer

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The relationship of hormonal factors to breast cancer is well established. Estrogens, in particular, have been implicated in the initiation and promotion of breast cancer and interference with estrogen agonism has represented the strategy for prevention trials. Selective estrogen receptor modulators (SERMs) represent the class of agents that has received the most intensive study. Impetus for the study of tamoxifen for prevention came from the identification of a reduction in contralateral breast cancers in a phase III placebo-controlled trial in the adjuvant setting, a finding which has repeated itself with the third-generation aromatase inhibitors. The findings