Friday, 19 March 2004 08:30–09:15

EUROPA DONNA TEACHING LECTURE

Risk factors for breast cancer

335 INVITED

Risk factors for breast cancer

F. Berrino. *Instituto Nazionale Tumori, Divisione di Epidemiologia, Milan, Italy*

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

R.W. Blamey[1], J. Mackay[2], D. Macmillan[3]. *On behalf of FABRECAN working group. [1]Nottingham City Hospital, Breast Institute, Nottingham, UK; [2]Institute of Child Health, Clinical Genetics, London, UK; [3]Nottingham City Hospital, Breast Institute, Nottingham, UK*

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

A. Decensi. *European Institute of Oncology, Chemoprevention Unit, Milan, Italy*

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.

338 INVITED

Endocrine prevention of breast cancer

J.N. Ingle. *Mayo Clinic, Rochester, Minnesota, USA*

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

from the trials of tamoxifen and raloxifene, particularly NSABP P1 and the MORE trial, respectively, demonstrated the ability of this class of agents to reduce, at least in the short term, the incidence of breast cancer. The large 19,000 patient STAR trial should complete accrual in the near future and provide information on the relative efficacy and, importantly, toxicity of these 2 SERMs.

The third-generation aromatase inhibitors have become established for management of women in the metastatic disease and adjuvant therapy settings. Strong evidence is available from clinical trials for the non-steroidal aromatase inhibitors anastrozole and letrozole in the first-line metastatic setting to choose one of these agents over tamoxifen based on efficacy and tolerability. In the adjuvant setting, two large placebo-controlled trials have been reported which demonstrate substantial reduction in the incidence of contralateral breast cancers with anastrozole (ATAC) and letrozole (MA.17). These findings plus the fact that aromatase inhibtors are associated with a lower incidence of thromboembolism and endometrial pathology than tamoxifen has made them attractive for study in the prevention setting. IBIS II is evaluating anastrozole against placebo and MAP3 will study the steroidal aromatase inhibitor exemestane (with or without celecoxib) against placebo. In the latter trial, the cyclooxygenase-2 inhibitor celecoxib has been selected for study because of preclinical data showing inhibition of both ER-positive and ER-negative breast cancers and value of combining this agent with exemestane. In addition, long-term NSAID use has been associated with decreased breast cancer risk. The implications of profound lowering of estrogens are clear and close evaluation of end organ effects is recognized.

A major problem with the large prevention trials to date is the large patient sample sizes, thus long time and high cost, required. Research is being conducted to evaluate surrogate endpoint biomarkers that would facilitate smaller trials able to be completed in shorter time-frames.

In addition to estrogen action through the estrogen receptor, the generation of genotoxic metabolites of estradiol represents a potential mechanism of breast carcinogenesis. Estrogen genotoxicity represents an area of ongoing investigation with numerous potential therapeutic strategies.

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Intraductal techniques in surveillance

J. O'Shaughnessy. *U.S. Oncology, Chemoprevention Res. Programme, Dallas, Texas, USA*

Atypical hyperplasia develops along the continuum of breast intraepithelial neoplasia (IEN), the genotypic and phenotypic epithelial cell changes that evolve into and accompany invasive cancer, and may be an obligate precursor of invasive breast cancer. Although there are no prospective studies that have evaluated whether high-risk women with cytologically-identified hyperplasia with atypia derive as much benefit from tamoxifen as do women with pathologically defined atypical hyperplasia, many experts believe that the breast cancer risks of both groups are similarly elevated and that tamoxifen treatment is indicated for both. Random, periareolar bilateral breast FNA in women at elevated risk for developing breast cancer on the basis of a family history or an elevated 10-year Gail risk score has been shown to detect breast epithelial cell atypia in 21% of high-risk women. Although nipple aspirate fluid (NAF) can be collected by experienced hands from approximately 60% to 80% of women, cellular yields for cytologic analysis are often low. Ductal lavage has been developed as a minimally invasive way of facilitating retrieval of intraductal epithelial cells to identify women who are at markedly elevated risk of developing breast cancer due to the presence of atypical epithelial cells. The primary purpose of ductal lavage is risk stratification- to provide additional information to women who are at elevated risk on the basis of their 5-year Gail risk score and to distinguish between those who are at elevated versus high risk. In a large study by Dooley, et al., ductal lavage was 3.2 times more sensitive in detecting abnormal cells than was NAF when samples from the same breast were compared. Ductal lavage is an excellent tool for evaluating the effectiveness of new breast IEN treatment agents in high-risk women. Several clinical trials have been initiated or are planned to serially monitor atypical breast epithelial cells in high-risk women who are taking an aromatase inhibitor or a novel investigational risk reduction agent such as celecoxib. Ductal lavage is being used to investigate the molecular characteristics of breast epithelial cells and proteins in ductal lavage effluent. Promising molecular markers under study include LOH of DNA markers, methylated genes, and abnormal protein patterns on mass spectroscopy.

340 INVITED

Prophylactic mastectomy in high risk women

J.G.M. Klijn. *Erasmus MC, Daniel den Hoed Cancer Center, Medical Oncology, Rotterdam, The Netherlands*

Current risk-reduction strategies aimed at prevention of breast cancer and death by cancer include changes in lifestyle, early detection of cancer by regular surveillance, prophylactic mastectomy (PM), prophylactic oophorectomy (PO) and chemoprevention. Early studies on the possible interest in PM in untested high-risk women showed a wide range of outcomes. At our family cancer clinic 51% of unaffected women with a proven gene mutation choose PM, and 64% PO. Until recently, only case reports and retrospective studies of the outcome of prophylactic mastectomy (mainly subcutaneous, and thus often incomplete) have been published. However, Hartmann and colleagues reported an approximate 90% risk reduction by PM in 639 women with a family history of breast cancer after a median follow-up of 14 years. In a very small group of 18 women with a confirmed BRCA1 or BRCA2 mutation no breast cancers were observed after PM after a median follow-up of 13 years. After these retrospective studies, we performed the first prospective comparative study in 139 BRCA1/2 mutation carriers. No cases of breast cancer were observed after bilateral total PM after a mean follow-up of 2.9 year in 76 BRCA1/2 mutation carriers (mean age 37.7 yr) in contrast to 8 breast cancers in the surveillance group (n=63, mean age 39.5 yr, mean follow-up 3.0 year) resulting in a hazard ratio of 0 (95% CI: 0–0.36; p=0.003). After a recent preliminary update at 5.2 yr of follow-up this risk reduction (92%) was still highly significant ($p<0.02$), also after adjustment for PO ($p<0.03$). In our affected BRCA1/2 mutation carriers with primary breast cancer, 35% of the patients opted for prophylactic bilateral/contralateral mastectomy, also resulting in a strong risk reduction for a second primary breast cancer, but till thusfar without a significant effect on overall survival. The strong protective effect of PM must be weighed against possible surgical complications by breast reconstruction, psychological problems and quality of life. In our experience only 5% did regret PM, but at 3 years of follow-up a significant number of women reported some negative effects on body image and sexuality. Endocrine prevention by PO or chemoprevention resulted in a risk reduction of about 50% for breast cancer.

In conclusion: thusfar prophylactic bilateral total mastectomy is the most effective way of prevention, but PO is a reasonable alternative, while chemoprevention has to be preferably applied in clinical trials.

Friday, 19 March 2004 14:15–15:45

SYMPOSIUM

Breast conserving surgery – 30 years of experience

341 INVITED

Breast conservation: overview and future perspectives

U. Veronesi. *European Institute of Oncology, Milan, Italy*

The revolution in breast cancer treatment was ushered in by our work in the 1970s with conservative surgical approach. A randomized trial began in Milan in 1973 to compare small size breast cancer patients treated by Halsted mastectomy (the standard operation till that time) with those receiving breast sparing – quadrantectomy – plus axillary dissection and 50 Gy radiotherapy administered in two tangentially opposed fields using high energy equipment, plus a boost of 10 Gy on the scar with orthovoltage equipment (QUART).

The survival curves showed that QUART gave identical results to Halsted mastectomy, and that subdivision of patients by tumor size, site and age still did not reveal any difference between the treatments.

An important development of conservation surgery refers to the possibility of avoiding axillary dissection when axillary nodes are negative. Although axillary dissection is an important staging procedure, more and more patients present themselves with small carcinomas and all too often axillary dissection reveals only healthy lymph-nodes. We studied the ability of sentinel node biopsy to predict the status of the axilla in order to obtain information on the safety of foregoing axillary dissection when the sentinel node is negative. A randomized trial on the safety and efficacy of sentinel node biopsy was conducted in the years 1998–1999 and the data published in N Engl J Med. We recruited 516 patients, who were randomized between routine total axillary dissection and elective axillary dissection, only in cases where a positive sentinel node biopsy was present. The 5-year rate of local-regional recurrences and survival was not different in the two arms.

In the field of complementary treatments, intraoperative radiotherapy (ELIOT: Electron Intraoperative Therapy) could become one of the other main issues in the management of early breast cancer.

The theoretical gain of the use of ELIOT in the treatment of breast cancer is the delivery of a high dose radiotherapy to a very limited area of the body (and of the breast itself), with a good spare of normal tissues and organs. The incidence of local relapse is in fact higher just in the site of tumour resection, with a much lower probability of relapse in the other quadrants of the same breast.