Wednesday, 30 September 1998 **16:00-18:00**

PARALLEL SESSION

Epidemiology and prevention

93 INVITED

Chemoprevention of breast cancer – An update

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Because breast cancer is the commonest form of cancer in women in the Western world, a large amount of effort has been put into trying to discover its causes and possible means of prevention. Mammographic screening offers one approach to preventing mortality by detecting cancers at an earlier more treatable stage, but it will not prevent the development of cancers. At the other extreme there is interest in trying to reduce the incidence of breast cancer by restricting dietary fat intake or increasing the amount of exercise taken. However, in the short to medium term chemoprevention with hormonally active agents is likely to be the most effective approach. Four trials of tamoxifen prophylaxis have been undertaken and their current status will be reviewed. A range of new agents could also be considered including tamoxifen analogues such as raloxifene, pure anti-oestrogens, aromatase inhibitors, and phyto-oestrogens.

94 ORAL

Geographic distribution within the Netherlands of families with specific mutations in BRCA1 and BRCA2

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Purpose: To determine the origin within the Netherlands of families with a number of specific mutations in the breast cancer susceptibility genes, BRCA1 and BRCA2.

Methods: Families were identified through the family cancer clinic of the Daniel den Hoed Cancer Center and the department of clinical genetis, Erasmus University, Rotterdam. The origin of families with various specific Dutch founder mutations was mapped out. The place of birth was determined for the ancestors, most likely to have transmitted a mutation in each of the families.

Results: Presence of a BRCA1 or BRCA2 germline mutation was detected in 70 and 14 families, respectively. 6 BRCA1 and 1 BRCA2 mutation that were previously described as specific Dutch founder mutations were detected ≥ 5 times. 4 of these mutations appear to be originated from distinct regions in the south-west Netherlands. One of these mutations, a large 3.8 kb genomic deletion encompassing exon 13 of the BRCA1 gene is the most frequently encountered BRCA1 mutation within the Rotterdam famillies (n = 15, 21% of 70 BRCA1 families). All of the families with this mutation originated from one small region with approximately 150.000 inhabitants. Breast cancer incidence among these families was heterogeneous and no specific breast or ovarian cancer phenotype could be assigned to any of these founder mutations.

Conclusion: For some of the specific Dutch founder mutations in BRCA1 and BRCA2, the origin within the Netherlands can be traced back to distinct regions.

95 ORAL

Mutations in the BRCA1 and BRCA2 genes: Uptake of presymptomatic DNA test, preventive choices and breast cancer risk after prophylactic mastectomy

Hanne Meijers-Heijboer[1], Leon Verhoog[2], Cecile Brekelmans[2], Bert van Geel[2], Caroline Seynaeve[2], Anja Wagner[1], Ans van den Ouweland[1], Petra Frets[1], Martinus Niermeijer[1], Jan Klijn[2]. *Department of Clinical Genetics, University Hospital Rotterdam; [2]Family Cancer Clinic, Daniel den Hoed Cancer Center/University Hospital Rotterdam, Netherlands*

Purpose: Mutations in the BRCA1/2 genes in females cause a 60%–85% and a 20–60% risk for breast-and ovarian cancer respectively. Mutations in these two genes attribute to approximately 5% of the total of breast cancers. We wanted to determine the uptake of presymptomatic. BRCA1/2 DNA testing (PST) in families in which a mutation was known. In addition we analysed the chosen preventive interventions and the incidence of breast cancer after prophylactic mastectomy.

Methods: After a mutation was detected in breast cancer prone families, the initial counsellee informed their family members about the possibility of PST. This was accompanied with written information on the pros and cons of DNA testing. The uptake of PST was determined after at least 6 months. We analysed the preventive choices made by female mutation carriers. We determined the incidence of breast cancer after prophylactic mastectomy (n = 93). This group consisted of 48 BRCA1/2 mutation carriers (18 breast cancer patients and 30 healthy women) and 45 women from high-risk breast cancer prone families (32 breast cancer patients and 13 healthy women).

Results: 196 healthy at risk persons applied for PST (5.8 persons per family). 113 out of 188 healthy female 50%-risk carriers (60.1%) and 44 out of 150 male 50%-risk carriers (29.3%) were tested. In 57 healthy women a mutation was found. Of these 32 underwent prophylactic mastectomy (56%). 22 out of 32 women who were older than 35 years underwent prophylactic oophorectomy (69%). Especially women in their thirties and forties decided for both PST and prophylactic mastectomy. In the prophylactic mastectomy group we expected 5 breast cancer patients during the period of follow up. Until now (mean 2.5 years) no cases of breast cancer occurred.

Conclusion: The majority of Dutch women from high-risk families wants a presymptomatic BRCA1/2 DNA test and take prophylactic surgical measures in case they carry a mutation. Our data suggest that prophylactic mastectomy reduces the risk for breast cancer in high-risk women.

96 ORAL

Ethnicity, diet, and mammographic density patterns

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Purpose: Mammographic density patterns refer to the distribution of fat, connective, and epithelial tissue in the healthy female breast and are strong predictors of breast cancer risk. This project investigated the hypothesis that ethnicity and diet are related to mammographic densities.

Methods: In a cross-sectional design, more than 400 White, Hawaiian, Chinese, and Japanese women with normal mammograms completed a reproductive history and a food frequency questionnaire. After digitizing the cranio-caudal mammographic films, the area with densities and the total area of the breast were measured using a computerized method.

Results: The mean dense area in the mammograms was approximately 15% smaller in Asian than in White and Hawaiian women. However, because of their relatively smaller breast size, the percent of the breast occupied by dense tissue in Asian women was equal to or higher than in White women. In a multiple linear regression model, daily intake of fruits, vegetables, soy products, as well as age, body mass index, age at menarche, and parity were inversely related to mammographic densities, while age at first live birth showed a positive association with densities.

Conclusion: Women from ethnic groups with low breast cancer risk have smaller areas of mammographic densities than women from high risk groups. A diet rich in fruits, vegetables, and soy foods may be related to mammographic density patterns that protect against breast cancer.

97 ORAL

The risk of breast cancer in women with affective or neurotic disorders

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Purpose: To test the hypothesis that women admitted into psychiatric departments with affective or neurotic disorders have an increased incidence of breast cancer compared to the general population of women adjusted for age and calendar period.

Methods: The base population comprised all 66,648 women registered during the period 1970–1993 in the nation-wide Danish Psychiatric Case Registry with a psychiatric admission including a diagnosis of affective or neurotic disorder.

Results: In all 1,270 affective or neurotic women developed breast cancer compared to 1,242 expected. SIR = 1.02; 95% CI: 0.97–1.08.

We found no statistical effect on the relative risk of type of psychopathology, years of follow-up, age after first admission and alcohol abuse.

Conclusion: We found no support for the hypothesis of an increased risk of breast cancer among women with admission into psychiatric department with affective or neurotic disorder.

98 ORAL

Breast cancer and risk factors: A comparative study between a low and a high risk population

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Aims: To study breast cancer risk factors in two epidemiologically different populations caracterised by low and high incidence rates for breast cancer. To define minor and major risk factors and determinants. To evaluate futur epidemiological changes and options in public health interventions in breast cancer.

Materiel and Method: A comparative epidemiologic study was performed between Geneva, Switzerland and Shanghai, China. We included 2000 women, 1000 in each group. We study minor risk factors, i.e reproductive (menarche, menopause, age at first pregnancy), hormonal (oral contraception, hormonal substitution), live style (diet) factors; major risk factors (family or personal history of benign breast diseases or cancer) were also studied.

Results: Mean age is 50 in each group, respectively Geneva and Shanghai. Results about minor risk factors demonstrated an early menarche and late menopause (before 40 y.o.) in Geneva (13 vs 15 y.o; 22.9 vs 31.6%). Nulliparity and first pregnancy age (before 25 y.o.) is most frequent in Geneva (14.2 vs 6.7%; 31.4 vs 53.7%) Contraceptive and hormonal substitution are unusual in Shanghai (10 vs 1.2%; 11 vs 0%). Fatty diet and obesity is more frequent in Geneva (5 vs 0.3%). Personal and family history of breast cancer is very high in Geneva (2.2 vs 2.2%; 10.3 vs 0.9%)

Conclusion: These results confirm well known minor and major breast cancer risk factors. Diversity of involved risk factors and future epidemiological changes-specially in diet and hormonal use-make difficult futures predictions and public health interventions.

99 ORAL

Worse survival of patients with endometrial cancer following tamoxifen treatment for breast cancer: A study with 309 second tumors

L. Bergman[1], M.L.R. Beelen[1], M.P.W. Gallee[1], J. Benraadt[2], F.E. van Leeuwen[1]. *[1]The Netherlands Cancer Institute; [2]Comprehensive Cancer Center Amsterdam, Netherlands*

Purpose: We conducted a nationwide case-control study to assess the effect of tamoxifen on the risk and prognosis of endometrial cancer.

Methods: Through the population-based Netherlands Cancer Registry and two older, hospital-based registries we identified 310 cases with endometrial cancer after breast cancer and 861 matched controls with breast cancer in whom endometrial cancer had not developed. Detailed information on breast cancer treatment, risk factors and prognostic factors of endometrial cancer was obtained through a review of the medical records.

Results: Tamoxifen had been used by 36% of the cases and 29% of controls (RR 1.5 [95% CI 1.1–1.9]). The median time between diagnosis of breast cancer and endometrial cancer was 40 (4–235) months. There was a strong increase in risk of endometrial cancer with longer duration of tamoxifen use ($p < .001$): RR 2.0 (95% CI 1.2–3.2) for 2–5 years of use and 6.9 (95% CI 2.4–19.4) for ≥ 5 years of use compared to never use. FIGO stage 3 and 4 endometrial cancers occurred more frequently in long-term (≥ 2 yrs) tamoxifen users than in nonusers (17.4% vs 5.4%, $p = .006$). Eleven of 110 tamoxifen-treated women and 10 of 200 non-users died of endometrial cancer after median follow-up of 30 months. Three-year actuarial endometrial cancer-specific survival was significantly worse for long-term tamoxifen users (≥ 2 yrs) than for non-users (80% vs. 94%; $p = .002$). Cox proportional hazard analyses showed that the worse survival of long-term users was related to their less favourable FIGO stage. Additional immunohistochemical analyses of the tissue blocks of all endometrial cancers are currently being performed to evaluate whether advanced FIGO stage after long-term tamoxifen use reflects specific molecular genetic alterations.

100 POSTER

Serum and nipple aspirate levels of vitamin A and vitamin E and lack of an association with breast cancer

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Purpose: Epidemiological evidence suggests that diets low in antioxidants could lead to an increased risk of breast cancer. Vitamin A and E are two antioxidants that have been shown experimentally to inhibit the development of mammary tumours. Our aim was to determine the levels of vitamin A and E in serum and nipple aspirates of women attending the South Manchester Breast Clinic and the association with breast cancer.

Methods: One-hundred and six women were studied, with a median age of 44 years (range 16–82). Forty-four patients had breast cancer and 62 had either benign or no detectable breast disease. Serum and/or nipple aspirate samples were collected from each patient and paired nipple aspirate and serum data were available for 35 women. Vitamin levels were measured by HPLC.

Results:

Median levels (mg/ml)	Serum (benign patients)	Serum (cancer patients)	Nipple aspirate (benign breast)	Nipple aspirate (malignant breast)	Serum (non smokers)	Serum (smokers)
Vit A	0.5	0.50	0.29	0.25	0.50	0.50
(IQ range)	*(0.40–0.62)*	*(0.40–0.57)*	*(0.13–0.44)*	*(0.17–0.40)*	*(0.41–0.59)*	*(0.34–0.57)*
Vit E	11.3	12.35	12.20	11.10	11.70	10.8*
(IQ range)	*(9.3–12.6)*	*(9.–15.08)*	*(6.40–21.4)*	*(5.50–16.40)*	*(9.8–14.3)*	*(8.75–12.45)*

* $p < 0.05$

Serum vitamin A and E rose significantly with age and with the menopause (pœ 0.01) Nipple aspirate antioxidant levels were unaffected by smoking ($p > 0.2$) and breast cancer had no affect upon nipple aspirate or serum antioxidant levels.

Conclusion: We have found no evidence of an association between breast cancer and level of Vitamin A and E.

101 POSTER

Individual breast cancer risk in premenopausal women

R.M. de Souza[1], A.R. Lazzaron[1], R. Defferrari[1], A.A. Borba[2], L. Scherer[2], A.L. Frasson[3]. *[1]Faculdade de Medicina, UFRGS; [2]Centro de Ecografia e Radiologia, Hospital São Rafael; [3]Faculdade de Medicina, PUC/RS, Brazil*

Purpose: There is an increasing demand for prediction of individual women's risk for breast cancer. We delineated an equation to estimate premenopausal women's breast cancer risk for a period of one year, based on the absolute risk and the excess risk from identified risk factors.

Methods: We tested this method in 1681 women who underwent mammography in a private clinic. After calculating the individual risk for each of the patients, we divided them in quartiles. We also divided the population in arbitrary risk levels: low, intermediate, and high. Then, we compared the number of cases expected with the number of cases diagnosed.

Results: The breast cancer incidence was higher in the highest quartile of risk (3.5%) as compared to the lowest (1.0%) ($P = 0.02$). The breast cancer incidence was also higher in arbitrary high risk level group (5.1%) as compared to the low risk (1.5%) ($P = 0.01$). The relative risk of presenting the disease was 3.25 in the highest quartile of risk compared to the lowest ($P < 0.05$), and was 3.26 in the high risk level compared to the low risk ($P = 0.01$). There was a significant correlation in the expected/observed ratio between subgroups ($r = 0.99$; $P < 0.001$).

Conclusion: This new method might be useful in the evaluation of individual breast cancer risk in premenopausal women.

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Individual breast cancer risk assessement in postmenopausal women

R.M. de Souza[1], A.R. Lazzaron[1], R. Defferrari[1], A.A. Borba[2], L. Scherer[2], A.L. Frasson[3]. *[1]Faculdade de Medicina, UFRGS; [2]Centro de Ecografia e Radiologia, Hospital São Rafael; [3]Faculdade de Medicina, PUC/RS, Brazil*

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