in the expression of hTERT mRNA between cancerous and non-cancerous breast tissue. There is potentially a use for hTERT as a diagnostic marker for breast malignancy, particularly using a cut-off point for significant levels of expression. However there is no correlation with tumour stage, suggesting that post-transcriptional modification of hTERT mRNA may be altering the amount of active enzyme that is produced, since telomerase enzyme activity has been shown to correlate with tumour size and nodal status.

460 ORAL

cDNA microarray gene expression profiles as a potential prognostic and predictive tool for an improved management of breast cancer

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Aim: The purpose of this study is to correlate gene expression patterns generated from cDNA microarrays with clinico-pathological characteristics and clinical outcome in breast cancer.

Methods: RNAs from a randomly selected group of breast cancer patients with known clinical outcome were analyzed using a 7600 gene cDNA microarray constructed at the National Cancer Institute. Permutation-based multiple comparisons procedures were used to identify individual genes differentially expressed between groups defined by the standard clinicopathologic variables ER status, grade, menopausal status, nodal status, and tumor size. Hierarchical clustering and principal components methods were applied for unsupervised analyses of expression patterns. Cox proportional hazards regression with adjustment for standard clinical and pathological variables was used to identify genes significantly associated with survival.

Results: Gene expression patterns were found to be strongly associated with ER status and moderately associated with grade, but not strongly associated with menopausal status, nodal status, or tumor size. Cluster analyses suggested 2 or 3 clusters, and these appeared related to, but not completely explained by ER status. Sets of genes significantly ($p < 0.001$) associated with relapse free survival and breast cancer-specific survival after adjustment for standard clinico pathological variables were identified. These genes were involved in a variety of molecular pathways, including differentiation (CRIP2), immune (CCBP2), and stress response (HSPA5).

Conclusions: ER phenotype is associated with distinct gene expression signatures. Furthermore, our results suggest some candidate genes potentially associated with relapse free survival and breast cancer-specific survival.

461 ORAL

The prevalence of the 4G4G genotype polymorphism of the plasminogen aktivator inhibitor (pai-1) 4G5G gene, in patients with breast cancer

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Plasmatic PAI activity/concentrations and tumor tissue concentrations are elevated in patients with breast and other kind of cancers whereas this increase correlates with poor prognosis of patients. The 4G/5G deletion/insertion polymorphism is in the promoter region of the PAI *1 gene whereas the 4G allele is associated with increased gene transcription in cell lines in vitro and with increased PAI-1 concentrations in carriers. The prevalence of 4G allele in breast cancer patients and healthy women was investigated and compared with the plasmatic PAI activity.

Blood samples were drawn from 48 nonconsecutive and unselected women with a first diagnosis of breast cancer the morning (8oo * 10oo) prior to surgery. Another 48 healthy women served as controls. Investigations of the 4G/5G polymorphism were performed at the university of Munster using PCR and PAI activity was estimated with a chromogenic uPA dependent test (DADE * Behring, Liederbach, Germany).

Breast cancer patients were significantly older than the controls (58.5 $\pm$ 10.2 y vs. 50.8 $\pm$ 13.2 y; $p < 0.05$). The prevalence of the 4G4G * allele in breast cancer patients (43.8%) was significantly higher as compared to the controls (14.6%; $p < 0.001$). For PAI activity a cut-off level of 3.8 U/ml was used (Thromb. Haemost 1999). The mean PAI activity was 4.8 $\pm$ 2.1 U/ml and significantly higher as compared to the controls (3,4 $\pm$ 1.3 U/ml; $p < 0.001$). In breast cancer patients the prevalence of the 4G/4G-allele was associated with an elevated PAI activity being present in 67% of carriers.

This is the first study that investigated the 4G/5G deletion/insertion polymorphism of the PAI * 1 gene in breast cancer patients. These preliminary results show a surprisingly high prevalence of the 4G4G allele in breast cancer patients. These results are hypothesis generating with respect to a contribution to the fibrinolytic/proteolytic potential of breast cancer cells that is an important prerequisite for successful tumor invasion and metastasis. Further studies including other gynecologic cancer types are on their way

Saturday, 23 March 2002 9:00–10:30

PROFFERED PAPERS

Epidemiology and prevention

462 ORAL

Breast cancer in women treated with supradiaphragmatic radiation therapy for hodgkin's disease: the Mayo Clinic experience

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Objective: To evaluate overall risk, contributing risk factors, detection, pathology, and management of breast cancer (BC) in women previously treated with supradiaphragmatic radiation therapy (SDRT) for Hodgkin's disease (HD).

Methods: Medical records of 2,202 women seen at the Mayo Clinic (MC) for HD between 1950-93 were reviewed. The records of 653 women treated with SDRT at MC were abstracted and follow-up (FU) questionnaires mailed.

Results: Patient Characteristics: Median age of 653 patients (pts) at SDRT was 31.9 years (y) (range (r) 2.6-86.5 y), median FU was 8.3 y (r 0-47.9 y). Thirty pts developed 34 BC, their median age at SDRT was 22.7 y (r 13.2-51.5 y). Median interval between SDRT and BC was 19.9 y (r 0.7-42.3 y). Median age at diagnosis of BC was 44.4 y (r 27.5-70.8 y). BC Risk: Standard morbidity ratio (SMR) was 3.0 (09% CI 2.0-4.3) ($p<0.001$). A significant increase in SMR was seen after 15 y of FU and continued through 30 y of FU. SMR was inversely related to age at SDRT up to age 30. For pts > age 30 at SDRT the SMR was 1.2 (95% CI 0.5-2.2) vs. SMR 8.8 (95% CI 5.4-13.4) for pts < age 30 ($p<0.0001$). A family history (FH) of BC, and splenectomy significantly increased BC risk by univariate analysis ($p=0.002$, $p=0.0134$ respectively) and multivariate analysis ($p=0.009$, $p=0.023$ respectively). The impact of FH of BC and the impact of splenectomy were greatest in pts 30 y or older ($p=0.0055$, $p=0.021$ respectively). BC Characteristics: Mode of detection in 32 BC: 15 by self-exam, 13 by mammogram, and 14 by clinical exam. Location (65% upper outer quadrant) and histology were similar to those in general population. Stages (St) of 30 BC: 7-St 0, 11-St I, 9-St II, 3-St III. All 34 BC were treated with modified radical mastectomy.

Conclusion: The risk of BC is increased in women treated with SDRT for HD before age 30 and in women who have undergone splenectomy. Patients and physicians should be aware of this risk.

463 ORAL

Clinical presentation, treatment and prognosis of tubular carcinomas of the breast: a population-based study

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Background: Tubular carcinoma of the breast is a rare, well-differentiated histologic subtype of invasive carcinoma, known for its favorable prognosis. Our objective was to evaluate clinical and pathological features of these tumors, assess long-term outcome and clinical management of these patients (pts), particularly the need of axillary lymph node dissection.

Methods: This study includes all pts with primary tubular carcinoma of the breast (n=50), ie < 1% of 5392 breast cancer cases recorded at the regional population-based cancer registry between 1980 and 1999. We studied patients' characteristics, method of discovery, tumor size, surgical margins, axillary node involvement, hormonal receptors, nuclear grade, type of surgery and use of adjuvant therapy. Survival was calculated using Kaplan-Meier method from the date of initial diagnosis and factors modifying prognosis were determined by the Cox model.

Results: The median age was 56 years (range: 26-90). The stage distribution was as follows: I in 39 (78%), II in 9 (18%) and IV in 2 (4%) pts. An axillary lymph node dissection was performed in 37 (74%) pts. Axillary lymph nodes were positive in 2 pts (4%), respectively with 1 and 3 nodes. Chemotherapy was given in 9 pts (18%), hormonal therapy in 7 pts (14%) and radiation therapy in 32 pts (64%). With a median follow-up of 6.5 years (range: 1.2-19), 38 pts (76%) were alive, 4 died of disease (8%) and 7 (14%) died of other causes. Five- and 10- year disease- specific survival were 95% and 87% respectively.

Conclusion: Tubular carcinomas have an excellent long-term prognosis. Nodal metastases are unfrequent. As for other rare breast tumors, standard recommendations need to be proposed to avoid over-treatment.

464 ORAL

Factors underlying the improvement in mortality from breast cancer

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Possible reasons for the fall in mortality from breast cancer in the UK are earlier detection (ED) and adjuvant therapies (AT).

ED works by increasing the numbers in the good prognostic groups, AT by increasing survival within prognostic groups. These have been analysed using the Nottingham prognostic Index (NPI), for women with operable cancers diagnosed in 1980–84 (prior to use of adjuvant therapy and to screening of women aged 50+) and 1990–94.

Age 50–70	1980–84		1990–94		
NPI	%	(Surviving at 10 yrs)	%	(Surviving at 10 yrs)	Expected to survive without AT
GPG	29.5	(23.6)	41.6	(37.0)	33.2
MPG	56.2	(30.3)	46.4	(33.4)	25.1
PPG	14.2	(2.1)	12.0	(3.4)	1.8
Total	100	(56.0)	100	(73.8)	60.1

In women aged 50–70 10 year OS rose from 56% to 74%, ED. A higher percentage of cases in NPI Good Group (GPG) accounted for part of this.

AT (largely Tamoxifen) Survival rose WITHIN all NPI groups; in the moderate group (MPG) the rise was from 56% to 72%.

Both ED and AT have reduced mortality in breast cancer.

465 ORAL

Male breast cancer in Lithuania 1991-2000 year

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In Lithuania where lives over 3 millions inhabitants and the female breast cancer is one of the most common disease in women, male breast cancer occurs infrequently, but it can affect men as well, as women. Because male breast cancer is so uncommon, it has been difficult to accumulate extensive data. In our study we analyzed statistical data about 98 cases of male breast cancer during 1991-2000 year period. We noticed, that men represent mostly new cases of breast cancer after age 60 year (87,7%), about 55% male breast cancer was in stage III, and it was due in great part to fixation of the tumor to the skin, 81,6% was invasive ductal carcinoma and in 40,8% axillary metastases were absent and 59,1% present. Men were thought to have a poorer prognosis than women do, but in our study we found that differences in prognosis are slight. From 57 cases of disease in stage III 5 years survived 29 (29,5%).

Summary: 1. In contrast to women with breast cancer men with breast cancer are older and have a more advanced disease. 2. The disease is morphological similar to women. 3. There are not significant differences in prognosis between male and female breast cancer.

466 ORAL

Use of oral contraceptives and breast cancer risk: the women's lifestyle and health study

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Background: Use of oral contraceptives slightly increases risk for breast cancer, but prospective data relevant to currently used regimens are sparse. We report here findings from a large, population based cohort study in Norway and Sweden with detailed assessment of exposure. This cohort consists of young women whose main exposure consist of current used brands of hormonal contraceptives.

Methods: We used information collected in the 'Women's Lifestyle and Health Study' in Norway and Sweden. The analysis was based on data from 102 801 women who were aged 30-49 years when they responded to a questionnaire in 1991-92, that included questions on hormonal contraceptive use and other lifestyle characteristics. Complete follow-up through 1997, accomplished by linkage of the cohort members to nationwide databases, revealed 740 incident primary invasive breast cancers. Proportional hazard regression was used to calculate relative risks (RR) with adjustment for age and other confounders.

Results: We found a 19% increased risk of breast cancer among ever-users of oral contraceptives, compared with never-users (multivariate RR=1.19; 95% CI 1.00-1.42). Women with current use had higher risk (RR=1.51; 95% CI 1.11-2.06), particularly among those aged 45 years or more (RR=2.23; 95% CI 1.33-3.67). We found no increased risk among women who used oral contraceptives before age 20 years or before first full-term pregnancy.

Conclusions: Use of oral contraceptives increases breast cancer risk, particularly when used in the late period of reproductive life.

467 ORAL

The Norwegian Breast Cancer Screening Program; Is re-attendance related to screening outcome and the women's attitude and experiences to the program?

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The aim of this study was to identify attitudes to and experiences with the Norwegian Breast Cancer Screening Program (NBCSP) among women with different screening outcome and investigate whether those factors were connected to actual re-attendance.

The NBCSP started as a four-year pilot project in four counties in 1996. Women (50-69 years) are invited to screening every second year in stationary or mobile units. Eventually recall examinations take place at breast diagnostic centers, at University or County-hospitals.

All women invited to the NBCSP receive an invitation package, which among other factors consist of an epidemiological questionnaire (EQ). An especially designed questionnaire was made for this study (SQ). The SQ was sent to 1221 randomly selected women with five different screening outcome; non-attendees (300), women screened negative (300), women recalled due to a false positive mammogram (300), women recalled due to technical unsatisfied mammograms (87) and women diagnosed with a histological verified breast cancer (234). The SQ was dispatched one to ten months after invitation to screening. Totally 989 women filled in the SQ. The response rate was 92.2% for the attendees and 46.7% for the non-attendees to the NBCSP. Data from the 989 women who filled in the SQ were linked to the epidemiological questionnaire (EQ), which among other things contained data with possible relation to experienced pain. Of the 989 women who filled in the SQ, 610 (61.7%) had filled in the EQ. These women were included in analyses related to experienced pain. Almost all the invited women reported a positive attitude to the program and recommended others to participate. Even 85.5% of non-attendees recommended others to participate. Among women who were screened negative, 97.9% reported willingness to re-attend, 87.7% actually did. Corresponding figures for women with a false positive mammogram were 96.2% and 85.4%. The proportion of non-attendees who wanted to attend the next screening round was 64.2% and 42.3% actually did. About one fourth of the attended women reported no pain during screening examination, while one third of the recalled women reported no pain during recall examination. Experienced pain during screening examination seemed to be influenced by hormonal factors.

The reported attitude to and experiences with the NBCSP are unison positive and probably affect the attendance and re-attendance in a favorable way.