O-111. FREQUENCY OF BREAST AND OTHER CANCERS AMONG RELATIVES OF MALE BREAST CANCER PATIENTS

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We have previously reported the frequency of BRCA2 gene mutations in a series of male breast cancer patients and shown that carriage of a BRCA2 mutation has no effect on prognosis. Other studies have suggested that BRCA2 mutations are associated not only with an increased risk of male and female breast cancer, but other cancers also e.g. pancreas, ovary, prostate and bladder.

DNA samples from 64 male breast cancer cases were screened for mutations in BRCA2 by use of polymerase chain reaction, heteroduplex analysis, protein truncation testing and sequencing. Living patients were interviewed about family history. An experienced genealogist constructed family pedigrees through access to the Scottish public records of births, deaths and marriages. Ethics committee approval was obtained.

Germline BRCA2 mutations were identified in 12 of the 64 (19%) male breast cancer cases. 8/35 (23%) of female first-degree relatives of mutation carriers had breast cancer compared to 5/132 (4%) female first-degree relatives of non-carriers ($p = 0.0007$, Yates corrected $\chi^2 = 11.48$, 1 d.f.). There were no significant differences between relatives of mutation carriers and non-carriers in terms of the frequencies of pancreatic, ovarian, prostatic, bladder, renal, lung, gastric and colorectal cancers.

Presence of a germline BRCA2 mutation in a proband is associated with a significantly increased frequency of breast cancer in relatives, but any increase in incidence of other cancers is below the limits of detection for a series of this size. This implies that absolute numbers of other cancers will be low within BRCA2 mutation carrying families, therefore it is perhaps questionable that screening for other cancers in relatives of male breast cancer patients is worthwhile.

O-112. THE HISTORY OF BREAST CYSTS IS NOT ASSOCIATED WITH THE DIAGNOSIS OF BREAST CANCER

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Background: The significance of a history of benign cysts to the development of breast cancer is disputed.

Aim: To investigate the relationship of a history of breast cysts to the diagnosis of breast cancer in women attending a symptomatic breast clinic.

Method: Between Jan 1996 and May 1999, 15,205 patients were referred by their GP to the Edinburgh Breast Unit. A structured history was taken; they were specifically asked if they had a cyst previously aspirated or removed surgically. All patients were examined and investigated by a standard protocol. Women over the age of 35 routinely had bilateral mammography. Ultrasound, fine needle aspiration and core biopsy were performed if indicated. Patients were then categorised into 3 groups (normal, benign, malignant). The association between a previous history of benign breast cysts and disease category was tested for statistical significance using a stratified chi-squared tests.

Results: Of the 15,205 patients seen 4,330 (28.5%) were found to be normal, 9,204 (61.2%) had benign disease and 1,571 (10.3%) were found to have malignant disease. The observed numbers of patients with previous cysts in each disease category, compared to the expected number if there was no association is shown in Table 1. There was a substantial excess of normal subjects, with 6% fewer than expected with benign disease and 36% fewer than expected with malignant disease. Analysis within age groups shows similar results.

Diagnostic Group	Previous history of benign cysts	
	Observed No.	Expected No.
Normal	351	275.7
Benign	525	560.5
Malignant	72	111 8

Statified chi squared test. chi squared = 3.96, $p < 0.001$

Conclusion: In women attending a symptomatic breast clinic the history of previous cysts is not associated with the diagnosis of breast cancer.

O-113. THE ZEBRA STUDY: ZOLADEX™ IS AS EFFECTIVE AS CMF IN PRE-/PERIMENOPAUSAL PATIENTS WITH OESTROGEN RECEPTOR POSITIVE, NODE-POSITIVE EARLY BREAST CANCER

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The ZEBRA (Zoladex™ Early Breast Cancer Research Association) study is a large (n = 1640), multicentre, randomized trial initiated in 1990 to compare disease-free survival (DFS), overall survival (OS) and side-effects between Zoladex (goserelin; 3.6 mg every 28 days for 2 years) and cyclophosphamide/methotrexate/5-fluorouracil (CMF; 6 × 28-day cycles) in pre-/perimenopausal patients with node-positive early breast cancer. The efficacy population included 1614 patients: 797 randomized to Zoladex and 817 randomized to CMF. Protocolled subgroup analyses by oestrogen receptor (ER) status showed a highly significant interaction between treatment and ER status ($p = 0.0016$). In ER-positive patients (74% of patients), Zoladex was equivalent to CMF for DFS (HR = 1.01; 95% CI 0.84, 1.20; $p = 0.94$), whereas in ER-negative patients (19% of patients), Zoladex was inferior to CMF for DFS (HR = 1.76; 95% CI 1.27, 2.44; $p = 0.0006$). Over 95% of Zoladex patients achieved amenorrhoea by 6 months compared with approximately 59% of CMF patients. Amenorrhoea was reversible in the majority of Zoladex patients but permanent with CMF: only 23% of Zoladex patients remained amenorrhoeic at 3 years (i.e. 1 year after cessation of Zoladex treatment) compared with 77% of CMF patients. In

CMF treated patients DFS was substantially better in those with amenorrhoea.

Elicited side-effects (WHO grades ≥ 1) typical of chemotherapy, e.g. alopecia, nausea/vomiting and infection, were substantially higher with CMF than Zoladex during the 6-month CMF treatment period. Menopausal symptoms, e.g. vaginal dryness and hot flushes, were initially lower with CMF but remained unchanged post-treatment, whereas on cessation of Zoladex, they were markedly reduced to a level below that observed in the CMF group. In summary, in pre-/perimenopausal patients with ER-positive, node-positive early breast cancer, Zoladex demonstrates equivalent efficacy to CMF with a considerably better side-effect profile but without permanent ovarian suppression associated with chemotherapy.

O-114. OVARIAN SUPPRESSION PLUS TAMOXIFEN (TAM) VERSUS CHEMOTHERAPY (CT) IN PATIENTS WITH EARLY BREAST CANCER: RESULTS OF A META-ANALYSIS OF THREE ADJUVANT TRIALS

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A meta-analysis of 3 clinical trials comparing LHRH-A [goserelin (G) or triptorelin (TP)] plus TAM (ET) versus CT (either CMF or CEF) was carried out.

The primary end point of the comparison was survival (OS). Disease-free (DFS) and local DFS were secondary end points. Individual patient (pt) data were collected for 1638 pts, of whom 814 had been assigned to ET and 824 to CT. Virtually all the pts enrolled had ER positive and/or PgR positive tumours. Trial information is provided below.

Assigned treatment	ABC		GROCTA		FASG	
	TAM+G 3-yr	CMF 1,8 ×6	TAM+G 2-yr	Classical CMF ×6	TAM+TP 3-yr	CEF ×6
Randomised pts	526	535	124	120	164	169
Median f.u. time (mos)	55	52	83	83	65	63
Total died (%)	41 (7.9)	50 (9.5)	25 (20.2)	23 (19.2)	10 (6.1)	19 (11.3)
Total relapsed (%)	88 (17.0)	104 (19.8)	50 (40 3)	44 (36.7)	25 (15.3)	37 (22.0)
Locally relapsed (%)	21 (4.1)	41 (7 8)	9 (7.3)	10 (8.3)	7 (4.3)	12 (7.1)

Results are summarized in the table.

Conclusions: The combination of TAM with ovarian suppression appear to be superior to standard CT (either CMF or CEF) in terms of both DFS and local DFS. Both treatments appear to yield comparable results in terms of OS. ET might represent an alternative to CT in breast cancer pts with ER or PgR positive tumours.

	Total	ET	CT	P value	
				Log-rank	Wilcoxon
Total died (%)	168	76 (9.4)	92 (11.3)	0.16	0.12
Total relapsed (%)	348	163 (20.2)	185 (22.8)	0.089	0.056
Locally relapsed (%)	100	37 (4.6)	63 (7.8)	0.004	0.003

O-115. THE ZEBRA STUDY: EARLY BENEFITS IN QUALITY OF LIFE IN GOSERELIN-TREATED *VS* CMF-TREATED PRE-/PERIMENOPAUSAL PATIENTS WITH NODE-POSITIVE EARLY BREAST CANCER

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The large (n = 1640), multicentre, randomized ZEBRA (Zoladex™ Early Breast Cancer Research Association) study has previously reported that goserelin (Zoladex; 3.6 mg every 28 days for 2 years) is as effective as cyclophosphamide/methotrexate/5-fluorouracil (CMF; 6 × 28-day cycles) In pre-/perimenopausal patients with oestrogen receptor (ER) positive early breast cancer. In a protocolled sub-study, quality of life (QoL) was assessed using the Rotterdam Symptom Checklist (RSCL) at 3 and 6 months and 1, 2 and 3 years in patients from 86 centres (goserelin, n = 514 [n = 247 at 3 years]; CMF, n = 496 [n = 243 at 3 years]). Only patients with a baseline score and at least one post-baseline score were included In the analysis. Patient and disease characteristics between the groups were comparable as were all baseline QoL scores. The improvement from baseline in overall QoL score was significantly greater in the goserelin group than the CMF group during the first 3–6 months ($p < 0.0001$). However, at 1, 2 and 3 years, there were no significant differences in overall QoL score between groups. Early QoL benefits for goserelin were also noted for the physical symptom distress, activity level and effort to cope with illness dimensions of the RSCL during the first 3–6 months of therapy, compared with patients receiving CMF ($p < 0.0001$); however, no significant differences in these scores were observed between groups after 6 months. In contrast, the change in score for the hormonal effects dimension was significantly worse in the goserelin group during their 2-year treatment period ($p < 0.01$); however, at 3 years, this trend was reversed. No significant differences were observed between the two treatment groups for the psychological distress or social effects dimensions during or after treatment. Analysis of QoL in the ER-positive sub-group resulted in qualitatively comparable conclusions as the overall QoL population for each RSCL dimension. In summary, goserelin for the treatment of node-positive early breast cancer in pre-/perimenopausal patients offers an improved overall QoL during the CMF 6-month treatment period. Coupled with equivalent efficacy in ER-positive patients, these data support the use of goserelin as an alternative to CMF in this patient population.