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Adjuvant endocrine therapy in pre- and postmenopausal women with primary breast cancer. A 25-year report of the Copenhagen Breast Cancer Trials.

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Background: In the beginning of the 1970 Tamoxifen (TAM) - a new antioestrogen - was shown to be safe and effective in advanced disease and the response was correlated to the content of estrogen receptor protein (ER) in the tumor cells. The effect of diethylstilboestrol (DES) was also related to the ER status of the disease. The objectives of the studies were to evaluate the efficacy and safety of adjuvant endocrine therapy and to correlate the effect to the ER status of the tumor.

Material and methods: 360 consequetive patients with stage I-III breast cancer were entered from 1975 to 1978 into two controlled double-blind studies. Premeonpausal patients were randomised to receive either placebo (PL) or Tamoxifen 30mg daily for two years. Postmenopausal patients received either PL, TAM or DES 3mg daily for two years. Postoperative radiotherapy were administered to all. The tumor cells were in most patients analysed for content of estrogen receptor protein.

Results: Updated results after 25 years of observation will be presented and compared to the results of an extensive analysis after 10 years of oberservation.

Breast cancer genetics and biology

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Molecular analysis of eighteen most recurrent mutations in the BRCA1 gen in 59 Chilean breast cancer families

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BRCA1 accounts for nearly all families with multiple cases of early onset breast and/or ovarian cancer and about 45% of families with breast cancer only. Although to date more than 1.237 distinct mutations, polymorphism and variants have been described, several mutations have been found to be recurrent in the gene. We have analyzed 59 Chilean breast/ovarian cancer families (Table 1) for the eighteen most recurrent mutations in the BRCA1 gene.

Table 1. Chilean breast cancer families at high risk for breast cancer predisposing mutations

Case category for selection	Mean age at diagnosis of individual (years)[b]	Number of families (% total families)
Multiple-case families (* 3[a])	51.10	29 (49.1%)
Multiple-case families (2[a])	50.00	14 (23.7%)
Early onset (≤ 40 years) breast cancer	34.33	7 (11.9%)
Bilateral breast cancer	47.67	5 (8.5%)
Male and ovarian cancer	74.30	1 (1.7%)
Breast cancer and ovarian cancer	47.00	4 (5.1%)
Total	49.45	59 (100%)

a: Number of breast cancer cases per family, including first-degree, second-degree, and distant relatives. b: Mean age at onset of all individuals in the family affected with breast and/or ovarian cancer (whether sampled or not).

The analysis of the five exons and two introns where these mutations are located was made using mismatch PCR assay, ASO, restriction analysis, allele specific PCR assay and sequentiation techniques. Two BRCA1 recurrent mutations (185delAG and 300T→ G) and one variant of uncertain significance (3867 G→ A) were found in four of our families. Also, a new mutation (4185delCAAG) and one polymorphism previously described (3232 A→ G) were found in other two families (Table 2). The 185delAG was found in a 3.38% of the families and each of the others were present only in one of the families of this cohort. Therefore these mutations are not especially recurrent in the Chilean population. The variant of uncertain significance and the polymorphism detected could represent a founder effect of Spanish origin.

Abstract 403 – Table 2. Germline BRCA1 mutations

Family	Female breast cancer	Average Age (years)	Ovarian Cancer	Average Age (years)	Male breast cancer	Cancer at other sites[b]	BRCA1 mutation	Exon	Effect
F4	2	50	–	–	0	Prost, Ut	185delAG	2	Ter codon 39
F46	3	56	3	43,3	0	Pan, Test, Co, Melan	185delAG	2	Ter codon 39
F13	4	40.25	–	–	0	Prost, St, Kid, Lu, Bo	300T→ G	5	Cys to Gly
F14	3	41.5	–	–	0	Ut	3867G→ A	11	Glu to Lys
F21	3	47	–	–	0	–	4185del4	11	Ter codon 1364
F25	3	45.6	–	–	0	Ut, Pan, St	3232 A/G	11	Polymorphism

F: Family; Ov: Ovarian cancer, Prost: Prostate cancer, Ut: Uterus cancer, Co: Colon cancer, Pan: Pancreatic cancer, Melan: Melanoma, Test: Testicular cancer, St: Stomach cancer, Kid: Kidney cancer, Lu: Lung cancer, Bo: Bone Cancer.

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G-protein coupled receptors and anti-apoptotic signalling by estrogen independent of estrogen receptor

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Introduction: In breast cancer, steroids in particular estrogen, functioning through its receptors (ER) contribute to tumour progression by regulating the transcription of target genes. Recent studies however suggest that estrogen may mediate some of cell survival properties through an ER-independent mechanism involving mitogen-activated protein kinase (MAPK) pathway.

Methods: The ER-positive MCF-7 and the ER-negative SKBR3 human breast cancer cell lines were incubated in the presence and absence of EGF and estrogen with or without G-protein coupled receptor (GPCR) inhibitor, pertussis toxin and EGF receptor inhibitor, AG 1478. Phospho-c-raf, phospho-Erk, phospho-cdc2 and survivin expression were detected using western blotting techniques.

Results: In MCF-7 and SKBR3 human breast cancer cells, we have found that EGF and estrogen stimulation rapidly increased the phosphorylation of c-raf, Erk and subsequently an increase in cdc2 phosphorylation and an up-regulation of survivin expression. A further increase was noted in the presence of EGF in combination of estrogen. Moreover, estrogen induced a translocation of phospho-cdc-2 from the cytosol to the nucleus indicating activation of the phospho-cdc-2/survivin complex. The effects of EGF on phosphorylation of c-raf, Erk, cdc2 and survivin were attenuated by AG1478. The effects of estrogen on phosphorylation of c-raf, Erk, cdc2 and survivin were attenuated by pertussis toxin and to the lesser extent by AG1478.

Conclusion: These observations implicate estrogen in the MAPK cell survival mechanism and survivin anti-apoptotic pathway. Elucidation of ER-independent estrogen survival pathways may in part explain clinical observations of steroid therapy resistance in breast cancer.

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Modeling the effect of age in T1-T2 breast cancer

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Purpose: 1) To determine the functional form of age (i.e. determine the relationship between age and survival or mortality without making rigid assumptions), while adjusting for the effect of other known variables; 2) to search for a parsimonious algebric representation of that functional form.

Material and Methods: Women from the US Surveillance, Epidemiology, and End Results Program, with histologically confirmed pT1-2 pN0-1 M0 breast carcinoma diagnosed in 1988-1997. The martingale residuals obtained from a multivariate proportional hazards (PH) model in node-negative (N0) cases were analyzed by a Poisson regression procedure applied to the age covariate. Non-linearity of age on the log hazard ratio