431 Proffered paper oral

Diagnostic radiation exposure and risk of breast cancer in BRCA1/2 mutation carriers in the GENE-RAD-RISK study: a report from the GENEPSO, EMBRACE, and HEBON Collaborators' group

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Background: Exposure to ionizing radiation is an established risk factor for breast cancer in the general population, but at low doses (<0.1 Gy), usually a modest or no increase in breast cancer risk is observed. Because of the role of the BRCA proteins in DNA repair, BRCA1/2 mutation carriers might be more sensitive to ionizing radiation than the general population.

Methods: A retrospective European collaborative cohort study (GENE-RAD-RISK) of 1,993 BRCA1/2 mutation carriers from France, the UK and the Netherlands was performed using self-reported exposure to diagnostic radiation. Risk of breast cancer was analyzed using a time-varying weighted Cox proportional hazards model with a 5 year time lag. A unique feature of this study is the individually estimated cumulative breast dose score.

Results: When compared to no exposure, having had more than 2 fluoroscopies or 4 X-rays before age 20 increased the risk of breast cancer ($HR_{fluoroscopies}$=2.46, 95% CI = 1.09–5.54, P_{trend}=0.102; HR_{X-rays}=1.53, 95%=0.74–3.17, P_{trend}=0.041). Ever having had a mammogram before age 30 increased the risk of breast cancer 1.5-fold (HR = 1.54, 95% CI = 1.03–2.28) and a dose-response trend ($HR_{>4\ mammograms}$=2.41, 95% CI = 0.90–6.49, P_{trend}=0.040) of greater risk with higher number of mammograms was observed, which could not be attributed to confounding by indication because of family history of breast cancer (analysis in Dutch subgroup only: $P_{interaction}$ = 0.727). Other exposure types were not significantly associated with breast cancer risk. Exposure to any diagnostic radiation before age 30 increased the risk of breast cancer (HR = 1.73, 95% CI = 1.20–2.48). The risk of breast cancer was greater with increasing cumulative dose: the risks for a cumulative dose score <0.002 Gy, ⩾0.002–0.0066 Gy, ⩾0.0066–0.0174 Gy, and ⩾0.0174 Gy were 1.45 (0.92–2.27), 1.70 (1.03–2.79), 1.74 (0.89–3.39), and 3.29 (1.83–5.93), respectively, when compared to no exposure. Results on Excess Relative Risk estimates will be presented.

Conclusions: Exposure to diagnostic radiation before age 30 was associated with at least a 1.5-fold increase in breast cancer risk in BRCA1/2 mutation carriers. This relative risk was observed for doses that are at least an order of magnitude lower than those for which in previous studies significant associations were observed. The data supported a dose-response model. A potential difference in mechanism between BRCA1 and BRCA2 needs to be investigated in future studies.

Friday, 26 March 2010 15:30–17:00

CLINICAL SCIENCE SYMPOSIUM

Multi-targeting therapies in breast cancer

434 Invited

Synthetic lethal strategies in ER/HER2 negative breast cancers

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Breast cancer comprises a diverse collection of diseases with distinct biological features and clinical behaviour. Both pre-clinical and clinical research now commonly targets specific sub-groups of breast cancer with the aim of identifying biological markers or genetic phenotypes, which reveal specific therapeutic targets or indicators of prognosis for each of these groups. Examples include the targeting of oestrogen receptor (ER) driven breast cancers with endocrine therapies, and sub-group of breast cancers driven by the receptor tyrosine kinase ErbB2 (HER2) by targeting this receptor using the monoclonal antibody (e.g. trastuzumab) or the small molecule inhibitor lapatinib. In each case, extensive preclinical research followed by large, multi-centre, randomised controlled trials has led to improved disease free survival and overall survival. These novel targeted agents are, however, of no benefit to a substantial number of women whose breast cancers lack ER, PR and HER2 receptors; the so called "triple negative" sub-group. Increasing knowledge of the molecular pathology of and relationships between "triple negative" and "basal-like" breast cancers reveals some recurrent genetic, epigenetic and gene expression changes associated with these sub-types. These are now being used to inform early phase clinical trials in "triple negative" and "basal-like" breast cancer subtypes. There is a significant link between loss of function of BRCA1 and triple negative breast cancer. Abnormalities in the DNA damage response and specialised DNA repair processes may be prevalent in triple negative breast cancers. Our group and others have explored the concept of targeting abnormal DNA repair. Given that cancer cells with a dysfunctional BRCA1 pathway have been shown to display an exquisite sensitivity to DNA cross-linking agents and PARP inhibitors, clinical trials are now testing whether these agents can be used for the management of patients with hereditary BRCA cancers and sporadic carcinomas with "triple negative" and "basal-like" phenotypes. The rationale for, nature of and early results of such clinical trials examining synthetic lethal strategies will be discussed.

435 Proffered paper oral

Prognostic and predictive value of central and local hormone receptor assessment in the HERA trial

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Background: HER-2-positivity of breast cancers (BC) has been associated with poor prognosis and response to endocrine therapy. Adjuvant trastuzumab significantly improves disease-free survival (DFS) and overall survival in patients with HER-2 positive early BC. Our aim was to establish whether the benefit of trastuzumab differed according to the status of positivity of hormone receptors in patients enrolled in the HERA trial.

Patients and Methods: This study investigated estrogen (ER) and progesterone (PR) receptor status, endocrine treatments and DFS in patients in the 1 year and observation groups of the HERA trial. ER and PR were measured by immunohistochemistry (local and central assessments). ER and PR were defined using Allred scores and were considered positive if the score was 3−8. Cox proportional hazards regression analysis was used to estimate hazard ratios (HR) and 95% confidence intervals. HRs were used to compare DFS in randomized groups among subgroups of patients.

Results: 3,401 patients were enrolled in the 1 year and observation groups of HERA and the median follow-up in this analysis is 23.5 months. A central assessment of ER and/or PR was possible for 3,002 out 3401 patients (88.3%). Among those patients with central and local data available, central ER concordance with local assessment was 91% (ER negative) and 73% (ER positive) while central PR concordance was 84% (PR negative) and 81% (PR positive). There was a trend for patients with a higher HER-2 copy number to have a lower central ER score. HR according to central/local ER status is shown in table below (1 year trastuzumab and observation groups).

Subgroup	# Pts*	Hazard Ratio (95% CI)	# Pts receiving endocrine therapy*	# Pts with DFS Event*
Central *and* Local ER+	981	0.60 (0.40–0.91)	963	97
Central ER+, Local ER−	150	1.10 (0.43–2.70)	42	18
Central ER−, Local ER+	359	0.56 (0.33–0.95)	333	58
Central *and* Local ER−	1506	0.55 (0.44–0.70)	144	287

* number of patients refers to the number of patients in the observation and 1-year trastuzumab groups combined.

Conclusion: Accurate hormone receptor status results are important when deciding the appropriate treatment for a patient. Discordance rates in hormone receptor status results found were higher than those reported in patients not selected for HER-2 positivity and this may reflect the difficulties imposed by lower levels of ER even in ER+HER-2+ patients.

Better standardisation for assessment of hormone receptors should take place worldwide.