attenuated after adjusting for confounders (REM – 1.50, 1.38 and 1.27).

Conclusion: We confirmed poorer BCRS in older women in our region. This was partially explained by known prognostic factors. Further research is needed to determine whether biological differences or sub-optimal management can explain the residual excess mortality.

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O-42 EARLY OPERABLE PRIMARY BREAST CANCER IN OLDER (⩾70 YEARS) WOMEN (EPCS) – BIOLOGY AND CLINICAL SIGNIFICANCE

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Introduction: Biology of breast cancer appears to change with age. Most studies are small/from multiple centres limiting their importance.

Methods: From 1973 to 2009, 2000+ EPCs were managed in Nottingham. Oestrogen receptor (ER) was assessed by immunohistochemistry (giving an H-score) on core biopsy for all patients. A total of 831 patients had primary surgery and 575 had good quality tumour samples available for tissue microarray analysis.

Results: Comparing these 831 patients with a younger (<70 years) series ($N = 1809$), expression of ER ($p < 0.001$), p53, HER4, CK14, bcl2 ($p < 0.000$) and CK 17 ($p < 0.05$) was found to increase with age, while reverse was seen with CK 7/8 ($p < 0.002$), ki67 and E-Cadherin ($p < 0.000$). No change was observed in PR, HER2, CK5/6, CK19 and MUC1 expression.

At 66-month median follow-up, for those who did not receive adjuvant systemic therapy ($N = 306$), tumour size ($p < 0.042$), grade ($p < 0.046$), axillary stage ($p < 0.000$) and PR ($p < 0.017$) were found to be independent prognostic factors.

At 49-month median follow-up, for patients with ER+ (H-score ⩾ 50) tumours, those with H-score ⩾ 250 had equivalent 5-year breast cancer specific survival (BCSS) regardless of primary treatment (surgery vs primary endocrine therapy (PET) 95% versus 93%, $p = 0.715$). For patients on PET, all those with H-score ⩾ 250 achieved clinical benefit as compared to 11 patients with H-score < 250 who progressed, at 6 months ($p < 0.03$), the former also had better BCSS ($p < 0.01$).

Conclusion: The pattern suggests a less aggressive tumour phenotype with advancing age. The ER H-score appears as an excellent surrogate for clinical outcome for ER+ EPCs. It is available at diagnosis and has a great value in guiding discussion of therapeutic options.

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O-43 A KRAS MICRORNA BINDING SITE VARIANT IS A GENETIC MARKER OF RISK FOR TRIPLE NEGATIVE BREAST CANCER

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Introduction: MiRNAs exert their regulatory effect on gene expression by binding to the 3′ untranslated region (UTR) of target mRNAs. The let-7 miRNA family are global genetic regulators critically important for controlling oncogene expression (e.g. *KRAS*). Dysregulated let-7 expression is associated with many malignancies including breast cancer, and it is hypothesized that defective interaction between let-7 and its target *KRAS* underpins this association and oncogenesis. We hypothesized that a single nucleotide polymorphism (SNP) in the *let-7*-binding site in *KRAS* disrupts *let-7* regulation of the oncogene and thus predisposes to breast cancer.

Methods: A population analysis of the association of the *KRAS* variant and breast cancer was performed on a cohort of 1010 breast cancer patients and 1497 age-matched healthy controls. Genomic DNA isolated from all participants was amplified using PCR assays designed specifically to identify the T (wild type) or G (variant) allele. Genotyping results were correlated with patients' clinicopathological parameters.

Results: The *KRAS* variant was present in 15% of all breast cancer patients, compared with baseline prevalence of <7%. In particular the *KRAS*-variant predicted a significantly increased risk of developing triple negative breast cancer in premenopausal women (OR = 4.78, CI = 1.71–13.38, $p = 0.015$), and patients with the variant allele were significantly more likely to present with advanced stage disease ($p = 0.03$).

Conclusion: These seminal findings suggest that the *KRAS*-variant acts as a genetic marker of risk for developing triple negative breast cancer. Predicting risk for this subtype is critically important, to permit early screening and intervention for 'at-risk' individuals.

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O-44 GENE–ENVIRONMENT INTERACTIONS IN 7610 WOMEN WITH BREAST CANCER: PROSPECTIVE EVIDENCE FROM THE MILLION WOMEN STUDY

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Background: Genome-wide association studies, together with analyses of specific candidate polymorphisms, have identified a number of low-penetrance breast cancer susceptibility loci. Information is scarce about the combined effects on breast cancer incidence of these genetic variants and of environmental factors (reproductive, behavioural, and anthropometric risk factors for

breast cancer). To test for evidence of gene–environment interactions, we compared genotypic relative risks for breast cancer across categories of the environmental risk factors.

Methods: We tested gene–environment interactions in 7610 women who developed breast cancer and 10,196 controls without the disease in a large UK prospective study, studying the effects of 12 polymorphisms (*FGFR2*-rs2981582, *TNRC9*-rs3803662, 2q35-rs13387042, *MAP3K1*-rs889312, 8q24-rs13281615, 2p-rs4666451, 5p12-rs981782, *CASP8*-rs1045485, *LSP1*-rs3817198, 5q-rs30099, *TGFB1*-rs1982073, and *ATM*-rs1800054) in relation to prospectively collected information about 10 established environmental risk factors (age at menarche, parity, age at first birth, breastfeeding, menopausal status, age at menopause, use of hormone replacement therapy, body-mass index, height, and alcohol consumption).

Results: We will present findings from this systematic investigation of gene–environment interactions in relation to breast cancer risk in the Million Women Study. Results from a meta-analysis of these and published data will also be shown when possible.

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O-45 CHILDHOOD ADIPOSITY AND BREAST CANCER INCIDENCE IN WOMEN IN MIDDLE AGE

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Among 397,339 postmenopausal women, breast cancer incidence increases with increasing body mass index (BMI), while adiposity in childhood has been found to lower risk. Few epidemiological studies have been able to investigate joint effects of both childhood and adult adiposity.

In a large, prospective study of postmenopausal middle-aged women, adjusted relative risks (RR), according to BMI in middle age and relative adiposity at age 10, were estimated by Cox regression. (Analyses were confined to non-users of hormone replacement therapy, which can mask the effects of BMI on breast cancer risk.)

Among 397,339 women, there were 6189 incident breast cancers over 5.2 years mean follow-up (average age at diagnosis: 63 years). As expected, women with a high BMI in middle age had a greater breast cancer risk ($P < 0.001$). In contrast, women who were plumper than average at age 10 had a lower risk of breast cancer than women who were about average ($P < 0.001$). A similar apparently protective effect of childhood adiposity was observed at each level of women's BMI in middle age ($P = 0.08$, NS, for interaction). These relationships were not altered by height ($P = 0.9$), age at menarche ($P = 0.8$), or other reproductive and hormonal risk factors ($P > 0.1$).

Despite the increase in risk of breast cancer with increasing BMI among postmenopausal women, greater childhood adiposity lowers risk in the same women. The reason for the persistent and apparently protective effect of childhood adiposity is unclear.

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O-46 MACROPHAGE INFILTRATION IS ASSOCIATED WITH POOR OUTCOME IN BREAST CANCER PATIENTS AND A REDUCED TREATMENT RESPONSE TO LETROZOLE AND ZOLEDRONATE

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Background: Macrophage infiltration augments tumour recurrence whilst Zoledronic acid suppresses macrophage protumourigenicity. In the ZO-FAST and ABCSG 12 trials, oestrogen receptor (ER) positive breast cancer patients received Zoledronate in combination with an aromatase inhibitor, Letrozole, demonstrating an increased disease-free survival. We aimed to investigate macrophage infiltration and patient prognosis and the early biological effects of adjunctive Zoledronate on patient and macrophage response to treatment in breast cancer.

Methods: Tissue microarrays from 179 breast cancer 'FasA Cohort' patients were immunohistochemically stained with CD68, a universal macrophage marker. A randomised pre-operative trial allocated ER-positive breast cancer patients ($n = 110$) to 14 days pre-operative treatment of Letrozole, Letrozole and Zoledronate, or placebo. Pre- and post-treatment specimens were collected and immunohistochemically stained for CD68 and the proliferation marker, Ki67.

Results: The FasA cohort found links between macrophage frequency and tumour grade ($P < 0.01$), size ($P < 0.05$), recurrence ($P < 0.05$) and lymph node status ($P < 0.05$). Ki67 reductions of 52% ($P < 0.001$) were seen in the aromatase inhibitor group, with no additional benefit following Zoledronate treatment. Macrophage infiltrate (Mean = 37; Range = 3–117) was positively associated with pre and post Ki67 levels ($P < 0.05$, $P < 0.01$). Additionally, low post-treatment macrophage infiltrate (Mean = 29; Range = 3–66) was associated with a greater reduction in Ki67 following aromatase inhibition ($P < 0.05$).

Conclusion: Macrophage infiltrate correlates with poor outcome in breast cancer. Aromatase inhibition but not Zoledronate lowered proliferation and macrophage infiltration in ER-positive breast cancer. For the first time we have shown novel treatment effects on the tumour stromal compartment.

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O-47 THE BASO II TRIAL AT MEDIAN 15 YEARS OF FOLLOW-UP

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BASO II tested whether adjuvant radiotherapy or endocrine therapy were required following Wide Local Excision: Grade I/node negative/$\leqslant$2 cm diameter.

The mean endpoint was Local Recurrence (in breast) (LR).

Entry was to 4-way randomisation: RT only, Tamoxifen (TAM) only, neither, both.