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

Benjamin J. Cairns, TienYu Owen Yang, Gillian K. Reeves, Valerie Beral, on behalf of the Million Women Study Collaborators. *Cancer Epidemiology Unit, University of Oxford, Oxford, UK*

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

A. Lee, R. Lamb, H. Gregson, A. Cramer, J. Morris, L. Renshaw, M. Winter, R.E. Coleman, J.M.J. Dixon, G. Landberg, N.J. Bundred. *Breakthrough Breast Centre, Manchester, UK*

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

R.W. Blamey, A. Oates, data manager, on behalf of the Contributors to BASO II. *Nottingham City Hospital, UK*

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.

Results:

	n	% 10 Year LR free
RT + TAM	98	100 ± 0
RT only	110	93 ± 3
TAM only	107	93 ± 3
Neither	96	82 ± 4

Entry was also allowed to *2-way randomisation* for units which had opted to give RT or TAM to all their cases. Analysis by randomisation then allowed RT versus no RT with both arms including some cases receiving TAM by elective choice of Unit (or) TAM versus no TAM, both including some cases receiving elective RT.

Results:

	n	% 10 Year LR free	% 15 Year LR free	W-G	*p*
RT	571	97 ± 1	93 ± 1	20.5	<0.000
No RT	568	88 ± 2	86 ± 2		
TAM	213	96 ± 2	92 ± 4	12.3	<0.000
No TAM	217	87 ± 3	83 ± 3		

Analysis by treatment received confirms that results from randomisation (intention to treat).

Survival overall (all cases) is 91 ± 1% at 10 years.

Conclusion:

1. Omission of any adjuvant therapy led to a recurrence rate of 1.8% per annum. This was reduced by the use of either TAM only or RT only.
2. Use of both TAM and RT produced no LR's.

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O-48 THE POST-OPERATIVE RADIOTHERAPY IN MINIMUM-RISK ELDERLY (PRIME) RANDOMISED TRIAL OF ADJUVANT RADIOTHERAPY AFTER BREAST CONSERVING SURGERY: IMPACT ON QUALITY OF LIFE AND COST-EFFECTIVENESS AT 5 YEARS

I.H. Kunkler [a], L.J. Williams [b], R.J. Prescott [b], C.C. King [b], W. Jack [a], J.M. Dixon [a], M. van der Pol [c], T.T. Goh [c], R. Lindley [d], J. Cairns [e]. [a] *Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK.* [b] *Centre for Population Health Sciences, University of Edinburgh, UK.* [c] *Health Economics Research Unit, University of Aberdeen, UK.* [d] *Westmead Hospital, University of Sydney, Australia.* [e] *London School of Hygiene and Tropical Medicine, London, UK*

Objectives: To assess whether in older women with 'low risk' axillary node negative breast cancer (T0–2, N0, M0) treated by breast conserving surgery and adjuvant endocrine therapy the omission of post-operative radiotherapy affects quality of life and is cost-effective.

Design: Randomised controlled multicentre trial.

Participants: Patients (255) with follow up to 5 years from the end of recruitment.

Interventions: Whole breast radiotherapy (40–50 Gy) or no breast radiotherapy.

Main outcome measures: Quality of life, anxiety and depression, cost effectiveness.

Results: No difference in overall quality of life or anxiety and depression was found. However, in the subscales of the EORTC QLQ C30 and BR23 questionnaires, there were significantly higher levels of insomnia within the non-irradiated group. By contrast, the irradiated patients reported higher levels of breast symptoms, and social function was slower to recover. The mean Quality Adjusted Life Years were similar in the two arms with marginally higher levels in the radiotherapy arm. The additional cost of providing radiotherapy was £2128 per patient. Local recurrence rates at 5 years were 6% (95% CI 0–12%) in the non-irradiated group and 0% in the irradiated group.

Conclusion: Breast radiotherapy is tolerated well by most older breast cancer patients without impairing their overall health related quality of life (HRQOL). Concerns about HRQOL should not be a primary consideration when deciding whether or not to recommend postoperative radiotherapy after breast conserving surgery and adjuvant endocrine therapy. The 'no radiotherapy option' is cost effective in the short term.

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O-49 THE INFLUENCE OF PATIENT-RELATED AND SURGICAL FACTORS ON OVERALL COSMESIS AND LATE TOXICITY AFTER ADJUVANT BREAST RADIOTHERAPY: RESULTS FROM THE CAMBRIDGE INTENSITY MODULATED RADIOTHERAPY (IMRT) TRIAL

Gillian C. Barnett [a], Gordon C. Wishart [b], Jennifer C. Wilkinson [c], Anne M. Moody [c], Charles B. Wilson [c], Nicola Twyman [c], Neil G. Burnet [a], Charlotte E. Coles [c]. [a] *University of Cambridge, Department of Oncology, Cambridge, UK.* [b] *Cambridge Breast Unit, Cambridge, UK.* [c] *Oncology Centre, Addenbrooke's Hospital, Cambridge, UK*

Background: The Cambridge Breast IMRT Trial demonstrated that improving dose distribution using IMRT leads to significant reduction in telangiectasia at comparatively early follow-up. The secondary aim was to elucidate the influence of patient-related and surgical factors on late toxicity and cosmesis.

Method: The influence of such factors on late toxicity assessed using photographic, clinical and patient-reported endpoints at 2 years following radiotherapy was analysed in 1014 patients.

Results: Patients with a moderate or poor baseline surgical cosmesis had an increased risk of moderate or poor overall cosmesis (odds ratio (OR) = 38.19; 95% CI 21.9–66.7; $p < 0.0005$), and of developing any clinically assessed breast shrinkage (OR = 4.96; 95% CI 3.67–6.71, $p < 0.0005$) and induration (OR = 2.78; 95% CI 1.92–4.01, $p < 0.0005$) at 2 years. Increased breast volume was significantly associated with the development of several late toxicity endpoints ($p < 0.0005$). Current smokers had an increased risk of developing pigmentation (OR = 2.09, 95% CI 1.23–3.54; $p = 0.006$). Post-operative infection requiring antibiotics was associated with increased risk of telangiectasia (OR = 3.39, 95% CI 1.94–5.91; $p < 0.0005$) and breast oversensitivity (OR = 1.78, 95% CI 1.27–2.49; $p = 0.001$).