Body: Introduction
Breast cancer radiotherapy cures many women, but, as with other therapies, can cause late side-effects.

Methods
We undertook meta-analyses of individual patient data from the trials of breast cancer radiotherapy, relating various characteristics of the regimens tested to cause-specific mortality rate ratios (RRs) and second cancer incidence RRs.

Doses to cardiac structures were calculated for trials with some heart disease death(s), lung doses were calculated for megavoltage trials with some lung cancer(s) in the second decade after radiotherapy, and oesophagus doses were calculated for megavoltage trials with some oesophageal cancer(s). Trial radiotherapy regimens were reconstructed for a woman with typical anatomy using virtual simulation and 3-dimensional CT planning (and, for a few regimens, manual planning).

Results
Information was available on 40,781 women in 75 evenly randomised comparisons of radiotherapy versus not. Median follow-up was 9.7 years and 20,345 died, 6064 without recurrence. Smoking information for included women was unavailable.

Mean normal tissue radiation doses for irradiated women were: heart 6.3 Gy (range <1-18), ipsilateral lung 17.2 Gy (range 5.8-27.2) and oesophagus 10.5 Gy (range <1-27.3).

Allocation to radiotherapy increased non-breast-cancer mortality (RR=1.15, 95% CI 1.09-1.22, 2p<0.0001), due mainly to heart disease (RR=1.30, 1.15-1.46, 2p<0.0001). The heart disease death rate was strongly related to the estimated heart radiation dose, and increased approximately linearly by 4.1% per Gy (95% CI 2.4-6.2, 2p<0.00001).

Second cancer incidence was increased (RR=1.23, 1.12-1.36, 2p<0.0001). The site with most events was the contralateral breast (RR=1.20, 1.08-1.33, 2p=0.0006 with 881 versus 673 cases). Excluding the first decade, lung cancer incidence was increased (RR=2.10, 1.48-2.98, 2p=0.00003 with 94 versus 40 cases after the first decade). There were also excesses of oesophageal cancer (RR=2.42, 1.19-4.92, 2p=0.01), mainly in trials where the internal mammary chain and supraclavicular fossa were irradiated, and leukaemia (RR=1.71, 1.05-2.79, 2p=0.03).

Conclusions
Since these trials, normal tissue doses from breast cancer radiotherapy have at least halved so the excess relative risks will be at least halved. Background disease rates have also changed, so the absolute risks will be different for women today. Modelling the effects of such changes suggests that for women who have smoked throughout adult life and will continue smoking, even modern radiotherapy may cause an absolute lung cancer risk of a few per cent, making this the main late side-effect in smokers. However, for non-smokers (and ex-smokers) with healthy hearts who would, under current guidelines, be offered radiotherapy, the expected reduction in breast cancer mortality greatly outweighs any increase in other mortality.