Web appendix: Supplementary information

Estimation of underlying incidence

The life tables for a cohort of women not being screened and a cohort of women receiving regular screening from age 50 to 69 were developed using population-based data for breast cancer incidence, breast cancer mortality and all cause mortality for England and Wales, 2009 (web table).

Web table: Population incidence and mortality data used to develop the life tables

Age group	Breast cancer incidence		All cause mortality	Breast cancer mortality	Other mortality
	1988	2009	2009	2009	2009
50-	.0014043	.002433	.0035	.000411	0.003089
55-	.0016285	.002425	.005407	.000535	0.004872
60-	.0017751	.00318	.008095	.000696	0.007399
65-	.0019942	.003476	.013008	.000828	0.01218
70-	.0020904	.002686	.02204	.001029	0.021011
75-	.0022037	.003337	.039795	.001325	0.03847
80-	.0024239	.003628	.072125	.001821	0.070304
85+	.0028713	.003893	.170101	.002968	0.167133

Population based incidence and mortality data reflect the fact that approximately 75 per cent of women aged 50-69 have regular mammographic screening through the NHS breast screening programme [1]. In order to estimate the underlying incidence in the absence of screening we used population incidence data for England and Wales in five-year age bands for 1988 (web table) when there was no national screening programme. Age-specific incidence in one-year age bands in 1988 was based on a regression of the log of the observed incidence against age from age 50 to age 90. Thus,

$$\log_e(\text{incidence}_{1988}) = -7.485587 + \text{age} * .0183122$$

The expected background incidence for the non-screened cohort for 2009 in one-year age bands was then obtained my multiplying the 1988 incidence by a factor of 1.35 to allow for the background increase in incidence over time - this is the relative difference in the incidence in women aged 45-49 and 80-85 comparing 2009 with 1988.

The incidence of breast cancer in the cohort of screened women was estimated by assuming that screening increases the incidence of breast cancer by both relative overdiagnosis and by advancing the diagnosis of breast cancer by five years on average from age 50 to 69 and then to result in a ten per cent reduction in incidence after screening stops. These values were chosen empirically so that the predicted population age-specific breast cancer incidence based on a weighted average of the incidences for the screened and unscreened cohorts of women used in the model approximated the observed population incidence for 2009 (web figure 5) assuming that 75% of women undergo screening. In addition to the probabilistic sensitivity analysis used to evaluate impact of uncertainty for other parameters used in the model, we re-ran the models and probabilistic sensitivity analyses under five alternative scenarios with screening advancing diagnosis by 3, 5 or 7 years and with a ten or twenty per cent reduction in incidence post screening.

Estimation of breast cancer specific mortality

Breast cancer specific mortality rates in the screened and unscreened cohorts were derived using population breast cancer specific mortality rates for England and Wales, 2009. We assumed that these rates reflect a weighted average of mortality rates in screened and unscreened cohorts in a population where 75 per cent of women had regular screening between the age of 50 and 69. The breast cancer mortality rate in the screened cohort was assumed to be proportionately reduced

(breast cancer specific mortality relative risk reduction) from five years after the start of screening until 10 years after screening is stopped (the end of the follow-up period).
Thus

$$\text{Breast cancer mortality in screened} = \frac{\text{observed breast mortality in population} * \text{relative risk reduction}}{0.75 * \text{relative risk reduction} + 0.25}$$

$$\text{Breast cancer mortality in unscreened} = \frac{\text{observed breast mortality in population}}{0.75 * \text{relative risk reduction} + 0.25}$$

It is likely that the observed breast cancer specific mortality in the population is the result of a more complex function than this simple, weighted average as women who attend screening are different from non-attenders. For example, attenders tend to be of higher socio-economic status. While this is associated with an increased risk of incident breast cancer, it is also associated with a lower case-fatality for reasons that are complex and incompletely understood. Thus relationship between screening attendance and breast cancer mortality is complex. However, for the purposes of the cost-utility analysis the simple weighted average is analogous to the difference in mortality rates that would be observed in a randomised controlled trial.

Sampling distributions for input parameters in uncertainty models

In the probabilistic sensitivity analyses the input parameters were sampled independently from distributions reflecting the underlying uncertainty in their estimates.

Relative risk of breast cancer specific mortality associated with regular mammographic screening: The estimate of the relative risk reduction of breast cancer specific mortality reported by the independent review – 20 per cent – was used for the base-case scenario[2]. The statistical uncertainty of this estimate is reflected in a 95 per cent confidence interval of 11 to 27 per cent. Reviews by the Canadian Task Force on Preventive Health Care[3] and the US Preventive Services Task Force[4] reached similar conclusions, but a meta-analysis conducted by the Nordic Cochrane Centre based on the studies with adequate randomisation suggested that the benefit is likely to be less than this[5]. Furthermore, there is substantial additional uncertainty relating to a lack of knowledge about the mortality benefit of screening using modern digital mammography in an era of modern surgery, adjuvant chemotherapy and adjuvant hormone therapy. It seems reasonable to believe that the effects of modern therapy would be more likely to reduce the effectiveness of screening than to increase the effects of screening, although neither is assumed to be true. In order to reflect this in the probabilistic sensitivity analysis, the log relative risk reduction was sampled from a gamma distribution such that the modal relative risk was 0.8 and the distribution slightly skewed towards 1.

Log_e(relative risk breast cancer specific mortality) = 0.7+rgamma(6,.08)*.25, truncated at -0.288 and -0.051

Relative risk of non-BC mortality in breast cancer cases: This was set at 1.06 for the base-case scenario. This was based on the assumption that the excess mortality associated with surgery is extremely small, but that adjuvant radiotherapy is associated with a 12 per cent increase in mortality from other causes [6] and that 50 per cent of breast cancer patients are treated with radiotherapy (based on data from the Eastern Cancer Registration and Information Centre). In the probabilistic sensitivity analysis this parameter was sampled from a right-skewed, gamma distribution with a mode of 1.06.

Relative risk of non-BC mortality in breast cancer cases = 1+0.1*Gamma(7,0.1)

Relative overdiagnosis: The estimate of the relative overdiagnosis during screening from the independent review [2] – 19 per cent – was used for the base case scenario. However, a wide variety of methodologies have been used to produce estimates for over diagnosis ranging from -4 per cent to over 50 per cent[7]. We sampled this parameter from a log-normal distribution with a mean of 0.174 and standard deviation 0.035.

Log_e(Relative overdiagnosis associated with screening) = Normal(0.174,0.035)

Age specific health-related quality-of-life: Data from the Health Survey from England has shown the average health-related utility weight in the general population to be 0.85 (SD=0.01) and to decline by 0.0.0043 units per year from age 50 to age 80[8]. In the probabilistic sensitivity analyses these were sampled from the following distributions

Health-related utility weight for a woman aged 50 = Normal(0.85, 0.01).

Annual reduction in utility = Normal(0.0043, 0.001)

Health utility associated with a diagnosis of breast cancer: In a recent, comprehensive review of studies evaluating health-related quality-of-life in breast cancer, Peasgood et al concluded that it is not feasible to generate a definitive list of health-state utility values that can be used in future economic evaluations [9]. Nevertheless, estimates of the short term mean health-related quality-of-life were provided. Based on these, we assumed that the mean health-related utility decrement in the year after diagnosis of breast cancer was around 0.7 compared to women of the same age. This is likely to improve rapidly over time with some women having residual long-term morbidities associated with treatment and other women returning to a quality of life similar to that of women of the same age who have not had breast cancer. The average person-years of survival time after a diagnosis of breast cancer was 10 years and so an average health-related utility decrement of 0.9 was used for the baseline model – equivalent to a utility of 0.7, 0.8 and 0.9 in the three years following diagnosis and 0.95 thereafter. In the probabilistic sensitivity analysis, this parameter was sampled from a right-skewed, gamma distribution with a mode of 0.9. Total quality adjusted life years were calculated by applying this value to the person years lived after a diagnosis of breast canceradjusted for the age specific health-related quality-of-life.

Health-related quality-of-life associated with diagnosis of breast cancer = 0.85 + 0.167*Gamma(4,0.1), right truncated at 1

Annual cost of the NHS breast screening programme: The cost of the screening programme can be considered to be equivalent to the annual steady state cost of the current NHS breast screening programme, which has been estimated to be £96 million (http://www.cancerscreening.nhs.uk/breastscreen/cost.html) or £4.8 million for each year of screening over 20 years. The is little information available to assess the uncertainty around this parameter, but it seems reasonable to assume that the true value is unlikely to be more third more or one third less than this value. In the probabilistic sensitivity analyses this was sampled from a normal distribution with a mean of 4.8 million and standard deviation of 0.8 million so that 95 per cent of values will lie within one third of the mean.

Annual cost of breast screening programme = Normal(4.8 million, 0.8 million)

Relative cost of treating a clinically detected cancer compared to the same cancer diagnosed earlier through screening: A clinically detected case would be expected to be less advanced if it had been detected earlier by screening and so the cost of treating the cases that are not over-diagnosed would be expected to be lower than in the unscreened cohort. However, there is little evidence on which to estimate this difference. A 10 per cent increase in costs for cases occurring in the unscreened population was assumed – a relative cost of 1.1. This parameter was sampled from a normal distribution with mean 1.1 and standard deviation 0.04 in the probabilistic sensitivity analysis.

Relative cost of treating a clinically detected cancer compared to the same cancer diagnosed earlier through screening = Normal(1.1,0.04), left truncated at 1.05

Cost of managing over-diagnosed cases in screened cohort: The cost of managing over-diagnosed cases was estimated by assuming that the majority would be in situ or micro-invasive disease and treated with surgery and radiotherapy. In 2011, 72 per cent of these cases detected by the NHS BSP were treated with local surgery and 27 per cent with mastectomy [1]. The 2011 NHS reference costs for these procedures, weighted for unilateral/bilateral with varying degrees of complications and with/without reconstruction according to NHS activity, are £1450 and £2810 respectively. Assuming 20 per cent of these patients also receive radiotherapy at a cost of £1,800, the average cost of treatment for an over-diagnosed case is £2,163. For the probabilistic sensitivity analysis this parameter was sampled from a gamma distribution with a mode of £2,000.

Cost of treating overdiagnosed breast cancer = 1800+Gamma(3,.1)*1000

Cost of treating metastatic breast cancer: The additional cost of treating patients who died from breast cancer was assumed to be £20,000, the same as the cost of treating metastatic breast cancer (NICE 2009). This parameter was sampled from a right-skewed gamma distribution with mode £20,000 in the probabilistic sensitivity analysis.

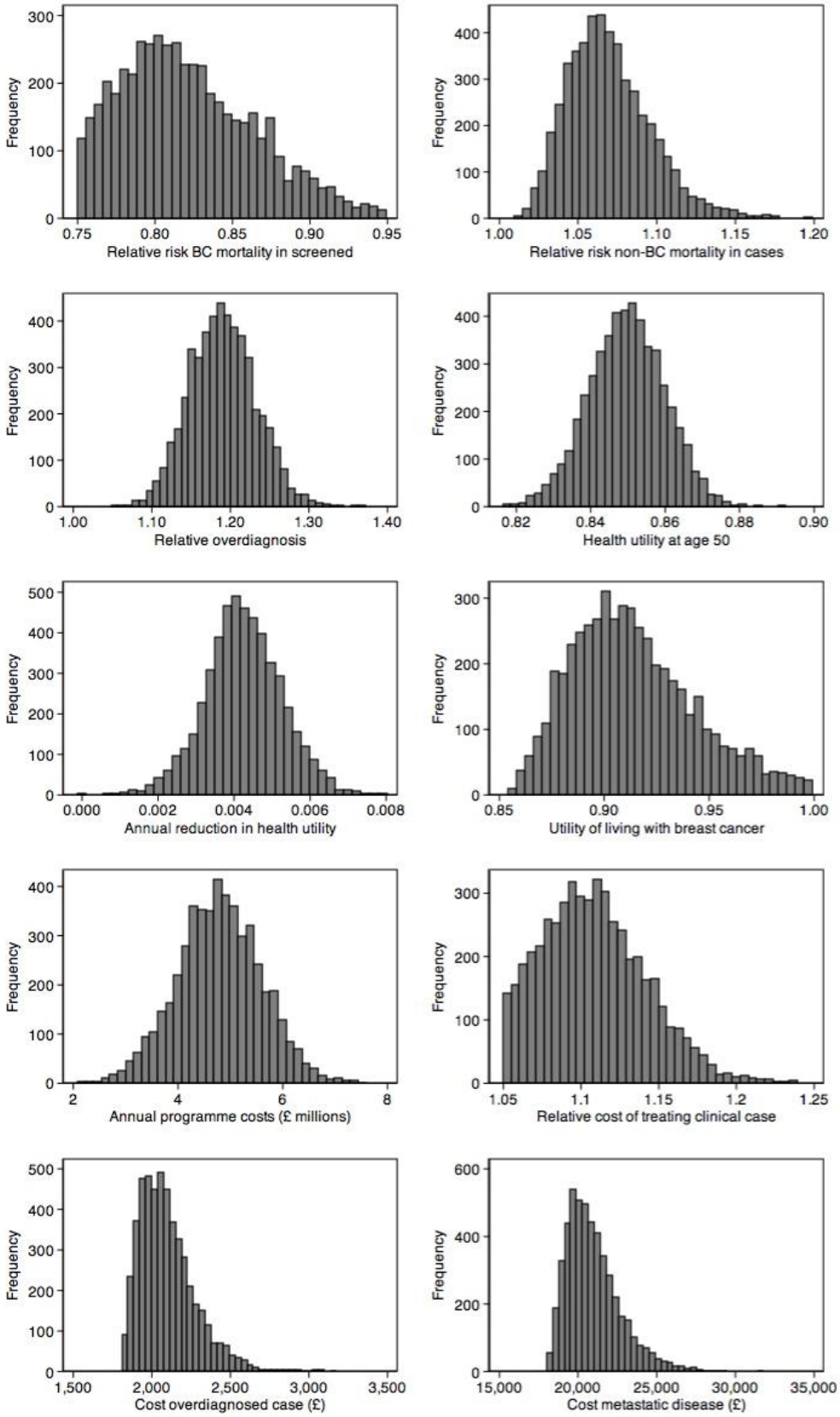
Cost of treating metastatic cancer = 18000+Gamma(3,.1)*10000

Web References

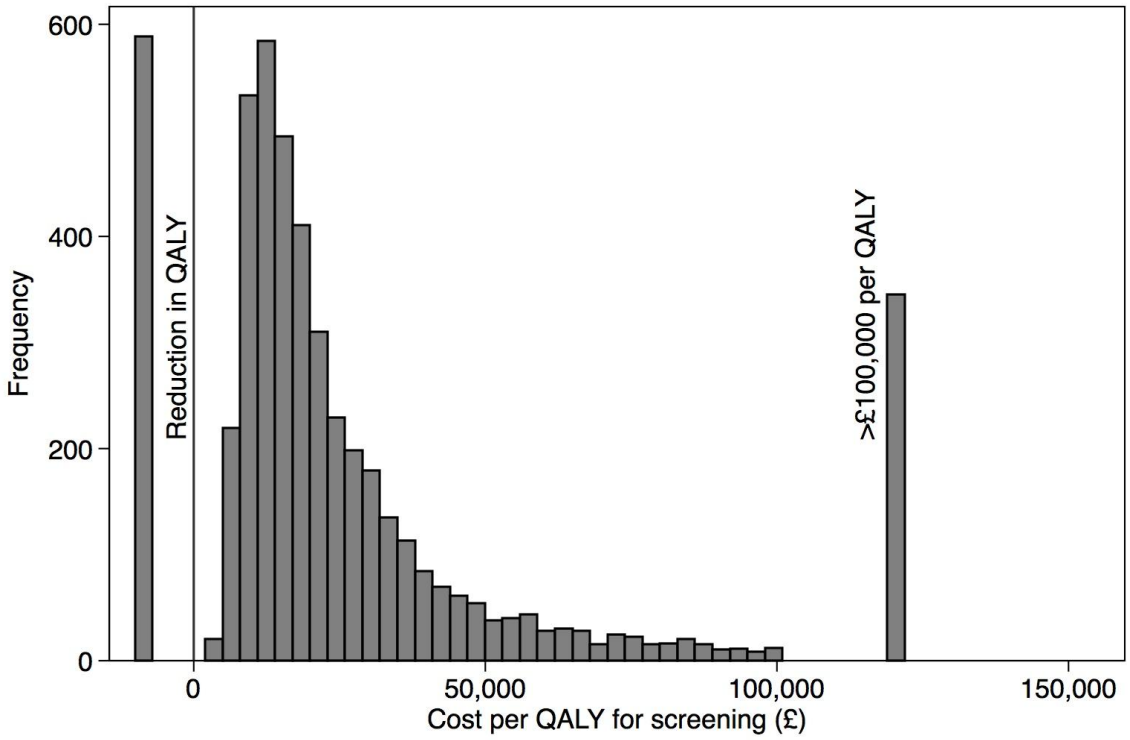
1. NHS Breast Screening Programme: Annual Review, 2011.
2. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012.
3. Tonelli M, Gorber SC, Joffres M, Dickinson J, Singh H, Lewin G, et al. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. *CMAJ* 2011;183(17):1991-2001.
4. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009;151(10):727-37, W237-42.
5. Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database of Systematic Reviews* 2011;2011(1).
6. Early Breast Cancer Trialists Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366(9503):2087-106.
7. de Gelder R, Heijnsdijk EA, van Ravesteyn NT, Fracheboud J, Draisma G, de Koning HJ. Interpreting overdiagnosis estimates in population-based mammography screening. *Epidemiol Rev* 2011;33(1):111-21.
8. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health* 2011;14(4):539-45.
9. Peasgood T, Ward SE, Brazier J. Health-state utility values in breast cancer. *Expert Rev Pharmacoecon Outcomes Res* 2010;10(5):553-66.

Web figures

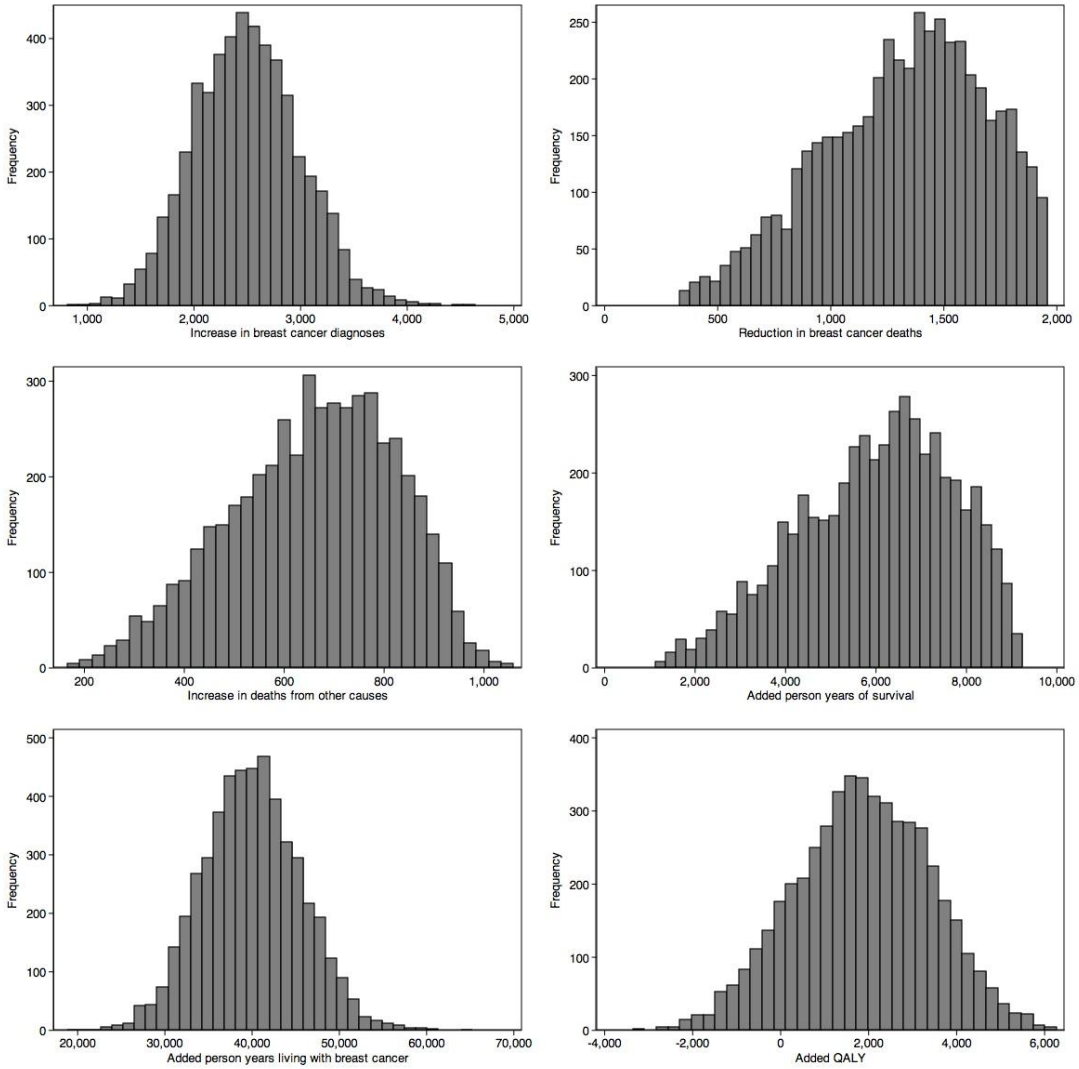
Web figure 1: Distribution of input parameters using in each of 5000 model runs in sensitivity analysis under the base-case scenario for the effect of screening on breast cancer incidence



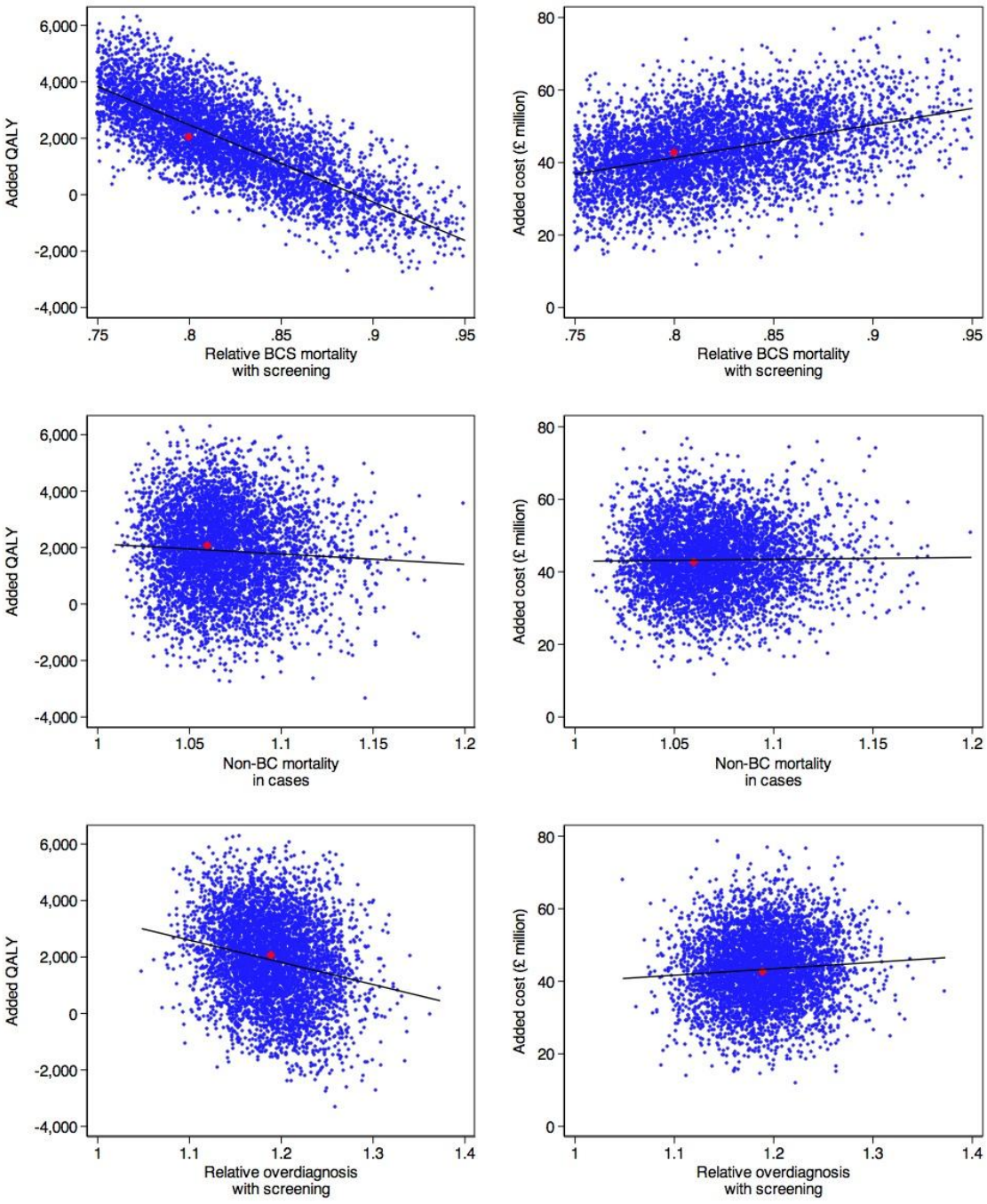
Web figure 2: Distribution of cost per quality adjusted life-year for a population based screening programme based on 5000 runs of the probabilistic sensitivity analysis under the base-case scenario for the effect of screening on breast cancer incidence



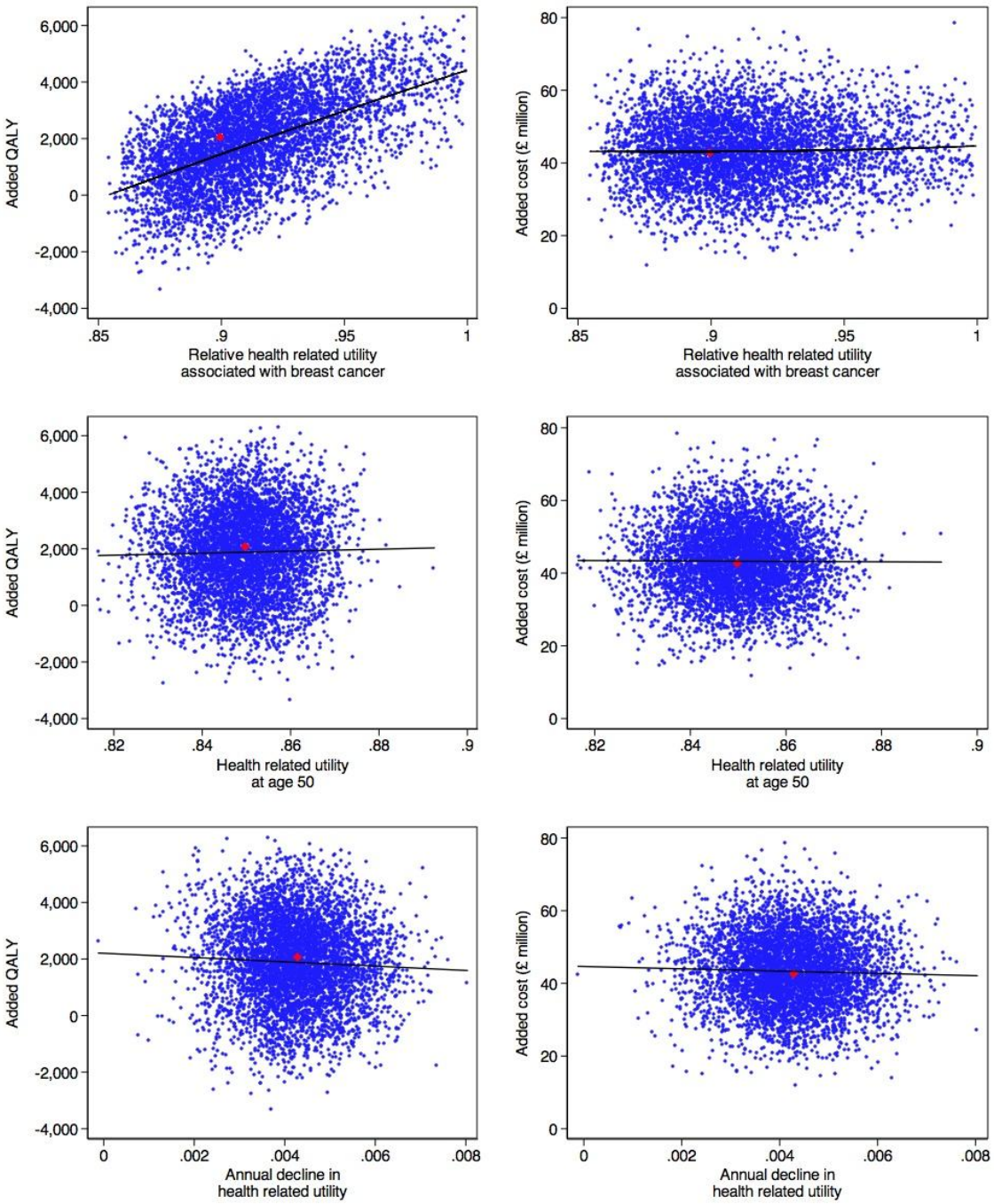
Web figure 3: Distribution of key output parameters for a population based screening programme based on 5000 model runs in sensitivity analysis under the base-case scenario for the effect of screening on breast cancer incidence



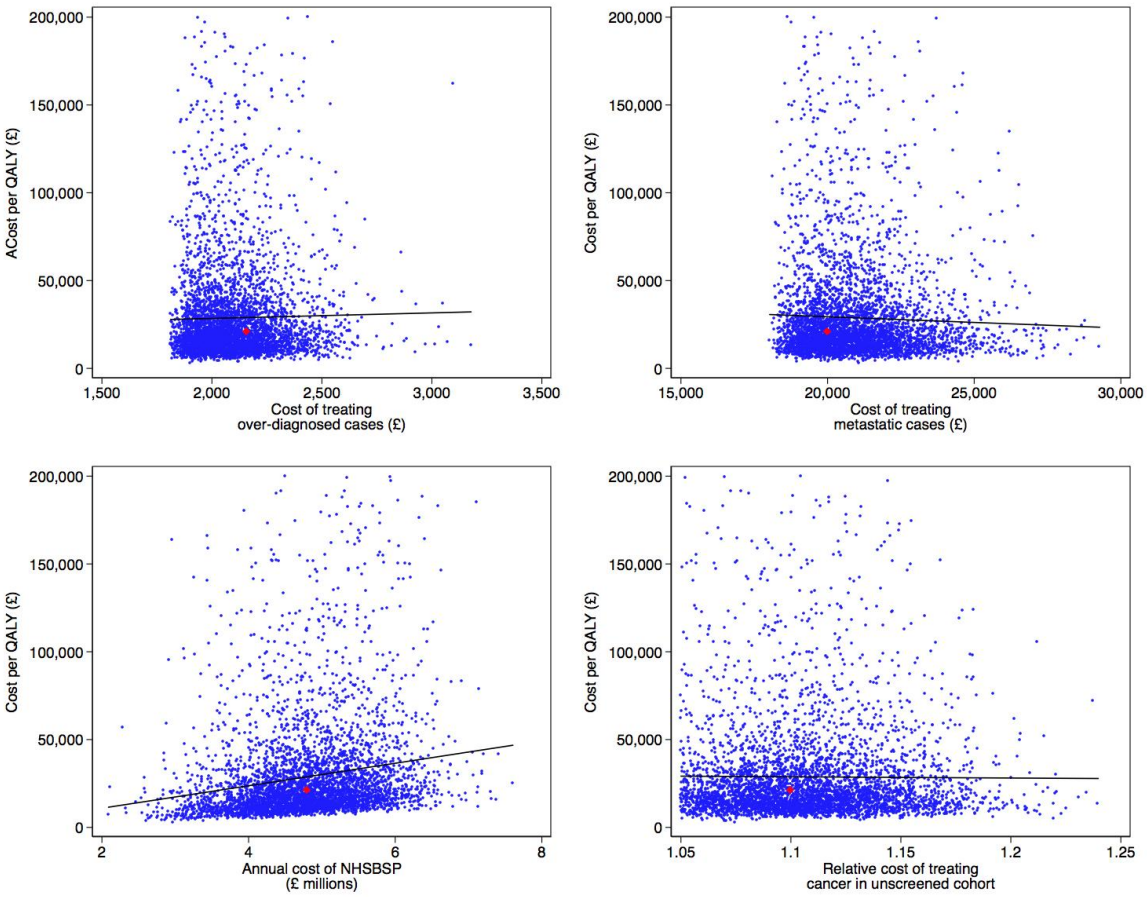
Web figure 4: Association between three input parameters (breast cancer mortality relative risk, relative over diagnosis and relative risk of non-breast cancer mortality in cases) and two primary model outputs (QALYs gained and added cost of screening) under the base-case scenario for the effect of screening on breast cancer incidence



Web figure 5: Association between three input parameters (health-related utility at age 50, annual decline in health-related quality-of-life and health-related quality-of-life decrement after a diagnosis of breast cancer) and two primary model outputs (QALYs gained and added cost of screening) under the base-case scenario for the effect of screening on breast cancer incidence



Web figure 6: Association between four cost-related parameters (annual cost of NHSBSP, relative cost of treating a clinically detected cancer, cost of treating a primary cancer and cost of treating a metastatic cancer) and incremental cost-effectiveness ratio (cost per QALY) under the base-case scenario for the effect of screening on breast cancer incidence



Web figure 7: Model based prediction of age-specific breast cancer incidence in population compared to observed age-specific incidence for 2009 (under the base-case scenario for the effect of screening on breast cancer incidence)