

Supplementary Online Content

Pashayan N, Morris S, Gilbert FJ, Pharoah PDP. Cost-effectiveness and benefit-to-harm ratio of risk-stratified screening for breast cancer: a life-table model. *JAMA Oncology*. Published online July 5, 2018. doi:10.1001/jamaoncol.2018.1901

eTable 1. Model input parameters

eTable 2. Outcomes of three scenarios of screening – no screening, age-based screening, and risk-targeted screening

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eFigure 8D. Deterministic sensitivity analysis - Incremental cost-effectiveness ratios by risk threshold considering risk distribution variance of 0.28, 0.43, and 0.58

eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

Table 1: Model input parameters

| Input parameter | Description (base-case value) | PSA Distribution (α, β) (mean, SD)* | Median [IQR] | eReferences |
|---|---|--|-------------------|-------------|
| Life table | | | | |
| Age-specific incidence of breast cancer in the absence of screening | <ul style="list-style-type: none"> Expected one-year age band incidence in 2009 derived by multiplying the 1998 incidence by a factor of 1.45 to allow for the background increase in incidence over time | | | 1;3 |
| Age-specific incidence of screen-detected breast cancer | <ul style="list-style-type: none"> Assuming that screening increases the incidence of breast cancer by both relative overdiagnosis and by advancing the diagnosis of breast cancer by seven years on average from age 50-69 and then incidence is dropped by ten per cent after screening stops Assuming that 75 per cent of women undergo screening These values were chosen empirically so that the predicted incidence approximates the observed population incidence for 2009 | | | 1 |
| Age-specific mortality from breast cancer | <ul style="list-style-type: none"> Derived from the breast cancer specific mortality rates in England and Wales, 2009 Assuming these rates reflect weighted average of mortality rates in screened and unscreened cohorts in a population where 75 per cent had regular screening between ages 50 to 69 Breast cancer mortality in screened = (observed breast mortality in the population * relative risk reduction) / (0.75*relative risk reduction+0.25) Breast cancer mortality in unscreened = (observed breast mortality in the population) / (0.75*relative risk reduction+0.25) | | | 1;3 |
| Age-specific mortality from other causes | <ul style="list-style-type: none"> Derived from the mortality rates in England and Wales, 2009 | | | 1;3 |
| Relative mortality reduction with screening | <ul style="list-style-type: none"> Relative risk of breast cancer mortality associated with regular mammographic screening (0.8) Relative mortality risk reduction = $0.7 + \text{Log-Gamma}(6, 0.08) * 0.25$ | Log-Gamma (6, 0.08) | 0.81 [0.78, 0.85] | 1;2 |

| | | | | |
|---|---|-------------------------------|-----------------------------|-----|
| Relative risk of death from non-breast cancer in women diagnosed with breast cancer | <ul style="list-style-type: none"> Assuming the excess mortality with surgery is extremely small and adjuvant radiotherapy is associated with 12 per cent increase in mortality from other causes Based on cancer registration data, 50 per cent of breast cancer patients receive adjuvant radiotherapy (1.06) Relative risk of death=$1+\text{Log-Gamma}(7,0.1)*0.1$ | Log-Gamma (7, 0.1) | 1.07 [1.05, 1.09] | 1;4 |
| Proportion overdiagnosed | <ul style="list-style-type: none"> Proportion of the cancers diagnosed during the active screening period (19%) | Log-Normal (0.174, 0.035)* | 17.5% [15%, 20%] | 1;2 |
| Utility | | | | |
| Health related utility | <ul style="list-style-type: none"> Mean health related utility weight for a 50 year old woman without breast cancer (0.85) | Normal (0.85, 0.01)* | 0.85 [0.84, 0.86] | 1 |
| Annual decline in health related utility | <ul style="list-style-type: none"> Annual decline in utility from age 50 to 80 (0.0043) | Normal (0.0043, 0.001)* | 0.0043 [0.0036, 0.005] | 1;5 |
| Relative reduction in quality of life associated with living after a diagnosis of breast cancer | <ul style="list-style-type: none"> Mean health related utility decrement following diagnosis (0.9) Assuming the mean health-related utility decrement of 0.7, 0.8, and 0.9 in the three years following diagnosis and 0.95 thereafter compared to women of the same age Health related quality of life associated with diagnosis of breast cancer =$0.85+0.167*\text{Gamma}(4,0.1)$; right truncated | Gamma (4, 0.1) | 0.91 [0.89, 0.94] | 1;6 |
| Cost | | | | |
| Cost of the screening programme for each year of screening (Million) | <ul style="list-style-type: none"> Estimated cost of the NHS breast screening programme £96 million Annual cost of the programme (£4.8 million) | Normal (4.8, 0.8)* | 4.8 [4.2, 5.3] | 1;7 |
| Cost of treating primary breast cancer | <ul style="list-style-type: none"> If 72 per cent of cases detected by the NHSBSP were treated with local surgery and 27 per cent with mastectomy and 20 per cent of the patients also received radio therapy Average cost of treating primary breast cancer $\text{£}1,450*0.72 + \text{£}2,810*0.27 + \text{£}1,800*0.20$ (£2,163) Cost of treating primary cancer = $1800+\text{Gamma}(3,0.1)*1000$ | Gamma (3, 0.1) | £2,066 [£1,971, £2,186] | 1;8 |
| Cost of treating advanced | <ul style="list-style-type: none"> Cost of treating metastatic breast cancer (£20,000) | Gamma | £20,658 [£19,714, | 1;9 |

| | | | | |
|--|---|-----------------------|----------------------|---|
| metastatic breast cancer | <ul style="list-style-type: none"> Cost of treating metastatic cancer = $18000 + \text{Gamma}(3, 0.1) * 10000$ | (3, 0.1) | £21,864] | |
| Relative cost of treating a clinically detected patient with breast cancer compared with the cost if it had been detected earlier by screening | <ul style="list-style-type: none"> Assuming clinically detected cancer to be more advanced than screen-detected cancer and the cost of treatment of the former would be higher Assuming 10 per cent increase in cost for treating cases in the unscreened group (1.1) | Normal (1.1, 0.04) | 1.10 [1.07, 1.13] | 1 |
| Cost of risk assessment | <ul style="list-style-type: none"> Empirical estimate based on per variant research cost of genotyping (£50) Cost of risk assessment = $\text{Gamma}(50, 0.1) * 10$ | Gamma (50, 0.01) | £50 [£45, £55] | |

PSA – Probabilistic sensitivity analysis
IQR – Interquartile range

eTable 2: Outcomes of three scenarios of screening – no screening, age-based screening, and risk-targeted screening.

| Proportion at highest risk (%) | Breast cancer cases among the unscreened | Total breast cancer cases | Over-diagnosed cases | Breast cancer deaths | Other causes deaths | PYRS | QALY | Cost (£) |
|--------------------------------|--|---------------------------|----------------------|----------------------|---------------------|-----------|-----------|-------------|
| No screening | | | | | | | | |
| | 26,826 | 26,826 | - | 10,631 | 239,113 | 6,421,926 | 4,696,181 | 163,486,827 |
| Age-based screening | | | | | | | | |
| | - | 31,889 | 3,819 | 8,718 | 240,301 | 6,430,124 | 4,698,098 | 205,365,932 |
| Risk-based screening | | | | | | | | |
| 1 | 25,604 | 26,761 | 7 | 10,505 | 239,180 | 6,422,481 | 4,712,717 | 180,862,880 |
| 2 | 24,725 | 26,772 | 21 | 10,436 | 239,218 | 6,422,780 | 4,712,873 | 180,373,280 |
| 3 | 23,959 | 26,798 | 39 | 10,378 | 239,250 | 6,423,035 | 4,712,999 | 180,073,328 |
| 4 | 23,263 | 26,834 | 61 | 10,326 | 239,280 | 6,423,265 | 4,713,107 | 179,886,912 |
| 5 | 22,617 | 26,875 | 85 | 10,279 | 239,307 | 6,423,475 | 4,713,202 | 179,780,480 |
| 6 | 22,010 | 26,919 | 112 | 10,234 | 239,333 | 6,423,671 | 4,713,288 | 179,735,312 |
| 7 | 21,435 | 26,967 | 141 | 10,192 | 239,357 | 6,423,855 | 4,713,366 | 179,739,472 |
| 8 | 20,887 | 27,017 | 171 | 10,153 | 239,380 | 6,424,030 | 4,713,438 | 179,784,720 |
| 9 | 20,361 | 27,069 | 204 | 10,115 | 239,402 | 6,424,197 | 4,713,504 | 179,865,152 |
| 10 | 19,856 | 27,122 | 237 | 10,078 | 239,424 | 6,424,356 | 4,713,566 | 179,976,176 |
| 11 | 19,369 | 27,177 | 272 | 10,044 | 239,444 | 6,424,509 | 4,713,623 | 180,114,256 |
| 12 | 18,898 | 27,232 | 308 | 10,010 | 239,464 | 6,424,656 | 4,713,676 | 180,276,544 |
| 13 | 18,442 | 27,289 | 345 | 9,978 | 239,484 | 6,424,798 | 4,713,727 | 180,460,672 |
| 14 | 17,999 | 27,346 | 384 | 9,946 | 239,503 | 6,424,936 | 4,713,774 | 180,664,704 |
| 15 | 17,569 | 27,404 | 423 | 9,916 | 239,521 | 6,425,068 | 4,713,818 | 180,887,008 |
| 16 | 17,150 | 27,462 | 463 | 9,886 | 239,539 | 6,425,198 | 4,713,860 | 181,126,144 |
| 17 | 16,743 | 27,521 | 503 | 9,857 | 239,556 | 6,425,323 | 4,713,899 | 181,380,912 |
| 18 | 16,345 | 27,580 | 545 | 9,829 | 239,573 | 6,425,445 | 4,713,937 | 181,650,224 |
| 19 | | | | | | | | |

| Proportion at highest risk (%) | Breast cancer cases among the unscreened | Total breast cancer cases | Over-diagnosed cases | Breast cancer deaths | Other causes deaths | PYRS | QALY | Cost (£) |
|--------------------------------|--|---------------------------|----------------------|----------------------|---------------------|-----------|-----------|-------------|
| | 15,957 | 27,640 | 587 | 9,802 | 239,590 | 6,425,563 | 4,713,972 | 181,933,152 |
| 20 | 15,578 | 27,699 | 630 | 9,776 | 239,606 | 6,425,678 | 4,714,005 | 182,228,864 |
| 21 | 15,207 | 27,759 | 673 | 9,750 | 239,622 | 6,425,791 | 4,714,037 | 182,536,608 |
| 22 | 14,844 | 27,820 | 716 | 9,724 | 239,637 | 6,425,901 | 4,714,067 | 182,855,744 |
| 23 | 14,490 | 27,880 | 761 | 9,700 | 239,653 | 6,426,008 | 4,714,095 | 183,185,664 |
| 24 | 14,142 | 27,940 | 805 | 9,675 | 239,668 | 6,426,112 | 4,714,122 | 183,525,792 |
| 25 | 13,802 | 28,001 | 850 | 9,652 | 239,682 | 6,426,215 | 4,714,147 | 183,875,648 |
| 26 | 13,468 | 28,061 | 896 | 9,628 | 239,697 | 6,426,315 | 4,714,172 | 184,234,800 |
| 27 | 13,141 | 28,122 | 941 | 9,606 | 239,711 | 6,426,412 | 4,714,195 | 184,602,800 |
| 28 | 12,820 | 28,182 | 987 | 9,584 | 239,725 | 6,426,508 | 4,714,216 | 184,979,296 |
| 29 | 12,505 | 28,242 | 1,034 | 9,562 | 239,738 | 6,426,602 | 4,714,237 | 185,363,936 |
| 30 | 12,196 | 28,303 | 1,080 | 9,540 | 239,752 | 6,426,694 | 4,714,257 | 185,756,384 |
| 31 | 11,892 | 28,363 | 1,127 | 9,519 | 239,765 | 6,426,784 | 4,714,275 | 186,156,320 |
| 32 | 11,594 | 28,423 | 1,173 | 9,499 | 239,778 | 6,426,872 | 4,714,293 | 186,563,504 |
| 33 | 11,301 | 28,483 | 1,220 | 9,479 | 239,790 | 6,426,958 | 4,714,310 | 186,977,632 |
| 34 | 11,014 | 28,543 | 1,268 | 9,459 | 239,803 | 6,427,043 | 4,714,326 | 187,398,496 |
| 35 | 10,731 | 28,603 | 1,315 | 9,439 | 239,815 | 6,427,126 | 4,714,341 | 187,825,840 |
| 36 | 10,453 | 28,662 | 1,362 | 9,420 | 239,827 | 6,427,208 | 4,714,355 | 188,259,488 |
| 37 | 10,180 | 28,721 | 1,409 | 9,401 | 239,839 | 6,427,288 | 4,714,368 | 188,699,200 |
| 38 | 9,911 | 28,780 | 1,457 | 9,383 | 239,851 | 6,427,366 | 4,714,381 | 189,144,816 |
| 39 | 9,647 | 28,839 | 1,504 | 9,365 | 239,863 | 6,427,443 | 4,714,393 | 189,596,128 |
| 40 | 9,387 | 28,898 | 1,552 | 9,347 | 239,874 | 6,427,519 | 4,714,404 | 190,053,008 |
| 41 | 9,132 | 28,956 | 1,599 | 9,330 | 239,885 | 6,427,593 | 4,714,415 | 190,515,280 |
| 42 | 8,880 | 29,015 | 1,646 | 9,312 | 239,896 | 6,427,666 | 4,714,425 | 190,982,768 |
| 43 | 8,633 | 29,072 | 1,694 | 9,296 | 239,907 | 6,427,738 | 4,714,435 | 191,455,376 |

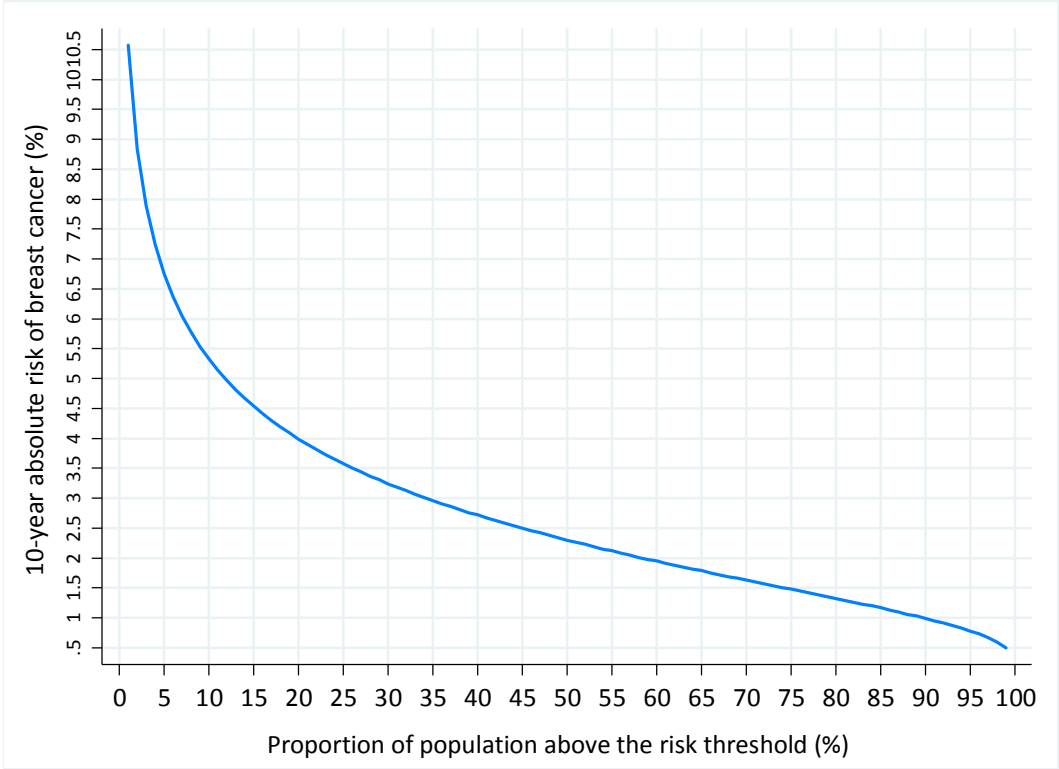
| Proportion at highest risk (%) | Breast cancer cases among the unscreened | Total breast cancer cases | Over-diagnosed cases | Breast cancer deaths | Other causes deaths | PYRS | QALY | Cost (£) |
|--------------------------------|--|---------------------------|----------------------|----------------------|---------------------|-----------|-----------|-------------|
| 44 | 8,390 | 29,130 | 1,741 | 9,279 | 239,918 | 6,427,808 | 4,714,444 | 191,932,960 |
| 45 | 8,150 | 29,187 | 1,788 | 9,263 | 239,928 | 6,427,877 | 4,714,452 | 192,415,360 |
| 46 | 7,915 | 29,244 | 1,835 | 9,247 | 239,938 | 6,427,945 | 4,714,460 | 192,902,480 |
| 47 | 7,683 | 29,301 | 1,882 | 9,231 | 239,949 | 6,428,011 | 4,714,467 | 193,394,240 |
| 48 | 7,455 | 29,357 | 1,929 | 9,215 | 239,959 | 6,428,077 | 4,714,474 | 193,890,480 |
| 49 | 7,230 | 29,413 | 1,975 | 9,200 | 239,969 | 6,428,141 | 4,714,480 | 194,391,120 |
| 50 | 7,010 | 29,469 | 2,022 | 9,185 | 239,978 | 6,428,204 | 4,714,486 | 194,896,064 |
| 51 | 6,792 | 29,525 | 2,068 | 9,170 | 239,988 | 6,428,267 | 4,714,492 | 195,405,216 |
| 52 | 6,578 | 29,580 | 2,114 | 9,156 | 239,997 | 6,428,327 | 4,714,497 | 195,918,480 |
| 53 | 6,368 | 29,634 | 2,160 | 9,142 | 240,007 | 6,428,387 | 4,714,501 | 196,435,792 |
| 54 | 6,161 | 29,689 | 2,206 | 9,128 | 240,016 | 6,428,446 | 4,714,506 | 196,957,072 |
| 55 | 5,957 | 29,742 | 2,251 | 9,114 | 240,025 | 6,428,504 | 4,714,509 | 197,482,208 |
| 56 | 5,756 | 29,796 | 2,296 | 9,100 | 240,034 | 6,428,561 | 4,714,513 | 198,011,168 |
| 57 | 5,559 | 29,849 | 2,341 | 9,087 | 240,042 | 6,428,617 | 4,714,516 | 198,543,872 |
| 58 | 5,365 | 29,902 | 2,386 | 9,074 | 240,051 | 6,428,671 | 4,714,519 | 199,080,272 |
| 59 | 5,174 | 29,954 | 2,430 | 9,061 | 240,059 | 6,428,725 | 4,714,522 | 199,620,272 |
| 60 | 4,986 | 30,006 | 2,474 | 9,049 | 240,068 | 6,428,778 | 4,714,524 | 200,163,840 |
| 61 | 4,801 | 30,058 | 2,518 | 9,036 | 240,076 | 6,428,830 | 4,714,526 | 200,710,896 |
| 62 | 4,619 | 30,109 | 2,561 | 9,024 | 240,084 | 6,428,881 | 4,714,527 | 201,261,440 |
| 63 | 4,441 | 30,159 | 2,604 | 9,012 | 240,092 | 6,428,931 | 4,714,529 | 201,815,360 |
| 64 | 4,265 | 30,209 | 2,647 | 9,000 | 240,100 | 6,428,980 | 4,714,530 | 202,372,640 |
| 65 | 4,092 | 30,259 | 2,689 | 8,989 | 240,107 | 6,429,028 | 4,714,531 | 202,933,232 |
| 66 | 3,923 | 30,308 | 2,731 | 8,978 | 240,115 | 6,429,075 | 4,714,531 | 203,497,104 |
| 67 | 3,756 | 30,357 | 2,772 | 8,966 | 240,122 | 6,429,122 | 4,714,532 | 204,064,224 |
| 68 | | | | | | | | |

| Proportion at highest risk (%) | Breast cancer cases among the unscreened | Total breast cancer cases | Over-diagnosed cases | Breast cancer deaths | Other causes deaths | PYRS | QALY | Cost (£) |
|--------------------------------|--|---------------------------|----------------------|----------------------|---------------------|-----------|-----------|-------------|
| | 3,592 | 30,405 | 2,814 | 8,956 | 240,130 | 6,429,167 | 4,714,532 | 204,634,544 |
| 69 | 3,431 | 30,453 | 2,854 | 8,945 | 240,137 | 6,429,212 | 4,714,532 | 205,208,016 |
| 70 | 3,273 | 30,501 | 2,894 | 8,934 | 240,144 | 6,429,256 | 4,714,532 | 205,784,624 |
| 71 | 3,118 | 30,547 | 2,934 | 8,924 | 240,151 | 6,429,298 | 4,714,531 | 206,364,352 |
| 72 | 2,966 | 30,594 | 2,974 | 8,914 | 240,158 | 6,429,340 | 4,714,530 | 206,947,168 |
| 73 | 2,817 | 30,640 | 3,012 | 8,904 | 240,164 | 6,429,381 | 4,714,529 | 207,533,024 |
| 74 | 2,670 | 30,685 | 3,051 | 8,895 | 240,171 | 6,429,421 | 4,714,528 | 208,121,952 |
| 75 | 2,527 | 30,729 | 3,089 | 8,885 | 240,177 | 6,429,460 | 4,714,527 | 208,713,904 |
| 76 | 2,386 | 30,774 | 3,126 | 8,876 | 240,183 | 6,429,499 | 4,714,526 | 209,308,864 |
| 77 | 2,248 | 30,817 | 3,163 | 8,867 | 240,189 | 6,429,537 | 4,714,524 | 209,906,848 |
| 78 | 2,113 | 30,860 | 3,199 | 8,858 | 240,196 | 6,429,573 | 4,714,523 | 210,507,824 |
| 79 | 1,981 | 30,903 | 3,235 | 8,850 | 240,201 | 6,429,609 | 4,714,521 | 211,111,808 |
| 80 | 1,852 | 30,945 | 3,270 | 8,841 | 240,207 | 6,429,644 | 4,714,519 | 211,718,784 |
| 81 | 1,726 | 30,986 | 3,304 | 8,833 | 240,213 | 6,429,678 | 4,714,517 | 212,328,784 |
| 82 | 1,603 | 31,027 | 3,338 | 8,825 | 240,218 | 6,429,711 | 4,714,514 | 212,941,808 |
| 83 | 1,483 | 31,067 | 3,371 | 8,817 | 240,224 | 6,429,744 | 4,714,512 | 213,557,856 |
| 84 | 1,366 | 31,106 | 3,404 | 8,810 | 240,229 | 6,429,774 | 4,714,509 | 214,176,976 |
| 85 | 1,252 | 31,145 | 3,436 | 8,802 | 240,234 | 6,429,805 | 4,714,507 | 214,799,184 |
| 86 | 1,141 | 31,183 | 3,467 | 8,795 | 240,239 | 6,429,835 | 4,714,504 | 215,424,544 |
| 87 | 1,033 | 31,220 | 3,497 | 8,788 | 240,244 | 6,429,863 | 4,714,501 | 216,053,056 |
| 88 | 928 | 31,257 | 3,527 | 8,782 | 240,248 | 6,429,891 | 4,714,498 | 216,684,816 |
| 89 | 827 | 31,293 | 3,556 | 8,775 | 240,253 | 6,429,918 | 4,714,495 | 217,319,904 |
| 90 | 729 | 31,328 | 3,584 | 8,769 | 240,257 | 6,429,943 | 4,714,492 | 217,958,368 |
| 91 | 635 | 31,362 | 3,611 | 8,763 | 240,261 | 6,429,968 | 4,714,489 | 218,600,352 |
| 92 | 545 | 31,396 | 3,637 | 8,758 | 240,265 | 6,429,991 | 4,714,485 | 219,245,984 |

| Proportion at highest risk (%) | Breast cancer cases among the unscreened | Total breast cancer cases | Over-diagnosed cases | Breast cancer deaths | Other causes deaths | PYRS | QALY | Cost (£) |
|---------------------------------------|---|----------------------------------|-----------------------------|-----------------------------|----------------------------|-------------|-------------|-----------------|
| 93 | 458 | 31,428 | 3,662 | 8,753 | 240,269 | 6,430,013 | 4,714,482 | 219,895,440 |
| 94 | 375 | 31,460 | 3,686 | 8,748 | 240,273 | 6,430,034 | 4,714,478 | 220,548,928 |
| 95 | 297 | 31,491 | 3,709 | 8,743 | 240,276 | 6,430,054 | 4,714,474 | 221,206,768 |
| 96 | 224 | 31,520 | 3,730 | 8,738 | 240,279 | 6,430,073 | 4,714,471 | 221,869,344 |
| 97 | 156 | 31,549 | 3,750 | 8,735 | 240,282 | 6,430,089 | 4,714,466 | 222,537,232 |
| 98 | 94 | 31,575 | 3,768 | 8,731 | 240,285 | 6,430,104 | 4,714,462 | 223,211,392 |
| 99 | 40 | 31,601 | 3,784 | 8,728 | 240,287 | 6,430,116 | 4,714,458 | 223,893,568 |

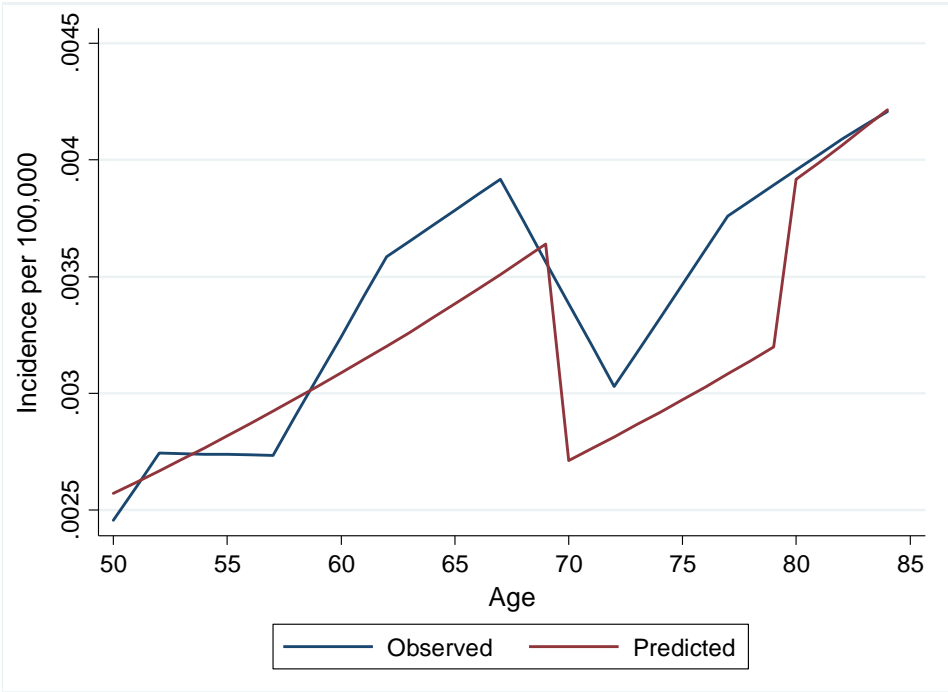
PYRS – Person years of survival
 QALY – Quality adjusted life years
 Discounted at 3.5% per year
 Average of 2000 simulations

eFigure 1: 10-year absolute risk of being diagnosed with breast cancer for women aged 50 years in England and Wales at each percentile of risk threshold. The variance of the risk distribution is 0.43.

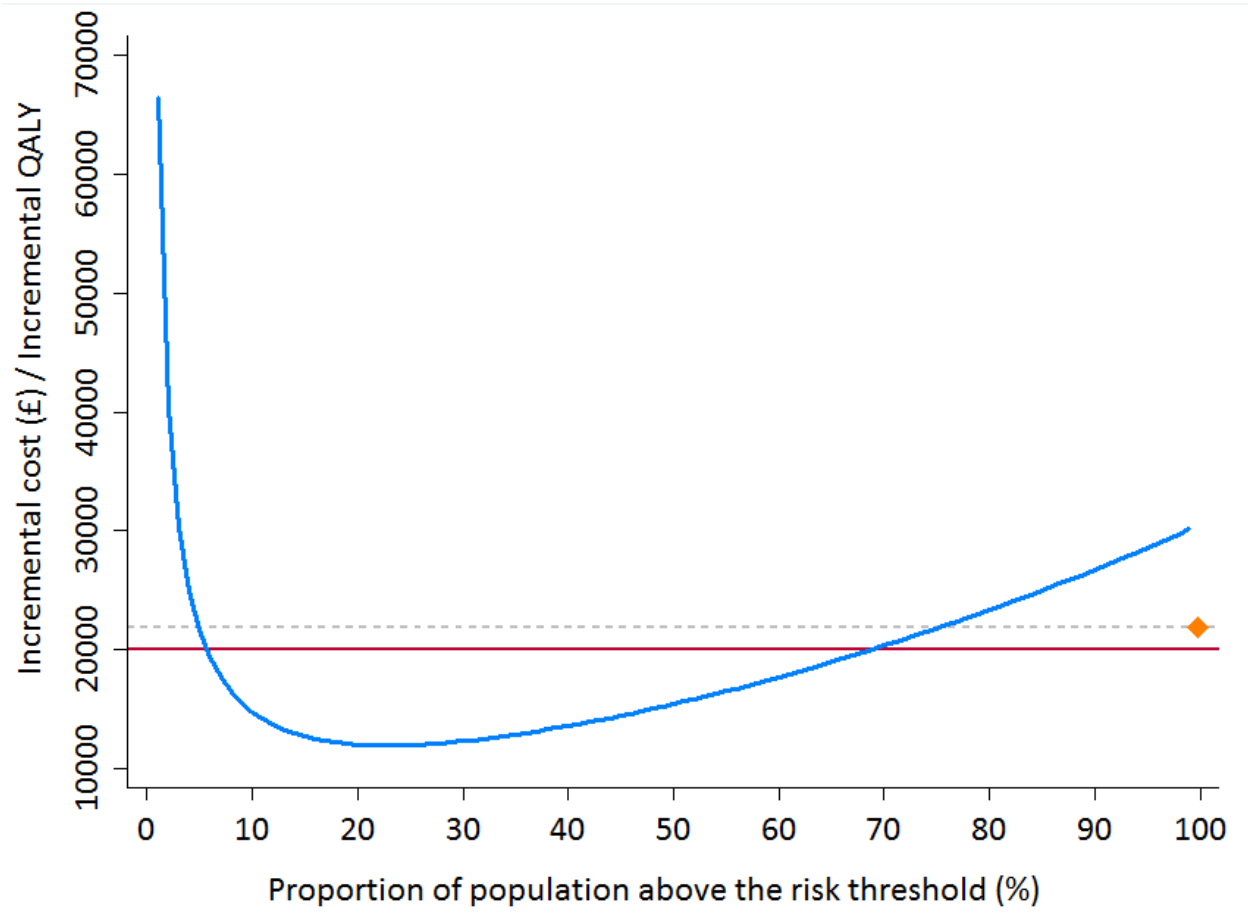


The population average 10-year risk is 2.85%.

eFigure 2: Model based prediction of age-specific breast cancer incidence in population compared to observed age-specific incidence for 2009.



eFigure 3: Incremental cost effectiveness ratios by risk-threshold (no screening is the comparator)



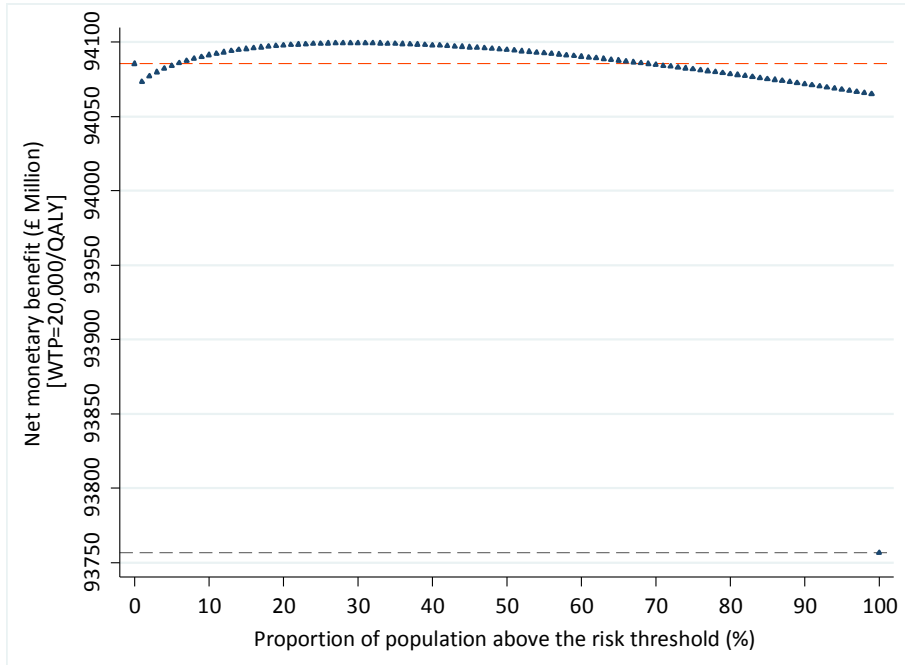
Red line: Threshold of £20,000 per QALY gained

Diamond: Incremental cost-effectiveness ratio for age-based screening

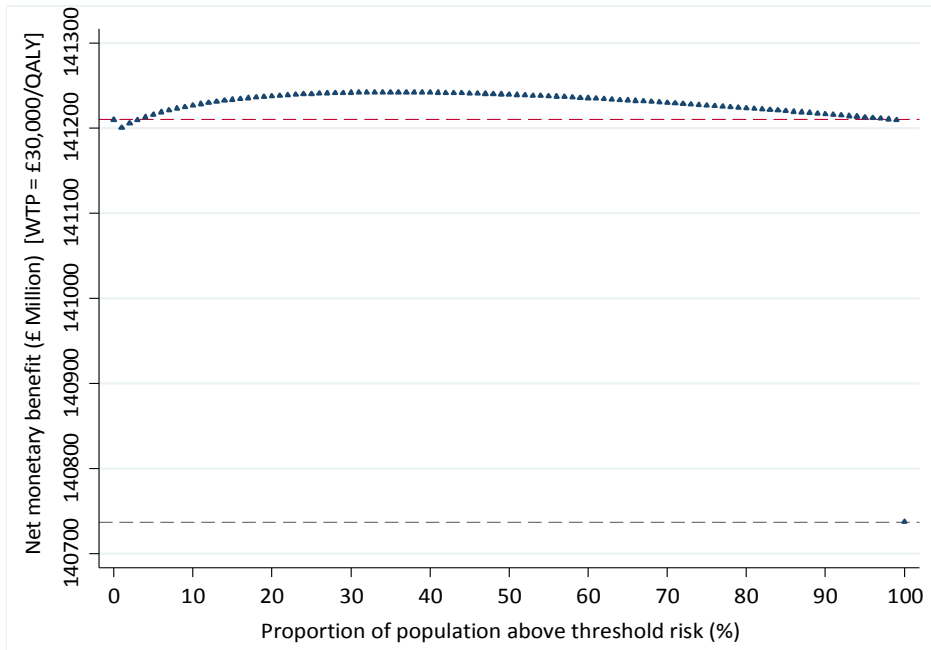
Incremental cost-effectiveness ratio is the difference in mean costs (based on 2,000 simulations) between the screened and unscreened cohorts divided by the difference in mean QALYs between the two cohorts.

eFigure 4. Net monetary benefits at willingness to pay (WTP) of £20,000 per QALY gained (a) and £30,000 per QALY gained (b) for no screening, age-based and risk-stratified screening scenarios.

a. WTP £ 20,000 per QALY

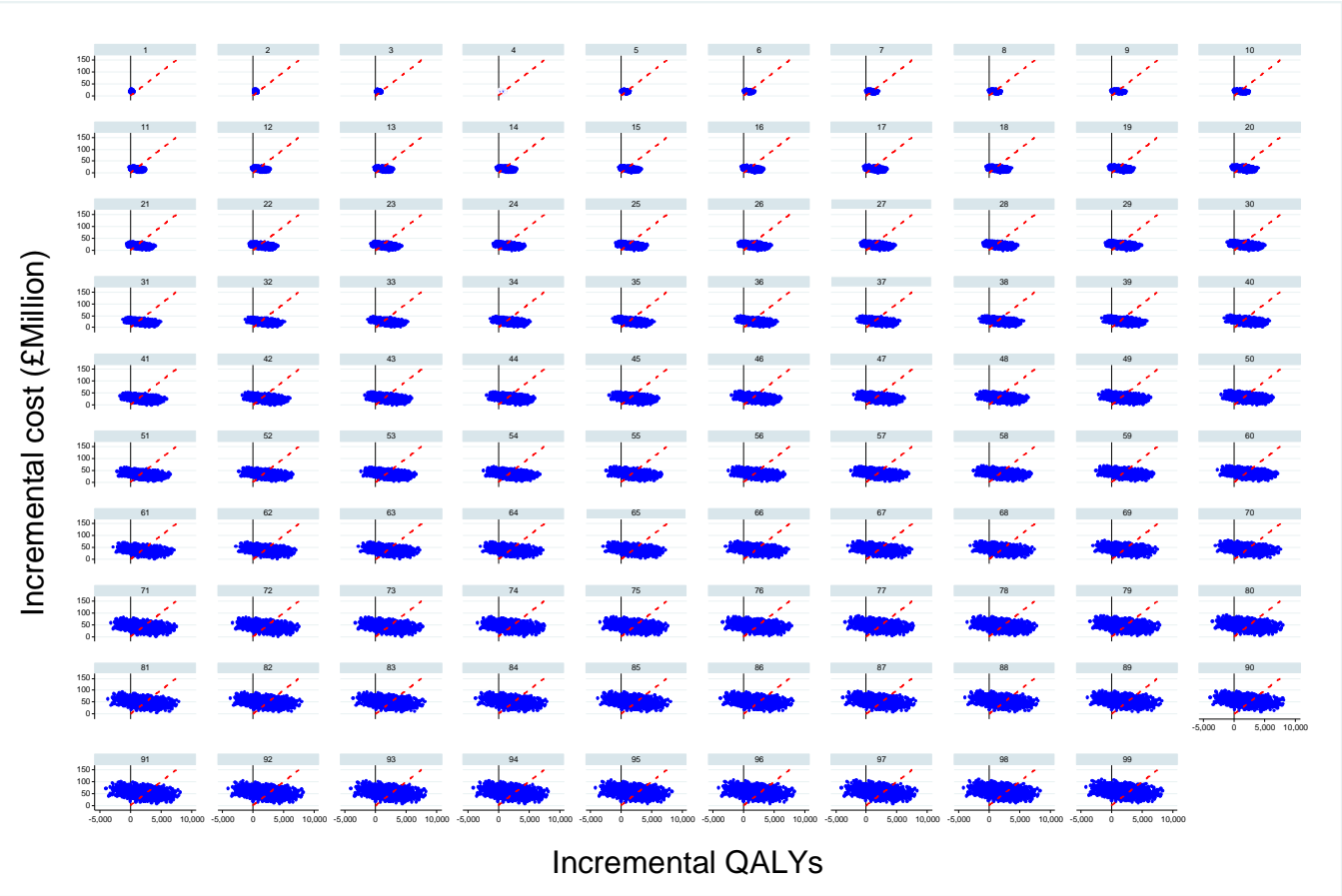


b. WTP £30,000 per QALY



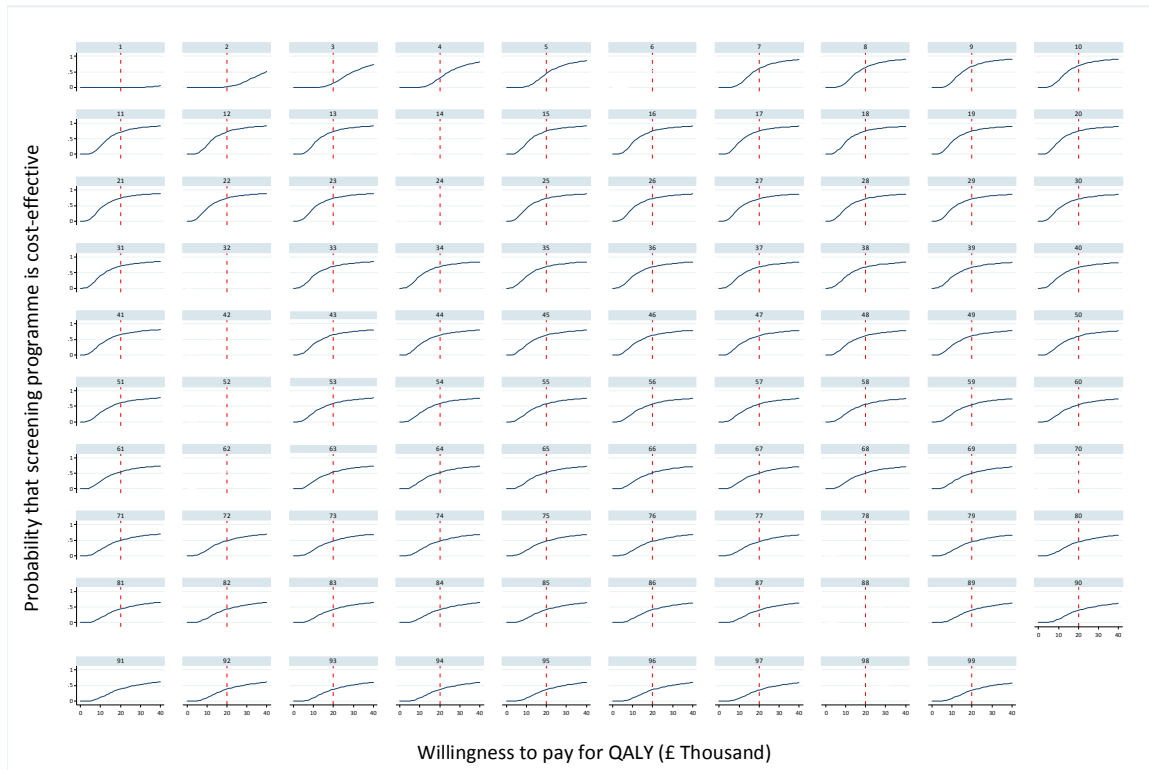
Red dashed line indicates the NMB of no screening
 Grey dashed line indicates the NMB of age-based screening
 The highest NMB value corresponds to the most-cost-effective scenario: in a. targeting screening to 30% women at highest risk and in b. to 35% of women at highest risk.

eFigure 5: Cost-effectiveness planes of incremental cost vs. incremental QALYs of risk-stratified screening scenarios as compared to no screening. Results are based on 2,000 simulations.



Each graph represents percentile risk threshold for risk-stratified screening strategy. The first graph is for 99th percentile risk threshold and the last graph for the 1st percentile.

eFigure 6: Cost-effectiveness acceptability curves for risk-stratified screening strategies for each percentile of risk threshold, considering willingness to pay (WTP) of 100 to 40,000 per QALY.

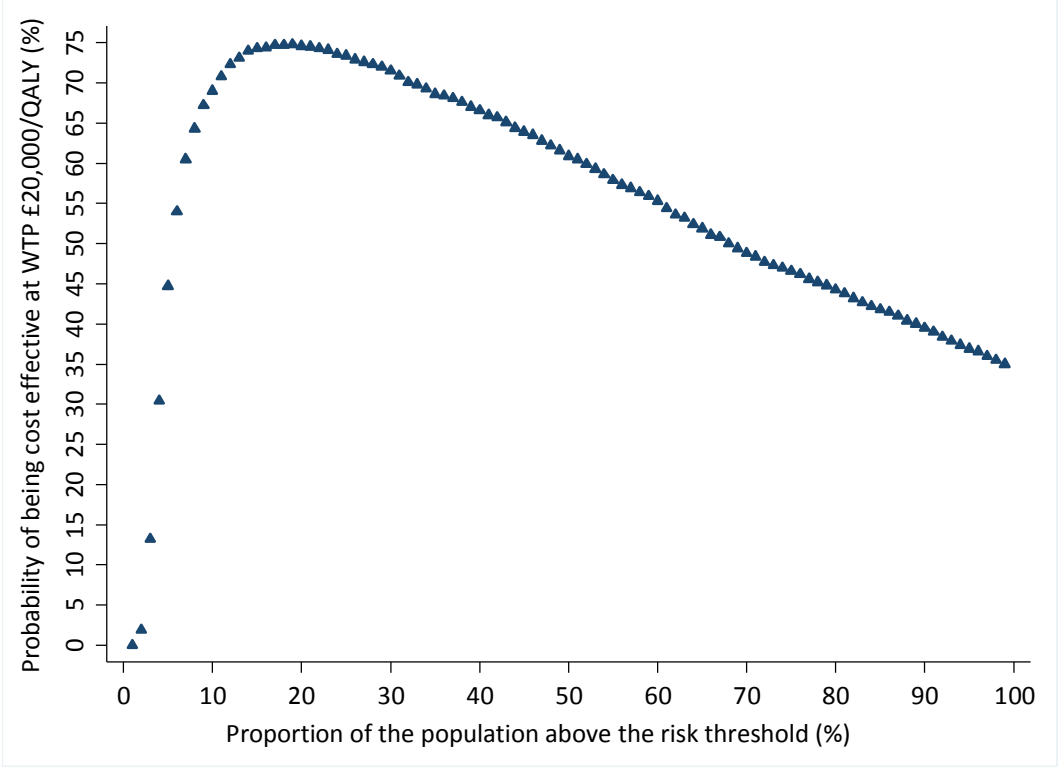


Each graph represents percentile risk threshold for risk-stratified screening strategy. The first graph is for 99th percentile risk threshold and the last graph for the 1st percentile.

The red line represents WTP of 20,000 per QALY.

The analysis is based on net monetary benefit (NMB) approach using 2,000 simulations.

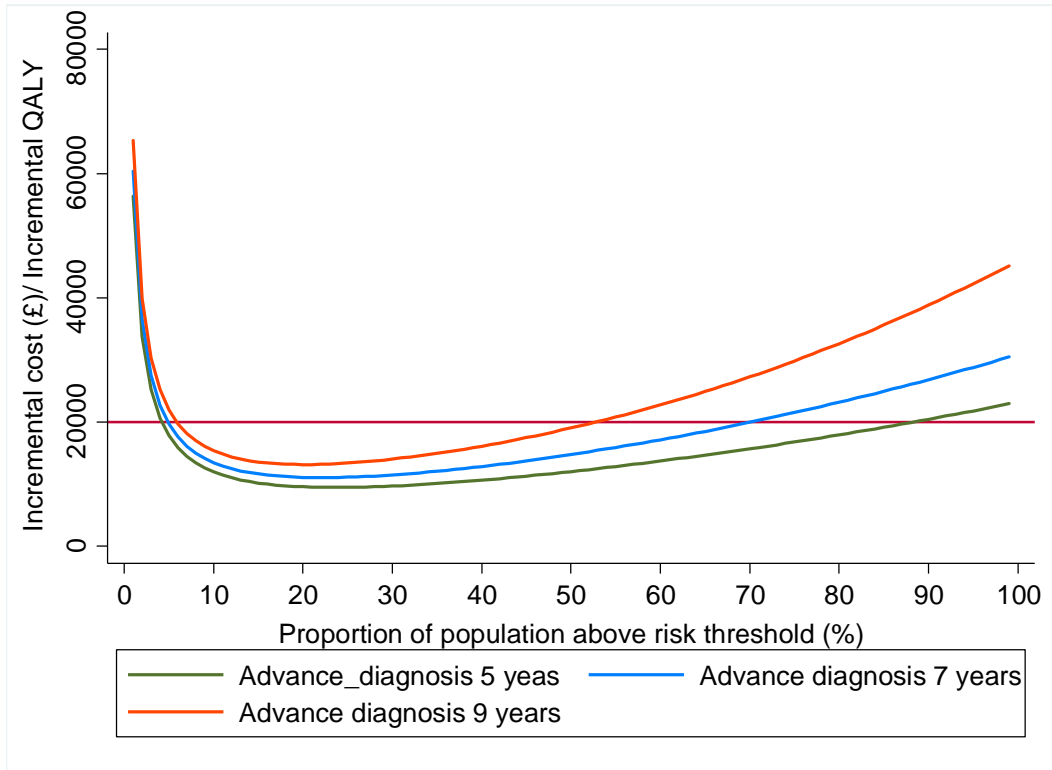
eFigure 7: The probability of each risk-stratified screening strategy of being cost-effective at willingness to pay (WTP) of £20,000 per QALY.



The analysis is based on net monetary benefit (NMB) approach using 2,000 simulations.

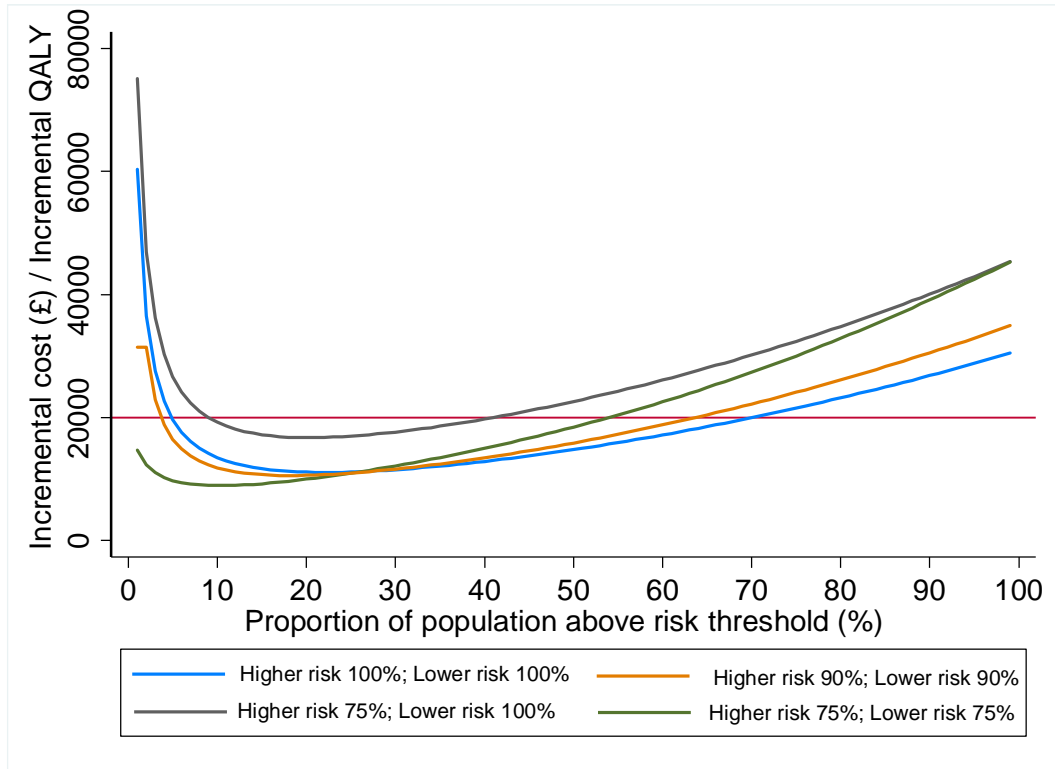
eFigure 8A: Deterministic sensitivity analyses –

- a. **Incremental cost-effectiveness ratios by risk threshold considering breast cancer incidence rate where screening advances the diagnosis by 5 years, 7 years, and 9 years**



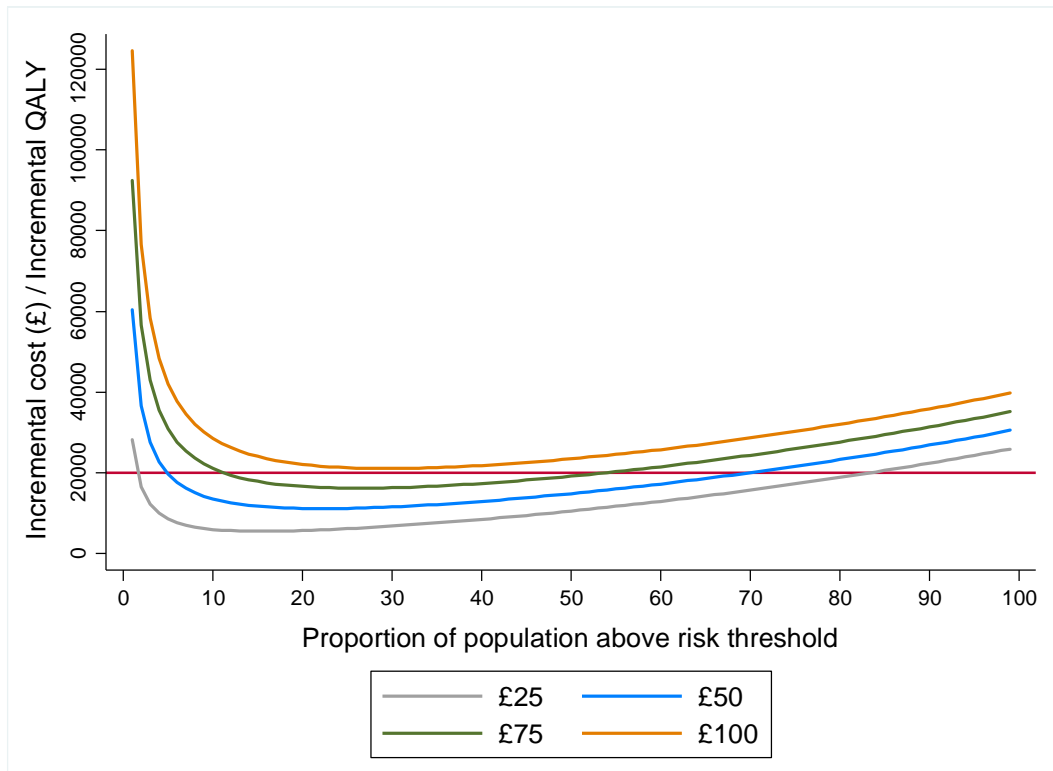
Red line: Threshold of £20,000 per QALY gained

b. eFigure 8B. Incremental cost-effectiveness ratios by risk threshold considering 100%, 90% and 75% adherence to the screening recommendation for the higher and lower risk groups.



Red line: Threshold of £20,000 per QALY gained

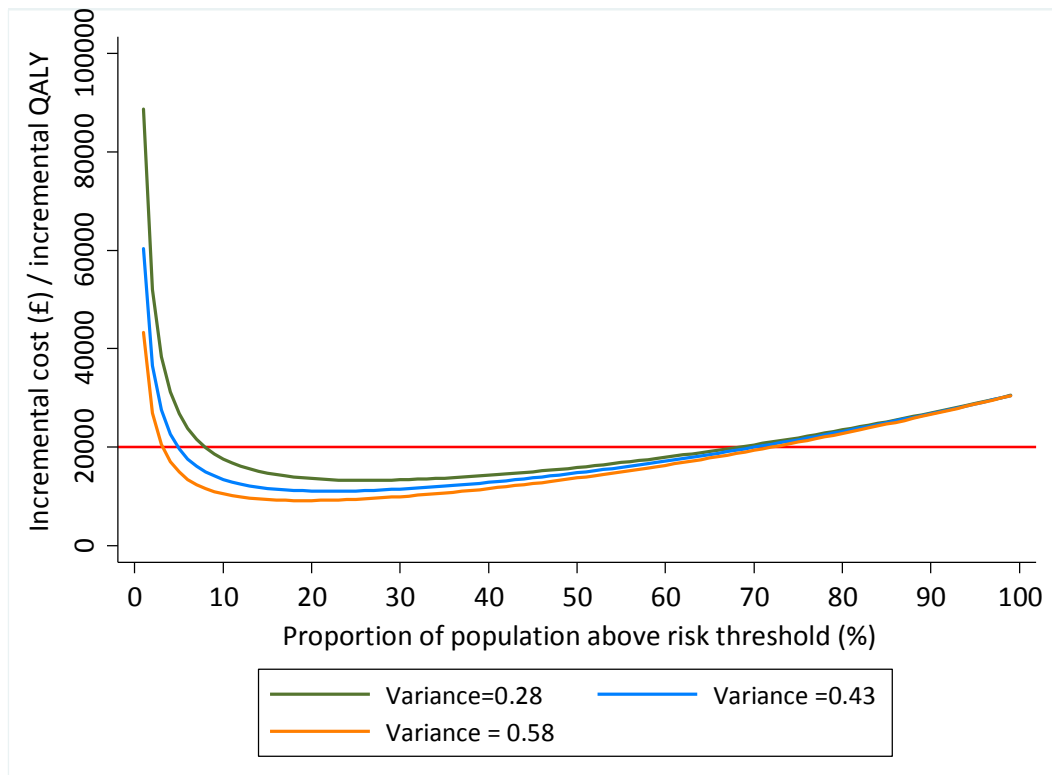
c. eFigure 8C. Incremental cost-effectiveness ratios by risk threshold considering cost of risk assessment of £25, £50, £75, and £100.



Red line: Threshold of £20,000 per QALY gained

Risk is based on polygenic profiling of the breast cancer germline genetic susceptibility variants and questionnaire based epidemiological risk factors (age at menarche, parity, age at first birth, combined menopausal hormone therapy, body mass index, benign breast disease, alcohol intake, smoking, and family history of breast cancer in first-degree relatives)

d. eFigure 8D. Incremental cost-effectiveness ratios by risk threshold considering risk distribution variance of 0.28, 0.43, and 0.58.



Red line: Threshold of £20,000 per QALY gained

In univariate deterministic sensitivity analyses, the baseline incidence of breast cancer (assuming screening advances the diagnosis by 5 and 9 years among women 50-69 years of age), adherence to screening recommendation (75% and 90%), cost of risk assessment (£25, £75 and £100) were varied. In each case, with higher baseline incidence, lower adherence, and higher cost of risk assessment, the ICER would fall below £20,000/QALY at higher percentile of risk threshold. Varying the variance of the risk distribution (0.28 and 0.58) did not materially affected the result.

The ICER, WTP, and what is deemed acceptable benefit-harm trade off will vary across healthcare systems. However, the different sensitivity analyses indicate that risk-based screening improves the cost-effectiveness of the screening programme – this trend is likely to apply to other healthcare systems, though the optimal risk threshold for targeted screening would vary across healthcare systems.

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