

# INFERENCE OF LONG TERM EFFECTS AND OVERDIAGNOSIS IN PERIODIC CANCER SCREENING

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## Supplementary Material

This appendix includes simulation results described in Section 3 in the main paper. The main programming codes written in C/C++ are in separate files.

## S1 Simulation Results in Section 3

The simulation results presented here include the following scenarios: age at initial screening  $t_0 = 50$ , screening interval  $\Delta = 6, 12, 24$  months, the screening sensitivity  $\beta = 0.3, 0.7, 0.9$ . The parametric models for the transition probability density  $w(t)$  and the sojourn time distribution  $q(x)$  were:

$$w(t) = \frac{0.2}{\sqrt{2\pi\sigma t}} \exp \left\{ -(\log t - \mu)^2 / (2\sigma^2) \right\}, \quad (\text{S1.1})$$

$$q(x) = \frac{\kappa x^{\kappa-1} \rho^\kappa}{[1 + (x\rho)^\kappa]^2}, \quad \text{or} \quad q(x) = \lambda e^{-\lambda x}. \quad (\text{S1.2})$$

The 0.2 in the  $w(t)$  is the upper limit of making a transition from the disease-free state to the preclinical state. The parameters  $(\mu, \sigma^2) = (4.2, 0.1)$ , so that the mode of the transition density is about 60 years old. The parameter was choosen for  $\kappa = 2.5$  and  $\rho = 0.661, 0.264, 0.132, 0.066$  and  $\lambda = 0.5, 0.2, 0.1, 0.05$ , such that the mean sojourn time is 2, 5, 10 and 20 years when using either the log logistic or the exponential as the sojourn time distribution.

In Table 1 and 2, the first column “MST” is the mean sojourn time in years; the next 4 columns are the conditional probabilities of each of the four cases, that is,  $P(\text{Case } i|A, T \geq t_0)$ ,  $i = 1, 2, 3, 4$ , corresponding to the probability of symptom-free-life, no-early-detection, true-early-detection, and over-diagnosis; and summation of the 4 probabilities in each row should be 1. The last two columns are the conditional probability of True-Early-Detection and Over-Diagnosis given that it is a the screen-diagnosed case; it is calculated by  $P(\text{Case } i|A, T \geq t_0) / [P(\text{Case } 3|A, T \geq t_0) + P(\text{Case } 4|A, T \geq t_0)]$ ,  $i = 3, 4$ . The probabilities are reported as percentages in the tables.

Table 1: Simulation of probabilities ( $\times 100$  %): when the sojourn time is log-logistic

| MST                                                                                | $^aP(\text{SympF})$ | $^aP(\text{NoED})$ | $^aP(\text{TrueED})$ | $^aP(\text{OverD})$ | $^bP(\text{TrueED} \text{ScrD})$ | $^bP(\text{OverD} \text{ScrD})$ |
|------------------------------------------------------------------------------------|---------------------|--------------------|----------------------|---------------------|----------------------------------|---------------------------------|
| <b>screening interval <math>\Delta = 6</math> month, <math>\beta = 0.3</math></b>  |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.47               | 4.08               | 7.13                 | 0.29                | 96.08                            | 3.92                            |
| 5                                                                                  | 87.91               | 1.58               | 9.44                 | 1.04                | 90.06                            | 9.94                            |
| 10                                                                                 | 87.22               | 0.61               | 9.71                 | 2.44                | 79.95                            | 20.05                           |
| 20                                                                                 | 86.52               | 0.22               | 8.16                 | 5.08                | 61.66                            | 38.34                           |
| <b>screening interval <math>\Delta = 6</math> month, <math>\beta = 0.7</math></b>  |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.34               | 1.00               | 10.21                | 0.42                | 96.07                            | 3.93                            |
| 5                                                                                  | 87.70               | 0.20               | 10.82                | 1.25                | 89.66                            | 10.34                           |
| 10                                                                                 | 86.98               | 0.07               | 10.25                | 2.67                | 79.31                            | 20.69                           |
| 20                                                                                 | 86.27               | 0.03               | 8.35                 | 5.33                | 61.06                            | 38.94                           |
| <b>screening interval <math>\Delta = 6</math> month, <math>\beta = 0.9</math></b>  |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.31               | 0.39               | 10.83                | 0.45                | 96.00                            | 4.00                            |
| 5                                                                                  | 87.66               | 0.06               | 10.97                | 1.29                | 89.49                            | 10.51                           |
| 10                                                                                 | 86.94               | 0.02               | 10.30                | 2.71                | 79.15                            | 20.85                           |
| 20                                                                                 | 86.23               | 0.01               | 8.37                 | 5.37                | 60.94                            | 39.06                           |
| <b>screening interval <math>\Delta = 12</math> month, <math>\beta = 0.3</math></b> |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.56               | 6.39               | 4.82                 | 0.20                | 95.96                            | 4.04                            |
| 5                                                                                  | 88.12               | 3.45               | 7.57                 | 0.83                | 90.08                            | 9.92                            |
| 10                                                                                 | 87.52               | 1.66               | 8.66                 | 2.13                | 80.26                            | 19.74                           |
| 20                                                                                 | 86.88               | 0.63               | 7.75                 | 4.71                | 62.20                            | 37.80                           |
| <b>screening interval <math>\Delta = 12</math> month, <math>\beta = 0.7</math></b> |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.42               | 2.66               | 8.55                 | 0.34                | 96.18                            | 3.82                            |
| 5                                                                                  | 87.81               | 0.72               | 10.30                | 1.14                | 90.03                            | 9.97                            |
| 10                                                                                 | 87.10               | 0.23               | 10.09                | 2.56                | 79.79                            | 20.21                           |
| 20                                                                                 | 86.39               | 0.08               | 8.30                 | 5.21                | 61.46                            | 38.54                           |
| <b>screening interval <math>\Delta = 12</math> month, <math>\beta = 0.9</math></b> |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.37               | 1.45               | 9.77                 | 0.39                | 96.20                            | 3.80                            |
| 5                                                                                  | 87.74               | 0.25               | 10.77                | 1.21                | 89.88                            | 10.12                           |
| 10                                                                                 | 87.01               | 0.07               | 10.26                | 2.64                | 79.54                            | 20.46                           |
| 20                                                                                 | 86.30               | 0.02               | 8.36                 | 5.29                | 61.24                            | 38.76                           |
| <b>screening interval <math>\Delta = 24</math> month, <math>\beta = 0.3</math></b> |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.64               | 8.30               | 2.91                 | 0.13                | 95.75                            | 4.25                            |
| 5                                                                                  | 88.36               | 5.72               | 5.31                 | 0.60                | 89.85                            | 10.15                           |
| 10                                                                                 | 87.97               | 3.48               | 6.85                 | 1.69                | 80.20                            | 19.80                           |
| 20                                                                                 | 87.54               | 1.62               | 6.77                 | 4.06                | 62.49                            | 37.51                           |
| <b>screening interval <math>\Delta = 24</math> month, <math>\beta = 0.7</math></b> |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.52               | 5.15               | 6.06                 | 0.24                | 96.12                            | 3.88                            |
| 5                                                                                  | 87.99               | 2.05               | 8.97                 | 0.96                | 90.33                            | 9.67                            |
| 10                                                                                 | 87.32               | 0.76               | 9.56                 | 2.33                | 80.38                            | 19.62                           |
| 20                                                                                 | 86.63               | 0.24               | 8.14                 | 4.97                | 62.11                            | 37.89                           |
| <b>screening interval <math>\Delta = 24</math> month, <math>\beta = 0.9</math></b> |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.47               | 3.79               | 7.42                 | 0.29                | 96.22                            | 3.78                            |
| 5                                                                                  | 87.88               | 0.99               | 10.04                | 1.07                | 90.34                            | 9.66                            |
| 10                                                                                 | 87.17               | 0.26               | 10.06                | 2.49                | 80.19                            | 19.81                           |
| 20                                                                                 | 86.46               | 0.07               | 8.31                 | 5.14                | 61.81                            | 38.19                           |

<sup>a</sup> The probability of each outcomes, i.e.  $P(\text{Case } i|A, T \geq t_0)$ .<sup>b</sup> The conditional probability of True-Early-Detection and of Over-Diagnosis given that it is a screen-diagnosed case.

Table 2: Simulation of probabilities ( $\times 100$  %): when the sojourn time is exponential

| MST                                                                                | $^aP(\text{SympF})$ | $^aP(\text{NoED})$ | $^aP(\text{TrueED})$ | $^aP(\text{OverD})$ | $^bP(\text{TrueED} \text{ScrD})$ | $^bP(\text{OverD} \text{ScrD})$ |
|------------------------------------------------------------------------------------|---------------------|--------------------|----------------------|---------------------|----------------------------------|---------------------------------|
| <b>screening interval <math>\Delta = 6</math> month, <math>\beta = 0.3</math></b>  |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.45               | 4.75               | 6.46                 | 0.32                | 95.34                            | 4.66                            |
| 5                                                                                  | 87.91               | 2.62               | 8.33                 | 1.12                | 88.16                            | 11.84                           |
| 10                                                                                 | 87.34               | 1.53               | 8.51                 | 2.60                | 76.64                            | 23.36                           |
| 20                                                                                 | 86.81               | 0.84               | 7.23                 | 5.09                | 58.65                            | 41.35                           |
| <b>screening interval <math>\Delta = 6</math> month, <math>\beta = 0.7</math></b>  |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.33               | 2.17               | 9.04                 | 0.43                | 95.43                            | 4.57                            |
| 5                                                                                  | 87.73               | 0.99               | 9.96                 | 1.30                | 88.48                            | 11.52                           |
| 10                                                                                 | 87.13               | 0.53               | 9.51                 | 2.81                | 77.22                            | 22.78                           |
| 20                                                                                 | 86.58               | 0.27               | 7.79                 | 5.33                | 59.41                            | 40.59                           |
| <b>screening interval <math>\Delta = 6</math> month, <math>\beta = 0.9</math></b>  |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.30               | 1.53               | 9.69                 | 0.46                | 95.45                            | 4.55                            |
| 5                                                                                  | 87.69               | 0.66               | 10.30                | 1.33                | 88.54                            | 11.46                           |
| 10                                                                                 | 87.09               | 0.34               | 9.70                 | 2.84                | 77.33                            | 22.67                           |
| 20                                                                                 | 86.54               | 0.17               | 7.90                 | 5.36                | 59.54                            | 40.46                           |
| <b>screening interval <math>\Delta = 12</math> month, <math>\beta = 0.3</math></b> |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.54               | 6.68               | 4.53                 | 0.22                | 95.29                            | 4.71                            |
| 5                                                                                  | 88.10               | 4.23               | 6.72                 | 0.93                | 87.88                            | 12.12                           |
| 10                                                                                 | 87.61               | 2.66               | 7.38                 | 2.33                | 76.00                            | 24.00                           |
| 20                                                                                 | 87.14               | 1.54               | 6.53                 | 4.77                | 57.76                            | 42.24                           |
| <b>screening interval <math>\Delta = 12</math> month, <math>\beta = 0.7</math></b> |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.40               | 3.67               | 7.54                 | 0.36                | 95.39                            | 4.61                            |
| 5                                                                                  | 87.82               | 1.82               | 9.13                 | 1.20                | 88.35                            | 11.65                           |
| 10                                                                                 | 87.23               | 1.00               | 9.04                 | 2.70                | 76.99                            | 23.01                           |
| 20                                                                                 | 86.69               | 0.53               | 7.54                 | 5.21                | 59.11                            | 40.89                           |
| <b>screening interval <math>\Delta = 12</math> month, <math>\beta = 0.9</math></b> |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.35               | 2.74               | 8.47                 | 0.41                | 95.43                            | 4.57                            |
| 5                                                                                  | 87.76               | 1.25               | 9.70                 | 1.27                | 88.46                            | 11.54                           |
| 10                                                                                 | 87.16               | 0.66               | 9.38                 | 2.77                | 77.19                            | 22.81                           |
| 20                                                                                 | 86.62               | 0.34               | 7.73                 | 5.29                | 59.37                            | 40.63                           |
| <b>screening interval <math>\Delta = 24</math> month, <math>\beta = 0.3</math></b> |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.62               | 8.37               | 2.84                 | 0.14                | 95.27                            | 4.73                            |
| 5                                                                                  | 88.34               | 6.10               | 4.85                 | 0.69                | 87.58                            | 12.42                           |
| 10                                                                                 | 88.02               | 4.22               | 5.82                 | 1.92                | 75.16                            | 24.84                           |
| 20                                                                                 | 87.71               | 2.62               | 5.45                 | 4.21                | 56.44                            | 43.56                           |
| <b>screening interval <math>\Delta = 24</math> month, <math>\beta = 0.7</math></b> |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.49               | 5.61               | 5.60                 | 0.27                | 95.36                            | 4.65                            |
| 5                                                                                  | 87.98               | 3.15               | 7.80                 | 1.05                | 88.17                            | 11.83                           |
| 10                                                                                 | 87.43               | 1.84               | 8.20                 | 2.51                | 76.59                            | 23.41                           |
| 20                                                                                 | 86.91               | 1.01               | 7.06                 | 5.00                | 58.56                            | 41.44                           |
| <b>screening interval <math>\Delta = 24</math> month, <math>\beta = 0.9</math></b> |                     |                    |                      |                     |                                  |                                 |
| 2                                                                                  | 88.44               | 4.53               | 6.68                 | 0.32                | 95.40                            | 4.60                            |
| 5                                                                                  | 87.88               | 2.28               | 8.67                 | 1.15                | 88.33                            | 11.67                           |
| 10                                                                                 | 87.30               | 1.25               | 8.79                 | 2.64                | 76.94                            | 23.06                           |
| 20                                                                                 | 86.76               | 0.65               | 7.41                 | 5.15                | 59.03                            | 40.97                           |

<sup>a</sup> The probability of each outcomes, i.e.  $P(\text{Case } i|A, T \geq t_0)$ .<sup>b</sup> The conditional probability of True-Early-Detection and of Over-Diagnosis given that it is a screen-diagnosed case.