OPTIMAL SCHEDULING OF MEDICAL EXAMS:

THE CASE OF BREAST CANCER

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DP# 91-A16
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November 18, 1991
Abstract

Screening for early detection is currently one of the most effective ways to control breast cancer. As the incidence of breast cancer is strongly dependent on age, the question arises of how such dependence should affect the spacings between screening times. Various facets of this general question, such as the appropriateness of screening before age 50 and the efficacy of biannual examinations, have been at the center of the debate on breast cancer screening in the last few years.

This paper illustrates the use of a decision theoretic model for determining the best sequence of examination ages for the early detection of breast cancer. Policies are evaluated on the bases of the expected number of examinations involved and of the expected reduction in mortality. Trade-off curves between these two quantities are calculated for the optimal schedule as well as the optimal periodic schedule with arbitrary age of first screen; the results are used to compare the available alternatives, including the policies currently recommended by various scientific and professional organizations. One indication emerging from the analysis is that periodic screening examinations, if properly scheduled, do not entail a substantially higher risk than optimally scheduled examinations. Screening before age 50, biannual examinations and the impact of improved sensitivity of mammographies are also discussed.
1 Introduction

Based on the evidence collected in various large scale studies, there currently is consensus that early detection may be effective in reducing mortality from breast cancer (see, for example, American Medical Association 1991). Therefore mammographic screening is recommended by various scientific, professional and governmental organizations. However, recommendations differ with regard to the age of first screen and the frequency of screens (Miller 1991).

Theoretical models for optimal scheduling of screening examinations for the early detection of chronic disease have been proposed by Kirch and Klein (1974), Shahani and Crease (1977), Eddy (1980) and more recently by Parmigiani (1990b) and Zelen (1991). In particular, the model proposed in Parmigiani (1990b) accounts explicitly for the dependence of incidence on age in determining optimal strategies. As breast cancer incidence is strongly dependent on age, this model appears to provide the appropriate tool. The purpose of this paper is twofold. First I intend to illustrate the aforementioned new methodology in a case which at present is of great practical concern. Second, I use the results to help evaluate the current screening recommendations.

The discussion proceeds as follows. In section 2, I introduce the basic assumption of the model. In section 3, I discuss the data analysis used in the calculation of the risks, and in section 4, I carry out the derivation and evaluation of the optimal policies.

2 Problem Formulation

Similarly to Shwartz (1983), I assume that the natural history of breast cancer in a patient can be described by a four-state stochastic process. In state I there is no cancer, or undetectable cancer, in state II there is detectable asymptomatic cancer, in state III (clinical) there is symptomatic cancer, and in state IV the patient dies. Transitions are always from state I to II, II to III, or from any stage to IV. A process is then fully defined by the specification of the probabilities of the above transitions as a function of age. Let the time spent in state I be the random variable
Y. A patient leaving state I can move to state II or state IV. Let \( f(y) \) represent the density of transitions from I to II, and \( \hat{f}(y) \) the density of transitions from I to IV. Next, let \( U \) be the sojourn time in state II; then \( Y + U \) is the age of the patient at the time of the surfacing of symptoms. Let \( h(u|y) \) and \( \hat{h}(u|y) \) be the conditional transition densities to states III and IV respectively, given an arrival in state II at time \( y \). It is important to allow for a dependence between \( Y \) and \( U \) as younger women tend to contract faster growing cancer. All densities are assumed to be continuous. Then, if no screening takes place, the probability of eventually contracting cancer and reaching the detectability point is \( \xi = \int_0^\infty f(y)dy \). Also, the probability of reaching the clinical stage, given an arrival in state II at time \( y \) is given by \( \theta(y) = \int_0^\infty h(u|y)du \), and the marginal probability of contracting cancer and reaching the clinical stage is \( \hat{\theta} = \int_0^\infty \theta(y)f(y)dy \).

Let \( \beta \) denote the sensitivity of the screening test. To the purpose of this problem, the specificity can be assumed to be unity with no loss of generality. Usually, positive mammograms are followed by a highly specific biopsy. Therefore, the screening problem does not terminate unless the illness is actually present. A low specificity of the test will, however, have an impact on the expected costs, since it will imply a more frequent use of the biopsy.

Examinations are scheduled for patients in states I and II, and terminate as soon as state III or state IV are reached, or state II is detected. Let an examination schedule be denoted by \( \tau = \{\tau_1, \ldots, \tau_i, \ldots\} \), where \( \tau_i \) is time of the \( i \)-th examination, \( \tau_i > \tau_{i-1} \) and \( \tau_0 = 0 \). The number of planned examinations is \( n \), which may be finite or infinite. Also, let \( \mathcal{I}(\tau) \) be the number of examinations actually performed for the schedule \( \tau \); \( \mathcal{I}(\tau) \) is a random variable since it is a function of \( Y \) and \( U \). Designing an optimal screening program consists of choosing the best \( \tau \) according to some criterion. This choice addresses at once the problems of optimal timing, of whether or not screening is worthwhile for an individual with the given transition densities, and of when to stop screening.

A widely accepted criterion for evaluating the effectiveness of screening programs for breast cancer is their effect on mortality. It then seems natural to base the loss function on the mortality curves under early and late detection. An estimation of such mortality curves based on the HIP data is presented in Walter and Stitt (1987). Their estimate is corrected for lead time bias. The
five-year survival probability is .833 in case of early detection versus .690 in case of detection at the surfacing of symptoms. For ten-year survival the values are .693 and .501.

More generally, one would like to be able to account for the age of the tumor at detection and for the age of the patient at time of detectability. The latter issue, in particular, is important in determining whether or not it is worthwhile to screen women under fifty years of age, since it is commonly believed that the incidence of faster growing tumors is higher in younger women. To incorporate this information it would be necessary to adopt an age-dependent loss function. However, information on age-specific mortality curves and on the dependence of the prognosis on the age of the tumor does not seem to be sufficient for a reliable assessment of the losses.

Therefore, the end point chosen for the analysis is the probability $\mathcal{L}(\tau)$ of death within 5 years of detectability, conditional on contraction of the disease. Conversion of the results to time periods other than five years or to marginal rather than conditional probability of death require simply a linear transformation of the scale, so that all comparisons between policies are unchanged.

In addition to reduced mortality, screening obviously involves costs, so that a sensible analysis should include those as well. In practice, specification of an exchange rate to evaluate both costs and mortality on the same scale may be very troublesome, and an attractive tool is provided by trade-off curves, originally proposed in this context by Shahani and Crease (1977). For a fixed value $e$ of the expected number of examinations, one can solve the constrained maximization of $\mathcal{L}(\tau)$ with respect to the screening times, by minimising

$$A(\tau) = \ell [T(\tau) - e] + \mathcal{L}(\tau),$$

(1)

Changing $e$ and repeating the procedure yields a graph of $\mathcal{L}$ versus $T$; this graph can be derived without specifying the exchange rate between dollars and reduction in mortality. If a single policy is chosen, such exchange rate can be recovered by looking at the Lagrange multiplier $\ell$ in (1).
The following are explicit expressions of $I$ and $L$ in terms of an arbitrary policy $\tau$.

\[
I(\tau) = \sum_{i=0}^{n} \int_{\tau_i}^{\tau_{i+1}} \left\{ i \hat{f}(y) + \sum_{j=0}^{n-i} (i+j+1)(1-\beta)^j[p_{ij}(y) + \beta q_{ij}(y)]f(y) \right\} dy
\]

\[
L(\tau) = \sum_{i=0}^{n} \int_{\tau_i}^{\tau_{i+1}} \sum_{j=0}^{n-i} (1-\beta)^j[L_{III}p_{ij}(y) + L_{II}q_{ij}(y)]f(y)dy,
\]

where $p_{ij}(y) = H(\tau_{i+j+1} - y|y) - H(\tau_{i+j} - y|y)$ and $q_{ij}(y) = 1 - H(\tau_{i+j+1} - y|y)$. Also, equations (2) and (3) are obtained under the assumption that $\theta(y) = 1$. Empirical support for this assumption is discussed in section 4.

Calculation of the optimal schedule is simplified by the fact that for fixed $k$ and $c$, the optimal sequence satisfies the following recursive conditions.

\[
H(\delta_{i+1}|\tau_i) = \int_{0}^{\delta_i} h(x|\tau_i - x) \frac{f(\tau_i - x)}{f(\tau_i)} dx - \frac{k}{c(L_{III} - L_{II})} \left( \frac{\hat{f}(\tau_i)}{f(\tau_i)} + 1 \right) \quad i = 1, \ldots, n.
\]

Details on the optimization algorithms can be found in Parmigiani (1990b).

3 Transition Densities

The evaluation of $I(\tau)$ and $L(\tau)$ and the computation of the optimal screening policy require the assessment of the probability densities defining a patient's history. There are four such densities. These describe transitions from state I to II and IV, and from state II to III and IV.

3.1 Mortality and Incidence of Breast Cancer

Moolgavkar, Stevens and Lee (1979) developed a general model to estimate the incidence of breast cancer in the female population. The model accounts for both age and cohort effect, and yields estimates of incidence and mortality as a function of age alone. The feature of separating the cohort effect from the age effect makes their estimates suitable for use in the context of this paper, since I have assumed that the patient's age is the appropriate time scale regardless of the date of birth. As the cohort effect seems to be strong, this is an important advantage. This study can be used to estimate the number of transitions from state I to state III.
Transitions from state I to state IV, can be derived using life tables. The resulting values are used to evaluate the density \( \hat{f} \). \( \hat{f} \) is assumed to be a Weibull density:

\[
\hat{f}(y) = \frac{a}{b} \left( \frac{y}{b} \right)^{a-1} e^{-\left( \frac{y}{b} \right)^a}
\]

Least squares yields parameter estimates of \( a = 7.233 \) and \( b = 82.551 \). The Weibull provides a good fit and is computationally very convenient, due to the closed form of the cdf. Use of the Gumbel or other distributions improves the fit only marginally and leaves the conclusion substantially unchanged.
3.2 Sojourn Time in the Detectable Pre-clinical Stage

The distribution of the sojourn time in the pre-clinical stage is perhaps the most important and controversial of the evaluations required for the computation of the risk. Several models have been proposed for its estimation. In particular, Louis, Albert and Heghiniyan (1978) developed a non-parametric estimation, Walter and Day (1984) and Brookmeyer, Day and Moss (1986) considered the joint estimation of test sensitivity and sojourn time, and Spratt, Greenberg and Heuser (1986) obtained estimates of the sojourn time that depend on the age of the patient.

Because patient age is an important effect, I use the latter study. At each age, the authors assumed a lognormal distribution:

\[ p(u) = \frac{1}{\sqrt{2\pi su}} e^{-\frac{1}{2s^2} (\log u - m)^2} \]

The rationale for this choice is that the tumor is believed to follow a growth undergoing an exponential retardation with increasing size. This is captured by the decreasing failure rate of the lognormal distribution. In terms of the four-state model adopted here, their results can be used to evaluate the density of the sojourn time in the detectable pre-clinical stage, conditional on a transition to state III, that is, conditional on the patient not dying of other causes while in state II. In the notation used previously, this is the density \( h' \) of the random variable \( U' \). The appropriate constant to convert this into the distribution \( h \) of transitions from II to III is evaluated at the end of the section.

To evaluate screening policies it is necessary to provide a sojourn-time distribution for ages not covered in the study of Spratt, Greenberg and Heuser. Moreover, the estimated parameters display a somewhat noisy behavior. Therefore, I proceed by modeling the parameters of the lognormal distribution as functions of age, and adopting the resulting predicted values as input in the risk evaluation. In particular, the location parameter \( m \) is increasing with age, but the behavior of the scale parameter seems more erratic, and the data do not provide sufficient grounds for reliably modeling age dependence. Therefore, I model age dependence through the parameter \( m \) only.
A suitable family of functions for \( m \) seems to be the logistic:

\[
\log(m_0 - m(y)) = m_1 + m_2 y,
\]

where \( y \) is age. I specified \( m_0 \) to approach linearity and constant variance in the regression; a convenient choice is \( m_0 = 1.4 \). This yields least squares estimates of \( m_1 = 1.6 \) and \( m_2 = -0.038 \). Figure 1 illustrates the fit.

![Figure 1: Fit of the logistic model for the mean parameter of the sojourn time distribution.](image)

Due to the highly noisy information, I considered the parameter \( S \) unknown. Consequently, \( U' \) given \( Y = y \) and \( S = s \) is lognormal with parameters \( m_0 - e^{m_1 + m_2 y} \) and \( s \). I then specified
a prior distribution on $S$, based in part on the above evidence. An inverse gamma prior seems a sufficiently flexible and tractable choice:

$$
\pi(s) = \frac{1}{\Gamma(a)b^a s^{a+1}} e^{-\frac{1}{b} s}
$$

If the values of $a$ and $b$ are chosen to match the mean and variance of the values of $s$ obtained by Spratt, Greenberg and Heuser, then $a = 6.33$ and $b = 3.36$. After integrating out $S$, the distribution of $U'$ given $Y = y$ is:

$$
h'(u'|y) = \frac{B(a, b)}{u'} \sqrt{\frac{b}{2}} \left[ 1 + \frac{b}{2} \left( \log u' - m_0 + e^{m_1 + m_2 y} \right) \right]^{-\frac{a+b+1}{2}}.
$$

This is the density that will be used in calculating the optimal policy, with parameters at noted above.

3.3 Time to Detectability

Using the information described so far it is possible to construct an estimate of the density of the transitions from state I to state II. One approach is to estimate the distribution of the sum of $Y$ and $U$ using the data on cases of breast cancer, and then derive the distribution of $Y$ via a convolution. However, the distribution of $Y$ plays an essential role in the calculations of the optimal examination schedule, and it would be very convenient to have a direct expression for it, instead of having to resort to numerical convolution every time the density needs to be evaluated.

One way to achieve this is estimating the number of individual moving from stage I to stage II at any given age, based on the table of cases of breast cancer and on the assumption on the sojourn time discussed in the previous section. Then a parametric can be fitted directly to the derived table. Therefore, I proceed by first constructing a density estimate for the number of cases of breast cancer, and then computing the convolution of it with the density of the sojourn time in the detectable pre-clinical stage. The latter provides the desired estimate of the number of transitions. To keep the amount of modeling to a minimum during this phase, I estimated the
density of cases using a cubic spline curve. A Weibull density was finally fitted to the resulting values. Parameters are $a = 4.48$ and $b = 65.52$.

3.4 Mortality During the Detectable Pre-clinical Stage

The final element necessary for the full specification of the stochastic process representing a patient’s history is the probability density of transitions from state II to state IV, governing deaths from causes other than breast cancer while in the detectable pre-clinical stage. In this context it can be safely assumed that this density is the same as in state I: having contracted pre-clinical breast cancer does not modify the incidence of other causes of death. This assumption may be unrealistic when the tumor metastasizes at a very early stage, so that other forms of cancer surface first, but, as it will be clear shortly, this possibility is of no consequence here.

Under the above assumption, the sojourn time in II, conditional on a transition from II to IV, has density: $h''(u|y) = \frac{f(u+y)}{1-H(y)}$. If $U''$ is a random variable with density $h''$, the probability of a transition from state II to state III given a detectability time $Y$, is given by $\theta(y) = P(U' < U''|Y = y)$ The above equation provides the normalizing constant for the distributions of the sojourn time in the detectable pre-clinical stage, that is: $h(u|y) = h'(u'|y)\theta(y)$ and

$$\hat{h}(u|y) = h''(u|y)(1 - \theta(y)) = \frac{\hat{f}(u+y)}{1 - \hat{H}(y)}(1 - \theta(y))$$

The values of $\theta$ at different ages, under the distributions postulated so far, are given in Table 1.

<table>
<thead>
<tr>
<th>Age</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
</tr>
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<td>$\theta$</td>
<td>0.9995</td>
<td>0.9978</td>
<td>0.9938</td>
<td>0.9876</td>
<td>0.9803</td>
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</table>

Table 1: Probability of transition from II to III as a function of age.

These values suggest that, in the rest of the analysis, it is not important to account for mortality due to competing causes of death while in the detectable pre-clinical stage. Henceforth, I assume that $\theta(y) = 1$. This brings remarkable computational simplifications. When the results of the model with variable $\theta(y)$ are compared to the case $\theta(y) = 1$, the difference is negligible.
3.5 Sensitivity

The sensitivity of mammography varies substantially with the technology employed, the expertise of the radiologist, and physiological features of the patient such as amount of fat tissues in the breast and others. In addition, the estimation of sensitivity is complicated by the fact that any statistical model has to jointly estimate sensitivity and distribution of the sojourn time in the detectable pre-clinical stage. For example, the presence of symptoms six months after a negative mammogram, may be evidence of either fast growth or poor sensitivity. Therefore, assumptions on the growth of the tumor are necessary, and the estimates of sensitivity depend strongly on them. Difficulties are more severe when trying to evaluate how the sensitivity of the test depends on size or age of the tumor.

Most of the estimates available are based on rather restrictive models, and, in particular, assume that the sensitivity is constant (see Walter and Day, 1984 and Brookmeyer, Day and Moss, 1986). In general, however, these studies seem to indicate that the sensitivity was of the order of .8 for the mammography technology adopted in the HIP study.

Finally, it has to be noted that the mammographic techniques are constantly improving, and that the most advanced xerographic films are now achieving very high sensitivity, so that, in planning future schedules, it may be sensible to consider the case $\beta = 1$.

4 Trade-off Curves and Optimal Schedules

4.1 Highly Sensitive Tests

In this Section, I present the trade-off curve between $L(\tau)$ —that is the probability of dying within five years of the detectability time conditional on contracting breast cancer WRONG!!!! itzemarglina—— and the expected number of examinations. I consider four families of schedules: the optimal schedule, the optimal schedule within the sub-family of periodic schedules with arbitrary year of first screen and the optimal periodic schedule with year of first screen constrained to be 40 years and 50 years respectively.
Figure 2: Trade-off curve under optimal scheduling and under optimal periodic scheduling.

Figure 2 displays the trade-off curve for the optimal schedules versus the optimal periodic schedules with arbitrary first examination time. The values of $k/c$ range from $1/100$ to $1/5000$. The values of $u(x)$ are expressed in percentage points, and if no screening takes place, $u_0 = 0.395$. Note that the curve for the optimal periodic policy is very close to the optimum. In terms of overall risk, the advantage of optimal schedules over optimal periodic schedule is always less than one percentage point, which is negligible.

This may appear to contradict the fact that $f$ has a rapidly increasing failure rate. In this case, however, there is a strong effect of competing causes of death, whose failure rate
increases more rapidly than that of the cases of breast cancer. Moreover, the time dependence in the distribution of the sojourn time in the detectable pre-clinical stage can, as illustrated in the previous section, offset the effect of log-concavity. The combination of these two factors generates optimal policies where the increasing failure rate of $f$ is not even sufficient to produce decreasing times between examinations.

In addition, the advantages of nonperiodic examinations, whether the spacings are increasing or decreasing, is reduced by the moderate prevalence. Marginally, the probability of contracting breast cancer is .1. With a higher incidence, the same departure from a periodic schedule in terms of policy would have a larger impact on the risk.

Table 2 contains the optimal schedule at $k = 1$ and $c = 200$, and Table 3 contains the optimal schedule at $k = 1$ and $c = 500$. The values were chosen to produce optimal ages of first screen close to the current recommendations. Notice that the times between examinations are not monotonic, being slightly decreasing at the beginning, and then becoming sparse at later ages. When the time dependence in the density $h$ is suppressed, the times between examination keep decreasing for a longer time, but eventually they will still start to increase, due to the effect of competing causes of death in older women.

A periodic schedule with arbitrary time of first screen can be identified by the pair $(\tau_1, \delta)$, with the time of the $i$-th examination given by $\tau_1 + (i - 1)\delta$.

It appears from examining the optimal schedules that the choice of an age of first screen around 47 or 48 years implies, at least in this model, that a consistent optimal continuation should be based on screens more that two years apart. To explicitly address this issue, consider policies with optimal frequency and with age of first screen constrained to be 40 or 50 years respectively, and compared them with the current recommendations.

Figure 3 displays the resulting trade-off curves, and the points corresponding to policies with first screen at 40 and 50 years, followed by annual or biannual tests; the trade-off curve of the optimal periodic policy is also graphed for reference. The advantage of optimal periodic schedules over some of the current recommendations may be significant. In particular, it appears that biannual policies approach optimality at both $\tau_1 = 40$ and $\tau_1 = 50$ for appropriate values.
Figure 3: Trade-off curve to evaluate current screening recommendations

of the cost parameters. On the other hand, annual policies show a significantly high expected number of screens, not rewarded by an adequate reduction in mortality.

4.2 Sensitivity Analysis

The sensitivity of the results to changes in the values of the parameters was assessed for all parameters. The level of uncertainty about the density \( f \) of transitions from state I to state II is moderate, so that small changes in the parameters are appropriate. Age of first screen and frequency of examinations are somewhat sensitive to shifts in the distribution. The loss in
efficiency due to periodic schedules and the relation between age of first screen and frequency of examination seem, however, much more robust. Similar considerations apply to the density \( \hat{f} \), with the added caveat that uncertainties concern mostly the functional form and the bias introduced by not accounting for the generation effect. Changes in parameters can therefore provide only a limited picture of the sensitivities of interest.

The parameters of the distribution \( h \) of the sojourn time in the pre-clinical stage are, in general, influential, especially on the frequency of examinations. Moreover, their assessment is uncertain, so that significant deviations from the postulated values need to be considered. There are five parameters entering \( h \): two hyperparameters for the unknown scale parameter of the lognormal, and three parameters for the logistic model describing the expectation of the lognormal as a function of age. Of the latter three, \( m_1 \) and \( m_2 \) were estimated using least squares, and \( m_0 \) was arbitrarily selected in a best transformation search. Table 4 illustrates the changes of various quantities of interest following 10% changes in the values of \( m_0 \), \( m_1 \) and \( m_2 \) at \( k = 1 \) and \( c = 200 \). Of the displayed quantities, the most sensitive are the times between checks. In particular an increase of 10% in \( m_0 \) results in an increase of 9% in \( \delta_1 \) and 17% in \( \delta_{10} \). A similar, although less pronounced, effect results from changes in \( m_2 \).

As mentioned earlier, the very good performance of periodic examinations depends on the relatively low prevalence. In groups at higher risk, non-periodic examination may be more advantageous. The larger advantage, however, is in terms of absolute rather than relative difference. To illustrate this point, I replicated the calculations assuming that the marginal prevalence is four times as large as estimated, and that the relative standings of age-specific incidences remain unchanged.

Figure 4 illustrates the new trade-off curve. Again the relative difference is within one percentage point, but in this case this is a much more significant figure in terms of number of lives saved.

The sensitivity of the results to some of the structural assumptions is more difficult to assess. In particular, the conclusions concerning the relation between age of first screen and frequency of examinations depend on the assumption of constant losses. It is plausible that an analysis
Figure 4: Trade-off curve under optimal scheduling and under optimal periodic scheduling.

Based on age-specific mortality curves would provide different conclusions. However, the studies available do not yet provide sufficient information to adequately assess such losses, particularly for women aged 40 to 49 years.

4.3 Mammographies with Sensitivity .8

In this section, I assume that the sensitivity $\beta$ of the mammographic technique used for screening is .8, and carry out some of the calculations presented in the previous section. The general conclusions of the analysis are similar. Some differences, however, are worth mentioning.
To illustrate the modifications on the component of the risk induced by the lower sensitivity, in Tables 5 and 6, I compare the expected number of examinations and the expected losses of various policies, under $\beta = 1$ and $\beta = .8$. It is noticeable that the effect of lowering $\beta$ is substantially larger on the expected losses than it is on the expected number of screens. The reason is that, due to the short duration of the detectable pre-clinical stage relative to the screening frequency, most false negative tests will result in a late detection, the chances of having a second attempt at an early detection being slim. Accordingly, the increase in expected loss is much larger in biannual policies —8% to 10%— than in annual policies —1% to 2%. Therefore, it can be expected that the advantages of biannual policies over annual policies emphasized by Figure 3 should be mitigated in this case.

Figure 5 replicates Figure 3 for $\beta = .8$. The conclusion seems to be that annual policies are inefficient if the test is highly sensitive, but become more competitive as the sensitivity decreases. In particular, if the age of first screen is 40 years, annual examinations appear a very reasonable choice at $\beta$ as large as .8, for appropriate values of the costs.

5 Conclusions

The assumption of a constant sensitivity throughout the pre-clinical stage is heroic in this case, and is introduced for convenience. The pre-symptomatic phase is characterized by a continuous growth of the tumor that typically leads to continuously easier detectability.

High risk groups

References

Figure 5: Trade-off curve to evaluate current screening recommendations when $\beta = .8$.


<table>
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<tr>
<th>$i$</th>
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<td>0.35</td>
</tr>
<tr>
<td>19</td>
<td>95.69</td>
<td>3.18</td>
<td>0.94</td>
<td>0.32</td>
</tr>
<tr>
<td>20</td>
<td>98.74</td>
<td>3.05</td>
<td>0.97</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Table 2: Optimal policy at $k = 1$, and $c = 200$. 
<table>
<thead>
<tr>
<th>$i$</th>
<th>$\tau_i$</th>
<th>$\tau_i - \tau_{i-1}$</th>
<th>$F(\tau_i) + \hat{F}(\tau_i)$</th>
<th>$H(\tau_i - \tau_{i-1})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39.13</td>
<td>39.13</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>2</td>
<td>40.8</td>
<td>1.69</td>
<td>0.00</td>
<td>0.84</td>
</tr>
<tr>
<td>3</td>
<td>42.48</td>
<td>1.64</td>
<td>0.00</td>
<td>0.72</td>
</tr>
<tr>
<td>4</td>
<td>44.13</td>
<td>1.65</td>
<td>0.01</td>
<td>0.62</td>
</tr>
<tr>
<td>5</td>
<td>45.80</td>
<td>1.67</td>
<td>0.01</td>
<td>0.54</td>
</tr>
<tr>
<td>6</td>
<td>47.50</td>
<td>1.70</td>
<td>0.02</td>
<td>0.47</td>
</tr>
<tr>
<td>7</td>
<td>49.23</td>
<td>1.73</td>
<td>0.02</td>
<td>0.41</td>
</tr>
<tr>
<td>8</td>
<td>51.01</td>
<td>1.77</td>
<td>0.03</td>
<td>0.36</td>
</tr>
<tr>
<td>9</td>
<td>52.84</td>
<td>1.82</td>
<td>0.04</td>
<td>0.32</td>
</tr>
<tr>
<td>10</td>
<td>54.71</td>
<td>1.86</td>
<td>0.05</td>
<td>0.29</td>
</tr>
<tr>
<td>15</td>
<td>64.82</td>
<td>2.13</td>
<td>0.16</td>
<td>0.19</td>
</tr>
<tr>
<td>20</td>
<td>76.36</td>
<td>2.43</td>
<td>0.43</td>
<td>0.16</td>
</tr>
<tr>
<td>25</td>
<td>89.52</td>
<td>2.76</td>
<td>0.83</td>
<td>0.18</td>
</tr>
<tr>
<td>28</td>
<td>98.11</td>
<td>2.89</td>
<td>0.96</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Table 3: Optimal policy at $k = 1$, and $c = 500$. 
Table 4: Sensitivity to the parameters of the distribution of the sojourn time in the detectable pre-clinical stage.

<table>
<thead>
<tr>
<th></th>
<th>$m_0 + 10%$</th>
<th>$m_0 - 10%$</th>
<th>$m_1 + 10%$</th>
<th>$m_1 - 10%$</th>
<th>$m_2 + 10%$</th>
<th>$m_2 - 10%$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R(x)$</td>
<td>63.164</td>
<td>61.507</td>
<td>64.919</td>
<td>64.232</td>
<td>62.234</td>
<td>61.943</td>
</tr>
<tr>
<td>$U(x)$</td>
<td>0.2564</td>
<td>0.2519</td>
<td>0.2626</td>
<td>0.2615</td>
<td>0.2531</td>
<td>0.2521</td>
</tr>
<tr>
<td>$n$</td>
<td>20</td>
<td>18</td>
<td>21</td>
<td>20</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>$r_1$</td>
<td>47.684</td>
<td>46.625</td>
<td>49.105</td>
<td>49.083</td>
<td>46.713</td>
<td>46.531</td>
</tr>
<tr>
<td>$\delta_2$</td>
<td>2.3193</td>
<td>2.5279</td>
<td>2.5110</td>
<td>2.1510</td>
<td>2.1497</td>
<td>2.5179</td>
</tr>
<tr>
<td>$\delta_{10}$</td>
<td>2.5703</td>
<td>3.0248</td>
<td>2.7885</td>
<td>2.5313</td>
<td>2.3626</td>
<td>2.8516</td>
</tr>
</tbody>
</table>

Table 5: Effect of test sensitivity on the expected number of examinations associated with selected policies.

<table>
<thead>
<tr>
<th></th>
<th>40 + annual</th>
<th>40 + biannual</th>
<th>50 + annual</th>
<th>50 + biannual</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta = 1$</td>
<td>36.580</td>
<td>18.539</td>
<td>26.909</td>
<td>13.699</td>
</tr>
<tr>
<td>$\beta = .8$</td>
<td>36.582</td>
<td>18.541</td>
<td>26.911</td>
<td>13.701</td>
</tr>
</tbody>
</table>

Table 6: Effect of test sensitivity on the expected loss associated with selected policies.

<table>
<thead>
<tr>
<th></th>
<th>40 + annual</th>
<th>40 + biannual</th>
<th>50 + annual</th>
<th>50 + biannual</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta = 1$</td>
<td>0.228</td>
<td>0.236</td>
<td>0.252</td>
<td>0.255</td>
</tr>
<tr>
<td>$\beta = .8$</td>
<td>0.234</td>
<td>0.259</td>
<td>0.256</td>
<td>0.274</td>
</tr>
</tbody>
</table>