Mathematical Modeling of Dynamic Breast Cancer Screening Policies

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Breast Cancer Statistics and Motivation

General Breast Cancer Facts

- Risk
  - 1 in 3
    - female cancer diagnoses is breast cancer (excluding skin)
  - 1 in 8
    - lifetime risk of developing breast cancer
  - 1 in 28
    - lifetime risk of dying from breast cancer
- Survival
  - lifetime survival rate
    - localized, 80%
    - regional, 55%
    - distant metastatic, 20%

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General Breast Cancer Facts: Screening

- The earlier breast cancer is detected and followed by appropriate treatment, the greater the chance of survival
- Mammography is the “single most effective method of early detection”
  - 80% sensitivity
  - 95% specificity
- Current screening policy recommendation (static)
  - annual mammograms (and CBE) starting at age 40
    - adherence: 30% of women over 50 do not have a yearly mammogram

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Age Effects

- Incidence
  - increases with age
- Aggression
  - decreases with age
- Survival
  - increases with age
    - due to more responsive tumors
- Mammogram efficacy
  - increases with age
    - due to lower tissue density

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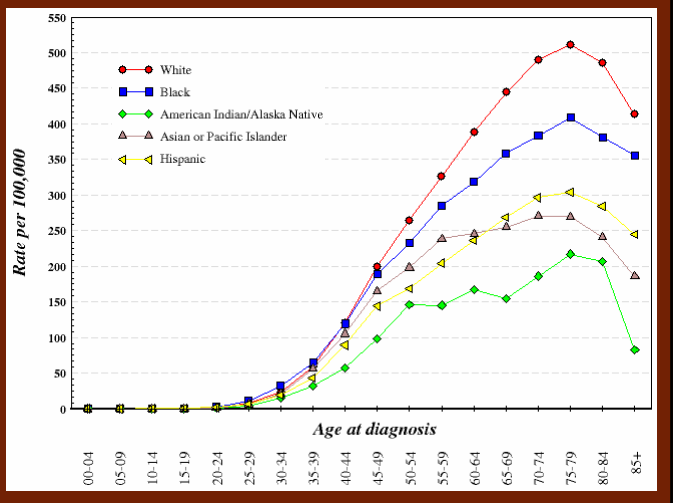
Age Effects: Incidence

- By age 25
  - 1 in 19,608
- By age 35
  - 1 in 622
- By age 45
  - 1 in 93
- By age 55
  - 1 in 33
- By age 65
  - 1 in 17
- By age 75
  - 1 in 11
- By age 85
  - 1 in 8



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Age Effects: Aggression

- Mean sojourn time of the detectable preclinical phase
  - 40-49: 2.4 years
  - 50-59: 3.7 years
  - 60-69: 4.2 years
  - 70-79: 4 years
- Median doubling time
  - 40-49: 80 days
  - 50-70: 157 days
  - over 70: 188 days

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Age Effects: Survival

- Lifetime survival by stage at detection
  - under 60
    - localized 79%
    - regional 51%
    - distant 19%
  - 60-69
    - localized 82%
    - regional 56%
    - distant 21%
  - over 70
    - localized 86%
    - regional 66%
    - distant 30%

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Age Effects: Mammography Efficacy

- Sensitivity (true+)
  - under 40: 54%
  - 40-49: 77%
  - 50-64: 78%
  - older than 64: 81%
- Specificity (true-)
  - 40-49: 92%
  - 50-59: 93%
  - 60-69: 95%
  - 70-79: 96%

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Controversy

- "While annual screening likely is *more* beneficial for all women, the importance of annual screening clearly is greater in premenopausal women (<55) compared with postmenopausal women." ACS 2003
- "…data do not support different screening recommendations in women aged 40-49 years." Rosenberg et. al. 1998

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Research Question and Approach

Research Question

- Given these opposing dynamics…
  - over time
    - ⇧ incidence
    - ⇩ aggression
    - ⇧ survival
    - ⇧ efficacy
- …is there value in considering dynamic screening policies?
  - policies with screening intervals that change over time

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Approach

- Divide life into two intervals
  - premenopause (“young”), < 55
  - postmenopause (“old”), > 55
- Restrict attention to “two-phase” policies
  - one, fixed pre-menopausal interval
  - one, fixed post-menopausal interval
- Define “value” in terms of lifetime mortality risk
- Formulate a partially observed Markov chain model
- Analyze a broad set of policies and construct insightful tradeoff curves

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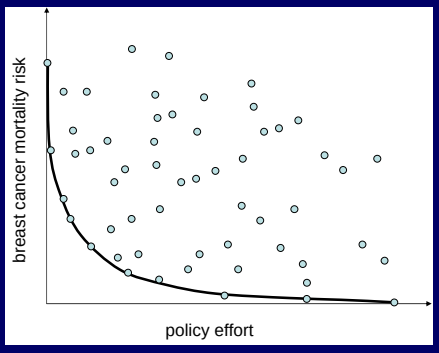
Tradeoff Curve Schematic



- Which policies will fall on the frontier?
- An individual can select a policy on the frontier based on her
  - risk preference
  - insurance
  - willingness to face false positive results
  - etc…

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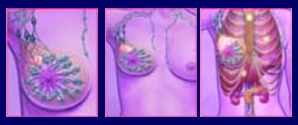
Natural History

- state 0
  - Cancer free
- state 1
  - Stage 0
    - cancer cells present
  - Stage I
    - 2 cm or less
- state 2
  - Stage II
    - 2-5 cm
  - Stage III
    - 5 cm+
  - Stage IV
    - metastic cancer
- Breast cancer death — state 3
- state 4: non-breast cancer death



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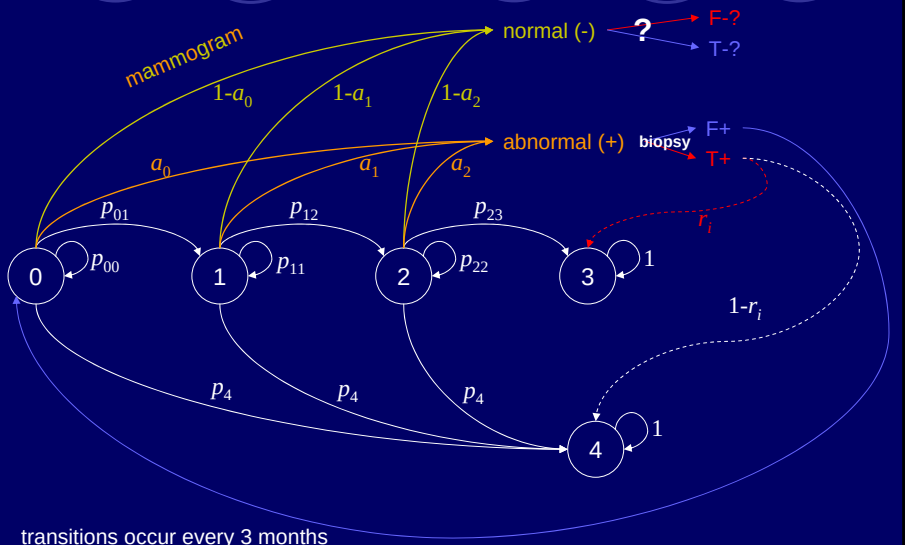
Markov Chain Model (Pre-Menopause)



transitions occur every 3 months

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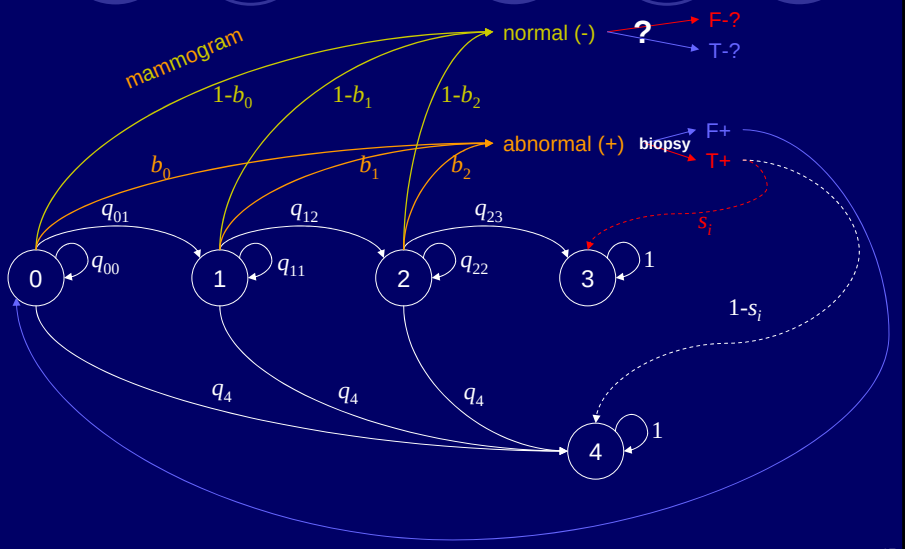
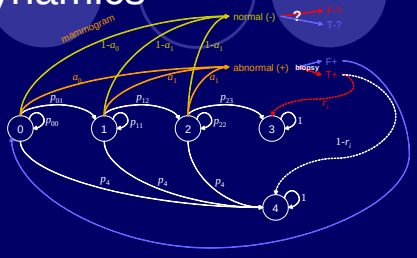
Markov Chain Model (Post-Menopause)



Pre- Post-Menopause Dynamics

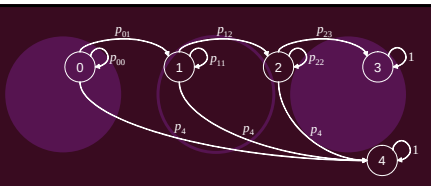
- After menopause
  - ⇧ incidence
  - ⇩ aggression
  - ⇧ efficacy
  - ⇧ survival
  - ⇧ comorbidity



	incidence		aggression		efficacy		survival		comorbidity	
pre-meno pause	p_{01}	$p_{01} < q_{01}$	p_{12}	$p_{12} > q_{12}$ $(p_{23} = q_{23})$	a_0 a_1 a_2	$a_0 > b_0$ $a_1 < b_1$ $a_2 < b_2$	r_1 r_2	$r_1 > s_1$ $r_2 > s_2$	p_4	$p_4 < q_4$
post-meno pause	q_{01}		q_{12}		b_0 b_1 b_2		s_1 s_2		q_4	

Policy Evaluation Procedure

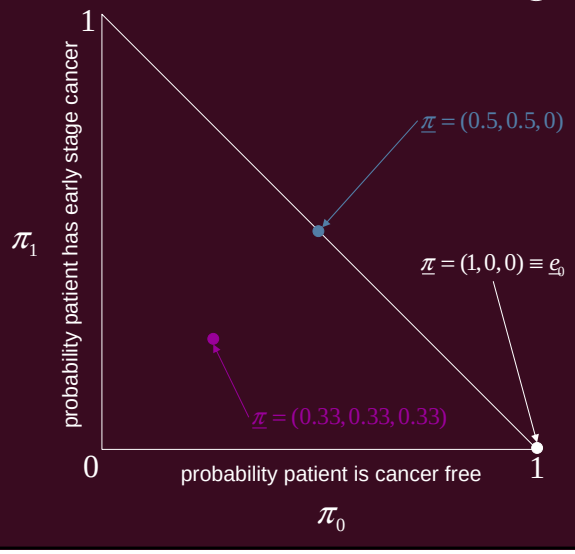
State Space



- Set of possible states

  $\underline{\pi} = (\pi_0, \pi_1, \pi_2)$

- $\pi_2 = 1 - \pi_0 - \pi_1$



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Pre-Menopause Sample Path

- If the current state is…… $\underline{\pi} = (\pi_0, \pi_1, \pi_2)$
- and we don't screen this transition and don't die, then updated state is… $\underline{\pi}'(\underline{\pi})$

$$\pi_i'(\underline{\pi}) = \frac{(\underline{\pi}P)_i}{(1-\pi_2 p_{23} - (\pi_0 + \pi_1 + \pi_2)(p_4))}$$

- and we do screen now and get
  - normal (-)…… $\underline{\pi}''(\underline{\pi})$

$$\pi_i''(\underline{\pi}) = \frac{\pi_i(1-a_i)}{(\pi_0(1-a_0) + \pi_1(1-a_1) + \pi_2(1-a_2))}$$

  - abnormal (+) and
    - false (F+)…… $\underline{e}_0 \equiv (1,0,0)$
    - true (T+)…… process ends

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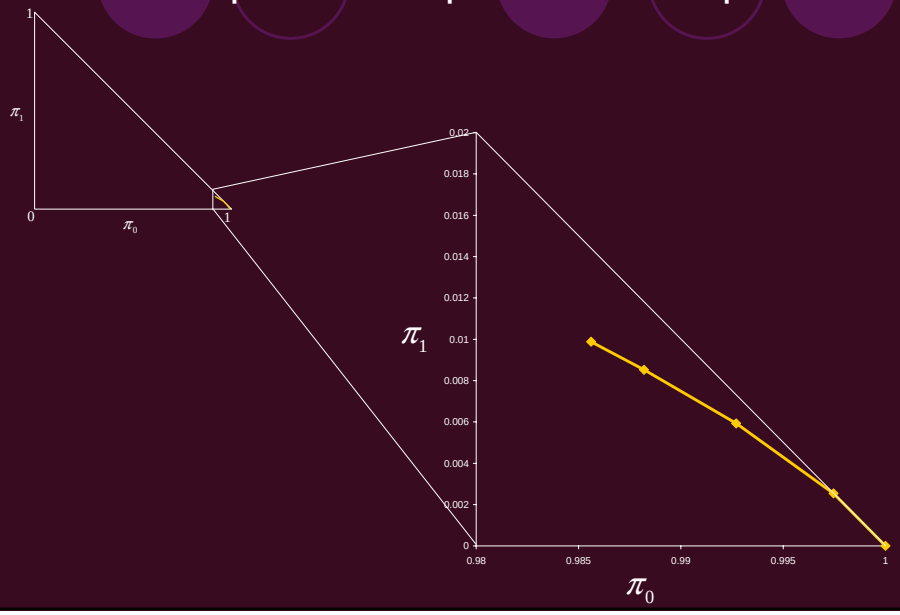
Pre-Menopause Sample Path Example



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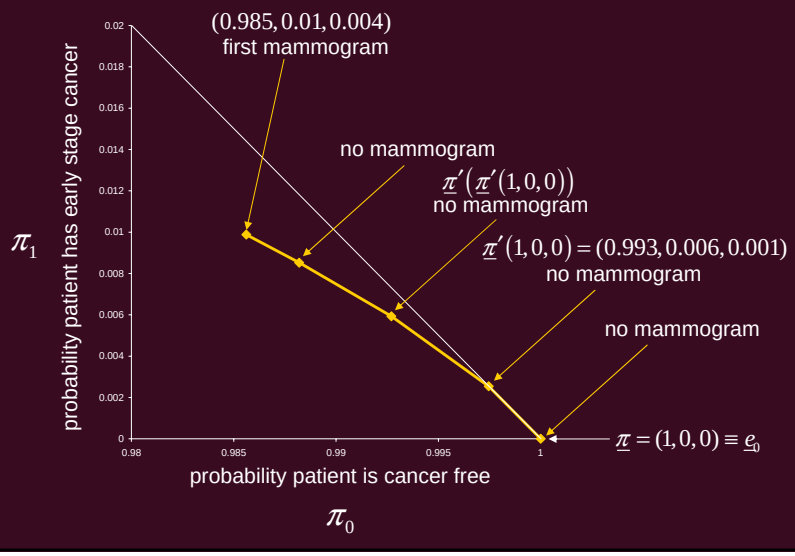
Pre-Menopause Sample Path Example



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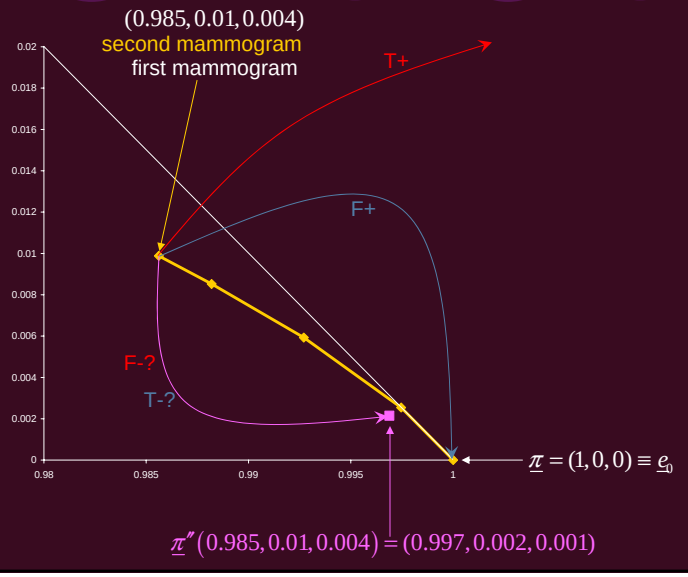
Pre-Menopause Sample Path Example



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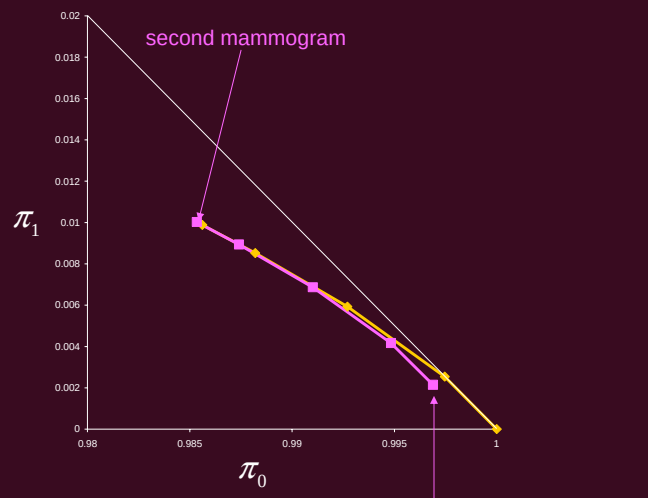
Pre-Menopause Sample Path Example



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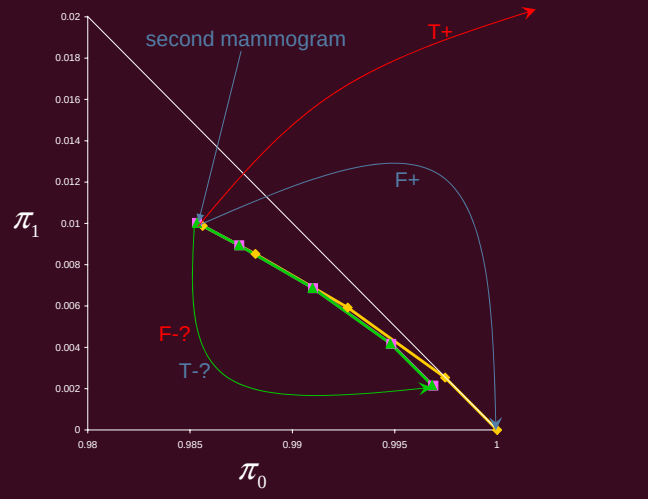
Pre-Menopause Sample Path Example



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Pre-Model

- $W^n_{pre}(\underline{\pi})$
  - probability that a patient will eventually die from breast cancer if
    - she's currently alive with occupancy distribution $\underline{\pi}$
    - her current age is 30+3*n*/12 years < 55 years

$$W^n_{pre}(\underline{\pi}) = \begin{cases} DN^n_{pre}(\underline{\pi}), & \text{if } n\text{th pre epoch is a do nothing epoch} \\ M^n_{pre}(\underline{\pi}), & \text{if } n\text{th pre epoch is a mammogram epoch} \end{cases}$$

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Post-Model

- $W^n_{post}(\underline{\pi})$
  - probability that a patient will eventually die from breast cancer if
    - she's currently alive with occupancy distribution $\underline{\pi}$
    - her current age is 55+3*n*/12 years

$$W^n_{post}(\underline{\pi}) = \begin{cases} DN^n_{post}(\underline{\pi}), & \text{if } n\text{th post epoch is a do nothing epoch} \\ M^n_{post}(\underline{\pi}), & \text{if } n\text{th post epoch is a mammogram epoch} \end{cases}$$

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Pre-Model

$$W^n_{pre}(\underline{\pi}) = \begin{cases} DN^n_{pre}(\underline{\pi}), & \text{if } n\text{th pre epoch is a do nothing epoch} \\ M^n_{pre}(\underline{\pi}), & \text{if } n\text{th pre epoch is a mammogram epoch} \end{cases}$$

BC death in next 3 months

other death in next 3 months

$$DN^n_{pre}(\underline{\pi}) = \overbrace{\pi_2 p_{23}(1)}^{\text{BC death in next 3 months}} + \overbrace{(\pi_0+\pi_1+\pi_2)(p_4)(0)}^{\text{other death in next 3 months}}$$
$$+ (1-\pi_2 p_{23} - (\pi_0+\pi_1+\pi_2)(p_4)) W^{n+1}_{pre}\left(\underline{\pi}'(\underline{\pi})\right)$$

} live through next 3 months

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Pre-Model

$$W^n_{pre}(\underline{\pi}) = \begin{cases} DN^n_{pre}(\underline{\pi}), & \text{if } n\text{th pre epoch is a do nothing epoch} \\ M^n_{pre}(\underline{\pi}), & \text{if } n\text{th pre epoch is a mammogram epoch} \end{cases}$$

BC death in next 3 months

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$$+ (1-\pi_2 p_{23} - (\pi_0+\pi_1+\pi_2)(p_4)) W^{n+1}_{pre}\left(\underline{\pi}'(\underline{\pi})\right)$$

} live through next 3 months

$$W^0_{post}\left(\underline{\pi}'(\pi)\right)$$

if n is the last pre-epoch

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Pre-Model

$$W^n_{pre}(\underline{\pi}) = \begin{cases} DN^n_{pre}(\underline{\pi}), & \text{if } n\text{th pre epoch is a do nothing epoch} \\ M^n_{pre}(\underline{\pi}), & \text{if } n\text{th pre epoch is a mammogram epoch} \end{cases}$$

$$M^n_{pre}(\underline{\pi}) = \overbrace{\pi_0 a_0 DN^n_{pre}(\underline{e}_0)}^{\text{false+}} + \overbrace{\pi_1 a_1 (r_1(1) + (1-r_1)(0)) + \pi_2 a_2 (r_2(1) + (1-r_2)(0))}^{\text{true+}}$$
$$+ (\pi_0(1-a_0) + \pi_1(1-a_1) + \pi_2(1-a_2)) DN^n_{pre}(\underline{\pi}''(\underline{\pi})) \quad \Big\} \text{ negative}$$

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Optimization vs. Evaluation Approach

- Normally, operations researchers would
  - assign a “cost” to performing a mammogram and
  - solve the resulting dynamic program for the
  - optimal screening policy
- We take a policy evaluation approach instead which allows us to
  - compare the relative value of different policies, which may have different utilities for different patients
  - simplify the state space

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Preliminary Results

Parameter Estimates

pre	post
$P = \begin{pmatrix} 0.99939 & 0.00021 & 0 & 0 & 0.0004 \\ 0 & 0.4996 & 0.5 & 0 & 0.0004 \\ 0 & 0 & 0.9196 & 0.08 & 0.0004 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$	$Q = \begin{pmatrix} 0.980566 & 0.000466 & 0 & 0 & 0.018968 \\ 0 & 0.731032 & 0.25 & 0 & 0.018968 \\ 0 & 0 & 0.901032 & 0.08 & 0.018968 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$
$a = [0.078 \quad 0.54 \quad 0.58]$	$b = [0.044 \quad 0.81 \quad 0.98]$
$r = [0.53 \quad 0.76]$	$s = [0.53 \quad 0.76]$

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Additional Parameters to Specify

- Non-policy parameters
  - problem start age
    - age at which the Markov chain applies
    - 30 years
  - menopause onset age
    - 55 years
  - problem end age
    - age after which breast cancer mortality is zero
    - 100 years

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Additional Parameters to Specify

- Policy parameters
  - screening start age
  - pre-screening interval (if applicable)
  - post-screening interval
  - screening stop age
    - 100 years

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No Screening

- Under no screening, at age 100
  - 3.62% dead from breast cancer
  - 93.63% dead from other causes
  - 2.75% still living
- Benchmark lifetime mortality risk
  - 1 in 28 = 3.57%

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Screening Starting at Age 40

pre interval	post interval	lifetime mortality risk	max # mammograms
40, 6mo	1yr	3.04% (1in 33)	76
40, 6mo	2yr	3.16% (1in 32)	53
40, 6mo	3yr	3.21% (1 in 31)	46
40, 1yr	1yr	3.14% (1in 32)	61
40, 1yr	2yr	3.26% (1in 31)	38
40, 1yr	3yr	3.31% (1 in 30)	31

pre interval	post interval	lifetime mortality risk	max # mammograms
40, 2yr	1yr	3.26% (1in 31)	53
40, 2yr	2yr	3.37% (1 in 30)	31
40, 2yr	3yr	3.40% (1 in 29)	23
40, 3yr	1yr	3.27% (1 in 31)	51
40, 3yr	2yr	3.43% (1 in 29)	28
40, 3yr	3yr	3.44% (1 in 29)	21

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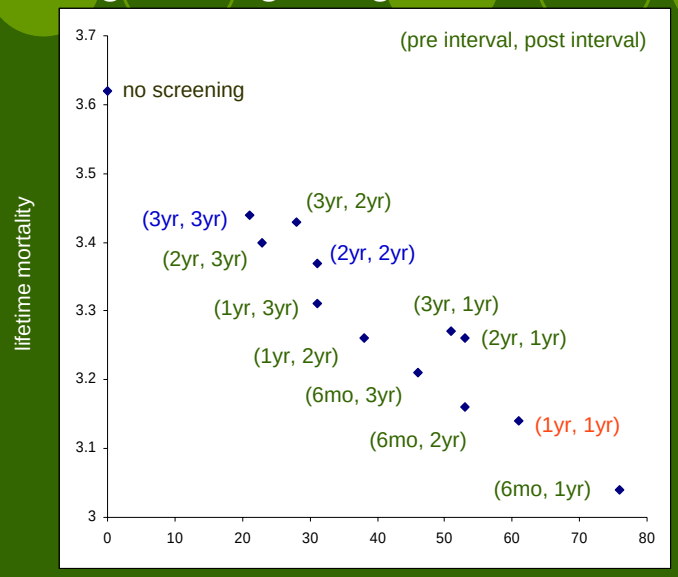
Screening Starting at Age 40



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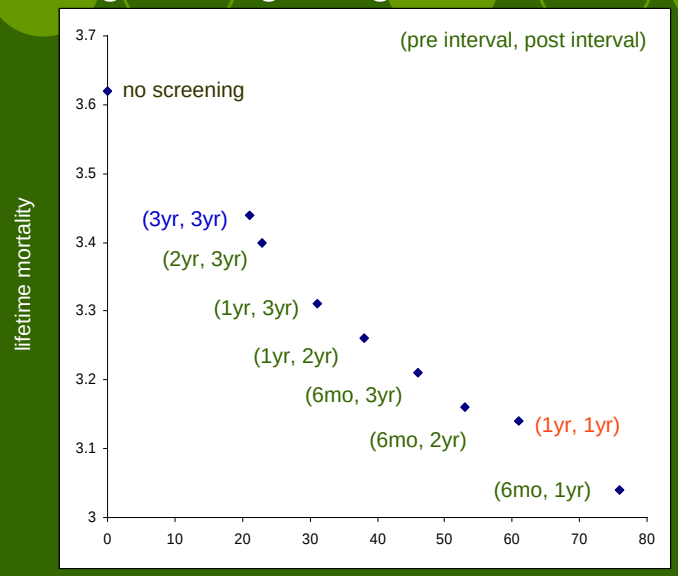
Screening Starting at Age 40



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Screening Starting at Age 40

- A patient can achieve a mortality risk “in between” that of two routine policies by using a two-phase policy
- The current recommendation, (1yr, 1yr), is on the frontier of screening policies that start at 40
- If annually after 40 sounds like “too much” effort, then
  - it’s better to screen
    - more often pre-menopause
    - and less often post-menopause
  - than vice versa
- The routine policy (2yr, 2yr) is dominated by two-phase policy (1yr, 3yr)

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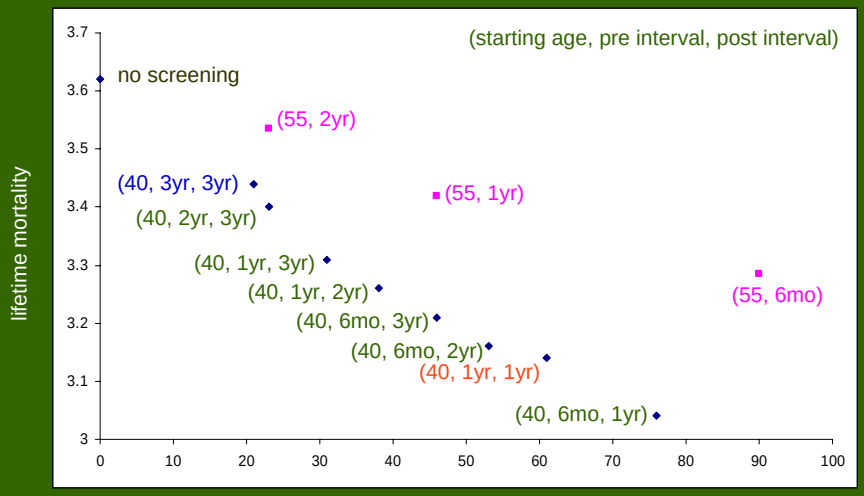
Screening Starting at Menopause



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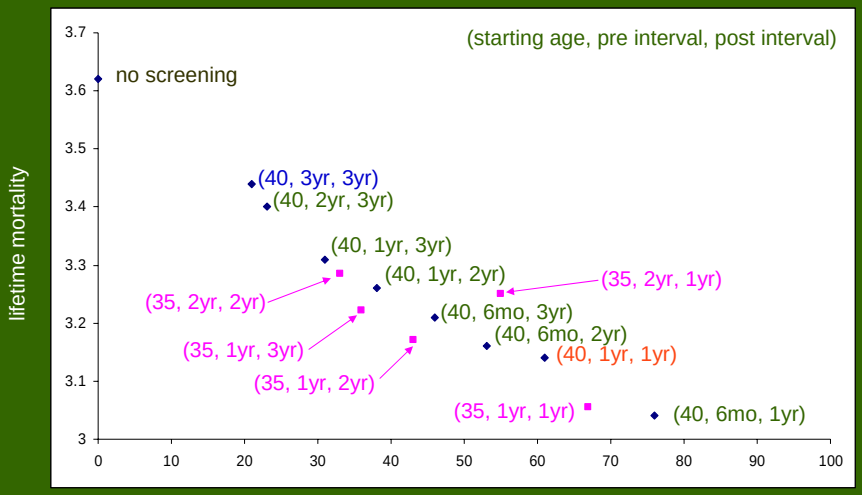
Screening Starting at Age 35



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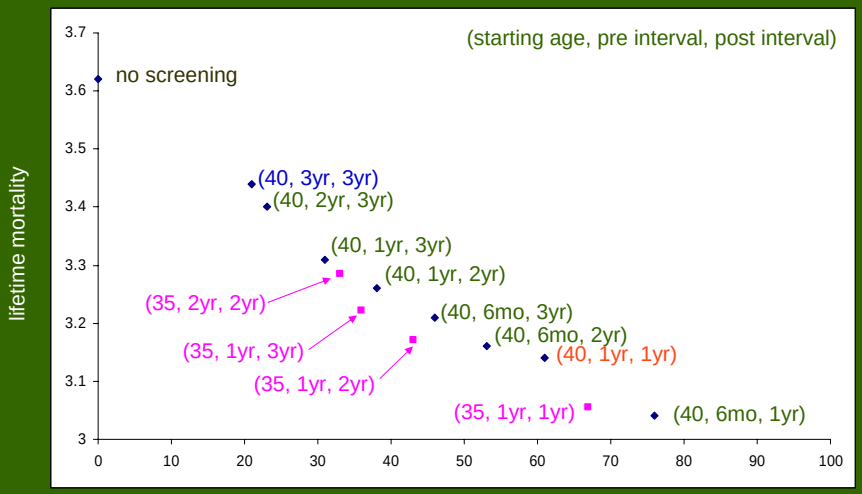
Screening Starting at Age 35



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Screening Starting at Age 35

- Again, if annually is “too often,”
  - it’s better to “front load” your screening in terms of overall policy effort
- However,
  - if a patient prefers to delay screening until after age 40
    - she can achieve the same risk as if she started at age 35, but
    - with a greater number of mammograms pre-menopause

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