# Mathematical Modeling of Dynamic Breast Cancer Screening Policies

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Supported by NSF grants DMI-423090 and DMI-0423410

# 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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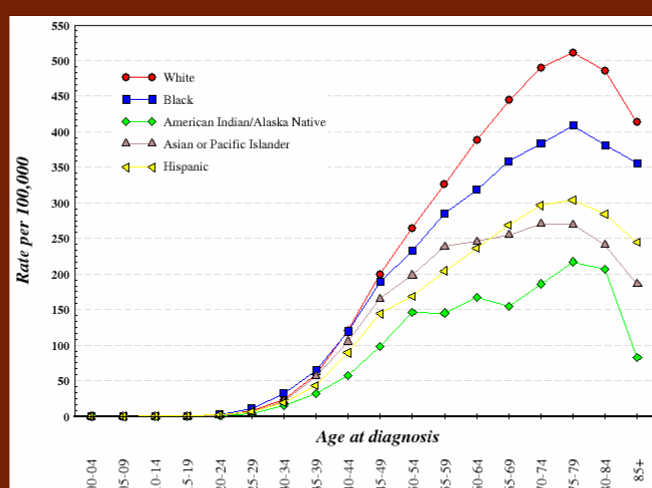
# Age Effects: Incidence

- 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

## 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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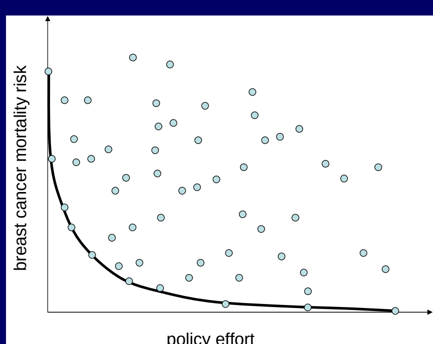
## Tradeoff Curve Schematic




- 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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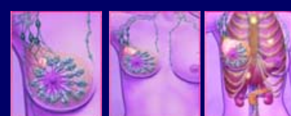
# Natural History

- state 0
  Cancer free
- Stage 0 — state 1
  - cancer cells present
- Stage I
  - 2 cm or less

- Stage II
  - 2-5 cm
- Stage III — state 2
  - 5 cm+
- Stage IV
  - metastic cancer

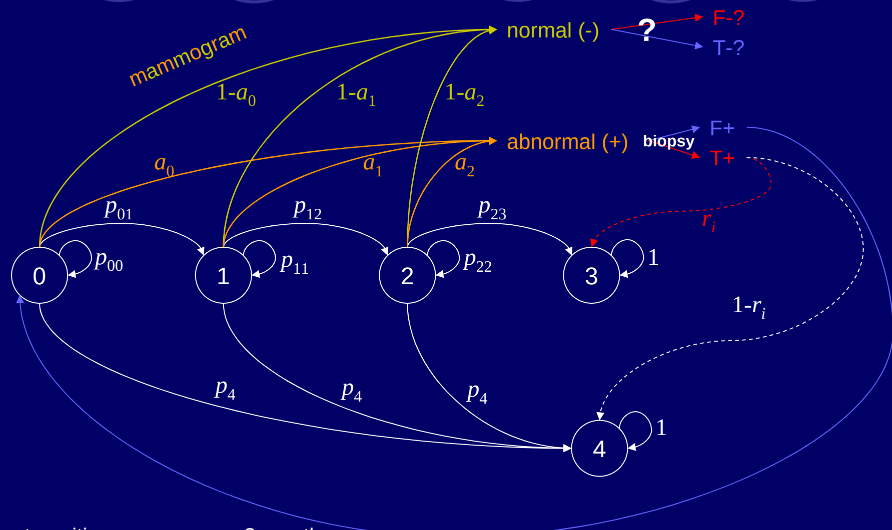


- Breast cancer death — state 3

state 4: non-breast cancer death

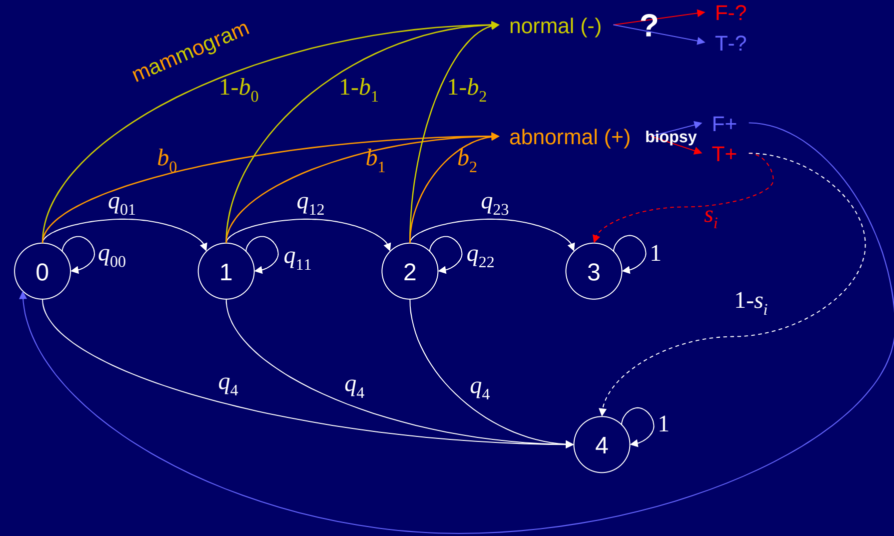


# Markov Chain Model (Pre-Menopause)




transitions occur every 3 months

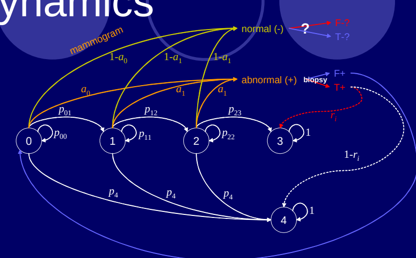
# Markov Chain Model (Post-Menopause)






# Pre- Post-Menopause Dynamics

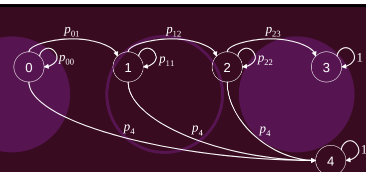
- After menopause
  - ⇧ incidence
  - ⇩ aggression
  - ⇧ efficacy
  - ⇧ survival
  - ⇧ comorbidity




| | 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

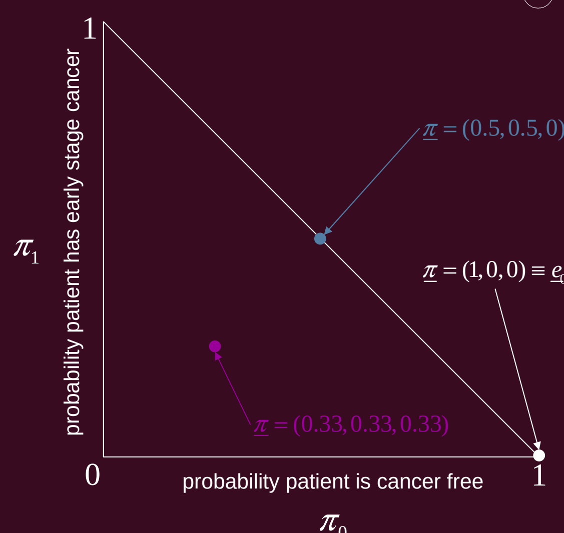
## State Space




- 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… $\underline{\pi}'(\underline{\pi})$

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

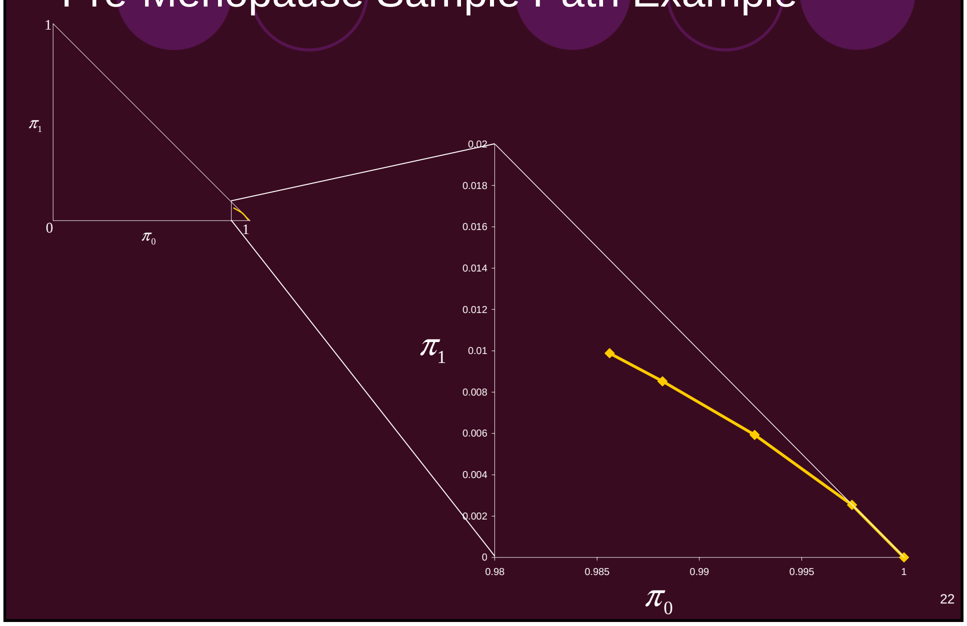
- and we do screen now and get
  - normal (-)……………………………… $\underline{\pi}''(\underline{\pi})$

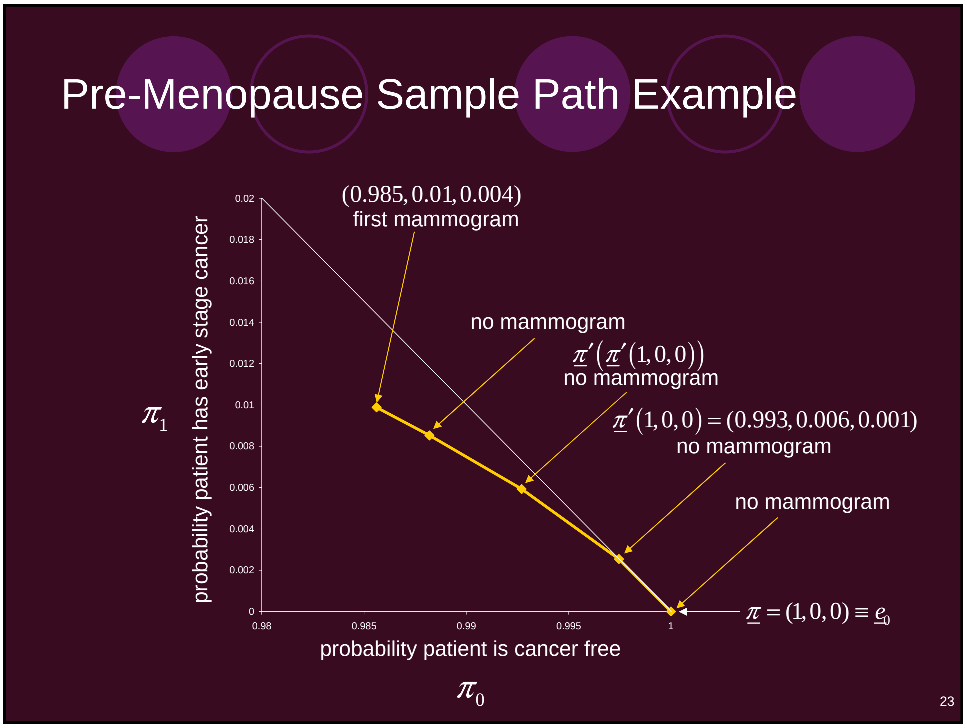
$$\pi_i''(\underline{\pi}) = \frac{\pi_i(1-a_i)}{(\pi_0(1-a_0) + \pi_1(1-a_1) + \pi_2(1-a_2)}$$

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



## Pre-Menopause Sample Path Example




Pre-Menopause Sample Path Example
(0.985, 0.01, 0.004)
first mammogram
no mammogram
π′(π′(1,0,0))
no mammogram
π′(1,0,0) = (0.993, 0.006, 0.001)
no mammogram
no mammogram
π = (1,0,0) ≡ e0
π1
probability patient has early stage cancer
probability patient is cancer free
π0
0
0.002
0.004
0.006
0.008
0.01
0.012
0.014
0.016
0.018
0.02
0.98
0.985
0.99
0.995
1
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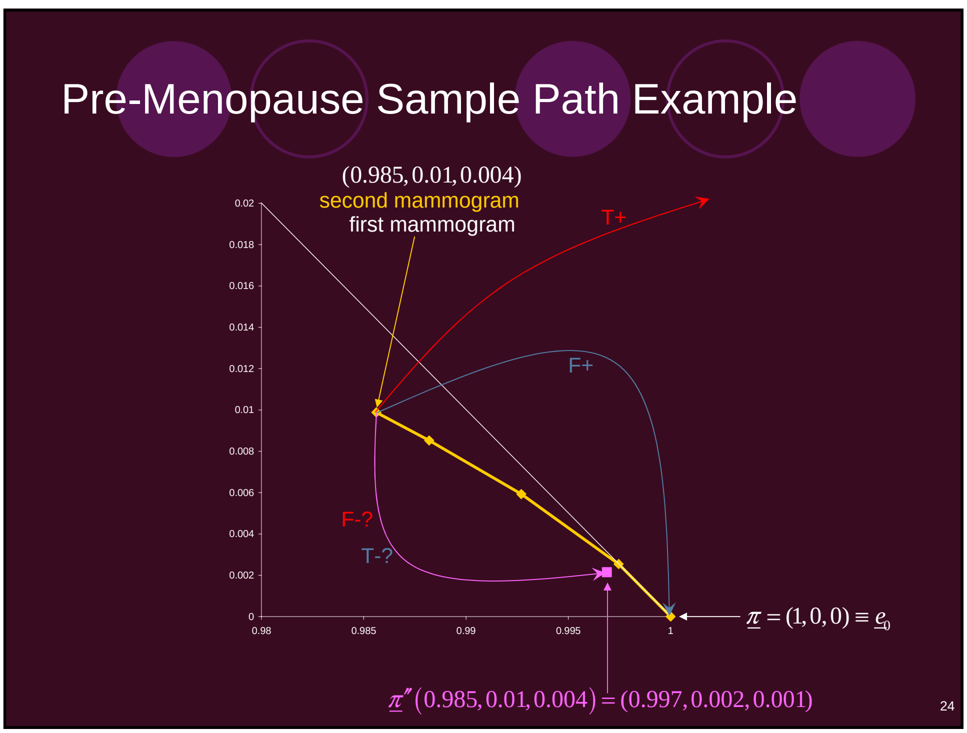
Pre-Menopause Sample Path Example
(0.985, 0.01, 0.004)
second mammogram
first mammogram
T+
F+
F-?
T-?
π = (1,0,0) ≡ e0
π″(0.985, 0.01, 0.004) = (0.997, 0.002, 0.001)
0
0.002
0.004
0.006
0.008
0.01
0.012
0.014
0.016
0.018
0.02
0.98
0.985
0.99
0.995
1
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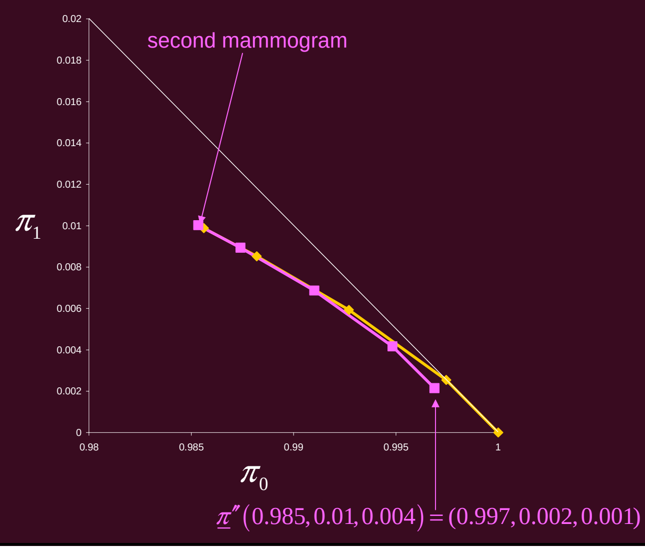
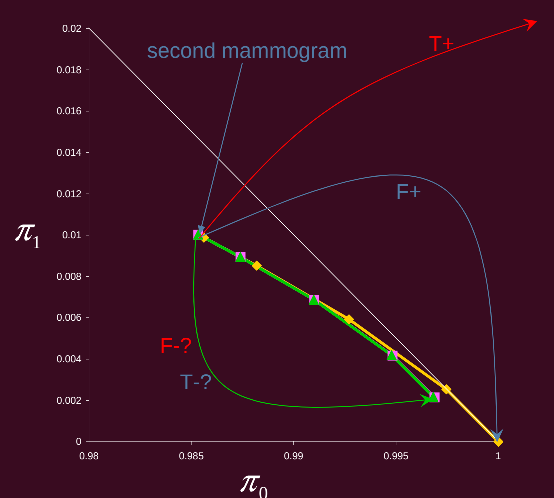
# Pre-Menopause Sample Path Example






# Pre-Menopause Sample Path Example



## Pre-Model

- $W_{pre}^{n}(\underline{\pi})$
  - 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

$$W_{pre}^{n}(\underline{\pi}) = \begin{cases} DN_{pre}^{n}(\underline{\pi}), & \text{if } n\text{th pre epoch is a do nothing epoch} \\ M_{pre}^{n}(\underline{\pi}), & \text{if } n\text{th pre epoch is a mammogram epoch} \end{cases}$$

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## Post-Model

- $W_{post}^{n}(\underline{\pi})$
  - 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

$$W_{post}^{n}(\underline{\pi}) = \begin{cases} DN_{post}^{n}(\underline{\pi}), & \text{if } n\text{th post epoch is a do nothing epoch} \\ M_{post}^{n}(\underline{\pi}), & \text{if } n\text{th post epoch is a mammogram epoch} \end{cases}$$

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# Pre-Model

$$W_{pre}^{n}(\underline{\pi}) = \begin{cases} DN_{pre}^{n}(\underline{\pi}), & \text{if } n\text{th pre epoch is a do nothing epoch} \\ M_{pre}^{n}(\underline{\pi}), & \text{if } n\text{th pre epoch is a mammogram epoch} \end{cases}$$

$$DN_{pre}^{n}(\underline{\pi}) = \overbrace{\pi_2 p_{23}}^{\text{BC death in next 3 months}}(1) + \overbrace{(\pi_0+\pi_1+\pi_2)(p_4)}^{\text{other death in next 3 months}}(0)$$

$$\underbrace{+\left(1-\pi_2 p_{23}-(\pi_0+\pi_1+\pi_2)(p_4)\right)W_{pre}^{n+1}\left(\underline{\pi}'(\underline{\pi})\right)}_{\text{live through next 3 months}}$$



# Pre-Model

$$W_{pre}^{n}(\underline{\pi}) = \begin{cases} DN_{pre}^{n}(\underline{\pi}), & \text{if } n\text{th pre epoch is a do nothing epoch} \\ M_{pre}^{n}(\underline{\pi}), & \text{if } n\text{th pre epoch is a mammogram epoch} \end{cases}$$

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$$\underbrace{+\left(1-\pi_2 p_{23}-(\pi_0+\pi_1+\pi_2)(p_4)\right)W_{pre}^{n+1}\left(\underline{\pi}'(\underline{\pi})\right)}_{\text{live through next 3 months}}$$

$$W_{post}^{0}\left(\underline{\pi}'(\pi)\right) \quad \text{if } n \text{ is the last pre-epoch}$$

## Pre-Model

$$W_{pre}^{n}\left(\underline{\pi}\right)=\begin{cases} DN_{pre}^{n}\left(\underline{\pi}\right), & \text{if } n\text{th pre epoch is a do nothing epoch} \\ M_{pre}^{n}\left(\underline{\pi}\right), & \text{if } n\text{th pre epoch is a mammogram epoch} \end{cases}$$

$$\begin{aligned} M_{pre}^{n}\left(\underline{\pi}\right) = {} & \overbrace{\pi_0 a_0 DN_{pre}^{n}\left(\underline{e}_0\right)}^{\text{false+}} + \overbrace{\pi_1 a_1\left(r_1(1)+(1-r_1)(0)\right)+\pi_2 a_2\left(r_2(1)+(1-r_2)(0)\right)}^{\text{true+}} \\ & \left.+\left(\pi_0(1-a_0)+\pi_1(1-a_1)+\pi_2(1-a_2)\right)DN_{pre}^{n}\left(\underline{\pi}''\left(\underline{\pi}\right)\right) \qquad \right\}\text{negative} \end{aligned}$$



## 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

# 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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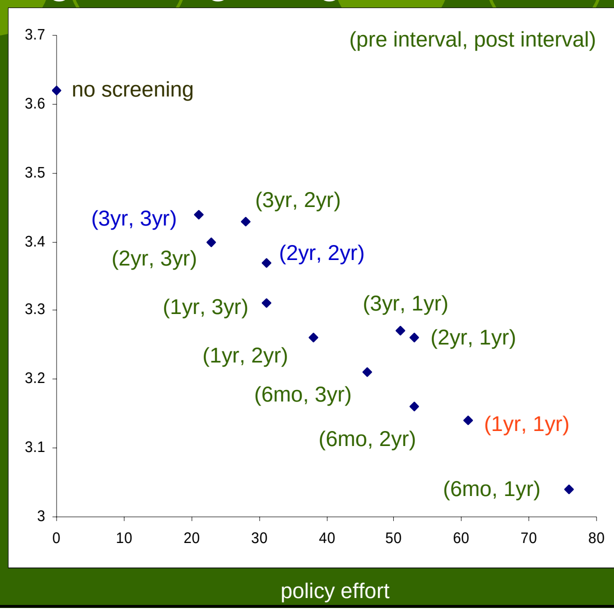
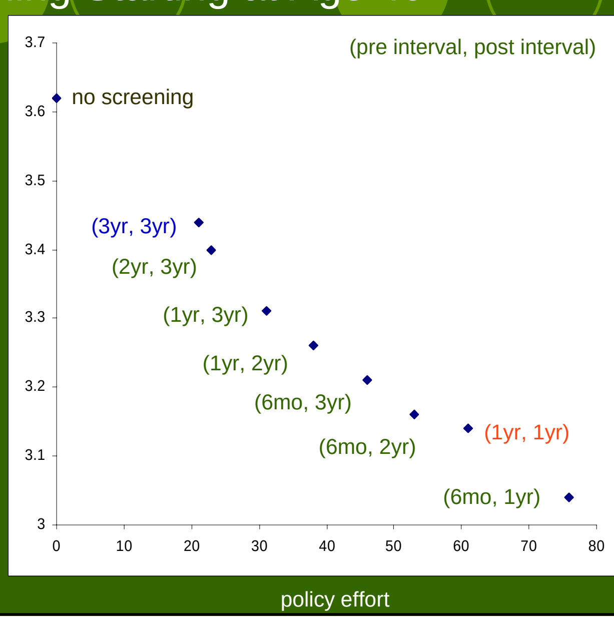
## Screening Starting at Age 40




## Screening Starting at Age 40



## 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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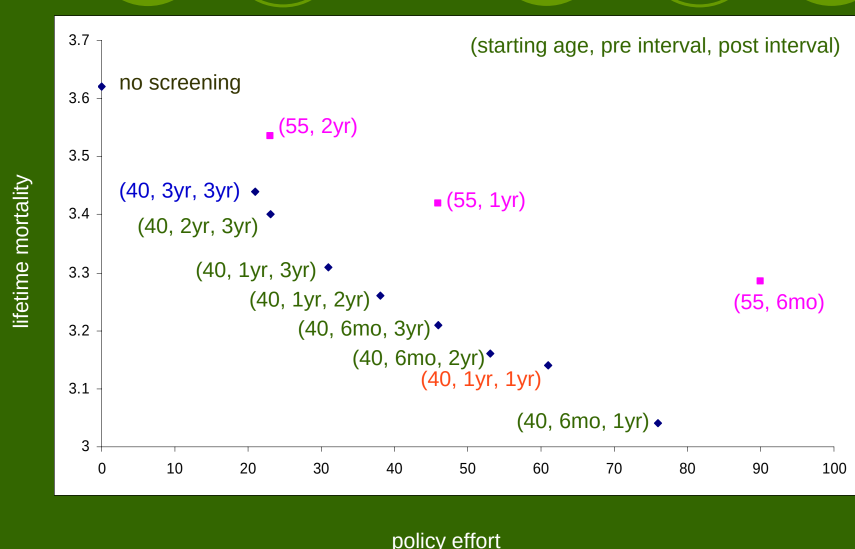
## Screening Starting at Menopause

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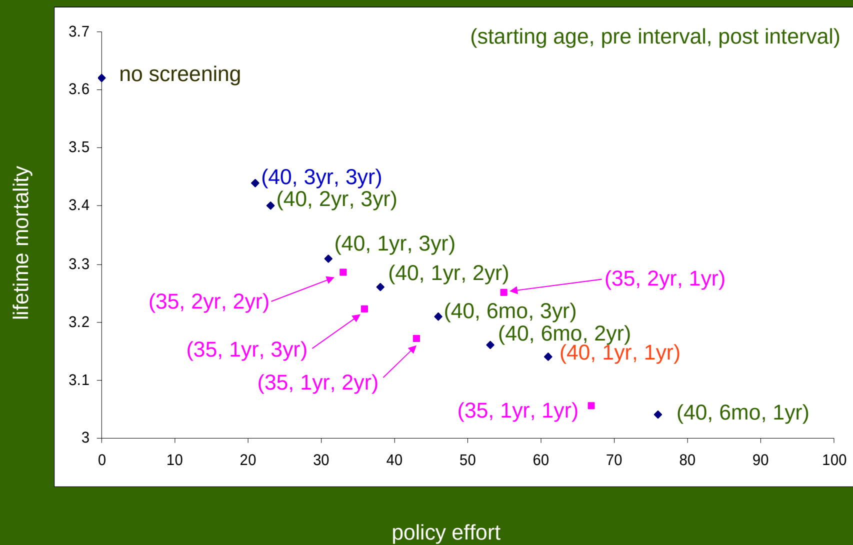
## Screening Starting at Age 35

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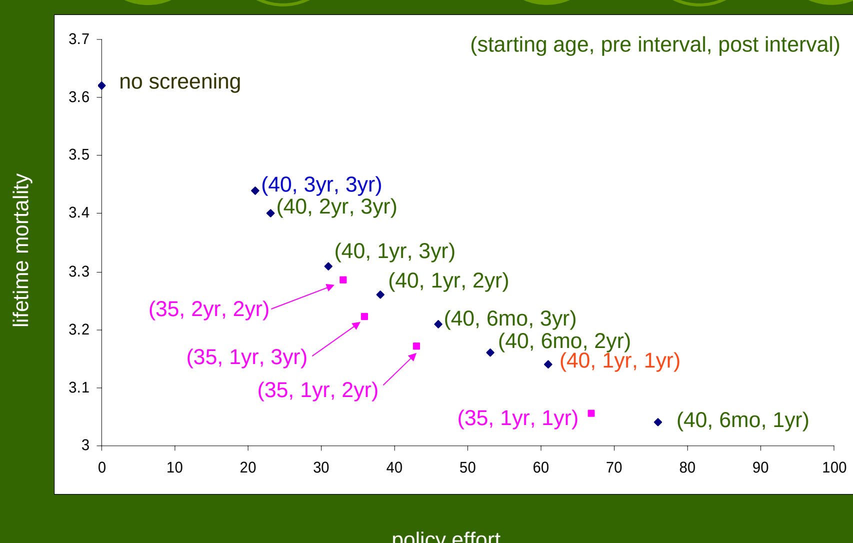
## Screening Starting at Age 35

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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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