

Collaborative Modeling for Cancer Screening

Sandra J. Lee

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Outline

- Stochastic Models for Early Detection of Cancer
- Collaborative Modeling: Cancer Intervention and Surveillance Modeling Network (CISNET), Breast Working Group (BWG)
- Breast Cancer Screening
- Risk-Based Screening
- Melanoma Screening
- Remarks

Introduction

Rationale for Screening

- Early Detection of Disease: Screening asymptomatic individuals for chronic disease is rapidly growing public health initiative.
- Goal: To diagnose disease in early stage using special screening exams.
- Motivation: To enhance treatment benefit and result in more cures and possibly lower mortality.

Early Detection of Cancer: Screening Test for Cancer

- Breast: Mammography (film, digital, digital tomosyntheses), Physical Exam, MRI
- Melanoma: Whole Body Examination
- Cervical Cancer: Pap test
- Colon: FOBT, Sigmoidoscopy, Colonoscopy
- Prostate: PSA, DRE
- Ovarian: CA125
- Lung: CXR, CT, PET-CT

Consideration of Screening Program

- Available screening test / treatment
- Screening Programs
 - Who should be screened (Targeted vs. Population)?
 - When to begin?
 - How often?
 - When to stop?
 - High-risk population?
- Randomized screening trials are prohibitive
- Role of models

Issues in Early Detection of Cancer

Breast Cancer

- Eight randomized screening trials 1960-1990's
- General agreement on beneficial effect of mammogram for women 50-65
- Controversial Issues:
 - Women in 40's
 - Screening intervals?
 - Stopping age?
 - Screening strategies for the high risk group?
 - Harms of screening – overdiagnosis?

Melanoma

- Screening modality
- Mortality benefit?

Collaborative Modeling



CISNET

- Cancer Intervention and Surveillance Modeling Network (<http://cisnet.cancer.gov>)
- National Cancer Institute (NCI) sponsored consortium of investigators
- Initiated in September 2000
- Breast, Prostate, Colorectal, Lung, Esophageal, Cervical Cancer
- Focus: To use modeling to improve our understanding of the impact of cancer control interventions (e.g., prevention, screening, treatment) on population trends in incidence and mortality

CINSNET Breast Working Group (BWG)

- Dana- Farber Cancer Institute (Model D) - Lee
- Erasmus University (Model E) - de Koning
- Georgetown University/Einstein Medical Center (Model GE) - Mandelblatt/Schechter
- MD Anderson Cancer Center (Model M)- Berry
- Stanford University (Model S) – Plevritis
- Wisconsin University (Model W) – Trentham-Dietz/Stout/Alagoz
- [Rochester University (Model R)- Yakovlev]

Natural History of Disease Progression and Case Finding Process

Dana-Farber Model (Model D)

Model Assumptions

- Progressive Disease (Invasive Breast Cancer, Melanoma)

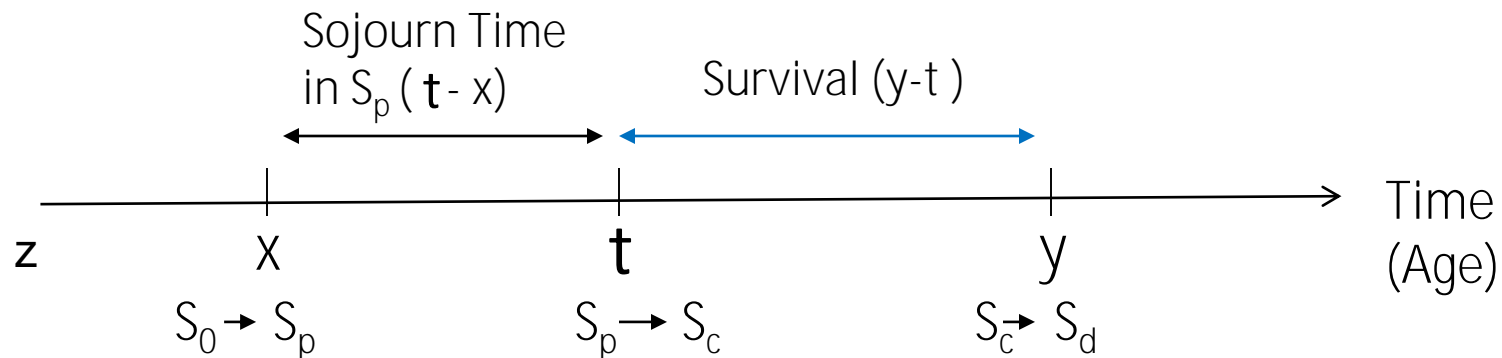
$$S_0 \longrightarrow S_p \longrightarrow S_c \longrightarrow S_d$$

- S_0 : Disease free state – disease free or undetectable stage
 - S_p : Pre-clinical state - asymptomatic with no signs/symptoms
 - S_c : Clinical state – when diagnosed by routine methods
 - S_d : Death state (death due to disease)
- Stage Shift – Screening test finds cases in an earlier stage (S_p)
 - Lee and Zelen (*JASA* 1998, *Annals of Oncology* 2003, *JNCI* 2006, *Biometrics* 2008)

(1) Dynamics of the Natural History: No Screening

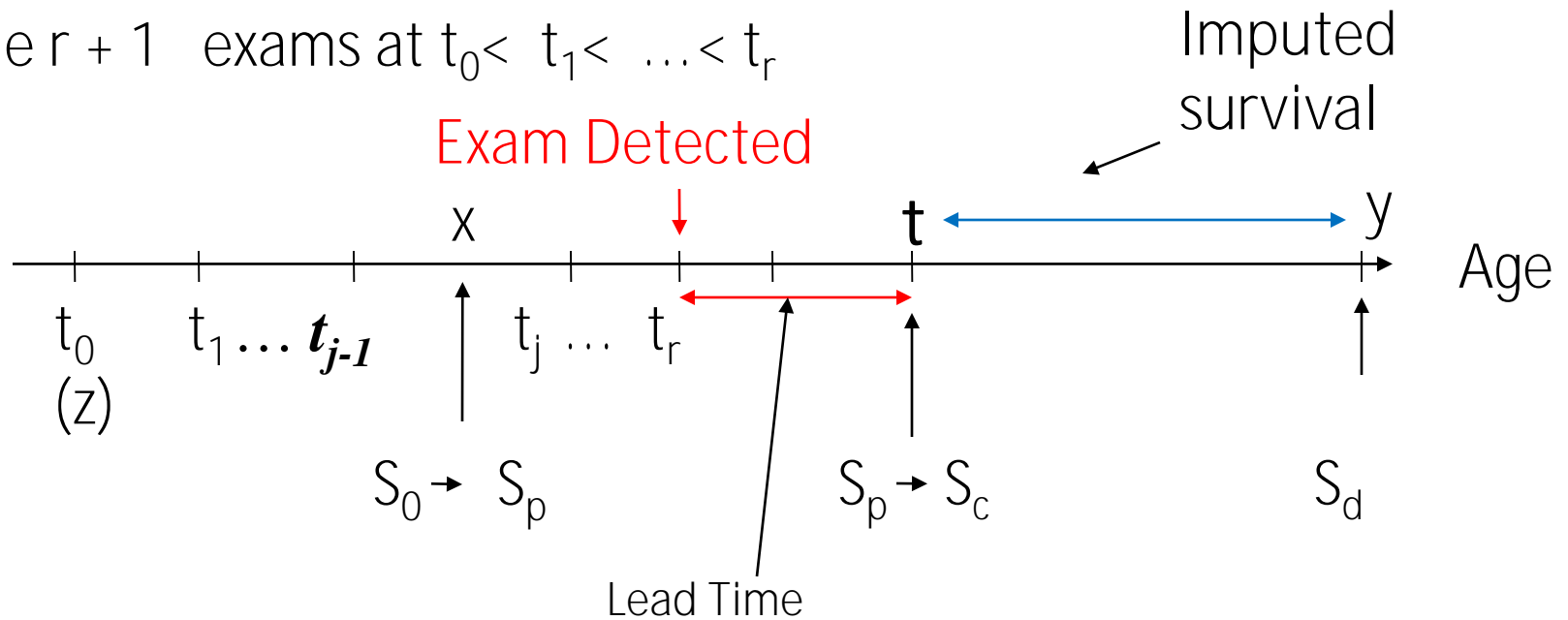
- S_0 : Disease free state – disease free or undetectable stage
- S_p : Pre-clinical state - asymptomatic with no signs/symptoms
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Progressive Disease Model



(2) Dynamics of Case Finding Process: Screen-Detected Case at t_r

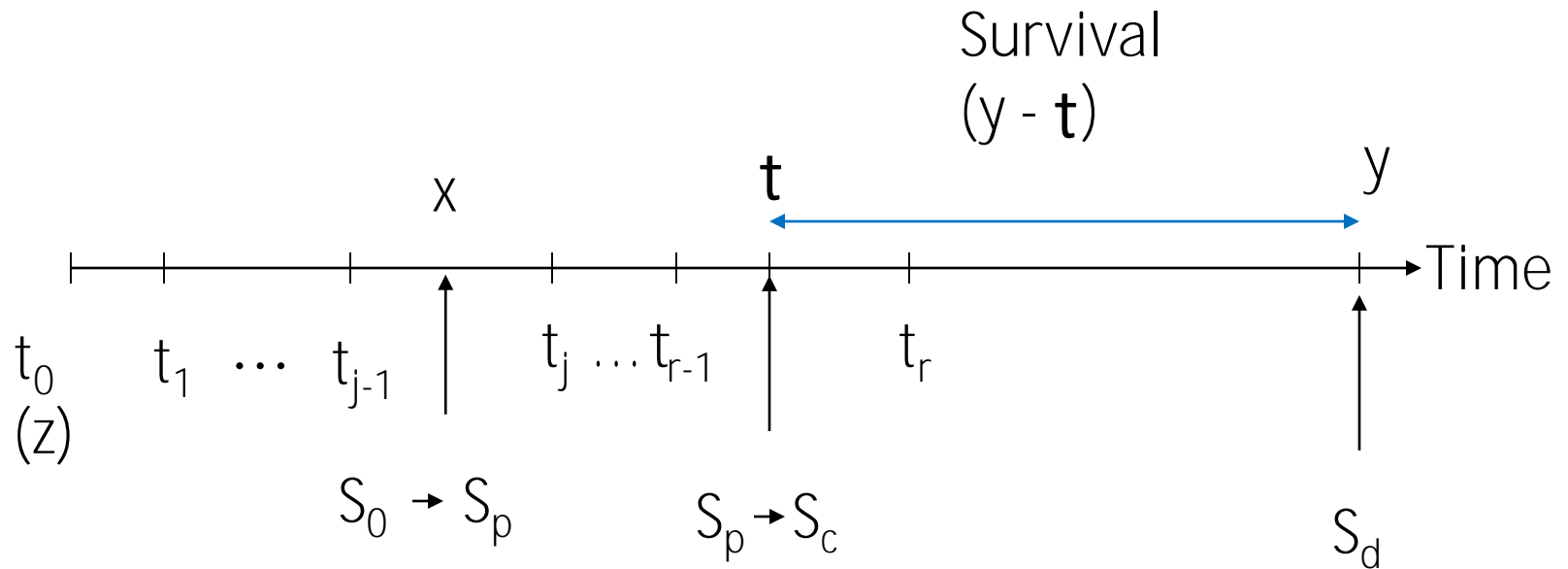
Assume $r + 1$ exams at $t_0 < t_1 < \dots < t_r$



- Ages t and x are not observed. $(t - t_r)$ is lead time.
- Observed survival time $(y - t_r)$
- Imputed survival time $(y - t)$

(3) Dynamics of Case Finding Process: Interval Cases

Case diagnosed between t_{r-1} and t_r



Exams at $t_0 < t_1 < \dots < t_{r-1}$

Mortality Modeling

- Probability of disease-specific death at age T for birth cohort v

$$d_v(T) = \int_T^{T+1} \left\{ \int_0^y S_v(\tau) I_v(\tau) g_v(y-w|\tau) d\tau \right\} dy.$$

- Probability of disease-specific death at age T for birth cohort v with screening history H

$$d_v(T|H) = \int_T^{T+1} \left\{ \int_0^y D_v(t|H) + I_v(t|H) dt \right\} dy$$

- Mortality Reduction (MR%)

$$MR\% = \frac{\sum_{T=A}^I \{d_v(T)S_v^*(T) - d_v(T|H)S_v^{**}(T)\}}{\sum_{T=A}^I d_v(T)S_v^*(T)} \times 100$$

Outcome Measures

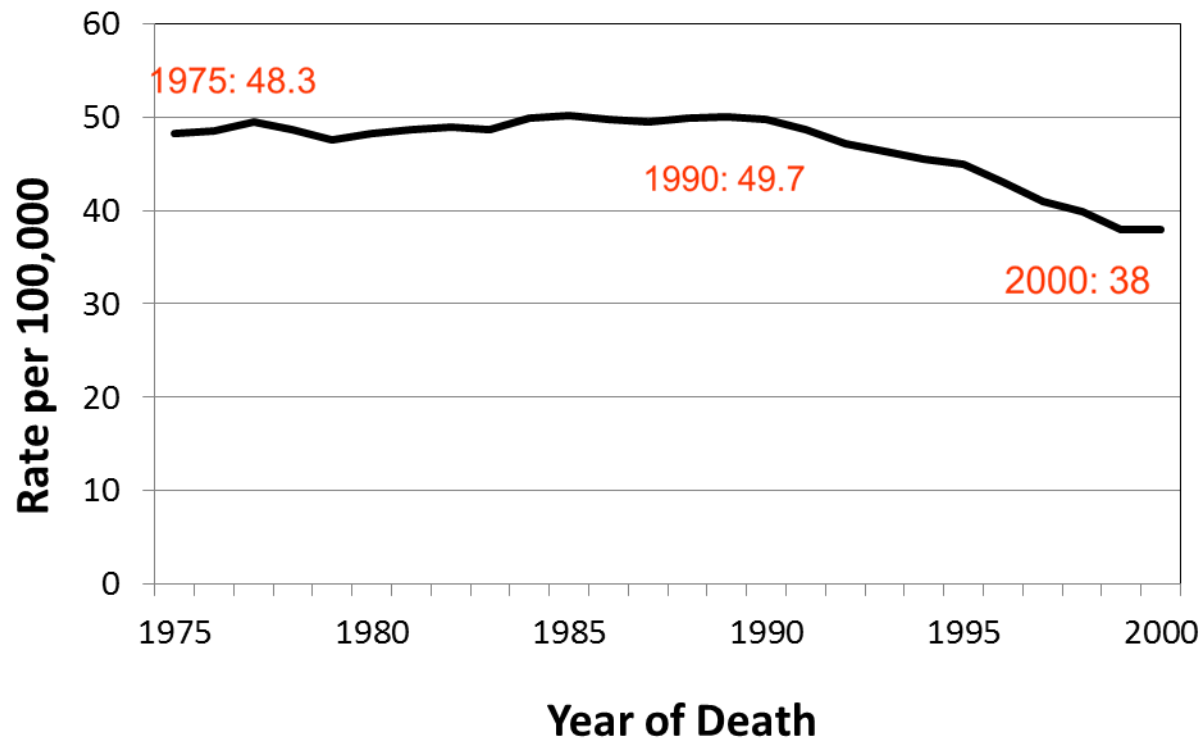
- Benefits
 - Mortality Reduction (MR%)
 - Life years gained
 - Deaths averted
- Harms
 - False positive screens
 - Overdiagnosis – screening exams finding cases who will never have clinical symptoms in their life time (i.e. lead time > residual survival time)
- Cost Effectiveness
 - Total cost of screening programs
 - Cost per life-year gained
 - Cost per quality adjusted life-year gained

Collaborative Modeling: CISNET Examples

Motivating Problem

Example 1: CISNET BWG Base Case I

Role of Screening and Adjuvant Therapy on Reducing the U.S. Breast Cancer Mortality in 1975-2000?



U.S. Breast Cancer Mortality Rate Age Adjusted for Women 30-79; *NEJM* (2005)

U.S. Population Breast Cancer Mortality Modeling

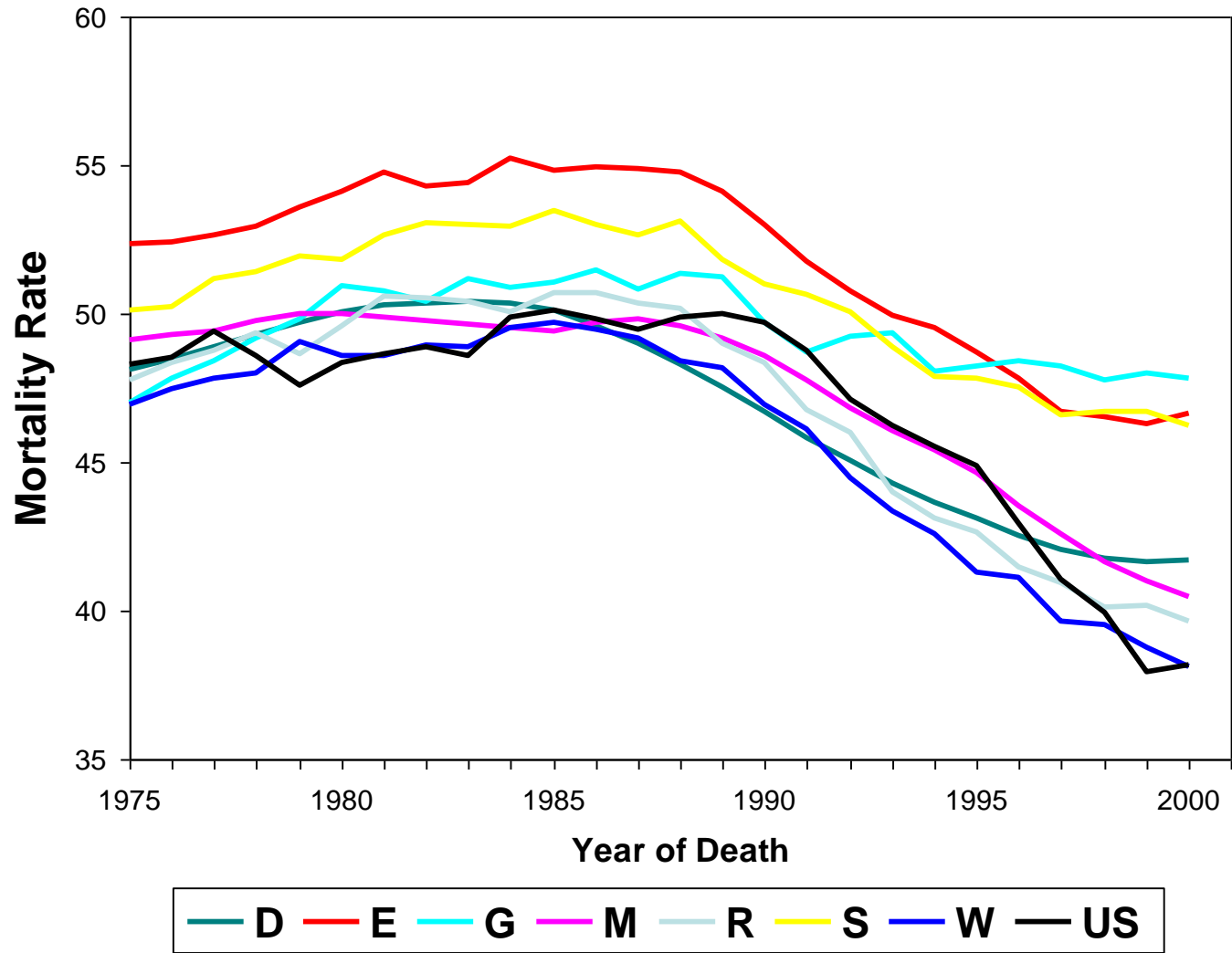
Input Parameters

- Survival distributions
- Stage distributions
- Natural history model parameters
- Sensitivity of mammography
- Screening disseminations in the U.S. (total no. of exams, intervals, FU time)
- Treatment disseminations in the U.S.
- Treatment efficacy of adjuvant therapies

Data Sources

- US SEER data
- Breast Cancer Screening Trials
- BCSC (Breast Cancer Surveillance Consortium)
- NCI – model treatment and screening dissemination patterns
- Treatment efficacy – Early Breast Cancer Trialists' Collaborative Group

CISNET Results



CISENT Base Case I: Summary

- All models showed reduction is due to both screening and treatment.
- Relative contribution of screening ranged from 28% to 65% (median: 46%).
- Relative contribution of treatment benefit ranged from 35% to 72% (median: 54%).
- *NEJM 2005*

Example 2: U.S. Preventive Services Task Force

- Independent panel of experts in prevention and primary care, sponsored by the Agency of Healthcare Research and Quality (AHRQ)
- Conduct rigorous assessments of the scientific evidence for the effectiveness of broad range of clinical preventive services, including mammography screening
- 2008, 2015 – TF collaboration using CISNET models to explore breast cancer screening schedules
- 2008: Models generated outcomes under various screening schedules (*Ann Intern Med* 2009)
 - TF revised recommendation on breast cancer screening
 - TF 2009 recommendation: Biennial screening 50-74 (change from 2002 guideline of 1-2 years for 40+)

Example 2: U.S. Preventive Services Task Force (2)

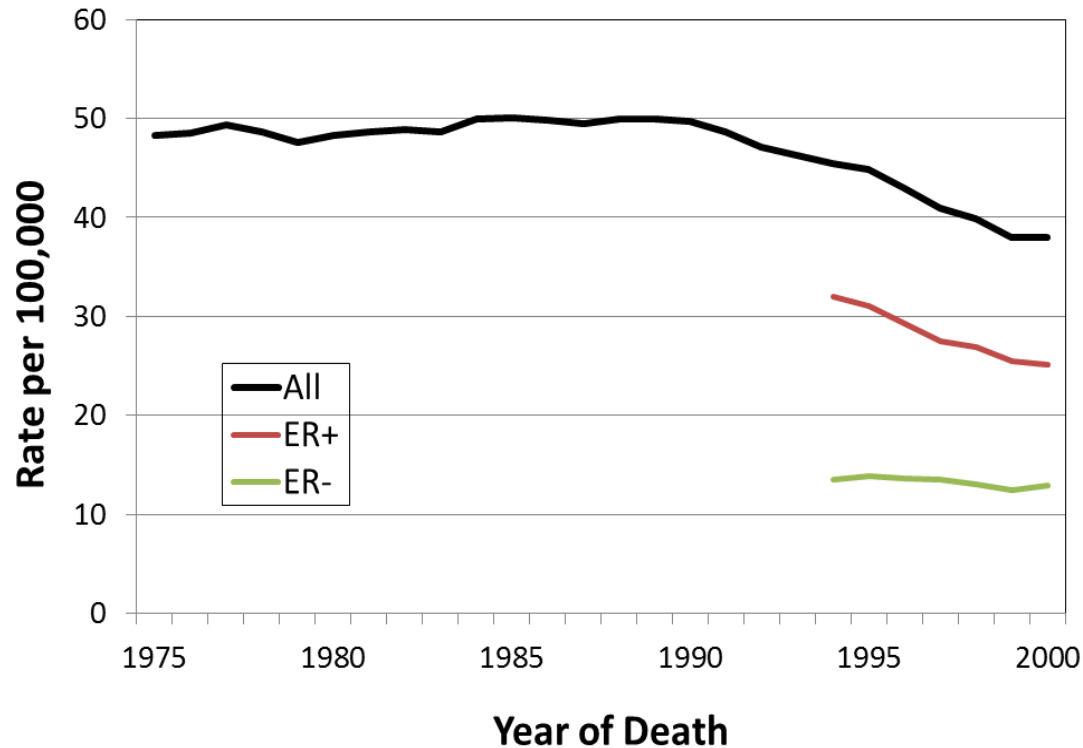
- 2015 – TF collaboration using CISNET models to explore breast cancer screening schedules
- Models generated outcomes under various screening schedules (*Ann Intern Med* 2016)
 - Eight strategies starting at 40,45, 50 years, stop at 74; annual, biennial, hybrid screening intervals
 - Breast Density, Risk status, Hormonal status (ER/HER2) incorporated
 - TF 2016 recommendation: Biennial screening 50-74
 - Higher risk group – fewer false positives per 1000 screened, lower ratio of overdiagnosis per breast cancer death averted than average women
 - Lower breast density - greater detection rate, larger MR%
 - Higher breast density- greater absolute number detected, more life-year saved

Other CISNET Collaborations

- Example 3: Tipping the balance of benefits and harms to favor screening mammography starting at age 40 years: a comparative modeling study of risk (*Ann Intern Med* 2012)
 - Women aged 40-49 with a 2 fold increased risk have similar harms/benefit (false positive/deaths averted) ratio for biennial screening MM as normal-risk women aged 50-74
- Example 4: Benefits, harms and costs for breast cancer screening after U.S. implementation of digital mammography (*JNCI* 2014)
 - Digital mammography screening increased total costs for small added health benefits

Example 5: CISNET BWG Base Case II

Effects of Screening and Systemic Adjuvant Therapy on ER-Specific US Breast Cancer Mortality?



U.S. Breast Cancer Mortality Age 30-79, adjusted *JNCI* 2014

Table 2. Age-adjusted reduction in breast cancer mortality rates (per 100 000 women) in 2000 attributed to adjuvant treatment and/or screening relative to no screening and no adjuvant treatment for women aged 30 to 79 years*

Model	All breast cancer cases					ER+ breast cancer cases					ER- breast cancer cases				
	Tam	Chemo	TX	SCR	SCR+TX	Tam	Chemo	TX	SCR	SCR+TX	Tam	Chemo	TX	SCR	SCR+TX
D	6	5	11	9	19	6	2	8	7	15	0	3	3	2	5
E	9	8	16	9	22	9	4	12	7	16	0	4	4	3	6
G-E	8	5	13	14	24	8	3	10	10	18	0	3	3	4	6
M	8	4	12	8	15	8	2	10	6	13	0	2	2	2	3
S	13	6	16	14	26	13	3	15	11	21	0	2	2	3	5
W	10	6	16	10	24	10	3	12	7	18	0	4	4	3	6
Median	8	6	14	10	23	8	3	11	7	17	0	3	3	3	5

* Mortality reductions are absolute reductions, computed as the difference between the rate predicted in the absence of both screening and adjuvant treatment and the rate predicted with one or both interventions. Chemo = chemotherapy; ER = estrogen receptor; SCR = screening mammography; SCR+TX = screening mammography and tamoxifen and chemotherapy; Tam = tamoxifen; TX = tamoxifen and chemotherapy.

Main Findings:

ER+: higher contribution from adjuvant therapy than screening

ER-: similar contribution

ER-: less likely to be screen-detected, screen-detected cases had better mortality benefit

Example 6: Web-Calculator for Mammography Choices for Women in 40's

- USPSTF – MM recommendation 50-74 biennial
- No routine screening in their 40's, individual decision considering benefits/harms - "individual decision taking one's context into account including the patient's values regarding specific benefits and harms"
- How to assess benefits and harms?
- Using Collaborative Simulation Modeling to Develop a Web-based Tool
- To Support Policy-level Decision Making about Breast Cancer Screening Initiation Age

Risk-Based Screening:

Periodic vs. Threshold Generated Screening Schedules

Risk-Based Screening

- Reformulate the problem of screening as a risk-based problem
- For example: age, breast density, family history etc.
- Define "Risk" as: Probability of having undiagnosed pre-clinical disease at age t
- Choose a screening examination schedule that is bound by this "risk"

Risk-Based Screening

Risk Definition:

$S(t)$ = Probability of having undiagnosed pre-clinical disease at age t

No Screening



$q(t)$ ~ exponential distribution with mean 2-4 years for invasive breast cancer

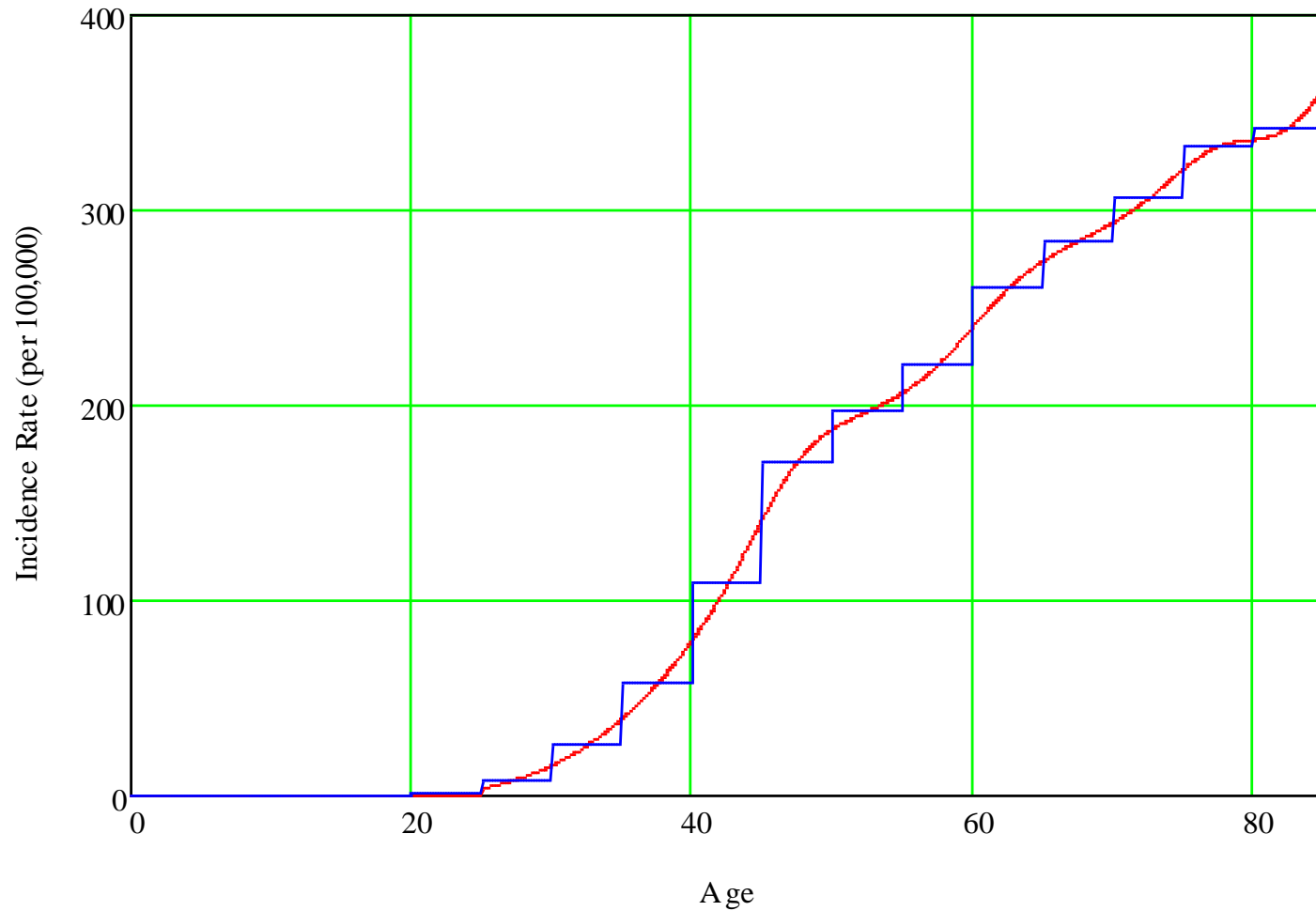
S_0 : Disease-free or Undetectable State

S_p : Pre-clinical State (Asymptomatic)

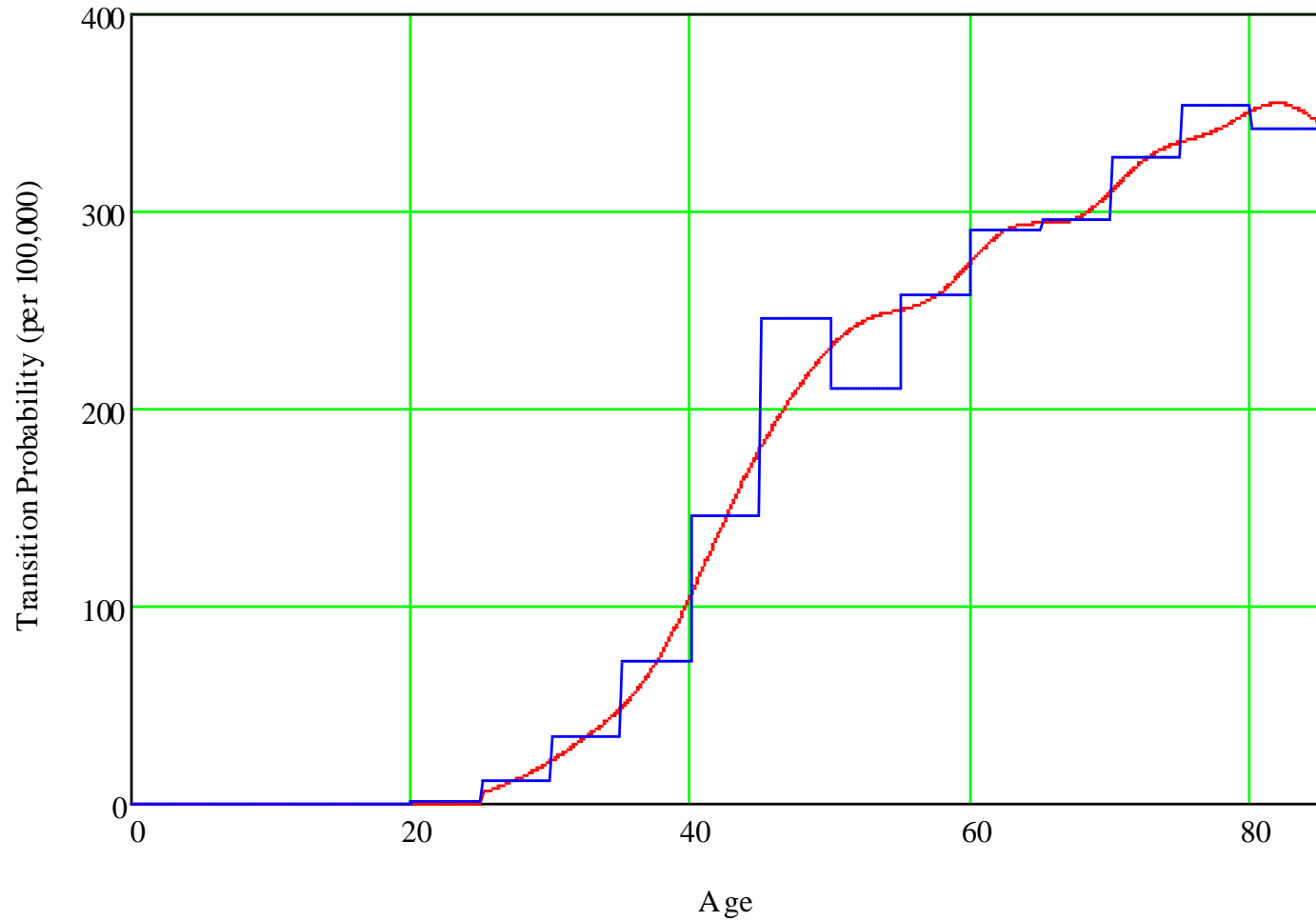
S_c : Clinical State

SEER 1975-1979 Incidence Rate

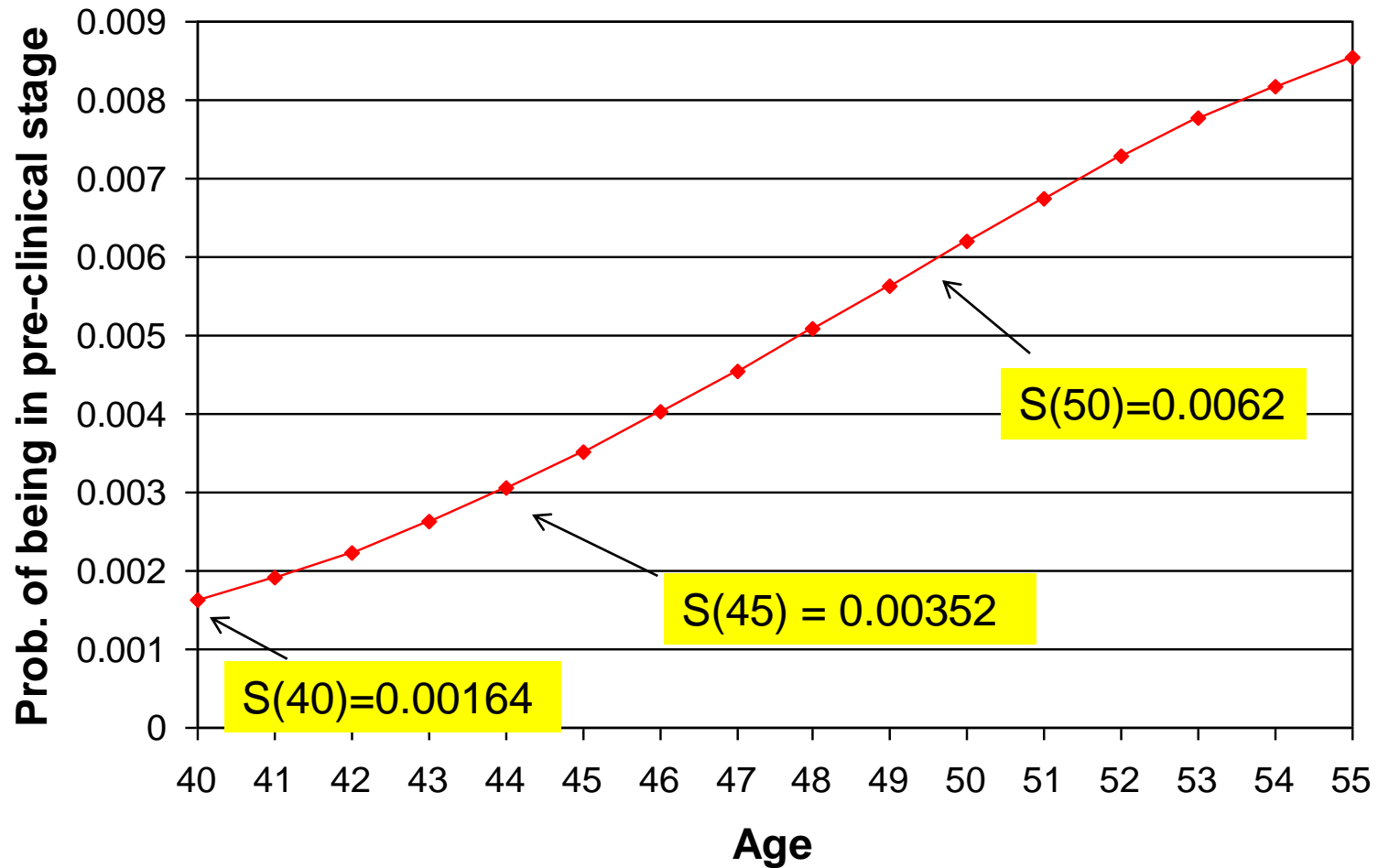
Estimate Transition Probability $i(t): S_p \rightarrow S_c$



Estimate Transition Probability $w(t): S_0 \rightarrow S_p$



$S(t)$: Probability of having undiagnosed pre-clinical disease at age t



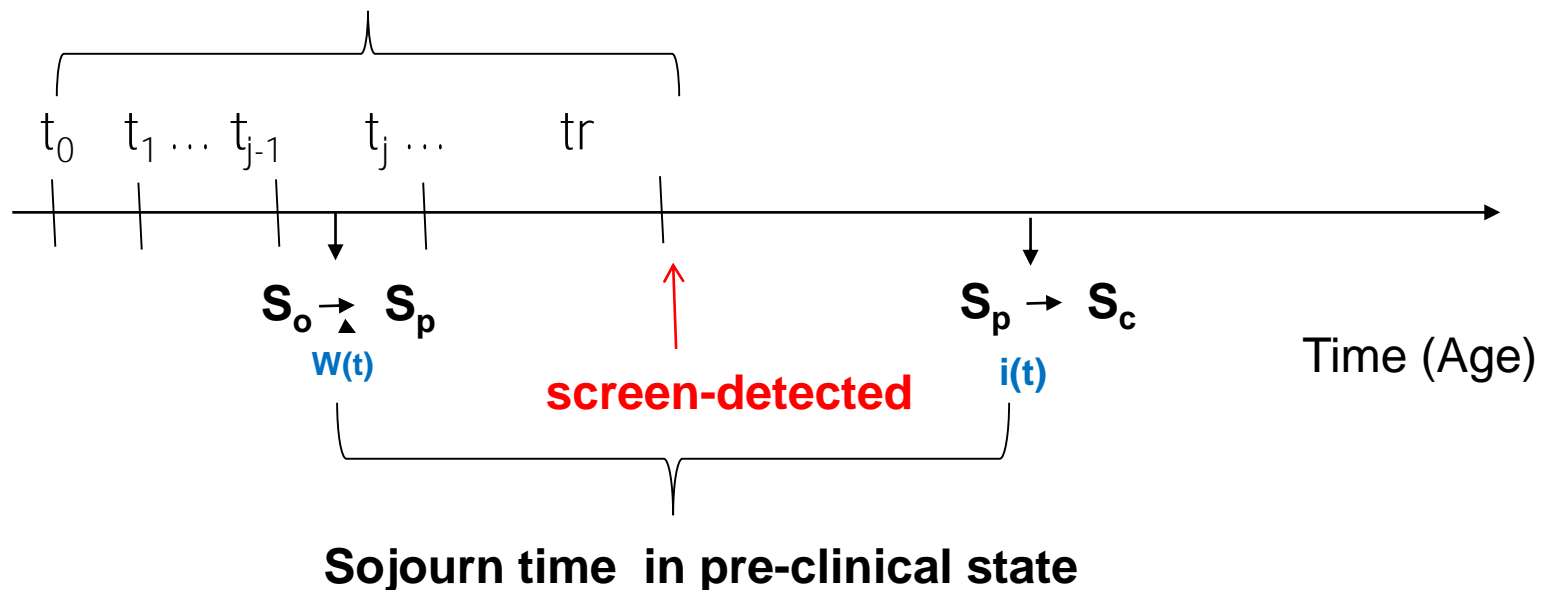
Estimation of Risk in with Screening : Model

Risk: $S(t)$ = Probability of having undiagnosed pre-clinical disease at t

More complicated to estimate:

- Function of exam schedules and Sensitivity $q(t)$

Exam Schedules $q(t) \sim$ exponential distribution with mean 2-4 years



Risk-Based Screening

$$S(t) = \sum_{r=1}^n \Phi(t - t_{r-1}) \\ \times \{1 - \Phi(t - t_r)\} P(t|r) + \Phi(t - t_n) P(t|n+1)$$

$$P(t|r) = (1 - \beta)^r P_0(t_0) Q_0(t - t_0) + \Phi(r - 2)$$

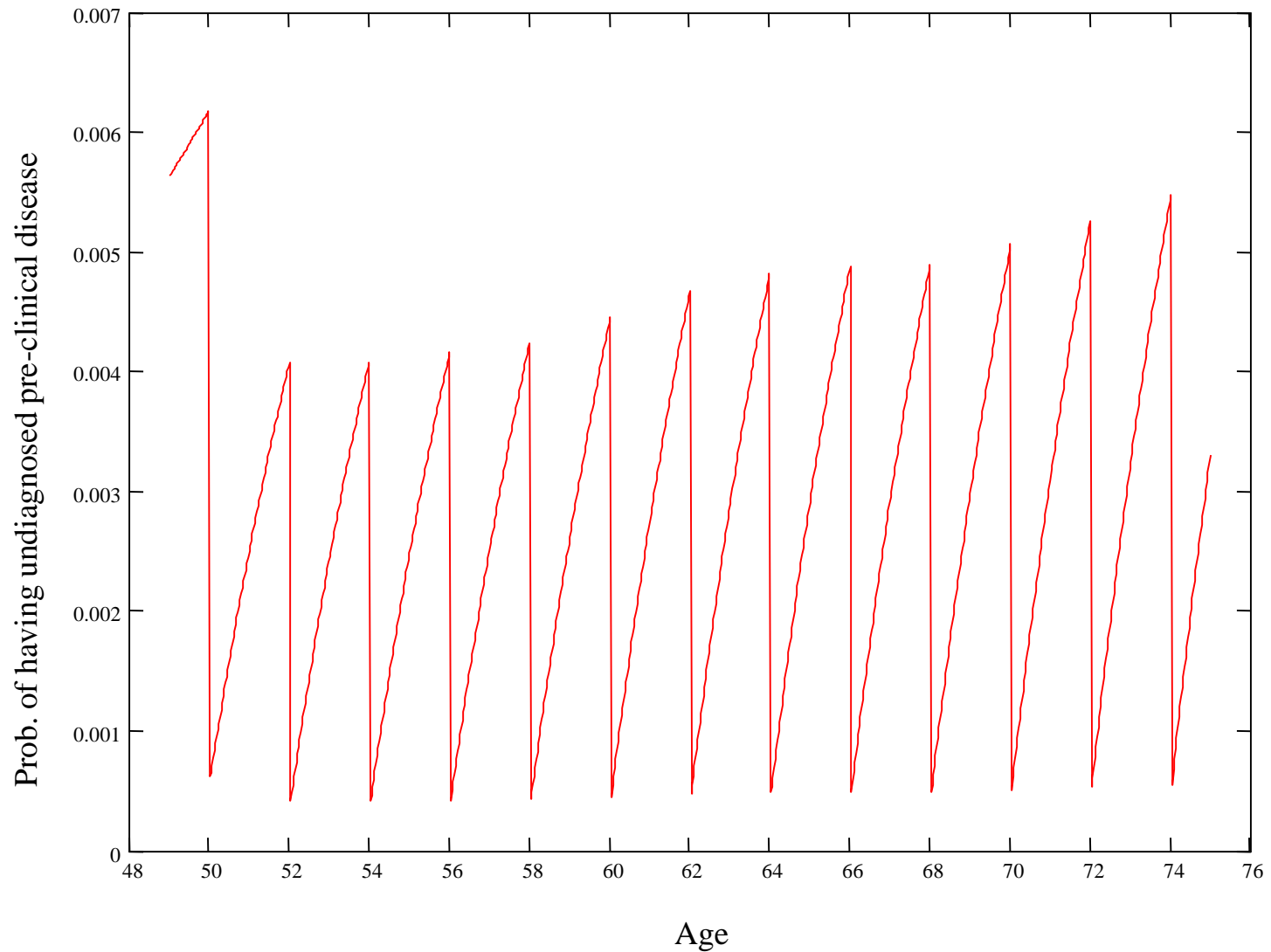
$$\times \sum_{k=1}^{r-1} (1 - \beta)^{r-k} \int_{t_{k-1}}^{t_k} w(x) Q(t - x) dx \\ + \int_{t_{r-1}}^t w(x) Q(t - x) dx,$$

where

$$\Phi(x) = \begin{cases} 1 & \text{if } x \geq 0 \\ 0 & \text{otherwise.} \end{cases}$$

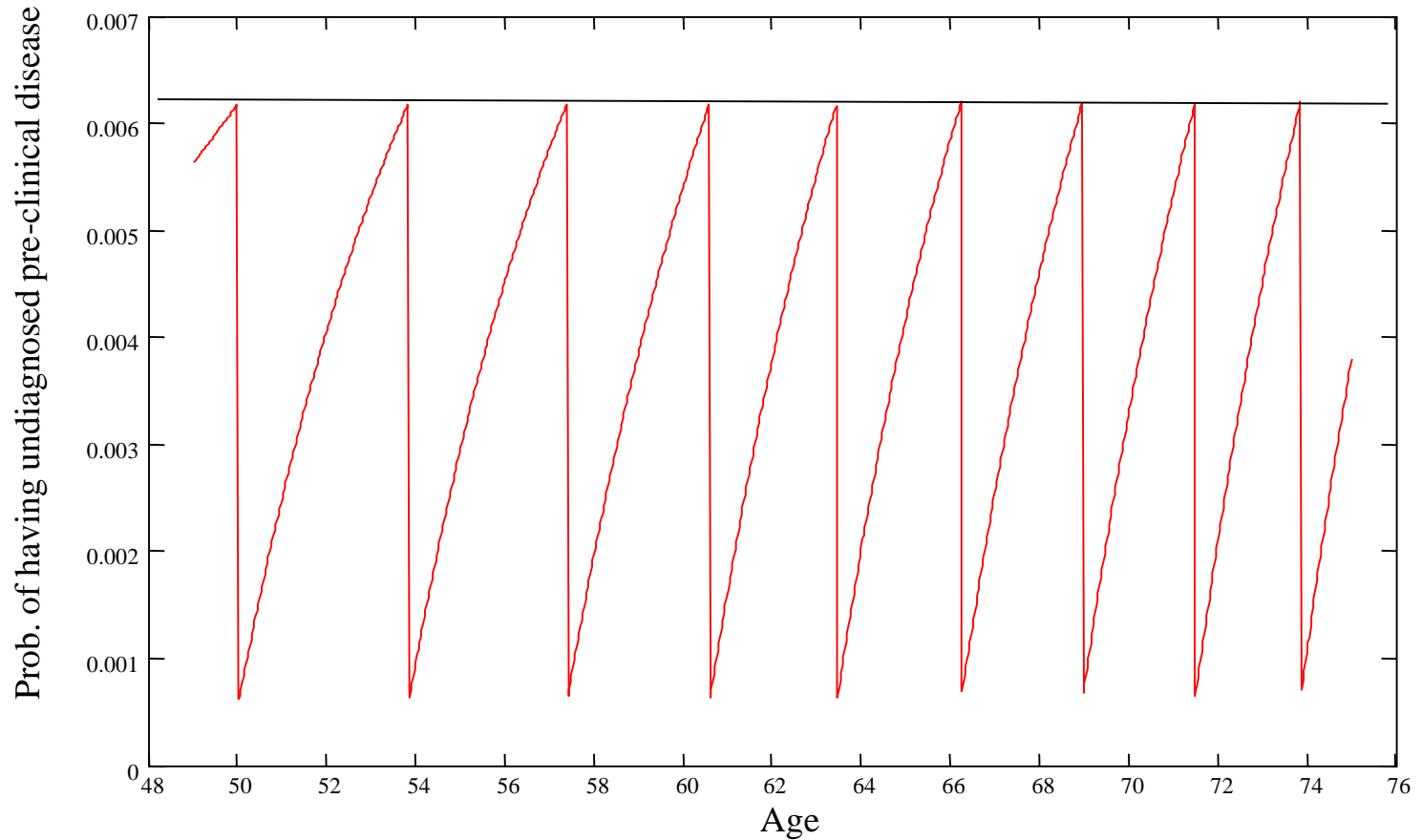
$$S(t) = \text{Prob}(\text{Undiagnosed Pre-clinical Disease})$$

Following Biennial Exam Schedule with $(t) = .90$ for $[50, 74]$



$S(t) = \text{Prob}(\text{Undiagnosed Pre-Clinical Disease})$

Exam Schedule with $S(50) = .0062$ (Threshold Value)

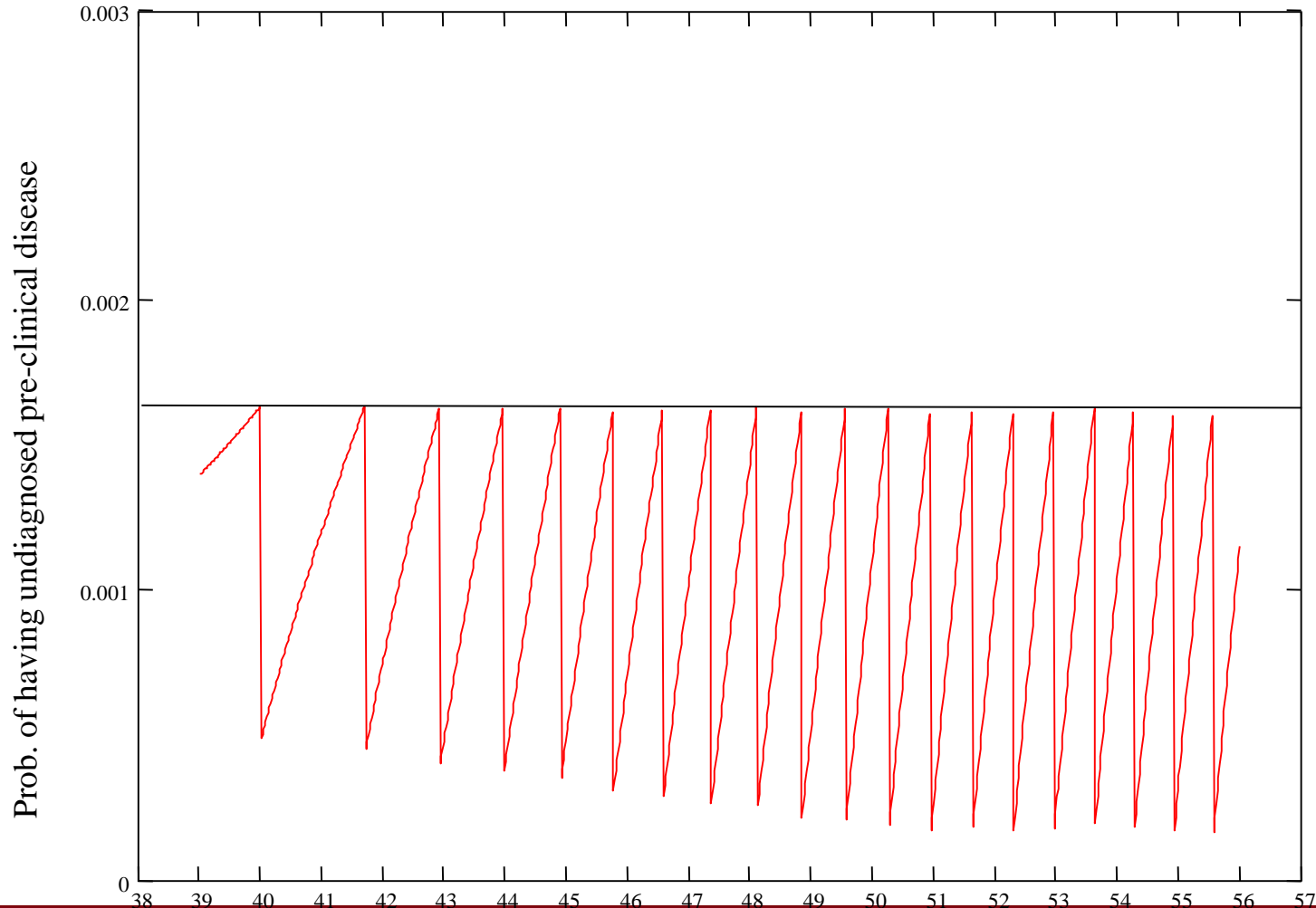


Risk Based-Screening Schedules

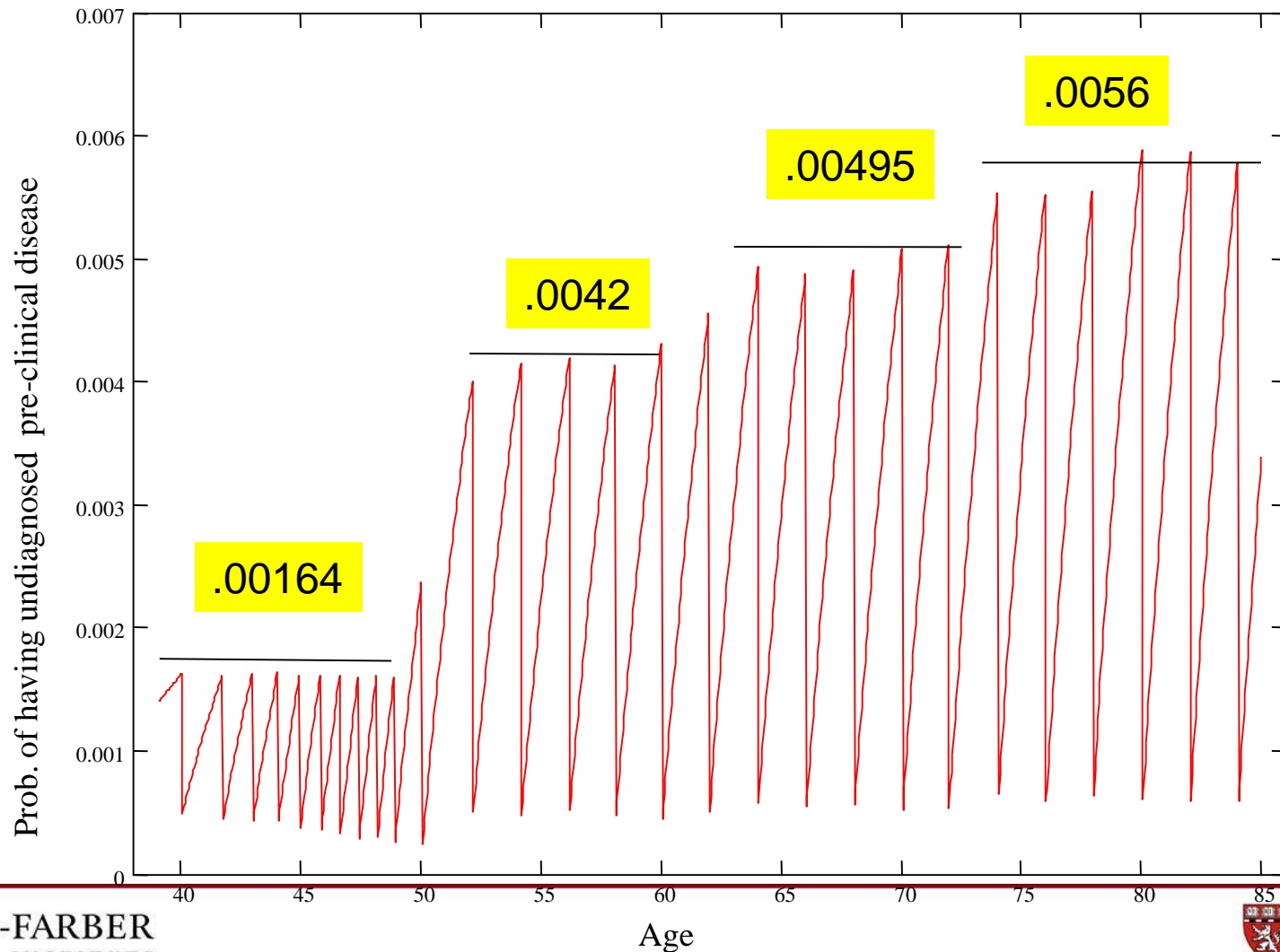
- Threshold Method (Lee & Zelen, *JASA* 1998): Screening schedule where risk is bound by a threshold value – can use to select initial age and screening intervals.
- Examples for Screening in [50, 74]:
 - Biennial – 13 exams: MR%= 21.5%
 - Threshold – 9 exams: MR%= 19%
 - (Annual – 25 exams: MR%= 26.2%)
 - Control Group – no screening [40,85]

$S(t) = \text{Prob}(\text{Undiagnosed Pre-Clinical Disease})$

Exam Schedule with $S(40) = 0.00164$ (Threshold Value)



S(t) with Threshold Method Starting at Age 40 Using Non-Constant Threshold Values



Screening Schedule for [40,84]

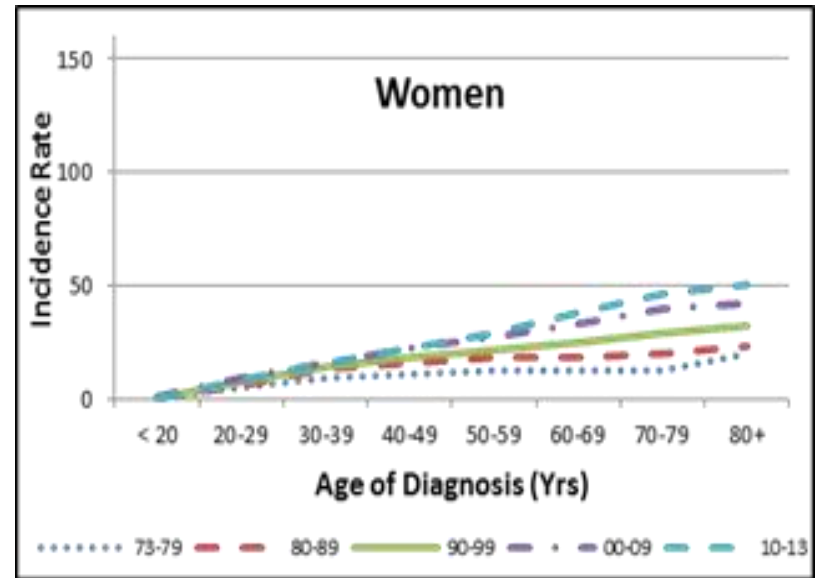
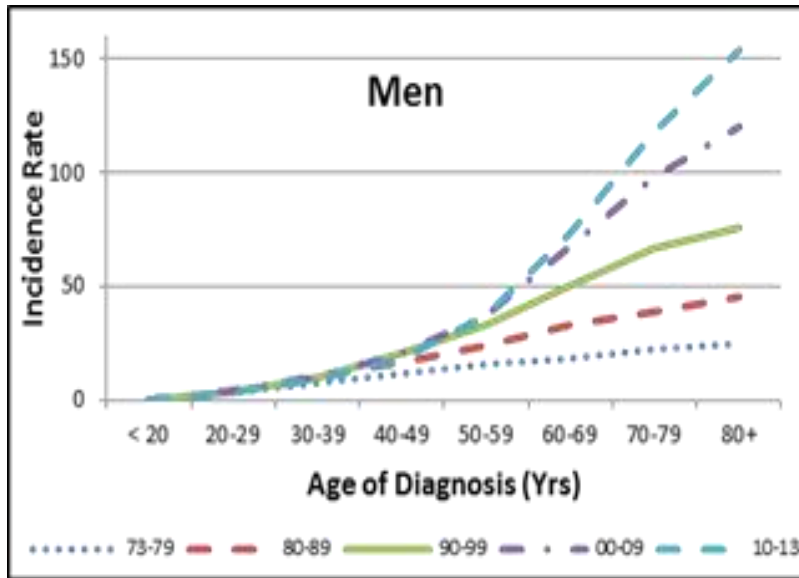
- Threshold value was chosen to find 80% of the cases at screening exams for [40,50), [50, 60), [60,70), [70,84]
 - Total Number of Exams: 28
 - MR%=27.9% (using no screening [40,85] as a control group)
- Yield – benefit is small when screening women in 40's

Applications to High-Risk Group

- High-Risk Group
 - Natural history by risk status
 - Estimate the risk while incorporating other risk factors (prior breast procedure, first degree family with breast cancer, age at birth of first child, breast density etc.)
 - BCSC data
 - Apply “threshold” method

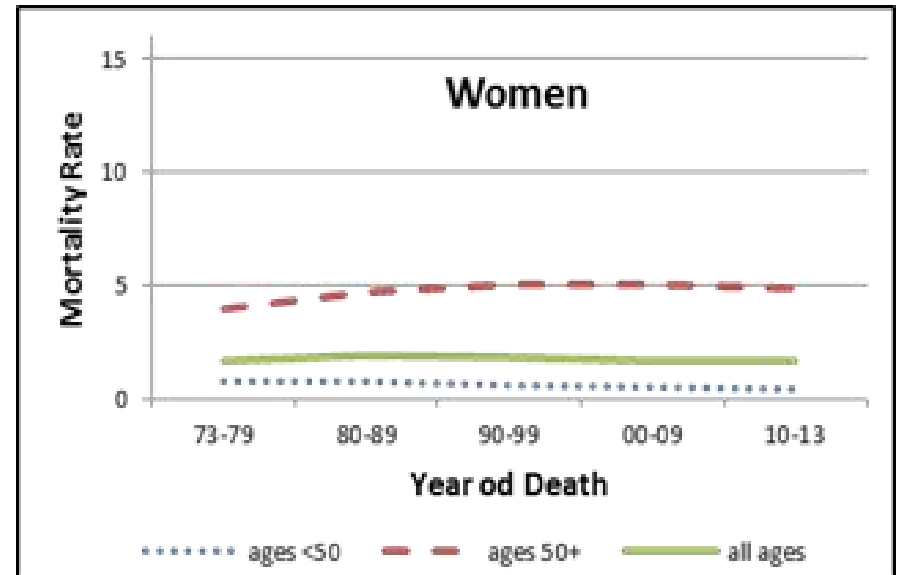
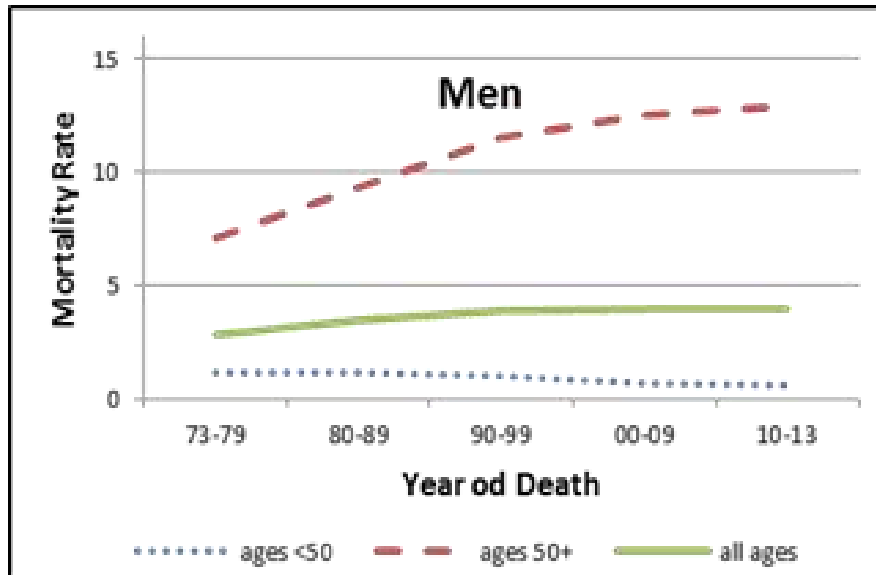
Melanoma Screening

Melanoma Incidence in the U.S.



U.S. SEER (Surveillance Epidemiology End Results) Data
Age-Specific Melanoma Incidence Rate /100,000

Melanoma Mortality in the U.S.



U.S. SEER (Surveillance Epidemiology End Results) Data
Melanoma Mortality Rate /100,000

Melanoma Screening Studies

- Germany SCREEN study in Schleswig-Holstein region in 2003
 - Primary physician trained to evaluate skin cancer
 - N=360,288 enrolled
 - After 5 years, decline in 0.8 deaths per 100,000 in comparison regions
 - *Cancer* 2008
- Germany National Screening Program in 2008
 - 2008 starting at age 35
 - No measurable decline in death rates as of 2013
 - *Archives of Dermatology* 2012. *Deutsches Arzteblatt International* 2015
- Large scale program implemented within a U.S. Healthcare System in 2014
 - Thinner melanoma among screen-detected cases
 - *Cancer* 2016, *JAMA oncology* 2017

USPSTF Recommendation in 2016

- Limited evidence was identified for skin cancer screening, wrt potential benefit of skin cancer screening and melanoma mortality
- Future research on skin cancer screening should focus on targeted screening in those considered to be at higher risk for skin cancer
- *JAMA* 2016

Targeted Screening for Melanoma

- Risk of Developing Melanoma
 - Well Known Risk Factors: personal history of melanoma, presence of atypical nevi, increased nevus count, large/giant congenital nevi, non-melanoma skin cancer, actinic damage, family history of melanoma, and melanoma susceptibility genes (such as CDKN2A, CDK4, CDKN2A, MC1R)
- Risk of Fatal Melanoma
 - Same risk factors?
- Associations between risk of developing melanoma and fatal melanoma?
 - Preliminary data (n=1,700) using the pilot database from Beth Israel Deaconess Medical School, Harvard Medical School

Mortality Modeling in Men and Women

- Natural History of Melanoma for Men and Women
 - Preliminary data: Men with shorter sojourn time in pre-clinical state S_p
- Stochastic Models for Early Detection of Melanoma
 - “Early Stage” – defined as localized tumor with $< .8$ mm
 - Assume stage shift of 20% from screening
 - Compared to no screening [40,79]

Total Exams	Intervals	Screening Horizon	MR% Men	MR% Women
5	5 yr	[50-70]	8.6%	14.7%
7	5 yr	[40-70]	10%	19%
9	5 yr	[40-79]	11.2%	20.1%
14	3 yr	[40-79]	14.5%	26.6%

Targeted Screening for Melanoma

- Risk Prediction Model for Developing Melanoma
- Risk Prediction Model for Fatal Melanoma
- Targeted Screening in Men and Impact on the Melanoma Mortality in the U.S.?

Remarks

Remarks (1)

- Stochastic models for early detection of breast cancer and melanoma
- Model structures, assumptions, input parameters, validations
- Models enhance our understanding wrt benefits or harms of early detection
- Stochastic models may lead to a deeper understanding of observed phenomena and be applied to public health related issues

Remarks (2)

- Collaborative Modeling – in-depth analysis of screening outcomes based on common input data
- Screening Programs for High-Risk Groups
 - Identify sub groups at higher risk
 - Special programs based on risk
 - Estimate “risk” using the risk profile and past screening history
 - Apply the risk-based screening program
- Population vs. Targeted Screening Programs

Thanks!

Collaborators:

- Marvin Zelen Ph.D. (HSPH, DFCI)
- Hui Huang M.S. (DFCI)
- Xiaoxue Li Ph.D (DFCI, HSPH)
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- Julie Najita, Ph.D. (DFCI, HSPH)
- Harald Weedon-Fekjaer Ph.D.
(University of Oslo)
- CISNET Breast Working Group



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