Simulating Screening Bias in Case-control Risk-factor Studies

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Presenter Disclosures

Rick Jansen

(1) The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No Relationships to disclose

Outline

- ***Overview***
  - ***Nature of the problem***
  - ***Goals of the research***
  - ***Types of screening bias***
  - ***Extent of the problem***
- Mathematical model and components
- Nested case-control studies
- Results
- Summary and conclusions

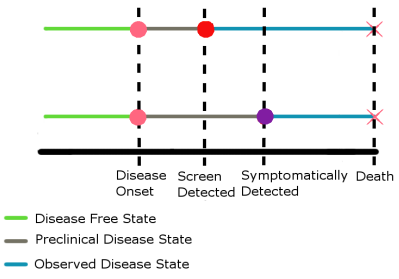
What is the Problem?

- Screening use may affect observational risk-factor estimates
  - Differential screening behaviors across risk factor strata
    - Screening frequency and proportion
  - Modifies sampled population
    - Screening excludes/includes some cases
    - Differences in disease histories (e.g. disease progression and disease stage at detection)

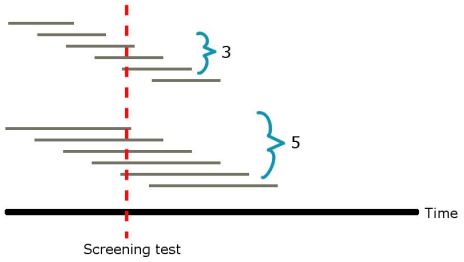
Goals of the Research

- Determine if screening bias is a problem in case-control studies of lung cancer incidence nested within the PLCO trial
- Determine how the risk-factor study design and model parameterization influence the amount of predicted bias.
- Explore if the mathematical model for screening bias provided here corresponds well with the observed risk ratio (RR).
- Provide design suggestions for future risk-factor studies to minimize the potential affect of screening bias.

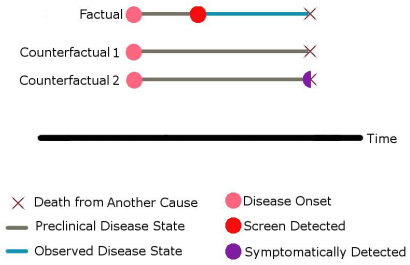
Screening Bias – Lead-Time



Screening Bias - Length

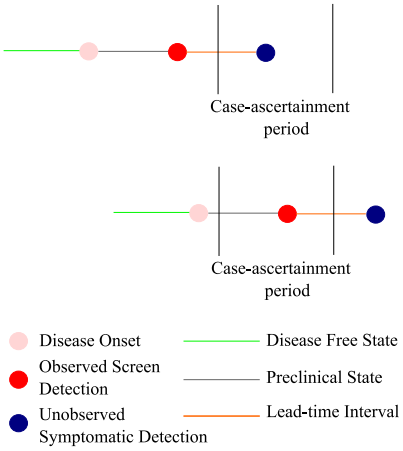


Screening Bias - Overdiagnosis

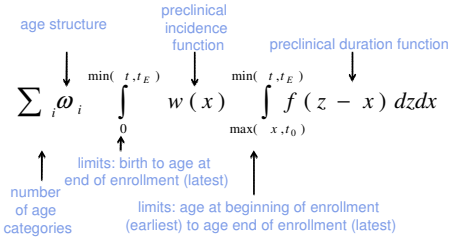


Outline

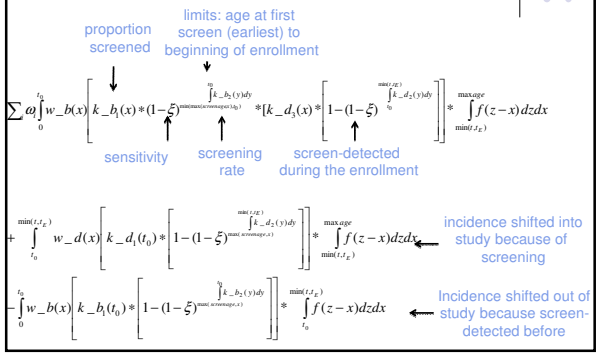
- Overview
- **Mathematical model and components**
  - **Influence of screening on case selection**
  - ***Complete model***
- Nested case-control studies
- Results
- Summary and conclusions



Mathematical Model for Incidence (Unscreened)



Mathematical Model for Incidence (Screened)



Theoretical Bias Adjustment

- Apply models (under different screening conditions) to each risk-factor stratum
- Under double null hypothesis in unbiased study, the ratio of risk-factor strata incidence rates = 1; any deviation represents screening bias
- To theoretically correct for screening bias, multiply observed risk estimate by 1/simulated risk estimate
- Model must be validated before use as a correction

Outline

- Overview
- Mathematical model and components
- **Nested case-control studies**
  - ***PLCO study - overview***
  - ***PLCO study - lung cancer***
  - ***Purpose of different designs***
- Results
- Summary and conclusions

PLCO Study Overview

- PLCO: Prostate, Lung, Colorectal, and Ovarian cancer screening trial
- ~77,000 men and ~77,000 women aged 55-74 randomized to intervention or usual-care group followed for minimum of 13 years
  - Enrollment: 1993 – 2001 at 10 sites around the U.S.
- Demographic characteristics, known risk-factors for studied cancers, and screening history were collected from all participants at baseline

PLCO Study Lung Cancer

- Screening method that PLCO focused on was chest x-ray. PLCO collected smoking and lung cancer information.
- Opportunity to explore screening bias when there is a known large risk-factor effect
- Subjects in the intervention group were screened at baseline (T_0) and annually for 3 years thereafter (T_1-T_3) until December 1998 when the third annual screen (T_3) was discontinued for never smokers
- Within group at other study times, screening behavior similar between risk-factor strata

Scheduled Screens

- Interventional arm scheduled to receive a chest x-ray screen
- Usual care arm assumed to continue screening behavior as reported for the 3 years prior to enrollment
- After 1998, nonsmokers no longer schedule for screen
- Screening behavior assumed to be same in both arms as reported for 3 years prior to beginning of PLCO enrollment

Recorded Screening Behavior

	Average Screening Contamination Within 3 Years Prior to Enrollment (%)	Average Screening Compliance at Study Time T0 (%)	Average Screening Compliance at Study Time T1 (%)	Average Screening Compliance at Study Time T2 (%)	Average Fraction Screened at T3 (%)
Ever Smokers	56.3	87.9	84.5	83.1	78.7
Never Smokers	49.0	89.2	86.7	85.7	25.9
Combined	52.9	88.5	85.6	84.3	54.3

Study Designs

- Twenty-seven studies: between PLCO study years T0 and T5
- Random sample of 200 Cases and use incidence density sampling to select 4 controls at diagnosis date of each case
- Repeated sampling 100 times for each of the 27 designs

Purpose of Different Designs

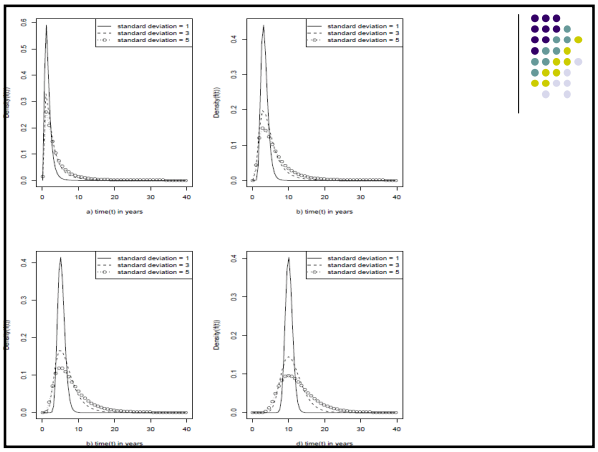
- To identify the effect of selecting a sample:
  - from all calendar enrollment years, 1993-2001 compared to selecting only after protocol change, 1995-2001
  - from intervention group compared to usual-care group
  - over varying lengths of case-ascertainment period

Outline

- Overview
- Mathematical model and components
- Nested case-control studies
- **Results**
  - ***Parameterization of model***
  - ***Simulation results***
  - ***Nested case-control results***
  - ***Comparison***
- Summary and conclusions

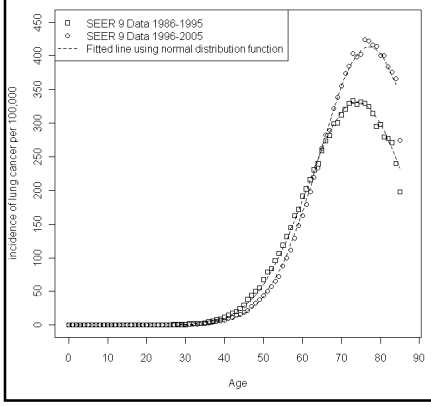
Parameterization of Model for Lung Cancer Case-control Studies

- Use study specific age group distribution
- Use literature-based screening sensitivity
- For the preclinical duration, used several modes (1,3,5,10) and standard deviations (1,3,5) for the log normal distribution
- Overdiagnosis was explicitly incorporated by mixing in a proportion with a preclinical duration with mode (20) and standard deviation (5)

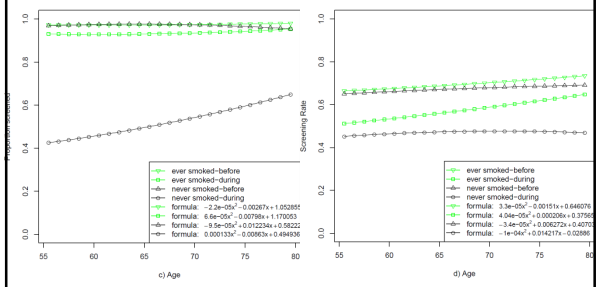


Parameterization of Model (Continued)

- Use SEER incidence data from years 86-05
  - 86-95: pre-study rates
  - 96-05: in-study rates
  - adjusted by mean of preclinical duration distribution = preclinical incidence functions
- Proportion screened and screening rate functions estimated from study data
  - Proportion: age-dependent 2° polynomial for the fraction of individuals screened
  - Rate: age-dependent 2° polynomial for frequency of screening among those screened



Screening Functions



Simulation Results

- Determine if screening bias has the potential to affect the observed RR
- Use two study designs representative of the extremes for screening behavior differential
  - Sampled from intervention group affected by procedural modification (enrolled between 95-01)
  - Sampled from usual-care group from entire PLCO enrollment period (93-01)

Simulated RRs for Case-Control Study With Enrollment Period T3-T5

a) Usual-care group sampled from entire enrollment period: Simulation results using smoked variable: Lognormal distribution for preclinical duration with no overdiagnosis and chest x-ray sensitivity of 86%

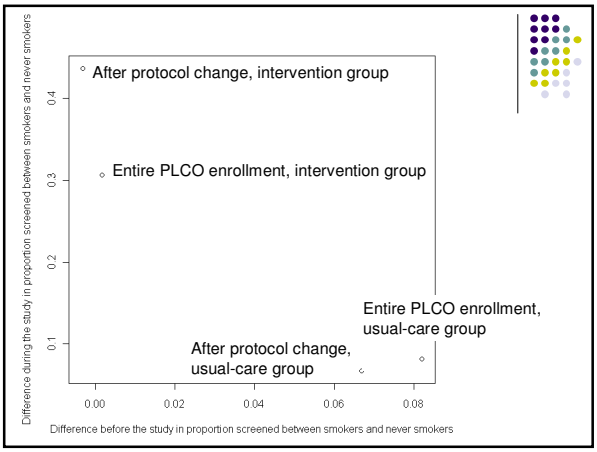
	Mode = 1	Mode = 3	Mode = 5	Mode = 10
Standard dev. = 1	1.01	1.02	1.04	1.09
Standard dev. = 3	1.02	1.03	1.05	1.10
Standard dev. = 5	1.02	1.04	1.06	1.11

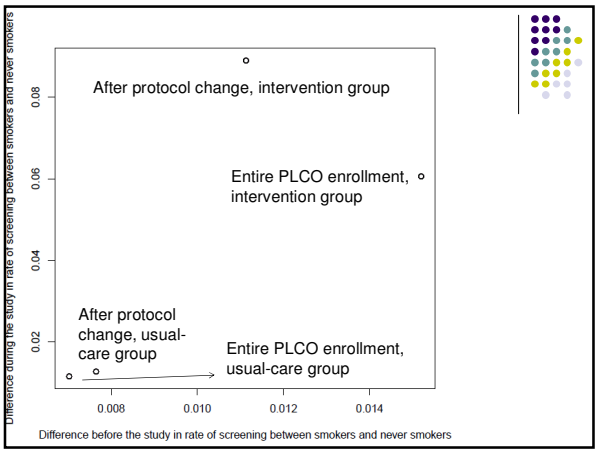
b) Intervention group sampled after procedural modification: Simulation results using smoked variable: Lognormal distribution for preclinical duration with no overdiagnosis and chest x-ray sensitivity of 86%

	Mode = 1	Mode = 3	Mode = 5	Mode = 10
Standard dev. = 1	1.13	1. 46	1.79	1.94
Standard dev. = 3	1.25	1.54	1.78	1.94
Standard dev. = 5	1.31	1.59	1.78	1.93

Simulation Results – Parameter Influence

- How do components of the mathematical model influence the simulated RR
  - Screening behavior differential
  - Different mode and standard deviations for the preclinical duration lognormal distribution
  - Look at model sensitivity to overdiagnosis and chest x-ray screening sensitivity
- Add two study designs
  - Corresponding study sampled from either intervention or usual-care group missing from previous pair





Model Sensitivity to Chest X-ray Sensitivity in Intervention Group

b) Intervention group sampled after procedural modification: Simulation results using smoked variable: Lognormal distribution for preclinical duration with no overdiagnosis chest x-ray sensitivity of 46%

	Mode = 1	Mode = 3	Mode = 5	Mode = 10
Standard dev. = 1	1.09	1.32	1.64	1.99
Standard dev. = 3	1.19	1.43	1.67	1.98
Standard dev. = 5	1.24	1.49	1.70	1.97

b) Intervention group sampled after procedural modification: Simulation results using smoked variable: Lognormal distribution for preclinical duration with no overdiagnosis and chest x-ray sensitivity of 66%

	Mode = 1	Mode = 3	Mode = 5	Mode = 10
Standard dev. = 1	1.13	1. 46	1.79	1.94
Standard dev. = 3	1.25	1.54	1.78	1.94
Standard dev. = 5	1.31	1.59	1.78	1.93

b) Intervention group sampled after procedural modification: Simulation results using smoked variable: Lognormal distribution for preclinical duration with no overdiagnosis and chest x-ray sensitivity of 86%

	Mode = 1	Mode = 3	Mode = 5	Mode = 10
Standard dev. = 1	1.18	1. 57	1.83	1.86
Standard dev. = 3	1.31	1.62	1.79	1.85
Standard dev. = 5	1.37	1.64	1.78	1.85

Model Sensitivity to Overdiagnosis in Intervention Group

b) Intervention group sampled after procedural modification: Simulation results using smoked variable: Lognormal distribution for preclinical duration with no overdiagnosis chest x-ray sensitivity of 46%

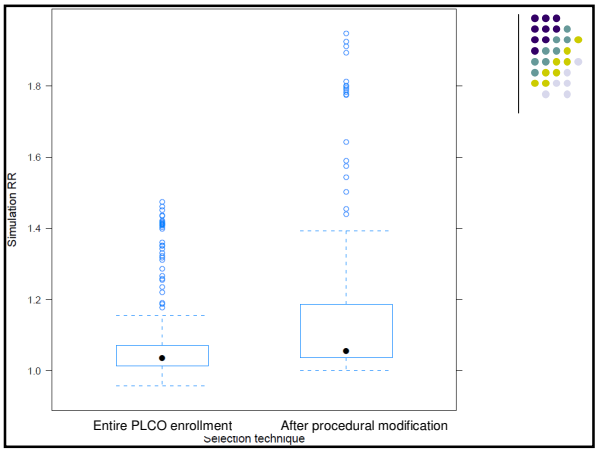
	Mode = 1	Mode = 3	Mode = 5	Mode = 10
Standard dev. = 1	1.09	1.32	1.64	1.99
Standard dev. = 3	1.19	1.43	1.67	1.98
Standard dev. = 5	1.24	1.49	1.70	1.97

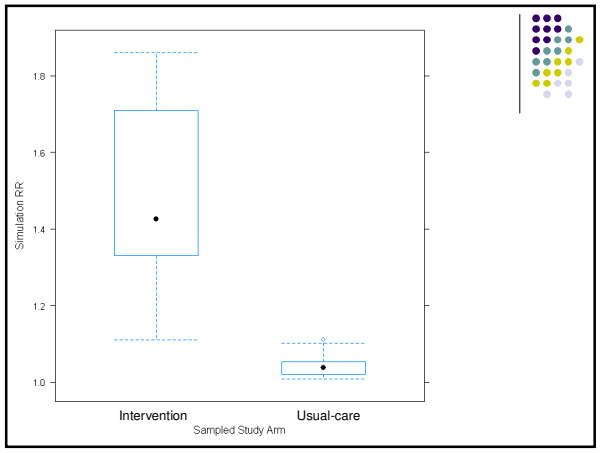
d) Intervention group sampled after procedural modification: Simulation results using smoked variable: Lognormal distribution for preclinical duration with 20% overdiagnosis and chest x-ray sensitivity of 46%

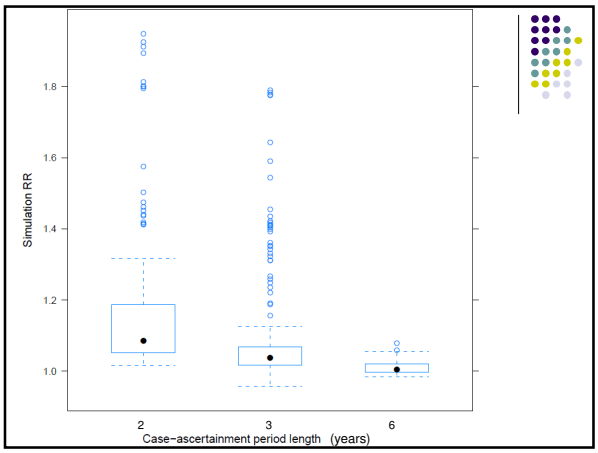
	Mode = 1	Mode = 3	Mode = 5	Mode = 10
Standard dev. = 1	2.07	2.05	2.04	2.03
Standard dev. = 3	2.07	2.06	2.05	2.04
Standard dev. = 5	2.07	2.06	2.05	2.04

Simulation Results – Study Design Influence

- Selection of sampled population: entire PLCO enrollment vs. after procedural modification
- Sampled study arm: intervention or usual-care
- Length of the case-ascertainment period





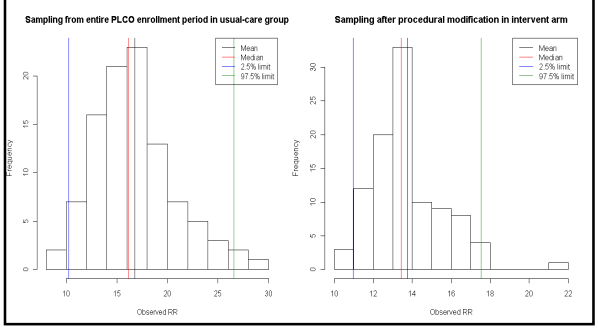


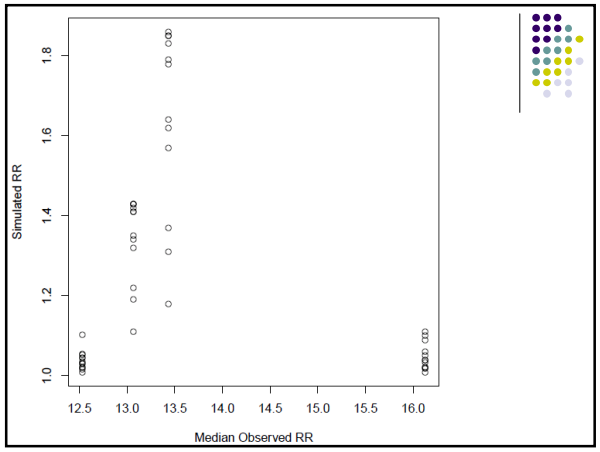
Do Simulated RRs Correspond With Observed RRs

- Empirically compare pairs of nested case-control studies and the simulation of those studies
  - Obtain a ratio of observed median RRs between the two studies
  - Obtain a ratio of simulated RRs between the two studies
  - Create a variable, ρ, that is the ratio of the simulated RR ratio to observed RR ratio

$$\frac{Ratio\ of\ RR_{simulated-1-2}}{Ratio\ of\ RR_{median-1-2}} = \rho$$

Distribution of Observed RRs for the 100 Resamples





Entire PLCO Enrollment Control vs. Intervention, no Overdiagnosis

ρ	Mode=1	Mode=3	Mode=5	Mode=10
Std Dev = 1	0.74	0.63	0.59	0.62
Std Dev = 3	0.69	0.62	0.61	0.62
Std Dev = 5	0.68	0.62	0.61	0.64

Entire PLCO Enrollment Control vs. Intervention, 20% Overdiagnosis

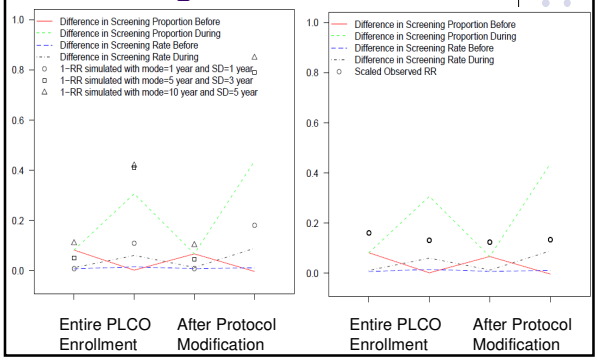
ρ	Mode=1	Mode=3	Mode=5	Mode=10
Std Dev = 1	0.62	0.62	0.61	0.63
Std Dev = 3	0.63	0.64	0.64	0.65
Std Dev = 5	0.64	0.64	0.65	0.66

Comparison for Each Design Pair; ρ = 1 is goal

Mode=1, Standard deviation=1

ρ	Entire,intervention	After,usual-care	After,intervention
Entire,usual-care	0.74	0.78	0.71
Entire,intervention		1.06	0.97
After,usual-care			0.92
After,intervention			
Mode=5, Standard deviation=3			
Entire,usual-care	0.61	0.78	0.49
Entire,intervention		1.30	0.81
After,usual-care			0.62
After,intervention			
Mode=10, Standard deviation=5			
Entire,usual-care	0.64	0.78	0.50
Entire,intervention		1.24	0.79
After,usual-care			0.64
After,intervention			

Relationship Between RRs and Screening Difference



Summary – Parameter Influence

- Simulation results suggest increased bias with:
  - increased difference in screening behavior (i.e., proportion and rate) between smoking strata
  - increased preclinical duration (i.e., mode and standard deviation)
  - Increased chest x-ray sensitivity
  - Overdiagnosis

Summary- Design Influence

- Simulation results suggest increased bias with:
  - Shorter case-ascertainment period
  - Sampling only from the intervention group
  - Sampling only after screening procedural modification

Conclusions

- In the presence of differential screening under plausible assumptions about preclinical incidence and duration, the simulations suggest the possibility for screening bias from chest x-ray to affect the risk smoking has on the development of lung cancer by up to 99%.
- The observed RRs have a large amount of variability between study designs, maybe indicating that some bias is present, though not as much as some of the simulations indicate.

Conclusions

- There are likely other types of bias (besides screening bias) also influencing these observed RRs making validation of the mathematical model using the described empirical comparison technique difficult
- When conducting observational studies where screening bias may arise in addition to using a design to minimize screening bias, a collection of detailed screening information is suggested

Future Research

- Test if screening bias can be adequately adjusted for using detailed screening variables in a regression model.
- Test the model sensitivity to adjustment of the underlying assumptions such as identifying how incorporating a risk-factor disease association influences the simulation results.
- Use an optimization procedure to find “best” set of parameters for model including overdiagnosis
- Validate that the mathematical model can predict the amount of screening bias in an observational study of lung cancer incidence so it can be used as a correction factor.
- Include additional variables in the mathematical model as identified from a casual diagram
- Modify and apply the mathematical model to other diseases and their forms of early detection.

Thank you

- Committee members and U of MN SPH
- NCI and PLCO Investigators & Coordinators
- Question or comments?