Evolution from Universal to Precision Screening

Estimating the Unbiased Benefits of Universal and Precision Screening Programs Using Advanced Modeling Approaches

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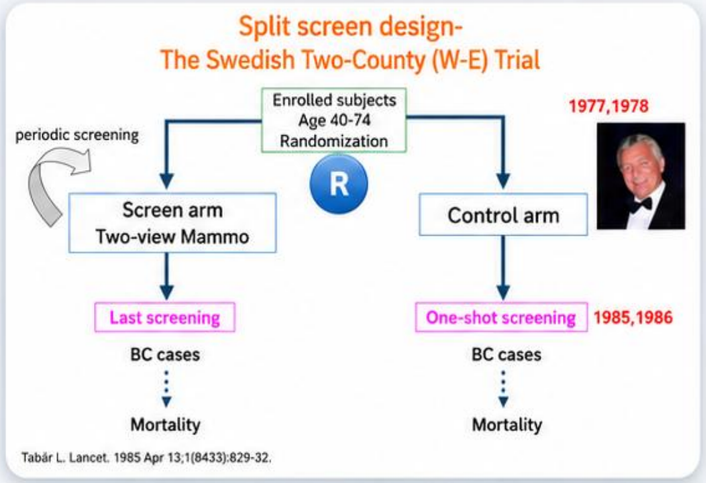
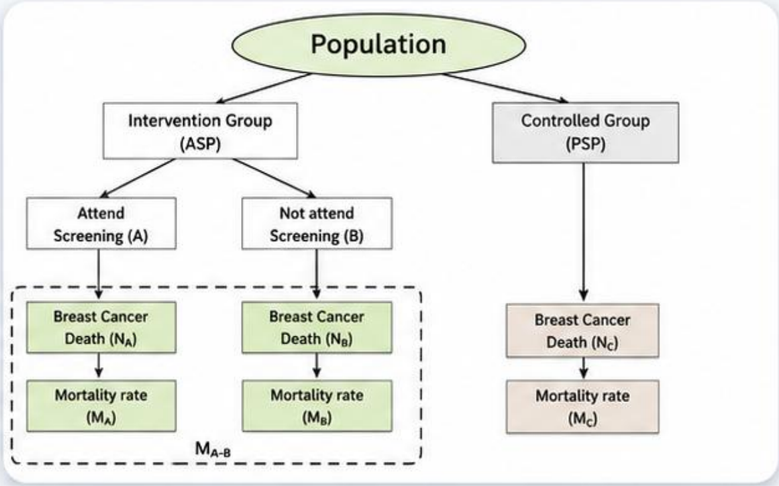
International Asian Cancer and Chronic Disease Screening Network | IACCS 2026

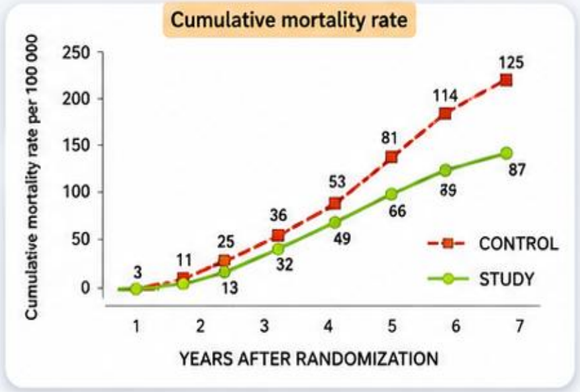
Evolution of Breast Cancer Prevention



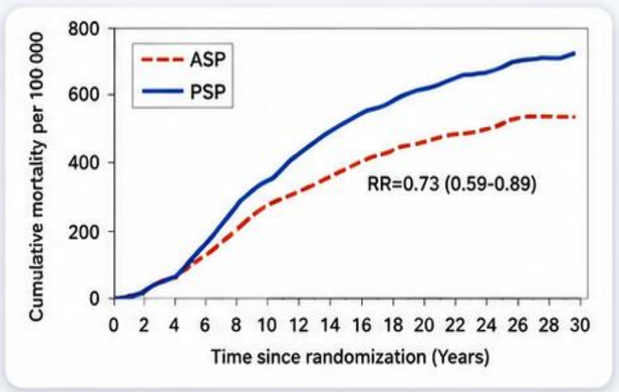


1 Before screen era - 1977 | 2 Trial period 1977-1988 | 3 Service screening programme 1988 -

Assessment



Evidence-based Health Policy Making



Assurance

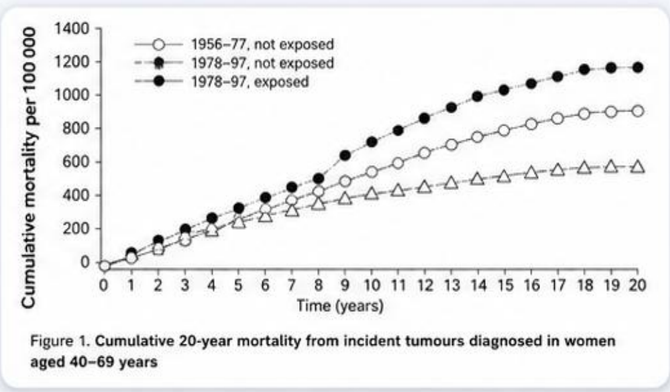


Figure 1. **Cumulative 20-year mortality from incident tumours diagnosed in women aged 40–69 years**

Biases in the Evaluation for Service Screening Program

1 Traditional Evaluation: Randomized Controlled Trials (RCTs)

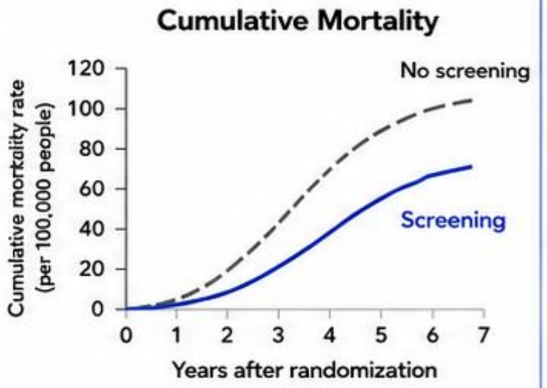
Eligible population

Population meeting eligibility criteria (potential participants)

R — Randomization

Screening group (receives screening)

No-screening group (usual care)



RCTs compare important outcomes (e.g., mortality).

Examples of Screening Evaluated in RCTs

- Mammography (breast cancer)
- FOBT / FIT (colorectal cancer)
- LDCT (lung cancer screening)
- PSA (prostate cancer screening)

Strengths

- Randomization minimizes selection bias.
- Provides high-quality evidence for mortality reduction.

Limitations

- Nationwide implementation takes time and resources.
- Not feasible for ongoing program evaluation.

RCTs can establish effectiveness under controlled conditions.

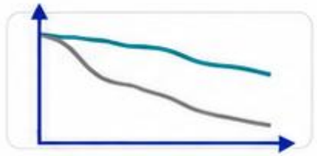
Key Question: After nationwide implementation, how can we evaluate screening effectiveness when a randomized control group no longer exists?

2 Real-World Evaluation: Observational Comparisons in Practice

Screened population (people who receive screening)

Unscreened population (people who do not receive screening)

Real-world data from routine practice (e.g., registries, claims data, EHRs)



Compare outcomes (e.g., survival, mortality)

Key Question

How can we evaluate screening effectiveness in the real world when a randomized control group no longer exists?

Limitations: Traditioonal Approaches Are Subject to Major Biases

Lead-time Bias
Earlier diagnosis looks better, even if the time of death is unchanged.

Length Bias
Slow-growing tumors are more likely to be detected by screening.

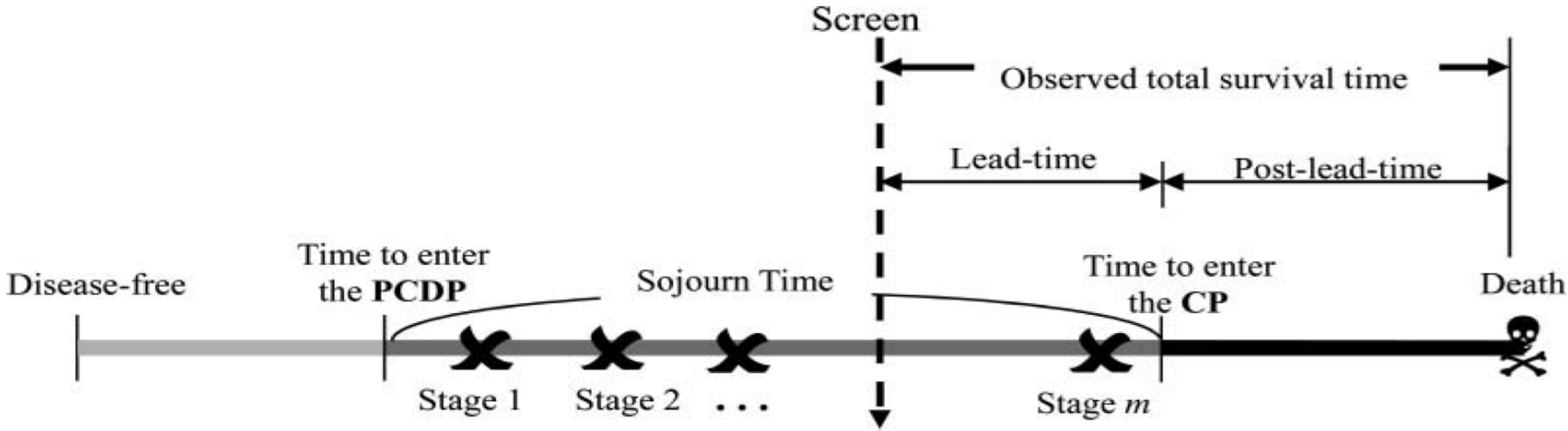
Self-selection Bias
People who participate in screening are healthier and have different risk profiles.

Takeaway: RCTs provide the most reliable evidence for screening effectiveness.

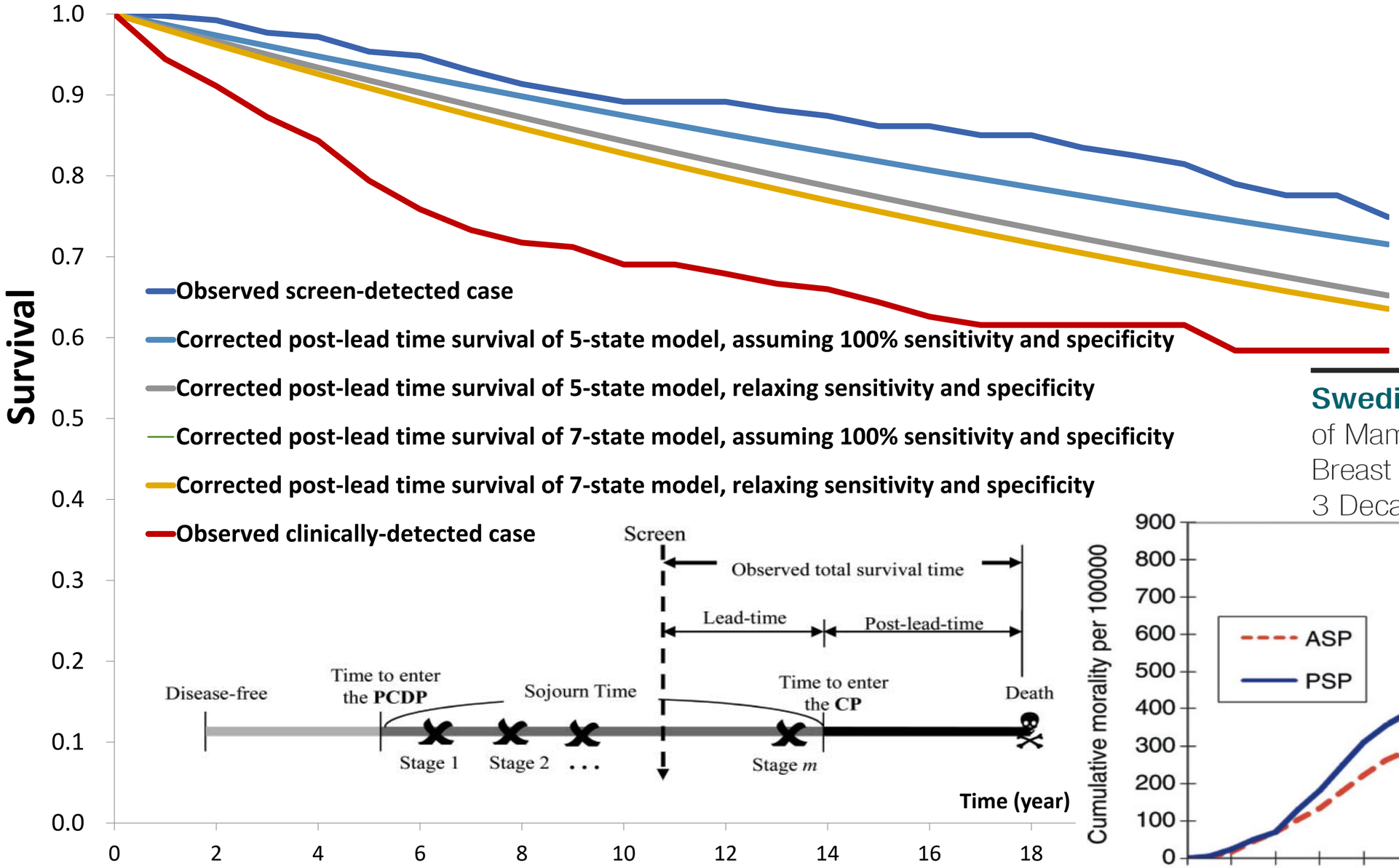
In real-world settings, careful study design and analytic strategies are essential to address biases and generate valid insights.

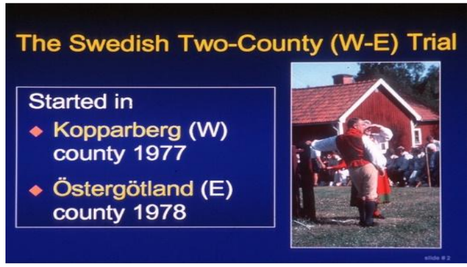
Breast Cancer Timeline

Free of BC → **Preclinical (PCDP)** → **Clinical (CP)**



Estimating the Benefits of Universal Screening Program

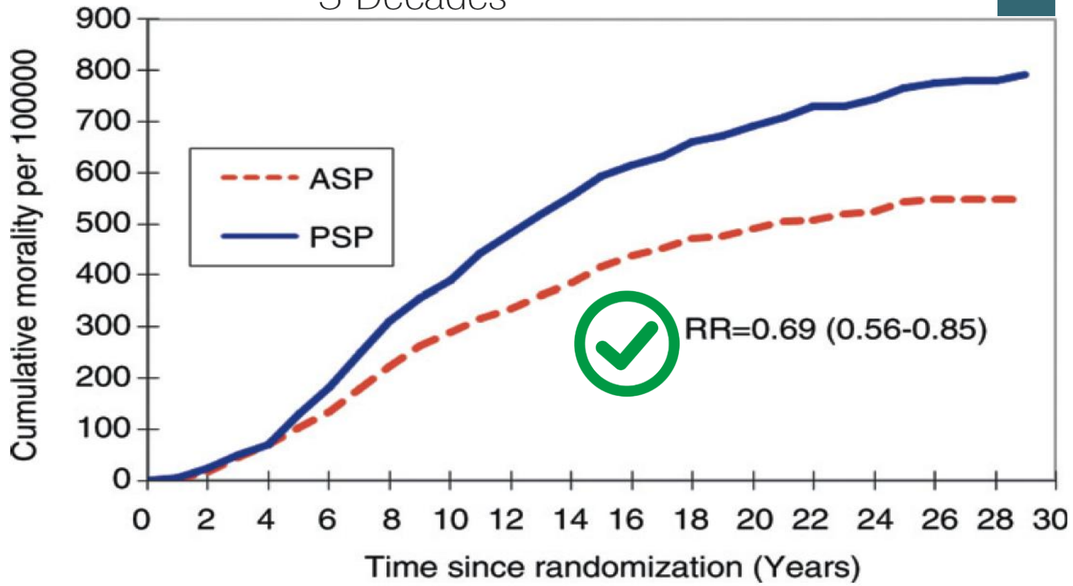




RR=0.43 (95% CI: 0.33-0.56)
RR=0.55 (95% CI: 0.41-0.71)
RR=0.67 (95% CI: 0.47-0.89)
RR=0.70 (95% CI: 0.52-0.89)
RR=0.70 (95% CI: 0.52-0.89)
RR=1.00

Swedish Two-County Trial: Impact of Mammographic Screening on Breast Cancer Mortality during 3 Decades[1]

Radiology



Hsiu-Hsi Chen , Amy Ming-Fang Yen & Laszlo Tabár (2012): A Stochastic Model for Calibrating the Survival Benefit of Screen-Detected Cancers, JASA, 107:500, 1339-1359

Is it Possible to Evaluate Screening Program Dispensing with Data from the Entire Cohort?

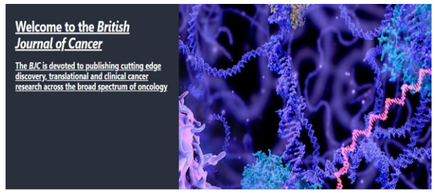
Clinical | Open access | Published: 10 June 2003

A case–cohort study for the disease natural history of adenoma–carcinoma and *de novo* carcinoma and surveillance of colon and rectum after polypectomy: implication for efficacy of colonoscopy

C-D Chen, M-F Yen, W-M Wang, J-M Wong & TH-H Chen

British Journal of Cancer **88**, 1866–1873 (2003) | Cite this article

8310 Accesses | **130** Citations | **7** Altmetric | Metrics



Research Article

Stochastic model for non-standard case–cohort design

Tony Hsiu-Hsi Chen, Ming-Fang Yen, Ming-Neng Shiu, Tao-Hsin Tung, Hui-Min Wu

First published: 23 January 2004 | https://doi.org/10.1002/sim.1610 | VIEW METRICS

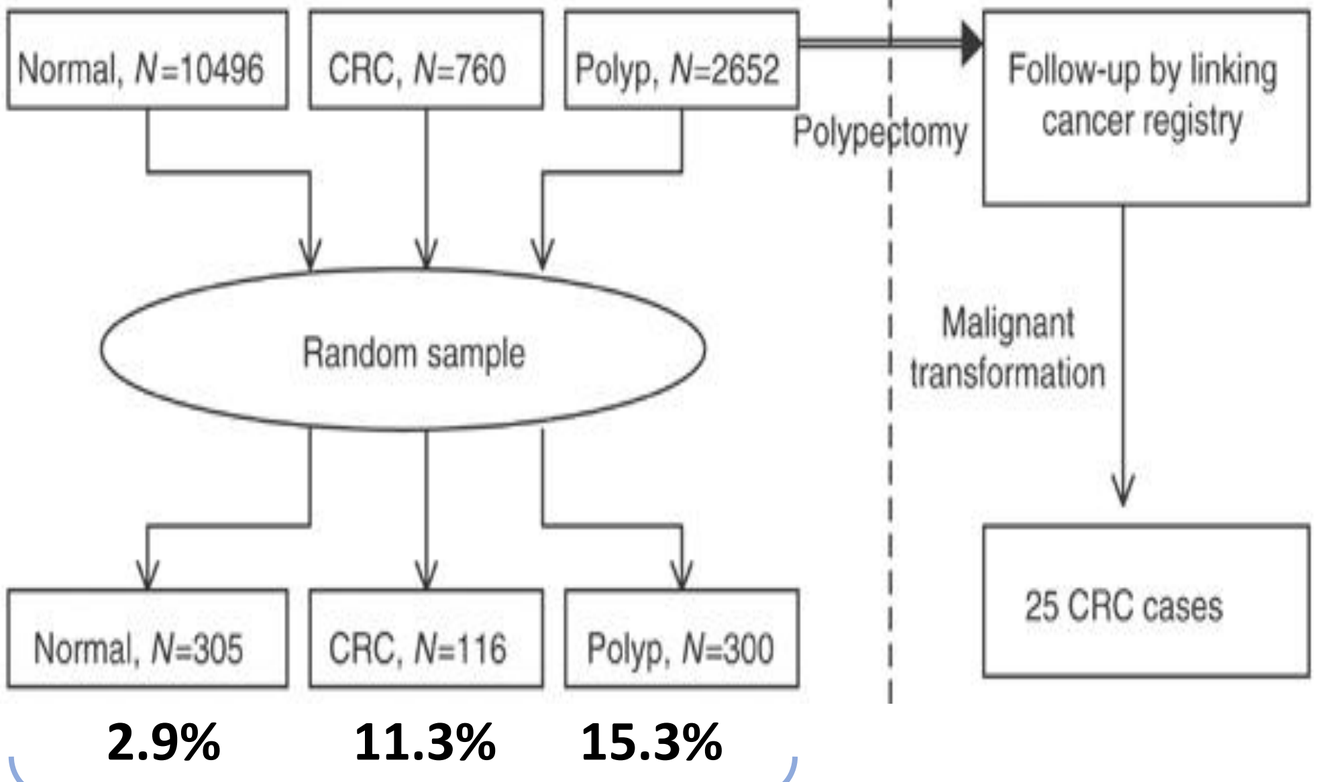
Aims

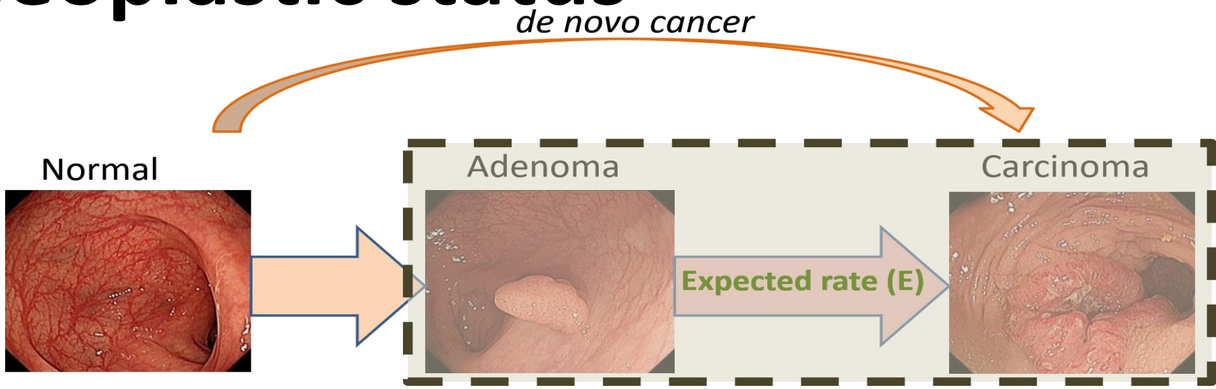
1. Estimate **progression rates** from normal mucosa to carcinoma
2. Estimate **malignant transformation** after polypectomy
3. Assess the effectiveness of polypectomy
4. Compare progression by adenoma size and histological type

Sampling Scheme for Colorectal Neoplastic status

Part I
Estimating of Parameters Associated with Disease Natural History (Expected)

Part II
Malignant Transformation Rate After Polypectomy (Observed)



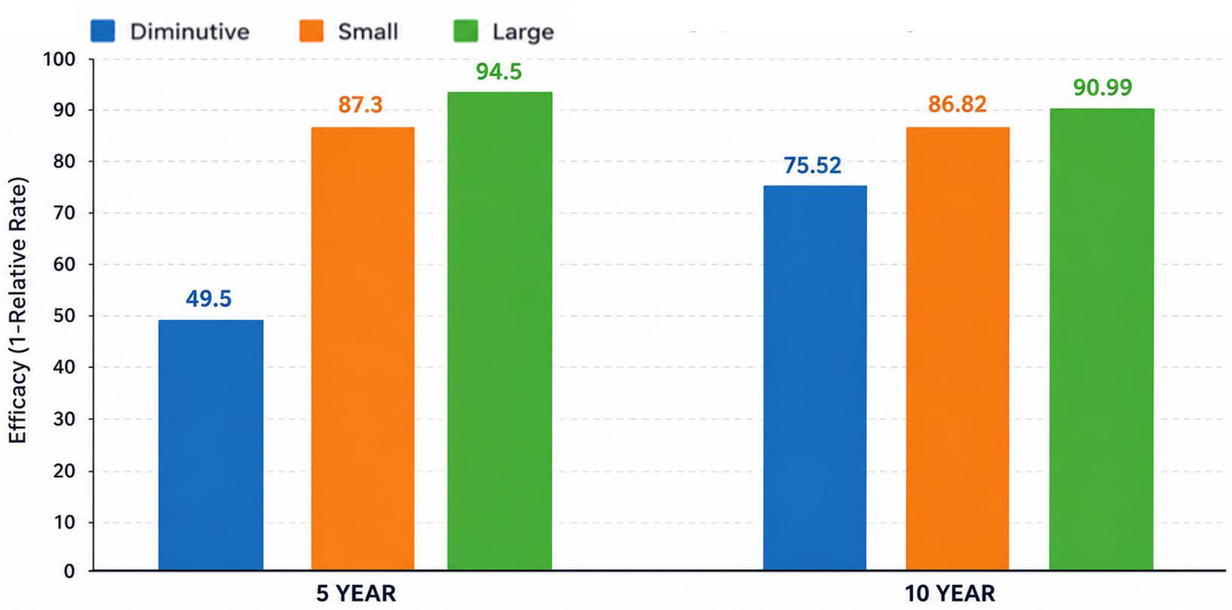


Without considering de novo cancers

$$88\%\left(=\left(1-\frac{0.0026}{0.022}\right)\times 100\%\right)$$

Considering de novo cancers

$$73\%\left(=\left(1-\frac{0.0026}{0.0095}\right)\times 100\%\right)$$



Efficacy=1-O/E

O: observed rate of disease progression

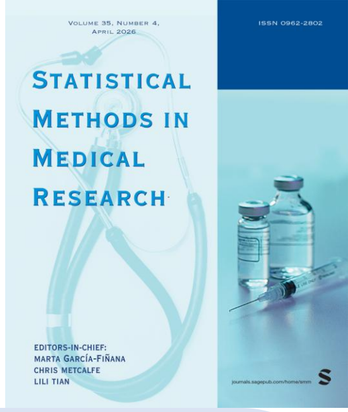
E: expected rate of disease progression

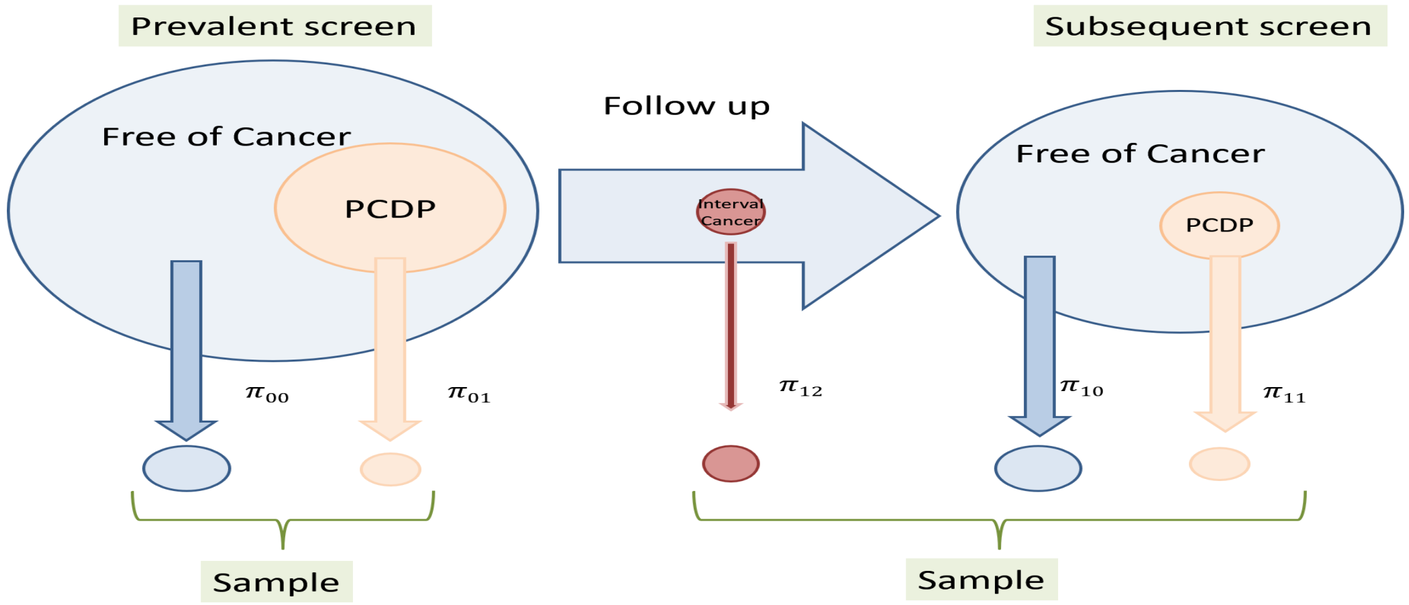
Restricted access | Research article | First published online November 20, 2019 | Request permissions

Sampling-based Markov regression model for multistate disease progression: Applications to population-based cancer screening program

Chen-Yang Hsu, Wen-Feng Hsu, Amy Ming-Fang Yen, and Hsiu-Hsi Chen View all authors and affiliations

Volume 29, Issue 8 | https://doi.org/10.1177/0962280219885400

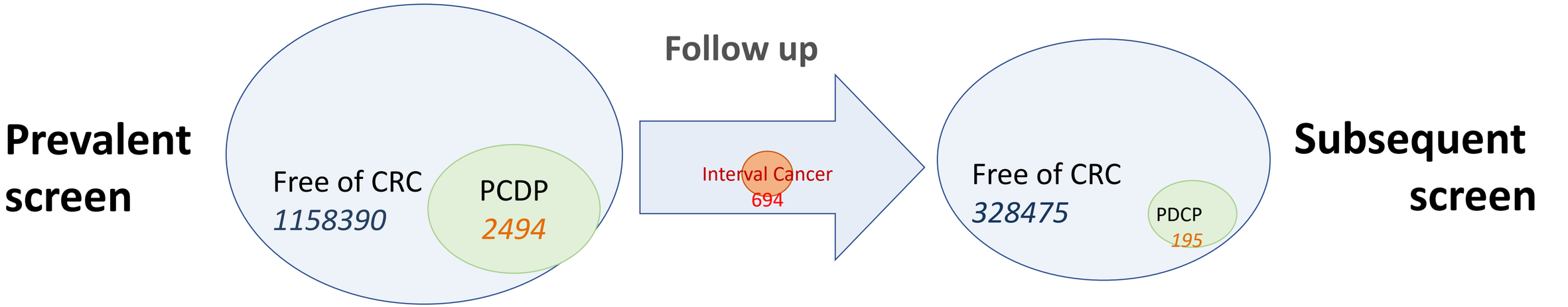




Aims

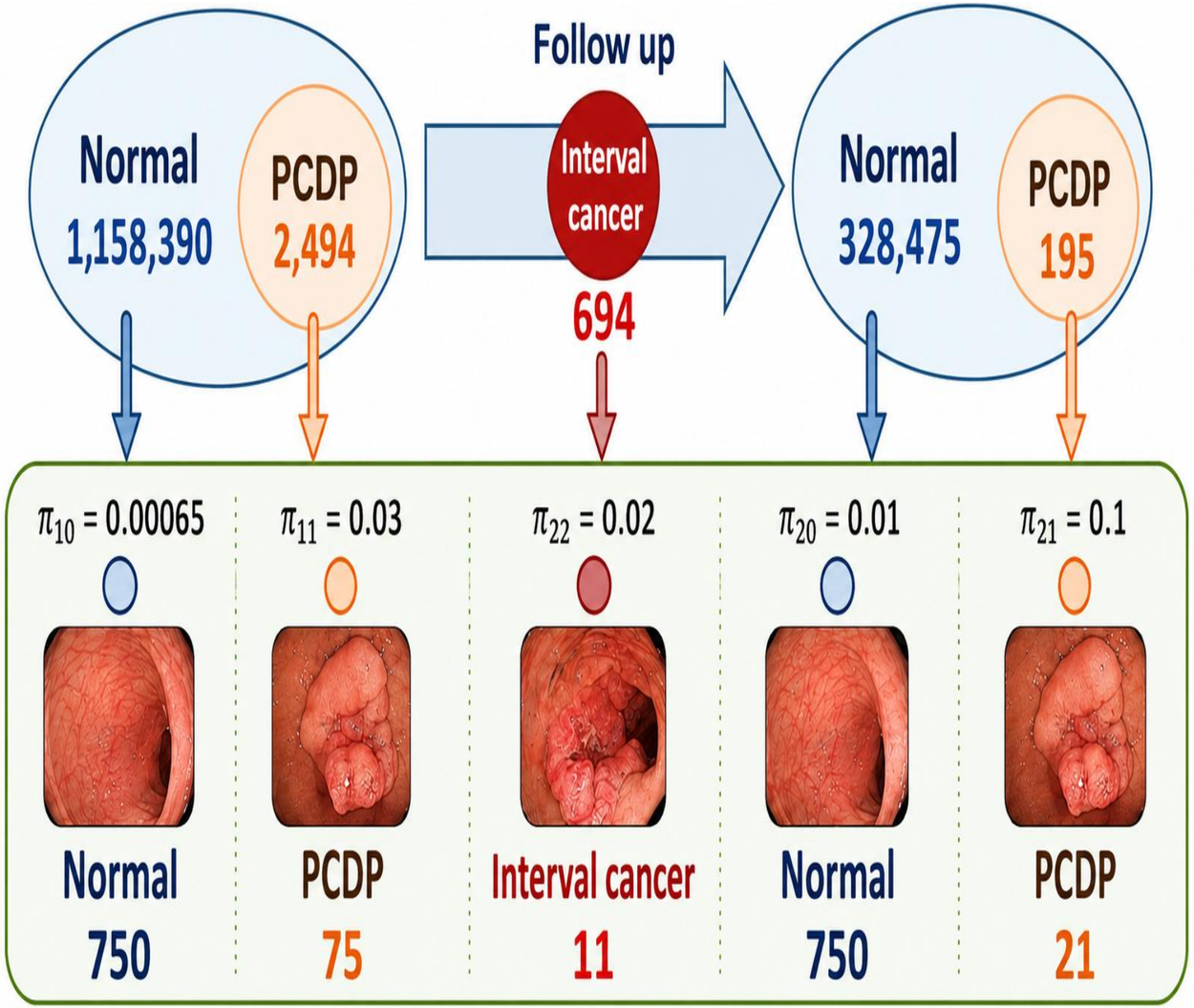
- Extent the **non-standard case-cohort design** from cross-sectional study to follow-up study
- Incorporation measurement error in the model
- Elucidate multistate **disease progression**
- Assess the **state-specific effect** of subject-specific characteristics with efficiency

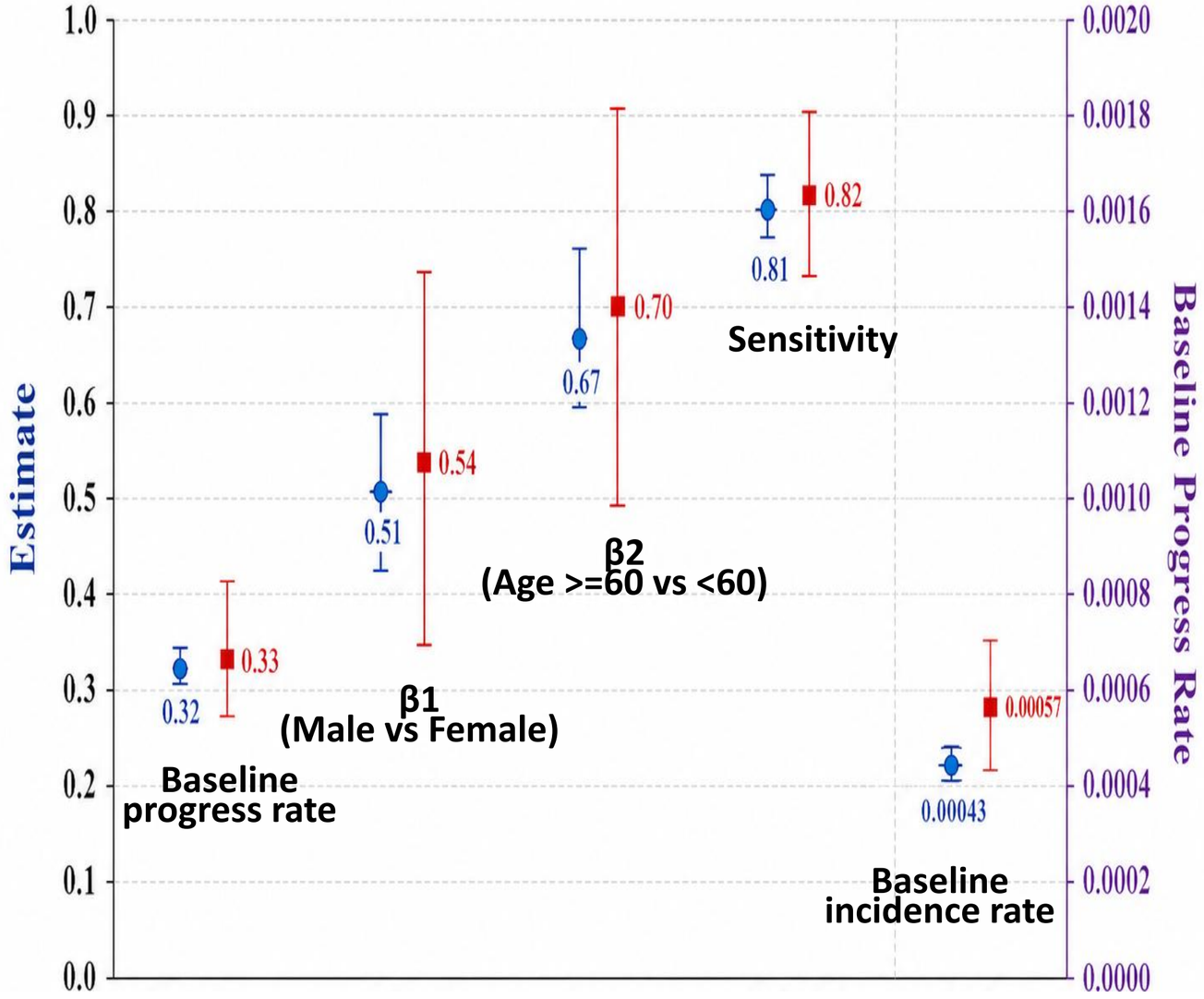
Data on population-based screening for colorectal cancer in Taiwan



	Normal		PCDP		Interval cancer	
	Frequency	*(%)*	*Frequency*	*(%)*	*Frequency*	*(%)*
Prevalent screen						
Overall	1158390	(99.8)	2494	(0.2)	-	
Male	444937	(38.4)	1347	(54.0)	-	
Age ≧ 60	442793	(38.2)	1424	(57.1)	-	
Subsequent screen						
Overall	328475	(99.7)	195	(0.06)	694	(0.21)
Male	110862	(33.8)	99	(50.8)	340	(49.0)
Age ≧ 60	168966	(51.4)	130	(66.7)	214	(30.8)

Unbiased Estimates for Disease Evolution Parameters using Sampled Data of Empirical CRC Screening Data





Unbiased Estimates for Disease Evolution Parameters using Sampled Data of Simulated Breast Cancer Data

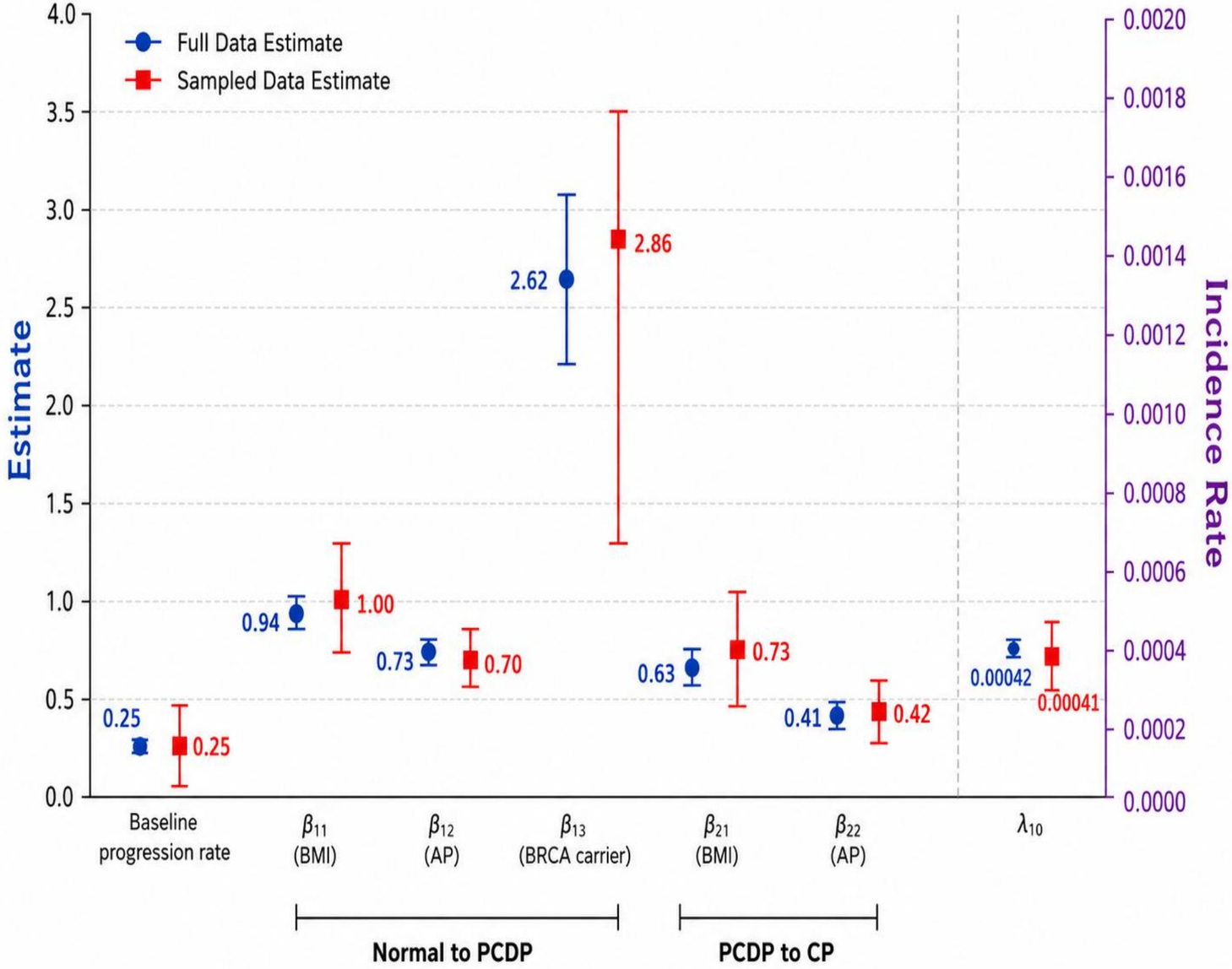
Free of BC → Preclinical (PCDP) → Clinical (CP)

Full Data

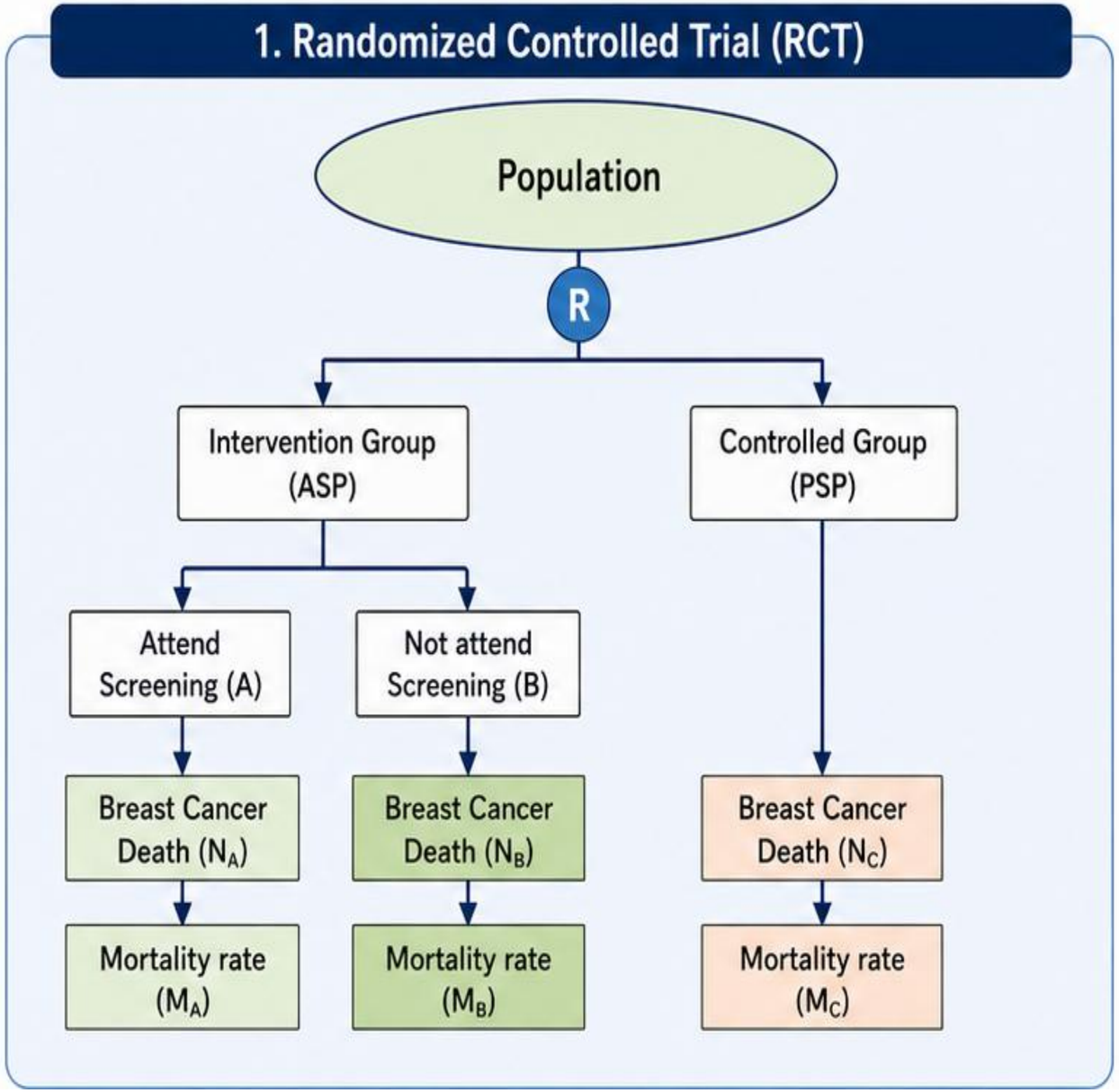
Prevalent screen			Follow up	Subsequent screen	
Free of BC	Preclinical (PCDP)		Clinical (CP) / Interval cancer	Free of BC	Preclinical (PCDP)
997,721	2,279		777	995,639	1,305

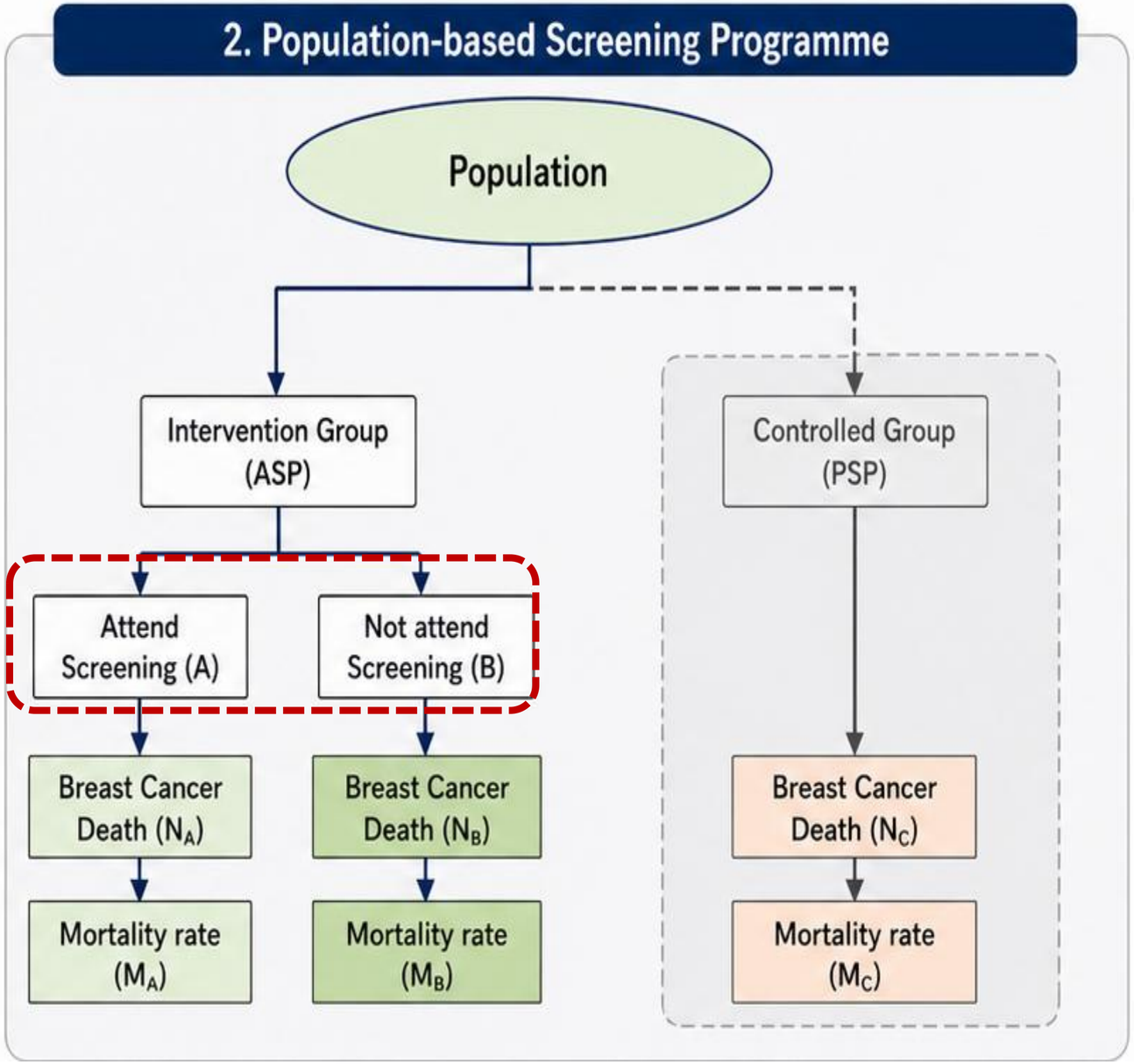
Sampled Data

Free of BC Prevalent screen	Preclinical (PCDP) Prevalent screen	Clinical (CP) / Interval cancer	Free of BC Subsequent screen	Preclinical (PCDP) Subsequent screen
$\pi_{10} = 0.01$	$\pi_{11} = 0.07$	$\pi_{22} = 0.05$	$\pi_{20} = 0.005$	$\pi_{21} = 0.06$
Sampled count	Sampled count	Sampled count	Sampled count	Sampled count
6,000	160	40	4,800	80



Evaluation for Population-based Service Screening Program: Self-Selection Bias

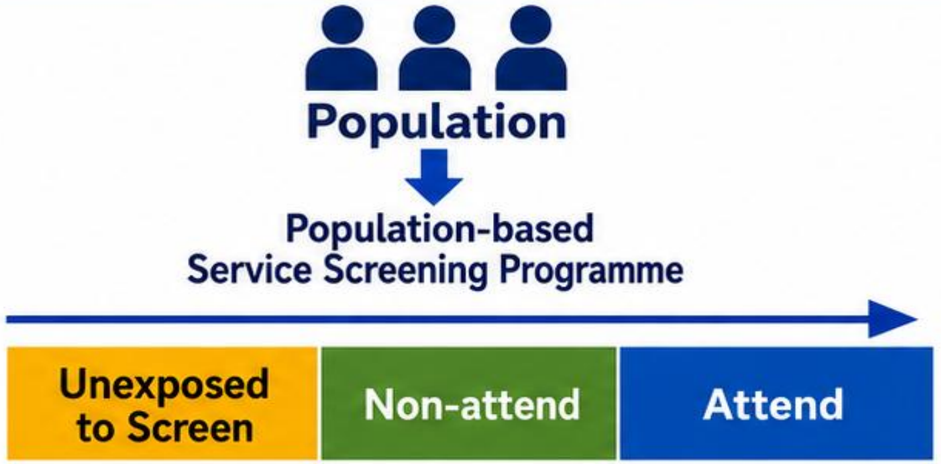




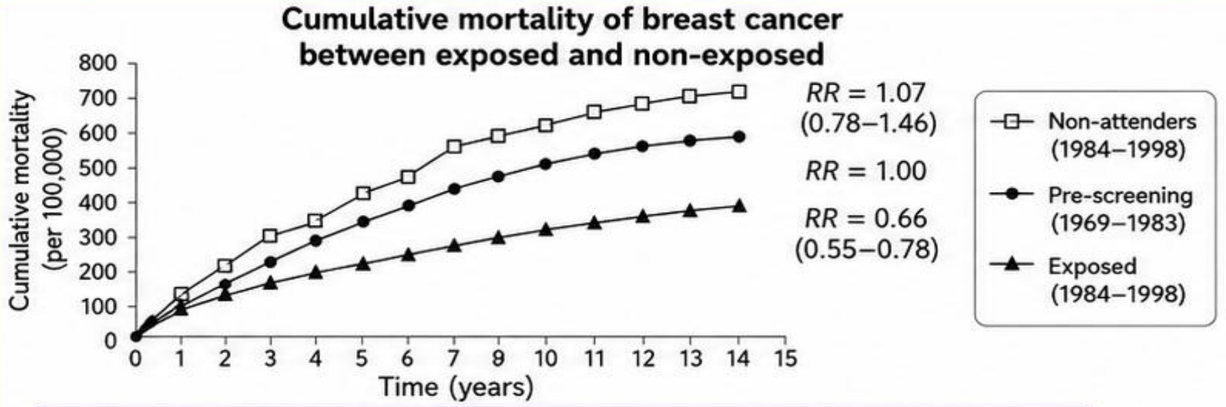
Selection Bias Adjustment in Service Screening

Adjusting for different cumulative mortality between attendees and non-attendees

1. Study Design (Quasi-experimental Design)



2. Why Adjustment Is Needed



Non-attenders have higher cumulative mortality than attendees.
Without adjustment, the screening benefit may be underestimated.

3. Adjustment Formula and Calculation

Formula

$$RR = [\text{attendance rate}] \times \frac{M_A}{M_C} + [1 - \text{attendance rate}] \times \frac{M_B}{M_C}$$

Attend Screening (A) — Mortality rate: M_A / M_C

Not Attend Screening (B) — Mortality rate: M_B / M_C

Illustrative Calculation

Attend (A): $RR = 0.66$ (M_A / M_C)

Not attend (B): $RR = 1.07$ (M_B / M_C)

Adjusted RR

$RR = [\text{attendance rate}] \times 0.66 + [1 - \text{attendance rate}] \times 1.07$

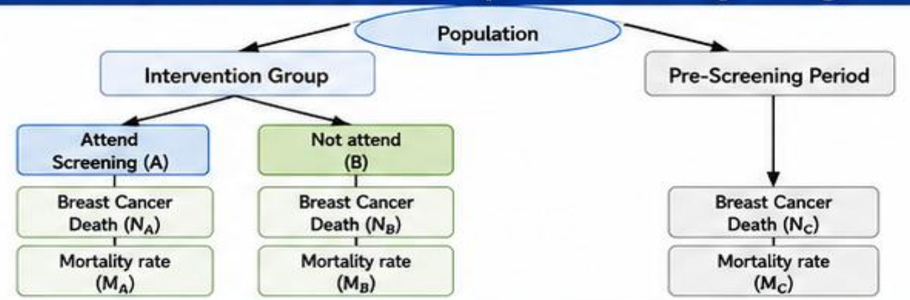
Example: attendance rate = 0.38

$RR = 0.38 \times 0.66 + 0.62 \times 1.07$

$RR \approx 0.90$

More accurate estimate of screening effect

4. How the Formula Maps to the Study Design



$$RR = [\text{attendance rate}] \times \frac{M_A}{M_C} + [1 - \text{attendance rate}] \times \frac{M_B}{M_C}$$

Poisson Regression model for full adjustment (Self-selection, Period, Age) RR: 0.59

Tabar: Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. Lancet 2003

Study Population: Pirkanmaa, Finland (1988–2000)

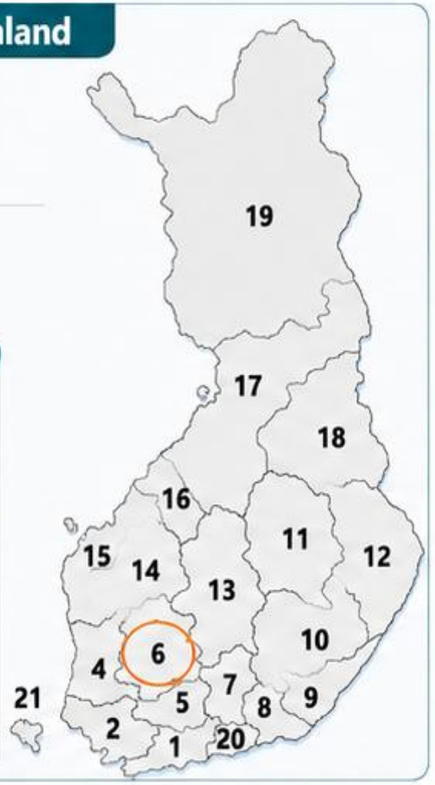
Region Overview: Pirkanmaa, Finland

Finland Population
~ 5.4 millions

Pirkanmaa Population
~ 0.49 millions

Available Regions (National Level)

1. Uusimaa
2. Varsinais-Suomi
3. Satakunta
4. Kanta-Häme
5. Päijät-Häme
6. **Pirkanmaa**
7. Kymenlaakso
8. Etelä-Karjala
9. Etelä-Savo
10. Pohjois-Savo
11. Pohjois-Karjala
12. Keski-Suomi
13. Etelä-Pohjanmaa
14. Pohjanmaa
15. Keski-Pohjanmaa
16. Pohjois-Pohjanmaa
17. Kainuu
18. Lappi
19. Itä-Uusimaa
20. Åland
21. Åland



95,057 Total invitations

84,812 Attendants

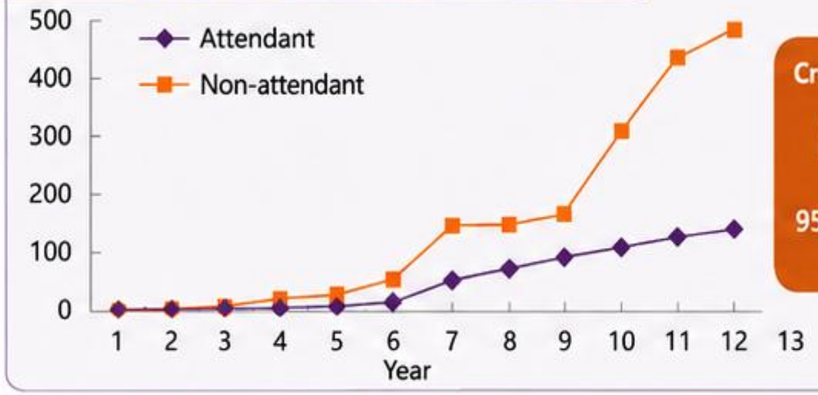
89.2% Average attendance rate

Cohort followed	Women	Share
Total followed	33,375	100%
Exposed (attended ≥1 screen)	31,192	93.5%
Non-exposed (never attended)	2,183	6.5%

Invitations, Attendance and Attendance Rate by Year

Year	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	Total
Invitations	4553	5039	7142	6452	8024	6923	6885	8183	7558	7910	8125	9665	8598	95057
Attendants	4005	4358	6340	5728	7187	6162	6176	7288	6779	7018	7309	8677	7786	84812
Attendance rate (%)	87.96	86.49	88.77	88.78	89.57	89.01	89.70	89.06	89.69	88.72	89.96	89.78	90.56	89.22

Cumulative Mortality (per 100,000)



Crude relative rate
0.27
95% CI 0.12–0.61
— biased

Age Group (years)	Study Outcomes by Age Group								Unexposed	
	Exposed									
	Prevalent cases		Incident cases		Interval cases[a]		Interval cases[b]			
	Death	No.	Death	No.	Death	No.	Death	No.	Death	No.
50–54	7	101	4	65	6	65	0	2	1	9
55–59	0	29	2	94	11	64	1	9	6	11
Total	5	130	6	159	17	129	1	11	7	20

[a] Interval cases: Diagnosed between screens

[b] Interval cases: Diagnosed after last screen

Wu JC et al. Evaluation of breast cancer service screening programme with a Bayesian approach: mortality analysis in a Finnish region. Breast Cancer Res Treat. 2010 Jun;121(3):671-8.

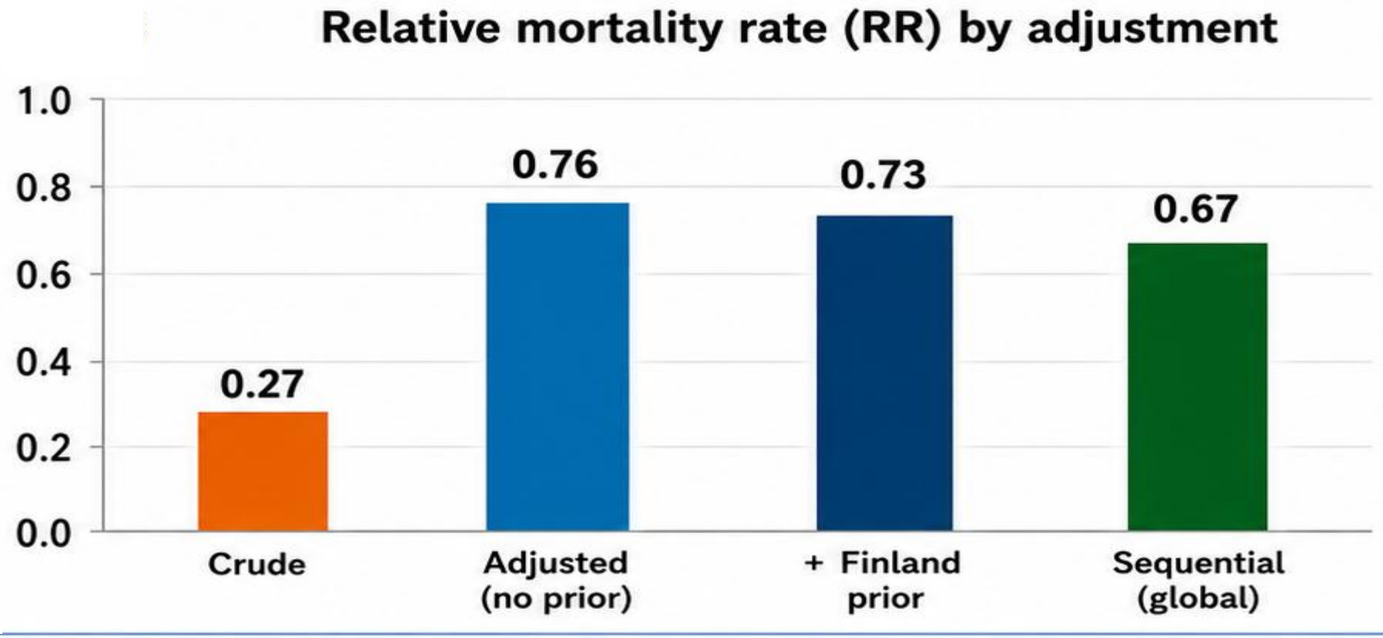
Unbiased Estimate of Breast Cancer Screening Benefit in Pirkanmana

A Finland data only – Pirkanmaa

Prior specification	Adjusted RR (95% CI)
Non-informative prior no prior	0.76 (0.49–1.15)
Informative prior from Hakama nationwide study	0.73 (0.57–0.93)

B Sequential Bayesian (global, chronological updating)

#	Study / year / region	Sequential posterior RR (95% CI)
1	Tabár et al. / 1977 / Dalarna, Sweden	0.46 (0.29–0.72)
2	Bjurstam et al. / 1982 / Gothenburg, Sweden	0.69 (0.51–0.92)
3	Hakama et al. / 1987 / Finland	0.70 (0.56–0.86)
4	**Current study / 1988 / Pirkanmaa, Finland**	**0.67 (0.55–0.80)**



Validation: The Method Recovers RCT Results

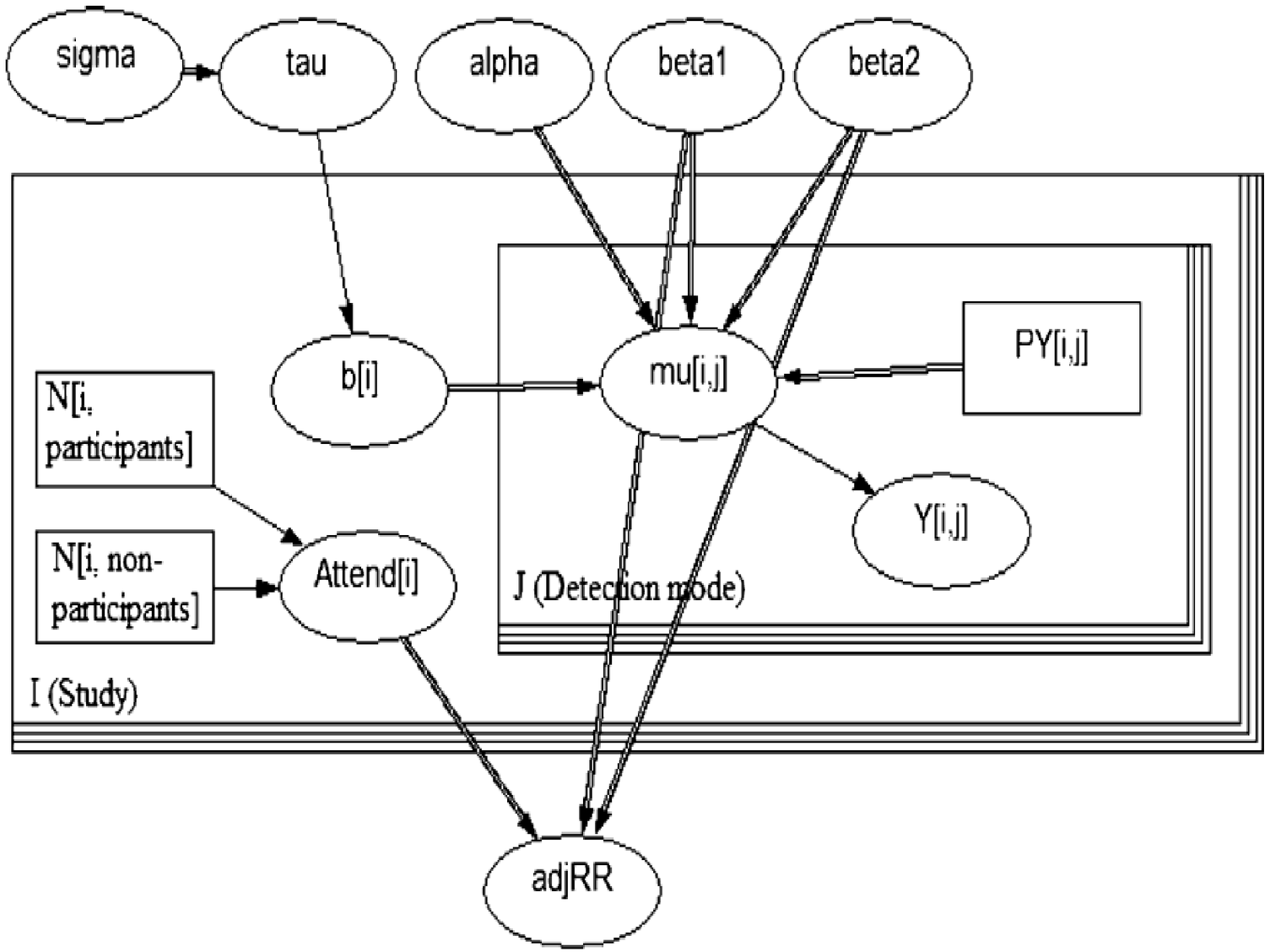
Study (age 50–59)	Bayesian self-selection adjustment	Randomized trial (ITT)
Dalarna-county trial	0.47 (0.29–0.72)	0.46 (0.29–0.73)
Gothenburg trial	0.93 (0.60–1.34)	0.91 (0.61–1.36)
Finnish nationwide program	0.77 (0.54–1.10)	0.76

Across three Nordic trials the bias-adjusted estimates closely match the trial results — evidence the self-selection correction works.

Wu JC et al. Evaluation of breast cancer service screening programme with a Bayesian approach: mortality analysis in a Finnish region. Breast Cancer Res Treat. 2010 Jun;121(3):671-8.

Bayesian Model for Self-selection Bias Adjustment

Evaluation of breast cancer service screening program with a Bayesian approach: mortality analysis in a Finnish region



Mortality Model

$$\log\left(\frac{\mu_{ij}}{\mathrm{PY}_{ij}}\right) = \alpha + \beta_1 I_S + \beta_2 I_{\overline{S}} + b_i$$

where

- μ_{ij} : expected mortality rate in study i, detection mode j
- PY_{ij} : person-years at risk in study i, mode j
- I_S : indicator for participants
- $I_{\overline{S}}$: indicator for non-participants
- b_i : random effect for study i (captures between-study heterogeneity)

Adjustment for Self-selection Bias

$$\mathrm{adjRR} = \mathrm{Attend} \times \exp(\beta_1) + (1 - \mathrm{Attend}) \times \exp(\beta_2)$$

where Attend = attendance rate (proportion who participated)

Wu JC et al. Evaluation of breast cancer service screening programme with a Bayesian approach: mortality analysis in a Finnish region. Breast Cancer Res Treat. 2010 Jun;121(3):671-8.

Taiwan CRC screening program

2004-2023

Real World Data

Note that the program has extended to 45-49 age group in 2025

- **6.3 million** individuals screened
- **17.5 million** FITs performed
- (ascertain **104,052** advanced adenomas and **33,909 CRCs**)

Eligible Population aged 50-74

Have had a FIT screening in the past two years?

Yes

No

Questionnaire + **FIT Screening**

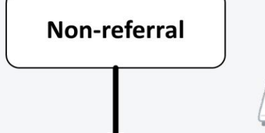
6.9%

FIT Positive

FIT Negative

Non-referral

Health Bureau



70%

Referral to Colonoscopy exam

Adenoma/ Colorectal Cancer

Normal

Treatment / Surveillance

Next Screening

Cancer Screening Data Monitoring Center

Data Analysis

- ✓ Screening Rate
- ✓ Screening Statistics
- ✓ Indicators Monitor

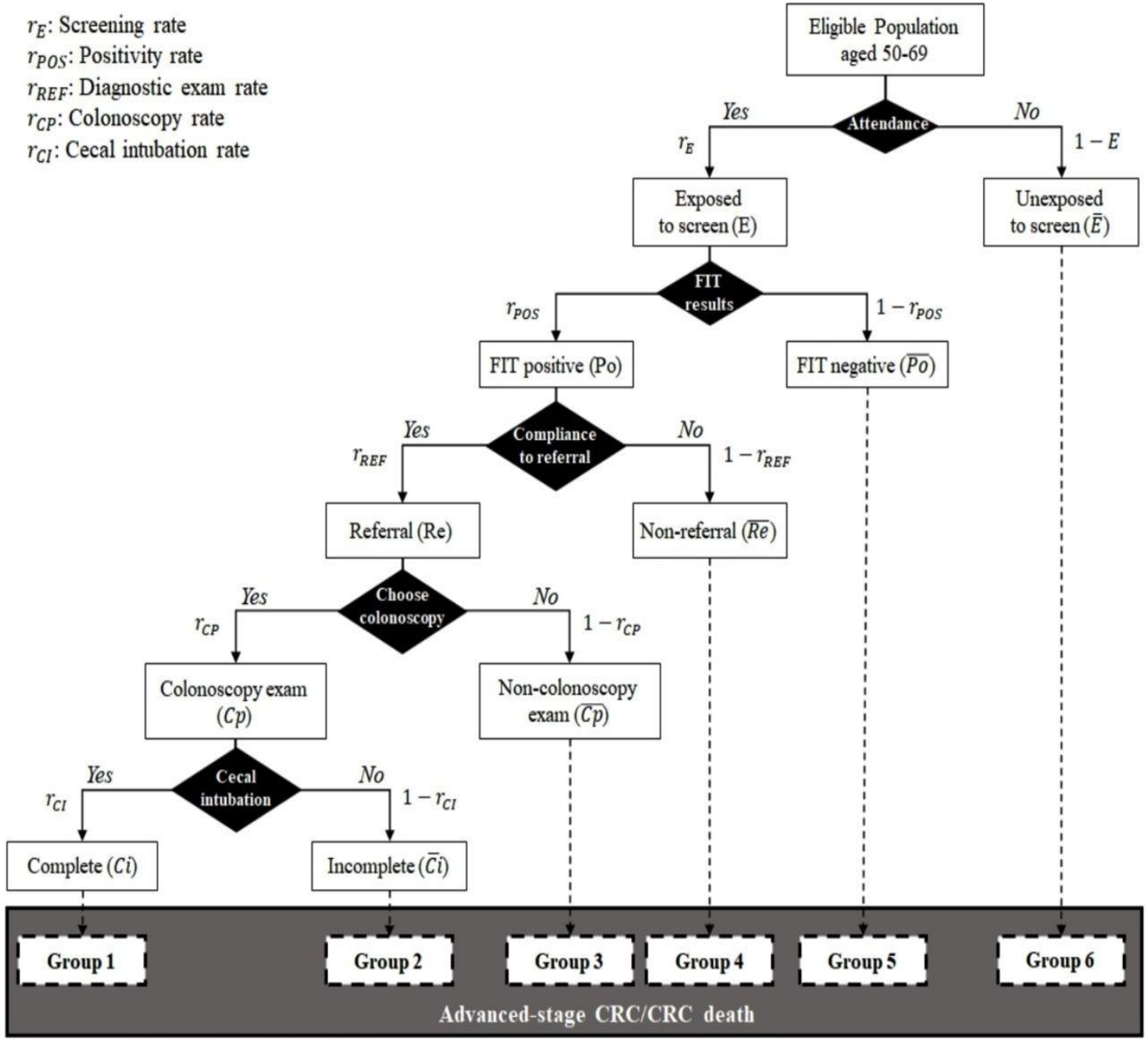
Health Promotion Administration

Universal Biennial Screening Benefit

	aRR_2 (full adjustment)‡
Incidence of advanced cancer†	
Overall	0.66 (0.63 to 0.70)
Proximal	0.84 (0.77 to 0.92)
Distal	0.61 (0.58 to 0.64)
Mortality	
Overall	0.60 (0.57 to 0.64)
Proximal	0.72 (0.66 to 0.80)
Distal	0.56 (0.53 to 0.59)

Chiu et al, Long-term effectiveness of faecal immunochemical test screening for proximal and distal colorectal cancers 2021 *Gut*

r_E: Screening rate
r_{POS}: Positivity rate
r_{REF}: Diagnostic exam rate
r_{CP}: Colonoscopy rate
r_{CI}: Cecal intubation rate



Adjustment with Bayesian DAG Poisson Regression

1 MODEL

Let Y be the number of advanced-stage CRC or CRC deaths in each group.
Assume $Y \sim \text{Poisson}(\mu)$.
The model links exposure status and covariates (age, sex) while accounting for time trend.

$$\log(\mu) = \log(PY) + \beta_b + \sum_{i=1}^{8} \beta_i X_i$$

- PY = person-years (offset)
- X_i = covariates (indicator variables for the six pathways, age group, sex)
- β_b = background growth (natural log-linear trend of incidence)
- Estimated as 0.0443 (se = 0.000243) from pre-screening time trend

2 INTERPRETATION OF COEFFICIENTS

Taking exponent of coefficients gives six relative rates (RRs) compared with the uninvited (control) group:

Coefficient	Pathway (vs uninvited)	Meaning	$RR = e^{\beta_i}$
β_1	$E \rightarrow Po \rightarrow Re \rightarrow Cp \rightarrow Ci$	Reached cecum with colonoscopy	e^{β_1}
β_2	$E \rightarrow Po \rightarrow Re \rightarrow Cp \rightarrow \overline{Ci}$	Colonoscopy but incomplete	e^{β_2}
β_3	$E \rightarrow Po \rightarrow Re \rightarrow \overline{Cp}$	Referred but no colonoscopy	e^{β_3}
β_4	$E \rightarrow Po \rightarrow \overline{Re}$	Positive FIT but not referred	e^{β_4}
β_5	$E \rightarrow \overline{Po}$	Negative FIT	e^{β_5}
β_6	$\bar{E}$	Non-attender (unexposed)	e^{β_6}

3 ADJUSTED RELATIVE RATE (aRR)

using ITT with self-selection bias adjusted

The adjusted RR (aRR_2) corresponding to equation (7):

$$\begin{aligned} aRR_2 &= e^{\beta_1} \cdot r_{CI} \cdot r_{CP} \cdot r_{REF} \cdot r_{POS} \cdot r_E \\ &+ e^{\beta_2} \cdot (1 - r_{CI}) \cdot r_{CP} \cdot r_{REF} \cdot r_{POS} \cdot r_E \\ &+ e^{\beta_3} \cdot (1 - r_{CP}) \cdot r_{REF} \cdot r_{POS} \cdot r_E \\ &+ e^{\beta_4} \cdot (1 - r_{REF}) \cdot r_{POS} \cdot r_E \\ &+ e^{\beta_5} \cdot (1 - r_{POS}) \cdot r_E \\ &+ e^{\beta_6} \cdot (1 - r_E) \end{aligned}$$

- r_{CI} = proportion reaching cecum with colonoscopy (contingent on being referred)
- r_{CP} = proportion complete colonoscopy (contingent on reaching cecum)
- r_{REF} = proportion referred (contingent on positive FIT)
- r_{POS} = proportion positive FIT among invitees
- r_E = proportion invited (ITT uptake rate)

Thank you for your attention