

Module 3 Study Design for Evaluation of Disease Screening-

Quasi-experimental Design

(Ref: Chen LS, Yen AM, Duffy SW, et al. Computer-aided system of evaluation for population-based all-in-one service screening (CASE-PASS): from study design to outcome analysis with bias adjustment. *Annals of epidemiology*. 2010; 20(10): 786-96.)

3.1 Study design of population-based disease service screening

Population-based cancer service screening programs, which are not based on randomized design, have been suggested in either developed or developing countries as a means to reduce mortality. However, despite the effectiveness of mass screening with randomized controlled design, it does not imply the same benefits that result from population-based screening programs as the related factors or parameters cannot be appropriately regulated or well controlled with a good quality assurance program. For example, a lower coverage rate, attendance rate, sensitivity, specificity, referral rate, and delay to treatment due to known or unrecognized factors may provide a small benefit.

Several obstacles exist for the analysis of data from population-based cancer service screening programs. The current study design used for this evaluation of effectiveness in population-based service screening (non-randomized property) differs from those usually employed in a randomized controlled trial. First, in a randomized controlled trial, the control group (the uninvited) is well managed through a randomization design compared to population-based service screening programs in which the comparator can either come from the historical cohort in the absence of

screening, or from the non-attendees during the contemporaneous period with the attendee. Second, as the evaluation of the effectiveness of population-based service screening requires parameters set at both the population and individual levels, processing is both time-consuming and demanding. One must therefore develop a systematic health information system that incorporates the various registered data, including the population registry, mass screening data, cancer registry data, and mortality registry data.

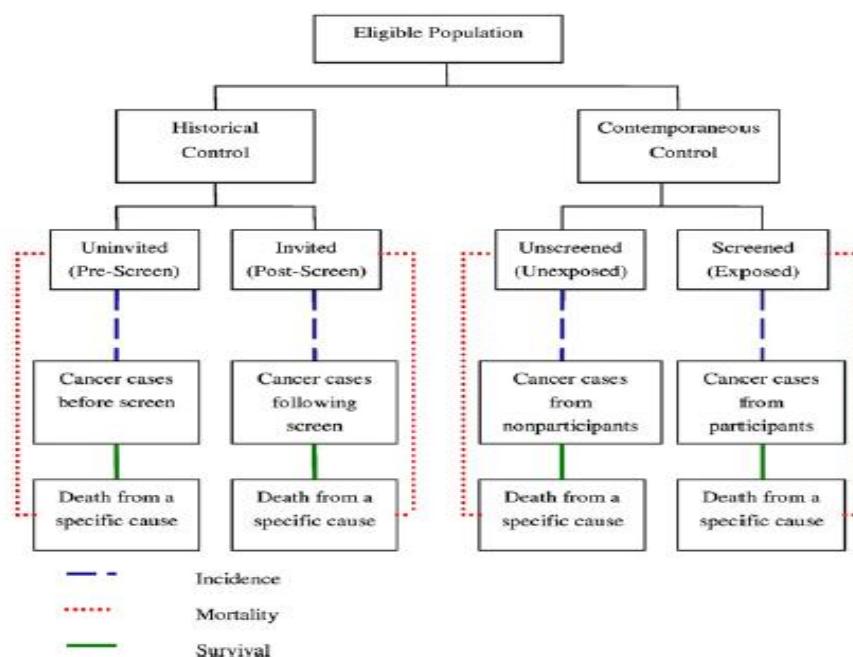


Figure 3-1 Diagram of the study design on the evaluation of population-based cancer service screening

3.1.1 Historical Control (Before and After Design)

The One-Group Pretest-Posttest Design

$$O_{x-} \quad X \quad O_{x+}$$

3.1.2 Contemporaneous Control

Posttest-Only Design with Nonequivalent Group

$$\begin{array}{ll}
 X+ & O \text{ (Exposed)} \\
 X- & O \text{ (Unexposed)}
 \end{array}$$

3.2 Service Screening for Breast Cancer in Sweden

3.2.1 Organized breast cancer service screening in Sweden

(Ref: Tabar et al., *Lancet*, 2003)

Articles

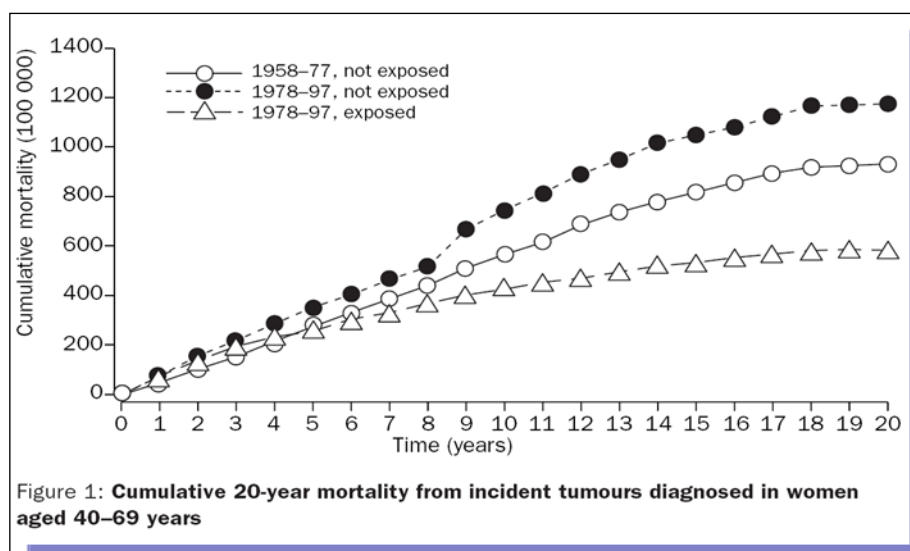
Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening

Laszlo Tabar, Ming-Fang Yen, Bedrich Vitak, Hsiu-Hsi Tony Chen, Robert A Smith, Stephen W Duffy

The long term effect of mammographic service screening is not well established. We aimed to assess the long-term effect of mammographic screening on death from breast cancer, taking into account potential biases from self-selection, changes in breast cancer incidence, and classification of cause of death.

We compared deaths from breast cancer diagnosed in the 20 years before screening was introduced (1958–77) with those from breast cancer diagnosed in the 20 years after the introduction of screening (1978–97) in two Swedish counties, in 210 000 women aged 20–69 years.

We also compared deaths from all cancers and from all causes in patients diagnosed with breast cancer in the 20 years before and after screening was introduced. In the analysis, data were stratified into age-groups invited for screening (40–69 years) and not invited (20–39 years), and by whether or not the women had actually received screening.



The unadjusted risk of death from breast cancer dropped significantly in the second screening period compared with the first in women aged 40–69 years (relative risk [RR] 0.77 [95% CI 0.7–0.85]; $p < 0.0001$). No such decline was seen in 20–39 year olds.

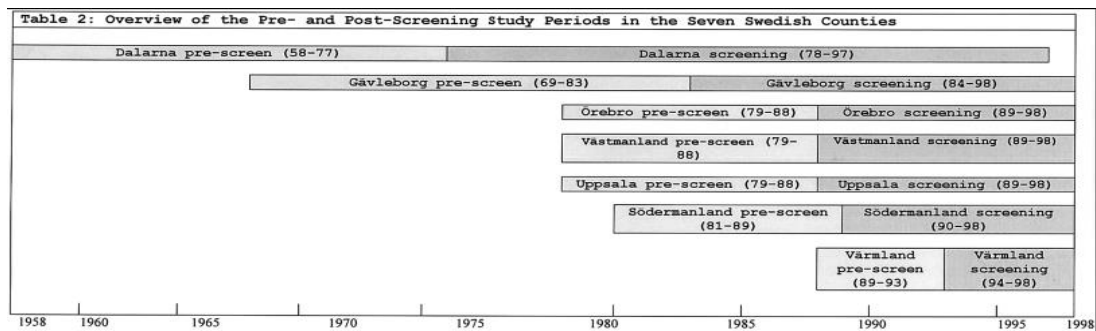
After adjustment for age, self-selection bias, and changes in breast-cancer incidence in the 40–69 years age-group, breast-cancer mortality was reduced in women who were screened (0.56; 0.49–0.64 $p < 0.0001$), in those who were not screened (0.84 [0.71–0.99]; $p = 0.03$), and in screened and unscreened women combined (0.59 [0.53–0.66]; $p < 0.0001$).

	Person-years ($\times 10^4$)	Breast-cancer cases (rate/ 10^4)	Breast-cancer deaths		
			Number (rate/ 10^4)	Relative risk (95% CI)	
				Unadjusted*	Adjusted†
20–39 years					
1958–77 (not exposed)	1624	181 (11.2)	68 (4.2)	1.00	1.00
1978–97 (not exposed)	1788	317 (17.7)	88 (4.9)	1.18 (0.85–1.62)	0.73 (0.50–1.06)
40–69 years					
1958–77 (not exposed)	2416	3151 (130.5)	1129 (46.7)	1.00	1.00
1978–97 (exposed)	1647	3594 (218.3)	401 (24.4)	0.52 (0.46–0.59)	0.56 (0.49–0.64)
1978–97 (not exposed)	752	1308 (173.9)	457 (60.8)	1.30 (1.16–1.45)	0.84 (0.71–0.99)
1978–97 (all)	2399	4902 (204.4)	858 (35.8)	0.77 (0.70–0.85)	0.59 (0.53–0.66)

*Adjusted for age, changes in breast cancer incidence, and self-selection bias. †Relative to the period 1958–77.

3.2.2 Service screening for breast cancer in seven Swedish counties

(Ref: Duffy et al., Cancer, 2002)



(Pre Screen vs. Screen)

TABLE 3
Comparison of Breast Carcinoma Mortality from Incident Tumors between the Prescreening and Screening Epochs (Exposed and Unexposed Women Combined in the Latter Group)

County	Epoch	Deaths	Person-years	Rate/100,000	RR (95% CI)
Värmland	Pre	36	159,783	22.5	1.00 (-)
	Screen	37	163,411	22.6	1.00 (0.64-1.59)
Södermanland	Pre	98	396,206	24.7	1.00 (-)
	Screen	79	422,007	18.7	0.76 (0.56-1.02)
Västmanland ^a	Pre	112	448,442	25.0	1.00 (-)
	Screen	85	470,961	18.0	0.84 (0.64-1.12)
Uppsala	Pre	110	389,156	28.3	1.00 (-)
	Screen	112	471,834	23.7	0.84 (0.65-1.09)
Örebro	Pre	133	476,420	27.9	1.00 (-)
	Screen	108	489,298	22.1	0.79 (0.61-1.02)
All counties with ≤ 10 years screening ^b	Pre	489	1,870,007	26.1	1.00 (-)
	Screen	421	2,017,511	20.9	0.82 (0.72-0.94)
Gävleborg	Pre	311	795,110	39.1	1.00 (-)
	Screen	219	786,032	27.9	0.71 (0.60-0.85)
Dalarna ^a	Pre (1)	187	511,629	36.5	1.00 (-)
	Pre (2)	182	516,318	35.2	0.96 (0.78-1.18)
	Screen (1)	138	498,803	27.7	0.76 (0.61-0.95)
	Screen (2)	97	512,984	18.9	0.57 (0.44-0.73)
All counties with > 10 years screening ^b	Pre	680	1,823,057	37.3	1.00 (-)
	Screen	454	1,797,819	25.3	0.68 (0.60-0.77)

RR: relative risk; 95% CI: 95% confidence interval; Pre: prescreening epoch; Screen: screening epoch.

^a Corrected for lead time.

^b Adjusted for county.

(Exposed vs. Unexposed)

TABLE 4
Comparison of Breast Carcinoma Mortality between Screened and Unscreened Women within the Screening Epochs, with RRs and 95% CIs

County	Exposure status	Deaths	Person-years	Rate/100,000	RR (95% CI) ^a
Värmland	Unscreened	17	43,636	39.0	1.00 (-)
	Screened	20	119,775	16.7	0.72 (0.53-0.98)
Södermanland	Unscreened	34	97,965	34.7	1.00 (-)
	Screened	45	324,042	13.9	0.66 (0.51-0.85)
Västmanland ^b	Unscreened	26	36,831	70.6	1.00 (-)
	Screened	59	434,130	13.6	0.41 (0.32-0.54)
Uppsala	Unscreened	48	85,598	56.1	1.00 (-)
	Screened	64	386,245	16.6	0.56 (0.44-0.71)
Örebro	Unscreened	68	177,022	38.4	1.00 (-)
	Screened	40	312,276	12.8	0.59 (0.46-0.76)
Gävleborg	Unscreened	49	124,748	39.3	1.00 (-)
	Screened	170	661,284	25.7	0.95 (0.73-1.22)
Dalarna (1988-1997) ^b	Unscreened	33	62,881	52.5	1.00 (-)
	Screened	64	450,103	14.2	0.54 (0.42-0.69)
All counties	Unscreened	275	628,681	43.7	1.00 (-)
	Screened	462	2,687,855	17.2	0.61 (0.55-0.68)

Organized service screening in 7 Swedish counties, covering approximately 33% of the population of Sweden, resulted in a 40–45% reduction in breast carcinoma mortality among women actually screened. The policy of offering screening is associated with a mortality reduction in breast

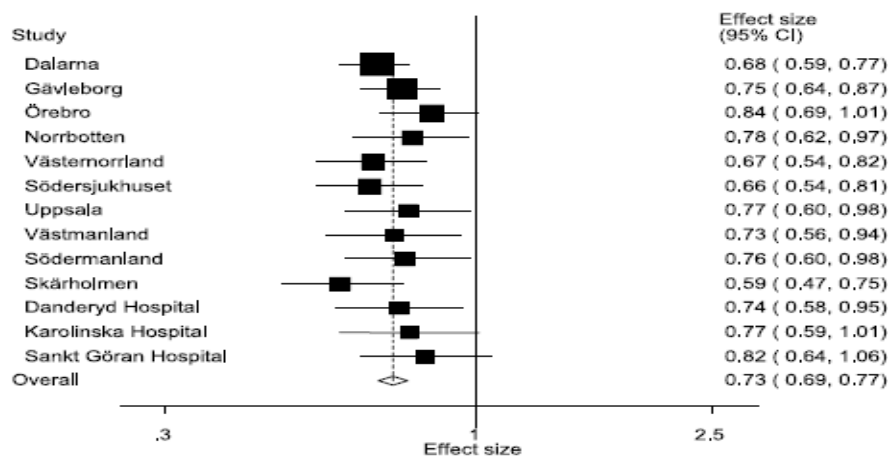
carcinoma of 30% in the invited population, exposed and unexposed combined.

3.2.3 Organized service screening for 13 large area in 9-county

(Ref: Tabar et al., *CEBP*, 2006)

Table 4. Deaths from tumors diagnosed in the screening epoch and the corresponding person-years, by exposure status and area

Area	Unexposed to screening		Exposed to screening	
	Deaths	Person-years	Deaths	Person-years
Dalarna	150	233,632	214	886,713
Gävleborg	66	116,907	207	776,281
Örebro	102	279,317	89	407,706
Norrbottn	54	158,272	84	466,271
Västernorrland	46	123,318	102	447,817
Södersjukhuset	84	197,091	68	369,382
Uppsala	39	92,059	80	438,099
Västmanland	30	64,351	69	454,871
Södermanland	48	112,882	68	405,705
Skärholmen	59	159,724	56	269,820
Danderyd Hospital	64	131,237	57	258,904
Karolinska Hospital	57	125,840	44	238,374
Sankt Görän Hospital	61	135,891	44	192,369
Overall	860	1,930,521	1,182	5,612,312



These results indicate a reduction in breast cancer mortality of between 40% and 45% in association with screening, after adjustment for self-selection bias.

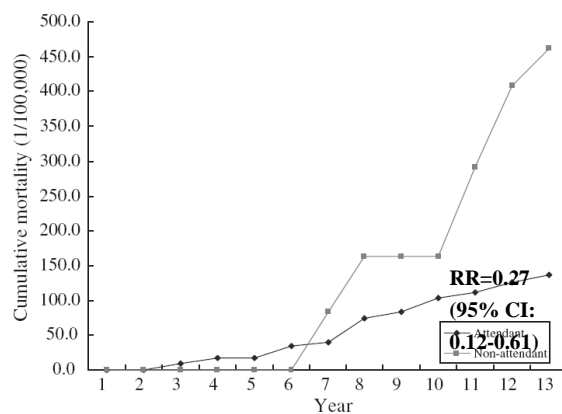
3.3 Service Screening for Breast Cancer in Finland

3.3.1 Evaluation of long-term effectiveness of population-based breast cancer service screening program in a small geographic area may suffer from self-selection bias and small samples

(Ref: Wu et al., *Breast Cancer Res Treat*, 2010)

Bayesian acyclic graphic model for correcting self-selection bias with or without incorporating evidence from previous studies with similar design (*exchangeable) by chronological order applied it to an organized breast cancer service screening program in Pirkanmaa center of Finland.

3.3.1.1 Cumulative mortality curves



Year	1988	1989	1990	1991	1992	1993	1994
Invitations	4553	5039	7142	6452	8024	6923	6885
Attendants	4005	4358	6340	5728	7187	6162	6176
Attendance rate (%)	87.96	86.49	88.77	88.78	89.57	89.01	89.70

Year	1995	1996	1997	1998	1999	2000	Total
Invitations	8183	7558	7910	8125	9665	8598	95057
Attendants	7288	6779	7018	7309	8677	7786	84812
Attendance rate (%)	89.06	89.69	88.72	89.96	89.78	90.56	89.22

3.3.1.2 Estimated Results with Bayesian Approach

External Sources	Types of Prior and Prior Estimates	Data for Likelihood / Posterior Estimates	Adjusted RR (95% CI)
1. Finland Data only	Non-informative Prior - All regression coefficients are assigned as $N(0, 10^6)$	Pirkanmaa / $\alpha \sim (-8.47, 0.13^2)$ $\beta_1 \sim (-0.54, 0.23^2) \beta_2 \sim (0.73, 0.41^2)$	0.76 (0.49-1.15)
	Informative Prior from Hakama study- $\alpha \sim (-8.47, 0.13^2)$ $\beta_1 \sim (-0.41, 0.19^2) \beta_2 \sim (0.30, 0.29^2)$	Pirkanmaa/ $\alpha \sim (-8.47, 0.11^2)$ $\beta_1 \sim (-0.48, 0.14^2) \beta_2 \sim (0.46, 0.25^2)$	0.73 (0.57-0.93)
2. Outside Finland		Dalarna / $\alpha \sim (-7.79, 0.16^2)$ $\beta_1 \sim (-0.92, 0.25^2) \beta_2 \sim (-0.05, 0.40^2)$	0.46 (0.29-0.72)
(1) Tarbar et al /1977/Dalarna, Sweden	Non-informative Prior- All regression coefficients are assigned as $N(0, 10^6)$	Gothenburg / $\alpha \sim (-6.99, 0.11^2)$ $\beta_1 \sim (-0.64, 0.18^2) \beta_2 \sim (0.25, 0.25^2)$	0.69 (0.51-0.92)
(2) (Bjurstam et al /1982/ Gothenburg in Sweden)	Informative prior-from the posterior distribution of (1)/ $\alpha \sim (0, 10^6)$ $\beta_1 \sim (-0.92, 0.25^2) \beta_2 \sim (-0.05, 0.40^2)$	Finland (Hakama) / $\alpha \sim (-8.42, 0.10^2)$ $\beta_1 \sim (-0.53, 0.13^2) \beta_2 \sim (0.26, 0.19^2)$	0.70 (0.56-0.86)
(3) (Hakama et al / 1987/Finland)	Informative prior-from the posterior of (2) / $\alpha \sim (0, 10^6)$ $\beta_1 \sim (-0.64, 0.18^2) \beta_2 \sim (0.25, 0.25^2)$	Pirkanmaa / $\alpha \sim (-8.41, 0.09^2)$ $\beta_1 \sim (-0.55, 0.11^2) \beta_2 \sim (0.34, 0.17^2)$	0.67 (0.55-0.80)
(4) (Current study / 1988 / Pirkanmaa in Finland)	Informative prior-from the posterior distribution of (3) / $\alpha \sim (-8.42, 0.10^2)$ $\beta_1 \sim (-0.53, 0.13^2) \beta_2 \sim (0.26, 0.19^2)$		

3.4 Service Screening for Cancer in Taiwan

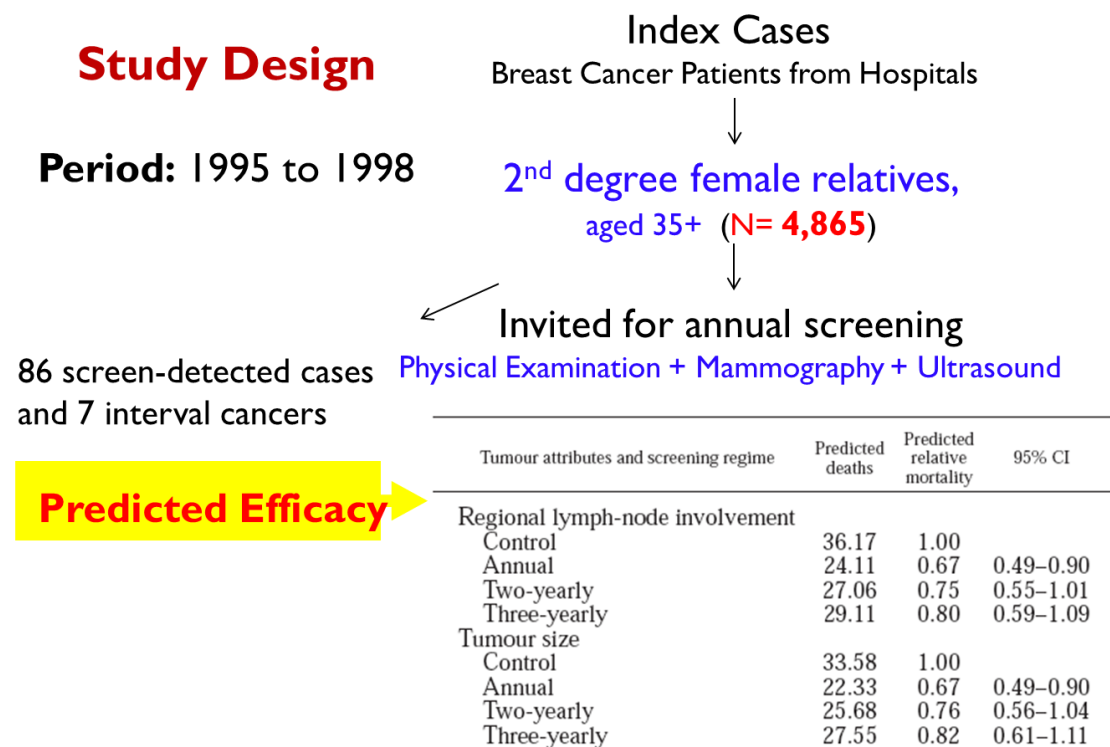
3.4.1 Evaluation of Breast Cancer Screening in Taiwan

3.4.1.1 Phase I: Breast Cancer Screening for Female Relatives of Breast-Cancer-Index Case

(Ref: Lai et al., 1998 IJC; Wu et al., 2006 JMS)

EFFICACY OF BREAST-CANCER SCREENING FOR FEMALE RELATIVES OF BREAST-CANCER-INDEX CASES: TAIWAN MULTICENTRE CANCER SCREENING (TAMCAS)

Mei-Shu LAI¹, Ming-Fang YEN², Hsu-Sung KUO², Shin-Lan KOONG¹, Tony Hsiu-Hsi CHEN^{3*} and Stephen W. DUFFY⁴



3.4.1.2 Phase II: Mass Screening with Physical Examination

(Ref: Wu et al., 2006 JMS)

The program was conducted from 1999 to 2001. Total of 899,383 women aged 35 years or more participated. Among them, 33,073 women also received breast ultrasound. 947 breast cancer cases were found (detection rate=1.05‰)

3.4.1.3 Phase III: Two-stage Model

(Ref: Wu et al., 2006 JMS)

Given the concern over clinical capacity and cost of mammogram given the incidence rate which is still not so high as western countries albeit the time trend has been increasing, two-stage model was adopted between 2002 and 2004. The first stage was to apply the questionnaire to select high-risk group according to family history, menstrual factor and reproductive factor (see below).

Score= $-0.03 \times (\text{age at screening} - 60) + 2.00 \times (\text{age at menarche} \leq 14) - 2.00 \times (\text{no. of parity} = 1) - 5.00 \times (\text{no. of parity} = 2) - 6.00 \times (\text{no. of parity} = 3) - 9.00 \times (\text{no. of parity} \geq 4) + 0.50 \times (25 \leq \text{age at first full term pregnancy} \leq 29) + 1.50 \times (\text{age at first full term pregnancy} \geq 30) - 3.00 \times (\text{breast feeding}) + 9.00 \times (\text{family history of breast cancer}) + 7.00 \times (\text{previous benign breast cancer}) + 8.00 \times (\text{other previous cancer}) + 2.00 \times (\text{history of oral contraceptive}) + 3.00 \times (\text{history of hormone replacement therapy})$

3.4.2 Evaluation of Colorectal Cancer Screening in Taiwan

Evaluation of a Selective Screening for Colorectal Carcinoma

The Taiwan Multicenter Cancer Screening (TAMCAS) Project

(Ref: Chen etl., Cancer, 1999)

A multicenter design was devised to identify high risk groups without clinical symptoms related to CRC; these subjects were identified through the study of index cases of CRC in Taiwan. Colonoscopy, in combination with a fecal occult blood test or double-contrast barium enema, was used to screen high risk groups. A total of 8909 subjects were invited to attend screening. Of 8909, 81 with asymptomatic CRC were detected in one-shot screening.

	Estimated no. of cases					RR of death from CRC	95% CI
	First screening	Second screening	Interval cancer	Death from CRC	OCD		
Annual	70.46	130.85	25.03	41.97	38.68	0.74	(0.50–1.10)
Biennial	70.46	110.05	43.88	43.47	39.53	0.77	(0.52–1.14)
Triennial	70.46	93.63	58.08	44.94	40.35	0.79	(0.53–1.17)
Control	68.64	—	132.94	56.58	46.83	1	

CRC: colorectal carcinoma; OCD: other causes of death; RR: relative risk; CI: confidence interval.

Predictions of mortality reduction for people who received annual, biennial, and triennial screening regimes compared with controls were 26% (95% CI, 0–50%), 23% (95% CI, 0–48%), and 21% (95% CI, 0–47%), respectively.

3.4.3 Evaluation of Cervical Cancer Screening in Taiwan

Efficacy and cost-effectiveness of nationwide cervical cancer screening in Taiwan

Shin-Lan Koong, Amy Ming-Fang Yen and Tony Hsiu-Hsi Chen

(Koong et al., 2006, *JMS*)

The annual cervical screening programme using the Papanicolaou (Pap) smear test was launched for women aged 30 years and over from 1995 in Taiwan. Annual Pap smear screening with 100% compliance was estimated to lead to an approximate 80% reduction in deaths from cervical cancer. With 50% compliance, around a 40% reduction was expected.

Compliance/age group	% Reduction in invasive carcinoma by interval			% Reduction in death from cervical cancer by interval		
	1	3	5	1	3	5
100%						
30–34	97	82	65	82	64	52
35–39	97	84	70	80	63	51
40–49	97	85	72	79	62	51
50–59	98	87	76	75	60	51
60–69	98	90	80	78	66	56
70%						
30–34	68	57	45	61	47	38
35–39	68	57	48	59	46	38
40–49	68	58	49	58	45	37
50–59	68	60	52	54	43	36
60–69	68	62	55	56	48	41
50%						
30–34	48	38	31	44	34	28
35–39	48	40	33	43	34	28
40–49	48	41	34	43	34	27
50–59	48	41	36	40	32	26
60–69	48	43	38	41	35	30

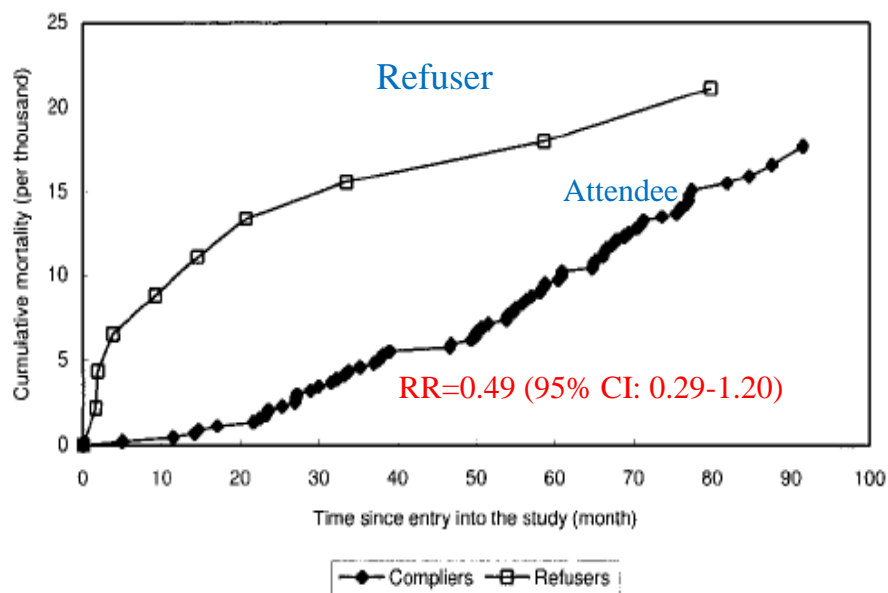
Intervention efficacy for ages 30–69 (calculated using first screen progression estimates) by inter-screening interval and assumed compliance, assuming an average sensitivity of 82%

3.4.4 Evaluation of Hepatocellular Carcinoma Screening in Taiwan

ULTRASOUND SCREENING AND RISK FACTORS FOR DEATH FROM HEPATOCELLULAR CARCINOMA IN A HIGH RISK GROUP IN TAIWAN

(Ref: Chen et al., 2002, *IJC*)

A 2-stage screening program since 1991 was designed to identify a high risk group in 7 townships in Taiwan by 6 markers (of risk for HCC) and repeated US screening was further applied to those with at least 1 positive result for the 6 markers (Positive HBsAg, Positive anti-HCV, AFP \geq 20 ng/mL, AST \geq 40 IU/L, ALT \geq 45 IU/L, Family history of HCC).



3.5 Epidemiological aspects for study design

The following examples show the fallacy without considering RCT.

(A) Can estrogen therapy reduce CHD recurrence in postmenopausal women?

(Selection-bias)

In Observational Studies

A group: Take postmenopausal estrogen

B group: Not to take postmenopausal estrogen

CHD in A << CHD in B

Estrogen use is effective in secondary prevention of CHD

Argument : Women who choose to take hormones are healthier and have a more favourable CHD profile than those who do not.

Selection bias: Absence of comparability between groups being studied

- (1) Participant and non-participants selection: Participants are frequently educated, healthier, lead better lifestyle, and have few complication
- (2) A hospital-based case-control study on myocardial infarction will underestimate relative risk (Neyman bias).
- (3) Knowledge of the exposure may lead to an increased rate of admission to hospital (OC and thrombembolism)
- (4) Detection bias: An exposure may facilitate the unmasking of disease (estrogen and endometrial cancer)

(B) Retinopathy of pre-maturity and hospital-Nursery lighting :

Retinopathy of pre-maturity is the main factor for childhood blindness. It is postulated that premature infant exposure to light increased retinopathy of pre-maturity. By collecting data on the two groups of premature infant: heavy light (A) and standard light (B), we compared the incidence of retinopathy between the two groups. We found $A > B$:

Exposure to light → increase the risk of retinopathy

Con:

The majority receiving heavy light were more likely to receive high levels of inspired oxygen (one of cause leading to free radicals in the retina). The culprit is the levels of inspired oxygen that resulted in retinopathy of pre-maturity.

✕The RCT (Reynolds et al 1998; 338:1572-6) proved

Light reduction does not reduce the frequency of retinopathy of prematurity.

This is, in fact, related to "**Simpson's paradox**"

(C) In Chicago, the boss of Hawthorne factory found the poor production of output may result from the poor lighting facility. He therefore improved these facilities and the output therefore increased.

Argument : An increase in output may be due to the encouragement of staffs' motivation because the output is stable even having the poor facility of lighting. This is called "**Hawthorne effect**".

(D) The statin was developed to reduce cholesterol. The administration of statin after six months led to the reduction of cholesterol. Is this a true effect?

Argument : Statistical Regression Toward the mean

(E) To enhance reading ability, a program was conducted for first grade student of primary school. After two years, reading ability has been enhanced. Is the program effective in enhancing reading ability?

Argument : Reading ability increased with **Maturation**.

(F) After 921 earthquake, health promotion was provided to recall the patients with chronic disease. After three months, patients compliance with medical regime was improved.

Argument : The effectiveness of improving compliance may be due to **“History Effect”**.

3.6 Statistical approach for self-selection bias adjustment: Bayesian Acyclic Graphic Model for Adjusting for Selection-bias

Let Y_{ij} denote the observed numbers of breast cancer death in the i th study with the j detection mode ($j=1$ for exposed, 2 =non-exposed, and 3 =uninvited, respectively). Hence, Y_{ij} follows a Poisson distribution with the expected value of μ_{ij} . Attendance rate (r_i) in the i th study is treated as a random variable specified by a beta distribution, $\text{Beta}(N_{i, \text{exposed}}, N_{i, \text{non-exposed}})$.

$N_{i,exposed}$ and $N_{i,non-exposed}$ are numbers of the exposed and the non-exposed group from the i th study.

Following the framework of generalized linear model, the relationship between the outcome Y and detection modes was regressed through a logarithm link function like the following:

$$\log\left(\frac{\mu_{i,j}}{Person-years_{i,j}}\right) = \alpha + \beta_1 \times I_S + \beta_2 \times I_{\bar{S}} + b_i$$

I_S and $I_{\bar{S}}$ are two indicator variables for participant and non-participant, respectively, opposed to the uninvited group (baseline group). Two hyper parameters, β_1 and β_2 , are the corresponding coefficients indicating the magnitudes of the risk for breast cancer death for the participant group and the non-participant group compared with the uninvited group. Note that b_i is a latent variable (random-effect) for capturing the heterogeneity across studies. We suppose b_i follows a normal distribution with 0 and τ as the mean value and the variance.

Once β_1 and β_2 are estimated, the self-selection bias was calculated with the following formula.

$$adjRR = r\% \times \exp(\beta_1) + (1 - r\%) \times \exp(\beta_2)$$

which is similar to previous formula for the adjustment of self-selection bias,

$RR_1 = (r\% \times P_S + (1 - r\%) \times P_{\bar{S}}) / P_I$, a function of attendance rate ($r\%$) and the mortality ratio for the participant group (P_S) and the non-participant group ($P_{\bar{S}}$) compared to the uninvited group (P_I).

The other measure is the estimate of the relative risk associated with actually being screened in those who would comply if invited, the noncompliance adjustment for randomized controlled trial as

$$RR_2 = \frac{(r\% \times P_s / P_i)}{1 - (1 - r\%) \cdot P_s / P_i}$$