

DOCTOR OF PHILOSOPHY PROGRAM IN EPIDEMIOLOGY AND BIostatISTICS

(INTERNATIONAL PROGRAM)

Evaluation of Cancer and Chronic Disease Screening

June 2013

Professor Hsiu-Hsi Chen and

Taiwanese DHCG Group: Dr. Sam Li-Sheng Chen,

Dr. Amy Ming-Fang Yen, , Dr. Sherry Yueh-Hsia Chiu,

Dr. Jean Ching-Yuan Fann, Dr. Wendy Yi-Ying Wu



Faculty of Public Health, Khon Kaen University

123 Mitraparp Road, Khon Kaen 40002, Thailand

Tel.: +66 (0) 4334 7057

Fax.: +66 (0) 4334 7058

Website: // ph.kku.ac.th/

PH Ref. No. 0514.11.1/๑๖๒๓

June 11, 2013

Prof. Tony Hsiu-Hsi Chen, Ph.D.
Graduate Institute of Epidemiology and Prevention Medicine,
College of Public Health, National Taiwan University
Room 533, 17 Hsuehshow Road, Taipei 100, Taiwan
Tel: +886-2-33668033
Fax: +886-2-33668042
E-mail: chenlin@ntu.edu.tw

Dear Professor Dr. Hsiu-Hsi Chen,

It is a great pleasure of the Faculty of Public Health, Khon Kaen University (KKU), Thailand to invite you to be a speaker and a trainer in the workshop on "Evaluation of Cancer and Chronic Diseases Screening" at Khon Kaen University during June 27, 2013 – July 2, 2013

This workshop will be mutual benefits for staff and students of the Faculty of Public Health since it is an opportunity to explore and exchange knowledge and experiences with the experts in public health. In addition, this is a great initiation for future academic collaboration such staff and student exchange, join research and teaching. The Faculty of Public Health will support you for the traveling, accommodation, lecture and expense allowance during the workshop.

Your kind consideration of this request and the participation of the invited guest to the workshop will be gratefully acknowledged. We are convinced that this project will strengthen our collaboration and will eventually of benefit to the people in the region.

We look forwards to seeing you in the near future.

Sincerely yours,

Asst. Prof. Dr. Somsak Pitaksanurat
Dean of the Faculty of Public Health
Khon Kaen University
Thailand





Faculty of Public Health, Khon Kaen University
123 Mitraparp Road, Khon Kaen 40002, Thailand
Tel.: +66 (0) 4334 7057
Fax: +66 (0) 4334 7058
Website: // ph.kku.ac.th/

PH Ref. No. 0514.11.1/ 0025

June 11, 2013

Dr. Li-Sheng Chen
Associate Professor,
School of Oral Hygiene, College of Oral Medicine,
Taipei Medical University, Taipei, Taiwan

Dear Dr. Li-Sheng Chen,

It is a great pleasure of the Faculty of Public Health, Khon Kaen University (KKU), Thailand to invite you to be a trainer in the workshop on "Evaluation of Cancer and Chronic Diseases Screening" at Khon Kaen University during June 27, 2013 – July 2, 2013

This workshop will be mutual benefits for staff and students of the Faculty of Public Health since it is an opportunity to explore and exchange knowledge and experiences with the experts in public health. In addition, this is a great initiation for future academic collaboration such staff and student exchange, join research and teaching. The Faculty of Public Health will support you for the accommodation and expense allowance during the workshop.

Your kind consideration of this request and the participation of the invited guest to the workshop will be gratefully acknowledged. We are convinced that this project will strengthen our collaboration and will eventually of benefit to the people in the region.

We look forwards to seeing you in the near future.

Sincerely yours,

Asst. Prof. Dr. Somsak Pitaksanurak
Dean of the Faculty of Public Health
Khon Kaen University
Thailand



Faculty of Public Health, Khon Kaen University
123 Mitraparp Road, Khon Kaen 40002, Thailand
Tel.: +66 (0) 4334 7057
Fax: +66 (0) 4334 7058
Website: // ph.kku.ac.th/

PH Ref. No. 0514.11.1/ 0026

June 11, 2013

Dr. Ming-Fang Yen
Assistant Professor,
School of Oral Hygiene, College of Oral Medicine,
Taipei Medical University, Taipei, Taiwan

Dear Dr. Ming-Fang Yen,

It is a great pleasure of the Faculty of Public Health, Khon Kaen University (KKU), Thailand to invite you to be a trainer in the workshop on "Evaluation of Cancer and Chronic Diseases Screening" at Khon Kaen University during June 27, 2013 – July 2, 2013

This workshop will be mutual benefits for staff and students of the Faculty of Public Health since it is an opportunity to explore and exchange knowledge and experiences with the experts in public health. In addition, this is a great initiation for future academic collaboration such staff and student exchange, join research and teaching. The Faculty of Public Health will support you for the accommodation and expense allowance during the workshop.

Your kind consideration of this request and the participation of the invited guest to the workshop will be gratefully acknowledged. We are convinced that this project will strengthen our collaboration and will eventually of benefit to the people in the region.

We look forwards to seeing you in the near future.

Sincerely yours,

Asst. Prof. Dr. Somsak Pitaksanurak
Dean of the Faculty of Public Health
Khon Kaen University
Thailand



Faculty of Public Health, Khon Kaen University
123 Mitraparp Road, Khon Kaen 40002, Thailand
Tel.: +66 (0) 4334 7057
Fax: +66 (0) 4334 7058
Website: // ph.kku.ac.th/

PH Ref. No. 0514.11.1/ 0027

June 11, 2013

Dr. Yueh-Hsia Chiu
Assistant Professor,
Department of Health Care Management,
College of Management, Chang Gung University,
Tao-Yuan, Taiwan

Dear Dr. Yueh-Hsia Chiu,

It is a great pleasure of the Faculty of Public Health, Khon Kaen University (KKU), Thailand to invite you to be a trainer in the workshop on "Evaluation of Cancer and Chronic Diseases Screening" at Khon Kaen University during June 27, 2013 – July 2, 2013

This workshop will be mutual benefits for staff and students of the Faculty of Public Health since it is an opportunity to explore and exchange knowledge and experiences with the experts in public health. In addition, this is a great initiation for future academic collaboration such staff and student exchange, join research and teaching. The Faculty of Public Health will support you for the accommodation and expense allowance during the workshop.

Your kind consideration of this request and the participation of the invited guest to the workshop will be gratefully acknowledged. We are convinced that this project will strengthen our collaboration and will eventually of benefit to the people in the region.

We look forwards to seeing you in the near future.

Sincerely yours,

Asst. Prof. Dr. Somsak Pitaksanurak
Dean of the Faculty of Public Health
Khon Kaen University
Thailand



Faculty of Public Health, Khon Kaen University
123 Mitraparp Road, Khon Kaen 40002, Thailand
Tel.: +66 (0) 4334 7057
Fax: +66 (0) 4334 7058
Website: // ph.kku.ac.th/

PH Ref. No. 0514.11.1/ 0028

June 11, 2013

Dr. Ching-Yuan Fann
Assistant Professor,
Department of Health Industry Management,
School of Healthcare Management, Kainan University,
Tao-Yuan, Taiwan

Dear Dr. Ching-Yuan Fann,

It is a great pleasure of the Faculty of Public Health, Khon Kaen University (KKU), Thailand to invite you to be a trainer in the workshop on "Evaluation of Cancer and Chronic Diseases Screening" at Khon Kaen University during June 27, 2013 – July 2, 2013

This workshop will be mutual benefits for staff and students of the Faculty of Public Health since it is an opportunity to explore and exchange knowledge and experiences with the experts in public health. In addition, this is a great initiation for future academic collaboration such staff and student exchange, join research and teaching. The Faculty of Public Health will support you for the accommodation and expense allowance during the workshop.

Your kind consideration of this request and the participation of the invited guest to the workshop will be gratefully acknowledged. We are convinced that this project will strengthen our collaboration and will eventually of benefit to the people in the region.

We look forwards to seeing you in the near future.

Sincerely yours,

Asst. Prof. Dr. Somsak Pitaksanurak
Dean of the Faculty of Public Health
Khon Kaen University
Thailand



Faculty of Public Health, Khon Kaen University
123 Mitraparp Road, Khon Kaen 40002, Thailand
Tel.: +66 (0) 4334 7057
Fax: +66 (0) 4334 7058
Website: // ph.kku.ac.th/

PH Ref. No. 0514.11.1/ 0029

June 11, 2013

Dr. Wendy Yi-Ying Wu
Institution of Public Health & Department of Public Health,
National Yang-Ming University

Dear Dr. Wendy Yi-Ying Wu,

It is a great pleasure of the Faculty of Public Health, Khon Kaen University (KKU), Thailand to invite you to be a trainer in the workshop on "Evaluation of Cancer and Chronic Diseases Screening" at Khon Kaen University during June 27, 2013 – July 2, 2013

This workshop will be mutual benefits for staff and students of the Faculty of Public Health since it is an opportunity to explore and exchange knowledge and experiences with the experts in public health. In addition, this is a great initiation for future academic collaboration such staff and student exchange, join research and teaching.

Your kind consideration of this request and the participation of the invited guest to the workshop will be gratefully acknowledged. We are convinced that this project will strengthen our collaboration and will eventually of benefit to the people in the region.

We look forwards to seeing you in the near future.

Sincerely yours,

Asst. Prof. Dr. Somsak Pitaksanurak
Dean of the Faculty of Public Health
Khon Kaen University
Thailand



Schedule: 27th June ~ 2nd July

Program:

Module 1 (8:30am-12:00am, 27th Jun)

Basic Concept of Cancer and Chronic Disease Screening (2.5 hours)

Computer Practice of Data Analysis on Cancer and Chronic Disease Screening
(1 hour)

Module 2 (13:00pm-17:00pm, 27th Jun)

Study Design for Evaluation of Disease Screening-Experimental Design (3 hours)

Computer Practice of Evaluation for Randomized Controlled Trial of Screening
(1 hour)

Module 3 (8:30am-12:00am, 28th Jun)

Study Design for Evaluation of Disease Screening- Quasi-experimental Design
(2.5 hours)

Computer Practice of Evaluation for Service Screening Program (1 hour)

Module 4 (13:00pm-17:00pm, 28th Jun), (8:30am-12:00am, 1st Jul)

Temporal Natural History Model in Cancer and Chronic Disease Screening (6.5 hours)

Computer Practice of Temporal Natural History Model (1 hour)

Module 5 (13:00pm-17:00pm, 1st Jul)

Bias Adjustment in Cancer and Chronic Disease Screening (3 hours)

Computer Practice of Data Analysis on Bias Adjustment in Screening (1 hour)

Module 6 (8:30pm-15:00pm, 2nd Jul)

Cost-effectiveness Analysis of Screening Program (5.5 hours)

Computer Practice of Cost-effectiveness Analysis of Screening Program (1 hour)

Module 1 Basic Concept of Cancer and Chronic Disease Screening

1.1 Concepts and Framework of Disease Screening (Figure 1-1)

1.1.1 Setting, population, and disease natural history

In any prevention of specific cancer death, several aspects should be delineated including setting, population of interest, disease natural history, referral and treatment, effectiveness, and cost (money). Settings under the context in health care field may include community, ambulatory health care center, hospital, and institution. Different settings may imply different intervention point relating to disease natural process or prognosis. Intervention at community usually identified several types of participants, including the refuser that are invited to intervention but never come. This group often follows the disease natural course with the progression from asymptomatic phase to clinical phase at very late stage due to severe clinical symptom and sign. Due to advanced stage, the treatment is fruitless and complication and disability may often call for institution care. They may die early. The second group from the general population is amenable to intervention if invited. The disease natural history of this group is often altered by the introduction of organized service screening program to interrupt the disease natural history at asymptomatic phase and administered by early treatment or therapy. The third group is participants offered with so-called opportunistic screening in the realm of screening and with self-referral for intervention in the field of primary prevention even in the absence of invited and organized intervention. They have high awareness to access to medical care by themselves. However, the proportion of this group in general population is often related to economic level.

The selection of comparator against the intervention program should be clearly defined under this context. In enhanced awareness program or screening program, the comparator may include subjects with opportunity to screening even in the absence of organized service screening. The dotted lines at the bottom of the box of general population represent the disease natural history without being interrupted by screening regime and are often unobservable. This part will be handled by using Markov models (see the module 6).

1.1.2 Level of prevention

The intervention programs within the context of primary prevention include health education program for changing life style or awareness program for enhancing the accessibility to early detection and possible prophylactic intervention such as the administration of hormone to high risk group or prophylactic mastectomy for high risk group carrying with susceptible genetic gene. The aims of these intervention programs are to reduce the incidence of breast cancer. Although economic appraisal for these interventions can be modeled in a similar manner, the current study does not give a scenario for this part.

For the level of secondary prevention, the screening methods used may highly depend on different levels of economic development. In the context of state-of-the art breast cancer screening, breast self-examination, physical examination, mammographic examination and other emerging techniques may be applied in the light of the order of efficacy together with the level of economic development. In highly-economically developed country, economic evaluation of new emerging technique may be of great interest whereas simple and cheap screening like physical examination in conjunction with clinical

awareness program may take precedence over other screening methods. For tertiary prevention, economic appraisal is tailored for evaluation of alternative treatments and novel therapy in the wake of a large proportion of early-detected breast cancer as a result of screening or perhaps enhanced awareness program.

1.1.3 Economic appraisal

Figure 1-1 shows other components, particularly related to screening program, involved in economic appraisal of intervention program. The effectiveness is defined by a series of outcome including the reduction of BC for primary prevention, the proportion of screen-detected cancers among total breast cancers identified from the screening program (including screening-detected cases, interval cancer and refuser), reassurance, false alarm, advanced cancer, severe complication and disability, and specific-cause mortality, breast cancer for instance. These outcomes can be adjusted by utility usually defined by QAL or measured by another popular estimate of the maximum amount of willing (WTP) used in cost-benefit analysis. The final column describes the relevant direct and indirect costs. Note that as time horizon for early investment on intervention is different from that for costs for later treatment. Discount rate is therefore applied to time preference.

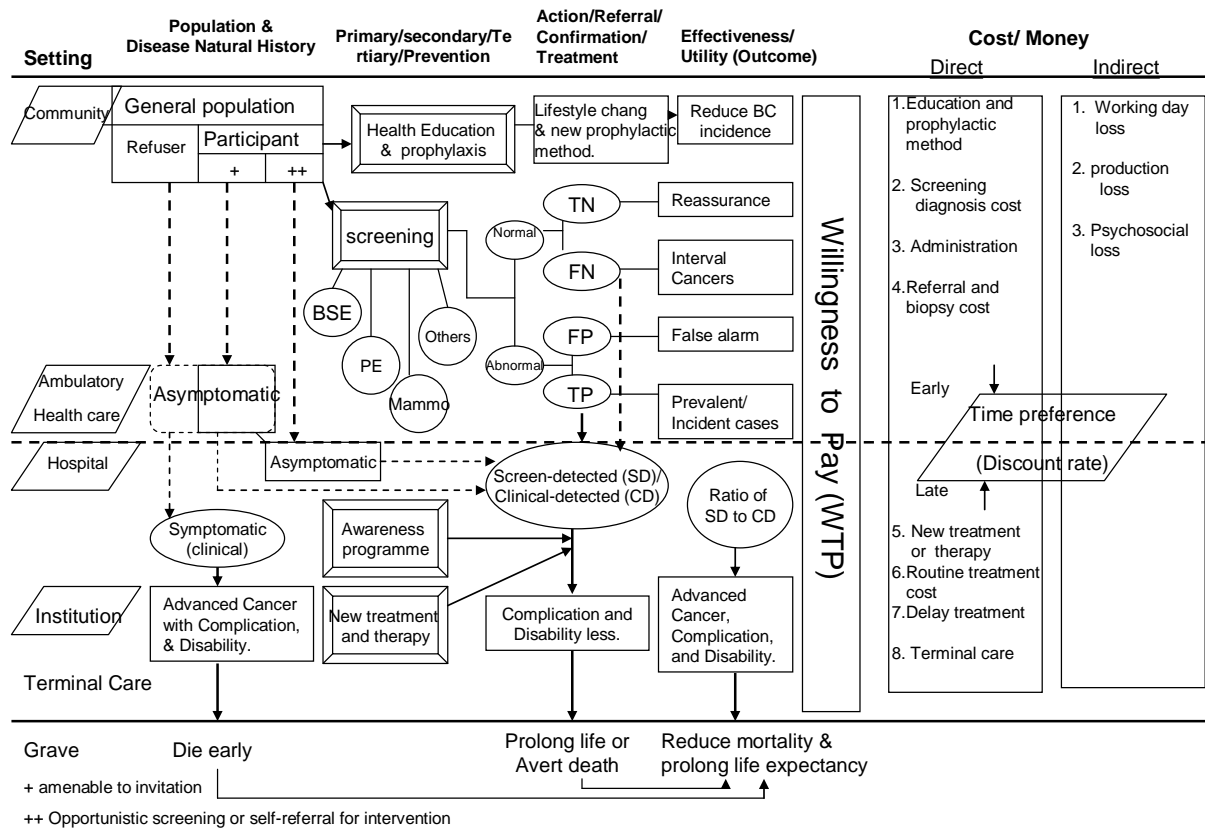


Figure 1-1. Framework of economic appraisal of intervention program of breast cancer

1.2 Detection mode in screening

1.2.1 Definition of detection modality

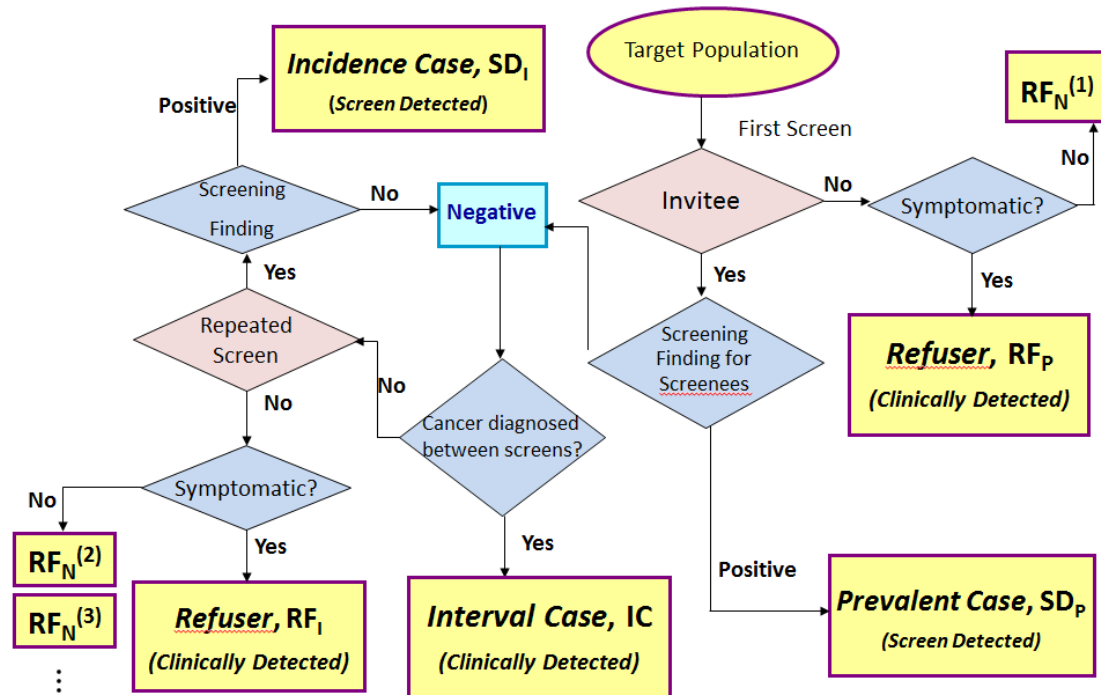
(A) Screen-detected cases

- Prevalent screen (Normal → PCDP)
- Subsequent screen (Normal → PCDP)

(B) Clinically-detected cases (Normal → clinical phase)

- Interval cancer (Cancer diagnosed between screens)
- Refuser
- Control group

Detection Mode in Mass Screening



1.3 Components on evaluation of disease screening

Components related to evaluation of mass screening included several aspects that are delineated in the following section (see Table 1-1)

Table 1-1 Evaluation System of KCIS program

Components	Methods / Data sources	◆Indicators / Selected results from the KCIS program /comments
1. Quality assurance		
(1) Consistency	Self-reported disease from KCIS data vs. claim data from national health insurance (NHI)	◆Sensitivity and specificity for Self-reported disease (yes or no) cross-tabulated by data from NHI i.e. <u>Type 2 diabetes</u> : Sen:76.37%, Spe:97.52%
(2) Comprehensiveness or delay report of national cancer register	Proportion of cancers reported to national cancer registry among screen-detected cases at of specific time	◆Cases reported to cancer registry/cases from the KCIS program until 2003 i.e. <u>Colorectal cancer</u> : 74.42% (32/43) i.e. <u>Hepatoma</u> : 88.41% (122/ 138)
(3) Interval Cancer Rate	Interval cases found by linking normal subjects at screen cancers with national cancer registry	◆Program sensitivity=[1-(Interval cancer rate/ the expected incidence rate)]×100% i.e. <u>CRC</u> : 85%
(4) Cumulative Survival Rate	Number of death from screen-detected cases or clinically-detected cases by the linkage of the KCIS data with national cancer registry	1-yr, 5-yr, or 10-yr cumulative survival rate
(5) Data quality of questionnaire	(a) Any key variables of questionnaire were missing	(a)◆Missing records / Total records i.e. <u>Missing Rate</u> (2000-2002) : 2.27%→0.00%
	(b) Duplicate cases within a year	(b)◆Duplicate attendants / Total attendants i.e. <u>Duplicating Rate</u> (2000-2002) : 3.97%→ 0.02%
	(c) Data logical checking	(c)◆Error records / Total records i.e. <u>Inaccurate Rate</u> (2000-2002) : 0.86%→0.00%
	(c) Household coverage rate	(d)◆Households of KCIS / Total households i.e. 35.8% (48166/134607)
2. Organization		
(1) Coverage rate	Proportion of population served with the KCIS	◆Total attendants / Total population

Components	Methods / Data sources	◆Indicators / Selected results from the KCIS program /comments
	project	i.e. age 30-79(2000-2002) : 19.5%→28.4%
(2) Outreach/opportunistic Screening	Linkage of the KCIS data with claim data from NHI for adult health check-up	◆Attendants of outreach since from the KCIS/ attendant from opportunistic visit i.e. <u>adult health checkup</u> : 43%; <u>KCIS attendants</u> : 57%
(3) Health manpower involved in on-site screening	Number and composition (volunteer social worker vs. professional health manpower) of health manpower	(a)◆Average served attendants per manpower : 2.2 (2000)→4.4 (2003) (b)◆The proportion of volunteer social worker on professional health manpower : 25.4%(2000)→32.1%(2003)
(4) Referral and confirmatory diagnosis	Clinical capacity for referral and confirmatory diagnosis	(a) Mean waiting time for referral and confirmatory diagnosis (b) Times of referral
(5) Age ranges and inter-screening interval	Depending on diseases	◆ <u>Colorectal Cancer</u> : 50-79, annually ◆ <u>Cervical cancer</u> : 30-79, every 3 yrs
(6) Clinical surveillance	Depend on characteristic of screening finding	◆Pre-cancer lesion : <u>colorectal cancer</u> <1cm adenoma : 3-6 yrs after the initial polypectomy ≥1cm adenoma : within 3yrs after initial polypectomy

3. Basic findings

(1) Attendance rate	Attendance rate of before and post KCIS projects	◆Attendants / Number of Invitation i.e. <u>Cervical Cancer</u> : Before: 55.5%→Post: 80.5%
(2) Abnormal Rate	Abnormal rates of screening test	◆Positive of test / total attendants i.e. <u>FOBT positive rate</u> (2001-2003) :

Components	Methods / Data sources	♦Indicators / Selected results from the KCIS program /comments
		4.1%,4.5%, 3.7%
(3) Referral performance	Calculated data by referral part of database	♦Referral cases / abnormal finding (2000-2002) i.e. <u>Colonoscopy for CRC</u> : 67.13%→73.97% i.e. <u>Ultrasonography for HCC</u> : 77.37%→88.52%
(4) Biopsy rate	Confirmatory biopsy of abnormal findings	♦Biopsy cases/ abnormal cases i.e. <u>Breast cancer</u> : 2.87%
4.Effectiveness		
(1) Prevalence/Incidence ratio	Prevalence rate (P) from the KCIS and incidence (I) from national cancer registry	♦Prevalence rate from screen / Incidence from cancer registry. Average duration of pre-clinical phase (in year). i.e. <u>CRC</u> : 3.7 yr (1.52×10^{-3} / 4.1×10^{-6})
(2) I/E ratio	See the point (3) of quality assurance mentioned above	See above
(3) Proportion or cumulative incidence rate of advanced cancers or	Proportion or cumulative incidence rate of large tumor, lymph nodes, and poor differentiation	♦Number of tumor characteristic / Cancer cases i.e. <u>Dukes stages of CRC</u> : Dukes A: 13 (39.4%), Dukes B:13 (39.4%), Dukes C: 6 (18.2%), Dukes D: 1 (3.0%)
(4) abnormal outcomes of relative chronic disease	Proportion of abnormal outcomes of chronic diseases	♦Hyperlipidemia: Total cholesterol ≥ 240 ng/dl / Total Hyperlipidemia : 12.7%
(5) Long-term mortality	Linkage data to ascertain date of death and cause of death (a) Empirical data (b) Project: Monte Carlo Computer simulation	Relative mortality rate for screened vs unscreened
5.Co-morbidity profiles		
	Attendants have more than one disease simultaneously	♦Attendants of ≥ 2 types of disease/Total attendants i.e. chronic disease : two:20.7%, three:

Components	Methods / Data sources	♦Indicators / Selected results from the KCIS program /comments
		7.0% and four: 0.9%
6.Behavior risk factor surveillance	Life-style factors and biochemical data from the KCIS program	Monitor the changes of these factors and biochemical markers through repeated screens in the KCIS program
7.Decision / Economic evaluation		
(1) Cost-effectiveness analysis	Markov Decision analysis (see Figure 4.1) of cost and effectiveness for the following comparisons	Incremental cost-effectiveness or utility ratio expressed by Cost per life year gained or Cost per quality-adjusted life-year gained
(2) Cost-utility analysis	(1) Multiple / single screening (2) Single screening / none	
8. Epidemiological profiles	Linkage to national cancer registry to ascertain incident tumors and active follow-up of chronic disease	(a) A series of longitudinal outcomes for elucidating causal relationships between baseline covariates and cancer or chronic disease through case-cohort or nested case-control study (b) Family-based epidemiological design for family aggregation or genetic contribution
9. Social aspect		
(1) Cue to attending KCIS	Survey by random sampling	♦ heard about the KCIS / total survey cases 49.3% (2000)→ 65.6%(2003)
(2) Satisfaction toward the KCIS	Survey by random sampling from attendants in the KCIS	♦ Number of attendants toward satisfaction / Total samples : 81.4% (2000)→93.9% (2003)
(3) Interaction with local primary care or public health system	Participation and engagement from primary care unit or specialist	Proportion of GP or social works included in the KCIS involved in the KCIS program

1.3.1 Organizational aspects

Evaluation of disease screening program with respect to the organizational aspects includes coverage rate, outreach/opportunistic proportion, health manpower at on-site screening and referral and confirmatory diagnosis. This is illustrated by our KCIS (Keelung community-based Integrated Screening) program. (Table 1-1)

1.3.2 Basic outcomes

Basic characteristics of mass screening included attendance rate, positive results of screening, referral rate, biopsy rate, detection rate of asymptomatic neoplasm or non-neoplastic chronic diseases, sensitivity and specificity, positive predictive value and negative predictive value for the yield of screening.

1.3.3 Effectiveness of screening

The assessments of the effectiveness of screening include short-term and long-term indicators. The former consist of prevalence/incidence (P/I) ratio, the incidence rate of interval cancer as a percentage of the expected incidence rate from the underlying population (I/E ratio), cumulative incidence rate of advanced cancer such as tumor larger than 2 cm or nodes positive.

The higher P/I ratio, the lower I/E ratio, and the lower the proportion or the cumulative incidence rate of advanced cancers, the better the benefit of screening achieved.

1.3.4 Quality assurance data

There are four main domains that reflect data quality on screening program. These include accuracy of disease status and information, delay reporting of cancer registry, ascertainment of interval cancers, and survival by detection mode

1.3.5 Co-morbidity profiles

Screening, particularly multiple disease screening, provides an opportunity for ascertaining co-morbidity of diseases in each individual.

1.3.6 Behavior risk factor surveillance

The screening program provides a platform for bridging screening with primary education, particularly pertaining to a health promotion program for prevention of chronic diseases. Repeated biochemical data together with life-style factors obtained from questionnaires offer an opportunity to monitor changes in behavior risk factors, including the cessation rate of smoking and the changes of blood pressure, blood lipids, fasting blood level, dietary habits and status of physical activity after the introduction of a series of primary education programs, by comparing the mean or median for each specific biochemical variable before and after intervention.

1.3.7 Decision/economic evaluation

As mentioned above, screening program enables us to evaluate the effectiveness of mortality reduction in single or multiple disease screening. For example, Markov decision analysis is applied to estimating multiple benefits for early detection of two non-neoplastic chronic diseases (including

asymptomatic type 2 diabetes, and hypertension) and four common cancers (cervical neoplasm, oral neoplasm, breast cancer and colorectal neoplasm).

1.3.8 Epidemiological profiles

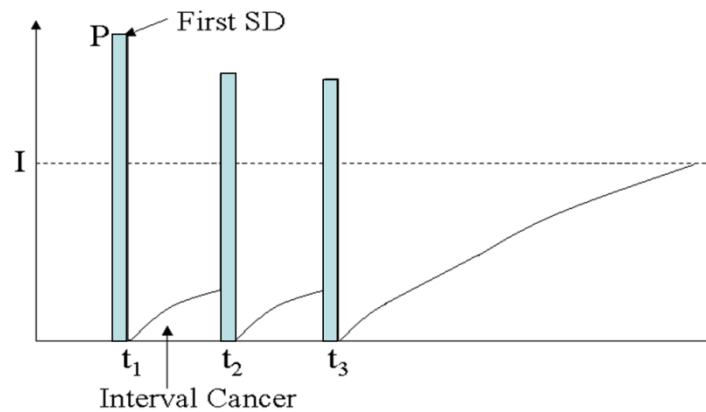
The follow-up of normal subjects in the KCIS program will yield a series of longitudinal incident cases regarding chronic diseases or cancers rather than single ones, which not only provides the chance of elucidating the associations between different outcomes but also throw light on causal relationships between baseline or time-dependent covariates and cancers or chronic diseases. In addition, household data from the KCIS program offers an opportunity to investigate family aggregation or genetic contribution using family-based epidemiological design.

1.3.9 Social aspects

From the social aspect, evaluation also included the assessment of satisfaction with the screening program. For example, approximately 200 people each year, randomly selected from the population registry in Keelung City were interviewed through the telephone to assess whether they have heard about the KCIS program. In this survey, the proportion of attendants who heard about the KCIS program increased from 49% in 2000 to 66% in 2003. Of those who participated in the KCIS program, 82% in 2000 to 94% in 2003 were satisfied with the program. The social impact regarding interaction with local primary care or public health system should be also included.

1.4 Epidemiological profiles and mass screening for cancer and chronic diseases

1.4.1 Prevalence and incidence in mass screening

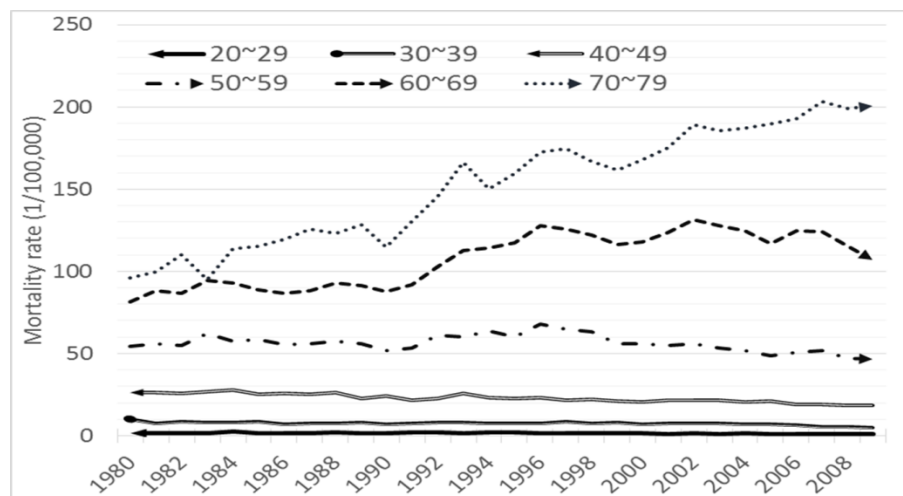


The prevalence of cancer increased remarkably at first screen because of PCDP cases. Assuming 100% sensitivity, the incidence right after prevalent screen levels off to zero, and starts to climb up gradually with occurrence of the interval cases. Subsequent screens led to an abrupt level of incidence. One screens stop, the incidence rate of interval cancer grows until it reaches the level of background incidence rate.

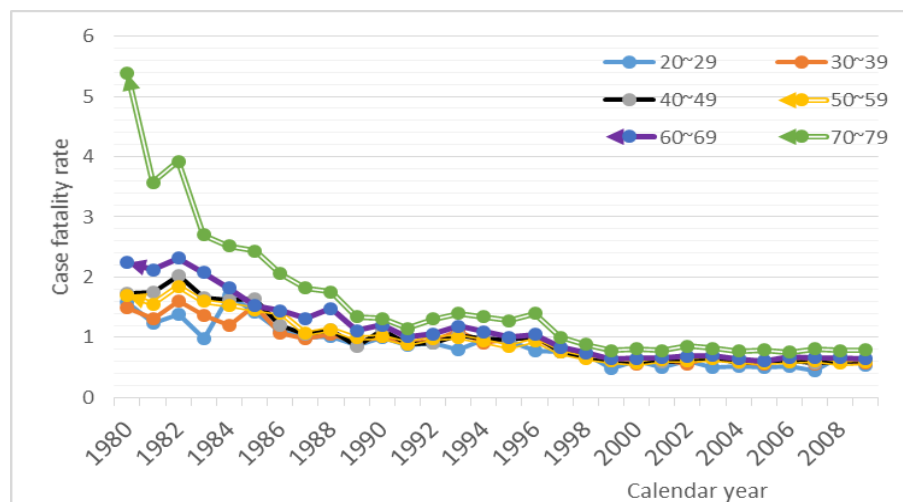
1.4.2 Mortality is a function of incidence and case-fatality

Figure 1-2 Hepatocellular carcinoma in Taiwan

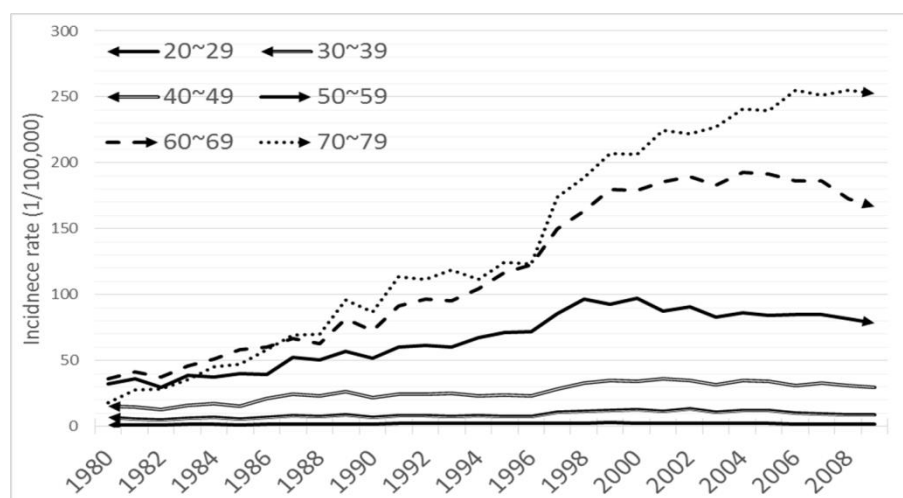
(A) Mortality



(B) Fatality



(C) Incidence



1.4.3 Increasing incidence of colorectal cancer after the introduction of screening in Taiwan

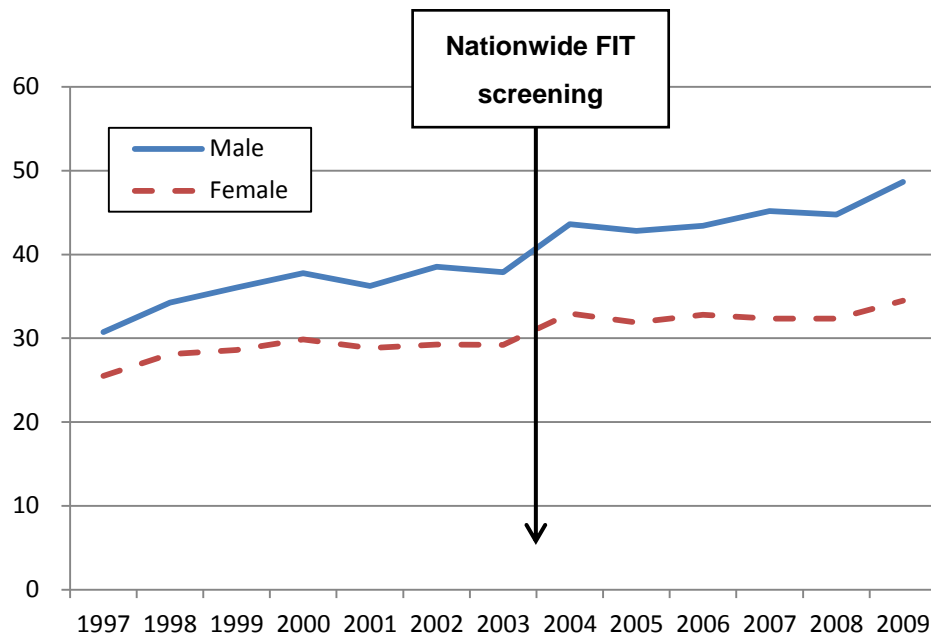


Figure 1-4 Incidence of colorectal cancer in 1997-2009, Taiwan

1.5 Statistical aspects on mass screening for cancer and chronic disease

1.5.1 Set theory and sample space

In the disease natural history, the sample space

$$S = \{ N, \text{PCDP}, \text{CP}, D_1, \text{and } D_2 \}$$

In the screening program, the sample space contains outcomes

$$S = \{ N_p, N_s, SD_p, SD_l, IC, RF_p, RF_l, D_1, \text{and } D_2 \}$$

1.5.2 Sigma algebra

A collection of S is called sigma algebra (or Borel field) denoted by β .

A probability function is a function P with domain β that satisfies

$$P(A) \geq 0 \text{ for all } A \in \beta$$

$$P(S) = 1$$

If A_1, A_2, \dots belonging to β are pairwise disjoint, then $P(\bigcup_{i=1}^{\infty} A_i) = \sum_{i=1}^{\infty} P(A_i)$

Defining probabilities $P(\{N_p\} + \{SD_p\} + \{RF_p\}) = 1$

1.5.3 Poisson distribution

Definition

A random variable (*r.v.*) Y is said to have a Poisson distribution with parameter μ (>0) if its probability mass function (p.m.f.) is defined by

$$P_Y(y) = \frac{e^{-\mu} \mu^y}{y!} \quad y=0,1,2,\dots$$

Interpretation

A Poisson *r.v.* Y is the number of occurrence of cancer; which was a rare event, during some fixed time period. The expected number of cancer is μ and individual occurrences of cancer are independent.

Binomial and Poisson distribution

The Poisson p.m.f can be derived by taking the limit of a binomial p.m.f. as $n \rightarrow \infty$ under the assumption that np remain constant.

Let $\mu=np$ and substituting for p in the formula for binomial probability

$$\begin{aligned} C_y^n P^y (1-P)^{n-y} &= \frac{n!}{(n-y)! y!} P^y (1-P)^{n-y} \\ &= \frac{n!}{(n-y)! y!} \left(\frac{\mu}{n}\right)^y \left(1 - \frac{\mu}{n}\right)^{n-y} \\ &= \frac{n(n-1) \dots (n-y+1)}{n^y} \times \frac{\mu^y}{y!} \left(1 - \frac{\mu}{n}\right)^n \left(1 - \frac{\mu}{n}\right)^{-y} \\ &\rightarrow 1 \cdot \frac{\mu^y}{y!} \cdot e^{-\mu} \cdot 1 \end{aligned}$$

($\because \lim_{n \rightarrow \infty} \left(1 - \frac{\mu}{n}\right)^n = e^{-\mu}$ with the application of L'Hôpital's rule)

Mean and Variance

$$E(Y) = \mu$$

$$\text{Var}(Y) = \mu$$

Suppose that $N_t \sim \text{Poisson}(\lambda t)$ for each t

$$\begin{aligned} \Pr(T > t) &= \Pr(\text{first cancer after time } t) \\ &= \Pr(\text{no cancers in } [0, t]) \\ &= \Pr(N_t = 0) \\ &= e^{-\lambda t} \end{aligned}$$

$$\begin{aligned}\Pr(\text{Exp}(\lambda) > t) &= \Pr(\text{Poisson}(\lambda t) = 0) \\ \rightarrow \Pr(\text{Exp}(\lambda) \leq t) &= \Pr(\text{Poisson}(\lambda t) > 0)\end{aligned}$$

1.5.4 The exponential distribution

Definition

A r.v. Y is said to have an exponential distribution with parameter λ if its probability density function (p.d.f.) is defined by

$$\begin{aligned}f_Y(y) &= \lambda e^{-\lambda y} & y \geq 0 \\ &= 0 & y < 0\end{aligned}$$

Poisson and Exponential distribution

Consider a sequence of cancers arrivals over time. Let T be the time until the first cancer arrival and, for each t , let N_t be the number of arrivals in the time interval $[0, t]$. Hence, the survival function of T is given by

$$S_T(t) = e^{-\lambda t} \quad t \geq 0$$

The probability density function of T is

$$f_T(t) = \lambda e^{-\lambda t} \quad t \geq 0$$

Hazard Function for Exponential Distribution

Consider a woman that has a constant risk of breast cancer. This means that the hazard function for this woman is constant

$$\lambda(t) = \lambda \quad t \geq 0$$

Hence, from the general formula derived above

$$S_T(t) = \exp\left(-\int_0^t \lambda \, dt\right) = e^{-\lambda t} \quad t \geq 0$$

$$H(t) = -\log S_T(t) = \lambda t$$

$$\log H(t) = \log \lambda + \log t$$

Concept of hazard rate and incidence rate

Concept and variable	Hazard rate	Incidence rate
1. Field	Clinics	Public Health
2. Epidemiology level	Individual	Population
3. Time to event	Death, metastasis, recurrence	Onset of disease (time to event is unknown)
4. Numerator	p.d.f. (continuous) Exponential –survival time	p.m.f. (discrete) Poisson—count
5. Denominator	Survival function	Person years
6. Sufficient statistics	(1) Total time & total events (2) Ordinal data of survival time (3) Absolute survival time	Minimum sufficient statistics: total events and total person-time

