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糞便免疫化學法大腸癌族群篩檢之間隔癌統計方法

Statistical Methods for Interval Cancers from Fecal Immunochemical Test in Population-based Screening for Colorectal Cancer

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本論文係 許文峰 君（學號 D04849009）在國立臺灣大學流行病學與預防醫學研究所完成之博士學位論文，於民國 108 年 07 月 26 日承下列考試委員審查通過及口試及格，特此證明。

口試委員：陳秀勇（簽名）

（指導教授）

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中文摘要

研究背景

當糞便潛血檢查被廣泛使用於以族群為主之大腸癌篩檢時，對於利用潛血檢測之兩階段篩檢下之篩檢間隔癌相關品質確保議題，無論如何強調都不為過。篩檢間隔癌有許多類型，包含腸鏡後的篩檢間隔癌及因潛血檢測所產生的篩檢間隔癌，雖然兩者已有清楚定義，但對於兩類篩檢間隔個案之相關量性研究迄今仍十分缺乏，包含兩類篩檢間隔個案在大腸癌自無症狀至有症狀之進展表現上，對第一階段糞便潛血檢查及第二階段腸鏡檢查之效度影響、以及在存活分析上，兩類篩檢間隔個案與其他篩檢偵測癌症在考量截切資料及前導期校正後之比較，以及與未轉介、未參加篩檢之大腸癌個案存活互相比較。此外，在區分篩檢間隔個案為新發個案或篩檢工具造成偽陰性個案之方法學發展，也是相當有興趣的議題，而這些也可能伴隨因第二階段腸鏡檢查之工具效度、不同篩檢間隔、不同篩檢率、與不同個人特質而形成更為複雜之議題。

研究目的

本論文旨在

1. 進行系統性文獻回顧估計不同類型糞便潛血檢查(化學法及免疫法)之敏感度，並考慮篩檢參與率及大腸鏡檢轉介率，
2. 發展一新穎統計模式估計與大腸直腸癌疾病進展相關的參數以及因應此兩階段篩檢模式在免疫法糞便潛血與大腸鏡檢階段所對應的敏感度，進一步估算篩檢間隔癌來自於新發生癌症及前次篩檢偽陰性兩種可能所佔的比例，及這兩個比例在篩檢間隔變換或應用於不同人口學特質之差異，
3. 發展一進階統計模式估計估算在免疫法糞便潛血後之間隔癌(FIT Interval Cancer)與大腸鏡檢後之間隔癌(Colonoscopy Interval Cancer)其分別來自新發癌症及前次偽陰性之比例，並模擬不同篩檢間隔之下之差異，
4. 比較免疫法糞便潛血後之間隔癌(FIT Interval Cancer)、大腸鏡檢後之間隔癌(Colonoscopy Interval Cancer)及篩檢偵測個案之長期存活狀況，並與調整前導期之篩檢偵測個案及進一步調整截切之首次篩檢偵測個案、大腸鏡檢未順從個案、及未參與篩檢癌症個案之長期追蹤狀況進行比較，
5. 估算篩檢間隔由 2 年改為 3 年後因免疫法糞便潛血後之間隔癌(FIT Interval Cancer)與大腸鏡檢後之間隔癌(Colonoscopy Interval Cancer)增加後所造成死亡人數增加後的潛在人命年損失(Potential Years of Life Lost, PYLL)。

研究方法

1. 貝氏 **Beta-binominal 統合分析**

   利用糞便潛血化學法為主之篩檢系統性文獻回顧資料及現行台灣糞便潛血免疫法篩檢之資料進行三種敏感度包含工具敏感度、整體敏感度及計畫敏感度之貝氏 Beta-binominal 統合分析。
2. 廣義非線性測量誤差迴顧模式

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本論文發展廣義非線性測量誤差迴歸模式以對臨床症前期癌症發生率及自無症狀轉移至臨床症狀之速率以三階段馬可夫模式分別以貝氏及非貝氏方法進行估計，模式並考量二階段篩檢之敏感度。為評估篩檢間隔癌在不同篩檢間隔及篩檢工具之影響，就不同年齡層、性別之個別速率及敏感度之估計結果應用於不同假設設計之試驗設計上。

更進一步將進階廣義非線性測量誤差迴歸模式，對臨床症前期癌症發生率及自無症狀轉移至臨床症狀之速率進行估計外，並分別估計腸鏡敏感度及潛血檢測敏感度，用以反映腸鏡後的篩檢間隔癌及因潛血檢測所產生的篩檢間隔癌。

3. 比較不同大腸癌偵測型態存活，包含篩檢偵測大腸癌、因潛血檢測所產生的篩檢間隔癌、腸鏡後的篩檢間隔癌、以及臨床偵測大腸癌包含未轉介鏡檢大腸癌以及未參加篩檢之大腸癌個案。此部份除利用寇斯比例風險迴歸模型進行多變量分析，亦對篩檢測偵個案進行截切資料及前導期校正。

資料來源

本論文資料來源因應上述三個部份描述如下：

1. 利用文獻搜尋找到以糞便檢測為主之族群大腸直腸癌篩檢之文獻，共取得 5 篇以化學法為工具及 2 篇以免疫法為工具的研究，
2. 利用臺灣大規模族群大腸直腸癌篩檢計畫估計廣義非性迴歸測量誤差模式相關參數，該篩檢計畫的目標族群為 50-69 歲民眾，篩檢間隔為兩年，篩檢資料區間介於 2004 年至 2014 年間，
3. 利用參與上述篩檢計畫目標族群在 2004 年至 2012 年間發生的大腸直癌個案，計 8992 名個案，依照不同偵測模式追蹤其後續存活狀況至 2016 年止。

結果

第一部份：不同類型糞便潛血檢查工具之敏感度

統合分析結果顯示化學法糞便潛血篩檢工具敏感度為 52.5% (95%信賴區間: 51.2%-53.8%)，整體敏感度為 49.6% (95 信賴區間: 48.3%-50.9%)，計畫敏感度則降至 33.3% (95%信賴區間: 32.0%-34.5%)。而在糞便潛血免疫法為篩檢工具的分析結果中，工具敏感度為 80.9% (95%信賴區間: 80.0%-81.7%) 整體敏感度為 65.7% (95%信賴區間: 64.6%-67.3%)。其中工具及整體的敏感度皆高於化學法篩檢工具(gFOBT)，但因為較低的篩檢參與率，免疫法的計畫敏感度卻較化學法低，為 34.7% (95%信賴區間: 33.7%-35.7%)。

第二部份：以免疫糞便潛血法進行篩檢之篩檢間隔個案

應用馬可夫二階段方法，以台灣兩年一次大腸直腸癌篩檢資料估計結果得到基礎發生率為 0.00151 (95%信賴區間: 0.00147-0.00155)，疾病進展速率為 0.36 (95%信賴區間: 0.34-0.38)。若將測量誤差也納入考量之模型，工具敏感度估計為 75.47% (95%信賴區間: 72.99%-77.80%)。性別及年齡在癌症發生中扮演的角色，男性的影響程度為女性的 1.75 倍(95%信賴區間: 1.68-1.82)，老年為年輕的 1.79 倍 (95%信賴區間: 1.73-1.86)。性別及年齡在癌症疾病進展中扮演的角色而言，男性的影響程度為女性的 0.82 倍(95%信賴區間: 0.77-0.87)，老年為年輕的 0.91 倍 (95%信賴區

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間:0.86-0.97)。

在兩年一篩的間隔個案中大多數為新發生的大腸癌個案(約佔 68.8%)，若對應至篩檢政策為一年一篩時會降低至 61.1%，若為三年一篩時則增加至 74.7%。對兩階段糞便潛血篩檢，使用廣義非線性錯誤分類迴歸模式所估計之糞便潛血敏感度為 71.9% (95%信賴區間: 71.0-72.8%)，大腸鏡檢敏感度為 93.6% (95%信賴區間: 91.9-94.9%)。依據此估計結果，就糞便潛血篩檢而言，分別有 61%的篩檢間隔為新發篩檢間隔癌，而有 39%為偽陰性篩檢間隔癌。就大腸鏡檢間隔癌而言，分別有 88%的篩檢間隔為新發篩檢間隔癌，而有 12%為偽陰性篩檢間隔癌。

第三部份：不同偵測模式大腸直腸存活分析

在調整年齡、性別、病灶位置及治療後，相較於未參與篩檢個案，大腸鏡檢未順從個案、免疫法糞便潛血後之間隔癌、大腸鏡檢後之間隔癌、第一次及後續篩檢偵測個案死於大腸癌的調整危險對比值分別為 0.56(0.50-0.64)、0.57 (0.52-0.64)、0.42 (0.32–0.54)、0.30 (0.27-0.33)及 0.22 (0.19-0.26)。對篩檢測偵個案進行截切資料及前導期校正後，後續及第一次篩檢偵測個案死於大腸癌的調整危險對比值分別為 0.25 (0.22-0.30)及 0.63 (0.58–0.69)。

利用廣義非線性聯合測量誤差模式的估計結果及不同偵測模式個案之存活率，可以得到兩年一次篩檢改為三年一次篩檢將會導致 2337 年的潛在人年損失，其 2314 人年損失是來自糞便潛血檢查、23 人年損失來自大腸鏡。

結論 本論文發展一新穎廣義非線性測量誤差迴歸模式，用以評估大規模大腸直腸癌篩檢計畫因糞便潛血及大腸鏡在間隔癌個案的分別貢獻程度，在考量前導期及截切性質下的存活分析後，估算篩檢間隔改變對大腸直腸癌死亡減少的影響。

關鍵詞: 大腸直腸癌; 大腸癌篩檢; 糞便潛血免疫法; 大腸鏡; 間隔癌症

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Abstract

Background. While fecal immunochemical test (FIT) has widespread use in population-based colorectal cancer (CRC) screening quality assurance of interval cancers (ICs) ensuing from two-stage screening with FIT test cannot be over emphasized. Various types of ICs (including colonoscopy ICs and FIT ICs) and sensitivity have been defined but there are no formal quantitative studies yet addressing how both ICs in relation to the disease progression of CRC from asymptomatic phase to symptomatic phase, the performance of screening with FIT at first stage and colonoscopic examination at second stage, and their survival rates in comparison with screen-detected CRCs with adjustment for truncation and lead-time, and CRCs from non-referral, and non-participants. One of intractable methodological issues in modelling ICs is that newly developed CRCs after screening cannot be directly separated from false negative CRCs missed at the previous screen on the basis of empirical data. This issue is further complicated by the performance of the second-stage confirmatory method such as colonoscopy, inter-screening interval, and screening rate, and demographic features.

Aims. The objectives of this thesis are to **1.** conduct a systematic review and meta-analysis of estimating different types of sensitivity for g-FOBT and FIT making allowance for attendance rate of the uptake of screening and non-referral of colonoscopy; **2.** develop a new statistical model for estimating the transition parameters pertaining to the disease natural history of CRC and the sensitivity of the overall two-stage screening resulting from FIT and colonoscopy in order to quantify the respective contributions of false-negative and newly developed CRCs to total ICs and to estimate the corresponding figures varying with different inter-screening interval and demographic features; **3.** develop an advanced statistical model to quantifying the respective contributions of false-negative and newly developed CRCs to FIT ICs and colonoscopy ICs, respectively, to quantify the respective contributions of false-negative and newly developed CRCs to total ICs and to estimate the corresponding figures varying with different inter-screening intervals; **4.** elucidate and compare the long-term survival of FIT ICs and colonoscopy ICs in comparison with the lead-time and truncation adjusted survival of prevalent screen-detected CRC and subsequent screen-detected CRC, non-referral (not complying with colonoscopy) CRC, and CRCs from non-participants. **5.** estimate potential years of life lost (PYLL) when excess deaths attributed to FIT ICs and colonoscopy ICs were averted by changing inter-screening interval.

Methods. Part I: Bayesian Beta-binominal Meta-analysis

Three degree of sensitivity: test, episode and program sensitivity in gFOBT-based and FIT-based screening programs of previous studies and the current Taiwanese study were systematically reviewed and a meta-analysis was conducted by Bayesian beta binomial

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meta-analysis to account for differences of these three sensitivities between gFOBT screening program and FIT screening program.

Part II: Generalized non-linear measurement error regression model

A generalized non-linear measurement error regression model was developed to estimate the pre-clinical incidence rate and the transition rate from asymptomatic phase to symptomatic phase underpinning a three-state Markov model and the sensitivity of two-stage screening program with Bayesian and non-Bayesian method. To assess the impact of inter-screening interval on interval CRC, the estimated results on age and sex specific rates and sensitivities were further applied to the proposed multi-arm trials. Another advanced generalized non-linear measurement error regression model was further developed to estimate the pre-clinical incidence rate and the transition rate from asymptomatic phase to symptomatic phase underpinning a three-state Markov model and the joint estimates of FIT-based and of colonoscopy-based sensitivity to reflect FIT ICs and colonoscopy ICs. To assess the impact of inter-screening interval on two separate types of interval CRC were further applied to the proposed multi-arm trials.

Part III: Lead-time- and Truncation-adjusted Survival

The survival status of CRCs was compared stratifying with different detection modes: screen-detected CRC, FIT IC, colonoscopy IC, and clinically diagnosed CRC (colonoscopy noncompliers, and screening non). Multivariable analyses were conducted with Cox proportional hazards regression models. We also further adjusted the lead-time and truncation adjustment for screen-detected CRCs.

Data Sources. There are three parts of retrieving data for this thesis. The first part consists of studies on evaluating the sensitivity of tests for colorectal cancer were derived from 5 gFOBT-based screening programs, and 2 FIT-based screening programs. The second part is to use the empirical data on Taiwanese Nationwide Colorectal Cancer Screening Program recruiting residents aged 50 to 69 years to have the uptake of a biennial FIT during 2004-2014 for estimating the parameters encoded in generalized non-linear regression measurement error model. The third part is to use the data of CRCs with various detection modes resulting from Taiwanese population-based FIT screening program. Totally 8,992 CRCs were identified from the cohort who were considered as eligible for screening during 2004-2012 in Taiwanese CRC Screening Program and were followed up until 2016.

Results. Part I: Meta-analysis of Different Types of Stool-based Sensitivity

The results of gFOBT-base screening program based on meta-analysis show that the pooled test sensitivity was 52.5% (95CI: 51.2%-53.8%), and the episode sensitivity was 49.6% (95CI: 48.3%-50.9%). The program sensitivity was 33.3% (32.0%-34.5%). The results of FIT-based screening program based on meta-analysis show that the test sensitivity was 80.9% (95CI: 80.0%-81.7%) and episode sensitivity was 65.7% (95CI:

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64.6%-67.3%). The program sensitivity of FIT-based screening program was reduced to 34.7% (95 CI: 33.7%-35.7%).

Part II: Interval cancer in FIT-based screening program

The baselined incidence rate and progress rate were estimated as 0.00151 (95% CI: 0.00147-0.00155) and 0.36 (95%CI:0.34-0.38), respectively. The sensitivity of screening test was estimated as 75.47% (95%CI:72.99%-77.80%). The effect size of male sex and old age on the occurrence of CRC was estimated as 1.75 (95%CI:1.68-1.82) and 1.79 (95%CI:1.73-1.86), respectively. The effect size of male sex and old age on the progression of CRC was estimated as 0.82 (95%CI:0.77-0.87) and 0.91 (95%CI:0.86-0.97), respectively. FIT interval CRCs from biennial regime mainly resulted from newly developed CRCs (68.8%). The corresponding figures were reduced to 61.1% for annual program but increased to 74.7% for triennial program. The estimated results based on the generalized non-linear joint measurement error model gave the sensitivity of 71.9% (95% CI: 71.0-72.8%) and 93.6% (95% CI: 91.9-94.9%) for FIT and colonoscopy, respectively. Based on these estimates, 61% and 39% of ICs resulted from the path of newly develop and false negative, respectively for FIT screen. The corresponding figure for colonoscopy is 88% for newly developed, and 12% for false negative.

Part III: Survival by detection model

After adjusting for age, sex, location, and treatment, compared with that for CRCs in screening nonparticipants, aHR of was 0.56(0.50-0.64) for CRC in colonoscopy noncompliers, 0.57 (0.52-0.64) for FIT IC, 0.42 (0.32–0.54) for colonoscopy IC, 0.30 (0.27-0.33) for prevalent screen-detected CRC, and 0.22 (0.19-0.26) for subsequent screen-detected CRC. After adjustment for lead-time and truncation, the aHR was 0.25 (0.22-0.30) for subsequent screen-detected CRC, and 0.63 (0.58–0.69) for prevalent screen-detected CRC. Based on the estimated results of generalized non-linear joint measurement error model and survival for each detection modes, the biennial program compared with triennial one resulted in the life-year gained by 2337 person-years, among which 2314 person-years and 23 person-years resulted from FIT test and colonoscopy, respectively.

Conclusions. A new generalized non-linear measurement error regression models was developed to model contributory causes of FIT and Colonoscopy ICs to estimate the impact of inter-screening interval on the reduction of deaths from CRC attributed to each type of ICs making use of the lead-time and truncation-adjusted survival model.

Key words: Colorectal cancer; Colorectal cancer screening; Fecal immunochemical test; Colonoscopy; Interval cancer

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Chapter 1 Introduction

1.1 Epidemiology of colorectal cancer

Colorectal cancer (CRC) is the third most common cancer accounting for 881,000 deaths, the fourth leading cause of cancer-related death, in 2018. It is the third most common cancer in men (1,006,019 cases, 10.9% of the total) and the second in women (794,958 cases, 9.5% of the total) worldwide (Bray et al. 2018) and is thus considered as one of the most threatening issues in global health (Torre et al. 2015). Despite the advance in medical technology and the increasing awareness among researchers, policymakers and the public the health impact of colorectal cancer remain remarkable and calls for the integration of a series of prevention strategies to reaching the aim of CRC prevention.

The urbanization and globalization further results in the soaring risk of CRC in Asia countries due to the change mainly in sedentary life style and dietary patterns. In Taiwan, 15,374 CRC cases are diagnosed each year and the annual death toll due to CRC is 5,722, which makes CRC the second most common cancer and the third leading cause of cancer-related death (Health Promotion Administration 2018).

1.2 Evolution of colorectal cancer

The lifetime risk of developing CRC in many regions is around 5%. Approximately

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45% of persons diagnosed with CRC death as a result of the disease, despite treatment (Ferlay et al. 2010). The majority of CRCs are considered to evolve from adenomatous colorectal polyps (Muto, Bussey and Morson 1975), and then progresses from early adenoma to invasive cancer takes years (Kuntz et al. 2011, Brenner et al. 2007). This feature of long-term progression through precursor lesions and the available stool-based test provide a good chance for reducing the risk of CRC mortality through early detection. The removal of precancerous lesion by using scopy-based modalities further brings the opportunity in reducing the incidence of CRC. As early as 1993, the National Polyp Study showed the effectiveness of colonoscopy in reducing CRC incidence by 76-90% through polypectomy (Winawer et al. 1993).

1.3 Colorectal cancer prevention with FIT-based screening program

The soaring incidence and high cost in treating advanced CRC together with the characteristics of long dwelling time in preclinical phase and curable precancerous lesion make CRC a suitable target for the application of population-based screening program as the secondary prevention strategy (Schreuders et al. 2015). From the viewpoint of secondary prevention, as the natural history for the evolution of CRC has been well-documented to be a relatively slow process starting from curable neoplastic lesions such as adenoma (Vogelstein et al. 1988, Chen et al. 2003), the identification of

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adenomas and lesions at early stage by mass screening became the paradigm of CRC prevention for recent decades. (Winawer et al. 1993, Mandel et al. 1993). The population-based screening programs is therefore adopted worldwide including Taiwan aimed to reduce CRC-related mortality and also its incidence. (Schreuders et al. 2015).

Among a variety of screening modalities, the stool-based tests including using guaiac fecal occult blood test (gFOBT) and Faecal immunochemical test (FIT) focusing on the detection of bleeding phenotype have increasingly gained attention in recent decades in population-based CRC prevention (Shaukat et al. 2013). These tests detect the blood reaction in stool samples at microscopic level by using either haem (gFOBTs) or human globin (FITs) as the target. The screening programs using gFOBT have been proven to be effective in reducing the mortality of CRC. A meta-analysis of four RCTs concluded that annual or biennial gFOBT screening shows the results of lacking of the benefit on CRC incidence reduction (in three out of the four studies included in the analysis) but led to an average 16% reduction in CRC-related mortality. Although the benefits of screening are well-established, no screening test will ever be perfect, the sensitivity is an indicator for the quality and effectiveness of a screening program. It is therefore indispensable to do systematic evaluation of the sensitivity of screening programs across different detection modalities including the use of gFOBT and FIT methods.

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1.4 Interval cancers in population-based screening program

While the effectiveness of this population-based strategy have been demonstrated in previous studies (Chiu et al., 2015), the sensitivity of screening tools and the impact of interval cancers occurred in the screening programs have gained attention in recent years. The major concern on the application of stool-based tests in population-based screening program lies within the ability in detecting asymptotic CRC, namely sensitivity for lesions. This is closely related to the occurrence of symptomatic case diagnosed between screens, namely interval cancer (Hewitson et al. 2008, Sanduleanu et al. 2015). Compared with screen-detected CRC, interval cancer is characterized by its advanced stage and worse survival (Hakama et al. 2007, Gill et al. 2012). The interval cancer rate is thus a cardinal indicator of the quality and effectiveness of population-based screening program (Sanduleanu et al. 2015, Scholefield et al. 2012, Brenner et al. 2012). Various types of interval cancers (including colonoscopy interval cancers and FIT interval cancers) and sensitivity have been defined but there are no formal quantitative studies yet addressing how both interval cancers in relation to the disease progression of CRC from asymptomatic phase to symptomatic phase, the performance of screening with FIT at first stage and colonoscopic examination at second stage, and their survival rates in comparison with screen-detected CRCs with adjustment for

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truncation and lead-time, and CRCs from non-referral, and non-participants.

In addition to FIT interval cancer as a result of the failure to detect CRCs being asymptomatic CRC already at the time of screening (false-negative CRC, lower part of Figure 1.1), the CRCs developed between screening rounds (newly developed CRC, upper part of Figure 1.1) may also account for interval cancer observed in screening program (Kaminski et al. 2010). Interval cancer caused by newly developed CRC begins from free of CRC status, passes through asymptomatic CRC status, and progresses to symptomatic CRC after negative screen. Notably, free of CRC status is defined by normal or with precancerous lesions such as small or advanced adenoma. (Figure 1.1) While the false-negative CRC is closely related to the ability of a screening tool to detect asymptomatic cancers, the newly developed CRC is strongly associated with inter-screening interval as the risk of developing CRC from adenoma is highly associated with the follow-up time.

The attempt to separate newly developed CRCs from false-negative CRCs relying on the observed FIT interval cancers is not possible. Mixing up newly developed CRCs with false-negative CRCs may lead to the underestimation of FIT sensitivity for detecting asymptomatic CRC. The relative contribution of newly developed and false negative cases to FIT interval CRCs may provide an insight into the design of inter-screening interval and the improvement of the quality assurance of screening program.

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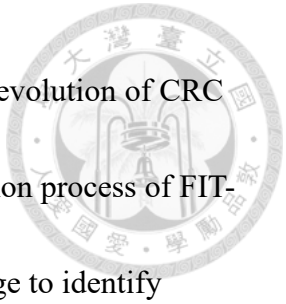

However, the elucidation of these issues is hampered by the evolution of CRC embedded within the two-stage screening process in which the common process of FIT-based screening program involved with the use of FIT test at first stage to identify subjects at increased risk of CRC followed by the referral for the confirmatory examination using colonoscopy as the major tool in the second stage. One of intractable methodological issues in modelling interval cancers is that newly developed CRCs after screening cannot be directly separated from false negative CRCs missed at the previous screen on the basis of empirical data. This issue is further complicated by the performance of the second-stage confirmatory method such as colonoscopy, inter-screening interval, and screening rate, and demographic features.

Aims

The objectives of this thesis are to

1. conduct a systematic review and meta-analysis of estimating different types of sensitivity for g-FOBT and FIT making allowance for attendance rate of the uptake of screening and non-referral of colonoscopy;
2. develop a new statistical model for estimating the transition parameters pertaining to the disease natural history of CRC and the sensitivity of the overall two-stage screening resulting from FIT and colonoscopy in order to quantify the respective

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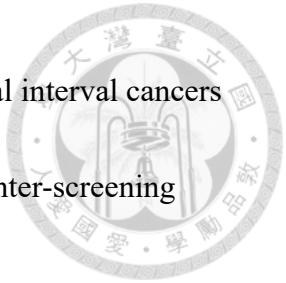

contributions of false-negative and newly developed CRCs to total interval cancers and to estimate the corresponding figures varying with different inter-screening interval and demographic features;

3. develop an advanced statistical model to quantifying the respective contributions of false-negative and newly developed CRCs to FIT interval cancers and colonoscopy interval cancers, respectively, to quantify the respective contributions of false-negative and newly developed CRCs to total interval cancers and to estimate the corresponding figures varying with different inter-screening intervals;
4. to elucidate and compare the long-term survival of FIT interval cancers and colonoscopy interval cancers in comparison with the lead-time and truncation adjusted survival of prevalent screen-detected CRC and subsequent screen-detected CRC, non-referral (not complying with colonoscopy) CRC, and CRCs from non-participants.
5. To estimate potential years of life lost (PYLL) when excess deaths attributed to FIT interval cancers and colonoscopy interval cancer were averted by changing inter-screening interval by using the combined information from 2 and 3.

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Chapter 2 Literature Review

2.1 Natural history of colorectal cancer

The three-state Markov model classifying disease process into three stages (CRC-free, pre-clinical detectable phase (PCDP), and clinical phase (CP)) has been proposed to quantify the temporal disease natural history of cancer. Owing to the multi-state property, the Markov model can estimate an occult transition, such as the PCDP to the CP, based on observed data by different detection modes, including disease-free at screening (CRC free→CRC-free), screen-detected (CRC-free→PCDP), and interval cancers (CRC free→CP). Besides, the simultaneous estimation on both incidence of the pre-clinical cancer and the mean sojourn time (MST, the inverse of transition rate from the PCDP to the CP under Markovian property), one could study the dependence between the two different transition rates.

Chen et al. applied the Markov model to a selective screening program in a multi-center screening program for colorectal cancer for high-risk group subjects in the Taiwan Multicenter Cancer Screening (TAMCAS) project (Chen et al. 1999). In their analysis, the preclinical incidence rate was estimated as 4 (95% CI: 2.9-5.0) per 1000, accompanying with 2.85-year MST (95% CI: 2.15-4.30). They also incorporated sensitivity into their model, and estimated the sensitivity of colonoscopy in combination with FOBT or double-contrast barium enema for this high-risk group as 94.98% (95%

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CI: 24.36-99.91%). As far as age and gender were concerned, subjects aged 50 years and older had 2.33-fold risk for the incident of preclinical CRC than young subjects, and male had a 1.10-fold risk. For the progression from the PCDP to the CP, the relative risks were 1.34 and 1.19 for elderly age and male, respectively.

The multi-state model can not only be applied to the entire cohort from a population-based service screening program, but also to only a fraction of samples retrieved from the hospital-based data or from a cohort. A case–cohort design may provide an efficient way of estimating parameters through selected samples instead of the entire cohort. Prentice et al. proposed a design involved covariate data only for cases experiencing failure and for members of a randomly selected subcohort (Prentice 1986). Importantly, estimation with case–cohort design is cost saving for biological markers that require a costly measurement. Kalbfleisch and Lawless used retrospective and case-cohort design with sampling procedures for parametric and semiparametric models (Kalbfleisch and Lawless 1988). Case–cohort design have been extended to multistate disease progression for the evaluation of disease natural history (Chen et al. 2003, Cain and Breslow 1988).

Chen et al. used such a case-cohort design to estimate the dwelling times of adenoma–carcinoma sequence by adenoma size and histological type, taking both multistate disease progression and de novo pathway of carcinoma into account (Chen et

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al. 2003). In the study of Chen et al., samples with the ratio of approximately 1:2 for normal or adenoma and cancer were used (Chen et al. 2003). The Bayesian inversion was applied to construct the total likelihood for multi-state Markov models for the entire cohort who underwent colonoscopy in a medical center (Cain and Breslow 1988). The proposed method provided an efficient way to elucidate the disease progress underpinning a multi-state disease progression (Cain and Breslow 1988). Chen et al. also applying the non-homogeneous model with case–cohort study design to elucidate the effect of betel quid, smoking and alcohol on three-state oral cancer progression as well as the efficacy of treatment (Hsiu-Hsi Chen et al. 2004). Furthermore, the stable convergence for parameter estimation with this Bayesian conversion enables the authors to put one more parameters governing the transition directly from CRC-free to invasive CRC, the so-called *de novo* carcinogenesis (Chen et al. 2003, Hsiu-Hsi Chen et al. 2004). Based on their estimated results with incidence of diminutive adenoma of 0.0021 and of *de novo* CRC as 0.00095, they successfully quantified some 32% of CRC arising from *de novo* sequence. However, in previous studies based on case-cohort design, the disease natural history was estimated using sampled data on non-cases and cases from the first examination only. A combination of data on first examination (prevalent screen), repeated examinations (subsequent screen), and interval cases (cases diagnosed in follow up and between examinations) is often encounter in disease screening. Two-

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stage sampling case–cohort design for disease natural history may provide an approach to an efficient utilization of such a follow up data with multistate disease outcome.

To evaluate treatment efficacy in reducing the rate of disease progression, we have to make comparison between the probability with and without intervention (Chen et al. 2003, Cain and Breslow 1988). The probability of malignant transformation after treatment can be derived from the observed data. However, without the randomized controlled study design, the probability of malignant transformation without intervention cannot be derived once the intervention is applied. Parameters derived from the natural history model of disease progression can shed light on the desired quantity.

2.2 Stool-based screening program for Screening program for CRC

2.2.1 Organized Screening program

An organized screening program involves a systematic process of inviting a target population to participate in screening and ensuring follow-up of those with a positive screen. An organized program should measure and report on the quality of each step in the screening process. The IARC outlines the following elements for organized screening programs, including

(1) an explicit policy with specified age categories, screening method and screening interval,

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(2) a defined target population,

(3) a management team responsible for implementation,

(4) a health care team for decisions, care and follow-up of patients with positive screening tests,

(5) a quality assurance structure for every step in the process, and

(6) a process for monitoring, evaluating and identifying cancer occurrence in the population (Cancer. , Lauby-Secretan et al. 2018).

2.2.2 Fecal occult blood test (FOBT)

In fecal occult blood test (FOBT)-based CRC screening programs, guaiac fecal occult blood tests (gFOBTs) have been the most commonly used occult stool tests for years. Randomized controlled trials have shown that screening with gFOBTs, and subsequent colonoscopy in case of a positive test, is associated with a 15%- 33% decrease in CRC-related mortality (Hardcastle et al. 1996, Kronborg et al. 1996, Mandel et al. 1993). Consequently, stool tests are widely used for CRC screening (Schreuders et al. 2015). At present, gFOBT is rapidly replaced by fecal immunochemical testing (FIT). FIT detects human-specific globin, whereas gFOBTs react with heme, including consumed non-human heme. FITs are more sensitive for the detection of CRC as well as its precursors than gFOBTs (Hol et al. 2009). Moreover, FITs allow single stool testing, are easier to handle, have higher participation rates and provide quantitative test results,

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which enables to adjust the positivity cut-off to match available resources (Kuipers, Rösch and Bretthauer 2013). Despite these advantages of FIT over gFOBT, gFOBT is still being used in several regions.

2.2.3 Guaiac fecal occult blood tests (gFOBT)

Randomized controlled trials have shown that screening with guaiac fecal occult blood tests (gFOBTs), and subsequent colonoscopy in case of a positive test, is associated with a 15%- 33% decrease in CRC-related mortality (Mandel et al. 1993, Kronborg et al. 1996, Hardcastle et al. 1996, Kewenter et al. 1994). Consequently, stool tests are widely used for CRC screening. A meta-analysis of four RCTs concluded that annual or biennial gFOBT screening had no effect on CRC incidence (in three out of the four studies included in the analysis) but led to an average 16% reduction in CRC-related mortality (Hewitson et al. 2008). The impact of the gFOBT is limited by the poor to moderate sensitivity for advanced adenomas and cancer (Brenner et al. 2014). (Table 2.2.1) For this reason, gFOBTs are typically used on multiple bowel movements per screening, and are implemented in repeated screening rounds. Other high-quality, nonrandomized study has also demonstrated similar results. The Burgundy study is a large-scale controlled trial using biennial screening (Hemoccult) in people aged 45–74 yr.(Faivre et al. 2004) After six screening rounds (and 11 yr of follow-up), the trial

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reported a 16% reduction in CRC mortality and a 23% reduction for people attending at least one round (Elwood et al. 1993). (Table 2.2.2)

In the dissertation, we evaluated the efficacy of screening program for CRC using gFOBT or FIT in terms the proportion of interval cancer of expected number of cases and the two components of interval cancer. For the comparison of interval cancer between studies using gFOBT and FIT, three randomized controlled studies using gFOBT as screening tool were enrolled. All of these three studies applying biennial screening program using gFOBT with the eligible age of enrollment ranged between 45-74 years or 60-64 years. Characteristics of these studies and details on the study design for the comparison were provided in Table 2.2.3 and Table 2.2.4.

2.2.4 Fecal immunochemical tests (FIT)

Due to that FITs are specific for human globin and do not require dietary restriction, FIT screening is generally associated with higher participation and higher detection rates of adenomas and CRCs compared with gFOBT screening (Hol et al. 2009, Van Rossum et al. 2008). Furthermore, quantitative FITs offer the opportunity to provide tailored screening by adjusting the positivity cut-off level. This can be used to adjust screening to available resources and colonoscopy capacity (Lansdorp-Vogelaar et al. 2009, Wilschut et al. 2011). A low cut-off increases the detection of advanced

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neoplasia, but lowers the positive predictive value and specificity thus demanding more colonoscopy resources (Hol et al. 2009). (Table 2.2.5) No RCT has reported the impact of FIT screening on CRC incidence and mortality. A recent ecological study compared regions in Italy with and without population FIT screening. CRC-specific mortality was 22% lower in areas with a FIT screening program compared with areas without a screening program (Zorzi et al. 2015). Chiu et al. suggested that the 21.4% coverage of the Taiwanese population receiving FIT led to a significant 10% reduction in CRC mortality (relative rate, 0.90; 95% CI, 0.84-0.95) after adjustments for a self-selection bias (Chiu et al. 2015). The higher uptake and sensitivity of FIT supports the assumption that biennial FIT screening at a low cut-off will have a larger impact than gFOBT on CRC incidence and mortality. Modelling studies suggest that the impact can approach that of colonoscopy if the adherence to multiple rounds is high (Zauber et al. 2009).

In previous study, Lee et al. (2018) reported a 1.64-fold (95% CI= 1.32 to 2.04) increased risk for CRC death for the noncolonoscopy group as opposed to the colonoscopy group adjusting for differences in baseline characteristics. A gradient relationship was noted between cumulative mortality and age- and sex-adjusted f-HbC categories with 1.31-fold (95% CI=1.04 to 1.71), 2.21-fold (95% CI=1.55 to 3.34), and 2.53-fold (95% CI=1.95 to 3.43) increased risk, respectively, for the 20–49, 50–99, and

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≧100 risk groups in the noncolonoscopy group compared with the colonoscopy group as summarized in Table 2.2.6 (Lee et al. 2017). These evidence show that higher f-HbC is associated with an increased risk of mortality from CRC in a dose response manner (Chen et al. 2011, Chiu et al. 2017b, Lee et al. 2017). In Yen's study, f-HbC may be useful for identifying cases requiring closer postdiagnosis clinical surveillance as well as being an early indicator of colorectal neoplasia risk in the general population (Yen et al. 2014). Dose-response findings may also be conducive to the development of the f-HbC-guided screening policy.(Table 2.2.7)

2.3 Interval Cancer

2.3.1 FIT interval cancer

The most common definition used for interval CRC of fecal testing was CRC detected after a negative fecal occult blood screening test and before the next invitation is due". However, the studies used various tests (guaiac fecal occult blood test (gFOBT) versus fecal immunochemical test (FIT)) at different frequency (yearly or biennially) and at different cut-off concentrations for a positive fecal occult blood test in diverse populations.(Sanduleanu et al. 2015) Lack of standardization in the reporting units for FIT (e.g., micrograms of hemoglobin per gram of feces) may have also contributed to

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differing results. (Fraser et al. 2012) According to the definition by WEO, within a FIT screening program, a CRC after a negative FIT screening test but before the next FIT is due would be designated as a 'FIT interval CRC'. (Sanduleanu et al. 2015)

Mass screening with FIT nested within a multiple screening model found the dose-response relationship between the quantitative value of FIT and the outcomes of interest related to FIT screening. Quantitative FIT permits the determination of an optimal cut-off for the fecal hemoglobin concentration(f-HbC) based on regional prevalence of CRCs. Several studies in Taiwan found that f-HbC is an independent predictor for CRC and interval cancer (IC) (including FIT IC and Colonoscopy IC), and is also a priority-setting indicator for colonoscopy. So, if the subjects receive FIT, f-HbC is an important predictor of risk stratification for precision prevention. In Chen's study, 44,324 with FIT negative result, 854 were non-referrals, and 814 were false-positive cases were followed up to ascertain cases of colorectal neoplasia (Chen et al. 2011). The incidence of colorectal neoplasia increased from 1.74 per 1000 person-years for those with baseline fecal hemoglobin concentration 1–19 ng/mL, to 7.08 per 1000 person-years for those with a baseline concentration of 80–99 ng/mL. (Table 2.3.1) The adjusted hazard ratios (HRs) increased from 1.43 (95% CI 1.08–1.88) for baseline fecal hemoglobin concentration of 20–39 ng/mL, to 3.41 (2.02–5.75) for a baseline concentration of 80–99 ng/mL (trend test $p<0.0001$), relative to 1–19 ng/mL. (Table 2.3.2) These results did

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not change when we included repeated FIT measurements. In this study, Quantitative fecal hemoglobin concentration at first screening predicts subsequent risk of incident colorectal neoplasia (Chen et al. 2011).

2.3.2 Colonoscopy Interval cancer

Colonoscopy with polypectomy reduces risk of subsequent CRC, and a negative examination portends a reduced risk as well (Brenner et al. 2010, Winawer et al. 1993). However, A number of observational studies have shown the risk of colorectal cancer (CRC) to be low within the 10-year screening interval commonly recommended after a negative colonoscopy(Singh et al. 2006, Brenner et al. 2006, Lakoff et al. 2008, Imperiale et al. 2008) CRC diagnoses after a negative or clearing colonoscopy during the recommended surveillance intervals (colonoscopy IC) is defined as colonoscopy IC or post-colonoscopy colorectal cancer, and suggest that the protective effect of colonoscopy is weaker than originally estimated.(Brenner et al. 2011, Martinez et al. 2009, Kaminski et al. 2010) Understanding how these cancers occur would inform interventions to optimize colonoscopy for CRC screening and prevention.

The interval between colonoscopies was determined by the responsible physician but usually according to Consensus Update by the US Multi-Society Task Force.(Lieberman et al. 2012) These recommendations (excepting patients with

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hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, or inflammatory bowel disease) can be simply summarized as follows:

(1) **5-year colonoscopy**: for individuals with a family history of CRC or personal history of 1-2 small adenomas;

(2) **3-year colonoscopy**: for individuals with a personal history advanced adenomas or at least 3 small adenoma; and

(3) **colonoscopy within 6-12 months**: if diagnostic procedure was incomplete or inadequate.

An "Interval" was defined as the period of time between 2 sequential colonoscopies.

As detailed in Tables 2.3.3 and 2.3.4, the reported proportions of interval CRC vary greatly, ranging from 0.8% of colonoscopic examinations46 to up to 9% of all diagnosed CRCs(Sanduleanu et al. 2015, Rex, Bond and Feld 2001, Baxter et al. 2011). Chiu et al. investigated whether and how f-HbC of FIT affected the risk prediction of IC caused by inadequate colonoscopy quality in a FIT-based population screening program (Chiu et al. 2017b). The estimated incidence of Colonoscopy IC was 1.14 per 1000 person-years of observation for the entire cohort. (Tale 2.3.5) Increased risk of IC was most remarkable in subjects with higher f-HbC (μg Hb/g faces) (100–149: aRR=2.55, 95% CI 1.52 to 4.29, ≥150: aRR=2.74, 95% CI 1.84 to 4.09) with adjustment for older age and colorectal neoplasm detected at baseline colonoscopy. (Table 2.3.6) Similar

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findings were observed for subjects with negative index colonoscopy (Chiu et al. 2017b).

There is now ample evidence that colonoscopy is highly operator-dependent, that significant miss rates occur for even advanced neoplasia, and that there is substantial variation in adenoma detection rates (ADRs). In one study of expert endoscopists the ADR varied almost 3-fold (range, 17%–47%) and there was even higher variability in detection rates of serrated polyps (range, 1%–18%). (Kahi et al. 2011) A systematic review of tandem colonoscopy studies by van Rijn et al combined results from 6 studies to include a total of 1650 polyps and found an overall adenoma miss rate of 22%, but the miss rate for adenomas of 10 mm or greater was only 2%.(Van Rijn et al. 2006) In contrast, a well-performed study of colonoscopy performed in tandem with computed tomography colonography found that 12% of lesions 10 mm or greater were missed with colonoscopy.(Pickhardt et al. 2003) There is little doubt that missed lesions occur commonly and contribute meaningfully to interval CRC risk.

Incomplete removal of adenomas is a second important cause of interval CRCs. There are now data that incomplete polypectomy is not only common but varies substantially among endoscopists. Pohl et al. reported an overall incomplete resection rate (IRR) of 10.1% with a 3.4-fold difference among endoscopists (range, 6.5%–22.7%).(Pohl et al. 2013) IRRs were significantly higher for larger polyps (5.8% for 5-

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to 7-mm polyps vs 23.3% for 15- to 20-mm polyps; OR, 3.21; 95% CI, 1.41–7.31) and for sessile serrated polyps in comparison with adenomas (31% vs 7.2%; OR, 3.74; 95% CI, 2.04–6.84). Although alarming, it is not surprising that larger and serrated lesions have higher IRRs.

The contribution of new rapidly progressing lesions to the interval cancer rate is the most difficult to determine because the rates of missed and incompletely resected lesions may well be underestimates. It is not known how much variability there is in the time-course of the sporadic adenoma-carcinoma progression, but the finding that it is shorter in Lynch syndrome is proof of principle that it can vary. Interval CRCs appear to have a different molecular profile than noninterval CRCs (Table 2.3.7): they are more likely to be microsatellite unstable, have the CpG island methylator phenotype, and have lower rates of KRAS45 mutations than noninterval CRCs. (Sawhney et al. 2006, Arain et al. 2010, Shaukat et al. 2012)These molecular features are characteristic of the serrated polyp pathway to CRC and support the concept that this pathway contributes disproportionately to interval CRCs.

2.4 Sensitivity of screening program

Previously, the most widely accepted methods to estimate sensitivity was ‘proportional incidence’ method. (Day and Walter 1984, Boer et al. 1994) This method

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estimates the interval cancer cases in a screened cohort population after the screening test, and estimates the expected cancer case in the absence of screening. Sensitivity is then calculated as the complement of the ratio between the number of observed interval cancers and those expected cancers. Unfortunately, in the full diagnostic process of a screening program, it is difficult to assess program sensitivity because of population coverage rate, colonoscopy referral rate, and colonoscopy quality(Zorzi et al. 2010). The original definition that refers to the test itself may be insufficient because screening as a public health policy is a process with a chain of actions involving population components, such as attendance, and clinical components, such as treatment, in addition to the actual testing of those intended to be screened. Hakama et al. defined three different level of sensitivity: test, episode and program sensitivity.(Hakama et al. 2007) Test sensitivity was defined as how much of the disease the screening test is able to identify in those screened, and we assumed that the colonoscopy referral rate was 100% while estimating test sensitivity. Episode sensitivity was defined as how much of the disease the screening test and diagnostic confirmation combined are able to identify in those screened. We took into account colonoscopy referral rate and colonoscopy quality while estimating episode sensitivity. Program sensitivity was defined as how much of the disease from invitation to diagnostic confirmation screening is able to identify in the total target population, and we further took into account screening coverage rate and

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screening uptake. (Figure 2.1) the formulas used for these three sensitivities were: test sensitivity=$1-\alpha P_{11}/[P_0-(1-\alpha)P_{10}]$ episode sensitivity=$1-\alpha P_1/[P0-(1-\alpha)P_{10}]$, and program sensitivity=episode sensitivity–episode sensitivity$\times P_{10}(1-\alpha)/P_0$, where α is the attendance rate, P_0 is the annual incidence among control group (during the screening interval), P_1 is the annual incidence between screens in people with a negative result of the screening episode, P_{10} is the annual incidence between screens in those were non-responders, and P_{11} is the annual incidence between screens in people with negative gFOBT/FIT results. In the study, the sensitivity of the guaiac fecal occult blood test (gFOBT) in Finland was 54.6%. Only a few interval cancers were detected among those with positive test results, hence the episode sensitivity of 51.3% was close to the test sensitivity. At the population level the sensitivity of the program was 37.5%.(Malila et al. 2008). Fecal immunochemical test (FIT) has a higher sensitivity at detecting CRC than the guaiac-based occult blood test, particularly for advanced adenoma detection.(John et al. 1993, Castiglione et al. 1996) However, the episode and program sensitivity are still unclear in FIT-based screening programs, and more importantly, none of the previous meta-analyses included program sensitivity in gFOBT-based or FIT-based screening programs.

2.5 Systemic review for FOBT-based sensitivity

We conducted an electronic search on PubMed and Cochrane databases using the

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following terms: Colorectal cancer; colorectal cancer screening; interval colorectal cancer; post colonoscopy colorectal cancer; fecal immunochemical test; FIT; guaiac fecal occult blood test; gFOBT; FOBT; fecal occult blood test; stool test. Searches were limited to English-language articles published from January 1985 to December 2018. Relevant studies included those in which identification of interval CRCs and person-year of CRC cancer screening population.

The following information was collected from each study, including publication date, country of origin, the methods used to CRC screening, person-years of screening population in whole cohort, person-years of subjects who were gFOBT/FIT negative in whole cohort, person-years of subjects who were non-attenders in whole cohort, person-years of control groups, gFOBT positive rate, FIT positive rate, gFOBT interval cancers, colonoscopy interval cancers, interval cancers after non-referral for colonoscopy, colorectal cancers from non-attenders, and colorectal cancers from control groups.

Of the 62455 articles identified using the above search strategy, 62426 were excluded after screening from the titles and abstracts (Figure 2.2). Another 11 duplicates were excluded because the same articles were searched from the PubMed and the Cochrane database. A total of 38 full articles and conference abstracts were further assessed for eligibility. After exclusion of duplicated articles (n=132), and studies that did not

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include non-attenders (n = 8) and those not included the data of person-year (n = 3), a total of 7 studies including 3 RCTs and 4 screening cohorts were eligible for inclusion in this meta-analysis. (Figure 2.2) The characteristics of the enrolled studies of gFOBT-based screening program were shown in Table 2.5.1, and FIT-based screening program in Table 2.5.2.

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Chapter 3 Data Sources

In this dissertation, we used a series of empirical tabular and individual data described as follows.

3.1 Taiwanese Nationwide CRC Screening Program

3.1.1 Screening Program

Taiwanese nationwide CRC screening program were used to estimate the disease natural history for CRC. The two-stage sampling schemes with multi-state model were further applied to data of a case-cohort design. A series of sampling proportions by different detection modes were tested for the effects of covariates on the incidence of preclinical CRC, and possible on the transition from the PCDP to the CP. The description of Taiwanese nationwide CRC screening program, the procedure for fecal immunochemical test (FIT) screening, and detection modes involved in this screening program were given below.

Specifically, the screening program with fecal immunochemical test (FIT) for the early detection of colorectal cancer was launched in 2004 in Taiwan. This population-based screening program targets at residents aged 50-69 years by providing FIT on the basis of a two-year interval. It turns out to be 5.5millions for the size of target population. Between January 1, 2004 and December 31, 2014, among 5,417,699 eligible subjects, there were 3,072,164 participants attended at least one screen, and 1,605,200

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(52.3%) received two or more screenings during the study period.

This Nationwide screen program involves the processes of invitation, distribution of FIT kits, test for fecal sample, the referral for colonoscopic examination, and the histopathological diagnosis which were performed in a stepwise manner at local public health units, clinics, and hospitals in each municipality. The whole screening was under regular monitor, including invitation, confirmatory examination, repeat screening, surveillance, and the collection of data on CRC cases and CRC death from the National Cancer Registry and the National Death Registry. Subjects who ever underwent screening examination was included in screening population, and the others were considered as refuser. For refusers, data were collected for those developing CRC or dying of CRC only who were identified from the National Cancer Registry Program and the National Death Registry.

Although this was a nationwide screening program, it was not compulsory for residents to undergo regular biennial FIT. Some attendees identified as normal at prevalent screen were eligible for attending subsequent screen rounds, but they may not receive FIT in two years. The inter-screening interval of these subjects would be longer than 2 years then. In this dissertation, we used data on screening between 2004 and 2014 with residents attending at least once.

3.1.2 FIT Test

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None of the subjects were advised for dietary or medication restriction before testing. A one-step commercial FIT kit with a serrated tipped sampling probe as a component of the sample collection device cap was given to the participants, and a single-spot sample was used for testing. Two major brands of FIT accounted for almost all FITs in use; these were the OC-Sensor (Eiken Chemical Co, Tokyo, Japan) and the HM-Jack (Kyowa Medex Co Ltd, Tokyo, Japan) tests with the respective cut-off concentrations of 100 and 8ng hemoglobin/mL buffer (Chiang et al. 2014).

All participants were asked to collect their fecal samples at home by using the sampler in at least 6 different areas of the feces, put into the collection tubes, then to submit them. Results of FIT were reported to the participants with telephone and mail. If the result was positive, the participants were referred for confirmatory diagnosis. If a subject had a normal result of FIT, they were defined as normal, and invited for attending subsequent screen rounds.

3.1.3 Confirmatory Diagnosis

A participant with a positive test was referred for the confirmatory diagnosis with either a total colonoscopy or sigmoidoscopy plus barium enema. Histology of colorectal neoplasm was classified according to the WHO classification. (Bosman et al. 2010) An advanced adenoma was defined as a lesion >10 mm with a villous component, high-

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grade dysplasia (HGD). If the participants were diagnosed as colorectal cancers, they were defined as screen-detected cases (in preclinical detectable phase (PCDP) of colorectal cancer). They would receive treatment, and not be invited for further screens. Participants without colorectal cancer in confirmatory diagnosis were also defined as normal, and invited for attending subsequent screen rounds.

The date and the occurrence of death and colorectal cancer for attendees were derived and verified by the linkage with the National Cancer Registry and the National Death Registry. Information on detection modes of the entire target population of the nationwide colorectal cancer screening including screening detected and clinical detected cases were thus obtained.

3.2 Data on colorectal cancer screening

Patients who participated in FIT screening and received confirmatory colonoscopy after positive FITs during the period from 2004 to 2009 were enrolled in the cohort. The cohort was followed up over time to ascertain colorectal neoplasia and the causes of death until 2014. Individual data including age, gender, date of colonoscopy, and the results of confirmatory diagnosis for adenoma and colorectal cancer were also collected.

3.3 Data on colorectal cancer survival

During the period of January 2004 to December 2012, 6,464,518 subjects aged 50 to 69

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years were considered to be eligible for screening. A total of 2,900,228 participated at least once FIT screening during 2004 to 2012. Totally 4,169 CRCs were detected at prevalent screening round, and 1,349 CRCs were detected at subsequent screening rounds. At the end of 2012, we identified 1,835 FIT ICs, 287 colonoscopy ICs, and 1,352 CRCs in colonoscopy noncompliers. Those subjects who had CRCs diagnosed within this program during 2004-2012 comprise the study cohort, and were followed up until the end of 2016.

3.3.1 Definition of CRC with different detection modes

CRC was categorized according to the mode of detection. CRCs detected at the first round of screening were defined as *prevalent screening–detected CRCs,* and those detected at subsequent screening rounds were defined as *subsequent screening–detected CRCs*. The definition of IC in the FIT-based screening program was based on the definition by the international expert panel convened by the World Endoscopy Organization (WEO) (Sanduleanu et al. 2015). *FIT IC* is defined as CRC diagnosed after a negative FIT screening test but before the next scheduled round of screening. In our program, patients who had negative results following FIT but became symptomatic and were diagnosed with a CRC within 2 years were referred to as FIT ICs. Based on the abovementioned WEO definition and currently recommended post-colonoscopy surveillance intervals, *colonoscopy IC* in the FIT-based screening program was defined

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as a CRC that was diagnosed within 3 years after the index colonoscopy with the finding of advanced adenoma, within 5 years with the finding of non-advanced adenoma and within 10 years with negative finding. If CRCs were diagnosed in patients who were FIT positive at a screening but refused or failed to receive confirmatory colonoscopy, then such CRCs were defined as *CRC in colonoscopy non-compliers*.

3.3.2 Locations and treatments of CRC.

The locations were assessed by the Taiwan Cancer Registry For the purpose of categorizing location, “proximal colon cancer” was defined as colon cancers that were diagnosed proximal to the splenic flexure (cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure). “Distal colorectal cancer” was defined as CRCs that were diagnosed at splenic flexure to rectum (descending colon, sigmoid colon, rectosigmoid junction, and rectum). Treatment was assessed using the Taiwan Cancer Registry to determine whether cases underwent surgical resection, chemotherapy or target therapy, and radiation therapy.

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Chapter 4 Methods and Study Design

4.1 Generalized linear measurement error model for FIT test

4.1.1 Multistate Markov model for the evolution of CRC

The evolution of CRC from free of CRC (state 0), the state of preclinical detectable phase (PCDP, state 1), and surfacing to clinical phase (CP, state 2) can be depicted under the framework of multi-state Markov model. Let random variable X(t) representing the three-state progression of CRC mentioned above. The state space corresponding to the evolution of CRC is thus defined by Ω. The event history of CRC observed at each attendance of screening activity can be written by using the random variable (X(t)). Specifically, the probability of having observation on a sequence of the disease evolution is written as Pr(X(t_0), X(t_1), X(t_2),…,X(t_m)), where t_k corresponds to the time of kth round of screen, k=0,1,2,…,m, and X(0) is the initial state. For example, for a subject attending the first screen round at age t_1 with a CRC-free result and being detected as having CRC at the next round of screen after the time period of t_2, the probability of having such an observation can be written as

$$\Pr\left\{X\left(0\right)=0, X\left(t_1\right)=0, X\left(t_2\right)=1\right\}. \quad (4\text{-}1)$$

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The joint probability of the observed sequence representing repeated observations on CRC progression can be decomposed into the product of a series of conditional probabilities as follows

$$\begin{aligned}&\Pr\left\{X\left(0\right)=0, X\left(t_1\right)=0, X\left(t_2\right)=1\right\}\\&=\Pr\left\{X\left(0\right)=0\right\}\times\Pr\left\{X\left(t_1\right)=0\,|\,X\left(0\right)=0\right\}\times\Pr\left\{X\left(t_2\right)=1|\,X\left(t_1\right)=0\right\}\end{aligned} \tag{4-2}$$

, due to the Marko property and X(0) is the initial state as specified above.

Under the framework of continuous-time Markov process, the matrix of transition intensity kernel (**Q(*t*)**) for the three-state evolution of CRC is written as

$$\boldsymbol{Q}(\boldsymbol{t}) =$$

	Free of CRC	Asymptomatic CRC	Symptomatic CRC
Free of CRC	$-\lambda_1(t)$	$\lambda_1(t)$	0
Asymptomatic CRC	0	$-\lambda_2(t)$	$\lambda_2(t)$
Symptomatic CRC	0	0	0

(4-3)

The transition rate parameters, λ_1 (t) and corresponds to the incidence rate of CRC and λ_2(t) is the progression rate from PCDP to CP, respectively. The probabilities of CRC progression for a subject given period *t* can thus be modelled by using a three-state Markov process with the transition probabilities matrix, **P**(*t*), containing the parameters of interest, the incidence rate (λ_1(t)) and the progression rate (λ_2(t)) of CRC. The corresponding transition probability matrix is thus written as

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$$\boldsymbol{P}(\boldsymbol{t}) =$$

	Free of CRC	Asymptomatic CRC	Symptomatic CRC
Free of CRC	$P_{00}(t)$	$P_{01}(t)$	$P_{02}(t)$
Asymptomatic CRC	0	$P_{11}(t)$	$P_{12}(t)$
Symptomatic CRC	0	0	1

(4-4)

The zeros in the left lower triangle of the transition intensity matrix results from the biological fact that regression to less severe states for CRC is not possible and The probability one for the state of clinical CRC is due to the nature of absorbing state for CP in current three-state model for the evolution of CRC. A stochastic integration can be used for the derivation of the elements of the transition probability matrix **P**(t) as follows.

$$\begin{aligned}
P_{00}(t) &= \exp\left\{-\int_0^t \lambda_1(u)du\right\} \\
P_{01}(t) &= \int_o^t e^{-\int_0^s \lambda_1(u)du} \lambda_1(s) e^{-\int_{t-s}^t \lambda_2(v)dv} ds \\
P_{02}(t) &= 1 - P_{00}(t) - P_{01}(t) \\
P_{11}(t) &= \exp\left\{-\int_0^t \lambda_2(u)du\right\} \\
P_{12}(t) &= 1 - P_{11}(t)
\end{aligned} \tag{4-5}$$

The evolution of CRC with the continuous-time Markov process is thus realized by using the stochastic integration specified as above. Takin the probability of a subject being identified as PCDP during period *t*, $P_{01}(t)$, namely subsequent screen-detected

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case, as example, the probability derived by using the stochastic integration represented in (4-5) is

$$P_{01}(t) = \int_o^t e^{-\int_0^s \lambda_1(u)du} \lambda_1(s) e^{-\int_{t-s}^t \lambda_2(v)dv} ds$$

, which depicts the evolution of CRC from the state of free of CRC for time period *s* with the occurrence of PCDP at time *s* and hence the probability is written as the product of survival form $e^{-\int_0^s \lambda_1(u)du}$ and hazard $\lambda_1(s)$. The lesion then remain in the state of PCDP (state 1) for the rest of time period, *t-s* to *t* with the probability written with survival form $e^{-\int_{t-s}^t \lambda_2(v)dv}$. Under the context of screening program, the status of CRC for an attendee with the detection mode of subsequent screen detected case is observed during successive screening activity. The observed status for such a subject is normal in the initial screening round ($X(0)=0$), which turns into PCDP and being identified in the subsequent screening round attended after period *t* ($X(t)=1$). Although the exact time of the evolution of CRC from the state of free of CRC to PCDP for such a subject cannot be observed, it is for sure that the transition occurred during the period t, and hence the integration of *s* between 0 and time *t* was applied to the stochastic integration for $P_{01}(t)$. The rest of the elements of the transition probability matrix can be derived following the similar rationale.

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Assuming a homogenous process, the matrix of transition intensity kernel can be simplified to

$$\boldsymbol{Q} =$$

$$\begin{array}{c} \\ \text{Free of CRC} \\ \text{Asymptomatic CRC} \\ \text{Symptomatic CRC} \end{array} \begin{array}{c} \begin{array}{ccc} \text{Free of CRC} & \text{Asymptomatic CRC} & \text{Symptomatic CRC} \end{array} \\ \begin{bmatrix} -\lambda_1 & \lambda_1 & 0 \\ 0 & -\lambda_2 & \lambda_2 \\ 0 & 0 & 0 \end{bmatrix} \end{array} .$$

(4-6)

Following Cox and Miller (1965), and further elaborated by Chen et al. in 1996, the transition kernel can be derived by the general formulation by using the forward Kolmogorov differential equation $\mathbf{P}'(t) = \mathbf{P}(t)\mathbf{Q}$. The transition probability matrix in period t, $\mathbf{P}(t)$, can thus be derived as follows

$$\begin{aligned} P_{00}(t) &= e^{-\lambda_1 t}, \\ P_{01}(t) &= \frac{\lambda_1(e^{-\lambda_1 t} - e^{-\lambda_2 t})}{\lambda_2 - \lambda_1}, \\ P_{02}(t) &= 1 - \frac{\lambda_2 e^{-\lambda_1 t}}{\lambda_2 - \lambda_1} + \frac{\lambda_1 e^{-\lambda_2 t}}{\lambda_2 - \lambda_1}, \\ P_{11}(t) &= e^{-\lambda_2 t}, \\ P_{12}(t) &= 1 - e^{-\lambda_2 t}. \end{aligned} \qquad (4\text{-}7)$$

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4.1.2 Generalized non-linear model for CRC evolution with FIT-based test

For the derivation of generalized non-linear model for CRC evolution with FIT-based test, a general form can be developed for various detection modes, including prevalent screen, subsequent screen, and interval cancer mentioned above. Let I_{Prev}, I_{Subs}, and I_{IC} representing the indicator function for prevalent screen, subsequent screen, and interval cancer, respectively, the general form depicting the multistate outcomes of CRC under the context of screening program is written by

$$g(\mu_{Prev}, \mu_{Subs,}\mu_{IC}) \quad = f \ (\boldsymbol{X}_{Prev}\boldsymbol{\beta}_{Prev}, \boldsymbol{X}_{Subs}\boldsymbol{\beta}_{Subs}, \boldsymbol{X}_{IC}\boldsymbol{\beta}_{IC}) \quad (4\text{-}8)$$

, where μ_{Prev}, μ_{Prev}, and μ_{IC} represents the expected frequency of asymptomatic CRC detected in prevalent screen, subsequent screen, and interval cancer, respectively. The (4-8) is thus in the form of generalized multivariate non-linear model. Due to the stochastic integration required for the derivation of the two transition rates and the corresponding transition probabilities embedded in each detection modes, a non-linear function was applied for incorporating the effect of covariates on the force of transition between states as illustrated in (4-7). The transition probability is thus the function of transition intensity which in turn is associated with the state-specific predictor expressed by $\boldsymbol{X}_{Prev}\boldsymbol{\beta}_{Prev}, \boldsymbol{X}_{Subs}\boldsymbol{\beta}_{Subs}, \boldsymbol{X}_{IC}\boldsymbol{\beta}_{IC}$. The derivation of the generalized multivariate non-linear model is elaborated as follows. Based on the transition probabilities

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elaborated as above, a generalized non-linear regression model can be developed for each type of detection modes observed in screening program as follows.

Prevalent screen

In the scenario of cancer screening using FIT, only those without the condition of symptomatic CRC (state 2) are eligible for attending the prevalent screening round. The probability for attendees detected as having asymptomatic CRC during prevalent screen is thus a conditional probability written as

$$\frac{P_{01}(t_{0i})}{P_{00}(t_{0i})+P_{01}(t_{0i})} \qquad (4\text{-}9)$$

by truncating those cases with symptomatic cancers surfacing to CP prior to he/she being eligible for screening. The time t_{0i} is the age of the subject on attending prevalent screen for the *i*th type of subject. The probability for those who are identified as free-of-CRC in the prevalent screen is the complement,

$$\frac{P_{00}(t_{0i})}{P_{00}(t_{0i})+P_{01}(t_{0i})} \quad . \qquad (4\text{-}10)$$

Attendees of prevalent screen can be either in the status of normal or PCDP and hence can be modelled by using a binomial distribution written as

$$N_{\text{Previ}} \sim \text{Binomial}\left(N_{Pi}, \frac{P_{01}(t_{0i})}{P_{00}(t_{0i})+P_{01}(t_{0i})}\right) \quad , \qquad (4\text{-}11)$$

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where N_{Previ} is the frequency of asymptomatic CRC detected in prevalent screen and N_{Pi} represents the frequency of attendee in prevalent screen with age t_{0i}. Following the framework of generalized linear model, the random component is observed count on asymptomatic CRC detected in prevalent screen which can be associated with the predictors by using a logit link due to its characteristics of binomial distributed random variable. By using a logit link, the expected value, $E(N_{\text{Previ}})$, can be linked with the relevant predictors written as the follows

$$E(N_{\text{Previ}}) = N_{Pi} \times \frac{P_{01}(t_{0i})}{P_{00}(t_{0i}) + P_{01}(t_{0i})},$$

$$\text{logit}\left(\frac{P_{01}(t_{0i})}{P_{00}(t_{0i}) + P_{01}(t_{0i})}\right) = \eta_{Previ},$$

$$\eta_{Previ} = h\,(\mathbf{X}_{\text{Prev}}\boldsymbol{\beta}_{\text{Prev}}). \qquad (4\text{-}12)$$

where η_{Previ} is a systematic component including the covariate through the hazard function h.

Note that the effect of covariates (X) can be time-varying (i.e. depending on the round of screen) or time-invariants covariates). As specified by the multistate Markov process of CRC, the transition probabilities are dominated by the two transition intensities, the incidence rate of asymptomatic CRC (λ_1) and the progression rate of asymptomatic CRC to symptomatic CRC (λ_2), the effect of time-invariant covariates (such as age and gender) on the outcome of prevalent screen-detected CRC can be assessed through the

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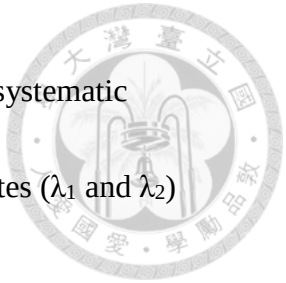

logit link function of the conditional transition probabilities with the systematic component through the hazard function in relation to the transition rates (λ_1 and λ_2) using a Cox proportional hazards form depicted as follows:

$$\lambda_1 = \lambda_{10}\exp(\mathbf{X}_1\boldsymbol{\beta}_1)$$

$$\lambda_2 = \lambda_{20}\exp(\mathbf{X}_2\boldsymbol{\beta}_2) \quad (4\text{-}13)$$

Subsequent screen

Attendees identified as disease free at prevalent screen are eligible for the subsequent screens and may be identified as normal or having PCDP. Unlike the prevalent screen, the kernel for the probability for attendees detected as having PCDP during subsequent screening rounds after interval t is thus $P_{01}(t)$ because the probability for yielding symptomatic CRC is capture by the following interval cancer. The probabilities of having observation on interval CRC, screening detected CRC, and subjects free of CRC and being identified as asymptomatic CRC in subsequent round are thus

Asymptomatic CRC: $P_{00}(t)$

Free of CRC: $P_{01}(t)$, (4-14)

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where *t* is the period of observation. For those detected as CRC or free of CRC in subsequent screening round, *t*=2 due to the biennial interscreening interval scheduled in Taiwan national CRC screening program. Similar to the prevalent screening, attendees of subsequent screen can be modelled by using a binomial distribution written as follows

$$N_{\text{Subsi}} \sim \text{Binomial}\ (N_{Si},\ P_{01}(t)), \qquad (4\text{-}15)$$

where N_{Subsi} is the random variable on the frequency of asymptomatic CRC identified in subsequent screening rounds following a binomial distribution index by parameter $P_{01}(t)$ and the frequency of total subjects attending subsequent screen, N_{Si}. A logit link can be applied to associated the random component with the predictors

$$E(N_{\text{Subsi}}) = N_{Si} \times P_{01}(t),$$

$$\text{logit}(P_{01}(t)) = \eta_{\text{subs}},$$

$$\eta_{\text{subs}} = h(\mathbf{X}_{\text{subs}}, \boldsymbol{\beta}_{\text{subs}}). \qquad (4\text{-}16)$$

Interval cancer

Attendees identified as in the normal status may surface to clinical phase before next screening round during interval *t* and are defined as symptomatic CRC (interval

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cancer) with probability $P_{02}(t)$ (Chen et al., 1996). For observed interval cancers with known exact time of diagnosis, the kernel for probability density function is written as follows:

$$P_{00}(t-\Delta t)P_{02}(\Delta t)+P_{01}(t-\Delta t)P_{12}(\Delta t). \quad (4\text{-}17)$$

There are two components constituting the probability density of state transition for interval cancer. The first part represents cancers that have rapid progression from disease-free state (state 0) to CP (state 1) at instantaneous time Δt but stay at disease-free state during the period of $t-\Delta t$. The second part represents the scenario of slow-growing lesions with the phenomenon that subjects arrive at the PCDP in the period of $t-\Delta t$ and hence the transition from the PCDP to the CP at instantaneous time of Δt (Chen et al., 1996). For infinitesimal Δt, this is equivalent to $dP_{02}(t)/dt$ and the probability density function for interval cancer is thus

$$P_{01}(t)\times\lambda_2 . \quad (4\text{-}18)$$

The observed frequency of interval cancer ,IC_i, among the normal subjects during the follow-up period PY_i, can be modelled by using a Poisson distribution specified as follows.

$$IC_i \sim \text{Poisson}\ (\mu_i) , \quad (4\text{-}19)$$

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The expected number of interval cancer the thus the Poisson parameter, μ_i, which is the product of PY_i and the probability density function of interval cancer

$$PY_i \times P_{01}(t) \times \lambda_2 . \quad (4\text{-}20)$$

A log link can be applied to associate the random component with systematic components as follows

$$\log(\mu_i) = h(\mathbf{X}_{IC}\boldsymbol{\beta}_{IC}). \quad (4\text{-}21)$$

Following the specification for the random components and link function for prevalent screen, subsequent screen, and interval cancer, the Generalized linear model for CRC evolution in (4-8) can be applied to Taiwan CRC screening program using FIT-based test.

Generalize non-linear measurement error model

The generalized non-linear regression model can be adapted with the incorporation of measurement errors applied to population-based screening test.

Since the accuracy of screening tool is not 100%, the parameter of measurement error was incorporated into the model. Following the notation of the state space and random variable of the observed stochastic process defined above. Let O^+ denote the

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observed result during screen detected as disease and O^- as non-disease. Let T^+ denote the true disease status and T^- as true non-disease. Two types of measurement error, sensitivity (*Sen*) and specificity (*Spe*), can be expressed as follows

$$\begin{aligned} Sen &= \Pr\left\{O^+ \mid T^+\right\}, \\ Spe &= \Pr\left\{O^- \mid T^-\right\}. \end{aligned} \tag{4-22}$$

The observed states in the model incorporating measurement error is a joint distribution of the observed states (O) and the underlying states (T) which can be derived by using a mixture of the product of observed state given the underlying states and the corresponding parameters involving with measurement error. A 100% specificity was assumed according to the characteristics of population-based screening program.

Due the imperfect sensitivity, some of asymptomatic CRC will be missed in screening round, which may progress to symptomatic CRC before next invitation (clinical-detected case, interval cancer) or being identified as have asymptomatic CRC (screen-detected case, PCDP). The proportion of attendees missed at prevalent screen can derived by the ratio of false negative to true positive, (1-*Sen*)/*Sen* (Chen et al., 1996; Chen et al., 2000). The expected number of CRC cases detected in prevalent screen and subsequent screen considering measurement error are

$$N_{\text{Previ}} \times \text{Sen} \frac{P_{01}(t_{0i})}{P_{00}(t_{0i}) + P_{01}(t_{0i})} \tag{4-23}$$

and

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$$N_{\text{Subsi}} \times P_{01}(t_i) \times Sen + F_0 \times \frac{1-Sen}{Sen} \times P_{11}(t_i) \quad (4\text{-}24)$$

, where number of cases detected in prior screening round was denoted by F_0. The expected number of subjects surfacing to interval cancer with the incorporation of measurement error after the period t_i can be derived by

$$PY_i \times P_{01}(t) \times \lambda_2 + F_0 \times \frac{1-Sen}{Sen} \times P_{11}(t) \times \lambda_2. \quad (4\text{-}25)$$

The effect of age and sex on sensitivity is modelled by using a logistic form

$$logit(Sen) = \boldsymbol{X}_{sen}\boldsymbol{r} \quad . \quad (4\text{-}26)$$

with the effect represents by vector **r**.

4.1.4 Estimating procedures for the generalized non-linear model

Moment method

The method used for the estimation of the two rates along with the covariate effects and FIT sensitivity was derived by equating the observed number of screen-detected CRC and interval CRC with the expected ones based on the moment method applying non-linear procedure (Chen et al., 1996).

Bayesian Markov Chain Monte Carlo Simulation

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To estimate parameters governing the natural history of colorectal cancer making allowance for sensitivity, a Bayesian directed acyclic graphic three-state Markov model is delinated in Figure 4.1. This framework is based on generalized linear model underpinning. Number of screen-detected cases are treated as binomial distribution specified by

r_s~Binomial (P_s (t), n_s),

where P_s (t) is the probability of detecting screen-detected colorectal cancer given numbers of screenee. Interval cancers consists of two components, newly-diagnosed colorectal cancer ($r_{newly.IC}$) and false-negative colorectal cancers($r_{fn.IC}$). The former is determined by a Poisson distribution, expressed by

$r_{newly.IC}$ =PY[i] x dP13(t), PY indicated the person years with specific i group. The false-negative CRC ($r_{fn.IC}$) is determined by case from subsequent sceen, transition probability P_{11}(t) and sensitivity (Sen). Sensitivity is expressed as logit transformation by exp(α)/1+exp(α). Normal distribution can be generaally appropriate for α . If there was no information given for the parameters, we will use non informative prior which means the prior distribution was assumed to follow normal distribution with mean equal to 0 and large variance set as N(0, 10^6). We let $\theta = r_{newly.IC} + r_{fn.IC}$. As interval cancer is rare, number of interval cancer with a Poisson distribution expressed as

$$r_{IC} \sim \text{Poisson}(\theta)$$

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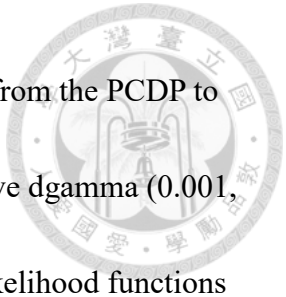

λ_1 is the preclinical incidence rate, and λ_2 is the transition rate from the PCDP to the CP, which can be approximated in Winbugs by the non-informative dgamma (0.001, 0.001) distribution. Applying backward Kolmogorov equation, the likelihood functions could be constructed with the transition probabilities given $P_{00}(t)$, $P_{01}(t)$, $P_{02}(t)$, $P_{11}(t)$, $P_{12}(t)$.

At the beginning, we will derive the estimates with posterior function after incorporating non-informative or informative priors into likelihood. By using prior information from the prior period (2004-2009) to derive posterior distribution, which is further taken as the prior information to combine the latter period data (2010-2014) from in-reach service screening phase to derive the updated posterior distribution. The prior estimates for average λ_1 was 0.00115 (SD= 8.93 x 10^6). The average λ_2 was 0.45 (SD= 0.0133) and the parameter of sensivity, α , was 1.25 (SD=0.1024).

4.2 Determination of the proportion of interval cancers from newly develop and missed pathway

The proportion of interval cancer arose from the pathway of newly developed and missed interval cancer can be determined based on the estimated results of the incidence rate of asymptomatic CRC and the progression rate of CRC as elaborated above. By using the (4-25) and (4-26), the number of CRCs arose from the newly developed

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pathway of interval cancer is derived by $PY_i \times P_{01}(t) \times \lambda_2$ and the false negative (missed) pathway is $F_0 \times P_{11}(t) \times \frac{1-Sen}{Sen} \times \lambda 2$. The proportion of false negative interval cancer is thus derived by

$$\frac{F_0 \times \frac{1-Sen}{Sen} \times P_{11}(t) \times \lambda_2}{PY_i \times P_{01}(t) \times \lambda_2 + F_0 \times \frac{1-Sen}{Sen} \times P_{11}(t) \times \lambda_2} . \quad (4\text{-}27)$$

Regarding the subsequent screening rounds, similar can be inferred for the proportion of asymptomatic CRCs due to the false negative pathway. The newly developed lesion after prevalent screening (Figure 1.1) is $N_{Subsi} \times P_{01}(t_i) \times Sen$ for subsequent screen-detected CRC and the number of CRCs arose from the false-negative pathway after prevalent screening is $F_0 \times \frac{1-Sen}{Sen} \times P_{11}(t_i)$.

The proportion of newly-developed CRC of FIT interval cancer can be calculated as

$$\frac{PY_i \times P_{01}(t) \times \lambda_2}{PY_i \times P_{01}(t) \times \lambda_2 + F_0 \times \frac{1-Sen}{Sen} \times P_{11}(t) \times \lambda_2}. \quad (4\text{-}28)$$

To assess the impact of inter-screening interval and screening tools on interval CRC, the estimated results on age and sex specific rates and sensitivities were further applied to the proposed multi-arm trials depicted in Figure 4.2 and Figure 4.2. Two stool-based scenarios were considered, one is aimed at testing the effect

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of interscreening interval on the efficacy of population-based screening program taking into account the risk levels in terms of the incidence of asymptomatic CRC and the progression rate of CRC (Figure 4.2). The other considering the use of a tool with improved sensitivity, FIT, compared with the traditional one, gFOBT to assess the impact of tool performance on the efficacy of population-based screening program (Figure 4.3). A simulation study using the parameters dominate the evolution of CRC derived from the empirical data in Taiwan using the generalized non-linear regression with the consideration of sensitivity and personal characteristics of age and sex on state-specific effect of CRC evolution was applied.

Regarding the gFOBT-based simulation, the kernel parameters was extracted from three published articles to reaching the aim of the comparison between FIT-based and gFOBT-based screening program. The proportion of interval cancer, divided into newly developed (true-negative interval cancer) and missed (false-negative interval cancer) during the six-year period of follow-up for the cohort of 100,000 subjects in each arm was used as the index for the comparison of efficacy for each strategy.

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4.3 Generalized non-linear joint measurement error model

The ascertainment of CRC detected in the FIT-based screening is a two stage process, which calls for the development of a generalized non-linear joint measurement error model for assessing the sensitivity of FIT and the sensitivity of colonoscopy together with the two rates of CRC evolution. This approach can further shed light on the identification of the proportion of paths of newly developed CRC and false negative CRC by the two tools in population-based CRC screening program. Screen attendants first receive FIT examination, those with positive results are then referred for colonoscopy for confirmatory diagnosis CRC. Those with negative colonoscopic examination, CRC may occurred before the next scheduled screen (colonoscopic interval cancer). In service screening program, a proportion of FIT-positive subjects may not comply with referral, among whom interval cancer may occur (interval cancer due to non-referral). Although attendants with negative FIT results are identified as normal with the subsequent screen scheduled at 2 years later, he/she may surface to symptomatic CRC and become interval cancers (FIT-interval cancer). Three measurement errors of FIT (S_1), colonoscopy (S_2), and referral rate (C) are involved in the FIT-based screening. The accordance of the two-stage process to the corresponding detection model are listed in Table 4.1.

This two stage process accounts for the proposal of test sensitivity and episode

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sensitivity by Hakama et al. (2007). The consideration of attendance rate further gives the program sensitivity in this previous work (Hakama et al., 2007). Although the proposal on the separating this two stage process with the development of a series of sensitivity indicator can be applied to assessing the performance of randomized controlled trial with the use of information from control group. This attempt cannot hold for the evaluation of service screening program. Furthermore, the previous method also unable to taking into account the time dimension on the evolution of CRC.

We used the moment method to estimate parameters of interest. The first moments by detection are derived as follows. The expected numbers of disease-free and screen-detected cases in the prevalent screen are

$$E\left(n_{dis-free}^{(1)}\right) = N^{(1)} \times \frac{P_{00}(age)+P_{12}(age)\times(1-s_c)]}{P_{00}(age)+P_{01}(age)}, \text{ and}$$

$$E\left(n_{SD}^{(1)}\right) = N^{(1)} \times \frac{P_{12}(age)\times s_c]}{P_{00}(age)+P_{01}(age)}, \quad (4\text{-}29)$$

respectively, where $N^{(1)}$ is the total number of participants attending the prevalent screen.

The expected number of disease-free and screen-detected cases in the second screen are

$$E\left(n_{dis-free}^{(2)}\right) = n_{dis-free}^{(1)} \times (P_{00}(t) + P_{01}(t) \times (1 - s_c)), \text{ and}$$

$$E\left(n_{SD}^{(2)}\right) = n_{dis-free}^{(1)} \times P_{01}(t) \times s_c + n_{SD}^{(1)} \times P_{11}(t) \times \frac{1-s_c}{s_c}, \quad (4\text{-}30)$$

respectively, where t is time since last screen.

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For FIT interval cancer, the expected number is

$$E(n_{FIT-IC}) = n^{(1)}_{dis-free,FIT(-)} \times P_{02}(t) + \left[n^{(1)}_{SD} + n_{non-ref\ IC} + n_{colonsp\ IC}\right] \times \frac{1-s_f}{s_f} \times P_{12}(t) \quad (4\text{-}31)$$

The expected number for colonoscopy interval cancer is expressed as

$$E\left(n_{Colonsp-IC}\right) = n^{(1)}_{dis-free,FIT(+)} \times P_{02}(t) + \left[n^{(1)}_{SD}\right] \times \frac{1-s_c}{s_c} \times P_{12}(t) \quad (4\text{-}32)$$

4.4 Assessing the efficacy of FIT-based screening program based on the survival by detection modes

4.4.1 Conventional Cox proportional hazards regression model

In addition to assessing the effectiveness of FIT-based screening program by using the population data, the comparison of CRC survival by each type of detection modes provides the clue for such an assessment. The Cox proportional hazards regression model using the time period from the diagnosis of CRC to the occurrence of CRC death or till the end of 2014 for censored subjects for the random variable for time-to-event analysis was applied. The detection modes of prevalent screen-detected, subsequent screen-detected, interval cancers due to FIT and colonoscopy, CRC in subjects with positive FIT but not compliant to referral, and CRC among non-participants were

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included in the analysis. The effects of age, sex, location of CRC, treatment administrated, and cancer stage on CRC survival were also incorporated in the assessment for the comparison of survival difference between detection modes. The Cox regression mode for the purpose is written as follows

$$h(t)=h_0(t)\exp(\boldsymbol{\beta}\mathbf{X}+\mathbf{r}\mathbf{Z}) , \qquad (4\text{-}33)$$

where **X** is the vector for a series of detection modes of CRC and **Z** is that of factors relevant with CRC survival as mentioned above. For assessing the effectiveness of screening, the detection modes of screen-detected cases in prevalent and subsequent screen, interval cancers, and non-referrals were combined. We also assess the difference in survival between two types of interval cancers. The Freedman statistics (1992) was used to assess the proportion of survival difference explained by the early detection through the comparison on the estimated results based on models with and without consideration cancer stage.

4.4.2 Lead-time and truncation adjustments

The effectiveness of CRC screening is often estimated by comparing CRC morality between screening participants and nonparticipants, but it has to collect population-based data with enormous costs. Here, we propose a statistical model only based on CRC cases with lead-time and truncation adjustments for evaluating the effectiveness of screening

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among different detection modes.

This model is derived from the time-dependent Cox proportional hazards regression model. For the lead-time adjustment, the lead-time is added to the age at diagnosis, which is randomly generated from an exponential distribution with parameter based on the estimated mean sojourn time in Table 5.1.3. The issue of truncation arises from the eligibility of screening. There are two possible routes leading to CRC death for the whole population. Some people who are eligible for CRC screening and without clinical symptoms are probably detected as asymptomatic CRCs. However, some people may progress to clinical CRCs before eligible age for screening. Thus, we use this concept to adjust the truncation effect by determining the eligibility for screening by comparing age for prevalent screen-detected case to the pseudo age at each time of event.

We create a time-dependent detection mode $D(t)$ for prevalent screen-detected CRC cases at event time t, which is determined by pseudo entry age ($A(t)^{se}$) and age at time t ($A(t)$).

$$D(t) = \begin{cases} \text{Prevelent screening} - \text{detected CRC}, & \text{if } \mathrm{A(t)^{se}} \geq \mathrm{A(t)} \\ \text{CRC in screening nonparticipants}, & \text{if } \mathrm{A(t)^{se}} < \mathrm{A(t)} \end{cases} \quad (4\text{-}34)$$

The procedure of this time-dependent Cox model is depicted by Figure 4.4. Firstly, we randomly generate a lead-time for all screen-detected cases and add it to the age at diagnosis. Here we use asterisk (*) to indicate the age after adjusting lead-time. Secondly,

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a time-dependent detection mode $D(t)$ for prevalent screen-detected CRC cases at event time t shows by the bar above the time line for each case. The process of determining $D(t)$ is as follows.

The first event happened to colonoscopy noncompliers after four-year follow-up and the corresponding age is 70 years old. At this time, the corresponding ages for two prevalent screen-detected cases are 63 and 60 years, respectively, both are younger than 70 years. The detection modes for these two subjects at the time of the occurrence of CRC are thus defined as nonparticipants. However, the second event happened to prevalent screen-detected case and the corresponding age is 62 years. At this time, age of another prevalent screen-detected is 65 which is older than 63 years. Thus, the detection mode for this case at this time is turned to prevalent screen-detected case. To take other covariates like sex, gender, tumor attributes, and treatments into account, we can easily incorporate these covariates into the proportional hazards form. The model can be written as follows.

$$h(t) = h_0(t)\exp[\beta_1 I(detection\ mode = Prevalent\ screening - detected\ cases)$$
$$+ \beta_2 I(detection\ mode = Subsequent\ screening - detected\ cases)$$
$$+ \beta_3 I(detection\ mode = Colonoscopy\ IC)$$
$$+ \beta_4 I(detection\ mode = FIT\ IC)$$
$$+ \beta_5 I(CRC\ in\ colonoscopy\ noncompliers)]$$

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(4-35)

The estimation depends on the multiplication of the partial likelihoods (L_i) at different event time. The overall likelihood (L) shows in (4.33).

$$L = \frac{\exp\left[\beta_5\right]}{1 + 1 + \exp\left[\beta_2\right] + \exp\left[\beta_3\right] + \exp\left[\beta_4\right] + \exp\left[\beta_5\right] + 1} \times \frac{\exp\left[\beta_1\right]}{\exp\left[\beta_1\right] + \exp\left[\beta_1\right] + \exp\left[\beta_2\right] + \exp\left[\beta_3\right] + \exp\left[\beta_4\right] + 1} \times \frac{\exp\left[\beta_4\right]}{1 + \exp\left[\beta_2\right] + \exp\left[\beta_3\right] + \exp\left[\beta_4\right] + 1} \times \frac{\exp\left[\beta_1\right]}{\exp\left[\beta_1\right] + \exp\left[\beta_2\right] + \exp\left[\beta_3\right] + 1}$$

(4-36)

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Chapter 5 Results

5.1 Meta-analysis of Different Types of Stool-based Sensitivity

5.1.1 gFOBT-based Screening Program

Table 5.1.1 showed the results of gFOBT-based screening program. Three RCTs were reported in 8 published articles (Funen(Kronborg et al. 1996, Jørgensen, Kronborg and Fenger 2002, Kronborg et al. 2004), Nottingham(Hardcastle et al. 1996, Robinson et al. 1999, Scholefield et al. 2002, Scholefield et al. 2011), Finland(Malila et al. 2008)). Three trials (Funen, Nottingham, and Finland) performed biennial screening with gFOBT. The attendance rates were higher in RCTs than in screening cohort studies. Two screening cohort was reported (France(Faivre et al. 2004), UK(Steele et al. 2009, Steele et al. 2012)). In UK screening cohort, no control group data was reported, and we instead used the CRC incidence rate of national report. For gFOBT–base screening program, meta-analysis showed that the pooled test sensitivity is 52.5% (95CI: 51.2%-53.8%), and the episode sensitivity is 49.6% (95CI: 48.3%-50.9%). The program sensitivity was 33.3% (32.0%-34.5%). (Table 5.2.1)

5.1.2 FIT-based Screening Program

Table 5.1.2. showed the results of FIT-based screening program. Two screening cohort were used for meta-analysis(Italy(Zorzi et al. 2011) and Taiwan(2019)). The test

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sensitivity and episode sensitivity were similar in Italy and Taiwan screening cohort. The test sensitivity was 81.9% (95CI: 77.1%-86.0%) and 80.9% (95CI: 80.0%-81.9%) for Italy and Taiwan screening cohort, respectively. The episode sensitivity was 77.9% (95CI: 72.2%-82.5%) and 65.7% (95CI: 64.3%-67.0%) for Italy and Taiwan screening cohort, respectively. However, in Taiwan screening cohort, the attendance rate of 0.57 and colonoscopy rate of 0.6 was lower than Italy screening cohort and gFOBT-based screening program, and the program sensitivity was only 34.4% (95CI: 33.4%-35.4%). Meta-analysis showed that the test sensitivity was 80.9% (95CI: 80.0%-81.7%) and episode sensitivity was 65.7% (95CI: 64.6%-67.3%), The test and episode sensitivity of FIT-based screening program was higher than gFOBT–base screening program. However, due to lower attendance rate in FIT-based screening cohort than the gFOBT-based RCT, at the population level the program sensitivity was 34.7% (95CI: 33.7%-35.7%).

5.2 Interval cancer in FIT-based screening program

5.2.1 Demographic Characteristics of Screening Attendants

Between January 1, 2004 and December 31, 2014, a total of 3,070,511 eligible Taiwanese residents attended the nationwide screening program for CRC. The

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demographic characteristics are listed in Table 5.2.1 Among the 3,070,511 attendees, 10,989 (0.36%) preclinical cases were identified at prevalent screen. A biennial screening regime was offered for 1,604,443 (52.3%) with negative FIT in prevalent screen, of whom 3,128 (0.19%) were identified as having preclinical disease at subsequent screens. A total of 9,641(0.6%) interval CRC diagnosed between two screens were ascertained. Male and elder subjects aged between 60 and 69 years had a higher risk of CRC.

5.2.2 Estimated results on generalized non-linear regression model for CRC revolution with FIT-based screening

The upper part of Table 5.2.2 shows the estimated incidence of PCDP and progression rate from the PCDP to the CP incorporating measurement error. The incidence of PCDP was estimated at 0.00151 (95% CI: 0.00147-0.00155). For the progress rate from PCDP to CP, the estimated result was 0.36 (95%:0.34-0.38). The lower part of Table 5.2.2 demonstrates the estimated results of generalized non-linear regression models with measurement error and incorporating the covariates of age and sex on both disease initiation, progression, and sensitivity. The effects of male and old age were significant for the development of PCDP with the hazard ratios estimate at 1.75 (95% CI: 1.68-1.82) and 1.79 (95% CI: 1.73-1.86). As to the progression of PCDP,

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the estimated hazard ratios for male and old age were 0.82 (95% CI: 0.77-0.87) and 0.91 (0.86-0.97), respectively. The effect of male and old age on sensitivity were also not statistically significant with the estimated hazard ratios at 0.84 (95% CI: 0.68-1.03) and 0.76 (95% CI: 0.63-0.92), respectively.

5.2.3 Age and Sex Specific Risk of CRC and Dwelling Time

Table 5.2.3 shows the estimated results on incidence rate, progression rate, and sensitivity based on the empirical data of Taiwan nationwide screening program for CRC. The incidence rate was estimated as 0.00151 per year (95% CI: 0.00147-0.00155). Annual transition rate from PCDP to clinical phase (CP) was 0.36 per year (0.34-0.38), giving a 2.78 (95% CI: 2.63-2.94) years of average dwelling time staying in the PCDP. It is very interesting to see the sensitivity for detecting CRC with FIT after separating newly developed cases from false negative cases among interval cancers was estimated as 75.5% (95% CI: 73.0%-77.8%).

The estimated results for age and gender specific risk of CRC are also listed in Table 5.2.3. Average dwelling times in males were 3.18 years and 3.49 years for 50-59 and 60-69 age groups, respectively. The corresponding figures were 2.60 years and 2.85 years in females, respectively. The sensitivity of FIT was the highest for women aged 50-59 years (78.73%), followed by men aged 50-59 years (75.61%), women aged 60-69

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years (73.79%), and men aged 60-69 (70.24%).

Figure 5.2.1 demonstrates the effect of age and sex incidence rate and progression rate on the probability of having preclinical case and clinical CRC with follow-up time. Given the same age range, men had higher probability of having clinical phase of CRC ((b) vs (d) and (c) vs (e), Figure 5.2.1). Given the same sex, the elder subjects had higher probability of having interval of CRC ((b) vs (c) and (d) vs (e), Figure 5.2.1).

5.2.4 Estimated results of applying the Bayesian directed acyclic graphic model for CRC revolution with FIT incorporating measurement error

Table 5.2.3 shows the estimated results on incidence rate, progression rate, and sensitivity based on the empirical data of Taiwan nationwide screening program for CRC. With the full data, from 2004-214, the incidence rate was estimated as 0.00151 per year (95% CI: 0.00150-0.00152). Annual transition rate from PCDP to clinical phase (CP) was 0.32 per year (0.31-0.32), giving a 3.13 (95% CI: 3.13-3.23) years of average dwelling time staying in the PCDP. The estimated α for sensitivity was 1.08 (95%CI: 1.00-1.05), as sensitivity with 74.6% (95% CI: 73.1%-76.0%). The lower part of Table 5.1.3 showed the similar results of later period Data, from 2010 to 2014) with prior period information (2004-2009). The incidence rate was estimated as 0.00149 per year

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(95% CI: 0.00147-0.00150). Annual transition rate from PCDP to clinical phase (CP) was 0.27 per year (0.26-0.28), giving a 3.70 (95% CI: 3.57-3.85) years of average dwelling time staying in the PCDP. The estimated α for sensitivity was 0.94 (95%CI: 0.86-1.02), as sensitivity with 71.9% (95% CI: 70.3%-73.5%).

The Diagnosis plots for parameter estimation with applying the Gibbs sampling were shoed in Figure 5.2.2

5.2.5 Effect of Screening Interval and Dwelling Time on Interval CRC

Figure 5.2.3 shows the simulated results based on the incidence rate, transition rate, and FIT sensitivity of Taiwan CRC screening program. The risk of developing interval cancer increased along with incremental inter-screening interval. The proportion of false-negative CRC accounted for 38.9% of FIT interval cancer for annual regime, 31.2% for biennial regime, and 25.3% for triennial regime whereas the counterpart proportion of newly developed CRCs explained 61.1% of FIT interval cancer for annual program, 68.8% for biennial program, to 74.7% for triennial program (General population, Figure 5.2.3). On the other hand, it should be noted that the proportions of newly developed CRCs were higher in those aged 50-59 years compared with those aged 60-69 years. Such finding did not substantially vary with gender.

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5.2.6 Effect of Screening Test on Interval CRC: gFOBT versus FIT

Figure 5.2.4 shows the results of interval cancers rate as percentage of the expected incidence rate (I/E ratio), and the percentage of each newly developed and false-negatives CRC among FIT interval cancers. The proportion of interval cancer (I/E ratio) was 29.8%, 38.5%, 35.7%, and 43.5% for Taiwan program, the Funen study (Kronborg et al. 1996), the Nottingham study (Hardcastle et al. 1996), and the Finland study (Malila, Anttila and Hakama 2005, Malila et al. 2008), respectively. Compared with the three gFOBT-based randomized controlled trials, screening with FIT had a lower proportion of interval cancer.

5.3 Estimated result for the generalized non-linear measurement error mode

Table 5.3.1 shows the estimated results based on the generalized non-linear joint measurement error model. The progression rate was estimated as 0.2899 (95% CI: 02885-0.2913). The estimated results based on the generalized non-linear joint measurement error model gave the sensitivity of 71.9% (95% CI: 71.0-72.8%) and 93.6% (95% CI: 91.9-94.9%) for FIT and colonoscopy, respectively.

Figure 5.3.1 shows the proportion of newly developed and false negative interval

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cancer by using FIT and colonoscopy as screening tool. Regarding the current biennial program, 61% and 39% of interval cancers resulted from the path of newly develop and false negative, respectively for FIT screen. The corresponding figure for colonoscopy is 88% and 12% for newly developed and false negative, respectively.

5.4 Survival by detection model

5.4.1 Study cohort and demographics of CRC with different detection modes

Figure 5.4.1. shows the disposition of the study population for CRC survival. A total of 2,900,228 participated at least once FIT screening during 2004 to 2012. Totally 4,169 CRCs were detected at prevalent screening round, and 1,349 CRCs were detected at subsequent screening rounds. At the end of 2012, we identified 1,835 FIT ICs, 287 colonoscopy ICs, and 1,352 CRCs in colonoscopy noncompliers, 34,877 in screening nonparticipants. The demographics of those CRC patients in association with their detection modes are presented in Table 5.4.1, and the distribution of cancer stages in association with detection modes is demonstrated in Figure 5.4.2. Among those 8,992 CRCs with complete staging information, screen-detected CRCs had significantly earlier stages compared with CRCs with other detection modes. Colonoscopy IC, FIT

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IC, and CRC in colonoscopy noncompliers were identified at more advanced stages (40.5%, 44.3%, and 42.7%, respectively, for stage III plus IV cancers) compared with screen-detected CRSs (Prevalent screening: 37.8%, subsequent screening: 35.3%). The information on treatment that administrated for those CRC patients is demonstrated in Table 5.4.2.

5.4.2 Survival analysis

The mean follow-up period of the study cohort was 5.43 years, with a total of 1,747 CRC deaths (19.4%) being observed during the study period. (Table 5.4.3) The survival rate and cumulative death rate was demonstrated in Figure 5.4.3. A significant difference in survival was evident amongst screen-detected CRCs, colonoscopy IC, FIT IC, and CRCs in colonoscopy noncompliers (P<0.001). CRC detected at subsequent screening had better survival than CRC detected at prevalent screening, followed by colonoscopy IC, FIT IC, CRCs in colonoscopy noncompliers, and CRCs in screening nonparticipants. Compared with that for CRCs in screening nonparticipants, the hazard ratio (HR) and 95% confidence interval (95%CI) for CRC death were 0.57(0.51-0.63) for colonoscopy noncompliers, 0.57 (0.52-0.62) for FIT IC, 0.43 (0.34–0.55) for colonoscopy IC, 0.28 (0.26-0.30) for prevalent screen-detected CRC, and 0.21 (0.18-0.25) for subsequent screen-detected CRC. (Table 5.4.4.) Compared with colonoscopy

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IC, FIT IC was associated with more unfavorable survival. (Log-rank test: p=0.04) (Table 5.4.5)

In the multivariable analysis using a Cox proportional hazards regression model and after adjusting for age, sex, location, and treatment(model 1), the adjusted HR (aHR) was 0.56(0.50-0.64) for colonoscopy noncompliers, 0.57 (0.52–0.64) for FIT IC, 0.42(0.32–0.54) for colonoscopy IC, 0.30 (0.27-0.33) for prevalent screen-detected CRC, and 0.22 (0.19-0.26) for subsequent screen-detected CRC (Table 5.4.4). After further adjustment for cancer stage (model 2), the trend was similar and showed an aHR of 0.67(0.59-0.76) for colonoscopy noncompliers, 0.64 (0.57-0.71) for FIT IC, 0.53 (0.41–0.69) for colonoscopy IC, 0.40 (0.36-0.44) for prevalent screen-detected CRC, and 0.32 (0.27-0.38) for subsequent screen-detected CRC.

As for IC, we performed similar analyses for comparing colonoscopy IC and FIT IC. (Table 5.4.5) The risk of CRC death was significantly higher for FIT IC with aHR of 1.42 (1.09–1.85) as compared with colonoscopy IC. After further adjustment for cancer stage, such risk was still higher for FIT IC but statistically non-significant with aHR of 1.22 (0.93–1.59).

For lead-time and truncation adjustment, the results were showed in Table 5.4.6. Compared with that for CRCs in screening nonparticipants, the hazard ratio (HR) and

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95% confidence interval (95%CI) for CRC death were 0.37 (0.35-0.39) for CRC in screening participants. After further adjustment for lead-time and truncation, the aHR was 0.51 (0.49–0.54) for CRC in screening participants, and 0.56 (0.54–0.59) after further adjusting for age, sex, location, and treatment. Table 5.4.7 showed the results for different detection mode, including Screen-detected CRC, Colonoscopy IC, FIT IC, CRC in colonoscopy noncompliers, and CRC in screening nonparticipants. After adjustment for lead-time and truncation, the aHR was 0.61 (0.55-0.67) for CRC in colonoscopy noncompliers, 0.61 (0.56–0.66) for FIT IC, 0.46(0.36–0.59) for colonoscopy IC, 0.43 (0.40-0.46) for screen-detected CRC. After further adjustment for age, sex, location, and treatment, the trend was similar and showed an aHR of 0.61 (0.55-0.67) for CRC in colonoscopy noncompliers, 0.61 (0.56–0.66) for FIT IC, 0.46(0.36–0.59) for colonoscopy IC, 0.43 (0.40-0.46) for screen-detected CRC.

In Table 5.4.8, screen-detected CRCs were distinguished as subsequent screen-detected CRC, and prevalent screen-detected CRC. After adjustment for lead-time and truncation, the aHR was 0.56 (0.52-0.61) for prevalent screen-detected CRC, and 0.23 (0.19-0.27) for subsequent screen-detected CRC. After further adjustment for age, sex, location, and treatment, the aHR was 0.63 (0.58-0.69) for prevalent screen-detected CRC, and 0.25 (0.22-0.30) for subsequent screen-detected CRC.

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Based on the estimated results of generalized non-linear joint measurement error model and survival for each detection modes, the biennial program compared with triennial one resulted in the life-year gained by 2337 person-years, among which 2314 person-years and 23 person-years resulted from FIT test and colonoscopy, respectively.

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Chapter 6 Discussion

6.1 Meta-analysis of the sensitivity for different types of stool-based test

In the dissertation, we reported the test, episode, and program sensitivity of FOBT-base screening on population-based CRC screening program. In the Kronborg's RCT study, the attendance rate was 67%, and the program sensitivity was 51.7%. After we combined evidence from the RCTs and cohort studies, the program sensitivity of FIT screening program was lower to 33.3%. The results show that increasing coverage rate and the uptake of screening is a high priority in CRC screening program. In Taiwan screening cohort, the episode sensitivity was 65.7%, and is lower than test sensitivity, 80.9%. The finding demonstrated that the efficacy was attenuated gradually during the process of multi-step screening program. FIT-positive persons represent a group with very high-risk of advanced adenoma and cancer, and all persons with positive results should receive colonoscopy. Colonoscopy referral rate and colonoscopy quality play important role in the episode sensitivity. In addition to the willingness of FIT-positive subjects for colonoscopy, colonoscopy capacity within a FOBT-based screening program is an important resource, and should be considered in the estimate of the national capacity to provide colorectal cancer screening to all eligible persons in

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screening program.(Seeff et al. 2004) In Taiwan population-base screening program, the colonoscopy rate for FIT-positive individuals was around 80% in the inaugural period, but then declined to 60% after entering the roll-out period as a result of a significant increase in demand for colonoscopy but limited capacity to perform the procedure.(Jen et al. 2018)

However, the reporting methods actually can only be applied under the scenario of randomized controlled trials. As presented in the results derived by applying the method provided by Hakama et al. to the two FIT-based serviced screening programs, the results are misleading.

Because this method proposed by Hakama is only suitable in the RCT study design, when we would like to estimate the sensitivities in the prospective cohort design of population-based screening program, it neglects the aspect of time dimension in the method, and not all subjects receive the screening examination regaularly . Therefore, we can utilize the concept of disease natural history to recalculate the episode sensitivity $(1–\alpha P_1/[P0–(1–\alpha)P_{10}])$. In the denominator, it means we exclude the annual incidence for non-responders from the annual incidence among control group, then we can replace it with the annual incidence for attendees, which can be derived by parameters estimated from screen data. The estimated three-state progressive model for CRC gives the

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incidence rate of 0.00133 and the progression rate of 0.382. The corresponding transition probability matrix is thus as follows.

$$\mathbf{P}(\mathrm{t}) = \begin{bmatrix} P_{00}(t) & P_{01}(t) & P_{02}(t) \\ 0 & P_{11}(t) & P_{12}(t) \\ 0 & 0 & 1 \end{bmatrix}$$

Under our current screening policy, we provide the biennial CRC screening program, so we take t=2 into the transition probability matrix that is given by

$$\mathbf{P}(2) = \begin{bmatrix} 0.9973 & 0.0019 & 0.0008 \\ 0 & 0.4658 & 0.5342 \\ 0 & 0 & 1 \end{bmatrix}$$

Hence, the annual incidence for attendees in the denominator is $1 - P_{00}(2) = 1 - 0.0027$.

In the numerator, it represents the incidence for people with a negative result (interval cancer), which is $P_{02}(2) = 0.0008$. Therefore, the episode sensitivity can be reformed from $1–\alpha P_1/[P0–(1–\alpha)P_{10}]$ to $1\text{-}P_{02}(2)/[1\text{-}P_{00}(2)]$, resulting in 70%.

6.2 Contributory causes of FIT interval colorectal cancer

The study in the dissertation is the first one focusing on the decomposition of FIT interval cancer into two components, namely the newly developed and the false-negative CRCs. Based on a population-wide FIT-based screening program we demonstrated that newly developed CRCs accounted for 68.8% of FIT interval cancer.

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The sensitivity of detecting asymptomatic CRC after separating newly developed CRC from FIT interval cancers was elevated to 75.5% compared with 70.2% traditional estimate of sensitivity based on 29.8% of the complementary of the rate of interval cancer as a percentage of expected incidence rate.

Interval cancer, one of the core measures of the quality of cancer screening program, is greatly affected by sensitivity. Compared with gFOBT, FIT has a higher sensitivity in detecting CRC and are more likely to have the potential to reduce interval cancer in screening program (Chiu et al. 2017a, John et al. 1993, Allison et al. 1996). Wieten et al. reported that the ratio between interval cancer and screen-detected CRC was 1:1.2 for gFOBT, and 1:2.6 for FIT (Wieten et al. 2019). Our results confirmed a lower proportion of interval cancer for FIT-based screening program compared with that using gFOBT. Our results show that the ratio between interval cancer and screen-detected CRC was 1:2.4 in the FIT-based screening program and the proportion of interval cancer from false-negative CRC was lower. This is consistent with the finding of Wieten's study.

The sensitivity of Taiwan FIT-based screening program was 70.2% based on the proportional incidence method which was lower than the estimated result of 75.5% derived from direct estimation based on generalized non-linear measurement error

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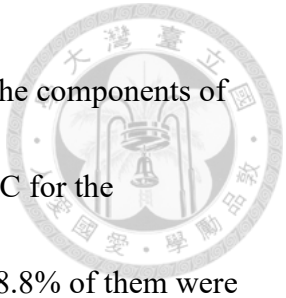

regression model. This was mainly due to the difference in handling the components of interval cancer, namely newly developed CRC and false-negative CRC for the estimation of sensitivity. Among the observed FIT interval cancers, 68.8% of them were newly developed CRCs and were disguised as being missed at screening activity according to conventional proportional incidence method. On the other hand, the generalized non-linear regression model taking into account these newly developed CRCs, namely newly developed cancers following the previous negative FIT result, to derive an accurate evaluation of FIT sensitivity.

In our study, the sensitivity of FIT was higher for subjects aged 50-59 years compared with those aged 60-69 years, and for women compared with men. There are evidence show a higher incident rate of proximal CRC among subjects older than 60 years (Kim, Shin and Ahn 2000, Sung et al. 2015). Since the sensitivity of FIT was lower for proximal CRC (Chiang et al. 2014), this difference in CRC risk for proximal and distal colon may be the biological reason accounting for our finding.

As far as Bayesian approach is concerned, we used the inaugural period (2004-2009) as prior distribution and the rolling-out period (2010-2014) as the likelihood, and the estimated results on sensitivity of 71.9% (95% CI: 70.3-73.5%) applying the Bayesian approach, which was similar by the generalized non-linear measurement error

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regression model. However, the progression rate was lower for the rolling out period (0.27, 95% CI: 0.26-0.28).

Moreover, we used the generalized non-linear joint measurement error model to evaluate the sensitivity of FIT and colonoscopy in screening episode. The sensitivity colonoscopy of colonoscopy was 93.6%. and resulted in 88% of colonoscopy IC resulted from newly developed CRC. The possible explanation for such finding is that the missed lesion form colonoscopy more likely are proximal advanced neoplasms, sessile serrated adenomas/polyps (SSA/P), or nonpolypoid neoplasms, and these lesions may progress from advanced adenoma to symptomatic CRC faster than polypoid lesion. Previous studies have shown that SSA/P is more likely to be located at the proximal colon, and Bettington et al. reported that SSA/Ps containing dysplasia/carcinoma are predominantly small (<10 mm) (Bettington et al. 2017). It has also been reported that when dysplasia develops in such a lesion, then the clinical course may speed up and lead to poorer outcome (Bettington et al. 2017, García-Solano et al. 2011, van Rijnsoever et al. 2002). In our study, the subjects with advanced adenoma are still at free of CRC status, and if endoscopist miss these lesions, and the subjects may be diagnosed with CRC very soon after colonoscopy examination.

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6.3 CRC survival and detection mode in FIT screening

The results from this study confirmed that screen-detected CRC was associated with more favorable long-term survival compared with other CRCs, including both FIT and colonoscopy IC, and CRCs in colonoscopy noncompliers after positive FITs. As expected, screen-detected CRC had more favorable survival than ICs, and the FIT IC and CRCs from the colonoscopy noncompliers had the worst survival as compared to CRCs with other detection modes. Such findings are consistent with those from a previous study by Govindarajan et al. showing that post-colonoscopy CRCs were associated with a higher risk of emergent presentation, a lower likelihood of surgical resection, and significantly worse oncologic outcomes. Still, these patients had better outcomes than did patients who had not received a recent colonoscopy (Govindarajan et al. 2016). The current study compared FIT IC and colonoscopy IC and showed that the former was associated with more unfavorable survival compared with the latter. However, after adjusting for disease stage, there were no significant difference in mortality between these two detection modes. The finding meant that FIT interval cancer had worse survival is mainly due to late stage at diagnosis. Such a finding has rarely been reported previously in large-scale population-based FIT screening programs and is quite intriguing. However, a trend toward worse survival for FIT IC was noted,

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even though it is statistically non-significant. The possible explanation for such finding is that FIT fails to detect invasive cancers or precancerous neoplasms with a more unfavorable biological nature and clinical course compared with cancers missed by colonoscopy. Our previous study demonstrated that FIT had lower sensitivity for SSA/P, especially when the size of the lesion was small or conventional adenoma was absent (Chang et al. 2017). Nonpolypoid neoplasms, especially the nongranular type of laterally spreading tumor, have been reported to be associated with a much higher rate of malignant transformation and deep invasion (Bogie et al. 2018). FIT, however, has lower sensitivity to detect nonpolypoid neoplasms, and patients with such lesions are more likely to have false-negative FIT results, leading to the occurrence of FIT ICs (Chiu et al. 2013, Alwers et al. 2019, Phipps et al. 2015). Colonoscopy may also miss significant lesions, especially nonpolypoid ones, leading to colonoscopy IC, as mentioned previously.

The lead time is the difference between the age of screening detected CRC and the onset of the clinical symptoms without screening. Screening detected CRC will appear to lengthen the time from diagnosis until death.(Wu, Rosner and Broemeling 2007) In our study, after we adjusted for the lead-time and truncation, the aHR of screen-detected CRC, compared with CRC in screening nonparticipants, was elevated from 0.37 to 0.51.

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The lead time was quantities with the estimated result of CRC natural history, and was critical in the assessment of the likely benefits of screening program. On the other aspect, the screening program is an artificial policy, the initial age for screening is limited. For example, in the Taiwan screening program, the initial age for screening is 50 years old. Therefore, the subjected who joins the screening program have to be older than 50 years old, and, also, the screen-detected CRC is older than 50 years old. If one subject is diagnosed with CRC or dies from colorectal cancer younger than 50 years old, then he or she would not be able to become a screen-detected CRC. So, the CRC cases with worse condition may be excluded from screen-detected CRC due to the policy factor, and then it may result in the over-estimated benefit of prevalent screen-detected CRC. After adjusting for the truncation for prevalent screen-detected CRC, and the aHR was elevated from 0.28 to 0.56. These models can be used for further effectiveness analysis of screening program, and avoid the over-estimated benefit of screening detected CRC..

Nevertheless, the different survival of CRCs with various detection modes, its implication on the entire screening program may be another matter and the magnitude of CRC with individual detection mode should be carefully considered. For evaluation the effectiveness of screening program, based on the estimated results of generalized

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non-linear joint measurement error model and survival for each detection modes, the biennial program compared with triennial one resulted in the life-year gained by 2, 337 person-years, among which 2,314 person-years and 23 person-years resulted from FIT test and colonoscopy, respectively. Hence, it is quite clear that decreasing the FIT interval cancer is currently the first priority task of the screening organizer. The findings from this study provide new insights about FIT screening and may further help improve various aspects of the screening program, thereby maximizing the effectiveness of the screening program.

6.4 Limitation

There are several limitations in current study. Although the effect of age and sex on the occurrence and progression of CRC were incorporated in current Markov regression mode, factors such as family history were not considered. The effect of family history on CRC evolution can be incorporated in the future which will shed light on the development of CRC prevention strategies for this subpopulation. Regarding the comparison of CRC survival by detection modes, the characteristics of CRC cases not identified through the screening process (nonparticipants) may vary from cities and counties. As these CRCs may be detected by self-paid screening colonoscopy, especially

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in the metropolitan area, the estimated results on the risk of CRC death through defined detection modes may be different across areas in Taiwan. Further exploration of CRC survival by detection modes through different areas will provide inside into this possibility.

6.5 Conclusion

A new generalized non-linear measurement error regression models was developed to model contributory causes of FIT and Colonoscopy interval cancers to estimate the impact of inter-screening interval on the reduction of deaths from CRC attributed to each type of interval cancer making use of the lead-time and truncation-adjusted survival model.

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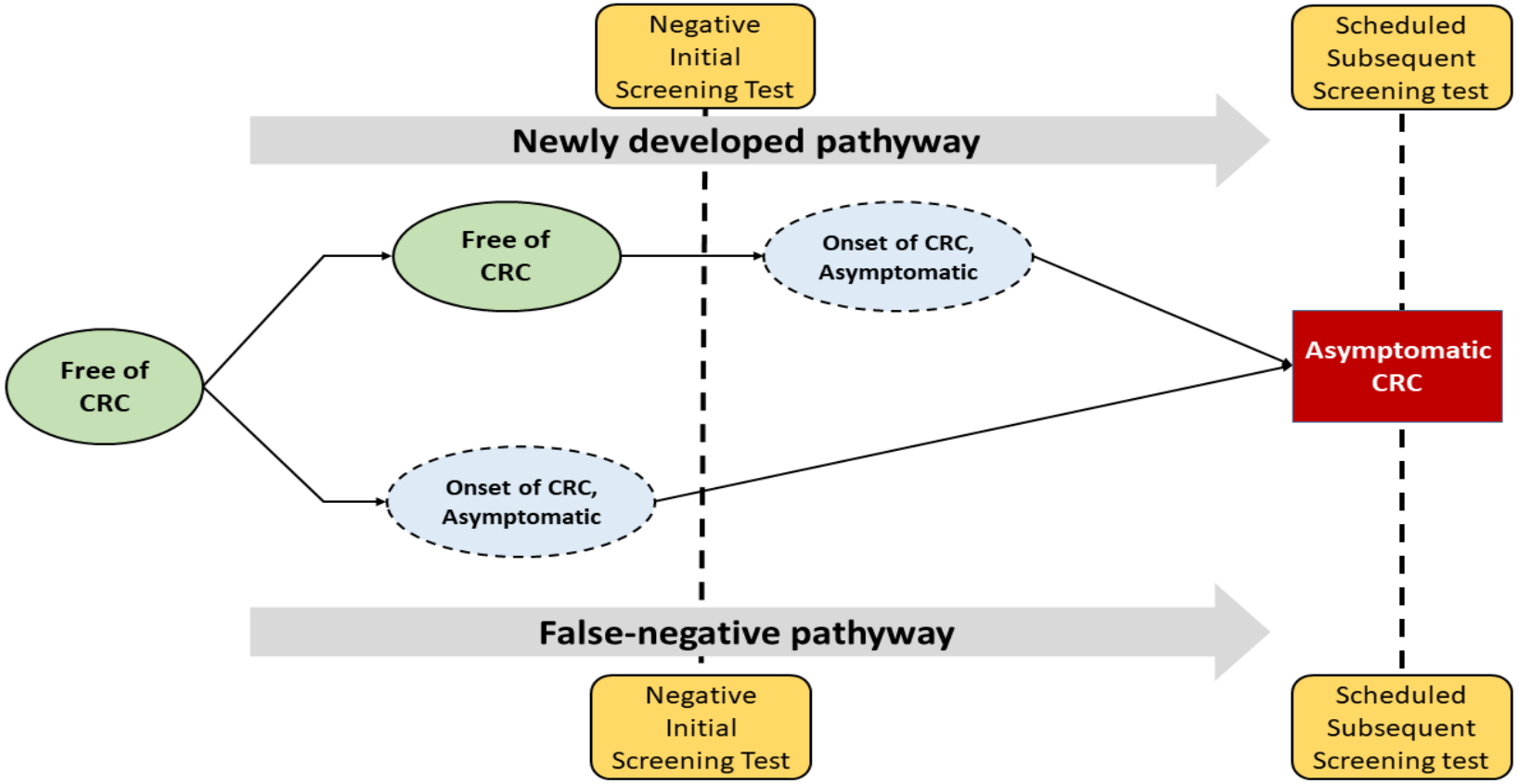
Figure 1.1 Component and pathway for subsequent screen-detected CRC and FIT interval cancer

A. subsequent screen-detected CRC



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B. FIT interval cancer

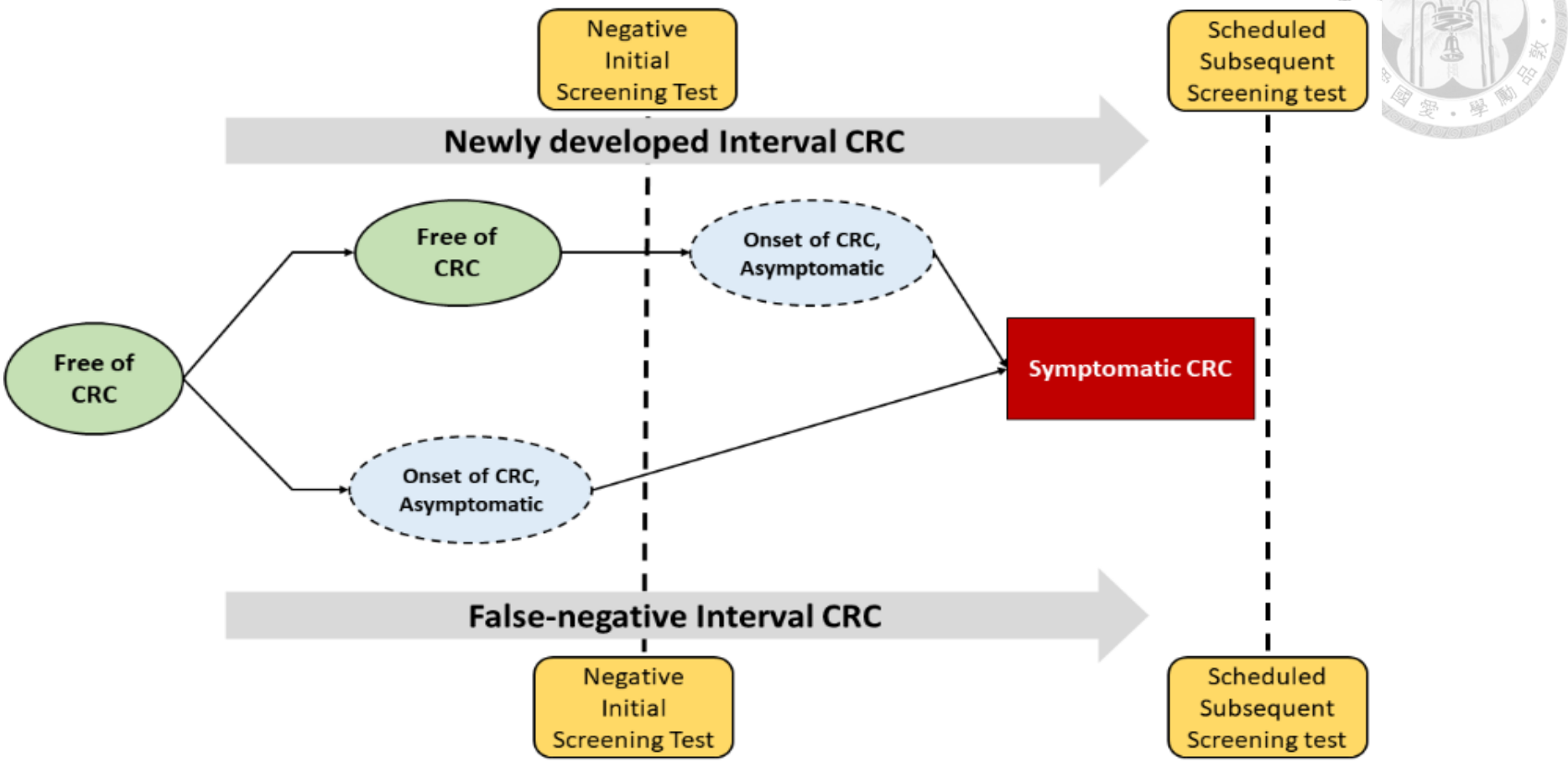

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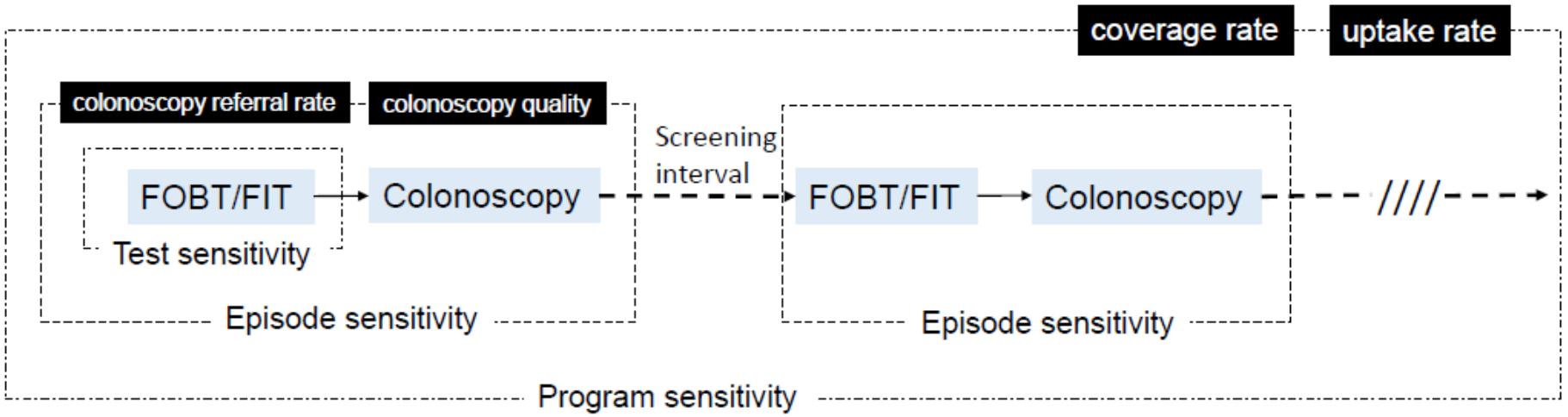
Figure 2.1 Test sensitivity, episode sensitivity, and program sensitivity



Test sensitivity—Assume 100% colonoscopy referral rate and 100% sensitivity of colorectal examination

Episode sensitivity—Take into account colonoscopy referral rate and colonoscopy quality

Program sensitivity—Further take into account screening coverage rate and screening uptake rate

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Figure 2.2 Flow chart of literature search and selection for FOBT-based sensitivity

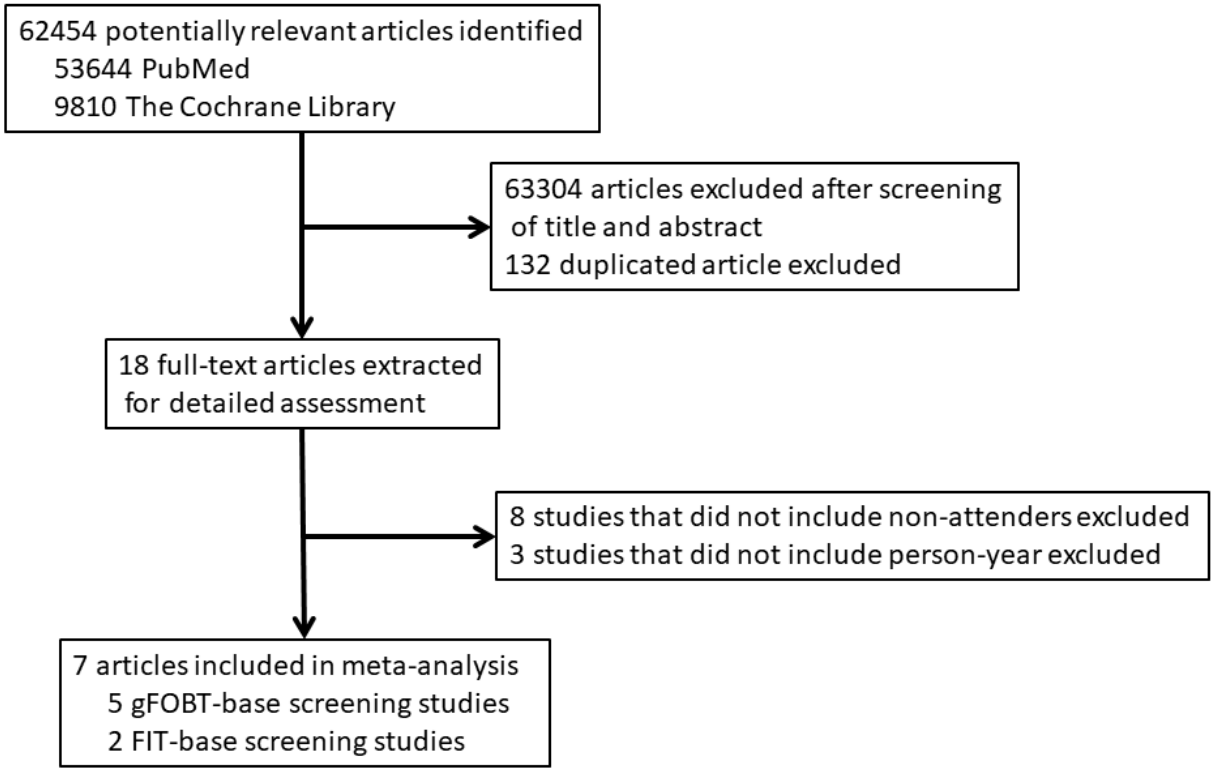

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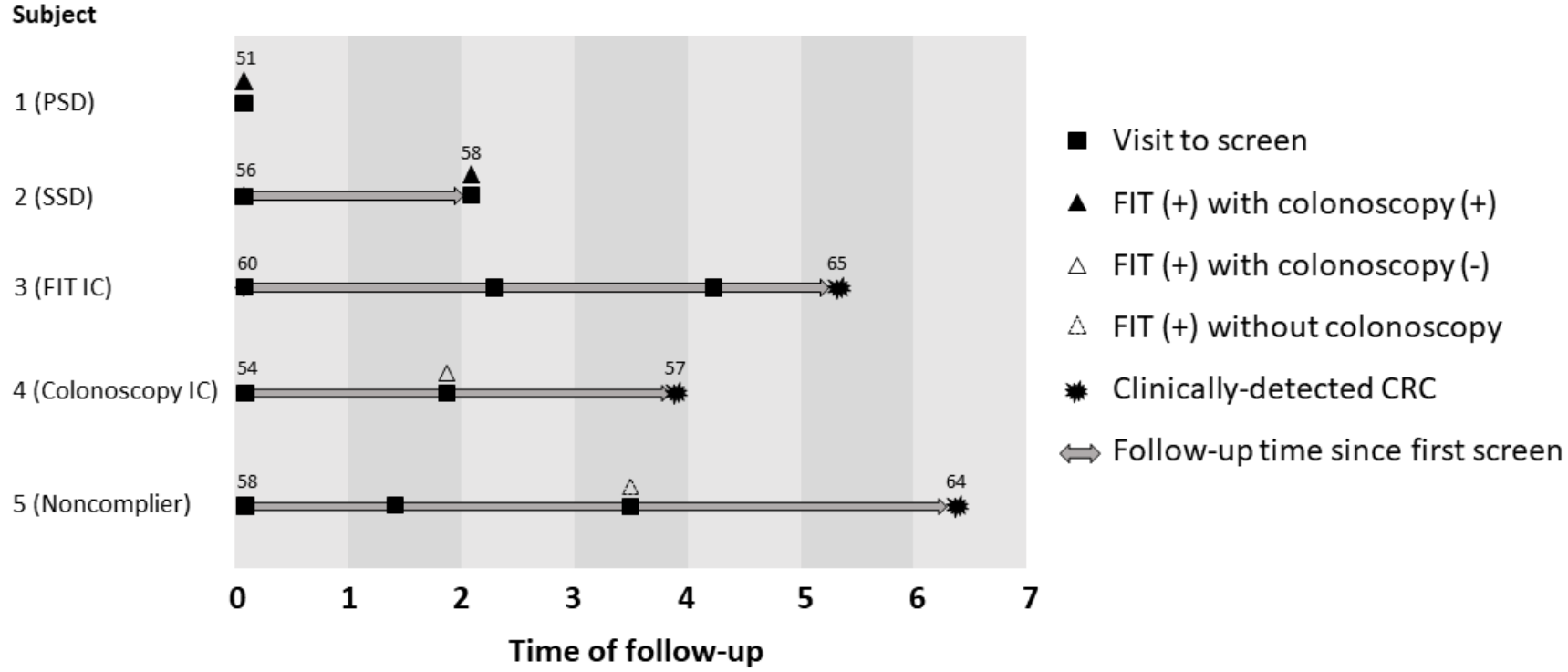
Figure 3.1 CRCs with different detection mode within FIT-based screening program



PSD: Prevalent screen-detected CRC

SSD: Subsequent screen-detected CRC

IC: Interval cancer

FIT: Fecal immunochemical test

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Figure 4.1 The Bayesian directed acyclic graphic three-state Markov model

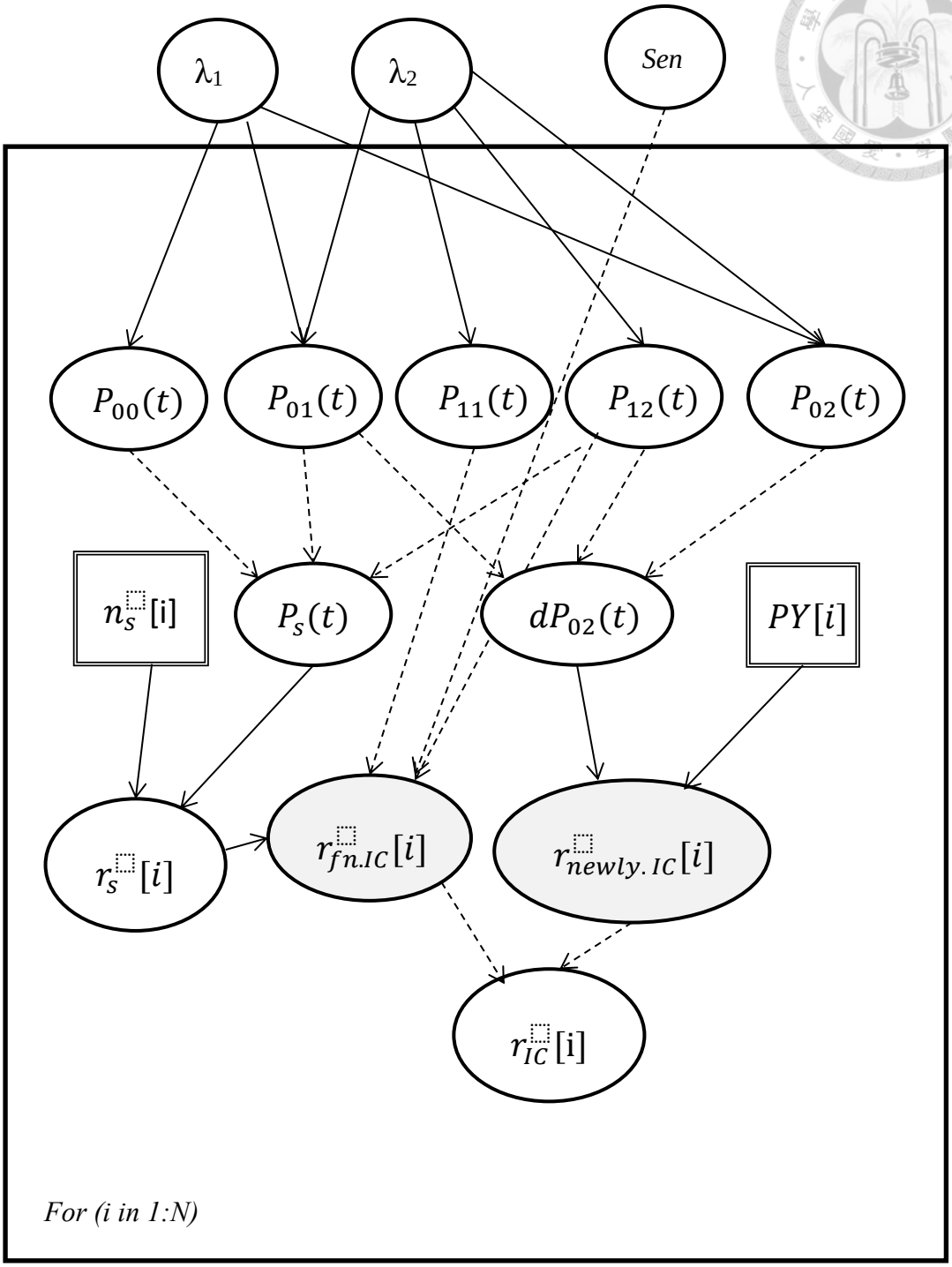

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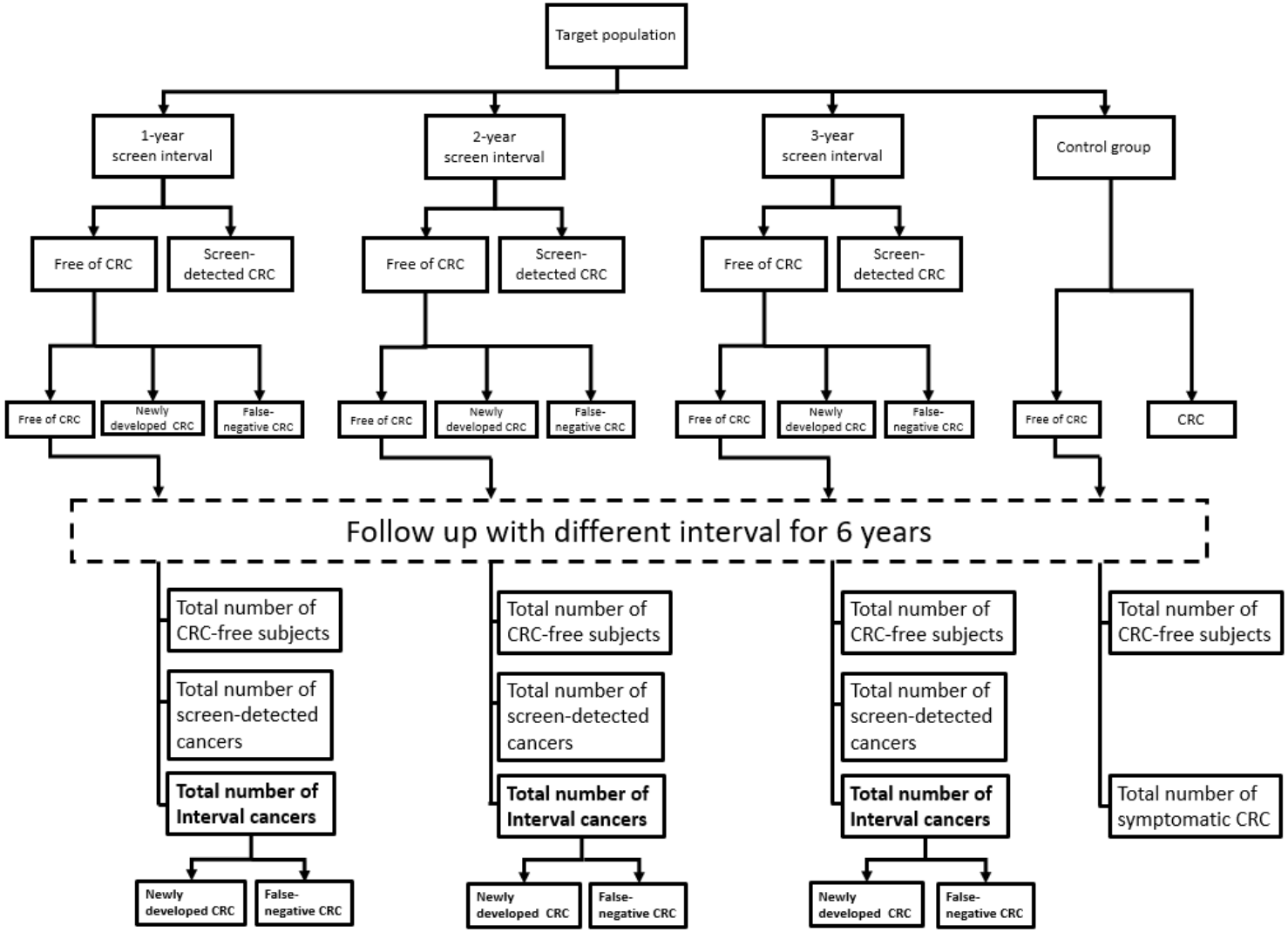
Figure 4.2 Study design for comparing the components of FIT interval cancer (Newly developed interval CRC, False-negative interval CRC) for the effect of screening intervals (1-year, 2-year, and 3-year)*



*IC: interval cancer

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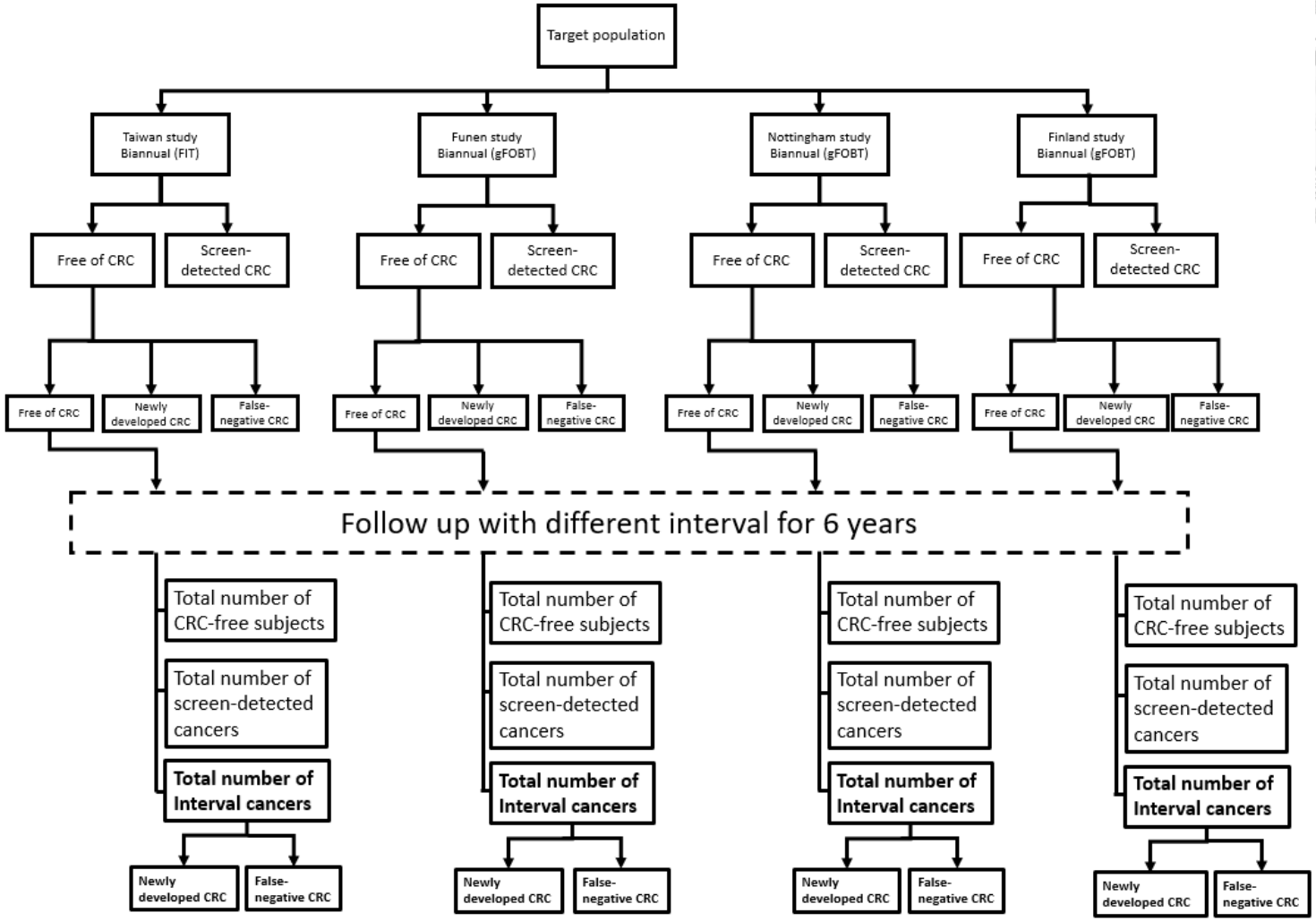
Figure 4.3 Study design for comparing the components of interval CRC (Newly developed CRC, False-negative CRC) for FIT screening program and studies using gFOBT*



*IC: interval cancer

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Figure 4.4 The procedure of time-dependent Cox model

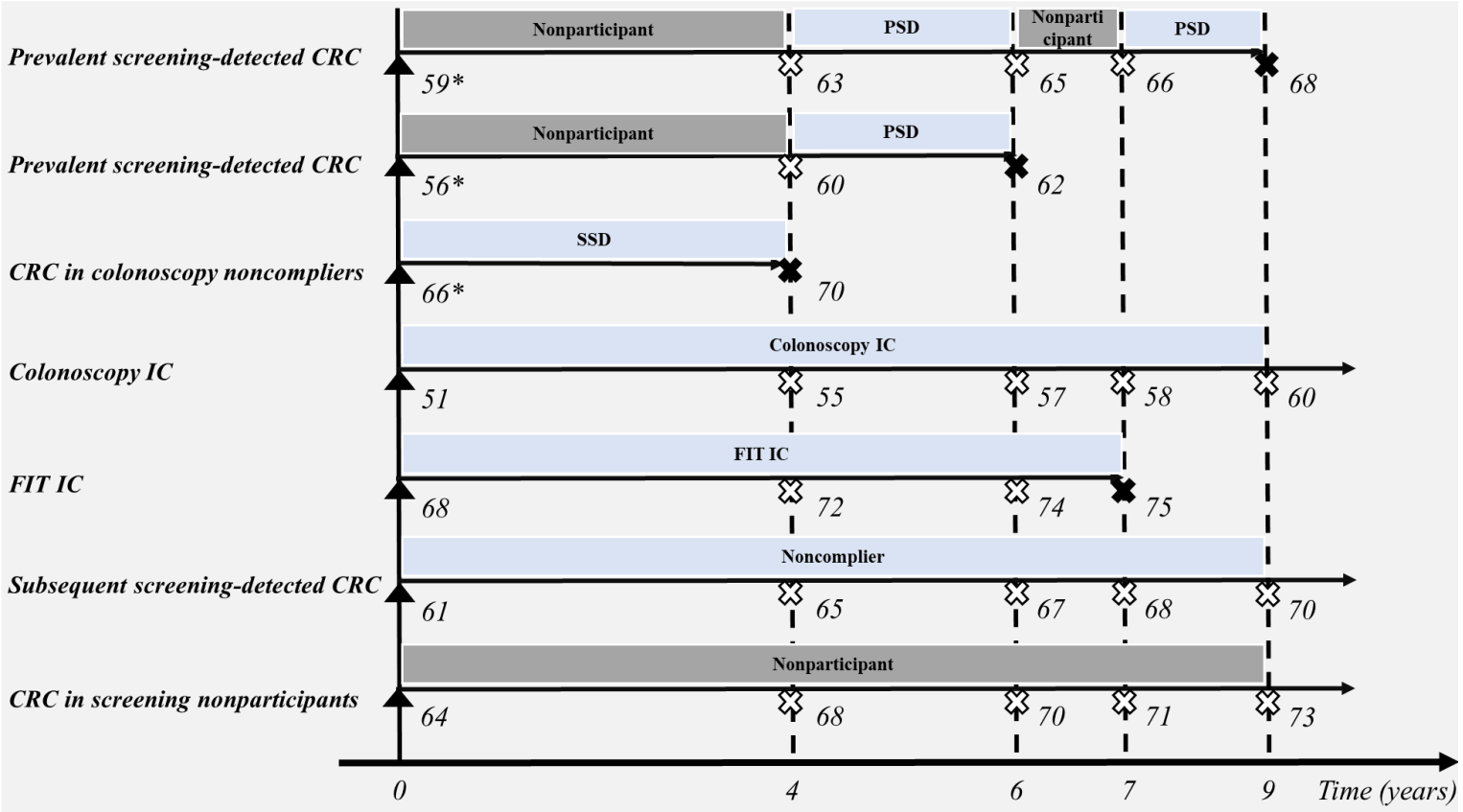

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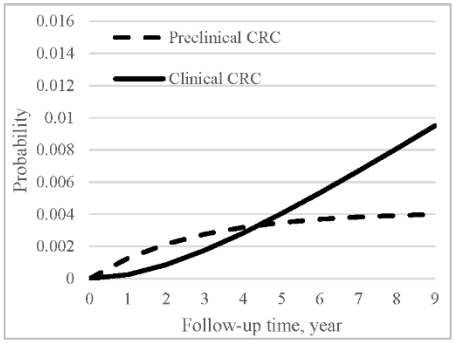
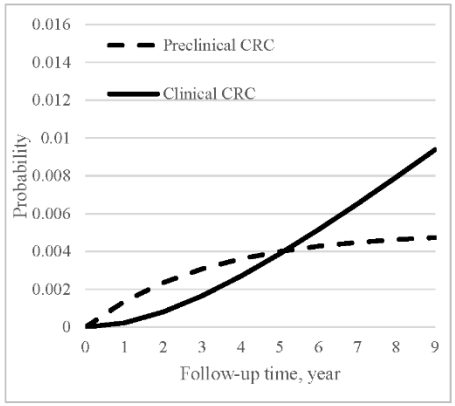
Figure 5.2.1 Proportions of preclinical phase and clinical phase of CRC based on the empirical data on Taiwan CRC screening

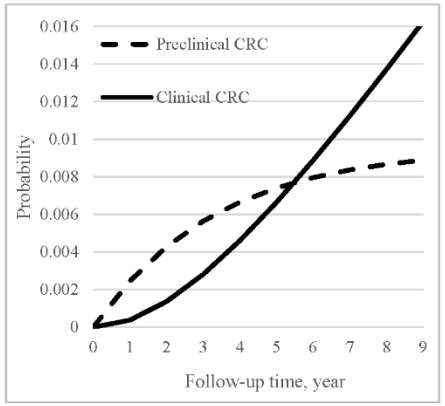
(a) Overall (incidence 151per 100,000, progression rate 0.36 per year)



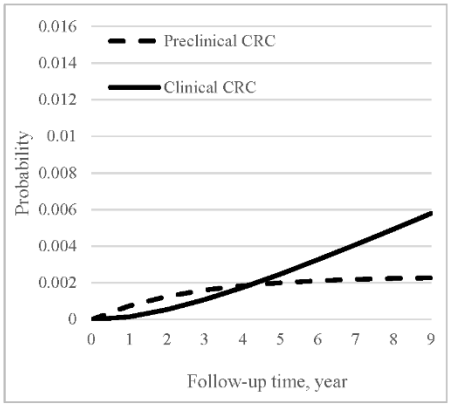
(b) Male, 50-59 years



(c) Male, 60-69 years



(d) Female, 50-59 years



(e) Female, 60-69 years

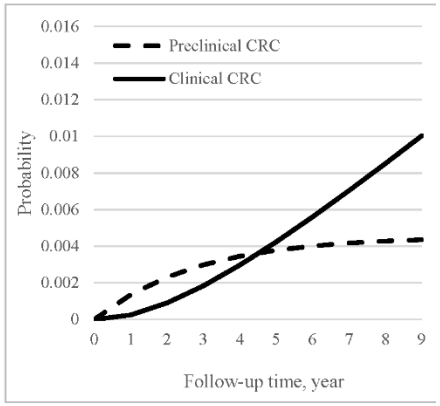


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Figure 5.2.2 Diagnosis plots for parameter estimation with applying the Gibbs sampling (b1: incidence rate of PCDP;b2: progress rate of PCDP; bs: parameter of sensitivity)

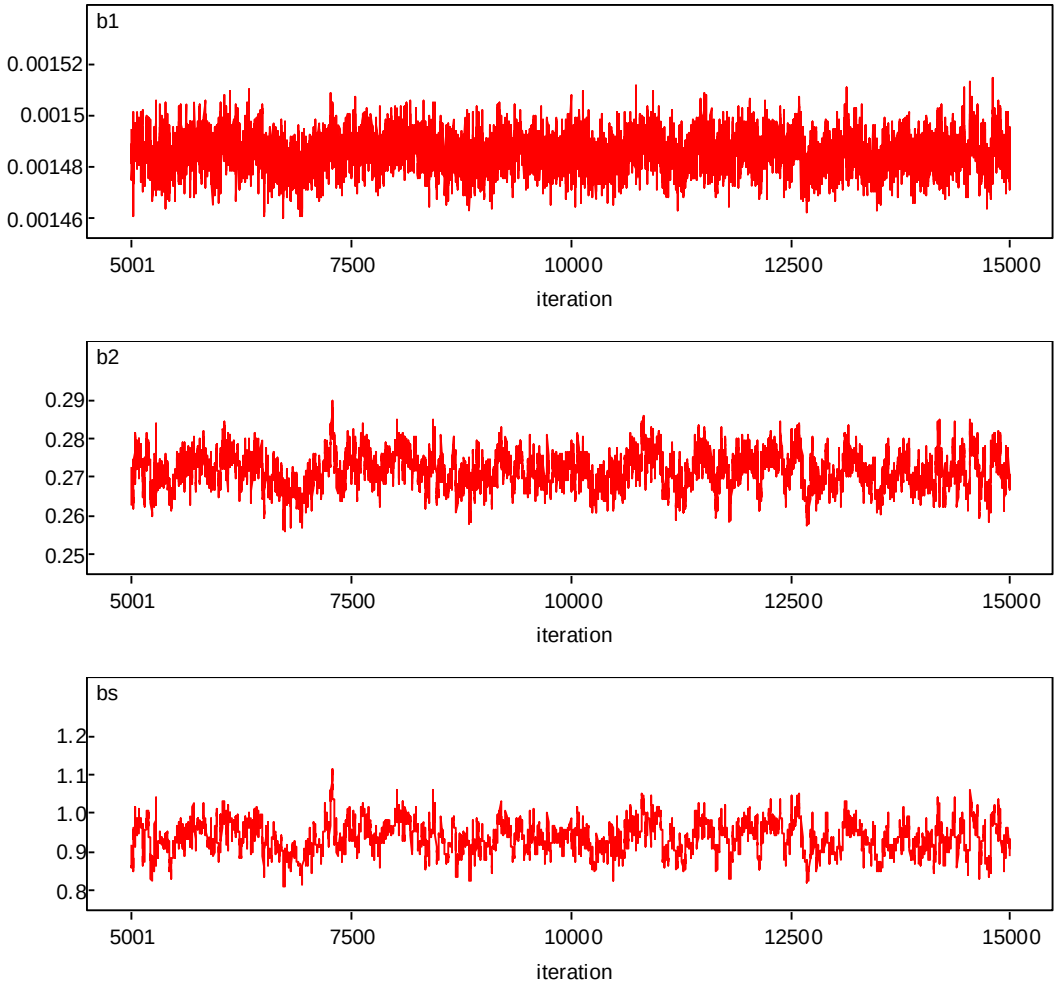

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Figure 5.2.3. Frequencies and proportions of newly developed and false-negative CRC by inter-screening intervals and characteristics of subjects

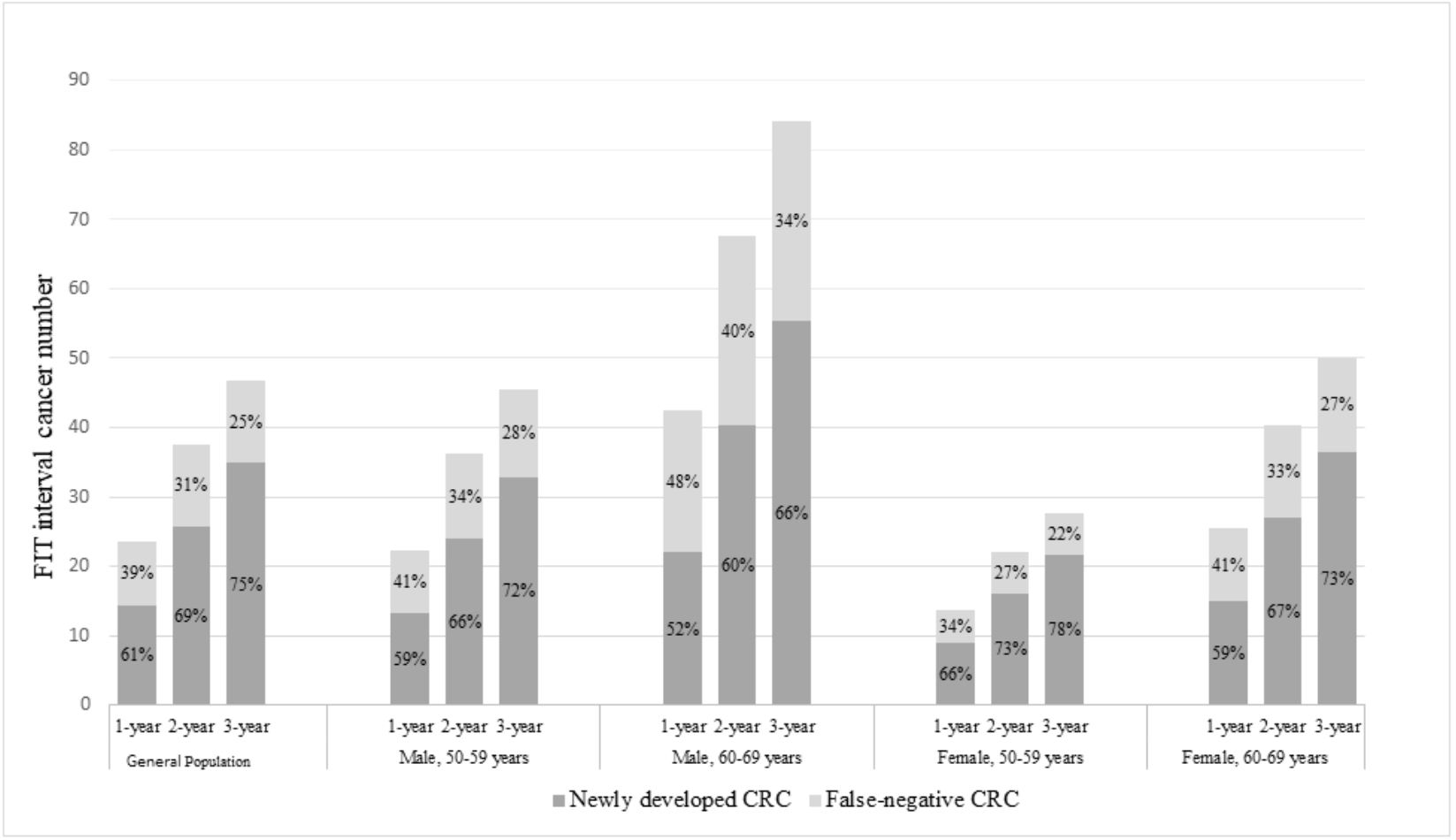

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Figure 5.2.4 Interval CRC as a percentage of the expected incidence by g-FOBT (Funen, Nottingham, and Finland) and FIT (Taiwan) studies

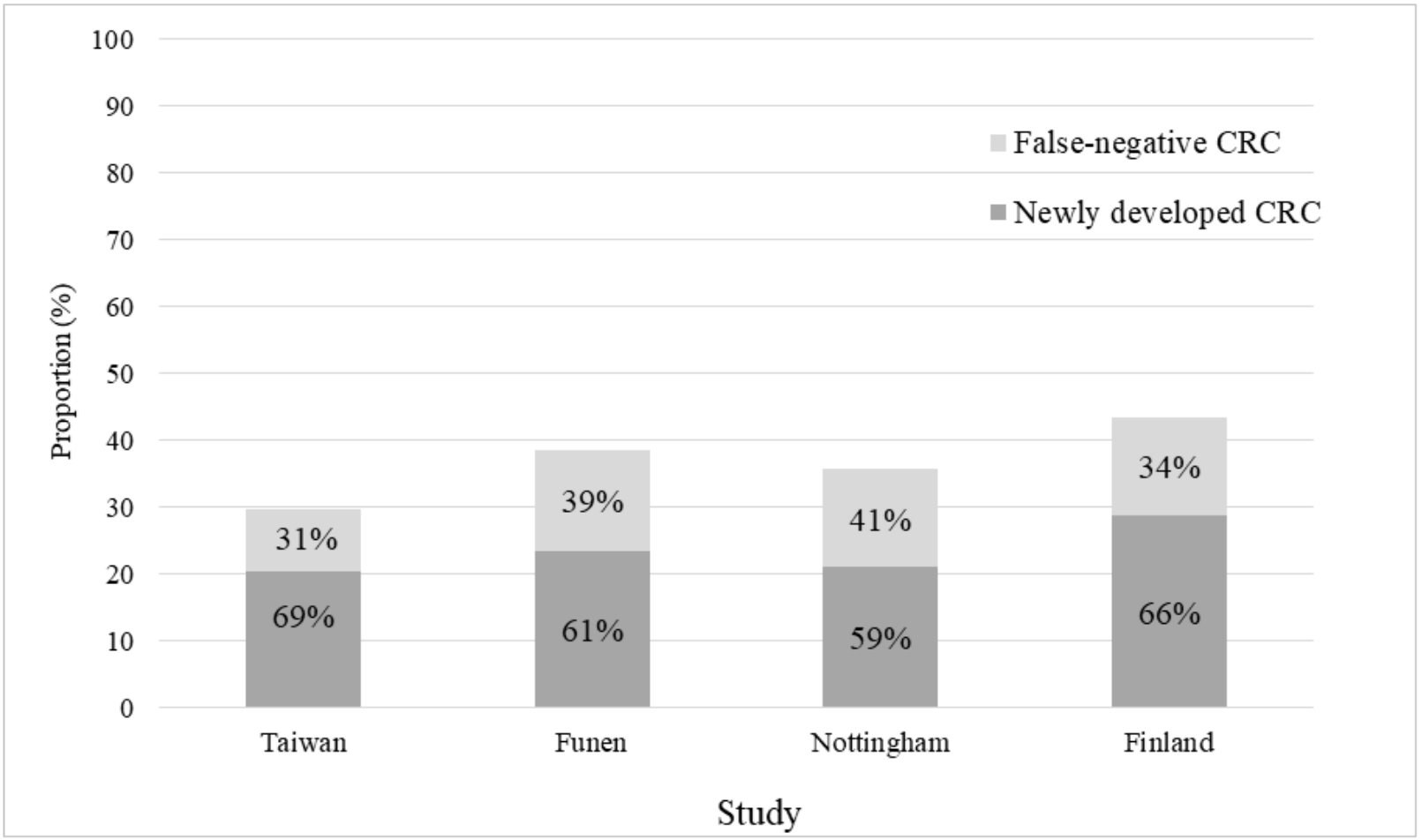

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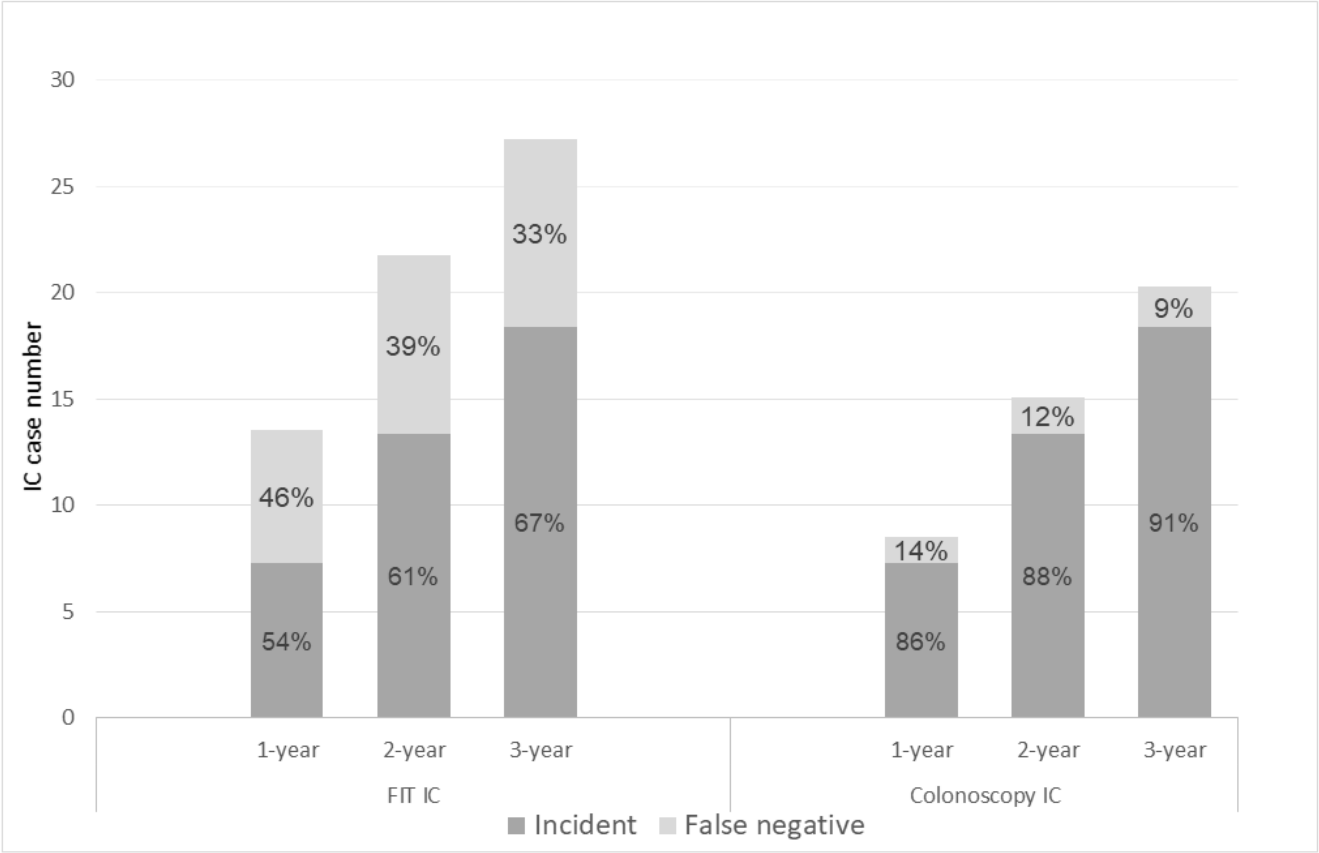
Figure 5.3.1 Frequencies and proportions of newly developed and false-negative CRC of FIT IC and colonscopy IC by inter-screening intervals and characteristics of subjects*



*IC: interval cancer

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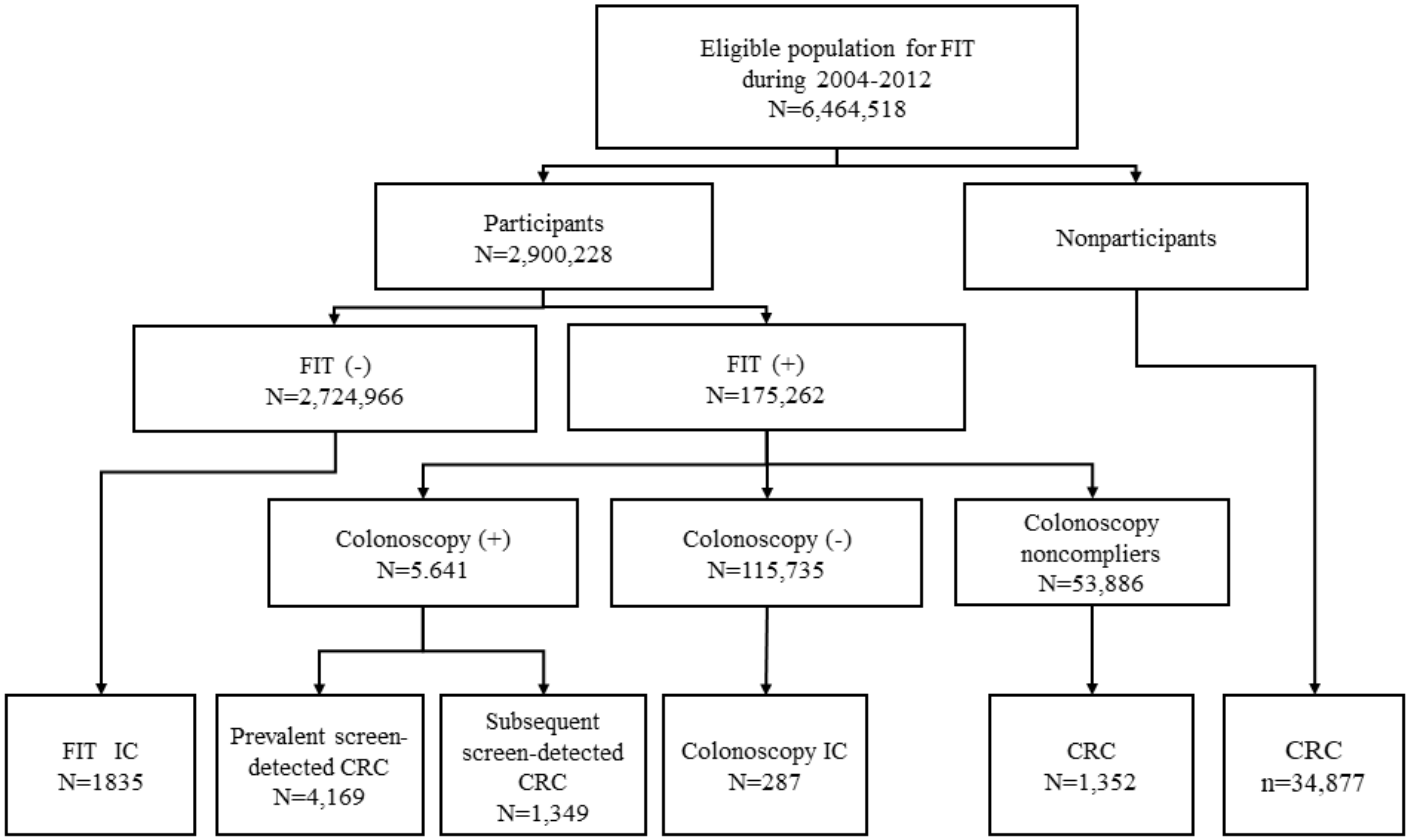
Figure 5.4.1 Diagram showing CRC with different detection mode within FIT screening program in Taiwanese Nationwide CRC Screening Program*



***FIT: fecal immunochemical test; CRC: colorectal cancer; IC: interval cancer.**

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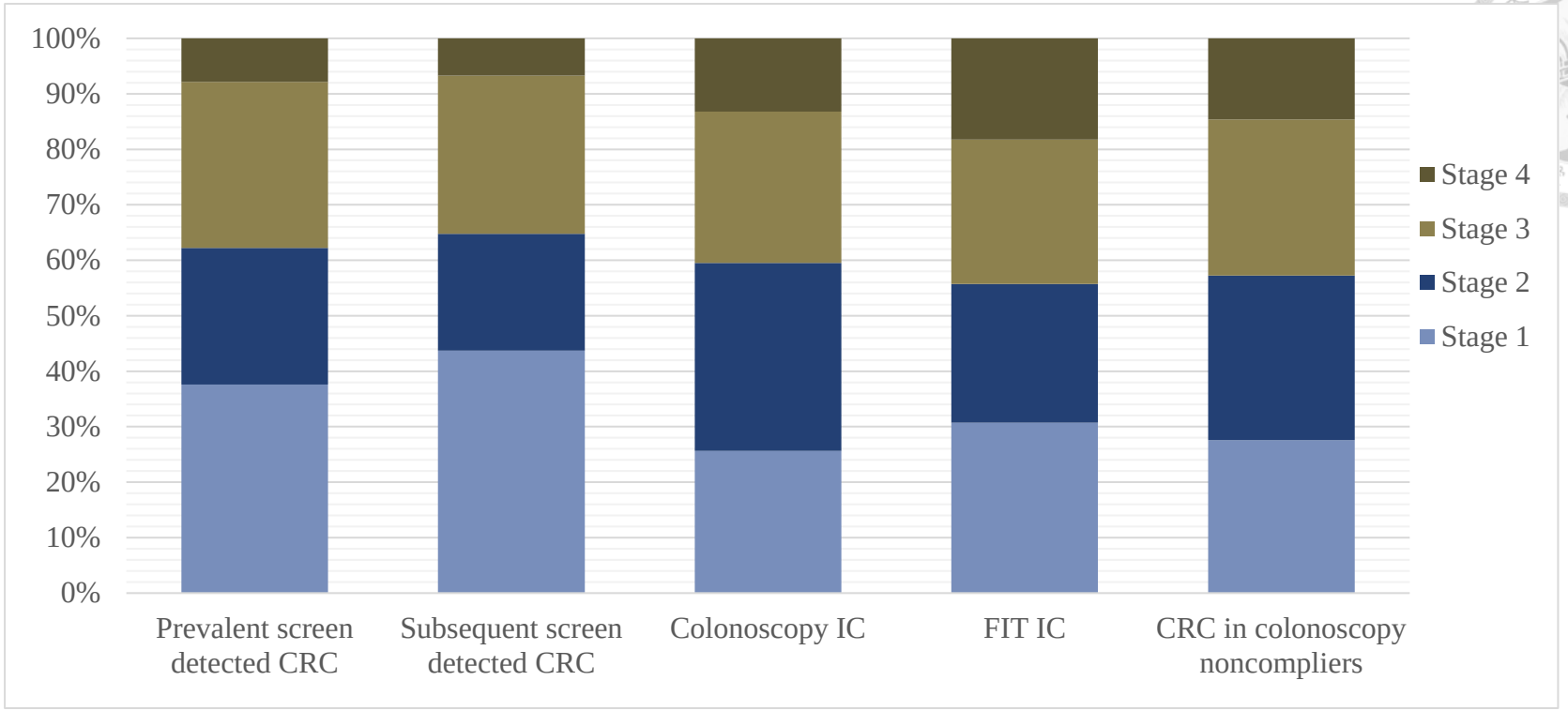
Figure 5.4.2 Stage distribution of CRC with different detection modes in screening participants



FIT: fecal immunochemical test; CRC: colorectal cancer; IC: interval cancer.

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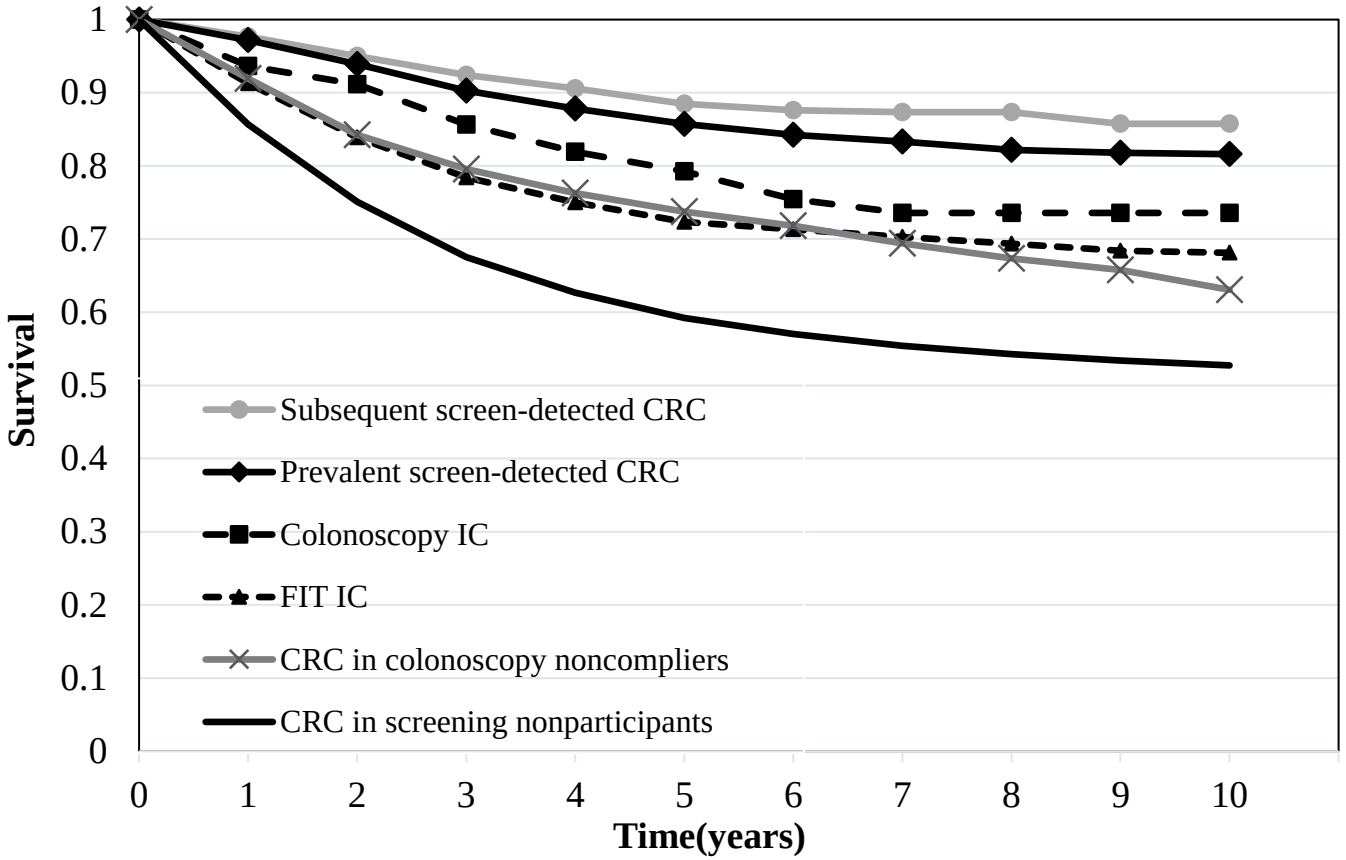
Figure 5.4.3. Long-term outcomes of CRCs with different detection modes



FIT: fecal immunochemical test; CRC: colorectal cancer; IC: interval cancer.

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Table 2.2.1 Study and test characteristics of gFOBT studies

Study	Country	Time period	N. of stools/ n. of samples per stool	Participants n	Total screen detected CRCs n	Detection rate (%)	Total gFOBT ICs n	Incidence rate per 100,000 pys (95% CI)
Mandel et al. 1989, 1993	USA	1957-1982	3/2	39,259	183	0.47	22	11 (7-17)
Souques et al. 2000	France	1980-1995	3/2	9,153	15	0.16	10	16 (8-29)
Hardcastle et al. 1996	UK	1981-1991	3/1 or 2	44,838	236	0.53	147	27 (23-32)
Kewenter et al. 1988	Sweden	1982-1985	3/2	9,040	35	0.39	16	106 (65-173)
Cummings et al. 1986	USA	1984	3/2	11,497	14	0.12	1	4 (1-31)
Kronborg et al. 1996	Denmark	1985-1995	3/2	20,672	120	0.58	146	71 (60-83)
Faivre et al. 2004	France	1988-1998	3/2	24,009	196	0.82	219	76 (67-87)
Bouvier et al. 1999	France	1991-1994	n.d.	71,307	152	0.21	100	47 (38-57)
Rennert et al. 2001	Israel	1992	3/2	22,193	58	0.26	10	16 (9-29)
Zappa et al. 2001	Italy	1992-1997	n.d.	16,765	66	0.39	45	67 (50-90)
Steele et al. 2012	Scotland	2000-2007	3/2	167,415	698	0.42	635	63 (58-68)
Paimela et al. 2010	Finland	2004-2006	3/2	37,514	66	0.18	35	49 (35-68)
Denters et al. 2012	Netherlands	2006-2008	3/2	2,119	8	0.38	4	94 (35-251)
Levi et al. 2011	Israel	2008-2011	3/2	2,266	8	0.35	5	110 (46-265)

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Table 2.2.2 Studies about the gFOBT screening and CRC mortality reduction

Study	gFOBT		Control		Mortality Reduction(%)
	No. of person-yr	No. of deaths	No. of person-yr	No. of deaths	
Funen(Kronborg et al. 1996)	431,142	363	431,000	431	16%
Gotebrog(Kewenter et al. 1994, Kewenter et al. 1988)	-	252	-	300	16%
Minnesota(I) (Mandel et al. 1993)	180597	121	177000	177	33%
Minnesota (II) (Mandel et al. 1993)	187,341	148	177000	177	21%
Nottingham (Hardcastle et al. 1996)	847,142	593	844,444	684	13%
Faivre et al. 2004	476911	254	477,773	304	16%

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Table 2.2.3 Characteristics of randomized controlled trials for CRC screening program using gFOBT

Study	Study period	Country	gFOBT kit	Screening Frequency	Age range (years)
Funen(Kronborg et al. 1996)	1985-1995	Denmark	Haemoccult-II	Biennial	45-75
Nottingham(Hardcastle et al. 1996)	1981-1991	UK	Haemoccult (Rohm Pharma, weiterstadt, Germany)	Biennial	45-74
Finland(Malila et al. 2005, Malila et al. 2008)	2004-2006	Finland	Haemoccult (Beckman Coulter, USA)	Biennial	60-64

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Table 2.2.4 Derivation of progress rate for the Funen, Nottingham, and Finland randomized controlled trial from literature

Study	λ_1	λ_2	λ_3	λ_4	gFOBT Sensitivity	Incidence rate	Dwelling time (years)	Progression rate
Funen (Kronborg et al. 1996)	0.00158	0.3247	0.2801	0.6478	64%	0.00158	2.48	0.40
Nottingham (Hardcastle et al. 1996)	0.00146	0.2754	0.2142	0.7627	64%	0.00146	2.78	0.36
Finland (Malila et al. 2005, Malila et al. 2008)	0.00111	0.4849	0.3214	0.7350	65%	0.00111	2.06	0.49

λ_1 is the incidence rates of localized preclinical detectable phase (PCDP), λ_2 is the progression rates from localized PCDP to non-localized PCDP, λ_3 is the progression rate from localized PCDP to localized clinical CRC, and λ_4 is the progression rate from non-localized PCDP to non-localized clinical CRC(Chiu et al. 2011, Chiu et al. 2017a). The dwelling time for Funen (Kronborg et al. 1996), Nottingham (Hardcastle et al. 1996), and Finland (Malila et al. 2005, Malila et al. 2008) randomized controlled trial was derived by

$$\frac{1}{\lambda 2+\lambda 3}+\frac{\lambda 2}{(\lambda 2+\lambda 3)\times\lambda 4}$$

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Table2.2.5 Study and test characteristics of FIT studies

Study	Country	Time period	No. of stools/ no. of samples per stool	FIT cut-off (μg Hb/g feces)	Participants n	Total screen detected CRCs n	Detection rate (%)	Total FIT ICs n	IC Incidence rate Per 100,000 pys (95% CI)
Namaka et al. 1996	Japan	1991	1/1	Qualitative	3,365	10	0.30	4	40 (15-106)
Itoh et al. 1996	Japan	1991-1992	1/1	10	27,860	77	0.28	12	22 (12-38)
Zappa et al. 2001	Italy	1992-1997	n.d./1	200-300	9,149	73	0.80	8	22 (11-44)
Chen et al. 2016	Taiwan	1994-2008	n.d./1	20	234,044	298	0.13	133	28 (24-34)
Castiglione et al. 2007	Italy	2000-2002	1/1	20	24,913	63	0.25	16	32 (20-52)
Launoy et al. 2005	France	2001-2003	2/1	≥67 in ≥1 FITs	7,421	24	0.32	4	27 (10-72)
Crotta et al. 2012	Italy	2001-2008	1/1	20	1,660	8	0.48	5	38 (16-90)
Zorzi et al. 2011	Italy	2002-2007	1/1	20	173,859	748	0.43	102	22 (18-26)
Shin et al. 2013	Korea	2004-2007	1/1	10	1,809,139	2,961	0.16	2,047	28 (27-30)
Chiu et al. 2015b, Chiu et al. 2017	Taiwan	2004-2009	1/1	20	1,160,895	2,728	0.23	968	14 (13-15)
Parente et al. 2013	Italy	2005-2007	1/1	100	38,807	165	0.43	8	10 (5-21)
De Girolamo et al. 2016	Italy	2005-2011	1/1	20	793,685	3,370	0.42	386	24 (22-27)
Rossi et al. 2015	Italy	2005-2012	1/1	20	121,796	575	0.47	29	3 (2-4)
Denters et al. 2012	Netherlands	2006-2008	1/1	10	2,871	21	0.73	4	70 (26-186)
Kapidzic et al. 2014	Netherlands	2006-2012	1/1	10	4,523	34	0.75	3	11 (4-34)
Jensen et al. 2016	USA	2007-2008	n.d./1	20	323,349	958	0.30	242	25 (22-28)
Levi et al. 2011	Israel	2008-2011	3/1	≥14 in ≥1 FITs	1,224	6	0.49	0	20 (1-327)
McNamara et al. 2014	Ireland	2008-2012	2/1	≥20 in ≥1 FITs	5,063	21	0.41	1	5 (1-35)
Digby et al. 2016	Scotland	2010-2011	n.d./1	80	30,893	30	0.10	31	50 (35-71)

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Table 2.2.6 Comparisons of colorectal cancer–specific mortality between the colonoscopy and noncolonoscopy groups

Variables	Relative risk* (95%CI)
Noncolonoscopy vs colonoscopy	1.64 (1.32 to 2.04)
Noncolonoscopy vs complete colonoscopy	2.31 (1.88 to 2.84)
Incomplete colonoscopy vs complete colonoscopy	1.65 (1.26 to 2.16)
Fecal hemoglobin concentration, μg Hb/g stool	
20–49	1.00
50–99	2.10 (1.61 to 2.73)
≥100	4.61 (3.61 to 5.89)

*Adjusted with age, gender, and screening round

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Table2.2.7 Hazard ratios and 95% confidence intervals from the accelerated failure time model for risk of CRC, colorectal adenoma

f-HbC (ng/ml)	CRC		Adenoma	
	HR	95%CI	HR	95%CI
Undetected	0.47	0.30-0.73	2.04	1.77-2.35
1-19	1.00	-	1.00	-
20-39	1.14	0.74-1.77	1.81	1.38-2.37
40-49	2.54	1.58-4.07	2.09	1.45-3.00
60-79	3.59	2.10-6.16	1.20	0.64-2.22
80-99	3.63	1.80-7.32	2.83	1.63-4.94
100-150	2.32	1.38-3.88	5.29	4.02-6.96
150-250	2.33	1.34-4.04	5.37	4.04-7.13
250-450	2.70	1.42-5.14	8.78	6.60-11.67
>450	14.00	10.20-19.22	11.19	8.87-14.12

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Table 2.3.1 Incidence of adenoma and colorectal cancer

f-HbC	Adenoma	CRC	Adenoma and CRC
	Incidence (cases per 1000 person-years)		
Undetected	1.36	0.32	1.67
1–19 ng/mL	1.18	0.55	1.74
20–39 ng/mL	2.20	0.59	2.78
40–59 ng/mL	2.64	1.27	3.90
60–79 ng/mL	1.70	2.32	4.01
80–99 ng/mL	3.80	3.33	7.08
≥100 ng/mL (non-referrals and false-positives)	2.91	5.61	8.49

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Table 2.3.2 Crude and adjusted HRs for risk of colorectal neoplasia

f-HbC	Crude HRs	adjusted HRs¢	adjusted HRs*
1–19	1.00	1.00	1.00
20–39	1.48 (1.13–1.95)	1.43 (1.08–1.88)	1.27 (0.74–2.17)
40–59	2.11 (1.47–3.01)	1.88 (1.31–2.71)	2.67 (1.47–4.84)
60–79	2.20 (1.35–3.57)	1.77 (1.06–2.94)	3.61 (1.81–7.23)
80–99	3.92 (2.36–6.51)	3.41 (2.02–5.75)	6.95 (3.47–13.90)
≥100 (non-referrals)	9.77 (7.07–13.51)	8.46 (6.08–11.76)	91.26 (65.61–126.94)
≥100 (false-positive cases)	0.93 (0.41–2.10)	0.70 (0.29–1.72)	

¢ Adjusted with age, gender, family history of CRC, meat consumption, BMI

*Time-dependent Cox regression model

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Table 2.3.3 Overview of studies on interval CRCs after colonoscopy in asymptomatic populations, showing that variation in the definitions used for an interval CRC affects the estimated rates

Studies	Definition iCRC	Design	Outcomes	Stage of CRC (I–II vs. III–IV)	Location of CRC (proximal vs. distal)	Risk factors/ possible etiology
Brenner et al (2012) Germany	1–10 years after negative colonoscopy	Population-based; 1945 CRC cases; 2399 controls	433 screen detected vs. 78 iCRCs	Screen detected: 282 vs. 149 iCRCs: 39 vs.39	Screen detected: 167 vs. 243 iCRC 44 vs. 32	Predictors of CRCs
Strock et al (2011) Luxembourg	All CRCs after index colonoscopy	Retrospective; 8950 patients after screening CS	19 iCRCs in 47 725 person-years follow-up	Not specified	iCRC: 6 vs. 13	N/A
Kaminski et al (2010) Poland	CRC diagnosed between screening and surveillance examination	Retrospective. 45 026 patients in colonoscopy screening program	CRC incidence; 42 iCRCs in 188 788 person-years of follow-up	Not specified	iCRC: 12 vs. 25	Macroscopic appearance (5 depressed, 2 flat)
Matsuda et al (2009) Japan	<36 months	Observational, cohort study, NPS; 5309 patients patients	Incidence of advanced neoplasms after CS: 13 iCRCs within 3 years	iCRC: 12 vs. 1	iCRC: 5 vs. 8	Macroscopic appearance (5 depressed, 2 flat)
Kahi et al (2009) USA	Not defined	Retrospective. screening cohort of 715 patients vs. SEER data	5 screen detected; 7 iCRCs in 10 492 person-years follow-up	Screen detected 5 vs.0 iCRC: 4 vs. 3	Screen detected 2 vs. 3 iCRC: 6 vs. 1	N/A
Lieberman et al (2007) USA	<5 years after screening colonoscopy	Prospective. 3121 screenees	1.7 per 1000 person years follow-up	iCRC: 10 vs. 4	iCRC: 7 vs. 7	N/A

ADR, adenoma detection rate; CRC, colorectal cancer; CS, colonoscopy; iCRC, interval CRC; N/A, not applicable; NPS, National Polyp Study; SEER, Surveillance, Epidemiology and End Results.

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Table 2.3.4 Overview of studies on interval CRCs after colonoscopy in a mix of symptomatic and asymptomatic populations, showing that variation in the definitions used for an interval CRC influences the estimated rates

Studies	Definition iCRC	Design	Outcomes	Stage of CRC (I–II vs. III–IV)	Location of CRC (proximal vs. distal)	Risk factors/ possible aetiology
Corley *et al* (2014) USA	6 months-10 years after colonoscopy	Retrospective, population-based, 314 872 colonoscopies 712 patients with iCRC	712 iCRC in 927 523 person-years follow-up; 8.2% of all CRCs were iCRCs	iCRCs: 457 vs. 255	iCRC: 427 vs. 267 (18 unknown)	Inverse association between ADR and risk of iCRC, advanced iCRC
Erichsen *et al* (2013) Denmark	1–5 years	Retrospective, 982 patients with iCRC vs. 358 patients with colonoscopy >10 years vs.35 704 patients with sporadic CRCs	982/38 064=2.6% iCRCs	Sporadic CRC: 12 995 vs. 17 982 iCRC: 377 vs. 414	Sporadic CRC: 9782 vs. 23 979 iCRC: 441 vs. 433	Predictors of iCRCs
le Clercq *et al* (2013) The Netherlands	<5 years	Retrospective, population-based, 5107 patients with CRC	147/5107=2.9% iCRCs	Sporadic CRC: 2499 vs. 2531 iCRC: 79 vs. 63	Sporadic CRC: 1634 vs. 3522 iCRC: 87 vs. 59	Predictors of iCRCs
Cooper *et al* (2012) USA	6–36 months	Retrospective. SEER-Medicare database with 57 839 CRC patients	7.2% had prior colo 53.647 detected CRC 4192 iCRCs	Screen detected: 29 172 vs. 18 778 iCRCs: 2444 vs. 1291	Screen detected: 25 870 vs. 17 921 iCRC: 2851 vs. 819	N/A
Huang *et al* (2012) China	<5 years	1764 patients with adenomas under surveillance	14/1794 iCRCs=0.78% =2.9 cases per 1000 person-years follow-up	iCRCs: 9 vs. 4	iCRC: 11 vs. 3	Possible aetiology
Horiuchi *et al* (2011)	<5 years after negative	Prospective cohort of	9 iCRCs within 5 years	iCRC: 7 vs. 2	iCRC: 6 vs. 3	N/A

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Studies	Definition iCRC	Design	Outcomes	Stage of CRC (I–II vs. III–IV)	Location of CRC (proximal vs. distal)	Risk factors/ possible aetiology
Japan	colo	3212 patients with negative CS				
Baxter *et al* (2011) Canada	7–36 months	Observational study of 14 064 CRC patients	Incidence iCRC: 9.0% of all diagnosed CRCs	Not specified	iCRC: 676 vs. 584	N/A
Leung et al (2010) USA	Average 41 months; range 11–83 months	Prospective. Continued follow-up study (PPT)	9 CRCs over 7626 person-years observation (1.2/1000)	iCRC: 7 vs. 2	iCRC: 8 vs. 1	Risk factors and possible aetiology
Ferrández et al (2010) Spain	<36 months	Retrospective. 16.866 colonoscopy reports	386 CRC patients of whom 27 (7.0%) had prior CS	Not specified	iCRC: 6 vs. 21	N/A
Singh *et al* (2010) Canada	6–36 months	Population based study of 4883 CRC patients	Incidence iCRC: 7.9% (n=388)	iCRC 70 vs. 67	iCRC: 225 vs. 147	Risk factors
Lakoff *et al* (2008) Canada	>6 months	110 402 patients with negative colonoscopy; 14 year follow-up Control: general population	1.3% (n=1461) of cohort-patients develop CRC vs. 2.2% of controls	Not specified	Controls: 19 056 vs 33 195 iCRC: 610 vs. 443	N/A
Imperiale *et al* (2008) USA	<5 years	2436 with negative CS, 5-year follow-up	No iCRCs diagnosed	N/A	N/A	N/A
Bressler *et al* (2007) Canada	6–36 months	Retrospective. Claims-based administrative data; 31 074 CRC patients	12 487 had prior colo Detected: 12 057 New/missed: 3.4% (n=430)	Not specified	Detected: 3827 vs. 8422 New/missed: 238 vs. 192	Risk factors

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Studies	Definition iCRC	Design	Outcomes	Stage of CRC (I–II vs. III–IV)	Location of CRC (proximal vs. distal)	Risk factors/ possible aetiology
Farrar *et al* (2006) USA	<5 years	Retrospective. 830 CRC patients; 45 iCRCs vs. 90 sporadic CRCs	iCRC incidence: 5.4% of all diagnosed CRCs	Sporadic: 52 vs. 38 iCRC: 30 vs. 15	Sporadic: 26 vs. 64 iCRC: 23 vs. 22	Possible aetiology
Pabby *et al* (2005) USA	CRC detected during surveillance at year 1 or year 4	Prospective; 2079 patients with 5810 person-years of observation (PPT)	13 iCRC cases (2.2/ 1000 person-years observation)	iCRC: 8 vs. 5	iCRC: 7 vs. 6	Possible aetiology
Robertson *et al* (2005) USA	Any cancer diagnosed after a clearing colonoscopy	Prospective; 2915 patients, mean follow-up: 3.7 years (3 chemoprevention trials)	19 CRCs in 2915; 1.74/ 1000	iCRC 16 vs. 3	iCRC 10 vs. 9	Possible aetiology
Leaper *et al* (2004) New Zealand	>6 weeks	Retrospective; patients undergoing CS	17 of 286 (5.9%) were missed by CS	iCRC: 10 vs. 7	iCRC 13 vs. 4	Possible aetiology

ADR, adenoma detection rate; CRC, colorectal cancer; CS, colonoscopy; iCRC, interval CRC; PPT, Polyp Prevention Trial; N/A, not applicable.

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Table 2.3.5 Interval cancer rates of the whole cohort and subjects with negative colonoscopy

	IC rate per 1000 PY of observation (95% CI)	
	Whole cohort	Subjects with negative colonoscopy
Fecal hemoglobin concentration (μg Hb/g feces)		
20-49	0.73 (0.51 to 0.95)	0.60 (0.36 to 0.84)
50-99	1.03 (0.67 to 1.39)	0.89 (0.48 to 1.30)
100-149	1.79 (1.04 to 2.54)	1.38 (0.56 to 2.20)
≥150	1.85 (1.39 to 2.31)	1.56 (1.04 to 2.08)

IC: interval cancer; PY: person-year

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Table 2.3.6 Association of f-HbC concentration and risk of interval cancer

	Whole cohort		Subjects with negative colonoscopy	
	Crude RR	Adjusted RR* (95% CI)	Crude RR (95%CI)	Adjusted RR* (95% CI)
Fecal hemoglobin concentration (μg Hb/g feces)				
20-49	1.00	1.00	1.00	1.00
50-99	1.41(0.88-2.24)	1.48(0.93-2.37)	0.89 (0.48 to 1.30)	1.58(0.85-2.92)
100-149	2.45(1.46-4.11)	2.55(1.52-4.29)	1.38 (0.56 to 2.20)	2.45(1.20-5.02)
≥150	2.54(1.33-5.01)	2.74(1.84-4.09)	1.56 (1.04 to 2.08)	2.88(1.70-4.90)

Adjusted with age, gender, adenoma detection rate of setting, Index colonoscopy findings

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Table 2.3.7 Molecular Characteristics of Interval CRCs

Study	Interval CRC ratea	Molecular characteristic	Interval CRCsa	Noninterval CRCsb	OR (95% CI)
Sawhney et al	5.1% (51/993)	MSI	30.4% (14/46)	10.3% (10/97)	3.70 (1.50–9.10)
Arain et al	4.8% (63/1323)c	CIMP	57.0% (31/54)	33.0% (33/100)	2.41 (1.20–4.90)
Shaukat et al	4.8% (63/1323)c	BRAF	28.0% (15/54)	19.0% (21/110)	0.93 (0.36–2.38)
Shaukat et al	4.8% (63/1323)c	KRAS	12.9% (7/54)	28.9% (31/107)	0.36 (0.15–0.90)

CIMP, CpG island methylator phenotype; MSI, microsatellite instability.

[a]Interval CRC was defined as CRC within 5 years of a complete colonoscopy.

[b]Matched 1:2 by age and sex to patients with interval cancers.

[c]Analyses were performed on the same case series.

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Table 2.5.1 Characteristics of Studies of Colorectal Cancer Screening Using the gFOBT

gFOBT	Year	Country	gFOBT	Screening Frequency	Age range (yr)	Length of follow up (yr)	No. of Screening Rounds	FOBT IC		FOBT IC + colonoscopy IC + IC after non-referral for colonoscopy		FOBT refuser		Controls	
								No. of cancer	Person years	No. of cancer	Person years	No. of cancer	Person years	No. of cancer	Person years
Mandel et al. (I)	1993	U.S	Haemoccult	Annual	50-80	13	11			146	166112			356	181966
Mandel et al. (II)	1993	U.S	Haemoccult	Biennial	50-80	13	6			178	165356			356	181966
Kewenter et al.	1994	Sweden	Hemoccult II	Biennial	60-64	15.5	-	19	-	21	-	15	-	128	239148
Kronborg et al	1996	Denmark	Haemoccult	Biennial	45-75	17	9	232	298157	239	302596	306	128594	874	430755
Hardcastle et al	1996	U.K.	Haemoccult	Biennial	45-74	11.7	6	236	356172	249	356273	400	241671	856	596369
Zappa et al.	2001	Italy	Hemoccult II	Biennial	50-70	6	2			47	65723	-	-	94	65723
Faivre et al.	2004	France	Haemoccult	Biennial	45-74	11	6	219	263780	230	267756	218	216064	696	477773
Malila et al.	2008	Finland	Haemoccult	Biennial	60-64	3	2	32	69951	35	71344	26	28987	98	100475
Steele et al.	2009	UK	Hema-screen	Biennial	50-69	7	3	635	983301	756	1014690	525	849206	92.7	100000
Denters et al.	2012	Netherland	Hemoccult II	Biennial	50-74	2	1	6867	3713	4	4238	-	-	-	-

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Table 2.5.2 Characteristics of Studies of Colorectal Cancer Screening Using the FIT

Study	Year	Country	FIT	Screening Frequency	Age range (yr)	Length of follow up (yr)	No. of Screening Rounds	Test negative		Episode negative		Non-responders		Controls	
								No. of cancer	Person years	No. of cancer	Person years	No. of cancer	Person years	No. of cancer	Person years
Itoh et al.	1996	Japan	OC-HEMODIA	Biennial	≥40	2	1	-	-	12	52740	-	-	-	-
Zappa et al.	2011	Italy	OC-SENSOR	Biennial	50-69	6	-	102	465159	126	468306	121	100000	571	468306
Denters et al.	2012	Netherland	OC-SENSOR	Biennial	50-74	3	2	6	5742	-	-	-	-	-	-
Jensen et al	2016	U.S	OC FIT-CHEK	Annual	50-69	4	4	242	2566236	-	-	-	-	-	-
Digby et al	2016	Scotland	OC-SENSOR	Biennial	50–74	2	1	31	60280			-	-	-	-
Portillo et al	2017	Spain	OC-SENSOR	Biennial	50-69	7	-	186	-	204	-	-	-	-	-
van der Vlugt et al	2017	Netherland	OC-SENSOR	Biennial	50–76	8.5	3	27	-	36	-	109	-	72612	-
Chiu et al.	2019	Taiwan	OC-SENSOR HM-JACK	Biennial	50-69	5	-	1835	11642875	3474	12195094	30295	30823001	38544	43018095

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Table 4.1 The measurement errors under the context of population-based CRC screening program with FIT

FIT result	Referral	Colonoscopy result	Detection Mode
+ (S_f)	+ (C)	+ (S_c)	Prevalent screen-detected, Subsequent screen-detected
		− (1-S_c)	Interval cancer (colonoscopy)
	− (1-C)	X	Interval cancer (non-referral)
− (1-S_f)	X	X	Interval cancer (FIT)

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Table 5.1.1 Meta-analysis of Test sensitivity, episode sensitivity, and program sensitivity in gFOBT-base screening studies

gFOBT	Attendance rate	Test Sensitivity	95%CI	Episode Sensitivity	95%CI	Program Sensitivity	95%CI
Kronborg et al	0.67	60.70%	55.8%-65.7%	60.1%	55.2%-65.1%	51.7%	47.1%-56.3%
Hardcastle et al	0.60	48.50%	38.3%-58.9%	45.7%	35.5%-56%	24.6%	17.1%-32.2%
Faivre et al.	0.55	54.50%	47.8%-61.1%	52.9%	46.2%-59.5%	36.4%	30.8%-41.9%
Malila et al.	0.71	54.60%	32.6%-76.6%	51.3%	29.4%-73.3%	37.5%	18.8%-56.3%
Steele et al.	0.54	45.50%	41.5%-49.6%	39.6%	35.6%-43.7%	27.5%	24.2%-30.9%
Pool		52.5%	51.2%-53.8%	49.6%	48.3%-50.9%	33.3%	32.0%-34.5%

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Table 5.1.2. Meta-analysis of Test sensitivity, episode sensitivity, and program sensitivity in FIT-base screening studies

FIT	Attendance rate	Test Sensitivity	95%CI	Episode Sensitivity	95%CI	Program Sensitivity	95%CI
Zappa et al.	0.67	81.9%	77.1%-86.0%	77.9%	72.2%-82.5%	52.3%	44.3%-59.5%
Chiu et al.	0.57	80.9%	80.0%-81.9%	65.7%	64.3%-67.0%	34.4%	33.4%-35.4%
Pool		80.9%	80.0%-81.7%	65.7%	64.6%-67.3%	34.7%	33.7%-35.7%

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Table 5.2.1 Demographic characteristics of screening population

Detection mode	Total (frequency (%))	Sex (frequency (%))		Age group (frequency, %)	
		Female	Male	50≤age≤59	60≤age≤69
Prevalent screen					
Free of CRC	3,059,522 (99.6)	1,690,773 (99.8)	1,368,749 (99.5)	1,791,002 (99.7)	1,268,520 (99.5)
Screening detected CRC	10,989 (0.36)	4,115 (0.24)	6,874 (0.50)	4,570 (0.25)	6,419 (0.50)
Subsequent screen					
Free of CRC	1,601,315 (99.2)	977,052 (99.4)	624,263 (98.9)	1,067,693 (99.4)	533,622 (98.7)
Screening detected CRC	3,128 (0.19)	1,439 (0.15)	1,689 (0.27)	1,688 (0.16)	1,440 (0.27)
Interval CRC	9,641 (0.60)	4,137 (0.42)	5,504 (0.87)	4,325 (0.40)	5,316 (0.98)

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Table 5.2.2 Estimated results of applying the generalized non-linear regression model for CRC revolution with FIT incorporating measurement error and the effect of covariates

	Estimate	95% CI	HR	95% CI
Model without the effect of covariates				
Incidence rate of PCDP				
$\lambda_1(\times 10^4)$	15.1	(14.7, 15.5)		
Progress rate of PCDP				
λ_2	0.36	(0.34, 0.38)		
Sensitivity				
α	1.12	(0.99, 1.25)		
Incorporating the effect of covariates				
Incidence rate of PCDP				
$\lambda_1(\times 10^4)$	9.01	(8.70, 9.33)		
β_{21} (male)	0.56	(0.52, 0.60)	1.75	(1.68, 1.82)
β_{22} (Age $\geq$ 60)	0.58	(0.55, 0.62)	1.79	(1.73, 1.86)
Progress rate of PCDP				
λ_2	0.38	(0.36, 0.41)		
β_{21} (male)	-0.20	(-0.27, -0.14)	0.82	(0.77, 0.87)
β_{22} (Age $\geq$ 60)	-0.09	(-0.15, -0.03)	0.91	(0.86, 0.97)
Sensitivity				
α	1.31	(1.12, 1.51)		
β_{S1} (male)	-0.18	(-0.39, 0.03)	0.84	(0.68, 1.03)
β_{S2} (Age $\geq$ 60)	-0.27	(-0.46, -0.09)	0.76	(0.63, 0.92)

Model: $Incidence\ rate\ of\ PCDP = \lambda_1\ exp\{\beta_{11} sex + \beta_{12} age\ group\}$

$Progress\ rate\ of\ PCDP = \lambda_2\ exp\{\beta_{21} sex + \beta_{22} age\ group\}$

*Sensitivity=exp(α+β_{s1}*sex+β_{s2}*age group)/(1+exp(α+β_{s1}*sex+β_{s2}*age group))*

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Table 5.2.3 Estimated results on age and sex specific incidence rate, progression rate, and sensitivity

Population	Incidence rate (per year) (95% CI)	Progression rate (per year) (95% CI)	Dwelling time (years) (95% CI)	Sensitivity (95% CI)
Total	0.00151 (0.00147-0.00155)	0.36 (0.34-0.38)	2.78 (2.63-2.94)	75.47% (72.99%-77.80%)
Male, 50≤age≤59	0.00158 (0.00102-0.00213)	0.31 (0.30-0.33)	3.18 (3.03-3.33)	75.61% (72.57%-78.61%)
Male, 60≤age≤69	0.00283 (0.00184-0.00382)	0.29 (0.27-0.30)	3.49 (3.33-3.70)	70.24% (67.94%-72.53%)
Female 50≤age≤59	0.00090 (0.00058-00121)	0.38 (0.36-0.41)	2.60 (2.44-2.78)	78.73% (75.44%-81.99%)
Female, 60≤age≤69	0.00161 (0.00105-0.00121)	0.35 (0.33-0.38)	2.85 (2.63-3.03)	73.79% (69.79%-77.70%)

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Table 5.2.4 Estimated results of applying the Bayesian directed acyclic graphic model for CRC revolution with FIT incorporating measurement error

	Estimate	95% CI
Full data, 2004-2014		
Incidence rate of PCDP		
$\lambda_1(\times 10^4)$	15.1	(15.0, 15.2)
Progress rate of PCDP		
λ_2	0.32	(0.31, 0.32)
Sensitivity		
α	1.08	(1.00, 1.15)
Later period Data, 2010-2014 with prior period information (2004-2009)		
Incidence rate of PCDP		
$\lambda_1(\times 10^4)$	14.9	(14.7, 15.0)
Progress rate of PCDP		
λ_2	0.27	(0.26, 0.28)
Sensitivity($=exp(\alpha)/(1+exp(\alpha))$		
α	0.94	(0.86, 1.02)

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Table 5.3.1 Estimated results on the generalized non-linear joint measurement error model

	Estimate	95% CI
Incidence of asymptomatic CRC	9.27×10^{-5}	9.16×10^{-5} - 9.39×10^{-5}
Progression from asymptomatic to symptomatic CRC	0.2899	0.2885-0.2913
Sensitivity of FIT	71.9%	71.0%-72.8%
Sensitivity of colonoscopy	93.6%	91.9%-94.9

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Table 5.4.1 Demographics of the study cohort for CRC survival in screening participants

	Screen-detected CRC, n (%)		IC, n (%)		CRC in colonoscopy noncompliers, n (%)	Total, n (%)
	Prevalent screening	Subsequent screening	Colonoscopy IC	FIT IC		
Age at diagnosis						
50–59	1,950 (46.8)	443 (32.8)	77 (26.8)	699 (38.1)	503 (37.2)	3,672 (40.8)
≧60	2,219 (53.2)	906 (67.2)	210 (73.2)	1,136 (61.9)	849 (62.8)	5,320 (59.2)
Sex						
Male	2,504 (60.1)	639(47.4)	156 (54.4)	903 (49.2)	739 (54.7)	4,941 (55.0)
Female	1,665 (39.9)	710 (52.6)	131 (45.6)	932 (50.8)	613 (45.3)	4,051 (45.0)

FIT: fecal immunochemical test; CRC: colorectal cancer; IC: interval cancer.

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Table 5.4.2 Treatment that administrated for CRCs with different detection modes

	Surgery n (%)	Systemic therapy n (%)	Radiotherapy n (%)
Prevalent screen-detected CRC	3283(78.8)	1982 (47.5)	428 (10.3)
Subsequent screen-detected CRC	1072 (79.5)	620 (46.0)	123 (9.1)
Colonoscopy IC	220 (76.7)	161(56.1)	29 (10.1)
FIT IC	1294 (70.5)	935 (50.9)	255 (13.9)
CRC in colonoscopy noncompliers	1017 (75.2)	729 (53.9)	147 (10.9)

Treatment information was available for 8,484 (94.4%) among 8,992 CRCs.

Systemic therapy: Includes chemotherapy and/or target therapy

FIT: fecal immunochemical test; CRC: colorectal cancer; IC: interval cancer.

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Table 5.4.3 Number and survival status among CRCs with different detection modes

Detection mode	Screen-detected CRC		IC		CRC in colonoscopy noncompliers, n (%)	CRC in screening nonparticipants, n(%)
	Prevalent screening, n (%)	Subsequent screening, n (%)	Colonoscopy IC, n (%)	FIT IC, n (%)		
Survivors	3,531 (84.7)	1,193 (88.4)	223 (77.7)	1,316 (71.7)	982 (72.6)	19399(55.6)
CRC deaths	635 (15.3)	156 (11.6)	64 (22.3)	519 (28.3)	370 (27.4)	15478(44.4)
5 years survival rate	85.7%	88.5%	79.3%	72.3%	73.8%	59.2%

FIT: fecal immunochemical test; CRC: colorectal cancer; IC: interval cancer.

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Table 5.4.4 Risk of CRC death in relation to different detection modes

Detection mode	Univariable		Multivariable			
			Model 1		Model 2	
	HR	95% CI	aHR	95% CI	aHR	95% CI
Subsequent screen-detected CRC	0.21	(0.18-0.25)	0.22	(0.19-0.26)	0.32	(0.27-0.38)
Prevalent screen-detected CRC	0.28	(0.26-0.30)	0.30	(0.27-0.33)	0.40	(0.36-0.44)
Colonoscopy IC	0.43	(0.34–0.55)	0.42	(0.32-0.54)	0.53	(0.41-0.69)
FIT IC	0.57	(0.52–0.62)	0.57	(0.52–0.64)	0.64	(0.57-0.71)
CRC in colonoscopy noncompliers	0.57	(0.51-0.63)	0.56	(0.50-0.64)	0.67	(0.59-0.76)
CRC in screening nonparticipants	1	-	1	-	1	-

HR: hazard ratio; aHR: adjusted hazard ratio; FIT: fecal immunochemical test; CRC: colorectal cancer; IC: interval cancer; Model 1: adjusted for age, sex, location, and treatment; Model 2: adjusted for age, sex, location, treatment, and cancer stage.

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Table 5.4.5 Comparison of the risk of CRC death between FIT and colonoscopy ICs

Detection mode	Univariable		Multivariable			
			Model 1		Model 2	
	HR	95% CI	aHR	95% CI	aHR	95% CI
Colonoscopy IC	1	-	1	-	1	-
FIT IC	1.31	(1.01–1.70)	1.42	(1.09–1.85)	1.22	(0.93–1.59)

HR: hazard ratio; aHR: adjusted hazard ratio; FIT: fecal immunochemical test; CRC: colorectal cancer; IC: interval cancer; Model 1: adjusted for age, sex, location, and treatment; Model 2: adjusted for age, sex, location, treatment, and cancer stage.

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Table 5.4.6 Estimated results of Cox models with lead-time and truncation adjustment

	Univariable analysis			Univariable analysis with lead-time and truncation adjustment			Multivariable analysis* with lead-time and truncation adjustment		
	HR	**95% C.I.**		**HR**	**95% C.I.**		**HR**	**95% C.I.**	
CRC in screening participants	0.37	0.35	0.39	0.51	0.49	0.54	0.56	0.54	0.59
CRC in screening nonparticipants	1.00	-	-	1.00	-	-	1.00	-	-

*Adjusted for age, sex, location, and treatment

CRC in screening participants included prevalent, subsequent screening detected CRC, colonoscopy IC, FIT IC, and CRC in colonoscopy noncompliers.

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Table 5.4.7 Estimated results of Cox models with lead-time and truncation adjustment for different detection modes (I)

	Univariable analysis			Univariable analysis with lead-time and truncation adjustment			Multivariable analysis* with lead-time and truncation adjustment		
	HR	**95% C.I.**		**HR**	**95% C.I.**		**HR**	**95% C.I.**	
Screen-detected CRC	0.26	0.24	0.28	0.43	0.40	0.46	0.48	0.45	0.52
Colonoscopy IC	0.43	0.33	0.55	0.46	0.36	0.59	0.48	0.38	0.62
FIT IC	0.57	0.52	0.62	0.61	0.56	0.66	0.65	0.60	0.72
CRC in colonoscopy noncompliers	0.57	0.51	0.63	0.61	0.55	0.67	0.64	0.58	0.72
CRC in screening nonparticipants	1.00	-	-	1.00	-	-	1.00	-	-

*Adjusted for age, sex, location, and treatment

Screen-detected CRC included prevalent and subsequent screening detected CRC

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Table 5.4.8 Estimated results of Cox models with lead-time and truncation adjustment for different detection modes (II)

	Univariable analysis			Univariable analysis with lead-time and truncation adjustment			Multivariable analysis* with lead-time and truncation adjustment		
	HR	**95% C.I.**		**HR**	**95% C.I.**		**HR**	**95% C.I.**	
Subsequent screen-detected CRC	0.21	0.18	0.25	0.23	0.19	0.27	0.25	0.22	0.30
Prevalent screen-detected CRC	0.28	0.26	0.30	0.56	0.52	0.61	0.63	0.58	0.69
Colonoscopy IC	0.43	0.34	0.55	0.46	0.36	0.59	0.48	0.38	0.62
FIT IC	0.57	0.52	0.62	0.61	0.56	0.67	0.65	0.60	0.72
CRC in colonoscopy noncompliers	0.57	0.51	0.63	0.61	0.55	0.67	0.64	0.58	0.72
CRC in nonparticipants	1.00	-	-	1.00	-	-	1.00	-	-

*Adjusted for age, sex, location, treatment

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