Evaluation of a Selective Screening for Colorectal Carcinoma

The Taiwan Multicenter Cancer Screening (TAMCAS) Project

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BACKGROUND. Although the efficacy of mass screening for colorectal carcinoma (CRC) with a fecal occult blood test has been demonstrated in several randomized trials, a mass screening approach used in countries with intermediate or low incidence of CRC might be costly. Screening high risk people may be an alternative approach, to aid in the prevention of death from CRC. However, the efficacy of CRC screening for high risk people in such countries is uncertain.

METHODS. For this study, a multicenter design was devised to identify high risk groups without clinical symptoms related to CRC; these subjects were identified through the study of index cases of CRC in Taiwan. Colonoscopy, in combination with a fecal occult blood test or double-contrast barium enema, was used to screen high risk groups. A total of 8909 subjects were invited to attend screening. Of 8909, 81 with asymptomatic CRC were detected in one-shot screening. Markov models, in conjunction with a simulated approach, were proposed to estimate relevant parameters in relation to disease progression and to assess the effect of the interval between screenings on the efficacy of CRC screening for these high risk groups.

RESULTS. The estimated preclinical incidence rate was 0.00396 (95% confidence interval [CI], 0.002944–0.004985), which was 21 times that reported from a cancer registry in 1994. The simultaneous estimations of mean sojourn time (the average duration between the preclinical screen-detectable phase and the clinical phase) and sensitivity were 2.8 years (95% CI, 2.15–4.30) and 95.0% (95% CI, 24.4–99.9%), respectively. Predictions of mortality reduction for people who received annual, biennial, and triennial screening regimes compared with controls were 26% (95% CI, 0–50%), 23% (95% CI, 0–48%), and 21% (95% CI, 0–47%), respectively.

CONCLUSIONS. The efficacy of selective colorectal carcinoma screening has been demonstrated in this study. A high preclinical CRC incidence rate also suggests that such a screening strategy might be cost-effective for countries with intermediate or low incidence of CRC. Methods proposed in this study can be used to evaluate the efficacy of CRC screening in similar screening trials. ***Cancer* 1999;86:1116–28.**

KEYWORDS: colorectal carcinoma screening, selective multicenter screening, Markov model, high risk people.

Mass screening with the fecal occult blood test (FOBT) has been demonstrated to reduce mortality from colorectal carcinoma (CRC) by 15% (95% confidence interval [CI], 2–26%) in the Nottingham trial,[1] by 18% (95% CI, 1–32%) in a Danish trial,[2] and by 33% (95% CI, 13–50%) in a Minnesota trial[3] (annual screening vs. control group). However, in countries with intermediate or low incidence of CRC, it is questionable whether mass screening is appropriate. For

such countries, an alternative strategy based on selective screening of individuals at high risk of CRC is proposed.

Although CRC screening has been demonstrated to be effective in mass screening, the efficacy of screening for high risk groups is still unclear. Several small studies have reported the yield of screening colonoscopy for asymptomatic patients with a positive family history.[4–12] However, there were no definite results regarding the efficacy of colonoscopy screening for patients with a positive family history. This is partly because these studies were based on small sample sizes and partly because the study designs of several studies were based on retrospective surveys, which raises the question of whether patients identified in these studies were asymptomatic. A meta-analysis based on the above studies[13] also showed that there was not a substantial difference in the prevalence of adenoma and CRC between colonoscopy screening for high risk and average risk groups. Accordingly, the efficacy of colonoscopy screening for subjects with a positive family history may be questioned. In addition, in groups more susceptible to the occurrence of polyps and CRC than the general population, more intensive screening has been recommended and colonoscopy has been advocated as a screening tool.[14] However, results of the effectiveness of such screening policies have not been conclusive. Using colonoscopy, Luchtefeld et al.[8] found no significant difference in the occurrence of polyps in a group of asymptomatic individuals with relatives who had a history of CRC and a control group. However, the results were based on a small sample size, and strict criteria were used to select the asymptomatic patients. Only asymptomatic patients with a family history of CRC in one or two first-degree relatives were included. Patients were excluded if they had undergone barium enema or colonoscopy within 5 years or had a genetic disorder such as familial polyposis, Gardner syndrome, or hereditary nonpolyposis CRC.

Eddy et al. used a simulated model to demonstrate a positive result of the efficacy of screening for CRC on mortality from CRC in a high risk group ("high risk" meant having a first-degree relative with CRC).[15] However, because the parameters used for their simulation model were estimated from expert opinions (72 physicians) rather than directly from empiric data, results from their study are hypothetical. Ron,[16] in a screening project involving high risk subjects in Israel, found that subjects who had a family history of CRC were three times likely to develop the disease compared with those who did not have a family history. There was a significant increasing trend for the relation between the risk for colorectal neoplasm and number of relatives with CRC. It was also found that screening for these high risk subjects might detect CRC at an early stage. However, as the efficacy of CRC screening for these high risk subjects was not addressed in this study, it is still inconclusive whether the efficacy of CRC screening for high risk subjects is worthwhile.

It is well known that the efficacy of colorectal screening in reducing CRC mortality is highly dependent on the screening tool used; the compliance to the screening regimen; the natural history of the disease, particularly the rate at which tumors progress from preclinical to clinical disease; and the interscreening interval. For example, the success of CRC screening might be highly dependent on the screening test detecting CRC in the preclinical screen-detectable phase (PCDP). The duration between the PCDP and the clinical phase, usually called sojourn time, plays an important role in the optimal screening interval. Subjects at high risk may have a shorter sojourn time than the general population. If this is so, the optimal screening interval for the general population might be too long for high risk subjects.

As in the case of mass screening for the general population, the best way to evaluate the efficacy of screening and other subsidiary issues is through the use of randomized controlled trials. However, randomized trials are not without limitations. They usually require a large number of subjects followed for many years in order to achieve sufficient statistical power. Hence, time and cost frequently preclude them. Moreover, in the case of selective screening, a randomized trial is more likely to raise an ethical issue than a nonrandomized study. Given limited resources, a nonrandomized service program rather than a randomized trial may be considered for developing countries. It should be noted that evaluation of the efficacy of a service screening program for CRC is not straightforward. Unlike a randomized trial, there is no comparison group of people who are not invited to screening. Moreover, to assess the efficacy of screening using a primary endpoint (e.g., mortality) would require a long follow-up period. Therefore, it is necessary to apply methods to predict the efficacy of screening at an early stage, taking into account the natural disease history of CRC and the validity of the screening tool.

To develop some understanding of the natural history of CRC and to be able to predict the effectiveness of selective screening for CRC, one could either calculate some early indicators, such as the ratio of prevalence (the observed number of cancers detected at screening) to expected incidence (P/I ratio) and the interval cancer rate as a percentage of the expected incidence rate (I/E ratio). Alternatively, one could use

a stochastic process to estimate the transition rates through stages of the natural disease history (i.e., CRC free, preclinical CRC, clinical CRC, and death from CRC). From these, an estimate of the mean sojourn time (the duration of the preclinical screen detected phase, PCDP), the sensitivity of the screening tool, and the hazard rate of death from CRC could be obtained.

The sojourn time plays an important role not only in the efficacy of screening but in the determination of an optimal screening interval. The longer the sojourn time, the more lead time (the time of advancing early diagnosis) would be gained and the more benefit would be achieved via screening. The shorter the sojourn time, the more intensive the required screening, and vice versa. Estimation of mean sojourn time becomes important and can be made by using the P/I ratio or a stochastic model, as was done in this study. The program sensitivity is another factor affecting the efficacy of screening. The low value of this parameter suggests a considerable proportion of false-negative cases, which may discount the benefit of screening. Estimation of this parameter includes the traditional method, which assumes all interval cancers (cancers diagnosed between screenings) as false-negative cases, the I/E ratio of time since negative screening, and the stochastic process, taking sojourn time into account. The traditional method and the I/E ratio have long been criticized as being unable to distinguish new interval cases (cases diagnosed between screenings) from false-negative cases. For example, the high I/E ratio may be in part due to false-negative cases caused by poor sensitivity and in part due to the occurrence of new cases because of short sojourn time. Implications for two circumstances in the context of screening are different. If the sensitivity is poor, the quality of screening should be improved, whereas if the sojourn time is short, an intensive screening interval would be required. Because sojourn time may be highly correlated with the program sensitivity, simultaneous estimation of two parameters through the use of a stochastic model seems necessary.

For early indicators, I/E ratio for time since last negative screening was calculated for the published randomized trials. For the Nottingham trial,[1] the I/E ratios for 1 year and 2 years since last negative screening were 39.7% and 40.0%, respectively. This might suggest that the interval cancers include a proportion of false-negative cases. Using the traditional method to estimate sensitivity (whereby all interval cancers within x years of the last negative screening are assumed to be false-negative cases) gives 74.7%, 59.4%, and 55.3% for 1 year, 2 years, and 3 years since last negative screening, respectively. Another method for estimating sensitivity is to calculate (1-I/E). Calculation of this ratio results in estimates of 60.3%, 60.6%, and 69.4% for 1 year, 2 years, and 3 years since the last negative screening, respectively. Similar results were found in the Danish trial[2] (I/E = 49.6%, sensitivity = 50.4%, 2 years since the last negative screening). These results suggest that a greater benefit of FOBT screening would be achieved if the quality of FOBT could be improved or more intensive screening was performed.

In addition to these empiric early indicators of efficacy, a Markov model could be used to estimate relevant transition parameters and then to predict the efficacy of selective screening for CRC. Although the Markov chain model is sophisticated and requires the assumption of exponential distribution as a result of the Markov property, there are still several merits in employing Markov models. First, this method can be used to estimate an occult transition based only on states that are observable by the different detection modes. For instance, the transition from the PCDP to the clinical phase is usually occult but can be estimated using screen-detected cases and interval cancers. Second, the dependence between different transition rates can be considered. For example, CRC with a rapid progression from the PCDP to the clinical phase might lead to an increased risk of death from CRC. Third, it is relatively straightforward to estimate the effect of the interval between screenings on mortality using the estimated transition parameters.

Recently, a multicenter design for CRC screening of subjects at high risk for CRC (as defined below) was implemented in Taiwan. It is desirable to determine the efficacy of a selective screening approach in order to assess whether it is worthwhile screening high-risk subjects for CRC using this approach.

Accordingly, this article has two main aims. The first is to provide descriptive results of the Taiwan Multicenter Cancer Screening (TAMCAS) study, and in particular to do the following:

1. Estimate age specific and gender specific colorectal neoplasm prevalence rates by different high risk groups;
2. Estimate early indicators, such as P/I ratio and I/E ratio, in order to assess the efficacy of selective screening for CRC.

The second is to apply Markov models to data from the TAMCAS study in order to construct the disease natural history, and in particular to do the following:

3. Estimate age specific and gender specific preclinical incidence rates for CRC;
4. Estimate age specific and gender specific mean

TABLE 1
The Numbers of Attendants of First Screening and Repeat Screening by Different High Risk Groups, TAMCAS Project

	Family history		Disease history					
	CRC	≥2 first-degree relatives with cancers	Inflammatory bowel disease	Thyroid or breast carcinoma	Neoplasm[a]	Any combination of A, B, C, D		
	(A)	(B)	(C)	(D)	(E)	(F)	Unclassified	Total
No. attending first screening	3061	160	176	452	4489	173	398	8909
(% of first-screening exams)	(34.36)	(1.80)	(1.98)	(5.07)	(50.39)	(2.03)	(4.47)	(100)
No. of attending repeat screening	36	2	22	10	838	4	33	
(%) of first screening)	(1.18)	(1.25)	(12.5)	(2.21)	(18.67)	(2.31)	(8.29)	
Age-adjusted prevalence of CRC (%)								
Male	1.89	—	—	—	3.39	8.97		
Female	2.63	—	—	2.74	4.13	7.54		
Age-adjusted prevalence of adenoma (%)								
Male	25.59	24.41	9.07	20.58	37.64	29.68		
Female	17.21	24.64	7.98	11.58	28.33	24.70		

CRC: colorectal carcinoma.

[a] "Neoplasm" includes CRC and adenoma. Patients had CRC and underwent surgery 3 years previously (n = 2510) or had adenoma 1 year previously (n = 1979).

sojourn times (MST) and sensitivity simultaneously;
5. Estimate the hazard rates of death from CRC for preclinical and clinical CRC, allowing for other competing causes of death;
6. Predict the proportion of interval cancers for different screening frequencies based on the estimates from items 3 and 4 of this list;
7. Predict the effect of screening frequencies on mortality from CRC based on estimates from item 5.

Results from this study could also provide evidence of the efficacy of selective screening in other countries with intermediate or low CRC incidence.

MATERIALS AND METHODS

The TAMCAS for hepatocellular, colorectal, and breast carcinomas was launched by the Department of Health (DOH) in Taiwan in 1992. It is a hospital-based project that aims to identify early hepatocellular, colorectal, and breast carcinomas in individuals at high risk. There are 14–17 hospitals (including medical centers and regional hospitals) involved in the study. Subjects who met the criteria of the high risk group for each cancer were invited to screening between 1992 and 1997. For the CRC screening project, patients or relatives of patients without any clinical symptoms related to CRC were invited to screening if they met any of the following criteria for being at high risk:

1. First- or second-degree relatives of CRC case (high risk group A);
2. At least two first-degree relatives afflicted by any cancer (high risk group B);
3. Patients with familial polyposis or chronic ulceritis (high risk group C);
4. Thyroid or breast carcinoma patients (high risk group D);
5. Previous CRC treated with surgery at least 3 years ago or adenoma 1 year ago (high risk group E);
6. Any combination of 1, 2, 3, 4, and 5 (high risk group F).

The screening tool used in this study was colonoscopy in combination with FOBT or double-contrast barium enema. Subjects who showed signs of a focal mucosal lesion (i.e., morphologically suggestive for adenomas or cancers) after colonoscopy examination were defined as positive cases of adenoma or CRC. Biopsy was further performed to confirm diagnoses of adenoma or carcinoma. As regards FOBT or double-contrast barium enema, subjects who had positive reactions of chemical reagent or had a suspicious image were defined as positive cases. Biopsy was performed to ascertain diagnoses of adenoma or carcinoma. The positive predictive value (PPV) for the sole use of colonoscopy or the combination of colonoscopy with FOBT or double-air barium was calculated as the proportion of confirmed diagnosed cases among positive cases.

A total of 8909 subjects attended the first screening. Of 8909, only 945 subjects attended repeat screenings. Table 1 shows the number attending a first screening and repeat screening among attendants of

TABLE 2
Number of Cases by Detection Mode and Deaths from CRC or Other Causes

Detection mode	No. of cases
Prevalent screening	
CRC	81
Non-CRC	6318
Total	6399
Postscreening cases	
New cases	NK
False-negative cases	NK
Total	37
Preclinical → CRC death	6
Preclinical → OCD	3
CRC free → OCD	129

CRC: colorectal carcinoma; OCD: other causes of death.

the first screening in each of the high risk groups. The majority of subjects were in groups A (34%) and E (50%). Although we intended to invite all subjects to attend first and repeated screenings, few subjects attended the second screening. The very low rate of repeat screening may have be due to discomfort or inconvenience caused by the first colonoscopic examination. Accordingly, analysis of this study was limited to data from the first screening only. This provided an opportunity for evaluation of the efficacy of one-shot screening for CRC.

In order to estimate the MST and sensitivity, information on interval cancers was required. However, as most of the subjects only attended the first screening, there was no opportunity to identify interval cancers (cancers diagnosed between screenings) as used in other repeated screening projects.[1–2] We define cancers that arise after the first screening as postscreening cancers (PSCs). These cases are not equivalent to interval cancers as usual, but the clinical characteristics of both are similar because they are found due to the occurrence of clinical symptoms. To ascertain the cases of PSC, subjects in this study were matched to the cancer registry or records from the Bureau of National Health Insurance of Taiwan. Data in this study were also linked to the mortality registry to identify CRC deaths and deaths from other causes. It should be noted that patients with previous CRC treated with surgery at least 3 years previously (n = 2510) were excluded from the following Markov analysis, as we were only interested in estimating the preclinical incidence rate and other transition parameters for incident CRC. A total of 6399 subjects were included in our estimation of relevant parameters. Table 2 shows the number of asymptomatic CRCs detected

Let x_1 and x_2 denote age and gender, respectively, with the following definition:

$$x_1 = \begin{cases} 1 & \geq 50 \\ 0 & < 50 \end{cases}$$

$$x_2 = \begin{cases} 1 & \text{Male} \\ 0 & \text{Female} \end{cases}$$

In order to model preclinical incidence rate (λ_1) and the rate of transition (λ_2) from preclinical to clinical phase as a function of age and gender, the proportional hazards form is proposed to estimate relevant parameters, as follows:

$$\lambda_1 = K_0\left(R_{11}\, x_1 + R_{12}\, x_2\right)$$
$$\lambda_2 = m_0\left(R_{21} X_1 + R_{22} X_2\right) \qquad \text{(A-1)}$$

K_0 and m_0 are baseline rates for preclinical incidence and the transition from preclinical to clinical phase. R_{11}, R_{12}, R_{21}, and R_{22} are corresponding regression coefficients. The expression in (A-1) enables estimation of age specific and gender specific preclinical incidence rate and MST, respectively.

FIGURE 1. The procedure for estimating age specific and gender specific preclinical incidence rate and mean sojourn time (MST) is described.

at first screening, PSC cases, deaths from CRC, and other causes of death (OCD).

Because PSC cases consist of false-negative cases and new cases arising after first screen, and because we could not ascertain them separately, we therefore used a three-state Markov model to estimate relevant corresponding parameters, including the false-negative rate and the rate of transition from the preclinical phase to the clinical phase.

A three-state Markov model was used to estimate the preclinical incidence rate and the MST. Details of the methodology are described by Duffy et al.[17] To estimate age specific and gender specific preclinical incidence rates and MSTs, a three-state exponential regression Markov model was first proposed, in which the preclinical incidence rate and the rate of transition from the PCDP to the clinical phase was modeled as a function of age and gender in a proportional hazards form. The detailed procedure is given in Figure 1.

In order to estimate survival for asymptomatic and symptomatic CRC, we then developed a five-state illness-and-death Markov model, which includes, in addition to parameters in the three-state model, death from CRC as a primary endpoint and death from other causes as competing causes of death. The natural history of disease progression is depicted in Figure 2.

This model is progressive and not allowed to

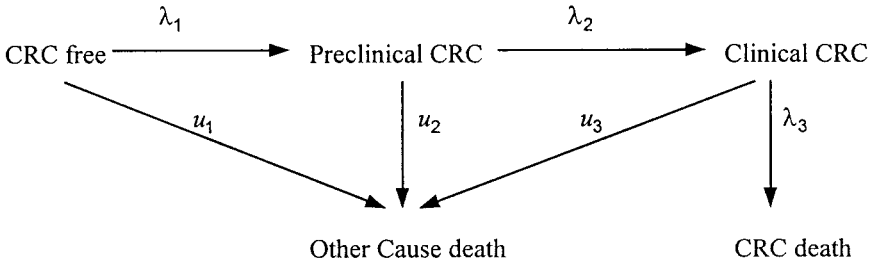

FIGURE 2. The natural history of the progression of colorectal carcinoma (CRC) is represented. λ_1: preclinical incidence of CRC; λ_2: the rate of transition from preclinical CRC to clinical CRC; λ_3: the hazard rate of death from CRC; u_1, u_2, and u_3: hazard rates of death from other causes for CRC free, preclinical CRC, and clinical CRC, respectively.

have the progression in more than two steps (i.e., from CRC free [state 0] to clinical CRC [state 2] at one time. Another feature of this model is that it not only considers death from CRC but also takes other competing causes of death into consideration. The interpretation of transition probabilities corresponding to the above natural disease history are outlined in the Figure 3.

This model is similar to one applied by Chen et al.[18] to evaluate breast carcinoma screening. Estimation of parameters for the Markov model was performed using the SAS NLIN procedure.[19]

To assess the effect of interscreening interval on the efficacy of CRC screening for this high risk group, a simulation program was designed. The study design is based on a split design.[20] This design is a variant of stop-screen design. The unique characteristic of this design is that at the time the last screening is offered to the screened group, a screening is also offered to all those in the control group. The merit of this design is that it enhances the comparability of cancer cases identified in the control and intervention arms.[20] From the practical aspect of screening, this may also partly resolve the ethical issue for the control group. This design was used in some Swedish randomized trials for breast carcinoma, such as the Stockholm trial and the Two-County trial. A hypothetical population of 25,596 subjects was randomly assigned to four groups: annual, biennial, and triennial screening regimes and a control group. Each group consists of 6399 subjects, similar to the sample size in the current study. One hundred percent attendance and 100% sensitivity was assumed. To predict the number of cases of preclinical and clinical CRC and the corresponding deaths from CRC, transition probabilities for 1-year, 2-year, and 3-year interscreening intervals were calculated using the estimated transition parameters from the 5-state Markov model. Taking the control group as a baseline group, relative mortalities for annual, biennial, and triennial regimes were predicted.

Let 0, 1, 2, 3, 4 denote states of CRC free, preclinical CRC, clinical CRC, CRC death, and other causes of death, respectively. Transition probabilities for a five-state illness-and-death Markov model are derived as follows:

Transition probabilities:
According to the Cox and Miller method,[29] transition probabilities corresponding to λ_1, λ_2, λ_2, u_1, u_2, and u_3 could be written down as follows:

$$\begin{array}{c} \\ 0 \\ 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{array}{c} \begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \end{array} \\ \begin{pmatrix} P_{00}(t) & P_{01}(t) & P_{02}(t) & P_{03}(t) & P_{04}(t) \\ 0 & P_{11}(t) & P_{12}(t) & P_{13}(t) & P_{14}(t) \\ 0 & 0 & P_{22}(t) & P_{23}(t) & P_{24}(t) \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix} \end{array} \qquad \text{(A-2)}$$

Note that λ_1, λ_2, λ_2, u_1, u_2, and u_3 give instantaneous potential for the transition from state to state per unit time. The forward Kolomogorov equation[29] relates these parameters to the transition probability, P_{ij} (t), in expression (A-2), which represents the probability of transition from state i to state j during time t. For example, P_{01}(t) denotes the probability of transition from CRC free to preclinical CRC during time t. Other transition probabilities could be defined in a similar way. It should be noted that since the model is not allowed to have the progression more than two steps at one time, the instantaneous rate from state 0 to state 2 is zero. However, there will exist a positive transition probability for such a transition, provided that the duration of t is sufficiently large. Like interval cancers (from state 0 to state 2), they may progress from CRC free (state 0), then preclinical CRC (state 1), and finally to clinical CRC, given a specified interscreening interval. This explanation can be applied to other similar transition probabilities, such as state 0 to 3. The method of deriving the detailed formula for the above transition probabilities refer to Chen et al.[18]

FIGURE 3. The interpretation of transition probabilities corresponding to the natural history of colorectal carcinoma is outlined.

TABLE 3
The Estimated Result for Preclinical Incidence Rate, MST (in Years), and Sensitivity, TAMCAS Project

Parameters	Estimates	95% CI
CRC free → preclinical	0.0039645	(0.002944–0.004985)
Preclinical → clinical	0.3513	(0.2373–0.4652)
MST (yrs)	2.8466	(2.1495–4.2969)
Sensitivity	0.9498	(0.2436–0.9991)

MST: mean sojourn time; CI: confidence interval.

TABLE 4
The Estimated Result for Preclinical Incidence Rate and MST (in Years) by Age and Gender, TAMCAS Project

Parameter	Estimate	95% CI
1. Female, age <50 yrs		
Preclinical incidence	0.002447	(0.00060–0.004293)
MST	3.6819	(2.0924–15.3140)
2. Female, age ≥50 yrs		
Preclinical incidence	0.005712	(0.00068–0.02078)
MST	2.7482	(0.7461–23.9281)
3. Male, age <50 yrs		
Preclinical incidence	0.002679	(0.000363–0.008531)
MST	3.103	(0.9647–23.5661)
4. Male, age ≥50 yrs		
Preclinical incidence	0.006255	(0.0004084–0.041287)
MST	2.3148	(0.3440–36.8223)

MST: mean sojourn time; CI: confidence interval.

RESULTS

Descriptive Results

The prevalence of CRC in groups A and E increased with patient age (data not shown). However, the highest age-adjusted prevalence rate of CRC was observed in group F, followed by groups E and A (Table 1). Due to the rarity of cases, it was difficult to calculate age-adjusted rates of CRC for groups B, C, and D. Regarding adenoma, the prevalence also increased with patient age. The highest age-adjusted prevalence rate of CRC was observed in group E. The prevalence rate of group C peaked at around age 40 years (data not shown). This observation supports the postulate that cancers in this high risk group are caused by hereditary factors.

Regarding the performance of screening tools, 91% of the subjects were screened by FOBT and colonoscopy. Only 7% underwent colonoscopy alone and 2% received other combinations of screening tests. The positive predictive value (PPV) in detecting CRC was 27.6% when colonoscopy was used alone. This decreased to 9–11% when FOBT or double-air barium was combined with colonoscopy. The corresponding figures for adenoma were 82% and 43–60%, respectively. This suggests that the combined use of colonoscopy with FOBT or double-contrast barium enema will lead to a greater number of false-positive cases than the sole use of colonoscopy. The high PPV of colonoscopy for adenoma suggests that the use of colonoscopy for this high risk group may produce a higher yield for precursor lesions than for cancer, and therefore the rate of PPV for colonoscopy with the combination of FOBT or double-contrast barium enema is low partly because potentially precursor lesions are not included in the calculation.

For early indicators, the PSC/E ratio (analogous to the I/E ratio) was 16%, 20%, and 40% for 1 year, 2 years, and 3 years after a negative screening, respectively. The estimates of sensitivity based on the traditional method were 95.3%, 89.0%, and 68.7% for 1 year, 2 years, and 3 years, respectively. The corresponding figures using (1-PSC/E) were 84.1%, 80.0%, and 60.5%. These figures suggest a high program sensitivity for colonoscopy screening.

Results from Markov Models

Table 3 shows that the estimates of the annual preclinical rate (λ_1) and the rate of transition from PCDP to clinical phase (λ_2) based on a 3-state Markov model were 0.00396 (95% CI = 0.00294–0.0050) and 0.35 (95% CI = 0.24–0.47), respectively. The inverse of λ_2 gave an estimate of the MST of 2.8 years (95% CI = 2.15–4.30). The estimate of sensitivity, based on simultaneous estimation of the preclinical incidence rate, MST, and sensitivity using the Markov model, was 95% (95% CI = 24.4–99.9%).

Based on an exponential regression Markov model, the estimated results, stratified by age and gender simultaneously, are shown in Table 4. Because the incorporation of sensitivity into the model would have led to unstable estimation, sensitivity was therefore fixed at 95%, as estimated from the above 3-state model. The preclinical incidence among males was slightly higher than among females, regardless of age. The preclinical incidence for subjects ages 50 years or older doubled that for subjects younger than 50 years. Males were estimated to have a shorter sojourn time than females, and younger subjects had a longer sojourn time than older subjects. However, such differences in MST were not substantial.

Table 5 shows the estimated results for a five-state illness-and-death Markov model. Likewise, because the inclusion of sensitivity would have led to unstable parameter estimates, the sensitivity was also fixed at 94.5%, as above. The estimates of the preclinical incidence rate and MST were similar to those based on a three-state Markov model. The annual hazard rate

TABLE 5
The Estimated Results for a Five-State Markov Model, TAMCAS Project

Parameters	Estimates	95% CI
CRC free → preclinical	0.004086	0.003281–0.004891
MST (yrs)	2.8986	2.3025–3.8865
Clinical → CRC death	0.03116	0.0098–0.0525
Disease free → OCD	0.0001603	0.0001389–0.0001817
Preclinical → OCD	0.01625	0.001451–0.03104
Sensitivity	94.98%	43.41–99.79%

CRC: colorectal carcinoma; OCD: Other causes of death; CI: confidence interval.

from clinical CRC to death from CRC was approximately 3% (95% CI = 1–5%). It should be noted that the annual hazard rate from preclinical or clinical CRC to death from other causes was 1.6% (95% CI = 0.15–3.1%), which was higher than that from CRC free to death from other causes (0.016%, 95% CI = 0.014–0.018%).

By applying the estimated transition parameters from the five-state illness-and-death Markov model to transition probabilities, as shown in expression (A-2) (see Figure 3), we could obtain estimates of 10-year survival for preclinical and clinical CRC. Table 6 shows all possible transitions and estimated transition probabilities during a 10-year follow-up period. This yielded 10-year survival for patients with clinical and preclinical CRC. The 10-year survival for clinical CRC was 62.9%. The corresponding figure for preclinical CRC was 68.3% (66.1% + 2.2%). This gave a relative 10-year survival (for patients with clinical/preclinical CRC) of 0.92.

A Computer Simulation for Predicting Mortality Reduction from CRC by Annual, Biennial, and Triennial Screening

To predict the effect of the interscreening interval on the efficacy of CRC screening, we first calculated transition probabilities with respect to annual, biennial, and triennial screening regimes (see Table 7).

Table 7 shows that reducing the interscreening interval from 3 years to 1 year halved the risk for transition from preclinical to clinical CRC and would be expected to reduce the risk for transition from clinical CRC to death from CRC by 65% and the risk for transition from preclinical CRC to death from CRC by 86%.

To illustrate the effect of this on the number of predicted cases (preclinical and clinical CRC) and deaths (CRC deaths and OCD), a detailed calculation based on a 3-year screening regime is given in Figure 4. In order to estimate the efficacy of screening for CRC, the proportion of predicted interval cancers among the total cases (screen-detected plus interval cancers) by age, gender, and different screening regimes was calculated. As expected, the proportion of interval cancers increased with the length of interscreening interval (data not shown). For example, the proportion for males ages 50 years or older increased from 18.83% to 44.27% as the interscreening interval changed from 1 year to 3 years. Similar results were found for other combinations of age and gender. Table 8 shows that the relative mortalities for annual, biennial, and triennial screening regimes, compared with no screening, were 0.74 (95% CI = 0.50–1.10), 0.77 (95% CI = 0.52–1.14), and 0.79 (95% CI = 0.53–1.17), respectively. This indicates that there was no substantial difference among annual, biennial, and triennial screening regimes in the efficacy of screening these high risk subjects for CRC.

DISCUSSION

Using a selective multicenter screening strategy for certain high risk groups in Taiwan, we estimated 26% (95% CI = 0–50%), 23% (95% CI = 0–48%), and 21% (95% CI = 0–47%) mortality reduction from CRC for annual, biennial, and triennial screening regimes, respectively. This finding, together with the low estimate of early indicator of PSC/E and a long sojourn time, suggests that the efficacy of colonoscopy screening for these high risk subjects is worthwhile. Compared with the results reported by Eddy et al.,[15] that annual colonoscopy screening for high risk people can reduce mortality by 85%, our estimated benefit might be more conservative. There are three explanations for such disparity. First, the follow-up period in this study may still be too short. Second, the parameters used by Eddy et al. were obtained from expert opinion, whereas the parameters in our study were directly estimated from empiric data. Third, the parameters for estimating the efficacy of CRC screening were only based on one-shot screening, which might lead to less benefit of CRC screening than multiple repeat screenings. This suggests that prediction of the efficacy of colonoscopy screening for the high risk groups defined in this study might be underestimated. If the multiple repeat screenings were applied, more benefit of colonoscopy screening for high risk people would be expected. Although the follow-up period may be short, the statistical power in assessing the efficacy of CRC screening for high risk people is still more powerful, for two reasons. First, the target subjects in this study were selected from a high risk population rather than the general population. We believe that a total of 8909 subjects is large enough in that the high risk group would yield more incident cases, as demonstrated in this study. Second, the size of our study is

TABLE 6
Ten-Year Transition Probabilities for Five-State Markov Model, TAMCAS Project

	To				
From	CRC free	Preclinical CRC	Clinical CRC	CRC death	OCD
CRC free	0.9573	0.0104	0.0244	0.0032	0.0046
Preclinical CRC	0	0.0220	0.6611	0.1774	0.1395
Clinical CRC	0	0	0.6289	0.2396	0.1316
CRC death	0	0	0	1	0
OCD	0	0	0	0	1

CRC: colorectal carcinoma; OCD: other cause of death.

TABLE 7
Transition Probabilities with Respect to Annual (1-Year Interval), Biennial (2-Year Interval), and Triennial (3-Year Interval) Screening Regimes

		To				
From	Interval	CRC free	Preclinical CRC	Clinical CRC	CRC death	OCD
CRC free	1-year	0.99565	0.00348	0.00067	0.0000069	0.000194
	2-year	0.99132	0.00585	0.00233	0.0000498	0.000455
	3-year	0.98700	0.00745	0.00462	0.0001527	0.000780
Preclinical CRC	1-year	0	0.6827	0.29622	0.004758	0.016281
	2-year	0	0.4661	0.48503	0.016673	0.032155
	3-year	0	0.31825	0.60113	0.033083	0.047537
Clinical CRC	1-year	0	0	0.95467	0.02926	0.016067
	2-year	0	0	0.91140	0.05719	0.031405
	3-year	0	0	0.87009	0.083861	0.046048

CRC: colorectal carcinoma; OCD: other causes of death.

larger than previous studies of colonoscopy screening for patients with a positive family history.[4–12] In addition, unlike screening for the general population, the identification of high risk groups adds another difficulty to such a selective screening.

The estimates pertaining to the natural history of the disease indicate that it might be worthwhile to perform colonoscopy screening in high risk groups. For example, the estimated MST of 2.8 years suggests that there is a large window of opportunity for detecting asymptomatic CRCs at early PCDP. As the estimates of MST reported here are based on high risk subjects rather than the general population, it is valuable to compare the estimates in this study with those given by other studies for the general population. A study of mass screening for CRC in Calvados, France,[21] gave estimates of MST of 2.0 years for subjects ages 45–54 years, 3.3 years for subjects ages 55–64 years, and 6.7 years for subjects ages 65–74 years. However, in Calvados, screening was performed using FOBT, and hence sensitivity estimates were low (75%, 50%, and 40% for subjects ages 45–54, 55–64, and 65–74 years, respectively). A MST estimate of 2.65 (95% CI = 1.40–24.39) years was calculated for the Nottingham trial[1] based on published data. The estimate of sensitivity for the Nottingham trial based on published data was 71.1% (95% CI = 46.8–87.3%). These results suggest that the estimate of MST for high risk subjects in countries with low incidence of CRC is approximately equal that for the general population in countries with high incidence. As expected, the sensitivity for FOBT applied to population-based screening was lower than that for colonoscopy applied to a high risk population. This might also account for the higher I/E ratio in the Nottingham trial (39.7% for 1 year since last negative screening) compared with the estimates in this study. However, in contrast to age specific estimates of MST from mass screening for CRC in Calvados, our results do not show that the older subjects have a longer MST than the younger subjects. The high risk subjects employed in this study, rather than the general population, might account for this disparity. Ongoing research should be carried out to clarify this disparity between high risk people and the general population.

The estimates of age specific and gender specific preclinical incidence rate of CRC and MST might provide an important reference for establishing a screening policy for these high risk people. According to

(1) First screening: $(0\rightarrow1)$ (S_1)

$$S_1 = 6399 \times \frac{P_{01}(age)}{P_{00}(age) + P_{01}(age)} = 70.46$$

if age = 48.83 years

(2) Between first and second screening

(a) Interval cancers $(0\rightarrow2)$

$I_1 = (6399 - S_1) \times P_{02}(3) = 29.23$

(b) CRC free died from CRC $(0\rightarrow3)$

$D_1 = (6399 - S_1) \times P_{03}(3) = 0.97$

(c) CRC free died from OCD $(0\rightarrow4)$

$CD_1 = (6399 - S_1) \times P_{04}(3) = 4.94$

(3) Second screening: $(0\rightarrow1)$

$S_1 = (6399 - S_1) \times P_{01}(3) = 47.12$

(4) Between second and third screening

(a) Interval cancers $(0\rightarrow2)$

$I_2 = (6399 - I_1 - S_1 - D_1 - CD_1 - S_2) \times P_{02}(3) = 28.85$

(b) CRC free died from CRC $(0\rightarrow3)$

$D_2 = (6399 - I_1 - S_1 - D_1 - CD_1 - S_2) \times P_{03}(3) = 0.95$

(c) CRC free died from OCD $(0\rightarrow4)$

$CD_2 = (6399 - I_1 - S_1 - D_1 - CD_1 - S_2) \times P_{04}(3) = 4.87$

(5) Third screening: $(0\rightarrow1)$

$S_3 = (6399 - I_1 - S_1 - D_1 - CD_1 - S_2) \times P_{01}(3) = 46.51$

(6) 10-year cumulative deaths from CRC from preclinical CRC

$DS = (S_1 + S_2 + S_3) \times P_{13}(10) = 29.11$

(7) 10-year cumulative deaths from OCD for preclinical CRC

$CDS = (S_1 + S_2 + S_3) \times P_{14}(10) = 22.90$

(8) 10-year cumulative deaths from CRC for clinical CRC

$DI = (I_1 + I_2) \times P_{23}(10) = 13.91$

(9) 10-year cumulative deaths from OCD for clinical CRC

$CDI + (I_1 + I_2) \times P_{24}(10) = 7.64$

(10) The total number of 10-year cumulative deaths from CRC after screening

$T_{M3} = D_1 + D_2 + DI + DS = 44.94$

(11) The total number of 10-year cumulative deaths from OCD after screening

$T_{M3} = CD_1 + CD_2 + CDI + CDS = 40.35$

FIGURE 4. A detailed calculation of the effect of the interscreening interval on the number of predicted cases (preclinical and clinical) of colorectal carcinoma (CRC) and the number of deaths from CRC and other causes is outlined, based on a 3-year screening regime.

estimates of preclinical incidence rate and MST of CRC, the highest proportion of interval cancers will be predicted for males ages 50 years or older, and an increased proportion of interval cancers from annual to biennial screening regimes will be the most remarkable in this group. This suggests that the application of an interscreening interval in the target population should perhaps be dependent on age and gender. It should be noted that the proportion of interval cancers increases with the length of the interscreening interval. The higher proportion of interval cancers, the poorer the efficacy of the screening. Although our results confirm this correlation, the effect of different screening intervals on mortality reduction from CRC is not as substantial as that of the proportion of interval cancers because other factors, such as treatment and duration of follow-up, may also affect deaths from CRC.

The efficacy of screening is further increased by a high estimate of program sensitivity, thereby lowering the possibility of interval cancers due to false-negative cases. The program sensitivity of colonoscopy is estimated at 95% in this study. Although the confidence interval of this estimate is rather wide, we believe the estimate of this parameter is valid because this result is consistent with a previous finding in Israel[16] and because the estimates of early indicator based on the traditional method and 1-PSC/E, as shown in the "Results" section (both pertain to the sensitivity and can be estimated without the Markov model), suggests that the program sensitivity is good. Another reason for accounting for the wide confidence interval is that our calculation of the confidence interval for the sensitivity is based on the logit transformation, which may lead to a more conservative estimate.

It should be noted that although the screening tools used in this study were a combination of FOBT, colonoscopy, and air-contrast barium, it was difficult to evaluate the efficacy of screening for such a combination, because 90% of the subjects were screened by colonoscopy and FOBT. However, the Israeli study showed that the estimate of the sensitivity using FOBT in high risk subjects was approximately 14.4%. This suggests that the sole use of FOBT may not be appropriate for screening high risk subjects. The positive predictive value (PPV) for CRC and adenoma with colonoscopy was 84%. This estimate was slightly lower than that in the Israeli study.[16] Due to the sparse number of cases, we failed to estimate PPV for the use of FOBT alone. However, it should be noted that PPV for colonoscopy in combination with FOBT was reduced to 64.7%. This suggests that a greater proportion of false-positive cases occurred when FOBT screening was used. PPV for FOBT only in the Israeli study was 28.9%. Results from the estimated sensitivity and PPV suggest that an appropriate screening test for CRC in a high risk population would be colonoscopy rather than FOBT.

Whereas the efficacy of FOBT screening for CRC has been demonstrated in Western countries, an index approach used in this study to identify an appropriate high risk group for CRC screening provides an efficient method for countries with intermediate or low incidence of CRC. We believe this approach is considerably cost-effective because the estimate of the preclinical incidence rate in the high risk groups (0.00396)

TABLE 8
The Relative Mortalities for Patients Who Underwent Annual, Biennial, and Triennial Screening Regimes Compared with the Control Group, TAMCAS Project

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

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

was approximately 21 times the CRC incidence rate reported from cancer registry in 1994. Two possibilities account for the high estimate of preclinical incidence in this study. The first is that there is an underreporting of CRC incidence from cancer registry, which might occur in developing countries. The second postulate is that an unknown selective factor (possibly advice from relatives) might often prompt subjects in some high risk groups to visit hospitals.

To broaden the definition of groups at high risk for CRC, our criteria for the definitions of high risk groups are based on family or disease history. However, today genetic counseling and testing is an important tool for the identification of groups at high risk for CRC, mainly including two hereditary CRCs. One is familial adenomatous polyposis (FAP), which is caused by mutation of the APC gene and accounts for about 1% of all CRCs. The other is hereditary nonpolyposis colorectal carcinoma (HNPCC), which may be associated with four DNA mismatch repair genes (hMSH2, hMLH1, hPMS1, and hPMS2)[22–26] and accounts for 2–5% of all CRCs. Although our high risk groups may have included people with family history of two hereditary CRCs, genetic testing was not used in this study to identify these two hereditary cancers. Such genetic counseling and testing should be provided for people with a family history of FAP and HNPCC in order to see if they have gene carrier status. A knowledge of gene carrier status enables targted surveillance and the possibility of prophylactic surgical intervention, as suggested by Beck et al.[27]

From a methodologic viewpoint, the major advantage of using a five-state Markov model is the simultaneous estimation of transition rates for progression from the PCDP to the clinical phase and the hazard rate of transition from the clinical phase to death from CRC or other competing causes. This approach makes it possible to estimate the hazard rate of death from CRC, making allowance for lead time, which is one of

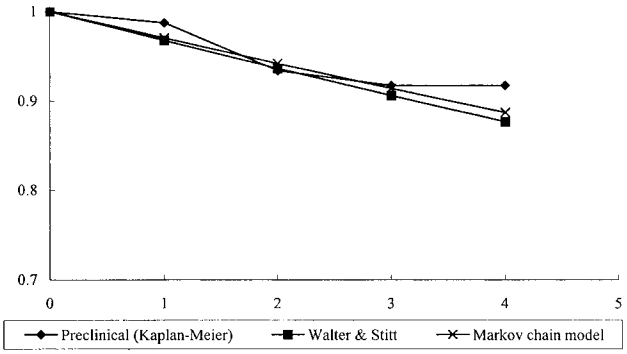

FIGURE 5. Adjusted lead time of cumulative survival for patients with preclinical CRC, determined by the method of Walter and Stitt and the Markov chain model, is compared with the observed cumulative survival for patients with preclinical CRC.

the threats to the validity of assessing the efficacy of screening in nonrandomized trials. One can also apply the method of Walter and Stitt[28] to calculate the post–lead time survival curve for screen-detected cases. Using their method gives an annual hazard rate of 0.0328, which is close to our estimate of 0.03116. Figure 5 shows that the two adjusted survival curves are almost identical. These two methods each have their own merits and drawbacks. Our method has one advantage over their method. The estimation of the sojourn time and the hazard rate of death from CRC can be performed simultaneously, whereas the lead time–adjusted hazard rate according to the method of Walter and Stitt is usually estimated by assuming a constant mean sojourn time or by an expectation-maximum (E-M) algorithm. However, in order to estimate two parameters simultaneously, we have to rely on interval cancers. In contrast, Walter and Stitt derive the adjusted hazard rate on the basis of screen-detected cases only. As the difference between the observed cumulative survival of preclinical CRC and the predicted cumulative survival adjusted by lead time is

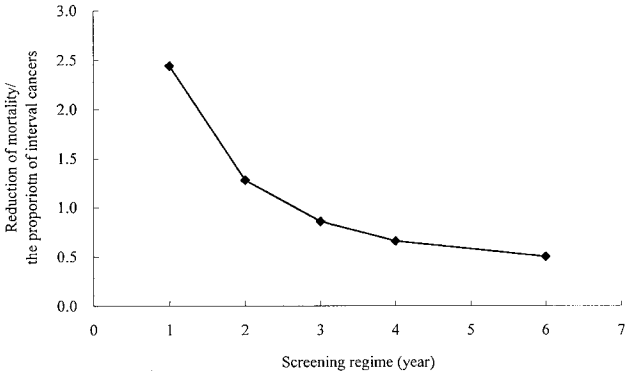

FIGURE 6. The ratio of the mortality reduction from CRC to the incidence of interval cancer as a percentage of the incidence expected rate.

not substantial (see Fig. 5), we believe the problem of lead time bias in this study is minor. We also validated the five-state Markov model by comparing the observed with the expected using a goodness-of-fit test. The result showed a lack of significant difference between the expected and the observed ($P = 0.79$).

Moreover, transition probabilities derived from the Markov model are also informative in clinical consultation because these figures can aid physicians in predicting the probability from state to state given a specific time interval, as shown in Tables 6 and 7. For example, if a high risk person is invited to have a colonoscopic examination and is diagnosed with CRC but has no suggested symptoms, such as bleeding or pain (defined as preclinical CRC in this study), the probability of dying from CRC after 10 years, based on Table 6, would be predicted as 18%. The corresponding figures for the normal finding and clinical CRC examined by colonoscopy are 0.3% and 24%, respectively. Table 7 has a similar application.

In order to propose a tentative suggestion for an optimal interscreening interval for these high risk subjects, we evaluated the relative efficacy by different screening regimes based on an indicator, the ratio of the reduction in mortality from CRC relative to the incidence of interval cancer as a percentage of the expected incidence rate. Figure 6 shows that the value of this indicator levels off when the interscreening interval is longer than 2 years. This suggests that an optimal screening interval for these high risk subjects might be 2 years.

In conclusion, colonoscopic screening of high risk groups in countries with a low incidence of CRC seems worthwhile. This is supported by the following evidence:

1. Early detection of CRC by biennial colonoscopy for high risk subjects might lead to a reduction in mortality of 23%;
2. A higher incidence rate due to selecting a high risk group as the target population might be more cost-effective;
3. A long MST and the high sensitivity of colonoscopy warrant the efficacy of selective screening for CRC.

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