Progression Rates of Colorectal Cancer by Dukes' Stage in a High-Risk Group: Analysis of Selective Colorectal Cancer Screening

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PURPOSE

The progression rates of colorectal cancer by Dukes' stage in a high-risk group were estimated and applied to evaluate the efficacy of different screening regimens.

PATIENTS AND METHODS

Of 6303 high-risk subjects invited to a colorectal cancer screening project with colonoscopy, 39 screen-detected cases and 16 postscreening cases were diagnosed with information available on Dukes' stage. A five-state Markov process was applied to estimate parameters pertaining to the disease natural history of colorectal cancer by Dukes' stage.

RESULTS

The estimates of the mean sojourn time in years were 3.10 for preclinical Dukes' A and B and 1.92 for preclinical Dukes' stages C and D. The predicted reductions of Dukes' stages C and D achieved by annual, biennial, 3-yearly, and 6-yearly screening regimens against the control group were 60%, 49%, 40%, and 25%, respectively. These, in turn, yield the corresponding predicted mortality reductions of 39%, 33%, 28%, and 18%.

CONCLUSIONS

These findings suggest that to achieve a 30% mortality reduction, as observed in annual fecal occult blood testing, a prudent interscreening interval with colonoscopy for this high-risk group should not be longer than 3 years. *(Cancer J 2004;10:160–169)*

KEY WORDS

Colorectal cancer screening, high-risk group, Dukes' stage, colonoscopy, Markov process

Dukes' stage plays an important role in the prognosis of colorectal cancer (CRC). Five-year survival rates are 90%–94% for Dukes' stage A, 75%–85% for Dukes' stage B, 52%–57% for Dukes' stage C, and zero to 2% for Dukes' stage D.[1,2] Dukes' stage is also a potentially powerful surrogate endpoint for evaluation of the efficacy of CRC screening in reducing mortality from CRC. Two population-based randomized trials, the UK Nottingham study[3] and the Denmark Funen study,[4] have found that the proportion of Dukes' stage A cases was much higher in the screened group than that in the control group. This in turn was associated with a 15%–25% mortality reduction based on a biennial screening regimen with the fecal occult blood test (FOBT) being applied to the general population. For this reason, quantifying the natural history of CRC by Dukes' stage not only throws light on how screening can work but can also predict the likely benefit of mortality reduction as a result of screening. For example, part of the benefit of the screening is to find presymptomatic Dukes' stage A and B cases, which would have progressed to Dukes' stages C and D and would have led to early death had screening not been performed. To obtain a clear understanding of such a down-staging, one should quantify how tumors progress from preclinical to clinical disease and between Dukes' stages during the preclinical phase.

The natural history of CRC by Dukes' stage is also

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crucial for the early detection of cases in selective screening of high-risk groups, which is often adopted in countries with low or intermediate incidence rates of CRC. It is postulated that tumor progression in this high-risk group may be more rapid than that in the underlying general population. A previous study based on the Taiwan Multi-center Cancer Screening (TAMCAS) project estimated a mean sojourn time (MST), the average duration of the preclinical screen-detectable phase, of approximately 3 years, which is shorter than the estimates of 4–5 years in the general population.[5] These results suggest that the natural history of CRC progression in a high-risk group is different from that in the background population. However, few studies have so far addressed the natural history of CRC by Dukes' stage because of the fact that transitions between preclinical Dukes' stages are not observable (although they can be inferred from stage at diagnosis of screen-detected and clinically arising tumors). Quantifying the disease progression of CRC by Dukes' stage is important for the determination of the interscreening interval because it enables us to evaluate the effects of different interscreening intervals on the consequent incidence of Dukes' stages C and D. The latter may be regarded as a surrogate endpoint for mortality, in that it gives an estimate of efficacy that is strongly related to mortality but is observable some years in advance.

The aims of this study were therefore to

1. quantify the natural history of CRC progression from normal, preclinical CRC, and clinical CRC, taking Dukes' stage into account;
2. assess whether the progression rate from preclinical Dukes' stages A and B to preclinical Dukes' stages C and D or that from preclinical Dukes' stages A and B to clinical stages A and B plays the more important role in the early detection of CRC; and
3. apply estimates from item 1 to assess the efficacy in reducing advanced disease, as classified by Dukes' stage and mortality, by different interscreening intervals.

PATIENTS AND METHODS

Five-State Disease Process by Dukes' Stage

To quantify the progression of CRC, the disease natural history of CRC by Dukes' stage is delineated in the middle panel of Figure 1. The malignant disease process for individuals begins with occurrence of preclinical Dukes' stages A and B that is often occult. These occult cases may transit to Dukes' stages C and D before the presence of clinical symptoms, such as bleeding or rectal pain, or may surface to the clinical phase with overt symptoms but still remain within Dukes' stages A and B. Subjects with occult Dukes' stages C and D eventually surface to the clinical phase with overt symptoms. The aforementioned disease process can be subdivided as Dukes' stages A, B, C, and D. However, because Dukes' stages A and B are widely regarded as early CRC on the defined as invasion within mucosa and Dukes' stages C and D as advanced CRC because of nodal involvement, the five-state disease natural history may be appropriate.

Clinical Scenario

In clinical practice, there are no data on transitions within individual presymptomatic cases because any such presymptomatic cases that are identified as a result of screening receive surgical and medical treatment, and the disease natural history is interrupted. Thus, the progression from presymptomatic Dukes' stages A and B to presymptomatic Dukes' stages C and D is occult and unobservable. Information required for estimating these progression rates with the use of modeling techniques is based on stage distributions in screen-detected and clinically detected cases. The former can be obtained from the first (prevalent) screening or repeated (incident) screenings. In the present study, we only have data from a prevalence screening, and tumors arising symptomatically in subjects screened negative at that screening.

Figure 1 illustrates the clinical scenario related to the disease progression for five hypothetical cases before first screening. Suppose time epochs for the duration between date of birth (t_0) and date of first screen (t_4) for the same birth cohort include t_1-t_4. Individual 1 is free of CRC before first screening. Individual 2 has onset of early CRC at t_4 and remains occult without further progression until first screening. Individual 3 has onset of early CRC at t_3 and progresses to advanced CRC without overt clinical symptoms at t_4 and remains presymptomatic until first screening. Individuals 4 and 5 surface to clinical disease and are diagnosed as having Dukes' stage C or D because of overt symptoms before first screening.

At the first screening, individuals 1–3 are classed respectively as free of CRC, presymptomatic early CRC, and presymptomatic advanced CRC. Individuals 4–5 are not eligible for first screening. We obtain information on screen-detected early CRC and advanced CRC from subjects like individuals 2 and 3. To obtain information on symptomatic CRC, we can monitor subjects who are free of CRC at first screening to ascertain symptomatic cases arising after first screening. Individuals 6 and 7 (see bottom of Fig. 1) represent these cases, which we call postscreening cases (PSCs). Screen-detected cases like individuals 1–3 and clinically detected cases like individuals 6 and 7 provide empirical data for quantifying progression rates of disease. We estimate progression

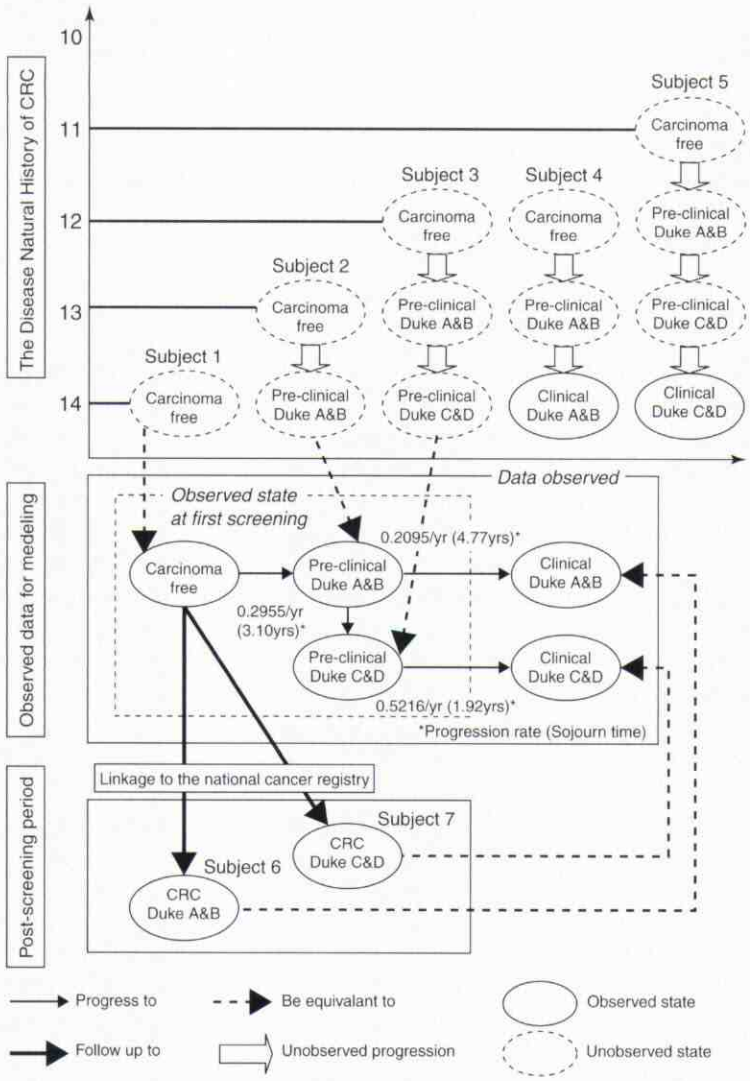

FIGURE 1 Clinical scenario and natural history of colorectal cancer (CRC) by Dukes' stage.

rates between five disease states: no malignancy; preclinical Dukes' stage A and B, preclinical C and D, clinical A and B, and clinical C and D.

Empirical Data

Data used to estimate parameters were derived from a CRC screening project in a high-risk group as detailed in a previous study.[6] Briefly, it is a hospital-based project, with 17 hospitals involved in the study. A total of 8909 individuals attended colonoscopy screening between 1992 and 1997. These individuals met the criteria of the high-risk group, including any combination of (1) first- or second-degree relatives with CRC, (2) at least two first-degree relatives affected by any cancer, (3) inflammatory bowel disease, (4) thyroid or breast cancer, or (5) previous CRC operated by surgery at least 3 years before or adenoma 1 year before. As mentioned in the previous study,[6] of 8909 subjects, only 945 subjects attended the repeated screenings, and analysis was limited to subjects attending the first screening. This is equivalent to one-shot screening.

To estimate the transition rates from the preclinical to the clinical phase in one-shot screening, information was obtained on PSCs, that is, the cancers arising after the first screening, as in individuals 6 and 7 in Figure 1. This is analogous to clinically detected interval cancers in traditional repeated screening.

We collected data on PSCs by linkage of the cohort to the cancer registry and records from national health insurance. Average follow-up time for PSCs was 2.14 years. Information on Dukes' stage was retrieved from pathological reports, which were reviewed by Dr. Wong, a senior physician in gastroenterology.

Because we are interested in estimating only the preclinical incidence rate and other transition parameters for new-incident CRC, subjects with previous CRC operated on surgically or those with a history of CRC ascertained by linkage with the national cancer registry were excluded from the following Markov analysis (but not

from the colonoscopy screening service). Thus, 6303 subjects aged less than 80 years were available. Of these, 77 screen-detected cases and 33 PSCs were identified. Only 51% (39/77) of preclinical cancers and 48% (16/33) of interval cancers have available information on Dukes' stage. Table 1 shows types of transition, numbers of transitions, and transition history.

Estimation of Progression Rates

The progression rates in Figure 1 were estimated with the use of a previously developed nonhomogeneous stochastic model.[7] Because the annual preclinical incidence rate of Dukes' stages A and B is likely to increase with age, a nonconstant preclinical incidence rate ($\lambda_1(t)$) was applied with the use of the Weibull distribution, with shape and scale parameters to be estimated from the data.[7] The remaining progression rates ($\lambda_2 - \lambda_4$) between the PCDP states or from the PCDP to clinical phase were modeled as a Markov process. The definition and notation of five-state Markov model are given in Appendix A. Essentially, we used a five-state Markov process, with states (0) no cancer, (1) preclinical cancer of Dukes' stage A or B, (2) preclinical cancer of Dukes' stage C or D, (3) clinical cancer of Dukes' stage A or B, and (4) clinical cancer of Dukes' stage C or D. We assumed that the sensitivity of colonoscopy to Dukes' stages C and D was 100%, and we estimated the sensitivity to Dukes' stages A and B in the statistical analysis. Because some CRC cases had missing data on Dukes' stage, a missing data adjustment was made, as shown in Appendix B. Confidence intervals were estimated with the use of the jacknife procedure.

Mean Sojourn Time and Cumulative Risk of Subsequent Progressions

In the relationship between screening for CRC and Dukes' stage, the health benefits as a result of early detection of preclinical Dukes' A and B are derived both from the reduction in subsequent progression from preclinical Dukes' stages A and B to clinical stages A and B and from the reduction in subsequent progression to preclinical stages C and D. The former is primarily related to the MST in preclinical Dukes' stages A and B before progression to clinical stages A and B, and the latter depends on the magnitude of relative transition rate (RTR) from preclinical Dukes' stages A and B to preclinical stages C and D compared with the transition rate to clinical stages A and B. If the RTR is greater than 1, the interscreening interval should be determined by the transition rate from preclinical Dukes' stages A and B to preclinical stages C and D. If the RTR is less than 1, the crucial factor determining the interscreening interval is the MST.

Because of the Markov property applied to $\lambda_2 - \lambda_4$, calculation of the MST for preclinical Dukes' stages C and D is performed by simply taking the inverse of annual rate of transition from preclinical stages C and D to clinical stages C and D, λ_4. However, the MST for preclinical Dukes' stages A and B depends on the rates of progression to clinical Dukes' stages A and B and of progression to preclinical Dukes' stages C and D, and thereafter to clinical Dukes' stages C and D. Calculation of two components is described by Chen et al[8] and is given as follows:

$$\frac{1}{(\lambda_2 + \lambda_3)} + \frac{\lambda_2}{(\lambda_2 + \lambda_3)\lambda_4}$$

Translation of progression rates into transition probabilities enabled us to calculate cumulative risks of progression from preclinical Dukes' stages A and B to clinical Dukes' stages A and B and C and D, respectively. The detailed calculations are already described.[8] In brief, let 0, 1, 2, 3, and 4 denote normal, preclinical Dukes' stages A and B, preclinical stages C and D, clinical stages A and B, and clinical stages C and D, respectively. The calculation of three transition probabilities, denoted as

TABLE 1 Types of Transition, Numbers of Transitions Observed in Our Data and Transition History for the Five-State Markov Model for Colorectal Cancer

Transition Types	Transition History (State i → State j, time)	Number of Transitions
Carcinoma free→ Carcinoma free	(0→0, age at first screen (A))	6226
Carcinoma free→ Preclinical Dukes' A & B	(0→1, age at first screen (A))	23
Carcinoma free→ Preclinical Dukes' C & D	(0→2, age at first screen (A))	16
Carcinoma free→ Clinical Dukes' A & B	(0→3, time since last negative screen (U))	10
Carcinoma free→ Clinical Dukes' C & D	(0→4, time since last negative screen (U))	6

$P_{12}(t)$, $P_{13}(t)$, and $P_{14}(t)$, gives cumulative risks of progression from preclinical Dukes' stages A and B to preclinical stages C and D, clinical stages A and B, and clinical stages C and D, respectively. Comparison of $P_{13}(t)$ with $P_{14}(t)$ or plotting of the cumulative risk of Dukes' stages C and D ($P_{12}(t) + P_{14}(t)$) helps determine the optimal interscreening interval for this high-risk group.

Computer Simulation of Effectiveness by Inter-Screening Interval

To determine the effect of interscreening interval on the reduction of Dukes' stages C and D and the reduction of mortality, a Monte Carlo computer simulation was performed as follows. A hypothetical cohort consisting of 50,000 residents with demographic characteristics (age and sex) identical to those in this high-risk group (Table 2) was randomly assigned to five screening regimens, annual, biennial, 3-yearly, 6-yearly, and an unscreened control group. The study period was 6 years. The study design was based on the split-stop design,[9] in which the control group received one-shot screening at the closure of the study. Monte Carlo computer simulation was performed to calculate the effectiveness of the four screening regimens compared with the control group, based on the disease progression rates estimated from our screening and PSC data. We assumed 100% attendance. Follow-up of CRCs for subsequent death from the disease lasted for 10 years in this simulation. The 10-year survival rates used in simulation were 80% for preclinical Dukes' stages A and B, 60% for clinical stages A and B, 40% for preclinical stages C and D, and 20% for clinical stages C and D, which were derived from the cancer registry in Taiwan. Life-table information from vital statistics in Taiwan was also used to adjust for competing causes of deaths in the simulations.

RESULTS

The proportions with Dukes' stage A in screen-detected cases and clinically detected cases were 28% and 13%, respectively. Estimated results for the five-state disease process are shown in Table 3. Sensitivity to Dukes' stage A and B disease was estimated to be 78%. Because the shape parameter was larger than 1, this suggests that the annual preclinical incidence rate increases with age, as expected. The transition rates from preclinical to clinical stage for Dukes' stages A and B and C and D were 0.2095 and 0.5216 per year, respectively. The RTR is equal to 1.41. The inverse of annual transition rate

TABLE 2 Age and Sex Distributions by Case State (% by Age in Parentheses)

Age, Years	Carcinoma Free (N = 6193)		CRC Cases (N = 110)		CRC Cases with Dukes' Data (N = 55)	
	Male	Female	Male	Female	Male	Female
< 50	1750 (52.55%)	1699 (59.34%)	15 (24.19%)	18 (37.50%)	5 (19.23%)	12 (41.38%)
50–59	652 (19.58%)	640 (22.35%)	17 (27.42%)	10 (20.83%)	5 (19.23%)	8 (27.59%)
60–69	657 (19.73%)	396 (13.83%)	17 (27.42%)	11 (22.92%)	9 (34.62%)	6 (20.69%)
70–79	271 (8.14%)	128 (4.47%)	13 (20.97%)	9 (18.75%)	7 (26.92%)	3 (10.34%)
Total	3330	2863	62	48	26	29

Abbreviation: CRC, colorectal cancer.

TABLE 3 Estimated Parameters for Progression of CRC

Parameter	Estimate	95% CI
CRC free → preclinical A & B		
Scale parameter	1.45×10^{-5}	1.0×10^{-5}–1.5×10^{-5}
Shape parameter	2.2824	2.2799–2.3506
Preclinical A & B → preclinical C & D	0.2955	0.2732–0.3029
Preclinical A & B → clinical A & B	0.2095	0.1946–0.2182
Preclinical C & D → clinical C & D	0.5216	0.5099–0.5220
Sensitivity to preclinical A & B	0.7874	0.7412–0.8083

[a]Pearson Chi-square for goodness of fit was 0.31.
Abbreviation: CRC, colorectal cancer.

of 0.5216 yields 1.92 years of MST for preclinical Dukes' stages C and D. Taking into account the probability that a Dukes' stage A and B preclinical case may progress to stage C and D then to clinical disease, the MST for preclinical Dukes' stages A and B is 3.10 years. This is approximately 60% greater than the MST of Dukes' stages C and D.

This also suggests that approximately 59% (0.2955/[0.2955 + 0.2095]) of the benefit as a result of early detection of preclinical Dukes' stages A and B is due to prevention of progression from preclinical Dukes' stages A and B to preclinical stages C and D, and 41% is due to prevention of progression from preclinical stages A and B to clinical stages A and B.

Cumulative Risk of Subsequent Progression for Preclinical Dukes' A and B

Application of progression rates in Table 2 gives the cumulative risk of subsequent progression for preclinical Dukes' stages A and B by follow-up time shown in Table 4. Cumulative risks for surfacing to clinical Dukes' stage A and B increased from 16% at the first year to 32% at the third year and to the plateau of approximately 40% after 5-year follow-up. Cumulative risks for the transition to preclinical Dukes' stages C and D declined from 21% at the second year to 11% at the fifth year and 2% at the tenth year. Cumulative risks for surfacing to clinical Dukes' stage C and D increased from 6% at the first year to 27% at the third year, 42% at the fifth year, and 56% at the 10th year. Figure 2 shows that in the early follow-up period, transition to clinical Dukes' stages A and B is more frequent than transition to clinical Dukes' stages C and D. Cumulative risk of clinical Dukes' stages C and D surpassed that of Dukes' stages A and B after 5 years of follow-up. The increased cumulative incidence of clinical Dukes' stage C and D disease at later years is largely due to high rates of progression to preclinical stages C and D in earlier years of follow-up. Figure 2 also shows that the cumulative risk of Dukes' stages C and D (preclinical and clinical combined) increased from 23% at the first year to 46% at the third year, and thereafter reached a plateau at around 58%.

Table 5 shows the results of simulations on effective-

TABLE 4 Cumulative Risk of Progression from Preclinical Dukes' A & B to Preclinical C & D, Clinical Colorectal Cancer by Dukes' Stage, and All Cases with Dukes' Stage C & D

Year of Follow-Up	Clinical Dukes' A & B, %	Preclinical Dukes' C & D, %	Clinical Dukes' C & D, %	Dukes' C & D, %
1	16.45	17.69	5.51	23.20
2	26.38	21.17	16.03	37.20
3	32.37	19.01	26.64	45.65
4	35.98	15.17	35.58	50.75
5	38.16	11.35	42.48	53.83
6	39.48	8.15	47.53	55.69
7	40.28	5.69	51.11	56.81
8	40.76	3.90	53.59	57.48
9	41.05	2.62	55.27	57.89
10	41.22	1.75	56.39	58.14

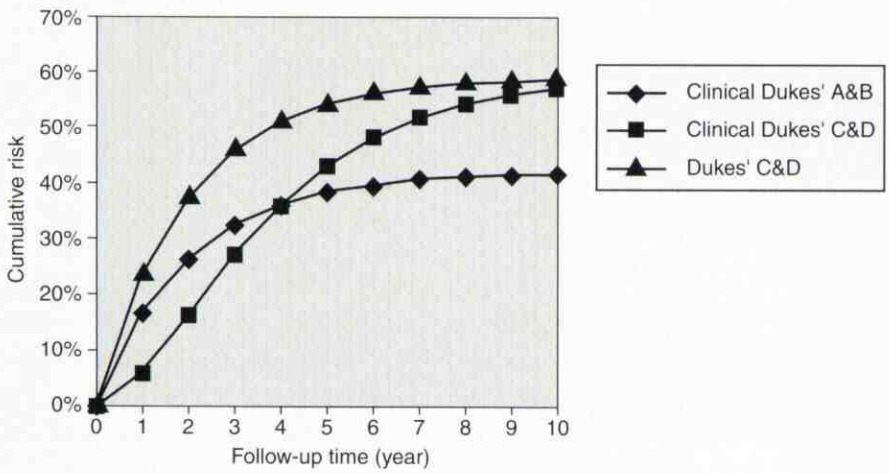

FIGURE 2 Cumulative risk of subsequent progression to clinical Dukes' stages A and B, clinical Dukes' stages C and D, and total Dukes' stages C and D (including preclinical and clinical Dukes' stages C and D) for preclinical Dukes' stages A and B.

TABLE 5 Results of Efficacy in Reducing Dukes' Stage C and D (RR_1) and Mortality from CRC (RR_2) by Different Screening Regimens (Annual, Biennial, 3-Yearly, and 6-Yearly)

Screening Regimens	Preclinical A & B	Preclinical C & D	Clinical A & B	Clinical C & D	C & D / Total CRC	Total Death	RR_1 (95% CI)	RR_2 (95% CI)
Annual	279.49	73.94	21.78	5.00	20.76%	128.41	0.40 (0.31–0.52)	0.61 (0.49–0.76)
Biennial	240.79	83.24	37.43	17.68	26.62%	141.49	0.51 (0.40–0.65)	0.67 (0.54–0.83)
3-Yearly	209.32	85.78	48.31	32.33	31.43%	151.14	0.60 (0.48–0.76)	0.72 (0.58–0.89)
6-Yearly	161.81	80.11	67.74	67.54	39.14%	171.45	0.75 (0.61–0.93)	0.82 (0.67–0.998)
Control	77.05	37.63	100.09	158.48	52.54%	210.09	1.00	1.00

Abbreviation: CRC, colorectal cancer.

ness of reducing advanced Dukes' stage C and D and deaths by different interscreening intervals. The proportion of Dukes' stages C and D increases as the interscreening interval lengthens. Approximately 60%, 49%, 40%, and 25% reductions in incidence of Dukes' stage C and D disease are expected for annual, biennial, 3-yearly, and 6-yearly screening, respectively, as compared with the control group. The predicted mortality reductions were 39%, 33%, 28%, and 18% for the four corresponding screening regimens in comparison with the control group.

DISCUSSION

Implications for Colorectal Cancer Screening in a High-Risk Group

Progression rates of CRC with respect to Dukes' stage in a high-risk group were estimated in this study. Results show that the rate of progression to clinical disease for preclinical Dukes' stages A and B is considerably lower than that for preclinical stages C and D, and the RTR is greater than 1. These findings suggest that early detection of CRC plays an important role in reducing the transition from preclinical Dukes' stages A and B to preclinical stages C and D and, to a lesser extent, in reducing the progression from preclinical stages A and B to clinical stages A and B. This suggests that selective screening with colonoscopy for this high-risk group is important for reducing Dukes' stage C and D disease, which in turn leads to a reduction in mortality from CRC.

Taking the control group as a baseline group, approximately 60%, 49%, 40%, and 25% reductions of Dukes' stages C and D are expected for annual, biennial, 3-yearly, and 6-yearly screening, respectively. Translation of this benefit into deaths averted by screening gives 39%, 33%, 28%, and 18% mortality reductions for annual, biennial, and 3-yearly screening, respectively, as compared with the control group. Our estimated sensitivity of 78% to Dukes' stage A and B disease is probably due to issues of technique in the early period of the program and may have improved since. In the meantime, to achieve an approximate 30% mortality reduction, as observed in annual FOBT screening for average-risk individuals, a prudent interscreening interval for colonoscopy in this high-risk group would be 3 years.

Such an inference was also upheld by analysis of number of PSCs by follow-up year. Among 33 PSCs, four cases were found at first year of follow-up, six cases between 1 and 2 years, 20 cases between 2 and 3 years, and three cases between 3 and 4 years. The small number after 3 years is due to the fact that follow-up was less than 3 years for more than half of the subjects. A large proportion of clinically detected cancers were found between the second and third year. Assuming that all these cases were due to false-negative results, the program sensitivities calculated by (PSC/[PSC + 77 screen-detected cases]) dropped from 95% at first year to 72% at the third year. This evidence suggests that 3-yearly screening regimen for this high-risk group is necessary, given limited costs.

The estimated mortality reductions are conservative in that we estimated only the deaths avoided from advancing the diagnosis from late malignant disease to early malignant disease, but we did not take account the benefit as a result of detection of premalignant adenomatous polyps, as demonstrated by Mandel et al,[10] who reported a 17%–20% incidence reduction with the use of FOBT screening.

Comparison Between High-Risk Group and General Population

The progression rate in the underlying general population is thought to be slower than that in a high-risk group. However, there is a lack of evidence on the

differences between the disease natural history by Dukes' stage for such a high-risk group and natural history for the underlying general population. The present study demonstrated that the proportion of Dukes' stage A in screen-detected cases (28%) is higher than that in clinically detected cases (13%). The benefit due to the reduction of Dukes' stage is slightly smaller in this study than in earlier findings from two randomized trials.[3,4] In these two studies, the percentage of Dukes' stage A disease in screen-detected cases was 41%, compared with 11% in the control group, a larger difference. Although individual information on Dukes' stage was not available from these studies, a three-state Markov model was fitted to the published tabular data, and the overall MST, given a 53.6% sensitivity of FOBT, was estimated to be 6.27 years in the Nottingham randomized trial.[3] This estimate is consistent with that from Launoy et al.[5] This suggests that the MST in the general population is approximately double that of this high-risk group. This may partially account for the smaller benefit in terms of Dukes' stage in our study.

Methodologic Considerations

From the methodologic viewpoint, there are several strengths of applying a multistate model to the evaluation of CRC screening. First, using such a model can throw light on the disease natural history, despite unobservable transitions within the clinical phase. The cumulative risks of these and other transitions can be predicted as in Table 2 and Figure 2. The five-state Markov model incorporating Dukes' stage into the disease natural history can further elucidate how screening works on pre-existing preclinical malignancy. Making use of this feature enables one to assess the relative contributions of reducing subsequent progression to preclinical Dukes' stages C and D (59%) and of reducing progression to clinical Dukes' stages A and B (41%). Also, the use of a surrogate endpoint such as Dukes' stage to assess the efficacy of treatment or screening is greatly helpful for nonrandomized studies, in which a control group is lacking but in which progression rates with respect to the surrogate endpoint can be estimated. In this way, we can also assess the effect of different screening frequencies on the outcome without long-term follow-up. Third, from the statistical viewpoint, the use of a surrogate endpoint may increase power. A comparison of actual mortality tends to have low power because the relevant standard deviation is based on only those subjects who die. Predicted mortality from stage has higher power because the standard deviation is based on the stage of all cases.[11]

Our method of estimating parameters takes missing data on Dukes' stage into account. This method, for the time being, assumes that information on Dukes' stage is missing completely at random. Although it is difficult to judge whether this assumption is valid, we can check whether the distributions of other relevant covariates, such as sex, age, and criteria of high-risk in subjects with Dukes' stage information, are similar to those in subjects without information on Dukes' stage. Results show no significant difference for sex, age, or risk criteria. Although the Dukes' stage data are unlikely to be missing completely at random, the similar distributions of these factors suggest that the missing completely at random assumption is a reasonable approximation. The proposed method provides the opportunity of understanding the disease natural history, even when the stage information cannot be available for all cases on some occasions, particular when the cancer registry is not completely developed to collect such information.

To check whether the Markov model was valid, we compared the expected and observed transitions, in which the expected number of transitions for each transition type was obtained from the product of total case number multiplied by the corresponding transition probability. The comparison between the observed and the expected numbers was not statistically significant ($\chi^2_{(1)} = 0.31$, $P = 0.4$). This suggests that the five-state Markov process used in this study to model the natural history by Dukes' stage was appropriate.

In conclusion, the natural history of CRC in a high-risk group was quantified with the use of a five-state disease process that modeled progression by Dukes' stage. Results from this study suggest that the optimal interscreening interval for a colonoscopy program in this high-risk group should be no more than 3 years.

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APPENDIX 1 Transition Parameters

According to the disease natural history model in Figure 1, transition parameters associated with this model can be expressed as an intensity matrix as follows:

$$Q = \begin{array}{c} \\ \text{Previous State} \end{array} \begin{array}{c} \begin{array}{ccccc} & & & \text{Current State} & \\ \text{Carcinoma Free} & \text{Preclinical Dukes' A \& B} & \text{Preclinical Dukes' C \& D} & \text{Clinical Dukes' A \& B} & \text{Clinical Dukes' C \& D} \end{array} \\ \begin{array}{r} \text{Carcinoma free} \\ \text{Preclinical Dukes' A \& B} \\ \text{Preclinical Dukes' C \& D} \\ \text{Clinical Dukes' A \& B} \\ \text{Clinical Dukes' C \& D} \end{array} \begin{pmatrix} -\lambda_1 & \lambda_1 & 0 & 0 & 0 \\ 0 & -(\lambda_2+\lambda_3) & \lambda_2 & \lambda_3 & 0 \\ 0 & 0 & -\lambda_4 & 0 & \lambda_4 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \end{array}$$

where $\lambda_1(a)$, λ_2, λ_3, and λ_4 denote the transition rates from carcinoma free to preclinical Dukes' stages A and B (at age a), from preclinical stages A and B to preclinical stages C and D, from preclinical stages A and B to clinical stages A and B, and from preclinical stages C and D to clinical stages C and D, respectively.

The transition probabilities, calculated from the forward Kolmogorov equation corresponding to λ_1, λ_2, λ_3, and λ_4, are denoted as follows:

$$P = \begin{array}{c} \\ \text{Previous State} \end{array} \begin{array}{c} \begin{array}{ccccc} & & & \text{Current State} & \\ \text{Carcinoma Free} & \text{Preclinical Dukes' A \& B} & \text{Preclinical Dukes' C \& D} & \text{Clinical Dukes' A \& B} & \text{Clinical Dukes' C \& D} \end{array} \\ \begin{array}{r} \text{Carcinoma free} \\ \text{Preclinical Dukes' A \& B} \\ \text{Preclinical Dukes' C \& D} \\ \text{Clinical Dukes' A \& B} \\ \text{Clinical Dukes' C \& D} \end{array} \begin{pmatrix} P_{00}(t) & P_{01}(t) & P_{02}(t) & P_{03}(t) & P_{04}(t) \\ 0 & P_{11}(t) & P_{12}(t) & P_{13}(t) & P_{14}(t) \\ 0 & 0 & P_{22}(t) & 0 & P_{24}(t) \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix} \end{array}$$

where $P_{ij}(t)$ 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 colorectal cancer free to preclinical Dukes' stages A and B during time t. Other transition probabilities could be defined in a similar way. The method of deriving the detailed formulas for the aforementioned transition probabilities are given by Chen et al.[12]

APPENDIX 2 Missing Data Adjustment

In order to estimate parameters, the total likelihood function, L, is required.

$$L = \prod_{i=1}^{6226}\left(\frac{P_{00}(A_i)\times\pi_0}{P_{00}(A_i)\times\pi_0 + P_{01}(A_i)\times\pi_1 + P_{02}(A_i)\times\pi_2}\right)$$
$$\times \prod_{j=1}^{23}\left(\frac{P_{01}(A_j)\times\pi_1}{P_{00}(A_j)\times\pi_0 + P_{01}(A_j)\times\pi_1 + P_{02}(A_j)\times\pi_2}\right)$$
$$\times \prod_{k=1}^{16}\left(\frac{P_{02}(A_k)\times\pi_2}{P_{00}(A_k)\times\pi_0 + P_{01}(A_k)\times\pi_1 + P_{02}(A_k)\times\pi_2}\right)$$
$$\times \prod_{l=1}^{10}\left(\frac{\pi_3 P_{03}(U_l)}{\pi_3 P_{03}(U_l) + \pi_4 P_{04}(U_l)}\right) \times \prod_{m=1}^{6}\left(\frac{\pi_4 P_{04}(U_m)}{\pi_3 P_{03}(U_m) + \pi_4 P_{04}(U_m)}\right)$$

$P_{0j}(.)$ represent transition probabilities given in Appendix A. The notations A and U represent age at first screening and time since last negative screening, and π_1, π_2, π_3, and π_4 are nonmissing fractions for preclinical Dukes' stages A and B, preclinical stages C and D, clinical stages A and B, and clinical stages C and D. The component of the total likelihood function can be decomposed into the following: the first, the second, and the third components are likelihoods for carcinoma free, preclinical Dukes' stages A and B, and preclinical stages C and D at first screening. Because subjects with pre-existing clinical colorectal cancer at first screening were excluded from the analysis, conditional probabilities were required in the aforementioned calculations. The fourth and the fifth components are likelihoods for postscreening cases: clinical Dukes' stages A and B and clinical Dukes' stages C and D. Because we assume that missing fractions are independent of Dukes' stage, this leads to $\pi_1 = \pi_2$, and $\pi_3 = \pi_4$. Dukes' stage information is available for only 51% (39/77) and 48% (16/33) of screen-detected and interval cancers, and assuming missing completely at random, missing data on Dukes' stage are treated as if one selects a random subset of the sample from all preclinical and clinical cancers. The algebra is based on the method of Chen et al.[12] The derivative of the score function and the information matrix based on first and second derivatives of the aforementioned likelihood function gives the point estimates and 95% confidence intervals in Table 2.