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Estimating the Unknown Parameters of the Natural History of Metachronous Colorectal Cancer Using Discrete-Event Simulation

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Abstract

Objectives—Some aspects of the natural history of metachronous colorectal cancer (MCRC), such as the rate of progression from adenomatous polyp to MCRC, are unknown. The objective of this study is to estimate a set of parameters revealing some of these unknown characteristics of MCRC.

Methods—The authors developed a computer simulation model that mimics the progression of MCRC for a 5-year period following the treatment of primary colorectal cancer (CRC). They obtained the inputs of the simulation model using longitudinal data for 284 CRC patients from the Mayo Clinic, Rochester.

Results—Five-year MCRC incidence and all-cause mortality were 7.4% and 12.7% in the patient cohort, respectively. Statistical analysis showed that 5-year MCRC incidence was associated with gender ($P = 0.05$), whereas both all-cause and CRC-related mortalities were associated with age ($P < 0.001$ and $P = 0.01$). Estimated annual probabilities of progression from adenomatous polyp to MCRC and from MCRC to metastatic MCRC were 0.14 and 0.28, respectively. Annual probabilities of mortality after MCRC and metastatic MCRC treatments were estimated to be 0.06 and 0.26, respectively. The estimated annual probability of mortality due to undetected MCRC was 0.16.

Conclusions—The results imply that MCRC, especially in women, may be more common than suggested by previous studies. In addition, statistics derived from the clinical data and results of the simulation model indicate that gender and age affect the progression of MCRC.

Keywords

colorectal cancer; discrete event simulation; simulation methods; operations research

Colorectal cancer (CRC) is one of the most common and deadly cancers. It is estimated that there were 146,000 new CRC cases and 49,000 CRC-related deaths in the United States in 2009.¹ Most CRC cases originate from adenomatous polyps in the colon and rectum.^{2–4} There is general consensus that adenomatous polyps grow over time and eventually progress to cancer. This pattern—polyp-to-cancer progression—allows for the use of colonoscopy for

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CRC prevention through the early detection and removal of adenomatous polyps before they become malignant.

Treatment modalities for CRC include curative surgery, systemic chemotherapy, and radiation therapy for rectal cancer. In many cases, these treatments, either alone or in combination, lead to increases in long-term survival. The overall 5-year survival for CRC in all-comers is 65.4%.⁵ However, some patients suffer from recurrence of their disease.^{6,7} In addition, patients who are successfully treated for CRC may suffer a metachronous CRC (MCRC) rather than metastatic disease.^{8,9} Several guidelines have suggested colonoscopy surveillance after CRC treatment for prevention and early detection of recurrent CRC and MCRC.^{2,10,11} For example, the American Gastroenterological Association (AGA) suggests that colonoscopy surveillance should start within the first year after CRC treatment.² If the first colonoscopy does not find a new neoplastic lesion (adenomatous polyp or MCRC), the next colonoscopy is recommended after 3 years. If the second colonoscopy is also negative for mucosal abnormalities, the interval is increased to 5 years.

Although CRC prevention and treatment procedures appear to be straightforward, there are many subtle issues discussed in the literature, including the true benefit of surveillance in CRC patients¹² and the impact of newer screening modalities, such as computed tomography (CT) colonography, on CRC prevention and treatment.¹³ In particular, clinicians need more guidance on choosing an appropriate preventive screening schedule for their patients.¹⁴

Most existing studies on MCRC have focused on determining incidence and mortality as well as identifying risk factors for MCRC.^{8,9,15} Several others have assessed the effectiveness of surveillance to prevent MCRC.^{16,17} However, there is limited research on estimating certain characteristics of the natural history of MCRC, such as how fast an adenomatous polyp progresses to MCRC in a patient with a known history of a malignancy, how fast MCRC progresses to metastatic MCRC (M-MCRC), and the probability of mortality due to MCRC-related causes. The uncertainty regarding these characteristics of MCRC progression impedes designing a better surveillance program to minimize MCRC risk in contrast to CRC prevention and early detection where such policy questions are well studied.^{18–25} The parameters that can reveal these unknown characteristics, such as polyp-to-MCRC progression probability, cannot be estimated from a database using conventional statistical tools due to the lack of appropriate data because of censoring (e.g., the detected adenomas are immediately removed, and no data can be collected on the growth rate of adenomas). Therefore, the use of a computational method, such as computer simulation, is necessary.

The purpose of this study is to estimate some unknown parameters of the natural history of MCRC, including the annual probability of polyp-to-MCRC and MCRC-to-M-MCRC progression and mortality due to MCRC-related causes. We estimated these parameters using a patient-level computer simulation model that mimics the progression of MCRC using a data set from the Mayo Clinic, Rochester (MCR) patient records. We also present some insightful statistics derived from our clinical data set such as 5-year MCRC incidence and mortality.

Analyzing the cost-effectiveness of colorectal cancer surveillance after CRC treatment to maximize the well-being of the patient is now more significant because of the advances in cancer treatments that have increased long-term cancer survival.²⁶ In this context, cost-effectiveness studies can directly benefit from the results provided in this article. Our study is also a novel application of inverse estimation, a method that obtains the physical parameters that characterize a certain model from observed outcomes data. There are similar

inverse problem studies that estimate the progression parameters of other cancer types²⁷ and the value of life for certain treatments such as dialysis.²⁸

METHODS

Patient Cohort

After obtaining institutional review board approval, we used a locally maintained tumor registry to identify patients who had been treated at the MCR for CRC during 1992 to 2006. We combined this information with an administrative billing database. We limited our analysis to only patients who resided within or immediately surrounding Olmsted County, Minnesota, where the MCR is located to ensure that we captured the majority of the specialty care received by our patient cohort. These local patients were identified using the county codes in their administrative billing data. We assumed that these patients, the vast majority of whom were first diagnosed and subsequently treated at the MCR, would receive their remaining cancer-related treatment at the MCR. Then, we matched these data to the Surgical Case Index (an MCR clinical database) to identify clinical information on the nature of lesions and polyps discovered during colonoscopies and curative surgeries. The surgical database was in free text format, so it required manual abstraction. Resource constraints only permitted us to abstract charts for 366 randomly chosen patients out of approximately 600 local patients who we identified. We excluded patients with known genetic-based CRC syndromes, familial adenomatous polyposis (FAP), and hereditary nonpolyposis colorectal cancer (HNPCC). There were no consensus guidelines for the surveillance of patients younger than 50 and older than 79 years at the time of the primary CRC treatment. Therefore, we limited our analysis to a final patient cohort of 284 patients who were between ages 50 and 79 at the time of their CRC treatment.

Input Parameters

The patients in our cohort were screened according to the AGA guidelines after their initial cancer treatment. We retrieved and abstracted the surgical charts and electronic records of these 284 patients to obtain various clinical information, including colonoscopy, surgical, and pathology reports as well as death certificates. We used this information to construct a longitudinal data set that included colonoscopy history, adenomatous polyp incidence (rate of patients with detected polyps), MCRC incidence (rate of patients with detected MCRC), and mortality for a 5-year period after the CRC treatment.

Adenomatous polyp occurrences were obtained from colonoscopy histories and pathology reports that provided details about the detected and removed polyps. We used these data to estimate the annual adenomatous polyp onset probability (an input in our simulation model) separately for each year after the initial treatment while accounting for the sensitivity of colonoscopy. We set the base values of the sensitivity of colonoscopy for detecting polyp and CRC as 85% and 90%, respectively.^{21,22} A patient may develop 1, 2, or 3 or more polyps with probabilities of 0.78, 0.13, and 0.09, respectively. We calculated this discrete probability distribution based on the number of detected polyps for each polyp occurrence. The case of developing 3 or more polyps is modeled as developing only 3 polyps for simplification. Although the patients in our cohort were frequently screened based on the AGA guidelines, some of the undetected adenomatous polyps may yet turn to MCRC. Such cases were identified from surgical reports to derive MCRC incidence, whereas mortality was calculated from death certificates. Known recurrent CRC cases and cancers that developed within the first 6 months after initial CRC treatment were excluded from the analysis to accurately distinguish MCRC from the recurrence of primary CRC. MCRC incidence and all-cause mortality rates from our clinical data were used as benchmark statistics to estimate the unknown parameters of the natural history of MCRC.

Calibration Procedure

We estimated the following unknown parameters of MCRC progression by calibrating our computer simulation model: 1) the annual polyp-to-MCRC progression probability, which represents the probability that an adenomatous polyp, which is either missed by colonoscopy surveillance or developed between 2 colonoscopy sessions, will progress to an MCRC lesion within 1 year; 2) MCRC-to-M-MCRC progression probability, which denotes the probability that an MCRC lesion will progress to an M-MCRC lesion within 1 year; 3) annual probability of mortality after MCRC treatment; 4) annual probability of mortality after M-MCRC treatment; 5) annual probability of mortality due to undetected MCRC (i.e., annual probability of death from a side effect of undetected CRC, including bowel obstruction); and 6) annual probability of mortality due to other reasons (P_{other}), which denotes annual probability of death because of a reason that cannot be associated with MCRC. Note that P_{other} defines lifetime without MCRC and depends on the gender and age group of the patients. For example, the probability that the lifetime of a patient without MCRC is longer than 5 years is equal to $(1 - P_{\text{other}})^5$.

Because clinical data do not provide necessary information about the progression of neoplastic lesions, these unknown parameters cannot be directly estimated from clinical data using conventional statistical methods such as regression. For example, the estimation of the annual polyp-to-MCRC progression probability requires information regarding when each patient developed an adenomatous polyp and when that polyp became MCRC, which is not available in clinical databases since detected polyps are immediately removed.

We therefore developed a computer simulation model in which these unknown parameters were key inputs. We then ran our model using every plausible combination of these unknown parameters and selected the combination that generated the output from the model that matched (with minimum mean square error) benchmark statistics (directly obtained from clinical data), including 5-year MCRC incidence and mortality rate. We calculated the mean square error (MSE) using the following formula, where MI_O , MR_O and MI_{SM} , MR_{SM} refer to the 5-year MCRC incidence (MI) and mortality rate (MR) observed from the clinical data and derived from the simulation model, respectively. This process is referred to as *calibration*.^{19,27}

$$MSE = [(MI_{SM} - MI_O)^2 + (MR_{SM} - MR_O)^2] / 2.$$

We made the following assumptions to reduce the complexity of the calibration process: 1) we assumed that the unknown parameters are time stationary because assuming otherwise increases the number of possible combinations of unknown parameters significantly. 2) We assumed that the annual probability of mortality after MCRC and M-MCRC treatments was proportional. Specifically, the latter probability was κ times the annual probability of mortality after MCRC treatment, where κ represents the ratio of the 5-year mortality rate of metastatic CRC from the Surveillance, Epidemiology and End Results (SEER) database to that of regional and local CRC combined. We use SEER data to estimate κ as 4.2. 3) We assumed that the annual probability of mortality after MCRC treatment was less than the annual probability of mortality due to undetected MCRC.

We specified a biologically plausible range for each unknown parameter given age and gender. We derived most of the initial plausible ranges (for the annual probability of polyp-to-MCRC progression, MCRC-to-M-MCRC progression, and mortality from other reasons) based on CRC progression probabilities from the literature and US life tables.^{21,22,29} For those parameters for which there was no guidance from the literature, we used plausible

ranges that would not contradict the clinical intuition. We then generated samples from this range using discrete step sizes. For example, if the range of unknown parameters is (0, 0.5] and the step size is 0.01, then we would evaluate 50 possible values ($\{0.01, 0.02, \dots, 0.5\}$) for each parameter using our simulation model. Although we had 6 unknown MCRC progression parameters to be estimated, we only calibrated 5 parameters because polyp-to-MCRC progression probability is κ times the annual probability of mortality after MCRC treatment. We therefore would simulate fewer than 50^5 combinations for the example given above as some of the combinations would not be feasible.

Several studies on CRC use a similar calibration process to ours to estimate unobservable CRC progression parameters using national CRC incidence from publicly available databases such as the SEER database as benchmark statistics.^{19,21,22} Among these studies, the one by Roberts and others¹⁹ is important as it builds a similar but more detailed discrete-time simulation model that mimics the progression of CRC. Another recent study uses a Markov model to represent the progression of MCRC in Korean males for a cost-effectiveness analysis of CRC surveillance³⁰; however, it does not explicitly present the parameters used to model MCRC progression.

Natural History of MCRC

Figure 1 shows the natural history of MCRC after the primary CRC treatment. We assumed that all patients are cancer and polyp free right after the treatment (see year 0 in Figure 1). A patient may develop an adenomatous polyp, stay polyp free, or die from a non-MCRC-related reason in the years following the treatment (see year 1 in Figure 1). We assumed that all MCRC cases arise from undetected adenomatous polyps (missed or that developed between 2 colonoscopy sessions). In a given year, if the patient does not die, an adenomatous polyp may grow and progress to MCRC with a particular probability or remain as a polyp (see year 2 in Figure 1). After an adenomatous polyp progresses to MCRC, one of the following occurs with a specific probability: 1) MCRC may stay as MCRC; 2) MCRC may progress to M-MCRC, which is detected and treated in the year it occurs; and 3) MCRC may result in death (see year 3 in Figure 1). Furthermore, a patient may develop a new adenomatous polyp each year after the MCRC treatment with a specific probability (see year 4 in Figure 1). The adenomatous polyp and MCRC progression probabilities depend only on age and gender.

Computer Simulation Model

Figure 2 describes our discrete-event system simulation model that mimics the progression of MCRC within 5 years following the primary CRC treatment for 6 age- and gender-based patient groups. In particular, the model specifies lesion appearance and progression as well as mortality as random events based on the natural history of MCRC. The model allows the existence of multiple colorectal lesions (adenoma and MCRC) at a given time and lets each lesion progress independently.

Our computer simulation model superimposes colonoscopy surveillance, which is scheduled based on the AGA guidelines, onto the natural progression of MCRC. When a patient undergoes a colonoscopy in a given year, the patient's lesions may be detected with a probability that is equal to the sensitivity of colonoscopy for an adenoma. We assumed that the detection and removal of each lesion are independent of other lesions. Patients undergo a treatment whenever colonoscopy surveillance detects an MCRC. Once a patient receives MCRC or M-MCRC treatment and survives the treatment, he or she becomes polyp and cancer free.

We constructed our simulation model using the JAVA programming language. We ran the model for 5 years or until the simulated patient died, whichever was sooner. We performed 5000 replications for each combination of unknown parameters and estimated several statistics, including MCRC incidence, MCRC risk, undetected MCRC rate, and all-cause mortality rate within 5 years after initial CRC treatment. We defined MCRC risk and all-cause mortality rate as the proportion of patients who have had MCRC and who died within 5 years after the initial treatment, respectively. In addition, we defined MCRC incidence as the proportion of patients who were diagnosed with MCRC or died from MCRC before diagnosis, and the rate of undetected MCRC was defined as the proportion of patients who had undiagnosed MCRC and stayed alive at the end of the fifth year.

Other Statistical Methods

We measured the significance of age and gender factors in adenomatous polyp incidence, MCRC incidence, and mortality using Pearson's chi-square test or Fisher's exact test when the former test was not applicable. We used SPSS (SPSS, Inc., an IBM Company, Chicago, IL) and R to compute Pearson's chi-square and Fisher's exact test calculations, respectively. In addition, we calculated the confidence intervals for the MCRC incidence and all-cause mortality using the following standard formula where n , M , and S^2 denote the sample size, mean, and variance, respectively ($\alpha = 0.05$).³¹

$$M(n) \mp t_{n-1, (1-\frac{\alpha}{2})} \sqrt{\frac{S^2(n)}{n}}.$$

Sensitivity Analysis

We conducted sensitivity analyses to assess the effect of uncertainties in the sensitivity of colonoscopy for detecting cancer lesions and the probability of missing polyps after initial CRC treatment. We set the sensitivity of colonoscopy for CRC lesions to be 90%, the average of the values reported in the literature.^{21,22} However, this sensitivity value could be higher than 90% because most cancer lesions are large and the patients who have a CRC history are likely to be screened more carefully. Hence, we repeated the calibration process by setting the sensitivity of colonoscopy for CRC lesions to 95%.

We also assumed that the patients are polyp free after they receive the initial CRC treatment. However, this assumption may not hold when the patients have CRC and adenomas simultaneously, which may be missed during the treatment and preoperative colonoscopy. It is reported that 36% of the patients who had an adenoma had multiple adenomas.³² We assumed that this proportion also holds for patients with CRC. Then approximately 5% ($36\% \times (100\% - 85\%)$) of the patients may have a missed adenomatous polyp after initial CRC treatment. Therefore, we repeat the calibration procedure for the case where the probability of missing a polyp is 0.05 instead of 0.

RESULTS

Polyp Incidence, MCRC Incidence, and Mortality from Clinical Data

There were a total of 284 patients in our cohort: 105 (37%) women and 179 (63%) men. Of those, 141 received CRC treatment before 2000, and 143 received it in or after 2000. Table 1 shows adenomatous polyp, MCRC, and mortality incidence within the 5 years following the CRC treatment stratified by gender and age. Colonoscopy exams detected 134 adenomatous polyps in 110 patients (39% of all patients). Table 1 implies that neither gender nor age was strongly associated with adenomatous polyp incidence ($P = 0.15$ and $P = 0.32$). In addition,

age was not strongly associated with adenomatous polyp incidence either among women or men ($P = 0.35$ and $P = 0.36$).

Within 5 years after the completion of CRC treatment, 21 (7.4%) of 284 patients had MCRC. MCRC cases appeared in 11% of women and 5% of men in our cohort; thus, MCRC was more common in women than men ($P = 0.05$). The MCRC incidence was highest in the 60 to 69 age group, but age alone was not significantly associated with MCRC incidence ($P = 0.20$). Age was not significantly associated with MCRC incidence among either women or men ($P = 0.73$ and $P = 0.22$).

Within 5 years following the CRC treatment, 36 patients (12.7% of our cohort) died. Of these 36 patients, 24 (17% of 141 patients) received the CRC treatment before 2000, and 12 (8% of 143 patients) received it in or after 2000. CRC was listed as a cause of death on the death certificate in 18 patients; 3 of these 18 patients were diagnosed with MCRC before they died. Only these 3 patients were assumed to have died from MCRC; the remaining 15 patients were assumed to have died from the complications related to initial CRC and its treatment. The mortality rates in Table 1 imply that gender was not significantly associated with 5-year all-cause and CRC-related mortality ($P = 0.32$ and 0.24 , respectively). Note that both all-cause and CRC-related mortalities were higher in older patients ($P < 0.001$ and $P = 0.01$, respectively).

Validation of the Computer Simulation Model

Our calibrated computer simulation model estimated the 5-year MCRC incidence and all-cause mortality as 7.3% and 12.7% for 50- to 79-year-old patients, respectively. The corresponding rates from our clinical data were 7.4% and 12.7%. Table 2 shows benchmark statistics produced by our simulation model; these were very similar to those statistics from the clinical data presented in Table 1. In addition, Table 3 shows the mean square error values and confidence intervals of MCRC incidence and all-cause mortality that cover the actual rates in Table 1. We therefore contend that our computer simulation model provides a helpful guide to evaluate counterfactual claims in the real world.

Our model also estimated the number of patients who developed MCRC within the 5 years after the CRC treatment, including patients with undetected MCRC at the end of the fifth year. An undetected MCRC occurs if the cancer is missed during the last colonoscopy or if it develops after the last colonoscopy within the 5-year period. The estimated 5-year MCRC risk was 7.9%, and thus the undetected MCRC rate was $7.9\% - 7.3\% = 0.6\%$. This implies that around 7.6% ($0.6/7.9 = 7.6\%$) of the MCRC cases that occurred in our patient cohort within 5 years following the primary CRC treatment could not be detected by the colonoscopy surveillance performed based on the AGA guidelines. Table 2 also shows 5-year MCRC risk and undetected MCRC rate by gender and age. As expected, 5-year MCRC risk was positively correlated with 5-year MCRC incidence, and both statistics followed the same pattern by gender and age. The 5-year undetected MCRC rate was slightly higher in women than in men. Furthermore, the undetected MCRC rate did not change with age in women, whereas the rate was minimum in the 60 to 69 age group in men.

Estimated Unknown Parameters of the Natural History of MCRC

Estimated unknown parameters of the natural history of MCRC are presented in Table 4 by gender and age. The annual polyp-to-MCRC progression probability was 0.14. This probability was higher in women as well as in younger and older age groups.

The MCRC-to-M-MCRC progression probability was 0.28 for our sample. The probability of progression from MCRC to M-MCRC did not vary by gender and age except among men

in the 50 to 59 age group. This result is consistent with existing studies, which have not reported any effect of gender or age on this probability for primary CRC.²¹

The annual probabilities of mortality after MCRC and M-MCRC treatments were 0.06 and 0.26, respectively. Mortality probabilities after MCRC and M-MCRC treatment were higher in older patients. In general, mortality probabilities after MCRC and M-MCRC treatment were slightly higher in women than in men.

The annual probabilities of mortality due to undetected MCRC and other reasons were 0.16 and 0.021, respectively. Note that mortality due to other reasons occurs when a patient dies due to a reason that cannot be associated specifically with MCRC. Both probabilities of mortality due to undetected MCRC and other causes were higher in older patients. The probability of mortality due to other reasons was slightly higher in women than in men. The probability of mortality due to undetected MCRC was the same for both genders in each age group except 60 to 69, where women were almost twice as likely to die from undetected MCRC as men. It should be noted that all mortality probabilities (last 4 columns of Table 4) increase with age.

Simulation Results for the Sensitivity Analysis

Table 5 illustrates the estimation of unknown parameters of natural history of MCRC with 95% sensitivity for CRC, whereas Table 6 shows the simulated 5-year MCRC incidence, MCRC, and undetected MCRC risks as well as 5-year mortality for this case. The estimated unknown parameters for the base case (Table 4) and the case for 95% sensitivity (Table 5) are very similar. As expected, 5-year MCRC incidence and mortality rates for both cases are almost identical because in both cases, the calibration process matched these simulation outcomes to the actual MCRC incidence and mortality from the clinical data. However, the case for 95% sensitivity is associated with slightly less MCRC risk and undetected MCRC because as the sensitivity increases, colonoscopy misses fewer adenomas that can progress to MCRC.

Table 7 illustrates the new estimation of unknown parameters of the natural history of MCRC when the probability of missing an adenoma is 0.05, whereas Table 8 shows the simulated 5-year MCRC incidence, MCRC and undetected MCRC risks, and 5-year mortality for this case. The estimated unknown parameters for the new case (Table 7) are very similar to those for the base case (Table 4). However, the annual probabilities of polyp-to-MCRC progression for the new case are lower than those for the base case because, in the new case, 5% of the patients will have more risk of developing MCRC than those in the base case. Therefore, a lower polyp-to-MCRC progression probability in this case is sufficient to enforce our simulation model to produce the same 5-year MCRC incidence and mortality results with the base case.

DISCUSSION

In this study, we estimated 6 unknown parameters of the natural history of MCRC using a computer simulation model and clinical data from a well-defined patient cohort at a single institution. We derived adenomatous polyp onset probabilities directly from clinical data, whereas the remaining unknown parameters were estimated via calibration. We also derived several important statistics from our data, such as metachronous polyp and MCRC incidence. These unknown parameters and statistics based on clinical data may help clinicians to better understand the natural history of MCRC and aid clinical researchers to build clinical decision models for MCRC and CRC surveillance.

Our findings are varied and novel. First, we find that MCRC may be more common than has previously been reported in the literature. Previous studies have reported lifetime MCRC risk of between 5% and 10%⁶ and that approximately 50% of MCRC cases occur within the first 5.5 years after diagnosis of the primary CRC.⁸ Thus, our finding of a 5-year MCRC incidence of 7.4% implies a higher lifetime MCRC risk in our patient cohort relative to the range of risk reported in the literature. Second, the 5-year adenomatous polyp incidence in our patient cohort, 39%, was relatively high compared with the reported range of long-run metachronous adenomatous polyp incidence of 30% to 50%.^{33–35} Note that there have been occasional reports of such high MCRC and metachronous adenomatous polyp incidence.³⁶

We also find that MCRC risk is higher in patients with CRC history than CRC risk in the general population.⁴ We concluded this because the MCRC incidence in our patient cohort (7.4%) was higher than the lifetime CRC risk (5.2%) based on 2003–2005 SEER data.⁵ Because MCRC incidence in our patient cohort was higher than CRC incidence in the US population, the calibrated unknown parameters of the natural history of MCRC were higher than corresponding estimated parameters for CRC in the literature.^{21–23}

The relatively high metachronous adenomatous polyp and MCRC incidence in our study may have been due to the composition of our patient cohort, which consisted of more men than women. On the other hand, the contribution of the gender distribution to a higher adenomatous polyp and MCRC incidence may not have been significant because men are slightly more prone to have CRC,⁵ and such gender differences were present in most patient cohorts in the literature.^{9,17,36,37} In addition, our patient cohort had a higher 5-year survival (87.3%) than the patients in the SEER data (64.4%),⁵ which may have been because our cohort had better access to high-quality health care from the MCR. Our patients were therefore more likely to survive until they developed colorectal lesions than patients in the SEER data.

Moreover, the 5-year survival rates among patients who received CRC treatment before 2000 and in or after 2000 were 83% and 92% in our patient cohort, respectively. This result implies that CRC survival increases in time as suggested in the literature.²⁶ Therefore, planning surveillance protocols of CRC patients to prevent MCRC may become more important for the long-term well-being of the patients in the future.

We also find that gender and age have an impact on MCRC progression. Although we did not find a significant difference in adenomatous polyp incidence between women and men in our cohort ($P = 0.15$), 5-year MCRC incidence was higher in women ($P = 0.05$). This observation may indicate that MCRC progression was more aggressive in women because although women had at most as many adenomatous polyps as men had, they had higher MCRC incidence. Thus, adenomatous polyps seem to have progressed to MCRC at a higher rate among women. Note that the estimated polyp-to-MCRC progression probabilities were higher in women than men due to higher MCRC incidence in women. Although most existing studies have reported no gender difference in MCRC incidence,⁸ few studies have reported higher recurrent CRC incidence in women after their primary CRC treatment.³⁷

Moreover, MCRC mortality probabilities produced by our simulation model were higher in women. Although this result may appear to be counterintuitive given that US life expectancy for women is higher than it is for men, our patient cohort differs from the general population because patients in our cohort received CRC treatment. In addition, some studies report lower survival in women both after CRC and bladder cancer treatments,^{38,39} and several studies report that women are more prone to have advanced-stage CRC than men, which may reduce posttreatment survival for women.^{40,41} Although MCRC mortality was higher in women, other-cause mortality rate, which was the difference between all-cause and CRC-

related mortality rate, was similar for men and women (Table 1). This shows that the gender-based differences in all-cause mortality (Table 1) in our patient cohort are primarily due to CRC-related causes.

Both rates of all-cause and CRC-related mortality were higher for older patients in our cohort ($P < 0.001$ and $P = 0.01$). Thus, we conclude that age affects MCRC progression. Similarly, the estimated probabilities of mortality after MCRC and M-MCRC treatment and mortality due to undetected MCRC were generally higher in older patients (Table 4). This may have been due to at least 2 reasons: 1) younger patients may have been more able to successfully complete treatment without any dose reduction, and 2) aggressive treatments, such as chemotherapy, may not have been used in older patients. Although age was not significantly associated with adenomatous polyp and MCRC incidence ($P = 0.32$ and $P = 0.20$, respectively), we observed certain age-based patterns in the polyp-to-MCRC progression probabilities. For example, polyp-to-MCRC progression probability was lowest in 60- to 69-year-old patients (Table 4).

Another important finding is that the estimated undetected MCRC rate, defined as the difference between MCRC risk and MCRC incidence, was higher in women (around 0.9% vs. 0.5%). This implies that undetected MCRC cases may have been more common among women. This may have been due to 2 reasons: 1) women in our patient cohort had a higher MCRC incidence than men, and 2) the proportion of men with detected adenomatous polyps was higher than that of women (42% vs. 33% in our patient cohort). Because physicians at the Mayo Clinic recommend increasing the frequency of colonoscopy sessions after a positive colonoscopy finding,² men on average received more colonoscopy exams than women. Thus, there were likely to have been fewer missed MCRC cases among men. Indeed, it has been previously reported that women had higher new or missed CRC incidence after colonoscopy screenings because they were less likely to be screened 3 years before the diagnosis of missed or new CRC.⁴²

Our study has several limitations. First, we had a small sample size, which may have caused sampling error in the estimation of unknown parameters such as the mortality probabilities for 50- to 59-year-old patients. However, we minimized other sources of sampling errors by collecting our data from a reliable single-institution data set through a careful and detailed data abstraction. Having a small sample size also prevented us from cross-validating our model using our clinical data. The cross-validation of our model's results to the published results also was not possible because of the lack of appropriate data for comparison. In addition, having a small sample size limited us to consider only a single type of adenomatous polyp and MCRC lesion in our model. Existing simulation models on CRC categorize adenomatous polyps based on size (small and large) and location (right colon, left colon, etc.) as well as considering cancer lesions in different stages (local and regional).^{19,22} Although categorizing adenomatous polyps and cancer lesions into subgroups is a more desirable approach, our patient cohort was not large enough to estimate the lesion progression probabilities based on different polyp and cancer lesion types. Furthermore, we restricted the surveillance period to 5 years because of the limited sample size. However, we conclude that this was reasonable because it has been reported that about half of all MCRC cases occur within the first 5.5 years after the CRC diagnosis.⁸

Second, our patient cohort largely consisted of whites, who are less likely than African Americans yet more likely than Asians to develop CRC.⁴³ Finally, we assumed that the compliance to CRC surveillance was 100% in our patient cohort, which is not an uncommon assumption in the literature.³⁰ To partially justify this assumption, we ensured that our cohort included only local patients who were very likely to comply with their colonoscopy surveillance schedules.

We present a natural history computer simulation model that mimics the progression of MCRC under the surveillance protocol suggested by the AGA. We describe how clinical data can be used to feed such a computer simulation model and refine it to estimate previously unknown parameters of the natural history of MCRC by calibrating some parameters of the model. Our results imply that MCRC may be more common relative to how it has been reported in the clinical literature. Our results also indicate that gender and age may affect certain characteristics of MCRC progression. Future opportunities with this model include a cost-effectiveness analysis for the evaluation of different colonoscopy surveillance schedules for patients with a prior history of CRC.

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References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun M. Cancer statistics, 2009. *CA Cancer J Clin.* 2009; 59:225–49. [PubMed: 19474385]
2. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. *Gastroenterology.* 2003; 124:544–60. [PubMed: 12557158]
3. Sack J, Rothman J. Colorectal cancer: natural history and management. *Hosp Physician.* 2000; 36:64–73.
4. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology.* 1997; 112:594–642. [PubMed: 9024315]
5. National Cancer Institute. Surveillance Epidemiology and End Results. Bethesda, MD: National Cancer Institute; 2008. Available from: <http://seer.cancer.gov.html>
6. Scholefield JH, Steele RJ. Guidelines for follow up after resection of colorectal cancer. *Gut.* 2002; 51:v3–v5. [PubMed: 12221030]
7. Kjeldsen BJ, Kronborg O, Fenger C, Jorgensen OD. A prospective randomized study of follow-up after radical surgery for colorectal cancer. *Br J Surg.* 1997; 84:666–9. [PubMed: 9171758]
8. Fajobi O, Yiu CY, Sen-Gupta SB, Boulos PB. Metachronous colorectal cancers. *Br J Surg.* 1998; 85:897–901. [PubMed: 9692559]
9. Park IJ, Yu CS, Kim HC, Jung YH, Han KR, Kim JC. Metachronous colorectal cancer. *Colorectal Dis.* 2006; 8:323–7. [PubMed: 16630238]
10. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *Gastroenterology.* 2006; 130:1872–85. [PubMed: 16697750]
11. Davila RE, Rajan E, Baron TH, et al. ASGE guideline: colorectal cancer screening and surveillance. *Gastrointest Endosc.* 2006; 63:546–57. [PubMed: 16564851]
12. Li Destri G, Di Cataldo A, Puleo S. Colorectal cancer follow-up: useful or useless? *Surg Oncol.* 2006; 15:1–12. [PubMed: 16891116]
13. Regueiro CR. AGA Future Trends Committee report: colorectal cancer: a qualitative review of emerging screening and diagnostic technologies. *Gastroenterology.* 2005; 129:1083–103. [PubMed: 16143145]
14. Pfister DG, Benson AB III, Somerfield MR. Clinical practice: surveillance strategies after curative treatment of colorectal cancer. *N Engl J Med.* 2004; 350:2375–82. [PubMed: 15175439]
15. Liang W. Age, sex and the risk of grade-specific second primary colorectal cancer: evidence for the protective effect of female hormone. *Eur J Cancer.* 2007; 43:1856–61. [PubMed: 17604155]

16. Vogel VG. Identifying and screening patients at risk of second cancers. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:2027–32. [PubMed: 17057026]
17. Bouvier AM, Latournerie M, Jooste V, Lepage C, Cottet V, Faivre J. The lifelong risk of metachronous colorectal cancer justifies long-term colonoscopic follow-up. *Eur J Cancer.* 2008; 44:522–7. [PubMed: 18255278]
18. Pickhardt P, Hassan C, Laghi A, Zullo A, Kim D, Morini S. Cost-effectiveness of colorectal cancer screening with computed tomography colonography. *Cancer.* 2007; 109:2213–21. [PubMed: 17455218]
19. Roberts S, Wang L, Klein R, Ness R, Dittus R. Development of a simulation model of colorectal cancer. *ACM Trans Model Comput Simul.* 2007; 18:4–30.
20. Hassan C, Pickhardt P, Laghi A, et al. Computed tomographic colonography to screen for colorectal cancer, extracolonic cancer, and aortic aneurysm: model simulation with cost-effectiveness analysis. *Arch Intern Med.* 2008; 168:696–705. [PubMed: 18413551]
21. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. *JAMA.* 2000; 284:1954–61. [PubMed: 11035892]
22. Vijan S, Hwang EW, Hofer TP, Hayward RA. Which colon cancer screening test? A comparison of costs, effectiveness, and compliance. *Am J Med.* 2001; 111:593–601. [PubMed: 11755501]
23. Song K, Fendrick A, Ladabaum U. Fecal DNA testing compared with conventional colorectal cancer screening methods: a decision analysis. *Gastroenterology.* 2004; 126:1270–9. [PubMed: 15131787]
24. Zauber A, Lansdorp-Vogelaar I, Knudsen A, Wilschut J, van Ballegooijen M, Kuntz K. Evaluating test strategies for colorectal cancer screening: a decision analysis for the US Preventive Services Task Force. *Ann Intern Med.* 2008; 149:659–69. [PubMed: 18838717]
25. Pignone, M.; Russell, L.; Wagner, J. *Economic Models of Colorectal Cancer Screening in Average-Risk Adults: Workshop Summary.* Washington, DC: National Academy Press; 2005.
26. Sun E, Jena A, Lakdawalla D, Reyes C, Philipson T, Goldman D. The contributions of improved therapy and earlier detection to cancer survival gains, 1988–2000. *Health Econ.* 2010; 13:1–20.
27. Stout N, Knudsen A, Kong C, McMahon P, Gazelle G. Calibration methods used in cancer simulation models and suggested reporting guidelines. *Pharmacoeconomics.* 2009; 27:533–45. [PubMed: 19663525]
28. Lee C, Chertow G, Zenios S. An empiric estimate of the value of life: updating the renal dialysis cost-effectiveness standard. *Value Health.* 2008; 12:80–7. [PubMed: 19911442]
29. Arias E. United States life tables, 2004. *Natl Vital Stat Rep.* 2007; 56:1–40. [PubMed: 18274319]
30. Park S, Kim S, Earle C, Jeong S, Yun Y. What is the most cost-effective strategy to screen for second primary colorectal cancers in male cancer survivors in Korea? *World J Gastroenterol.* 2009; 15:3153–60. [PubMed: 19575496]
31. Law, A.; Kelton, W. *Simulation Modeling and Analysis.* New York: McGraw-Hill; 2000.
32. van Stolk R, Beck G, Baron J, Haile R, Summers R. Adenoma characteristics at first colonoscopy as predictors of adenoma recurrence and characteristics at follow-up. *Gastroenterology.* 1998; 115:13–8. [PubMed: 9649453]
33. Neugut A, Lautenbach E, Abi-Rached B, Forde K. Incidence of adenomas after curative resection for colorectal cancer. *Am J Gastroenterol.* 1996; 91:2096–8. [PubMed: 8855728]
34. Schwartz R, McKenzie S. Update on postoperative colorectal cancer surveillance. *Curr Surg.* 2005; 62:491–4. [PubMed: 16125604]
35. Nusko G, Mansmann U, Wiest G, Brueckl W, Kirchner T, Hahn E. Right-sided shift found in metachronous colorectal adenomas. *Endoscopy.* 2001; 33:574–9. [PubMed: 11473327]
36. Balleste B, Bessa X, Pinol V, et al. Detection of metachronous neoplasms in colorectal cancer patients: identification of risk factors. *Dis Colon Rectum.* 2007; 50:971–80. [PubMed: 17468913]
37. Chu D, Chansky K, Alberts D, et al. Adenoma recurrences after resection of colorectal carcinoma: results from the Southwest Oncology Group 9041 calcium chemoprevention pilot study. *Ann Surg Oncol.* 2003; 10:870–5. [PubMed: 14527904]
38. Stiller C. Centralised treatment, entry to trials and survival. *Br J Cancer.* 1994; 70:352–62. [PubMed: 8054285]

39. Mungan N, Aben K, Schoenberg M, et al. Gender differences in stage-adjusted bladder cancer survival. *Urology*. 2000; 55:876–80. [PubMed: 10840099]
40. Mandelblatt J, Andrews H, Kao R, Wallace R, Kerner J. The late-stage diagnosis of colorectal cancer: demographic and socioeconomic factors. *Am J Public Health*. 1996; 86:1794–7. [PubMed: 9003140]
41. Schwartz K, Crossley-May H, Vigneau F, Brown K, Banerjee M. Race, socioeconomic status and stage at diagnosis for five common malignancies. *Cancer Causes Control*. 2003; 14:761–6. [PubMed: 14674740]
42. Bressler B, Paszat L, Chen Z, Rothwell D, Vinden C, Rabeneck L. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. *Gastroenterology*. 2007; 132:96–102. [PubMed: 17241863]
43. Surveillance, Epidemiology and End Results (SEER). Fast statistics. Available from: <http://seer.cancer.gov/faststats/selections.php?series=cancer>

Figure 1.

Natural history of MCRC. P_{polyp} , the annual probability of developing a polyp (calculated using patient cohort data); P_{MCRC} , the annual probability of polyp-to-MCRC progression (estimated via calibration); P_{M-MCRC} , the annual probability of MCRC-to-M-MCRC progression (estimated via calibration); P_{D0} , P_{D1} , the annual probability of mortality from other reasons that cannot be associated with MCRC (estimated via calibration); P_{D2} , the annual probability mortality from undetected MCRC (estimated via calibration); P_{D3} , the annual probability of mortality after M-MCRC treatment (estimated via calibration); MCRC, metachronous colorectal cancer; M-MCRC, meta-static MCRC.

Figure 2. Flowchart of the MCRC computer simulation model. MCRC, metachronous colorectal cancer; M-MCRC, metastatic MCRC; AGA, American Gastroenterology Association.

Five-Year First Metachronous Adenomatous Polyp, MCRC, and Mortality Incidences from the Mayo Clinic, Rochester Database

Table 1

Metachronous Adenomatous Polyp Incidence									
Age	Women			Men			Both Genders		
	Patients, <i>n</i>	Polyps, <i>n</i>	Rate, %	Patients, <i>n</i>	Polyps, <i>n</i>	Rate, %	Patients, <i>n</i>	Polyps, <i>n</i>	Rate, %
50-59	22	5	23	38	18	47	60	23	38
60-69	42	17	41	83	37	45	125	54	43
70-79	41	13	32	58	20	35	99	33	33
50-79	105	35	33	179	75	42	284	110	38.7

Metachronous Colorectal Cancer (MCRC) Incidence									
Age	Women			Men			Both Genders		
	Patients, <i>n</i>	MCRC, <i>n</i>	Rate, %	Patients, <i>n</i>	MCRC, <i>n</i>	Rate, %	Patients, <i>n</i>	MCRC, <i>n</i>	Rate, %
50-59	22	2	9	38	2	5	60	4	7
60-69	42	4	10	83	2	2	125	6	5
70-79	41	6	15	58	5	9	99	11	11
50-79	105	12	11	179	9	5	284	21	7.4

Mortality Due to All Causes									
Age	Women			Men			Both Genders		
	Patients, <i>n</i>	Mortality, <i>n</i>	Rate, %	Patients, <i>n</i>	Mortality, <i>n</i>	Rate, %	Patients, <i>n</i>	Mortality, <i>n</i>	Rate, %
50-59	22	0	0	38	0	0	60	0	0
60-69	42	5	12	83	7	8	125	12	10
70-79	41	11	27	58	13	22	99	24	24
50-79	105	16	15	179	20	11	284	36	12.7

Mortality Due to Colorectal Cancer-Related Causes									
Age	Women			Men			Both Genders		
	Patients, <i>n</i>	Mortality, <i>n</i>	Rate, %	Patients, <i>n</i>	Mortality, <i>n</i>	Rate, %	Patients, <i>n</i>	Mortality, <i>n</i>	Rate, %
50-59	22	0	0	38	0	0	60	0	0
60-69	42	3	7	83	4	5	125	7	6

Metachronous Adenomatous Polyp Incidence									
Age	Women			Men			Both Genders		
	Patients, <i>n</i>	Polyps, <i>n</i>	Rate, %	Patients, <i>n</i>	Polyps, <i>n</i>	Rate, %	Patients, <i>n</i>	Polyps, <i>n</i>	Rate, %
70–79	41	6	15	58	5	9	99	11	11
50–79	105	9	9	179	9	5	284	18	6.3

Table 2
Model Output: Five-Year MCRC Incidence, MCRC Risk, Mortality, and Undetected MCRC Rates

Age	Five-Year MCRC Incidence Rate, %			Five-Year MCRC Risk, %		
	Women	Men	Both Genders	Women	Men	Both Genders
50–59	9.1	5.2	6.7	10.0	5.8	7.3
60–69	9.4	2.4	4.7	10.4	2.6	5.3
70–79	14.1	8.4	10.7	15.0	9.0	11.5
50–79	11.2	4.9	7.3	12.1	5.4	7.9

Age	Five-Year Mortality Rate, %			Undetected MCRC Rate, %		
	Women	Men	Both Genders	Women	Men	Both Genders
50–59	0	0	0	0.9	0.5	0.7
60–69	11.9	8.5	9.6	1.0	0.3	0.5
70–79	26.8	22.4	24.2	0.9	0.7	0.8
50–79	15.2	11.2	12.7	0.9	0.5	0.6

MCRC, metachronous colorectal cancer.

Table 3
Model Output: CIs and Square Errors for 5-Year MCRC Incidence and Mortality Rates

Age	Five-Year MCRC Incidence Rate (%) for Women				Five-Year MCRC Incidence Rate (%) for Men			
	Mean	Lower 95% CI Limit	Upper 95% CI Limit	Square Error	Mean	Lower 95% CI Limit	Upper 95% CI Limit	Square Error
50-59	9.1	8.3	9.9	8.3×10^{-9}	5.2	4.6	5.9	5.3×10^{-8}
60-69	9.4	8.6	10.2	1.0×10^{-6}	2.4	1.9	2.8	2.5×10^{-7}
70-79	14.1	13.1	15.1	2.9×10^{-5}	8.4	7.6	9.1	5.8×10^{-6}

Age	Five-Year Mortality Rate (%) for Women				Five-Year Mortality Rate (%) for Men			
	Mean	Lower 95% CI Limit	Upper 95% CI Limit	Square Error	Mean	Lower 95% CI Limit	Upper 95% CI Limit	Square Error
50-59	0	0	0	0	0	0	0	0
60-69	11.9	11.0	12.8	2.3×10^{-9}	8.5	7.7	9.3	4.4×10^{-7}
70-79	26.8	25.6	28.0	8.6×10^{-9}	22.4	21.2	23.6	1.9×10^{-8}

The square errors are the square differences of rates from clinical data (Table 1) and simulation output (Table 2). CI, confidence interval; MCRC, metachronous colorectal cancer.

Table 4

Model Output: Estimation of Unknown Parameters of MCRC Progression

Gender	Age	Annual Probability of Polyp-to-MCRC Progression	Annual Probability of MCRC-to- M-MCRC Progression	Annual Probability of Mortality after MCRC Treatment	Annual Probability of Mortality after M-MCRC Treatment	Annual Probability of Mortality Due to Undetected MCRC	Annual Probability of Mortality Due to Other Causes
Women	50-59	0.235	0.20	0	0	0	0
	60-69	0.16	0.24	0.04	0.172	0.11	0.019
	70-79	0.295	0.32	0.16	0.688	0.37	0.042
Men	50-79	0.23	0.26	0.08	0.34	0.19	0.024
	50-59	0.095	0.12	0	0	0	0
	60-69	0.03	0.38	0.03	0.129	0.05	0.015
Both genders	70-79	0.15	0.28	0.11	0.473	0.37	0.039
	50-79	0.08	0.29	0.05	0.21	0.14	0.020
	50-79	0.14	0.28	0.06	0.26	0.16	0.021

MCRC, metachronous colorectal cancer; M-MCRC, metastatic MCRC.

Table 5
Estimation of Unknown Parameters of MCRC Progression When the Sensitivity of Colonoscopy for Colorectal Cancer Is 90%

Gender	Age	Annual Probability of Polyp-to-MCRC Progression	Annual Probability of MCRC-to-M-MCRC Progression	Annual Probability of Mortality after MCRC Treatment	Annual Probability of Mortality after M-MCRC Treatment	Annual Probability of Mortality Due to Undetected MCRC	Annual Probability of Mortality Due to Other Causes
Women	50-59	0.225	0.26	0	0	0	0
	60-69	0.160	0.25	0.05	0.22	0.13	0.019
	70-79	0.300	0.39	0.17	0.73	0.39	0.042
Men	50-79	0.23	0.31	0.09	0.37	0.2	0.02
	50-59	0.105	0.24	0	0	0	0
	60-69	0.030	0.25	0.03	0.13	0.05	0.015
Both genders	70-79	0.155	0.29	0.13	0.56	0.31	0.038
	50-79	0.09	0.26	0.06	0.24	0.14	0.02
	50-79	0.14	0.28	0.07	0.29	0.12	0.021

MCRC, metachronous colorectal cancer; M-MCRC, metastatic MCRC.

Five-Year MCRC Incidence, MCRC Risk, Mortality, and Undetected MCRC Rates When the Sensitivity of Colonoscopy for Colorectal Cancer Is 90%

Table 6

Age	Five-Year MCRC Incidence Rate, %			Five-Year MCRC Risk, %		
	Women	Men	Both Genders	Women	Men	Both Genders
50–59	9.0	5.3	6.6	9.7	5.6	7.1
60–69	9.4	2.5	4.8	10.2	2.8	5.3
70–79	14.1	8.4	10.8	14.8	9.0	11.4
50–79	11.1	5.0	7.3	11.9	5.4	7.8

Age	Five-Year Mortality Rate, %			Undetected MCRC Rate, %		
	Women	Men	Both Genders	Women	Men	Both Genders
50–59	0	0	0	0.7	0.4	0.5
60–69	11.9	8.4	9.6	0.8	0.3	0.5
70–79	26.8	22.4	24.2	0.7	0.6	0.6
50–79	15.2	11.2	12.7	0.7	0.4	0.5

MCRC, metachronous colorectal cancer.

Table 7
Estimation of Unknown Parameters of MCRC Progression When the Probability of Missing a Polyp Is 0.05

Gender	Age	Annual Probability of Polyp-to-MCRC Progression	Annual Probability of MCRC-to-M-MCRC Progression	Annual Probability of Mortality after MCRC Treatment	Annual Probability of Mortality after M-MCRC Treatment	Annual Probability of Mortality Due to Undetected MCRC	Annual Probability of Mortality Due to Other Causes
Women	50-59	0.175	0.2	0	0	0	0
	60-69	0.145	0.27	0.04	0.17	0.13	0.019
	70-79	0.280	0.33	0.13	0.56	0.29	0.042
Men	50-79	0.20	0.28	0.07	0.29	0.17	0.02
	50-59	0.100	0.22	0	0	0	0
	60-69	0.035	0.29	0.04	0.17	0.05	0.015
Both genders	70-79	0.120	0.33	0.11	0.47	0.41	0.038
	50-79	0.08	0.29	0.05	0.23	0.16	0.02
	50-79	0.12	0.28	0.06	0.25	0.16	0.02

MCRC, metachronous colorectal cancer; M-MCRC, metastatic MCRC.

Table 8
Five-Year MCRC Incidence, MCRC Risk, Mortality, and Undetected MCRC Rates When the Probability of Missing a Polyp Is 0.05

Age	Five-Year MCRC Incidence Rate, %			Five-Year MCRC Risk, %		
	Women	Men	Both Genders	Women	Men	Both Genders
50–59	9.1	5.2	6.6	10.0	5.7	7.2
60–69	9.4	2.4	4.8	10.2	2.7	5.2
70–79	14.1	8.4	10.7	15.1	8.9	11.5
50–79	11.2	4.9	7.2	12.1	5.4	7.8

Age	Five-Year Mortality Rate, %			Undetected MCRC Rate, %		
	Women	Men	Both Genders	Women	Men	Both Genders
50–59	0	0	0	0.9	0.5	0.5
60–69	11.9	8.4	9.6	0.8	0.3	0.5
70–79	26.8	22.4	24.2	1.0	0.5	0.6
50–79	15.2	11.1	12.7	0.9	0.4	0.6

MCRC, metachronous colorectal cancer.