How Much Can Current Interventions Reduce Colorectal Cancer Mortality in the U.S.?

Mortality Projections for Scenarios of Risk-Factor Modification, Screening, and Treatment

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BACKGROUND. Although colorectal cancer (CRC) is the second leading cause of cancer death in the U.S., available interventions to reduce CRC mortality are disseminated only partially throughout the population. This study assessed the potential reduction in CRC mortality that may be achieved through further dissemination of current interventions for risk-factor modification, screening, and treatment.

METHODS. The MISCAN-COLON microsimulation model was used to simulate the 2000 U.S. population with respect to CRC risk-factor prevalence, screening use, and treatment use. The model was used to project age-standardized CRC mortality from 2000 to 2020 for 3 intervention scenarios.

RESULTS. Without changes in risk-factor prevalence, screening use, and treatment use after 2000, CRC mortality would decrease by 17% by the Year 2020. If the 1995 to 2000 trends continue, then the projected reduction in mortality would be 36%. However, if trends in the prevalence of risk factors could be improved above continued trends, if screening use increased to 70% of the target population, and if the use of chemotherapy increased among all age groups, then a 49% reduction would be possible. Screening drove most (23%) of the projected mortality reduction with these optimistic trends; however, decreasing risk factors (16%) and increasing use of chemotherapy (10%) also contributed substantially. The contribution of risk factors may have been overestimated, because effect estimates could not be obtained from randomized controlled trials.

CONCLUSIONS. Currently available interventions for risk-factor modification, screening, and treatment have the potential to reduce CRC mortality by almost 50% by the Year 2020. However, without action now to further increase the uptake of current effective interventions, the reduction in CRC mortality may be only 17%. ***Cancer*** **2006;107:1624–33.** © *2006 American Cancer Society.*

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Colorectal cancer (CRC) is the second leading cause of cancer death in the U.S. For 2006, it is estimated that there will be 148,610 patients with newly diagnosed CRC and 55,170 deaths from CRC.[1] The Healthy People Consortium and the American Cancer Society (ACS) recognize the burden of CRC and have recommended the objective of reducing CRC mortality by 34% in 2010[2] and by 50% in 2015,[3] respectively.

CRC deaths can be prevented. Seventy percent of colon cancers in a cohort of middle-aged men in the U.S. potentially would be

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TABLE 1
Risk Factors for Colorectal Carcinoma in the MISCAN-COLON Microsimulation Model: Categories of Exposure and Assumed Relative Risks for Developing Colorectal Adenomas

Risk factor	Categories	RR for adenomas	Reference(s)
Smoking	Smoker 15 years ago vs. nonsmoker 15 years ago	1.8	Giovannucci et al., 1994[24,25]
Obesity	Body mass index ≥30 kg/m^2 vs. <30 kg/m^2	1.5	Giovannucci et al., 1995,[27] 1996[29]
Red meat consumption	≥2 Times per week vs. less	1.4	Giovannucci et al., 1994[26]
Physical activity	Level of physical activity according to current CDC guideline vs. not*	0.6	Giovannucci et al., 1995[27] and 1996[29]
Folate	Multivitamin use ≥4 times per week vs. less	0.7	Giovannucci et al., 1993[23] and 1995[30]; and Jacobs et al., 2003[32]
Aspirin	≥4 Times per week vs. less	0.5	Giovannucci et al., 1995[28]; Chan et al., 2004[31]; Rosenberg et al., 1991[33]

RR indicates relative risk; CDC, Centers for Disease Control and Prevention.
*CDC guideline: ≥30 minutes of moderate physical activity ≥5 days per week or ≥20 minutes of vigorous physical activity ≥3 days per week.

preventable by modifying risk-factor behavior, such as smoking and alcohol use.[4] Fecal occult blood testing (FOBT) may decrease CRC mortality by 15% to 33%.[5–7] Sigmoidoscopy reduced CRC mortality by 60% within the reach of the sigmoidoscope in case–control studies.[8,9] Recent breakthroughs in treatment have lengthened the median survival of patients diagnosed with metastatic CRC from 6 months (without any chemotherapy) to 20 months (with cytotoxic and targeted chemotherapy).[10] Similar improvements have been reported for patients with earlier stage disease.[11]

However, these interventions are disseminated only partially throughout the population. Obesity prevalence is currently 30% in the U.S. and is still increasing.[12] Despite recommendations of the ACS[13] and the U.S. Multisociety Task Force on CRC,[14] national data on CRC screening uptake show that only 47% of men and 43% of women age 50 years and older reported having either an FOBT within the past year, a sigmoidoscopy within the past 5 years, or a colonoscopy within the past 10 years.[15] Chemotherapy rates decline dramatically with chronologic age,[16] although a pooled analysis showed attenuated but still significant benefits of chemotherapy in elderly patients.[17] The objective of the current study was to assess the extent to which greater dissemination of current interventions for risk-factor modification, screening, and treatment can reduce CRC mortality in the general U.S. population.

MATERIALS AND METHODS

MISCAN-COLON Microsimulation Model

The Department of Public Health at Erasmus MC, the Netherlands, developed the MISCAN-COLON microsimulation model in collaboration with the National Cancer Institute (NCI) to assess the effect of different interventions on CRC. The MISCAN-COLON model simulates a large population of individuals in whom CRC can arise according to the adenoma-carcinoma sequence.[18,19] More than 1 adenoma can occur in an individual, and each adenoma can develop independently into CRC. Adenomas progress in size from small (1–5 mm), to medium (6–9 mm), to large (≥10 mm). Some adenomas eventually become malignant, transforming into Stage I cancer. The cancer then progresses from Stage I to Stage IV. In every stage, there is a chance of detecting the cancer because of symptoms. Survival after clinical detection depends on the stage in which the cancer is detected. The MISCAN-COLON model has been described previously in great detail.[20–22] In the model, we distinguish 3 types of interventions: risk-factor modification, screening, and treatment.

Risk-Factor Modification

In the MISCAN-COLON model, risk-factor behavior influences the incidence of adenomas. We included the established risk factors for CRC of smoking, obesity, and red meat consumption as well as aspirin use, supplemental folate use, and physical activity. The odds ratios, which were estimated from 2 long-term cohort studies (The Health Professionals Follow-Up Study and the Nurses Health Study)[23–31] and from the studies by Jacobs et al.[32] and Rosenberg et al.,[33] were used as approximations of the relative risks for adenoma incidence (Table 1) and were assumed to be multiplicative.

For smoking, recent studies have suggested that the induction period for CRC risk is from 35 years to 40 years.[34,35] Consequently, we required data for the prevalence of risk factors from as early as 1965. Data were obtained from the Cancer Progress Report.[12] Additional age-specific data were obtained directly from its underlying resources: the National Health Interview Survey (NHIS),[36] the National Health and

TABLE 2
Age-Adjusted Risk-Factor Prevalence, Screening Dissemination and Treatment Use for Colorectal Carcinoma in the MISCAN-COLON Microsimulation Model for Selected Years from 1965 to 2000

	Year							
	1965	1970	1975	1980	1985	1990	1995	2000
Risk factors								
Smoking (% adults current smokers)	42	37	36	33	30	26	25	23
Obesity (% adults obese)	13	13	14	14	17	21	25	31
Red meat (% adults consuming ≥2 times per week)	97	97	95	93	89	85	81	78
Physical activity (% adults adhering to guidelines)	25	25	25	25	25	24	25	26
Multivitamin (% adult-users)	0	0	5	12	20	27	34	38
Aspirin (% adult-users)	5	5	5	5	6	8	9	10
Screening								
Home-based FOBT (% adults age ≥50 years with home-based FOBT in past two years)	0	0	0	5	14	18	21	24
Endoscopy (% adults age ≥50 years ever had endoscopy)	0	0	0	8	21	30	35	39
Treatment (% of patients)								
Overall rate of adjuvant chemotherapy for Stage III	0	0	1	12	37	69	73	73
By regimen type:								
5-FU based regimens without other agents*	0	0	1	12	37	69	73	73
Infusional 5-FU and oxaliplatin	0	0	0	0	0	0	0	0
Overall rate of chemotherapy for metastatic disease	0	13	25	27	49	59	66	66
By regimen type:								
5-FU based regimens*	0	13	25	27	49	59	20	20
5-FU and irinotecan	0	0	0	0	0	0	46	46
5-FU, irinotecan and oxaliplatin	0	0	0	0	0	0	0	0
5-FU irinotecan, oxaliplatin, and the biologics (cetuximab and bevacizumab)	0	0	0	0	0	0	0	0

5-FU indicates 5-fluorouracil; FOBT fecal-occult blood testing.
* Includes regimens with 5-FU potentiating agents like leucovorin and levamisole.

Nutrition Examination Survey,[37] and the Behavioral Risk Factors Surveillance System.[38] For years in which data were not available, trends were extrapolated linearly. For modeling purposes, we assumed that the prevalences of risk factors was not associated (see Table 2 for risk factor prevalence from 1965 to 2000).

Screening

Screening and surveillance lead either to the removal of an adenoma and prevention of CRC or to the early detection of a carcinoma, possibly improving prognosis. We considered screening with FOBT and endoscopy (including flexible sigmoidoscopy and colonoscopy). Based on our prior work (see Loeve et al.[20,21]) and other studies,[39–41] we assumed the performance parameters of the screening tests that are shown in Table 3.

NHIS provided rates for ever being screened and time since last screening by 5-year age groups in 1987, 1992, 1998, and 2000. We assumed no screening prior to 1978. The screening rates between data points were estimated by linear extrapolation (see Table 2). Because of the poor performance characteristics of office-based FOBT,[42] we accounted only for home-based FOBT. Because NHIS did not distinguish between home-based and office-based FOBTs before 2000, we estimated that the percentage of home-based FOBTs for earlier years would be the same as it was in 2000.

Treatment

In the last 20 years, improvements to systemic CRC chemotherapy have increased the cure rate of locally advanced disease and prolonged the survival for patients with advanced disease. In the model, we distinguished 4 chemotherapy regimens, depending on the treatment strategies available to patients in the U.S. who were diagnosed in a particular time period. They were: 1) 5-fluorouracil, which was available before 1996; 2) 5-fluorouracil and irinotecan (1996–2001); 3) 5-fluorouracil, irinotecan, and oxaliplatin (2002–2003); and, 4) 5-fluorouracil, irinotecan, oxaliplatin, and bevacizumab/cetuximab (2004 onward). The efficacy of each of these treatment regimens was estimated by using the hazard ratios for disease-free survival from published clinical trials[11,43–54] that were

TABLE 3
Characteristics of Home-Based Fecal Occult Blood Testing, Sigmoidoscopy, and Colonoscopy in the MISCAN-COLON Microsimulation Model: Sensitivity for Small, Medium, and Large Adenomas and Cancers; Specificity; and Segments Screened

Parameter	Home-Based FOBT*	Sigmoidoscopy†	Colonoscopy‡
Sensitivity (%)			
Small adenomas (≤5 mm)	2	75	80
Medium adenomas (6–9 mm)	2	85	85
Large adenomas (≥10 mm)	5	95	95
Cancers	60	95	95
Specificity (%)	98	95§	90§
Segments screened‖	Whole colon and rectum	75% Reach descending colon, none reach beyond splenic flexure	95% Reach ascending colon, 70% reach cecum

FOBT indicates fecal occult blood testing.
* See Gyrd-Hansen et al., 1997.[39]
† See Loeve et al., 2000[21]; Hixson et al., 1991[40]; and Rex et al., 1997.[41]
‡ See Hixson et al., 1991[40] and Rex et al., 1997.[41]
§ Lack of specificity of sigmoidoscopy and colonoscopy is because of detection and removal of nonadenomatous polyps.
‖ Only adenomas and cancers within the reach of a screening test can be detected. Sensitivity applies to adenomas and cancers within reach of the test.

TABLE 4
Hazard Ratios of Dying from Colorectal Carcinoma for Various Chemotherapy Treatment Regimens Compared with no Adjuvant Chemotherapy in the MISCAN-COLON Microsimulation Model

	Hazard ratio			
	Adjuvant therapy for stage III disease		Therapy for metastatic disease	
Chemotherapy treatment regimens*	Age <75 years	Age ≥75 years†	Age <75 years	Age ≥75 years†
One cytotoxic agent (5-FU)‡	0.74§	0.82	0.70‖	0.80
Two cytotoxic agents (5-FU and irinotecan)	NA¶	NA¶	0.60**	0.70
Three cytotoxic agents (5-FU, irinotecan, and oxaliplatin)	0.61††	0.71	0.50‡‡	0.60
Three cytotoxic agents and effective biologic therapy (5-FU, irinotecan, and oxaliplatin with bevacizumab/cetuximab)	NA§§	NA§§	0.42‖	0.46

5-FU indicates 5-fluorouracil; NA, not applicable.
* Chemotherapy treatment regimens refer to the agents available for the treatment of colorectal carcinoma during a particular period.
† See Sargent et al., 2001.[17]
‡ Includes regimens with 5-FU potentiating agents like leucovorin and levamisole.
§ See Gill et al., 2004.[45]
‖ See Saltz et al., 2000[50] and de Gramont et al., 2000.[52]
¶ 5-FU and irinotecan were identified as ineffective for adjuvant therapy in a large United States randomized trial (Saltz et al., 2004[51]).
** See Saltz et al., 2000.[50]
†† See Andre et al., 2004.[11]
‡‡ See de Gramont et al., 2000[52]; Goldberg et al., 2004[53]; and Tournigand et al., 2004.[54]
§§ Adjuvant treatment trials of cytotoxic therapy plus biologic agents are just underway with no data yet available. Accordingly, the potential benefit of adding biologic therapy to adjuvant regimens was not considered.
‖ See Hurwitz et al., 2004[46] and Cunningham et al., 2004.[49]

applied to the stage-specific relative survival rates for 1975 to 1979 from the Surveillance, Epidemiology and End Results (SEER) Program. Hazard ratios for disease-free survival for elderly patients were attenuated modestly based on a meta-analysis of elderly adjuvant colon cancer chemotherapy trial participants[17] and on survival outcomes with and without adjuvant treatment in SEER-Medicare.[55,56] Table 4 provides a summary of the hazard ratios for the various chemotherapy strategies compared with a referent category of treatment without chemotherapy.

To estimate chemotherapy use by age and time period in the U.S. population, we used the SEER-Medicare linked data base.[55,56] This provided approximate treatment histories through 2002 for the population age 65 years and older who were diagnosed with CRC from 1991 to 1999. For the population younger than age 65 years, we used survey data and patterns-of-care studies.[57,58] For utili-

TABLE 5
Level of Risk-Factor Prevalence, Screening Use, and Treatment Use in 2020 by Scenario in the MISCAN-COLON Microsimulation Model

	Scenario		
	Frozen-2000	Continued-Trends	Optimistic-Trends
Risk factors			
Smoking (% adults current smokers)	23	17	11
Obesity (% adults obese)	31	45	34
Red meat (% adults consuming red meat ≥2 times per week)	78	69	41
Physical activity (% adults adhering to guidelines)	26	34	51
Multivitamin (% adult-users)	38	55	76
Aspirin (% adult-users)	10	15	15*
Screening			
Home-based FOBT (% adults age ≥50 years with home-based FOBT in past 2 years)	24	35	38
Endoscopy (% adults age ≥50 years ever had endoscopy)†	39	56	61
Treatment (% of patients)			
Overall rate of adjuvant chemotherapy for Stage III	73	76	84
By regimen type:			
5-FU-based regimens without other agents	73	27	0
Infusional 5-FU and oxaliplatin	0	49	84
Overall rate of chemotherapy for metastatic disease	66	70	83
By regimen type:			
5-FU-based regimens	20	6	0
5-FU and irinotecan	46	1	0
5-FU, irinotecan, and oxaliplatin	0	18	0
5-FU, irinotecan, and oxaliplatin and the biologics (cetuximab and bevacuzimab)	0	45	83

5-FU indicates 5-fluorouracil; FOBT, fecal occult blood testing.
*Because of adverse effects of bleeding (see Imperiale, 2003[60]), aspirin was not considered a possible intervention.
† Endoscopy utilization includes 65% of procedures by colonoscopy (including colonoscopies for surveillance and for diagnostic follow-up of positive FOBTs and sigmoidoscopies) and 35% of procedures by sigmoidoscopy.

zation patterns prior to 2000, estimates are available in Table 2.

Model Calibration and Validation

Accounting for the risk-factor dissemination before 1975 and the stage-specific survival rates from 1975 to 1979, the MISCAN-COLON model was calibrated to reproduce the 1975 to 1979 age-specific CRC incidence rates,[59] which were representative of the U.S. population prior to screening. Subsequently, we added trends in risk-factor prevalence and screening and treatment use from 1975 to 2000 to generate a population with the characteristics of the 2000 U.S. population. Model predictions for CRC incidence and mortality until 2000 all were within 6% of the observed incidence and mortality.

Scenarios

We considered 3 different hypothetical scenarios to project CRC mortality between 2000 and 2020.

The frozen-2000 scenario

Risk-factor prevalence and the use of screening and treatment remain at the levels observed in the Year 2000.

The continued-trends scenario

Observed trends in risk factors and screening from 1995 to 2000 continue at the current rates up until 2020. Recently approved treatment strategies are adopted rapidly, as illustrated in Table 5.

The optimistic-trends scenario

This scenario considers continued trends through 2004. From 2005 onward, the model assumes that risk-factor prevalence in the U.S. population improves by 4% per year (obesity stabilizes at its 2005 level, and aspirin was not considered a possible intervention because of adverse effects of bleeding[60]). CRC screening rates reach current levels of breast cancer screening (70%) by 2010, and all patients who are eligible for chemotherapy (those without significant comorbidities) receive the best currently available chemotherapy from 2005 onward. For this scenario we also estimated the contributions of risk-factor modification and increased use of screening and treatment separately on the reduction of CRC mortality.

The projected levels of risk-factor prevalence and screening and treatment use in 2020 associated with each of the scenarios described above are summar-

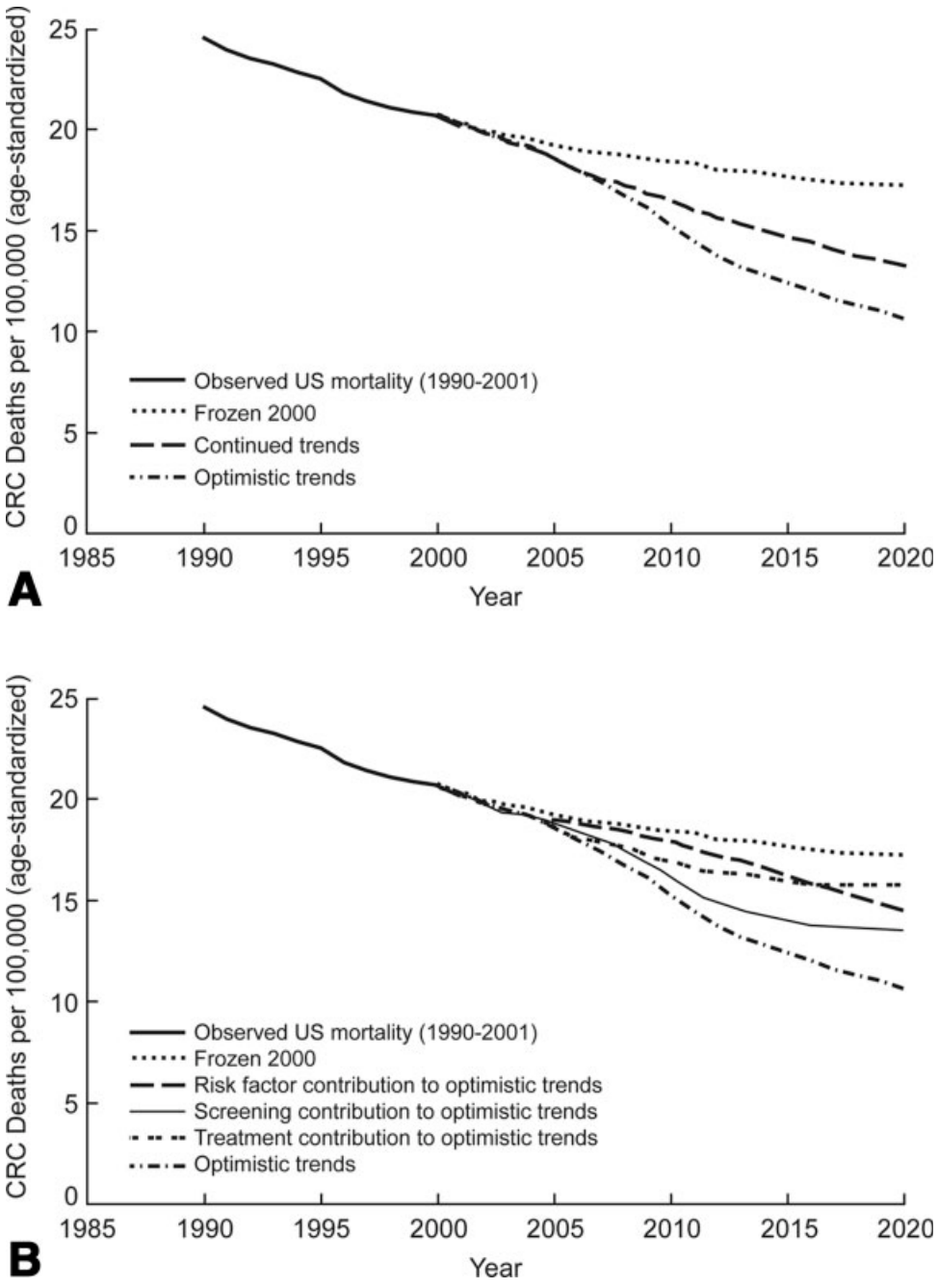

FIGURE 1. (A) Age-standardized colorectal carcinoma (CRC) mortality rates until 2001 are shown as observed (National Center for Health Statistics, 2001[62]) and from 2000 onward, as simulated by the frozen-2000, continued-trends, and optimistic-trends scenarios (2000–2020). (B) Age-standardized CRC mortality rates until 2001 as observed (National Center for Health Statistics, 2001[62]) and from 2000 onward, as simulated by the frozen-2000 and the optimistic-trends scenarios overall and with the separate contributions of risk-factor modification, increasing screening use and increasing treatment use for the optimistic-trends scenario.

ized in Table 5. Output was age-standardized to the U.S. 2000 standard population.[61]

RESULTS

Without further changes in risk-factor prevalence, screening use, and treatment use after 2000, the MISCAN-COLON model predicted that the CRC mortality rate per 100,000 population would decline from 20.8 in 2000, to 18.4 in 2010, and to 17.3 in 2020 (frozen 2000 trends) (Fig. 1A). CRC mortality was reduced by 11% between 2000 and 2010, and the mortality reduction leveled off at 17% by 2020. If the 1995 to 2000 trends continue, then MISCAN-COLON predicted mortality rates of 16.5 per 100,000 population in 2010 and 13.3 per 100,000 population in 2020 (continued trends) (Fig. 1A), representing a 21% reduction by 2010 and a 36% reduction by 2020 compared with 2000. With more optimistic trends, mortality rates of 15.3 per 100,000 population in 2010 and 10.7 per

100,000 population in 2020 were achieved, representing mortality reductions of 26% by 2010 and 49% by 2020 (optimistic trends) (Fig. 1A).

Figure 1B shows the separate effects of risk-factor modification, increased screening use, and increased treatment use on reducing CRC mortality in the optimistic-trends scenario. The frozen-2000 scenario was used as a referent point for additional mortality reduction. In 2010, screening achieved a CRC mortality of 16.6 per 100,000 population—a 9% additional mortality reduction over the 11% mortality reduction of the frozen-2000 scenario. The additional mortality reduction obtained through treatment is 6% with a CRC mortality of 17.2 per 100,000 population. The effect of risk-factor modification in the short-term was much smaller, an additional 1% reduction (CRC mortality of 18.1 per 100,000 population) over the frozen-2000 scenario. Over the 20-year period, however, risk-factor modification had a large impact, achieving an additional 12% mortality reduction beyond the estimate for the frozen-2000 scenario. The long-term additional CRC mortality reductions that were generated by increased screening use and increased treatment use were 17% and 7%, respectively.

DISCUSSION

The potential for reducing CRC mortality with currently available interventions is considerable. With a yearly 4% decrease in the prevalence of risk factors, an increase in CRC screening to 70%, and widespread use of the best available chemotherapy across all age groups, we estimate a 49% CRC mortality reduction by the Year 2020. The mortality reduction will be smaller if current trends continue (36% reduction) or if no further changes occur in the underlying contributors to CRC mortality (17% reduction). Of the 3 types of interventions considered, increasing screening has the largest effect on CRC mortality both after 10 years and after 20 years. Widespread use of currently available chemotherapy has an immediate effect on CRC mortality, but its effect ranks third by 2020. Risk-factor modification would take the longest to show an effect on CRC mortality but would provide an effect comparable to screening by the Year 2020.

Microsimulation is a powerful tool for assessing the benefit of different types of interventions simultaneously on a population level. Like all projections, uncertainty exists in underlying data and assumptions; therefore, the results should be interpreted with some caution. Given the lack of randomized controlled trials (RCTs) for most of the risk factors, our model assumptions for the relative risks for risk factors were based on the best estimates available from long-term cohort studies.[23–32] However, RCTs that estimated the effect of nonsteroidal antiinflammatory drugs on adenoma recurrence[63] showed a smaller effect than what was observed from cohort and case–control studies. Thus, in the current study, we may have overestimated the benefits of risk-factor modification.

Hormone replacement therapy (HRT) was not included as a risk factor in this analysis. Since the findings of the Women's Health Initiative (WHI) in 2002 that HRT use increases risk for cardiac events and breast cancer,[64] HRT use in the U.S. has declined sharply.[65] If HRT use is protective for CRC, then this decline will have a negative influence on CRC mortality trends in women. However, the potential effect will be modest: Only 25% of women age 40 years or older used HRT in 2001, and this rate declined to 15% in 2003. This 10% decline in women represents a $<5\%$ decline in the total population. Furthermore, with a possible relative risk of 0.8,[66] a protective effect of HRT would be modest. The U.S. Preventive Services Task Force recommends interpreting the evidence cautiously that suggests a protective effect of HRT. The WHI did show a reduction in CRC risk in women who used estrogen plus progestin and had an intact uterus, but patients with CRC in this intervention arm had more advanced disease and greater numbers of positive lymph nodes.[67] In women who underwent hysterectomy, no effect of only conjugated equine estrogen was found.[68] HRT, particularly estrogen only,[65] is used more commonly by women who have undergone a hysterectomy.[69]

In the model, we assume that risk factors only influence the incidence of adenomas. Risk factors also may influence the progression rate from adenoma to cancer. However, in this case, differences would be expected between the relative risks for cancers and adenomas. We observed only small differences between observed relative risks for adenomas and cancers.[23,27–31] Thus, it is unlikely that risk factors have a large effect on adenoma progression rates. It is possible that a longer follow-up would demonstrate differences in relative risks for adenomas and cancers.

For the current analysis, we assumed that there was no correlation between the prevalence of individual risk factors. Although this assumption often is incorrect (e.g., there is a known correlation between lack of physical activity and obesity), in a similar multiplicative model of the effect of risk factors on CRC, Cronin et al.[70] showed that the effect of a correlation on population-level risk is minimal. Their estimates for CRC incidence did not change significantly when they assumed an extreme correlation

between risk factors instead of no correlation. In addition, we did not consider correlations between risk-factor prevalence and the use of screening. Some studies of cancer screening have shown an association between low-risk patients and participation in screening.[71,72] This implies that individuals who currently are not being screened for cancer have a greater risk of developing it; therefore, increased screening presumably will reach a higher risk population. This would increase the overall effect of screening.

The model assumes that all positive FOBTs and sigmoidoscopies are followed by colonoscopy and that the compliance with initial diagnostic and surveillance colonoscopies is 100%. However, a recent study has shown that only 63% of physicians and 76% of gastroenterologists and general surgeons recommend complete diagnostic evaluation of patients who have a positive FOBT result.[73] If compliance with diagnostic follow-up and surveillance were 80% rather than 100%, then the additional benefit of screening would be reduced to 14% rather than 17%.

Although treatment provided the least mortality reduction of the 3 interventions, increased use of chemotherapy still contributes substantially to reducing CRC mortality, especially in the short term. The hazard ratios associated with the different chemotherapy regimens were obtained from RCTs. The model assumes that the observed treatment effects persist over the long term, even though the actual follow-up for the newer CRC treatments still is quite short. Studies in Europe and Australia have shown improvements in survival attributable to improvements in surgery and specialization.[74–77] However, such improvements have not been the subject of RCTs. This makes these other factors difficult to quantify. Inclusion and extrapolation of these improvements through 2020 would lead to a greater decline in mortality than when accounting for chemotherapy alone.

Despite the uncertainties in parameters and assumptions, our model reproduced observed past trends in CRC incidence and mortality between 1980 and 2000 very well. Furthermore, with continued trends for risk factors, screening, and treatment, we project 55,500 new CRC deaths in 2006, which differs by $<1\%$ from the ACS projection of 55,170 CRC deaths.

The Healthy People Consortium and the ACS have recommended an objective to reduce CRC mortality by 34% in 2010[2] and by 50% in 2015,[3] respectively. Our current analysis shows that, even with optimistic trends, achieving these objectives is not feasible with current interventions. Newer prevention, screening, and treatment options, such as effective, low-risk chemoprevention,[78] virtual colonoscopy, fecal DNA screening, and new combination chemotherapies, will be necessary and likely will be developed. Further developments in the field of genomics and proteomics may increase the potential for targeted intervention strategies.

The projections for this study were developed as part of the NCI-sponsored Cancer Intervention and Surveillance Modeling Network Consortium to evaluate cancer trends and project the impact of future interventions. A website[79] is available for an interactive presentation of these analyses. The current analysis will be part of this website and will be refined and updated when new data become available.

In this study we demonstrated that an almost 50% reduction in CRC mortality by 2020 already is possible with currently available interventions. However, future trends in CRC mortality depend greatly on the success of efforts to increase the use of current interventions. If we do not begin now to increase the uptake of current effective interventions, then CRC mortality reduction may be only 17%.

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