Published in final edited form as:

Dig Dis Sci. 2015 March ; 60(3): 681–691. doi:10.1007/s10620-015-3600-5.

The Impact of Screening on Colorectal Cancer Mortality and Incidence – Has It Really Made a Difference?

Ann G. Zauber, Ph.D.

Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York 10065, zauber@mskcc.org

Abstract

About sixty percent of the United States population of those age fifty and older are currently up to date with colorectal cancer screening recommendations. Has this level of screening made a difference for reducing colorectal cancer (CRC) incidence and/or mortality? Randomized controlled trials of guaiac-based fecal occult blood tests, which have relatively low sensitivity but high specificity for CRC, have shown a modest effect but with a long term reduction on CRC mortality. Newer fecal immunochemical tests are expected to have a greater effect. Randomized controlled trials of flexible sigmoidoscopy have also demonstrated a reduction in CRC mortality. Observational studies of screening colonoscopy suggest an effect of greater than fifty percent reduction for CRC mortality. We have assessed past trends of colorectal cancer screening in the US population which suggest that more than fifty percent of the decline in colorectal cancer mortality can be attributed to the increased acceptance and uptake in colorectal cancer screening. Current and future levels of increased screening could provide for even larger reductions for the US. Colorectal cancer screening has, and will, continue to make a significant impact on reducing colorectal cancer mortality.

Introduction

Despite declines in colorectal cancer (CRC) incidence and mortality of over 40% percent from 1975 to 2011 (Fig 1), colorectal cancer (CRC) remains the number two cause of cancer death in the United States [1]. In this chapter we address what effect screening has had on reducing CRC incidence and mortality in order to better understand how CRC screening may facilitate further declines in the burden of CRC. We discuss the empiric evidence for screening's effect based on the findings of randomized trials as well as observational studies and describe secular trends that suggest the impact of screening on CRC incidence and mortality. Understanding the ways to achieve the highest impact on CRC mortality will inform health policy makers regarding choices to further reduce the burden of this disease.

Randomized Controlled Trial Evidence for Impact of CRC screening

Randomized controlled trials (RCT), with long-term outcomes of site-specific incidence and mortality, are the gold standard for assessing the efficacy of a screening program. We now have results of such trials for Fecal Occult Blood tests (FOBT) and flexible sigmoidoscopy and randomized controlled trials for colonoscopy are now underway.

Randomized controlled trials of FOBT compared to usual care

(Table 1) Fecal occult blood testing was the first CRC screening test evaluated in randomized controlled trials that began in 1975 in the United States (US) and in 1981 in Europe, with publication in the 1990's [2,3,4]. The mortality reduction was higher for annual FOBT (33%) with rehydrated slides in the US [4] than for the programs with biennial screening (15% and 18%) [2,3]. An incidence reduction was also achieved in the US FOBT study for both annual (20%) and biennial screening (18%) after 18 years of follow up [5]. Longer-term follow-up to 30 years in this trial showed that screening with FOBT provided a long term mortality reduction of 32% for the annual screening and 18% for biennial screening. The authors attributed the long term sustained effect for CRC mortality reduction as a function of the polypectomy associated with the FOBT screening program [6].

The FOBT RCTs. These randomized controlled trials of FOBT [2–4] were included in a Cochrane review by Hewitson [7]. They all had CRC mortality as the primary endpoint and used the guaiac-based Hemoccult II test (gFOBT). The test requires two specimens from each of 3 stool samples, dietary restrictions for red meat and cruciferous vegetables, and provides a qualitative assessment of blood in the stool. In addition, these tests required active participation of the subject to plan adherence to dietary and medication restrictions, to obtain stool samples for 3 days, to return the samples collected and to repeat the FOBT every 1–2 years; those with positive tests were advised to have diagnostic colonoscopy. Overall, these guaiac based initial tests have shown only a modest effect on CRC mortality (Table 1).

A guaiac test with higher sensitivity Hemoccult SENSA, has been developed, but its higher sensitivity for CRC is associated with lower specificity (Table 2). There is a wide range of fecal immunochemical tests (FIT) using different laboratory methodologies to detect human hemoglobin in the feces. An advantage of FIT is there is no dietary restriction. Both qualitative and quantitative FIT tests are available but neither Hemoccult SENSA or FIT's have been studied in randomized controlled trials with CRC as the endpoint

Randomized controlled trials of flexible sigmoidoscopy compared to usual care

Large scale randomized controlled trials of flexible sigmoidoscopy were initiated in the late 1990's, with publication of long term (10 years or more) results in 2010 (UK Flexiscope Trial) [10], 2011 (Italy's SCORE trial)[11], 2012 (the US Prostate, Lung, Colorectal, and Ovarian Cancer trial) [12], and 2014 (Norway's NORCAPP) [13]. All have demonstrated a reduction in colorectal cancer incidence in the distal colon (the region within the reach of the flexible sigmoidoscope) (Table 1). CRC mortality was also significantly reduced for 3 of the 4 trials, with further reductions expected with continued follow-up. Three of the trials were based on the subjects' willingness to participate in a randomized controlled trial and one [13] was based on population sampling with the control group unaware of their inclusion in a randomized trial. The largest incidence effect was achieved in the UK flexiscope trial with 23% reduction in CRC mortality for intent to treat and 33% reduction for per protocol analysis, with the reduction primarily due to a 50% reduction in the distal colon. The Prostate Lung Colorectal and Ovarian Trial in the US reported less of a reduction in risk between the flexible sigmoidoscopy and usual care groups [12], but there was also an

estimated 50% cross-over to colonoscopy screening for both the flexible sigmoidoscopy and control groups, which would have mitigated the observed difference. Despite this new evidence from the flexible sigmoidoscopy RCT's demonstrating reductions in CRC incidence and mortality, the use of flexible sigmoidoscopy in the US has fallen steadily over the last 15 years; currently less than 3% of screening age population report having a sigmoidoscopy within the last 5 years [14]. The role of flexible sigmoidoscopy screening was questioned in an influential editorial in 2000 [15], which suggested that "in recommending flexible sigmoidoscopy to screen persons for colorectal cancer, we are promoting a suboptimal approach... "Flexible sigmoidoscopy is as clinically logical as performing mammography of one breast to screen women for breast cancer." Although this analogy is flawed, because two thirds of colorectal cancers are in the distal colon, it affected the willingness of physicians to recommend and subjects to participate in flexible sigmoidoscopy screening.

Randomized controlled trials of colonoscopy—Long term randomized controlled trials for colonoscopy are currently underway, with the endpoints of CRC incidence and mortality reduction, but these studies will not be reported until 2020 or beyond. These include the COLONPREV trial in Spain [16] ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00906997) NCT00906997), the CONFIRM trial in the US Veterans Administration (VA) ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01239082) NCT01239082) and the NordICC trial in Northern Europe [17] ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00883792) NCT00883792). Two of these trials are comparative effectiveness analyses of screening colonoscopy versus a program of fecal immunochemical test (FIT) with biennial FIT testing for the COLONPREV trial [16] and annual FIT testing for the VA trial. The Spanish COLONPREV trial [16] is a non-inferiority trial whereas the VA CONFIRM trial is a superiority trial of colonoscopy over a program of annual FIT. NordICC, the third large trial evaluating colonoscopy, is a classic effectiveness trial [17] designed to assess whether colonoscopy has reduced CRC mortality compared to usual care.

When do new screening tests require randomized controlled trials with CRC incidence and mortality endpoints?: In 1997 Winawer and Fletcher led the Multi-Society (GI) Task Force in developing guidelines for CRC screening based on the best evidence available [18]. They recognized that at that time only guaiac based fecal occult blood tests had been tested in RCT's. Given the limited impact of Hemoccult II screening on CRC mortality there was an expectation that new tests would be developed with improvements in test characteristics over Hemoccult II. This Multi-Society Task Force assessed the issue of whether each new test should require an evaluation with a RCT with long term outcomes of CRC incidence and mortality. They suggested that "it might be appropriate in the future to substitute a newer test for currently recommended ones if there was convincing evidence that the new test has... 1. comparable performance (e.g. sensitivity and specificity) in detecting cancers or adenomatous polyps at comparable stages, 2. is equally acceptable to patients [ie patients are adherent to this screening test] and 3. has comparable or lower complication rates and costs." They concluded that under these circumstances "it would not be necessary to submit each new technology to the original standard of proof, i.e., a randomized controlled trial with death from CRC as an outcome measure." The inclusion of the fecal immunochemical test (FIT) in the American Cancer Society Guidelines [19] in 2003 and the joint

MultiSociety and American Cancer Society Guidelines for CRC screening in 2008[20] was based on this type of comparison [18] of FIT characteristics with that of guaiac based fecal occult blood tests (gFOBT). The assumption is that better test parameters will provide higher incidence and mortality reduction. Of note, the earlier FIT had higher sensitivity but lower specificity than the Hemoccult II guaiac based test. Newer FIT tests are now available with high sensitivity and high specificity[21]

Comparative effectiveness of CRC screening tests: Comparative effectiveness approaches have been used to compare the various fecal screening tests. For example, Allison [22–25] summarized a number of comparative studies of “head to head” comparisons of guaiac FOBT and FIT and concluded that the FIT had higher sensitivity and higher specificity for distal CRC than the sensitive guaiac test. Brenner has shown superior diagnostic performance of FIT in a head-to-head comparison with guaiac based FOBT in a screening program for colonoscopy [26]. Recently a comparative effectiveness study of a stool DNA test plus a quantitative FIT test (Cologuard) [27] versus a quantitative FIT alone has shown higher sensitivity for colorectal cancer and advanced adenomas with the multi-target test than the FIT only but also with a higher false positive rate.

Other comparative effectiveness studies were designed to have follow-up for CRC mortality endpoint. Winawer and colleagues, for example, compared a screening program of rigid sigmoidoscopy plus a Hemoccult II FOBT to rigid sigmoidoscopy alone [28]; and found that sigmoidoscopy plus a FOBT decreased CRC mortality more than for sigmoidoscopy alone.

As noted above the COLONPREV [16] and CONFIRM trials are comparative effectiveness trials of colonoscopy versus a program of fecal immunochemical test (FIT). These colonoscopy screening trials were initiated in part to determine if regular testing with FIT, with its improved sensitivity for CRC (and even for advanced adenomas), might match the impact of screening colonoscopy. These studies should ultimately have long-term follow-up to assess CRC incidence and mortality.

Two large trials have compared CT-colonography with same-day optical colonoscopy [29,30]. In a Department of Defense study [30], the per adenoma test characteristics were 92% sensitivity of CT colonography for adenomas 10 mm or larger and 86% sensitivity for adenomas 6 mm or larger. Specificity was 96% for patients with adenomas 10 mm or larger and 80% for patients with adenomas 6 mm or larger. CTC results were not reported for lesions measuring less than 6 mm. The National CT Colonography Trial (NCTC) sponsored by the American College of Radiology Imaging Network (ACRIN 6664) [29] found that compared to colonoscopy, the sensitivity of CT colonography for adenomas or CRC 10 mm or larger was 84%. Sensitivity for adenomas 6 mm or larger was 70%. Specificity was 86% for patients with adenomas 10 mm or larger and 88% for patients with adenomas 6 mm or larger.

Observational studies of CRC screening—Case-control observational studies were also conducted for guaiac FOBT during the same time period as the randomized controlled trials and had similar results reporting a relatively small decrease in CRC mortality [31–37].

The original evidence for the impact of endoscopy on CRC mortality was based on two case-control studies [38,39]. Selby et al [38] showed that distal CRC deaths within the reach of the rigid sigmoidoscope were reduced by 59% in those who had had a sigmoidoscopy within the previous 10 years whereas there was no reduction of death from proximal CRCs. Newcomb et al [39] also found that the reduction in CRC risk with exposure to sigmoidoscopy was limited to the distal colon.

Initially, it was assumed that the beneficial effect observed in the distal colon with sigmoidoscopy could be used to estimate the effectiveness of colonoscopy for the entire colon. RCTs of colonoscopy screening were not started in the US until the late 1990's, in part because of the assumption that the endoscopy effect that would be found in the distal colon with flexible sigmoidoscopy in the Prostate Lung Colon and Ovarian trial would be indicative of what colonoscopy would be able to achieve in the proximal colon.

In the absence of long term results of screening with colonoscopy from randomized controlled trials, we can use the results of several high quality observational studies of colonoscopy for assessment of the effect on CRC mortality. An early case-control study from Ontario, Canada in 2009 suggested that colonoscopy reduced distal but not proximal colon cancer mortality [40]. This study was based on a time period when colonoscopy was rarely used for screening in Canada and those receiving colonoscopy were likely to have higher familial risk or be in need of diagnostic colonoscopy. Furthermore, a high percentage of non-gastroenterologists performed the procedure. Subsequent case-control studies, have shown a reduction of both distal and proximal CRCs but a consistently lower effect for the proximal colon [41,42]. This lower effect for colonoscopy in the proximal colon (Table 1c). has been attributed to flat and non-polypoid lesions which have not been visualized as well and which require somewhat different techniques for removal.

Prospective studies of endoscopy and colonoscopy: Several observational cohort studies of colonoscopy have been reported. Kahi determined that colonoscopic screening reduced CRC incidence by 67% compared to the general population in an Indiana cohort over an average of 15 years of follow up [43]. The sample size of this study was not large enough to evaluate a mortality reduction. Long-term follow-up of the prospective Nurses Health Study and the Health Professional Follow-up Study [44] reported incidence and mortality reductions for exposure to flexible sigmoidoscopy and to colonoscopy but with a larger effect for colonoscopy (Table 1c).

The current consensus from observational studies is that colonoscopy can provide a larger reduction in CRC mortality than has been achieved by flexible sigmoidoscopy, but that colonoscopy has thus far been less effective in the proximal colon than in the distal colon and rectum.

Colonoscopy as the screening test of choice: Colonoscopy is now the CRC screening test of choice for 90% those who are up to date with CRC screening in the US [14]. Colonoscopy has been used as the gold standard in assessing other screening tests with respect to sensitivity and specificity. As such, it is difficult to provide a measure of colonoscopy's own sensitivity and specificity. The original estimates for colonoscopy

sensitivity for adenomas by size were from back to back colonoscopy studies [45–47]. Comparative effectiveness studies of CT-colonography and colonoscopy found that both procedures missed pertinent lesions [29,30]. These CT-colonography studies alerted the medical community to the issue that colonoscopy is not a perfect “gold standard”.

It is now clear that there is no perfect screening test; all tests have false positives and false negative results. The best tests are those that minimize these false results and are acceptable to the population. We can evaluate colonoscopy screening by determining how well it performs in reducing CRC mortality in those that it has identified as having adenomas and in those identified as not having any adenomas. For positive findings of adenomas we can use the National Polyp Study prospective results to demonstrate that colonoscopic polypectomy of adenomas resulted in a marked reduction in CRC mortality of 53% as compared to the general population (Figure 2) [48]. Furthermore the higher risk adenoma population in the National Polyp Study (57% of this group had advanced adenomas), had a cumulative CRC mortality similar to those with no adenomas for the first 10 years after polypectomy (Figure 2).

Other studies[49,50], which used pathology registries to identify adenoma patients, have shown a smaller effect on CRC incidence [50] and mortality reduction [49] compared to the general population than found in the National Polyp Study (NPS). These registry studies did not link to endoscopy reports to ascertain whether all polyps had been removed or the quality of the endoscopic examination. In contrast, all baseline and surveillance colonoscopies were performed by study investigators and removal of all polyps and a successful intubation all the way to the cecum was required for the patient to be eligible for the NPS. The Robertson study of adenoma patients [51] enrolled in chemoprevention trials did not show an incidence reduction with polypectomy as compared to the general population. However, this study did not have per protocol colonoscopies for identification of the initial colonoscopy and the authors stated that the results “strongly suggested that prevalent neoplasia were missed at baseline”. The differences among these studies highlights the importance of high quality colonoscopy as critical to CRC screening programs [51,52].

The negative predictive value of colonoscopy (value of a negative exam in predicting a low metachronous CRC or advanced adenoma risk) can be assessed by the miss rate of colonoscopy in those with negative findings (no polyps) at the colonoscopy. The Veterans Affairs Cooperative Study No 380 found that 2.4% of those with negative findings at baseline had advanced neoplasia detected over 5 years with follow-up colonoscopy [53]. Similarly, Brenner et al [54] in Germany determined that no interval CRCs were detected in 533 with negative colonoscopies over an eleven year period and Singh et al in Manitoba observed an interval colorectal cancer rate of 0.1% for those with a negative colonoscopy examination over 11 years of follow-up [55,56]. Thus, a normal colonoscopy appears to have a high negative predictive value for CRC.

Another assessment of the impact of colonoscopy on CRC incidence is demonstrated in a large cohort of 136 gastroenterologists and 314,872 colonoscopies at Kaiser Permanente Northern California. In this analysis, 20% of the endoscopists had an adenoma detection rate

below 20% and patients having colonoscopy by endoscopists with lower adenoma detection rates had a significantly higher rate of interval cancers over 10 years post colonoscopy than patients of endoscopists with higher adenoma detection rates [57]. There was an estimated 3% decline in interval cancer rates with each 1% increase in the adenoma detection rate. Low adenoma detection rate was also associated with high interval cancer rates in Kaminski's study in Poland where 80% of the physicians had an adenoma detection rate less than 20% [58].

In summary these observational studies show a marked impact of colonoscopy to reduce colorectal cancer incidence and mortality through detection and removal of adenomas.

Adherence

A screening test must be well accepted to have a highly successful screening program. The impact of the screening program is a function of adherence to the completion rate and the efficacy of that screening test. As noted by Winawer "The best test is the one that gets done, and done well". However, in practice, adherence to CRC screening is quite variable. For example in the COLONPREV trial in Spain [16], Quintero reported adherence of 25% for colonoscopy and 34% for the initial FIT of a biennial screening program.

We have used microsimulation modeling in a decision analysis for the United States Preventive Services Task Force (USPSTF) to estimate the long term impact of age to begin, age to end, and intervals of screening for different CRC screening tests [59]. The microsimulation models are part of the Cancer Intervention and Surveillance Modeling Network (CISNET) of the National Cancer Institute. Given that the USPSTF recommendations would be for those subjects who were willing to be screened, we used 100% adherence with screening for our base case. Given such an assumption of 100% adherence, a program of screening using FIT, a high sensitive guaiac test, or flexible sigmoidoscopy with periodic FOBT could provide comparable life-years gained as screening colonoscopy every 10-years.

Population based trends of decreasing colorectal cancer incidence and mortality rates

Although we determine efficacy of CRC screening from randomized controlled trials, the ultimate measure of colorectal cancer screening effectiveness is the demonstration of a population level reduction in CRC incidence and mortality. Based on SEER results from 1975 to 2011, colorectal cancer incidence increased to a peak in the 1980's, with subsequent marked decreases continuing through the latest time period to 2011 (Figure 1). CRC mortality has also continued to decrease steadily, with consistent trends for whites and blacks and for men and women. Black CRC mortality rates have, however, been consistently higher than those of whites throughout this time period.

Impact of screening in reducing CRC incidence and mortality on the population basis

Past trends 1975 to 2000 in CRC incidence and mortality

We now address the central question of how much of the decreasing trends for CRC incidence and mortality in the past decades can be attributed to screening. We have used the CISNET MISCAN-Colon micro-simulation population model to partition out the impact of risk factors, and screening rates on CRC incidence changes, and risk factors, screening, and chemotherapy rates on CRC mortality rates over time [60,61]. We considered the risk factors that have been associated with increased risk of CRC (smoking, obesity and red meat consumption) as well as those which have been associated with decreases in CRC risk (physical activity, multivitamin use, and regular aspirin use.) The prevalence of risk factor exposures used in the model from 1965 to 2000 were based on Cancer Progress Report for risk factors. We assumed a smoking rate of 42% in 1965 to 23% in 2000; obesity rate of 13% in 1965 to 31% in 2000; and red meat consumption of 2 or more servings a week from 97% in 1965 to 78% in 2000; physical activity according to guidelines from 25% in 1965 to 26% in 2000; multivitamin use from 0 % in 1965 to 38% in 2000; regular aspirin use from 5% in 1965 to 10% in 2000. We used the prevalence of past screening with FOBT (in the past 2 years) or any endoscopy use from the National Health Interview Survey for adherence to CRC screening tests. We assumed no CRC screening until 1980 with an increase to 24% with recent FOBT and 39% with any endoscopy by 2000.

The results of the microsimulation model are shown in Fig 3. The overall observed decline in CRC incidence (Fig 3a) was 22% for 1975–2000. The MISCAN model-predicted decline without screening was 11%, indicating that changes in risk factors could account for about 50% of the overall decline in incidence rates during 1975–2000. Screening increased the CRC incidence rates in the short term but then accounted for 50% of the CRC incidence decline for the whole period.

The overall observed decline in CRC mortality was 26% for 1975–2000 (Fig 3b). The model predicted that with only changes in risk factors CRC mortality would have decreased by 9%, explaining 35% of the observed mortality decline. Screening was estimated to have decreased mortality by another 14%, explaining 53% of the mortality reduction, while treatment added another 3% decline, explaining the final 12% of the observed decline in CRC mortality

These modeling results strongly suggest that approximately 50% of the decline in CRC incidence and mortality between 1975 and 2000 could be due to CRC screening. We have now used a similar analysis for the time period up to 2010 and again estimated that CRC screening likely accounts for about 50% of the reduction in CRC mortality over the more recent period [62].

Future Trends in CRC Mortality Rates: Impact of Risk Factors, Screening, and Treatment—In the same analysis, we used microsimulation modeling to project future CRC mortality from 2000 to 2020 based on differing intensities of cancer control including

no change (pre-2000 frozen), continued trends, and optimistic trends in the prevalence of interventions (Fig 4a) [60,61]. Without changes in risk factors, screening and treatment (frozen as of 2000), the decline in CRC mortality may only be 17%. However the MISCAN-Colon model predicts a 36% overall decline in CRC mortality from 2000 to 2020 if current trends in risk factors, screening and treatment continue. If we could accelerate the projected trends, an overall CRC mortality reduction of 50% by 2020 is possible (Figure 4a).

We also projected out the microsimulation population modeling to 2020 as to whether risk factor reductions, increased CRC screening, or increased chemotherapy usage could provide the most impact by 2020. Figure 4b shows the contribution of the three types of intervention (risk factor modification, screening and treatment) on reducing CRC mortality if we could reach the level of optimistic trends. Increases in the proportion of adults screened could provide the largest reduction in future death rates followed by risk factor modification, and increasing use of current treatment practices.

Overall, microsimulation modeling suggests that declines in CRC incidence and/or death rates are consistent with a relatively large contribution from screening and with a smaller but demonstrable impact of risk factor reductions and improved CRC treatment. These declines are projected to continue if risk factor modification, screening, and treatment remain at current rates, but could be further accelerated with favorable trends in risk factors and higher utilization of screening and optimal treatment.

Colorectal cancer screening is now recommended by the US Preventive Services Task Force, the American Cancer Society, as well all the GI professional societies. Such recommendations are of importance in getting out the message to the general population to get screened for CRC. In the US, CRC screening remains largely opportunistic with the primary care physician or the patient requesting screening. Increased levels of screening are anticipated with the advent of the Affordable Care Act covering preventive care, given the increases that occurred when Medicare started covering colonoscopy screening. Large scale screening programs are already in place in systems such as Kaiser Permanente of Northern and of Southern California [63] and the Department of Veterans Affairs system among others.

Organized programs can decrease the barriers to CRC screening and can be monitored more easily for quality control. In Europe, population based CRC screening is organized by the state. We recognize that opportunistic screening will continue in the US but also expect more population based screening with high quality control for CRC testing will become prevalent in the US. These developments should lead to higher levels of CRC screening with appropriate diagnostic care for those with positive test.

Recently the “80% by 2018” initiative was launched by the National Colorectal Cancer Roundtable (NCCRT) to try to increase CRC screening from current rates (58% in 2010) to 80% by 2018. The goal is to get those who have not been screened or are not up to date with CRC screening to have screening. This is a very challenging proposal but feasible given the increased levels of screening anticipated with coverage in Medicare and the Affordable Care Act for preventive care and expansion of large scale screening programs by provider groups

[63]. Racial and income disparities [64] in access to screening and differences in screening levels for the uninsured and underinsured as well as low overall screening rates in some states [65] demonstrate areas where CRC screening can be improved.

Summary: Colorectal cancer screening has evolved from guaiac based occult stool blood testing to fecal immunochemical tests and onto colonoscopy itself as an option for the primary screening test. Based on the evidence from randomized controlled trials, observational studies, and microsimulation modeling, approximately fifty percent of the declines in colorectal cancer incidence and mortality on the population level can be attributed to the increases in CRC screening rates and to the use of more effective tests to detect and remove advanced adenomas as well as to detect early stage cancers.

Acknowledgements

This work is supported in part from the following grants: U01 CA-152959, U01 CA-151736, U54 CA-163262, R01 CA-079572, and P30 CA008748.

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Figure 1. Age adjusted rates from 1975 to 2011 for CRC Incidence and Mortality [1]
Red line is for CRC incidence and black line for CRC mortality. Source data from ref 1.

Figure 2. CRC Mortality in the National Polyp Study for Adenoma and Non-adenoma patients with comparison with the US incidence based mortality rates over up to 20 years

The number of subjects at risk per years followed is given for the adenoma (blue line) and non-adenoma (red line) cohorts. The cumulative incidence based mortality for the average risk US Population is taken from SEER data (black line). There were 25 CRC deaths expected in the general population of comparable age and sex distribution as the NPS adenoma cohort. There were 12 observed deaths in the NPS cohort with adenomas removed for a 53% reduction in CRC mortality compared to general population rates. Reproduced with permission from ref 48.

Figure 3. Partition of Past Trends in Colorectal Cancer Incidence and Mortality (1975–2000)
 Microsimulation model estimates of the contribution of risk factors and screening on CRC incidence (3a) and these factors as well as treatment on CRC mortality (3b). The **black line** is the observed SEER (9) delay-adjusted colorectal cancer incidence rates based on first primary colorectal cancer (Figure 3a) and the age-adjusted CRC mortality rates (Figure 3b) for 1975–2000. The green shaded area represents the estimate of the contribution of risk factor modification and the orange shaded area represents the estimate of the additional contribution of screening to the decline in CRC incidence (3a) and mortality (3b). The purple shaded area in 3b represents the estimate of the additional contribution of treatment to the decline in CRC mortality. Reproduced with permission from refs 60,61.

Figure 4. Projections of Colorectal Cancer Mortality

Microsimulation model projecting the effect of three levels of cancer control interventions on risk factors, screening, and treatment on CRC mortality (4a) and the estimated contribution of risk factors, screening and treatment to the optimistic projections for CRC mortality (4b). The **black line** is the age adjusted US mortality rate (1975–2006) by year of death. The **gray line** is the MISCAN modeling of the age-adjusted mortality 1975 to 2000 based on the past trends in risk factors, screening, and treatment (the purple line of Figure 3). In 4a, the **blue line** represents the projected CRC mortality if the upstream factors for risk factors, screening, and treatment remain at the same level as for 2000. This scenario is called Frozen (at 2000). The **orange line** represents the projected CRC mortality if the upstream factors continued according to the trend of these factors in 1995–2000. This scenario is called Continuing Trends. The **red line** represents the projected CRC mortality if the upstream factors for risk factors, screening, and treatment improve over and above that of continued trends to an optimistic level for each factor. This scenario is called optimistic trends. The **blue area** represents the improvement in CRC mortality based on the pre-2000 trends in upstream factors. The **yellow area** represents the additional impact of post-2000 continued trends in upstream factors. The red area represents the additional impact of post-2000 optimistic trends in upstream factors.

In 4b, the **heavy blue line** is the MISCAN model projection based on pre-2000 upstream factors (Frozen scenario) (blue line of 4a). The next lines represent the individual

components of the Opportunistic Trends models. The **green line** represents the projected age-adjusted CRC mortality if only optimistic *treatment* interventions are implemented. The **orange line** represents the age adjusted CRC mortality rate if only optimistic *risk factor* interventions were implemented. The **purple line** represents the CRC mortality rate if only optimistic *screening* were implemented. The **heavy red line** represents the CRC mortality rate for the combined effect of implementing risk factor, screening, and treatment interventions. Reproduced with permission from refs 60,61.

Table 1

A. Summary of Relative Risk and Percent Reduction in CRC Incidence and Mortality by CRC Screening Test Compared to Control Groups			
Randomized Controlled Trial	CRC Mortality		
	Annual Test	Biennial Test	
Fecal occult blood test (Hemoccult II)	RR (% ↓)	RR (% ↓)	
Minnesota[4,66] 30 Year Minnesota Follow-up[6]	0.67 (33%) 0.68 (32%)	0.94 (6%) 0.78 (22%)	
England[2]	-	0.82 (18%)	
Denmark [3]	-	0.85 (15%)	

B. Summary of Relative Risk and Percent Reduction in CRC Incidence and Mortality by CRC Screening Test for Intention to Screen and Per Protocol Analyses					
Randomized Controlled Trial		Intention to Screen		Per Protocol	
		Incidence	Mortality	Incidence	Mortality
Flexible Sigmoidoscopy	Adherence	RR (% ↓)	RR (% ↓)	RR (% ↓)	RR (% ↓)
United Kingdom[67]	71%	0.77 (23%)	0.69 (31%)	0.67 (33%)	0.57 (43%)
Italy[11]	58%	0.82 (18%)	0.78 (22%)	0.69 (31%)	0.62 (38%)
United States [12]	83%	0.79 (21%)	0.74 (26%)	-	-
Norway[13]	63%	0.73 (27%)	0.80 (20%)	0.69 (31%)	0.62 (38%)

C. Summary of Odds Ratio or Relative Risk and Percent Reduction in CRC Mortality for Colonoscopy Screening-Observational Studies				
Case Control	Overall CRC Mortality	Distal Mortality	Proximal Mortality	
	OR (% ↓)	OR (% ↓)	OR (% ↓)	
Ontario[40]	0.63 (37%)	0.33 (67%)	0.99 (1%)	
SEER – Medicare[41]	0.40 (60%)	0.24 (76%)	0.58 (42%)	
Four US Health Plans (Late Stage CRC)[42]	0.29 (71%)	0.26 (74%)	0.36 (64%)	
Prospective Cohort	Overall	Distal	Proximal	
	RR (% ↓)	RR (% ↓)	RR (% ↓)	
Nurses Health Study and Health Professional Study[44]	0.32 (68%)	0.18 (82%)	0.47 (53%)	

OR: Odds Ratio, RR: Relative Risk, Percent Reduction: % ↓

Test sensitivity and specificity by test and lesion size/type for commonly used CRC tests [59]

Table 2

	Adenoma 1–5mm	Adenoma 6–9mm	Adenoma 10+mm	Preclinical cancer	Per Subject Specificity
<i>Per Subject</i>					
Hemoccult II	0.02	0.17	0.42	0.40	0.98
Hemoccult SENSA *	0.08	0.12	0.24	0.68	0.92
FIT	0.05	0.10	0.22	0.70	0.95
<i>Per Lesion</i>					
SIG <i>per lesion in reach</i>	0.75	0.85	0.95	0.95	0.92
Colonoscopy	0.75	0.85	0.95	0.95	0.90