Research Article

Cancer Epidemiology, Biomarkers & Prevention

How Many Deaths from Colorectal Cancer Can Be Prevented by 2030? A Scenario-Based Quantification of Risk Factor Modification, Screening, and Treatment in Norway

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Abstract

Background: Colorectal cancer mortality can be reduced through risk factor modification (adherence to lifestyle recommendations), screening, and improved treatment. This study estimated the potential of these three strategies to modify colorectal cancer mortality rates in Norway.

Methods: The potential reduction in colorectal cancer mortality due to risk factor modification was estimated using the software Prevent, assuming that 50% of the population in Norway—who do not adhere to the various recommendations concerning prevention of smoking, physical activity, body weight, and intake of alcohol, red/processed meat, and fiber—started to follow the recommendations. The impact of screening was quantified assuming implementation of national flexible sigmoidoscopy screening with 50% attendance. The reduction in colorectal cancer mortality due to improved treatment was calculated assuming that 50% of the linear (positive) trend in colorectal cancer survival would continue to persist in future years.

Results: Risk factor modification would decrease colorectal cancer mortality by 11% (corresponding to 227 prevented deaths: 142 men, 85 women) by 2030. Screening and improved treatment in Norway would reduce colorectal cancer mortality by 7% (149 prevented deaths) and 12% (268 prevented deaths), respectively, by 2030. Overall, the combined effect of all three strategies would reduce colorectal cancer mortality by 27% (604 prevented deaths) by 2030.

Conclusions: Risk factor modification, screening, and treatment all have considerable potential to reduce colorectal cancer mortality by 2030, with the largest potential reduction observed for improved treatment and risk factor modification.

Impact: The estimation of these health impact measures provides useful information that can be applied in public health decision-making. *Cancer Epidemiol Biomarkers Prev; 26(9); 1420–6. ©2017 AACR.*

Introduction

Colorectal cancer is the third most common cancer and the fourth most common cause of cancer deaths worldwide (1). Colorectal cancer is a multifactorial disease with lifestyle, genetic, and environmental components, and is a marker of human development (2). Norway has one of the highest levels of the Human Development Index, as well as the incidence of colorectal cancer has tripled since 1953 (3), with declining colorectal cancer mortality since the mid-1990s (4, 5).

Colorectal cancer mortality and incidence can be reduced through different strategies that span the cancer control spectrum, from primary prevention (risk factor modification through adherence to lifestyle recommendations) via secondary prevention (preventive and early detection screening) through tertiary prevention (improved cancer care and treatment).

It has been estimated that about 50% of colorectal cancer risk can be attributed to five lifestyle factors, namely, smoking, diet, excess weight, alcohol, and physical inactivity (6), and that adherence to lifestyle recommendations reduced colorectal cancer risk (7–9). Once-only flexible sigmoidoscopy (FS) screening resulted in a 28% reduction in colorectal cancer mortality and a 20% reduction in colorectal cancer incidence, according to a meta-analysis by Brenner and colleagues (10). A national screening program has been shown to produce a reduction in colorectal cancer mortality in a number of countries (11, 12). In 1993, total mesorectal excision was implemented as the standard rectal resection technique in Norway, and this is probably the main reason for the increased 5-year survival of rectal cancer observed since then (13).

Few studies have investigated the prospects of improved treatment and corresponding reduction in colorectal cancer mortality, or the combined effect of risk factor modification, screening, and treatment on colorectal cancer mortality. The aim of this study was therefore to determine the individual and collective potential of

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risk factor modification, preventive and early detection screening, and treatment in reducing colorectal cancer mortality in the general population of Norway.

Materials and Methods

In this study, we compared estimated colorectal cancer mortality in the presence of specific strategies of risk factor modification, screening, and treatment with a reference scenario assuming no implementation and the continuation of existing trends described in detail below. For each strategy considered, we assumed that any intervention would be implemented at the start of 2014 and continued until the end of 2030. In addition to studying the impact for the whole population in Norway (all ages), results were also reported for premature mortality (deaths among people <70 years).

Reference scenario

We used data from Statistics Norway to obtain population data on January 1, 2014, in Norway in 1-year age groups by sex, and the forecasted population sizes for 2015 to 2030 in 5-year age groups by sex, based on medium national growth estimates (see Supplementary Figure S1 for an overview of the data sources). Data from the Cause of Death Registry at the Norwegian Institute of Public Health were used to obtain the colorectal cancer [International Classification of Diseases 10th Revision (ICD-10): C18–C20] mortality rate per 100,000 person-years in 5-year age groups by sex for Norway in 2014. Crude mortality rates for the reference scenario and for 2015 to 2030 were calculated by dividing the number of colorectal cancer deaths (assuming a constant mortality rate after 2014) in each year by the corresponding population size. The reference scenario assumed no changes in the risk factor prevalence in 2014, and equivalently, no implementation of screening programs, nor improvement in treatment beyond what was attained in 2014. This enabled us to use mortality in 2014 as the reference point with which to compare mortality reductions to 2030 based on cancer control implementation.

Risk factor modification

Selection of risk factors. Based on the report from the World Cancer Research Fund (WCRF), we selected modifiable risk factors shown to have a convincing effect on colorectal cancer risk (14). We also included smoking, which was not in the WCRF report, but is stated to be an established risk factor for colorectal cancer elsewhere (15). Thus, the following risk factors were finally included: smoking, low physical activity, excess body weight, high alcohol intake, high red/processed meat intake, and low fiber intake (Table 1).

Data. Three types of data were used to model risk factor modification: demographic data (the population size for 2014, the forecasted population for 2015–2030), risk factor data (prevalence and risk estimates), and colorectal cancer mortality rates for 2014. The prevalence of selected risk factors in Norway was obtained from national health examinations and interview surveys, whereas relative risks of each risk factor were taken from published meta-analyses of epidemiologic studies (refs. 16–21; Table 1). We prioritized the most recent meta-analyses and those that reported an association between the risk factor in question and colorectal cancer mortality (instead of the commonly reported incidence). All risk factors were modeled as dichotomized, categorical variables. Detailed information on the cutoff values of the risk factors and sources of exposure data is given in Supplementary Materials and Methods, in the Exposure Risk Data section.

Statistical analysis. To model the impact of risk factor modification on future colorectal cancer mortality, we used Prevent v.3.01. A detailed description of the mathematical calculations used by Prevent is given elsewhere (22, 23). As the beneficial effect of risk factor modification on mortality does not occur instantaneously, Prevent uses two time components, namely latency time (LAT) and lag time (LAG) (8). de Vries and colleagues define LAT as the time that risk remains unchanged after a decline in risk factor exposure, whereas LAG is the period during which reduction in risk factor exposure gradually affects cancer risk, leading to risk levels observed in the nonexposed (8). For smoking, low physical activity, high red/processed meat intake, and low fiber intake, we set LAT at 5 years and LAG at 20 years; the corresponding values for excess body weight and high alcohol intake were 1 and 15 years. Because there is little information in the literature on LAT and LAG, these values were based on previous applications of Prevent (8, 22). However, because we consider that LAG was too optimistic in previous studies, we expanded it to 15 or 20 years. Because the choice of LAT and LAG values influences the results, sensitivity analyses were performed (see Supplementary Table S1 and Figure S2). In addition, it is not realistic to assume that the risk factors would immediately disappear from 2015 onward. Therefore, we assumed that the prevalence of the risk factors was to be gradually reduced, e.g., by 10% in 2015, 20% in 2016, and up to 50% in 2019. Crude mortality rates with risk factor modification from 2015 to 2030 were calculated and used to estimate the percentage of reduction in colorectal cancer mortality in the forecasted population of Norway.

Screening

We assumed that once-only FS screening was established for men and women ages 55 to 64 years and offered over a 5-year

Table 1. Risk factors for colorectal cancer used in the Prevent model

		Prevalence in the population (%)		Relative risks		
Risk factor	Exposure	Men	Women	Men	Women	Reference
Smoking	Daily smokers	14	13	1.19	1.28	Botteri et al. 2008 (16)
Low physical activity	Physical activity less than 30 minutes 5 days a week	71	66	1.27	1.27	Je et al. 2013 (17)
Excess body weight	Body mass index $\geq$25 kg/m^2	53	36	1.30	1.06	Moghaddam et al. 2007 (18)
High alcohol intake	Alcohol intake >24 g/day for men and >12 g/day for women	21	20	1.23	1.23	Moskal et al. 2006 (19)
High red/processed meat intake	Red/processed meat intake $\geq$500 g/week	55	33	1.22	1.22	Chan et al. 2011 (20)
Low fiber intake	Fiber intake < 3 g/MJ	77	62	1.14	1.14	Aune et al. 2011 (21)

NOTE: Exposure groups not following recommended national guidelines, proportions of exposed in the Norwegian population, assumed relative risks for developing colorectal cancer, and reference to meta-analysis.

period (from 2014 to 2019), and consecutively for 55 year-olds from 2015 to 2030. The attendance rate was set at 50%.

Statistical analysis. To estimate the effect of FS screening on colorectal cancer mortality, we assumed no reduction during the first 5 years of screening, 50% of the effect was implemented 5 to 9 years after screening, and a full effect 10 years after implementation, which is similar to the study by Hakama and Hristova (24). Assumptions on the effect of FS screening were based on results from the Norwegian Colorectal Cancer Prevention (NORCCAP) trial, which reported a 27% [hazard rate ratio (HRR) = 0.73] reduction in colorectal cancer mortality among the invited group, with an attendance rate of 63% (25). For an FS screening coverage of 50%, an HRR of 0.79 was assumed based on the following formula: $\{1-(1-0.73\times[0.50\div0.63])\}$, as proposed by Geurts and colleagues (11). Furthermore, we assumed a similar effect for men and women. The age-specific mortality rates from 2015 to 2030 (assuming a constant mortality rate after 2014) were reduced by the percentage reduction in colorectal cancer mortality by age and calendar period (Table 2), to obtain age-specific mortality rates with screening. The crude mortality rates with screening from 2015 to 2030 were calculated and used to estimate the percentage reduction in colorectal cancer mortality in the forecasted population of Norway.

Treatment

Data. The number of patients diagnosed with colorectal cancer (ICD-10: C18–C20) from 1980 to 2014 was obtained from the Cancer Registry of Norway (CRN). Data on age, sex, year of diagnosis, tumor stage (8% missing), and vital status were available. Age-standardized incidence rates by sex for 2014 were also obtained from the CRN. A population life table stratified by age, sex, and calendar period was retrieved from Statistics Norway.

Statistical analysis. We assumed that colorectal cancer survival continued to improve from 2015 to 2030 utilizing an estimated linear trend to predict survival based on changing observed survival proportions for colorectal cancer patients diagnosed between 1980 and 2014. The effects of improved treatment were calculated from the assumption that 50% of the observed linear trend in survival continued from 2015 to 2030 (Fig. 1). Overall survival and interval-specific relative survival (RS) for 2015 to 2030 were estimated after fitting flexible parametric hazard models (26). Future colorectal cancer mortality rates were calculated using overall survival and interval-specific RS rates (reduced based on halving the linear trend; see Fig. 1), in addition to the incidence rate for 2014, as in Chu and colleagues (27). All models were adjusted for age at diagnosis, sex, tumor stage, and time-dependent effects of sex and age. Multiple imputation methods were used to account for missing values of tumor stage (28). More details on the statistical analysis are given in Supplementary Materials and Methods, in the Statistical Analysis Improved Survival section.

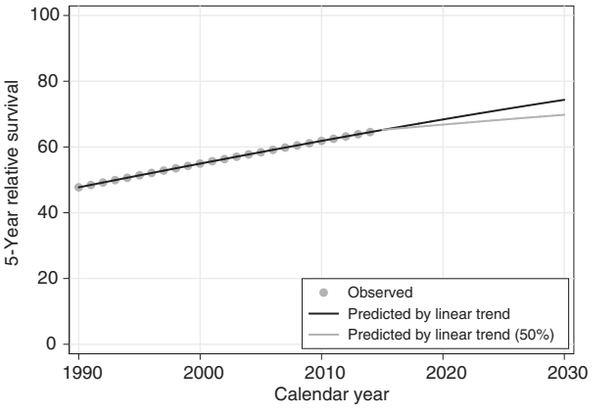

Figure 1.
Observed 5-year relative colorectal cancer survival for the calendar period 1980–2014 and predicted 5-year relative colorectal cancer survival based on linear trend and half of the linear trend for the calendar period 2015–2030.

Combined effect of all strategies

The combined effect of all three strategies was measured assuming independence and no correlation between the strategies, following the joint population attributable fraction rationale (29). When assuming independence between the strategies, the following multiplicative formula was applied:

$$\text{Combined effect} = 1 - \prod_{i=1}^{n}(1 - \text{Scenario}_i),$$

where $1 - \text{Scenario}_i$ is the proportion of the remaining disease that is not attributed to the ith scenario, $i = 1$ is the risk factor modification, $i = 2$ is the FS screening, and $i = 3$ is the treatment.

Table 2. Percentage reduction in colorectal cancer mortality by age and calendar period if FS screening was established in 2014 and covered 50% of the population ages 55 to 64 years

	Age (years)							
Calendar period	**50–54**	**55–59**	**60–64**	**65–69**	**70–74**	**75–79**	**80–84**	**≥85**
2014–2018	—	—	—	—	—	—	—	—
2019	—	—	2.2	2.2	—	—	—	—
2020	—	—	4.3	4.3	—	—	—	—
2021	—	—	6.5	6.5	—	—	—	—
2022	—	—	8.6	8.6	—	—	—	—
2023	—	—	10.8	10.8	—	—	—	—
2024	—	—	10.8	12.9	4.3	—	—	—
2025	—	—	10.8	15.1	8.6	—	—	—
2026	—	—	10.8	17.2	12.9	—	—	—
2027	—	—	10.8	19.4	17.2	—	—	—
2028	—	—	10.8	21.5	21.5	—	—	—
2029	—	—	10.8	21.5	21.5	4.3	—	—
2030	—	—	10.8	21.5	21.5	8.6	—	—

NOTE: Screening was implemented over a 5-year period (2014–2019).

Results

Reference scenario

Without further risk factor modification, no implementation of screening, and no improvement in treatment, the age-standardized ("European Standard Population") colorectal cancer mortality rate per 100,000 people in Norway would be 20.3 for both sexes combined in 2030, representing 2,236 expected colorectal cancer deaths. The colorectal cancer mortality rate per 100,000 would be 23.4 (1,196 expected colorectal cancer deaths) among men and 18.0 (1,040 expected colorectal cancer deaths) among women in 2030 in the Norwegian population.

Risk factor modification

Risk factor modification resulted in an 11% reduction in mortality in 2030 (Table 3), representing 227 prevented colorectal cancer deaths. The reduction was higher among men (12%; 142 prevented deaths) than among women (8%; 85 prevented deaths). The effect of risk factor modification on colorectal cancer mortality gradually increased from 2020 (2% among men and 1% among women) to 2025 (7% among men and 5% among women; Fig. 2A and B). The percentage reduction in colorectal cancer mortality by 2030 shown in Table 3 is also shown by risk factor. For excess body weight, a 3% reduction was seen for men compared with a 1% reduction for women. The results of sensitivity analyses (changing LAG and LAT values) for all risk factors showed a more rapid reduction in colorectal cancer mortality for sensitivity analysis 1 (based on previous applications with Prevent) compared with sensitivity analyses 2 and 3 (with extended LAG values; see Supplementary Materials and Methods, in the Sensitivity Analysis section for more details). The results for people <70 years of age showed a 15% reduction in colorectal cancer mortality (70 prevented deaths) in 2030.

Screening

Our results for FS screening showed a 7% reduction in colorectal cancer mortality, equivalent to 149 colorectal cancer deaths prevented in 2030 (Table 3). The effect of FS screening increased to a 4% reduction in 2025 among men (Fig. 2A). The results for people <70 years of age showed a 10% reduction in colorectal cancer mortality (57 prevented deaths) in 2030.

Treatment

If colorectal cancer survival continued to increase by 50% of the increase in previous years, the estimated reduction in colorectal cancer mortality would be 12%, corresponding to 228 prevented deaths in 2030 (Table 3). Our assumption that the reduction in colorectal cancer mortality due to continuously improved treatment of colorectal cancer was linear, resulting in a 5% reduction in 2020 and a 9% reduction in colorectal cancer mortality among men in 2025 (Fig. 2A). The results for men and women <70 years of age showed a 15% reduction in colorectal cancer mortality (66 prevented deaths) in 2030.

Combined effect of all strategies

The total combined effect of all three prevention strategies was estimated to reduce colorectal cancer mortality by 27%, which was equivalent to 604 prevented colorectal cancer deaths in 2030 (Table 3). For people <70 years of age, the total combined effect was 35% (193 prevented deaths).

Discussion

Our study showed that the investigated prevention and treatment strategies have the potential to individually and collectively reduce colorectal cancer mortality. Their combined effect indicated a potential reduction in colorectal cancer mortality of 27% (corresponding to 604 prevented deaths) by 2030. The largest effect was observed when assuming that 50% of the positive trend in colorectal cancer survival continued, thereby reducing colorectal cancer mortality by 12% (228 prevented deaths) in 2030. In addition, for risk factor modification, if 50% of the population of Norway adhered to the lifestyle recommendations on physical activity, nutrition, and smoking behavior, we estimated that colorectal cancer mortality would be reduced by 11% (227 prevented deaths) by 2030. A stronger effect of risk factor modification was observed among men (12%, 142 prevented deaths) than women (8%, 85 prevented deaths) due to a larger effect of losing weight among men (caused by both higher prevalence of excess body weight and larger relative risks among men compared with women). Furthermore, implementation of a national FS screening program in Norway would result in a 7% reduction (149 prevented deaths) in colorectal cancer mortality by 2030.

Few studies have investigated the combined effect of different prevention strategies for preventing colorectal cancer deaths. However, a microsimulation modeling study by Vogelaar and colleagues, with an optimistic trend scenario, projected that the combined effect of risk factor modification, screening, and improved treatment would reduce colorectal cancer mortality by 49% (30).

Favorable lifestyle changes at age 50 to 60 years were reported to prevent early death in Norway (31). Complete adherence to lifestyle recommendations was associated with a 16% reduction in the incidence of colorectal cancer in the overall European

Table 3. Percentage reduction in colorectal cancer mortality for different prevention strategies and different risk factors by sex for all ages and ages below 70 years in 2030

	Men		Women		Total	
Prevention strategy	**All ages**	**<70 years**	**All ages**	**<70 years**	**All ages**	**<70 years**
Risk factor modification for all factors combined	12	15	8	10	11	15
Recommended physical activity[a]	3	3	3	3	3	4
No obesity[a]	3	4	1	<1	3	4
Recommended alcohol intake[a]	2	2	2	3	2	3
Recommended red/processed meat intake[a]	2	2	1	1	2	2
Recommended fiber intake[a]	2	2	1	2	2	2
No smoking	<1	<1	<1	<1	<1	<1
FS screening	7	11	6	10	7	10
Treatment	12	15	12	15	12	15
All above scenarios combined	28	36	24	31	27	35

[a]50% of the population in Norway that do not adhere to the recommendation for prevention starts to follow the recommendations.

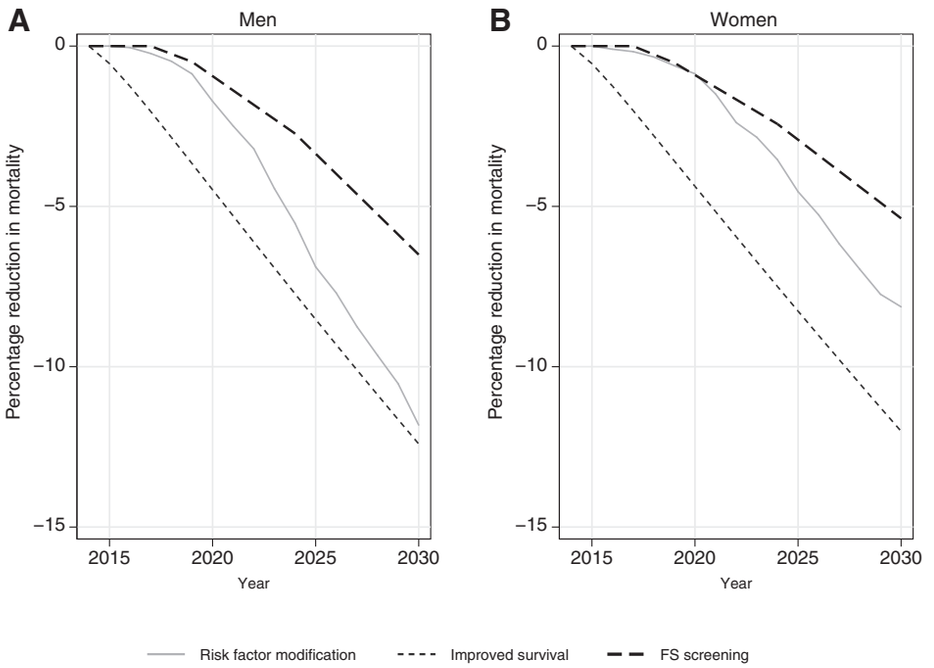

Figure 2.
Percentage reduction in colorectal cancer mortality from 2015 to 2030 by prevention strategy: risk factor modification, implementation of FS screening, and treatment (improved survival). Men **(A)** and women **(B)**.

Prospective Investigation into Cancer and Nutrition (EPIC) cohort (9) and 23% in the Danish cohort (7). Our macrosimulation study estimated a reduction in colorectal cancer mortality of 11% with 50% adherence to lifestyle recommendations. The difference is most likely explained by different exposures in the population, the size of the relative risk, and the prevention strategy investigated, that is, the difference in outcome between adherent and nonadherent groups (EPIC and Danish study) versus 50% adherence. Our smaller total effect of risk factor modification compared with these studies likely results from the more realistic 50% adherence. One strength of our study is that the prevalence of physical activity was based on actual activity (the use of an accelerometer to register the physical activity, see Supplementary Materials and Methods, in the Exposure Risk Data section) instead of self-report.

Because there is little information in the literature on the exact mechanisms by which each risk factor acts on colorectal cancer risk, it is difficult to determine LAT. Results from the sensitivity analyses, with changing LAT and LAG values, showed that these choices influence both the time to benefit from risk factor modification and the outcome in 2030. Sensitivity analysis 1, based on LAT and LAG values from previous applications with Prevent, showed a rapid effect of risk factor modification compared with sensitivity analyses 2 and 3 (with extended LAGs). However, when we selected values in sensitivity analysis 2, the time to benefit from risk factor modification was similar to the advanced microsimulation study from the United States, with lower short-term effect of risk factor modification followed by a steady decline (30).

It is considered advantageous to use a dynamic modeling approach, such as Prevent, when modeling the impact of risk factor modification, compared with the use of the standard population attributable risk approach (32). Indeed, in Prevent, it is possible to include time lags, which allow us to consider delayed changes in colorectal cancer mortality after risk factor exposure and take into account demographic changes in the study population. Nevertheless, the association between one risk factor and colorectal cancer mortality may be considerably modified by other risk factors. In the current version of Prevent, the effects of our investigated risk factors were assumed to be independent, but they are likely interrelated. For example, a lack of physical activity can cause an increased incidence of obesity (33), and associations between smoking and alcohol have also been observed (34). A positive correlation between risk factors may lead to an overestimation of the combined effect of all the risk factors (35).

In addition, the assumptions about the impact of risk factors on reduction in colorectal cancer mortality rely on the effects from meta-analyses being real/causal. These estimates are based on observational studies, which may lack adequate and similar adjustment (e.g., smoking, alcohol, and body mass) for confounding.

The likely impact of implementing a screening program on colorectal cancer incidence and mortality rates has been examined in several countries (11, 12, 24, 36), considering different tests and attendance rates. In our study, we estimated that colorectal cancer mortality was reduced by 7% in 2030 if FS screening were implemented, assuming a 50% attendance rate. Our estimates of screening benefit are lower than those from studies in the UK (11) and the United States (12). This is likely due to the different study designs and assumptions used (e.g., microsimulation models), the inclusion of colonoscopy, and the 80% attendance rate (compared with 50%) in the U.S. study. However, similar to studies using microsimulation models, we observed small effects in the first few years followed by larger effects (30, 36).

In addition to attendance rate, our prediction of the effect of screening depends on assumptions about mortality reduction due to screening, the age at invitation, and the time to benefit from FS screening. The estimate of mortality reduction after implementing FS screening was based on results from the NORCCAP trial; therefore, it was not affected by screening contamination in the control group. In addition, our results can be generalized to the

Norwegian population because of the random sampling of participants and controls in the NORCCAP trial, who were taken directly from the population registry, instead of relying on volunteers (25). The assumption of no reduction in the first 5 years after screening implementation is supported by the findings from meta-analyses estimating that a survival benefit could not be observed until 4.3 years after colorectal cancer screening began (25, 37).

In our study, we assumed a similar effect of FS screening in both men and women. However, some randomized control trials suggest a stronger effect of FS screening in men than in women (25, 38, 39). In our study, the slightly smaller effect observed for women was caused by a more elderly population compared with men.

Studies in Norway (40) and Europe (41) have shown that improvements in colorectal cancer survival can be attributed to improved surgery and care. By using colorectal cancer survival as an indicator of treatment efficacy, we assumed that the improvement in colorectal cancer survival was exclusively due to improved treatment. However, earlier and more frequent diagnoses of colorectal cancer due to better diagnostic tools and methods might also lead to improved colorectal cancer survival. In the model predicting future survival rates, we adjusted for stage in an effort to account for the issue of earlier diagnosis. In addition, we assume a halving of the linear trend and persistent improvement in colorectal cancer survival throughout the period. Using 50% of the linear trend seems reasonable; persistent improvement in colorectal cancer survival would only be problematic in long-term predictions if survival reached 100%, which was not the case in our study.

Only a few studies have investigated the prospects of improved treatment and corresponding reductions in colorectal cancer mortality. For example, Vogelaar and colleagues predicted a 10% reduction in colorectal cancer mortality, with increased use of chemotherapy as a proxy for improved treatment (30). Using the improvement in cancer-specific survival to estimate the improvement in treatment, our study predicted a similar effect of 12%. This approach was also used in a U.S. study that aimed to explain decreases in breast cancer mortality rates (42).

Cancer target projects often focus on deaths only among people <70 years of age (premature mortality). Our study observed a higher mortality reduction among people <70 years of age compared with the whole population (all ages) for all scenarios, which was due to the larger effect with risk factor modification caused by the long LAT (up to 20 years). Hence, those people > 70 years of age would not benefit in the short term from the effect of reduction in risk factor exposure. The larger effect of screening for the <70 age group compared with the >70 age group resulted from a greater reduction in colorectal cancer mortality for the population aged <70 years (Table 2).

In conclusion, the findings of this study show considerable potential for prevention of colorectal cancer mortality in the Norwegian population. It was possible to prevent nearly 30% of colorectal cancer mortality through the combined effects of risk factor modification, screening, and treatment. Improved treatment and adherence to lifestyle recommendations had the largest effect on men.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Development of methodology: K.D. Skyrud, T.Å. Myklebust, M.T. Eriksen, I.K. Larsen, B. Møller
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B. Møller
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.D. Skyrud, T.Å. Myklebust, T. de Lange, I.K. Larsen, B. Møller
Writing, review, and/or revision of the manuscript: K.D. Skyrud, T.Å. Myklebust, F. Bray, M.T. Eriksen, T. de Lange, I.K. Larsen, B. Møller
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K.D. Skyrud
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References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017;66:683–91.
3. Bray F, Wibe A, Dørum L, Møller B. Epidemiology of colorectal cancer in Norway. Tidssk Nor Legeforen 2007;127:2682–7.
4. Engholm G, Ferlay J, Christensen N, Bray F, Gjerstorff ML, Klint A, et al. NORDCAN–a Nordic tool for cancer information, planning, quality control and research. Acta Oncol 2010;49:725–36.
5. Engholm G, Ferlay J, Christensen N, Kejs A, Johannesen TB, Khan S, et al. NORDCAN: Cancer incidence, mortality, prevalence and survival in the nordic countries, Version 7.2 (16.12.2015). Association of the Nordic Cancer Registries. Danish Cancer Society. [cited 2016 Jun 6]. Available from: http://www.ancr.nu.
6. Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer 2011;105Suppl 2:S77–81.
7. Kirkegaard H, Johnsen NF, Christensen J, Frederiksen K, Overvad K, Tjonneland A. Association of adherence to lifestyle recommendations and risk of colorectal cancer: a prospective Danish Cohort Study. BMJ 2010;341:c5504.
8. de Vries E, Soerjomataram I, Lemmens VE, Coebergh JW, Barendregt JJ, Oenema A, et al. Lifestyle changes and reduction of colon cancer incidence in Europe: a scenario study of physical activity promotion and weight reduction. Eur J Cancer 2010;46:2605–16.
9. Aleksandrova K, Pischon T, Jenab M, Bueno-de-Mesquita HB, Fedirko V, Norat T, et al. Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. BMC Med 2014;12:168.
10. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality:

systematic review and meta-analysis of randomised controlled trials and observational studies. BMJ 2014;348:g2467.
11. Geurts SM, Massat NJ, Duffy SW. Likely effect of adding flexible sigmoidoscopy to the English NHS Bowel Cancer Screening Programme: impact on colorectal cancer cases and deaths. Br J Cancer 2015;113:142–9.
12. Meester RG, Doubeni CA, Zauber AG, Goede SL, Levin TR, Corley DA, et al. Public health impact of achieving 80% colorectal cancer screening rates in the United States by 2018. Cancer 2015;121:2281–5.
13. Wibe A, Moller B, Norstein J, Carlsen E, Wiig JN, Heald RJ, et al. A national strategic change in treatment policy for rectal cancer–implementation of total mesorectal excision as routine treatment in Norway. A national audit. Dis Colon Rectum 2002;45:857–66.
14. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Report. Food, nutrition, physical activity, and the prevention of colorectal cancer; 2011.
15. Tarraga Lopez PJ, Albero JS, Rodriguez-Montes JA. Primary and secondary prevention of colorectal cancer. Clin Med Insights Gastroenterol 2014; 7:33–46.
16. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. JAMA 2008;300: 2765–78.
17. Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA. Association between physical activity and mortality in colorectal cancer: a meta-analysis of prospective cohort studies. Int J Cancer 2013;133:1905–13.
18. Moghaddam AA, Woodward M, Huxley R. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. Cancer Epidemiol Biomarkers Prev 2007;16:2533–47.
19. Moskal A, Norat T, Ferrari P, Riboli E. Alcohol intake and colorectal cancer risk: a dose-response meta-analysis of published cohort studies. Int J Cancer 2007;120:664–71.
20. Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS One 2011;6:e20456.
21. Aune D, Chan DS, Lau R, Vieira R, Greenwood DC, Kampman E, et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. BMJ 2011;343: d6617.
22. Soerjomataram I, de Vries E, Engholm G, Paludan-Muller G, Bronnum-Hansen H, Storm HH, et al. Impact of a smoking and alcohol intervention programme on lung and breast cancer incidence in Denmark: an example of dynamic modelling with Prevent. Eur J Cancer 2010;46:2617–24.
23. Brønnum-Hansen H. How good is the Prevent model for estimating the health benefits of prevention. J Epidemiol Communtity Health 1999:300–5.
24. Hakama M, Hristova L. Effect of screening in the Nordic cancer control up to the year 2017. Acta Oncol 1997;36:119–28.
25. Holme O, Loberg M, Kalager M, Bretthauer M, Hernan MA, Aas E, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014;312:606–15.
26. Nelson CP, Lambert PC, Squire IB, Jones DR. Flexible parametric models for relative survival, with application in coronary heart disease. Stat Med 2007;26:5486–98.
27. Chu KC, Horm JW, Smart CR. Estimating cancer mortality rates from SEER incidence and survival data. Public Health Rep 1990; 105:36–46.
28. Nur U, Shack LG, Rachet B, Carpenter JR, Coleman MP. Modelling relative survival in the presence of incomplete data: a tutorial. Int J Epidemiol 2010;39:118–28.
29. Ezzati M, Vander Hoorn S, Rodgers A, Lopez AD, Mathers CD, Murray CJL. Estimates of global and regional potentil health gains from reducing muliple major risk factors. The Lancet 2003;362:271–80.
30. Vogelaar I, van Ballegooijen M, Schrag D, Boer R, Winawer SJ, Habbema JD, et al. How much can current interventions reduce colorectal cancer mortality in the U.S.? Mortality projections for scenarios of risk-factor modification, screening, and treatment. Cancer 2006;107:1624–33.
31. Berstad P, Botteri E, Larsen IK, Loberg M, Kalager M, Holme O, et al. Lifestyle changes at middle age and mortality: a population-based prospective cohort study. J Epidemiol Community Health 2017; 71:59–66.
32. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol 1985;122:904–14.
33. de Jong AE, Morreau H, Nagengast FM, Mathus-Vliegen EM, Kleibeuker JH, Griffioen G, et al. Prevalence of adenomas among young individuals at average risk for colorectal cancer. Am J Gastroenterol 2005;100:139–43.
34. Zisman AL, Nickolov A, Brand RE, Gorchow A, Roy HK. Associations between the age at diagnosis and location of colorectal cancer and the use of alcohol and tobacco: implications for screening. Arch Intern Med 2006;166:629–34.
35. Greenland S. Bias in methods for deriving standardized morbidity ratio and attributable fraction estimates. Stat Med 1984;3:131–41.
36. Coldman AJ, Phillips N, Brisson J, Flanagan W, Wolfson M, Nadeau C, et al. Using the cancer risk management model to evaluate colorectal cancer screening options for Canada. Curr Oncol 2015;22:e41–50.
37. Tang V, Boscardin WJ, Stijacic-Cenzer I, Lee SJ. Time to benefit for colorectal cancer screening: survival meta-analysis of flexible sigmoidoscopy trials. BMJ 2015;350:h1662.
38. Schoen RE, Pinsky PF, Weissfeld JL, Yokochi LA, Church T, Laiyemo AO, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366:2345–57.
39. Atkin W, Wooldrage K, Parkin DM, Kralj-Hans I, MacRae E, Shah U, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. Lancet 2017;389:1299–311.
40. Nedrebo BS, Soreide K, Eriksen MT, Dorum LM, Kvaloy JT, Soreide JA, et al. Survival effect of implementing national treatment strategies for curatively resected colonic and rectal cancer. Br J Surg 2011;98:716–23.
41. Oliphant R, Nicholson GA, Horgan PG, Molloy RG, McMillan DC, Morrison DS, et al. Contribution of surgical specialization to improved colorectal cancer survival. Br J Surg 2013;100:1388–95.
42. Narod SA, Iqbal J, Miller AB. Why have breast cancer mortality rates declined? Journal of Cancer Policy 2015;5:8–17.