ScienceDirect

Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/jval

Comparative-Effectiveness Research/HTA

Benefit-Harm Analysis for Informed Decision Making on Participating in Colorectal Cancer Screening: A Modeling Study

Henock G. Yebyo, PhD,* Francine van Wifferen, MSc,* Linda P.M. Pluymen, PhD, Mariska M.G. Leeflang, PhD, Evelien Dekker, PhD, Veerle M.H. Coupé, PhD, Milo A. Puhan, PhD, Marjolein J.E. Greuter, PhD, Inge Stegeman, PhD

ABSTRACT

Objectives: To facilitate informed decision making on participating in colorectal cancer (CRC) screening, we assessed the benefit-harm balance of CRC screening for a wide range of subgroups over different time horizons.

Methods: The study combined incidence proportions of benefits and harms of (not) participating in CRC screening estimated by the Adenoma and Serrated pathway to CAncer microsimulation model, a preference eliciting survey, and benefit-harm balance modeling combining all outcomes to determine the net health benefit of CRC screening over 10, 20, and 30 years. Probability of net health benefit was estimated for 210 different subgroups based on age, sex, previous participation in CRC screening, and lifestyle.

Results: CRC screening was net beneficial in 183 of 210 subgroups over 30 years (median probability [MP] of 0.79, interquartile range [IQR] of 0.69-0.85) across subgroups. Net health benefit was greater for men (MP 0.82; IQR 0.69-0.89) than women (MP 0.76; IQR 0.67-0.83) and for those without history of participation in previous screenings (MP 0.84; IQR 0.80-0.89) compared with those with (MP 0.69; IQR 0.59-0.75). Net health benefit decreased with increasing age, from MP of 0.84 (IQR 0.80-0.86) at age 55 to 0.61 (IQR 0.56-0.71) at age 75. Shorter time horizons led to lower benefit, with MP of 0.70 (IQR 0.62-0.80) over 20 years and 0.54 (IQR 0.48-0.67) over 10 years.

Conclusions: Our benefit-harm analysis provides information about net health benefit of screening participation, based on important characteristics and preferences of individuals, which could assist screening invitees in making informed decisions on screening participation.

Keywords: benefit-harm balance, colorectal cancer, informed decision making, microsimulation modeling.

VALUE HEALTH. 2024; 27(4):397–404

Introduction

Many decisions in healthcare require balancing of benefits against harms. However, most decision approaches and clinical guidelines tend to oversimplify, often emphasizing the benefits of interventions.[1] Screening for early detection of colorectal cancer (CRC) poses a particular challenge for decision making, necessitating an assessment of the balance between benefits and harms for the target individuals because not everyone would benefit from the screening.[2]

In The Netherlands, a CRC screening program has been implemented since 2014, where adults aged 55 to 75 years are invited biennially for fecal immunochemical testing (FIT).[3] Individuals with a positive FIT are referred for a diagnostic colonoscopy, where, depending on colonoscopy findings, they would be referred for treatment, colonoscopy surveillance, or invited for another screening round 10 years later. The screening program is perceived, on average, as beneficial for population health because the detection of polyps and early-stage CRC reduces incidence or progression to advanced CRC and CRC mortality.[4,5] However, not every individual will benefit from screening.[2] The benefit-harm balance for a specific individual depends on CRC risk factors such as age, sex and lifestyle and the risk of potential harms of the screening procedure, such as bleeding or perforation caused by the colonoscopy in FIT-positive individuals. The importance of screening outcomes and risk trade-offs also differs between individuals. A risk-averse or risk-accepting attitude of individuals toward specific outcomes may influence the decision whether to participate in screening. This should thus be accounted for in order to tailor decisions and meet the outcome needs of individuals.[6,7]

To enable informed decision making, individuals invited for screening should receive personalized, clear, and accurate information regarding the potential positive and negative outcomes of

*Henock G. Yebyo and Francine van Wifferen are shared first authors.

the screening. However, this process could be tremendously time consuming and challenging unless supported by systematic decision-making approaches. This is especially the case in national screening programs because, for example, in The Netherlands, over 2 million adults are invited for CRC screening annually.[8] More importantly, simultaneous processing of such information, preference elicitation, and weighing of negative and positive outcomes can be cognitively challenging, not only for screening invitees but also for clinicians. Quantitative benefit-harm balance modeling can be a useful method in this regard to facilitate tailored decisions for individuals, by simplifying the information load through a single summary measure of overall (net) health benefit.[9] This approach can be extended to develop an integrated decision aid within the screening procedure, simplifying information processing for assisting healthcare providers and screening participants in decision making.[1,10]

In this study, we assessed the benefit-harm balance of participating in CRC screening for finely stratified subgroups according to age, sex, levels of healthy lifestyle, and screening history over different time horizons.

Methods

Decision Context: Population and Outcomes

The benefit-harm balance modeling focused on individuals eligible for CRC screening in The Netherlands. We assessed the benefit-harm balance of participation in FIT-based CRC screening compared with non-participation over different time horizons. The benefits and harms of CRC screening were selected during a consensus meeting with 11 experts in research and implementation in the field of CRC screening, with additional sources from prior evidence. A description of this process can be found elsewhere.[10] We considered the screening benefits as reduced CRC detection and risk of death from CRC. Harms considered as related to the screening were risk of false-negative and false-positive test results, as well as complications from colonoscopy (Table 1). For participants, a false-negative test result indicates a risk of having undetected CRC; i.e., the FIT is negative while the participant has CRC. Additionally, if a patient is referred for a colonoscopy after a positive FIT result and the colonoscopy fails to detect CRC, this was also considered as undetected CRC. Non-participants, in contrast, do not experience the benefits or harms of screening but do have a risk of undetected CRC, which is expected to be significantly higher compared with participants.

Subgroups

The benefit-harm balance was assessed for different subgroups by sex, age (55 to 75 years with 2-years interval), history of CRC screening, and lifestyle, with a total of 210 subgroups (note, individuals aged 55 cannot have a history of CRC screening because they have not been invited before).[11-14] Because some lifestyle risk factors are known to cluster within individuals,[15] we defined a healthy lifestyle based on 5 healthy lifestyle factors (HLFs), including healthy weight, high physical activity, non-smoking, limited alcohol consumption, and a healthy diet, according to a large European cohort study.[14] The healthy lifestyle indicator consisted of 5 levels (0-1, 2, 3, 4, and 5), where higher scores indicated a healthier lifestyle. Although a family history of CRC and inflammatory bowel disease are strong risk factors for CRC, we did not consider them, as individuals with such risk are recommended to undergo regular surveillance, rather than participating in population-based screening.

Data

Our study integrated risk estimates of screening participants and non-participants over 10-, 20-, and 30-year of time horizons using microsimulation, the relative importance of CRC screening outcomes using a preference eliciting survey from the target population, and benefit-harm balance modeling.

Estimating absolute risks of benefits and harms: Microsimulation

We estimated the incidence proportion (IP) of benefits and harms using the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) model. The ASCCA model has been described extensively elsewhere.[16] In short, this microsimulation model simulates the natural history of CRC and the life trajectory of Dutch individuals from age 20 to age 90 or death, whichever comes first. It also includes a flexible screening component to simulate CRC screening. The model satisfactorily reproduces Dutch sex- and age-specific colorectal lesion prevalence rates,[17] as well as sex- and age-specific CRC incidence and mortality rates.[18] It is externally validated against several long-term CRC screening trials.[19] Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.006 describes the ASCCA model in detail.

We set up the ASCCA model to simulate biennial FIT screening between age 55 to 75 according to the Dutch screening program. Analyses were performed separately for each subgroup mentioned above. Because lifestyle was not included in the ASCCA model, we

Table 1. Definition of the benefit and harm outcomes of CRC screening.

Outcome	Definition
Reduced risk of being diagnosed with CRC	The difference in incidence proportion of a CRC diagnosis between participants and nonparticipants within 30, 20, or 10 years*
Reduced risk of death from CRC	The difference in incidence proportion to die from CRC between participants and nonparticipants within 30, 20, or 10 years
Risk of complications at colonoscopy	The incidence proportion over 30, 20, or 10 years of fatal and nonfatal complication during or after colonoscopy
Risk of undetected CRC†	The incidence proportion of having CRC that was not detected by screening within 30, 20, or 10 years.
Risk of a false-positive stool test result	The incidence proportion over 30, 20, or 10 years of a positive stool test without having CRC or a precursor lesion

CRC indicates colorectal cancer; FIT, fecal immunochemical testing.
*The risk of developing CRC was defined as the probability of a CRC diagnosis because individuals only know they have developed CRC because of the CRC diagnosis.
†For participants, this risk is the equivalent to the combined risk of a false-negative FIT result or a false-negative colonoscopy following a positive FIT result.

extended the model using the hazard ratios reported by Aleksandrova et al to obtain adenoma and serrated lesion specific incidence rates for each of the five HLF subgroups.[14] See a detailed description in Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.006.

For those with a history of participation, we assumed that they have participated in all previous rounds because the probability of participating again in a next round is high in The Netherlands (93%).[20] In addition, we assumed in the simulation that participants in a given screening round also participate in all subsequent rounds. For every screening round, we simulated 2 cohorts of 25 000 000 individuals for each of the 210 subgroups—ie, 1 for participants and 1 for non-participants.

We then calculated the difference in incidence proportion (IPD) of benefits and harms for participants versus non-participants of screening. Results were calculated over a 30-year time horizon, because the duration of an adenoma to develop into cancer may take more than 20 years. In the ASCCA model, the average adenoma dwell time is 24 years.[16,21] However, expecting a net health benefit after 30 years may be unattainable for some individuals because of a limited life expectancy. Therefore, we repeated the analysis for shorter time horizons of 10 and 20 years. As the ASCCA model simulates life trajectories until the age of 90, the 30-year time horizon was applied to those aged between 55 and 60 and gradually decreased to a time horizon of 15 years between age 60 and 75. The 20-year time horizon was applied to those aged between 55 and 70, after which it gradually decreased to 15 years.

Because the ASCCA model is a deterministic model, we additionally estimated the uncertainty (ie, variance) around the IPs for all benefit and harm outcomes using IPx(1-IP)/N. The sample size (N) was obtained from the original study used to inform the ASCCA model for the specific outcomes. For the IPs of CRC diagnosis and CRC-related death, the sample size of Aleksandrova et al was used.[14] For fatal and non-fatal complications, we considered Kooyker et al and the Dutch monitor, respectively.[3,22] For false-negative and false-positive test results, we used the sample size of a Dutch CRC screening trial.[23]

No discounting was applied because this study intends to provide personalized information about the benefits and harms of CRC screening by calculating and weighing the real health effects of screening.

Eliciting outcome preferences

A measure of the relative importance (or seriousness) of outcomes is necessary to assess the balance between different benefits and harms on a common scale. For this purpose, the preferences of the CRC-related outcomes were elicited in an online survey in adults (N = 265) recruited from the Dutch Health Care Consumer Panel of The Netherlands Institute for Health Services Research. Details of this study are reported in a previous publication.[10] In short, the preferences were elicited using a Best-Worst Scaling (BWS) survey. In the survey, individuals were asked to simultaneously select their most and least important outcomes from different sets of outcome combinations generated using a balanced incomplete block experimental design. Preference responses were aggregated within individual and across individuals to estimate the relative importance of the outcomes. Accordingly, CRC death was the most important outcome that individuals would like to avoid (odds ratio [OR] 4.5; 95% confidence interval [CI] 3.9-5.1), followed by CRC detection (OR 4.1; 95% CI 3.6-4.7), false-negative FIT result (OR 3.1; 95% CI 2.7-3.5), colonoscopy complications (OR 1.6; 95% CI 1.4-1.8), and a false-positive FIT result (OR 1.4; 95% CI 1.3-1.6).

Benefit-Harm Analysis

For the benefit-harm analysis, we used an approach originally developed by Gail et al that has been further developed and used to assess the benefit-harm balance in various healthcare decisions.[6,9,24]

The IPD of benefit and harm outcomes obtained with the ASCCA model were weighted by the respective preference weights of the outcomes. The preference-adjusted risks of benefit and harm outcomes were all summed to yield the benefit-harm index or net health benefit. The index shows whether the benefits outweigh the harms (positive index), vice versa (negative index), or an equipoise (index of 0). The analysis was done stochastically with 100 000 resampling accounting for the statistical uncertainty of the IPD of benefit and harms, as well as preferences providing a distribution of the net health benefit. Because the net health benefit was a product of several parameters, its interpretation can be complex. To simplify interpretation, we transformed the benefit-harm index to CRC-equivalent events per 1000 people, by dividing it solely by the preference for reduced CRC detection, where positive estimates signify the net events prevented and negative estimates signify net events induced by the screening. The CRC-equivalent event was used as an indicator of the absolute net health benefit and can be interpreted as CRC events prevented by screening without experiencing any important harm outcomes. The analyses included a bootstrapping method with 1000 replicate samples to estimate uncertainty about the net health benefit. We report 95% uncertainty intervals based on the 2.5th and 97.5th centiles in the distributions about the average CRC-equivalent events.

From the distribution of net health benefit indices, we calculated the probability that individuals would achieve a net health benefit over 30-, 20-, and 10-year time horizons after participating in screening. CRC screening was considered to be net beneficial when the probability of net health benefit reached at least 0.60. We chose 0.60, instead of 0.50, to ensure a certain benefit because the net benefit at a probability of 0.5 would be 0. It is also sensible to be slightly risk averse when participating in an intervention. We also provide the probabilities of net health benefit for each subgroup. Readers can use the 0.50 probability threshold to determine the net benefit where applicable.

The microsimulation was mainly performed in C++11 and benefit-harm balance in R version 4.0.2.

Sensitivity Analysis

The main analysis assumed that individuals who participate in the screening round of interest will also participate in all future rounds. We performed a sensitivity analysis assuming that individuals participate in 1 round only and not in subsequent rounds. Furthermore, we examined the sensitivity of the net health benefit to individual preferences, as opposed to aggregated preference values. That is, within each subgroup, we considered the preferences of individual people and examined how the net health benefit varied among them due to the influence of having different preferences. For this purpose, we obtained individual preferences estimated from the companion BWS survey data.[10]

Role of the Funding Source

The funders of the study had no role in the study design, data collection, data interpretation, writing of the report, or in the decision to submit for publication.

All data used in this study were available and aggregated; as such, no ethical approval was needed.

Results

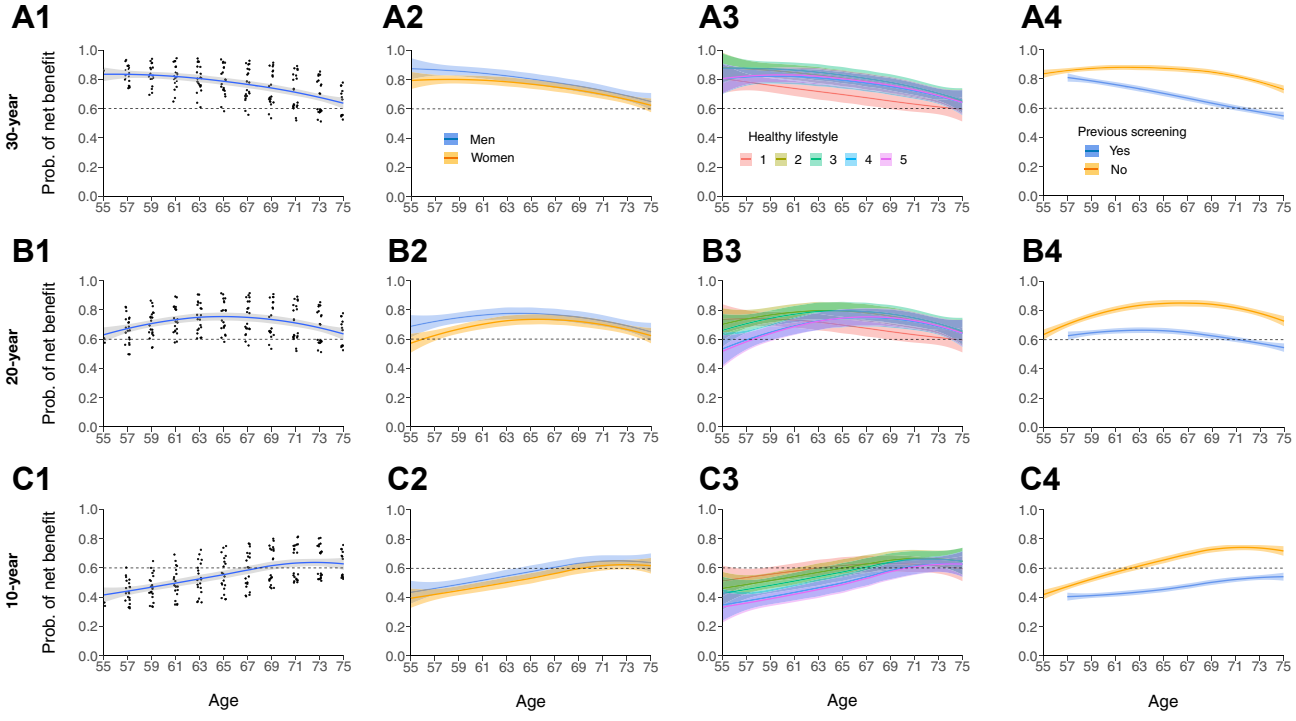
Risks of Benefits and Harms of CRC Screening

The IPDs of benefits and harms of CRC screening for the different subgroups based on sex, age, lifestyle, and screening history over 30-, 20-, and 10-year time horizons are presented in Appendix Figures C1-C6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.006. The IPDs of CRC diagnosis, CRC-related death and undetected CRC within 30 and 20 years were lower for those who previously participated in screening compared with those who did not, whereas the IPDs calculated over 10 years were roughly comparable between previous participants and previous non-participants (Appendix Figures C1-C3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.006). The IPDs of these outcomes increased with increasing age, meaning that screening benefit decreased with increasing age. The IPDs of a false-positive FIT result and of non-fatal and fatal colonoscopy complications over 30, 20, or 10 years decreased with increasing age (Appendix Figure C4-C6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.006). This is because the number of subsequent rounds decreases with increasing age, and we assumed that those who participate in the current round will also participate in all future rounds. Overall, IPDs were not substantially affected by lifestyle, except for those individuals with the unhealthiest lifestyle, and were lower when calculated over a shorter time horizon. Results are explained in detail in Appendix C in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.006.

Benefit-Harm Balance

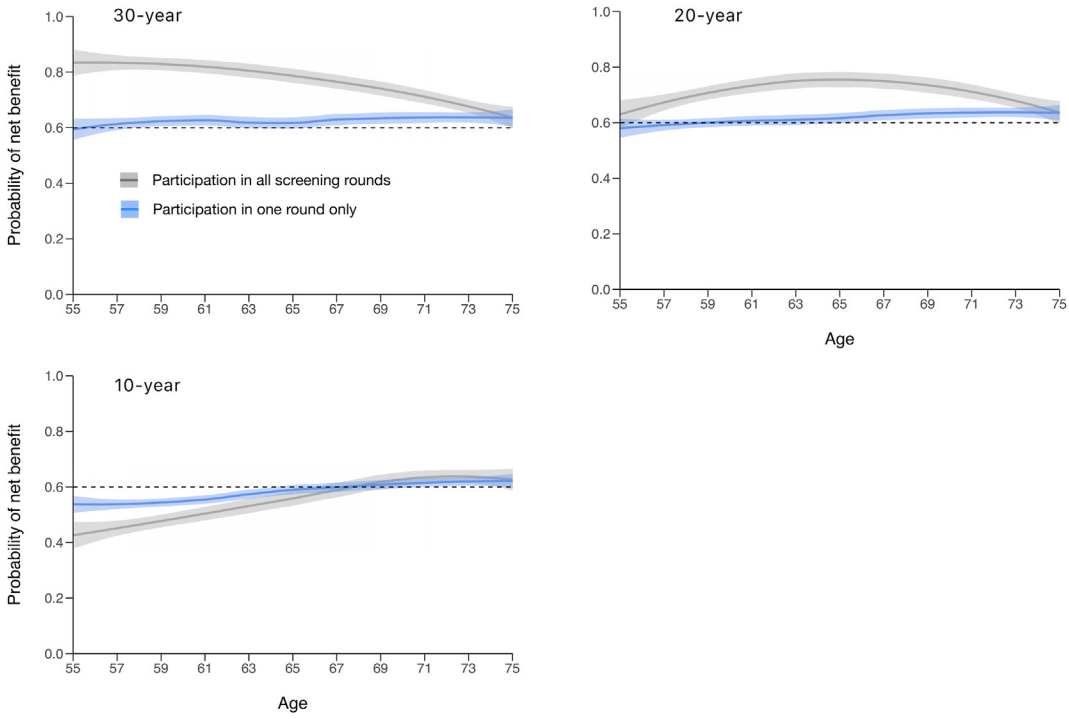
Figure 1 presents the summary results by subgroup (see Appendix D1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.006 for detailed results). The probability of net health benefit of CRC screening after 30 years ranged from 0.52 to 0.94 across various subgroups based on subgroups according to age, sex, lifestyle, and screening history (Figure 1, A1-A4). The MP between the groups was 0.79 (interquartile range [IQR] 0.69-0.85). 87% (183/210) of subgroups were more likely to achieve net health benefit from CRC screening because the probability of net health benefit exceeded the 0.60 benchmark. The subgroups that benefited from screening had between 10 (95% CI 8 to 13) and 83 (95% CI 79 to 86) CRC-equivalent events prevented per 1000 individuals over 30 years, with a median of 38 (IQR 26.5 to 52). See Appendix E in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.006 for details on CRC-equivalent events avoided by screening for the various subgroups. The remaining subgroups had an unfavorable benefit-harm balance. Those subgroups were characterized by having previously participated in screening, being older than 70 years (82%) and having an unhealthy lifestyle (0-1 HLF). The net health benefit diminished with increasing age, with MP of 0.84 (IQR 0.80-0.86) at 55 years and 0.61 (IQR 0.56-0.71) at 75 years. The probability of net health benefit was higher at all ages for men (MP 0.82, IQR 0.69-0.89) than for women (MP 0.76, IQR 0.67-0.83). When considering screening history, individuals who did not participate in previous screening rounds had higher net

Figure 1. Net health benefit of CRC screening versus no screening by subgroups over different time horizons. Plots (A1-A4) show the overall net health benefits and according to different characteristics over 30-year time horizons. (B1-B4) over 20-year horizons, and (C1-C4) over 10-year horizons. Lifestyle-related health factors had 5 scales, from 0 to 5 (higher value indicates healthier lifestyle), derived from different characteristics, including weight, physical activity, smoking, alcohol consumption, and diet. Screening starts at age 55, thereby the blue line in plots (A4), (B4), and (C4) start at age 57. The lines with the shaded bands are the median probability of net health benefit together with the interquartile range. The dots in panel (A1), (B1), and (C1) are the probability of net health benefit for each of the individual subgroups.



CRC indicates colorectal cancer.

Figure 2. Net health benefit of participating in CRC in the current round only compared with participating in all subsequent rounds according to 30-, 20-, and 10-year time horizons.



CRC indicates colorectal cancer.

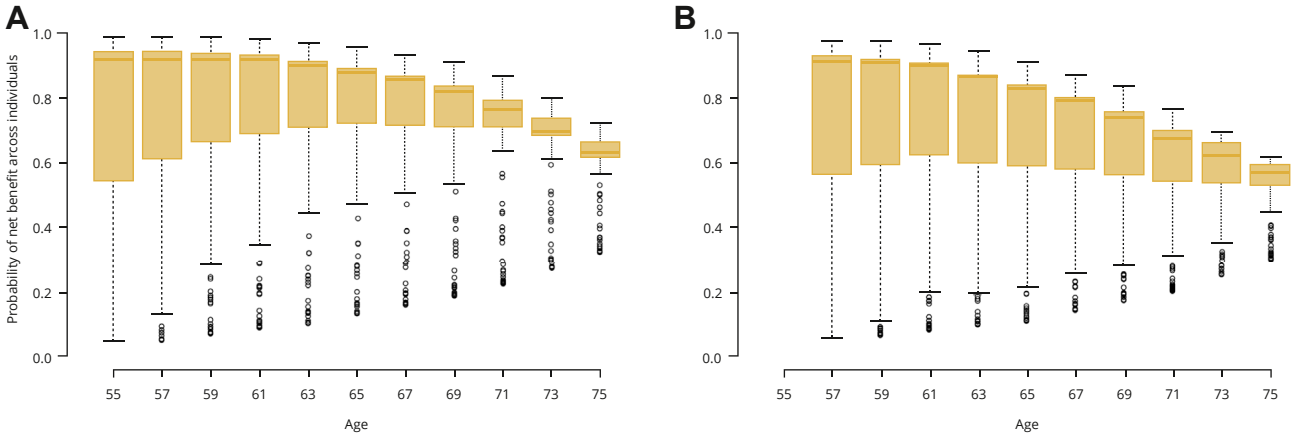
health benefit (MP 0.84, IQR 0.80-0.89) than those who previously participated (MP 0.69, IQR 0.59 to 0.75).

The results by time horizons showed that net health benefit was lower for 20- and 10-year time horizons, compared with assuming a 30-year time horizon (results described above), with MPs of 0.70 (IQR 0.62-0.80) and 0.54 (IQR 0.48-0.67), respectively (Figure 1, B1-B4 and C1-C4). This corresponded to 81% (171/210) and 34% (71/210) of subgroups deriving a net health benefit from screening over 20- and 10-year time horizons, compared with 87% of subgroups over a 30-year time horizon. The patterns of net health benefits across subgroups remained similar between the different time horizons.

Sensitivity Analysis

The net health benefit of participating in just 1 round was significantly lower when compared with participating in all subsequent rounds (Figure 2). Only 42% of subgroups would be likely

Figure 3. Preference-sensitivity of net health benefit for selected subgroups. Thirty-year benefit of CRC screening for individual participants of CRC screening. (A) Women of different ages with an average healthy lifestyle (3 of 5 health lifestyle indicator), with participation in prior screening rounds. (B) Women of different ages with an average healthy lifestyle, with no participation in prior screening rounds.



CRC indicates colorectal cancer.

to benefit from participating only in the current screening round. The MP of net health benefit between subgroups was 0.59 (IQR 0.56 to 0.69) for 30-year, 0.58 (IQR 0.56 0.68) for 20-year, 0.55 (IQR 0.53 to 0.65) for 10-year of time horizons, with no important differences between them. In this analysis, the net health benefit somewhat increased with age unlike the main analysis, particularly over the 10-year time horizon.

The sensitivity analysis in which we assumed varying preferences between individuals showed that the net health benefit was preference sensitive to some extent. Even within subgroups having homogenous characteristics, the net health benefit exhibited disparities between individuals, depending on their degree of risk-aversion or willingness to access risks. For example, when considering aggregated preference weights in the main analysis, a 55-year subgroup was more likely to benefit from screening. However, looking closely at the individual preferences within this subgroup, 25% of screening participants would be less likely to achieve a net health benefit over 30 years' time because of differences in preferences compared with non-participants (Figure 3). This percentage was even higher in certain subgroups, for example, in individuals with 0-1 HLFs.

Discussion

Our benefit-harm balance modeling shows that for most adults grouped by age, sex, healthy lifestyle, and screening history, FIT-based CRC screening is net beneficial (87% of subgroups benefit) over a 30-year time horizon. This percentage decreased to 81% and 34% when considering 20-year and 10-year time horizons, respectively. Our results further show that, for some individuals with different risk-accepting and risk-averse behaviors, the net health benefit would vary within subgroups, due to differences in perceived importance of benefit and harm outcomes.

Our analysis demonstrated that the net health benefit was more pronounced over long-term periods, which is expected because the benefits of FIT screening typically manifest later in life, whereas the harms tend to occur during or shortly after the screening. In the ASCCA model, the average time for an adenoma to progress to cancer is 24 years, making it difficult to detect adenomas with screening in a short time frame. Early assessment of the benefit-harm balance would result in an unfavorable benefit evaluation because the potential harms would tip the balance because of their early occurrence. Because the disease process cannot be directly observed, the exact duration of the adenoma dwell time is unknown. However, a validation study including 3 other microsimulation models found that only models with adenoma dwell times around 25 years could accurately predict the relative effects of screening on CRC incidence.[21] This roughly coincides with the 30-year time horizon over which our benefit-harm analysis demonstrated a net health benefit for most of the subgroups.

We observed a lower net health benefit for those with a history of participating in previous CRC screening rounds than those without. This is intuitive and in line with prior evidence that detection rates and positive predictive values are higher in the first screening round than in subsequent rounds.[25,26] This can be explained by the fact that most CRCs are detected in a single round, where the sensitivity of FIT ranges from 71% to 91%,[27] leading to a lower CRC detection rate in the next round. This decreased net health benefit in case of previous participation caused some subgroups to have little expected benefit from additional screening, namely, those who are both over 70 years and have an unhealthy lifestyle. Adults with an unhealthy lifestyle have a high risk of developing CRC. It is likely that CRC or precursor lesions would have been detected in previous screening rounds, providing less incremental benefit of subsequent rounds at later ages. In addition, unhealthy individuals have a high competing risk of non-CRC death and thus shorter remaining life expectancy that may hinder the realization of a net benefit of additional screening. This is consistent with a study by Cenin et al,[28] which also showed that the benefit-harm index for unhealthy adults, defined as having comorbidities, was favorable up to 66 years, and not beyond. In general, we observed a reduction in net health benefit for shorter life expectancies because the net health benefit decreased with increasing age. This can be anticipated because detected adenomas would have had a low chance to progress to cancer in the remaining lifetime. However, the most important factor in determining net health benefit was history of participation because all subgroups, regardless of age or lifestyle, experienced net health benefit when they had not yet participated in CRC screening before.[29]

Our findings showed that net health benefit was preference sensitive for some individuals within a subgroup. Depending on willingness to accept risks, individuals could decide to participate in screening differently because of different experiences and attitudes toward the benefit and harm outcomes. This underscores the significance of incorporating individual preferences and highlights that the results of this study are not intended to shape policy decisions regarding the implementation of screening. Instead, they are intended to assist individuals in making informed choices regarding their participation in screening. The former is not influenced by personal preferences, but the latter certainly is. Although further research is needed, the benefit-harm assessment approach can be integrated into decision support systems to facilitate informed decision making about screening participation at an individual level.

The strength of our study lies in the integrated approach using extensive risk estimation of the benefits and harms of screening using microsimulation modeling for a broad range of risk profiles, incorporation of preferences, and benefit-harm balance modeling for highly stratified subgroups. However, this analysis was not without limitations. First, it should be noted that our benefit-harm balance modeling was informed by outcome risks from the ASCCA model and preference weights from the BWS survey in The Netherlands. This may make the results in some sense specific to the Dutch population context. Generalization of the results to other countries should therefore be made with caution, which may need updates with setting-specific data. Second, the ASCCA model could not yield uncertainty estimates because this would be a computationally expensive and complex procedure with a microsimulation model consisting of more than 50 parameters. However, we did calculate uncertainty of IPs based on the original sample size from the studies informing the ASCCA model. Finally, we estimated risk profiles based on a restricted number of risk factors. The benefit-harm balance could possibly differ when more risk factors, such as race and comorbidity, are considered. We implicitly accounted for comorbidity by including an increase in risk of non-CRC death due to an unhealthy lifestyle or increasing age, but we did not account for younger individuals who suffer from comorbidity because of other causes than an unhealthy lifestyle.

In summary, our benefit-harm analysis shows that, in general, CRC screening is beneficial for most subgroups considering a time horizon of 30 years. The most important factor in determining net

health benefit was previous participation. With a shorter time horizon, the benefit from screening decreases. This study provides personalized information about the net health benefit of screening based on the characteristics and preferences of individuals, which could help individuals invited for screening to make informed decisions about screening participation.

Author Disclosures

Links to the individual disclosure forms provided by the authors are available here.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2023.12.006.

Article and Author Information

Accepted for Publication: December 6, 2023

Published Online: January 19, 2024

doi: https://doi.org/10.1016/j.jval.2023.12.006

Author Affiliations: University of Zurich, Epidemiology, Biostatistics and Prevention Institute, Zürich, Zürich, Switzerland (Yebyo, Puhan); Ldwig Maximilian University (LMU), Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Public Health and Health Services Research, Munich, Germany (Yebyo); Amsterdam UMC location Vrije Universiteit, Epidemiology and Data Science; De Boelelaan 1117, Amsterdam, The Netherlands (van Wifferen, Coupé, Greuter); Amsterdam Public Health, Methodology, Amsterdam, The Netherlands (van Wifferen, Pluymen, Leeflang, Coupé, Greuter, Stegeman); Amsterdam UMC location University of Amsterdam, Epidemiology and Data Science, Amsterdam, The Netherlands (Pluymen, Leeflang, Stegeman); Amsterdam UMC location University of Amsterdam, Gastroenterology and Hepatology, Amsterdam, The Netherlands (Dekker); University Medical Centre Utrecht, Department of Otorhinolaryngology and Head & Neck Surgery, Utrecht, The Netherlands (Stegeman); University Medical Centre Utrecht, Brain Centre, Utrecht, The Netherlands (Stegeman).

Correspondence: Francine van Wifferen, MSc, Amsterdam UMC location Vrije Universiteit, Epidemiology and Data Science, De Boelelaan 1117, Amsterdam, The Netherlands. Email: f.vanwifferen@amsterdamumc.nl

Author Contributions: *Concept and design:* Yebyo, van Wifferen, Pluymen, Leeflang, Dekker, Coupé, Puhan, Stegeman
Acquisition of data: Leeflang, Stegeman
Analysis and interpretation of data: Yebyo, van Wifferen, Pluymen, Coupé, Puhan, Greuter, Stegeman
Drafting of the manuscript: Yebyo, van Wifferen, Pluymen, Coupé, Stegeman
Critical revision of the paper for important intellectual content: Yebyo, van Wifferen, Pluymen, Leeflang, Dekker, Coupé, Puhan, Greuter, Stegeman
Statistical analysis: Yebyo, van Wifferen
Provision of study materials or patients: Leeflang, Dekker, Puhan
Obtaining funding: Leeflang, Puhan, Stegeman
Administrative, technical, or logistic support: Leeflang, Puhan
Supervision: Leeflang, Dekker, Coupé, Puhan, Greuter, Stegeman

Funding/Support: The study was funded by ZonMW (50-53125-98-155) and Swiss National Science Foundation (P400PM_194504).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Puhan MA, Singh S, Weiss CO, Varadhan R, Boyd CM. A framework for organizing and selecting quantitative approaches for benefit-harm assessment. *BMC Med Res Methodol*. 2012;12:173.
2. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol*. 2008;103(6):1541–1549.
3. Landelijke monitoring en evaluatie van het bevolkingsonderzoek naar Damkanker in Nederland - 2014-2017 - het eerste evaluatierapport. *Landelijk Evaluatie Team Voor COlorectaal Kanker Bevolkingsonderzoek (LECO)*. Erasmus MC: Antoni van Leeuwenhoek, Nederlands Kanker Instituut; 2019.
4. Greuter MJE, Demirel E, Lew JB, et al. Long-term impact of the Dutch colorectal cancer screening program on cancer incidence and mortality-model-based exploration of the serrated pathway. *Cancer Epidemiol Biomarkers Prev*. 2016;25(1):135–144.
5. Lin JS, Perdue LA, Henrikson NB, Bean SI, Blasi PR. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2021;325(19):1978–1998.
6. Yebyo HG, Braun J, Menges D, Ter Riet G, Sadatsafavi M, Puhan MA. Personalising add-on treatment with inhaled corticosteroids in patients with chronic obstructive pulmonary disease: a benefit-harm modelling study. *Lancet Digit Health*. 2021;3(10):e644–e653.
7. Rimer BK, Briss PA, Zeller PK, Chan ECY, Woolf SH. Informed decision making: what is its role in cancer screening? *Cancer*. 2004;101(5 suppl):1214–1228.
8. Timmermans D. *What Moves the Decision Maker? The Meaning of Well Considered and Informed Decision for Health and Prevention. [Wat Beweegt de Kiezer? Over de Betekenis van Weloverwogen en Geïnformeerde Keuzes Voor Gezondheid en Preventie.]*. ZonMW; 2013.
9. Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst*. 1999;91(21):1829–1846.
10. Pluymen LPM, Yebyo HG, Stegeman I, et al. Perceived importance of the benefits and harms of colorectal cancer screening: a best-worst scaling study. *Value Health*. 2023;26(6):918–924.
11. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Export Report 2018. Diet, Nutrition, Physical Activity and Colorectal Cancer. http://dietandcancerreport.org/. Accessed October 1, 2020.
12. White A, Ironmonger L, Steele RJC, Ormiston-Smith N, Crawford C, Seims A. A review of sex-related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK. *BMC Cancer*. 2018;18(1):906.
13. *IARC Working Group on the Evaluation of Cancer-Preventive Interventions. Colorectal cancer screening. Lyon (FR)*. International Agency for Research on Cancer; 2019.
14. Aleksandrova K, Pischon T, Jenab M, et al. Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. *BMC Med*. 2014;12:168.
15. Noble N, Paul C, Turon H, Oldmeadow C. Which modifiable health risk behaviours are related? A systematic review of the clustering of Smoking, Nutrition, alcohol and Physical activity ('SNAP') health risk factors. *Prev Med*. 2015;81:16–41.
16. Greuter MJE, Xu XM, Lew JB, et al. Modeling the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA). *Risk Anal*. 2014;34(5):889–910.
17. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. *Lancet Oncol*. 2012;13(1):55–64.
18. Nederlandse Kankerregistratie (NKR). IKNL. https://iknl.nl/nkr-cijfers. Accessed July 1, 2014.
19. Lew JB, Greuter MJE, Caruana M, et al. Validation of microsimulation models against alternative model predictions and long-term colorectal cancer incidence and mortality outcomes of randomized controlled trials. *Med Decis Mak*. 2020;40(6):815–829.
20. Darmkanker MB. *National Institute for Public Health and the Environment (RIVM), Netherlands Comprehensive Cancer Organisation (IKNL)*. 2021;2022.
21. Rutter CM, Knudsen AB, Marsh TL, et al. Validation of models used to inform colorectal cancer screening guidelines: accuracy and implications. *Med Decis Mak*. 2016;36(5):604–614.
22. Kooyker AI, Toes-Zoutendijk E, Opstal-van Winden AWJ, et al. Colonoscopy-related mortality in a fecal immunochemical test-based colorectal cancer screening program. *Clin Gastroenterol Hepatol*. 2021;19(7):1418–1425.
23. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology*. 2008;135(1):82–90.
24. Aschmann HE, Boyd CM, Robbins CW, et al. Balance of benefits and harms of different blood pressure targets in people with multiple chronic conditions: a quantitative benefit-harm assessment. *BMJ Open*. 2019;9(8):e028438.

25. Binefa G, Garcia M, Milà N, et al. Colorectal Cancer Screening Programme in Spain: results of key performance indicators after five rounds (2000-2012). *Sci Rep*. 2016;6:19532-19532.
26. Crotta S, Segnan N, Paganin S, Dagnes B, Rosset R, Senore C. High rate of advanced adenoma detection in 4 rounds of colorectal cancer screening with the fecal immunochemical test. *Clin Gastroenterol Hepatol*. 2012;10(6):633–638.
27. Imperiale TF, Gruber RN, Stump TE, Emmett TW, Monahan PO. Performance characteristics of fecal immunochemical tests for colorectal cancer and advanced adenomatous polyps: a systematic review and meta-analysis. *Ann Intern Med*. 2019;170(5):319–329.
28. Cenin DR, Tinmouth J, Naber SK, et al. Calculation of stop ages for colorectal cancer screening based on comorbidities and screening history. *Clin Gastroenterol Hepatol*. 2021;19(3):547–555.
29. Davidson KW, Barry MJ, Mangione CM, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2021;325(19):1965–1977.