Impact of demographic changes and screening colonoscopy on long-term projection of incident colorectal cancer cases in Germany: A modelling study

Thomas Heisser,[a,b]* Michael Hoffmeister,[a] Hanna Tillmanns,[c] and Hermann Brenner [a,d,e]

[a]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany
[b]Medical Faculty Heidelberg, University of Heidelberg, Heidelberg, Germany
[c]AOK Research Institute, Berlin, Germany
[d]Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany
[e]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

Summary

Background Demographic aging is expected to increase the number of colorectal cancer (CRC) cases in many countries. Screening for CRC can substantially reduce the disease burden but its use has remained rather limited in Germany. We aimed to quantify the expected impact of demographic aging on the future CRC burden and the potential to reduce that burden by increased use of screening colonoscopy offers in Germany.

Methods We obtained sex- and age-specific data on colonoscopy use from AOK, the biggest health insurance provider in Germany, and combined these with the projected demographic development and current CRC incidence rates. We estimated the number of new CRC cases until 2060, assuming screening colonoscopy use to be constant or to increase to between 1·5 and 3 times the current levels.

Findings Ten-year screening colonoscopy utilization rates were low (<20% in both sexes in all age groups). Assuming no change in screening colonoscopy use, the overall annual caseload was predicted to increase from approximately 62,000 cases in 2020 to more than 70,000 cases by the year 2040 and more than 75,000 cases by 2050. To avoid increasing case numbers, an increase of screening colonoscopy use to more than 3 times current levels would be needed.

Interpretation At current levels of screening use, the strong effects of the demographic aging imply that the CRC caseload will significantly increase in the decades to come. CRC screening efforts will need to be substantially increased to even maintain the current level of incident cases.

Keywords: Colorectal cancer; Screening; Forecasting; Colonoscopy; Adherence

Introduction

Although the colorectal cancer (CRC) incidence rate has declined by more than 20% over the last 16−18 years,[1] CRC remains the third most common cancer in Germany.[2] There is overwhelming evidence that screening reduces CRC incidence and mortality,[3−7] and screening is recommended to start at ages 45 or 50 for individuals at average risk.[8,9] Stool-test- and colonoscopy-based screening has been offered to the German general population since 1977 and 2002, respectively, and the strong incidence reductions over the last two decades are likely to be largely attributable to the uptake of population-wide screening offers.[10−12] An overview of the CRC screening offers in Germany is provided in Table 1.

Notably, the absolute number of incident CRC cases has also declined in the past two decades, but to a much lesser extent as compared to the incidence rates.[1] This is attributable to the demographic change in Germany,

*Corresponding author at: Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 581, 69120 Heidelberg, Germany.
E-mail address: t.heisser@dkfz.de (T. Heisser).

Research in Context

Evidence before this study

The demographic transition in Germany leads to a higher number and proportion of people at older age who are at higher risk of colorectal cancer (CRC) relative to the overall population. While screening colonoscopy strongly reduces CRC incidence, it is unknown to what extent screening efforts will need to be intensified to compensate for the expected increase in CRC case numbers.

Added value of this study

Assuming no change in screening colonoscopy use, the annual number of newly diagnosed CRC cases is expected to increase from approximately 62,000 in 2020 to more than 70,000 by the year 2040 and more than 75,000 cases by the year 2050. We demonstrate that an increase in 10-year use of screening colonoscopy to more than 3 times the current levels would be required to even maintain the number of incident CRC cases at current levels.

Implications of all the available evidence

The strong effects of the demographic transition in Germany imply that the number of newly diagnosed CRC cases will significantly increase in the decades to come. A substantial increase in use of effective screening offers will be needed to at least maintain the 2020 level of newly diagnosed cases.

leading to a higher number and proportion of people at older age. Even stronger demographic changes are expected in the years to come. The absolute number of men and women 67 years or older is expected to increase from approximately 16 million in 2019 (19% of total population) to more than 21 million in 2060 (28% of total population).[13] The considerably higher CRC risks in older age groups[14] suggest that even to maintain the current level of newly diagnosed CRC cases, screening uptake will need to increase substantially. However,

detailed evidence on screening uptake is sparse, as typically reported colonoscopy utilization rates do not discriminate between screening and diagnostic procedures, or are based on surveys highly prone to selection bias, with individuals interested in health topics being those most likely to respond.[15]

Combined with projections of the expected future CRC burden, the availability of such utilization data would allow for an estimation of the magnitude of potential effects of increases in uptake of screening offers. Such an analysis could provide vital guidance for policymakers as to healthcare planning, resource allocation and the evaluation of screen-related interventions.[16] The objective of this study therefore was, firstly, to assess the utilization of screening and diagnostic colonoscopies in Germany, and secondly, to project the expected numbers of annually diagnosed CRC cases in the decades to come. Thirdly, while fecal testing also contributes to CRC incidence reductions, screening colonoscopy constitutes the gold standard screening test for CRC, with high sensitivity even for non-advanced CRC precursor lesions. As an exemplary case study, we therefore sought to calculate the potential effect of increased screening colonoscopy utilization rates on the future CRC caseload.

Methods

Data sources

Utilization of colonoscopy and stool tests. Aggregated anonymized data on colonoscopy and stool tests use were provided by the scientific institute of the "Allgemeine Ortskrankenkasse" (AOK), as previously reported.[17−19] AOK is the biggest statutory health insurance company in Germany, which covers 26.9 million people all over Germany (approximately one-third of the German population). As all data were anonymized and de-identified prior to analysis, no approval by an institutional review board or informed consent was required.

The analysis on colonoscopy use was performed on consecutive insurance years from 2008 to 2017 in

Screening Test	Offers for Men	Offers for Women
Colonoscopy	Start of eligibility: age 50	Start of eligibility: age 55
	Up to two screening colonoscopies 10 years apart; 2nd screening colonoscopy only if 1st one was used before age 65	Up to two screening colonoscopies 10 years apart; 2nd screening colonoscopy only if 1st one was used before age 65
Fecal immunochemical test (FIT)[b]	Annually from age 50 to 54 if no screening colonoscopy is used	Annually from age 50 to 54
	Biennially from age 55 onwards if no screening colonoscopy is used	Biennially from age 55 onwards if no screening colonoscopy is used

Table 1: **Screening offer in Germany since April 2019.**[a]

[a] From October 2002 to March 2019, screening colonoscopy was offered from aged 55 on for both sexes. In April 2019, the eligibility age was lowered for men to age 50, while the offer for women remained unchanged.

[b] Following a positive FIT, diagnostic colonoscopy is warranted. The traditionally used guaiac-based stool tests were replaced by modern FITs in 2017.

subjects continuously insured within the study period. Based on these data, cumulative use rates of screening colonoscopy were derived, which is recommended every 10 years.[9] Subjects with CRC diagnosis (ICD-10 codes C18–C20) within the study period were excluded. In the study population, sex- and age-specific utilization rates of screening and diagnostic colonoscopies (i.e., colonoscopies for surveillance, workup of symptoms, or other screening tests) were determined by reviewing inpatient and outpatient prescription data (see Supplementary Text 1 for details).

For ancillary analyses, we obtained data on the biennial use of stool tests for the period 2015–2019. This includes data on the traditional guaiac-based stool tests as well as modern fecal immunochemical tests (FITs), which replaced the guaiac-based tests in 2017. We also obtained the number of individuals with diagnostic colonoscopy in the year 2019. As follow-up colonoscopies after a positive stool test are documented as diagnostic procedures, data on the potential use of FIT prior to a diagnostic colonoscopy were used as an additional proxy on screening utilization.

CRC incidence rates. We extracted sex- and age-group-specific absolute numbers of CRC cases as well CRC incidence rates for the German general population in the year 2018 (the most recent year available) from the interactive database of the German Centre for Cancer Registry Data[14] which provides combined and quality-checked data from epidemiological cancer registries in Germany.

Population forecasts up to the year 2060. We retrieved the results of the 14th coordinated population projection based on the year 2018 by the German Federal Office of Statistics, which covers the period up to 2060.[20] Its core consists of nine main variants, which illustrate the range of possible developments and show how the population development is influenced by the demographic components of fertility, mortality, and migration. For our analysis, we chose variant G2-L3-W3, which assumes moderate changes in fertility and life-expectancy and uses migration patterns averaged for the period 1990–2018.

Statistical analysis

Utilization of colonoscopy and stool tests. Colonoscopy utilization rates were summarized stratified by use (screening, diagnostic and combined), sex, and age-groups (10 year-steps, age as per end of the observation period; age groups 50–54 and 55–59 were reported separately as both sexes were eligible only from age 55 onwards during the study period (Table 1)). Use of stool tests was summarized for biennial periods (2015–2016,

2016–2017, 2017–2018, and 2018–2019) and stratified by age groups within the eligible target population for use of stool tests, starting at age 50 for both sexes (50–54; 55–59; 60–69; 70–79). As a proxy for the proportion of diagnostic colonoscopies due to a positive result of a stool test screening, we divided the number of individuals who had used a FIT within 184 days prior to a diagnostic colonoscopy through the number of individuals with a documented diagnostic colonoscopy in the year 2019.

Forecast of newly diagnosed CRC cases up to the year 2060. We calculated the numbers of CRC cases that would be expected in the years 2030, 2040, 2050 and 2060 in the absence of changes in sex- and age-specific incidence rates by multiplying the sex- and age-specific incidence rates for the year 2018 by the expected number of individuals projected to live in Germany in the corresponding years. Using the same methodology, we also calculated the number of CRC cases expected to have occurred in 2020 (not yet available from the German Centre for Cancer Registry).

Then, reductions of sex- and age-specific CRC case numbers that could be achieved by increasing use of screening colonoscopy were calculated for each sex- and age group as follows:

Let P_{curr} be the current prevalence of having had a colonoscopy within the past 10 years, I_0 the incidence of CRC among those who did not have a colonoscopy in the past 10 years, and RR the rate reduction of those who had a colonoscopy within the past 10 years compared to those who did not have a colonoscopy. RR was assumed to be 0.31 based on a meta-analysis of epidemiological studies.[4] Because CRC precursors are typically detected and removed at diagnostic colonoscopies in the same manner as at screening colonoscopies, the same rate reduction was assumed for both screening and diagnostic colonoscopies. In addition, we also assumed the same rate reduction for those who had both a screening colonoscopy and a diagnostic colonoscopy in the previous 10 years, i.e. we assumed no incremental protection from screening colonoscopy among people who also had a diagnostic colonoscopy.

Then the current, observed sex-and age-specific incidence rates within the respective sex-age-groups, denoted I_{curr} are given as

$$I_{curr} = P_{curr} \times RR \times I_0 + (1 - P_{curr}) \times I_0$$

$$= (P_{curr} \times RR + 1 - P_{curr}) \times I_0 \qquad (1)$$

from which sex- and age-specific values of I_0 were derived as

$$I_0 = I_{curr}/(P_{curr} \times RR + 1 - P_{curr}) \qquad (2)$$

Then, assuming I_0 to remain constant over time, the future sex- and age-specific incidence rates that would

be expected with increased prevalences of colonoscopy used (P_{inc}), denoted I_{fut}, were derived as

$$I_{fut} = (P_{inc} \times RR + 1 - P_{inc}) \times I_o. \quad (3)$$

For our calculations, we assumed P_{inc} to increase along corresponding increases of screening colonoscopy use of 50%, 100%, and 200% relative to the prevalence of having had a screening colonoscopy within the past 10 years as observed in the colonoscopy utilization data obtained from AOK. The use of diagnostic colonoscopies within the past 10 years was assumed to remain constant, and the increases in overall colonoscopy prevalences were assumed to exclusively result from increases in the proportion of individuals who used screening colonoscopy. As the starting age for screening colonoscopy eligibility in men was only recently lowered to age 50 (Table 1) (i.e., not yet captured in the utilization data obtained for this analysis), we assumed identical screening colonoscopy utilization rates for men aged 50−54 as for those aged 55−59.

By multiplying the resulting future sex- and age-specific incidence rates by the expected number of individuals projected to live in Germany in the years 2030−2060, we estimated the effect of increases in screening colonoscopy utilization on projected numbers of newly diagnosed CRC cases for the corresponding years. In addition, we calculated the difference in case numbers to the baseline estimate of the year 2020 assuming no change in screening colonoscopy uptake.

Finally, we estimated the numbers of CRC cases prevented by screening colonoscopy use by subtracting the numbers of CRC cases assuming current or increased levels of screening colonoscopy uptake (as calculated previously) from the number of CRC cases expected without any screening colonoscopy use.

It should be noted that calculating the effect of an increased use of only screening colonoscopy implicitly assumes the current level of uptake of fecal testing, which is also offered as a primary screening option in Germany, to remain constant. This may be a rather unrealistic assumption in practice, as, for instance, a higher CRC screening awareness of a population (leading to higher uptake) would likely manifest across all available screening options. Our calculations should therefore be understood as an exemplary case study on screening colonoscopy, which is commonly regarded as the gold standard screening test for CRC. Though it may be unlikely that our findings will be directly transferable to real-life screening settings, such case study will nonetheless provide a useful illustration of the impact of demographic changes and provide a first quantification of the extent to which screening efforts may need to be intensified.

Sensitivity analysis

To explore the impact of uncertainty related to this key parameter of the forecast, the RR of those who had a colonoscopy within the past 10 years compared to those who did not have a colonoscopy was either discounted by 20% (i.e., $RR = 0.25$) or increased by 20% (i.e., $RR = 0.37$). These sensitivity analyses reflect a possible even stronger or weaker effect of screening colonoscopy on CRC incidence reductions.

Role of the Funding Source

Results

Utilization of colonoscopy and stool tests

Figure 1 shows the cumulative proportions of colonoscopy utilization in men and women consistently insured by AOK from 2008 to 2017. In younger age groups, colonoscopy use was rare and exclusively driven by diagnostic colonoscopies, which also reflects the eligibility ages for screening colonoscopy (starting at age 55 during the study period). However, diagnostic colonoscopies made up for the larger proportion of overall colonoscopy utilization even in age-groups eligible for screening colonoscopy. In the first years of eligibility (age group 55−59), only 8% of men and women used a screening colonoscopy. Use of screening colonoscopy remained low (<20%) also in older age groups, peaking in those 60−69 of age, at only 17% in men and 19% in women.

Use of FIT within 2-year intervals was overall consistent across age groups (ranging from 16−21%, 15−21%, 14−19% and 13−17% for age groups 50−54, 55−59, 60−69, and 70−79, respectively) but varied slightly by observation period, with highest (17−21%) and lowest (13−16%) utilization rates observed for the years 2015−2016 and the years 2018−2019, respectively (Supplementary Figure 1). In 2019, the proportion of diagnostic colonoscopies with preceding fecal test ranged from 10% to 15% (Supplementary Figure 2).

Forecast of newly diagnosed CRC cases up to the year 2060

The projection of expected CRC cases by sex for the years 2030, 2040, 2050 and 2060 are shown in Figure 2. Assuming no changes in colonoscopy utilization levels and sex- and age-specific risks, the CRC burden will significantly increase along the projected demographic change in Germany. Based on the latest available incidence rates (from 2018), approximately 35,000 men and 27,400 women were newly diagnosed with CRC in 2020. For the years 2030, 2040, 2050 and 2060, these numbers are projected to increase to

A

Men

B

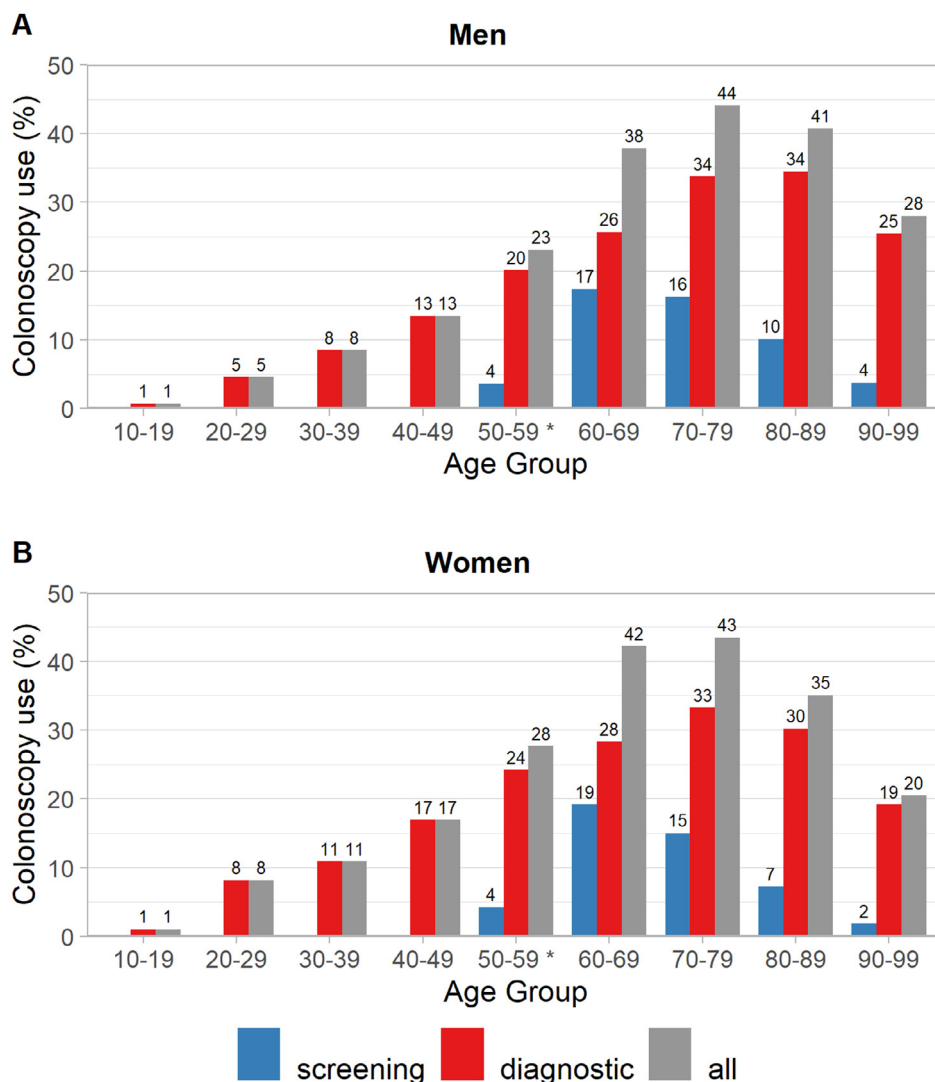## Women

screening   diagnostic   all

Figure 1. Cumulative use of colonoscopy from 2008 to 2017 in AOK insured men and women, stratified by use (screening vs for diagnostic clarification, and combined), sex and age group.

* Breakdown by age 50—54 and 55—59 as eligibility started at age 55 during the study period: age 50—54, 0%, age 55—59, 8% (identical for men and women).

Combined numbers may not add up as individuals may have had both screening and diagnostic colonoscopies during the study period. Indicated age is at end of the study period.

approximately 39,000, 42,600, 44,100, and 44,500 cases in men and 29,400, 31,900, 33,200, and 32,400 in women, respectively, reflecting an 11—27% (men) and an 8—21% (women) higher caseload versus the estimated numbers for the year 2020.

Effect of increased screening colonoscopy utilization

An overview of implied levels of total colonoscopy utilization assuming 50%, 100%, and 200% higher screening colonoscopy utilization rates relative to current levels is given in Table 2. Such increase in use of

screening colonoscopy would markedly alter the expected number of annually diagnosed and prevented CRC cases (Figures 3 and 4). Broadly, each 100% increase of (exclusive) screening colonoscopy use relative to the levels as observed in the AOK dataset would reduce the number of additionally expected cases by 3400—3700 (8%) in men and 2300—2400 (7—8%) in women, for all considered years as compared to the expected numbers when no change in screening colonoscopy use was assumed.

However, even substantial increases in screening colonoscopy utilization would not consistently lead to a

Figure 2. Projection of newly diagnosed colorectal cancer cases until 2060 assuming constant colonoscopy utilization levels.

Age group	Men			
	Use of any colonoscopy (%) assuming a change in screening colonoscopy use[a] by			
	+/− 0%	+50%	+100%	+200%
50−59	23	24	26	29
60−69	38	44	50	62
70−79	44	49	54	64
80−89	41	44	48	55
90−99	28	30	31	34
	Women			
50−59	28	30	32	36
60−69	42	49	56	70
70−79	43	48	53	63
80−89	35	38	40	45
90−99	20	20	21	22

Table 2: Projected 10-year cumulative use of any colonoscopy assuming no change, 50%, 100% or 200% increase in uptake of screening colonoscopy, stratified by sex and age-group.

[a] Relative to the current levels.

reduction of the expected number of CRC cases compared with the expected numbers for the year 2020. This is particularly evident for the years 2050 and 2060, when even a 200% relative increase of screening colonoscopy use would imply that the caseload as per 2020 would still slightly increase by 1–6%.

At the same time, reflecting the strong effects of the demographic transition, the numbers of prevented CRC cases were projected to slightly increase across all considered years even without changes in screening colonoscopy utilization patterns. Accordingly, assuming higher levels of colonoscopy uptake would translate into significantly higher numbers of prevented cases. For instance, a 200% increase of screening colonoscopy use by the year 2060 would result in approximately 11,200 and 7000 annually prevented CRC cases in men and women, respectively, an increase by 279% in men and 241% in women as compared to the 2020 baseline level.

An interactive analysis tool illustrating the effects of varying levels of increases in screening utilization is available from our website.[21]

Sensitivity analysis
Results of sensitivity analyses are shown in Supplementary Figures 3–4. Findings were robust when varying the incidence rate reduction by screening colonoscopy within a 40% range, as varying this assumption reproduced the overall picture seen in the base case analysis.

Discussion
This study illustrates the strong impact of the demographic change on the future CRC burden in Germany, and the potential mitigative effects of increases in

screening colonoscopy use. We first assessed current 10-year screening colonoscopy utilization rates in the German general population, which were found to be low (<20%) in all age groups in both men and women. Secondly, assuming the colonoscopy use to be constant, we forecasted the number of newly diagnosed CRC cases by the year 2060. The annual caseload for men and women combined was predicted to increase from approximately 62,000 cases in 2020 to more than 70,000 cases by the year 2040 and more than 75,000 cases by 2050. Finally, by modeling the effect of an increase of screening colonoscopy use on the forecasted numbers, we found that screening colonoscopy utilization rates would need to increase by more than 200% by the year 2050 to prevent an increase in numbers of incident cases compared to current numbers.

Findings in context
Overall, use of screening colonoscopy as reported in our study is in line with the latest reported utilization rates for the national level,[22] with minor differences likely attributable to different socioeconomic characteristics of our study population (AOK insured men and women only). However, the national registry does not provide data on diagnostic colonoscopy utilization. Overall colonoscopy use in Germany as reported in previous surveys or population-based studies reached up to 50% within 10 years.[10,15,23] However, none of these stratified for screening versus diagnostic use, and the studies are prone to selection bias, with individuals with a healthier lifestyle being more likely to participate. In addition, as survey data were collected from self-reports, reporting and recall biases cannot be ruled out.

Several previous studies forecasting the future CRC burden in Germany have been published, mostly relying on a methodology similar to our study.[24−28] More recently, both the International Agency for Research on Cancer[26,27] as well as a study by the University of Pittsburgh[28] predicted approximately 70,000 cases for Germany alone by the year 2040, which is in line with our estimates. Further studies assessing trends of the CRC burden[29,30] did not report estimates specifically for Germany or only reported estimates for mortality, but not incidence.

To our knowledge, no previous study has estimated the expected effect of increased screening use on the forecasted CRC caseload. Even though our findings may not be directly transferable to other healthcare systems, this case study for Germany may therefore provide guidance and an useful blueprint also for other European countries facing similar demographic trends, such as Italy and Spain.[31]

Implications for colorectal cancer screening
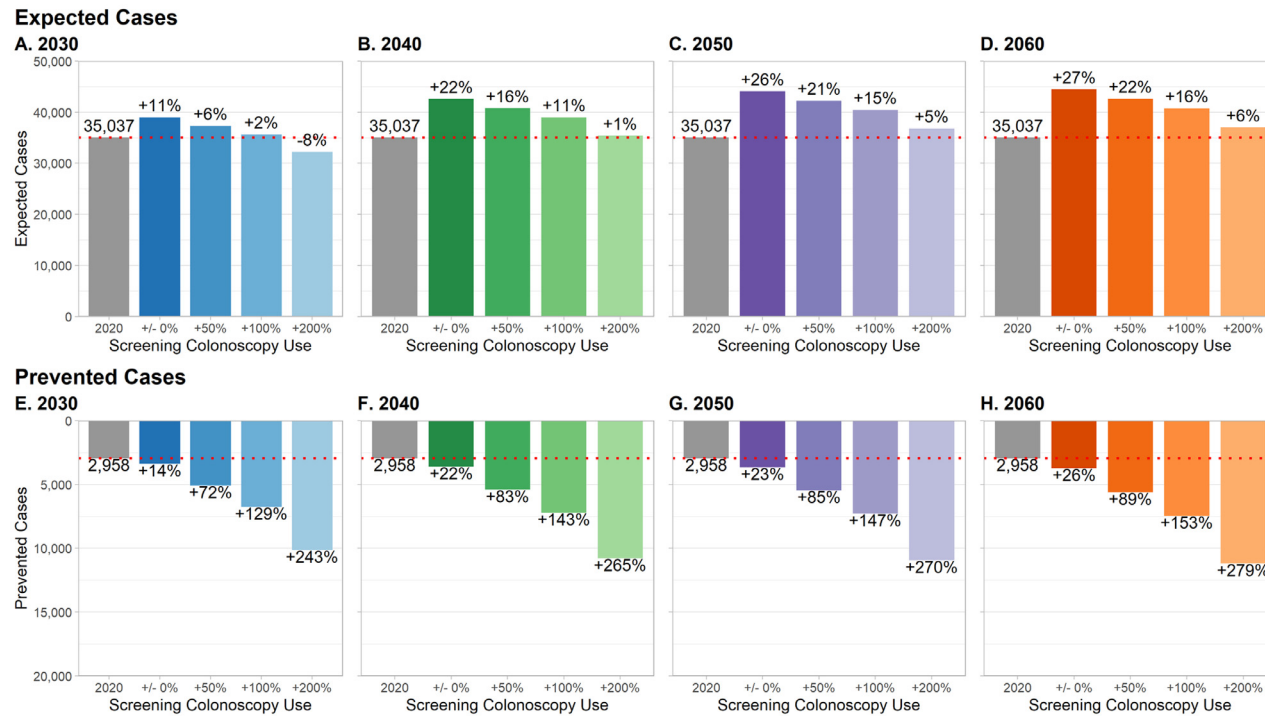The demographic transition in Germany and other industrialized countries has been foreseen for several

Expected Cases

Figure 3. Changes in numbers of expected (panels A−D) and prevented (panels E−H) colorectal cancer cases in Germany for the years 2030−2060 as compared to the year 2020, assuming no change, 50%, 100% or 200% increase in uptake of screening colonoscopy (men).
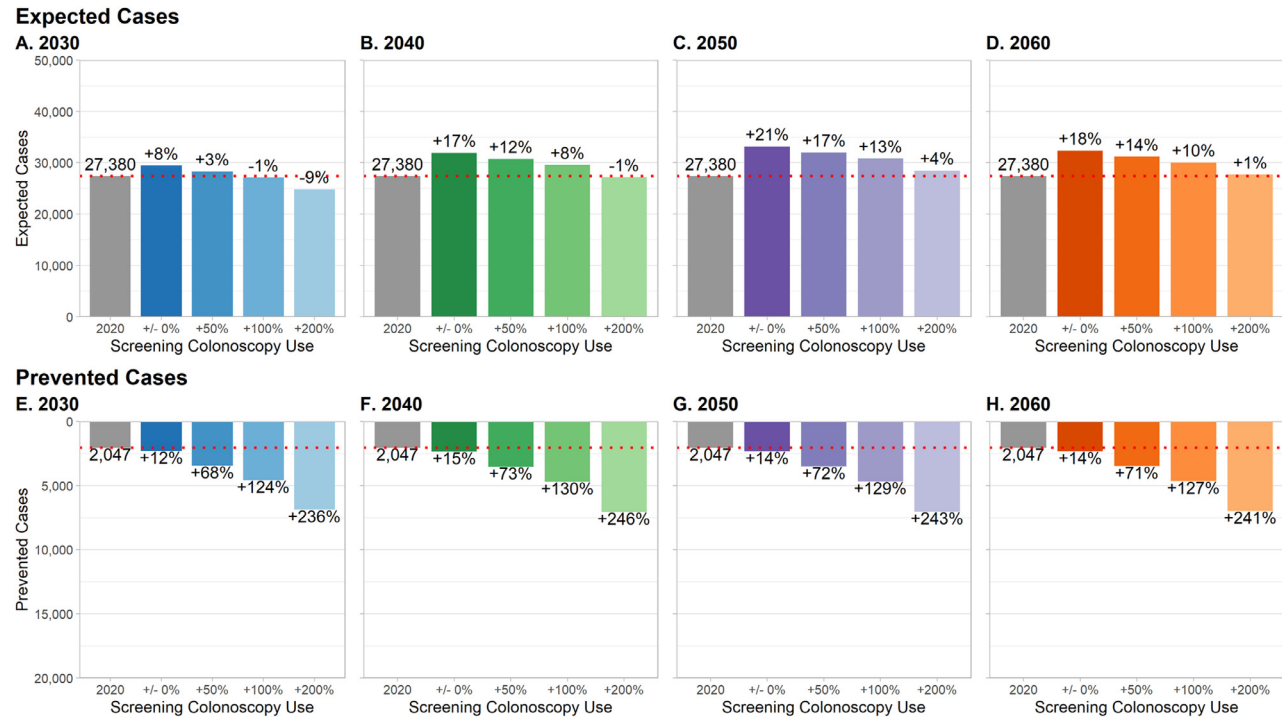
Figure 4. Changes in numbers of expected (panels A−D) and prevented (panels E−H) colorectal cancer cases in Germany for the years 2030−2060 as compared to the year 2020, assuming no change, 50%, 100% or 200% increase in uptake of screening colonoscopy (women).

Articles

decades,[24] and it is broadly known that the risk of CRC strongly increases with age.[32] While it might generally be recognized that these factors will lead to a trend of rising CRC case numbers, the strong decline of CRC incidence rates over the last two decades[1] may have fostered the misconception that this trend is already sufficiently counteracted by current CRC screening measures. Demonstrating that such an impression is misguided, our study illustrates that the strong effects of the demographic transition will require substantial increases of primary and secondary prevention efforts even to maintain the current level of incident CRC cases.

Firstly, diet and lifestyle were shown to have a major role in CRC, with approximately half of CRC cases assumed to be preventable by adopting healthy lifestyle behaviors (such as non-smoking, moderate alcohol consumption and physical activity).[33,34] Even though major changes to dietary and lifestyle patterns on a population level may be difficult to achieve, our findings may be used to underline the high relevance of primary prevention to policymakers, as well as to specifically target high-risk individuals.

Secondly, screening offers should be further improved. In particular, there are two features of the current design of the German early detection program for CRC that require reconsideration. One is that screening colonoscopy is offered from age 55 only for women. Along with the offer of annual stool testing at ages 50−54, there is strong potential for inefficient use of colonoscopy capacities in women who previously had multiple negative stool tests.[35] On the other hand, it could be shown that women would also benefit substantially from lowering the starting age for screening colonoscopy to age 50 in terms of CRC risk reduction.[36] Notably, evidence is accumulating in several countries that CRC risk increases in younger adults,[37,38] favoring even lower starting ages, e.g., age 45, for both sexes.[39]

Potentially even more concerning, screening colonoscopy is currently only offered twice, leading to an upper age limit at ages 60 for men and 65 for women, if the first screening colonoscopy was used as recommended. As CRC risks steeply increase with age and the life expectancy in Germany is set to exceed 80 years for both sexes soon,[40] complementary screening offers for the elderly would likely imply further sizeable reductions of the CRC burden.[36] Considering the findings of our study, additional screening offers for the elderly (e.g. an additional screening offer from age 70) should be implemented with even higher priority.

Thirdly, efforts to increase screening uptake need to be strongly enhanced. In our study, 10-year screening colonoscopy use in the eligible target population ranged from 4% to 17% in men and from 2% to 19% in women. Assuming an additional 2−3% of diagnostic colonoscopies related to FIT screening (as 10−15% of diagnostic colonoscopies were preceded by a FIT, and 20−34% of

individuals had a diagnostic colonoscopy), this implies that in most age-groups less than 20% of eligible individuals made use of screen-related colonoscopy.

Evidence on the determinants of adherence to CRC screening offers and measures to increase uptake is constantly evolving. In line with the findings of the ancillary analyses conducted for this study, screening by FITs tends to achieve higher uptake rates as compared to screening colonoscopy,[15] the gold standard screening test for early detection of CRC and its precursors. However, even though stool tests are significantly less sensitive in detecting CRC precursor lesions as compared to screening colonoscopy (which allows for detection and removal of precursor lesions at high sensitivity directly upon examination), increased uptake of FIT screening will likely also contribute to reducing the CRC caseload and should be promoted next to screening colonoscopy.

In our data, higher participation rates were seen in those aged 60 years or older versus younger ages, which is in accordance with findings of previous studies[15] and suggests that screening in younger adults should be particularly promoted. In the literature, an association was also reported for lifestyle factors and cultural background, suggesting that individuals with low socioeconomic status are less likely to use screening and thus may need to be targeted with priority.[41]

In Germany, a first step towards an organized screening program was made in 2019 with personal invitation letters sent out to the eligible population at ages 50, 55, 60 and 65. However, such single invitation letters every 5 years, which are accompanied by lengthy (>20 pages) and highly technical information brochures, are unlikely to achieve any relevant increase in use of screening offers, particularly among less educated high-risk groups. There is meanwhile overwhelming evidence, both from randomized clinical trials and real life experience from multiple countries, that well-organized screening programs that combine effective, easy to understand communication of screening offers with low-threshold access to screening may strongly increase adherence to effective screening offers.[42−45] Taking this evidence into account, policymakers should engage to carefully revise the current offers and invitation schemes of the German early cancer detection program for CRC.

Limitations

We made several simplifying assumptions when calculating the expected number of CRC cases in the future. For instance, sex- and age-group-specific CRC incidence in the absence of screening were assumed to be constant over time. Although observed incidence rates substantially declined in the past two decades,[1] this most likely primarily reflected the gradual increase in "cumulative" screening uptake, in particular of newly introduced screening colonoscopy, and only to a lesser

extent changes in lifestyle or birth-cohort effects. Although changes in major CRC risk factors may also have a substantial impact on age- and sex-specific incidence rates, the effects of such changes may partly cancel out. For example, whereas prevalence of smoking has started to decline and is expected to further decline in Germany,[46] prevalence of overweight and obesity are on the rise.[47] As well, since the actual incidence rates for the year 2020 were not yet available, we used the incidence rates observed in 2018 as a starting point for our calculations. However, given only minor changes in incidence rates from 2016 to 2018 (age-standardized rates varied by <1% in this period)[14] and in the absence of any recent major changes in screening practice, significant differences between 2018 and 2020 incidence rates appear unlikely.

The study is also limited by the use of colonoscopy utilization data from AOK, which, despite being the biggest statutory health insurance company in Germany, may not be fully representative for the whole German population due to differences in socio-economic characteristics. However, though slightly lower, we found the use of screening colonoscopy in our study to be overall comparable to the latest national utilization rates,[22] suggesting only marginal differences in colonoscopy use between those AOK insured and the German general population. On the same note, to derive the cumulative colonoscopy use rates, individuals with CRC diagnosis during the study period were excluded (regardless of mode of detection). The colonoscopy use rates in our study may therefore possibly be underestimated, and the required increase in uptake of screening colonoscopy to maintain a comparable caseload in the future may possibly be overestimated. However, as carcinomas are typically found in <1% of conducted screening colonoscopies,[22] this effect is likely negligible.

We also assumed a uniform relative risk for use versus non-use of colonoscopy for the whole of the study population although in practice, these parameters may vary between specific subgroups of patients, e.g., according to sex, age, family history, lifestyle, and previous use of screening tests. However, even though varied parameters by subgroups may have contributed to slightly improve the accuracy of our forecast, we believe our assumptions to be sufficiently robust to provide an overall impression of the impact of demographic transition on the future CRC caseload in Germany. This is also underpinned by the affirmative results seen in the sensitivity analyses. We purposely also abstained from rerunning the analyses with alternative assumptions with respect to the population projection as provided by German Federal Office of Statistics, as none of the variants varied considerably with respect to the screening-eligible population.

Finally, as further analyses were out of scope of this study, we limited the forecast to incident cases (but not mortality) and only considered the effect of increases in screening colonoscopy use (but not FIT screening). Specifically, further calculations on the effect of a possible increase in use of FIT screening would have added several layers of complexity and required additional assumptions, e.g., regarding longitudinal uptake patterns over time, as fecal testing is recommended at annual or biennial intervals.[48] However, given the benefits of FITs (e.g., they are easy to use and require little resources), there is also large potential and need for efforts to increase use of FITs whose effects should be evaluated in further research. Future studies should also focus on the forecasted number of CRC deaths in the future, as well as on the impact of increases in FIT screening use on the expected CRC burden.

Conclusion

Currently, less than 20% of the eligible population make use of screening colonoscopy offers. Assuming these participations rates to remain constant, the strong effects of the demographic transition in Germany imply that the number of newly diagnosed CRC cases will significantly increase in the decades to come. CRC screening efforts will need to be substantially increased to even maintain the current level of incident cases.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2022.100451.

References

1 Cardoso R, Zhu A, Guo F, Heisser T, Hoffmeister M, Brenner H. Incidence and mortality of proximal and distal colorectal cancer in Germany. *Dtsch Arztebl Int*. 2021;118:281–287.

2 Robert-Koch-Institut, Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. Krebs in Deutschland für 2017/2018 (Robert-Koch-institute and the society of epidemiological cancer registries in Germany: cancer in Germany for 2017/2018). 2021. https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/krebs_in_deutschland_node.html.

3 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;103:1541–1549.

4 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.

5 Atkin W, Wooldrage K, Parkin DM, 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;389:1299–1311.

6 Holme Ø, Schoen RE, Senore C, et al. Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. *BMJ*. 2017;356:i6673.

7 Miller EA, Pinsky PF, Schoen RE, Prorok PC, Church TR. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: long-term follow-up of the randomised US PLCO cancer screening trial. *Lancet Gastroenterol Hepatol*. 2019;4:101–110.

8 Bénard F, Barkun AN, Martel M, von Renteln D. Systematic review of colorectal cancer screening guidelines for average-risk adults: summarizing the current global recommendations. *World J Gastroenterol*. 2018;24:124–138.

9 Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). S3-Leitlinie Kolorektales Karzinom (Guideline program oncology (German cancer society, German Cancer Aid, AWMF): S3-guideline colorectal cancer). 2019; published online January. http://www.leitlinienprogramm-onkologie.de/leitlinien/kolorektales-karzinom/. Accessed 6 January 2021.

10 Guo F, Chen C, Schöttker B, Holleczek B, Hoffmeister M, Brenner H. Changes in colorectal cancer screening use after introduction of alternative screening offer in Germany: prospective cohort study. *Int J Cancer*. 2020;146:2423–2432.

11 Guo F, Chen C, Holleczek B, Schöttker B, Hoffmeister M, Brenner H. Strong reduction of colorectal cancer incidence and mortality after screening colonoscopy: prospective cohort study from Germany. *Am J Gastroenterol*. 2021;116:967–975.

12 Cardoso R, Guo F, Heisser T, et al. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. *Lancet Oncol*. 2021;22:1002–1013.

13 Statistisches Bundesamt (Federal Office of Statistics). Bevölkerungspyramide: altersstruktur Deutschlands von 1950 - 2060. (Population pyramid: Germany's age structure from 1950 to 2060). 2021. https://service.destatis.de/bevoelkerungspyramide/#!y=2060. Accessed 8 September 2021.

14 Zentrum für Krebsregisterdaten. Krebsstatistiken für Deutschland - interaktive datenbank (centre for cancer registry data: cancer statistics for Germany - interactive database). 2021; published online March 16. https://www.krebsdaten.de/Krebs/DE/Datenbankabfrage/datenbankabfrage_stufe1_node.html. Accessed 3 August 2021.

15 Cardoso R, Guo F, Heisser T, Hoffmeister M, Brenner H. Utilisation of colorectal cancer screening tests in european countries by type of screening offer: results from the european health interview survey. *Cancers (Basel)*. 2020;12:E1409.

16 Bray F, Møller B. Predicting the future burden of cancer. *Nat Rev Cancer*. 2006;6:63–74.

17 Tillmanns H, Schillinger G, Dräther H. Früherkennung bei Erwachsenen in der Gesetzlichen Krankenversicherung: Ergebnisse Einer AOK-Sekundärdatenanalyse (Early Detection among Adults in the Statutory Health Insurance System: Results of an AOK Secondary Data Analysis), Wissenschaftliches Institut der AOK (Scientific Institute of the AOK); 2019. https://doi.org/10.32745/9783954664023-3.

18 Tillmanns H, Schillinger G, Dräther H. Inanspruchnahme von Früherkennungsleistungen der Gesetzlichen Krankenversicherung Durch AOK-Versicherte im Erwachsenenalter 2009–2018 (Utilization of Early Detection Measures of the Statutory Health Insurance by Adult AOK-Insured Persons 2009–2018). Wissenschaftliches Institut der AOK (Scientific Institute of the AOK); 2020. https://doi.org/10.4126/FRL01-006425145. published online June 17.

19 Tillmanns H, Schillinger G, Dräther H, Sollmann S. Querschnittsanalyse zum Darmkrebs-Screening bei Versicherten der AOK (Cross-Sectional Analysis of Colorectal Cancer Screening in AOK Insured Persons). Wissenschaftliches Institut der AOK (Scientific Institute of the AOK); 2021. https://doi.org/10.4126/FRL01-006425261. published online Jan.

20 Statistisches Bundesamt (Federal Office of Statistics). 14. Koordinierte Bevölkerungs-Voraus-Berechnung - Basis 2018 [14th Coordinated Population Projection - base 2018]. Federal Statistical Office; 2019. published online June 27. https://www.destatis.de/EN/Themes/Society-Environment/Population/Population-Projection/update-population-projection.html. Accessed 13 September 2021.

21 German Cancer Research Center (DKFZ), Department clinical epidemiology and aging research. DKFZ prevention calculator. 2022; published online May. https://www.dkfz.de/en/klinepi/download/index.html. Accessed 5 March 2022.

22 Kretschmann J, El Mahi C, Lichtner F, Hagen B. Früherkennungskoloskopie. Jahresbericht 2019. [Screening Colonoscopy. Annual Report 2019]. 2021. https://www.zi.de/publikationen/studien/darmkrebs-frueherkennung. published online Dec 2.

23 Chen C, Stock C, Jansen L, Chang-Claude J, Hoffmeister M, Brenner H. Trends in colonoscopy and fecal occult blood test use after the introduction of dual screening offers in Germany: results from a large population-based study, 2003–2016. *Prev Med*. 2019;123:333–340.

24 Pritzkuleit R, Beske F, Katalinic A. [Demographic change and cancer]. *Onkologie*. 2010;33(suppl 7):19–24.

25 Quante AS, Ming C, Rottmann M, et al. Projections of cancer incidence and cancer-related deaths in Germany by 2020 and 2030. *Cancer Med*. 2016;5:2649–2656.

26 Ferlay J, Laversanne M, Ervik M, et al. Global cancer observatory: cancer tomorrow. 2020. https://gco.iarc.fr/tomorrow.

27 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249.

28 Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. *Transl Oncol*. 2021;14:101174.

29 Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66:683–691.

30 Araghi M, Soerjomataram I, Jenkins M, et al. Global trends in colorectal cancer mortality: projections to the year 2035. *Int J Cancer*. 2019;144:2992–3000.

31 United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects 2019, Online Edition, Rev. 1. 2019. https://population.un.org/wpp/.

32 Brenner H. Colorectal cancer screening for older adults. *BMJ*. 2015;350:9. https://doi.org/10.1136/bmj.h2029.

33 Carr PR, Weigl K, Jansen L, et al. Healthy lifestyle factors associated with lower risk of colorectal cancer irrespective of genetic risk. *Gastroenterology*. 2018;155:1805–1815.e5.

34 Carr PR, Weigl K, Edelmann D, et al. Estimation of absolute risk of colorectal cancer based on healthy lifestyle, genetic risk, and colonoscopy status in a population-based study. *Gastroenterology*. 2020;159:129–138.e9.

35 Heisser T, Weigl K, Hoffmeister M, Brenner H. Age-specific sequence of colorectal cancer screening options in Germany: a model-based critical evaluation. *PLoS Med*. 2020;17:e1003194.

36 Heisser T, Hoffmeister M, Brenner H. Model based evaluation of long-term efficacy of existing and alternative colorectal cancer screening offers: a case study for Germany. *Int J Cancer*. 2022;150:1471–1480.

37 Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut*. 2019;68:1820–1826.

38 Siegel RL, Torre LA, Soerjomataram I, et al. Global patterns and trends in colorectal cancer incidence in young adults. *Gut*. 2019;68:2179–2185.

39 US Preventive Services Task Force. Screening for colorectal cancer: US preventive services task force recommendation statement. *J Am Med Assoc*. 2021;325:1965–1977.

40 Statistia. Lebenserwartung in Deutschland - Durchschnittsalter bis zum Jahr 2060 (Life expectancy in Germany - Average age up to the year 2060). Statista. 2020. https://de.statista.com/statistik/daten/studie/273406/umfrage/entwicklung-der-lebenserwartung-bei-geburt—in-deutschland-nach-geschlecht/. Accessed 8 January 2021.

41 Klabunde C, Blom J, Bulliard J-L, et al. Participation rates for organized colorectal cancer screening programmes: an international comparison. *J Med Screen*. 2015;22:119–126.

42 Toes-Zoutendijk E, van Leerdam ME, Dekker E, et al. Real-time monitoring of results during first year of Dutch colorectal cancer screening program and optimization by altering fecal immunochemical test cut-off levels. *Gastroenterology*. 2017;152:767–775.e2.

43 Grobbee EJ, van der Vlugt M, van Vuuren AJ, et al. Diagnostic yield of one-time colonoscopy vs one-time flexible sigmoidoscopy vs multiple rounds of mailed fecal immunohistochemical tests in colorectal cancer screening. *Clin Gastroenterol Hepatol*. 2020;18:667–675.

44 Gruner LF, Hoffmeister M, Ludwig L, Meny S, Brenner H. The effects of differing invitation models on the uptake of immunological fecal occult blood testing. *Dtsch Arztebl Int*. 2020;117:423–430.

45 Gruner LF, Amitay EL, Heisser T, et al. The effects of different invitation schemes on the use of fecal occult blood tests for colorectal cancer screening: systematic review of randomized controlled trials. *Cancers (Basel)*. 2021;13:1520.

46 World Health Organization. European tobacco use. Trends report 2019. 2019. https://www.euro.who.int/en/health-topics/disease-prevention/tobacco/publications/2019/european-tobacco-use-trends-report-2019-2019. Accessed 16 February 2022.

47 NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet*. 2016;387:1377–1396.

48 Heisser T, Cardoso R, Guo F, Moellers T, Hoffmeister M, Brenner H. Strongly divergent impact of adherence patterns on efficacy of colorectal cancer screening: the need to refine adherence statistics. *Clin Transl Gastroenterol*. 2021;12:e00399.