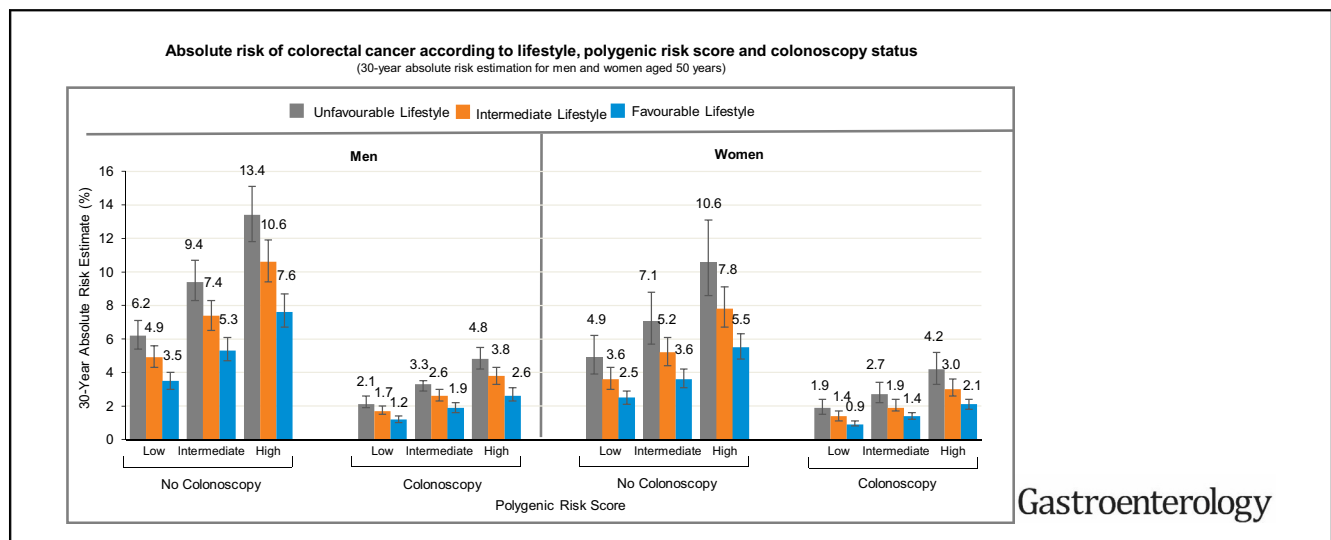




# Estimation of Absolute Risk of Colorectal Cancer Based on Healthy Lifestyle, Genetic Risk, and Colonoscopy Status in a Population-Based Study

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Gastroenterology

**BACKGROUND & AIMS:** Estimates of absolute risk of colorectal cancer (CRC) are needed to facilitate communication and better inform the public about the potentials and limits of cancer prevention. **METHODS:** Using data from a large population-based case-control study in Germany (Darmkrebs: Chancen der Verhütung durch Screening [DACHS] study, which began in 2003) and population registry data, we calculated 30-year absolute risk estimates for development of CRC based on a healthy lifestyle score (derived from 5 modifiable lifestyle factors: smoking, alcohol consumption, diet, physical activity, and body fatness), a polygenic risk score (based on 90 single-nucleotide polymorphisms), and colonoscopy history. **RESULTS:** We analyzed data from 4220 patients with CRC and 3338 individuals without CRC. Adherence to a healthy lifestyle and colonoscopy in the preceding 10 years were associated with a reduced relative risk of CRC in men and women. We observed a higher CRC risk in participants with high or intermediate genetic risk scores. For 50-year-old men and

women without a colonoscopy, the absolute risk of CRC varied according to the polygenic risk score and the healthy lifestyle score (men, 3.5%–13.4%; women, 2.5%–10.6%). For 50-year-old men and women with a colonoscopy, the absolute risk of developing CRC was much lower but still varied according to the polygenic risk score and the healthy lifestyle score (men, 1.2%–4.8%; women, 0.9%–4.2%). Among all risk factor profiles, the 30-year absolute risk estimates consistently decreased with adherence to a healthy lifestyle. **CONCLUSIONS:** In a population-based study, we found that a colonoscopy can drastically reduce the absolute risk of CRC and that the genetically predetermined risk of CRC can be further reduced by adherence to a healthy lifestyle. Our results show the magnitude of CRC prevention possible through colonoscopy and lifestyle at a predefined genetic risk. This observational study has been registered in the German Clinical Trials Register (DRKS00011793), which is a primary registry in the World Health Organization Registry Network.

Keywords: Colon Cancer; Epidemiology; Exercise; Food.

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer-related death worldwide.<sup>1</sup> It is a complex disease with both genetic and lifestyle factors contributing to individual risk of CRC.<sup>2,3</sup> Including the most recent genome-wide association studies (GWASs), more than 90 independent loci have been identified that are associated with the risk of CRC.<sup>4–16</sup> Although these individual genetic variants are only weakly associated with CRC, when aggregated into a polygenic risk score, they are predictive of CRC and provide a continuous and quantitative measure of genetic susceptibility of CRC.<sup>15,17</sup> Moreover, recent studies have also shown that these genetic risk variants may provide additional information that appears largely independent of a first-degree family history of CRC.<sup>15</sup>

In addition to the genetic susceptibility of CRC, there is well-established evidence that lifestyle factors such as smoking,<sup>18</sup> alcohol consumption,<sup>19</sup> poor diet,<sup>20–24</sup> physical inactivity,<sup>25</sup> and body fatness<sup>26,27</sup> are risk factors for CRC. Using data from a large population-based case-control study, we previously found that a healthy lifestyle score including 5 potentially modifiable lifestyle factors (nonsmoking, moderate alcohol consumption, a healthy diet, physical activity, and a healthy weight) was associated with lower risk of CRC and that risk further decreased with increasing adherence to the healthy lifestyle score.<sup>28</sup> Moreover, we found that adherence to a healthy lifestyle reduced the risk of CRC similarly in participants with higher and lower polygenic risk scores.

Although these results show that adherence to a healthy lifestyle was associated with reduced risk of CRC within each category of genetic risk, the results do not show the absolute risk or probability of developing CRC given a specific set of risk and protective factors. On the other hand, substantial evidence has shown that the risk of CRC can be greatly reduced through colonoscopy, allowing for the removal of precancerous lesions,<sup>29</sup> which may attenuate the influence of lifestyle and the genetic risk profile. Estimates of absolute risk are needed to facilitate communication and to better inform the public about the potentials and limits of cancer prevention.

Therefore, the aim of this analysis was to calculate detailed absolute risk estimates of CRC based on our healthy lifestyle score, an updated polygenic risk score, and information on colonoscopy history.

## Materials and Methods

### Study Design and Study Population

The Darmkrebs: Chancen der Verhütung durch Screening (DACHS) study is an ongoing population-based case-control study conducted in southwestern Germany since 2003. This analysis includes patients and control individuals recruited until 2016. Details of the DACHS study have been reported previously.<sup>30,31</sup> Briefly, patients with a histologically confirmed first diagnosis of CRC (*International Classification of Diseases*,

## WHAT YOU NEED TO KNOW

### BACKGROUND AND CONTEXT

Estimates of absolute risk of colorectal cancer (CRC) are needed to educate the public about the potentials and limits of cancer prevention.

### NEW FINDINGS

A population-based study showed that a colonoscopy greatly reduces the absolute risk of CRC. The genetically predetermined risk of CRC can be reduced by adherence to a healthy lifestyle.

### LIMITATIONS

The lifestyle factors in this study were treated as fixed variables that did not change, therefore, the authors cannot conclude how an individual's absolute risk may change if they make healthier lifestyle choices.

### IMPACT

Risk of CRC can be greatly reduced with colonoscopy screening and lifestyle modification for persons with all levels of genetic risk.

### LAY SUMMARY

In an analysis of a large population in Europe, the authors found that colonoscopy screening and healthy lifestyles greatly reduce risk of colorectal cancer, even in persons with genetic risk factors.

10th Revision codes C18–C20) are eligible to participate if they are at least 30 years of age (no upper age limit), can speak German, and are physically able to participate in an interview of approximately 1 hour. All 22 hospitals in the study area offering first-line treatment to patients with CRC are involved in recruitment. Approximately 50% of all eligible patients in the study area are recruited. Incomplete recruitment of patients is largely due to lack of time among the clinicians in charge of recruiting patients and notifying the study center in the routine setting. Community-based control individuals are randomly selected from population registries by using frequency matching with respect to age, sex, and county of residence (participation rate: 51%). The DACHS study was approved by the ethics committees of the University of Heidelberg and the state medical boards of Baden-Wuerttemberg and Rhineland-Palatinate. Written informed consent was obtained from each participant before taking part.

### Data Collection

Patients were informed about the study by their physicians, usually a few days after surgery. Patients participated in an

**Abbreviations used in this paper:** CI, confidence interval; CRC, colorectal cancer; DACHS, Darmkrebs: Chancen der Verhütung durch Screening; FFQ, food frequency questionnaire; GWAS, genome-wide association studies; OR, odds ratio; RR, relative risk; SNP, single nucleotide polymorphism.

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interview with trained interviewers who collected information on patients' sociodemographic, medical, and lifestyle history using a standardized questionnaire. In addition, we collected hospital discharge letters and pathology reports for all patients. Patients who could not be recruited during their hospital stay were contacted by mail shortly after discharge by clinicians or clinical cancer registries. The median time between CRC diagnosis and interview was 24 days. Control individuals were contacted by the study center through mail and follow-up calls, and interviews were scheduled at their homes. A minority of control participants not willing to participate in a personal interview provided some key information in a self-administered short questionnaire. However, because this questionnaire did not include a food frequency questionnaire (FFQ), these participants were excluded from this analysis.

### Derivation of the Healthy Lifestyle Score

A healthy lifestyle score was created by dichotomizing the information on 5 lifestyle factors (smoking, alcohol consumption, diet, physical activity, and body mass index) based on a priori knowledge of the risk factors for CRC.<sup>18–26,32–34</sup> The assessment of the lifestyle factors is described in the [Supplementary Methods](#), and further details on the derivation of the healthy lifestyle score were published recently.<sup>28</sup>

### Derivation of the Polygenic Risk Score

DNA was extracted from blood samples (in 99.1% of participants) or from buccal cells (in 0.9% of participants) using conventional methods. Details about genome-wide single-nucleotide polymorphism (SNP) analyses and imputation of missing genotypes in the DACHS study are provided in [Supplementary Table 1](#).

We considered a very recently reported set of 95 SNPs that were identified to be associated with a higher risk of CRC in the world's largest CRC GWAS in populations of European descent.<sup>2</sup> No linkage disequilibrium criterion was used for generating the polygenic risk score given the predefined SNP set; however, checks showed no high-linkage disequilibrium ( $D' \geq 0.95$ ) between any SNPs in our data set. Out of the reported 95 SNPs, a total of 90 SNPs could be extracted from our data set. The polygenic risk score was calculated as the sum of risk alleles as reported by Huyghe et al.<sup>2</sup>

### Information on Colonoscopy

Endoscopies before the diagnosis of CRC (excluding those leading to the current diagnosis) (case patients) or before the interview (control individuals) were assessed in detail during the interviews. We requested endoscopy and histology reports from the respective physicians for up to 3 prior endoscopies. Self-reported information was corrected if reported endoscopies could not be confirmed by medical records. Although we did not validate the information among all those who reported no prior endoscopy, we previously found the information to be accurate in a validation study.<sup>35</sup> Information on endoscopies leading to the current diagnosis were also assessed in detail during interviews. We classified a history of colonoscopy within the preceding 10 years of the reference time, including screening colonoscopies that led to the CRC diagnosis, as *yes* and *no* history of colonoscopy or *no* history of colonoscopy in

the preceding 10 years as *no* to reflect the decreased protective effect of colonoscopy beyond this time.<sup>36</sup>

### Statistical Analysis

The distribution of the demographic and lifestyle characteristics of the study population according to case-control status was evaluated in descriptive analyses using the Pearson chi-squared test or *t* test.

Multiple logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of the association of CRC risk with the healthy lifestyle score, polygenic risk score, and colonoscopy in the preceding 10 years. We stratified the model by sex (men and women) to allow for potential differential effects for men and women and included adjustment for age in all models. In these analyses, the lifestyle score was divided into 3 categories: favorable lifestyle (at least 4 of the 5 healthy lifestyle factors), intermediate (3 healthy lifestyle factors), or unfavorable (0, 1, or 2 healthy lifestyle factors), and the polygenic risk score was modeled as a categorical variable in tertiles (low, intermediate, and high genetic risk).

To replicate our findings published previously,<sup>28</sup> we performed analyses on the healthy lifestyle score stratified by polygenic risk score, using this expanded data set (which included a much larger number of participants and an updated polygenic risk score) and tested for interaction by including a cross-product term along with the main effect terms in the models, adjusting for the same covariates as previously.<sup>28</sup>

### Absolute Risk Calculations

We estimated the 30-year absolute risk and 95% CIs for developing CRC for 50-year-old men and women, with specific risk profiles, based on the principles of the modeling described by Freedman et al<sup>37</sup> and Pfeiffer and Petracchi,<sup>38</sup> considering only the healthy lifestyle score, the polygenic risk score, and colonoscopy. Briefly, the estimation of the absolute risk of CRC with this method includes estimating relative risks of CRC (calculated from population-based case-control data) and attributable risk parameters<sup>39</sup> and combining these estimates with baseline age-specific cancer hazard rates based on incidence rates and competing mortality rates from the German Centre for Cancer Registry Data, Robert Koch Institute (the German Federal Institute within the portfolio of the Federal Ministry of Health), to estimate the probability of developing CRC over a prespecified time interval (here, 30 years) given a person's age and risk factors (healthy lifestyle score, polygenic risk score, and colonoscopy status). The exact details of the calculations are provided in the [Supplementary Methods](#) ([Supplementary Tables 2–6](#)). In sensitivity analyses, we recalculated the absolute risks using different relative risks (RRs) for colonoscopy history: (1) the estimate reported in a meta-analysis on screening colonoscopy<sup>29</sup> (odds ratio [OR], 0.33) for both men and women and (2) an estimate closer to findings of a large cohort study<sup>40</sup> (RR, 0.50) for both men and women, in case the effect of colonoscopy was overestimated in our case-control study.

All analyses were performed using SAS, version 9.4 (SAS Institute Inc, Cary, NC), and R, version 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria) software. Statistical tests were 2-sided, with an alpha level of .05.

## Results

Overall, 4220 patients with CRC and 3338 control participants recruited in 2003–2016 were included in this analysis (Figure 1). The mean age of the case patients and control individuals was 68.4 years, and 61.5% of the participants were male (Table 1).

When comparing the baseline characteristics of the study participants, patients with CRC were more likely to have a lower level of education, smoke, and have a higher body mass index and were less likely to have had a colonoscopy in the preceding 10 years and to have participated in a health check-up. Control participants were more likely to be more physically active, less likely to have a family history of CRC, and more likely to use nonsteroidal anti-inflammatory drugs. Men with CRC were more likely to have a higher alcohol consumption, but no difference was seen among women. Overall, patients with CRC had a lower healthy lifestyle score compared to control participants and a higher polygenic risk score (median, case patients: 86.8; median, control individuals: 84.9) (Table 1).

### *Association of Adherence to a Healthy Lifestyle, Polygenic Risk Score, and Colonoscopy With Colorectal Cancer Risk in Men and Women*

In our study population, adherence to a healthy lifestyle was associated with reduced risk of CRC among both men and women after adjustment for age, polygenic risk score, and previous colonoscopy (Table 2). A higher CRC risk was observed among participants at high and intermediate genetic risk than among those at low genetic risk. A colonoscopy in the preceding 10 years was associated with a strong risk reduction of CRC, as reported previously<sup>30,36</sup> (Table 2).

### *Association of Adherence to a Healthy Lifestyle and Risk of Colorectal Cancer According to Polygenic Risk Score*

Among both men and women, multivariable analyses showed that within each tertile of the polygenic risk score, participants with a more favorable lifestyle had a lower risk of CRC (Supplementary Table 7). In an additional analysis, we assessed in this larger number of participants and using an updated polygenic risk score, the association of the healthy lifestyle score and CRC risk according to 2 groups of the polygenic risk score as published previously<sup>28</sup> and found similar results (Supplementary Table 8). Similar results were also seen when we stratified by tertiles of polygenic risk score (Supplementary Table 9).

### *Absolute Risk Estimates for Colorectal Cancer Based on Adherence to a Healthy Lifestyle Score, Polygenic Risk Score, and Previous Colonoscopy*

Table 3 presents estimates of the 30-year projected absolute risks of developing CRC for men and women separately, aged 50 years, combining information on polygenic risk score, adherence to a healthy lifestyle, and colonoscopy status, accounting for competing causes of death. The 30-year absolute risk of CRC was largely determined by

colonoscopy status. Without a colonoscopy, the 30-year absolute risk of developing CRC varied substantially depending on the individual risk profile, but across all risk factor profiles, the 30-year absolute risk estimates consistently decreased with higher adherence to a healthy lifestyle within each category of polygenic risk score, regardless of the colonoscopy status (Figure 2).

To illustrate, for a 50-year-old man with a high polygenic risk score, an unfavorable lifestyle, and without colonoscopy, the estimated 30-year absolute risk of developing CRC was 13.4% (95% CI, 11.8–15.1). In contrast, for a 50-year-old man with the same risk profile but adhering to a healthy lifestyle, the estimated 30-year absolute risk of CRC was 7.6% (95% CI, 6.7–8.7). Furthermore, a 50-year-old man with a favorable lifestyle who had a colonoscopy had an estimated 30-year absolute risk of CRC of only 2.6% (95% CI, 2.3–3.1).

For a 50-year-old woman with the highest risk profile (high genetic risk, unfavorable lifestyle, and without colonoscopy), the estimated 30-year absolute risk of CRC was 10.6% (95% CI, 8.6–13.1). With adherence to a healthy lifestyle, the 30-year absolute risk was much lower at 5.5% (95% CI, 4.8–6.3), and with colonoscopy, the 30-year absolute risk of CRC was estimated to be only 2.1% (95% CI, 1.8–2.4).

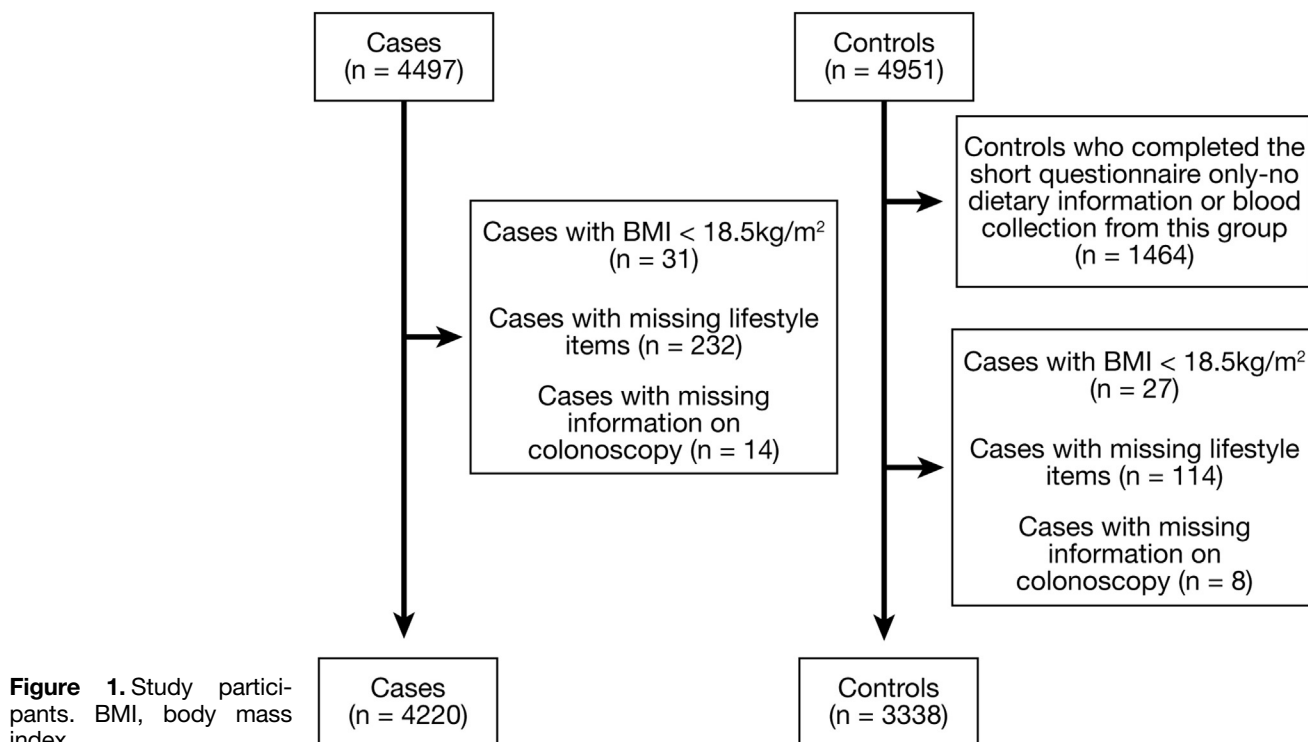
The estimated 30-year absolute risk of developing CRC for men with the lowest risk profile (50-year-old man with a low genetic risk and favorable lifestyle who had a colonoscopy) was 1.2% (95% CI, 1.0–1.4), and similarly, the estimated 30-year absolute risk of developing CRC for women with the lowest risk profile (50-year-old woman with a low genetic risk and favorable lifestyle who had a colonoscopy) was 0.9% (95% CI, 0.8–1.1).

In a sensitivity analysis where we used an estimate of CRC risk reduction closer to findings of a large cohort study (RR, 0.50), the absolute risk estimates were overall only slightly lower than in the main analyses; however, the same pattern was observed. Similar to the main analyses, the 30-year absolute risk estimates consistently decreased with adherence to a healthy lifestyle within each category of genetic risk, regardless of colonoscopy status (Supplementary Table 10 and Supplementary Figure 1).

## Discussion

Using data from a large epidemiologic study and population registry data, we present 30-year absolute risk estimates for developing CRC, combining information on adherence to a healthy lifestyle, polygenic risk score, and colonoscopy history. Of the 3 factors, colonoscopy status was the strongest preventive factor. If a colonoscopy was performed, absolute risks of CRC were overall much lower, and the range of absolute risks determined by lifestyle and polygenic risk score was narrower. However, adherence to a healthy lifestyle and genetic risk still played an important role. Within any polygenic risk category, increased adherence to a healthy lifestyle resulted in lower 30-year absolute risk estimates of CRC, suggesting that the genetically predetermined increased risk of CRC can be offset, at least to





some extent, by a healthy lifestyle. Healthy lifestyle and genetic risk played a much stronger role if no colonoscopy was performed.

The reduction of CRC risk associated with a healthy lifestyle has been well reported,<sup>28,41–46</sup> but we present for the first time, to our knowledge, absolute risk estimates of developing CRC based on genetic information, adherence to a healthy lifestyle, and history of colonoscopy. The absolute risk results together with the sensitivity analysis results support our previous findings that lifestyle factors may powerfully modify risk of CRC, regardless of the person's genetic profile.<sup>28</sup> Although individuals may perceive that having an increased genetic risk means that they are powerless against their genetic predisposition, our results show that a healthy lifestyle can still reduce CRC risk. Moreover, although the 30-year absolute risks associated with adherence to a healthy lifestyle were greatest in the group at high genetic risk and for those with no previous colonoscopy, these results still emphasize the benefit of everyone adhering to a healthy lifestyle.

Of the 3 factors included in our absolute risk calculations, history of colonoscopy was the strongest preventive factor. For a 50-year-old man or woman with a history of colonoscopy, the absolute risks of CRC were much lower, and variation of risk according to lifestyle and polygenic risk score was less pronounced. This is consistent with the well-established evidence that gastrointestinal endoscopy (in particular, polypectomy during sigmoidoscopy and colonoscopy) has a major protective effect against CRC.<sup>29</sup> Because most sporadic CRCs develop slowly over many years, the precursor lesions, adenomas and serrated polyps, can be detected and removed by colonoscopy.<sup>47</sup> Based on

the current available evidence, most national and international screening guidelines therefore recommend beginning CRC screening at age 50 years in adults at average risk.<sup>48,49</sup> In this large study, we considered only history of colonoscopy, although stool-based tests for blood (the guaiac-based fecal occult blood test and the fecal immunochemical test) were also used for CRC screening. In some countries, however, stool-based tests are used as the primary screening tests (for example, in the United Kingdom and The Netherlands).<sup>50</sup> Still, because we did not differentiate by indication for colonoscopy in this study, our results refer to colonoscopies for any reason, including those used to follow up positive stool test results. Also, although the effect of colonoscopy might be overestimated in our case-control study, the sensitivity analyses using an effect estimate closer to those reported in a large cohort study from the United States,<sup>40</sup> confirmed that the strongest risk reduction was still determined by colonoscopy and that with adherence to a healthy lifestyle, the 30-year absolute risk estimates consistently decreased within each category of genetic risk, regardless of colonoscopy status. However, the sensitivity analyses also showed that with less pronounced risk reduction of colonoscopy, the difference in the absolute risks between unfavorable and favorable lifestyle increased.

### Strengths and Limitations of This Study

The major strengths of the current study include the large sample size, which enabled the combination of genetic risk, lifestyle, and colonoscopy information in detail. Furthermore, we used an updated polygenic risk score for CRC using the most recently reported set of 95 SNPs that

**Table 1.** Baseline Characteristics of Participants by Case and Control Status

Characteristics	Total (n = 7558)	Case patients (n = 4220)	Control individuals (n = 3338)	P value
Sex, n (%)				
Female	2912 (38.5)	1636 (38.8)	1276 (38.2)	—
Male	4646 (61.5)	2584 (61.2)	2062 (61.7)	
Age, y				
Range	30–102	30–96	33–102	—
Mean (SD)	68.4 (10.6)	68.3 (10.7)	68.5 (10.5)	
Education, y, <sup>a</sup> n (%)				
≤9	4687 (62.1)	2795 (66.4)	1892 (56.8)	<.0001
10–11	1410 (18.7)	728 (17.3)	682 (20.5)	
≥12	1447 (19.2)	689 (16.4)	758 (22.8)	
Smoking status, n (%)				
Current or former smokers	1558 (20.6)	949 (22.5)	609 (18.2)	<.0001
Alcohol consumption, g/d, mean				
Women	5.4	5.2	5.7	.11
Men	21.2	22.5	19.5	<.0001
Dietary quality score, <sup>b</sup> mean	31.2	30.5	32.2	<.0001
Leisure time physical activity, MET-h/wk, mean	42.9	40.3	46.2	<.0001
BMI, kg/m <sup>2</sup> , mean	26.9	27.3	26.4	<.0001
First-degree family history of CRC, <sup>c</sup> n (%)				
Yes	971 (12.9)	616 (14.6)	355 (10.6)	<.0001
Colonoscopy in the preceding 10 years, n (%)				
Yes	2840 (37.6)	1140 (27.0)	1700 (50.9)	<.0001
Participation in a health check-up, <sup>d</sup> n (%)				
Yes	6624 (88.0)	3569 (84.9)	3055 (91.9)	<.0001
NSAIDs, <sup>e</sup> n (%)				
Yes	2184 (29.3)	1072 (25.8)	1112 (33.7)	<.0001
Healthy lifestyle score, n (%)				
Unfavorable lifestyle (0–2 factors)	2053 (27.2)	1321 (31.3)	732 (21.9)	<.0001
Intermediate lifestyle (3 factors)	2633 (34.8)	1504 (35.6)	1129 (33.8)	
Favorable lifestyle (4 or 5 factors)	2872 (38.0)	1395 (33.1)	1477 (44.2)	
Polygenic risk score, n (%)				
Low (T1)	2015 (26.7)	901 (21.4)	1114 (33.4)	<.0001
Intermediate (T2)	2506 (33.2)	1368 (32.4)	1138 (34.1)	
High (T3)	3037 (40.2)	1951 (46.2)	1086 (32.5)	
Mean (SD)	85.8 (5.7)	86.7 (5.6)	84.6 (5.6)	

MET, metabolic equivalent of task.

<sup>a</sup>Data missing for 14 participants.

<sup>b</sup>Diet quality score maximum: 50 points.

<sup>c</sup>Data missing for 6 participants.

<sup>d</sup>Data missing for 32 participants.

<sup>e</sup>Data missing for 93 participants.

were identified to be associated with a higher risk of CRC in the world's largest CRC GWAS in populations of European descent. Our model estimates the probability of developing CRC over a 30-year time interval using data from a large German population-based case-control study, incidence data from the German Centre for Cancer Registry Data, and data from national mortality rates. Thus, it is expected that our risk prediction models are mostly representative of the general German population. Moreover, this model includes information on lifestyle that can be easily ascertained in a clinical setting. Although genetic information is not available from the patients yet, it is increasingly being incorporated in electronic health records, particularly in the United States.<sup>51</sup> Also, our absolute risk estimates may facilitate communication about the risk of CRC, thereby allowing physicians to

improve their patient education, leading to better lifestyle management in patients at higher risk (even without knowledge of the genetic risk).

Our study also has some limitations. First, because we only had information collected at the reference time, the lifestyle factors were treated as fixed variables that did not change. However, diet and lifestyle behavior may change over a person's lifetime. Therefore, we cannot conclude how an individual's absolute risk may change if he or she makes healthier lifestyle choices. Second, in this model, we estimated the relative risks and attributable risks from a case-control study. Although case-control data has previously been used for the development of risk prediction models for CRC<sup>37</sup> or breast cancer,<sup>52,53</sup> our estimates could be subject to recall bias. The ascertainment of lifestyle was based on

**Table 2.** ORs of Risk Factors Associated With CRC Risk Stratified by Sex

Subgroup	Case patients n (%) / control individuals n (%)		OR (95% CI)	
	Men	Women	Men	Women
Healthy lifestyle score				
Unfavorable lifestyle	1013 (39)/590 (29)	308 (19)/142 (11)	1.00 (Ref)	1.00 (Ref)
Intermediate lifestyle	931 (36)/746 (36)	573 (35)/383 (30)	0.78 (0.67–0.90)	0.72 (0.57–0.93)
Favorable lifestyle	640 (25)/726 (35)	755 (46)/751 (59)	0.55 (0.47–0.64)	0.50 (0.40–0.63)
Polygenic risk score				
Low genetic risk	555 (21)/699 (34)	346 (21)/415 (33)	1.00 (Ref)	1.00 (Ref)
Intermediate genetic risk	851 (33)/699 (34)	517 (32)/439 (34)	1.54 (1.32–1.80)	1.45 (1.19–1.77)
High genetic risk	1178 (46)/664 (32)	773 (47)/422 (33)	2.24 (1.93–2.62)	2.23 (1.84–2.70)
Colonoscopy in the preceding 10 years				
No	1888 (73)/989 (48)	1192 (73)/649 (51)	1.00 (Ref)	1.00 (Ref)
Yes	696 (27)/1073 (52)	444 (27)/627 (49)	0.34 (0.30–0.39)	0.38 (0.32–0.44)

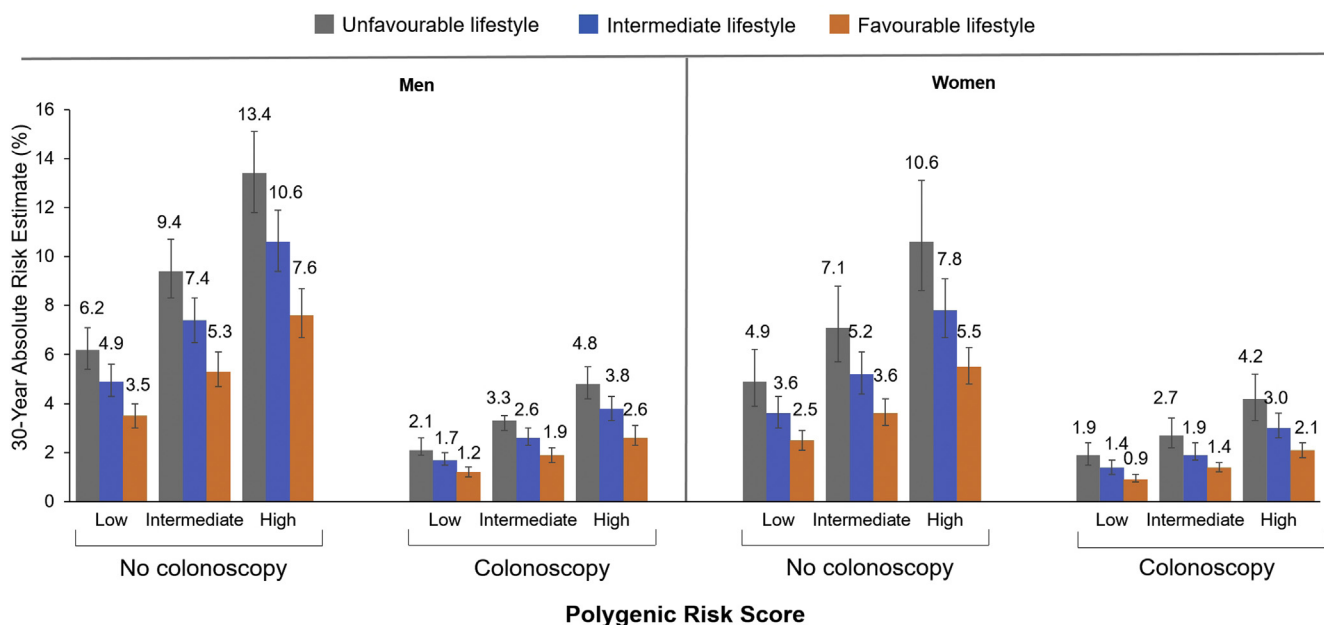
NOTE. The logistic regression models included age, healthy lifestyle score, polygenic risk score, and colonoscopy in the preceding 10 years.

self-reported information; therefore, the effects may be underestimated. In addition, we cannot rule out the possibility of selection bias, particularly in the recruitment of control individuals. Control participants may have been more health conscious and may have reported overall healthier lifestyles compared to the entire underlying

control population. For example, control participants who only provided a self-administered questionnaire were excluded from the analysis because of lack of information on diet and genetic risk score. These participants were slightly older (70.7 years vs 68.5 years) and reported less frequent participation in health check-ups (74.2% vs 91.9%), which

**Table 3.** 30-Year Absolute Risk Estimates of CRC for 50-Year-Old Men and Women

Subgroup	Case patients n (%) / control individuals n (%)		30-year risk, % (95% CI)	
	Men	Women	Men	Women
No colonoscopy				
Low genetic risk				
Unfavorable lifestyle	164 (40)/88 (26)	40 (15)/26 (12)	6.2 (5.4–7.1)	4.9 (3.9–6.2)
Intermediate lifestyle	157 (38)/123 (36)	101 (38)/53 (24)	4.9 (4.3–5.6)	3.6 (3.0–4.3)
Favorable lifestyle	87 (21)/134 (39)	123 (47)/143 (64)	3.5 (3.0–4.0)	2.5 (2.1–2.9)
Intermediate genetic risk				
Unfavorable lifestyle	260 (41)/97 (30)	76 (21)/20 (9)	9.4 (8.3–10.7)	7.1 (5.7–8.8)
Intermediate lifestyle	216 (34)/120 (37)	131 (36)/78 (35)	7.4 (6.5–8.3)	5.2 (4.4–6.1)
Favorable lifestyle	153 (24)/108 (33)	156 (43)/126 (56)	5.3 (4.7–6.1)	3.6 (3.1–4.2)
High genetic risk				
Unfavorable lifestyle	341 (40)/115 (36)	118 (21)/27 (13)	13.4 (11.8–15.1)	10.6 (8.6–13.1)
Intermediate lifestyle	302 (35)/105 (33)	199 (35)/57 (28)	10.6 (9.4–11.9)	7.8 (6.7–9.1)
Favorable lifestyle	208 (24)/99 (31)	248 (44)/119 (59)	7.6 (6.7–8.7)	5.5 (4.8–6.3)
Colonoscopy				
Low genetic risk				
Unfavorable lifestyle	53 (36)/80 (23)	7 (9)/21 (11)	2.1 (1.9–2.6)	1.9 (1.5–2.4)
Intermediate lifestyle	59 (40)/145 (41)	33 (40)/65 (34)	1.7 (1.5–2.0)	1.4 (1.1–1.7)
Favorable lifestyle	35 (24)/129 (36)	42 (51)/107 (55)	1.2 (1.0–1.4)	0.9 (0.8–1.1)
Intermediate genetic risk				
Unfavorable lifestyle	75 (34)/110 (29)	23 (15)/26 (12)	3.3 (2.9–3.1)	2.7 (2.2–3.4)
Intermediate lifestyle	80 (36)/126 (34)	60 (28)/60 (28)	2.6 (2.3–3.0)	1.9 (1.7–2.4)
Favorable lifestyle	67 (30)/138 (37)	88 (57)/129 (60)	1.9 (1.6–2.1)	1.4 (1.2–1.6)
High genetic risk				
Unfavorable lifestyle	120 (38)/100 (29)	44 (21)/22 (10)	4.8 (4.2–5.5)	4.2 (3.3–5.2)
Intermediate lifestyle	117 (36)/127 (37)	66 (32)/70 (32)	3.8 (3.3–4.3)	3.0 (2.6–3.6)
Favorable lifestyle	90 (28)/118 (34)	98 (47)/127 (58)	2.6 (2.3–3.1)	2.1 (1.8–2.4)



**Figure 2.** The 30-year absolute risk estimates of colorectal cancer for 50-year-old men and women, according to lifestyle, polygenic risk score, and colonoscopy status.

would result in some overestimation of the healthy lifestyle effect. However, on the other hand, it is possible that because of the dichotomization of risk factors in our healthy lifestyle score, the importance of healthy lifestyle is underestimated in this study. It is likely that with a more refined lifestyle score, relative risk and absolute risk estimates may be much more pronounced. In this study, we classified a small percentage of participants who had a colonoscopy more than 10 years ago together with participants who never underwent lower endoscopy, which may have led to an underestimation of the effects of colonoscopy. In addition, in rare cases, participants in our study may have had sigmoidoscopy or rectoscopy rather than colonoscopy,<sup>35</sup> but because these are rarely performed anymore in Germany, the results are likely to be unchanged. Finally, the population included in the present analyses were primarily people of European descent. Therefore, these results may not be generalizable to populations that are more diverse.

## Conclusion

In conclusion, after quantifying absolute risk estimates for CRC based on 3 major determinants of CRC risk—adherence to a healthy lifestyle, polygenic risk score, and history of colonoscopy—colonoscopy was the strongest preventive factor. We still found that better adherence to a healthy lifestyle was associated with much lower absolute risks of CRC within each category of genetic risk. These findings highlight the strong protective effect of colonoscopy and the potential of lifestyle interventions to reduce the risk of CRC across the population, even among those at high genetic risk of CRC and still among those who have had a colonoscopy. Our absolute risk estimates can be useful to facilitate communication and to better inform the public

about the magnitude, potentials, and limits of CRC prevention.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at <https://doi.org/10.1053/j.gastro.2020.03.016>.

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#### CRedit Authorship Contributions

Prudence Carr, PhD (Conceptualization: Supporting; Formal analysis: Equal; Writing – original draft: Lead); Korbinian Weigl, PhD (Writing – review & editing: Equal; Acquisition of data: Supporting); Dominic Edelmann, PhD (Formal analysis: Equal; Writing – review & editing: Supporting); Lina Jansen, PhD (Writing – review & editing: Equal; Acquisition of data: Equal); Jenny Chang-Claude, PhD (Funding acquisition: Equal; Project administration: Equal; Supervision: Equal; Writing – review & editing: Equal; Acquisition of data: Equal); Michael Hoffmeister, PhD (Conceptualization: Equal; Formal analysis: Supporting; Funding acquisition: Equal; Project administration: Equal; Supervision: Equal; Writing – review & editing: Equal; Acquisition of data: Equal)

#### Conflicts of interest

The authors disclose no conflicts.

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## Supplementary Methods

### Assessment of Lifestyle Factors in the DACHS Study

Extensive information on smoking history was collected during interviews. Participants provided information on their current and prior smoking behavior and, if applicable, the year in which they stopped smoking. Participants were classified as nonsmokers if they had never smoked regularly or were former smokers and smoked <30 pack years and as smokers if they were smoking at the time of diagnosis or recruitment to the study or were former smokers and smoked ≥30 pack years (classification of former smokers based on findings from Tsoi et al<sup>1</sup>) (Supplementary Table 2). Further details have also been reported previously.<sup>2</sup>

Information on alcohol consumption was assessed, where participants were asked how many drinks (beer [0.33 L], wine [0.25 L], or liquor [0.02 L]) they had consumed on average per week at ages 20, 30, 40, 50, 60, 70, and 80 years and in the last 12 months. The ethanol content of the beverage types (assuming 4, 8.6, and 33 g of pure ethanol in 100 mL of beer, wine, or liquor, respectively) was derived from food composition tables, and the average lifetime alcohol consumption was calculated based on self-recalled alcohol consumption at ages 20, 30, 40, 50, 60, 70, and 80 years. The mean daily lifetime amount of ethanol was calculated by dividing the total weekly ethanol amount by 7 days. Participants were classified as having moderate alcohol consumption if they were adherent to the World Cancer Research Fund/American Institute for Cancer Research recommendations: ≤24 g/d for men and ≤12 g/d for women<sup>3</sup> (Supplementary Table 2). Further details have also been reported previously.<sup>4</sup>

Participants were asked about the hours per week they spent with different physical activities over the past decades (ie, hard exhausting work, light work spent walking or standing, walking, cycling, or doing sports). Based on the task-specific metabolic equivalent of task (MET) values (3.3 MET-h/wk for each hour walking, 6 MET-h/wk for each hour cycling, and 8 MET-h/wk for each hour of sports), average recent nonoccupational physical activity (walking, cycling, or doing sports only) was calculated for each participant. Occupational activity (hard exhausting work, light work spent walking or standing) was not included in our physical activity variable given that most study participants were no longer engaged in occupational activity. Reported information from the most recent decade preceding the participant's current age was used to derive the activity-specific recent average MET-h/wk (eg, for patients aged 60–69 years, information from age 60 years was used). Further details on the assessment of physical activity in the DACHS study have been reported previously.<sup>5</sup> Participants were classified as being physically active if they met the World Health Organization Global Recommendations on Physical Activity for Health (at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an

equivalent combination of moderate and vigorous intensity physical activity [at least approximately 500 MET minutes]<sup>6</sup>) (Supplementary Table 2).

Dietary information was obtained by a 23-item FFQ, and consumption was assessed in 6 categories of predefined responses ranging from *never* to *multiple times per day*. Participants were asked to report their average frequency of consumption over the previous 12 months (control individuals) or before CRC diagnosis (case patients). A diet quality score was created based on the availability of data from the FFQ and the updated evidence from the 2017 World Cancer Research Fund/American Institute for Cancer Research diet recommendations for the prevention of CRC.<sup>7</sup> Six main food groups (red and processed meat [as a negative component], fish, whole grains, dairy foods, fruits, and vegetables [positive components]) were included in the diet quality score. Points were assigned depending on the frequency of consumption of the food groups and then summed up. The diet quality score ranged from 0 (lowest) to 50 (highest). Further details on the derivation of the diet quality score were published recently.<sup>8</sup> If information on any of the dietary items used to build the diet quality score was missing, the participants were excluded. Participants with a diet quality score in the highest 40% were considered to have a healthy diet (Supplementary Table 2). Further details on the assessment of diet in the DACHS study have been published previously.<sup>9,10</sup>

Participants reported their current weight and height and their past weight at each decade from age 20 to 80 years. Body mass index (BMI) was calculated from recent weight and height (5–14 years earlier). Participants with a BMI of <18.5 kg/m<sup>2</sup> were excluded. Participants with a healthy weight (BMI, >18.5 to <25 kg/m<sup>2</sup>) were assigned 1 point (Supplementary Table 2). Further details on the assessment of BMI in the DACHS study have been published previously.<sup>11</sup>

### Estimation of Absolute Risk for Developing Colorectal Cancer

We estimated the 30-year absolute risk of developing CRC for men and women separately given the healthy lifestyle score, the polygenic risk score, and colonoscopy status following the methods presented by Freedman et al.<sup>12</sup>

The estimated absolute risk of CRC included the following.

#### Estimating RR and attributable risk parameters from the case-control data (DACHS study data)

**Estimating the Relative Risk Models.** Because we were interested in calculating the absolute risk estimates of CRC according to adherence to a healthy lifestyle, the polygenic risk score, and colonoscopy, only these factors in addition to age (in 2 categories: ≤65 and >65 years) were included in the RR model. We analyzed all CRC cases together and used eligible control individuals from the DACHS study to estimate separate RR models for men and women. ORs and 95% CIs were computed from

unconditional logistic regression models. Statistical analyses were performed using R software, version 2.15.3.

**Attributable Risk Estimates.** The age- and sex-specific attributable risks (ARs) were calculated via

$$AR_j = 1 - \frac{1}{n_j} \sum_{i=1}^{n_j} \frac{1}{rr_{ij}},$$

where  $j$  is 1 of the 4 subgroups (men,  $\leq 65$  years; men,  $> 65$  years; women,  $\leq 65$  years; women,  $> 65$  years),  $n_j$  is the number of cases in the  $j$ th subgroup, and  $rr_{ij}$  is the relative risk of the  $i$ th case in the  $j$ th subgroup. The standard error of the AR estimate was calculated by using the influence function approach proposed by Graubard and Fears<sup>13</sup> (see also Freedman et al.<sup>12</sup>). Using the estimate of the standard error, confidence intervals were constructed assuming that distributions of the logit-transformed attributable risk are normally distributed.

*Estimating Baseline Age-Specific Cancer Hazard Rates (Based on the German Centre for Cancer Registry Data, Incidence Rates, and Robert Koch Institute [the German Federal Institute within the portfolio of the Federal Ministry of Health])*

**Estimating the Baseline Age-Specific Colorectal Cancer Hazard Rates.** As described by Freedman et al,<sup>12</sup> the baseline hazard rate was defined as the hazard rate for individuals for whom each of the risk factors are at the lowest risk level. The age-specific baseline hazard rates were computed by multiplying the age-specific incidence rates (from the Robert Koch Institute) by 1 – (the estimate of the AR) (Supplementary Table 3).

The age- and sex-specific incidence rates for colon and rectal cancer were obtained for Germany between 2003 and 2014 (Supplementary Table 4). For competing risks, the mortality rates for non-CRC-specific causes were calculated by subtracting the age- and sex-specific mortality rates for

CRC obtained also from the German Centre for Cancer Registry Data, Robert Koch Institute, from the overall mortality rates (Supplementary Table 5).

*Combining Competing Risks, Relative Risks, and Baseline Hazards to Estimate the Probability of Developing Colorectal Cancer Over a Prespecified Time Period (ie, 30 Years), Given a Person's Age and Risk Factors*

**Absolute Risk Estimates.** To calculate the absolute risk of CRC for a person given age  $a$  and risk factors  $\mathbf{x}$ , we proceeded as follows. First, we calculated the relative risk of this person,  $rr(\mathbf{x})$ , using the corresponding logistic model. Denoting the (sex-specific) baseline hazard rate for age  $k$  by  $h_{1k}$  and the (sex-specific) hazard rate of other-cause mortality by  $h_{2k}$ , the absolute risk of CRC in the following  $\tau$  years can then be calculated using formula (2) in Pfeiffer and Petracchi<sup>14</sup>:

$$r(a, \tau, \mathbf{x}) = \sum_{k=a}^{a+\tau-1} \frac{h_{1k} rr(\mathbf{x})}{h_{1k} rr(\mathbf{x}) + h_{2k}} [1 - \exp\{-(h_{1k} rr(\mathbf{x}) + h_{2k})\}]$$

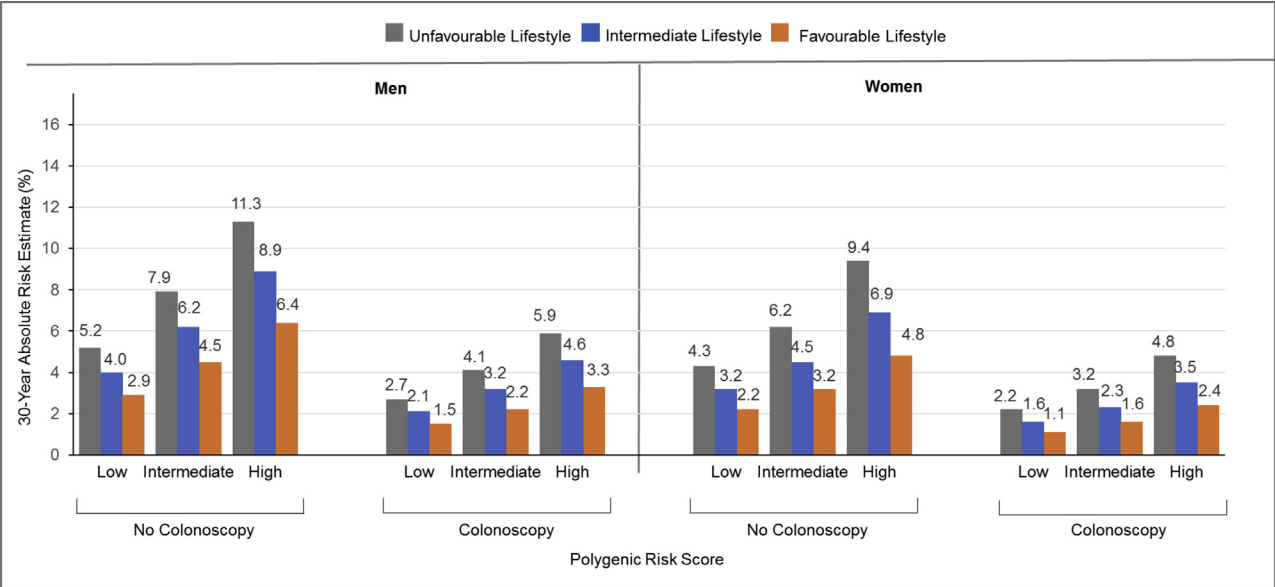
$$\exp\left\{-\sum_{l=a}^{j-1} (h_{1l} rr(\mathbf{x}) + h_{2l})\right\}.$$

The standard error was calculated using the influence function approach proposed by Pfeiffer and Petracchi.<sup>14</sup> Using the estimate of the standard errors, confidence intervals for the absolute risk estimates were constructed assuming that distributions of the logit-transformed absolute risk are normally distributed. To check the robustness of the obtained standard errors, we additionally calculated bootstrap standard errors for the absolute risk estimates. A comparison of the bootstrap standard errors and the standard errors obtained by the influence function approach are provided in Supplementary Table 6.



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**Supplementary Figure 1.** Sensitivity analysis: Recalculation of 30-year absolute risk estimates of CRC for 50-year-old men and women using a RR estimate for colonoscopy history closer to findings of a large cohort study (RR, 0.50).

**Supplementary Table 1.** Information About Genotyping and Imputation Within DACHS

Genotyping platform	Number of case patients	Number of control individuals	Recruitment Period	Imputation
Illumina (San Diego, CA) HumanCytoSNP	1593	1645	2003–2008	Cosmopolitan panel of reference haplotypes from phase 1 of the 1000 Genome Project
Illumina HumanOmniExpress	654	473	2007–2010	1000 Genome Project
Illumina HumanOmniExpress	1122	598	2010–2015	Haplotype Reference Consortium
Illumina Infinium OncoArray	851	622	2003–2016	(version r1.1.2016)

NOTE. Triallelic SNPs and those not assigned an rs number were excluded, as were genotyped SNPs when they had a low call rate ( $<98\%$ ), lack of Hardy-Weinberg equilibrium in control individuals ( $P < 1 \times 10^{-4}$ ), or low minor allele frequency ( $<0.1\%$ ). See Peters et al<sup>a</sup> and Schumacher et al<sup>b</sup> for more information about genotyping and imputation. Please note that data from the Illumina HumanCytoSNP and Illumina HumanOmniExpress with recruitment period from 2007 to 2010 have been used for previous analyses within the DACHS study.<sup>c</sup>

<sup>a</sup>Peters U, Jiao S, Schumacher FR, et al. Identification of genetic susceptibility loci for colorectal tumors in a genome-wide meta-analysis. *Gastroenterology* 2013;144:799–807.

<sup>b</sup>Schumacher FR, Schmit SL, Jiao S, et al. Genome-wide association study of colorectal cancer identifies six new susceptibility loci. *Nat Commun* 2015;6:7138.

<sup>c</sup>Weigl K, Chang-Claude J, Knebel P, et al. Strongly enhanced colorectal cancer risk stratification by combining family history and genetic risk score. *Clin Epidemiol* 2018;10:143–152.

**Supplementary Table 2.** Description of the Lifestyle Factors Used to Derive the Healthy Lifestyle Score

Lifestyle factor	Points	Description
Smoking	0 1	Smoking: current smoker or former smoker ( $\geq 30$ pack years) Nonsmoking: never smoker or former smoker ( $<30$ pack years)
Alcohol intake	0 1	Did not meet recommendations on alcoholic drinks <sup>a</sup> Met recommendation on alcoholic drinks <sup>a</sup>
Diet quality	0 1	Unhealthy diet quality: diet score $<34$ Healthy diet quality: diet score $\geq 34$ <sup>b</sup>
Physical activity	0 1	Did not meet physical activity guidelines <sup>c</sup> Met physical activity guidelines <sup>c</sup>
BMI	0 1	Overweight or obese (BMI $\geq 25$ kg/m <sup>2</sup> ) Healthy weight (18.5 $<$ BMI $<$ 25 kg/m <sup>2</sup> )

BMI, body mass index.

<sup>a</sup>World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) (2007) Recommendation on alcoholic drinks:  $\leq 24$  g/day men,  $\leq 12$  g/day women

<sup>b</sup>Diet score in the highest 40%

<sup>c</sup>The WHO Global Recommendations on Physical Activity for Health (2010) recommend adults to engage in at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate and vigorous intensity physical activity (At least  $\sim 500$  MET minutes).

**Supplementary Table 3.** Attributable Risk Estimates Stratified by Sex and Age

Sex, age group	n	Case patients, n	Attributable risk (95% CI)
Men, $>65$ y	2933	1596	0.75 (0.71–0.79)
Men, $\leq 65$ y	1713	988	0.78 (0.73–0.81)
Women, $>65$ y	1851	1062	0.71 (0.65–0.76)
Women, $\leq 65$ y	1061	574	0.73 (0.68–0.78)

**Supplementary Table 4.** Colorectal Cancer Incidence (Cases per 100,000) in Germany: Data From the German Center for Cancer Registry Data, Robert Koch Institute 2003–2014

Age, y	Men	Women
30–34	3.4	3.5
35–39	6.7	6.3
40–44	12.6	11.4
45–49	26.2	21.2
50–54	53.7	39.4
55–59	103.9	63.9
60–64	170.6	95.7
65–69	248.0	136.3
70–74	328.5	186.1
75–79	414.3	253.8
80–84	496.4	337.5
85+	526.6	403.4

**Supplementary Table 5.** Mortality (Deaths per 100,000) for Men and Women in Germany: Data From the German Center for Cancer Registry Data, Robert Koch Institute 2003–2014

Age, y	Men			Women		
	All cause	CRC	Other cause	All cause	CRC	Other cause
30–34	74.7	0.8	73.9	32.1	0.6	31.5
35–39	105.0	1.5	103.5	57.2	1.3	55.9
40–44	172.1	3.0	169.1	94.7	2.6	92.1
45–49	305.9	6.8	299.1	170.8	5.2	165.6
50–54	521.4	14.8	506.6	274.1	10.1	263.9
55–59	804.7	29.6	775.1	412.1	17.4	394.7
60–64	1249.0	53.3	1195.7	641.9	27.8	614.1
65–69	1874.8	84.6	1790.2	942.3	43.3	899.0
70–74	2812.2	124.1	2688.1	1496.2	66.1	1430.1
75–79	5128.7	181.4	4947.3	3034.6	105.7	2928.9
80–84	8059.0	259.6	7799.4	5850.8	171.0	5679.9
85+	15,551.0	360.9	15,190.1	14,964.1	286.8	14,677.3



**Supplementary Table 6.** Standard Error Calculation Using the Influence Function in Comparison to Bootstrap Standard Errors

Subgroup	Standard errors obtained by the influence function approach		Standard errors obtained by bootstrapping	
	Male	Female	Male	Female
No colonoscopy				
Low genetic risk				
Unfavorable lifestyle	0.0043	0.0059	0.0044	0.0060
Intermediate lifestyle	0.0033	0.0032	0.0033	0.0032
Favorable lifestyle	0.0025	0.0020	0.0025	0.0020
Intermediate genetic risk				
Unfavorable lifestyle	0.0059	0.0078	0.0060	0.0080
Intermediate lifestyle	0.0047	0.0043	0.0048	0.0044
Favorable lifestyle	0.0036	0.0026	0.0036	0.0027
High genetic risk				
Unfavorable lifestyle	0.0082	0.0114	0.0084	0.0118
Intermediate lifestyle	0.0064	0.0062	0.0066	0.0063
Favorable lifestyle	0.0050	0.0038	0.0050	0.0038
Colonoscopy				
Low genetic risk				
Unfavorable lifestyle	0.0017	0.0024	0.0017	0.0025
Intermediate lifestyle	0.0013	0.0014	0.0013	0.0014
Favorable lifestyle	0.0009	0.0008	0.0010	0.0008
Intermediate genetic risk				
Unfavorable lifestyle	0.0024	0.0032	0.0024	0.0033
Intermediate lifestyle	0.0019	0.0018	0.0019	0.0018
Favorable lifestyle	0.0014	0.0011	0.0014	0.0011
High genetic risk				
Unfavorable lifestyle	0.0033	0.0048	0.0034	0.0049
Intermediate lifestyle	0.0025	0.0027	0.0025	0.0026
Favorable lifestyle	0.0019	0.0016	0.0019	0.0016

**Supplementary Table 7.** Risk of CRC According to Polygenic Risk Score and Adherence to a Healthy Lifestyle

Subgroup	Colorectal cancer	
	n <sub>cases</sub> (%) / n <sub>controls</sub> (%)	OR (95% CI) <sup>a</sup>
Low genetic risk		
Unfavorable lifestyle	264 (29)/215 (19)	1.00 (Ref)
Intermediate lifestyle	350 (39)/386 (35)	0.75 (0.59–0.96)
Favorable lifestyle	287 (32)/ 513 (46)	0.45 (0.35–0.58)
P trend		<.0001
Intermediate genetic risk		
Unfavorable lifestyle	434 (32)/253 (22)	1.00 (Ref)
Intermediate lifestyle	470 (34)/384 (34)	0.71 (0.57–0.88)
Favorable lifestyle	464 (34)/501 (44)	0.60 (0.48–0.75)
P trend		<.0001
High genetic risk		
Unfavorable lifestyle	623 (32)/264 (24)	1.00 (Ref)
Intermediate lifestyle	684 (35)/359 (33)	0.86 (0.70–1.05)
Favorable lifestyle	644 (33)/463 (43)	0.61 (0.49–0.75)
P trend		<.0001

Ref, Reference.

<sup>a</sup>Model adjusted for matching factors age and sex and the factors school education, family history of CRC, colonoscopy, participation in a health check-up, and ever regular use of no-steroidal anti-inflammatory drugs.

**Supplementary Table 8.** Association Between the Healthy Lifestyle Score and CRC in the DACHS Study by Polygenic Risk Score

Polygenic risk score	Lifestyle score	CRC		<i>P</i> <sub>interaction</sub>
		<i>n</i> <sub>cases</sub> (%) / <i>n</i> <sub>controls</sub> (%)	OR (95% CI) <sup>a</sup>	
<Median	0 or 1	135 (9)/78 (5)	1.00 (Ref)	.08
	2	342 (23)/257 (15)	0.73 (0.52–1.04)	
	3	566 (37)/568 (34)	0.55 (0.40–0.76)	
	4	384 (25)/524 (31)	0.42 (0.30–0.58)	
	5	101 (7)/242 (15)	0.25 (0.17–0.37)	
	<i>P</i> trend		<.0001	
≥Median	0 or 1	216 (8)/89 (5)	1.00 (Ref)	
	2	628 (23)/308 (18)	0.86 (0.64–1.15)	
	3	938 (35)/561 (34)	0.73 (0.55–0.96)	
	4	699 (26)/477 (29)	0.63 (0.47–0.84)	
	5	211 (8)/234 (14)	0.38 (0.27–0.53)	
	<i>P</i> trend		<.0001	

Ref, reference.

<sup>a</sup>Model adjusted for matching factors age and sex and the factors school education, family history of CRC, colonoscopy, participation in a health check-up, and ever regular use of nonsteroidal anti-inflammatory drugs.**Supplementary Table 9.** Association Between the Healthy Lifestyle Score and CRC in the DACHS Study by Polygenic Risk Score (Tertiles)

Polygenic risk score	Lifestyle score	CRC		<i>P</i> <sub>interaction</sub>
		<i>n</i> <sub>cases</sub> (%) / <i>n</i> <sub>controls</sub> (%)	OR (95% CI) <sup>a</sup>	
Low genetic risk	0 or 1	76 (8)/46 (4)	1.00 (Ref)	
	2	188 (21)/169 (15)	0.62 (0.39–0.97)	
	3	350 (39)/386 (35)	0.52 (0.34–0.78)	
	4	230 (26)/348 (31)	0.37 (0.24–0.57)	
	5	57 (6)/165 (15)	0.18 (0.11–0.31)	
	Per 1 point increase in score		0.70 (0.63–0.77)	
	<i>P</i> trend		<.0001	
Intermediate genetic risk	0 or 1	127 (9)/56 (5)	1.00 (Ref)	.02
	2	307 (22)/197 (17)	0.71 (0.48–1.04)	
	3	470 (34)/384 (34)	0.54 (0.38–0.79)	
	4	363 (27)/351 (31)	0.50 (0.34–0.73)	
	5	101 (7)/150 (13)	0.35 (0.23–0.55)	
	Per 1 point increase in score		0.80 (0.74–0.87)	
	<i>P</i> trend		<.0001	
High genetic risk	0 or 1	148 (8)/65 (6)	1.00 (Ref)	
	2	475 (24)/199 (18)	1.06 (0.74–1.51)	
	3	684 (35)/359 (33)	0.89 (0.63–1.25)	
	4	490 (25)/302 (28)	0.74 (0.52–1.05)	
	5	154 (8)/161 (15)	0.42 (0.28–0.62)	
	Per 1 point increase in score		0.80 (0.74–0.87)	
	<i>P</i> trend		<.0001	

Ref, reference.

<sup>a</sup>Model adjusted for matching factors age and sex and the factors school education, family history of CRC, colonoscopy, participation in a health check-up, and ever regular use of nonsteroidal anti-inflammatory drugs.

**Supplementary Table 10.** Sensitivity Analysis: Recalculation of 30-Year Absolute Risk Estimates of CRC for 50-Year-Old Men and Women Using a RR Estimate for Colonoscopy History Closer to Findings of a Large Cohort Study (RR, 0.50)

Subgroup	Case patients n (%) / Control individuals n (%)		30-Year Risk, %	
	Men	Women	Men	Women
<b>No colonoscopy</b>				
Low genetic risk				
Unfavorable lifestyle	164 (40)/88 (26)	40 (15)/26 (12)	5.2	4.3
Intermediate lifestyle	157 (38)/123 (36)	101 (38)/53 (24)	4.0	3.2
Favorable lifestyle	87 (21)/134 (39)	123 (47)/143 (64)	2.9	2.2
Intermediate genetic risk				
Unfavorable lifestyle	260 (41)/97 (30)	76 (21)/20 (9)	7.9	6.2
Intermediate lifestyle	216 (34)/120 (37)	131 (36)/78 (35)	6.2	4.5
Favorable lifestyle	153 (24)/108 (33)	156 (43)/126 (56)	4.5	3.2
High genetic risk				
Unfavorable lifestyle	341 (40)/115 (36)	118 (21)/27 (13)	11.3	9.4
Intermediate lifestyle	302 (35)/105 (33)	199 (35)/57 (28)	8.9	6.9
Favorable lifestyle	208 (24)/99 (31)	248 (44)/119 (59)	6.4	4.8
<b>Colonoscopy</b>				
Low genetic risk				
Unfavorable lifestyle	53 (36)/80 (23)	7 (9)/21 (11)	2.7	2.2
Intermediate lifestyle	59 (40)/145 (41)	33 (40)/65 (34)	2.1	1.6
Favorable lifestyle	35 (24)/129 (36)	42 (51)/107 (55)	1.5	1.1
Intermediate genetic risk				
Unfavorable lifestyle	75 (34)/110 (29)	23 (15)/26 (12)	4.1	3.2
Intermediate lifestyle	80 (36)/126 (34)	60 (28)/60 (28)	3.2	2.3
Favorable lifestyle	67 (30)/138 (37)	88 (57)/129 (60)	2.2	1.6
High genetic risk				
Unfavorable lifestyle	120 (38)/100 (29)	44 (21)/22 (10)	5.9	4.8
Intermediate lifestyle	117 (36)/127 (37)	66 (32)/70 (32)	4.6	3.5
Favorable lifestyle	90 (28)/118 (34)	98 (47)/127 (58)	3.3	2.4