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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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Abstract

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 (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.

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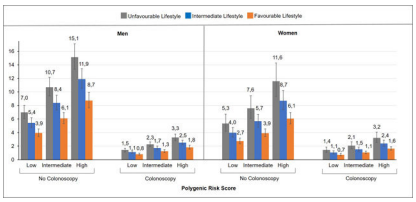
Registration: This observational study has been registered in the German Clinical Trials Register (DRKS00011793), which is a primary registry in the WHO Registry Network.

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 y 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% and 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% and women, 0.9%–4.2%). Among all risk factor profiles, the 30-y 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.

Graphical Abstract



Keywords

colon cancer; epidemiology; food; exercise

Introduction

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer related death worldwide[1]. It is a complex disease with both genetic and lifestyle factors contributing to individual risk of CRC[2, 3]. Including the most recent genome-wide association studies (GWAS), more than 90 independent loci have been identified that are associated with the risk of CRC[4–16]. 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[15, 17]. 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[15].

In addition to the genetic susceptibility of CRC, there is well established evidence that lifestyle factors such as smoking[18], alcohol consumption[19], poor diet[20–24], physical inactivity[25], and body fatness[26, 27] are risk factors for CRC. Using data from a large population based case-control study, we previously found that a healthy lifestyle score including five potentially modifiable lifestyle factors (non-smoking, moderate alcohol consumption, a healthy diet, physical activity, and a healthy weight) was associated with

lower risk of CRC and risk further decreased with increasing adherence to the healthy lifestyle score[28]. Moreover, we found that adherence to healthy lifestyle reduced the risk of CRC, similarly in participants with higher and lower polygenic risk scores.

Though 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[29], 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 & Methods

Study design and study population

The DACHS study (Darmkrebs: Chancen der Verhütung durch Screening) is an ongoing population-based case-control study conducted in southwest Germany since 2003. This analysis includes patients and controls recruited until 2016. Details of the DACHS study have been reported previously[30, 31]. Briefly, patients with a histologically confirmed, first diagnosis of CRC (International Classification of Diseases, 10th Revision [ICD-10] 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 about one 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 centre in the routine setting. Community-based controls are randomly selected from population registries 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 interview with trained interviewers who collected information on patients' socio-demographic, medical and lifestyle history using a standardized questionnaire. In addition, we collected hospital discharge letters and pathology reports for all cases. 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. Controls were contacted by the study

centre 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, as 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 five lifestyle factors (smoking, alcohol consumption, diet, physical activity and BMI) based on a priori knowledge of the risk factors for CRC[18–26, 32–34]. 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[28].

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 most 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[2]. No linkage disequilibrium criterion was employed for generating the polygenic risk score given the pre-defined SNP set, however, checks revealed no high linkage disequilibrium (D'≥0.95) between any SNPs in our dataset. Out of the reported 95 SNPs, a total of 90 SNPs could be extracted from our dataset. The polygenic risk score was calculated as the sum of risk alleles as reported by Huyghe et al[2].

Information on colonoscopy

Endoscopies prior to diagnosis of CRC (excluding those leading to the current diagnosis) (cases) or before the interview (controls) were assessed in detail during the interviews. We requested endoscopy and histology reports from the respective physicians for up to three 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[35]. 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 which 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[36].

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-square 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 three categories: favourable lifestyle (at least four of the five healthy lifestyle factors), intermediate (three healthy lifestyle factors), or unfavourable (zero, one or two healthy lifestyle factors), and the polygenic risk score was modelled as a categorical variable in tertiles (low, intermediate, and high genetic risk).

To replicate our findings published previously[28], we performed analyses on the healthy lifestyle score stratified by polygenic risk score, using this expanded dataset (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[28].

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 modelling described by Freedman et al[37] and Pfeiffer and Petracci[38], 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[39], 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 pre-specified time interval (here: 30 years) given a person's age and risk factors (healthy lifestyle score, polygenic risk score and colonoscopy status). Exact details of the calculations are provided in the Supplementary Methods. In sensitivity analyses, we recalculated the absolute risks using different RRs for colonoscopy history: 1. the estimate reported in a meta-analysis on screening colonoscopy[29], OR=0.33, for both men and women; 2. an estimate closer to findings of a large cohort study[40], 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 software version 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical tests were two-sided, with an alpha level of 0.05.

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 cases and controls 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, have a higher BMI, were less likely to have had a colonoscopy in the preceding 10 years, and were less likely 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 NSAIDs. Males 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 cases: 86.8; median controls: 84.9) (Table 1).

Association of adherence to a healthy lifestyle, polygenic risk score and colonoscopy with CRC 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[30, 36](Table 2).

Association of adherence to a healthy lifestyle and risk of CRC according to polygenic risk score

Among both men and women, multivariable analyses revealed that within each tertile of the polygenic risk score, participants with more favourable lifestyle had a lower risk of CRC (Supplementary Table 2). 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 two groups of the polygenic risk score as published previously[28] and found similar results (Supplementary Table 3). Similar results were also seen when we stratified by tertiles of polygenic risk score (Supplementary Table 4).

Absolute risk estimates for CRC 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, a 50-year-old male, with a high polygenic risk score, an unfavourable 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 male 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 male with a favourable 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 female, with the highest risk profile (high genetic risk, unfavourable 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 (5.5%, 95% CI 4.8%-6.3%), and with colonoscopy, the 30 year absolute risk of CRC was estimated to be 2.1% only (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 male, with a low genetic risk, favourable 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 female, with a low genetic risk, favourable 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 5, Supplementary Figure 1).

Discussion

Using data from a large epidemiological 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 three 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 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[28, 41–46], but we present for the first time 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[28]. 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, while 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 three 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, 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[29]. Since most sporadic CRCs develop slowly over many years, the precursor lesions, adenomas and serrated polyps, can be detected and removed by colonoscopy[47]. Based on the current available evidence, most national and international screening guidelines therefore recommend beginning CRC screening at age 50 in average risk adults[48, 49]. In this large study, we only considered history of colonoscopy although stool based tests for blood (the guaiac based faecal occult blood test [gFOBT] and the faecal immunochemical test [FIT]) were also used for CRC screening. In some countries however, stool-based tests are used as the primary screening tests (for example in the UK and the Netherlands)[50]. Still, as we did not differentiate by indication for colonoscopy in this study, our results refer to colonoscopies for any reason, including those to follow up positive stool tests. 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 US[40], 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 unfavourable and favourable 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 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 US[51]. 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 higher risk patients (even without knowledge of the genetic risk).

Our study also has some limitations. Firstly, since 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 behaviour may change over a person's lifetime. Therefore, we cannot conclude how an individual's absolute risk may change if they make healthier lifestyle choices. Secondly, 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[37] or breast cancer[52, 53] our estimates could be subject to recall bias. The ascertainment of lifestyle was based on 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 controls. 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 due to lack of information on diet and genetic risk score. These participants were slightly older (70.7 years vs 68.5 years) and reported less often participation in health check-ups (74.2% vs 91.9%), which would result in some overestimation of the healthy lifestyle effect. However, on the other hand, it is possible that due to 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[35], but since 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 three 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

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BMI	body mass index
CI	confidence interval
CRC	colorectal cancer
DACHS	Darmkrebs: Chancen der Verhütung durch Screening
FFQ	food frequency questionnaire
GWAS	genome-wide association studies
ICD-10	International Classification of Diseases, 10th Revision
NSAIDs	nonsteroidal anti-inflammatory drugs
OR	odds ratio
SNPs	single nucleotide polymorphisms

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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.

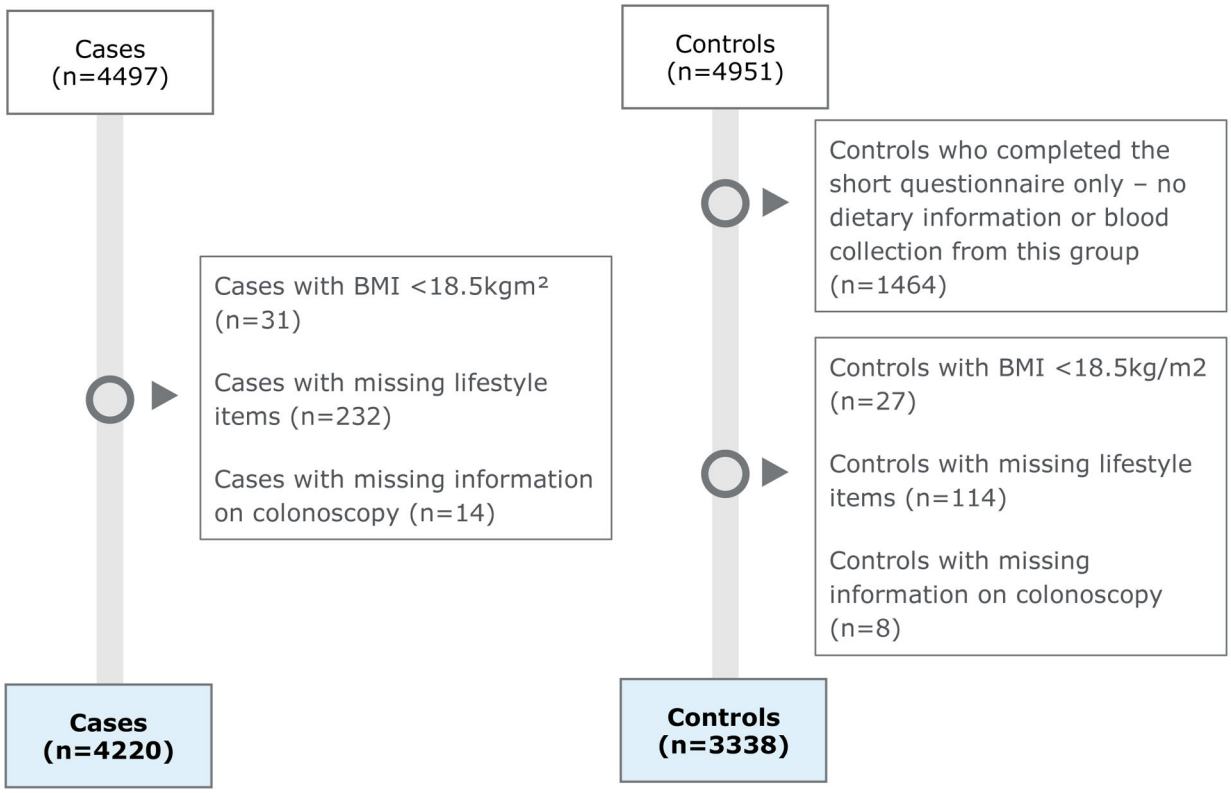

Figure 1.
Study participants

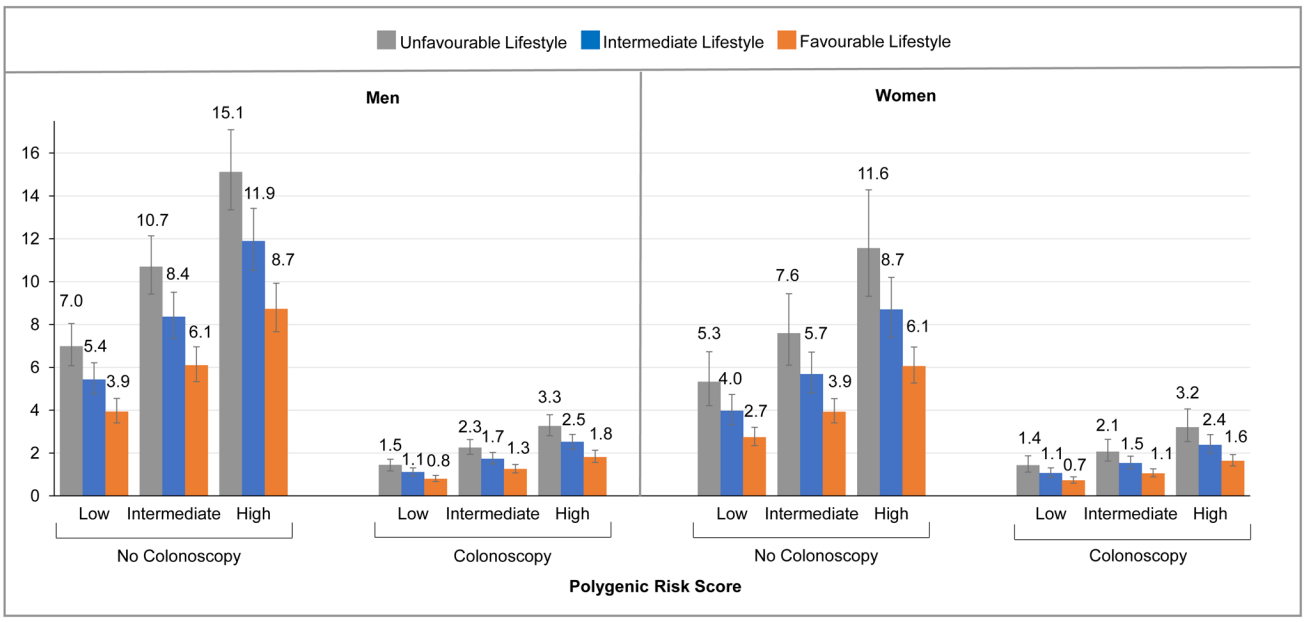

Figure 2.

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

Table 1.

Baseline characteristics of participants by case and control status.

Characteristics	Total N=7558	Cases N=4220	Controls N=3338	P value
Sex				
Female	2912 (38.5)	1636 (38.8)	1276 (38.2)	-
Male	4646 (61.5)	2584 (61.2)	2062 (61.7)	
Age				
Range	30–102	30–96	33–102	-
Mean, (SD)	68.4 (10.6)	68.3 (10.7)	68.5 (10.5)	
Education[1]				
≤9 years	4687 (62.1)	2795 (66.4)	1892 (56.8)	
10–11 years	1410 (18.7)	728 (17.3)	682 (20.5)	<0.0001
≥12 years	1447 (19.2)	689 (16.4)	758 (22.8)	
Smoking status				
Current or former smokers	1558 (20.6)	949 (22.5)	609 (18.2)	<0.0001
Alcohol consumption, g/day, mean				
Women	5.4	5.2	5.7	0.11
Men	21.2	22.5	19.5	<0.0001
Dietary quality score*, mean	31.2	30.5	32.2	<0.0001
Leisure time physical activity, MET-h/week, mean	42.9	40.3	46.2	<0.0001
BMI, kg/m^2, mean	26.9	27.3	26.4	<0.0001
1st degree family history of CRC[2]				
Yes	971 (12.9)	616 (14.6)	355 (10.6)	<0.0001
Colonoscopy in the preceding 10 years				
Yes	2840 (37.6)	1140 (27.0)	1700 (50.9)	<0.0001
Participation in a health check up[3]				
Yes	6624 (88.0)	3569 (84.9)	3055 (91.9)	<0.0001
NSAIDs[4]				
Yes	2184 (29.3)	1072 (25.8)	1112 (33.7)	<0.0001
Healthy lifestyle score				
Unfavourable lifestyle (0 or 1 or 2 factors)	2053 (27.2)	1321 (31.3)	732 (21.9)	
Intermediate lifestyle (3 factors)	2633 (34.8)	1504 (35.6)	1129 (33.8)	<0.0001
Favourable lifestyle (4 or 5 factors)	2872 (38.0)	1395 (33.1)	1477 (44.2)	
Polygenic risk score				
Low (T1)	2015 (26.7)	901 (21.4)	1114 (33.4)	
Intermediate (T2)	2506 (33.2)	1368 (32.4)	1138 (34.1)	<0.0001
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)	

Abbreviations: MET, metabolic equivalent of task; BMI, body mass index; CRC, colorectal cancer; NSAIDs, non-steroidal anti-inflammatory drug;

[1] Data missing for 14 participants;

[2] Data missing for 6 participants;

[3] Data missing for 32 participants;

[4] Data missing for 93 participants;

[*] Diet quality score max 50 points

Table 2.

Odds ratios of risk factors associated with colorectal cancer risk stratified by sex

	Cases n(%)/Controls n(%)		OR (95% CI)	
	Men	**Women**	**Men**	**Women**
Healthy lifestyle score				
Unfavourable 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)
Favourable 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)71073(52)	444(27)7627(49)	0.34 (0.30–0.39)	0.38 (0.32–0.44)

Abbreviations: OR, odds ratio; CI, confidence interval;

[1]The logistic regression models included age, healthy lifestyle score, polygenic risk score and colonoscopy in the preceding 10 years

Table 3.

30-year absolute risk estimates of colorectal cancer for 50-year-old men and women

Subgroup	Cases n(%)/Controls n(%)		30 Year Risk, % (95% CI)	
	Men	Women	Men	Women
No colonoscopy				
Low genetic risk				
Unfavourable 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)
Favourable lifestyle	87(21)/134(39)	123(47)/143(64)	3.5 (3.0–4.0)	2.5 (2.1–2.9)
Intermediate genetic risk				
Unfavourable 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)
Favourable lifestyle	153(24)/108(33)	156(43)/126(56)	5.3 (4.7–6.1)	3.6 (3.1–4.2)
High genetic risk				
Unfavourable 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)
Favourable 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				
Unfavourable 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)
Favourable lifestyle	35(24)/129(36)	42(51)/107(55)	1.2 (1.0–1.4)	0.9 (0.8–1.1)
Intermediate genetic risk				
Unfavourable 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)
Favourable lifestyle	67(30)/138(37)	88(57)/129(60)	1.9 (1.6–2.1)	1.4 (1.2–1.6)
High genetic risk				
Unfavourable 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)
Favourable lifestyle	90(28)7118(34)	98(47)7127(58)	2.6 (2.3–3.1)	2.1 (1.8–2.4)

Abbreviations: CI, confidence interval