Alcohol consumption, polygenic risk score, and early- and late-onset colorectal cancer risk

Xuechen Chen,[a,b] Hengjing Li,[a,b] Feng Guo,[a] Michael Hoffmeister,[a] and Hermann Brenner[a,c,d,]*

[a]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany
[b]Medical Faculty Heidelberg, Heidelberg University, Heidelberg, Germany
[c]German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Heidelberg, Germany
[d]Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Im Neuenheimer Feld 460, Heidelberg, Germany

eClinicalMedicine 2022;49: 101460
Published online xxx
https://doi.org/10.1016/j.eclinm.2022.101460

Summary

Background Evidence is lacking on the impact of alcohol consumption on colorectal cancer (CRC) risk (overall and by age at diagnosis) by polygenic risk score (PRS) levels, and it is unclear how the magnitude of CRC risk associated with alcohol consumption compares to the magnitude of genetically determined risk.

Methods Multiple logistic regression was used to assess the association between alcohol consumption and colorectal cancer (CRC) across PRS levels based on 140 CRC-related loci among 5104 CRC cases and 4131 controls from a large population-based case-control study. We compared the effects for alcohol consumption and PRS on CRC risk using the "Genetic Risk Equivalent (GRE)" for effective risk communication. Specific analyses were conducted for early-onset CRC (EOCRC, <55 years) and late-onset CRC (LOCRC, ≥55 years).

Findings High alcohol consumption, and to a lower extent, also alcohol abstinence were associated with increased CRC risk. Compared to low alcohol consumption (0·1-<25 g/d), lifetime average alcohol consumption ≥25 g/d was more strongly associated with EOCRC [odds ratio (OR) 1·8, 95% confidence interval (CI) 1·2−2·8] than with LOCRC risk (OR 1·3, 95% CI 1·1−1·4) (*P*-value for interaction with age =0·011). Interactions between alcohol consumption and PRS did not reach statistical significance for either EOCRC or LOCRC risk. The estimated impact of high lifetime alcohol consumption on EOCRC was equivalent to the effect of having 47 percentiles higher PRS (GRE 47, 95% CI 12−82), stronger than the impact on LOCRC (GRE 18, 95% CI 8−29).

Interpretation Excessive alcohol use was strongly associated with EOCRC risk, independent of PRS levels. Abstaining from heavy drinking could reduce risk for CRC, in particular for EOCRC to an extent that would be equivalent to having a much lower genetically determined risk.

Funding The first author (X.C.) was supported by the Guangzhou Elite Project (GEP). The DACHS study was supported by grants from the German Research Council (BR 1704/6−1, BR1704/6−3, BR 1704/6−4, BR 1704/6−6, CH 117/1−1, BR 1704/17−1, HO 5117/2−1) and the German Federal Ministry of Education and Research (01KH0404, 01ER0814, 01ER0815, 01GL1712).

Keywords: Early-onset colorectal cancer; Late-onset colorectal cancer; Alcohol consumption; Polygenic risk score; Genetic risk equivalentt

Introduction

Despite a significant decline in colorectal cancer (CRC) incidence among adults aged ≥50 years, many countries, in particular high-income countries, are now experiencing an increasing incidence of early-onset CRC (EOCRC).[1,2] Evidence has suggested distinct environmental and genetic risk factors and clinicopathological features of EOCRC and late-onset CRC (LOCRC).[3−5]

Excessive alcohol consumption is one of well-established risk factors for CRC[6−9] and has also been

Abbreviations: CI, confidence interval; CRC, colorectal cancer; DACHS, Darmkrebs: Chancen der Verhütung durch Screening; EOCRC, early-onset colorectal cancer; GRE, genetic risk equivalent; GWAS, genome-wide association study; LOCRC, late-onset colorectal cancer; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PRS, polygenic risk score; SNP, single nucleotide polymorphisms

*Corresponding author at: Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany.
E-mail address: h.brenner@dkfz-heidelberg.de (H. Brenner).

Research in context

Evidence before this study

We searched PubMed in title and abstract using keywords "((genome-wide association study) OR (polygenic risk score) OR (genetic risk score)) AND (colorectal cancer)", " (alcohol) AND (colorectal cancer)", "((early-onset) OR (young-onset) OR (late-onset)) AND (colorectal cancer)" during the period of Jan 1,1996 to Apr 1, 2022. Alcohol is one of best-established risk factors for colorectal cancer (CRC) and has also been suggested to increase early-onset CRC (EOCRC) risk, but little is known about its potential interaction with polygenic risk for CRC, which is of high relevance for enhanced risk stratification and targeted efforts of prevention. Latter require effective risk communication, which is difficult to achieve with traditional epidemiological metrics.

Added value of this study

We conducted a thorough analysis of the role of both lifetime and more recent alcohol consumption for overall CRC risk, EOCRC risk, and late-onset CRC (LOCRC) risk by polygenic risk score (PRS) levels, and compared its effect with the effect of genetic predisposition, for the first time, using the recently developed metric of "genetic risk equivalent". In our study, the association between heavy drinking and CRC risk was particularly strong for EOCRC, and this association was independent of genetic risk. The 85% increase in risk of EOCRC by heavy drinking was equivalent to the risk increase of having 47 percentiles higher PRS, which, conversely, can be interpreted as abstaining from heavy drinking could reduce risk of CRC, in particular risk of EOCRC, to an extent that would be equivalent to having a much lower genetically determined risk.

Implications of all the available evidence

This study contributes to enhanced quantification and communication of alcohol related CRC risk, especially EOCRC risk. The results underline the importance of enhanced efforts to prevent heavy drinking in adolescence and young adulthood and may support those efforts by enhanced risk communication. Further studies are needed to derive more precise estimates of the impact of various patterns of alcohol consumption in combination with PRS, other lifestyle factors, and comorbidities across various ethnic groups in the total population and young adults in particular.

suggested to increase EOCRC risk.[10–12] The causality underlying these observed associations has also been studied previously in Mendelian randomization studies which support a role of alcohol intake in CRC carcinogenesis.[13,14] Several studies have examined interactions of CRC-related single nucleotide polymorphisms (SNPs) identified in genome-wide association studies (GWASs) with environmental risk factors on CRC risk, but evidence of gene-environment interaction has remained limited.[15–18] Pertinent studies often suffer from the weak effects of single genetic variants and limited power, in particular given the need of adjustment for multiple testing. Statistical power might be much higher for analyses of interactions of environmental factors with integrative genetic metrics such as polygenic risk scores (PRS) that are based on multiple disease-related loci.[19] However, evidence is lacking on potentially differential associations of alcohol intake with CRC risk (overall and by age at diagnosis) across PRS levels. Such evidence could though be of high relevance for enhanced risk stratification and targeted efforts of prevention. Furthermore, it could be useful to compare the effects of reduced alcohol drinking to effects of predetermined genetic risk which may be helpful for effective risk communication.

The aims of this study were therefore to comprehensively assess associations of alcohol consumption with the overall CRC risk, EOCRC risk, and LOCRC risk at different levels of PRS, and to quantify the impact of alcohol drinking using the recently developed metric "Genetic Risk Equivalent (GRE)", which may help to compare risks from environmental and genetic factors and support effective communication in practice.[20–22]

Methods

Study design and study population

This study was based on CRC patients and control participants recruited within DACHS (Darmkrebs: Chancen der Verhütung durch Screening [German]) study, a large ongoing population-based case-control study on CRC in the Rhine-Neckar region in southwest Germany. The DACHS study was approved by the ethics committee of the Heidelberg Medical Faculty of Heidelberg University (protocol code 310/2001, date of approval 06.12.2001) and the state medical boards of Baden-Wuerttemberg (protocol code M-198–02, date of approval 08.01.2003) and Rhineland-Palatinate [protocol code 837.419.02 (3637), date of approval 30.12.2002]. Written informed consent was obtained from each participant. Details of the design of the DACHS study are provided in the Supplementary Text.

Assessment of alcohol consumption

Participants were asked about how many portions of beer (0·33 L), wine (0·25 L), and liquor (0·02 L) they consumed on average per week at each decade of life from age 20 until the time of interview (controls) or diagnosis (cases). According to food composition tables, 100 mL of beer, wine, and liquor on average contain 4, 8·6, and 33 g of pure ethanol.[23] Thus, standard portions of beer (330 ml), wine (250 ml), or liquor (20 ml) in the study region were assumed to contain 13·2 g, 21·5 g, and

6·6 g of pure ethanol. The mean daily doses at respective time points were derived from reported average alcohol consumption per week divided by 7 days. Lifetime average alcohol consumption was calculated using information from all decades. Latest alcohol consumption was calculated using information from the most recent decennial age preceding the participants' age. For example, information from age 60 was used for participants aged 60–69. Alcohol consumption was categorized into five groups with consistent cut-off points: none: 0 g/d; low: 0-<12 g/d adherent to the low-risk alcohol recommendation in Germany[24]; low-moderate: 12-<25 g/d; moderate-high: 25-<50 g/d; high: ≥50 g/d. In the association analyses by age at diagnosis/interview, sex, cancer location and stage, we regrouped them into three groups: 0 g/d, 0·1-<25 g/d, and ≥25 g/d allowing a reasonable sample size in each category.

Derivation of the polygenic risk score

Information about genotyping and imputation of missing genotypes for the study population is summarized in Supplementary Table S1. The PRS, based on 140 genetic variants (Supplementary Table S2) identified to be associated with CRC risk in populations of European descent in a recent GWAS (~120,000 participants which also included 6400 samples (5%) from the DACHS study),[25] was calculated as the sum of risk alleles of the respective variants (0, 1, or 2 copies of the risk allele for genotyped SNPs; imputed dosages for imputed SNPs). For comparison, we additionally calculated a weighted PRS which summed up all risk alleles with weights equal to the log of OR of the respective SNP and compared the association of unweighted and weighted PRS with CRC risk. Since associations of the weighted and unweighted results with CRC risk were very similar (Supplementary Table S3), we adopted the unweighted PRS in all further analyses.

Statistical analysis

First, we excluded participants without records of alcohol consumption in all decades. The proportion of missings was very small (0.4% among both cases and controls), and hence any potential impact of deviation from missingness at random would be expected to be very small. Then distribution of characteristics of the study population was assessed by descriptive analyses and compared between cases and controls, and also between EOCRC cases and LOCRC cases, using the Chi-square tests. Besides, we described the average alcohol consumption, overall and by specific beverages, separately for men and women for various decades of life in case and control groups.

Multiple logistic regression was used to assess the association between alcohol consumption and the overall CRC risk. Model 1 was adjusted for age (at diagnosis/interview) and sex. Model 2 was additionally adjusted for education, body mass index approximately 10 years before enrolment, lifetime average physical activity, smoking, red meat consumption within the past 12 months, history of colonoscopy, history of diabetes, history of cardiovascular disease including heart failure, myocardial infarction, angina pectoris, or stroke, family history of CRC in a first-degree relative, regular use of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥2 times/week for at least one year, current use of statins ≥1 time/week, and PRS (continuous variable). Detailed definitions of covariates are presented in Table 1. We then assessed the association by sex accounting for potential gender differences in alcohol consumption. Interactions on CRC risk were tested by additionally including a cross-product term of alcohol consumption and PRS in logistic regression models. In addition, dose-response relationships between alcohol consumption and CRC risk were modeled using restricted cubic splines.[26]

We explored the potentially differential effects of alcohol consumption with CRC risk between participants with low (below median of PRS among controls) and high (above median of PRS among controls) PRS using low alcohol consumption as the reference group. We also assessed the joint effects of alcohol consumption with PRS levels on CRC risk using low alcohol consumption in the low PRS subgroup as the uniform reference group. Individual associations of PRS with CRC risk, overall and by age of diagnosis, were also evaluated.

Similar associations analyses described above were conducted to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations of alcohol consumption with EOCRC and LOCRC risk adjusted for variables in model 2. There is no clear threshold age for defining EOCRC or LOCRC. Most studies have used 50 years according to the minimum age for CRC screening recommended in most countries' guidelines.[27] We extended this cut-off age to 55 years allowing an adequate number of cases in the younger population for our analyses. Interactions of PRS (or alcohol consumption) with age (binary variable) were tested by adding a cross-product terms of respective variables in regression models. We also carried out analyses using 50 years as the cut-off and provided results in Supplementary Table S4 to enable comparison of results with those from other studies using a cut-off at age 50.

ORs for CRC risk were also estimated by beverage types. In this analysis, we categorized participants into three subgroups according to consumption of different beverage types with the same cutoff points at 0 and 7 g/d to make the results comparable and to allow a reasonable sample size in each category. Seven grams of pure ethanol correspond to approximately 1/3 portion of beer, 1/2 portion of wine, and one portion of liquor in our study.[23] Furthermore, we assessed site-specific (proximal/distal) and stage-specific (stages I-III/stage IV) CRC risk.

Characteristics	Cases *N* (%)	Controls *N* (%)	*P*-values[g]
Total	5104	4131	
Sex			
Male	3076 (60·3)	2542 (61·5)	
Age (year)			
Median (Q1, Q3)	69 (62, 76)	70 (62, 76)	
Education (year)			
<9	3332 (65·3)	2280 (55·2)	
9—10	904 (17·7)	873 (21·1)	<0·0001
>10	859 (16·8)	972 (23·5)	
Lifetime average alcohol consumption (g/d)[a]			
None	905 (17·7)	614 (14·9)	
Low	2097 (41·1)	1894 (45·8)	
Low-moderate	1004 (19·7)	899 (21·8)	<0·0001
Moderate-high	783 (15·3)	555 (13·4)	
High	315 (6·2)	169 (4·1)	
Latest alcohol consumption (g/d)[a]			
None	1526 (29·9)	1107 (26·8)	
Low	1534 (30·1)	1410 (34·1)	
Low-moderate	951 (18·6)	867 (21·0)	<0·0001
Moderate-high	740 (14·5)	553 (13·4)	
High	353 (6·9)	194 (4·7)	
Smoking status			
Never	2279 (44·7)	2083 (50·4)	
Former	2039 (39·9)	1590 (38·5)	<0·0001
Current	766 (15·0)	447 (10·8)	
Physical activity (MET-hour/week)[b]			
Q1 (≤121·6)	1143 (22·4)	1033 (25·0)	
Q2 (121·7—178·4)	1247 (24·4)	1029 (24·9)	
Q3 (178·5—244·8)	1237 (24·2)	1028 (24·9)	0·0026
Q4 (≥244·9)	1420 (27·8)	1030 (24·9)	
Red meat intake[c]			
<1 time per week	409 (8·0)	471 (11·4)	
≥1 time per week and <1 time per day	4454 (87·3)	3514 (85·1)	<0·0001
≥1 time per day	233 (4·6)	143 (3·5)	
BMI (kg/m^2, 10 years before enrolment)			
<25	1534 (30·1)	1569 (38·0)	
25-<30	2364 (46·3)	1880 (45·5)	<0·0001
≥30	1139 (22·3)	650 (15·7)	
History of diabetes	970 (19·0)	558 (13·5)	<0·0001
History of cardiovascular disease[d]	1214 (23·8)	1004 (24·3)	·58
Family history of colorectal cancer in a first-degree relative	741 (14·5)	451 (10·9)	<0·0001
Use of NSAIDs[e]	1453 (28·5)	1570 (38·0)	<0·0001
Use of statins[f]	874 (17·1)	924 (22·4)	<0·0001
History of colonoscopy	1356 (26·6)	2490 (60·3)	<0·0001

***Table 1*: Distribution of characteristics in colorectal cancer patients and controls.**

NOTE: Missing values for cases/controls: education 9/6, smoking 20/11, physical activity 57/11, red meat intake 8/3, body mass index 67/32, history of diabetes 7/5, history of cardiovascular disease 3/2, family history of colorectal cancer in a first-degree relative 3/3, use of statins 2/5.

[a]Measured in gram ethanol. None: 0 g/d; Low: 0-<12 g/d; Low-moderate: 12-<25 g/d; Moderate-high: 25-<50 g/d; High: ≥50 g/d. Information from all decades were used to calculate lifetime average alcohol consumption. Information from the most recent decennial age preceding the participants' age was used to derive the latest alcohol consumption (e.g., for patients aged 60—69, information from age 60 was used).

[b]Lifetime average physical activity, measured in MET-hour/week and categorized according to the distribution of physical activity among controls.

[c]Consumption of red meat in the previous 12 months.

[d]History of heart failure, myocardial infarction, angina pectoris, or stroke.

[e]Defined as taking NSAIDs (including aspirin) at least 2 times a week for at least 1 year.

[f]Defined as current use of statins more than once a week.

[g]*P*-values were not reported for the matching factors age and sex.

Abbreviation: BMI, body mass index; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug; Q, quartile.

GREs were calculated as the ratio of coefficients for alcohol consumption categories and PRS percentiles from logistic regression models, providing an estimate of alcohol impact in terms of the equivalent difference in background genetic risk. Details of the derivation of GREs have been published recently,[20–22] and described specifically for this study in the Supplementary Text.

All analyses were performed with the R software, version 4.0.3. Two-sided *P*-values less than 0·05 were considered statistically significant.

Role of the funding source

The sponsors had no role in the study design and in the collection, analysis, interpretation of data, preparation of the manuscript, and decision to submit the paper for publication. All authors had full access to dataset used in this study and took the decision to submit for publication.

Results

Characteristics of study population

In total, 5104 cases with CRC (571 cases aged <55 years) and 4131 controls (417 controls aged <55 years) were included in our analysis after excluding participants (20 cases and 17 controls) with missing values of alcohol consumption in all decades (Supplementary Fig. S1). Descriptive characteristics of cases and controls are presented in Table 1. 60·3% of cases and 61·5% of controls were men, and the median age for cases and controls was 69 years and 70 years, respectively. Cases more often had a lower level of education, were heavy drinkers, abstainers, or current smokers, were overweight or obese, and had a history of diabetes or family history of CRC in a first-degree relative, when compared to controls. They less frequently used NSAIDs or statins, and less frequently had a previous colonoscopy. Baseline characteristics of cases also varied by age of diagnosis (<55/≥55 years). Details of comparison of characteristics between early- and late-onset CRC are presented in Supplementary Table S5. Detailed information on alcohol consumption over various decades of life is provided in Supplementary Fig. S2 and Supplementary Table S6, and described in the Supplementary Text.

Association of alcohol consumption and polygenic risk score with the overall CRC risk

Since ORs of different alcohol consumption categories with CRC risk did not vary by sex (*P*-value for the interaction of lifetime and latest alcohol consumption with sex was 0·57 and 0·055, respectively, Supplementary Table S7), we combined both sexes in the following analyses. After adjustment for multiple covariates, lifetime abstaining, moderate-high, and high alcohol consumption were significantly associated with a 16%, 22%, and 51% higher risk of CRC when compared to lifetime low alcohol consumption (Table 2). Very similar associations with CRC risk were seen for the latest alcohol consumption. The interaction between alcohol

Alcohol consumption (g/d)	Cases *N* (%)	Controls *N* (%)	Model 1[a] OR (95%CI)	Model 2[b] OR (95% CI)
Lifetime average alcohol consumption				
None	853 (17·3)	603 (14·9)	1·27 (1·12, 1·44)	1·16 (1·01, 1·34)
Low	2028 (41·1)	1858 (45·8)	Ref.	Ref.
Low-moderate	981 (19·9)	878 (21·7)	1·05 (0·94, 1·18)	0·98 (0·86, 1·11)
Moderate-high	768 (15·5)	552 (13·6)	1·32 (1·15, 1·50)	1·22 (1·05, 1·42)
High	309 (6·3)	164 (4·0)	1·79 (1·46, 2·20)	1·51 (1·20, 1·90)
P-interaction[c]				0·69/0·30
Latest alcohol consumption				
None	1446 (29·3)	1086 (26·8)	1·23 (1·11, 1·37)	1·09 (0·97, 1·23)
Low	1491 (30·2)	1386 (34·2)	Ref.	Ref.
Low-moderate	923 (18·7)	846 (20·9)	1·03 (0·91, 1·16)	1·01 (0·88, 1·15)
Moderate-high	732 (14·8)	544 (13·4)	1·28 (1·12, 1·47)	1·21 (1·04, 1·41)
High	347 (7·0)	193 (4·8)	1·72 (1·42, 2·09)	1·48 (1·19, 1·84)
P-interaction[c]				0·88/0·49

***Table 2*: Association of alcohol consumption with colorectal cancer risk.**

[a]Adjusted for age and sex.

[b]Additionally adjusted for education, body mass index, physical activity, smoking, red meat intake, history of colonoscopy, history of diabetes, history of cardiovascular disease, family history of colorectal cancer in a first-degree relative, use of statins, use of nonsteroidal anti-inflammatory drugs, and polygenic risk score (continuous variable).

[c]Interactions were tested by additionally including a cross-product term of polygenic risk score (continuous variable) and alcohol consumption (categorical/continuous) in models.

Abbreviation: CI, confidence interval; OR, odds ratio; Ref., reference.

consumption (categorical/continuous) and the PRS levels did not reach statistical significance. Results of dose-response analyses are shown in Supplementary Fig. S3, suggesting a J-shaped dose-response relationship between alcohol intake and CRC risk.

Dose-response relationships between alcohol consumption and CRC risk were similar among participants with low and high PRS (Supplementary Table S8). Lifetime abstaining, low, low-moderate, moderate-high, and high alcohol consumption in the high PRS group were associated with a 2·1-, 1·7-, 1·8-, 2·2-, and 2·6-fold increased risk of CRC, respectively, when compared to low lifetime alcohol consumption in the low PRS group (Supplementary Fig. S4). Again, very similar associations were seen for the latest alcohol consumption. As for individual effects of PRS on CRC risk, high PRS was significantly associated with 1.9-fold increased risk of CRC, EOCRC, or LOCRC when compared to low PRS level (Supplementary Table S9).

Association of alcohol consumption and polygenic risk score with EOCRC and LOCRC

We observed significant differences in associations between lifetime average alcohol consumption and CRC risk by age (Table 3). Lifetime average alcohol consumption ≥25 g/d was associated with 1·8-fold (95% CI 1·2−2·8) increased risk of EOCRC, stronger than the association with LOCRC (OR 1·3, 95% CI 1·1−1·4) (*P*-value for interaction with age on CRC risk =0·011, false discovery rate adjusted p-value =0.066), while we did not observe differential associations for the latest alcohol consumption. Interactions between alcohol consumption and PRS on either EOCRC or LOCRC risk likewise did not reach statistical significance. Stronger associations between alcohol consumption and EOCRC risk were also observed when we used 50 years as the cut-off year, even though the interaction between alcohol consumption and age on CRC risk did not reach statistical significance (*P*-value for interaction with age was 0.18 and 0.43, respectively, for lifetime or latest alcohol consumption, Supplementary Table S4). We likewise found an independent contribution of PRS and alcohol consumption to both EOCRC risk (<50 years) and LOCRC risk (≥50 years).

PRS was independently associated with both EOCRC and LOCRC, with highest risks seen among heavy drinkers with high PRS (Table 4). Compared to participants with low PRS and low alcohol consumption (0·1-<25 g/d), those who had a high PRS and drank heavily over life (≥25 g/d) had a 3.4-fold (95% CI 2.0−6.0) increased risk of EOCRC but a 2.3-fold (95% CI 2.0−2.8) increased risk of LOCRC. A similar pattern was observed for the latest alcohol consumption.

Age at diagnosis/interview	Alcohol consumption (g/d)	Cases *N* (%)	Controls *N* (%)	OR (95%CI)[a]	*P*-interaction Alcohol consumption × PRS[b]
<55 years	Lifetime average alcohol consumption				0·72
	0	108 (19·2)	89 (21·7)	0·89 (0·62, 1·28)	
	0·1-< 25	331 (58·8)	269 (65·5)	Ref.	
	≥25	124 (22·0)	53 (12·9)	1·84 (1·22, 2·79)	
	Latest alcohol consumption				0·74
	0	166 (29·5)	122 (29·7)	1·03 (0·74, 1·42)	
	0·1-< 25	303 (53·8)	236 (57·4)	Ref.	
	≥25	94 (16·7)	53 (12·9)	1·37 (0·90, 2·11)	
≥55 years	Lifetime average alcohol consumption				0·75
	0	745 (17·0)	514 (14·1)	1·22 (1·06, 1·42)	
	0·1-< 25	2678 (61·2)	2467 (67·7)	Ref.	
	≥25	953 (21·8)	663 (18·2)	1·26 (1·11, 1·44)	
	Latest alcohol consumption				0·85
	0	1280 (29·3)	964 (26·5)	1·09 (0·97, 1·23)	
	0·1-< 25	2111 (48·2)	1996 (54·8)	Ref.	
	≥25	985 (22·5)	684 (18·8)	1·28 (1·12, 1·46)	
P-interaction (alcohol consumption × age)[c] = 0·011/0·68					

***Table 3*: Association of alcohol consumption with early- and late-onset colorectal cancer.**

[a]Variable in the logistic regression models included age, sex, education, body mass index, physical activity, smoking, red meat intake, history of colonoscopy, history of diabetes, history of cardiovascular disease, family history of colorectal cancer in a first-degree relative, use of statins, use of nonsteroidal anti-inflammatory drugs, lifetime average/latest alcohol consumption, and PRS (continuous variable).

[b]Interactions were tested by including a cross-product term of lifetime average/latest alcohol consumption and PRS (continuous variable) in models.

[c]Interactions were tested by including a cross-product term of lifetime average/latest alcohol consumption and age at diagnosis/interview (binary variable) in models.

Abbreviation: CI, confidence interval; OR, odds ratio; PRS, polygenic risk score; Ref., reference.

Age at diagnosis/interview	PRS[a]	Alcohol consumption (g/d)	Cases *N* (%)	Controls *N* (%)	OR (95% CI)[b]	OR (95% CI)[c]
		Lifetime average alcohol consumption				
<55 years	Low	0	35 (18·9)	44 (22·2)	0·75 (0·42, 1·32)	0·76 (0·44, 1·32)
		0·1-< 25	115 (62·2)	128 (64·6)	Ref.	Ref.
		≥25	35 (18·9)	26 (13·1)	1·54 (0·80, 2·99)	1·44 (0·77, 2·71)
	High	0	73 (19·3)	45 (21·1)	0·95 (0·59, 1·56)	1·61 (0·99, 2·63)
		0·1-< 25	216 (57·1)	141 (66·2)	Ref.	1·67 (1·18, 2·37)
		≥25	89 (23·5)	27 (12·7)	2·09 (1·22, 3·67)	3·44 (2·01, 6·01)
≥55 years	Low	0	255 (16·9)	268 (14·7)	1·14 (0·91, 1·42)	1·19 (0·96, 1·48)
		0·1-< 25	905 (60·1)	1230 (67·3)	Ref.	Ref.
		≥25	346 (23·0)	329 (18·0)	1·34 (1·10, 1·64)	1·33 (1·10, 1·61)
	High	0	490 (17·1)	246 (13·5)	1·30 (1·07, 1·58)	2·35 (1·93, 2·87)
		0·1-< 25	1773 (61·8)	1237 (68·1)	Ref.	1·87 (1·66, 2·12)
		≥25	607 (21·1)	334 (18·4)	1·24 (1·04, 1·48)	2·34 (1·96, 2·80)
P-interaction (PRS × age)[d] = 0·34/0·80						
		Latest alcohol consumption				
<55 years	Low	0	62 (33·5)	63 (31·8)	0·89 (0·54, 1·46)	0·89 (0·55, 1·44)
		0·1-< 25	97 (52·4)	105 (53·0)	Ref.	Ref.
		≥25	26 (14·1)	30 (15·2)	0·89 (0·46, 1·70)	0·89 (0·47, 1·69)
	High	0	104 (27·5)	59 (27·7)	1·11 (0·72, 1·72)	1·77 (1·12, 2·80)
		0·1-< 25	206 (54·5)	131 (61·5)	Ref.	1·58 (1·08, 2·29)
		≥25	68 (18·0)	23 (10·8)	1·97 (1·10, 3·59)	2·92 (1·63, 5·37)
≥55 years	Low	0	446 (29·6)	493 (27·0)	1·05 (0·87, 1·25)	1·08 (0·90, 1·28)
		0·1-< 25	717 (47·6)	992 (54·3)	Ref.	Ref.
		≥25	343 (22·8)	342 (18·7)	1·27 (1·04, 1·56)	1·26 (1·03, 1·53)
	High	0	834 (29·1)	471 (25·9)	1·14 (0·98, 1·34)	2·04 (1·73, 2·40)
		0·1-< 25	1394 (48·6)	1004 (55·3)	Ref.	1·83 (1·60, 2·10)
		≥25	642 (22·4)	342 (18·8)	1·30 (1·09, 1·54)	2·39 (2·00, 2·87)
P-interaction (PRS × age)[d] = 0·33/0·75						

***Table 4*: Association of alcohol consumption with early- and late-onset colorectal cancer by polygenic risk score.**
[a]Participants were categorized into two groups (low=below median, high=above median) according to the median level of PRS among controls.
[b]Adjusted for age, sex, education, body mass index, physical activity, smoking, red meat intake, history of colonoscopy, history of diabetes, history of cardiovascular disease, family history of colorectal cancer in a first-degree relative, use of statins, and use of nonsteroidal anti-inflammatory drugs using participants with 0·1-<25 g/d alcohol consumption as the reference group.
[c]Variables mentioned above were adjusted but using participants with low PRS and 0·1-<25 g/d alcohol consumption as the reference group.
[d]Interactions were tested by including a cross-product term of PRS (continuous/binary variable) and age (binary variable) in models.
Abbreviation: CI, confidence interval; OR, odds ratio; PRS, polygenic risk score; Ref. reference.

Subgroup analyses by beverages types, cancer location, and cancer stage

Long-term wine, beer, and liquor abstaining were significantly associated with a 21%, 23%, and 11% higher risk of CRC when compared to the reference (pure ethanol: 0·1–7 g/d), respectively (Supplementary Table S10). Compared to the same reference group, lifetime high average consumption of alcohol (pure ethanol: >7 g/d) from beer and liquor was significantly associated with 21% and 50% higher CRC risk, respectively, but no risk increase was seen for high alcohol intake from wine. Similar results were obtained according to information on latest alcohol consumption except that the latest alcohol consumption from liquor >7 g/d was rare and the association with CRC risk was not significant and showed wide CIs. In the association analyses by CRC location and stage (Supplementary Table S11), the association of high lifetime alcohol consumption (pure ethanol: ≥25 g/d) with distal CRC risk (OR 1·38, 95% CI 1·20–1·59) seemed to be more pronounced than with proximal colon cancer risk (OR 1·14, 95% CI 0·96–1·35, *P*-heterogeneity=0·015). No statistically significant difference in associations between high alcohol consumption and CRC risk by cancer stage was observed.

GREs estimated for different alcohol consumption categories

The estimated effect of high lifetime alcohol consumption on CRC risk was equivalent to the effect of having 32 (GRE 32, 95% CI 14–50) percentiles higher PRS level (Table 5). The GRE for lifetime average alcohol

Variable	OR (95% CI)[a]	GRE (95% CI)
PRS per 10 percentiles	1·14 (1·12, 1·16)	
Lifetime average alcohol consumption (g/d)		
None	1·17 (1·02, 1·34)	12·0 (1·4, 22·6)
Low	Ref.	Ref.
Low-moderate	0·98 (0·86, 1·11)	−1·5 (−11·3, 8·2)
Moderate-high	1·23 (1·06, 1·42)	15·8 (4·4, 27·2)
High	1·52 (1·21, 1·91)	32·0 (14·2, 49·7)
Latest alcohol consumption (g/d)		
None	1·10 (0·97, 1·24)	7·3 (−1·9, 16·5)
Low	Ref.	Ref.
Low-moderate	1·01 (0·89, 1·15)	0·8 (−9·4, 10·9)
Moderate-high	1·21 (1·04, 1·41)	14·5 (2·9, 26·2)
High	1·49 (1·21, 1·85)	30·4 (13·6, 47·2)

***Table 5*: Genetic risk equivalents for different alcohol consumption categories with colorectal cancer risk.**
[a]Variables in the models included age, sex, education, body mass index, physical activity, smoking, red meat intake, history of colonoscopy, history of diabetes, history of cardiovascular disease, family history of colorectal cancer in a first-degree relative, use of statins, use of nonsteroidal anti-inflammatory drugs, lifetime average/latest alcohol consumption, and PRS (continuous variable, per 10 percentiles).
Abbreviation: CI, confidence interval; GRE, genetic risk equivalent; OR, odds ratio; PRS, polygenic risk score; Ref., reference.

consumption ≥25 g/d was particularly high for EOCRC (GRE 47, 95% CI 12–82), whereas it was less pronounced for LOCRC (GRE 18, 95% CI 8–29) (Figure 1 and Supplementary Table S12). Participants with high lifetime average liquor (>7 g/d) had the highest GRE of 31(95% CI 1–61), when compared to those with low lifetime alcohol consumption from liquor (Supplementary Table S10). The GRE was 15 (95% CI 4–25) for high lifetime average beer (>7 g/d). In addition, the GRE for lifetime average alcohol consumption ≥25 g/d was 23 (95% CI 13–33) for distal CRC risk, higher than that for proximal CRC risk (GRE 11, 95% CI −4 25) (Figure 1 and Supplementary Table S11).

Discussion

In this large population-based study, excessive alcohol consumption, and to a lower extent, also alcohol abstinence was associated with increased CRC risk. Long-term high beer and liquor but not wine consumption was significantly associated with increased CRC risk. The association between heavy drinking and CRC risk was stronger for EOCRC than for LOCRC risk, and more pronounced for distal CRC than for proximal CRC. The independent relationships between alcohol consumption and PRS levels with CRC risk enable more effective risk discrimination, in particular for EOCRC risk, through their joint consideration. Furthermore, the large GRE estimates indicate that the impact of avoiding heavy alcohol consumption on CRC risk could be equivalent to having a substantially lower predetermined polygenic risk.

That high alcohol consumption is associated with a moderately increased risk of CRC has been quite consistently found in previous studies.[6–9] Our results corroborate and extend these findings in demonstrating such associations to be consistent across various levels of genetically determined CRC risk. However, whether there are risk differences in CRC risk between light drinkers and non-drinker is subject to ongoing debate.[6,7,9,28] The inconsistent results could be possibly due to the different definitions of light drinkers. In addition, it has been suggested that the risk difference between abstainers and light drinkers might be due to their different lifestyles. For example, light drinkers might follow a healthier lifestyle than abstainers, and favorable lifestyle factors may mediate the apparent benefits of light alcohol intake. Also, some proportion of the abstainers may abstain from alcohol because of being older, ill, frail, or use of some medications. However, in our study the higher risk of abstainers persisted after comprehensive adjustment for such potential confounders, and it was equally evident for lifelong abstainers (i.e., after excluding abstainers who might have quit alcohol consumption due to health problems). Nevertheless, further large studies with comprehensive ascertainment of the lifetime history of alcohol consumption, other lifestyle factors, and medical conditions, as well as informative biomarkers are needed to more fully explore the potential benefit of drinking low amounts of alcohol.

Although a lower risk of CRC compared to abstaining was observed for low levels of alcohol consumption from all sources (wine, beer, and liquor), an increased risk of CRC at higher consumption levels was observed for beer and liquor only. Again, residual confounding by differences in lifestyle factors, but also substances other than alcohol included in the various alcoholic beverages might account for these differences.[29] For

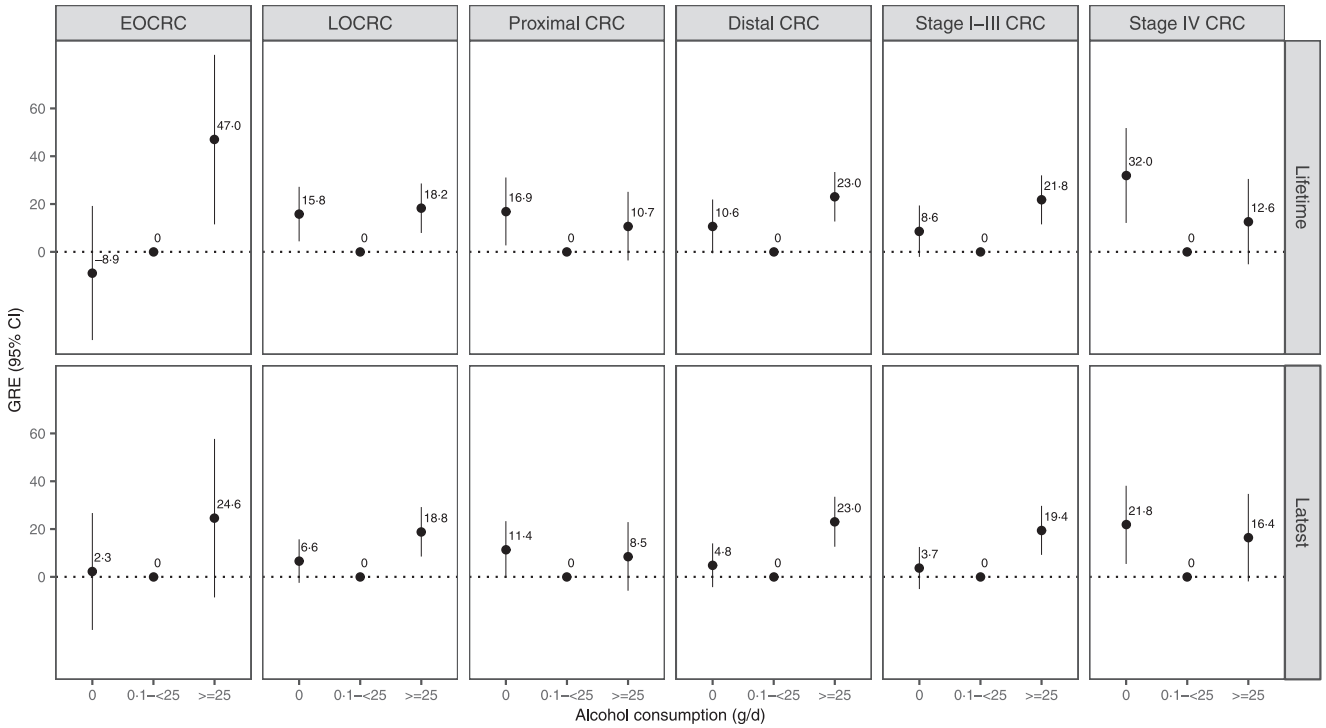

Figure 1. Genetic risk equivalents for comparisons between alcohol consumption with CRC risk by age at diagnosis or interview, cancer sites, and cancer stages. Note: Models were adjusted for age, sex, education, body mass index, physical activity, smoking, red meat intake, history of colonoscopy, history of diabetes, history of cardiovascular disease, family history of colorectal cancer in a first-degree relative, use of statins, use of nonsteroidal anti-inflammatory drugs, and polygenic risk score (continuous variable, per 10 percentiles) with 0•1-<25 g/d alcohol consumption as the reference group. Abbreviation: CI, confidence interval; CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; GRE, genetic risk equivalent; LOCRC, late-onset colorectal cancer.

example, resveratrol, abundant in grape skin, has various beneficial health effects including anti-inflammatory, lipid-lowering, and hypoglycemic effects, which might potentially offset some of the increased CRC risk at higher levels of alcohol consumption.[30] Again, however, further research is needed to more fully disclose and understand beverage-type specific effects on CRC risk.

Three recently published systematic reviews comprehensively summarized the evidence on non-genetic risk factors for EOCRC, and suggested alcoholic drinking as a potential risk factor for EOCRC, while only a few studies included in these reviews compared risk factors between early and late-onset CRC in multivariable models.[10–12] Although Syed et al. found a strong association of alcohol consumption with EOCRC, this association was not stronger than the association with LOCRC.[31] Similarly, the pooled analysis by Archambault et al. based on participants of genetically defined European descent (which included data of the DACHS study as a subset) did not find any risk factors (including alcohol consumption) that exhibited a stronger association with EOCRC than with LOCRC.[32] It is interesting to note that this pooled analysis also found a significantly increased risk of both EOCRC and LOCRC among alcohol abstainers.

However, no analysis for average lifetime alcohol consumption was performed.[31,32] Exposure to alcohol drinking in a lifetime course could impact cancer risk by increasing the duration of exposure to carcinogens and possibly increasing chances of existing effects at certain time frames when activation of driver mutations could render the young adult at risk of developing cancer.[33,34] In addition, a higher proportion of CRC in young patients occur in the distal colon or rectum compared to older patients.[3–5] Risk factors more strongly associated with distal colon or rectum cancer and increasing in prevalence are likely to contribute to the development of EOCRC. We found a stronger association between heavy drinking with distal CRC than proximal CRC, consistent with a recent meta-analysis study (4276 CRC cases, 15,802 controls) in which heavy alcohol consumption was associated with increased risk of distal colon and rectal cancer but not proximal colon cancer.[9] Given the limited evidence to date, further studies are warranted to validate our results, to more thoroughly assess the role of timing, trajectories, and cumulative amount of alcohol use throughout adolescence and adulthood, and to explore the mechanisms behind the observed patterns.

Our finding of the absence of an interaction between the PRS and alcohol consumption with respect to CRC risk is consistent with and corroborates findings from a recent study from the UK even though a larger number of cases were included.[18] We also extended the evidence from that study by assessing the effects of alcohol consumption on CRC risk by age at diagnosis. It is important to note, however, that both studies examined interaction on a multiplicative scale. Despite lack of interaction on the multiplicative scale, the impact of alcohol consumption will be stronger on an absolute scale for those with higher PRS levels. In other words, the same relative risk of heavy drinking implies a higher increase in absolute risk among people with higher PRS levels, due to their higher "baseline risk". People with high PRS will therefore benefit most from refraining from heavy alcohol consumption and from adopting other healthy lifestyles associated with CRC risk.[35] Finally, disclosing or disapproving interactions is also essential for the correct modeling of risk prediction based on genetic and environmental risk factors.

To our knowledge, our study is the first to report the impact of alcohol consumption and genetic risk in a directly comparative manner using the novel GRE metric. The GRE has recently been developed as a novel approach for improving risk communication to the public.[20–22] For example, the large GRE for heavy drinking in our study indicates that the impact of reduced alcohol consumption could be as strong as the impact of having a substantially lower predetermined polygenic risk for CRC, in particular EOCRC, which might help improve adherence to healthy guidelines, especially for those with a high genetic predisposition to CRC. In addition, variations regarding the relationship of heavy drinking with CRC risk by cancer location, and the estimated high GRE for distal CRC in our study further underscore the importance of targeted CRC cancer prevention.

This study has several strengths. The comprehensive assessment of CRC risk factors, phenotyping, and genotyping in this very large study enabled a thorough analysis of the role of both lifetime and more recent alcohol consumption for CRC risk overall, and by age groups and tumor sites and stages, in direct comparison with the role of genetic predisposition which was quantified, for the first time, in terms of the GRE. In-depth information collected by personal interviews and medical records allowed for thorough adjustment for potential confounders, and the size of the study enabled reasonably precise estimates of GRE even for subgroup analyses.

Certain limitations also have to be considered. Information bias such as recall bias cannot be ruled out as most data were gathered retrospectively through a standardized questionnaire. For example, information bias from imperfect recall, potentially combined with willful underreporting, is likely to have led to some underestimation of alcohol effects. Even though we conducted thorough dose-response analyses, we were unable to consider specific drinking patterns (such as binge drinking) which may also be relevant for CRC risk. Although we carefully controlled for a large number of potential confounders, we cannot exclude the possibility of residual confounding by less than perfect confounder

ascertainment and by incomplete information on additional factors potentially related to alcohol consumption and CRC risk. Another limitation is that the PRS used in this study is likely to reflect only a limited share of genetic predisposition. A large share of heritability for CRC remains unexplained and genetic predisposition most likely plays a larger role for EOCRC than for LOCRC.[36,37] With a more comprehensive characterization of genetic predisposition, its use for prediction of CRC risk, particularly EOCRC risk, in comparison and combination with alcohol consumption and other CRC risk factors is expected to become stronger. Despite the overall large sample size, the number of participants in some subgroups, especially for younger age groups, were relatively small which limited the power and precision of subgroup analyses. Given overlapping 95% confidence intervals of ORs and GREs, observed differences between subgroups need to be interpreted with caution. In addition, this study was based on the Caucasian population and thereby results need to be validated in other ethnic groups.

Despite these limitations, our study provides important evidence that alcohol use substantially contributes to increased CRC risk, particularly EOCRC risk, with substantial relative risks for heavy drinking irrespective of predetermined polygenic risk for CRC, and absolute risk increase being most pronounced for heavy drinkers with high PRS. On the other hand, this implies that the impact of avoiding heavy drinking can be as strong as having a substantially lower genetically determined increased CRC risk, as quantified by the large values of GRE, which further underscores the role of cutting down on alcohol in CRC prevention and may be helpful for more effective risk communication. Further research is needed to derive more precise estimates of the impact of various patterns of alcohol consumption in combination with PRS, other lifestyle factors, and comorbidities across various ethnic groups in the total population and young adults in particular.

Funding

The first author (X.C.) was supported by the Guangzhou Elite Project (GEP). The DACHS study was supported by grants from the German Research Council (BR 1704/6–1, BR1704/6–3, BR 1704/6–4, BR 1704/6–6, CH 117/1–1, BR 1704/17–1, HO 5117/2–1) and the German Federal Ministry of Education and Research (01KH0404, 01ER0814, 01ER0815, 01GL1712).

Contributors

Conceptualization, X.C., M.H., and H.B.; methodology, X.C., H.L., F.G., M.H., and H.B.; software, X.C.; formal analysis, X.C., H.L., F.G., M.H., and H.B.; resources, M.H. and H.B.; data curation, M.H. and H.B.; writing-original draft preparation, X.C.; writing-review and editing, X.C., H.L., F.G., M.H., and H.B.; supervision, H.B.; project administration, M.H. and H.B.; funding acquisition, H.B. All authors read and approved the final version of the manuscript.

Data sharing statement

Data are available from the corresponding author upon reasonable request.

Declaration of Interests

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101460.

References

1 Araghi M, Soerjomataram I, Bardot A, et al. Changes in colorectal cancer incidence in seven high-income countries: a population-based study. *Lancet Gastroenterol Hepatol*. 2019;4:511–518.
2 Siegel RL, Torre LA, Soerjomataram I, et al. Global patterns and trends in colorectal cancer incidence in young adults. *Gut*. 2019;68:2179–2185.
3 Hofseth LJ, Hebert JR, Chanda A, et al. Early-onset colorectal cancer: initial clues and current views. *Nat Rev Gastroenterol Hepatol*. 2020;17:352–364.
4 Stoffel EM, Murphy CC. Epidemiology and mechanisms of the increasing incidence of colon and rectal cancers in young adults. *Gastroenterology*. 2020;158:341–353.
5 Patel SG, Karlitz JJ, Yen T, Lieu CH, Boland CR. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. *Lancet Gastroenterol Hepatol*. 2022;7:262–274.
6 Fedirko V, Tramacere I, Bagnardi V, et al. Alcohol drinking and colorectal cancer risk: an overall and dose–response meta-analysis of published studies. *Ann Oncol*. 2011;22:1958–1972.
7 Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. *Br J Cancer*. 2015;112:580–593.
8 Vieira AR, Abar L, Chan DSM, et al. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. *Ann Oncol*. 2017;28:1788–1802.
9 McNabb S, Harrison TA, Albanes D, et al. Meta-analysis of 16 studies of the association of alcohol with colorectal cancer. *Int J Cancer*. 2020;146:861–873.
10 Breau G, Ellis U. Risk factors associated with young-onset colorectal adenomas and cancer: a systematic review and meta-analysis of observational research. *Cancer Control*. 2020;27:1073274820976670.
11 O'Sullivan DE, Sutherland RL, Town S, et al. Risk factors for early-onset colorectal cancer: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2021;29. https://doi.org/10.1016/j.cgh.2021.01.037. Published online JanS1542-3565(21)00087-2.
12 Puzzono M, Mannucci A, Grannò S, et al. The role of diet and lifestyle in early-onset colorectal cancer: a systematic review. *Cancers (Basel)*. 2021;13:5933.
13 Wang J, Wang H, Chen Y, Hao P, Zhang Y. Alcohol ingestion and colorectal neoplasia: a meta-analysis based on a Mendelian randomization approach. *Color Dis*. 2011;13:e71–e78.
14 Zhou X, Wang L, Xiao J, et al. Alcohol consumption, DNA methylation and colorectal cancer risk: results from pooled cohort studies and Mendelian randomization analysis. *Int J Cancer*. 2022. https://doi.org/10.1002/ijc.33945. published online Jan 31.

15 Hutter CM, Chang-Claude J, Slattery ML, et al. Characterization of gene–environment interactions for colorectal cancer susceptibility loci. *Cancer Res*. 2012;72:2036–2044.
16 Kantor ED, Hutter CM, Minnier J, et al. Gene–environment interaction involving recently identified colorectal cancer susceptibility loci. *Cancer Epidemiol Biomarkers Prev*. 2014;23:1824–1833.
17 Song N, Lee J, Cho S, Kim J, Oh JH, Shin A. Evaluation of gene-environment interactions for colorectal cancer susceptibility loci using case-only and case-control designs. *BMC Cancer*. 2019;19:1231.
18 Yang T, Li X, Farrington SM, et al. A Systematic analysis of interactions between environmental risk factors and genetic variation in susceptibility to colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2020;29:1145–1153.
19 Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. *Nature*. 2009;461:747–753.
20 Chen X, Jansen L, Guo F, Hoffmeister M, Chang-Claude J, Brenner H. Smoking, Genetic Predisposition, and Colorectal Cancer Risk. *Clin Transl Gastroenterol*. 2021;12:e00317.
21 Chen X, Guo F, Hoffmeister M, Chang-Claude J, Brenner H. Nonsteroidal anti-inflammatory drugs, polygenic risk score and colorectal cancer risk. *Aliment Pharmacol Ther*. 2021;54:167–175.
22 Chen X, Hoffmeister M, Brenner H. Red and processed meat intake, polygenic risk score, and colorectal cancer risk. *Nutrients*. 2022;14:1077.
23 Scherz H, and S.W. Souci, editors. *Food Composition and Nutrition Tables*. 5th edn Stuttgart (Germany): Medpharm Scientific Publishers; 1994.
24 Bundeszentrale für gesundheitliche Aufklärung. Alkohol? Kenn dein Limit. https://www.kenn-dein-limit.info/risikoarmer-konsum.html. Accessed 7 September 2021.
25 Thomas M, Sakoda LC, Hoffmeister M, et al. Genome-wide modeling of polygenic risk score in colorectal cancer risk. *Am J Hum Genet*. 2020;107:432–444.
26 lrm: logistic Regression Model. https://www.rdocumentation.org/packages/rms/versions/6.2-0/topics/lrm. Accessed 12 December 2021.
27 Ebell MH, Thai TN, Royalty KJ. Cancer screening recommendations: an international comparison of high income countries. *Public Health Rev*. 2018;39:7.
28 Bagnardi V, Rota M, Botteri E, et al. Light alcohol drinking and cancer: a meta-analysis. *Ann Oncol*. 2013;24:301–308.
29 Arranz S, Chiva-Blanch G, Valderas-Martínez P, Medina-Remón A, Lamuela-Raventós RM, Wine ER. Beer, Alcohol and Polyphenols on Cardiovascular Disease and Cancer. *Nutrients*. 2012;4:759–781.
30 Honari M, Shafabakhsh R, Reiter RJ, Mirzaei H, Asemi Z. Resveratrol is a promising agent for colorectal cancer prevention and treatment: focus on molecular mechanisms. *Cancer Cell Int*. 2019;19:180.
31 Syed AR, Thakkar P, Horne ZD, et al. Old vs new: risk factors predicting early onset colorectal cancer. *World J Gastrointest Oncol*. 2019;11:1011–1020.
32 Archambault AN, Lin Y, Jeon J, et al. Nongenetic determinants of risk for early-onset colorectal cancer. *JNCI Cancer Spectr*. 2021;5:pkab029.
33 Barreto SG. We asked the experts: providing the road map to uncovering the pathophysiology of young-onset cancer to guide treatment and preventive strategies. *World J Surg*. 2020;44:3212–3213.
34 Barreto SG, Pandol SJ. Young-onset carcinogenesis - the potential impact of perinatal and early life metabolic influences on the epigenome. *Front Oncol*. 2021;11: 653289.
35 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.
36 Huyghe JR, Bien SA, Harrison TA, et al. Discovery of common and rare genetic risk variants for colorectal cancer. *Nat Genet*. 2019;51:76–87.
37 Tenesa A, Dunlop MG. New insights into the aetiology of colorectal cancer from genome-wide association studies. *Nat Rev Genet*. 2009;10:353–358.