Lifestyle factors, obesity and the risk of colorectal adenomas in EPIC-Heidelberg

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Abstract
Objective We investigated the association of lifestyle and obesity with colorectal adenoma risk in a prospective setting.
Methods At recruitment (1994–1998), information on diet, anthropometry, lifestyle, and medication was assessed in 25,540 participants of the EPIC-Heidelberg cohort. Until June 2007, 536 verified incident colorectal adenomas were identified. Furthermore, participants with negative colonoscopy ($n = 3966$) were included in the analytic cohort.
Results In multivariate logistic regression analyses, participants with highest alcohol intake had an increased adenoma risk (odds ratio [OR] = 1.63; 95% CI 1.21–2.22) compared with lowest intake group. Folate consumption modified the ethanol effect (p-interaction = 0.03). Current smokers had a significantly increased adenoma risk compared with never smokers (OR = 1.40; 95% CI 1.16–1.84). Regular NSAID intake was associated with lower risk in subjects who reported their use at least twice compared with nonusers (OR = 0.70; 95% CI 0.53–0.93). Physical activity, body mass index, and waist-to-hip ratio were not consistently associated with adenoma risk.
Conclusions The results of this prospective cohort study showed that alcohol intake and smoking are important risk factors for colorectal adenoma, and regular NSAID use decreases the risk. The relationship between alcohol consumption and adenoma risk was modified by folate intake. However, we could not confirm an effect of obesity or physical activity on adenoma risk.

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Introduction

Colorectal adenomas are prevalent in ca. 10% of the population. They are positively associated with increasing age such that 20% or more of the subjects older than 60 years of age have an adenoma [1]. However, adenomas often do not cause symptoms and thus stay undetected. Adenomas have the potential to develop into colorectal cancer [1], which is one of the most common types of cancer in the Western world [2]. The worldwide incidence of colorectal cancer is very diverse and lifestyle factors such as obesity, smoking, diet, and ethanol intake are thought to play a role in the etiology. However, findings from epidemiologic studies on risk factors of adenomas are equivocal. Results appear to be most consistent for smoking and use of NSAIDs with an increased adenoma risk among former and current smokers [3] and a decreased risk among subjects with regular use of NSAIDs [4–7]. In contrast, results for alcohol consumption [7–20], obesity [7, 9, 16, 21–25], and physical activity [7, 9, 21, 22, 24, 26] are sometimes conflicting. Such diverse results may be due to several factors including study design (cohort vs. case–control studies), study population and possibly inherent genetic variation, or differences in the percentage of adenoma of different sites or morphology.

In this report, we used data of a prospective cohort study based in Heidelberg, Germany, to examine the associations

of lifestyle factors and obesity with risk of colorectal adenomas.

Subjects and methods

Study participants and questionnaires

As part of the European Prospective Investigation into Cancer and Nutrition (EPIC), the EPIC-Heidelberg cohort study was commenced in 1994 and recruited 25,540 participants (age range between 35 and 65 years) from the general population until 1998. With the help of questionnaires and face-to-face interviews, detailed information on diet and lifestyle was assessed.

Diet, including ethanol intake, was assessed via a validated food frequency questionnaire [27]. Subjects were asked to state how many glasses of beer, wine, liquor, or spirits they consumed per day or week. Individual ethanol intake was then calculated out of the frequency of consumption and the average ethanol levels of each specific beverage. To estimate average lifetime ethanol intake, participants were asked to state their alcohol consumption at different ages (20, 30, and 40). Average lifetime ethanol intake was calculated as a weighted mean of the intake at different ages and baseline, with weights equal to the total subject specific time under investigation. Smoking history and degree of physical activity were either levied using a lifestyle questionnaire or during a face-to-face interview. Intake of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, was assessed when asking for medication intake at baseline and during follow-up. Information on use of postmenopausal hormone therapy as well as menopausal status was assessed at baseline. Weight and height were measured in light underwear in a standardized procedure by trained personnel. Waist circumference was determined halfway between the lower costal arch and the upper iliac crest, and hip circumference was measured over the buttocks. An index of physical activity was established by cross-classifying categories of occupational activity with hours spent with cycling and sports [28].

Identification of cases

Since the recruitment of the study participants, three rounds of follow-up have been conducted in the EPIC-Heidelberg cohort. The aim of the follow-up is to collect, among others, information on the occurrence of major chronic diseases. Within these follow-ups, the study participants were asked to report the diagnosis of benign tumors, such as colorectal polyps. After three follow-ups (between September 1997 and 2007), 960 participants had declared the diagnosis of a colorectal polyp. Colorectal polyps reported by the study participants were verified by a trained physician by means of medical records. The second version of the International Classification of Diseases for Oncology was applied to code incident adenoma cases. Mortality data was coded according to the tenth revision of the International Classification of Disease, Injuries, and Causes of Deaths. Through verification, 536 were identified as incident colorectal adenomas and 167 as hyperplastic polyps. For sub-analysis, the colon was divided based on ICD-10 into right colon (C180, C181, C182, C183, C184, C1841, C1842, C1843, and C185), left colon (C186 and C187), and rectum (C199, C209, C2091, C2092, and C2093). The remaining 257 participants did not have an adenoma or a hyperplastic polyp and were included in the noncase group of our analysis.

Since colorectal adenomas are often without symptoms, they frequently remain undiagnosed. Due to this fact, only participants with a negative colonoscopy were included in the analyses. Of the 5,064 participants that reported a colonoscopy, we excluded all prevalent cancer cases (except nonmelanoma skin cancer; $n = 371$), hyperplastic polyps ($n = 171$), and three subjects with missing dietary information, leaving 4,519 participants for the analysis reported here.

All participants gave informed consent at study entry. This study was approved by the ethical committee of Heidelberg University Medical School.

Statistical analyses

The associations of anthropometric variables, ethanol intake, smoking habits, and physical activity with colorectal adenomas were evaluated with logistic regression. BMI was categorized into <25, 25–29, and ≥ 30 kg/m^2; waist-to-hip ratio (WHR) was classified into sex-specific quartiles. Daily ethanol intake at baseline and average lifetime ethanol intake were modeled as a categorical variable using four categories as follows: <5 g/d, 5–<15 g/d, 15–<30 g/d, and ≥ 30 g/d. Study participants were categorized into never, former, and current smokers as well as by pack-years of smoking. One pack-year incorporates the amount and duration of smoking and is defined as the daily consumption of one pack (20 cigarettes) over the time period of 1 year. In this study, the categories ≤ 0.075, 0.076–5, 6–10, 11–15, and >15 pack-years were used. Physical activity was classified into inactive, moderately inactive, moderately active, and active according to the above-mentioned index. NSAID use was classified into users or non-users at baseline as no information on amount or duration of medication intake has been assessed at baseline. Additionally, continuous NSAIDs use was defined by the reports of NSAID intake at baseline as well as during second and third follow-up of the Heidelberg–EPIC cohort. This variable was categorized

into never users, once (i.e., a report of NSAID use at baseline or at one of the follow-ups) and twice or three times (i.e., stated NSAID use at least two times, at baseline, or during follow-ups).

All analyses were adjusted for sex and age at recruitment. In multivariate regression models, we adjusted for energy intake without energy from alcohol (in quartiles), ethanol intake (<5, 5 to <15, 15 to <30, and ≥30 g/d), milk and milk products consumption (in quartiles), fiber consumption (in quartiles), folate intake (in quartiles), total red and processed meat intake (in quartiles), Body mass index (BMI, <25, 25–30, and ≥30 kg/m^2), family history of colorectal cancer (yes/no), physical activity (inactive, moderately inactive, moderately active, and active), intake of NSAIDs at baseline (yes/no), smoking status (never, former, current), pack-years of smoking (≤0.075, 0.076–5, 6–10, 11–15, and >15), education (none or primary, technical or professional school, secondary school, and university degree). Trend tests were performed by assigning a score ranging from 1 to maximum 5 to the categories/quartiles and using this score as a continuous variable into the Cox regression models. Subanalyses were performed by adenoma site (right colon [including colon transversum], left colon, and rectum) and gender. We also examined effects by adenoma size (<1 vs. ≥1 cm), but we did not observe major differences by size and, thus, decided not to present these results. We tested for interactive effects by including a cross-product term along with the main-effect terms in the Cox regression model. The statistical significance of the cross-product term was evaluated using the Wald test. All analyses were conducted using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

Results

More than 50% of the subjects without adenomas were women, but among cases, almost 64% were males (Table 1). Cases were on average 2 years older. BMI, waist circumference, and WHR differed significantly between cases and subjects without adenomas. Also, cases had a significantly higher intake of red and processed meat as well as ethanol as noncases. Among women, cases and subjects without adenomas differed by menopausal status.

Ethanol intake

We observed a statistically significant dose–response association between ethanol intake and the risk of adenoma (p-trend$_{\text{multivariate (mv)}}$ = 0.002; Table 2). Subjects in the third and fourth intake quartiles had an increased adenoma risk of OR = 1.57 (95% CI 1.20–2.07) and 1.63 (95% CI 1.21–2.22), respectively. Although the test for interaction was not statistically significant (Table 3), the association between ethanol intake and adenoma risk was stronger in men (fourth vs. first quartile OR$_{\text{mv}}$ = 1.82, 95% CI 1.21–2.74) than in women (OR$_{\text{mv}}$ = 1.45, 95% CI 0.84–2.51). The association for ethanol and adenoma was strongest in the rectum with an OR = 1.87 comparing the fourth with the first quartile of intake (95% CI: 1.02–3.44; Table 4).

Evaluating the association of average lifetime ethanol intake with adenoma showed a positive association in the unadjusted model, reaching statistical significance when comparing an average lifelong ethanol intake of ≥30 g/day with <5 g/day (OR = 1.55; 95% CI 1.13–2.11). This result was attenuated in the multivariate model (OR = 1.35; 95% CI 0.96–1.91; data not shown). This association was significant for adenomas of the rectum (OR = 3.43; 95% CI 1.66–7.12), but not for other sites or stratified by sex (data not shown).

The effect of ethanol intake was modified by folate consumption (p-interaction = 0.03). In participants with a low folate consumption (<median of 94.6 μg/d), the adenoma risk continuously increased with higher ethanol intake (p-trend = 0.0006). Comparing the highest ethanol intake with the lowest in this sub-group, the odds for adenomas was 2.08 (95% CI 1.35–3.18). For participants with a high folate consumption (≥94.6 μg/d), ethanol intake remained to increase adenoma risk, however, no longer with statistical significance (OR$_{\text{mv}}$ = 1.31, 95% CI 0.87–1.99) and without clear dose–response relationship (p-trend = 0.09). In a cross-classification, subjects with low folate and high ethanol intake (≥30 g/day) had an OR of 1.94 (95% CI 1.20–3.15), and those with high folate and high ethanol intake had an OR of 1.29 (95% CI 0.88–1.91), both compared with high folate and low ethanol (<5 g/day) intake as reference group (Fig. 1). We did not observe an effect modification by smoking status (p-interaction > 0.05).

Smoking habits

Former and current smokers had an increased adenoma risk, although the association was only statistically significant for current smokers (OR$_{\text{mv}}$ = 1.40, 95% CI: 1.06–1.84; Table 2). Also, the risk increased with increasing pack-years of smoking (p-trend$_{\text{mv}}$ = 0.001). We observed statistically significant effect modification by sex, with increased risk confined to women; the risk of current female smokers doubled compared with female nonsmokers (Table 3). Evaluating the data according to the adenoma location, positive associations were found for the left colon (p-trend for pack-years = 0.04) and the rectum (p-trend = 0.02), but not for the right colon (p-trend = 0.25; Table 4).

Table 1 Baseline Characteristics of colorectal adenoma cases and cohort participants with a negative colonoscopy in EPIC-Heidelberg

	Cases	Cohort participants with negative colonoscopy	*p* values[b]
n	536	3983	
Person years	5.4 (±2.4)	7.8 (±1.7)	
Location of adenomas			
Right colon[a], *n* (%)	156 (28.3)	—	
Left colon[a], *n* (%)	187 (35.5)	—	
Rectum[a], *n* (%)	117 (22.3)	—	
Missing, *n* (%)	72 (14.0)		
Morphology of adenomas			
Tubulovillous, *n* (%)	218 (40.9)	—	
Tubular, *n* (%)	307 (57.0)	—	
Others, *n* (%)	11 (0.1)	—	
Males, *n* (%)	341 (63.6)	1828 (45.9)	
Females, *n* (%)	195 (36.4)	2155 (54.1)	<.0001
Age (years), mean ± SD	55.1 ± 6.3	52.9 ± 7.6	<.0001
Hip circumference (cm), mean ± SD	103.5 ± 39.5	102.3 ± 29.5	0.52
Waist circumference (cm), mean ± SD	95.2 ± 56.8	89.4 ± 31.6	0.02
WHR, mean ± SD	0.92 ± 0.40	0.87 ± 0.10	0.008
BMI (kg/m^2), mean ± SD	26.6 ± 3.8	26.2 ± 4.0	0.02
Energy intake (kcal/d), mean ± SD	1994 ± 670	1935 ± 654	0.05
Vegetables (g/d), mean ± SD	115.9 ± 55.3	119.0 ± 58.8	0.25
Fruit (g/d), mean ± SD	113.2 ± 87.1	121.1 ± 86.2	0.05
Fiber intake (g/d), mean ± SD	20.0 ± 6.8	20.4 ± 7.3	0.27
Total folic acid (μg/d), mean ± SD	203.9 ± 57.7	205.8 ± 62.4	0.65
Red and processed meat (g/d), mean ± SD	91.3 ± 58.1	81.6 ± 60.8	0.0005
Ethanol (g/d), mean ± SD	23.2 ± 26.0	17.1 ± 21.8	<0.0001
Physical Activity Index (%)[c]			
Inactive	11.6	11.4	
Moderately inactive	38.5	37.1	
Moderately active	27.5	27.6	
Active	22.4	23.8	0.89
Regular NSAID use (yes, %)	9.5	9.3	0.90
Smoking status (%)			
Never	36.0	43.5	
Former	44.8	39.6	
Current	19.2	16.8	0.004
Education (%)			
None or primary school	30.7	29.8	
Technical or professional school	32.6	35.4	
Secondary school	5.4	5.4	
University degree	31.4	29.5	0.75
Family history of colon cancer (yes, %)	17.3	11.7	0.001
Menopausal status (%; among women only)[c]			
Premenopausal	33.5	19.8	
Postmenopausal	56.1	71.8	
Perimenopausal	10.5	8.5	0.0007
Use of hormone therapy (yes, %; among women only)[c]	35.9	42.3	0.08

[a] Right colon includes C180, C181, C182, C183, C184, C1841, C1842, C1843, and C185; left colon includes C186 and C187; rectum colon includes C199, C209, C2091, C2092, and C2093

[b] *t*-test for continuous variables or Chi-square test for categorical variables

[c] Missing information on physical activity for 121 participants; missing information on menopausal status for 293 women; and missing information on hormone therapy for 81 women

Table 2 Association of anthropometric and lifestyle variables and adenoma risk in EPIC-Heidelberg

Variable	Cases (*n*)	OR[a]	95% CI	OR[c]	95% CI
Ethanol intake					
<5 g/day	129	1.00	(Ref)	1.00	(Ref)
<15 g/day	125	1.22	(0.94, 1.58)	1.24	(0.95, 1.62)
<30 g/day	137	1.55	(1.19, 2.02)	1.57	(1.20, 2.07)
≥30 g/day	145	1.67	(1.27, 2.20)	1.63	(1.21, 2.22)
p-trend		0.0001		0.002	
BMI					
<25 kg/m^2	178	1.00	(Ref)	1.00	(Ref)
25–29 kg/m^2	278	1.20	(0.98, 1.48)	1.19	(0.96, 1.48)
≥30 kg/m^2	80	1.01	(0.76, 1.34)	1.03	(0.76, 1.38)
p-trend		0.59		0.73	
WHR[b]					
Q1	104	1.00	(Ref)	1.00	(Ref)
Q2	148	1.37	(1.05, 1.79)	1.26	(0.96, 1.66)
Q3	141	1.29	(0.98, 1.70)	1.19	(0.90, 1.57)
Q4	143	1.22	(0.92, 1.60)	1.07	(0.81, 1.43)
p-trend		0.31		0.75	
Smoking					
Never	193	1.00	(Ref)	1.00	(Ref)
Former	240	1.21	(0.98, 1.49)	1.17	(0.94, 1.45)
Current	103	1.50	(1.15, 1.95)	1.40	(1.06, 1.84)
Pack-years					
0 to ≤0.075	218	1.00	(Ref)	1.00	(Ref)
0.076 to ≤5	63	1.00	(0.74, 1.35)	0.96	(0.71, 1.30)
5 to ≤10	53	1.30	(0.94, 1.80)	1.26	(0.90, 1.75)
10 to ≤15	47	1.34	(0.95, 1.90)	1.32	(0.93, 1.87)
>15	155	1.50	(1.19, 1.88)	1.45	(1.14, 1.84)
p-trend		0.0002		0.001	
Physical activity					
Inactive	61	1.00	(Ref)	1.00	(Ref)
Moderately inactive	203	1.07	(0.80, 1.43)	1.07	(0.80, 1.45)
Moderately active	145	1.01	(0.74, 1.38)	1.04	(0.76, 1.42)
Active	118	0.96	(0.70, 1.33)	1.02	(0.74, 1.42)
p-trend		0.61		0.86	
NSAID use[d]					
Never	368	1.00	(Ref)	1.00	(Ref)
Once	85	0.85	(0.66, 1.08)	0.82	(0.64, 1.06)
Twice or three times	73	0.76	(0.58, 0.99)	0.70	(0.53, 0.93)

[a] Adjusted for age at baseline and sex

[b] Cut-points for quartiles are as follows: WHR: males 0.90, 0.94, 0.98, females 0.758, 0.80, 0.85

[c] All models are adjusted for age at baseline, sex, energy intake without alcohol (in quartiles), total red and processed meat intake (in quartiles), intake of milk and milk products (in quartiles), fiber intake (in quartiles), folate intake (in quartiles), family history of colorectal cancer (yes/no), and education (4 categories); additionally, adjusted for ethanol intake (4 categories), pack-years of smoking (5 categories), smoking status (3 categories), intake of NSAIDs (yes/no), BMI (3 categories), and physical activity (4 categories) where appropriate

[d] NSAID use was defined as follows: Never = no report of NSAID use at baseline or during the 2nd or the 3rd follow up; Once = reported at baseline or at follow-up 2 or follow-up 2; twice or three times = reported at least twice at baseline, the 2nd, or the 3rd follow-up

Table 3 Association of anthropometric and lifestyle variables and adenoma risk *by gender* in EPIC-Heidelberg

Variables	Men			Women			*p*-interaction
	Cases (*n*)	OR[b]	95% CI	Cases (*n*)	OR[b]	95% CI	
Ethanol intake							
<5 g/day	46	1.00	(Ref)	83	1.00	(Ref)	
<15 g/day	76	1.51	(1.01, 2.25)	49	1.03	(0.71, 1.50)	
<30 g/day	95	1.70	(1.15, 2.52)	42	1.51	(1.00, 2.28)	
≥30 g/day	124	1.82	(1.21, 2.74)	21	1.45	(0.84, 2.51)	0.88
p-trend		0.01			0.08		
BMI							
<25 kg/m^2	82	1.00	(Ref)	96	1.00	(Ref)	
25–29 kg/m^2	207	1.30	(0.97, 1.74)	71	1.09	(0.77, 1.53)	
≥30 kg/m^2	52	1.03	(0.70, 1.53)	28	1.02	(0.64, 1.63)	0.51
p-trend		0.60			0.94		
WHR[a]							
Q1	69	1.00	(Ref)	35	1.00	(Ref)	
Q2	91	1.21	(0.85, 1.72)	57	1.42	(0.90, 2.23)	
Q3	92	1.22	(0.86, 1.74)	49	1.16	(0.72, 1.86)	
Q4	89	1.05	(0.73, 1.51)	54	1.11	(0.69, 1.79)	0.56
p-trend		0.69			0.99		
Smoking							
Never	104	1.00	(Ref)	89	1.00	(Ref)	
Former	183	1.06	(0.81, 1.39)	57	1.27	(0.88, 1.83)	
Current	54	1.00	(0.68, 1.46)	49	2.06	(1.39, 3.08)	0.02
Pack-years							
0 to ≤0.075	127	1.00	(Ref)	91	1.00	(Ref)	
0.076 to ≤5	35	0.75	(0.50, 1.13)	28	1.29	(0.81, 2.04)	
5 to ≤10	30	0.96	(0.62, 1.50)	23	1.78	(1.08, 2.94)	
10 to ≤15	32	1.06	(0.69, 1.64)	15	1.87	(1.03, 3.38)	
>15	117	1.18	(0.88, 1.59)	38	2.05	(1.34, 3.13)	0.003
p-trend		0.17			0.0002		
Physical activity							
Inactive	36	1.00	(Ref)	25	1.00	(Ref)	
Moderately inactive	130	1.03	(0.69, 1.54)	73	1.08	(0.68, 1.71)	
Moderately active	94	0.93	(0.62, 1.41)	51	1.22	(0.74, 1.99)	
Active	76	0.93	(0.61, 1.44)	42	1.21	(0.72, 2.02)	0.39
p-trend		0.62			0.67		

[a] Cut-points for quartiles are as follows: WHR: males 0.90, 0.94, 0.98, females 0.758, 0.80, 0.85

[b] All models are adjusted for age at baseline, energy intake without alcohol (in quartiles), total red and processed meat intake (in quartiles), intake of milk and milk products (in quartiles), fiber intake (in quartiles), folate intake (in quartiles), family history of colorectal cancer (yes/no), and education (4 categories); additionally, adjusted for ethanol intake (4 categories), pack-years of smoking (5 categories), smoking status (3 categories), intake of NSAIDs (yes/no), BMI (3 categories), and physical activity (4 categories) where appropriate

Physical activity, body mass index, waist circumference, and waist-to-hip

We could detect neither an overall association between physical activity and adenoma risk (Table 2) nor an effect confined to gender (Table 3) or adenoma site (Table 4).

No consistent associations between BMI and adenoma risk were observed when considering all cases (Table 2). Interestingly, a high BMI was associated with an increased adenoma risk of the right colon, but not of the left colon or the rectum. There was no effect of BMI on adenoma risk when stratifying by sex (Table 3) or when examining the

Table 4 Association of anthropometric and lifestyle variables and adenoma risk *by adenoma site* in EPIC-Heidelberg

Variable	Right colon			Left colon			Rectum		
	Cases (*n*)	OR[b]	95% CI	Cases (*n*)	OR[b]	95% CI	Cases (*n*)	OR[b]	95% CI
Ethanol intake									
<5 g/day	40	1.00	(Ref)	47	1.00	(Ref)	28	1.00	(Ref)
<15 g/day	37	1.25	(0.78, 1.99)	47	1.23	(0.81, 1.88)	25	1.15	(0.66, 2.01)
<30 g/day	42	1.71	(1.06, 2.76)	43	1.33	(0.85, 2.08)	33	1.81	(1.05, 3.12)
≥30 g/day	37	1.43	(0.83, 2.48)	50	1.55	(0.95, 2.51)	31	1.87	(1.02, 3.44)
p-trend		0.14			0.14			0.02	
BMI									
<25 kg/m^2	36	1.00	(Ref)	74	1.00	(Ref)	47	1.00	(Ref)
25–29 kg/m^2	85	1.84	(1.21, 2.80)	84	0.87	(0.62, 1.23)	60	0.96	(0.63, 1.47)
≥30 kg/m^2	35	2.12	(1.29, 3.50)	29	0.93	(0.58, 1.48)	10	0.48	(0.23, 0.98)
p-trend		0.004			0.42			0.14	
WHR[a]									
Q1	26	1.00	(Ref)	39	1.00	(Ref)	24	1.00	(Ref)
Q2	43	1.38	(0.83, 2.29)	48	1.10	(0.71, 1.71)	39	1.51	(0.89, 2.56)
Q3	42	1.30	(0.78, 2.17)	50	1.15	(0.73, 1.78)	31	1.20	(0.69, 2.10)
Q4	45	1.19	(0.71, 1.99)	50	1.04	(0.66, 1.63)	23	0.83	(0.45, 1.52)
p-trend		0.63			0.86			0.45	
Smoking									
Never	64	1.00	(Ref)	65	1.00	(Ref)	40	1.00	(Ref)
Former	65	0.99	(0.68, 1.44)	84	1.26	(0.89, 1.79)	55	1.27	(0.82, 1.96)
Current	27	1.26	(0.77, 2.06)	38	1.54	(1.00, 2.39)	22	1.34	(0.76, 2.33)
Pack-years									
0 to ≤0.075	73	1.00	(Ref)	72	1.00	(Ref)	45	1.00	(Ref)
0.076 to ≤5	12	0.60	(0.32, 1.13)	28	1.33	(0.84, 2.10)	12	0.80	(0.42, 1.54)
5 to ≤10	14	1.06	(0.58, 1.92)	19	1.38	(0.81, 2.35)	13	1.43	(0.76, 2.72)
10 to ≤15	14	1.19	(0.65, 2.17)	16	1.44	(0.82, 2.55)	12	1.65	(0.85, 3.21)
>15	43	1.21	(0.80, 1.84)	52	1.50	(1.01, 2.23)	35	1.59	(0.98, 2.58)
p-trend		0.25			0.04			0.02	
Physical activity									
Inactive	16	1.00	(Ref)	17	1.00	(Ref)	14	1.00	(Ref)
Moderately inactive	63	1.26	(0.75, 2.14)	76	1.45	(0.86, 2.44)	40	0.91	(0.50, 1.65)
Moderately active	41	1.09	(0.62, 1.91)	52	1.35	(0.78, 2.34)	29	0.88	(0.47, 1.66)
Active	32	1.02	(0.56, 1.84)	40	1.24	(0.70, 2.20)	32	1.21	(0.64, 2.28)
p-trend		0.79			0.99			0.45	

[a] Cut-points for quartiles are as follows: WHR: males 0.90, 0.94, 0.98, females 0.758, 0.80, 0.85

[b] All models are adjusted for age at baseline, sex, energy intake without alcohol (in quartiles), total red and processed meat intake (in quartiles), intake of milk and milk products (in quartiles), fiber intake (in quartiles), folate intake (in quartiles), family history of colorectal cancer (yes/no), and education (4 categories); additionally, adjusted for ethanol intake (4 categories), pack-years of smoking (5 categories), smoking status (3 categories), intake of NSAIDs (yes/no), BMI (3 categories), and physical activity (4 categories) where appropriate

data of the women by menopausal status and hormone replacement therapy (HRT) intake (data not shown).

No association between waist circumference and adenoma risk was found (data not shown). For WHR, we observed an increased adenoma risk with increasing WHR in the simple, but not in the multivariate model (Table 2). No statistically significant associations were seen for WHR by sex (Table 3) or adenoma site (Table 4).

Use of NSAIDs

We did not observe statistically significant associations between the use of NSAIDs at baseline and colorectal adenoma risk in general or in sub-groups of the cohort (data not shown). However, we observed a statistically significantly decreased risk of colorectal adenomas in those subjects who reported use of NSAIDs at least twice during

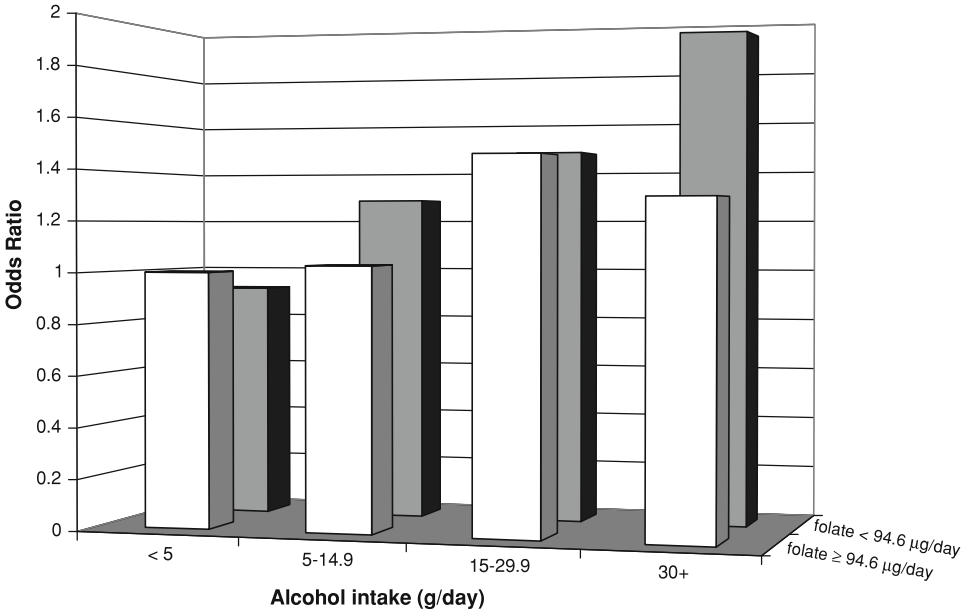

Fig. 1 Adenoma risk by categories of alcohol and folate intake in EPIC-Heidelberg

the study period, i.e., at baseline and during follow-up, compared with never users ($OR_{mv} = 0.70$; 95% CI 0.53–0.93; Table 2). However, this effect was confined to adenomas of the colon ($OR_{mv} = 0.72$; 95% CI 0.52–1.01, 2+ vs. never users); there was no association for rectal adenomas ($OR_{mv} = 0.93$; 95% CI 0.54–1.61, 2+ vs. never users).

Discussion

In this prospective cohort study, we observed an increased risk of colorectal adenomas in subjects with high intake of ethanol; the results were strongest for adenomas of the rectum. This effect of ethanol was statistically significantly affected by folate intake: persons with the highest ethanol consumption and lowest folate intake increased their adenoma risk by the factor 2. This effect was less strong and not statistically significant in participants whose folate intake was above median. Also, a dose–response relationship between adenoma risk and amount and duration of cigarette smoking was observed, especially in women. There were no consistent associations of physical activity, BMI, and WHR, as an indicator of central obesity with adenoma risk. Regular use of NSAIDs significantly reduced the risk of adenomas.

Alcohol consumption

We observed a 1.63-times higher adenoma risk in a subject who consumed more than 30 g ethanol/day when compared with <5 g/day. This positive association is supported by the observation of a risk increasing effect of high average lifetime ethanol intake on adenoma risk. Results from two large prospective cohort studies in the United States are in line with our findings [10]. A comparison of nondrinkers with persons consuming more than 30 g of ethanol per day resulted in an elevated risk of adenoma. However, this elevated risk was statistically significant for women, but not for men [10], whereas we observed a stronger association for men than for women. Similarly, Bourton et al. [29] found a positive association between alcohol consumption and large adenoma in men. Several aspects might contribute to a risk-increasing effect of alcohol consumption. First, acetaldehyde, the first metabolite of alcohol, is a well-known animal carcinogen and is classified as possibly carcinogenic to humans [30] Secondly, chronic alcohol consumption increases cytochrome P-450 and microsomal enzyme activity, which may result in an accelerated metabolism of tobacco carcinogens [31, 32]. Thirdly, high alcohol intake is often associated with a lower intake of fruit and vegetables [33]. However, not all studies show consistent results. While some case–control studies [8, 9, 11–13], a cross-sectional study [7] and a cohort study [10] supported the observed association between higher alcohol consumption and adenoma risk, other case–control studies [14–20] and one prospective study [21] could not confirm these results.

A literature review from 2002 summarized that almost all epidemiological studies that consider alcohol consumption while regarding folate status and colorectal adenoma found alcohol to be associated independently with higher risk [34]; however, the effect of alcohol consumption is pronounced when folate intake is low. A case–control study reported that drinkers of >3 drinks/week with a low folate consumption had a statistically significant

enhanced risk of colorectal adenoma when compared with nondrinkers with a high folate intake [35], confirming our study results. It has been postulated that acetaldehyde may decrease methionine synthesis [10, 36], leading to a depletion of *S*-adenosylmethionine and, consequently, induction of global DNA hypomethylation and finally carcinogenesis [37]; these effects might be especially pronounced with low dietary folate intake. It has been shown in a clinical trial that DNA hypomethylation can be reversed by physiologic intakes of folic acid [38]. Moreover, certain genetic dispositions may further increase the positive association between alcohol consumption and adenoma risk, again especially among persons with low folate intake [39].

Smoking

We found that former and current smokers had an increased adenoma risk, which is in line with a recent meta-analysis concluding that cigarette smoking is important for the formation as well as for the aggressiveness of adenomas [3]. Tobacco smoke contains a large number of carcinogens that may bind to DNA and form adducts, potentially causing irreversible genetic damage to cells of the colorectal mucosa [3]. In our study, positive associations were confined to women and to adenomas of the distal colon. However, Boutron et al. [29] found a statistically significant positive association between smoking (as pack-years) and adenoma incidence for men only. A further case–control study reported an association between cigarette smoking and adenoma at all sites, yet the most pronounced for rectal adenoma [11]. With respect to pack-years, our data confirmed the results of the meta-analysis [3], showing a positive association between pack-years and adenomas. Most other studies also confirmed the results of the meta-analysis [7, 8, 12–14], although some reported no associations between smoking and adenoma risk [9, 10, 13, 15]. Cope et al. [13] showed that a combination of high alcohol consumption and smoking increase the adenoma risk dramatically; however, we and others [11] did not detect a statistically significant interaction between the two variables.

Body mass index and physical activity

In our analysis, no consistent overall associations between BMI or WHR and adenoma risk were found. A positive association between WHR and adenoma risk was attenuated and no longer statistically significant after multivariate adjustment. However, stratification by colon site showed that persons with a BMI $\geq$ 30 kg/m^2 increased their risk for right colon adenoma more than twice compared with persons with a BMI $<$ 25 kg/m^2. In some previously published studies, no statistically significant associations between BMI and adenomatous polyps were detected in multivariate analysis [7, 16, 21]. Others, however, found that a high BMI was associated with an increased risk of large adenoma [9, 22–25]. It has been recommended to analyse data of women stratified by menopausal status and use of HRT. A case–control study has shown that obesity was associated with a strong increase in adenoma risk among premenopausal women, whereas only a weak association was detected among women after menopause [40]. Taking, additionally, HRT use into account, a cohort study observed that for postmenopausal women with abdominal obesity, and using HRT, the risk of colon cancer was not influenced, whereas women with the same characteristics, but not using HRT had an elevated risk of colon cancer [41]. In EPIC-Heidelberg, we observed no associations for BMI or WHR after stratifying for menopausal status and HRT use. However, the numbers of cases were small and, thus, the power to detect an association was limited.

In the EPIC-Heidelberg cohort, no association between the level of physical activity, defined by the amount of leisure time and occupational physical activity and adenoma risk, was observed. There was also no association with vigorous physical activity (data not shown). A protective relationship between physical activity and large adenoma was found in prospective [22, 24, 26] and case–control studies [7, 23, 24, 42–44], although some other studies could not confirm this [7, 9, 21]. In some studies, the effect was gender specific, the association being statistically significant for males only [45–47]. Another case–control study found a protective effect of physical activity on adenoma risk, however, only among those not using NSAIDs [44]; on the other hand, we did not observe such effect modification (data not shown). The underlying physiological mechanism of physical activity on adenoma risk remains unclear; however, a shorter transit-time of the fecal bolus in the colon and decreased amount of bile acid excretion may be possible contributing factors [48]. Furthermore, the observation of a protective effect of physical activity among non-users of NSAIDs suggests that the effect on adenomas may be driven through inflammatory mechanisms [44]; in addition, Giovannucci et al. [22] hypothesized that high levels of insulin may promote the enhanced risk of colorectal adenoma and cancer in obese as well as inactive persons.

Use of NSAIDs

We observed an approximately 25% lower risk of all adenomas and of colon adenomas in participants who

reported using NSAIDs at least twice during the study period compared with those who reported never taking NSAIDs. However, no association was seen when we used the information assessed at baseline only. This hints at an effect due to continuous use of NSAIDs rather than sporadic use only. Several epidemiologic studies have observed inverse associations between the intake of NSAIDs and risk of adenomas or adenoma recurrence [49, 50]. Clinical trials have confirmed the chemoprotective effect of NSAIDs on colorectal adenoma recurrence [51, 52] and several studies reported strongest associations between NSAID intake and adenoma risk among the most frequent users [4–7]. The main anti-neoplastic effect of NSAIDs is thought to be via the inhibition of cyclooxygenase (COX) enzymes, which catalyze the conversion of arachidonic acid to potentially proinflammatory prostaglandins [53]. NSAIDs are also able to restore apoptosis, induce cell-cycle arrest, and inhibit angiogenesis [54]. Further research suggests that the protective effect of NSAIDs on the colorectal adenoma risk may be dependent on certain genetic variants [55, 56].

Strengths and limitations

Strengths of this study include its prospective design, a high completeness of follow-up, and medically confirmed adenoma diagnoses. A further strong point of this study is the estimation of average lifetime ethanol intake as most other studies examined only effects of alcohol consumption at baseline, thus perhaps neglecting behavior at the time of initiating stages of adenoma development. Limitations of this study include possible misclassification, especially concerning the ethanol intake because subjects tend to underreport ethanol intake, perhaps even more so in high consumers. Also, persons with a very high ethanol intake may less likely to take part in a study and, thus, our results may not include the effect of very high ethanol intake. Furthermore, we only included subjects that had a colonoscopy with negative outcome in our control group. This has been done previously [57] and is justified by the fact that adenomas are frequently asymptomatic and participants are not aware of adenoma growth. However, this inclusion criterion may also cause bias since a colonoscopy may have been performed due to health complaints. On the other hand, this sub-group might be more health conscious and, therefore, more likely to participate in the colorectal screening program. Based on the structure of our questions in the follow-up questionnaires, we cannot differentiate between subjects who had a colonoscopy as part of a screening program or were referred to by their physician.

Conclusion

This prospective cohort study strengthens the evidence that subjects who smoke as well as subjects with high intake of ethanol have an increased risk of colorectal adenomas. The effects for alcohol were strongest for adenomas of the rectum and for participants with a low folate intake. A dose–response relationship between alcohol intake and amount and duration (pack-years) of cigarette smoking and adenoma risk was observed. No consistent associations between physical activity, BMI, and WHR and adenoma risk were detected, but we observed an inverse association between regular intake of NSAIDs and colorectal adenoma risk, which was confined to the colon.

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