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Research Article

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The Association between Glyceraldehyde-Derived Advanced Glycation End-Products and Colorectal Cancer Risk

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Abstract

Background: A large proportion of colorectal cancers are thought to be associated with unhealthy dietary and lifestyle exposures, particularly energy excess, obesity, hyperinsulinemia, and hyperglycemia. It has been suggested that these processes stimulate the production of toxic reactive carbonyls from sugars such as glyceraldehyde. Glyceraldehyde contributes to the production of a group of compounds known as glyceraldehyde-derived advanced glycation end-products (glycer-AGEs), which may promote colorectal cancer through their proinflammatory and pro-oxidative properties. The objective of this study nested within a prospective cohort was to explore the association of circulating glycer-AGEs with risk of colorectal cancer.

Methods: A total of 1,055 colorectal cancer cases (colon $n = 659$; rectal $n = 396$) were matchced (1:1) to control subjects. Circulating glycer-AGEs were measured by a competitive ELISA. Multivariable conditional logistic regression models were used to calculate ORs and 95% confidence intervals (95% CI), adjusting for potential confounding factors, including smoking, alcohol, physical activity, body mass index, and diabetes status.

Results: Elevated glycer-AGEs levels were not associated with colorectal cancer risk (highest vs. lowest quartile, 1.10; 95% CI, 0.82–1.49). Subgroup analyses showed possible divergence by anatomical subsites (OR for colon cancer, 0.83; 95% CI, 0.57–1.22; OR for rectal cancer, 1.90; 95% CI, 1.14–3.19; $P_{\text{heterogeneity}} = 0.14$).

Conclusions: In this prospective study, circulating glycer-AGEs were not associated with risk of colon cancer, but showed a positive association with the risk of rectal cancer.

Impact: Further research is needed to clarify the role of toxic products of carbohydrate metabolism and energy excess in colorectal cancer development. *Cancer Epidemiol Biomarkers Prev; 24(12); 1855–63. ©2015 AACR.*

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Introduction

Colorectal cancer is the third most common cancer in men and the second in women worldwide (1). The incidence of colorectal cancer varies approximately 25-fold in different world regions with high risk in developed countries (2). Moreover, it has been observed that the number of new colorectal cancer cases is increasing in countries adopting Western dietary and lifestyle patterns, observations which strongly suggest a role for environmental factors in its development (3). Many environmental factors, such as Western-type diet, physical inactivity, and abdominal obesity, have been implicated in colorectal cancer etiology (4). Some of the key metabolic consequences of these exposures are hyperinsulinemia, hyperglycemia, inflammation, and oxidative stress, all of which have been proposed as major underlying mechanisms for colorectal cancer development (5, 6). Interestingly, it has been proposed that interaction between processes of metabolic over-nutrition with inflammation and oxidative stress can lead to the production of reactive carbonyls, a group of highly toxic and possibly carcinogenic compounds, which in turn also have proinflammatory and pro-oxidative properties of their own (7). One example of this reaction, which has been well-observed *in vitro*, is the conversion of glyceraldehyde, an early product of glycolysis, to reactive carbonyls by reactive oxygen species (ROS; ref. 8). Glyceraldehyde contributes to the production of a group of compounds known as glyceraldehyde-derived advanced glycation end-products (glycer-AGEs; ref. 9). They belong to the larger family of advanced glycation end-products (AGEs), which are stable end-products of the nonenzymatic glycation reaction between reactive carbonyls and free amino groups of proteins, lipids, or nucleic acids (10, 11). They can be formed either exogenously in cooking and cigarette smoking processes or endogenously in tissues in the presence of ROS resulting from inflammation or other processes (12, 13). Glycer-AGEs are the main component of what is considered the most toxic subgroup of AGEs, also referred to as toxic-AGEs (14). It has been observed that glycer-AGEs can form *in vivo* from both reactive carbonyls and as a direct consequence of sugar metabolism (15, 16). Thus, it is plausible that the circulating concentration of glycer-AGEs, aside from having direct inflammatory and oxidative properties, may also be an indicator of the extent of direct exposures to reactive carbonyl species.

AGEs in general have been implicated in the development of diabetes (17, 18) and in ocular (19), renal (20), cardiovascular (21), and some neurodegenerative disorders (22), as well as in several cancers (23, 24). For their part, glycer-AGEs have been shown to be cytotoxic *in vitro* (25, 26), and findings from animal studies suggest involvement in the pathogenesis of insulin resistance and diabetes (27) as well as its complications (28). Human studies suggest the involvement of glycer-AGEs in the development of Alzheimer's disease (29), nonalcoholic steatohepatitis (30), vascular inflammation (31), and some rare disorders (32, 33). In addition to their potential direct effects, some evidence indicates that glycer-AGEs interact strongly with the receptor for AGEs (RAGE) to cause inflammatory and oxidative responses (28, 34)—which are suspected in the development of various cancers, including colorectal cancer (35–37). In view of their apparent direct cytotoxicity, adverse effects on cell function, and involvement in inflammatory and oxidative processes, a role for glycer-AGEs in colorectal cancer development is plausible, but has yet to be examined in studies on humans. In this study, nested within the large multinational European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, we investigated the association of circulating concentrations of glycer-AGEs with risk of colorectal cancer. We hypothesize that higher concentrations of glycer-AGEs would be positively associated with risk of colorectal cancer development.

Materials and Methods

Study population and data collection

We used a case–control design nested within the EPIC cohort, a large prospective cohort study with over 520,000 subjects enrolled from 23 centers in 10 Western European countries (Denmark, France, Greece, Germany, Italy, Netherlands, Norway, Spain, Sweden, and United Kingdom). The rationale and methods of EPIC, including information on dietary assessment methods, blood collection protocols, and follow-up procedures, have been previously reviewed (38). Briefly, individuals who were eligible for the study were selected from the general population of a specific geographical area, town, or province. Exceptions included the French subcohort, which is based on members of the health insurance system or state-school employees, the Utrecht (Netherlands) subcohort, which is based on women who underwent screening for breast cancer, and the Oxford (UK) subcohort,

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which targeted recruitment toward health-conscious people, including vegetarians. Between 1992 and 1998, standardized lifestyle and personal history questionnaires, anthropometric data, and blood samples were collected from most participants at recruitment. Diet over the previous 12 months was assessed at recruitment by validated country-specific questionnaires designed to ensure high compliance and improved measures of local dietary habits (39). In each of the study centers, either fasting or nonfasting blood samples of at least 30 mL were drawn from those participants who provided a blood sample and stored at 5°C to 10°C, protected from light, and transported to local laboratories for processing and aliquoting as previously described (38, 39). In all countries, except Denmark and Sweden, blood was separated in the local EPIC centers and stored at the International Agency for Research on Cancer (Lyon, France; −196°C, nitrogen vapor). In Denmark, blood samples were stored locally at −150°C under nitrogen vapor. In Sweden, samples were stored in −80°C freezers.

Follow-up for cancer incidence and vital status

Vital status follow-up (98.4% complete) is collected by record linkage with regional and/or national mortality registries in all countries except Germany and Greece, and the Italian center of Naples, where data are collected actively. Cancer incidence is determined through record linkage with regional cancer registries (Denmark, other Italian centers, the Netherlands, Norway, Spain, Sweden, and United Kingdom; for this analysis complete up to June 2003) or via a combination of methods, including linkage with health insurance records, contacts with cancer and pathology registries, and active follow-up through study subjects or their next-of-kin (France, Germany, and Greece; for this analysis complete up to June 2002).

Nested case–control study design and selection of study subjects

Case ascertainment and selection. Colon cancers were defined as incident tumors in the cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, and descending and sigmoid (C18.0–C18.7, according to the 10th Revision of the International Statistical Classification of Diseases, Injury, and Cause of Death), as well as tumors that were overlapping or unspecified (C18.8 and C18.9). Rectal cancers were defined as incident tumors occurring at the recto–sigmoid junction (C19) or rectum (C20). Subjects with anal canal tumors were excluded from the study. Colorectal cancer is defined as a combination of the colon and rectal cancer cases.

After exclusions (225 cases for insufficient remaining biosample, 26 cases for missing laboratory values of glycer-AGEs, and 29 cases with incomplete matching), a total of 1,055 first incident colorectal cancer cases (colon $n = 659$; rectal $n = 396$) were identified.

Control selection. For selection of control subjects, an incidence density sampling protocol was applied. For each case, one control subject was chosen at random among appropriate risk sets consisting of all cohort members alive and free of cancer (except nonmelanoma skin cancer) at the time of diagnosis of the index case. Matching characteristics were study center (to account for center-specific differences such as questionnaire design and blood collection procedures), sex, age, time of blood collection, and fasting status at the time of blood collection (less than 3 hours, 3–6 hours, and more than 6 hours). Women were also matched on menopausal status (premenopausal, peri-menopausal, postmenopausal, or surgically menopausal). Premenopausal women were matched on phase of the menstrual cycle at blood collection, and postmenopausal women were matched on current use of hormone replacement therapy.

Laboratory analyses

Serum levels of glycer-AGEs were measured with a competitive enzyme-linked immunosorbent assay (ELISA) at Kanazawa Medical University, Japan, by using immunopurified glycer-AGEs antibody as described previously (15). Briefly, 96-well microtiter plates were coated with 1 μg/mL glycer-AGEs to each well and incubated overnight in a cold room. Wells were washed three times with 0.3 mL of PBS-Tween-20 (PBS-Tween-20). Wells were then blocked by incubation for 1 hour with 0.2 mL of a solution of PBS containing 1% BSA. After washing with PBS-Tween-20, test samples (50 μL) were added to each well as a competitor for 50 μL of glycer-AGEs antibody (1:1,000), followed by incubation for 2 hours at 30°C with gentle shaking on a horizontal rotary shaker. Wells then were washed with PBS-Tween-20 and developed with an alkaline phosphatase–linked anti-rabbit IgG utilizing p-nitrophenyl phosphate as the colorimetric substrate. Results are expressed as glycer-AGEs units (U) per milliliter (mL) of serum, with 1 U corresponding to 1 μg of glycer-AGEs standard. Sensitivity and intra- and interassay coefficients of variation were 0.01 U/mL, 6.2% and 8.8%, respectively (31, 40). For all analyses, laboratory technicians were blinded to the case–control status of the samples, and cases and matched controls were run on the same plate.

Some existing biomarker measures on the same cases and matched controls were also utilized for this study. Measurements of glycated hemoglobin (HbA1c) were previously run on erythrocyte hemolysate using high performance liquid chromatography method (Bio-Rad Variant II instrument, Bio Lad Laboratories) with intrabatch coefficient of variations of 2.5% (41). High-sensitivity C-reactive protein (hs-CRP) and high-density lipoprotein (HDL) cholesterol concentrations were measured using a high-sensitivity assay (Beckman-Coulter) and a colorimetric method, respectively, on a Synchron LX-20 Pro autoanalyzer (Beckman-Coulter). The interassay coefficients of variation were 6.0% to 6.5% and 3.4% to 4.1% at various concentrations of hs-CRP and HDL cholesterol, respectively (42).

Statistical analysis

The distributions of selected baseline demographic and dietary characteristics between colon and rectal cancer cases and the matched controls were described.

Conditional logistic regression was used to estimate the ORs and 95% confidence intervals (CI) of colorectal cancer, and by anatomical subsite of cancers of the colon and rectum in relation to levels of circulating glycer-AGEs. Glycer-AGEs levels were ranked into quartiles whose cut-points were determined based on the distribution among the controls with the lowest quartile as the reference category.

Risk estimates were computed as both univariate analyses based on the matching factors, and multivariable analyses, with additional adjustments for potential confounders, including smoking status (status/duration/intensity of smoking), body mass index (BMI, kg/m^2), education level (as an indicator variable

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for socioeconomic status), total alcohol consumption (g/day), physical activity (combined recreational and household activity; expressed as sex-specific categories of metabolic equivalents), total energy intake (kcal/day), total daily intakes of fiber (g/day), fruits and vegetable (g/day), and red/processed meats (g/day; refs. 43–48), and diabetes status (49, 50). Subjects were classified as diabetic if they had baseline HbA1c levels $\geq$6.5% and/or self-reported diabetes at recruitment ($n = 174$). For all models, collinearity was assessed and tests for linear trend were performed using a score variable with values from 1 to 4, consistent with the quartile grouping. Statistical tests for heterogeneity to test whether the associations differ by anatomical subsites of colon and rectal cancer were based on χ^2 statistics.

We also assessed effect modification by several factors; sex and tumor location were hypothesized as effect modifiers at the time of study design because of their modifying effect of some colorectal cancer risk factors in previous studies (4), while smoking, alcohol, and BMI were examined for hypothesis generation. The product term of glycer-AGEs (in quartiles) and each potential effect modifier was included in the model and evaluated by a likelihood ratio test. In the sensitivity analysis, we repeated the main multivariable-adjusted models after excluding cases that occurred in the first 2 years of the follow-up ($n = 142$ for colon and $n = 82$ for rectum) and their matched controls to avoid possible reverse causality, and subjects with diabetes and their matched cases and controls ($n = 180$ for colon and $n = 128$ for rectum). Heterogeneity tests were based on χ^2 statistics.

Logistic restricted cubic spline models were used to explore possible deviation from nonlinear relationships between glycer-AGEs and colorectal cancer, with 4 knots specific at the median of each quartile of glycer-AGEs levels.

A two-tailed P value < 0.05 was considered to be statistically significant. All statistical analyses were performed with SAS version 9.3 (SAS Institute) statistical software package.

Results

Baseline characteristics of cases and controls

Selected baseline characteristics of the colon and rectal cancer cases and their matched controls are compared in Table 1. Colon and rectal cancer cases were on average 59 years and 58 years old and had mean follow-up times of 3.7 and 3.9 years, respectively. Colon cancer cases included a higher proportion of individuals who reported being physically inactive (15.8% vs. 11.5%), had higher average hs-CRP levels (3.1 vs. 2.2 mg/L), and consumed less fruits and vegetables (369 g/d vs. 418 g/d) than their matched controls. Both colon and rectal cancer cases were more likely to be diabetic (10.2% vs. 6.9% for colon and 11.7% vs. 8.0% for rectal cancer) than their counterparts. No significant case–control differences were observed in other baseline characteristics.

Associations of glycer-AGEs with colorectal cancer

Table 2 presents ORs and 95% CIs for the association between glycer-AGEs levels, in quartiles using the lowest category as a referent, and colorectal cancer. Overall, models with adjustments for matching factors showed very similar results with the multivariable models with adjustments for established confounding factors in addition to matching factors. Elevated glycer-AGEs levels were not associated with colorectal cancer risk (multivariable adjusted OR, 1.10; 95% CI, 0.82–1.49, comparing highest vs. lowest quartiles; $P_{trend} = 0.87$). When analyses were run separately for colorectal cancer subsites, no association was observed between glycer-AGEs and risk of colon cancer (multivariable adjusted OR, 0.83; 95% CI, 0.57–1.22; $P_{trend} = 0.25$), whereas a statistically significant positive association was observed with rectal cancer (multivariable adjusted OR, 1.90; 95% CI, 1.14–3.19; $P_{trend} = 0.04$), although the test for heterogeneity was not statistically significant ($P_{heterogeneity} = 0.14$).

After testing potential effect modification by various factors relevant for colorectal cancer risk and glycer-AGEs concentrations, alcohol consumption showed a statistically significantly modifying effect on the association between glycer-AGEs level and rectal cancer ($P_{interaction} = 0.03$). Further stratification by level of alcohol consumption (dichotomized based on the sex-specific median values of total alcohol consumption among controls; men, 18.1 g/d; women, 5.7 g/d) showed a significant, positive association for rectal cancer among high alcohol consumers (> median) group (multivariate adjusted OR, 2.70; 95% CI, 1.29–5.62; $P_{trend} = 0.01$; Table 3). No significant effect modifications, including alcohol consumption, were observed for colon cancer.

Sensitivity analysis

After exclusion of cases which occurred during the first 2 years of follow-up and their matched controls, the overall findings did not change substantially for either of the colorectal cancer, colon, or rectum anatomical sites. The associations between glycer-AGEs and colorectal cancer, colon, and rectal cancer risks were also similar after excluding subjects with diabetes. Spline models confirmed that associations between glycer-AGEs and risk of colon or rectal cancers were linear.

Discussion

In this nested case–control study within the large prospective EPIC cohort, we did not observe any overall association between increasing circulating levels of glycer-AGEs and colorectal cancer. However, subgroup analyses by anatomical subsite showed a statistically significant positive association with risk of rectal cancer, particularly among those with higher alcohol consumption. We found no association between glycer-AGEs and colon cancer risk.

A role for AGEs in colorectal cancer development has been hypothesized (37) but not yet fully explored. This may be due to the complexity of this family of compounds, whose heterogeneous structures are far from being fully understood (51). Of the handful of different AGEs species identified, *N*-(carboxymethyl)-lysine (CML) is probably among the most studied and is inferred as an indicator of overall AGEs exposure. The only evidence to date from prospective studies on blood CML measures shows no association with risk of colorectal cancer (36) or pancreatic cancer (52), results which are in line with our present findings for colorectal cancer, although we studied a different and possibly more toxic species of AGEs (14).

Our subgroup observations of a risk for rectal but not colon cancer are interesting. One explanation is chance, given the limited sample size of the rectal cancer subgroup and the non-statistically significant test for heterogeneity of effect between the anatomical subsites. However, there are some possible biologic explanations for this observation: (a) Colon and rectal tissues may

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Table 1. Description of cases and matched controls, by anatomical site

	Colon cancer		Rectal cancer	
Characteristics	**Cases**	**Matched controls**	**Cases**	**Matched controls**
Men, *n*	297	297	213	213
Women, *n*	362	362	183	183
Total	659	659	396	396
Age, years, mean (SD)				
At recruitment	58.8 (7.2)	58.8 (7.2)	58.1 (6.8)	57.7 (6.6)
At blood collection	59.0 (7.2)	58.9 (7.2)	58.1 (6.8)	57.8 (6.5)
BMI, kg/m^2, mean (SD)	26.8 (4.5)	26.3 (3.9)	26.6 (4.0)	26.4 (3.8)
Waist circumference, cm, mean (SD)	90.4 (13.3)	88.0 (12.1)	90.4 (12.9)	89.8 (12.9)
Smoking status/duration/intensity, *n* (%)				
Never smokers	276 (41.9)	291 (44.2)	155 (39.1)	156 (39.4)
Ex-smokers, duration of smoking <10 years	40 (6.1)	43 (6.5)	21 (5.3)	29 (7.3)
Ex-smokers, duration of smoking ≥10 years	160 (24.3)	165 (25.0)	103 (26.0)	93 (23.5)
Ex-smokers, missing duration of smoking	15 (2.3)	12 (1.8)	4 (1.0)	8 (2.0)
Smokers, <15 cigarettes a day	110 (16.7)	96 (14.6)	79 (19.9)	65 (16.4)
Smokers, ≥15 to <25 cigarettes a day	41 (6.2)	39 (5.9)	24 (6.1)	34 (8.6)
Smokers, ≥25 cigarettes a day	9 (1.4)	6 (0.9)	7 (1.8)	5 (1.3)
Missing smoking status	8 (1.2)	7 (1.1)	3 (0.8)	6 (1.5)
Physical activity, *n* (%)				
Inactive	104 (15.8)	76 (11.5)	57 (14.4)	58 (14.6)
Moderately inactive	201 (30.5)	206 (31.3)	115 (29.0)	99 (25.0)
Moderately active	288 (43.7)	293 (44.5)	176 (44.4)	169 (42.7)
Active	62 (9.4)	78 (11.8)	48 (12.1)	61 (15.4)
Missing/unspecified	4 (0.6)	6 (0.9)	0	9 (2.3)
Education level, *n* (%)				
None/primary	256 (38.8)	288 (43.7)	147 (37.1)	163 (41.2)
Technical/professional	151 (22.9)	161 (24.4)	108 (27.3)	110 (27.8)
Secondary	113 (17.1)	83 (12.6)	54 (13.6)	41 (10.3)
University or higher	117 (17.7)	109 (16.5)	75 (18.9)	75 (18.9)
Missing/unspecified	22 (3.3)	18 (2.7)	12 (3.0)	7 (1.8)
Diabetes status, %				
Self-reported diabetes at recruitment, *n* (%)	29 (5.3)	29 (5.3)	24 (6.9)	16 (4.6)
Subjects HbA1c ≥ 6.5%, *n* (%)	54 (10.0)	25 (6.1)	36 (11.1)	22 (8.6)
Self-reported diabetes or HbA1c ≥ 6.5%, *n* (%)	65 (10.2)	42 (6.9)	45 (11.7)	30 (8.0)
Dietary variables [g/day, median (IQR)]				
Total energy, kcal/day	2,070 (1,690–2,490)	2,060 (1,730–2,450)	2,150 (1,730–2,560)	2,110 (1,720–2,560)
Total fat intake	77 (60–96)	77 (61–96)	79 (60–104)	80 (63–103)
Fiber intake	22 (17–27)	23 (18–27)	22 (18–28)	23 (18–28)
Fruit and vegetable intake	369 (246–524)	418 (263–566)	356 (244–504)	364 (250–524)
Red meat intake	48 (25–77)	48 (26–76)	56 (34–84)	54 (31–82)
Processed meat intake	25 (13–41)	23 (12–42)	27 (14–47)	26 (13–47)
Alcohol intake	9 (1–23)	8 (1–21)	12 (2–31)	11 (2–25)
Hs-CRP, mg/L, median (IQR)	3.1 (1.3–5.7)	2.2 (1.1–4.7)	2.3 (1.0–4.4)	2.3 (1.0–4.2)
Cholesterol, mmol/L, median (IQR)	6.3 (5.5–7.1)	6.4 (5.6–7.2)	6.4 (5.6–7.1)	6.5 (5.8–7.3)
HDL, mmol/L, median (IQR)	1.4 (1.1–1.7)	1.4 (1.2–1.8)	1.4 (1.2–1.7)	1.4 (1.2–1.7)
LDL, mmol/L, median (IQR)	4.2 (3.5–4.8)	4.2 (3.5–4.9)	4.2 (3.4–4.8)	4.3 (3.6–5.0)
Glycer-AGEs, U/mL, median (IQR)	6.8 (5.3–8.3)	7.0 (5.5–8.7)	7.2 (5.8–9.1)	7.1 (5.4–8.6)

NOTE: Cases and controls were matched on age (within 2.5 years), gender, administrative center, hormone therapy and menopausal status (among women), fasting status, and date of blood collection (within 45 days).
Abbreviations: IQR, interquartile range; LDL, low-density lipoprotein.

differ in expression level of the receptors that either bind AGEs (i.e., RAGE) and then elicit various protumorigenic effects (53), or those that act as competitive inhibitors of RAGE-mediated signaling pathways, i.e., soluble form of RAGE (sRAGE; ref. 54). Glycer-AGEs have been shown to have high binding affinity for RAGE (34), and decreased circulating sRAGE levels have been observed in colorectal cancer (36). If RAGE and sRAGE expression and activity levels differ between colon and rectal tissues, then a difference of effect associated with AGEs exposure may be plausible. In the current literature, there is some evidence indicating an increase in RAGE expression in human colon tissues in Crohn's disease (55), and in the colon tissue of diabetic rats (56), but direct comparisons of human colon versus rectal normal and tumor tissues have not been reported and would warrant further study. (b) AGEs-induced effects and AGEs accumulation may vary in tumors from different anatomical sites (24), resulting in tissue-specific effects of glycer-AGEs or AGEs in general. And (c) colon and rectal tumors differ by gene mutations (e.g., *K*-ras and *APC* gene) and biologic behavior (57–59), indicating that they may arise from different mechanisms of carcinogenesis and hence be differentially affected by various endogenous and exogenous factors, such as AGEs. Thus, although they are plausible, our findings of a differential association between the colon and rectal anatomical subsites require both replication and further study.

A related incidental observation in our subgroup analyses was a statistically significant effect modification of alcohol on

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Table 2. Circulating glycer-AGEs concentration and the risk of cancers of the colorectum, colon, and rectum

	Glycer-AGEs				
	Q1 (reference)	Q2	Q3	Q4	
Type of cancer	OR	OR (95% CI)	OR (95% CI)	OR (95% CI)	P_{trend}
Colorectum					
Cut-point [U/mL][a]	≤5.42	>5.42 and ≤7.03	>7.03 and ≤8.65	>8.65	
Mean (SD), median [U/mL]	4.3 (0.9), 4.4	6.3 (0.5), 6.3	7.8 (0.4), 7.7	10.5 (1.7), 10.0	
Number of cases/controls	249/264	301/264	237/263	266/263	
Matching factors[b]	1.00	1.19 (0.94–1.50)	0.95 (0.74–1.23)	1.07 (0.81–1.42)	0.95
Multivariate adjusted[c]	1.00	1.18 (0.92–1.51)	0.94 (0.72–1.24)	1.10 (0.82–1.49)	0.87
Colon					
Cut-point [U/mL][a]	≤5.48	>5.48 and ≤6.99	>6.99 and ≤8.68	>8.68	
Mean (SD), median [U/mL]	4.3 (0.9), 4.5	6.3 (0.5), 6.2	7.7 (0.5), 7.7	10.5 (1.7), 10.0	
Number of cases/controls	174/166	184/165	157/164	144/164	
Matching factors[b]	1.00	1.03 (0.77–1.37)	0.88 (0.64–1.20)	0.78 (0.55–1.11)	0.12
Multivariate adjusted[c]	1.00	1.04 (0.76–1.42)	0.86 (0.61–1.22)	0.83 (0.57–1.22)	0.25
Rectum					
Cut-point [U/mL][a]	≤5.36	>5.36 and ≤7.12	>7.12 and ≤8.61	>8.61	
Mean (SD), median [U/mL]	4.2 (1.0), 4.4	6.3 (0.5), 6.4	7.8 (0.4), 7.7	10.3 (1.7), 9.5	
Number of cases/controls	77/99	115/100	79/98	125/99	
Matching factors[b]	1.00	1.49 (0.99–2.23)	1.14 (0.73–1.80)	1.90 (1.17–3.10)	0.03
Multivariate adjusted[c]	1.00	1.47 (0.96–2.27)	1.11 (0.68–1.80)	1.90 (1.14–3.19)	0.04

Abbreviation: Q, quartile.

[a]Based on control participants only.

[b]Model based on matching factors (age, gender, administrative center, time of the day at blood collection, fasting status, and menopausal status among women) only.

[c]Model based on matching factors plus adjustments for smoking status/duration/intensity, BMI, total physical activity, education level, diabetes status, total dietary energy consumption, and intakes of alcohol, red and processed meat, fiber, and fruits and vegetables.

the association between glycer-AGEs and rectal cancer risk. Although alcoholic beverages may be important exogenous sources of AGEs (60) and several studies, including our own (48), have observed a stronger association between higher alcohol consumption and development of rectal than colon cancer (61, 62), these observations do not explain the modifying effect of alcohol on the association of AGEs with rectal cancer that we observed. The reasons for this modification are therefore unclear and, if the modification were replicated, would warrant further study.

The present study has several strengths. The foremost is the prospective design and the prediagnostic collection of dietary/lifestyle information and blood samples from the cohort participants. Our study was also large and well powered to explore associations with colorectal cancer, but size was a limiting factor in our subgroup analyses. A key limitation of

Table 3. ORs (95% CI) for colon and rectal cancer according to quartiles of circulating glycer-AGEs by alcohol intake status

	Glycer-AGEs[a]				
Sex-specific categories of dietary	Q1	Q2	Q3	Q4	
alcohol intake level (g/day)	OR	OR (95% CI)	OR (95% CI)	OR (95% CI)	P_{trend}
Colon					
Low alcohol status (≤ median)[b]					
Number of cases/controls	135/130	145/137	119/119	104/124	
Matching factors[c]	1.00	0.97 (0.69–1.37)	0.79 (0.54–1.15)	0.71 (0.46–1.10)	0.08
Multivariate adjusted[d]	1.00	1.01 (0.69–1.47)	0.79 (0.52–1.20)	0.82 (0.51–1.33)	0.29
High alcohol status (> median)[b]					
Number of cases/controls	39/36	39/28	38/45	40/40	
Matching factors[c]	1.00	1.48 (0.68–3.20)	0.92 (0.40–2.07)	1.11 (0.47–2.58)	0.95
Multivariate adjusted[d]	1.00	1.10 (0.46–2.61)	0.78 (0.31–1.95)	1.17 (0.46–3.03)	0.95
Rectum					
Low alcohol status (≤ median)[b]					
Number of cases/controls	51/64	70/57	38/46	57/63	
Matching factors[c]	1.00	1.56 (0.92–2.65)	0.95 (0.52–1.73)	1.14 (0.66–1.97)	0.95
Multivariate adjusted[d]	1.00	1.48 (0.85–2.58)	0.95 (0.51–1.78)	1.14 (0.64–2.03)	0.99
High alcohol status (> median)[b]					
Number of cases/controls	26/35	45/43	40/52	68/36	
Matching factors[c]	1.00	1.39 (0.69–2.77)	1.14 (0.57–2.29)	2.85 (1.41–5.79)	< 0.01
Multivariate adjusted[d]	1.00	1.41 (0.69–2.88)	1.07 (0.52–2.19)	2.70 (1.29–5.62)	0.01

Abbreviation: Q, quartile.

[a]Quartile cut-offs are same as in Table 2.

[b]Alcohol consumption level was dichotomized based on the sex-specific median values of lifetime alcohol consumption among controls.

[c]Model adjusted for matching factors (age, gender, administrative center, time of the day at blood collection, fasting status, and menopausal status among women) only.

[d]Model adjusted for matching factors plus smoking status/duration/intensity, BMI, total physical activity, education level, diabetes status, total dietary energy consumption, red and processed meat, fiber, and fruits and vegetables.

our study is that we only had a single measure of glycer-AGEs, taken at time of recruitment into the cohort (baseline). Although there is no information as to what extent a single measure of AGEs reflects long-term exposure, random errors in measuring long-term exposure would be expected to reduce any observed disease risk associations toward the null. The finding of a significant association between glycer-AGEs and the risk of rectal cancer suggests that any measurement error was not sufficient to obscure the association, though the relative risks we observe may underestimate the strength of the true association.

In summary, in this prospective study in European populations, circulating glycer-AGEs were not associated with overall risk of colorectal cancer. Further research is needed to investigate the role of glyer-AGEs and AGEs in general in colorectal cancer development.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

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