LETTER

Yogurt consumption and risk of conventional and serrated precursors of colorectal cancer

Davenport *et al*[1] underscored the urgent need to identify new modifiable factors for colorectal adenomas. A few studies[2 3] reported that higher yogurt intake may reduce the risk of colorectal cancer (CRC), potentially mediated by the gut microbiome. However, no study has yet evaluated the association between yogurt intake and precursors of CRC.

We prospectively evaluated the association between yogurt intake and risk of conventional adenoma and serrated lesion, among 32 606 men in the Health Professionals Follow-up Study (HPFS) and 55 743 women in the Nurses' Health Study (NHS), who have undergone lower endoscopy between 1986 and 2012. These participants provided detailed information on demographics, lifestyle and diet including yogurt consumption every 4 years. Multivariable logistic regressions were used to calculate ORs and 95% CIs associated with cumulative average of yogurt intake. We examined the associations by adenoma type (conventional adenomas only, serrated lesions only or both), malignant potential (for conventional adenomas: high-risk (≥1 cm or with villous component or high grade/severe dysplasia, or ≥3 adenomas) vs low risk; for serrated lesions: ≥1 vs <1 cm) and anatomical site (proximal, distal or rectum).

We documented 5811 adenomas in men and 8116 adenomas in women. In men, compared with individuals without yogurt consumption, men who consumed ≥2 servings/week had a lower risk of conventional adenoma (multivariable OR=0.81, 95% CI=0.71 to 0.94, p_{trend}=0.01; table 1). This inverse association was more pronounced for adenomas with high malignant potential (OR=0.74, 95% CI=0.59 to 0.92, p_{trend}=0.01) than those with low risk (p_{trend}=0.25) (figure 1A). Also, stronger inverse associations were observed for colon (OR=0.82, 95% CI=0.70 to 0.95, p_{trend}=0.01) than for rectal adenomas (p_{trend}=0.95) (figure 1B). Overall, among men, no apparent association was observed for serrated lesions (p_{trend}=0.34), but a trend toward inverse association for lesions ≥1 cm was seen (OR=0.48, 95% CI=0.25 to 0.95, p_{trend}=0.04) (figure 1A). In women, no associations were observed for conventional adenomas and/or serrated lesions (table 1) or according to adenoma subtype or anatomical sites (online supplementary table S1).

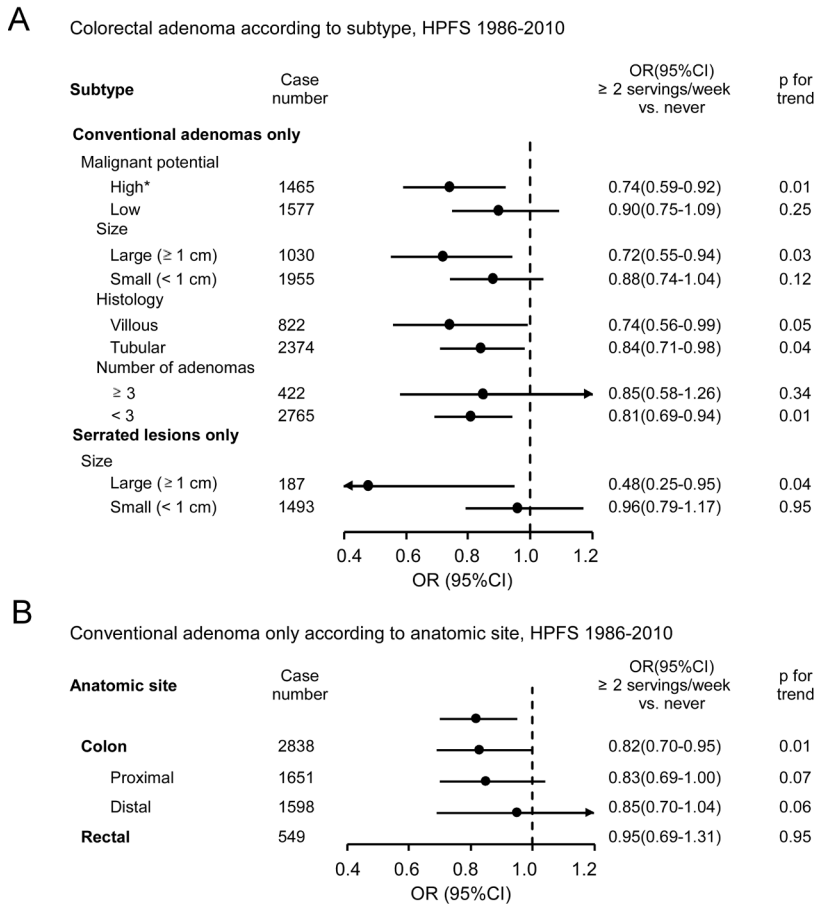

Figure 1 Yogurt intake and risk of colorectal adenoma according to subtype (A); yogurt intake and risk of conventional adenoma only according to anatomical site (B) in the Health Professionals Follow-up Study (HPFS). *High-risk adenomas include adenomas ≥1 cm, or with tubulovillous/villous histology or high grade/severe dysplasia or ≥3 adenomas. OR was adjusted for the covariates denoted in table 1. P for trend was calculated using the median of each yogurt intake category as a continuous variable.

Yogurt has been recommended by the Dietary Guidelines for Americans as part of fat-free and low-fat dairy[4]; however, its intake is low. We found that yogurt intake may reduce risk of conventional adenoma, in particular those of high malignant potential, and independent of calcium and non-yogurt dairy intake. We also reported the probable inverse association with risk of large serrated lesions, an emerging clinical phenotype that also requires extensive surveillance. Taking together, yogurt may help prevent precursors of CRC, potentially through both adenoma-to-carcinoma sequence and serrated pathway. A number of possible mechanisms have been postulated. Products of the two common probiotics used in yogurt, *Lactobacillus bulgaricus* and *Streptococcus thermophilus*, may reduce levels of carcinogens such as nitroreductase, faecal activated bacterial enzymes and soluble faecal bile acids.[5–7] The stronger link between yogurt intake and colon versus rectal adenomas may in part due to the lower pH in the colon, which is more hospitable for probiotics.[8] Yogurt may also reduce adenoma risk by exerting anti-inflammatory effects on colon mucosa and ameliorating gut barrier dysfunction.[9] As male patients with adenoma present with increased gut permeability,[10] yogurt may benefit more for men compared with women.

The strengths of the study include prospective and updated assessments of yogurt intake with large number of cases of conventional adenomas and serrated lesions. Future studies in different racial/ethnical groups are warranted to confirm these findings and elucidate underlying biological mechanisms associated with sex and anatomical site differences.

Table 1 Yogurt intake and risk of conventional adenoma and serrated lesion, HPFS and NHS 1986–2010

	Yogurt intake				
	Never	1–3/month	1–<2/week	≥2/week	P for trend*
Men (HPFS)					
Conventional adenomas only					
No of cases (n=3196)	1701	687	542	266	
Age-adjusted OR (95% CI)†	1(Ref)	0.91 (0.83 to 1.00)	0.91 (0.82 to 1.00)	0.74 (0.65 to 0.84)	<0.001
Multivariable-adjusted OR (95% CI)‡	1(Ref)	0.96 (0.87 to 1.05)	0.97 (0.87 to 1.07)	0.81 (0.71 to 0.94)	0.01
Serrated lesions only					
No of cases (n=1800)	924	392	323	161	
Age-adjusted OR (95% CI)†	1(Ref)	0.93 (0.83 to 1.05)	0.98 (0.86 to 1.12)	0.81 (0.68 to 0.96)	0.02
Multivariable-adjusted OR (95% CI)‡	1(Ref)	0.99 (0.88 to 1.12)	1.05 (0.92 to 1.21)	0.89 (0.74 to 1.07)	0.34
Conventional adenomas and serrated lesions					
No of cases (n=815)	439	176	138	62	
Age-adjusted OR (95% CI)†	1(Ref)	0.90 (0.75 to 1.07)	0.87 (0.71 to 1.05)	0.66 (0.50 to 0.86)	0.001
Multivariable-adjusted OR (95% CI)‡	1(Ref)	0.98 (0.82 to 1.18)	0.97 (0.79 to 1.18)	0.78 (0.59 to 1.04)	0.10
Women (NHS)					
Conventional adenomas only					
No of cases (n=3896)	1347	870	1041	638	
Age-adjusted OR (95% CI)†	1(Ref)	1.02 (0.94 to 1.12)	1.00 (0.92 to 1.09)	0.95 (0.86 to 1.05)	0.24
Multivariable-adjusted OR (95% CI)‡	1(Ref)	1.05 (0.96 to 1.15)	1.03 (0.94 to 1.12)	0.98 (0.88 to 1.09)	0.55
Serrated lesions only					
No of cases (n=3230)	1100	707	900	523	
Age-adjusted OR (95% CI)†	1(Ref)	0.98 (0.89 to 1.08)	0.99 (0.90 to 1.08)	0.88 (0.79 to 0.98)	0.03
Multivariable-adjusted OR (95% CI)‡	1(Ref)	1.03 (0.94 to 1.14)	1.02 (0.93 to 1.13)	0.92 (0.82 to 1.04)	0.14
Conventional adenomas and serrated lesions					
No of cases (n=990)	331	223	281	155	
Age-adjusted OR (95% CI)†	1(Ref)	1.05 (0.89 to 1.25)	1.02 (0.87 to 1.20)	0.88 (0.73 to 1.07)	0.17
Multivariable-adjusted OR (95% CI)‡	1(Ref)	1.12 (0.94 to 1.34)	1.09 (0.91 to 1.30)	0.94 (0.76 to 1.17)	0.46

*Calculated using the median of each yogurt intake category as a continuous variable.
†Adjusted for age, time period of endoscopy, number of reported endoscopies, time since most recent endoscopy and reason for current endoscopy.
‡Additionally adjusted for height (continuous), body mass index (in quintiles), family history of CRC (yes/no), diabetes (yes/no), pack-years of smoking (never, 1–4.9, 5–19.9, 20–39.9, ≥40 pack-years), alcohol intake (never, 0.1–4.9, 5–14.9, 15–29.9, ≥30 g/day), physical activity in METs (in quintiles), regular use of aspirin (yes/no), regular NSAIDs use (yes/no), total vitamin D intake (in quintiles), non-yogurt dairy intake (in quintiles), total calorie intake (in quintiles), red and processed meat intake (in quintiles), dietary fibre intake (in quintiles), total folate intake (in quintiles), Alternative Healthy Eating Index-2010 (in quintiles), total calcium intake (in quintiles), menopausal status (premenopausal/postmenopausal, NHS only) and menopausal hormone use (never/past/current, NHS only).
CRC, colorectal cancer; HPFS, Health Professionals Follow-up Study; METs, metabolic equivalent tasks; NHS, Nurses' Health Study; NSAIDs, non-steroidal anti-inflammatory drugs.

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Contributors XiZ, YC and XuZ had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: XiZ, YC, XuZ. Acquisition of data: KW, MS, ATC, ELG, YC. Analysis and interpretation of data: all coauthors. Drafting of the manuscript: XiZ, YC, XuZ. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: XiZ, YC. Obtained funding: SO, ATC, ELG, XuZ. Administrative, technical or material support: YC, XuZ. Study supervision: YC, XuZ.

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Competing interests Charles S. Fuchs reports consulting role for Agios, Bain Capital, Bayer, Celgene, Dicerna, Five Prime Therapeutics, Gilead Sciences, Eli Lilly, Entrinsic Health, Genentech, KEW, Merck, Merrimack Pharmaceuticals, Pfizer, Sanofi, Taiho, and Unum Therapeutics. He also serves as a Director for CytomX Therapeutics and owns unexercised stock options for CytomX and Entrinsic Health.

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