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Yogurt consumption and colorectal polyps

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TCPS Study: MJS, WZ, HJM designed and implemented the study. RN, WES, MJS, XZ participated in data collection. MJS and XZ provided the overall statistical analysis and oversight. MJS wrote the manuscript. All authors provided the critical review of the manuscript and approved the final manuscript.

Biofilm Study: CLS and FMG designed and implemented the study and reviewed all data. EHS, GEM, DK, LL, JLD, JJG, LMH participated in data collection. SBR analyzed the data and performed statistical analysis. SBR, CLS, FMG wrote the manuscript. All authors provided the critical review of the manuscript and approved the final manuscript.

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Abstract

Diet modifies the risk of colorectal cancer (CRC) and inconclusive evidence suggests yogurt may protect against CRC. We analyzed data collected from two separate colonoscopy-based case-control studies. The Tennessee Colorectal Polyp Study (TCPS) and Johns Hopkins Biofilm Study included 5,446 and 1,061 participants, respectively, diagnosed with hyperplastic polyp (HP), sessile serrated polyp (SSP), adenomatous polyp (AP), or without any polyps. Multinomial logistic regression models were used to derive odds ratios (ORs) and 95% confidence intervals (95% CI) to evaluate comparisons between cases and polyp-free controls and case-case comparisons between different polyp types. We evaluated the association between frequency of yogurt intake and probiotic use with the diagnosis of colorectal polyps. In the TCPS, daily yogurt intake vs no/rare intake was associated with decreased odds of HP (OR= 0.54; 95%CI: 0.31–0.95) and weekly yogurt intake was associated with decreased odds of AP among women (OR= 0.73; 95%CI: 0.55–0.98). In the Biofilm study, both weekly yogurt intake and probiotic use were associated with a non-significant reduction in odds of overall AP (OR=0.75; 95%CI: 0.54, 1.04) and (OR=0.72; 95%CI: 0.49, 1.06) in comparison to no use, respectively. In summary, yogurt intake may be associated with decreased odds of HP and AP and probiotic use may be associated with decreased odds of AP. Further prospective studies are needed to verify these associations.

Keywords

Yogurt; probiotics; colorectal polyps; adenomatous polyps; sessile serrated polyps; hyperplastic polyps; serrated polyps

INTRODUCTION

Colorectal cancer (CRC) accounts for a substantial burden of disease and mortality worldwide as the third leading cause of cancer in women and men in the United States and globally[(1)].CRC represents a heterogeneous collection of cancers resulting from several genetic and epigenetic changes [(2)]. There are at least two different premalignant polyps, adenomatous polyps (AP) and sessile serrated polyps (SSP), with different etiologies and pathways leading to CRC and, possibly, different risk factors[(3–14)].

A majority of CRC cases are attributed to modifiable lifestyle factors including diet, obesity, physical activity, alcohol intake, and tobacco use[(6,13,15–20)]. Dietary behavior modification represents a potential strategy to prevent CRC. Mounting evidence suggests red and

processed meat and saturated fats increase the risk, whereas fiber, fruits and vegetables may protect against CRC[15,21,22]. Fermentable dairy foods and yogurt specifically may also offer protection against colon cancer although accumulating evidence is limited and inconclusive.

Yogurt consumption in European countries accounts for up to 32% of dairy intake[23]. In the US, the prevalence of yogurt consumption has been increasing particularly as a means for obtaining health benefits[23,24]. While there is significant variation in commercially available products, yogurt is a source of protein, dietary minerals including calcium, magnesium, and B vitamins[23]. A growing literature suggests that yogurt consumption and probiotic use may have multiple health benefits including osteoporosis, obesity and metabolic disease, cardiovascular disease, chronic kidney, mental health disease aside from possible gastrointestinal (GI) benefits[23,25–30].

At the turn of the 20th century, Metchnikoff first proposed that lactic acid-producing bacteria present in yogurt, including *Lactobacillus bulgaricus, Streptococcus thermophiles, Lactobacillus acidophilus,* and *Bifidobacterium* might protect against colon cancer by inactivating toxins produced by pathologic bacteria[18,31,32]. With better understanding of the interaction between the gut microbiome and colon health, preliminary evidence supports an anti-tumor effect of lactic acid-producing bacteria contained in yogurt and probiotics whereby these bacteria may optimize the environment of the colon[31,33–37].

Few epidemiologic studies have evaluated the relationship between yogurt and CRC and, of these, several found an inverse association[38–42] and the rest were null[43–50]. Lack of associations may be due to a limited statistical power to detect a difference in CRC risk from either a small sample size or a low prevalence of and/or limited variability in yogurt consumption. Fewer studies evaluated the association between yogurt intake and risk of colorectal AP[42,45,51,52]. None have evaluated SSP, recently recognized with the potential for malignant transformation [4], although a recent cohort study found a null association among all serrated polyps, evaluating HP and SSP as one entity [53]. Furthermore, just one small randomized controlled trial performed in a Japanese population with prior colorectal tumors evaluated the association between probiotic supplement use and risk of colorectal tumors (adenomas and early colorectal cancers), but not sessile serrated polyps. This investigation found an inverse association between probiotic use alone and recurrence of metachronous AP with moderate atypia or higher[54]. Thus, we evaluated the association between yogurt consumption and odds of polyps in two colonoscopy-based case-control studies; in one study, probiotic supplement use in relation to odds of polyps was also assessed.

EXPERIMENTAL METHODS

Study Populations

Tennessee Colorectal Polyp Study—The Tennessee Colorectal Polyp Study (TCPS) is a colonoscopy-based case-control study conducted from February 2003 to October 2010. Institutional approval for human subjects' research was granted through the VUMC and VA Institutional Review Boards (IRB) and the VA Research and Development Committee. The study design has been previously described[55]. In brief, participants were recruited from

those presenting for routine colonoscopy at two medical centers in Nashville, TN. Eligible participants were aged 40–75 years, and did not have any of the following: inflammatory bowel disease, a personal or family history of any hereditary CRC syndromes, a prior history of colorectal AP, previous colectomy, or a history of cancer other than non-melanoma skin cancer.

In all, 12,585 individuals were approached for participation in TCPS and 7,621 (60.6%) provided informed consent. This analysis is limited to the 5,446 participants diagnosed with a hyperplastic polyp (HP), SSP, AP, or without any polyps who also completed a telephone interview and food frequency questionnaire (FFQ) with a reported daily consumption of at least 600 kcal/day and with complete data on yogurt intake.

Participants also completed an interviewer-administered questionnaire which solicited information on the participant's demographics, medication use, family history, and other lifestyle factors and a self-administered FFQ with 108 food items which has been previously described[56]. Total energy intake (kcal/day) was also derived from the FFQ that asks about dietary patterns over the last 12 months.

Johns Hopkins Biofilm Study—The Biofilm Study recruited patients undergoing colonoscopy for routine care at three endoscopy study sites, Green Spring Station Endoscopy Center in Lutherville, MD, White Marsh Endoscopy Center in Baltimore, MD and Reading Endoscopy Center in Wyomissing, PA between August, 2016, and April, 2018. Prior to colonoscopy, the participant met with the endoscopist and the research coordinator, enrollment was discussed and written informed consent was obtained. A total of 1,061 patients were enrolled and had complete data (~43% of all eligible). The study was reviewed and approved by the Johns Hopkins Medical Institute (JHMI) IRB for human research. The inclusion criteria included adults (ages 40–85) with an intact colon. Individuals with inflammatory bowel disease, a history of using blood thinners including warfarin or antiplatelet drugs, individuals with a hemicolectomy and pregnant women were excluded.

Participants completed a questionnaire including socio-demographic information, risk factors for CRC (including detailed questions regarding their medical and surgical history), medication use (including antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDS), aspirin, hormone therapy), family history of CRC, patterns of tobacco use, alcohol use and physical activity, and history of prior colonoscopy and pertinent findings. Participants were defined as having diabetes mellitus, hypertension or hyperlipidemia if they self-reported a prior history of those conditions. In addition, they answered basic questions regarding their dietary patterns regarding the frequency of consumption of meat, fish, eggs, cheese, milk, and yogurt during the last 12 months. The questionnaire is available in the Appendix.

Yogurt Intake and Probiotic Use—In TCPS, yogurt intake frequency was defined as never/rarely, monthly but less than weekly (1–3/month), weekly but less than daily (1–6/week), and daily (1+/day). Amount of yogurt intake per day was calculated as the usual portion size (0.25, 0.5, or 1 cup) multiplied by the frequency of intake per day and was categorized into four groups: never/rarely (never or rarely consumed) and tertiles based on the consumption among controls.

In the Biofilm study, frequency of yogurt intake (1 cup serving size) was collected as never, within the last year, more than once a month, and more than once a week. For this analysis and to more closely match the TCPS categories, intake was categorized as never/rarely (never or within the last year), monthly less than weekly (more than once a month), and weekly (more than once a week). Information on daily consumption was not available. Probiotic use was defined as taking a probiotic supplement within the last week.

Case and Control Definitions—The TCPS process to standardize polyp diagnosis has been previously described in detail[6]. In brief, all polyps were systematically reviewed by the study pathologist under the guidance of a senior GI clinical and research pathologist to standardize polyp diagnosis. SSP were diagnosed based upon the diagnostic criteria from expert panel standards (at least one distorted, dilated, or horizontally branched crypt within the polyp) by joint review of cases[57]. The Biofilm Study abstracted the polyp diagnosis from the medical record to classify study participants. The precise location, size, diagnosis and other characteristics of the colorectal polyps were collected from the colonoscopy and pathology reports. In both studies, cases were classified according to the presence, number, and synchronicity of HP, SSP, and AP. The HP cases had one or more HP without any synchronous AP or SSP. The AP cases had one or more tubular, tubulovillous, or villous AP with or without dysplasia and with or without synchronous HP. The SSP cases had one or more SSP, with or without synchronous HP and AP. Location was defined relative to the splenic flexure with cecum, ascending and transverse categorized as proximal colon and descending, sigmoid and rectum as distal colon. Due to their rarity, traditional serrated adenomas were excluded from this analysis (n=12 for TCPS and n=1 for Biofilm). AP were defined as advanced if they were 1 cm or greater, or contained villous or dysplastic components. Controls in both studies had a complete colonoscopy with visualization of the cecum without any evidence of polyps at the present colonoscopy although some controls in the Biofilm Study, but not TCPS, may have had a personal history of adenoma (50% of study participants).

Statistical analysis—Supplementary Figures 1 and 2 show the participant flowcharts for the two studies. For both studies, descriptive comparisons between case and control groups were calculated using general linear models (for continuous variables) or Mantel-Haenszel χ^2 testing (for categorical variables) with adjustments for age (5-year age categories from 40–75) and sex, where appropriate. Odds ratios (ORs) and 95% confidence intervals (95% CI) were derived from multinomial logistic regression models which permitted case-control and case-case comparisons. Potential confounders and established risk factors within the studies were adjusted for in the models. In TCPS, models were adjusted for sex, age, study site (academic/VA), educational attainment, body mass index (BMI, kg/m^2), physical activity in the past 10 years (yes/no), regular alcohol drinking (current, former, never), cigarette smoking status (current, former, never), NSAIDS use (ever/never), red meat intake (g/day), dietary energy intake (kcal/day), and frequency of non-yogurt dairy intake (never/rarely, monthly less than weekly, weekly less than daily, daily). In the Biofilm Study, risk factors were included in the final model both if they were established risk factors or had a p value ≤ 0.05 in the univariate analysis which included sex, age, cigarette use (current, former, never), overweight (BMI less than or greater than 25 kg/m^2), prior colon polyp (yes/

no), history of cholecystectomy (yes/no), diabetes mellitus diagnosis (yes/no), hypertension diagnosis (yes/no), hyperlipidemia diagnosis (yes/no), alcohol use (never/<14 alcoholic drinks/week/>14 alcoholic drinks/week) and moderate or vigorous physical exercise (yes/no). Tests for trend were derived by including the categorical variable as a continuous factor in the model. TCPS statistical analyses were completed using SAS Enterprise 7.15. Biofilm statistical analyses were completed using PC SAS 9.4. P values of ≤0.05 (2-sided probability) were considered statistically significant in all analyses.

We performed power calculations for TCPS and the Biofilm study. In TCPS analysis, the minimally detectable ORs are 0.69, 0.52, and 0.31 for AP, HP, and SSP, respectively, assuming a statistical power of 80% and a two-sided alpha of 0.05. Assuming the same power and two-sided alpha, the Biofilm study afforded minimally detectable ORs for AP, HP, and SSP of 0.68, 0.48, and 0.52, respectively.

RESULTS

Demographic characteristics for each study by case-control status are shown in Table 1. A limited number of demographics were collected between both studies (age, sex, race, smoking, BMI, alcohol and physical activity). Among these features, sex, smoking, alcohol use, physical activity and history of colonic polyps differed the most between studies, whereas, the patients in both studies were of similar age and most were Caucasian. In both studies, polyp cases were more likely to have a personal history of smoking. Within TCPS, polyp cases were slightly older, and more likely to be male and overweight, to have lower educational attainment, to consume more red meat, and less likely to exercise, use NSAIDs, and to consume dairy in comparison to controls. In the Biofilm Study, cases with AP or SSP were more likely to have had a cholecystectomy and a history of colon polyps and less likely to have had GI surgery in comparison to controls. Biofilm Study AP cases were older and more likely to be male and overweight, whereas SSP cases were less likely to be overweight and heavily use alcohol and HP cases were more likely to be male and less likely to use aspirin than polyp-free controls.

The associations between yogurt intake and odds of polyp type are presented in Table 2 and online supplemental tables. In TCPS, frequency was inversely associated with odds of serrated polyps (SP; HP and SSP). In comparison to those who did not consume yogurt, daily intake was associated with a 50% decreased odds of HP (OR= 0.54; 95%CI: 0.31–0.95) and a similar, but non-significant reduced odds of SSP (OR=0.49; 95% CI: 0.19–1.24). The association with HP was even stronger among males (OR= 0.28; 95%CI: 0.09–0.91). Daily intake of yogurt was inversely associated with odds of SP without synchronous AP and, particularly, with decreased odds of SP and AP (Supplementary Table 1) overall and separately among men and women. Frequency and amount of yogurt intake was not associated with overall odds of AP, although weekly intake of yogurt was significantly associated with a reduced odds of AP among women (OR= 0.73; 95%CI: 0.55–0.98). The association with daily use was also reduced, but no longer significant with fewer numbers and reduced power (OR= 0.68; 95%CI: 0.44–1.06).

The Biofilm Study also demonstrated a non-significant reduction in odds of SSP for regular yogurt consumption (OR=0.75; 95% CI: 0.44–1.28 for weekly intake vs no/rare intake) with similar magnitude for both men and women. However, unlike TCPS, yogurt intake was not associated with a reduced odds of HP (OR=1.12; 95%CI: 0.62, 2.02), but was associated with a non-significant reduction in overall AP odds (OR=0.75; 95%CI: 0.54, 1.04) that also did not vary by gender. A similar reduction in odds of AP was also observed for probiotic use (OR=0.72; 95%CI: 0.49, 1.06), which was more apparent among women than among men. Twenty four percent and 11% of women and men, respectively, reported using probiotics. To evaluate whether the differences between TCPS and the Biofilm study were due to the inclusion of individuals with a history of polyps in the Biofilm study, we performed a sensitivity analysis in which we restricted the Biofilm study analysis to people without a prior polyp (data not shown). This sensitivity analysis eliminated approximately 50% of the study population, as 55% of women and 44% of men did not have a history of polyps. Among those without a history of polyps, the association between weekly yogurt intake and AP odds became significant (OR=0.54; 95%CI:0.33–0.89) particularly among women, the association between probiotic use and AP became stronger but not significant (OR=0.56; 95%CI:0.30–1.04) although the association with SSP odds was similar.

To evaluate whether the associations between polyp odds and yogurt and probiotic intake varied by region of the colorectum, we evaluated the associations comparing polyp-free controls, left-sided polyps, right-sided polyps, and synchronous right- and left-sided polyps (Supplementary Table 2). The studies varied in their association by region. In TCPS, daily yogurt intake was inversely associated with left-sided polyps (OR=0.56; 95%CI: 0.38–0.83) in comparison to no intake and was most apparent among women. In the Biofilm study, yogurt intake at least weekly was non-significantly inversely associated with odds of polyps only on the right side (OR=0.70; 95%CI: 0.48–1.04). Probiotic use was associated with a non-significant reduced odds of right-sided only polyps (OR=0.69; 95%CI: 0.43–1.11) although this was limited to women (OR=0.67; 95%CI: 0.38–1.18). There was no relationship between yogurt intake and odds of advanced adenomas (Supplementary Table 3).

DISCUSSION

We found in two colonoscopy-based case-control studies that frequency of yogurt consumption was associated with a trend towards decreased odds of colorectal polyps. While both studies found an inverse association between yogurt and colorectal polyps and the Biofilm study found an inverse association between probiotics and colorectal polyps, the findings differed between the two studies in terms of polyp type, polyp location and statistical significance. In TCPS, daily yogurt intake was associated with a decreased odds of SP, particularly HP. Weekly, but not daily yogurt intake, was associated with decreased odds of AP among women, whereas in the Biofilm Study weekly consumption or more of yogurt was associated with a non-significant decreased odds of overall AP. Daily yogurt intake was associated with a decreased odds of left-sided lesions particularly among women in TCPS, and decreased odds of right-sided polyps in the Biofilm Study, respectively. Probiotic use was not associated with a statistically significant polyp risk reduction overall, although it was associated with a borderline reduced odds of AP and right-sided polyps among women.

Lactic acid-producing bacteria are present in probiotic supplements and in fermented milk products such as yogurt. There are several proposed mechanisms by which these bacteria may prevent colon carcinogenesis. Lactic-acid bacteria may decrease the risk of colon polyp formation by stimulating the mucosal immune system, increasing cytokine production, modulating T cell function, and/or increasing Natural Killer (NK) cells and IgA-secreting lymphocytes that then may modify microbiome function[33–37,58]. In addition, these bacteria may also act to decrease CRC risk by decreasing inflammation. In a randomized controlled trial of pediatric patients with active ulcerative colitis, use of probiotics led to resolution of endoscopic and mucosal inflammation 2.5 times more frequently than in controls[34,36,37,59]. Lactic-acid bacteria may also reduce the concentration of secondary bile acids and dietary carcinogenic metabolites produced by meat ingestion including N-nitroso compounds and heterocyclic aromatic amines (HCAs) by binding to and inactivating them and reducing their bioavailability[35,60,61]. Further, certain bacterial strains may reduce bacterial enzyme activities present in the colon such as β-glucuronidase and nitroreductase, which hydrolyze and activate carcinogenic molecules contained in burnt and processed meat products[31,62]. Finally, lactic acid-producing bacteria secrete short chain fatty acids, including butyrate, which is the primary colonocyte energy source and proposed to possess antitumorigenic properties. Butyrate inhibits histone deacetylase and thereby decreases cell proliferation and promotes apoptosis [63–65]. Decreases in butyrate-producing bacteria and enrichment of pathogenic bacteria is a common finding in studies comparing differences between CRC cases and controls[66–69].

Our finding of a possible inverse association between yogurt and probiotic consumption and colorectal neoplasia risk is consistent with prior studies. In the only randomized trial of probiotic use that assessed the effect on AP, Ishikawa et al. randomized individuals with recent colorectal tumors (AP or early cancers) to one of four arms: diet instruction, *Lactobacillus casei*, wheat bran or both *L. casei* and wheat bran[54]. At the end of 4 years, individuals who took *L. casei* had a lower prevalence of metachronous AP with moderate or greater atypia. Although this trial included only a single probiotic bacterium, it provides initial evidence of a possible preventive role for probiotic bacteria in colorectal carcinogenesis. In our analysis, we also observed a decreased odds of AP associated with probiotics consumption.

There are a limited number of epidemiological studies evaluating the relationship between yogurt and CRC risk and their results are inconclusive. In case-control and cohort studies, there have been reports of inverse [38–42] associations with CRC risk, although most have been null[43–50]. Two cohorts out of eight observed an inverse association and three case control studies out of five reported an inverse association[38–50]. When an inverse association has been observed, it has been reported with rectal cancer (38), colon cancer[39–41], Japanese men[38], and among Italians[39]. A pooled analysis of 10 cohort studies examined 5,734 CRC cases and observed a weak inverse association between consumption of yogurt with CRC risk that was of borderline significance[70]. Conversely, previous epidemiologic studies were more consistent regarding the relationship between yogurt intake with AP risk although there are no studies evaluating risk for SSP. Three[42,50,51] previous European case-control studies observed an inverse association between colorectal AP and yogurt intake, but two European cohorts found no association[45,52]. The observed relationships were modest and

limited to large or advanced adenomas. One recent report from two large US cohort studies found an inverse association only among men who consumed yogurt and risk of AP, but no associations were found for SP risk or for polyp risk among women[53]. Instead we found a possible weak association with overall AP odds in the Biofilm study and a significant association with AP odds among women and a strong association with HP in TCPS. The heterogeneity in the design of these studies may contribute to the differences including variation in exposure definition (several assessed broader categories including fermented dairy products)[38–43], extreme heterogeneity of available probiotics and yogurt products (including both the types and quantities of lactic acid-producing bacteria strains contained in each), the underlying population and diet, and analytic methods including controlling for confounders[42,44–53]. Another possible explanation for the inconsistent findings may be misclassification of polyp status in many of the previous studies given the recent understanding of enhanced risk with SSP. Finally, the studies with small sample sizes may be inadequately powered to detect an association.

Our study is strengthened by the use and comparison of two study populations to evaluate the association between yogurt consumption and colorectal polyps, despite some differences between the studies and their findings. Differences may be due to variations in amount of yogurt ingestion and bacterial strains. These two studies were conducted during different eras of yogurt consumption. Yogurt has been growing in popularity in the US population due to companies marketing its health benefits. The prevalence of yogurt consumption in the American diet has increased from 4% to 9% of adults reporting weekly intake from 2004 to 2012[24]. Using National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2014, we also found the intake of yogurt increased over time from 6.1% to 9.2% and the amount of yogurt consumed increased from 10.0 to 17.9 g per day (unpublished data). Among controls, weekly or more frequent consumption of yogurt was slightly higher in the Biofilm Study (45.5%) than in TCPS (40.7%). Unlike in TCPS, daily yogurt intake was not able to be evaluated in the Biofilm study. Thus, the observed association for weekly consumption in the Biofilm Study may reflect daily intake or may also reflect a dilution of the true association for daily users. Moreover, the types of yogurt available and sold in stores has also evolved during the time period between the two studies. In 2010 when TCPS enrollment was ending, Greek yogurt (a more concentrated yogurt with higher protein and reduced sugar content and higher bacterial count) began replacing regular yogurt intake in the US population[71]. In addition, with increasing publicity regarding yogurt health benefits, yogurt companies began modifying yogurt products to include additional bacterial strains (yogurt and probiotic products) with advertisements regarding the health benefits including symptomatic relief from GI symptoms[71]. It is possible that the observed differences between the two studies, and with previous studies, are a result of increased frequency of use or differences in yogurt types or strains.

The Biofilm Study also included participants who had prior polyps and therefore represents a higher risk population. Yogurt use might act differently in these two populations because of a dissimilar underlying risk of forming colorectal polyps. However, when the analysis was restricted to the participants in the Biofilm Study without a history of colorectal polyps the association was stronger and significant for AP and unchanged for SSP and HP. In contrast, polyp-free controls with a prior history of polyps are predisposed to form polyps, but

predisposed individuals may not have had enough time to form polyps between their last colonoscopy and the current colonoscopy. Finally, the two studies employed two different methods to diagnose SSP and HP. As TCPS was conducted prior to the distinction between HP and SSP, this study performed a thorough review of all serrated polyps to update the diagnoses. The colonoscopies performed during the Biofilm study were done after the change in clinical practice and therefore the HP or SSP diagnosis could be audited directly from the medical records. Within the TCPS, the use of one pathologist to diagnose the outcome might have standardized the diagnosis and review of difficult cases with a senior GI pathologist might have improved the accuracy of diagnosis.

As with prior studies, power remains an issue in the two present studies especially in subgroup analyses by polyp type. While the overall sample sizes of the two studies were adequate based on power calculations (see Methods), after performing subgroup analyses by polyp type the samples sizes and power were reduced, especially for SSP given the relative rarity of these polyps. With the collective SSP between both studies, our power to detect a 30% decrease in odds among people who consumed yogurt at least weekly compared to never/rarely was only 18%. Our power to detect a 30% decrease in odds in AP was 67%. Finally, residual confounding may also explain differences between the two studies or with previous findings. In the Biofilm Study, we did not collect overall energy intake, which is a known confounder when assessing for effects of nutrients on colon polyps[72]. The effects of probiotics may be stronger when consumed with prebiotics, such as indigestible fiber that lactic acid-producing bacteria consume and which is proposed to enhance the benefits of probiotic ingestion[73]. Prebiotic use was not collected in the Biofilm Study. Total fiber intake was collected in the TCPS, however, adjustment for fiber did not substantially alter the associations between yogurt and polyps.

The collection of probiotic supplementation in the Biofilm Study is a strength as there are limited data available regarding the effect on colon cancer in epidemiological studies. However, it is important to note we only collected information regarding use in the week prior to colonoscopy and no data regarding frequency of probiotic use or duration of use were collected. This may lead to misclassification of exposure if there were significant differences in intensity and duration of probiotic use among this population.

Overall, using two colonoscopy studies, we were able to observe that both yogurt and probiotics, two different products containing lactic acid-producing bacteria, have independent inverse associations with colorectal polyp odds that were either statistically significant or of borderline significance. We observed a reduced odds of AP in the Biofilm Study and reduced odds of AP among women and reduced odds of SP, particularly HP, in TCPS, associated with yogurt intake. We observed a non-significant reduced odds of AP associated with probiotic use in the Biofilm study. Our collective results raise the possibility of a protective effect of lactic-acid bacteria, but are limited due to differences in study design, lack of clear dose-response relationships and small number of cases to draw inferences, especially in the smaller Biofilm study and in subgroup analyses. Future, rigorous studies to assess the effect of bacterial strains and yogurt types on polyp types and the dose and duration of yogurt intake and probiotic use needed for prevention are warranted, particularly in light of recent results challenging the positive benefit of probiotic

products[74–77]. Further research might prove that interventions with yogurt and probiotics may be potential low-cost strategies for CRC prevention, particularly considering the global surge in CRC and among individuals under 50 years of age[1,78].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CRC	colorectal cancer
HP	hyperplastic polyp
SSP	sessile serrated polyp
AP	adenomatous polyp
SP	serrated polyp

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Table 1:

Characteristics of the Study Participants in the Tennessee Colorectal Polyp Study and Biofilm Study

Characteristic	No Polyp Controls	Hyperplastic Polyps	Adenomatous Polyps	Sessile Serrated Polyps	$p_{heterogeneity}$	No Polyp Controls	Hyperplastic Polyps	Adenomatous Polyps	Sessile Serrated Polyps	$p_{heterogeneity}$
	Tennessee Colorectal Polyp Study[a]					Johns Hopkins Biofilm Study[b]				
-	n=3258	n=471	n=1536	n=181	-	n=579	n=63	n=333	n=96	
Age (years; least square means)	57.6	57.1	59.2[e]	58.2	<0.001	60.2	58.6	62.4[e]	60.0	<0.001
Sex (% Female)	45.4	36.5 [e]	28.1[e]	36.5 [e]	<0.001	59.6	55.1	47.7 [e]	54.2	0.007
Race (% Caucasian)	91.8	91.7	89.9	93.3	0.10[c]	88.6	91.6	90.5	96.1	0.10[c]
Study Site of (%)										
VUMC	76.1	68.2 [e]	70.7 [e]	74.6	<0.001					
VA-Nashville Campus	23.9	31.8	29.3	25.4						
Educational Attainment (%)										
High School or Less	22.1	27.6 [e]	28.0 [e]	24.1	<0.001[c]					
Some College	27.6	28.0	27.8	26.1						
College Graduate	22.2	23.1	21.7	27.9						
Graduate/Professional School	28.1	21.3	22.5	21.9						
Employment Status (%)										
Employed						65.7	59.4	60.7	63.7	0.35[c]
Disabled						1.9	5.3[e]	2.7	1.1	
Retired						29.1	28.8	32.6[e]	31.8	
Unemployed						3.3	6.5	4.0	3.5	
Indication for Colonoscopy (%)										
Average Risk Screening	57.6	54.9	55.7	57.3	0.33[c]	63.2	52.2	60.5	52.1	0.02[c]
Family History	13.1	14.3	12.9	16.2						
Diagnostic/Follow Up	21.1	20.3	22.8	14.6		13.4	15.1	7.8 [e]	15.1	

Characteristic	No Polyp Controls	Hyperplastic Polyps	Adenomatous Polyps	Sessile Serrated Polyps	$P_{heterogeneity}$	No Polyp Controls	Hyperplastic Polyps	Adenomatous Polyps	Sessile Serrated Polyps	$P_{heterogeneity}$
	Tennessee Colorectal Polyp Study[a]					Johns Hopkins Biofilm Study[b]				
-	n=3258	n=471	n=1536	n=181	-	n=579	n=63	n=333	n=96	
Surveillance	-	-	-	-		23.4	32.6 [e]	31.7 [e]	32.8 [e]	
Other	8.2	10.5	8.5	12.0		-	-	-	-	
Family History of Colorectal Cancer (%)	9.0	8.8	9.6	11.4	0.04[c]	18.8	23.8	19.3	13.7	0.40[c]
Regular Alcohol Intake (%)										
Never	60.4	54.2 [e]	56.3 [e]	56.5	0.02[c]					
Former	20.0	22.3	23.0	19.4						
Current	19.6	23.5	20.7	24.0						
Never						48.6	56.7	49.4	45.7	0.08[c]
< than 14 drinks/wk						41.8	25.2 [e]	41.7	41.8	
> than 14 drinks/wk						9.6	18.1 [e]	8.9	12.5 [e]	
Cigarette Smoking Status (%)										
Never	54.7	32.0 [e]	44.2 [e]	37.0 [e]	<0.001[c]	63.9	45.7	53.0	55.2	<0.001[c]
Former	34.7	40.3	32.8	34.3		28.6	41.8	30.5	28.9	
Current	10.6	27.7	23.0	28.6		7.5	12.4	16.6 [e]	15.9 [e]	
Regular Physical Activity in the Past 10 Years (%)[d]	58.8	51.3 [e]	52.7 [e]	53.0	<0.001[c]	79.8	74.4	76.2	81.9	0.57[c]
Current Use of NSAIDs (%)	51.4	51.5	46.2 [e]	48.1	0.009[c]	27.4	38.2	29.3	27.0	0.38[c]
Body Mass Index (kg/m^2; least square means)	27.8	28.9 [e]	28.5 [e]	28.6	<0.001[c]	29.5	30.4	29.2	29.5	0.06[c]
Personal History of Colorectal Polyp (%)										
Yes						29.7	30.9	33.5 [e]	32.2 [e]	0.0002[c]
No						68.4	63.1	63.6	66.7	
Unknown						2.0	6.0	2.9	1.1	

Characteristic	No Polyp Controls	Hyperplastic Polyps	Adenomatous Polyps	Sessile Serrated Polyps	$P_{heterogeneity}$	No Polyp Controls	Hyperplastic Polyps	Adenomatous Polyps	Sessile Serrated Polyps	$P_{heterogeneity}$
	Tennessee Colorectal Polyp Study[a]					Johns Hopkins Biofilm Study[b]				
-	n=3258	n=471	n=1536	n=181	-	n=579	n=63	n=333	n=96	
Personal History of Cholecystectomy (%)						8.7	9.9	14.8 [e]	19.8 [e]	0.006[c]
Red meat consumption (g/ day, least square means)	51.0	65.9 [e]	62.4 [e]	67.2 [e]	<0.001[c]					
Daily Energy Intake (kcal; least square means)	2051	2033 [e]	2163 [e]	2178	<0.001[c]					
Frequency of Dairy Intake Excluding Yogurt (%)										
Never/Rarely	1.7	1.3	3.0 [e]	0.3	0.02[c]					
Monthly Less than Weekly	5.0	5.8	5.7	4.9						
Weekly Less than Daily	37.3	39.7	40.5	43.4						
Daily	56.0	53.2	50.8	51.4						
Frequency of Yogurt Intake (%)										
Never/Rarely	48.5	53.7 [e]	53.8 [e]	56.0	0.002 [c]	33.3	31.0	42.1	37.1	0.06[c]
Monthly Less than Weekly	18.1	17.7	18.3	18.4						
Weekly Less than Daily	25.9	24.2	21.8	22.0						
Daily	7.4	4.4	6.2	3.6						
1 or more/month						21.0	22.5	21.3	26.8	
1 or more/week						45.6	46.5	36.6 [e]	36.1 [e]	
Daily Amount of Yogurt Intake (cups)	0.13	0.10 [e]	0.11 [e]	0.09 [e]	0.004 [c]					
Use of a Probiotic Supplement (%)						20.5	21.1	13.8 [e]	14.4 [e]	0.04[c]

[a] Data presented as least square mean of log transformed data (continuous) or frequencies standardized to age (5 year categories) and sex distribution of controls with exception of age, sex and study site, which are presented as n and percentages for categorical data and mean values and standard deviation for continuous data.

[b] Data presented as least square mean of log transformed data (continuous) or frequencies standardized to age (5 year categories) and sex distribution of controls with exception of age and sex, which are presented as n and percentages for categorical data and mean values and standard deviation for continuous data.

[c] P-values adjusted for age (5-year categories) and sex.

[d] Current Moderate/Vigorous Physical Activity (%)

[e] Case group least square mean or frequencies are significantly different from the control group.

Table 2.

Associations between yogurt consumption and probiotic use with risk of colorectal polyps.

	Case-Control Comparisons					Case-Case Comparisons				
	No Polyp Controls	Hyperplastic Polyps (HP)		Adenomatous Polyps (AP)		Sessile Serrated Polyps (SSP)	AP vs. HP	SSP vs. HP	SSP vs. AP
	n	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Tennessee Colorectal Polyp Study										
Frequency of yogurt intake[a]										
ALL										
Never/Rarely	1581	268	1.00 (ref)	914	1.00 (ref)	108	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Monthly Less than Weekly	591	82	1.01(0.76–1.35)	251	1.00(0.83–1.20)	28	0.82(0.51–1.31)	0.98(0.72–1.34)	0.81(0.48–1.37)	0.83(0.51–1.34)
Weekly Less than Daily	845	105	1.00(0.76–1.33)	290	0.92(0.77–1.10)	39	0.94(0.61–1.45)	0.92(0.68–1.24)	0.94(0.57–1.54)	1.02(0.65–1.60)
Daily	241	16	0.54(0.31–0.95)	81	0.93(0.69–1.25)	6	0.49 (0.19–1.24)	1.72(0.95–3.11)	0.90(0.31–2.61)	0.52(0.20–1.36)
P_{trend}			0.23		0.37		0.26	0.56	0.73	0.45
MALES										
Never/Rarely	1129	206	1.00 (ref)	754	1.00 (ref)	86	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Monthly Less than Weekly	288	46	1.02(0.7–1.47)	150	0.95(0.75–1.21)	10	0.51(0.25–1.05)	0.94(0.64–1.38)	0.50(0.23–1.09)	0.53(0.26–1.11)
Weekly Less than Daily	286	43	1.04(0.71–1.53)	156	1.08(0.85–1.38)	16	1.03(0.57–1.86)	1.04(0.69–1.56)	0.99(0.51–1.93)	0.95(0.52–1.74)
Daily	77	4	0.28(0.09–0.91)	45	1.19(0.79–1.79)	3	0.71(0.21–2.37)	4.27(1.29–14.14)	2.54(0.49–13.2)	0.6(0.18–2.03)
P_{trend}			0.32		0.41		0.55	0.16	0.97	0.37
FEMALES										
Never/Rarely	452	62	1.00 (ref)	160	1.00 (ref)	22	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Monthly Less than Weekly	303	36	1(0.63–1.6)	101	0.99(0.73–1.35)	18	1.29(0.64–2.59)	0.99(0.59–1.64)	1.28(0.57–2.88)	1.3(0.63–2.7)
Weekly Less than Daily	559	62	1(0.66–1.52)	134	0.73(0.55–0.98)	23	0.97(0.48–1.92)	0.73(0.46–1.17)	0.96(0.44–2.1)	1.32(0.64–2.71)
Daily	164	12	0.73(0.37–1.45)	36	0.68(0.44–1.06)	3	0.41(0.09–1.84)	0.93(0.43–2)	0.56(0.11–2.84)	0.6(0.13–2.81)
P_{trend}			0.58		0.02		0.42	0.33	0.67	0.86
Daily amount of yogurt intake[a]										
None/rarely	1581	268	1.00 (ref)	914	1.00 (ref)	108	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)

	Case-Control Comparisons					Case-Case Comparisons			
	No Polyp Controls	Hyperplastic Polyps (HP)		Adenomatous Polyps (AP)		Sessile Serrated Polyps (SSP)	AP vs. HP	SSP vs. HP	SSP vs. AP
	n	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
>0 to 0.06 cups	559	75	0.99(0.74–1.34)	226	0.97(0.8–1.17)	22	0.75(0.46–1.24)	0.76(0.43–1.33)	1.25(0.77–2.03)	0.78(0.46–1.3)
0.07 to 0.20 cups	565	71	0.99(0.73–1.35)	204	0.92(0.75–1.12)	31	1.01(0.63–1.61)	1.01(0.60–1.73)	1.09(0.65–1.83)	1.10(0.68–1.79)
>0.20 cups	544	55	0.79(0.55–1.12)	189	0.98(0.79–1.22)	20	0.77(0.43–1.36)	0.98(0.51–1.87)	1.12(0.62–1.99)	0.78(0.44–1.41)
P_{trend}			0.34		0.59		0.46	0.91	0.88	0.62
Johns Hopkins Biofilm Study										
Frequency of yogurt intake[b]										
ALL										
Does not eat yogurt/ rarely	196	20	1.00 (ref)	139	1.00 (ref)	36	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1 or more/month	110	14	1.45 (0.69–3.04)	72	1.00 (0.68–1.46)	25	1.29 (0.72–2.31)	0.68 (0.32–1.45)	0.89 (0.37–2.14)	1.32 (0.72–2.42)
1 or more/week	271	29	1.27 (0.68–2.39)	122	0.75 (0.54–1.04)	35	0.76 (0.44, 1.29)	0.60 (0.31–1.15)	0.60 (0.27–1.30)	1.00 (0.57–1.75)
P_{trend}			0.51		0.08		0.27	0.13	0.19	1.00
MALES										
Does not eat yogurt/ rarely	106	9	1.00 (ref)	88	1.00 (ref)	21	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1 or more/month	34	8	3.06 (1.06–8.84)	38	1.41 (0.80–2.49)	10	1.57 (0.65–3.77)	0.46 (0.16–1.33)	0.51 (0.15–1.81)	1.12 (0.47–2.69)
1 or more/week	93	12	2.13 (0.81–5.61)	50	0.71 (0.44–1.09)	13	0.75 (0.34–1.68)	0.33 (0.12–0.90)	0.35 (0.11–1.16)	1.06 (0.46–2.46)
P_{trend}			0.11		0.20/		0.54	0.03	0.09	0.87
FEMALES										
Does not eat yogurt/ rarely	90	11	1.00 (ref)	51	1.00 (ref)	15	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1 or more/month	76	6	0.71 (0.24–2.07)	34	0.76 (0.44–1.32)	15	1.13 (0.50–2.55)	1.07 (0.35–3.29)	1.59 (0.45–5.64)	1.49 (0.62–3.58)
1 or more/week	178	17	0.77 (0.33–1.79)	72	0.74 (0.46–1.17)	22	0.73 (0.35–1.54)	0.96 (0.39–2.34)	0.95 (0.33–2.72)	0.99 (0.45–2.19)
P_{trend}			0.57		0.21		0.35	0.91	0.85	0.90
Use of a probiotic supplement[b]										
ALL										
Yes	119	12	1.01 (0.51–2.00)	47	0.72 (0.49–1.06)	13	0.66 (0.34–1.24)	0.73 (0.35–1.52)	0.65 (0.27–1.57)	0.88 (0.44–1.74)

	Case-Control Comparisons					Case-Case Comparisons			
	No Polyp Controls	Hyperplastic Polyps (HP)		Adenomatous Polyps (AP)		Sessile Serrated Polyps (SSP)	AP vs. HP	SSP vs. HP	SSP vs. AP
	n	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
No	458	51	1.00 (ref)	286	1.00 (ref)	83	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
					MALES					
Yes	27	1	0.29 (0.04–2.27)	21	1.10 (0.58–2.09)	3	0.54 (0.15–1.92)	3.86 (0.48–31.0)	1.88 (0.18–20.0)	0.49 (0.14–1.78)
No	206	28	1.00 (ref)	155	1.00 (ref)	41	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
					FEMALES					
Yes	92	11	1.46 (0.66–3.23)	26	0.56 (0.34–0.92)	10	0.69 (0.32–1.48)	0.38 (0.16–0.92)	0.47 (0.17–1.34)	1.23 (0.53–2.86)
No	252	23	1.00 (ref)	131	1.00 (ref)	42	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)

[a] Adjusted for sex, study location, age, regular alcohol drinking status, BMI, smoking status, physical activity in the past 10 years, educational attainment, NSAID use, red meat intake, dietary energy intake, and frequency of non-yogurt dairy intake

[b] Adjusted for sex, age, cigarette use (current/former/never), overweight (BMI less than or greater than 25 kg/m^2), prior colon polyp (yes/no), history of cholecystectomy (yes/no), diabetes mellitus diagnosis (yes/no), hypertension diagnosis (yes/no), hyperlipidemia diagnosis (yes/no), physical activity (yes/no) and >10 alcohol drinks/week (yes/no)

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