Characteristics and risk factors for early-onset metachronous colorectal adenoma

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Aim: Compare risk factors for early-onset-metachronous colorectal adenoma (EOMCA) among individuals <50 versus ≥50 years. Materials & methods: Descriptive statistics compared clinical/demographic characteristics for individuals <50 and ≥50. Logistic regression estimated associations between demographic and clinical attributes and EOMCA. Results: N = A total of 1623 participants. Individuals <50 years (vs ≥50) had higher smoking rates, greater intake of red meat, monounsaturated fatty acids, total fat and less sleep, sedentary behavior, aspirin intake, supplemental calcium use and higher mean energy-adjusted dietary inflammatory index (E-DII™) score (pro-inflammatory diet) (all p ≤ 0.001). Odds of EOMCA were higher among smokers and participants reporting previous polyp(s). Overall odds of EOMCA were lower among individuals <50. Conclusion: History of previous polyps and smoking were risk factors for EOMCA. Lifestyle factors require further research.

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Keywords: colorectal adenoma • colorectal adenoma recurrence • colorectal cancer • early-onset colorectal cancer • metachronous colorectal adenoma • risk factors

Colorectal cancer (CRC) is the second leading cause of cancer-related death among men and women in the USA combined and can be prevented by the detection and removal of colorectal adenomatous polyps [1,2]. Over the past several decades, overall CRC incidence has been decreasing with a recent (2011–2016) decline of 3.3% per year. However, during this same time period, early-onset CRC incidence among individuals <50 years of age has been steadily increasing at a rate of 2.2% per year from 2012 to 2016 [3–6]. A recent study has demonstrated a particularly...
high increase in incidence among individuals aged 49–50 [7]. Yet, the risk factors and causes of early-onset CRC are still not well understood.

Studies demonstrate that early-onset CRC is often present in the distal (or left sided) colon and rectal locations, presents at later stages and has disproportionately affected non-Hispanic whites [8–14]. The lack of screening and education targeted toward individuals younger than 50 years of age has contributed to key symptoms going unrecognized by both patients and clinicians [15,16]. These studies suggest that preclinical manifestations of CRC, such as colorectal adenomas, may remain undiagnosed in both asymptomatic and symptomatic adults younger than the current screening age. However, improved understanding of risk factors may improve our ability to identify the at-risk population for early-onset CRC.

There is currently limited understanding of the underlying etiology or risk factors for early-onset CRC. Studies suggest that the increased incidence of early-onset CRC is attributable to modifiable risk factors such as obesity [17], sedentary behavior [18] and dietary factors including alcohol and processed meat consumption [16,19]. It has also been suggested that the gut microbiome in combination with a host of factors including a western dietary pattern (inherently inflammatory in nature), synthetic food dyes, antibiotics and stress also influence early-onset CRC development [20]. Many of these same modifiable risk factors also have been linked to the development of early-onset colorectal adenomatous polyps in individuals [21,22]. Evidence suggests that risk factors for early-onset adenomas also includes diabetes [23], certain dietary patterns [24], smoking [25], metabolic syndrome [25], elevated triglycerides [25] and greater waist circumference [22]. Understanding the drivers of the initiation and recurrence of early-onset colorectal adenomas is paramount to promoting effective prevention and control of CRC in this population.

It is well documented that CRC is known to arise from colorectal adenomas [26]. Once an individual is diagnosed with a colorectal polyp, the risk of another polyp developing, frequently described as metachronous colorectal polyp, varies according to patient and polyp (size, number, histology) characteristics [27–29]. Individuals with a family history of CRC or advanced adenoma in one or more first-degree relatives are at increased risk of developing adenomas and earlier screening and more frequent surveillance are also recommended due to increased risk [30–33]. However, factors linked to early-onset adenomas are understudied in this age group.

Evidence is limited for the risk factors related to metachronous colorectal adenomas among individuals <50 years of age. In the current study, risk factors for early-onset metachronous colorectal adenoma are compared with older-onset cases. Moreover, associations between modifiable and non-modifiable factors that may impact the likelihood of metachronous colorectal adenoma in a young population are examined. The results of the current study may help inform strategies for risk assessment and risk stratification and influence targeted screening approaches for individuals under 50 years of age.

Materials & methods

Study participants

We conducted a pooled analysis among participants enrolled in the Wheat Bran Fiber (WBF) and Ursodeoxycholic Acid (UDCA) Phase III randomized, double-blind, placebo controlled, chemoprevention trials conducted at the University of Arizona Cancer Center. Study participants were recruited from 1990 to 1999 and a total of 2502 participants completed both trials. Both trials have been described in detail previously [34,35]. Briefly, eligible participants were recruited from three clinical sites in the Phoenix metropolitan area and included males and females ranging in age from 40 to 80 years who had one or more colorectal adenoma(s) removed during a colonoscopic evaluation within a six-month period prior to study registration. Accordingly, individuals ≥50 years of age are compared with individuals from 40 to <50 years of age in this study.

Baseline polyp characteristics were recorded according to size, number of polyps removed, histology and location in the colon/rectum. Individuals with self-reported inherited syndromes, such as familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer were ineligible. The objective of the WBF trial was to investigate the effect of a daily wheat-bran fiber supplement (13.5 vs 2.0 g/d) on the risk of metachronous adenomatous polyps. The aim of the UDCA trial was to compare the effect of UDCA (administered at 8–10 mg/kg of body weight) versus placebo on prevention of metachronous adenoma recurrence.

The primary study outcome (metachronous colorectal adenoma) in both trials was defined as the occurrence of one or more pathologically confirmed colorectal adenomas detected by colonoscopic evaluation at least 6 months after the qualifying colonoscopy. Adenomas were categorized as nonadvanced (<10 mm in size, tubular histology and no high-grade dysplasia) or advanced (≥10 mm in size and/or tubulovillous/villous histology and/or the
presence of high-grade dysplasia and/or cancer). Incident and metachronous adenomas are reported as single groups in the current report because there were insufficient participants in the <50 study population with incident or metachronous adenomas to merit subgroup analyses of participants with advanced adenomas. Serrated adenoma histology was not routinely reported at the time of the WBF and UDCA trials. The mean follow-up time from baseline colonoscopy and polypectomy (i.e., randomization) to the study indicated follow-up colonoscopy for the WBF and UDCA trials was 3.1 and 3.2 years, respectively. There was no evidence that either the WBF supplement or the UDCA treatment decreased risk of colorectal adenoma recurrence in the primary study analyses (35,36). Institutional review boards of the participating clinical sites and the University of Arizona reviewed and approved both studies. Written informed consent was obtained from each participant prior to study enrollment.

Assessment of baseline characteristics
All baseline data collection and procedures were conducted during the screening phase of the study. A variety of questionnaires were administered to collect baseline information such as medication use and other risk factor data including diet and physical activity. Dietary intake was assessed using the validated (37), self-administered, scannable, semi-quantitative Arizona Food Frequency Questionnaire that evaluates usual dietary intake over the past few months in the previous year. Energy-adjusted dietary inflammatory index (E-DII™) scores were derived from the Arizona Food Frequency Questionnaire data as describes by Harmon et al. (38), which, in turn, is based on the method for computing the Dietary Inflammatory Index (DII™) by Shivappa et al. (39). Physical activity over the previous 4 weeks was assessed using the validated, self-administered, scannable Arizona Activity Frequency Questionnaire (AAFQ) (40), including 59 items categorized by leisure, recreational, household and ‘other’ categories of activity. Endoscopic and pathologic information on colorectal adenoma characteristics (e.g., anatomic location, size, number, histology) were obtained from the qualifying procedure as part of the review for eligibility. A previous polyp is one that was identified during a colonoscopy that occurred in the patient’s history, prior to study enrollment.

Statistical analysis
Baseline and clinical characteristics including age, gender, family history, BMI, waist circumference, race/ethnicity, family history, smoking status, previous colorectal polyp(s), use of low-dose aspirin (81 mg daily), physical activity, dietary intake and colorectal adenoma characteristics were compared by age strata (<50 vs ≥50 years old). Calcium, energy, protein, total fat, saturated fat and supplemental folate intake were rescaled by a factor of 100 in order to provide a large enough coefficient estimation to reasonably capture the change in each variable and its respective effect on metachronous adenoma. Summary statistics were calculated using Pearson chi-square tests for categorical variables, student t-test for normally distributed continuous variables and the Kruskal–Wallis test for non-normally distributed continuous variables.

Three categories of activity were created based on the self-reported data available from the AAFQ. Using the guidelines developed by the Sedentary Behavior Research Network, behaviors ≤1.5 metabolic equivalent of tasks (METs) were classified as ‘sedentary behavior’, physical activities between 1.5–3 METs were designated as ‘light-intensity physical activity’ and activities ≥3 METs were categorized as ‘moderate-vigorous physical activity’ (39,40). Within each of these categories, quartiles were generated for assessment of sedentary behavior and physical activity in this study. Red and processed meat consumption is one of the established risk factors for colorectal cancer. The American Institute for Cancer Research recommends up to 18 ounces of red and processed meat per week (approximately nine 3-ounce servings or 511 g) (41). For this reason, we created cut points of red meat for <511 and ≥511 g per week. We also created gender-specific cut points for fiber following the Institute of Medicine recommendations (25 g of fiber for women and 38 g of fiber for men) which considers energy intake for each gender (42). Gender-specific cut points for waist circumference (35 inches for females and 44 inches for males) were also generated.

Bivariate logistic regression models were used to assess the association of risk factors with metachronous colorectal adenoma. Potential risk factors were identified in the literature and from our analysis of statistically significant factors identified in the analysis of baseline characteristics mentioned above. We further evaluated the relationship between subjects’ demographic and clinical characteristics by conducting multivariate logistic regression using significant variables identified in the bivariate logistic regression analysis. Using the same set of variables included in the multivariate regression, we performed a subgroup analysis by age. Models yielded adjusted odds ratio (ORs) and corresponding 95% CI. Likelihood ratio tests comparing models with and without interaction terms were used.
Participants who completed the wheat bran fiber and ursodeoxycholic acid clinical trials (n = 2502)

Participants excluded because they did not have complete baseline physical activity data from the Arizona Activity Frequency Questionnaire (AFFQ) (n = 772)

Participants included in analysis for early-onset metachronous colorectal adenoma (n = 1730)

Participants excluded because of missing data for family history and previous polyps (n = 107)

Participants eligible for participation in this study (n = 1623)

Figure 1. Eligible study participants.

to evaluate interactions by age. All individuals missing data for family history and previous polyp were excluded.
All the statistical analyses were done in Stata SE 14.0 (TX, USA).

Results

Our analysis included 1623 individuals (selection of participants presented in Figure 1). By design, the mean age of the groups was significantly different, with an average age of 45.9 ± 2.6 and 67.1 ± 7.3 for those <50 years (n = 92) and those ≥50 years (n = 1531), respectively (Table 1). The majority of both the <50 and ≥50 populations were male (62.0 and 68.8%, respectively) and white (90.0 and 95.0%, respectively). There were three areas of investigation in this study. The first was a descriptive analysis of baseline characteristics among individuals <50 and ≥50 who had a metachronous adenoma removed during the study period. The second was a logistic regression analysis to evaluate odds of metachronous colorectal adenoma and age. The third was a multivariate logistic regression analysis, stratified by individuals <50 and ≥50 years of age, to evaluate the association of risk factors (baseline characteristics) and odds of colorectal metachronous adenoma.

Descriptive analysis

Table 1 presents the results of the descriptive analysis. Younger individuals (<50 years of age) were less likely to be non-Hispanic white individuals (90.1 vs 95.3%, p = <0.043), have reported a history of previous polyps (from a screening procedure conducted before the qualifying adenoma) (18.4 vs 44.4%, p = <0.001), report aspirin use (14.1 vs 31.0%, p = <0.001), report use of supplemental folate (163.0 vs 224.3 g/d, p = 0.023) and calcium (72.7 vs 235.9 mg/d, p = <0.001) and report more hours of sedentary behavior per day (6.0 vs 8.8, p = <0.001). Participants <50 years of age were also less likely to have a metachronous colorectal adenoma (25.0 vs 46.4%, respectively, p = <0.001) at time of follow-up colonoscopy.

Younger individuals (<50 years of age) were more likely to be current smokers (25.0 vs 11.8%, p = 0.001); have a higher intake of protein (79.5 ± 29.2 vs 73.0 ± 29.6 g/d, p = 0.03), higher intake of total fat (74.9 ± 31.2 vs 64.1 ± 31.1 g/d, p = <0.001), higher intake of monounsaturated fatty acids (29.0 ± 12.3 vs 24.5 ± 12.1 g/d, p = 0.001), higher intake of polyunsaturated fat (15.0 ± 6.5 vs 13.6 ± 6.6 g/d, p = 0.049), higher intake of red meat (67.1 ± 48.0 vs 53.0 ± 39.1 g/d, p = 0.001) and have a more pro-inflammatory diet as indicated by the E-DII score (-1.2 vs -1.9, p < 0.001) compared with individuals ≥50 years of age. Individuals <50 years of age, compared with those ≥50 years of age, were also more likely to report more hours of sleep compared with those 50 years of age and older (6.7 ± 1.2 vs 7.5 ± 1.2 h, p = 0.001).

BMI, waist circumference and intake of other dietary factors (fiber, alcohol and total energy [kcals/day]) were not significantly different between the two age groups. Baseline colorectal adenoma characteristics also were examined (i.e., multiple ≥3 adenomas, size ≥1 cm), villous architecture, proximal location. There were no significant
<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics of study participants who had a colorectal adenoma removed (n = 1623).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
</tr>
<tr>
<td>Age (&lt;50 (n = 92)</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>White, not Hispanic, n (%)</td>
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<tr>
<td>Family or personal history of CRC or polyps‡</td>
</tr>
<tr>
<td>Family history CRC, n (%)</td>
</tr>
<tr>
<td>Previous polyps§, n (%)</td>
</tr>
<tr>
<td>Lifestyle characteristics</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
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<tr>
<td>Aspirin#, n (%)</td>
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<tr>
<td>Sedentary behavior (h per day)</td>
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<tr>
<td>Light-intensity physical activity (MET-h per day)</td>
</tr>
<tr>
<td>Moderate to vigorous physical activity (MET-h per day)</td>
</tr>
<tr>
<td>Dietary intake</td>
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<tr>
<td>Energy (kcal/day)</td>
</tr>
<tr>
<td>Protein (g/day)</td>
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<tr>
<td>Total fat (g/day)</td>
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<tr>
<td>Saturated fat (g/day)</td>
</tr>
<tr>
<td>Total fiber (g/day)</td>
</tr>
<tr>
<td>Calcium (mg/day)</td>
</tr>
<tr>
<td>Alcohol (g/day)</td>
</tr>
<tr>
<td>Monounsaturated fatty acid (g/day)</td>
</tr>
<tr>
<td>Polyunsaturated fatty acid (g/day)</td>
</tr>
<tr>
<td>Supplemental folate (g/day)</td>
</tr>
<tr>
<td>Supplemental calcium (mg/day)</td>
</tr>
<tr>
<td>Red meat (g/day)</td>
</tr>
<tr>
<td>Energy-adjusted dietary inflammatory index (DII™) score</td>
</tr>
<tr>
<td>Sleep (h/day)</td>
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<tr>
<td>Anthropometrics</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>BMI categories</td>
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<tr>
<td>Underweight/normal, &lt;25 kg/m², n (%)</td>
</tr>
<tr>
<td>Overweight, 25 to &lt;30 kg/m², n (%)</td>
</tr>
<tr>
<td>Obese, ≥30 kg/m², n (%)</td>
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<tr>
<td>p-Trend</td>
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<tr>
<td>Waist circumference</td>
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<tr>
<td>Waist circumference, males</td>
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<tr>
<td>Waist circumference, females</td>
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<tr>
<td>Colorectal adenoma – baseline characteristics (on index colonoscopy)</td>
</tr>
<tr>
<td>Multiple (≥3) adenomas, n (%)</td>
</tr>
<tr>
<td>Size ≥1 cm, n (%)</td>
</tr>
<tr>
<td>Villous architecture, n (%)</td>
</tr>
<tr>
<td>Proximal location, n (%)</td>
</tr>
<tr>
<td>Distal location, n (%)</td>
</tr>
<tr>
<td>Metachronous colorectal adenoma (on follow-up colonoscopy)</td>
</tr>
<tr>
<td>Metachronous adenoma, n (%)</td>
</tr>
</tbody>
</table>

1 p-values were generated for categorical variables using chi square tests; all p-values for continuous variables were generated using student t-tests.
2 Numbers may not add up to the total due to missing data. Data are missing for race/ethnicity (white), family history of colorectal cancer, previous polyps, large adenoma, villous architecture, proximal location, distal location and BMI.
3 Colorectal cancer in one or more first-degree relatives.
4 History of colorectal polyps prior to qualifying colonoscopy.
5 Regular use of aspirin 4 weeks prior to enrollment.
BMI: Body mass index; CRC: Colorectal cancer; E-DII™: Energy-adjusted dietary inflammatory index; MET: Metabolic equivalent of task.
Table 2. Odds of metachronous colorectal adenoma among participants <50 and ≥50 years of age.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total, n (%)</th>
<th>Metachronous adenoma, n (%)</th>
<th>OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>1531 (94.33)</td>
<td>710 (46.4)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>92 (5.67)</td>
<td>23 (25)</td>
<td>0.39 (0.24, 0.62)</td>
</tr>
</tbody>
</table>

p-trend = <0.001

† Odds ratio and 95% CI adjusted for waist circumference, gender, energy and trial arm.
OR: Odds ratio.

Table 3. Odds of metachronous colorectal adenoma stratified by age group, results from multivariate regression.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.69 (0.360, 7.895)</td>
<td>0.507</td>
<td>1.13 (0.824, 1.543)</td>
<td>0.45</td>
</tr>
<tr>
<td>Previous polyps</td>
<td>5.48 (1.190, 25.233)</td>
<td>0.029</td>
<td>1.34 (1.068, 1.678)</td>
<td>0.01</td>
</tr>
<tr>
<td>Current smoking</td>
<td>5.40 (1.248, 23.399)</td>
<td>0.024</td>
<td>1.43 (1.024, 1.989)</td>
<td>0.04</td>
</tr>
<tr>
<td>Multiple (≥3) adenomas</td>
<td>0.54 (0.059, 4.857)</td>
<td>0.58</td>
<td>2.27 (1.671, 3.083)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large adenoma (≥1 cm)</td>
<td>1.58 (0.336, 7.141)</td>
<td>0.563</td>
<td>1.25 (0.980, 1.586)</td>
<td>0.07</td>
</tr>
<tr>
<td>Villous histology</td>
<td>0.97 (0.159, 5.923)</td>
<td>0.973</td>
<td>1.56 (1.162, 2.082)</td>
<td>0.003</td>
</tr>
<tr>
<td>Proximal location</td>
<td>0.71 (0.163, 3.072)</td>
<td>0.645</td>
<td>1.44 (1.147, 1.808)</td>
<td>0.002</td>
</tr>
<tr>
<td>Distal location</td>
<td>1.43 (0.500, 4.112)</td>
<td>0.502</td>
<td>0.92 (0.744, 1.134)</td>
<td>0.43</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>1.05 (0.935, 1.170)</td>
<td>0.435</td>
<td>1.03 (1.002, 1.808)</td>
<td>0.037</td>
</tr>
<tr>
<td>Supplemental folate†</td>
<td>0.68 (0.465, 1.001)</td>
<td>0.051</td>
<td>0.97 (0.928, 1.014)</td>
<td>0.18</td>
</tr>
<tr>
<td>E-DII™</td>
<td>1.06 (0.809, 1.377)</td>
<td>0.69</td>
<td>1.03 (0.970, 1.099)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Red meat

≤511 g/week | Ref. | Ref. |
>511 g/week | 0.84 (0.233, 3.021) | 0.79 | 1.11 (0.859, 1.444) | 0.42 |
Calcium (mg/day)† | 1.01 (0.898, 1.145) | 0.82 | 0.98 (0.960, 0.998) | 0.03 |

† Calcium and supplemental folate were rescaled by 100 when put in the models.
E-DII™: Energy-adjusted dietary inflammatory index; MET: Metabolic equivalent of task; OR: Odds ratio.

Differences among various clinical characteristics of adenomas removed at baseline (index colonoscopy) between the two age groups.

Table 2 presents the results of logistic regression modeling of the association between age group and odds of metachronous colorectal adenoma. We observed a statistically significant reduced odds of metachronous colorectal adenoma among individuals <50 years of age compared with those aged 50 or older, with an OR (95% CI) 0.39 (0.24, 0.62), p trend = <0.001 (adjusted for waist circumference, gender, energy and trial arm).

Table 3 presents the results of multivariate logistic regression modeling stratified by age group. We observed that the odds of metachronous colorectal adenoma among individuals <50 years of age was associated with a history of previous polyps (OR [95% CI] 5.48 [1.19, 25.23], p = 0.029) and current smoking (OR [95% CI] 5.40 [1.25, 23.40], p = 0.024). In the ≥50-year-old group only, metachronous colorectal adenoma was related to polyps detected prior to study entry (OR [95% CI] 1.34 [1.07, 1.68], p = 0.011), smoking (OR [95% CI] 1.43 [1.02, 1.99], p = 0.036), multiple adenomas (OR [95% CI] 2.27 [1.67, 3.08], p = <0.001), villous architecture, (OR [95% CI] 1.56 [1.16, 2.08], p = 0.003), proximal location (OR [95% CI] 1.44 [1.15, 1.81], p = 0.002), waist circumference (OR [95% CI] 1.03 [1.00, 1.81], p = 0.037) and calcium (OR [95% CI] 0.98 [0.96, 1.00], p = 0.029). No statistically significant effect modification by age was observed (data not shown).

Discussion
The results of the present study demonstrate that individuals with early-onset metachronous colorectal adenomas were more likely to be current smokers, have higher intake of protein and fat (monounsaturated and polyunsaturated), consume more red meat, have a generally more pro-inflammatory diet and sleep more than older individuals included in the study. In contrast, older adenoma patients were more likely to report non-Hispanic white ethnicity,
greater aspirin use, a history of previous polyps, use of supplemental folate and calcium and engaging in more hours of sedentary behavior compared with their younger counterparts. BMI, waist circumference, intake of protein, fiber, alcohol and total energy (kcal/day) were not statistically significantly different between the two groups. Metachronous colorectal adenomas were observed in 25.0 and 46.4% of <50 and ≥50 populations, respectively.

The magnitude of effect for early- compared with later-onset metachronous colorectal adenoma was stronger if the participant had a history of previous polyps (OR [95% CI] 5.5 [1.2, 25.2] vs 1.4 [1.1, 1.7]) or reported being a current smoker at baseline (OR [95% CI] 5.4 [1.3, 23.4] vs 1.4 [1.0, 2.0]). A case–control study at the Cleveland Clinic by Nagpal et al. [43] support the current finding that recurrence of any adenoma is more common in adults 50 years of age or older. The rates of advanced neoplasia at postpolypectomy colonoscopy, however, were similar between the younger and older age groups, even after adjusting for gender and smoking. The sample size of the Nagpal et al. study was relatively small and there was a significant difference in follow-up times of colonoscopy in the young adults compared with the older cohort. Recent studies found similar results for differences in risk of metachronous adenomas in younger and older populations [44,45].

It is well established that a history of previous polyps is associated with the development of future polyps and individuals with advanced adenomas have a 15.9–19.3% risk of metachronous advanced adenomas [46]. This may explain why there was a higher odds of metachronous adenoma associated with history of previous polyps in both the <50 and ≥50 groups, as it may override the effect of age alone on adenoma development. Moreover, among the ≥50 year old participants, having a villous adenoma at baseline confers a 1.6-fold increased odds for metachronous adenoma, having multiple (≥3) removed at baseline confers 2.3-fold increased odds of metachronous colorectal adenoma and having a baseline adenoma proximally located confers a 1.4-fold increased risk of metachronous colorectal in this age group. These findings parallel established risk estimates describing higher likelihood of metachronous advanced colorectal neoplasia in those with advanced polyps at baseline [47]. Given these observations, it appears that the established clinical characteristics associated with metachronous colorectal adenoma apply to the older population and not the young. This, in turn, supports current literature suggesting younger onset colorectal tumorigenesis is different from that of older onset disease [20,48].

In terms of nonmodifiable risk factors, such as gender and race/ethnicity, Pendergrass et al. showed in an epidemiologic necropsy study that the frequency of adenomas was highest in males in a population 20–49 years of age [49]. A South Korean population of 40–49 years who underwent screening colonoscopies, were male and were current smokers were independent predictors of advanced adenoma [50]. Interestingly, no differences in odds of metachronous colorectal adenoma among non-Hispanic whites were observed in our univariate analysis (data not shown). While this was somewhat unexpected given the epidemiological literature revealing increases of early-onset colorectal cancer in the non-Hispanic white population, it points to a limitation of our investigation given that our population was predominantly (over 90%) white.

Previous studies that evaluated certain modifiable risk factors such as smoking, physical activity and dietary intake in a younger population with colorectal adenomas have shown similar results to this study. It is widely documented that smoking is one of the leading modifiable risk factors for chronic disease and strongly associated with colorectal polyps [22,25]. Moreover, in Korean study by Kwak et al. [51] found that current tobacco use (OR 1.48, 95% CI: 1.14–1.91) in 20–39-year-old adults was associated with increased risk of adenoma development. Jacobson et al. also reported a significant increased risk for a metachronous or recurrent adenoma in the highest quartile of smokers compared with never smokers among men (OR [95% CI] 1.8 [1.0, 3.4]) [52]. Earlier literature also indicated that the association of smoking with adenomas was observed to be stronger in younger subjects (<50 years) [53]. The data presented in this study support previous findings from colorectal adenoma recurrence studies that current cigarette smoking is associated with an increased risk for metachronous colorectal adenoma [52,54] and this relationship was observed for both the <50 and ≥50 groups in our study.

It has been observed that individuals <50 years of age smoke fewer cigarettes per day compared with those ≥50 and individuals ≥50 have smoked for a longer duration compared with those younger [55]. Therefore, finding that the odds of metachronous adenoma among the <50 participants who reported smoking at baseline was greater than those ≥50 was unexpected. One potential explanation we explored was the fact that smoking is associated with distal lesions [56] and typically early-onset colorectal cancer is most often manifested as distal tumors [57]. However, in the present study, the <50 participants were not more likely to have distal lesions compared with those ≥50. Another potential explanation could be the difference in colonic mucosa and the ensuing epigenetic alterations among those <50 years of age that promote an environment uniquely susceptible to metachronous
adenoma in the presence of tobacco smoke. This could include differences in the formation of DNA adducts, chronic inflammation, cytokines and chemokines [58].

Physical activity has been associated with colorectal cancer [59-61] and adenomas [62-66] although consistency has been lacking in the measurement tool used across studies. In the current study, baseline physical activity was assessed over previous 4 weeks using the validated self-administered Arizona Activity Frequency Questionnaire with 59 items. However, no significant association between baseline physical activity and odds of metachronous adenoma colorectal was observed for either age group. There are a few potential explanations for this result. The majority of the <50 and ≥50 population did not achieve sufficient daily levels of physical activity to produce an effect. For example, a previously conducted adenoma recurrence study [62] investigating adenoma recurrence and physical activity found a protective effect among men engaging in five or more hours per day of vigorous activity, which only 20.6 and 25.3% of age <50 and ≥50 population, respectively, were in the highest category of moderate-to-vigorous physical activity. Another potential explanation may be that the protective effect of physical activity has been found to be stronger for the development of advanced adenomas [67]. As described in Colbert et al. [68], inherent limitations also include measurement error which may have misclassified some individuals and therefore impacted the resulting association. Finally, the duration and intensity of physical activity required to reduce risk of colorectal adenoma recurrence has not been well established; however, some studies suggest that moderate-intensity activity to higher overall physical activity is sufficient to reduce risk [69-73].

Previous studies in this population report a statistically significant association between sedentary behavior and colorectal adenoma recurrence among men [74]. However, in the present study, higher sedentary behavior was not significantly associated with metachronous colorectal adenoma in either age group, possibly due to the comparatively small sample sizes that arose when participants are categorized by age.

Red and processed meat consumption has been established as a risk factor for colorectal cancer [75]; however, in the present study no differences in the relationship between red meat and metachronous colorectal adenoma were observed between the two age groups. This finding is parallel with previous literature that has reported a weak association between colorectal adenoma recurrence and consumption of red meat [76] and results are generally inconsistent among other studies [77]. One potential explanation for the lack of association in the ≥50 group is due to the fact that red meat consumption (53.0 ± 39.1 g/d) did not meet the threshold for increased risk [41]. In the younger population, we could speculate that the duration of meat exposure was inadequate to produce an effect and two large cohort studies [78,79] also suggest that early exposure to red and processed meat may not impact adenoma development until later in life. Finally, it is currently unclear which stages of carcinogenesis red meat plays the largest and most detrimental role [80].

We observed that the diets of the <50-year-old subjects were more pro-inflammatory (though still in the anti-inflammatory range) compared with those ≥50 years old. Stratified logistic regression results showed no significant association, perhaps because the E-DII scores were skewed toward lower values in both groups. Also, sample size was small and resulting precision was low in the <50 year group. So, even though the point estimate was larger than in the older group (a 6% increase in odds per E-DII point vs a 3% increase) it was not statistically significant. Additionally, the E-DII scores were calculated using the baseline AAFQ which only allowed the inclusion of 27 out of 45 parameters included in the E-DII score calculation, therefore several important micronutrients in the form of various vitamins and minerals were omitted. Availability of this information could have impacted the scoring and eventually the results. In a previous publication conducted in the Iowa Women’s Health Study, DII calculated from both diet and supplements had a higher risk of CRC than when DII was computed just from diet [81]. It is also important to point out that a 6% increase in risk that we see per unit E-DII score among the population under 50 years of age is right in the range of what we typically find in most of our studies with respect to relative differences in risk of CRC according to DII/E-DII [82]. Finally, a previous study conducted by our group in this same population did not observe a statistically significant association between a proinflammatory diet and metachronous colorectal adenoma overall [83]. However, additional investigations using case–control and cross sectional study designs observed a positive association between a proinflammatory diet and odds of colorectal adenomatous polyps [84] and a higher prevalence of colorectal adenomas, particularly in men, consuming a more proinflammatory diet [85]. While beyond the scope of the current work, further investigating the role inflammation initiated through diet and its role on metachronous adenoma development would be a worthwhile exploration.

There are several strengths and limitations of the current study. Strengths include the overall large study population for colorectal adenoma patients with detailed health behavior and pathology measures. There are few studies that have collected evaluable data on colorectal adenoma recurrence among patients less than 50 years of age.
The secondary data analysis presented in this study, which pools the WBF and UDCA datasets, was selected for analyses as these two original Phase III studies provide extensive dietary and physical activity data as well as colonoscopy data on this young population. Unfortunately, the sample size for early-onset adenomas was relatively small in comparison to older adults. This is not unexpected; however, the results should be aimed at hypothesis generating for future studies. Additionally, there is no control group to this study so we do not know what is the significance of the finding in relation to the population with no polyps at that population. Moreover, recruitment for both the WBF and UDCA trials was conducted largely in the 1990's this is both a limitation and strength of the study; it may limit the comparability of our study with more current studies, but our unique pooled cohort of participants also provides an early snapshot of the EOCRC burden that was about to manifest and can be viewed as a strength of this work (the recent surge in research and subsequent publications about early-onset CRC over the past 5–10 years comes a decade or more after the colorectal adenoma data reported here were gathered. It is generally accepted that colorectal tumors are slow-growing lesions and that it takes at least a decade for a colorectal adenoma to progress to adenocarcinoma).

Conclusion
The clinical Implications and public health impact of this work are notable. In this study, we have identified that a history of polyps and current smoking status is strongly and independently associated with metachronous colorectal adenoma in young adults <50 years old. There are currently no dedicated recommendations for surveillance colonoscopy in young adults so professional society guidelines for adult populations are applied to this group [29]. Our results can be extrapolated to suggest that improved surveillance and possibly even targeted screening using these factors may be warranted. Large adenomas with high-grade dysplasia and villous histology at baseline are strong predictors of recurrent advanced adenomas [86]. Clinically important adenoma characteristics in our study included location, size, number and histologic features. We found no significant difference among the various characteristics of adenomas removed at baseline; however, in the ≥50 group, it was observed that they were more likely to have recurrent colorectal adenomas. Efforts to further investigate specific risk factors and the biologic/molecular basis for the increasing incidence and mortality of young-onset colorectal cancer are warranted.

Author contributions
CS Molmenti had access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. CS Molmenti and J Yang were primarily responsible for the data analysis and interpretation. N Shivappa and JR Hébert computed the DII and E-DII scores. EA Hibler, JM Kolb, J Yang, M Hussain, P Lance, DS Alberts, AI Neugut, JR Hébert, N Shivappa and ET Jacobs were responsible for assisting with manuscript preparation and editing as well as assisting with data analysis and interpretation.

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This work was supported by a grant from NCI R25T CA094061-12. CS Molmenti has consulted for Pfizer. AI Neugut has consulted for Otsuka Pharmaceuticals, Eisai, Pfizer, Hospira and United Biosource Corp. AI Neugut is on the Medical Advisory Board of EHE Intl. Dr Warren Andersen is supported by R00 CA207848. Dr James R Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr Nitin Shivappa is an employee of CHI. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research
Institutional Review Boards of the participating clinical sites and the University of Arizona reviewed and approved both studies. Written informed consent was obtained from each participant prior to study enrollment.

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Practice points

- For the past several decades, colorectal cancer incidence among individuals <50 years of age has been increasing, with little epidemiologic or molecular evidence to explain its underlying cause and limited potential strategies for prevention and control.
- Recently published data reported a dramatic increase in colorectal cancer incidence from age 49–50; this is of major concern as it suggests that the preclinical manifestations of colorectal cancer remain undiagnosed in young people prior to screening.
- Colorectal adenomas, the major precursor lesions to the majority of colorectal cancer cases, are diagnosed in the under 50 population, yet little is known about the specific risk factors that are associated with increased risk for metachronous colorectal adenoma.
- History of previous polyps is associated with development of future polyps and colorectal cancer.
- The results of this study demonstrate that individuals ≥50 years of age exhibited greater aspirin use, reported previous polyps, had greater intake of supplemental folate and calcium and engaged in more hours of sedentary behavior compared with their younger counterparts. Participants <50 years of age were more likely to be current smokers, have higher intake of protein and fat (monounsaturated and polyunsaturated), consume a more pro-inflammatory diet, consume more red meat and sleep more than older participants.
- This study observed that history of previous polyps prior to study entry and smoking were risk factors for metachronous colorectal adenoma among those <50 years of age compared with those ≥50 years of age.
- No significant differences were observed among the various characteristics of adenomas removed at baseline; however, in the ≥50 group it was observed that they were more likely to have metachronous colorectal adenomas.
- It appears that the established clinical characteristics associated with adenoma recurrence apply to the older population and not the young, which supports current literature suggesting younger onset colorectal tumorigenesis is different from that of older onset disease.

References


