Title

Systematic Review of Prevalence, Risk Factors, and Risk for Metachronous Advanced Neoplasia in Patients With Young-Onset Colorectal Adenoma

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Title: Young onset colorectal adenoma: a systematic review of prevalence, risk factors, and risk for metachronous advanced neoplasia.

Short Title: Systematic review of young onset adenoma

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Abbreviations: BMI: Body mass index; CI: Confidence interval; CRC: Colorectal cancer; FDR: First degree relative; NOS: Newcastle-Ottawa Quality Assessment Scale; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; YOA: Young onset adenoma.

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BACKGROUND AND AIMS: Incidence and mortality from early onset colorectal cancer (CRC) is rising. Adenoma detection, removal and subsequent endoscopic surveillance may modify risk of CRC diagnosed prior to age 50 (early onset CRC). We conducted a systematic review of young onset adenoma (YOA) prevalence, associated risk factors, and rate of metachronous advanced neoplasia after YOA diagnosis.

METHODS: Through a systematic search of multiple electronic databases through 2/12/2019, we identified studies with individuals age 18 to 49 years which reported on prevalence of adenoma, risk factors for adenoma, and/or risk for metachronous advanced neoplasia. Summary estimates were derived using random effects meta-analysis, when feasible.

RESULTS: Pooled overall prevalence of YOA was 9.0% (95% CI: 7.1%-11.4%) based on 24 studies including 23,142 individuals. On subgroup analysis, pooled prevalence of YOA for autopsy studies was 3.9% (95% CI: 1.9%-7.6%), while prevalence for colonoscopy studies was 10.7% (95% CI: 8.5%-13.5). Only advancing age was identified as a consistent risk factor for YOA based on 4 studies including 78,880 individuals. Pooled rate of metachronous advanced neoplasia after baseline YOA diagnosis was 6.0% (95% CI: 4.1%-8.6%), based on 3 studies including 1,493 individuals undergoing follow-up colonoscopy, with only 1 CRC case reported. Overall there were very few studies reporting metachronous advanced neoplasia, and no studies evaluating whether routine surveillance colonoscopy decreases risk of CRC.

CONCLUSIONS: Prevalence of YOA is estimated to be 9% and increases with age. Risk for metachronous advanced neoplasia after YOA diagnosis is estimated to be 6%. More research is needed to understand the prevalence, risk factors, and risk of CRC associated with YOA.

KEY WORDS: Colorectal Adenoma; Colorectal Neoplasia; Prevalence; Young Adult

INTRODUCTION

Colorectal cancer (CRC) is the 3rd most common cancer worldwide, and the 2nd most common cause of cancer mortality, with an incidence of 1.8 million and 881,000 deaths in 2018.[1] In the United States, CRC incidence and mortality have been declining among older adults.[2] In contrast, CRC incidence and mortality have increased among adults younger than age 50. Between 1975-1980, the overall incidence rate of early onset CRC was 9.9 per 100,000, with an increase to 11.7 per 100,000 between 2010-2014.[3] While factors responsible are not well understood, postulated risk factors include male sex, obesity, smoking, alcohol intake, antibiotic exposure, and dietary changes such as exposure to more processed foods[4].[5-9]

Adenomas are the precursors of most CRCs, and adenoma removal can reduce CRC incidence and mortality.[10-14] Based on observation of the impact of polypectomy and surveillance outcomes among older individuals, systematic detection and removal of adenomas with subsequent surveillance may have the ability to improve early detection and prevention of early onset CRC.[11-15] Clinical experience suggests that adenomas are detected among individuals under age 50 (Young onset adenoma). However, young onset adenoma (YOA) prevalence, risk factors associated with YOA, rates of metachronous advanced neoplasia and CRC after polypectomy, and whether surveillance has potential to reduce risk for advanced adenoma or CRC on follow up have not been well characterized. Clarifying these issues will help determine if detection, removal, and surveillance of adenomas has potential to address rising early onset CRC incidence and mortality.

To address this literature gap, we conducted a systematic review of the prevalence, risk factors, and risk of metachronous advanced neoplasia and CRC in individuals with YOA, to specifically address the following key questions:

1. Among individuals age 18 to 49, what is the prevalence of YOA?
2. Among individuals age 18 to 49, what are potential risk factors associated with YOA?
3. Among individuals with YOA, what is the risk for metachronous advanced neoplasia on follow up colonoscopy?

4. Among individuals with YOA, what is the risk for subsequent CRC on follow up colonoscopy?
5. Among individuals with YOA, does exposure to surveillance colonoscopy, versus no surveillance, reduce risk for colorectal cancer on follow up?

METHODS

Study Design

We conducted and reported a systematic review following the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16] Details of the protocol for this systematic review were registered on PROSPERO (registration #CRD42019125508).[17]

Search Strategy

We searched the Embase (Elsevier) and Pubmed from inception until February 12, 2019. The search was developed with the help of an experienced librarian (KMH; see Supplementary Material). Additional records were identified through review of reference sections of included studies, and reviewed in full text if they met title and abstract review criteria (see Supplementary Material for full search strategy).

Selection Criteria

Two individuals (NE and MYC) independently reviewed identified abstracts for eligibility. All abstracts reporting on outcomes related to our key questions for individuals age 18-49 years were selected for full-text review. Disagreements were resolved by involving a third author (SG). The same 2 reviewers then conducted a full text review of articles meeting inclusion criteria and of articles for which there was some uncertainty as to eligibility (See Supplementary Material for full selection criteria). Articles focused on patients with inflammatory bowel disease, hereditary colorectal cancer syndromes, or family history of CRC were excluded.

Data Abstraction and Risk of Bias/Quality Assessment

Two individuals (NE and MYC) conducted data abstraction, including study characteristics such as author, year of publication, study design/setting, time period of colonoscopy and the total sample size. Outcome data abstracted included risk factors for young onset adenoma and their

respective odds ratios from multivariate analysis, number of patients with young onset adenoma receiving follow-up colonoscopy, proportion of individuals with baseline adenoma with advanced neoplasia on follow up, and proportion of individuals with baseline adenoma with CRC on follow up. Risk of bias/quality were assessed by both reviewers for each study using a structured approach (See Supplementary material for details)

Data Synthesis and Statistical Analyses

Key Question 1 on the prevalence of young onset adenoma, and Key Question 3 on the rate of metachronous neoplasia on follow up had sufficient data for pooled estimates. For these two questions, we pooled corresponding data using the random effects model described by DerSimonian and Laird.[18]

For adenoma prevalence, the outcome was expressed as a pooled proportion, with 95% confidence intervals (CIs). Pre-planned subgroup analyses based on study type (colonoscopy vs. autopsy studies), and publication date (pre- vs post-1995). The year 1995 was used as the cutoff for this publication date analyses because it was the year after which early onset CRC began to rise.[3] For rate of metachronous neoplasia on follow up, the outcome was expressed as a proportion, with 95% confidence intervals. We assessed statistical heterogeneity using I^2 statistic.[19] All analyses were performed using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ). Small study effects were assessed by examining funnel plot asymmetry (See Supplementary material for detail on data syntheses and analyses).

RESULTS

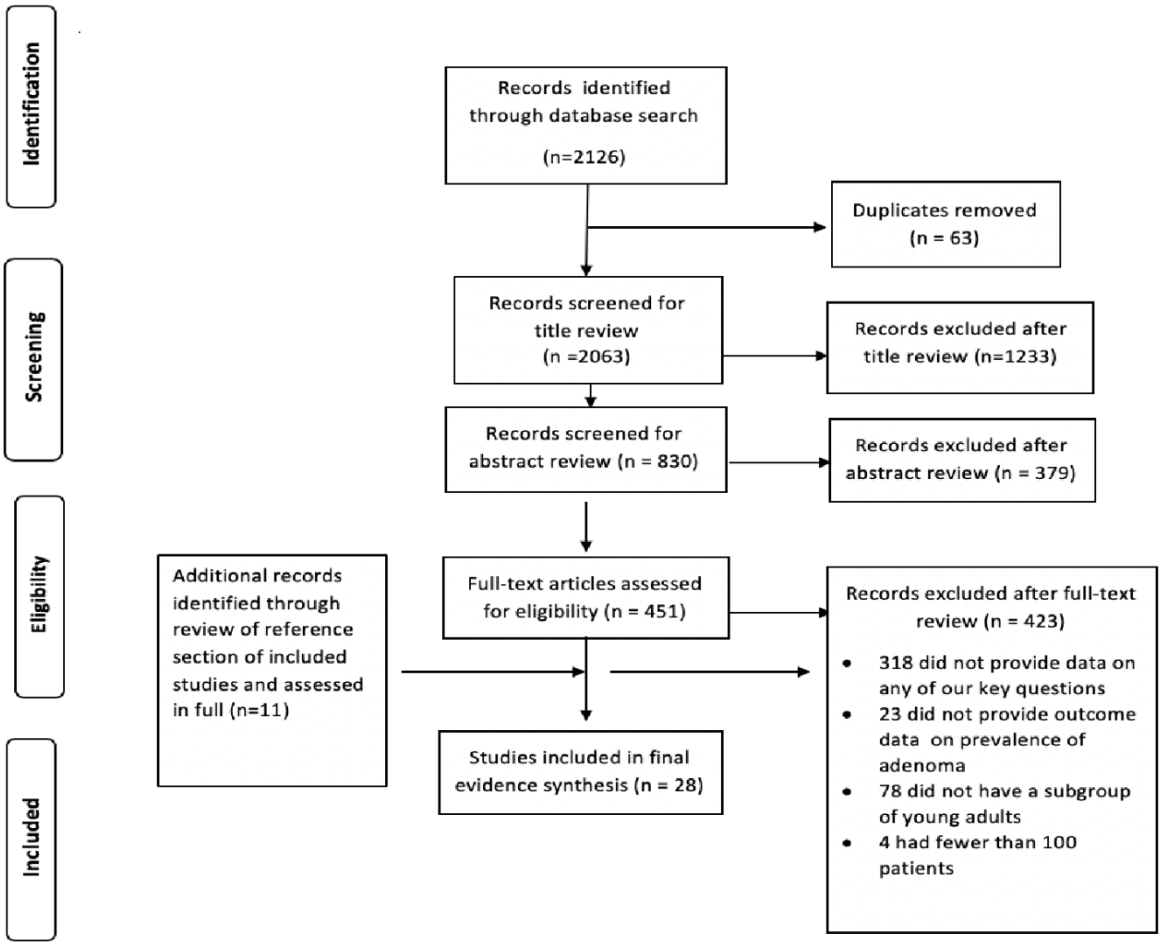
Literature Review

Figure 1 summarizes the literature review process. Out of 2,063 unique references, 830 were selected for abstract review based on title assessment, 451 were selected for full text review after abstract assessment, and an additional 11 studies were identified after reviewing the reference sections of included studies. Ultimately, 28 studies were included in the systematic review based

on pre-specified criteria.[20-44] Our search strategy did not identify any paper that addressed the impact of surveillance colonoscopy in patients with YOA on incidence and mortality from CRC.

Supplementary Table 1 describes the characteristics and quality of each included study, assessed as low, moderate or high quality. Overall 89% (n=25/28) of included studies were judged to be of at least moderate quality, with the remaining 11% (n=3/28) judged to be of low quality.

Figure 1: Study selection PRISMA flow diagram.

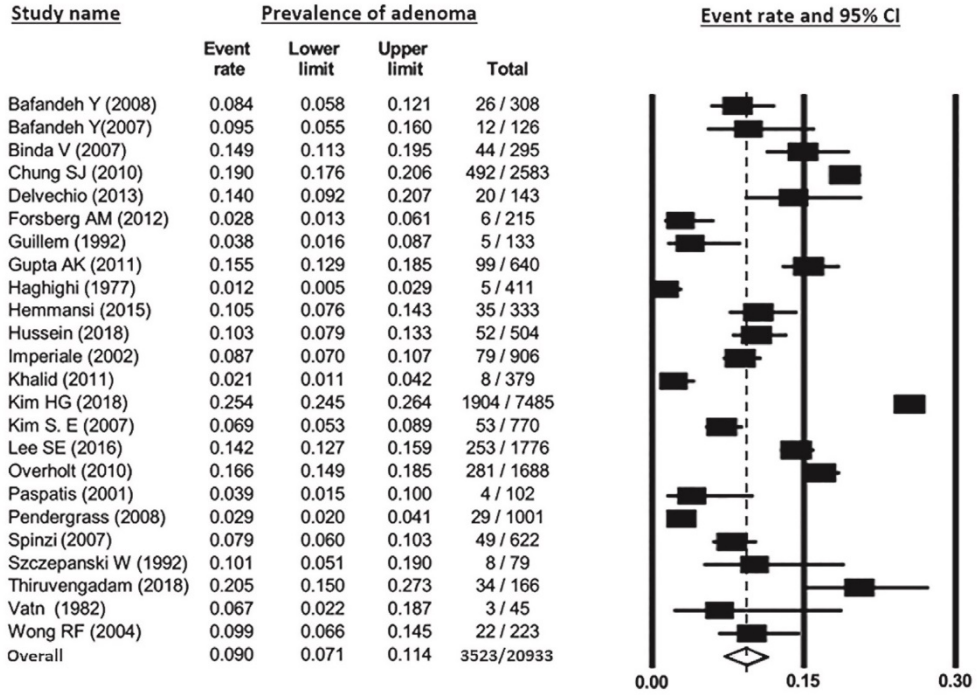


Key Question 1: Among individuals age 18-49, what is the prevalence of YOA?

The 24 studies addressing YOA prevalence included 5 autopsy studies (n=1,638)[36-40] and 19 studies of patients undergoing colonoscopy (n=19,295; Supplementary Table 2).[20-26, 28-32, 34, 35, 41-43, 45, 46]. Of the 19 studies of patients undergoing colonoscopy, 7 studies were performed on symptomatic patients alone[20, 21, 23, 30, 32, 41, 43], 6 on asymptomatic patients[22, 28, 31, 34, 43, 47], and 6 did not specify whether patients were symptomatic or not[24, 26, 29, 35, 42, 45]. The time period for assessment of our outcome data ranged from 1972 to 2017, with 19 of them conducted in patients undergoing colonoscopy after the year 1995, 3 studies prior to 1995, and 2 that began prior to 1995, but continued past this time. All the autopsy studies were performed before 1995. Of the studies providing prevalence data, 7 studies were performed in North America (all in the US), 1 study in South America (Brazil), 6 studies in Europe (2 Italy, 1 Poland, 1 Greece, 1 Sweden, 1 Norway), 6 studies in the Middle East (4 Iran, 1 Pakistan, 1 Lebanon), and four studies in East Asia (South Korea). These were grouped into Western studies (14 studies), and Afro-Asian studies (10 studies) (Supplementary Table 3).

Pooled prevalence of YOA was estimated to be 9.0% (95% CI: 7.1%-11.4%), with a range of 1.2%-25.4% across studies (Figure 2). Substantial heterogeneity was noted (I^2 =96%). On subgroup analysis, the pooled prevalence of YOA among autopsy studies was 3.9% (95% CI: 1.9%-7.6%), while prevalence among colonoscopy studies was 10.7% (95% CI: 8.5%-13.5%), p-value for difference between subgroups was P< 0.01 (Figure 3). Pooled prevalence of YOA based on colonoscopies performed prior to 1995 was 4.2% (95% CI: 7.4%-12.0%), while prevalence was 10.0% (95% CI: 7.8%-12.8%) based on studies performed after 1995 (Figure 4). Pooled prevalence based on colonoscopies performed on asymptomatic patients was 13.9% (95% CI: 9.5%-20.1%), while pooled prevalence based on colonoscopies performed on symptomatic patients was 8.6% (95% CI: 6.2%-11.7%; p-value for differences between subgroups = 0.05). Pooled prevalence based on Western studies was 9.0% (95% CI: 6.6%-12.1%) versus 9.2% for Afro-Asian studies (95% CI: 6.5%-12.9%; p = 0.919; Supplemental Figure A). To assess whether any one study had a dominant effect on the pooled prevalence estimate, each study was individually excluded and its effect on the main summary estimate and I^2 test for heterogeneity was evaluated. No study markedly influenced the overall prevalence of young onset adenoma, or degree of heterogeneity. Since considerable heterogeneity was observed across all studies, evaluation of publication bias using funnel plot was not conducted.

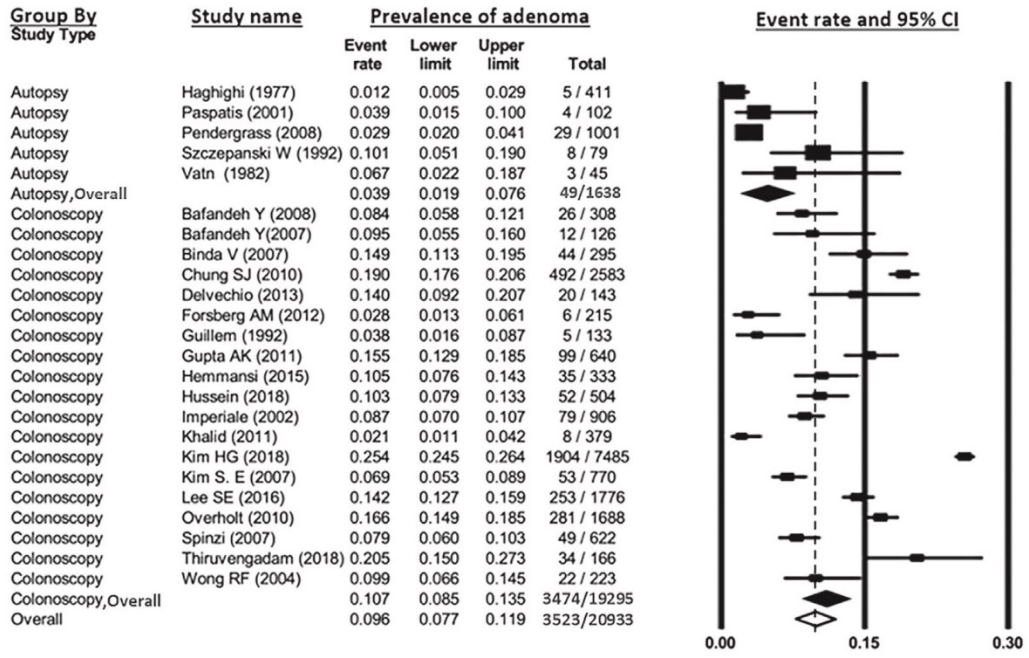
Figure 2: Pooled prevalence of YOA Legend: rectangles denote the pooled estimate for each study; the open diamond denote the overall pooled estimate for all studies.



Study name	Prevalence of adenoma			
	Event rate	Lower limit	Upper limit	Total
Bafandeh Y (2008)	0.084	0.058	0.121	26 / 308
Bafandeh Y(2007)	0.095	0.055	0.160	12 / 126
Binda V (2007)	0.149	0.113	0.195	44 / 295
Chung SJ (2010)	0.190	0.176	0.206	492 / 2583
Delvechio (2013)	0.140	0.092	0.207	20 / 143
Forsberg AM (2012)	0.028	0.013	0.061	6 / 215
Guillem (1992)	0.038	0.016	0.087	5 / 133
Gupta AK (2011)	0.155	0.129	0.185	99 / 640
Haghighi (1977)	0.012	0.005	0.029	5 / 411
Hemmansi (2015)	0.105	0.076	0.143	35 / 333
Hussein (2018)	0.103	0.079	0.133	52 / 504
Imperiale (2002)	0.087	0.070	0.107	79 / 906
Khalid (2011)	0.021	0.011	0.042	8 / 379
Kim HG (2018)	0.254	0.245	0.264	1904 / 7485
Kim S. E (2007)	0.069	0.053	0.089	53 / 770
Lee SE (2016)	0.142	0.127	0.159	253 / 1776
Overholt (2010)	0.166	0.149	0.185	281 / 1688
Paspatis (2001)	0.039	0.015	0.100	4 / 102
Pendergrass (2008)	0.029	0.020	0.041	29 / 1001
Spinzi (2007)	0.079	0.060	0.103	49 / 622
Szczepanski W (1992)	0.101	0.051	0.190	8 / 79
Thiruvengadam (2018)	0.205	0.150	0.273	34 / 166
Vatn (1982)	0.067	0.022	0.187	3 / 45
Wong RF (2004)	0.099	0.066	0.145	22 / 223
Overall	0.090	0.071	0.114	3523/20933

Figure 2. Pooled prevalence of young-onset adenoma. *Rectangles* denote pooled estimate for each study; *open diamond* denotes overall pooled estimate for all studies. CI, confidence interval.

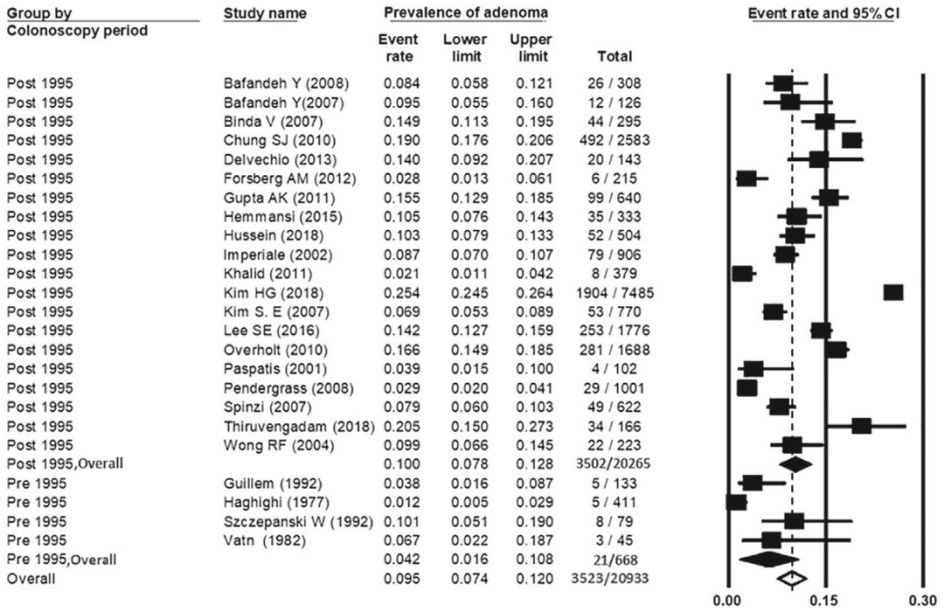
Figure 3: **Pooled prevalence of YOA, grouped by autopsy versus colonoscopy based-studies.** Legend: rectangles denote the pooled estimate for each study; the filled diamonds denote pooled estimates for the two subgroups, while the unfilled diamond denote overall pooled estimate for all studies.



Group By Study Type	Study name	Prevalence of adenoma			
		Event rate	Lower limit	Upper limit	Total
Autopsy	Haghighi (1977)	0.012	0.005	0.029	5 / 411
Autopsy	Paspatis (2001)	0.039	0.015	0.100	4 / 102
Autopsy	Pendergrass (2008)	0.029	0.020	0.041	29 / 1001
Autopsy	Szczepanski W (1992)	0.101	0.051	0.190	8 / 79
Autopsy	Vatn (1982)	0.067	0.022	0.187	3 / 45
Autopsy,Overall		0.039	0.019	0.076	49/1638
Colonoscopy	Bafandeh Y (2008)	0.084	0.058	0.121	26 / 308
Colonoscopy	Bafandeh Y(2007)	0.095	0.055	0.160	12 / 126
Colonoscopy	Binda V (2007)	0.149	0.113	0.195	44 / 295
Colonoscopy	Chung SJ (2010)	0.190	0.176	0.206	492 / 2583
Colonoscopy	Delvechio (2013)	0.140	0.092	0.207	20 / 143
Colonoscopy	Forsberg AM (2012)	0.028	0.013	0.061	6 / 215
Colonoscopy	Guillem (1992)	0.038	0.016	0.087	5 / 133
Colonoscopy	Gupta AK (2011)	0.155	0.129	0.185	99 / 640
Colonoscopy	Hemmansi (2015)	0.105	0.076	0.143	35 / 333
Colonoscopy	Hussein (2018)	0.103	0.079	0.133	52 / 504
Colonoscopy	Imperiale (2002)	0.087	0.070	0.107	79 / 906
Colonoscopy	Khalid (2011)	0.021	0.011	0.042	8 / 379
Colonoscopy	Kim HG (2018)	0.254	0.245	0.264	1904 / 7485
Colonoscopy	Kim S. E (2007)	0.069	0.053	0.089	53 / 770
Colonoscopy	Lee SE (2016)	0.142	0.127	0.159	253 / 1776
Colonoscopy	Overholt (2010)	0.166	0.149	0.185	281 / 1688
Colonoscopy	Spinzi (2007)	0.079	0.060	0.103	49 / 622
Colonoscopy	Thiruvengadam (2018)	0.205	0.150	0.273	34 / 166
Colonoscopy	Wong RF (2004)	0.099	0.066	0.145	22 / 223
Colonoscopy,Overall		0.107	0.085	0.135	3474/19295
Overall		0.096	0.077	0.119	3523/20933

Figure 3. Pooled prevalence of young-onset adenoma, grouped by autopsy versus colonoscopy based-studies. *Rectangles* denote pooled estimate for each study; *filled diamonds* denote pooled estimates for the 2 subgroups; *unfilled diamond* denotes overall pooled estimate for all studies. CI, confidence interval.

Figure 4: Pooled prevalence of YOA, grouped by studies conducted pre versus post 1995. Legend: rectangles denote the pooled estimate for each study; the filled diamonds denote pooled estimates for the two subgroups; the unfilled diamond denote overall pooled estimate for all studies.



Group by Colonoscopy period	Study name	Prevalence of adenoma			
		Event rate	Lower limit	Upper limit	Total
Post 1995	Bafandeh Y (2008)	0.084	0.058	0.121	26 / 308
Post 1995	Bafandeh Y(2007)	0.095	0.055	0.160	12 / 126
Post 1995	Binda V (2007)	0.149	0.113	0.195	44 / 295
Post 1995	Chung SJ (2010)	0.190	0.176	0.206	492 / 2583
Post 1995	Delvechio (2013)	0.140	0.092	0.207	20 / 143
Post 1995	Forsberg AM (2012)	0.028	0.013	0.061	6 / 215
Post 1995	Gupta AK (2011)	0.155	0.129	0.185	99 / 640
Post 1995	Hemmansi (2015)	0.105	0.076	0.143	35 / 333
Post 1995	Hussein (2018)	0.103	0.079	0.133	52 / 504
Post 1995	Imperiale (2002)	0.087	0.070	0.107	79 / 906
Post 1995	Khalid (2011)	0.021	0.011	0.042	8 / 379
Post 1995	Kim HG (2018)	0.254	0.245	0.264	1904 / 7485
Post 1995	Kim S. E (2007)	0.069	0.053	0.089	53 / 770
Post 1995	Lee SE (2016)	0.142	0.127	0.159	253 / 1776
Post 1995	Overholt (2010)	0.166	0.149	0.185	281 / 1688
Post 1995	Paspatis (2001)	0.039	0.015	0.100	4 / 102
Post 1995	Pendergrass (2008)	0.029	0.020	0.041	29 / 1001
Post 1995	Spinzi (2007)	0.079	0.060	0.103	49 / 622
Post 1995	Thiruvengadam (2018)	0.205	0.150	0.273	34 / 166
Post 1995	Wong RF (2004)	0.099	0.066	0.145	22 / 223
Post 1995,Overall		0.100	0.078	0.128	3502/20265
Pre 1995	Guillem (1992)	0.038	0.016	0.087	5 / 133
Pre 1995	Haghighi (1977)	0.012	0.005	0.029	5 / 411
Pre 1995	Szczepanski W (1992)	0.101	0.051	0.190	8 / 79
Pre 1995	Vatn (1982)	0.067	0.022	0.187	3 / 45
Pre 1995,Overall		0.042	0.016	0.108	21/668
Overall		0.095	0.074	0.120	3523/20933

Figure 4. Pooled prevalence of young-onset adenoma, grouped by studies conducted before versus after 1995. *Rectangles* denote pooled estimate for each study; *filled diamonds* denote pooled estimates for the 2 subgroups; *unfilled diamond* denotes overall pooled estimate for all studies. CI, confidence interval.

Key Question 2: Among individuals ages 18 to 49, what are potential risk factors associated with YOA?

Risk factors for YOA were addressed by 4 studies including 78,880 individuals (Supplemental Table 4).[22, 29, 35, 48] There were 2 studies conducted in South Korea, 1 study in China, and 1 study in the US. There was 1 multi-center study, and 3 single center studies.

The most consistent significant risk factor across all studies was increasing age. Three out of four studies assessed age as a continuous variable and observed that the likelihood of YOA significantly increased with each unit increase in age (Supplementary Table 4).[29, 35, 48] One study assessed age as a categorical variable and observed a significant increase in the prevalence of young onset adenoma as the age category increased: 10.4% in 30-39 years group versus 22.2% in the 40-49 years group (P <0.001).[22] Male sex was the second most consistently assessed risk factor, and was significantly associated with YOA in 2 out of 4 studies: Chung et al., (OR: 2.18, 95% CI: 1.02-4.63), and Gupta et al. (OR: 1.16, 95% CI: 1.03-1.31).[29, 49] Body mass index (BMI)

was assessed in 3 out of 4 studies, and only 1 of the studies found that the odds of YOA increased with each unit increase in BMI (OR: 1.05, 95% CI: 1.01-1.08)[48]. Current smoking status was assessed in 2 studies, with 1 observing a significant association with young onset adenoma (OR: 2.05, 95% CI: 1.16-3.65).[22] Family history of CRC was assessed in 2 studies, but was not significantly associated with YOA in either study.

Key Question 3: Among patients with YOA, what is the risk for metachronous advanced neoplasia on follow up?

The risk of metachronous advanced neoplasia on subsequent follow up of patients with YOA was reported in 4 papers including 78,880 individuals (Supplementary Table 5). Three of the four papers were conducted in South Korea, while 1 was conducted in the United States. Two of the studies were single center studies,[50, 51] while the other 2 were multi-center studies.[33,46] Follow-up times ranged from 33.6 to 49.0 months. One study estimated cumulative incidence (rate) of metachronous advanced neoplasia; this report only provided cumulative incidence for the low and high risk adenoma groups separately and did not provide an overall incidence rate for all adenoma patients combined.[46] Three studies reported risk of metachronous advanced neoplasia, defined as the proportion of individuals with baseline adenoma with advanced neoplasia on follow up. [52 33, 53] Pooled analysis of metachronous advanced neoplasia was limited to these three studies, because the study by Kim NH et al.[54] did not provide sufficient data regarding number with adenoma at baseline and number with advanced neoplasia at follow up to allow for pooling. Pooled risk of metachronous advanced neoplasia was estimated to be 6.0% (95% CI: 4.1%-8.6%; Figure 5). Substantial heterogeneity was noted (I^2 =56%).

Figure 5: Pooled rate of metachronous advanced neoplasia after baseline YOA diagnosis.
Legend: rectangles denote pooled estimate for each study; the unfilled diamond denote overall pooled estimate for all studies.

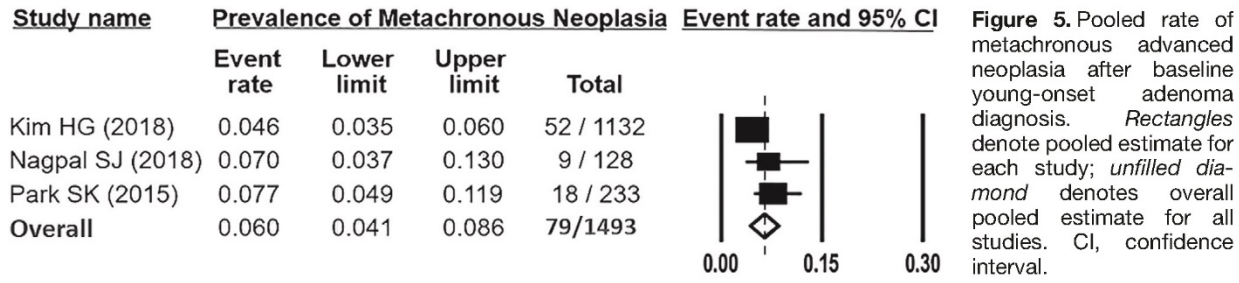


Figure 5. Pooled rate of metachronous advanced neoplasia after baseline young-onset adenoma diagnosis. *Rectangles* denote pooled estimate for each study; *unfilled diamond* denotes overall pooled estimate for all studies. CI, confidence interval.

Two studies stratified the rate or risk of advanced neoplasia on follow up based whether low risk (defined as having 1-2 tubular adenomas measuring <10mm in size) vs. high risk (defined as having advanced adenomas or ≥3 adenomas) adenomas were present.[33, 46] Kim HG et al. found that the cumulative rate of advanced neoplasia was 4.9% among 798 individuals with low risk adenoma at baseline, and 3.9% among 334 individuals with high risk adenoma at baseline. Kim NH et al. found that the 5 year risk of advanced neoplasia on follow up among individuals with low risk adenoma at baseline was 2.8% for ages 30-39, and 3.3% for ages 40-49, and that the 3 year risk among individuals with high risk adenoma at baseline was 1.9% for ages 30-39, and 3.6% for ages 40-49.

Key Question 4: Among patients with YOA, what is the risk for subsequent CRC?

The 4 papers (n=78,880) that addressed Question 3 on the risk of metachronous advanced neoplasia, also addressed Question 4 (Supplementary Table 6). Across these studies, only 1 case of CRC was reported amongst 9,341 patients (0.01%).

Key Question 5 :Among patients with young onset adenoma, does exposure to surveillance colonoscopy, versus no surveillance, reduce risk for colorectal cancer on follow up?

We did not identify any study reporting the impact of surveillance colonoscopy in patients with young onset adenoma on incidence and mortality from CRC.

DISCUSSION

Adenomas are found in individuals younger than 50, but prevalence, risk factors, and subsequent management and impact have not been previously well characterized. In a systematic review focusing on 5 key questions concerning YOA, we observed that the prevalence of YOA was 9%. Estimated risks of metachronous advanced neoplasia and CRC were 6% and 0.01%, respectively, though there is a paucity of data for this outcome. Increasing age was found to be the most consistent risk factor for YOA. We did not identify any studies on the impact of routine colonoscopic surveillance in patients with YOA on incidence and mortality from CRC. Our findings may inform current clinical practice, as well as future research on YOA and strategies for reducing incidence and mortality from early onset CRC.

Young onset adenoma prevalence

In a meta-analysis of 24 studies contributing data from 20,933 individuals, we found the pooled prevalence of YOA was estimated to be 9.0%. Prevalence was substantially lower among autopsy studies (3.9%) compared to colonoscopy studies (10.7%). The lower prevalence observed in autopsy studies could be because these studies are more representative of the general population, or because of variation in the protocols used to assess presence of adenomas.[55] Higher prevalence observed in colonoscopy studies could be because colonoscopy is more sensitive for adenoma detection than routine autopsy, or because the group of patients referred for colonoscopy under age 50 (most often for specific signs or symptoms of disease or family history of CRC), are not representative of the general population. Indeed, 14 out of 19 studies included in this evidence synthesis reported findings from patients undergoing colonoscopy for signs or symptoms of possible disease.

In a subgroup analysis, pooled adenoma prevalence was estimated to be 4.2% before, and 10.0% after 1995, the year around which early onset CRC incidence began to increase. This observation could be due to actual increases in YOA prevalence driven by risk factors overlapping with risk factors for early onset CRC, or temporal trends such as changes in attention to adenoma detection as a quality measure,[56] and introduction of high definition colonoscopes. Indeed, in 1 study, observed prevalence of young onset adenoma increased from 11.2% in the period between

1999-2006 prior before to 18.8% in the 2007-2009 period after high definition colonoscopes were adopted in their institution.[29]

Taken together, our study suggests that prevalence of YOA may be as high as 11.4% (the upper bound of the 95% CI around our estimated prevalence of 9%), but that data are insufficient to determine whether there has been an increase prevalence of YOA over time. We acknowledge that conventional statistical measures of heterogeneity (I^2 value) suggest high heterogeneity. However, these measures were designed for comparative studies in which summary estimates were odds ratio, relative risk, etc. Interpreting these measures for prevalence studies is challenging, and all meta-analyses of prevalence studies have high I^2 value.[57-59] Sources of heterogeneity in our study include the long time span of our included studies (from 1977-2018), the limited number of studies addressing this key question, and the diverse patient population (spanning different continents). We sought to minimize heterogeneity at a conceptual level by limiting analyses to studies that were as homogenous as possible, excluding modeling and cost-effectiveness studies, and by using a rigorous protocol. We also evaluated potential sources of heterogeneity by examining pooled prevalence in specific predefined subgroups. Our findings are similar to a recent narrative review, which concluded that colorectal adenomas are increasingly detected in young people,[60] and extend their conclusions by presentation of evidence from a systematic review and meta-analysis.

Young onset adenoma risk factors

Across 4 studies contributing data from 78,880 individuals, we found increasing age, male sex, and increasing BMI reported as risk factors for YOA. Only increasing age, a non-modifiable risk factor, was consistently identified as a risk factor across all studies.[22, 29, 35, 48] Formal meta-analysis was not possible due to study design heterogeneity. Thus, there is a lack of available data to provide significant insights into factors associated with YOA. Future research should utilize large cohorts of individuals with YOA (such as those identified through colonoscopy) to further understand risk factors associated with young onset adenoma diagnosis and assess overlap with risk factors for early onset CRC.

Metachronous advanced neoplasia and colorectal cancer after young onset adenoma

A common clinical challenge is determining whether individuals with YOA discovered during colonoscopy represent a group at increased risk for metachronous advanced neoplasia, and whether this group requires specialized surveillance. Across 3 studies contributing data from 1,493 individuals, we found that the pooled risk for metachronous advanced neoplasia was 6%. A 4th study reporting on data from 7,848 individuals with YOA over 40.8 months of follow up reported a cumulative incidence of metachronous advanced neoplasia of less than 4%, both among patients with high and low risk adenomas at baseline. Across the 4 included studies, just 1 individual was reported to develop CRC on follow-up. Sparse data were available to inform assessment of outcomes among individuals with baseline low risk versus high risk young onset adenoma. One study reported a 5 year metachronous advanced neoplasia rate of 4.9% after baseline low risk adenoma, and a 3 year rate of 3.9% after baseline high risk YOA diagnosis.[33] Comparisons of risk of advanced metachronous neoplasia for young adults vs adults over 50 have not been widely reported. One study comparing the risk of metachronous advanced neoplasia on follow-up among patients aged 20-49 vs 50-54, found the 5 year risk of advanced neoplasia on follow-up after baseline low risk adenoma in patients aged 20-49 years was 4.8% vs 5.0% in patients aged 50-54 years. After baseline high risk adenoma, the 3 year risk of metachronous advanced neoplasia was 3.9% in patients aged 20-49 years vs 3.8% in patients aged 50-54 years.[33] Another study including 128 young adults <50 years and 123 older adults who underwent baseline colonoscopy found the risk of advanced neoplasia on follow up did not differ between younger and older adults (7% vs 12.2% p=0.16).[61] Taken together, available evidence suggests that individuals with young onset adenoma have a relatively low rate of metachronous advanced neoplasia on follow up, at under 8.6% (the upper bound of the 95% CI for our estimated rate of 6%), but available evidence is insufficient to conclude whether rate of metachronous neoplasia in individuals with YOA is lower, similar to, or higher than individuals with adenomas diagnosed over age 50. A limitation of all studies included was that a substantial fraction of patients with baseline young onset adenoma did not receive surveillance colonoscopy for ascertainment of the outcome of metachronous advanced neoplasia. This decreased the sample size of individuals available for outcome ascertainment and potentially could have introduced bias of unknown direction. Larger cohort studies are needed to better characterize the risk for metachronous advanced neoplasia, including risk for CRC, among patients with young onset adenoma. Factors that might influence risk for metachronous advanced neoplasia (such as

family history of CRC) also merit investigation. In the interim, based on currently available data, evidence suggests that YOA patients should not be recommended surveillance colonoscopy more frequently than individuals with adenomas diagnosed at ages 50 and older. However, we suggest surveillance recommendations be individualized based on factors such underlying comorbid conditions, family history of CRC, and quality of baseline bowel preparation pending generation of new evidence.

Impact of colonoscopy surveillance after young onset adenoma diagnosis

We did not identify any studies that specifically addressed the impact of surveillance colonoscopy among patients with YOA. Understanding whether surveillance improves outcomes could clarify whether YOA patients require close surveillance and help reinforce participation in surveillance. Lack of evidence to support importance of surveillance may contribute to recommendations for surveillance, as well as adherence to surveillance (which may be as low as 24.7% among YOA patients[62]). Future large cohort studies should examine whether surveillance colonoscopy after YOA diagnosis improves outcomes. Randomized trials can also be considered, but feasibility may be a major challenge due to the very large sample size likely required to show differences in outcomes.

Strengths and limitations

To our knowledge, this is the first systematic review and comprehensive evidence synthesis of the 5 key questions regarding young onset adenoma we posed. We utilized best practices for our literature review and evidence synthesis, including: 1) pre-specifying the key questions of interest; 2) registering the protocol with PROSPERO; 3) utilizing best practices for the protocol, including a comprehensive literature review, having more than one reviewer for assessing inclusion/exclusion criteria and abstracting data; and assessing quality of individual studies. We also, for two questions, were able to perform meta-analyses that have not yet, to our knowledge, been reported.

Several limitations may be considered in interpreting our report. Despite a rigorous, pre-specified search strategy, all relevant publications may not have been identified. We chose to focus on published manuscripts and did not include abstracts from scientific meetings. Most of the data

available were from retrospective cohort studies, which may be subject to bias in data collected and challenged by presence of unmeasured confounding variables. Most of the data synthesized comes from patients undergoing colonoscopy for signs or symptoms of suspected gastrointestinal disease. As such, the findings are not representative of the general population of individuals under age 50. We were unable to stratify our analyses of adenoma prevalence under age 50 by age categories (such as by age decade) due to a lack of granular data on age-specific prevalence. Future research may help to clarify how much adenoma prevalence varies by age categories under age 50. Similarly, our systematic review and meta-analysis did not include a focus on variation in adenoma characteristics (e.g. high vs low risk adenoma) by age or over time; these areas may also be targeted for future research.

At the meta-analysis level, we observed significant heterogeneity in the pooled estimates of prevalence of young onset adenoma, risk of recurrent advanced neoplasia, and risk of CRC during follow up of patients with young onset adenoma. Prior studies have documented heterogeneity in providing prevalence estimates from meta-analyses.[63] The noted heterogeneity could be from a patient level (different levels of comorbidities, different patient ethnicity, presence or absence of various risk factors contributing to polyp formation), or from a study design setting (differences in study design; inclusion/exclusion criteria such as asymptomatic vs. symptomatic patient populations; study setting; definition of outcomes such as advanced neoplasia). To minimize this heterogeneity, at the conceptual phase of our study, we used strict inclusion and exclusion criteria. We also performed pre-planned subgroup analyses to explore sources of heterogeneity. Despite these steps, observed heterogeneity contributed to lowering our assessment of the quality of evidence to support answers to our key questions. Another limitation of our study pertaining to our analysis of the risk of advanced neoplasia on follow-up of patients with young onset adenoma (Key Question 3) is the that the pooled studies utilized varying length of surveillance intervals, precluding ability to use a consistent follow up time point after baseline polypectomy (e.g. 3 or 5 years) to estimate proportion with metachronous advanced neoplasia on follow up. This may have contributed to heterogeneity in our pooled estimates.

CONCLUSION

In a comprehensive systematic review and meta-analysis, we found that the pooled prevalence of YOA is estimated to be 9%. Evidence is insufficient to determine whether prevalence is increasing over time. Risk factors for YOA reported by currently available literature include age, male sex, increasing BMI, and smoking, with age being the most consistently reported risk factor across studies. More research on risk factors for YOA are needed, particularly to determine whether early onset CRC and YOA share common risk factors. Pooled risk for metachronous advanced neoplasia on follow-up after young onset adenoma diagnosis was estimated to be 6%. Evidence was insufficient to determine whether risk for metachronous advanced neoplasia differs by baseline adenoma characteristics, or to precisely estimate risk for CRC on follow up; both of these areas require further study. Evidence was insufficient to assess the impact of surveillance colonoscopy on outcomes of individuals with YOA. Overall, current evidence suggests that YOA is common, and associated with a relatively low for metachronous advanced neoplasia, but that more research is required to determine prevalence, risk factors, and optimal management, including whether detection, removal, and surveillance of YOA has potential to impact early onset CRC incidence and mortality.

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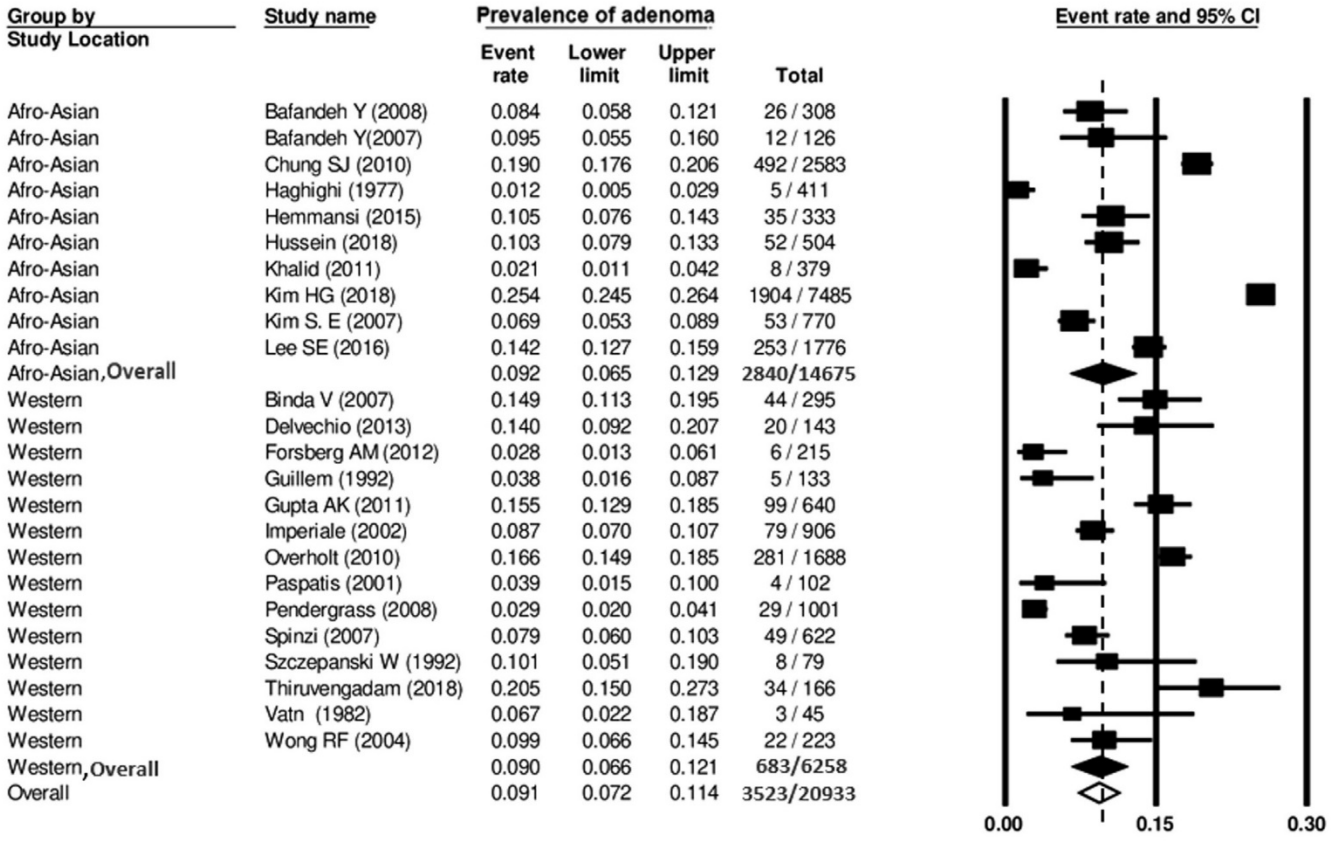
Supplemental Figure A: Pooled prevalence of YOA (Western vs Afro-Asian regions). Legend: rectangles denote pooled estimate for each study; the filled diamonds denote pooled estimates for the two subgroups; the unfilled diamond denote overall pooled estimate for all studies.



Supplementary Figure 1. Pooled prevalence of young-onset adenoma (Western vs Afro-Asian regions). *Rectangles* denote pooled estimate for each study; *filled diamonds* denote pooled estimates for the 2 subgroups; *unfilled diamond* denotes overall pooled estimate for all studies. CI, confidence interval.

SUPPLEMENTARY MATERIAL

METHODS

Study Design

We conducted and reported a systematic review following the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16] Details of the protocol for this systematic review were registered on PROSPERO (registration #CRD42019125508).[17]

Search Strategy

We searched the following databases from the inception until February 12, 2019: Embase (Elsevier) and Pubmed. The search was developed with the help of an experienced librarian (KMH; see Supplementary Material). Studies were excluded if they were review articles, editorials, non-English, animal studies, modeling studies, cost-analysis studies, qualitative studies, case studies, systematic reviews/meta-analyses, did not include individuals younger than age 50, had a sample size of <100 subjects, focused only on a special population (e.g. comprised solely of patients with a history of radiation for cancer therapy, or patients with genetic cancer syndrome), or included only children younger than age 18. Autopsy studies were included, if they answered any of the key questions. Additional records were identified through review of the reference sections of included studies, and reviewed in full text if they met title and abstract review criteria.

Selection Criteria

Two individuals (NE and MYC) independently reviewed identified abstracts for eligibility. All abstracts reporting original adenoma and/or CRC prevalence data with specified subgroup of 18-49 years were selected for full-text review. If the age range of the study population was not specified in the abstract, the abstract was also selected for review to determine if the age group 18-49 years was listed as a subgroup in the manuscript. Disagreements were resolved by involving a third author (SG). The same 2 reviewers then conducted a full text review of articles that met the inclusion criteria and of articles for which there was some uncertainty as to eligibility.

We included cohort studies conducted in adults 18-49 years of age, undergoing colonoscopy (or autopsy), and reporting (a) prevalence of adenoma, (b) risk factors associated with adenoma, (c) risk of metachronous advanced neoplasia and/or CRC, and/or (d) impact of CRC surveillance in subset of patients with adenoma on long-term incidence and mortality from CRC. If there were articles based on overlapping study participants, the original authors were contacted to help determine which article to include.

Data Abstraction and Risk of Bias Assessment

Two individuals (NE and MYC) conducted data abstraction. Data abstraction included: study characteristics such as author, year of publication, study design/setting (single center vs. multi-center, cohort vs. randomized trial); time period of colonoscopy, the inclusion and exclusion criteria for each study; the mean age of the study population, and the total sample size. Outcome data abstracted included: the number of adenomas for each study, risk factors for young onset adenoma and their respective odds ratios from multivariate analysis, the number of patients with young onset adenoma receiving follow-up colonoscopy, the proportion of individuals with baseline adenoma with advanced neoplasia on follow up, and the proportion of individuals with baseline adenoma with CRC on follow up. If a study also included data on adults 50 and above, we limited our data abstraction to adenoma data for adults aged 18-49.

The same two individuals (NE and MYC) individually assessed each included manuscript for quality. The 2017 Joanna Briggs Institute critical appraisal tool for prevalence studies was used to assess the quality of studies addressing prevalence of young onset adenoma.[18] The Newcastle-Ottawa-Quality Assessment Scale (NOS) was used to assess the quality of all other studies.[19] In this scale, observational studies were scored across 3 categories: selection (4 questions) and comparability (2 questions) of study groups and ascertainment of the outcome of interest (3 questions); all questions had a score of 1 except for comparability of study groups, in which separate points were awarded for controlling age and/or sex (maximum of 2 points). Studies with a cumulative score of $\geq$7 were considered high quality.

Data Synthesis and Statistical Analyses

Two key questions had sufficient data available to perform meta-analyses: Key Question 1 on the prevalence of young onset adenoma, and Key Question 3 on the rate of metachronous neoplasia on follow up. For these two questions, we pooled corresponding data using the random effects model described by DerSimonian and Laird.[20]

For adenoma prevalence, the outcome was expressed as a pooled proportion, with 95% confidence intervals (CIs). We also conducted pre-planned subgroup analyses based on colonoscopy vs. autopsy studies, indication for colonoscopy (symptomatic vs. asymptomatic) and location (Western vs. Afro-Asian). We also conducted time trend analysis by abstracting data on the proportion of patients found with adenomas on autopsy or colonoscopy prior to year 1995 vs. after 1995. The year 1995 was used as the cutoff for this subgroup analysis because it is the year after which the rise in early onset CRC has been observed.[3] For rate of metachronous neoplasia on follow up, the outcome was expressed as a proportion, with 95% confidence intervals. We did not perform any subgroup analyses based on the year of publication as these did not reflect the time of patient recruitment. We assessed statistical heterogeneity using I^2 statistic, which estimates the proportion of total

variances across studies was due to heterogeneity rather than chance.[21] Values over 50% indicate substantial heterogeneity. Publication bias was assessed qualitatively by visual inspection of funnel plots. For all tests except for publication bias, a probability level <0.05 was considered statistically significant. All analyses were performed using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ). Small study effects were assessed by examining funnel plot asymmetry.

Literature Search Terms:

PubMed Search Terms:
Search (("Young Adult"[Mesh] OR "Adult"[Mesh:noexp] OR (young adult[tiab] OR young adult,[tiab] OR young adulthood[tiab] OR young adults[tiab]) OR younger adults[tiab] OR "Age of Onset"[Mesh] OR young[tiab] OR younger[tiab]) AND ("Colonoscopy"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Early Detection of Cancer"[Mesh] OR screening[tiab] OR early detection[tiab] OR surveillance[tiab] OR "Incidence"[Mesh] OR "Prevalence"[Mesh] OR incidence[tiab] OR prevalence[tiab] OR "Risk Factors"[Mesh] OR (risk factor[tiab] OR risk factor's[tiab] OR risk factore[tiab] OR risk factored[tiab] OR risk factors[tiab] OR risk factors,[tiab] OR risk factory[tiab]) OR "Neoplasms, Second Primary"[Mesh] OR second primary colorectal cancer[tiab] OR "Neoplasm Recurrence, Local"[Mesh] OR (recurren[tiab] OR recurrenc[tiab] OR recurrence[tiab] OR recurrence'[tiab] OR recurrence's[tiab] OR recurrence20[tiab] OR recurrenceassociated[tiab] OR recurrencebut[tiab] OR recurrencec[tiab] OR recurrenced[tiab] OR recurrencee[tiab] OR recurrencefree[tiab] OR recurrencegrey[tiab] OR recurrencegtv[tiab] OR recurrencein[tiab] OR recurrencel[tiab] OR recurrenceless[tiab] OR recurrenceliterature[tiab] OR recurrencemva[tiab] OR recurrencen[tiab] OR recurrencent[tiab] OR recurrenceof[tiab] OR recurrenceonline[tiab] OR recurrencerate[tiab] OR recurrencerates[tiab] OR recurrenceree[tiab] OR recurrencerelative[tiab] OR recurrences[tiab] OR recurrences'[tiab] OR recurrencescore[tiab] OR recurrencesed[tiab] OR recurrenceses[tiab] OR recurrencesor[tiab] OR recurrencess[tiab] OR recurrencew[tiab] OR recurrencewithout[tiab] OR recurrencia[tiab] OR recurrencial[tiab] OR recurrencias[tiab] OR recurrencies[tiab] OR recurrencs[tiab] OR recurrenct[tiab] OR recurrency[tiab] OR recurrencys[tiab] OR recurrend[tiab] OR recurrene[tiab] OR recurrened[tiab] OR recurreness[tiab] OR recurrens[tiab] OR recurrens'[tiab] OR recurrenstam3[tiab] OR recurrent[tiab] OR recurrent'[tiab] OR recurrentabortion[tiab] OR recurrentacutepancreatitis[tiab] OR recurrentbladder[tiab] OR recurrentbrca1alleles[tiab] OR recurrente[tiab] OR recurrente12[tiab] OR recurrented[tiab] OR recurrentes[tiab] OR recurrentgastric[tiab] OR recurrentgeneralized[tiab] OR recurrential[tiab] OR recurrentis[tiab] OR recurrently[tiab] OR recurrentnasal[tiab] OR recurrentpleural[tiab] OR recurrentpolyhedritis[tiab] OR recurrentpregnancy[tiab] OR recurrentpulmonary[tiab] OR recurrents[tiab] OR recurrentspontaneousabortion[tiab] OR recurrenttumors[tiab] OR recurrentvte[tiab] OR recurrenty[tiab]))) AND (("colon"[MeSH Terms] OR "colon"[tiab]) AND (("Adenomatous Polyps"[Mesh] OR "Adenoma, Villous"[Mesh] OR "adenoma*"[tiab]) OR ("Colonic Polyps"[Mesh] OR ((("colon"[MeSH Terms] OR "colon"[All Fields]) OR ("colon"[MeSH Terms] OR "colon"[All Fields] OR "colonic"[All Fields])) AND polyp[tiab] OR polyps[tiab]))))

Embase Search Terms:
(('colonoscopy'/syn AND 'adenomatous polyp'/syn OR (adenomatous AND polyp) OR 'adenomatous polyp' OR adenoma OR metachronous OR (colorectal AND adenomas) OR 'colorectal adenoma') AND 'polypectomy surveillance' OR (polypectomy AND surveillance) OR (adenoma AND surveillance) OR 'adenoma surveillance' OR ('post polypectomy' AND surveillance) OR 'post-polypectomy surveillance') AND ('risk factor' AND 'adenomatous polyp'/syn OR (adenomatous AND poly) OR 'adenomatous polyp' OR adenoma OR metachronous OR (colorectal AND adenomas) OR 'colorectal adenoma') AND ‘Young Adult’/syn OR ‘young” OR ‘younger’ or ‘young adults’
+
**riskfactors for YOA
risk AND factors AND adenomatous AND polyp AND young

('colonoscopy'/syn AND 'adenomatous polyp'/syn OR (adenomatous AND polyp) OR 'adenomatous polyp' OR adenoma OR metachronous OR (colorectal AND adenomas) OR 'colorectal adenoma') AND 'polypectomy surveillance' OR (polypectomy AND surveillance) OR (adenoma AND surveillance) OR 'adenoma surveillance' OR ('post polypectomy' AND surveillance) OR 'post-polypectomy surveillance'

Supplemental Tables 1-6

Supplementary Table 1: Characteristics of included studies (n=28 studies including 103,668 individuals)

Study Name	Study Period	Quality	Ages included in each study	Location	Indication for Colonoscopy	Key Question (KQ) Addressed
Bafandeh Y (2008)	2005-2007	Moderate	18-49	Tabriz, Iran	Colonoscopy for unexplained lower GI symptoms in patients <50 years	KQ1: Prevalence of YOA
Bafandeh Y (2007)	2005-2007	Moderate	30-49	Tabriz, Iran	Colonoscopy for unexplained lower GI symptoms in patients <50 years	KQ1: Prevalence of YOA
Binda V (2007)	1999-2000	Moderate	40-49	Brazil	Colonoscopy for unexplained lower GI symptoms in patients <50 years	KQ1: Prevalence of YOA
Chen HM (2011)	1990-2009	Low	18-49	China	Consecutive subjects <49 years who received colonoscopy for bloody stool	KQ2: Risk factors for YOA
Chung SJ (2010)	2004-2007	Moderate	30-49	Seoul, South Korea	Asymptomatic screening colonoscopy as part of annual health checkup in patients <50 years	KQ1: Prevalence of YOA KQ2: Risk factors for YOA
Delvechio G (2013)	2006-2008	Moderate	40-49	Rome, Italy	Patients aged 40-49 years with at least 1FDR (40 to ≥70 years of age) with CRC	KQ1: Prevalence of YOA
Forsberg AM (2012)	2002-2006	High	18-45	Stockholm, Sweden	Colonoscopy performed (regardless of indication) on a sample of patients ≤45 drawn from the Swedish population register	KQ1: Prevalence of YOA
Guillem JG (1992)	1980-1990	Moderate	20-49	New York, USA	Patients aged 20-49 with FDR with CRC	KQ1: Prevalence of YOA
Gupta AK (2011)	1999 -2009	Moderate	40-49	Michigan, USA	Patients aged 40-49 years with FDR with CRC	KQ1: Prevalence of YOA KQ2: Risk factors for YOA
Haghighi P (1977)	1962-1973	High	20-49	Southern Iran	Prospective review by an experienced colon pathologist of all colon	KQ1: Prevalence of YOA

					specimens removed from consecutive autopsies in ages 20-49	
Hemmansi G (2015)	2009-2012	Low	40-49	Firoozgan, Iran	Asymptomatic patients aged 40-49 undergoing colonoscopy for screening	KQ1: Prevalence of YOA
Hussein K (2018)	2016-2018	Moderate	18-49	Lebanon	Colonoscopy for unexplained lower GI symptoms, and family history of IBD or CRC in patients <50	KQ1: Prevalence of YOA
Imperiale TF (2002)	1995-2000	Moderate	40-49	Indianapolis, USA	Asymptomatic patients aged 40-49 years undergoing colonoscopy for screening	KQ1: Prevalence of YOA
Khalid AB (2011)	2007-2009	Moderate	18-49	Karachi, Pakistan	Patients aged 18-49 with symptoms of fresh blood per rectum in the previous 6 months	KQ1: Prevalence of YOA
Kim HG (2018)	2006-2010	Moderate	20-49	Guangdong, Seoul, South Korea	Asymptomatic patients aged 20-49 undergoing screening colonoscopy and subsequent surveillance colonoscopy	KQ1: Prevalence of YOA KQ3: Risk of metachronous advanced neoplasia on follow-up KQ4: Risk of CRC on follow-up
Kim NH (2018)	2010-2017	Moderate	30-49	Seoul and Suwon, South Korea	Asymptomatic patients aged 30-49 undergoing screening colonoscopy, and subsequent surveillance colonoscopy	KQ3: Risk of metachronous advanced neoplasia on follow-up KQ4: Risk of CRC on follow-up
Kim SE (2007)	2005	Moderate	30-49	Seoul, South Korea	Asymptomatic patients aged 30-49 undergoing screening colonoscopy	KQ1: Prevalence of YOA
Lee SE (2016)	2012-2014	Moderate	18-49	Goyan, South Korea	Symptomatic and asymptomatic patients age< 50 undergoing colonoscopy as a part of routine health checkups	KQ1: Prevalence of YOA KQ 2: Risk factors for YOA

Nagpal SJ (2018)	1984-2012	Moderate	18-49	Cleveland, USA	Patients age < 40 who underwent polypectomy and subsequent colonoscopy for surveillance	KQ3:Risk of metachronous advanced neoplasia on follow-up KQ4: Risk of CRC on follow-up
Overholt BF (2010)	2007	Moderate	40-49	USA, Canada	Patients aged 40-49 undergoing colonoscopy as a part of routine health checkups, regardless of symptoms	KQ1: Prevalence of YOA
Park SK (2015)	2009-2012	Moderate	18-49	Seoul, South Korea	Patients who underwent initial colonoscopy with polypectomy, and a subsequent surveillance colonoscopy	KQ3: Risk of metachronous advanced neoplasia on follow-up KQ4: Risk of CRC on follow-up
Paspatis GA (2001)	1997-1999	High	18-49	Crete, Greece	Forensic postmortem autopsies with examination of the colon (performed for cases age <50 with sudden or violent or undiagnosed deaths)	KQ1: Prevalence of YOA
Pendergrass CJ (2008)	1985-2004	High	20-49	Baltimore, USA	Postmortem autopsy of cases aged 20-49, without any documented GI symptoms, GI diagnosis, or family history of CRC	KQ1: Prevalence of YOA
Spinzi G (2007)	2002	Moderate	30-49	Italy	Patients age 30-49 undergoing colonoscopy for hematochezia	KQ1: Prevalence of YOA
Szczepanski W (1992)	1974-1978	High	18-49	Krakow, Poland	Prospective study of consecutive autopsies with examination of the colon under a magnifying lens in cases age< 50	KQ1: Prevalence of YOA
Thiruvengadam R (2018)	2013-2018	Low	18-40	California, USA	Retrospective review of colonoscopy performed by a single provider with ADR of 70%, in asymptomatic patients <40 years old	KQ1: Prevalence of YOA
Vatn M (1982)	1972-1973	High	18-40	Oslo, Norway	Prospective study of consecutive autopsies with examination of the	KQ1: Prevalence of YOA

					colon under a magnifying lens in cases <40 years old	
Wong RF (2004)	1997-1999	Moderate	18-49	Utah, USA	Consecutive veterans age <50 who underwent colonoscopy for rectal bleeding	KQ1: Prevalence of YOA

Abbreviations: ADR, Adenoma detection rate; CRC, colorectal cancer; FDR, First degree relative; GI, Gastrointestinal; IBD, Inflammatory bowel disease; KQ: Key Question ; YOA, Young onset adenoma.

Supplementary Table 2. Findings from studies addressing KQ1: What is the prevalence of young onset adenoma? (n=24 studies including 20,933 individuals)					
Study Name	**Study Period**	**Quality**	**Location**	**Indication of Colonoscopy**	**Adenoma Prevalence**
Colonoscopy Studies					
Bafandeh Y (2008)	2005-2007	Moderate	Tabriz, Iran	Colonoscopy for unexplained lower GI symptoms in patients younger than 50	Age <30: 4.6% (n=5/108), Age 30-39: 9.1% (n=10/110) Age 40-49: 12.2% (n=11/90) Overall: 8% (n=26/308)
Bafandeh Y (2007)	2005-2007	Moderate	Tabriz, Iran	Colonoscopy for unexplained lower GI symptoms in patients younger than 50	Age 30-39: 7.9% (n=6/76) Age 40-49: 12% (n= 6/50) Overall: 11% (n=12/126)
Binda V (2007)	1999-2000	Moderate	Brazil	Colonoscopy for unexplained lower GI symptoms anemia and weight loss in patients younger than 50	14.9% (n=44/295)
Chung SJ (2010)	2004-2007	Moderate	Seoul, South Korea	Asymptomatic screening colonoscopy as part of annual health checkup in patients <50	Age 30-39: 10.4% (n=63/608) Age 40-49: 22.0% (n=429/1930) Overall:19% (n= 492/2583)
Delvechio G (2013)	2006-2008	Moderate	Rome, Italy	Patients aged 40-49 with at least one FDR (40 to ≥70 years of age) with CRC	14% (n=20/143)
Forsberg AM (2012)	2002-2006	High	Stockholm, Sweden	Colonoscopy performed (regardless of indication) on a sample of patients age ≤45 drawn from the Swedish population register	2.8% (n=6/215)
Guillem JG (1992)	1980-1990	Moderate	New York, USA	Patients aged 20-49 with FDR with CRC	FDR: Age 20-29: 0% (n=0/5) Age 30-39: 2% (n=1/49) Age 40-49: 8.3% (n=4/48) Control: Age 20-29: 0% (n= 0/0) Age 30-39: 0% (n= 0/7) Age 40-49: 0% (n= 0/24) Overall: 3% (n=5/133)
Gupta AK (2011)	1999-2009	Moderate	Michigan, USA	Patients aged 40-49 old with FDR with CRC	Age 40-44: 9.2% (n=9/314) Age 45-49: 21.5% (n=70/326). Overall: 12% (n= 99/640)

Hemmansi G (2015)	2009-2012	Low	Firoozgan, Iran	Asymptomatic patients aged 40-49 undergoing colonoscopy for screening	Male: 12.2% (n=19/156) Female: 9.0% (n=16/177) Overall: 10.5% (n=35/333)
Hussein K (2018)	2016-2018	Moderate	Lebanon	Colonoscopy for unexplained lower GI symptoms, abnormal imaging, and family history of IBD or CRC in patients <50	Age 18-40: 3.6% (n=12/330) Age 40-49: 23.0% (n=40/174) Overall: 10% (n=52/504)
Imperiale TF (2002)	1995-2000	Moderate	Indianapolis, USA	Asymptomatic patients aged 40-49 undergoing colonoscopy for screening	Overall: 8.7% (n=79/906)
Khalid AB (2011)	2007-2009	Moderate	Karachi, Pakistan	Patients aged 18-49 with symptoms of fresh blood per rectum in the previous 6 months	Overall: 2.1% (n=8/379)
Kim HG (2018)	2006-2010	Moderate	Guangdong, Seoul, South Korea	Asymptomatic patients aged 20-49 undergoing screening colonoscopy and subsequent surveillance colonoscopy	Age 20-39: 19% (n=243/1278) Age 40-49: 26.7% (n=1661/6207) Overall: 25.4% (n=1904/7485)
Kim SE (2007)	2005	Moderate	Seoul, South Korea	Asymptomatic patients aged 30-49 undergoing screening colonoscopy	Male: Age 30-39: 2.7% (n= 4/149) Age 40-49: 12.3% (n=34/275) Female: Age 30-39: 1.6% (n= 2/127) Age 40-49: 5.9% (n=13/219) Overall: 7% (n= 53/770)
Lee SE (2016)	2012-2014	Moderate	Goyan, South Korea	Symptomatic and asymptomatic patients younger than age 50 undergoing colonoscopy as a part of routine health checkups	Age 18-40: 8.8% (n=61/694) Age 40-44: 14.7% (n=87/591) Age 45-49: 21.3% (n=105/491) Overall: 8% (n= 253/1776)
Overholt BF (2010)	2007	Moderate	USA, Canada	Patients aged 40-49 undergoing colonoscopy as a part of routine health checkups, regardless of symptoms	Overall:16.7% (n= 281/1688)
Spinzi G (2007)	2002	Moderate	Italy	Patients aged 30-49 undergoing colonoscopy for hematochezia	Age 30-40: 4.5% (n=14/312) Age 41-50: 11.3% (n=35/310) Overall: 8% (n=49/622)
Thiruvengadam R (2018)	2013-2018	Low	California, USA	Retrospective review of colonoscopy performed by a single provider with ADR of 70%, in asymptomatic patients younger than age 40	Age 18-30: 6.8% (n=4/59) Age 31-40: 28% (n=30/107) Overall: 39% (n=34/166)

Wong RF (2004)	1997-1999	Moderate	Utah, USA	Consecutive veterans younger than age 50 who underwent colonoscopy for rectal bleeding	Overall: 9.9% (n= 22/223)
Autopsy Studies					
Haghighi P (1977)	1962-1973	High	Southern Iran	Prospective review with a magnifying lens by an experienced colon pathologist of all colon specimens removed from consecutive autopsies in ages 20-49	Age 20-30: 0.7% (n=1/140) Age 30-40: 1.3% (n=2/150) Age 40-50: 1.7% (n=2/121) Overall: 1% (n=5/411)
Paspatis GA (2001)	1997-1999	High	Crete, Greece	Forensic postmortem autopsies with examination of the colon (performed for cases <age 50 with sudden or violent or undiagnosed deaths)	Male: 5.5.% (n=4/72) Female 0% (n=0/30) Overall: 4% (n=4/102)
Pendergrass CJ (2008)	1985-2004	High	Baltimore, USA	Postmortem autopsy of cases aged 20-49, without any documented GI symptoms, GI diagnosis, or family history of CRC	Age 20-29: 1.4% (n=2/144) Age 30-39: 2.4% (n=8/334) Age 40-49: 3.6% (n=19/523) Overall: 2.9% (n=29/1001)
Szczepanski W (1992)	1974-1978	High	Krakow, Poland	Prospective study of consecutive autopsies with examination of the colon under a magnifying lens in cases younger than age 40	Male: 15.9%(n= 7/44) Female: 2.9% (n= 1/35) Overall: 10% (n= 8/79)
Vatn M (1982)	1972-1973	High	Oslo, Norway	Prospective study of consecutive autopsies with examination of the colon under a magnifying lens in cases younger than age 40	Overall: 6.7% (n= 3/45)

Abbreviations: ADR, Adenoma detection rate; CRC, colorectal cancer; FDR, First degree relative; GI, Gastrointestinal; IBD, Inflammatory bowel disease; KQ, Key question; YOA, Young onset adenoma.

Supplementary Table 3: Key Question 1 studies grouped by region and symptom status					
Study Name	**Study Period**	**Quality**	**Location**	**Region**	**Indication of Colonoscopy**
Bafandeh Y (2008)	2005-2007	Moderate	Tabriz, Iran	Afro-Asian	Symptomatic
Bafandeh Y (2007)	2005-2007	Moderate	Tabriz, Iran	Afro-Asian	Symptomatic
Binda V (2007)	1999-2000	Moderate	Brazil	Western	Symptomatic
Chung SJ (2010)	2004-2007	Moderate	Seoul, South Korea	Afro-Asian	Asymptomatic
Delvechio G (2013)	2006-2008	Moderate	Rome, Italy	Western	Not specified
Forsberg AM (2012)	2002-2006	High	Stockholm, Sweden	Western	Not specified
Guillem JG (1992)	1980-1990	Moderate	New York, USA	Western	Not specified
Gupta AK (2011)	1999 -2009	Moderate	Michigan, USA	Western	Not specified
Haghighi P (1977)	1962-1973	High	Southern Iran	Afro-Asian	Not applicable
Hemmansi G (2015)	2009-2012	Low	Firoozgan, Iran	Afro-Asian	Asymptomatic
Hussein K (2018)	2016-2018	Moderate	Lebanon	Afro-Asian	Symptomatic
Imperiale TF (2002)	1995-2000	Moderate	Indianapolis, USA	Western	Asymptomatic
Khalid AB (2011)	2007-2009	Moderate	Karachi, Pakistan	Afro-Asian	Asymptomatic
Kim HG (2018)	2006-2010	Moderate	Guangdong, Seoul, South Korea	Afro-Asian	Asymptomatic
Kim SE (2007)	2005	Moderate	Seoul, South Korea	Afro-Asian	Asymptomatic
Lee SE (2016)	2012-2014	Moderate	Goyan, South Korea	Afro-Asian	Not specified
Overholt BF (2010)	2007	Moderate	USA, Canada	Western	Not specified
Paspatis GA (2001)	1997-1999	High	Crete, Greece	Western	Not applicable
Pendergrass CJ (2008)	1985-2004	High	Baltimore, USA	Western	Not applicable
Spinzi G (2007)	2002	Moderate	Italy	Western	Symptomatic
Szczepanski W (1992)	1974-1978	High	Krakow, Poland	Western	Not applicable
Thiruvengadam R (2018)	2013-2018	Low	California, USA	Western	Asymptomatic
Vatn M (1982)	1972-1973	High	Oslo, Norway	Western	Not applicable
Wong RF (2004)	1997-1999	Moderate	Utah, USA	Western	Symptomatic

Supplementary Table 4. Findings from studies addressing KQ2: What are potential risk factors associated with young onset adenoma? (n=4 studies including 78,880 individuals)

Study Name	Study Period	Quality	Location	Sample Size	Indication of Colonoscopy	Risk factors for YOA
Chen HM (2011)	1990-2009	Low	China	74,526	Consecutive subjects 40 years or younger who received colonoscopy for bloody stool	**Significant Risk Factors:** Rectal bleeding: OR 1.40 (1.03–1.91) Age: OR 1.11 (1.07–1.13) BMI: OR 1.05 (1.01–1.08) **Non-Significant Risk Factors:** Male sex: OR 1.30 (0.95–1.77)
Chung SJ (2010)	2004-2007	Moderate	Seoul, South Korea	2,538	Asymptomatic screening colonoscopy as part of annual health checkup in patients younger than 50	*Age 30-39:* **Significant Risk Factors:** Male sex: OR 2.18 (1.02–4.63) Current smoker: OR 2.05 (1.16–3.65) **Non-Significant Risk Factors:** Alcohol: OR 0.72 (0.35–1.47) Family history of CRC: OR 1.38 (0.55–3.46) BMI >25.0: OR 0.68 (0.31–1.48) Abdominal obesity: OR 1.08 (0.51–2.27) *Age 40-49:* **Significant Risk Factors:** Male sex: OR 2.09 (1.52–2.87) Current smoker: OR 1.37 (1.06–1.79) **Non-Significant Risks Factors:** BMI≥25: OR 0.82 (0.61–1.12) Abdominal obesity: OR 1.10 (0.89–1.96) Alcohol: OR 1.01 (0.76–1.33) Family history of CRC: OR 1.38 (0.91–2.09)
Gupta AK (2011)	1999-2009	Moderate	Michigan, USA	640	Patients aged 40-49 years old with FDR with CRC	**Significant Risk Factors:** Age: OR 1.16 (1.03-1.31) Male sex: OR 2.1 (1.06-4.40) **Non-Significant Risk Factors:** FDR >60y at diagnosis: OR 2.01 (0.94-4.27) Obesity: OR 1.67 (0.80-3.45) Diabetes: OR 0.56 (0.08-3.90)

						Aspirin: OR 0.26 (0.03-2.30) ≥2 FDRs with CRC: OR 1.72 (0.33-8.80)
Lee SE (2016)	2012-2014	Moderate	Goyan, South Korea	1,176	Patients <50 years old undergoing colonoscopy as a part of routine health checkups, regardless of symptoms	**Significant Risk Factors:** Age (45-49, Ref): Age 40-44: OR 0.64 (0.46-0.88) Age<40: OR 0.39 (0.28-0.56 Waist circumference: OR 1.72 (1.15-2.55) **Non-Significant Risk Factors:** Male sex: OR 1.43 (0.89-2.28) Metabolic syndrome: OR 0.88 (0.53-1.46) BMI (18.5-24.9, Ref): 25.0-29.9: OR 0.90 (0.61-1.33) ≥30: OR 0.55 (0.24-1.27) Diabetes mellitus: OR 1.29 (0.71-2.35) Current alcohol: 1.04 (0.77-1.40) Smoking status (Never, Ref): Former: 1.23 (0.79-1.93) Current: 1.60 (1.07-2.41)

Abbreviations: ADR, Adenoma detection rate; BMI, body mass index; CRC, colorectal cancer; FDR, First degree relative; GI, Gastrointestinal; IBD, Inflammatory bowel disease; KQ, Key question; OR, Odds ratio; Ref, Reference group; YOA, Young onset adenoma.

Supplementary Table 5. Findings from studies addressing KQ3: Among patients with young onset adenoma, what is the risk for advanced neoplasia on follow up? (n=4 studies including 9,341 individuals)

Study Name	Study Period	Quality	Location	Number of Patients	Mean Follow Up Time	Risk for Advanced Neoplasia on Follow Up
Kim HG (2018)	2006-2010 for baseline exam and up to 2015 for surveillance	Moderate	Guangdong, Seoul, South Korea	1,132	Not reported	*High risk adenoma at baseline:* 3 year rate: 3.9% (n=13/334) *Low risk adenoma at baseline:* 5 year rate: 4.9% (n=39/798)
Kim NH (2018)*	2010-2014 for baseline exam and up to 2017 for surveillance	Moderate	Seoul and Suwon, South Korea	7,848	40.8 months	*Low risk adenoma at baseline:* 5 year cumulative rate: 30-39. 2.8% 40-49: 3.3% *High risk adenoma at baseline:* 3 year cumulative rate: 30-39: 1.9% 40-49: 3.6%
Nagpal SJ (2018)	1984-2012	Moderate	Cleveland, USA	128	33.6 months	Advanced neoplasia 7.0% (n=9/128)
Park SK (2015)	2009-2012	Moderate	Seoul, South Korea	233	49.0 months	Advanced neoplasia 7.7% (n=18/233)

*Not included in pooled estimate, as reported cumulative risk of metachronous adenoma, and did not provide a denominator for our pooled estimate
Low risk adenoma at baseline defined as having 1-2 tubular adenomas measuring <10mm in size.
High risk adenoma at baseline defined as having advanced adenomas or ≥3 adenomas.
Abbreviations: KQ, Key question.

Supplementary Table 6. Findings from studies addressing KQ4: Among patients with young onset adenoma, what is the risk for subsequent colorectal cancer? (n=4 studies including 9,341 individuals)

Study Name	Study Period	Quality	Location	Number of Patients	Mean Follow Up Time	Rate of Subsequent Colorectal Cancer (CRC)
Kim HG (2018)	2006-2010 for baseline exam and up to 2015 for surveillance	Moderate	Guangdong, Seoul, South Korea	1,132	Not reported	*Low risk adenoma at baseline:* 5 year risk of CRC: n=0/798 *High risk adenoma at baseline:* 3 year risk of CRC: n=0/334
Kim NH (2018)	2010-2014 for baseline exam and up to 2017 for surveillance	Moderate	Seoul and Suwon, South Korea	7,848	40.8 months	CRC risk: n=1/7848
Nagpal SJ (2018)	1984-2012	Moderate	Cleveland, USA	128	33.6 months	CRC risk: n= 0/128
Park SK (2015)	2009-2012	Moderate	Seoul, South Korea	233	49.0 months	CRC risk: n=0/233

Low risk adenoma at baseline defined as having 1-2 tubular adenomas measuring <10mm in size.
High risk adenoma at baseline defined as having advanced adenomas or ≥3 adenomas.
Abbreviations: KQ, Key question.