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). 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 (eg, composed 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, 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 whether the age group 18–49 years was listed as a subgroup in the article. 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 (1) prevalence of adenoma, (2) risk factors associated with adenoma, (3) risk of metachronous advanced neoplasia and/or CRC, and/or (4) 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, MYC) conducted data abstraction. Data abstraction included study characteristics such as author, year of publication, study design/setting (single center vs multicenter, 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 YOA and their respective ORs from multivariate analysis, the number of patients with YOA 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 older, we limited our data abstraction to adenoma data for adults aged 18–49.

The same 2 individuals (NE, MYC) individually assessed each included article for quality. The 2017 Joanna Briggs Institute critical appraisal tool for prevalence studies was used to assess the quality of studies addressing prevalence of YOA.[18] The Newcastle-Ottawa-Quality Assessment Scale 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 ≥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 YOA and Key Question 3 on the rate of metachronous neoplasia on follow-up. For these 2 questions, we pooled corresponding data by using the random-effects model described by DerSimonian and Laird.[18]

For adenoma prevalence, the outcome was expressed as a pooled proportion, with 95% 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 before 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% CIs. We did not perform any subgroup analyses based on the year of publication because these did not reflect the time of patient recruitment. We assessed statistical heterogeneity by using I^2 statistic, which estimates the proportion of total variances across studies that was due to heterogeneity rather than chance.[21] Values greater than 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 <.05 was considered statistically significant. All analyses were performed by 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 recurrence-free[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 recurrence-score[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'

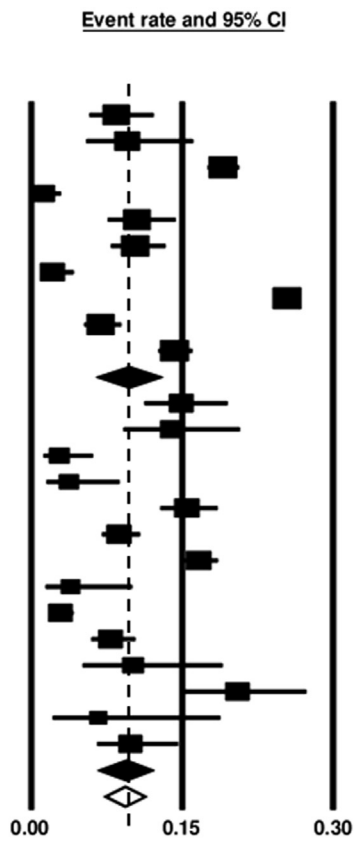
+

**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'.

Group by Study Location	Study name	Prevalence of adenoma Event rate	Lower limit	Upper limit	Total
Afro-Asian	Bafandeh Y (2008)	0.084	0.058	0.121	26 / 308
Afro-Asian	Bafandeh Y(2007)	0.095	0.055	0.160	12 / 126
Afro-Asian	Chung SJ (2010)	0.190	0.176	0.206	492 / 2583
Afro-Asian	Haghighi (1977)	0.012	0.005	0.029	5 / 411
Afro-Asian	Hemmansi (2015)	0.105	0.076	0.143	35 / 333
Afro-Asian	Hussein (2018)	0.103	0.079	0.133	52 / 504
Afro-Asian	Khalid (2011)	0.021	0.011	0.042	8 / 379
Afro-Asian	Kim HG (2018)	0.254	0.245	0.264	1904 / 7485
Afro-Asian	Kim S. E (2007)	0.069	0.053	0.089	53 / 770
Afro-Asian	Lee SE (2016)	0.142	0.127	0.159	253 / 1776
Afro-Asian,Overall		0.092	0.065	0.129	2840/14675
Western	Binda V (2007)	0.149	0.113	0.195	44 / 295
Western	Delvechio (2013)	0.140	0.092	0.207	20 / 143
Western	Forsberg AM (2012)	0.028	0.013	0.061	6 / 215
Western	Guillem (1992)	0.038	0.016	0.087	5 / 133
Western	Gupta AK (2011)	0.155	0.129	0.185	99 / 640
Western	Imperiale (2002)	0.087	0.070	0.107	79 / 906
Western	Overholt (2010)	0.166	0.149	0.185	281 / 1688
Western	Paspatis (2001)	0.039	0.015	0.100	4 / 102
Western	Pendergrass (2008)	0.029	0.020	0.041	29 / 1001
Western	Spinzi (2007)	0.079	0.060	0.103	49 / 622
Western	Szczepanski W (1992)	0.101	0.051	0.190	8 / 79
Western	Thiruvengadam (2018)	0.205	0.150	0.273	34 / 166
Western	Vatn (1982)	0.067	0.022	0.187	3 / 45
Western	Wong RF (2004)	0.099	0.066	0.145	22 / 223
Western,Overall		0.090	0.066	0.121	683/6258
Overall		0.091	0.072	0.114	3523/20933



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 Table 1. Characteristics of Included Studies (n = 28 Studies Including 103,668 Individuals)

Study name	Study period	Quality	Ages included in each study (*y*)	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 y	KQ1: Prevalence of YOA
Bafandeh Y (2007)	2005–2007	Moderate	30–49	Tabriz, Iran	Colonoscopy for unexplained lower GI symptoms in patients <50 y	KQ1: Prevalence of YOA
Binda V (2007)	1999–2000	Moderate	40–49	Brazil	Colonoscopy for unexplained lower GI symptoms in patients <50 y	KQ1: Prevalence of YOA
Chen HM (2011)	1990–2009	Low	18–49	China	Consecutive subjects <49 y 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 y	KQ1: Prevalence of YOA KQ2: Risk factors for YOA
Delvechio G (2013)	2006–2008	Moderate	40–49	Rome, Italy	Patients aged 40–49 y with at least 1 FDR (40 to ≥70 y 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 y drawn from the Swedish population register	KQ1: Prevalence of YOA
Guillem JG (1992)	1980–1990	Moderate	20–49	New York	Patients aged 20–49 with FDR with CRC	KQ1: Prevalence of YOA
Gupta AK (2011)	1999–2009	Moderate	40–49	Michigan	Patients aged 40–49 y 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 experienced colon pathologist of all colon specimens removed from consecutive autopsies in ages 20–49	KQ1: Prevalence of YOA
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 y	KQ1: Prevalence of YOA
Imperiale TF (2002)	1995–2000	Moderate	40–49	Indianapolis, IN	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 mo	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 part of routine health checkups	KQ1: Prevalence of YOA KQ 2: Risk factors for YOA
Nagpal SJ (2018)	1984–2012	Moderate	18–49	Cleveland, OH	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 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 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, MD	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 aged 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 aged <50	KQ1: Prevalence of YOA
Thiruvengadam R (2018)	2013–2018	Low	18–40	California	Retrospective review of colonoscopy performed by a single provider with ADR of 70%, in asymptomatic patients <40 y old	KQ1: Prevalence of YOA
Vatn M (1982)	1972–1973	High	18–40	Oslo, Norway	Prospective study of consecutive autopsies with examination of the colon under a magnifying lens in cases <40 y old	KQ1: Prevalence of YOA
Wong RF (2004)	1997–1999	Moderate	18–49	Utah	Consecutive veterans age <50 who underwent colonoscopy for rectal bleeding	KQ1: Prevalence of YOA

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 y	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 1 FDR (40 to ≥70 y 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 aged ≤45 drawn from the Swedish population register	2.8% (n = 6/215)
Guillem JG (1992)	1980–1990	Moderate	New York	Patients aged 20–49 with FDR with CRC	FDR: Age 2-–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	Patients aged 40–49 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 y	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, IN	Asymptomatic patients aged 40–49 undergoing colonoscopy for screening	Overall: 8.7% (n = 79/906)

Supplementary Table 2. Continued

Study name	Study period	Quality	Location	Indication of colonoscopy	Adenoma prevalence
Khalid AB (2011)	2007–2009	Moderate	Karachi, Pakistan	Patients aged 18–49 with symptoms of fresh blood per rectum in the previous 6 mo	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 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 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	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	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 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)

Supplementary Table 2. Continued

Study name	Study period	Quality	Location	Indication of colonoscopy	Adenoma prevalence
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, MD	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)

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	Western	Not specified
Gupta AK (2011)	1999–2009	Moderate	Michigan	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, IN	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, MD	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	Western	Asymptomatic
Vatn M (1982)	1972–1973	High	Oslo, Norway	Western	Not applicable
Wong RF (2004)	1997–1999	Moderate	Utah	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 y 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) Nonsignificant risk factors: Male sex: OR 1.30 (0.95–1.77)
Chung SJ (2010)	2004–2007	Moderate	Seoul, South Korea	2538	Asymptomatic screening colonoscopy as part of annual health checkup in patients younger than 50	Age 30–39 y Significant risk factors: Male sex: OR 2.18 (1.02–4.63) Current smoker: OR 2.05 (1.16–3.65) Nonsignificant 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 y Significant risk factors: Male sex: OR 2.09 (1.52–2.87) Current smoker: OR 1.37 (1.06–1.79) Nonsignificant risk 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	640	Patients aged 40–49 y with FDR with CRC	Significant risk factors: Age: OR 1.16 (1.03-1.31) Male sex: OR 2.1 (1.06-4.40) Nonsignificant risk factors: FDR >60 y 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	1176	Patients <50 y undergoing colonoscopy as 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) Nonsignificant 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)

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 9341 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	1132	Not reported	High risk adenoma at baseline: 3-y rate: 3.9% (n = 13/334) Low risk adenoma at baseline: 5-y rate: 4.9% (n = 39/798)
Kim NH (2018)[a]	2010–2014 for baseline exam and up to 2017 for surveillance	Moderate	Seoul and Suwon, South Korea	7848	40.8 mo	Low risk adenoma at baseline: 5-y cumulative rate: 30–39. 2.8% 40–49: 3.3% High risk adenoma at baseline: 3-y cumulative rate: 30–39: 1.9% 40–49: 3.6%
Nagpal SJ (2018)	1984–2012	Moderate	Cleveland, OH	128	33.6 mo	Advanced neoplasia 7.0% (n = 9/128)
Park SK (2015)	2009–2012	Moderate	Seoul, South Korea	233	49.0 mo	Advanced neoplasia 7.7% (n = 18/233)

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

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 9341 Individuals)

Study name	Study period	Quality	Location	Number of patients	Mean follow-up time	Rate of subsequent colorectal cancer
Kim HG (2018)	2006–2010 for baseline exam and up to 2015 for surveillance	Moderate	Guangdong, Seoul, South Korea	1132	Not reported	Low risk adenoma at baseline: 5-y risk of CRC: n = 0/798 High risk adenoma at baseline: 3-y 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	7848	40.8 mo	CRC risk: n = 1/7848
Nagpal SJ (2018)	1984–2012	Moderate	Cleveland, OH	128	33.6 mo	CRC risk: n = 0/128
Park SK (2015)	2009–2012	Moderate	Seoul, South Korea	233	49.0 mo	CRC risk: n = 0/233

NOTE. Low risk adenoma at baseline defined as having 1–2 tubular adenomas measuring <10 mm in size. High risk adenoma at baseline defined as having advanced adenomas or ≥3 adenomas.
CRC, colorectal cancer; KQ, key question.

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