Methods

### Systematic Review of Young-Onset Adenoma 10.e1

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1165 Study design. We conducted and reported a system-1166 atic review following the recommendation of the 1167 Preferred Reporting Items for Systematic Reviews and 1168 Meta-Analyses (PRISMA) statement.<sup>16</sup> Details of the 1169 protocol for this systematic review were registered on 1170 PROSPERO (registration #CRD42019125508).<sup>17</sup>

Supplementary Material

1171 **Search strategy.** We searched the following databases 1172 from the inception until February 12, 2019: Embase 1173 (Elsevier) and PubMed. The search was developed with 1174 the help of an experienced librarian (KMH). Studies were 1175 excluded if they were review articles, editorials, non-1176 English, animal studies, modeling studies, cost-analysis 1177 studies, qualitative studies, case studies, systematic 1178 reviews/meta-analyses, did not include individuals 1179 younger than age 50, had a sample size of <100 subjects, 1180 focused only on a special population (eg, composed 1181 solely of patients with a history of radiation for cancer 1182 therapy or patients with genetic cancer syndrome), or 1183 included only children younger than age 18. Autopsy 1184 studies were included if they answered any of the key 1185 questions. Additional records were identified through 1186 review of the reference sections of included studies and 1187 reviewed in full text if they met title and abstract review 1188 criteria.

1189 Selection criteria. Two individuals (NE, MYC) inde-1190 pendently reviewed identified abstracts for eligibility. All 1191 abstracts reporting original adenoma and/or CRC prev-1192 alence data with specified subgroup of 18-49 years were 1193 selected for full-text review. If the age range of the study 1194 population was not specified in the abstract, the abstract 1195 was also selected for review to determine whether the 1196 age group 18-49 years was listed as a subgroup in the 1197 article. Disagreements were resolved by involving a third 1198 author (SG). The same 2 reviewers then conducted a full-1199 text review of articles that met the inclusion criteria and 1200 of articles for which there was some uncertainty as to 1201 eligibility.

1202 We included cohort studies conducted in adults 1203 18-49 years of age, undergoing colonoscopy (or au-1204 topsy), and reporting (1) prevalence of adenoma, (2) risk 1205 factors associated with adenoma, (3) risk of metachro-1206 nous advanced neoplasia and/or CRC, and/or (4) impact 1207 of CRC surveillance in subset of patients with adenoma 1208 on long-term incidence and mortality from CRC. If there 1209 were articles based on overlapping study participants, 1210 the original authors were contacted to help determine 1211 which article to include.

1212 Data abstraction and risk of bias assessment. Two in-1213 dividuals (NE, MYC) conducted data abstraction. Data 1214 abstraction included study characteristics such as author, 1215 year of publication, study design/setting (single center 1216 vs multicenter, cohort vs randomized trial), time period 1217 of colonoscopy, the inclusion and exclusion criteria for 1218 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.<sup>18</sup> The Newcastle-Ottawa- Q11 Quality Assessment Scale was used to assess the quality of all other studies.<sup>19</sup> 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 metaanalyses: 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.<sup>18</sup> Q12

1250 For adenoma prevalence, the outcome was expressed 1251 as a pooled proportion, with 95% CIs. We also conducted 1252 pre-planned subgroup analyses based on colonoscopy vs 1253 autopsy studies, indication for colonoscopy (symptomatic 1254 vs asymptomatic), and location (Western vs Afro-Asian). 1255 We also conducted time trend analysis by abstracting 1256 data on the proportion of patients found with adenomas 1257 on autopsy or colonoscopy before 1995 vs after 1995. The 1258 year 1995 was used as the cutoff for this subgroup analysis 1259 because it is the year after which the rise in early-onset 1260 CRC has been observed.<sup>3</sup> For rate of metachronous 1261 neoplasia on follow-up, the outcome was expressed as a 1262 proportion, with 95% CIs. We did not perform any sub-1263 group analyses based on the year of publication because 1264 these did not reflect the time of patient recruitment. We 1265 assessed statistical heterogeneity by using  $l^2$  statistic, 1266 which estimates the proportion of total variances across 1267 studies that was due to heterogeneity rather than 1268 chance.<sup>21</sup> Values greater than 50% indicate substantial 1269 heterogeneity. Publication bias was assessed qualitatively 1270 by visual inspection of funnel plots. For all tests except for 1271 publication bias, a probability level <.05 was considered 1272 statistically significant. All analyses were performed by 1273 using Comprehensive Meta-Analysis version 2 (Biostat, 1274 Englewood, NJ). Small study effects were assessed by 1275 examining funnel plot asymmetry. 1276 1277 Literature search terms. PubMed search terms. Search 1278 (("Young Adult"[Mesh] OR "Adult"[Mesh:noexp] OR 1279 (young adult[tiab] OR young adult,[tiab] OR young 1280 adulthood[tiab] OR young adults[tiab]) OR younger adults[tiab] OR "Age of Onset"[Mesh] OR young[tiab] OR 1281 1282 younger[tiab]) AND ("Colonoscopy"[Mesh] OR "Follow-1283 Up Studies" [Mesh] OR "Early Detection of Cancer" [Mesh] 1284 OR screening[tiab] OR early detection[tiab] OR surveil-1285 lance[tiab] OR "Incidence" [Mesh] OR "Prevalence" [Mesh] 1286 OR incidence[tiab] OR prevalence[tiab] OR "Risk Fac-1287 tors"[Mesh] OR (risk factor[tiab] OR risk factor's[tiab] 1288 OR risk factore[tiab] OR risk factored[tiab] OR risk fac-1289 tors[tiab] OR risk factors,[tiab] OR risk factory[tiab]) OR 1290 "Neoplasms, Second Primary" [Mesh] OR second primary colorectal cancer[tiab] OR "Neoplasm Recurrence, 1291 1292 Local"[Mesh] OR (recurren[tiab] OR recurrenc[tiab] OR 1293 recurrence[tiab] OR recurrence'[tiab] OR recurrence's 1294 [tiab] OR recurrence20[tiab] OR recurrenceassociated 1295 [tiab] OR recurrencebut[tiab] OR recurrencec[tiab] OR 1296 recurrenced[tiab] OR recurrencee[tiab] OR recurrence-1297 free[tiab] OR recurrencegrey[tiab] OR recurrencegtv 1298 [tiab] OR recurrencein[tiab] OR recurrencel[tiab] OR 1299 recurrenceless[tiab] OR recurrenceliterature[tiab] OR 1300 recurrencemva[tiab] OR recurrencen[tiab] OR recurren-1301 cent[tiab] OR recurrenceof[tiab] OR recurrenceonline 1302 [tiab] OR recurrencerate[tiab] OR recurrencerates[tiab] 1303 OR recurrenceree[tiab] OR recurrencerelative[tiab] OR 1304 recurrences[tiab] OR recurrences'[tiab] OR recurrence-1305 score[tiab] OR recurrencesed[tiab] OR recurrenceses [tiab] OR recurrencesor[tiab] OR recurrencess[tiab] OR 1306 1307 recurrencew[tiab] OR recurrencewithout[tiab] OR 1308 recurrencia[tiab] OR recurrencial[tiab] OR recurrencias [tiab] OR recurrencies[tiab] OR recurrencs[tiab] OR 1309 1310 recurrenct[tiab] OR recurrency[tiab] OR recurrencys 1311 [tiab] OR recurrend[tiab] OR recurrene[tiab] OR recurr-1312 ened[tiab] OR recurreness[tiab] OR recurrens[tiab] OR 1313 recurrens'[tiab] OR recurrenstam3[tiab] OR recurrent 1314 [tiab] OR recurrent'[tiab] OR recurrentabortion[tiab] OR 1315 recurrentacutepancreatitis[tiab] OR recurrentbladder 1316 [tiab] OR recurrentbrca1alleles[tiab] OR recurrente[tiab]

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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'.

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## **2020**

## Systematic Review of Young-Onset Adenoma 10.e3

	Group by	Study name	Prevale	nce of ac	enoma		Event rate and 95% CI 14
1394	Study Location		Event	Lower	Upper	-	14
1395			rate	limit	limit	Total	14.
1396	Afro-Asian	Bafandeh Y (2008)	0.084	0.058	0.121	26/308	
1397	Afro-Asian	Baranden Y(2007) Chung SI (2010)	0.095	0.055	0.160	12/120	
1398	Afro-Asian	Haghighi (1977)	0.012	0.005	0.029	5/411	
1399	Afro-Asian	Hemmansi (2015)	0.105	0.076	0.143	35/333	
1400	Afro-Asian	Hussein (2018)	0.103	0.079	0.133	52/504	
1401	Afro-Asian	Khalid (2011)	0.021	0.011	0.042	8/379	
1402	Afro-Asian	Kim HG (2018)	0.254	0.245	0.264	1904 / 7485	
1403	Alro-Asian Afro-Asian	NM S. E (2007)	0.069	0.053	0.089	253/1776	
1404	Afro-Asian, Overall	Lee OL (2010)	0.092	0.065	0.129	2840/14675	
1405	Western	Binda V (2007)	0.149	0.113	0.195	44/295	14
1406	Western	Delvechio (2013)	0.140	0.092	0.207	20/143	14
1407	Western	Forsberg AM (2012)	0.028	0.013	0.061	6/215	
1408	Western	Guillem (1992)	0.038	0.016	0.087	5/133	
1409	Western	Gupta AK (2011)	0.155	0.129	0.185	99/640 70/006	
1410	Western	Overholt (2010)	0.166	0.149	0.185	281 / 1688	
1411	Western	Paspatis (2001)	0.039	0.015	0.100	4/102	
1412	Western	Pendergrass (2008)	0.029	0.020	0.041	29/1001	
1413	Western	Spinzi (2007)	0.079	0.060	0.103	49/622	
1/1/	Western	Szczepanski W (1992)	0.101	0.051	0.190	8/79	
1414	Western	Thiruvengadam (2018)	0.205	0.150	0.273	34/166	
1415	Western	Wong RF (2004)	0.067	0.022	0.167	3/40	
1416	Western Overall	wong m (2004)	0.090	0.066	0.140	683/6258	
141/	Overall		0.091	0.072	0.114	3523/20933	$ $ $\overline{\Phi}$ $ $ $ $ $ $ $ $
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1419	Supplementary Fig	ure 1. Pooled prevalend	ce of yo	ung-onse	et adeno	ma (Western	Afro-Asian regions). Rectangles denote
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## 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 ${<}50 \text{ y}$	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
Delvechio G (2013)	2006–2008	Moderate	40–49	Rome, Italy	Patients aged 40–49 y with at least 1 FDR (40 to $\geq$ 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 v 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
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
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	KQ4: Risk of CRC of follow-up 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	Symptomatic and asymptomatic patients age <50 undergoing	KQ1: Prevalence of 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

Clinical Gastroenterology and Hepatology Vol. ■,

No.

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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

 $\begin{array}{c} 1683\\ 1684\\ 1686\\ 1686\\ 1686\\ 1686\\ 1686\\ 1686\\ 1690\\ 1691\\ 1692\\ 1692\\ 1692\\ 1693\\ 1695\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1696\\ 1700\\ 1700\\ 1701\\ 1702\\ 1706\\ 1770\\ 1726\\ 1726\\ 1772\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1726\\ 1734\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\ 1736\\$ 

ADR, adenoma detection rate; CRC, colorectal cancer; FDR, first-degree relative; GI, gastrointestinal; IBD, inflammatory bowel disease; KQ, Key Question; YOA, young-onset adenoma.

Systematic Review of Young-Onset Adenoma

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### 10.e6 Enwerem et al

## Clinical Gastroenterology and Hepatology Vol. ■, No. ■

1799

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	2005–2007	Moderate	Tabriz, Iran	Colonoscopy for	Age <30: 4.6% (n = 5/108),
(2008)				unexplained lower GI	Age 30–39: 9.1% (n = 10/110
				symptoms in patients	Age 40–49: 12.2% (n = 11/90
				younger than 50	Overall: 8% (n = 26/308)
Bafandeh Y	2005–2007	Moderate	Tabriz, Iran	Colonoscopy for	Age $30-39$ : 7.9% (n = 6/76)
(2007)				unexplained lower GI	Age 40–49: 12% (n = $6/50$ )
				symptoms in patients	Overall: 11% (n = $12/126$ )
Binda V (2007)	1999_2000	Moderate	Brazil	Colonoscopy for	14.9% (n - $44/295$ )
	1000 2000	Moderate	Diazii	unexplained lower GI	14.070(11 - 44/200)
				symptoms, anemia.	
				and weight loss in	
				patients younger than	
				50	
Chung SJ (2010)	2004–2007	Moderate	Seoul, South	Asymptomatic screening	Age 30–39: 10.4% (n = 63/
			Korea	colonoscopy as part of	608) Ago 40, 40: 00,00/ (- , 400/
				in patients <50 v	Age 40-49: 22.0% (n = 429/
				in patients < 30 y	Overall: $19\% (n - 402/2583)$
Delvechio G	2006-2008	Moderate	Rome. Italv	Patients aged 40-49 with	14% (n = 20/143)
(2013)			,	at least 1 FDR (40 to	
				$\geq$ 70 y of age) with CRC	
Forsberg AM	2002-2006	High	Stockholm,	Colonoscopy performed	2.8% (n = 6/215)
(2012)			Sweden	(regardless of	
				indication) on a sample	
				of patients aged $\leq$ 45	
				Swedish population	
				register	
Guillem JG (1992)	1980–1990	Moderate	New York	Patients aged 20-49 with	FDR:
				FDR with CRC	Age 229: 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	Age 40-44: 9.2% (n = 9/314)
				FDR with CRC	Age 45–49: 21.5% (n = 70/
					326)
	0000 0010	1		A	Overall: $12\%$ (n = 99/640)
Hemmansi G	2009-2012	LOW	⊢iroozgan,	Asymptomatic patients	IVIAIE: $12.2\%$ (n = $19/156$ ) Female: $9.0\%$ (n = $16/177$ )
(2013)			lidli	ayeu 40-49 unuergoing	Overall: 10.5% (n = $35/333$ )
				screening	
Hussein K (2018)	2016-2018	Moderate	Lebanon	Colonoscopy for	Age 18–40: 3.6% (n =12/330)
. ,				unexplained lower GI	Age 40-49: 23.0% (n = 40/
				symptoms, abnormal	174)
				imaging, and family	Overall: 10% (n = 52/504)
				history of IBD or CRC in	
Imperiale TF	1995-2000	Moderate	Indianapolis	Asymptomatic natients	Overall: 8.7% (n = $79/906$ )
(2002)			IN	aged 40-49 undergoing	- / c. a c. / / (i) - / (/ 000)
· · /				colonoscopy for	
				screening	

## **2020**

## Systematic Review of Young-Onset Adenoma 10.e7

Study name	Study period	Quality	Location	colonoscopy	Adenoma prevalence
Khalid AB (2011)	2007–2009	Moderate	Karachi, Pakistan	Patients aged 18–49 with symptoms of fresh blood per rectum in the	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)
Lee SE (2016)	2012–2014	Moderate	Goyan, South Korea	Symptomatic and asymptomatic patients younger than age 50 undergoing colonoscopy as part of routine health shockups	Overall: 7% (n = 53/770) 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 = 252/1776)
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	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)

## Clinical Gastroenterology and Hepatology Vol. ■, No. ■

### 1973 Supplementary Table 2. Continued

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10.e8

Study name	Study period	Quality	Location	colonoscony	Adenoma prevalence
Paspatis GA	1997–1999	High	Crete,	Forensic postmortem	Male: 5.5.% (n = $4/72$ )
(2001)			Greece	autopsies with	Female: $0\%$ (n = 0/30) Overall: $4\%$ (n = $4/102$ )
				colon (performed for	Overall: $4\%$ (II = $4/102$ )
				cases $<$ age 50 with	
				sudden or violent or	
				undiagnosed deaths)	
Pendergrass CJ	1985–2004	High	Baltimore,	Postmortem autopsy of	Age 20–29: 1.4% (n = 2/144)
(2008)			MD	cases aged 20-49,	Age 30–39: 2.4% (n = 8/334)
				without any	Age 40–49: $3.6\%$ (n = 19/523
				documented Gi	Overall: $2.9\%$ (n = $29/1001$ )
				diagnosis or family	
				history of CRC	
Szczepanski W	1974–1978	High	Krakow,	Prospective study of	Male: 15.9% ( n = 7/44)
(1992)		5	Poland	consecutive autopsies	Female: 2.9% (n = 1/35)
				with examination of the	Overall: 10% (n = 8/79)
				colon under a	
				magnifying lens in	
				cases younger than age	
Vata M (1982)	1072_1073	High	Oslo Norway	40 Prospective study of	Overall: 6.7% (n $- 3/45$ )
vali ivi (1302)	1372 1373	riigii	USIO, NOIWAY	consecutive autopsies	
				with examination of the	
				colon under a	
				magnifying lens in	
				magninying iono in	
				cases younger than age	
ADR, adenoma detection roung-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YO
ADR, adenoma detection roung-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detection young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-o	degree relative; GI, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detection young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-o	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YO/
ADR, adenoma detection young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-o	degree relative; Gl, ga	astrointestinal; IBD, inflammatory bo	wel disease; KQ, key question; YOA
ADR, adenoma detection young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-o	degree relative; GI, ga	astrointestinal; IBD, inflammatory bo	wel disease; KQ, key question; YOA
ADR, adenoma detection young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-o	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detection young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detectior young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detectior voung-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detection young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-o	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YO/
ADR, adenoma detection young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-o	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detection young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-o	degree relative; Gl, ga	astrointestinal; IBD, inflammatory bo	wel disease; KQ, key question; YOA
ADR, adenoma detectior /oung-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-o	degree relative; GI, ga	astrointestinal; IBD, inflammatory bo	wel disease; KQ, key question; YO
ADR, adenoma detectior /oung-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-o	degree relative; Gl, ga	astrointestinal; IBD, inflammatory bo	wel disease; KQ, key question; YOA
ADR, adenoma detectior /oung-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; GI, ga	ases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detection /oung-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; GI, ga	astrointestinal; IBD, inflammatory bo	wel disease; KQ, key question; YOA
ADR, adenoma detection /oung-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; GI, ga	astrointestinal; IBD, inflammatory bo	wel disease; KQ, key question; YOA
ADR, adenoma detection young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detection young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detection young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YO/
ADR, adenoma detection /oung-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detectior young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detectior young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detectior young-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detectior /oung-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA
ADR, adenoma detectior /oung-onset adenoma.	n rate; CRC, colorectal	cancer; FDR, first-o	degree relative; Gl, ga	cases younger than age 40	wel disease; KQ, key question; YOA

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### Systematic Review of Young-Onset Adenoma 10.e9

### 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	Woderate	Utan	vvestern	Symptomatic

Supplementary Table 4. Findings From Studies Addressing KQ2: What Are Potential Risk Factors Associated With Young-

Indication of

colonoscopy

Consecutive subjects 40 y Significant risk factors:

Onset Adenoma? (n = 4 Studies Including 78,880 Individuals)

74,526

Location Sample size

#### 10.e10 Enwerem et al

Study name

Chen HM

Study

period

1990-2009 Low

Quality

China

### Clinical Gastroenterology and Hepatology Vol. ■, No. ■

Risk factors for YOA

(2011)					or younger who	Rectal bleeding: OR 1.40 (1.03-1.91)	
					received colonoscopy	Age: OR 1.11 (1.07–1.13)	
					for bloody stool	BMI: OR 1.05 (1.01–1.08)	
						Nonsignificant risk factors:	
Chung C I	0004 0007	Madarata	Cooul Couth	0500	A our montamatic a arran in a	Male sex: OR 1.30 (0.95–1.77)	
Chung SJ (2010)	2004-2007	woderate	Seoul, South	2538	Asymptomatic screening	Age 30–39 y Significant risk factors:	
(2010)			Kulea		annual health checkup	Significant fisk factors. Male sev: $OR = 2.18 (1.02-4.63)$	
					in patients younger	Current smoker: OB 2 05 (1 16–3 65)	
					than 50	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:	
						BIVII $\geq$ 25: OR 0.82 (0.61–1.12)	
						Abdominal obesity: OR 1.10 (0.69–1.96)	
						Eamily history of CBC: OB 1.38 (0.91-	
						2.09)	
Gupta AK	1999–2009	Moderate	Michigan	640	Patients aged 40-49 v with	Significant risk factors:	
(2011)			0		FDR with CRC	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)	
Loo SE	2012_2014	Moderate	Govan	1176	Patients <50 v undergoing	ZEPDAS WILLICHC. OR 1.72 (0.33-0.00) Significant risk factors:	
(2016)	2012-2014	Moderate	South	1170	colonoscopy as part of	Age $(45-49$ Ref)	
(2010)			Korea		routine health	Age 40–44: OB 0.64 (0.46–0.88)	
					checkups, regardless of	Age <40: OR 0.39 (0.28–0.56	
					symptoms		
						Waist circumference: OR 1.72 (1.15–	
						2.00)	
						Malo sov: OP 1 42 (0 80, 2 28)	
						Metabolic syndrome: OB 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 $(0.71-2.35)$	
						Smoking status (Never Ref)	
						Former: 1 23 (0 70-1 93)	
						Current: 1.60 (1.07–2.41)	
	detection rate;	BMI, body mas	s index; CRC, colored	tal cancer; F	DR, first-degree relative; GI, gast	rointestinal; IBD, inflammatory bowel disease;	
ADR, adenoma	ວn; OR, odds rat	lio; Ret, referen	ce group; YOA, youn	g-onset ader	noma.		
ADR, adenoma KQ, key questic							
ADR, adenoma KQ, key questic							
ADR, adenoma KQ, key questic							
ADR, adenoma KQ, key questic							

	Studies Includ	ing 9341 Indiv	viduals)			
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) <sup>a</sup>	2010–2014 for baseline exam and up to 2017 for	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%
	surveillance					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)

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)

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.

<sup>a</sup>Not included in pooled estimate, as reported cumulative risk of metachronous adenoma, and did not provide a denominator for our pooled estimate.

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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

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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.