SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
IRCCS Istituto di Ricovero e Cura a Carattere Scientifico

Lo screening basato sul rischio
Le raccomandazioni delle società scientifiche

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Colorectal Cancer Risk Factors

- Age
- Family History/Familial syndromes
- History of colon cancer/colonic polyps
- Obesity/dietary factors
- Smoking
- Alcohol consumption
- Long-standing inflammatory bowel diseases

We always think about family history but …

Hereditary Sindromes >>> Familial >> Sporadic

Hereditary vs. Familial

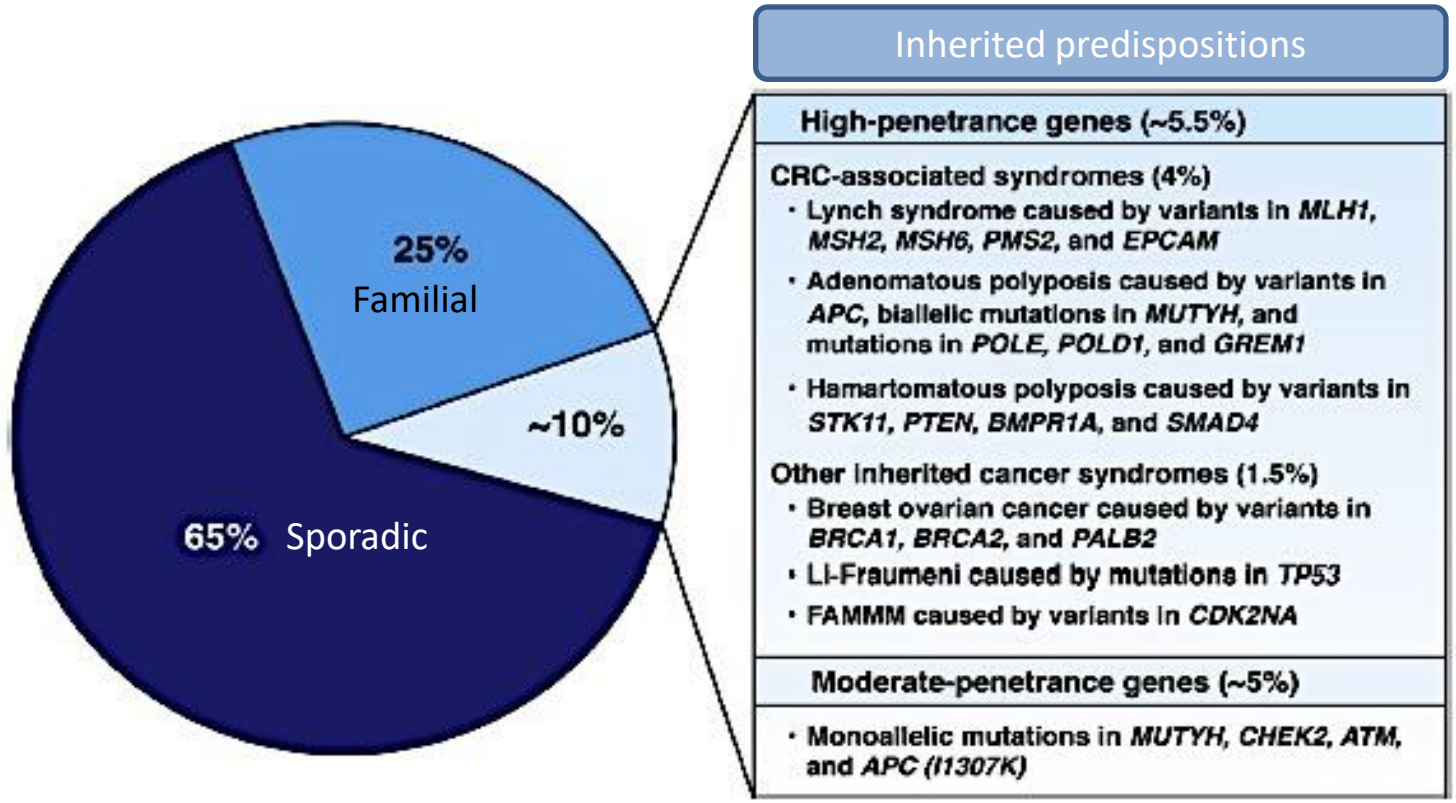
- In Hereditary, a genetic mutation is the cause of the disease
  - Dominant
  - Recessive
- In Familial, there could be an underlying common risk factor within the family pre-disposing to the disease

Family History and CRC

- Approx. 5% of the western world population has a positive family history of CRC.
- Some will have just one relative with CRC diagnosed at an older age, whereas others may have two or more relatives diagnosed before age 50 years.
- One first-degree relative → 2-fold higher risk of CRC
  Two or more relatives → a 4 to 6-fold increased risk, independent of age at diagnosis

Ramsey SD et al. Genet Med 2006;8:571 – 5.
Hakama M. Lancet 2006;368:101 – 3.
Butterworth AR et al. Eur J Cancer 2006;42:216 – 27.

Genetic risk of CRC and main players in genetic predispositions



Stoffel, *Gastreonterology,* **2020**

Familial Cancer

RECOMMENDATION

ESGE recommends definition of familial risk of colorectal cancer as the presence of at least two first-degree relatives with colorectal cancer or at least one first-degree relative with colorectal cancer before the age of 50 years. Strong recommendation, moderate quality evidence, level of agreement 92%.

RECOMMENDATION

ESGE recommends colonoscopy surveillance in first-degree relatives of CRC cases in families that fulfill the definition of familial risk of colorectal cancer.
Strong recommendation, moderate quality evidence, level of agreement 100%.

Van Leerdam et al. GIE 2019

- RR among cohort studies of 1.67 (95%CI 1.52 – 1.82) and a pooled RR among case–control studies of 2.22 (95%CI 2.00 – 2.48) in the presence of **at least one FDR with CRC**
- Higher pooled RR was found in the presence of **two or more FDRs**, with pooled RRs of CRC of 2.40 (cohort) and 2.81 (case–control)
- When **CRC was diagnosed before the age of 50 years in an FDR**, the pooled RRs were 3.26 (95%CI 2.82 – 3.77; cohort) and 3.57 (95%CI 1.07 – 11.85; case–control)

Roos VH, et al Clin Gastroenterol Hepatol 2019:

Familial Cancer

RECOMMENDATION

ESGE recommends starting colonoscopy surveillance at the age of 40 years when there is a familial risk of colorectal cancer.

Strong recommendation, moderate quality evidence, level of agreement 92%.

Van Leerdam et al. GIE 2019

- Hemminki reported in a large prospective cohort a SIR of 2.01 (95%CI 1.71 – 2.33) for individuals aged 40 – 49 years at diagnosis, with at least one affected FDR with CRC, compared with an SIR of 1.18 (95 %CI 0.99 – 1.39) for individuals over 50 years at diagnosis

Hemminki K, et al. Int J Cancer 2001; 94: 743–748

Familial Cancer

RECOMMENDATION

ESGE recommends a 5-year surveillance interval for colonoscopy after a normal high quality baseline examination in the setting of familial risk of colorectal cancer.

Strong recommendation, low quality evidence, level of agreement 83%.

RECOMMENDATION

ESGE recommends that follow-up after polyp excision in individuals with familial risk of colorectal cancer should follow the surveillance guidelines for the general population.

Strong recommendation, moderate quality evidence, level of agreement 92%.

Van Leerdam et al. GIE 2019

- Brenner et al found that the odds ratio (OR) for developing CRC for individuals **with at least one FDR** with CRC was 0.66 (95%CI 0.27 – 1.58) within 5 – 9 years after a negative colonoscopy and 0.47 (95 %CI 0.14 – 1.59) more than 10 years after a negative colonoscopy
- Samadder et al. found that in individuals with at least one FDR with CRC this risk reduction only extends until 5 years after a negative colonoscopy

Brenner H et al. J Clin Oncol 2011; 29: 3761–3767

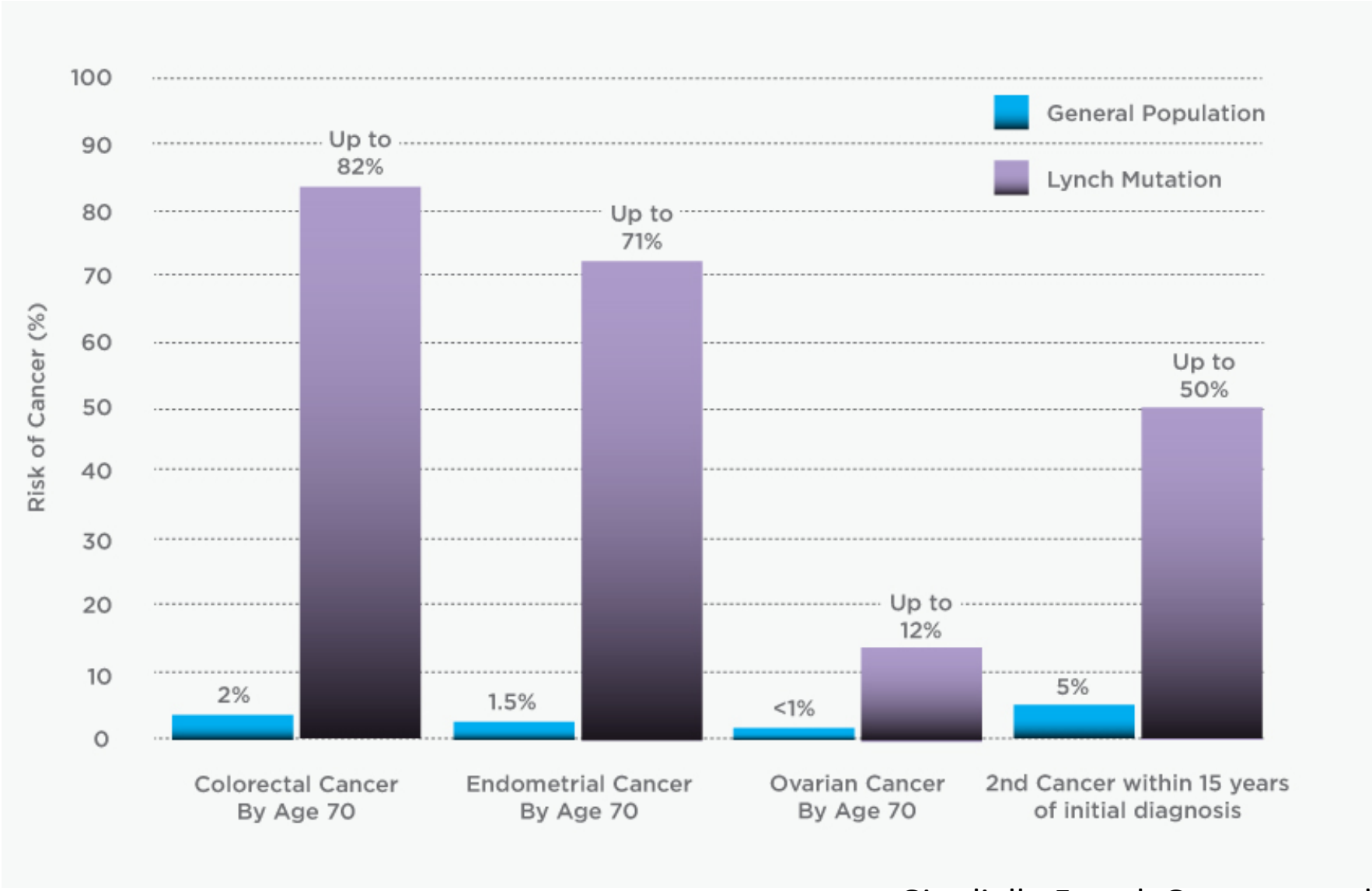
Samadder NJ et al. Am J Gastroenterol 2017; 112: 1439–1447

ACG Guidelines CRC screening

9	We suggest initiating CRC screening with a colonoscopy at age 40 or 10 yr before the youngest affected relative, whichever is earlier, for individuals with CRC or advanced polyp in 1 first-degree relative (FDR) at age <60 yr, or CRC or advanced polyp in ≥2 FDR at any age. We suggest interval colonoscopy every 5 yr	Conditional	Very low
10	We suggest consideration of genetic evaluation with higher familial CRC burden (higher number and/or younger age of affected relatives)	Conditional	Very low
11	We suggest initiating CRC screening at age 40 or 10 yr before the youngest affected relative and then resuming average-risk screening recommendations for individuals with CRC or advanced polyp in 1 FDR at age ≥60 yr.	Conditional	Very low
12	In individuals with 1 second-degree relative (SDR) with CRC or advanced polyp, we suggest following average-risk CRC screening recommendations	Conditional	Low

Am J Gastroenterol 2021;116:458–479

Cancer risk for LS mutation carriers



Giardiello F et al. Gastroenterology 2014

Dwell time of advanced adenomas and CRC in LS

	Advanced Adenoma	CRC
Mean±SD (range)	33.0±16.2 (12-56)	35.2±22.3 (7-96)

CGH 2011;9;340-345

Lynch Syndrome Guidelines

RECOMMENDATION

ESGE recommends starting colonoscopy surveillance at the age of 25 years for *MLH1* and *MSH2* mutation carriers and at the age of 35 years for *MSH6* and *PMS2* mutation carriers.

Strong recommendation, moderate quality evidence, level of agreement 100 %.

Van Leerdam et al. GIE 2019

Incidence of cancers in relation to genotype

Table 2 Cumulative incidence of cancers in groups of organs from 25 years of age up to the age indicated in the column Age, stratified on carriers of *path_MMR* variants in the different genes and 95% CIs in parentheses. Gynaecological cancer include endometrial and ovarian cancer. Upper gastrointestinal cancer include stomach, duodenum, bile duct, gall bladder or pancreas cancer. Genitorurinary tract cancer include urinary bladder, ureter or kidney

			Cumulative incidence at age (% (95% CI))			
ICD9	**Organ**	**Age**	***path_MLH1***	***path_MSH2***	***path_MSH6***	***path_PMS2***
	Any cancer	40	16.8 (12.2 to 21.3)	14.3 (8.0 to 20.3)	0	0
		50	40.2 (34.7 to 45.7)	37.2 (29.4 to 45.1)	18.1 (8.0 to 28.3)	0
		60	58.7 (52.8 to 64.6)	57.6 (49.3 to 65.9)	39.0 (25.8 to 52.2)	18.2 (0.0 to 41.0)
		70	71.7 (64.7 to 78.7)	71.6 (61.9 to 81.2)	53.6 (38.6 to 68.6)	18.2 (0.0 to 41.0)
		75	75.8 (68.5 to 83.2)	80.4 (69.8 to 90.9)	60.9 (42.7 to 79.0)	52.1 (0.1 to 100.0)
153, 154	Colorectal cancer	40	12.7 (8.6 to 16.9)	8.9 (4.0 to 13.7)	0	0
		50	25.0 (20.0 to 30.0)	19.4 (13.0 to 25.8)	1.8 (0.0 to 5.4)	0
		60	34.6 (28.9 to 40.3)	27.1 (19.9 to 34.3)	5.6 (0.0 to 11.9)	0
		70	40.1 (33.5 to 46.7)	40.8 (31.6 to 50.1)	15.0% (3.3 to 26.6)	0
		75	45.8 (37.8 to 53.9)	43.0 (33.2 to 52.8)	15.0 (3.3 to 26.6)	0

Moller P et al. GUT 2018

Lynch Syndrome Guidelines

RECOMMENDATION

ESGE recommends a high quality surveillance colonoscopy every 2 years in asymptomatic individuals with Lynch syndrome.

Strong recommendation, moderate quality evidence, level of agreement 90%.

RECOMMENDATION

ESGE recommends to repeat complete colonoscopy within 3 months in the case of a colonoscopy of suboptimal quality (poor bowel preparation or incomplete procedure).

Strong recommendation, moderate quality evidence, level of agreement 90%.

Van Leerdam et al. GIE 2019

- No randomized controlled trials for surveillance in LS mutation carriers → therefore retrospective or prospective observational studies only that indirectly compare rates of post-colonoscopy CRC and their stage distribution with different surveillance intervals.
- No data on colonoscopy quality in the studies comparing different surveillance intervals

Colorectal Cancer Incidence or Stage at Detection by Colonoscopy Among 3 Countries With Different Lynch Syndrome Surveillance Policies

- Data from 16,327 colonoscopies (conducted from 1984 through 2015) of 2747 patients with Lynch syndrome (pathogenic variants in the MLH1, MSH2, or MSH6 genes)
- 23,309 person-years of cumulative observation time.
- Time from the index colonoscopy to incident CRC or adenoma
- **Colonoscopies performed 1-2 or 3-yearly**
- **No significant differences in cumulative CRC incidence or CRC stage at detection among countries.**
- There was no significant association between CRC stage and time since last colonoscopy.

Engel et al. Gastroenterology 2018

European guidelines from the EHTG and ESCP for Lynch syndrome

Table 1 Recommendations that achieved consensus based on GRADE

	Strength of recommendation	% of voters agreeing
Colorectal surveillance		
For *path_MLH1*, *path_MSH2* and *path_MSH6* carriers, 2- or 3-yearly colonoscopic surveillance is recommended‡	Strong*	75
For *path_PMS2* carriers, colonoscopic surveillance should be performed to reduce mortality and incidence of colorectal cancer	Strong*	82
For *path_PMS2* carriers, 5-yearly surveillance may be considered	Weak†	80
For patients with LS with a history of CRC and segmental colectomy, biennial colonoscopies should be performed	Strong*	88
For patients with LS with a history of CRC and segmental colectomy, biennial rectosigmoidoscopies should be performed	Strong*	88
There is no evidence at the moment to support different surveillance colonoscopy intervals for men and women	Strong*	100
Chromoendoscopy is equivalent to high-definition white-light endoscopy in specialist centres. It may be an adjunct to be considered in the absence of high-definition endoscopy or in centres with lower adenoma detection rates	Weak†	92
If bowel preparation is not entirely adequate, a repeat procedure at 1 year is recommended. If the bowel preparation is completely inadequate or the examination incomplete, an immediate repeat colorectal surveillance procedure should be requested (within next 6 weeks)	Weak, based on very low-quality evidence (expertopinion)	85
Age at onset of surveillance colonoscopy should be stratified according to genotype	Strong*	100
For *path_MLH1* or *path_MSH2* carriers, surveillance colonoscopies should be initiated at the age of 25 years	Moderate†	94
For *path_MSH6* or *path_PMS2* carriers, surveillance colonoscopies should be initiated at the age of 35 years	Moderate†	93
Age at onset of surveillance should not be stratified by gender	Moderate*	88

BJS, 2021, 108, 484–498

Thieme

Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2020

Authors
Cesare Hassan[1], Giulio Antonelli[1], Jean-Marc Dumonceau[2], Jaroslaw Regula[3], Michael Bretthauer[4], Stanislas Chaussade[5], Evelien Dekker[6], Monika Ferlitsch[7], Antonio Gimeno-Garcia[8], Rodrigo Jover[9], Mette Kalager[4], Maria Pellisé[10], Christian Pox[11], Luigi Ricciardiello[12], Matthew Rutter[13], Lise Mørkved Helsingen[4], Arne Bleijenberg[6], Carlo Senore[14], Jeanin E. van Hooft[6], Mario Dinis-Ribeiro[15], Enrique Quintero[8]

RECOMMENDATION

2020 statement

ESGE recommends that patients with 10 or more adenomas should be referred for genetic counselling.

Strong recommendation, moderate quality evidence.

2013 statement

Incorporated unchanged into 2020 statement above.

Hassan et al. GIE 2020

Hereditary gastrointestinal polyposis syndromes

Polyp subtype	Polyposis syndrome	Gene	Germline mutation found	Incidence	Clinical criteria	CRC risk	References
Adenomatous	Familial adenomatous polyposis (FAP)	*APC*	70%–90%	1 in 10000	Classic: >100 adenomas in colon/rectum at age 25	100%	[4,5,23,24]
					Attenuated: <100 adenomas in colon/rectum at age 25	69%	
	MUTYH-associated polyposis (MAP)	*MUTYH*	16%–40%	1–4 in 10000	20–100 adenomas in colon/rectum	19%–43%	[6,25,26]
Hamartomatous	Peutz–Jeghers syndrome (PJS)	*STK11/LKB1*	80%–94%	1 in 250000	**1** ≥2 histologically confirmed Peutz–Jeghers polyps **2** any number of Peutz–Jeghers polyps in an individual with a positive family history of PJS **3** presence of characteristic mucocutaneous pigmentations in an individual with a positive family history of PJS **4** any number of Peutz–Jeghers polyps in an individual with characteristic mucocutaneous pigmentation	15%–57%	[7–9,27,28]
	Juvenile polyposis syndrome (JPS)	*SMAD4, BMPR1A*	40%–60%	1–1.6 in 100000	**1** ≥5 juvenile polyps are present in the colon/rectum or in other parts of the gastrointestinal tract **2** any number of juvenile polyps in a patient with one or more relatives affected with JPS	39%–68%	[10–13]

Van Leerdam et al. GIE 2019

Hereditary gastrointestinal polyposis syndromes

▶ **Table 2** Summary table of colonoscopy surveillance statements.

Polyposis syndrome	Starting age	Surveillance interval	Treatment indication
(Attenuated) familial adenomatous polyposis	12–14 years	Every 1–2 years	Pre- and post-colectomy: remove all polyps > 5 mm
MUTYH-associated polyposis	18 years	Every 1–2 years	Pre- and post-colectomy: remove all polyps > 5 mm
Peutz–Jeghers syndrome	Baseline: 8 years Routine: 18 years	Baseline: if polyps found, every 1–3 years Routine: every 1–3 years	Elective polypectomy
Juvenile polyposis syndrome	12–15 years	Every 1–3 years	Elective polypectomy for polyps > 10 mm
Serrated polyposis syndrome	NA	1 year: after ≥ 1 advanced polyp or ≥ 5 non-advanced clinically relevant polyps 2 years: after no advanced polyps or < 5 non-advanced clinically relevant polyps	Clearing/surveillance phase: remove all polyps ≥ 5 mm and all polyps of any size with optical suspicion of dysplasia

NA, not applicable.

Van Leerdam et al. , Endoscopy 2019

UC– ECCO guidelines

- Longstanding colitis increases the risk of developing colon cancer.
- **Population based studies have shown that this is less than previously thought, and mainly limited to sub-groups (e.g. onset before adulthood; duration> 10y; concomitant PSC)**.
- Histologic or macroscopic pancolitis carries the highest risk, with no increased risk for patients with proctitis.
- Disease activity, post-inflammatory polyps and possibly a family history of CRC are additional risk factors.
- Colonoscopy can be considered in all patients with at least distal colitis 8 years following symptom onset, but annually at any time point following diagnosis of PSC

http://www.e-guide.ecco-ibd.eu/interventions-investigational/colorectal-carcinoma-surveillance

UC– ECCO guidelines

5-yearly colonoscopy :

- Colitis affecting less than 50% of the colon surface area
- Extensive colitis with mild endoscopic or histological active inflammation

3-yearly colonoscopy :

- Post-inflammatory polyps
- Colorectal cancer in a first-degree relative older than 50 years
- Extensive colitis with moderate or severe endoscopic or histological inflammation

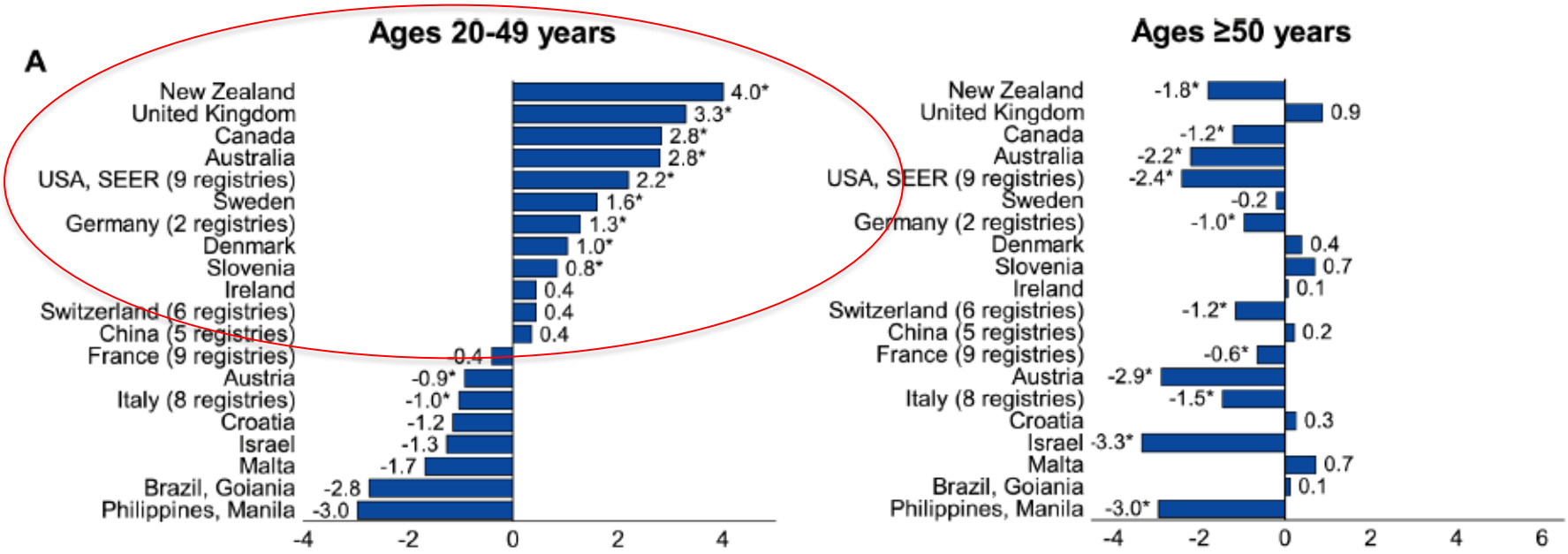
Annual colonoscopy

- Stricture within the past 5 years
- Dysplasia within the past 5 years in a patient who declines surgery
- PSC (including post-orthotopic liver transplant) from time of diagnosis of PSC
- Colorectal cancer in a first-degree relative younger than 50 years

Pan-colonic chromoendoscopy (e.g. 0.1% indigo-carmine solution) should be undertaken, with targeted biopsies of any lesion and 2 biopsies taken each 10 cm to assess disease activity and extent. If only white light colonoscopy is performed, 4 biopsies should be taken every 10 cm although this is clearly an inferior surveillance strategy. Polypectomy depends on type of lesion.

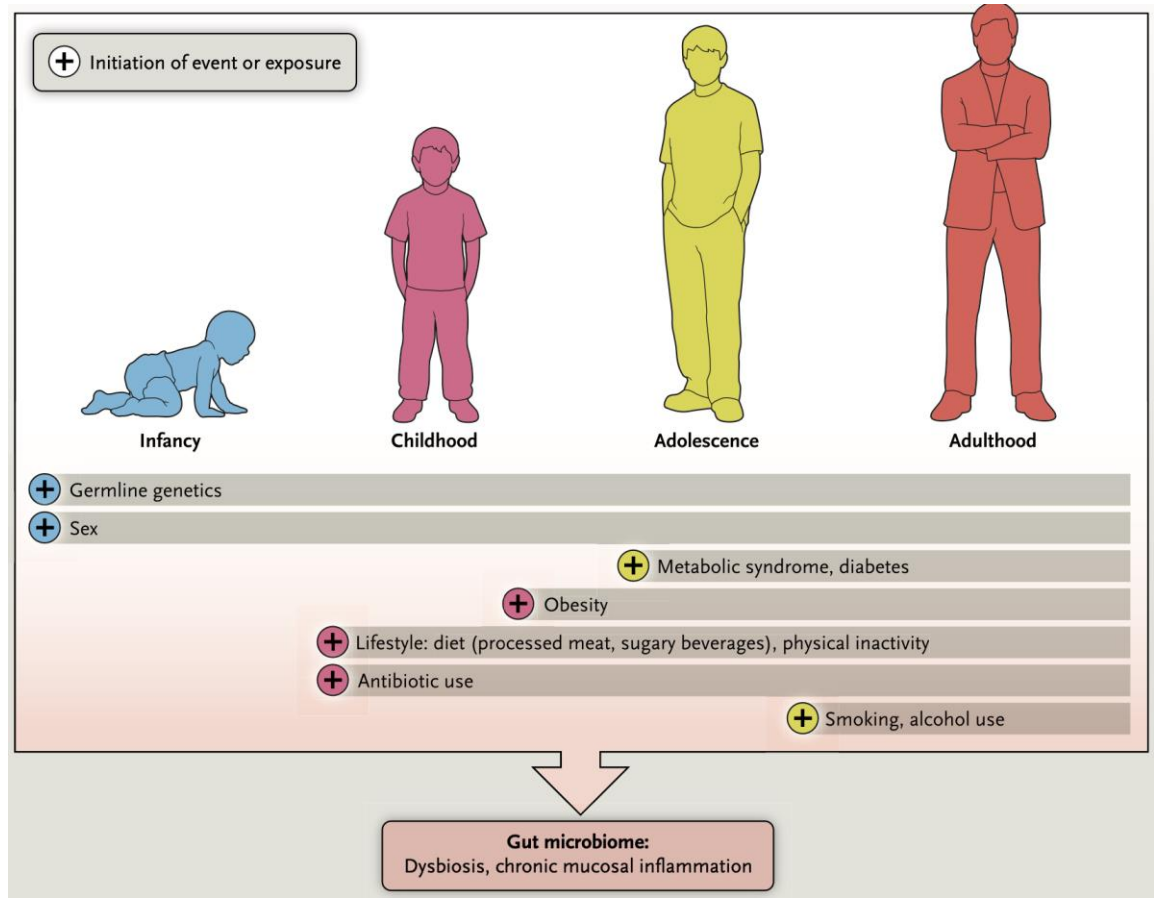
http://www.e-guide.ecco-ibd.eu/interventions-investigational/colorectal-carcinoma-surveillance

Trends in Colorectal Cancer Incidence across five continents



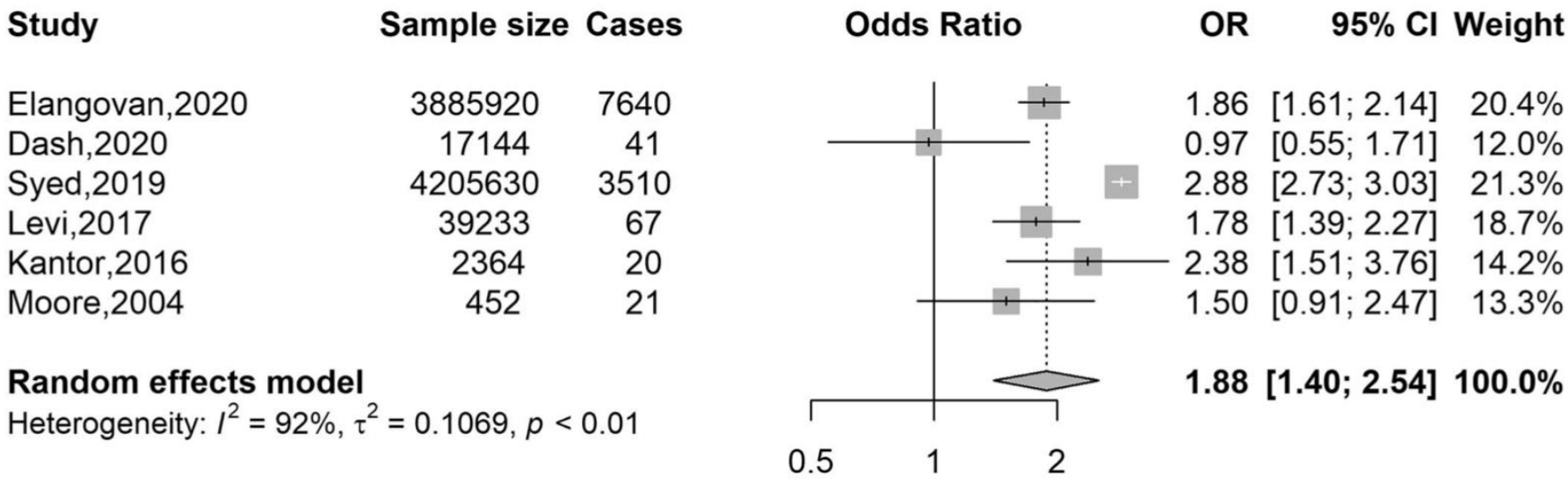
Siegel RL, et al. Gut 2019;68:2179–2185

Factors influencing EO CRC



Sinicrope FA, NEJM 2022

Association of Body Mass Index With Risk of Early-Onset Colorectal Cancer: Systematic Review and Meta-Analysis



Li et al. Am J Gastroenterol 2021;116:2173–2183.

	CRC screening start age	CRC screening stop age
MSTF, 2021	"We suggest that clinicians offer CRC screening to all average-risk individuals age 45-49 (weak recommendation; low-quality evidence)."	"We suggest that individuals who are up to date with screening and have negative prior screening tests, particularly high-quality colonoscopy, consider stopping screening at age 75 years or when life expectancy is less than 10 years (weak recommendation, low-quality evidence)."
	"For average-risk individuals who have not initiated screening before age 50, we recommend that clinicians offer CRC screening to all average-risk individuals beginning at age 50 (strong recommendation, high-quality evidence)."	"We suggest that persons without prior screening should be considered for screening up to age 85, depending on consideration of their age and comorbidities (weak recommendation, low-quality evidence)."
NCCN, 2021[66]	"Average risk: age ≥45. The panel has reviewed existing data for beginning screening of average-risk individuals at age <50 years. Based on their assessment, the panel agrees that the data are stronger to support beginning screening at 50 years but acknowledges that lower-level evidence supports a benefit for screening earlier. When initiating screening for all eligible individuals, the panel recommends a discussion of potential harms/risks and benefits, and the consideration of all recommended CRC screening options."	Not provided
American College of Gastroenterology, 2021[67]	"We recommend CRC screening in average-risk individuals between ages 50 and 75 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC." Strong recommendation; moderate-quality evidence "We suggest CRC screening in average-risk individuals between ages 45 and 49 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC." Conditional recommendation; very low-quality evidence	"We suggest that a decision to continue screening beyond age 75 years be individualized (conditional recommendation strength, very low-GRADE quality of evidence)."
USPSTF, 2021[90]	Grade A: "The USPSTF recommends screening for colorectal cancer in all adults ages 50 to 75 years." Grade B: "The USPSTF recommends screening for colorectal cancer in adults aged 45 to 49 years."	Grade C: "The USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults aged 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health, prior screening history, and preferences."
ACP, 2019[91]	"Clinicians should screen for colorectal cancer in average-risk adults between the ages of 50 and 75 years."	"Clinicians should discontinue screening for colorectal cancer in average-risk adults older than 75 years or in adults with a life expectancy of 10 years or less."
ACS, 2018[52]	"The ACS recommends that adults aged 45 and older with an average risk of CRC undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. As a part of the screening process, all positive results on non-colonoscopy screening tests should be followed up with timely colonoscopy."	"Average-risk adults in good health with a life expectancy of greater than 10 years continue CRC screening through the age of 75 years (qualified recommendation)."
	"The recommendation to begin screening at age 45 is a qualified recommendation."	Clinicians should "individualize CRC screening decisions for individuals aged 76 through 85 years based on patient preferences, life expectancy, health status, and prior screening history (qualified recommendation)."

Patel S et al Gastroenterology 2022

Obesity and Risk of High-risk adenomas

	NO LESIONS ($n=1751$)	HIGH-RISK ADENOMAS ($n=1349$)	
	n (%)	*n* (%)	OR (95% CI)
BMI			
Underweight	12 (0.7)	6 (0.4)	0.74 (0.27–2.02)
Normoweight	738 (42.2)	547(35.1)	1.0
Overweight	694 (39.7)	597 (44.3)	1.18 (1.0–1.39)
Obesity	306 (17.5)	272 (20.2)	1.29 (1.05–1.60)
Ever smoking			
No	1300 (74.2)	905 (67.1)	1.0
Yes	451 (25.8)	444 (32.9)	1.45 (1.24–1.71)

Colussi D et al. UEG Journal (2018)

Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: A BMJ Rapid Recommendation

1 - Colorectal cancer screening with faecal immunochemical testing (FIT), sigmoidoscopy or colonoscopy: A BMJ Rapid Recommendation

Weak recommendation

For healthy, screening-naïve adults aged 50-79 with < 3% estimated risk of colorectal cancer at 15 years
(Estimate your 15-year risk of cancer here https://qcancer.org/15yr/colorectal/index.php)

We suggest no screening

Remark: Find evidence summaries, decision aids and practical issues in user-friendly formats here: https://magicevidence.org/match-it/190220dist/

Weak recommendation

For healthy, screening-naïve adults aged 50-79 with > 3% estimated risk of colorectal cancer at 15 years
(Estimate your 15-year risk of cancer here https://qcancer.org/15yr/colorectal/index.php)

We suggest screening with FIT (every or every two years) or a single sigmoidoscopy or colonoscopy

Remark: Find evidence summaries, decision aids and practical issues in user-friendly formats here: https://magicevidence.org/match-it/190220dist/

About you

Age (25-84): 64

Sex: Male Female

Ethnicity: White or not stated

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status: non-smoker

Alcohol status: none

Do you have a family history of ...

gastro-intestinal cancer?

Women only: have you had any of these cancers?

breast cancer?

uterine cancer?

ovarian cancer?

cervical cancer?

Men only: have you had any of these cancers?

(These cancers did not pass our statistical test for significance for women.)

oral cancer?

lung cancer?

cancer of the blood?

Do you currently have...

Diabetes: none

ulcerative colitis?

colonic polyps?

Leave blank if unknown

Body mass index

Height (cm):

Weight (kg):

Calculate risk over 15 years. Calculate risk

Welcome to the QCancer®(15yr,colorectal) risk calculator

Welcome to the QCancer-®(15yr,colorectal) web calculator. You can use this calculator to work out your risk of developing colorectal cancer by answering some simple questions.

This version of the calculator differs from the main QCancer®-10yr calculator in two ways. First, the number of years that risk can be calculated over has been raised to 15 years. Second, it is a cut down version of the main calculator, and presents the risk of developing colorectal cancer only. The main QCancer®-10yr calculator, which shows the risk of developing several cancers over a 10 year period, is here.

The QCancer®-10yr algorithms have been developed by Julia Hippisley-Cox and Carol Coupland and are based on routinely collected data from many thousands of GPs across the country who have freely contributed data to the QResearch database for medical research.

QCancer®-10yr has been developed for the UK population, and is intended for use in the UK. All medical decisions need to be taken by a patient in consultation with their doctor. The authors and the sponsors accept no responsibility for clinical use or misuse of this score.

This colorectal cancer risk calculator was originally intended to show risk over a 1 to 10 year period, we have extended this to a 1 to 15 year period to inform a clinical practice guideline on colorectal cancer screening.

The science underpinning the QCancer®-10yr equations has been published in BMJ Open. See the publication page for a link.

Conclusions

- Risk-based screening strategies are defined by Scientific Societies for:
  - Familial CRC
  - Lynch Syndrome
  - Hereditary polyposis
  - IBD

- US average risk population is at «higher risk» → screening lowered to 45 yrs
- Need more data for risk stratification approaches for CRC screening in average risk population