

Epidemiologi, riskfaktorer, genetik, screening

Bethany Van Guelpen

Postgraduatekurs i gastrointestinal cancer

Märsta, 2024



UMEÅ
UNIVERSITET



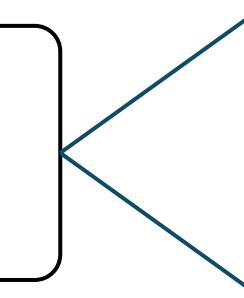
Outline

Epidemiology

Etiology and
prevention

Genetically
high-risk
populations

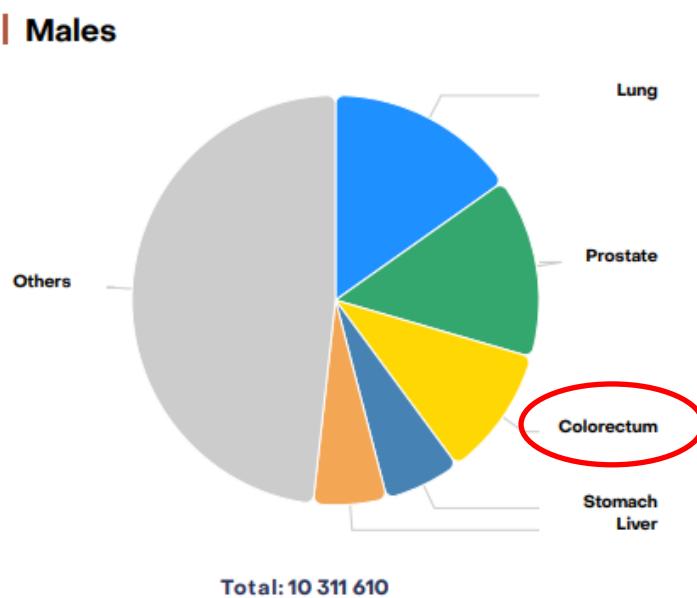
”Normal-risk”
populations



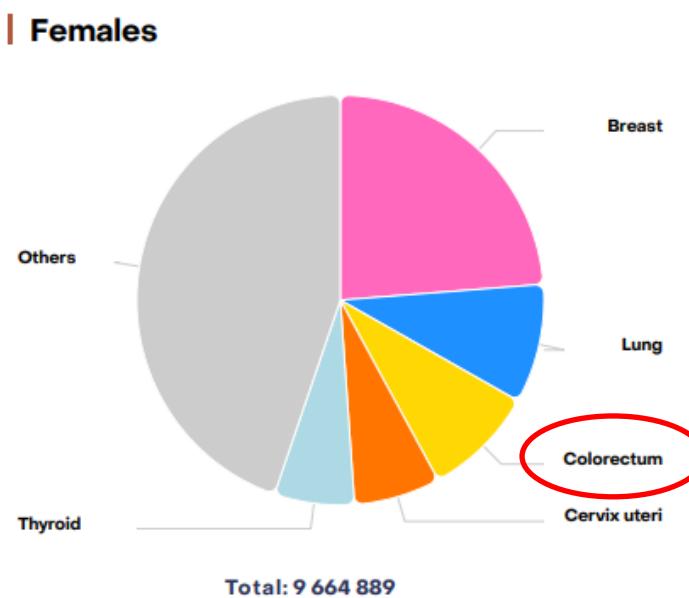
Epidemiology

Lifetime risk approximately 1/20
3rd highest incidence, 2nd highest mortality

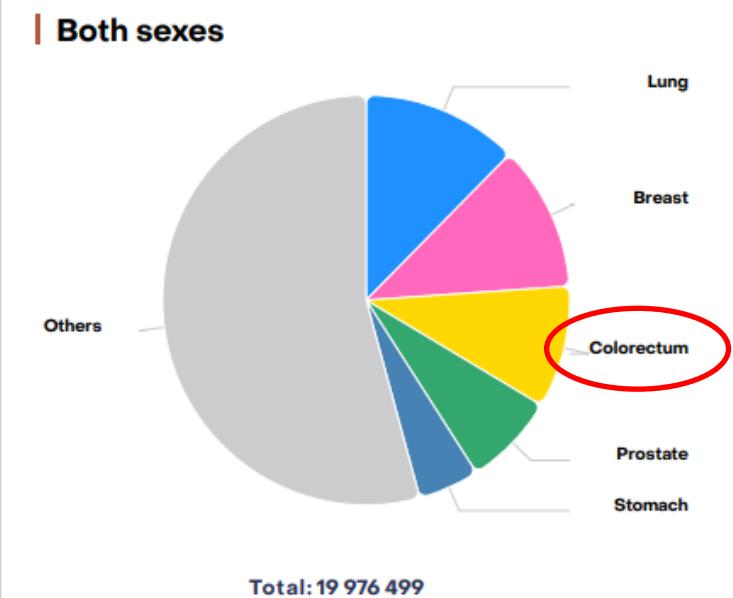
| Males



| Females



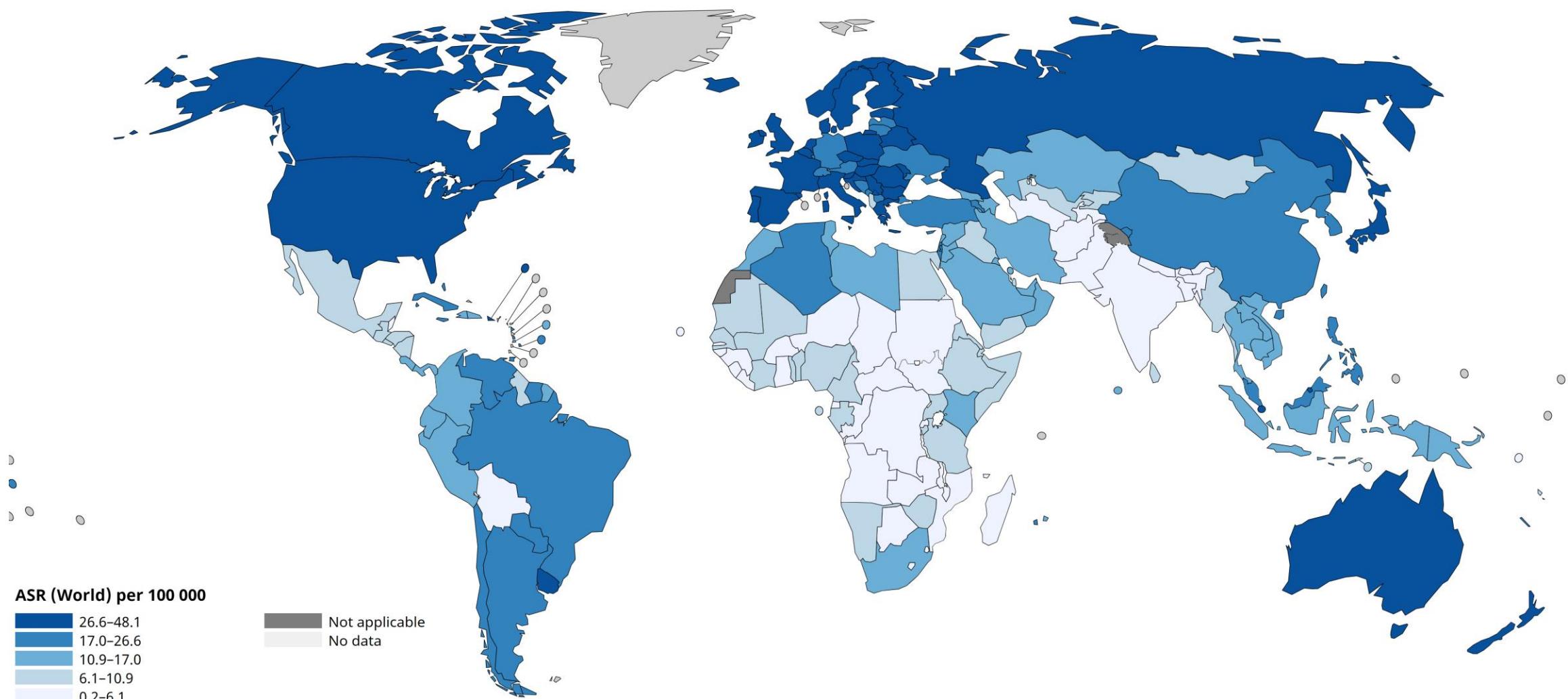
| Both sexes



Global colorectal cancer incidence

Age-Standardized Rate (World) per 100 000, Incidence, Both sexes, in 2022

Colorectum



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Cancer TODAY | IARC
<https://gco.iarc.who.int/today>
Data version: Globocan 2022 (version 1.1) - 08.02.2024
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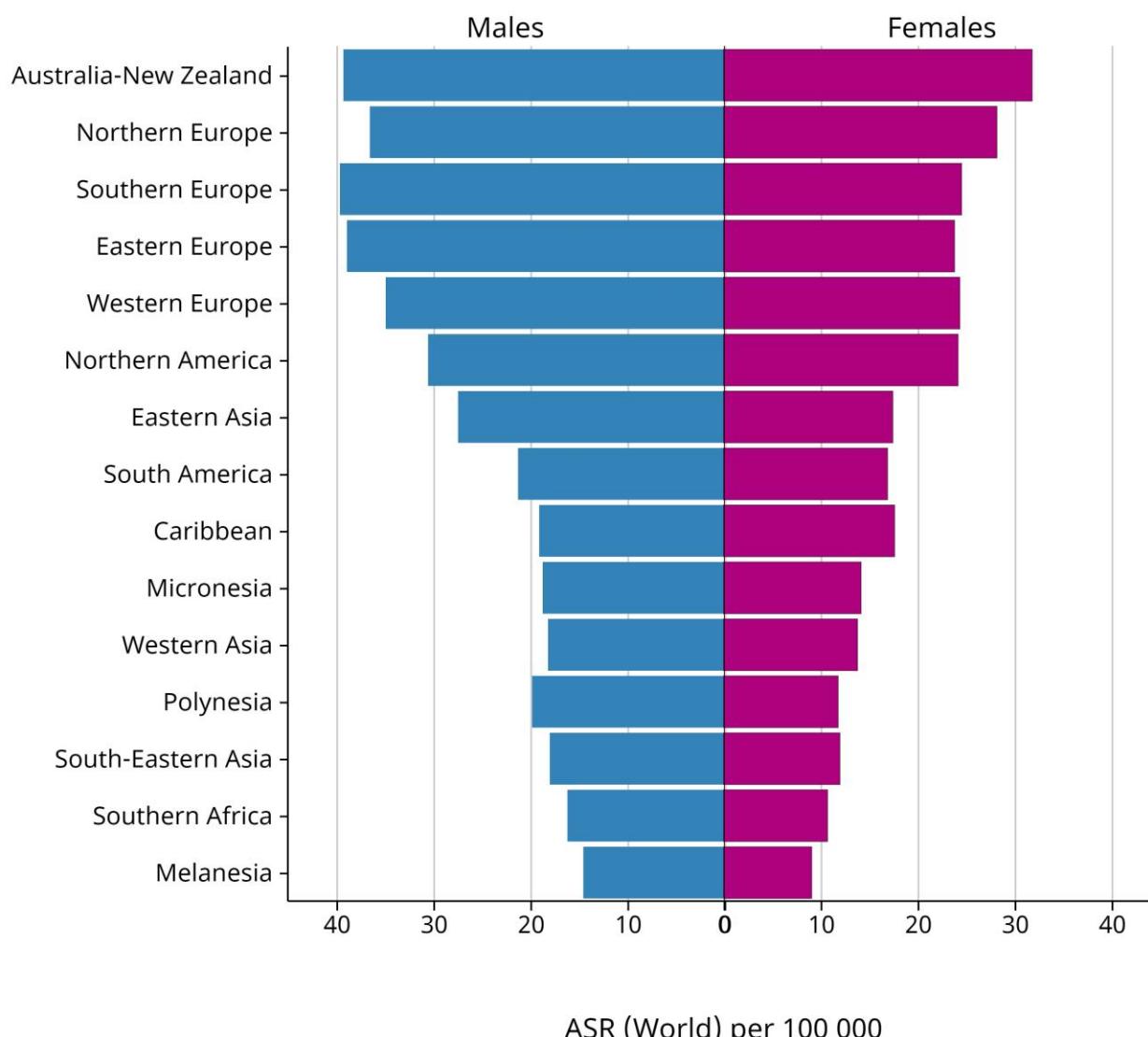
International Agency
for Research on Cancer

World Health
Organization

Age-Standardized Rate (World) per 100 000, Incidence, Males and Females, in 2022

Colorectum

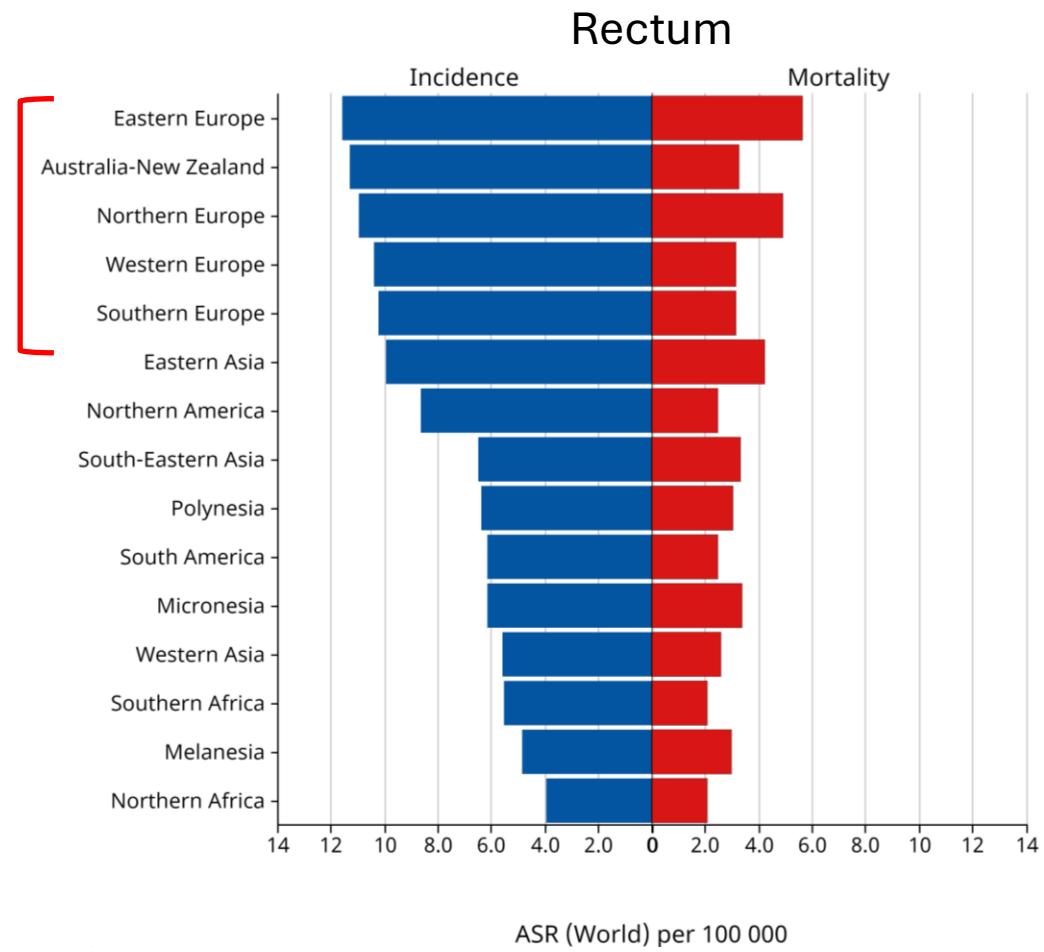
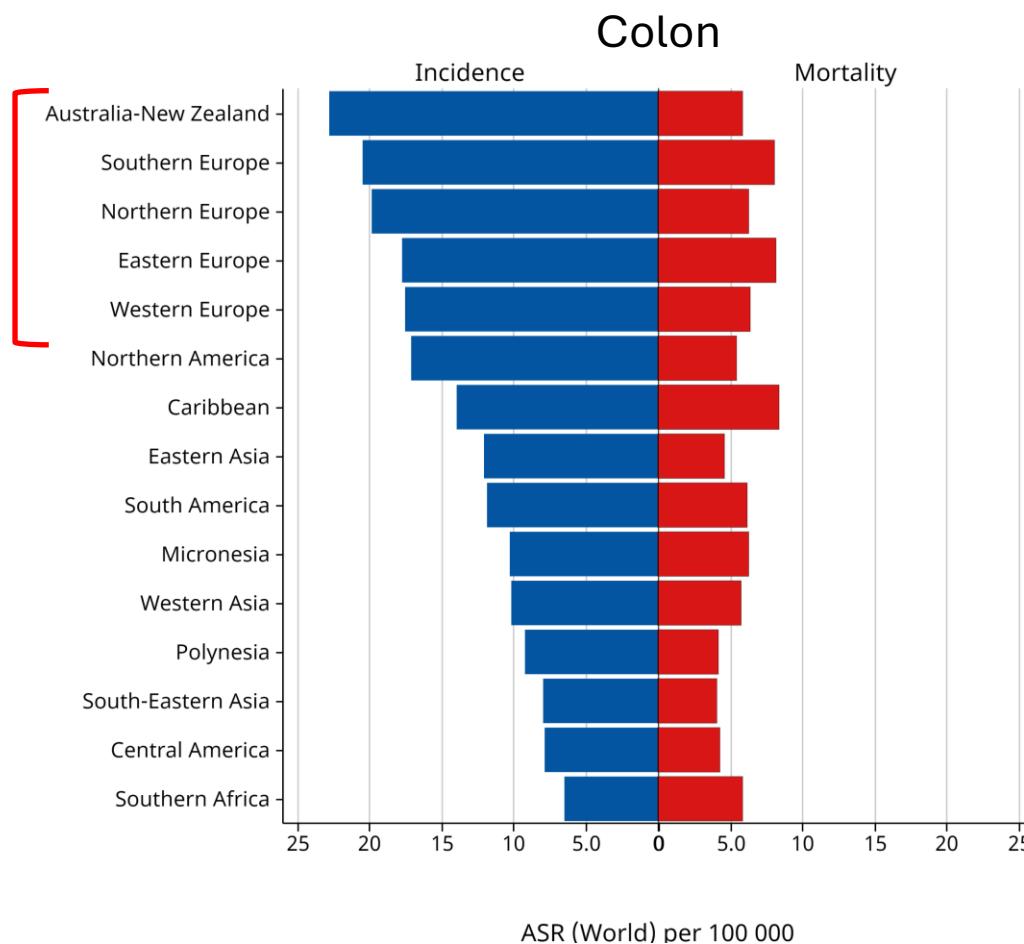
UN Regions (Top 15)



Sex differences are generally greater for rectal cancer than colon cancer in the high-incidence countries.

Age-standardized incidence and mortality (world) per 100 000, in 2022

UN regions (top 15)



Mortality - ASR (World) vs Incidence - ASR (World), Both sexes, in 2022

Colorectum

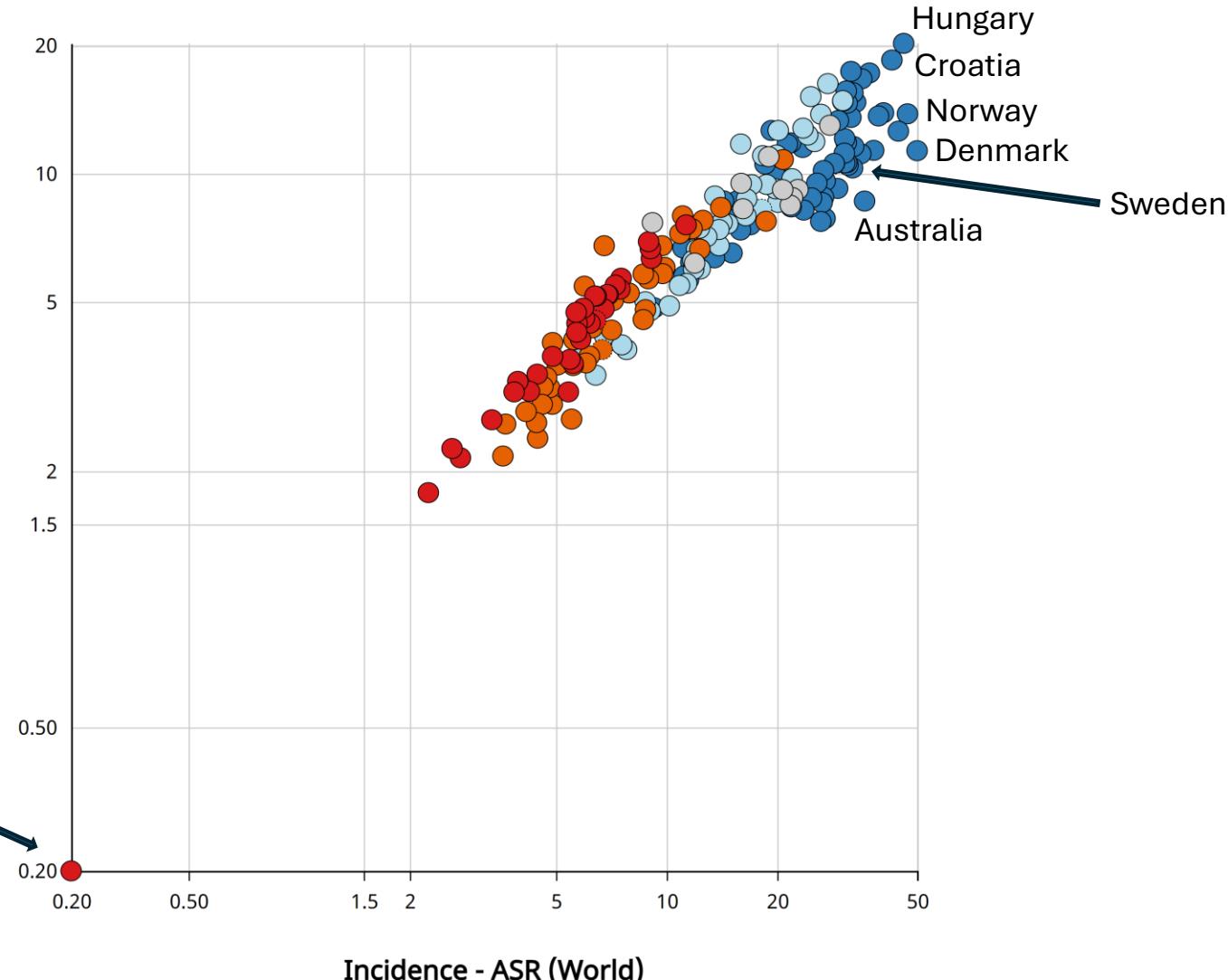
ASR (World)

HDI

- Very high HDI
- High HDI
- Medium HDI
- Low HDI
- Not applicable

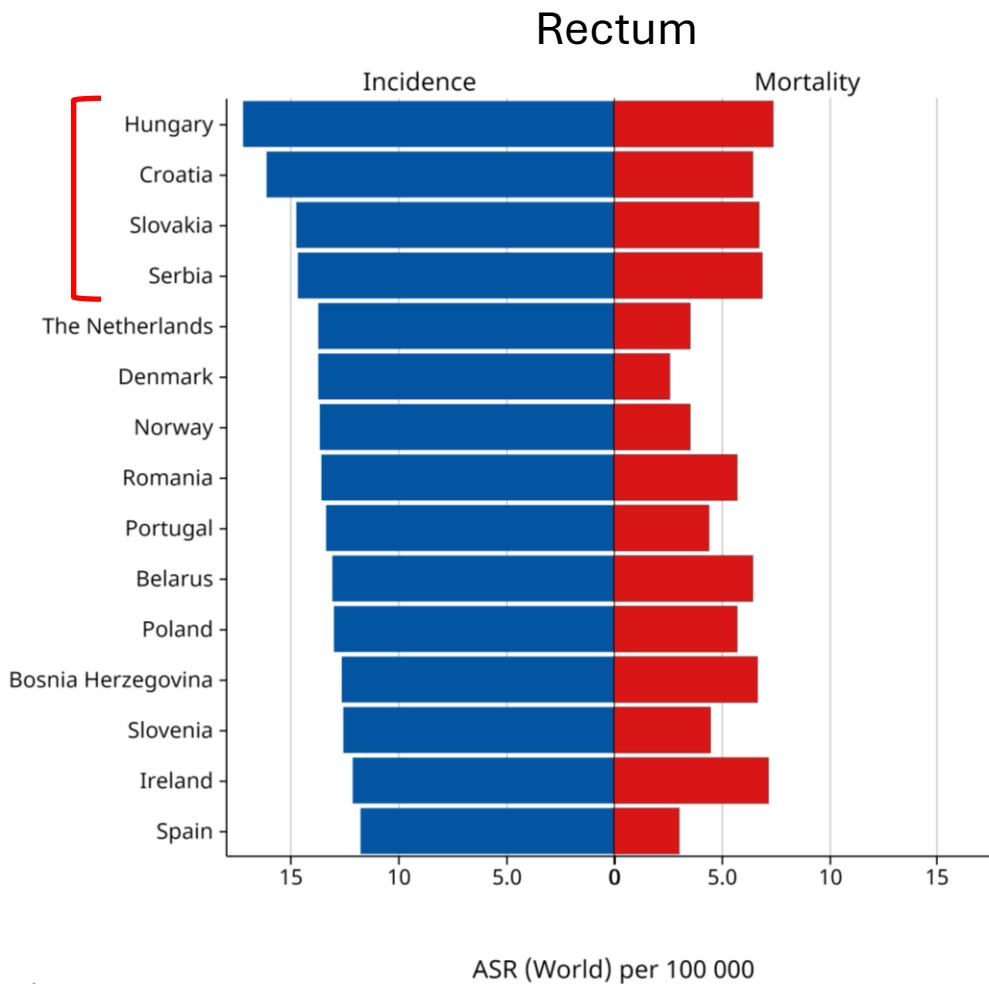
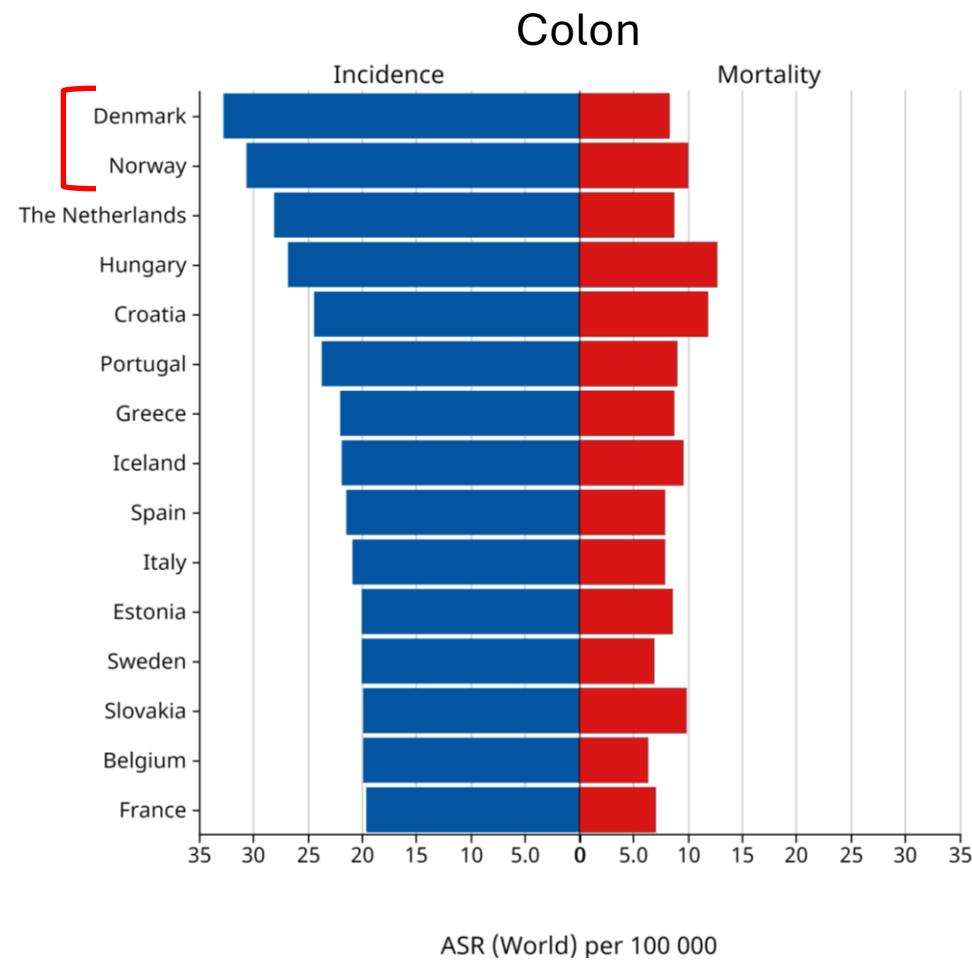
HDI: human development index (life expectancy, schooling, gross national income)

Sierra Leone
Data out reflects
data in...



A closer look at Europe

Age-standardized incidence and mortality (world) per 100 000, in 2022
European countries (top 15)





Time trends in Sweden

Women

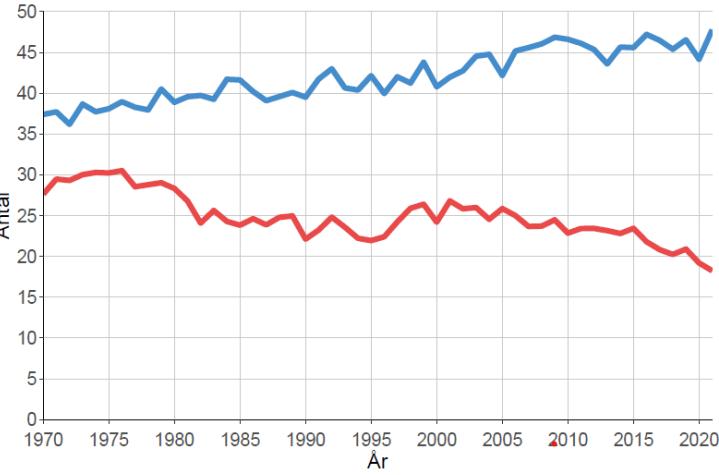
Men

Koloncancer 2022

Nationell kvalitetsrapport för år 2022
från Svenska Kolorektalcancerregistret

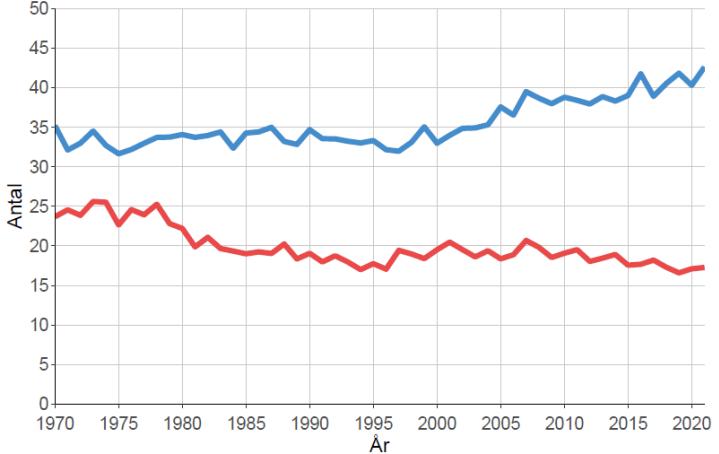
Colon

— Incidens — Mortalitet



Figur 4.2. Ålderstandardiserad incidens och mortalitet per 100 000 invånare i Sverige, män, 1970-2021

— Incidens — Mortalitet



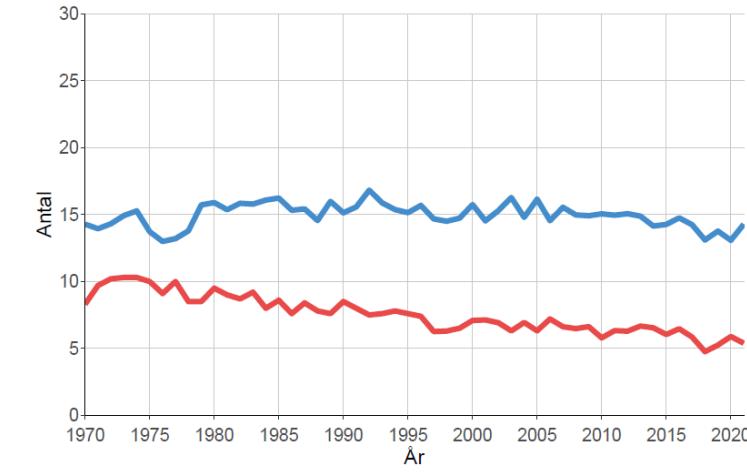
Figur 4.3. Ålderstandardiserad incidens och mortalitet per 100 000 invånare i Sverige, kvinnor, 1970-2021

Rektalcancer 2022

Nationell kvalitetsrapport för år 2022
från Svenska Kolorektalcancerregistret

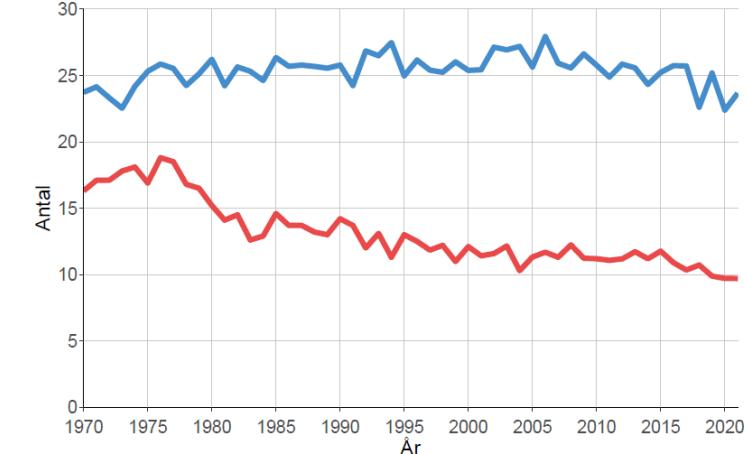
Rectum

— Incidens — Mortalitet



Figur 4.3. Ålderstandardiserad incidens och mortalitet per 100 000 invånare i Sverige, män, 1970-2021.

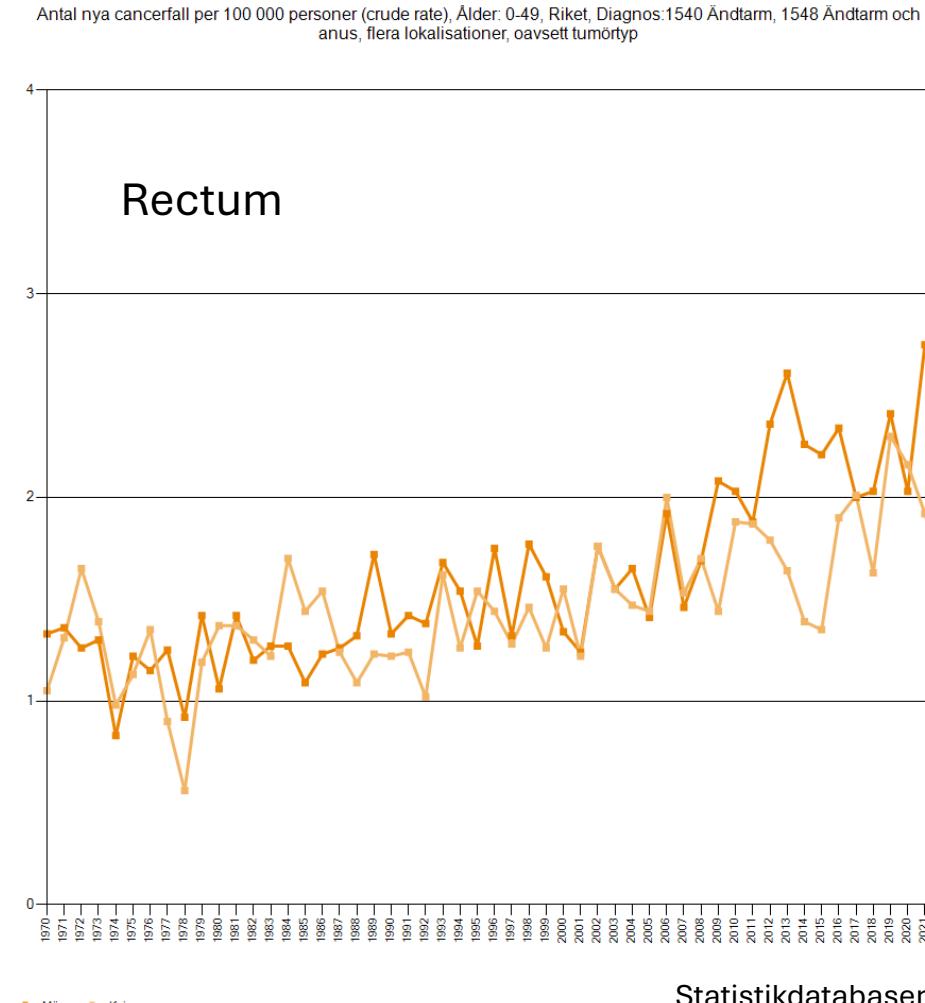
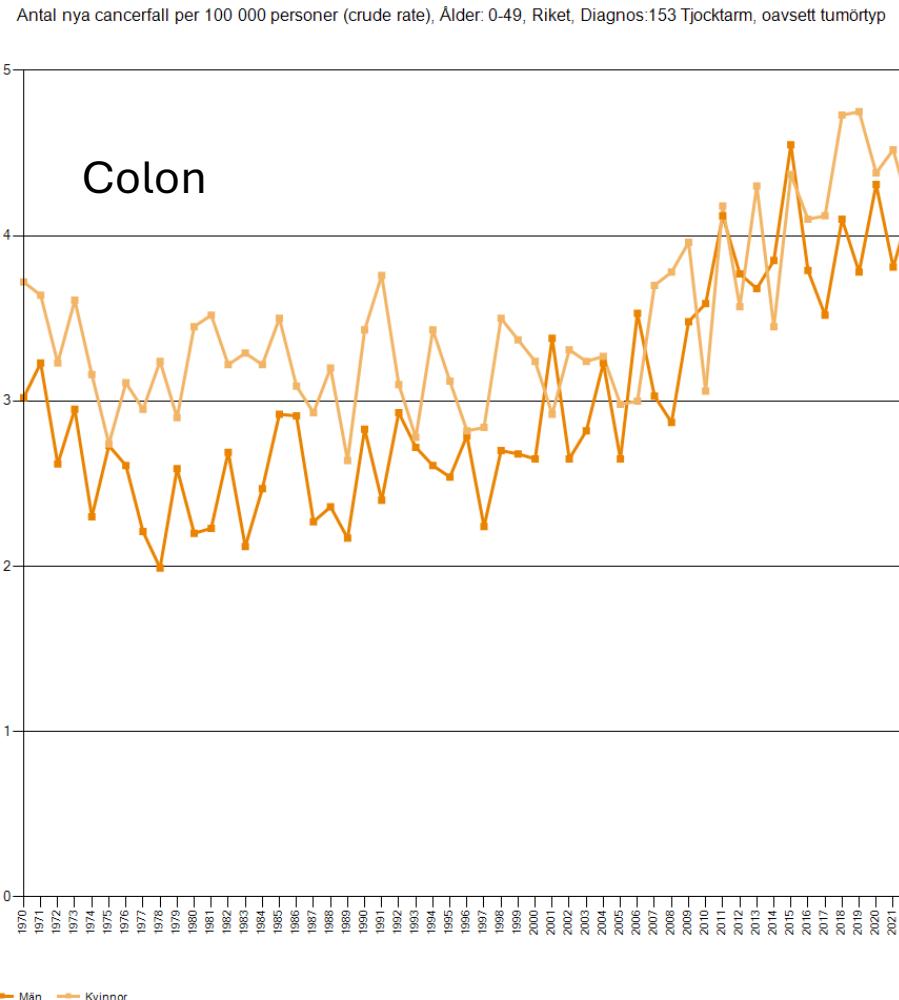
— Incidens — Mortalitet



Figur 4.2. Ålderstandardiserad incidens och mortalitet per 100 000 invånare i Sverige, kvinnor, 1970-2021.

Increasing incidence <50 years but from low numbers...

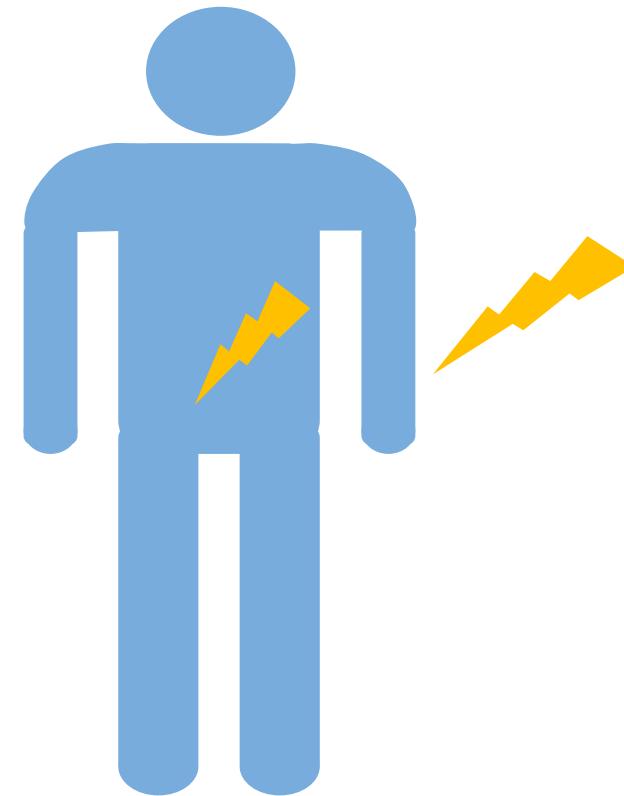
Birth cohort phenomenon?



Etiology and Prevention

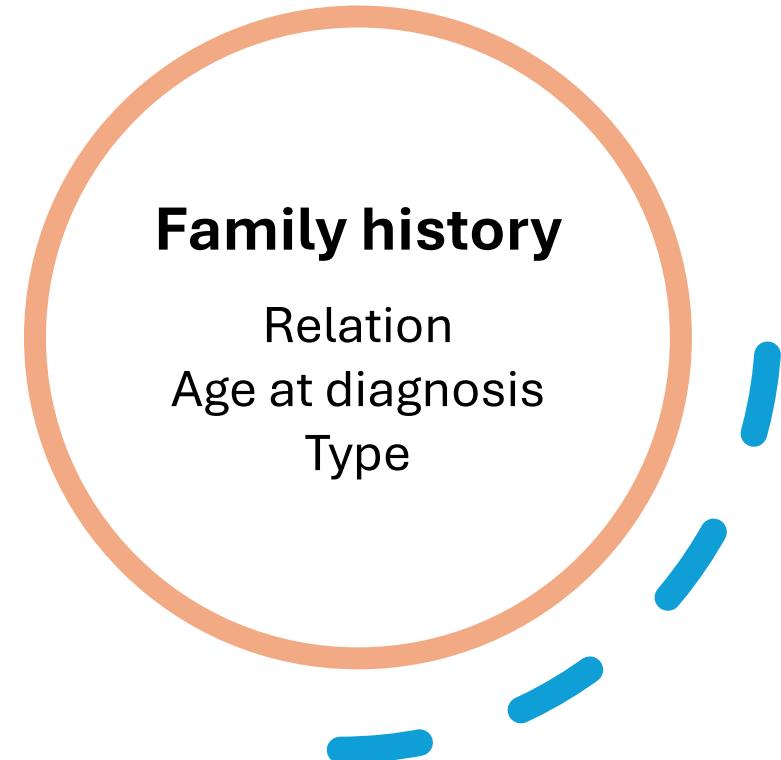
Non-modifiable risk factors

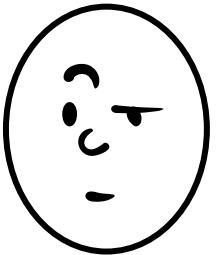
- Age
- Biological sex
- Height
- Heredity/genetics
- (Ethnicity)



Genetics

- Hereditary (Lynch, FAP etc.)
- Familial
- Risk variants

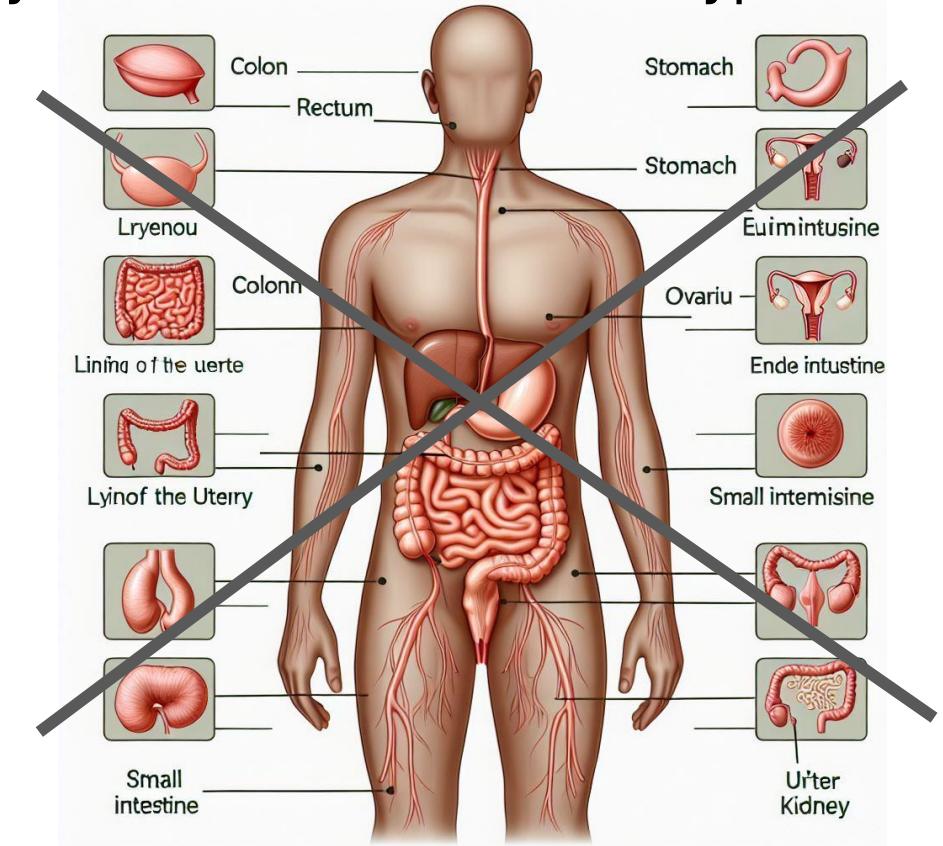




Lynchs syndrom

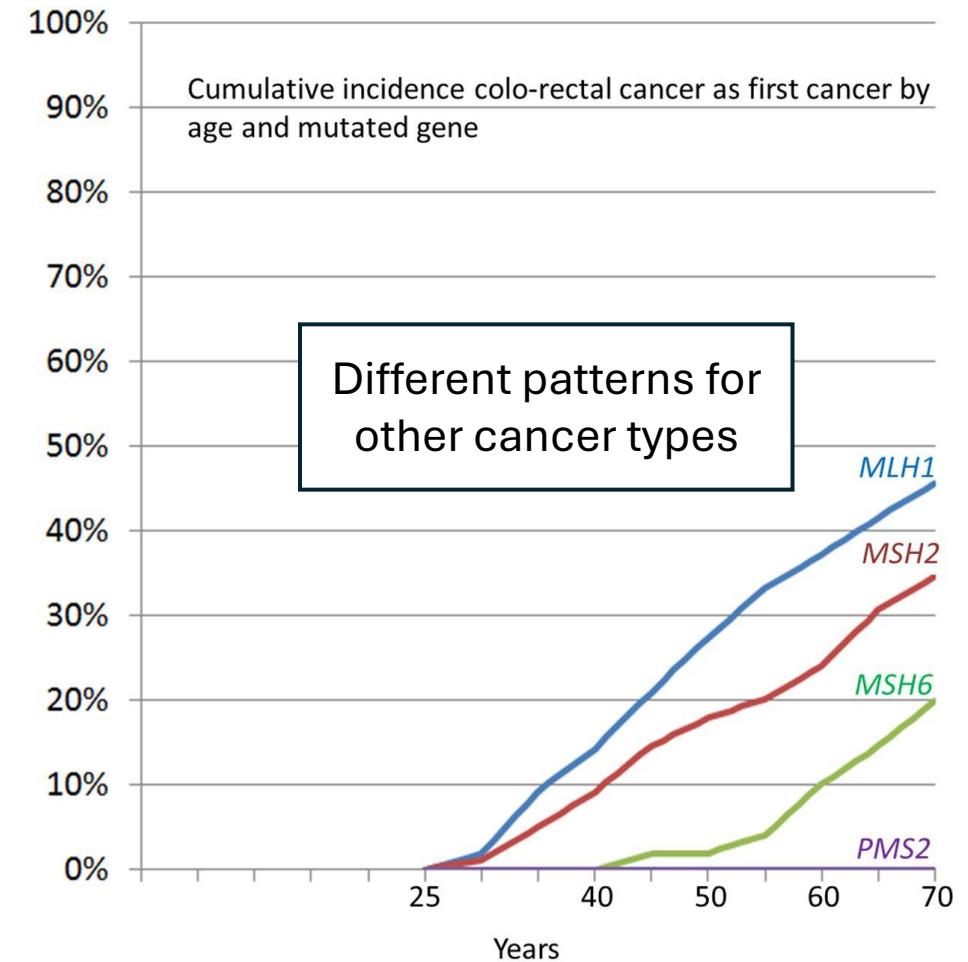
- Prevalence 1/300
- 500 known families in Sweden, probably many undiagnosed
- Risk for colorectal cancer 30-70%
- 1-3% of all colorectal cancer
- More often proximal colon, mucinous, high lymphocyte infiltration
- Uterus (40-60% risk), ovarian, stomach, pancreas, urinary tract, prostate

”Lynch-associated cancer types”



”Prevention” in Lynch – surveillance colonoscopy

- Typically 2-year interval
- Starting age:
 - *MLH1*: 25 years
 - *MSH2*: 25 years
 - *MSH6*: 30 years
 - *PMS2*: 35 years
- Consider modifying:
 - Younger age of diagnosis in family
 - Other risk factors, e.g. heavy smoking history, obesity, male sex, inflammatory bowel disease.



Prevention in Lynch

Pharmacoprevention:

- >75 mg ASA (CAPP2 600 mg, CAPP3 and AAS-Lynch ongoing)
- Resistant starch? (CAPP2, noncolonic cancers)

Lifestyle:

- Body size
- Smoking
- Alcohol
- Physical activity
- Diet

Burn J et al. Lancet 2020;395:1855-1863

Mathers J et al. Cancer Prev Res. 2022;15(9):623-634

Mohavedi M et al. J Clin Oncol. 2015;33(31):3591-7



CAPP2:



Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG)

Kevin J Monahan Nicola Bradshaw, ³ Sunil Dolwan, ⁴ Bianca Desouza, ⁵ Malcolm G Dunlop, ⁶ James E East, ^{7,8} Mohammad Iyas, ⁹ Asha Kaur, ¹⁰ Fiona Lalloo, ¹¹ Andrew Latchford, ¹² Matthew D Rutter, Ian Tomlinson, Huw J W Thomas, ¹³ James Hill, ¹¹ Hereditary CRC guidelines eDelphi consensus group

having a family history of a first-degree relative (FDR) or second-degree relative (SDR) with CRC. While many predisposing conditions, such as Lynch syndrome (LS), familial adenomatous polyposis (FAP) and other polyposis syndromes account for only 5–10% of all CRC diagnoses, advances in genetic diagnosis, and genetic counselling, facilitate targeted risk-reducing interventions, including endoscopic surveillance, preventative surgery and chemoprophylaxis, which provide opportunities for cancer prevention. This guideline is an update from the 2010 British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland (BSG/ACPGBI)

Received 20 September 2019
Revised 25 October 2019

EJS, 2021, 108, 484–498

DOI: 10.1002/ejs.11902
Review

OXFORD

European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender

T. T. Seppälä ^{1,2}, A. Latchford ^{3,4}, A. Sampalo ^{5,6}, R. Jiménez-Rodríguez ^{7,8}, L. Sánchez-Guillem ^{9,10}, D. G. Evans ⁵, N. Ryan ¹¹, E. J. Crosbie ¹², M. Domínguez-Valella ¹³, J. Burns ⁸, M. Kloos ^{14,15}, M. von Knebel Doeberitz ^{16,17}, F. J. van Duijnhoven ¹⁸, P. Quirke ¹⁹, J. R. Sampson ²⁰, P. Meller ^{21,22}, G. Möslan ^{23,24}, on behalf of the European Hereditary Tumour Group (EHTG) and European Society of Coloproctology (ESCP)

¹Department of Surgery, Helsinki University Hospital, and University of Helsinki, Helsinki, Finland

²Department of Gastroenterology, John Hopkins Hospital, Baltimore Maryland, USA

³Department of Cancer and Surgery, Imperial College London, UK

⁴St Mark's Hospital, London North West Healthcare NHS Trust, London, UK

⁵Manchester Centre for Genomic Medicine, Division of Evolution and Genomic Sciences, University of Manchester, Manchester University Hospitals NHS Foundation Trust, UK

⁶Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, St Mary's Hospital, Manchester, UK

⁷Centre for Academic Women's Health, University of Bristol, Bristol, UK

⁸Faculty of Medical and Dental Sciences, Middle Ulster University, Belfast, Northern Ireland, UK

⁹Pathology and Data Analytics, School of Medicine, University of Leeds, Leeds, UK

¹⁰Institute of Medical Genetics, Division of Cancer and Genetics, Cardiff University School of Medicine, Heath Park, Cardiff, UK

¹¹Department of Surgery, Emergency Hospital of Bucharest, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

¹²Department of Surgery, Hospital Universitario Virgen del Rocío, Seville, Spain

¹³Colorectal Unit, Department of General Surgery, Elche University General Hospital Elche, Alicante, Spain

¹⁴Department of Pathology, University Hospital of North Norway, Tromsø, Norway

¹⁵Department of Applied Tumour Biology, Institute of Pathology, University Hospital Heidelberg, Germany

¹⁶Cooperation Unit Applied Tumour Biology, German Cancer Research Centre, Heidelberg, Germany

¹⁷Centre for Hereditary Tumours, Bethesda Hospital, Duesseldorf, Germany

¹⁸Department of Surgery, University Hospital of Göttingen, Göttingen, Germany

¹⁹Division of Human Nutrition and Health, Wageningen University and Research, Wageningen, the Netherlands

*Correspondence to: T. T. Seppälä, PO Box 340, 00290 HUS, Helsinki, Finland. E-mail: tori.seppala@finmed.fi; t.ori@lanchford.co.uk; tori_seppala@helsinki.fi; @ToriSeppala; @CAPP2_EHTG; @EHTG_Tweets; @EHTG_tweets; @YouESCP; @seppala_tori; @LynchsyndromeUK; @Colorectal_rv; @HertsGenetics; @LynchsyndromeUK; @Colorectal_rv; @HertsGenetics

Abstract

Background: Lynch syndrome is the most common genetic predisposition for hereditary cancer but remains underdiagnosed. Large prospective observational studies have recently increased understanding of the effectiveness of colonoscopic surveillance and the heterogeneity of cancer risk between genotypes. The need for gene- and gender-specific guidelines has been acknowledged.

Methods: The European Hereditary Tumour Group (EHTG) and European Society of Coloproctology (ESCP) developed a multidisciplinary working group consisting of surgeons, clinical and molecular geneticists, pathologists, epidemiologists, gastroenterologists, and patient representation to conduct a graded evidence review. The previous Mallorca guideline format was used to revise the clinical guidance. Consensus for the guidance statements was acquired by three Delphi voting rounds.

Results: Recommendations for clinical and molecular identification of Lynch syndrome, surgical and endoscopic management of Lynch syndrome-associated colorectal cancer, and preventive measures for cancer were produced. The emphasis was on surgical and gynaecological aspects of the syndrome. The Manchester consensus guidelines for gynaecological management were endorsed. Executive and layperson summaries were provided.

Conclusion: The recommendations from the EHTG and ESCP for identification of patients with Lynch syndrome, colorectal surveillance, surgical management of colorectal cancer, lifestyle and chemoprevention in Lynch syndrome that reached a consensus (at least 80 per cent) are presented.

Received: March 24, 2020. Revised: May 16, 2020. Accepted: June 14, 2020

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Familial adenomatous polyposis (FAP)

- Prevalence 35/1 000 000
- 200 families in Sweden
- >25% de novo mutation
- Small intestine, desmoid, osteoma of jaw, papillary thyroid cancer (1-12% risk), hepatoblastoma in childhood

Prevention of FAP

- Surveillance colonoscopy usually annually from 12-15 years
- Prophylactic surgery when the number and size of polyps becomes unmanageable

Summary of monogenic variants

Replication repair deficiency

- Multiple cancer types
- High microsatellite instability and tumor mutational burden
- Colorectal cancer more often proximal colon, mucinous, high lymphocyte infiltration
- Therapeutic prediction: immune checkpoint inhibitors (positive), chemotherapy (negative)
- Lynch: mismatch repair protein: MLH1, MSH2, MSH6, PMS2
- Polymerase-proofreading associated polyposis: POLE, POLD
- Other genes: EPCAM (mutation causes MSH2 promoter methylation), MSH3, MLH3

Polyposis syndromes

- 1% of colorectal cancer
- Pathogenic variant found:
 - Most patients with >100 polyps
 - Few patients with 10-100 polyps
- Familial adenomatous polyposis (FAP) and attenuated FAP (AFAP): APC
- MUTYH-associated polyposis (MAP), NTHL1, MSH3 (all recessive)
- Polymerase-proofreading (POLE, POLD)
- Hamartomatous e.g. STK11 (Peutz-Jegher), PTEN (Cowden) etc
- Juvenile polyposis (BMPR1A, SMAD4)
- Serrated polyposis (no genes?)

A growing list...



Vilka bör erbjudas cancergenetisk utredning?

- Individ som insjuknat i tjock- och ändtarmscancer eller livmoderkroppscancer före 50 års ålder
- Familj där två eller flera 1a eller 2a grads-släktingar med tjock- och ändtarmscancer eller Lynchs syndrom-associerade tumörer* i samma släktgren varav en insjuknat före 60 års ålder
- Individ med metakron eller synkron tjock- och ändtarmscancer cancer eller Lynch syndrom-associerade tumörer*
- Misstanke om ärftligt polypossyndrom
- Påvisad dMMR med förlust av MSH2, MSH6 och/eller isolerad PMS2-förlust
- Påvisad dMMR med förlust av MLH1 vid avsaknad av BRAF-mutation (BRAF vildtyp)

Är det någonsin bråttom att utreda?

* Tjock- och ändtarmscancer samt cancer i livmoderkropp, äggstockar, tunntarm, magsäck eller urinvägar.

Familial colorectal cancer

- 1 first degree relative with colorectal cancer at age <50 years: one-time colonoscopy at age 55
- 2 first degree relatives with colorectal cancer: one-time colonoscopy at age 55
- 3 first degree relatives with colorectal cancer: colonoscopy after 5 years starting 5 years before the earliest case
- Normal findings → return to screening
- Adenoma/polyps → polyp follow-up protocol
- Renewed assessment after 5-10 years

Prevention in other higher-risk populations



An AI-generated image of “a polyp” (Copilot).
September 2024



- Inflammatory bowel disease
- After polypectomy

Svensk Gastroenterologisk Förening
Swedish Society of Gastroenterology



Nationell riktlinje

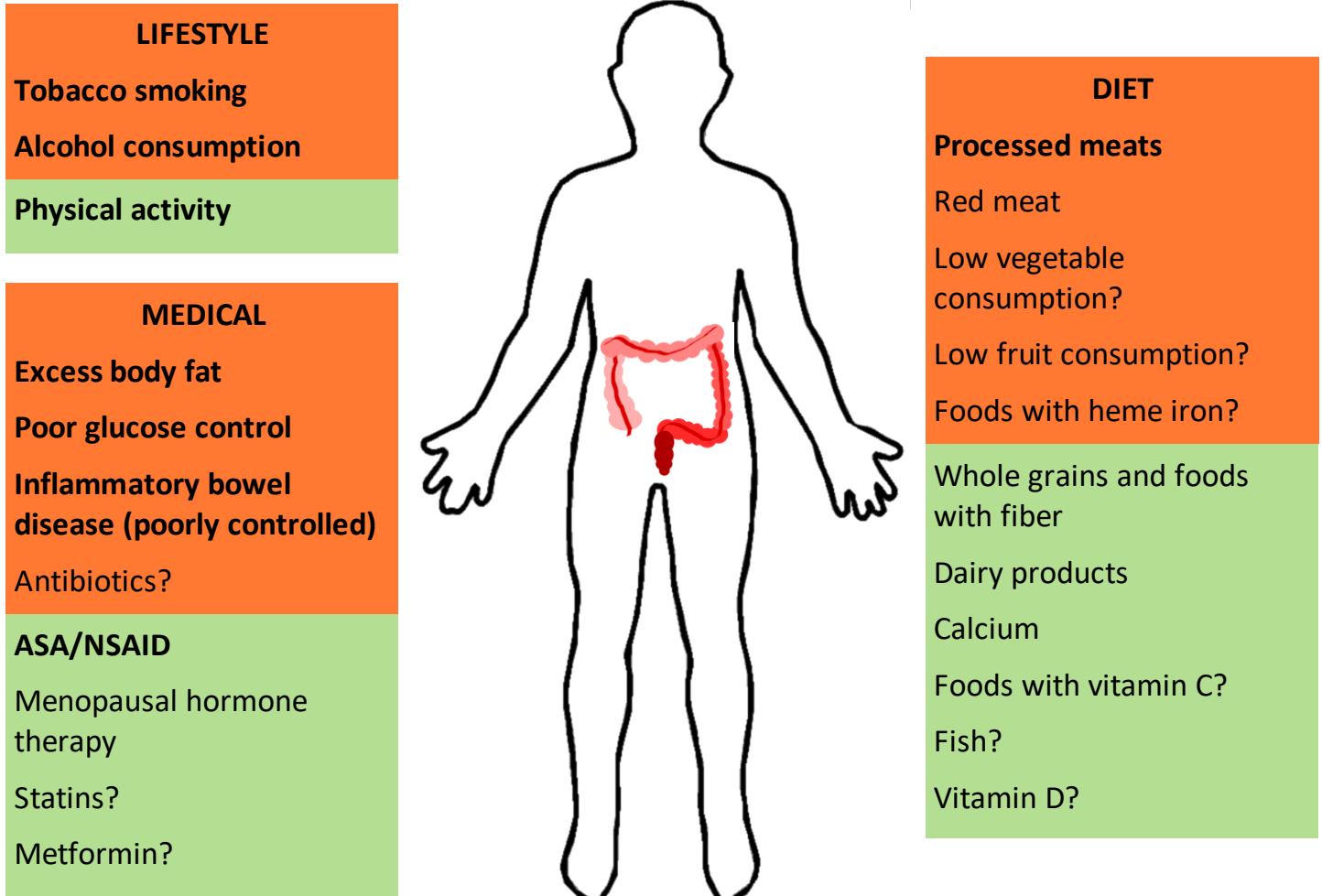
2021

På uppdrag av Svensk Gastroenterologisk Förenings styrelse

**Endoskopisk uppföljning efter
kolorektal polypektomi**

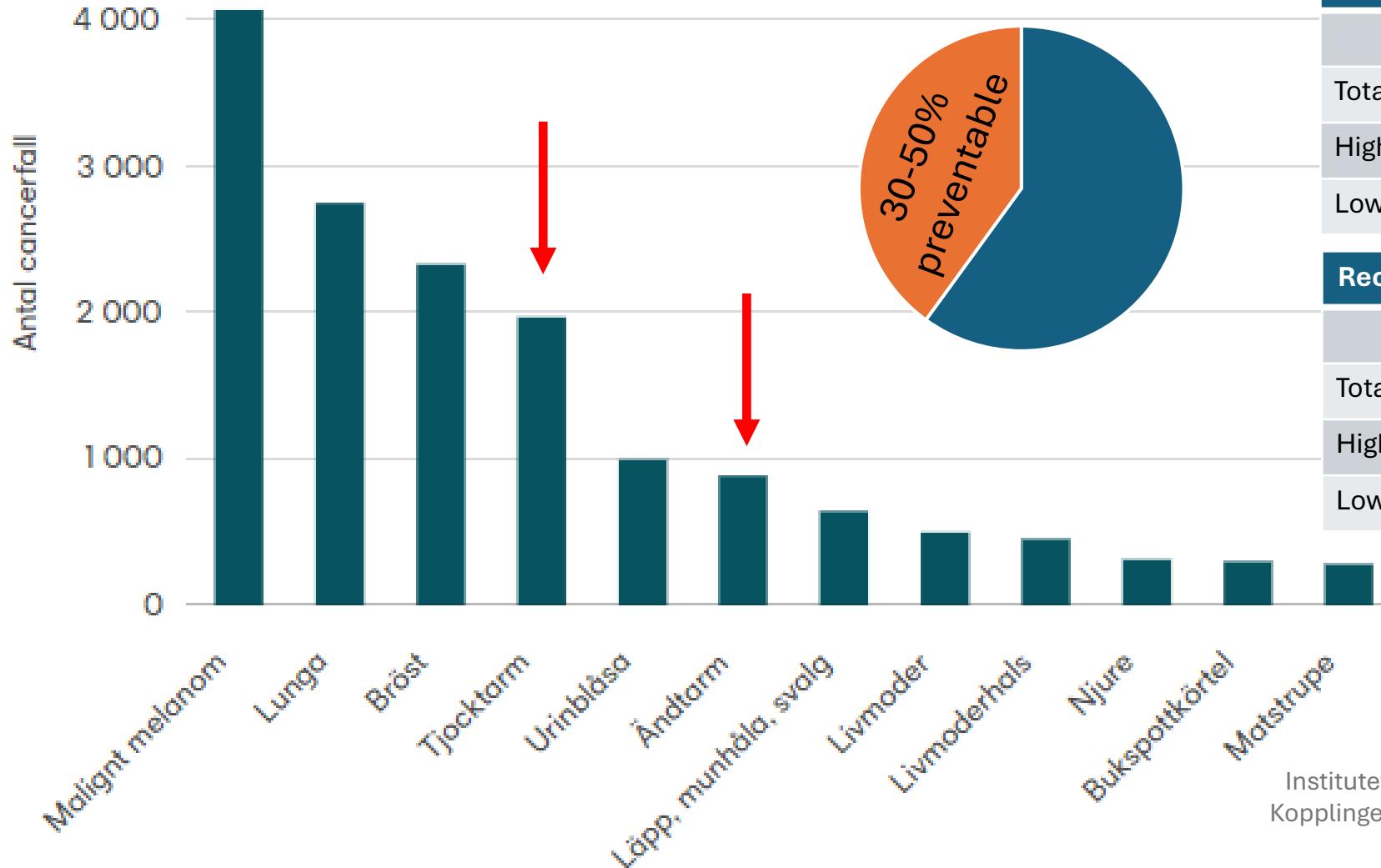
Datum för fastställande: 2021-10-28
Datum för översyn: 2022-11-30
Datum för revidering: 2025-11-30

Modifiable risk factors



Established risk factors in bold. Increased risk in orange, decreased risk in green

Preventable cases in Sweden

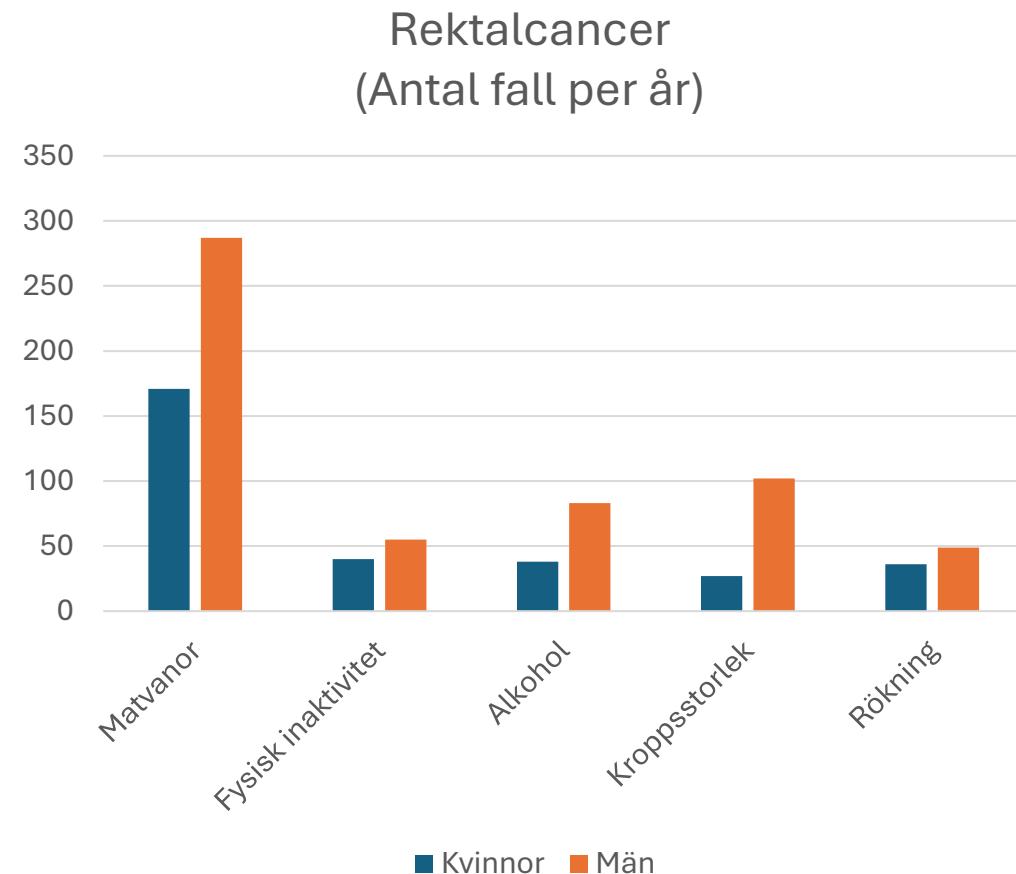
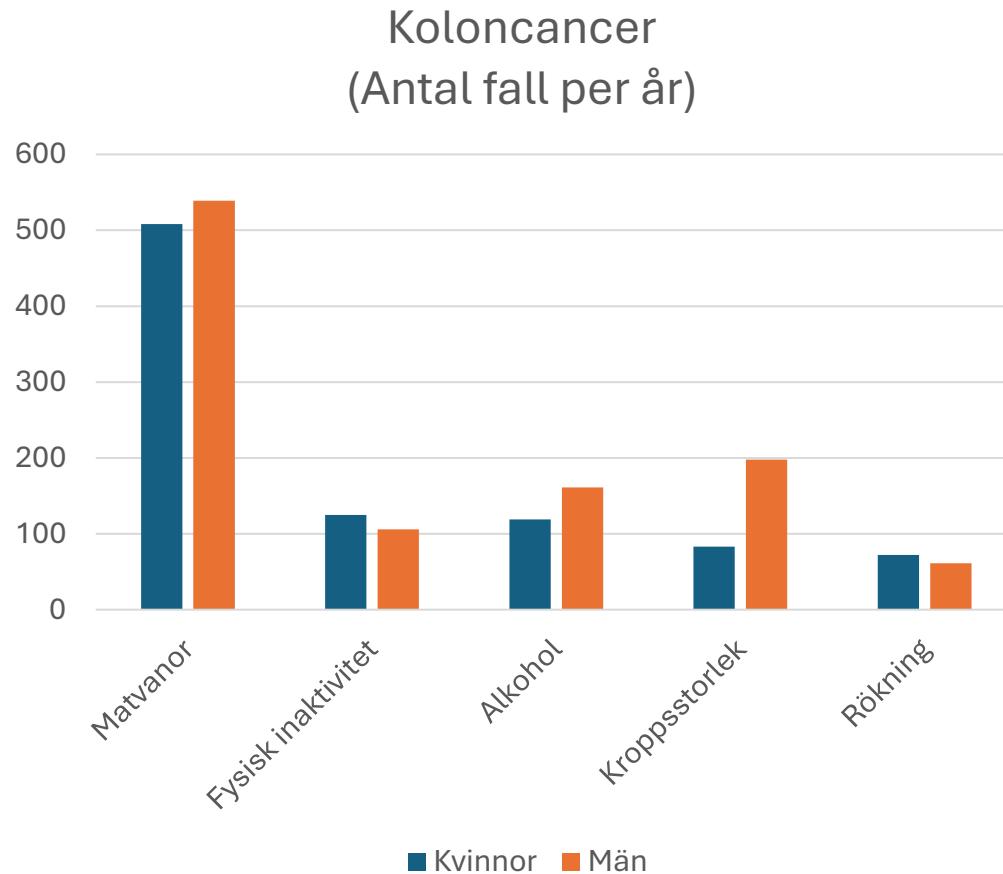


Colon cancer		
	Men	Women
Total	43.1%	35.9%
Higher education	40.6%	35.9%
Lower education	44.6%	35.9%

Rectal cancer		
	Men	Women
Total	44.3%	37.5%
Higher education	41.0%	34.4%
Lower education	46.2%	39.7%

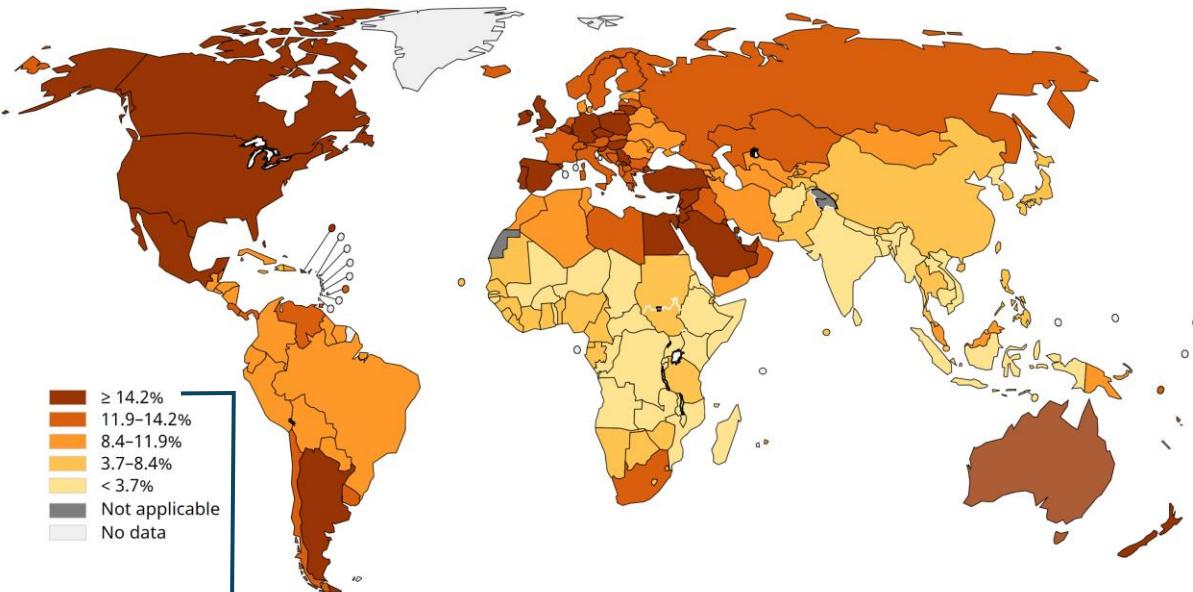
Institutet för Hälso- och Sjukvårdsekonomi (IHE) rapport, 2023
Kopplingen mellan påverkbara riskfaktorer och cancer i Sverige;
totalt och uppdelat efter utbildningsnivå

Relative importance of lifestyle-related factors



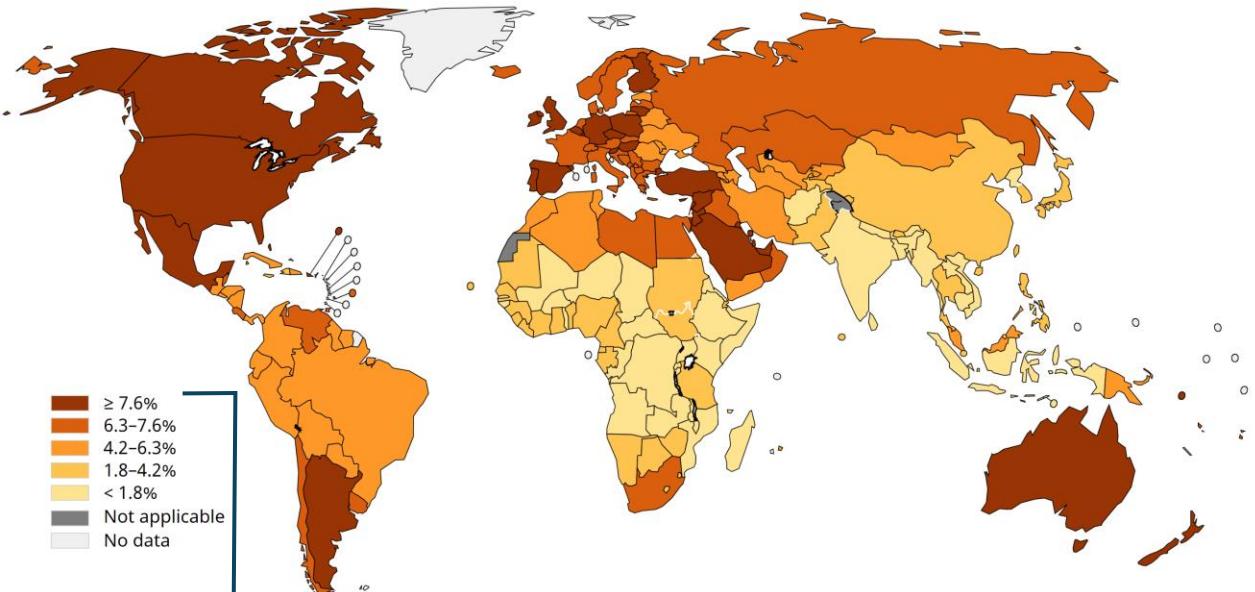
Proportion of cases attributable to excess BMI

Colon cancer



14%

Rectal cancer



7.5%

International Agency for Research on Cancer



GLOBAL CANCER
OBSERVATORY

Prevention in “normal-risk” populations

- Society level
- Population level
- Individual level



Society-level prevention

The infographic features a collage of images arranged in a grid-like pattern. At the top left is a splash of brown liquid. Below it are two cans (one red, one silver), a gold coin, a white bowl filled with colorful vegetables, and a soccer ball. To the right of these are a pink circular object, a green apple, a speedometer-like gauge with markings from 20 to 280, and a small white bowl containing fruit. The central text reads "Taxes on sugary drinks: Why do it?" in red.

TOGETHER
LET'S BEAT NCDs
#beatNCDs

World Health Organization

Taxes on
sugary drinks:
Why do it?

ERFONDEN

Logga in

åvoshop Om cancer Minska risken Forskning Råd & Stöd Om oss

Producentavgift på socker i dryck

Producentavgift på socker i dryck

Sverige behöver en producentavgift på sockersötade drycker. Som ett steg mot mer hälsosamma levnadsvanor vill Cancerfonden att en producentavgift på socker i drycker som läsk införs. Evidensen är tydlig. En producentavgift skulle sänka sockerinnehållet.

Population-level prevention

- Lifestyle recommendations
- General screening programs
- Screening awareness campaigns
- Self-exam campaigns (thankfully not for colorectal cancer)
- Standardized care pathways

12 WAYS TO REDUCE YOUR CANCER RISK

BASED ON THE EUROPEAN CODE AGAINST CANCER.

Did you know that about half of all cancers could be avoided?

What can you do to reduce your risk of cancer?

4 BE PHYSICALLY ACTIVE IN EVERYDAY LIFE
Limit the time you spend sitting and aim for at least 30 minutes of moderate physical activity a day.
 30 min

9 RADIATION
Find out if you are exposed to radiation from naturally high radon levels in your home. Find out more information on radon levels from the Environmental Protection Agency: www.epa.ie

5 HAVE A HEALTHY DIET
Eat fruit, vegetables, whole grains and pulses. Limit foods high in sugar, salt and fat. Avoid processed meat and limit red meat.

10 ADVICE FOR WOMEN
Breastfeeding is proven to reduce the risk of cancer. HRT is a hormonal drug for menopausal symptoms which increase risk of certain cancers. Limit HRT.

11 GET VACCINATIONS
Some cancers are spread by viruses and bacteria. Ensure your children take part in vaccination programmes for Hepatitis B (for newborns) and Human papillomavirus (HPV) (for girls over 12 years).

12 GET SCREENED FOR CANCER
Screening is checking for cancer or conditions that may lead to cancer in people that may have no symptoms. Take part in organised cancer screening programmes for bowel cancer (men and women), breast cancer (women) and cervical cancer (women).
www.cancerscreening.ie

1 DO NOT SMOKE
One in three of all cancers is related to smoking. Cut out the cigarettes and cut your cancer risk.

6 AVOID ALCOHOL
Drinking alcohol can cause at least seven types of cancer. Cutting back - or even better - avoiding alcohol altogether will reduce your risk.

2 AVOID SECOND-HAND SMOKE
Keep your home and workplace smoke free. Second-hand smoke increases the risk of lung cancer and heart disease in non-smokers.

7 AVOID TOO MUCH SUN
Skin cancer is the most common cancer in Ireland with over 10,000 new cases diagnosed in 2011. Be SunSmart: protect your skin when outdoors (sunscreen is not enough) and avoid sunbeds.

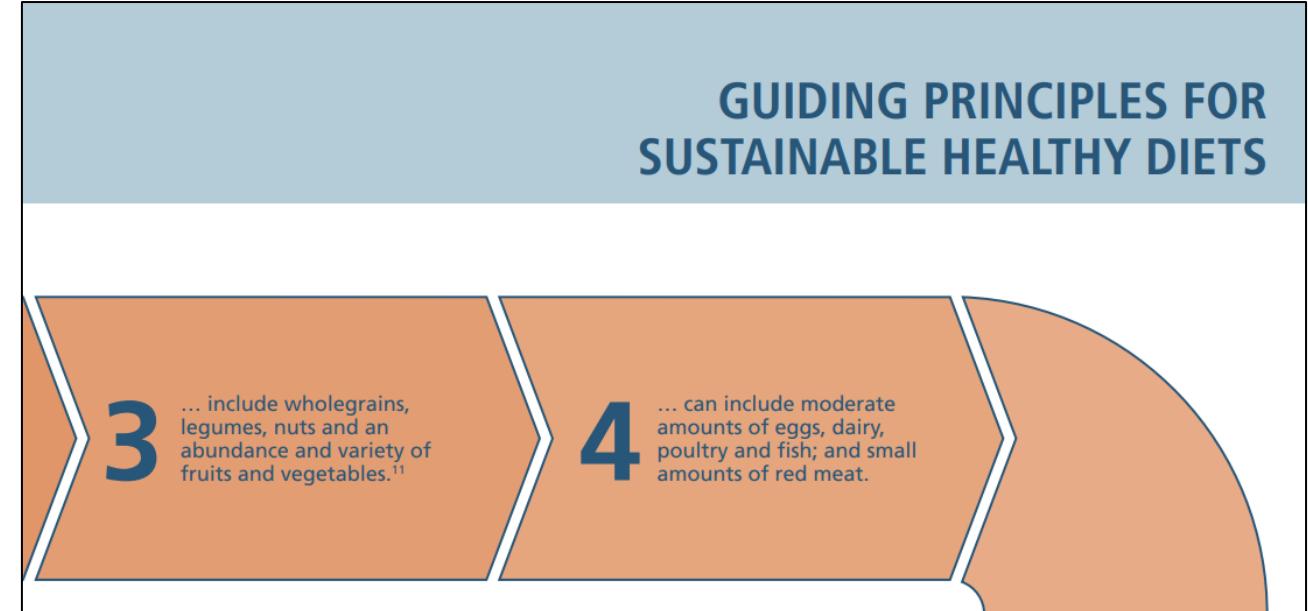
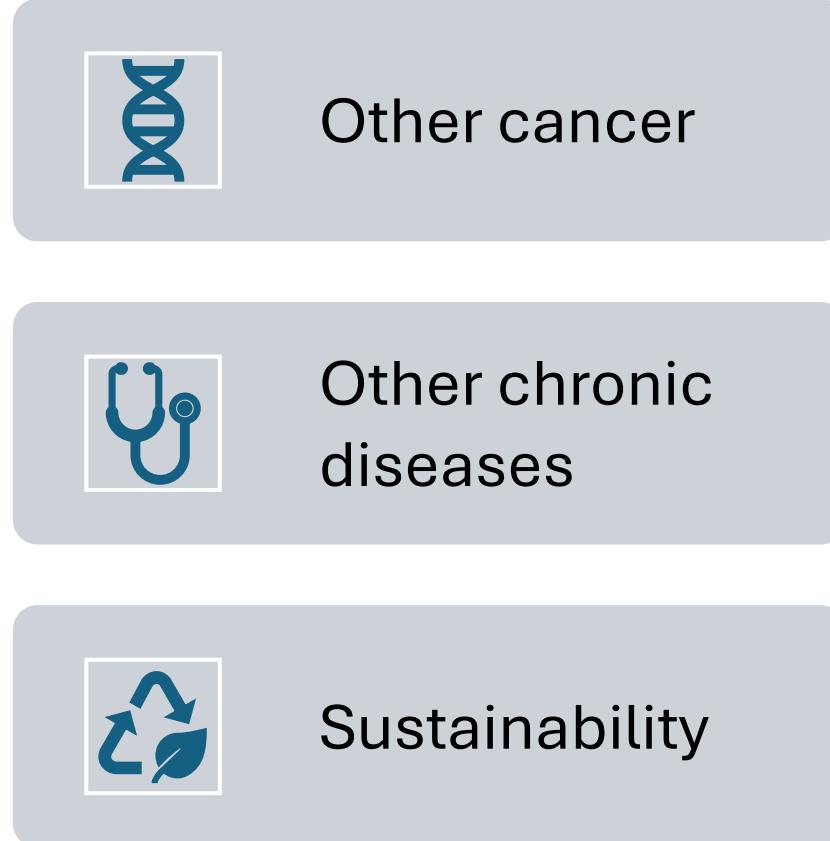
3 BE A HEALTHY WEIGHT
As the amount of fat in the body increases, so does the chance of developing certain cancers. Take action to have a healthy body weight by being physically active and eating a healthy diet.

8 POLLUTANTS
Protect yourself in your workplace and follow health and safety instructions.

Cancer specialists and scientists from across Europe compiled the code based on the latest scientific evidence on cancer prevention. This code was developed by the International Agency for Research on Cancer and the European Commission 2014.

Irish Cancer Society, based on the European Code Against Cancer

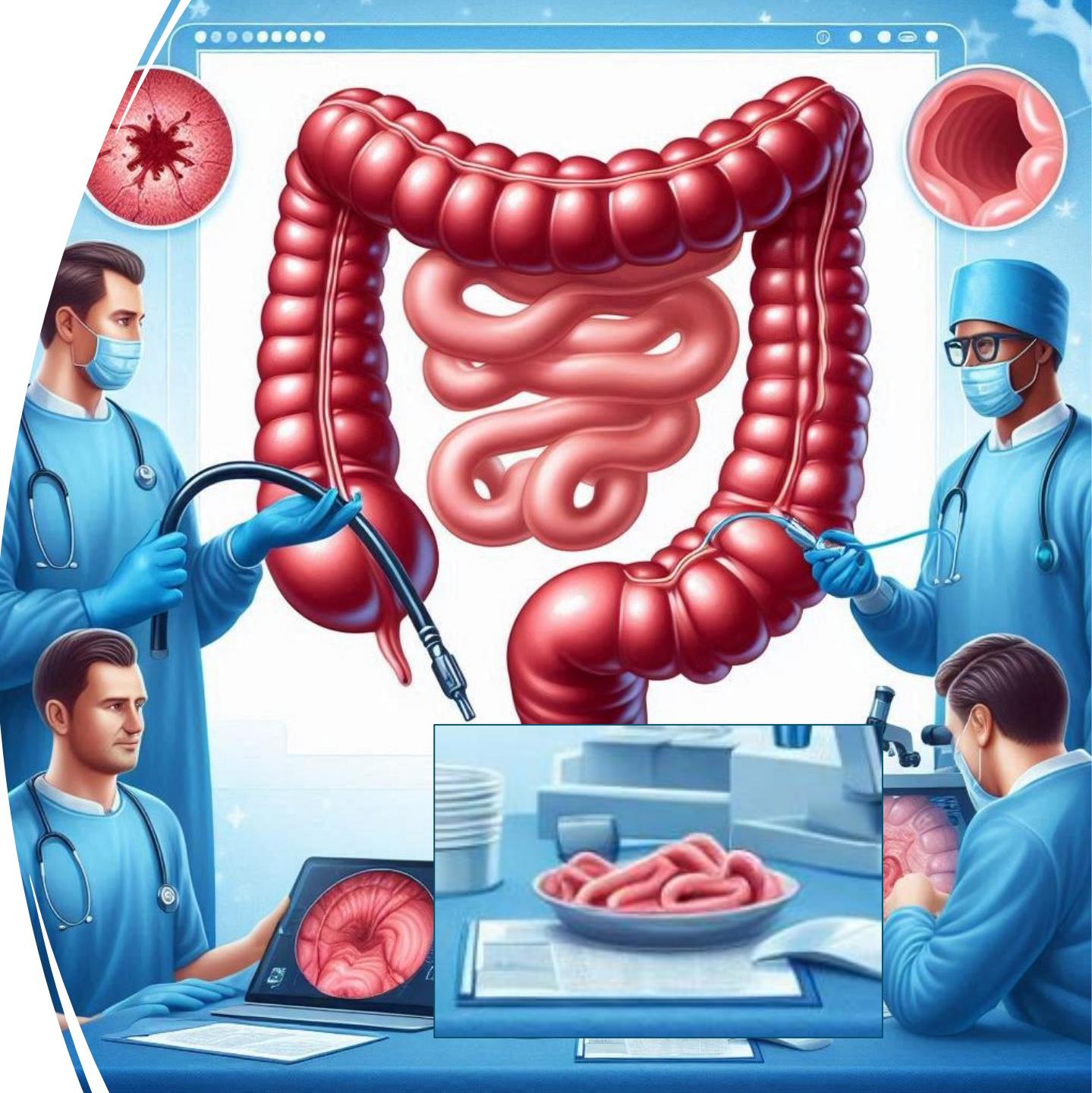
Lifestyle recommendations – the bigger picture



... include whole grains,
legumes, nuts and an
abundance and variety
of fruits and vegetables

... can include
moderate amounts of
eggs, dairy, poultry
and fish; and small
amounts of red meat.

Prevention through screening



Overview of screening principles

“Medical”

- Important health problem
- Natural history adequately understood
- Recognizable asymptomatic phase
- Suitable test or examination
- Test and diagnostics acceptable to the population
- Accepted treatment for patients with recognized disease
- Treatment more effective in early phase than clinically diagnosed disease
- Health gains outweigh negative effects of screening
- Screening program ethically acceptable

”Structural”

- Cost effective
- Feasible (facilities, resources)
- Information to target population
- Equality aspects clear
- Plan for evaluation of effects

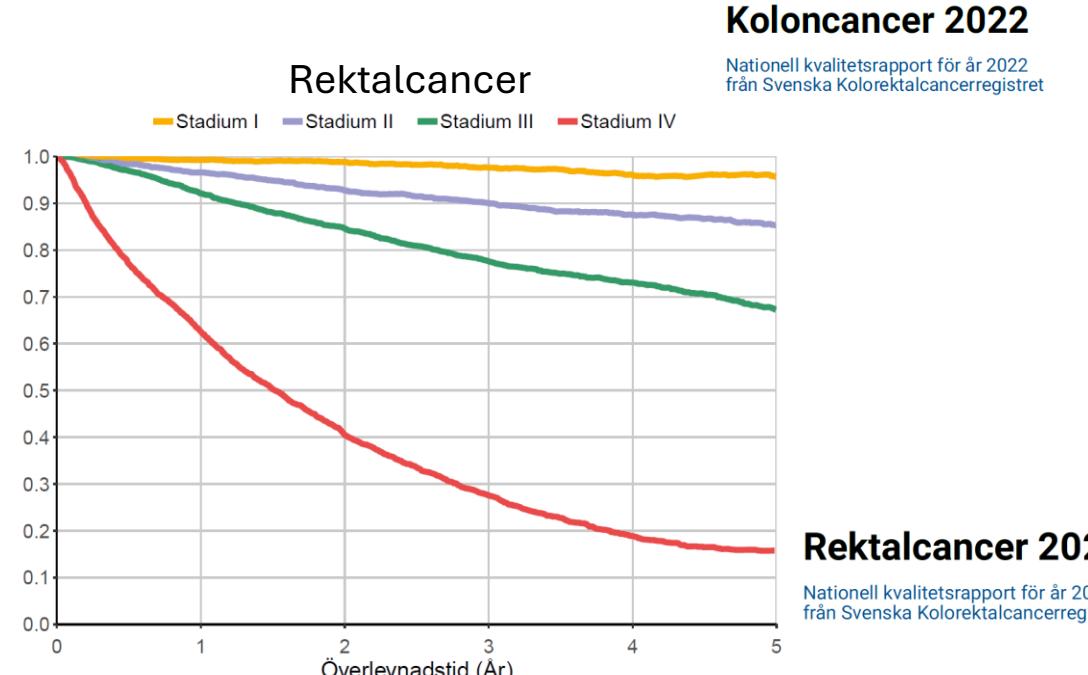
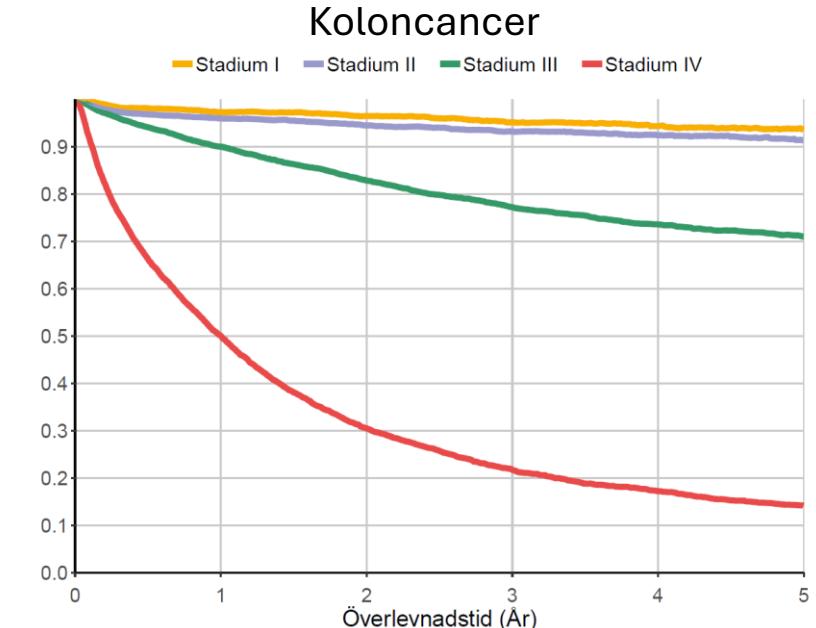
These lists are a summary of several sources and are modified in wording but not content. The division into medical and structural is my view. Key references are:

World Health Organization, Wilson, J. M. G. & Jungner, G. (1966). The principles and practice of screening for disease. World Health Organization.

Socialstyrelsen. Nationella screeningprogram. Modell för bedömning, införande och uppföljning. Socialstyrelsen artikelnummer 2019-4-12 Stockholm2019 [2020-12-09].

Colorectal cancer screening

- **Prevention:** removal of precancerous lesions
- **Early detection:** "40-45% of cases shift from more advanced stages to stage I, i.e. in absolute terms an increase from approximately 10-15% to 20-25%"
- **Lower mortality:** "Approximately 300 colorectal cancer deaths annually in Sweden can be prevented"



Screening methods

- Stool-based tests
 - **Fecal immunochemical test (FIT)**
 - High-sensitivity guaiac fecal occult blood test (gFOBT)
 - Stool DNA test
- Direct tests
 - **Colonoscopy**
 - Flexible sigmoidoscopy
 - CT colonography



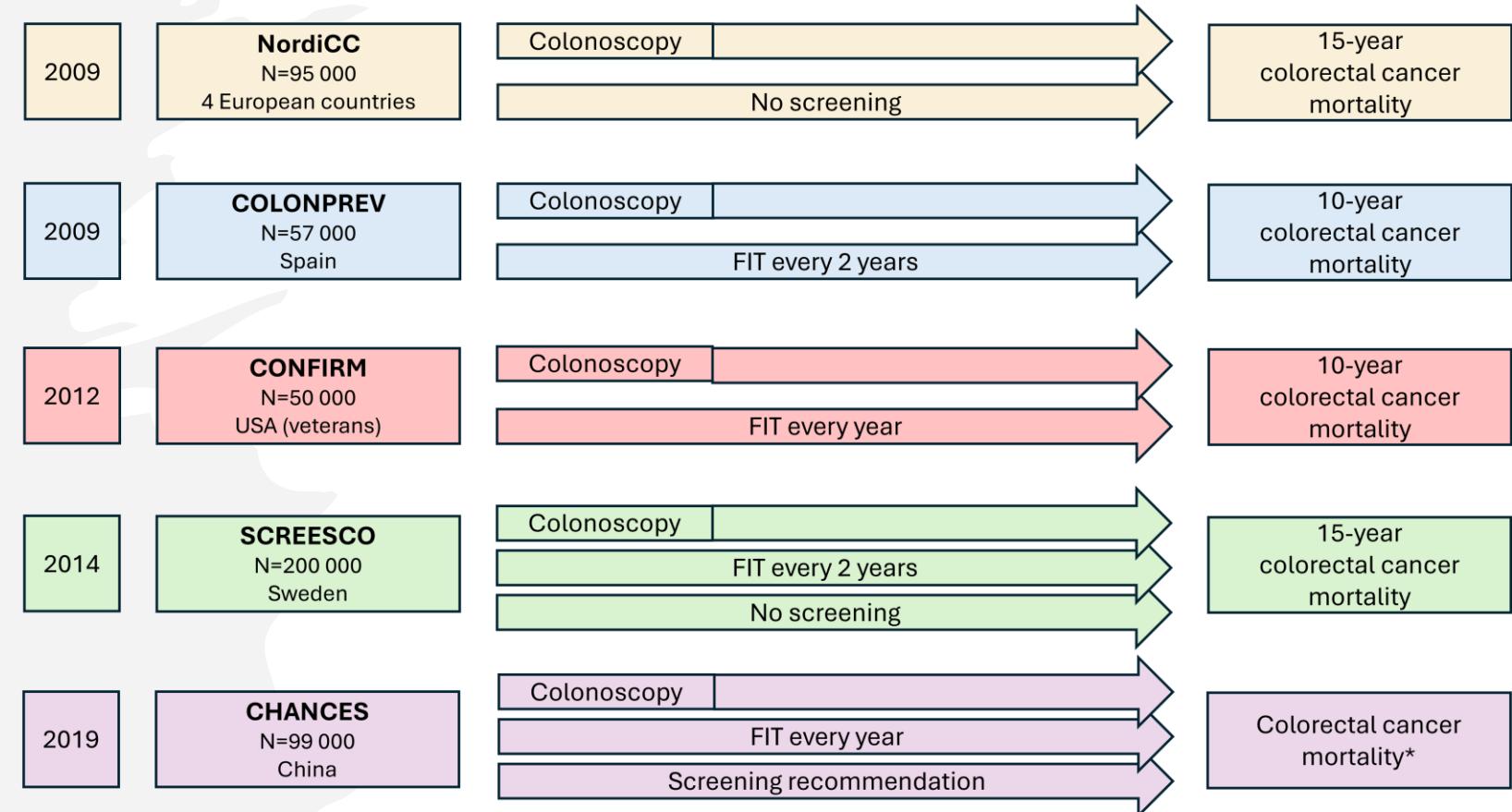
	Sick	Healthy	
Positive test	True positive	False positive	PPV $\frac{\text{true positives}}{\text{all positives}}$
Negative test	False negative	True negative	NPV $\frac{\text{true negatives}}{\text{all negatives}}$
	Sensitivity $\frac{\text{true positives}}{\text{all sickies}}$	Specificity $\frac{\text{true negatives}}{\text{all healthies}}$	
	FIT: 75-80%	FIT: 95%	

"Spin": high specificity rules in.
"Snout": high sensitivity rules out.
Positive and negative predictive values depend on prevalence.

USA:

- High-sensitivity gFOBT or FIT annually
- sDNA-FIT every 1-3 years
- CT colonography every 5 years
- Flexible sigmoidoscopy every 5 years
- Flexible sigmoidoscopy every 10 years + FIT annually
- Colonoscopy screening every 10 years

Large-scale colonoscopy studies



*Secondary outcome. (Combined lung and colorectal cancer screening study)

Screening effectiveness

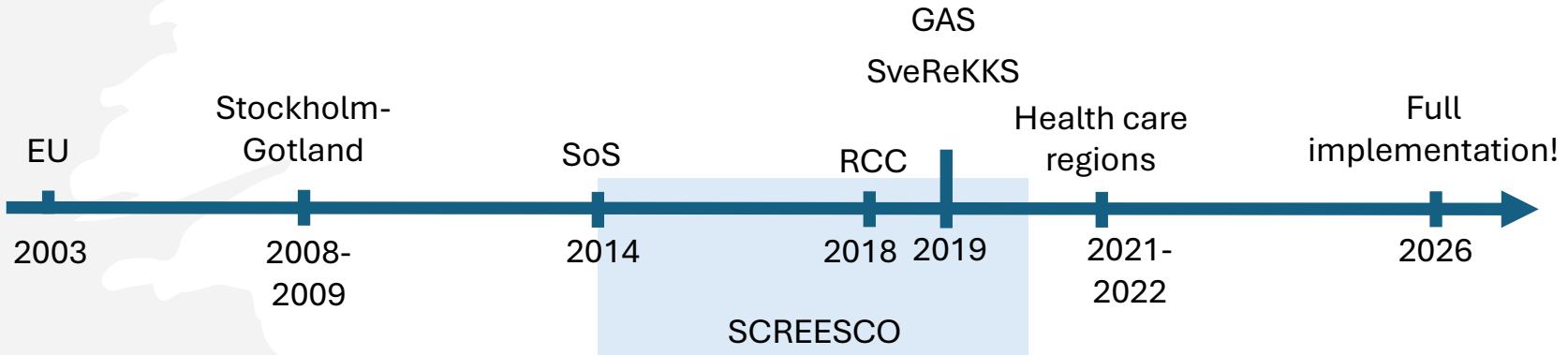
Colonoscopy studies - NordiCC

- Intention to treat:
 - Incidence reduction 18%
 - Colorectal cancer mortality reduction 10%
- Per protocol:
 - Incidence reduction 31%
 - Colorectal cancer mortality reduction 50%

Sigmoidoscopy studies

- Incidence reduction 20%, limited to left-sided colorectum (16% in women, 25% in men, mostly in higher age group)
- Colorectal cancer mortality reduction 20% (also more in men than women)

Screening in Sweden



- "...samtliga personer med normalrisk för tjock- och ändtarmscancer i åldern 60–74 år får erbjudande om att testa sig för eventuell förekomst av ockult blod i avföringen vartannat år"
- "De individer som testas positivt kallas till vidare utredning med koloskopi"



Map of "Sweden" and flag generated with AI (Copilot – September 2024)

Screening age – when to start?

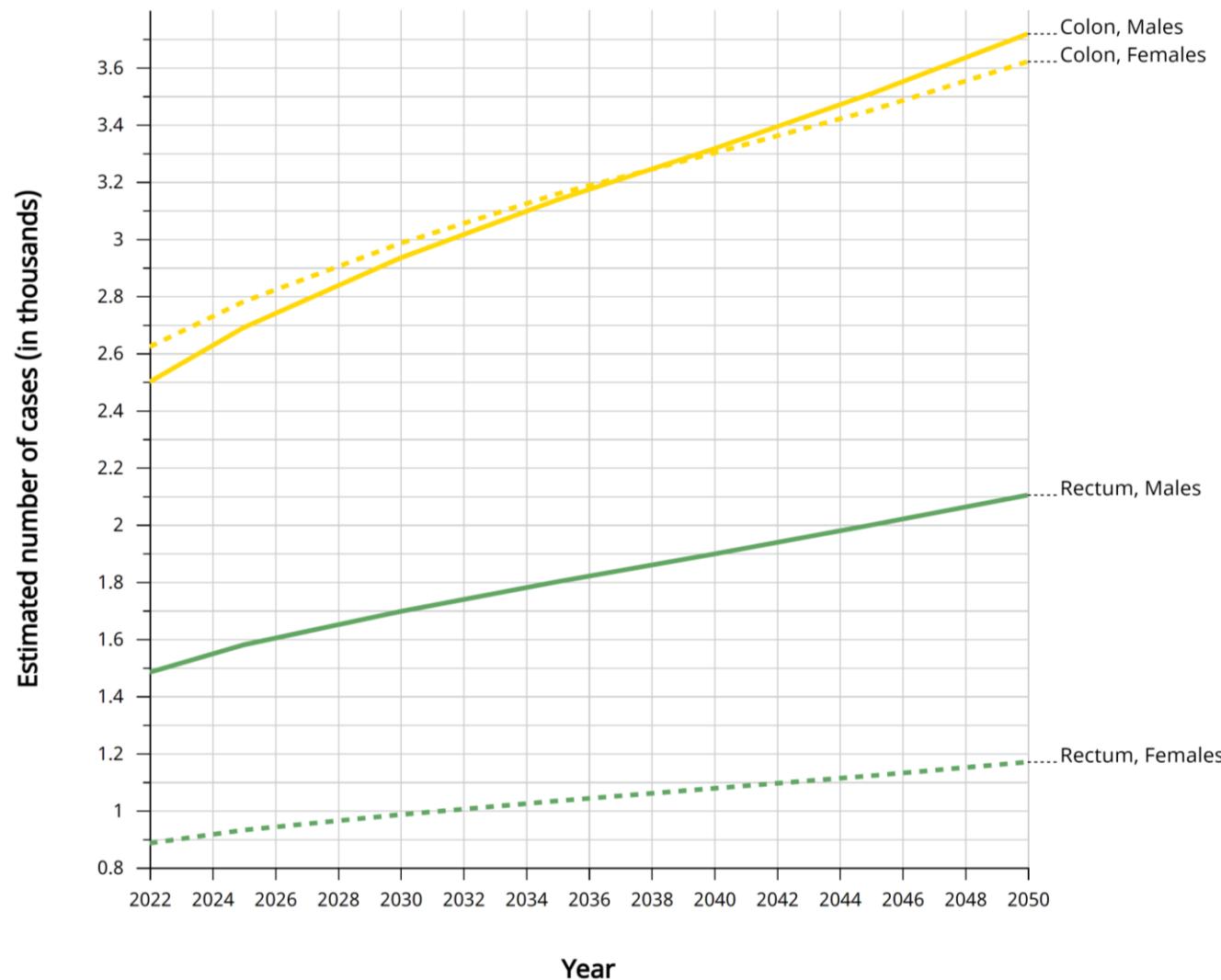
- Sweden: 60 years
- Europe: 50 years
- USA: 45 years
- Early-onset colorectal cancer is on the rise, but still only 6% cases in Sweden.

/ INRIKES



Hur vanligt är tarmcancer bland unga? Vilka symtom ska man vara uppmärksam på? Och vilka är riskfaktorerna? Se professor i kirurgi Anna Martling berätta om tre viktiga fakta om tarmcancer. Foto: Midhat Poturovic

Estimated number of new cases from 2022 to 2050, Males and Females, age [0-85+]
Sweden



Predicted increases in incidence

	Men	Women
Colorectal	38%	30%
Colon	40%	32%
Rectal	35%	27%

Predicted increases in mortality

	Men	Women
Colorectal	49%	39%
Colon	50%	40%
Rectal	46%	38%

All increases are <20% for 0-74 y

Other aspects

Potential downsides:

- Cancer worry
- False negatives
- False sense of security
- Physical discomfort
- Complications of colonoscopy (perforation, bleeding, 1/200)
- Overdiagnosis of polyps
- Overtreatment of cancer (negligible on group level)

Potential challenges:

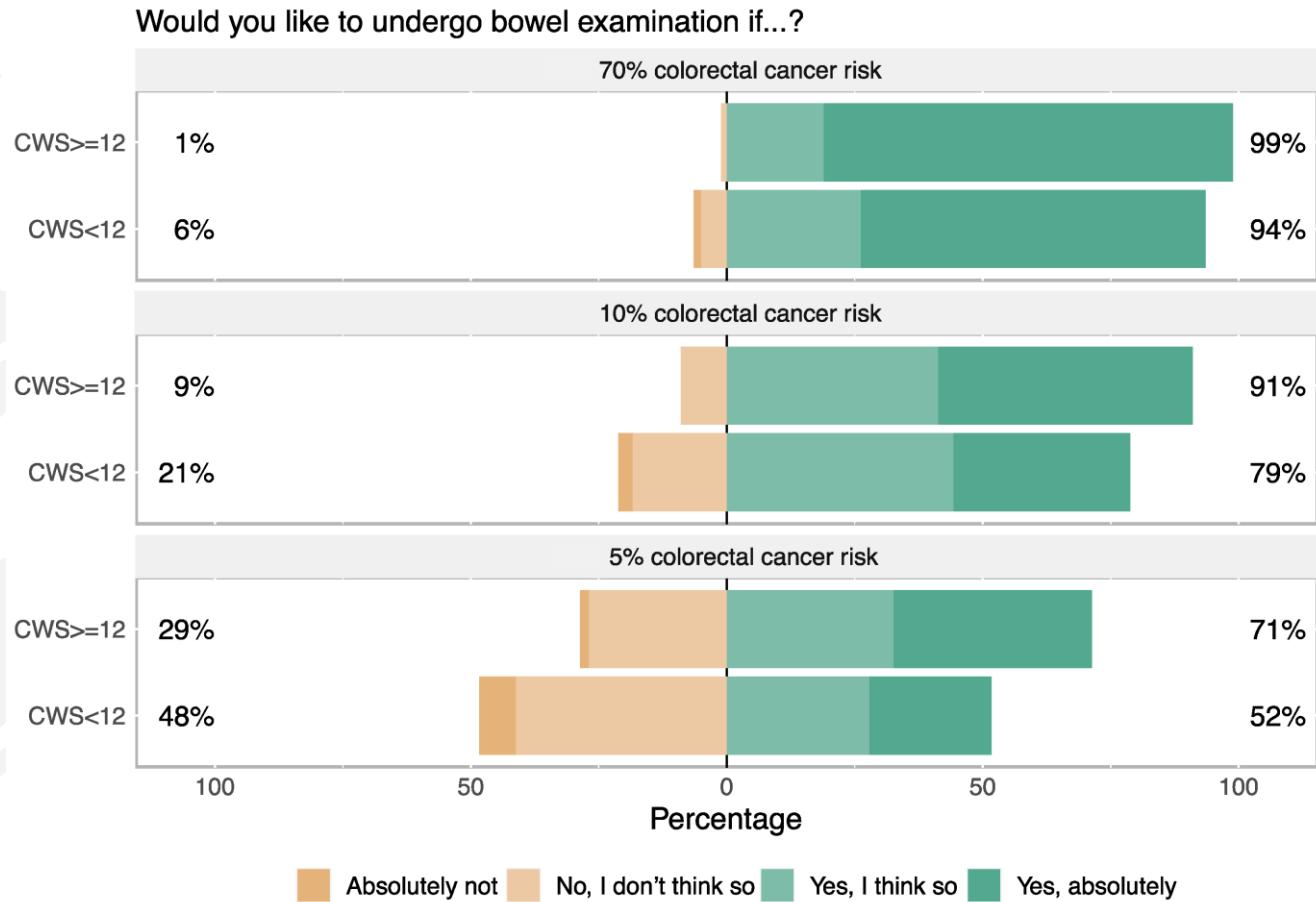
- Compliance
- Healthy screenee bias (health equity)
- Access to colonoscopists
- Colonoscopy quality measures (bowel prep, cecal intubation rates, adenoma detection rates)

Screening compliance

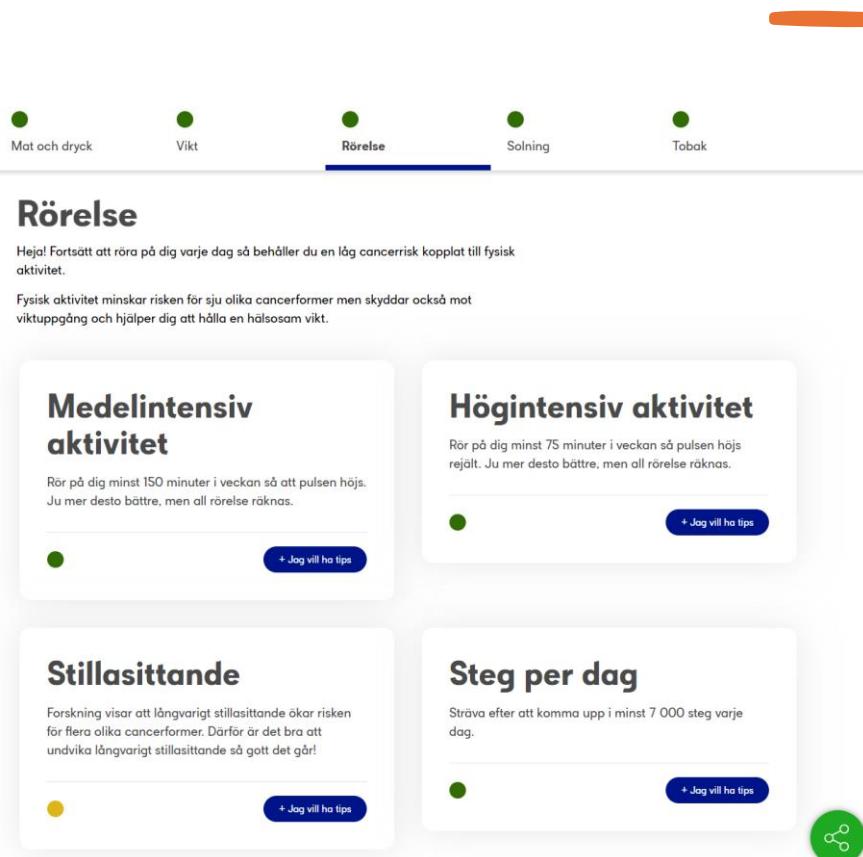
“Risk tools improved patient risk perception, knowledge, and screening intentions, but not necessarily screening behavior.”



Anna Rosén



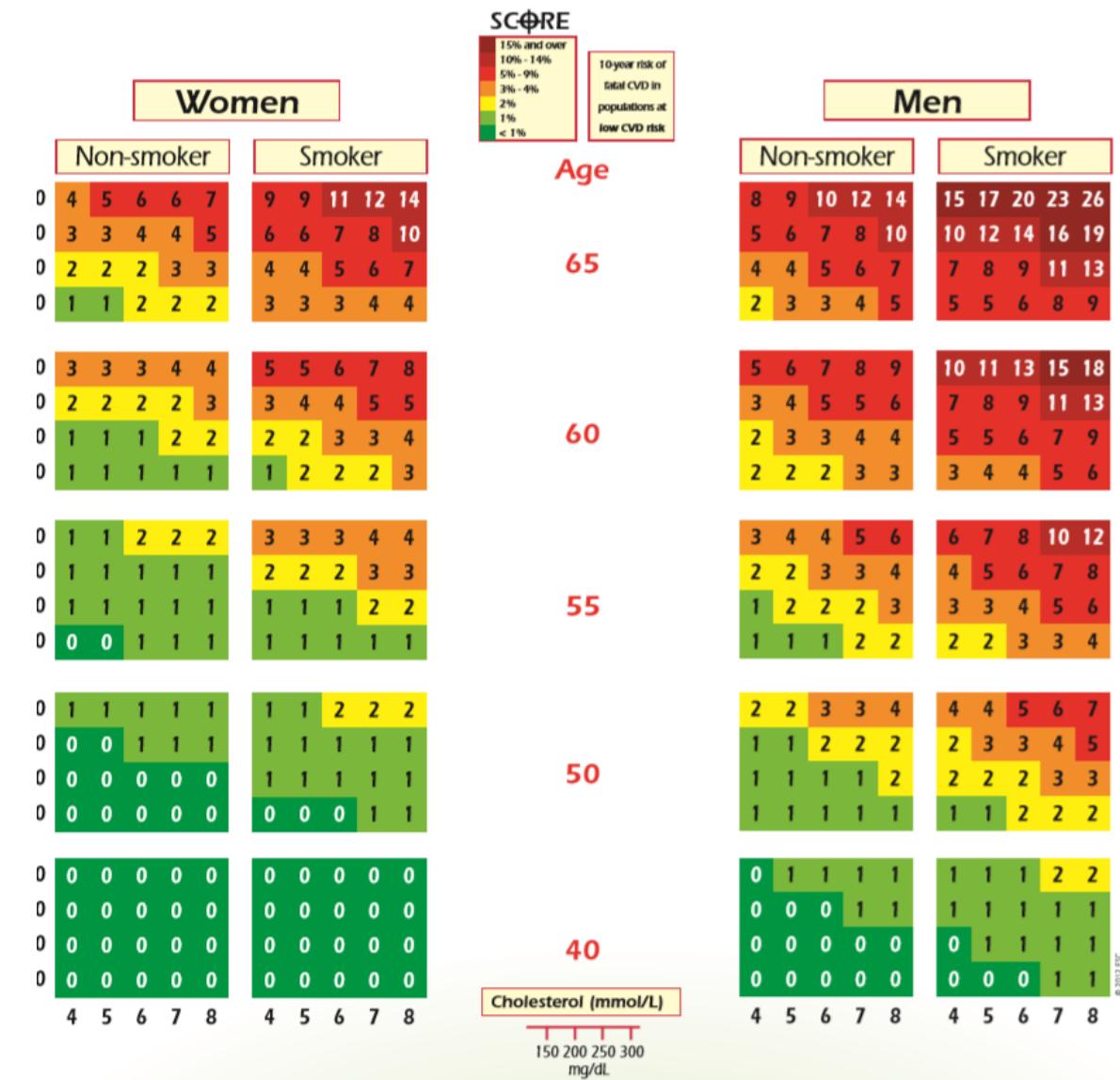
Individual-level (precision?) prevention

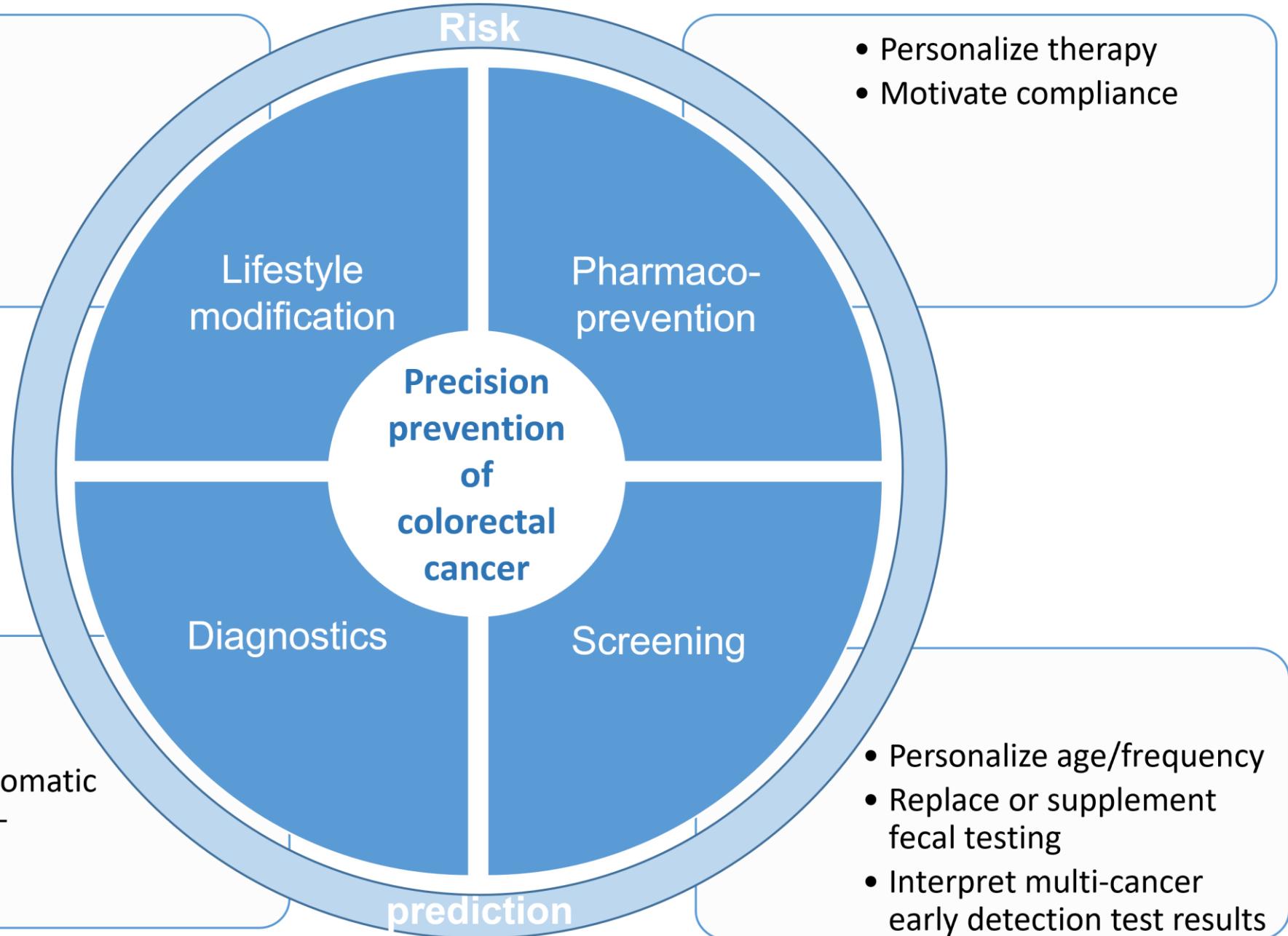


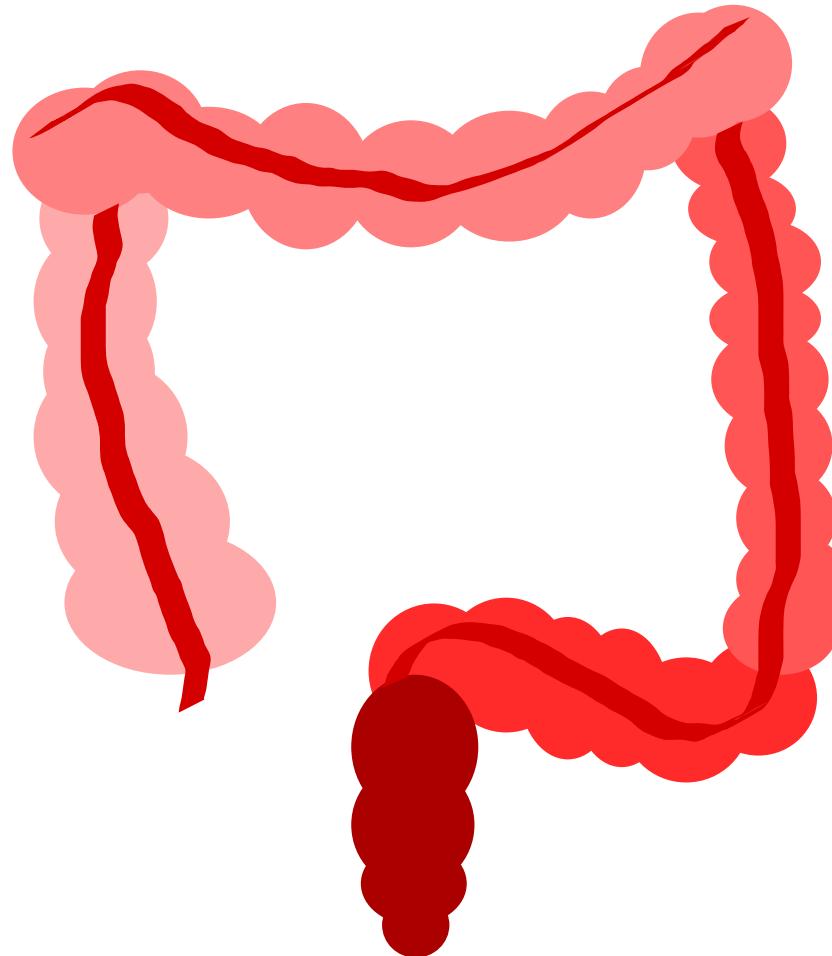


Risk of death due to cardiovascular disease within 10 years.

Example: male, 65 yr old smoker with high blood pressure and high cholesterol, risk 20-25%







The End