



Early-onset colorectal cancer – Is there a case to begin screening at age 45?

Jill Tinmouth MD PhD

Feb 29, 2020



Ontario Health
Cancer Care Ontario



Sunnybrook
HEALTH SCIENCES CENTRE

when it matters
MOST



Conflict of Interest

(Over the past 24 months)
Jill Tinmouth

Commercial or Non-Profit Interest	Relationship
Ontario Health (Cancer Care Ontario)	Lead Scientist, ColonCancerCheck Program



CanMEDS Roles

X	Medical Expert (as <i>Medical Experts</i> , physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. <i>Medical Expert</i> is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
	Communicator (as <i>Communicators</i> , physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
X	Collaborator (as <i>Collaborators</i> , physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
X	Leader (as <i>Leaders</i> , physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
	Health Advocate (as <i>Health Advocates</i> , physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
X	Scholar (as <i>Scholars</i> , physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
	Professional (as <i>Professionals</i> , physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)





Objectives

1. To describe and understand recent CRC trends in persons under age 50
2. To discuss potential intended and unintended consequences of initiating CRC screening at age 45
3. To discuss what we should do in light of recent trends in early-onset colorectal cancer



More Young People Are Dying of Colon Cancer

August 22, 2017



An X-ray of the colon shows constriction from a tumor. Getty Images

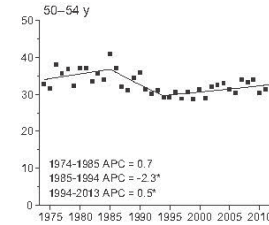
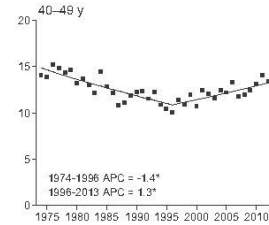
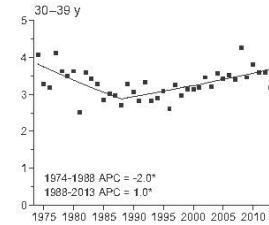
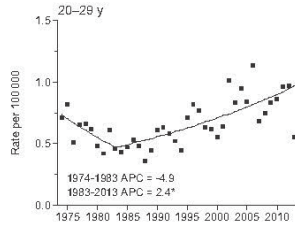


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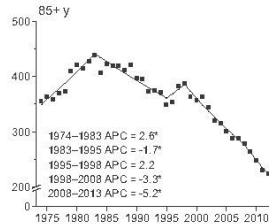
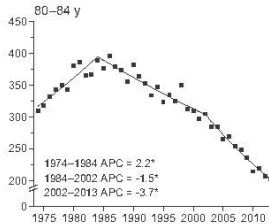
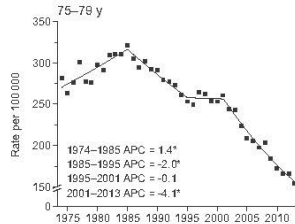
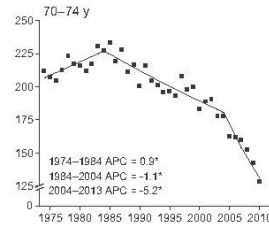
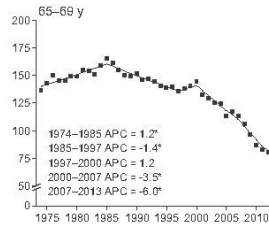
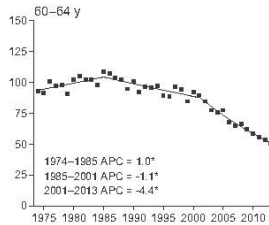
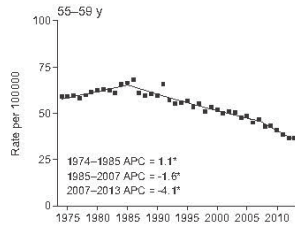


Incidence of colon cancer, US 1974-2013

< 54 y.o.



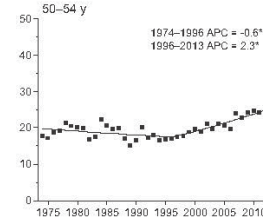
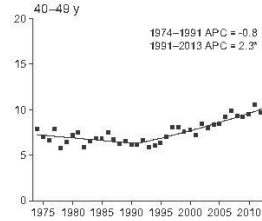
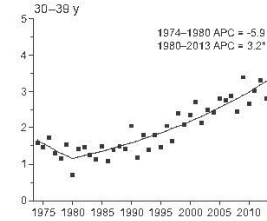
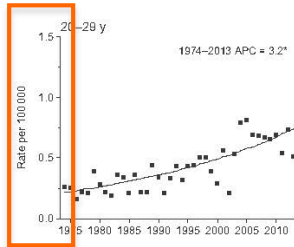
≥ 55 y.o.



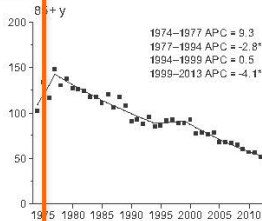
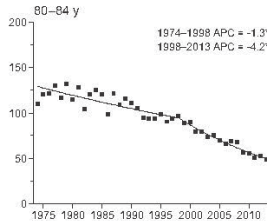
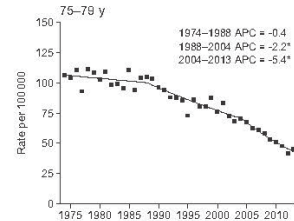
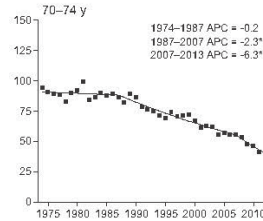
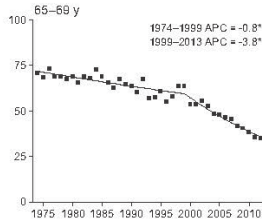
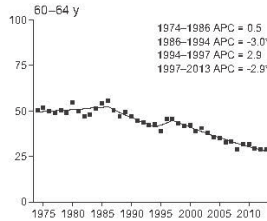
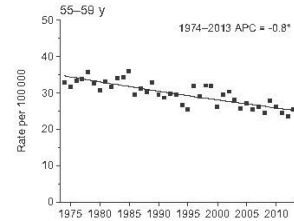


Incidence of rectal cancer, US 1974-2013

< 54 y.o.



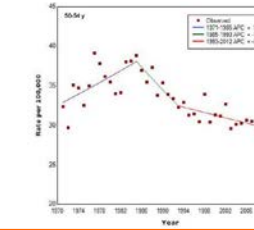
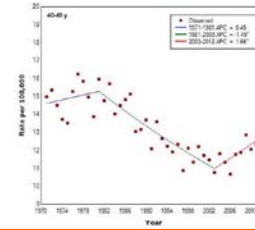
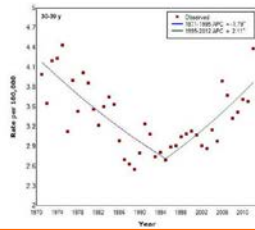
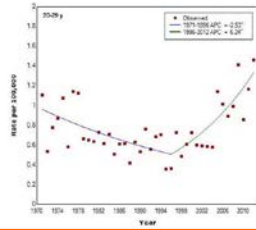
≥ 55 y.o.





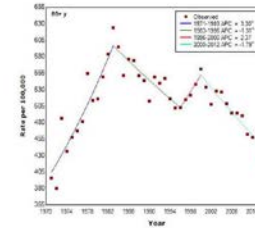
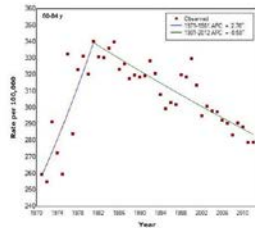
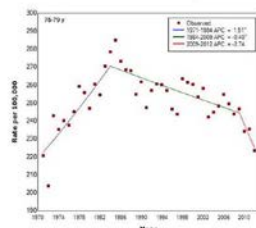
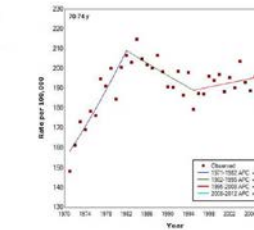
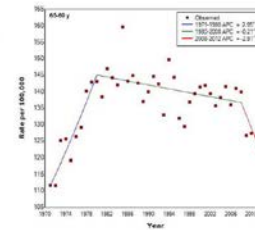
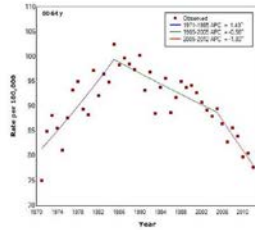
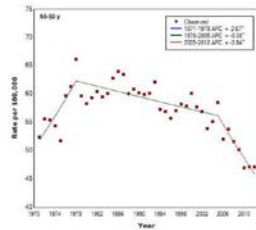
Incidence of colon cancer, Canada 1971-2012

< 54 y.o.



↑ Mid 1990s

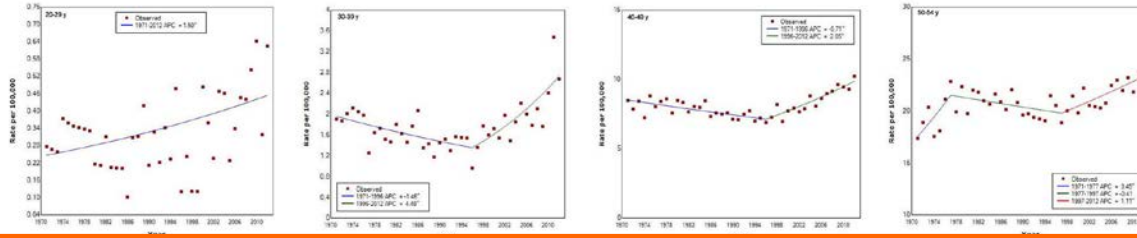
≥ 55 y.o.



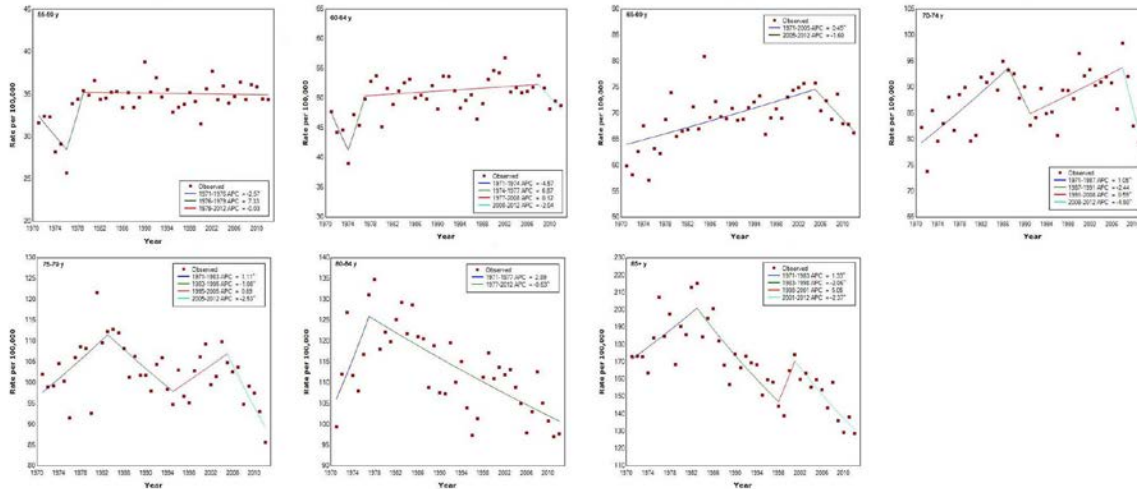


Incidence of rectal cancer, Canada 1971-2012

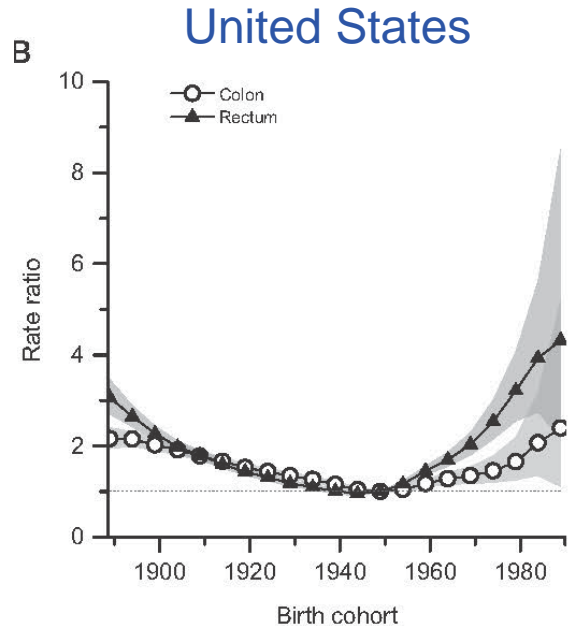
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≥ 55 y.o.



Incidence rate ratios by birth cohort

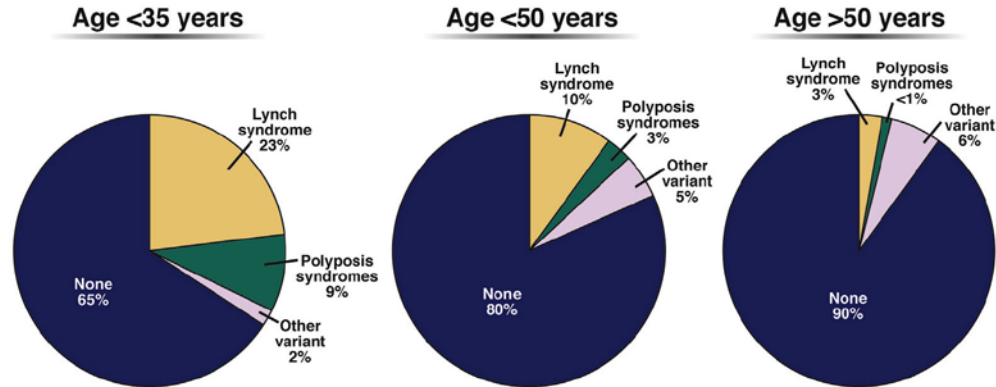




Clinical Features of Early vs Late Onset CRC

- Higher proportion of distal tumors
- Disproportionately affects African Americans and Hispanics in USA
- Survival same, despite more aggressive treatment
- More aggressive tumors (histopathology and molecular profile)
- Delays in diagnosis?

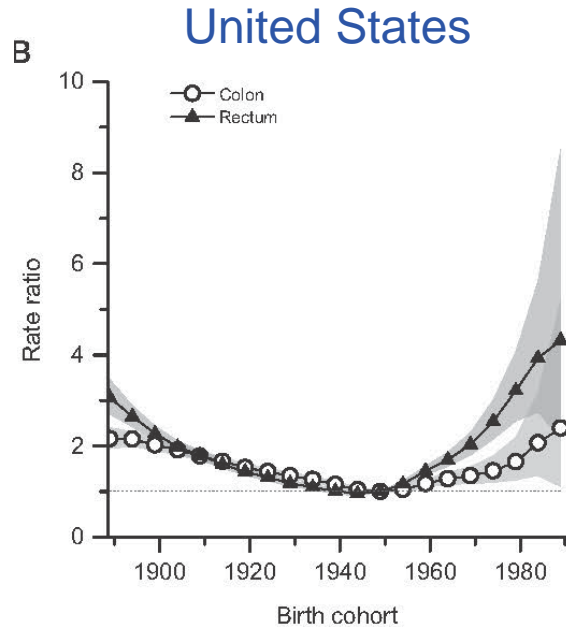
Role of genetics



Lynch syndrome	Polyposis syndromes	Other pathogenic variants	
		High penetrance	Moderate/low penetrance
<i>MLH1</i>	<i>APC</i>	<i>BRCA1</i>	<i>CHEK2</i>
<i>MSH2</i>	<i>MUTYH</i>	<i>BRCA2</i>	<i>ATM</i>
<i>MSH6</i>	<i>SMAD4</i>	<i>TP53</i>	<i>NBN</i>
<i>PMS2</i>	<i>BMPR1A</i>	<i>PALB2</i>	<i>BARD1</i>
	<i>PTEN</i>	<i>CDKN2A</i>	<i>BRIP1</i>
	<i>POLE</i>		



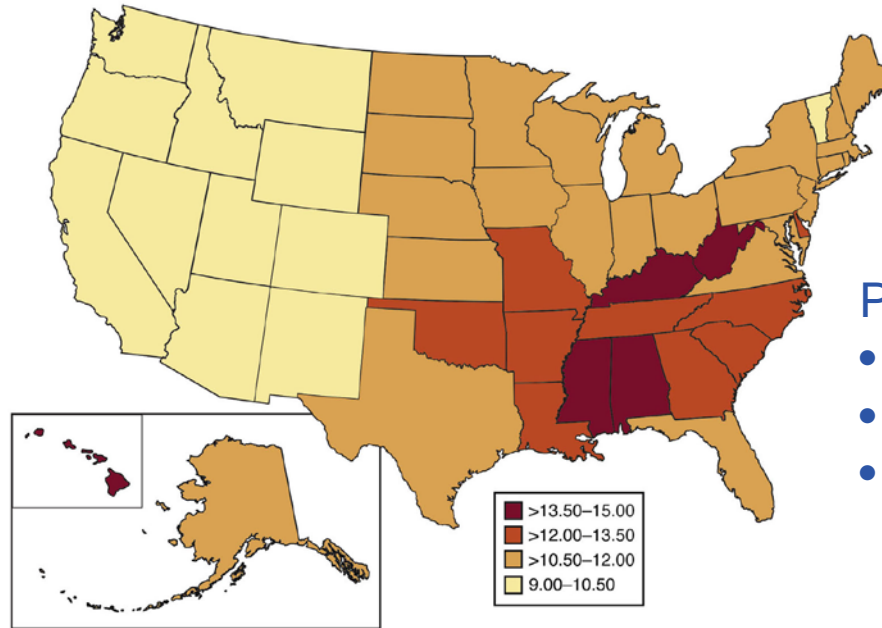
Birth cohort effect



Suggest exposures early in life or more freq experienced by younger generations

The geography of early onset CRC incidence, USA

- Mississippi
Delta/Appalachia:
- Poverty
 - Unemployment
 - Poor health care access



- Pathogenic exposures?
- Environmental
 - Lifestyle
 - Occupational



Role of lifestyle factors

- Established risk factors
 - Obesity
 - Diabetes
 - Diet
 - Habits
 - NSAIDS/ASA
 - IBD
 - Possible risk factors
 - Antibiotics
 - Breastfeeding/C-section
 - Childhood obesity
 - Birthweight
 - Infectious agents
- Microbiome**



AGE OF INITIATION OF SCREENING

Canadian Task Force for Preventive Health	50 years of age – WEAK REC 60 years of age – STRONG REC
Canadian Association of Gastroenterology	50 years of age
US Preventive Services Task Force	50 years of age – ‘GRADE A’
US Multi-Society Task Force	50 years of age – STRONG REC
UK Bowel Cancer Screening Programme Standards	60 years of age

d test or
onoscopy



Pros and cons of starting screening at age 45?

Potential Intended Consequences:

- ↓ CRC in 45-49 y.o.
- ↓ CRC in high risk minority groups
- ↑ Screening in >50 y.o.



Potential Unintended Consequences:

- Diversion of resources to ↓ risk groups
- ↑ Screening disparities
- Substantial cost
- Real benefits may fall short
- Lost research opportunity



Potential Favorable Intended Consequences

Possible PRO: ↓ CRC in 45 to 49 year olds

Outcomes per 1000 40-year-olds

Modality and Age to Start/Age to End/Interval, Years	No. of Stool Tests	No. of SIGs	No. of CTCs	No. of COLs	LYG	Complications	CRC Deaths Averted ^a	ER ^b	ER < Benchmark ^c	LYG ≥ 90% of Benchmark	Model-Recommended Strategy ^d
COL											
COL 45/75/10 ^e	0	0	0	5646	429	23	37	32	-	-	Yes
Stool tests											
FIT 45/75/3	8038	0	0	1619	310	11	27	5	Yes	No	
FIT 45/75/2	10,973	0	0	1994	352	13	30	9	Yes	No	
HSgFOBT 45/75/3	7405	0	0	2024	310	13	27	Dominated	-	No	
FIT-DNA 45/75/5	4949	0	0	2157	333	14	29	Dominated	-	No	
HSgFOBT 45/75/2	9776	0	0	2516	354	15	30	Dominated	-	No	
FIT-DNA 45/75/3	6644	0	0	2640	376	16	32	Dominated	-	No	
FIT 45/75/1	17,835	0	0	2698	403	16	34	14	Yes	Yes	Yes
HSgFOBT 45/75/1	14,366	0	0	3364	403	18	34	Dominated	-	Yes	
FIT-DNA 45/75/1	12,019	0	0	3851	426	19	36	50	No	Yes	
Flexible sigmoidoscopy											
SIG 45/75/10	0	2691	0	3314	373	19	33	9	Yes	No	
SIG 45/75/5	0	3865	0	3761	403	20	35	15	Yes	Yes	Yes
CT colonography											
CTC 45/75/10	0	0	3045	2106	322	14	29	6	Yes	No	
CTC 45/75/5	0	0	4630	2666	390	16	34	8	Yes	Yes	Yes

Abbreviations: COL, colonoscopy; CRC, colorectal cancer; CTC, computed tomographic colonography; ER, efficiency ratio; FIT, fecal immunochemical test; FIT-DNA, multitarget stool DNA test; HSgFOBT, high-sensitivity guaiac-based fecal occult blood test; LYG, life-years gained; SIG, flexible sigmoidoscopy.

^a In the absence of screening, the model predicted 45 deaths from CRC.

^b Calculated as $\frac{\text{incremental colonoscopies w-r previous efficient strategy}}{\text{incremental LYG w-r previous efficient strategy}}$. It is an incremental burden-to-benefits ratio.

^c A strategy can only be recommended by the model if it has an ER lower than the ER of the benchmark strategy (COL every 10 years from ages 45 to 75 years).

^d A strategy is recommended by the model if it is an efficient strategy (i.e., the LYG compared with the benchmark strategy (COL screening every 10 years from ages 45 to 75 years)).

^e This strategy was selected by the model when an ER threshold was reached.

Peterse et al, Cancer 2018;124:2964-73



Possible PRO: ↓ CRC in 45 to 49 year olds

Outcomes per 1000 40-year-olds

Model (test/start/stop/int)	No. stool tests	No. COL	Δ No. COL	LYG	Δ LYG
COL, 45/75/10	-	5646		429	
COL, 50/75/10	-	4836		404	
FIT, 45/75/1	17835	2698		403	
FIT, 45/75/2	10973	1994		352	
FIT, 50/75/2	8839	1762		325	

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Peterse et al, Cancer 2018;124:2964-73

the LYG compared with the benchmark strategy (COL screening



Possible PRO: ↓ CRC in 45 to 49 year olds

Outcomes per 1000 40-year-olds

Model (test/start/stop/int)	No. stool tests	No. COL	Δ No. COL	LYG	Δ LYG
COL, 45/75/10	-	5646	+810	429	+25
COL, 50/75/10	-	4836	-	404	-
FIT, 45/75/1	17835	2698		403	
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FIT, 45/75/1	17835	2698	+936	403	+78
FIT, 45/75/2	10973	1994		352	
FIT, 50/75/2	8839	1762	-	325	-

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- Early detection of CRC in 45 to 49 y.o.
- Prevention of CRC in 50-60 y.o.
- Realize societal benefits of early detection (>life years, productivity)

sensitivity guaiac-based fecal occult blood test; LYG, life-years gained; SIG, flexible sigmoidoscopy.

^a In the absence of screening, the model predicted 45 deaths from CRC.

^b Calculated as $\frac{\text{incremental colonoscopies w-r previous efficient strategy}}{\text{incremental LYG w-r previous efficient strategy}}$. It is an incremental burden-to-benefits ratio.

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Peterse et al, Cancer 2018;124:2964-73





Other possible PROs

↓ CRC in high risk minority groups

- Less is known about assn btw early onset CRC and race/ethnicity in Canada

↑ Screening in >50 y.o



Potential Unfavorable Unintended Consequences



Possible CONs: Substantial cost

(per 1000)

Strategy (test/start/stop/int)	No. stool tests	CRC averted	CRC death averted	Δ No. COL	Cost/QAL Y
COL, 45/75/10 vs COL, 50/75/10	-	4	2	758	\$33,900
FIT, 45/75/1 vs FIT, 50/75/1	3242	4	1	267	\$7700



Possible CONs: Shifting resources to ↓ risk groups

Table 1. Age-adjusted incidence rates (per 100 000 persons) of colorectal cancer in 2009–2013 vs 1984–1988 by 10-year age group*

Age group, y	Incidence rate, 1984–1988	Incidence rate, 2009–2013	Relative change, %	Absolute difference
20–29	0.8	1.8	+125.0	+1.0 per 100 000
30–39	4.5	7.1	+57.8	+2.6 per 100 000
40–49	19.4	23.6	+21.6	+4.2 per 100 000
50–59	73.5	61.2	–16.7	–12.3 per 100 000
60–69	188.9	104.1	–44.9	–84.8 per 100 000
70–79	356.3	190.2	–46.6	–166.1 per 100 000

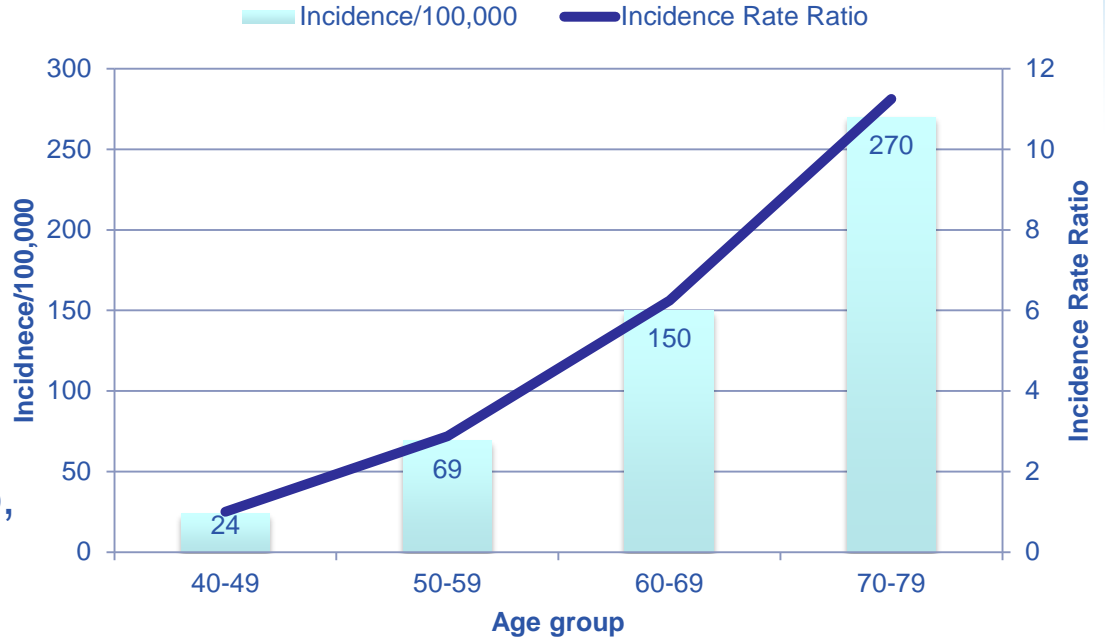
*Age-adjusted incidence, calculated using the 2000 US standard population, was obtained by using SEER*Stat version 8.3.2, Surveillance, Epidemiology, and End Results 9 registries, 1973–2013 (3).



Possible CONs: Shifting resources to ↓ risk groups

48-68%

'Up-to-date' any CR test, 50-74 yo, Canada, 2014



Absolute incidence by age, Canada, 2013-15

Possible CONs: Shifting resources to ↓ risk groups

	Scenario 1: start screening colonoscopy every 10 years at age 45 instead of 50 years	Scenario 2: provide screening colonoscopy every 10 years to currently unscreened 55-year-olds	Scenario 3: provide screening colonoscopy every 10 years to currently unscreened 65-year-olds	Scenario 4: increase follow-up colonoscopy completion rate after abnormal FIT result from 60% to 90% in cohort currently participating in annual FIT ^a
Cohort size, n	1000	231	342	3935 ^b
Incremental number of colonoscopies required over a lifetime, n	758	758	758	758
CRC cases averted, n	4	13	14	22
CRC deaths averted, n	2	6	7	10
Absolute gain in QALYs (discounted)	14	28	27	36
Absolute incremental cost (discounted) ^c	\$486,500	(\$163,700)	(\$445,800)	(\$843,900)



Other possible CONs:

- May increase CRC screening disparities
 - Fundamental causes theory
- Real benefits may fall short
 - Model assumptions/interpretation, effectiveness (age, biology)
- Lost opportunity to study screening in <50 y.o.
 - Best screening strategy (which test, risk scores?)





So what do we do **NOW?**

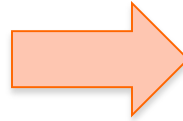
- **Investigate symptoms** in those <50 y.o. promptly
- **Public health strategies** to reduce established risk factors
- **Research** to better understand pathogenesis and best approach to screening



So what do we do **IN THE FUTURE?**

2010

- 5% of colon ca
- 10% of rectal ca



2030

- 11% of colon ca
- 23% of rectal ca

CRCs in US <50 y.o., US



So what do we do **IN THE FUTURE?**

- Burgeoning health problem
- Likely, ‘start age’ of 45 will come in time
- Not ‘all comers’ – use of risk scores
- Not with colonoscopy





Thank you

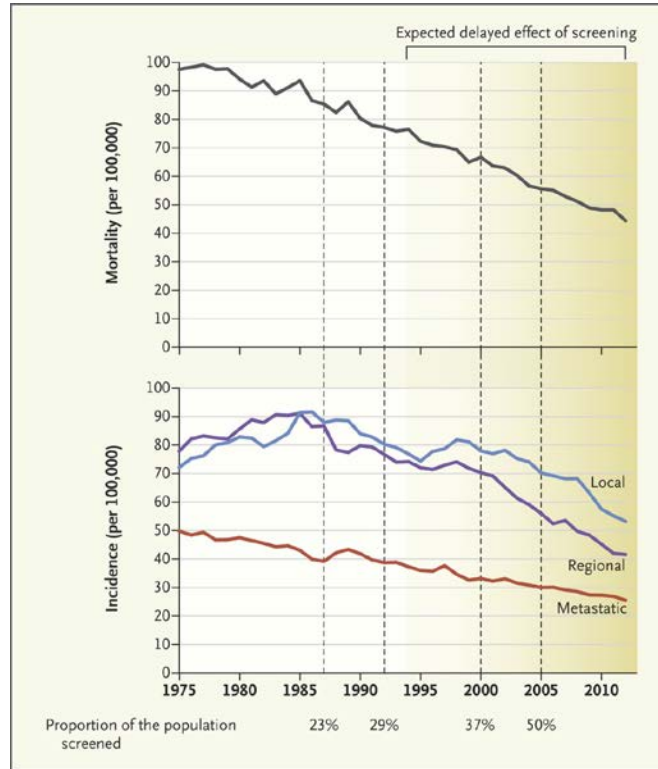


Extra slides



Role of CRC screening?

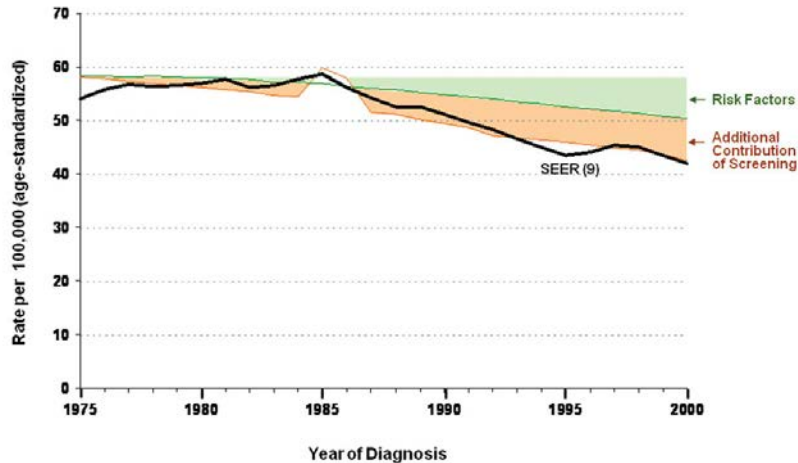
CRC Mortality and Stage-Specific Incidence among People 50 Years of Age or Older in the United States, 1975–2012



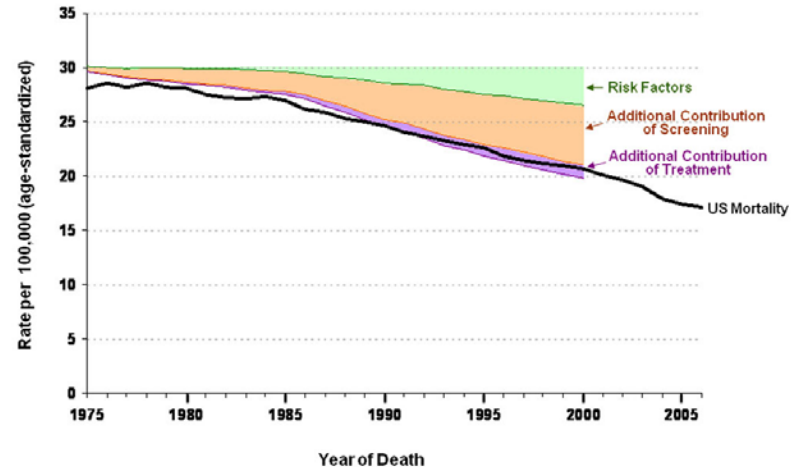


Role of other factors

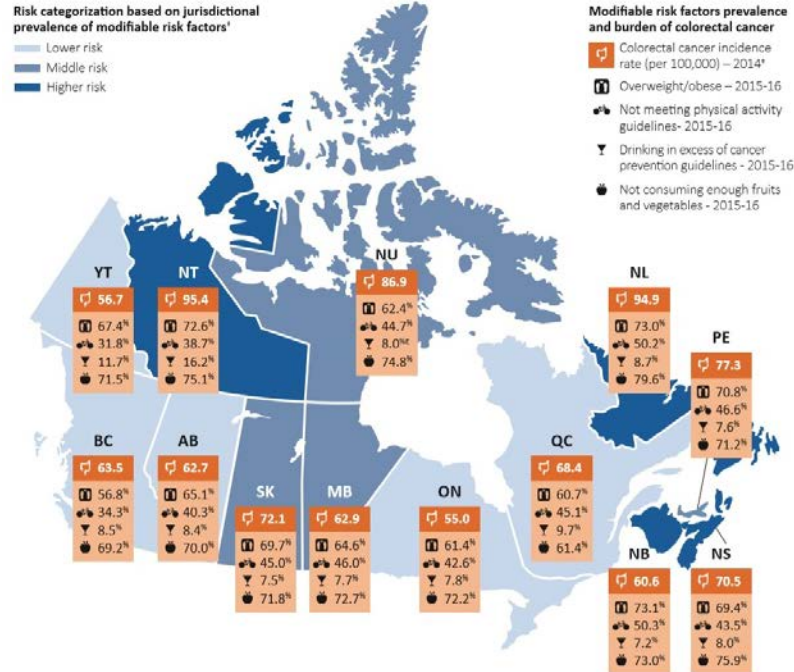
CRC Incidence, US 1975-2000



CRC Mortality, US 1975-2000



Canadian CRC Incidence – All Ages, 2014



Possible PRO: ↓ CRC in 45 to 49 year olds

Outcomes per 1000 40-year-olds

Model (test/start/stop/int)	No. stool tests	No. COL	Δ No. COL	LYG	Δ LYG
COL, 45/75/10	-	5646	+2948	429	+26
COL, 50/75/10	-	4836		404	
FIT, 45/75/1	17835	2698	-	403	-
FIT, 45/75/2	10973	1994		352	
FIT, 50/75/2	8839	1762		325	

^c A strategy can only be recommended by the model if it has an EN lower than the EN of the benchmark strategy (COL every 10 years from ages 45 to 75 years).

^d A strategy is recommended by the model if it is an efficient choice every 10 years from ages 45 to 75 years).

^e This strategy was selected by the model when an ER threshold

Peterse et al, Cancer 2018;124:2964-73

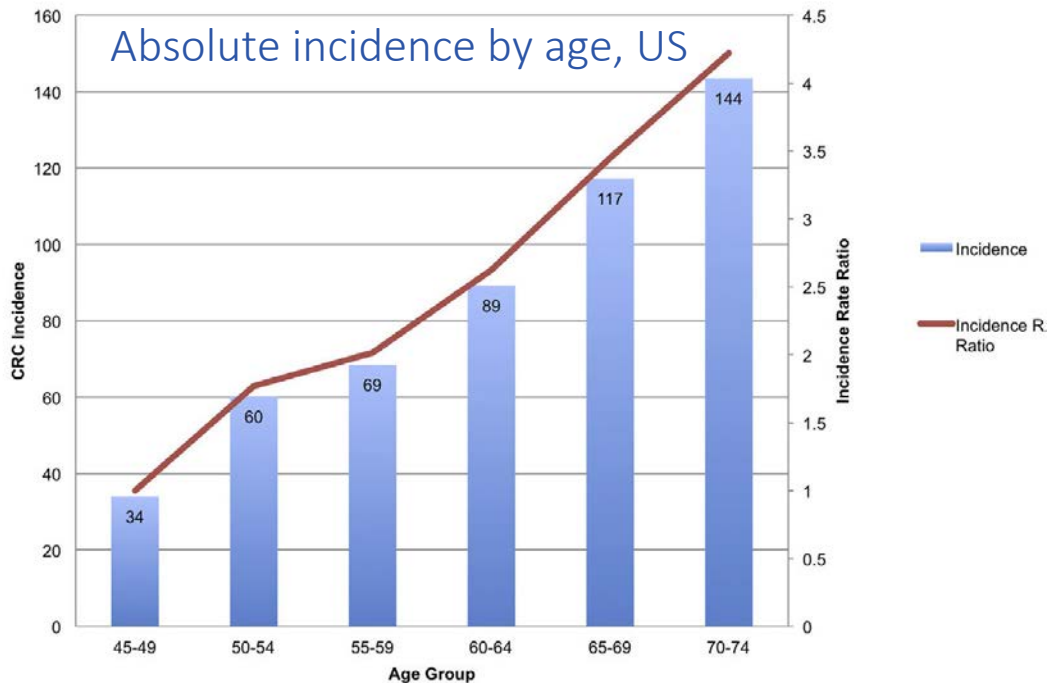
the LYG compared with the benchmark strategy (COL screening



Possible CONs: Shifting resources to ↓ risk groups

48-68%

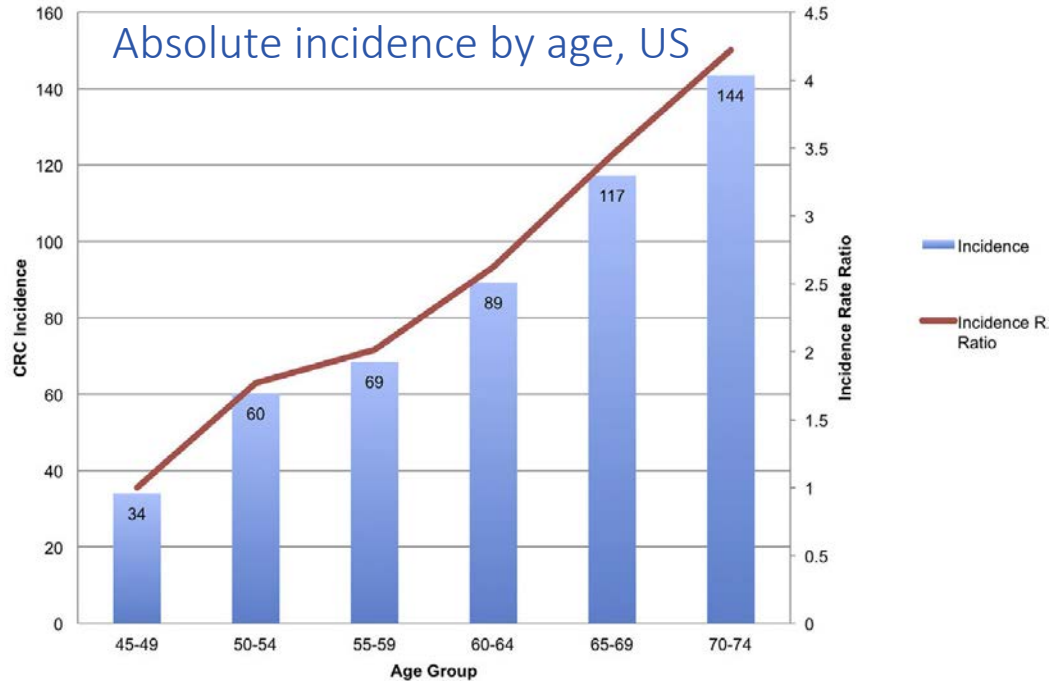
'Up-to'date' any test, 50-74 yo,
Canada, 2014



Possible CONs: Shifting resources to ↓ risk groups

63-83%

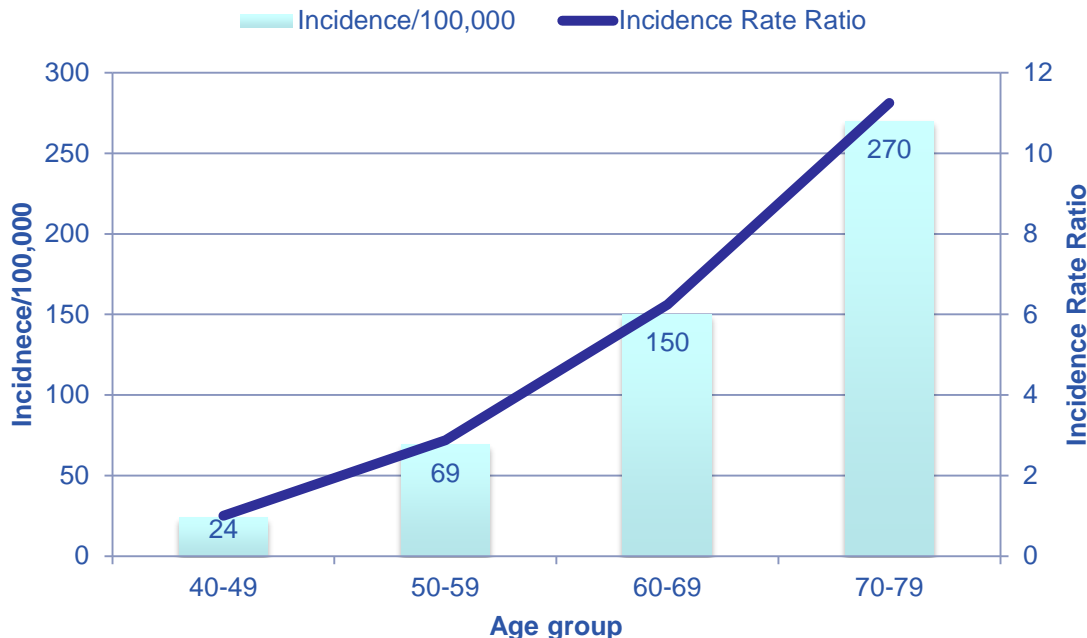
F/U after abnormal fecal test,
Canada, 2013-4



Possible CONs: Shifting resources to ↓ risk groups

63-83%

F/U after abnormal fecal test,
Canada, 2013-4



Absolute incidence by age, Canada, 2013-15



Possible CONS: May ↑ disparities in CRC screening

- **The fundamental causes theory:** Those w/ lower SES are less likely to benefit from new health interventions than those more knowledge and money
- Simply put, higher SES 45 y.o. are those most likely to be screened
- In a resource constrained environment, may lead to fewer low SES 50+ y.o. being screened