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Age at Initiation of Lower Gastrointestinal Endoscopy and Colorectal Cancer Risk Among US Women

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IMPORTANCE In the past 4 years, the American Cancer Society and the US Preventive Services Task Force updated recommendations to initiate colorectal cancer (CRC) screening at 45 years of age to address the increasing incidence of CRC among adults younger than 50 years. However, empirical evidence evaluating the potential benefits of screening in younger populations is scant.

OBJECTIVE To examine the association between endoscopy initiation at different ages and risk of CRC among US women.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study used data from the Nurses' Health Study II, which included US female health professionals followed up from 1991 through 2017. Data analysis was performed from August 2020 to June 2021.

EXPOSURE Age at initiation of sigmoidoscopy or colonoscopy for screening (routine screening or because of family history) or symptoms.

MAIN OUTCOMES AND MEASURES Incident CRC, confirmed by medical records, pathology reports, and the National Death Index. Cumulative incidence of CRC in each group was estimated with age as the time scale, and the absolute risk reduction associated with endoscopy initiation at different ages through 60 years was calculated. Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% CIs, stratified by age and calendar year of questionnaire cycle and adjusted for CRC risk factors in the multivariable models.

RESULTS Among 111 801 women aged 26 to 46 years (median, 36 years) at enrollment, 519 incident CRC cases were documented over 26 years, encompassing 2 509 358 person-years of follow-up. In the multivariable analysis, compared with no endoscopy, undergoing endoscopy was associated with a significantly lower risk of incident CRC for age at initiation before 45 years (HR, 0.37; 95% CI, 0.26-0.53), 45 to 49 years (HR, 0.43; 95% CI, 0.29-0.62), 50 to 54 years (HR, 0.47; 95% CI, 0.35-0.62), and 55 years or older (HR, 0.46; 95% CI, 0.30-0.69). The absolute reduction in the estimated cumulative incidence of CRC through 60 years of age was 72 per 100 000 persons for initiation of endoscopy at 45 to 49 years of age vs 50 to 54 years of age. Compared with no endoscopy, initiation of endoscopy before 50 years of age was also associated with a reduced risk of CRC diagnosed before 55 years of age (<45 years: HR, 0.45 [95% CI, 0.29-0.70]; 45-49 years: HR, 0.43 [95% CI, 0.24-0.76]).

CONCLUSIONS AND RELEVANCE In this cohort study, compared with no endoscopy, initiation of endoscopy before 50 years of age was associated with a reduced risk of CRC, including CRC diagnosed before 55 years of age. Screening before 50 years of age was associated with greater absolute reduction in CRC risk compared with initiation of CRC screening at 50 years of age or later.

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Supplemental content

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Colorectal cancer (CRC) is associated with significant morbidity and mortality in the US. Among all cancers, it has the third highest incidence and is the third greatest cause of death in both men and women.[1] Although the overall incidence of CRC has decreased in recent decades, there has been a steady increase among individuals younger than 50 years,[2] a group of people for whom routine screening was not recommended. In the past 4 years, the American Cancer Society[3] and the US Preventive Services Task Force[4] recommended lowering the age for screening initiation to 45 years for individuals at average risk. This recommendation was based on benefits vs burden estimated by comparative modeling approaches using microsimulation models of CRC screening in a hypothetical cohort of 40-year-old US individuals.[5,6] Recommended screening strategies include stool-based tests and endoscopic screening methods, the latter of which represent important strategies for CRC prevention by removal of precancerous lesions that could later become malignant or detection of early-stage cancers that can be more effectively treated. Evidence from randomized clinical trials and prospective cohort studies has shown that endoscopic screening can reduce the incidence of and mortality from CRC.[7-9] However, limited empirical data are available regarding the effectiveness of endoscopic screening in younger populations.

Thus, to evaluate the associations between endoscopy initiated at different ages and CRC risk, we conducted a prospective cohort study of lower gastrointestinal endoscopy among women enrolled in the Nurses' Health Study II beginning in 1991 who were followed up for subsequent risk of CRC through 2017. Because participants were aged 26 to 46 years at enrollment, this cohort provided a unique opportunity to examine the association of age at initiation of endoscopic screening with risk according to family history of CRC as well as potential benefits according to subsite and stage of the disease. We also estimated the absolute risk reduction associated with endoscopy initiated at different ages.

Key Points

Question Is initiation of lower gastrointestinal endoscopy before 50 years of age associated with a reduction in the risk of colorectal cancer among US women?

Findings In this cohort study of 111 801 US women, compared with no endoscopy, initiation of endoscopy before 50 years of age was associated with reduced risk of colorectal cancer and specifically colorectal cancer diagnosed before 55 years of age. Initiation of endoscopy from 45 to 49 years of age was associated with a greater reduction in the absolute risk of colorectal cancer through 60 years of age compared with initiation from 50 to 54 years of age.

Meaning These findings support guidelines recommending initiation of colorectal cancer screening before 50 years of age among women.

Methods

Study Population

This prospective cohort study included 111 801 women from the Nurses' Health Study II, a large cohort of registered nurses residing in 14 US states.[10] In brief, in 1989, 116 429 female nurses aged 24 to 44 years who completed a baseline questionnaire were enrolled; every 2 years, participants returned mailed questionnaires providing information on demographics, medical history, and lifestyle factors, with a follow-up rate greater than 85% of available person-time. We used the return of the 1991 questionnaires as our baseline, when we first queried information about endoscopy. After exclusion of participants with a history of cancer (except for nonmelanoma skin cancer, n = 360), inflammatory bowel disease (n = 1214), and colorectal polyps (n = 14); those who died (n = 34); those with missing information on age (n = 17) or major lifestyle factors (n = 348); and those with information on endoscopy missing from all the questionnaires so that the age at initiation of endoscopy could not be determined (n = 2641), a total of 111 801 women were included in our analysis. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital, Harvard T.H. Chan School of Public Health, and participating registries as required. Return of the questionnaires was considered to imply written informed consent. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Assessment of Lower Gastrointestinal Endoscopy

Details of endoscopy assessment and confirmation are provided in the eMethods in the Supplement. From 1991 through 2015, participants were asked whether they had undergone either sigmoidoscopy or colonoscopy in the past 2 years and, if so, the reason for the examination (eg, routine screening, family history of CRC, or symptoms). Endoscopic and pathologic reports were reviewed for participants who reported polypectomy.

Ascertainment of CRC and Death

A diagnosis of CRC was confirmed with the use of medical records and pathology reports. We also identified unreported, fatal CRC cases through family members or the postal system or sought information from the National Death Index, tumor registries, and death certificates (details included in the eMethods in the Supplement). The primary cause of death was assigned according to *International Classification of Diseases, Ninth Revision* codes (153-154 for death from CRC).

Statistical Analysis

Data analysis was performed from August 2020 to June 2021. Details of the statistical analysis are included in the eMethods in the Supplement. We defined the age at initiation of endoscopy based on responses from biennial questionnaires and categorized it into 5 groups (no endoscopy, <45 years, 45-49 years, 50-54 years, and ≥55 years). We updated this as a time-varying variable to account for changes during follow-up (ie, a person contributed person-time to the no endoscopy group before the time of first endoscopy and then switched to the corresponding age group according to the age at the time of first endoscopy).

Our primary end point was overall CRC incidence. We included incidence of younger-onset CRC (CRC diagnosed before 55 years of age) and CRC mortality as secondary outcomes. Consistent with a prior study from our group,[9] to

minimize the influence of endoscopies performed for the diagnostic evaluation of CRC, we examined endoscopy before the diagnosis of CRC, death from any cause, or the end of follow-up in 2017, whichever came first.[11] In sensitivity analysis, we allowed further delay by adopting 2-year lagged exposure. We used Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% CIs, stratified by age in years and calendar year of the questionnaire cycle and adjusted for CRC risk factors in the multivariable models.

To examine the absolute benefit of initiation of endoscopy at different ages, we estimated multivariable-adjusted cumulative incidence of CRC in each group with age as the time scale. We applied the effect of endoscopy after the participants reached the corresponding age. We then assessed the absolute risk reduction from 33 (the lowest age in this analysis) through 60 years of age associated with endoscopy initiation by calculating the difference of mean estimated cumulative incidence in the no endoscopy group vs the endoscopy group.

We conducted a priori subgroup analyses and examined whether the associations between age at endoscopy initiation and risk of incident CRC differed according to the indication for endoscopy, findings on endoscopy, updated age during follow-up, and family history of CRC. We examined tumor subsite- and stage-specific associations by fitting a cause-specific Cox proportional hazards regression model using a duplication method.[12,13]

Statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc). All *P* values were 2-sided, and $P < .05$ was considered statistically significant.

Results

A total of 111 801 women aged 26 to 46 years (median, 36 years) at enrollment were included in the study, encompassing 2 509 358 person-years of follow-up. We present characteristics of participants throughout the study period according to age at initiation of endoscopy in **Table 1** (characteristics of the group aged 55 years [the median age in the endoscopy group] are shown in eTable 1 in the Supplement). Compared with

Table 1. Characteristics of Participants According to Age at Initiation of Lower Gastrointestinal Endoscopy in Nurses' Health Study II[a]

Characteristic	No endoscopy	Age at initiation of endoscopy, y			
		<45	45-49	50-54	≥55
Person-years	1 611 054	273 207	169 773	336 210	119 114
Age, mean (SD), y[b]	43.7 (7.3)	49.6 (7.3)	54.7 (5.2)	57.2 (4.1)	61.5 (3.4)
Race and ethnicity, %					
Asian	1.6	1.0	1.4	1.6	1.7
Hispanic	1.6	1.7	1.3	1.3	1.6
Non-Hispanic African American	1.5	1.6	1.5	1.7	1.9
Non-Hispanic White	92.1	92.1	92.3	92.5	91.8
Other[c]	3.2	3.6	3.5	2.9	3.0
Family history of CRC, %	9.2	22.3	23.0	11.4	9.8
Median family income, mean (SD), $	79 680 (31 481)	81 720 (32 286)	83 428 (26 215)	84 223 (21 579)	79 653 (15 758)
Body mass index, mean (SD)[d]	25.7 (5.7)	26.0 (5.8)	26.4 (4.6)	26.1 (3.6)	26.7 (2.8)
Menopausal hormone use, %					
Premenopausal	62.9	60.3	39.5	21.4	3.2
Postmenopausal, never hormone user	17.3	15.0	24.7	36.0	42.4
Postmenopausal, past hormone user	9.6	10.6	17.0	23.2	34.0
Postmenopausal, current hormone user	10.2	14.1	18.8	19.4	20.4
Alcohol, mean (SD), g/d	3.6 (6.3)	3.6 (6.0)	4.2 (5.2)	4.7 (4.5)	4.6 (3.5)
Physical activity, mean (SD), MET-h/wk	21.9 (24.0)	22.4 (24.2)	20.9 (16.8)	21.8 (13.5)	20.5 (10.1)
Past smoker, %	25.9	26.7	30.1	30.3	33.0
Current smoker, %	9.8	8.4	6.3	5.0	5.9
Multivitamin use, %	48.5	48.7	51.0	53.4	50.5
Aspirin use, %	21.0	23.0	29.5	34.3	39.3
Other NSAID use, %	40.1	43.7	45.8	46.2	45.1
Hypertension, %	20.0	24.8	32.8	35.9	43.6
Diabetes, %	4.1	5.8	7.3	7.3	10.0
Hypercholesterolemia, %	30.4	39.9	48.3	52.7	59.1
Myocardial infarction, %	0.6	0.8	1.1	0.9	1.4
Cancer, %	2.3	3.3	5.1	5.2	5.9
Total energy intake, mean (SD), kcal/d	1803 (485)	1830 (489)	1815 (373)	1801 (304)	1786 (236)
Calcium intake, mean (SD), mg/d	1110 (412)	1151 (433)	1214 (344)	1282 (282)	1265 (222)
Folate intake, mean (SD), μg/d	528 (233)	551 (236)	575 (173)	601 (139)	594 (109)
Red and processed meat intake, mean (SD), serving/d	0.9 (0.6)	0.9 (0.6)	0.9 (0.4)	0.9 (0.3)	0.9 (0.3)

Abbreviations: CRC, colorectal cancer; MET, metabolic equivalent; NSAID, nonsteroidal anti-inflammatory drug.

[a] Values were updated during follow-up and standardized to the distribution of age groups of the study population with the exception of age.

[b] According to our definition of age at initiation of endoscopy, a person contributed person-time to the no endoscopy group before the time of endoscopy initiation and then switched to the corresponding age group according to the age at the time of endoscopy initiation. Thus, the no endoscopy group includes person-time before the initiation of endoscopy.

[c] Detailed categorization was not available.

[d] Calculated as weight in kilograms divided by height in meters squared.

women who initiated endoscopy at 50 years of age or later, women who initiated endoscopy before 45 years of age or from 45 to 49 years of age were more likely to have a family history of CRC and lower prevalence of hypertension, hypercholesterolemia, diabetes, and cancer. Substantially higher percentages of endoscopies were performed because of symptoms rather than family history or routine reasons for endoscopies initiated before 50 years of age compared with 50 years of age or later (**Figure 1**).

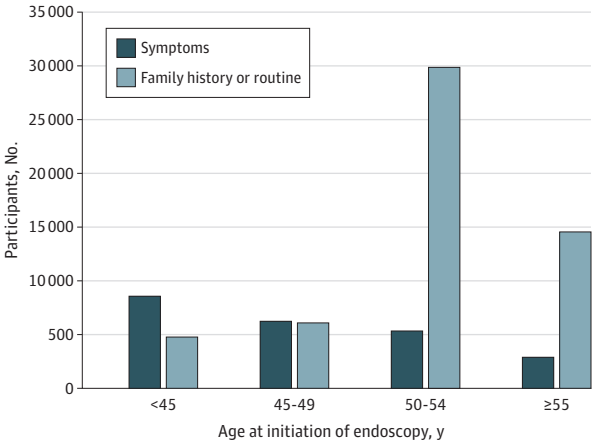
We documented 519 incident CRC cases. Compared with no endoscopy, initiation of a lower gastrointestinal endoscopy was associated with a significantly lower risk of incident CRC in models with adjustment for age, family history, and lifestyle risk factors for CRC (**Table 2**). Compared with the no endoscopy group, the multivariable HRs for CRC risk according to age at endoscopy initiation were 0.37 (95% CI, 0.26-0.53) before 45 years, 0.43 (95% CI, 0.29-0.62) for 45 to 49 years, 0.47 (95% CI, 0.35-0.62) for 50 to 54 years, and 0.46 (95% CI, 0.30-0.69) for 55 years or older.

We then estimated the multivariable-adjusted cumulative incidence of CRC and calculated the absolute risk reduction associated with each age group at endoscopy initiation (**Figure 2**). Compared with the no endoscopy group, the estimated reduction in incident CRC cases per 100 000 persons from 33 through 60 years was 435 (64%) among those who initiated screening before 45 years of age, 356 (52%) for initiation from 45 to 49 years of age, 284 (41%) for initiation from 50 to 54 years of age, and 153 (22%) for initiation at 55 years or older. This translated to a reduction in the cumulative incidence of CRC of 72 per 100 000 persons through 60 years of age for endoscopy initiation at 45 to 49 years of age vs 50 to 54 years of age.

We documented 299 younger-onset CRC cases. Initiation of endoscopy was associated with a lower risk of CRC diagnosed before 55 years of age. Compared with the no endoscopy group, the multivariable HRs were 0.45 (95% CI, 0.29-0.70) for initiation before 45 years of age, 0.43 (95% CI, 0.24-0.76) for 45 to 49 years of age, and 0.50 (95% CI, 0.27-0.92) for 50 to 54 years of age.

In stratified analyses, the associations of endoscopy initiation before 50 years of age and at 50 years of age or later with CRC incidence did not significantly differ according to current age or family history of CRC (**Figure 3**A). For example, initiation of endoscopy before 50 years of age was associated with a risk reduction of 63% (95% CI, 48%-73%) among participants without a family history of CRC and a risk reduction of 50% (95% CI, 13%-71%) among those with a family history of CRC (P = .34 for interaction). When stratified according to anatomic subsites, initiation of endoscopy, regardless of age, was associated with risk of developing distal colon cancer and rectal cancer but not with risk of proximal colon cancer (Figure 3B). The multivariable HRs for incident CRC among participants who initiated endoscopy before 50 years of age compared with no endoscopy were 0.58 (95% CI, 0.33-1.02) for proximal colon cancer, 0.13 (95% CI, 0.05-0.33) for distal colon cancer, and 0.35 (95% CI, 0.20-0.60) for rectal cancer (P = .01 for heterogeneity). The HRs for the associations of initiation of endoscopy before 50 of age and at 50 years or later with CRC incidence were similar across TNM stages of the disease.

Figure 1. Age at Initiation of Lower Gastrointestinal Endoscopy According to Indication



Data are from participants who reported at least 1 endoscopy from 1991 to 2015 in the Nurses' Health Study II (N = 78 305).

We documented a total of 89 CRC-related deaths during follow-up. Initiation of endoscopy for screening at 50 years of age or later was associated with a reduction in the risk of CRC mortality, but there was no association between endoscopy initiation before 50 years of age and risk of mortality (eTable 2 in the Supplement). Compared with no endoscopy, the multivariable HRs for CRC mortality were 0.59 (95% CI, 0.28-1.28) for endoscopy initiated before 50 years of age and 0.42 (95% CI, 0.23-0.78) for endoscopy initiated at 50 years of age or later. The association between endoscopy initiated at 50 years of age or later and reduced risk of mortality remained after further adjustment for comorbidities.

We found that initiation of endoscopy before 50 years of age was associated with lower incidence of CRC and younger-onset CRC in sensitivity analysis with 2-year lagged exposure (eTable 3 in the Supplement). The associations between initiation of endoscopy and CRC were similar regardless of the reported indication for the procedure (eTable 4 in the Supplement). For example, compared with no endoscopy, the HRs for incident CRC were 0.40 (95% CI, 0.27-0.58) for initiation of endoscopy for screening reasons (family history or routine) and 0.39 (95% CI, 0.27-0.55) for initiation because of symptoms before 50 years of age. In analyses according to findings on endoscopy, we observed a reduction in CRC risk associated with normal findings on sigmoidoscopy or colonoscopy initiated both before 50 years of age and at 50 years of age or later (eTable 5 in the Supplement).

Discussion

In this large, prospective cohort study of US women, we found that initiation of endoscopy before 50 years of age was associated with reduced risk of CRC, including CRC diagnosed before 55 years of age. This inverse association was observed primarily for distal colon cancer. Furthermore, we demonstrated that earlier initiation of endoscopy was associated with

Table 2. Age at Initiation of Lower Gastrointestinal Endoscopy and Risk of Colorectal Cancer[a]

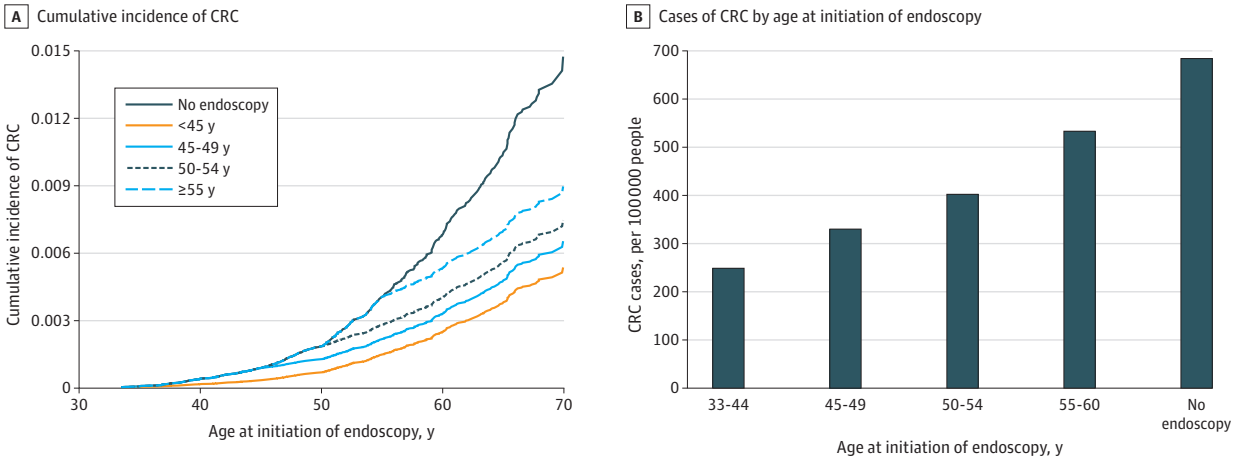
		Age at initiation of endoscopy, y			
	No endoscopy	<45	45-49	50-54	≥55
Any colorectal cancer					
Cases, No.	335	36	35	78	35
Person-years, No.	1 611 054	273 207	169 773	336 210	119 114
Age-adjusted HR (95% CI)	1 [Reference]	0.40 (0.28-0.57)	0.46 (0.32-0.66)	0.46 (0.34-0.61)	0.45 (0.30-0.68)
Multivariable-adjusted HR (95% CI)	1 [Reference]	0.37 (0.26-0.53)	0.43 (0.29-0.62)	0.47 (0.35-0.62)	0.46 (0.30-0.69)
Onset of colorectal cancer before 55 y of age[b]					
Cases, No.	249	24	13	13	NA
Person-years, No.	1 522 656	215 833	103 173	137 733	NA
Age-adjusted HR (95% CI)	1 [Reference]	0.51 (0.33-0.78)	0.47 (0.26-0.83)	0.49 (0.27-0.89)	NA
Multivariable-adjusted HR (95% CI)	1 [Reference]	0.45 (0.29-0.70)	0.43 (0.24-0.76)	0.50 (0.27-0.92)	NA

Abbreviations: HR, hazard ratio; MET, metabolic equivalent; NA, not applicable.

[a] Cox proportional hazards regression models were stratified by age (years) and questionnaire cycle, and multivariable models were further adjusted for family history of colorectal cancer (yes or no), menopausal status and hormone use (premenopausal, postmenopausal [never hormone use, current hormone use, and past hormone use]), smoking (never, past, and current smoker), aspirin use (yes or no), other nonsteroidal anti-inflammatory drug use (yes or no), multivitamin use (yes or no), body mass index (calculated as weight in kilograms divided by height in meters squared), physical activity (MET-h per week), alcohol consumption (grams per day), and intakes of total calories (kilocalories per day), calcium (milligrams per day), folate (micrograms per day), or red and processed meat (servings per day) (all continuously).

[b] Participants were censored at 55 years of age.

Figure 2. Estimated Cumulative Incidence of Colorectal Cancer (CRC)

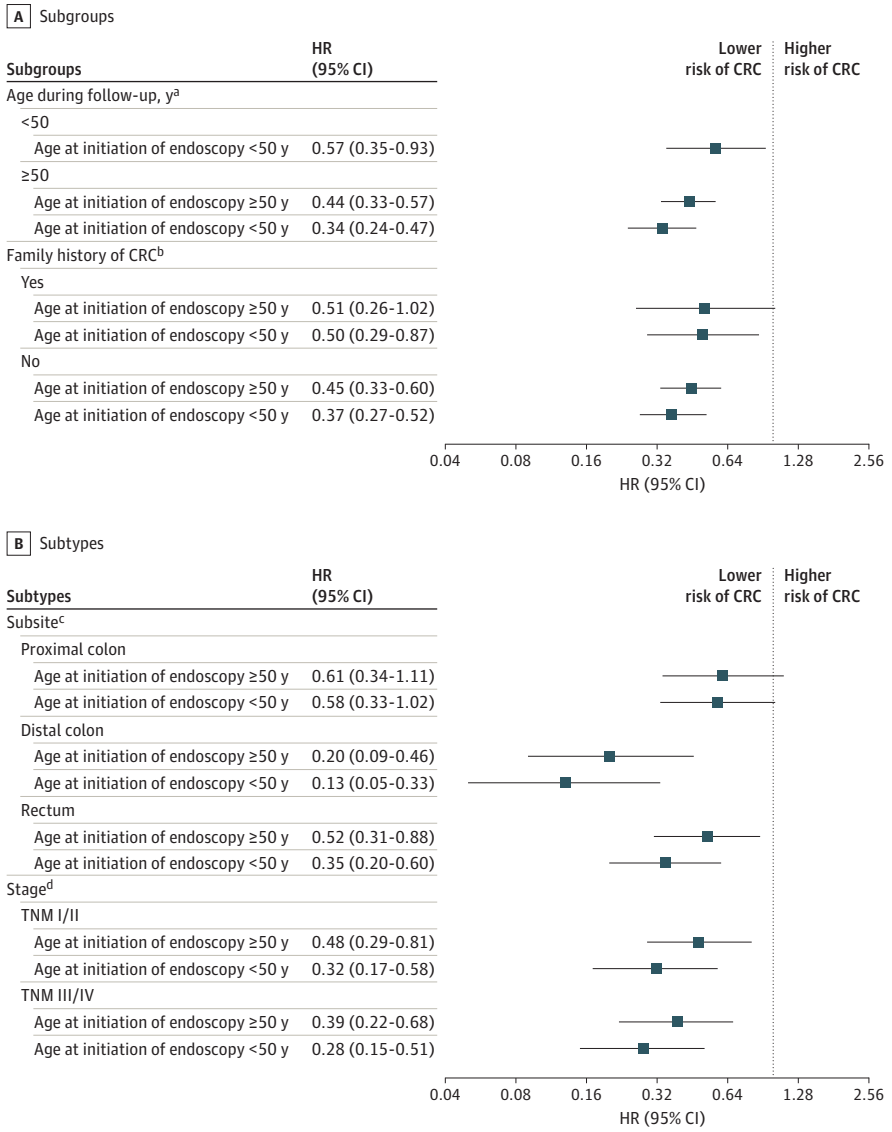


Cox proportional hazards regression models were applied to estimate cumulative incidence associated with each age group at initiation of endoscopy, with adjustment for family history of CRC, menopausal status and hormone use, body mass index, physical activity, smoking, alcohol consumption, aspirin use, other nonsteroidal anti-inflammatory drug use, multivitamin use, and intake of total calories, calcium, folate, or red and processed meat.

a greater reduction in the absolute risk of CRC compared with initiation at later ages. There was no association between initiation of endoscopy before 50 years of age and risk of CRC mortality. Our study suggests a benefit of initiation of endoscopy before 50 years of age for decreasing CRC risk.

Epidemiologic data showed a 51% increase in CRC incidence among individuals younger than 50 years from 1974 to 2013.[14] In 2018, the American Cancer Society provided a qualified recommendation for starting screening for adults who are at average risk at 45 years of age rather than 50 years of age.[3] This recommendation was based on a comparative modeling study using the Microsimulation Screening Analysis-Colon model that suggested that initiating colonoscopy screening at 45 years of age and repeating screening every 10 years yielded the lowest burden to benefit ratio (efficiency ratio; 32) and 25 (6.2%) more life-years gained per 1000 persons screened compared with initiating screening at 50 years of age.[5] Recently, the US Preventive Services Task Force also updated their recommendation of initiating regular CRC screening at 45 years of age based on updated modeling using 3 microsimulation models.[4,6] However, there have been few empirical data regarding the effectiveness of screening in younger individuals. A recent retrospective cohort study using Florida's statewide linkage database showed that colonoscopy at 45 to 49 years of age was associated with a reduction in CRC risk of 50% and colonoscopy at 50 to 54 years of age was associated with

Figure 3. Age at Initiation of Lower Gastrointestinal Endoscopy and Risk of Colorectal Cancer (CRC)



Cox proportional hazards regression models were stratified by age and questionnaire cycle and adjusted for family history of CRC, menopausal status and hormone use, body mass index, physical activity, smoking, alcohol consumption, aspirin use, other nonsteroidal anti-inflammatory drug use, multivitamin use, and intake of total calories, calcium, folate, or red and processed meat. No endoscopy was the reference category. A, *P* for interaction was calculated using a likelihood ratio test by comparing the model with main effects of the exposure and the factor and a cross-product term of the 2 to a model with only main effects of the exposure and the factor. B, *P* for heterogeneity was calculated using a likelihood ratio test by comparing the model in which the association with exposure was allowed to vary by subtype to a model in which all associations were held constant. Markers indicate hazard ratios (HRs), with horizontal lines indicating 95% CIs.

[a] *P* = .07 for interaction.

[b] *P* = .34 for interaction.

[c] *P* = .01 for heterogeneity for age at initiation before 50 years of age; *P* = .06 for heterogeneity for age at initiation at 50 years of age or later.

[d] *P* = .76 for heterogeneity for age at initiation before 50 years of age; *P* = .59 for heterogeneity for age at initiation at 50 years of age or later.

a reduction in CRC risk of 68%.[15] However, that study did not evaluate site- and stage-specific CRC incidence or CRC mortality, nor did it account for CRC risk factors. Moreover, absolute benefits of endoscopic screening before 50 years of age have not been evaluated. Our study adds to the evidence base by providing novel data regarding potential absolute benefits of endoscopy initiation at 45 to 49 years of age compared with initiation at 50 to 54 years of age and a more comprehensive assessment of location and stage of CRC and CRC mortality. Given the challenge of conducting randomized clinical trials of endoscopic screening with sufficient follow-up, our data contribute to addressing this evidence gap.

The effectiveness of endoscopy at younger ages might be associated with the baseline risk of colorectal neoplasia or the natural history of the disease. Compared with late-onset CRC, younger-onset cancers tend to have distinct clinical features, more advanced stage at diagnosis, and poorer overall survival rates; a larger proportion of the increase in CRC among individuals younger than 50 years has been shown to be attributable to distal colon and rectal cancer compared with colon cancer.[16,17] However, a study suggested that the cut point at 50 years of age might be arbitrary in a biological sense because the prevalence of tumor LINE-1 hypomethylation in CRC gradually increased with decreasing age at diagnosis without demarcation at 50 years of age.[18]

Although some studies[19-21] have suggested that lifestyle factors, such as a Western diet, and obesity may be associated with the increase in younger-onset CRC, the etiopathogenesis remains largely unknown.[22] In our study, endoscopy initiation before 50 years of age was similarly associated with lower risk of CRC compared with initiation after 50 years of age in relative scale, but greater absolute risk reduction may be achieved if endoscopy were initiated earlier. Moreover, initiation of endoscopy before 50 years of age was associated with

reduced risk of primarily distal colon cancer. These results suggest that initiating screening before 50 years of age may be associated with reduced incidence of CRC, particularly younger-onset CRC, which may have a more substantial public health impact because morbidity and premature death at a younger age are associated with substantially greater loss of high-quality life-years and productivity.[23] We found that endoscopy initiation before 50 years of age was not associated with risk of CRC mortality. However, the power for the mortality analysis was limited because of the small number of deaths from CRC in this younger cohort.

Although earlier initiation of CRC screening was associated with reduced risk of incident CRC compared with no endoscopy, unfavorable or unintended consequences need to be considered.[23] The current screening uptake and colonoscopy follow-up with abnormal stool test findings are suboptimal for individuals aged 50 to 75 years in certain racial and ethnic groups, uninsured individuals, or individuals with lower socioeconomic status.[24,25] Thus, a universal recommendation of screening initiation at 45 years of age may divert resources to low-risk, younger populations and away from high-risk, older populations. In addition, the benefits associated with earlier initiation of endoscopy have to be balanced against considerations of adverse events (eg, perforation, bleeding), more invasive follow-up tests, and potential overdiagnosis. However, the rates of complications are expected to be lower in younger populations.[26] Finally, lowering the screening age from 50 to 45 years may be associated with substantially increased costs.[5] From a societal perspective, the incremental benefit of earlier initiation of CRC screening must be considered alongside the cost and other health care needs of the population.

Strengths and Limitations

This study has several strengths. First, the biennial prospective collection of endoscopy data over 2 decades of follow-up allowed us to capture changes in endoscopy status throughout adulthood and assess the associations of endoscopy initiation at different ages with subsequent risk, both relative and absolute, of incident CRC and CRC mortality. Second, as indicated in our validation studies, the accuracy of the classification according to endoscopy status was high because all participants were health care professionals. Third, the prospectively and repeatedly collected detailed information on lifestyle factors reduced the potential for confounding and recall bias.

This study also has limitations. As with other observational studies, we cannot eliminate the possibility of residual or unmeasured confounding. However, our estimates for the benefit of endoscopic screening after 50 years of age are consistent with results from prior studies,[15,27,28] supporting the validity of our methods. Of note, because of the inherent lag between endoscopy status and CRC diagnosis based on information from biennial questionnaires, we were not able to accurately identify screening-detected CRC as done in randomized clinical trials of screening. Thus, our results should be interpreted as the long-term association of endoscopy with CRC incidence and mortality. The power for mortality analysis was limited, and we were not able to provide definite estimates for lifetime absolute risk reduction. Moreover, our cohort included only women and mostly White health care professionals, and studies in other populations are needed considering potential gender differences and racial and ethnic disparities in risk of CRC. In addition, we focused on initiation of endoscopy without accounting for surveillance colonoscopies, which were beyond the scope of the study and are worth further investigation. Additional studies are also needed to examine the potential impact of initiating screening at an earlier age with noninvasive modalities, such as fecal immunochemical testing or fecal DNA tests, which were not assessed in our cohort questionnaires.

Conclusions

Using repeatedly collected information on endoscopy and disease over 26 years in a large, prospective cohort of women, we found that compared with no endoscopy, initiation of endoscopy before 50 years of age was associated with a reduced risk of CRC, including CRC diagnosed before 55 years of age and primarily of the distal colon. Earlier initiation of endoscopy was associated with a greater absolute risk reduction of CRC compared with initiation at later ages. Our findings support guidelines from the past 4 years that recommend screening for CRC at 45 years of age and provide empirical evidence for patients, physicians, and policy makers to consider when making decisions about CRC screening in a younger population.

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