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Iron deficiency and symptoms in women aged 20–49 years and relation to upper gastrointestinal and colon cancers

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ABSTRACT

Objective Iron deficiency anaemia (IDA) in women aged 20–49 years may be caused by menses or gastrointestinal cancer. Data are sparse on the yield of endoscopy/colonoscopy in this population. Our aim was to determine the association of IDA and symptoms with cancers.

Design Retrospective cohort study within Kaiser Permanente Northern California. Participants were women aged 20–49 years tested for iron stores and anaemia during 1998, 2004 and 2010 and followed for 5 years for outcomes of oesophageal, gastric and colon cancers. Symptoms from the three prior years were grouped into dysphagia, upper gastrointestinal (UGI), lower gastrointestinal (LGI), rectal bleeding and weight loss.

Results Among 9783 anaemic women aged 20–49 years, there were no oesophageal, 6 gastric and 26 colon cancers. Incidences per 1000 for gastric cancer with and without iron deficiency (ID) were 0.60 (95% CI 0.23 to 1.55) and 0.63 (95% CI 0.17 to 2.31), and for colon cancer, 2.72 (95% CI 1.72 to 4.29) and 2.53 (95% CI 1.29 to 4.99). Endoscopies for UGI or dysphagia symptoms rather than bidirectional endoscopy for ID yielded more gastric cancers (n=5 and n=4, respectively) with fewer procedures (3793 instead of 6627). Colonoscopies for LGI or rectal bleed instead of for ID would detect more colon cancers (n=19 and n=18) with about 40% of the procedures (=2793/6627).

Conclusions UGI and colon cancers were rare in women of menstruating age and when controlled for anaemia were as common without as with ID. Using symptoms rather than IDA as an indication for endoscopy found equal numbers of cancers with fewer procedures.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Iron deficiency anaemia can be caused by gastrointestinal cancer, but in women of menstruating age, it is most commonly caused by menses. Professional organisations disagree whether their rate of cancer is sufficient to warrant endoscopic gastrointestinal examination irrespective of symptoms.

WHAT THIS STUDY ADDS

⇒ In anaemic women aged 20–49 years, gastrointestinal cancers were as common with iron deficiency as in those without iron deficiency. Performing endoscopies or colonoscopies for symptoms found more cancers with fewer procedures than performing endoscopy and colonoscopy in all those with iron deficiency.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that in anaemic women aged 20–49 years, the decision to perform UGI endoscopy or colonoscopy should be dictated by symptoms and not by iron deficiency.

INTRODUCTION

Iron deficiency anaemia (IDA) in adults in the developed world is commonly caused by bleeding in the gastrointestinal (GI) tract, with the most feared cause being cancer. The finding of IDA thus commonly leads to referral for endoscopic examination of the upper gastrointestinal (UGI) and lower gastrointestinal (LGI) tracts. In women of menstruating age, IDA is more commonly caused by blood loss with menses, occurring in 5%–15.7% of US women aged 20–49 years.[1 2] This raises the question of whether these women should be offered endoscopy, given that GI cancers occasionally occur in this age group. Most studies of the incidence of malignancy in this population are small and performed in those referred for endoscopy, with case series ranging in size from 19 to 187 women.[3–10] A recent Veterans Administration study was large and population based but did not examine the role of symptoms.[11] Data are even more scarce in those with iron deficiency (ID) without anaemia.[12] In order to examine the inter-relation of ID, anaemia and symptoms on the incidence of major GI cancers in women of menstruating age, we undertook a retrospective cohort study.

METHODS

We identified women between the ages of 20 and 49 years who had test results for ID and anaemia within Kaiser Permanente Northern California (KPNC) electronic health records (EHRs). The Kaiser population is

representative of the overall Northern California population.[13] Additional selection criteria included: (1) continuous membership in the study entry (or index) year; (2) continuous membership for 36 months preceding the index year without any endoscopic procedures in that time; and (3) 36 or more active membership months in 4 years following the index year or until an eligible cancer was diagnosed. Exclusion criteria included prior hysterectomy or diagnosis of gastrointestinal cancer or inflammatory bowel disease (IBD) and childbirth in index or preceding year. Entry years were 6 years apart, 1998, 2004 and 2010, with 1995 the first year for which a complete electronic data set was available. Each woman could be a study subject of one entry year only. The study entry (index) date was defined as the first date within a study year that tests for ID were done.

ID was defined as ferritin less than the lower limits of normal (LLN; 10–22 µg/L during this period). In those without available ferritins, we used total iron binding capacity greater than upper limits of normal (428 µg/dL), which has a higher correlation with ferritin than does iron saturation.[12 13] Anaemia was defined as the LLN in our laboratories, haemoglobin <11.5 g/dL or haematocrit <34%, obtained during the year prior to the study entry date. When multiple tests were found, the test closest to the index date was used.

Women with anaemia were the primary cohort, and those without anaemia were a secondary cohort. Each cohort was further divided into: (1) ID versus no ID and (2) had endoscopy versus no endoscopy. We use 'endoscopy' in this study as a generic term encompassing any UGI endoscopy or colonoscopy performed within 1 year after the index date.

Outcomes

Primary outcomes included oesophageal cancers, gastric cancers and colon cancers within 5 years of the study entry date and were compiled from the KPNC Cancer Registry, with diagnosis confirmed by review of pathology records. Small carcinoids (<1 cm) were excluded as their biological behaviour is usually benign. We included two secondary outcomes: (1) we analysed findings in those undergoing endoscopy within 1 year of study entry date in order to examine biases introduced by selection for early endoscopy. (2) We examined the rates of selected non-cancer causes of IDA, acknowledging that their diagnosis is imperfect without endoscopy. The included causes were oesophagitis, ulcers or IBD, compiled from International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

Comorbidities and symptoms

Comorbidities and symptoms in the 3 years preceding the index date were identified using ICD-9-CM codes. Comorbidities of interest included diabetes mellitus, kidney disease, cardiovascular disease, pulmonary disease, menorrhagia and cirrhosis. Charlson Comorbidity Index score was calculated using EHR records from this time period. Symptoms were grouped into five categories: (1) UGI symptoms, (2) dysphagia, (3) lower GI symptoms, (4) rectal bleeding and (5) weight loss (online supplemental etable 1).

Patient demographics

Age at study entry date was calculated as a continuous variable and further grouped into 20–29, 30–39 and 40–49 years. Race/ethnicity included Hispanic/Latino, non-Hispanic white, non-Hispanic black, Asian/Pacific Islanders and other.

Statistical analysis

Distributions of demographics and clinical characteristics were calculated and expressed as frequencies (%) or mean (±SD) as appropriate. The incidence (per 1000 patients) of each cancer or secondary outcome was calculated by age groups, including 95% CI, according to: (1) ID status, (2) undergoing endoscopy within 1 year of ID testing or (3) presence or absence of symptom groups. We calculated the number needed to detect (NND) a cancer as a proxy for the number of endoscopies needed to detect one cancer and used it to compare the outcomes of different criteria for performing endoscopy. Comparisons in bivariate analyses included χ^2 or Fisher's exact tests for categorical variables as appropriate and independent two-sample t-tests for continuous variables.

Multivariable logistic regression analyses were used to assess the risk of being ID and (1) having cancer and (2) undergoing endoscopy, each stratified by anaemia status and controlling for symptom groups, patient race/ethnicity, Charlson score and patient age by deciles. All analyses were performed using SAS V.9.4 (SAS Institute Inc, Cary, North Carolina, USA) with the threshold of significance set at two-sided $p<0.05$.

RESULTS

Findings in anaemic women

Demographics

A total of 32 440 women were tested for ID, of whom 9783 were anaemic (primary cohort), 22 657 were not anaemic (secondary cohort) and 942 had unknown status. The demographic and clinical characteristics of the anaemic cohort are shown in table 1. Women with ID were more likely to be Hispanic and less likely to be black and had a lower Charlson score and more menorrhagia than non-ID anaemic women. Those who underwent endoscopy were more likely to be ID, older, white and had higher Charlson score and more symptoms.

Cancers

Thirty-two cancers were identified in anaemic women after we excluded one carcinoid less than 1 cm. There were no oesophageal, 6 gastric and 26 colon cancers.

Table 1 Demographic and clinical characteristics in women aged 20–49 years with anaemia who were tested for iron deficiency

Characteristics	Entire cohort n=9783 (100)	Iron deficiency n (%)		Had endoscopy* n (%)	
		Yes (n=6627)	No (n=3156)	Yes (n=653)	No (n=9130)
Iron deficiency	7919 (65.5)	–	–	527 (80.70%)	6100 (66.81%)
Had endoscopy*	1036 (8.6)	527 (7.95)	126 (3.99)	–	–
Age groups (year)					
20–29	648 (5.4)	379 (5.72)	269 (8.52)	15 (2.30)	633 (6.93)
30–39	2591 (21.4)	1656 (24.99)	935 (29.63)	118 (18.07)	2473 (27.09)
40–49	6544 (54.2)	4592 (69.29)	1952 (61.85)	520 (79.63)	6024 (65.98)
Age (year), mean±SD	43.1±7.3				
Charlson comorbidity index score		0.5±0.9	0.9±1.4	0.9±1.5	0.6±1.1
Mean±SD	0.7±1.2	2134 (32.2)	1367 (43.31)	282 (43.19)	3219 (35.26)
≥1	4568 (37.8)	379 (5.72)	269 (8.52)	15 (2.30)	633 (6.93)
Race/ethnicity					
White	3686 (30.5)	1886 (28.46)	865 (27.41)	228 (34.92)	2523 (27.63)
Black	2397 (19.8)	1178 (17.78)	793 (25.13)	95 (14.55)	1876 (20.55)
Hispanic	2480 (7.8)	1660 (25.05)	466 (14.77)	164 (25.11)	1962 (21.49)
Asian	2574 (21.3)	1417 (21.38)	754 (23.89)	114 (17.46)	2057 (22.53)
Other†	947 (7.8)	486 (7.33)	278 (8.81)	52 (796)	712 (7.80)
Any comorbidity	3292 (27.2)	1661 (25.06)	826 (26.17)	172 (26.34)	2315 (25.36)
Diabetes mellitus	1304 (10.8)	548 (8.27)	376 (11.91)	72 (11.03)	852 (9.33)
Kidney disease	333 (2.8)	66 (1.00)	162 (5.13)	21 (3.22)	207 (2.27)
Cardiovascular disease	238 (2.0)	63 (0.95)	72 (2.28)	13 (1.99)	12 (1.34)
Pulmonary disease	330 (2.7)	140 (2.11)	115 (3.64)	17 (2.60)	238 (2.61)
Menorrhagia	1712 (14.2)	1059 (15.98)	286 (9.06)	87 (13.32)	1258 (13.78)
Cirrhosis	40 (0.3)	10 (0.15)	17 (0.54)	9 (1.38)	18 (0.20)
Any symptoms	6372 (52.7)	3411 (51.47)	1667 (52.82)	506 (77.49)	4572 (50.08)
UGI symptoms	4688 (38.8)	2504 (37.78)	1201 (38.05)	424 (64.93)	3281 (35.94)
Dysphagia	390 (3.2)	183 (2.76)	103 (3.26)	44 (6.74)	242 (2.65)
LGI symptoms	3060 (25.3)	1622 (24.48)	849 (26.90)	251 (38.44)	2220 (24.32)
Rectal bleed	710 (5.9)	402 (6.07)	175 (5.54)	82 (12.56)	495 (5.42)
Weight loss	291 (2.4)	135 (2.04)	85 (2.69)	28 (4.29)	192 (2.10)
Any gastric symptoms: UGI and/or dysphagia	3705 (37.9)	2504 (37.8)	1201 (38.1)	424 (64.9)	3281 (35.9)
Any colon symptoms: LGI and/or rectal bleed	2471 (25.3)	1622 (24.5)	849 (26.9)	251 (38.4)	2220 (24.3)
Endoscopy within 5 years of study entry	1498 (15.3)	1101 (16.6)	397 (12.6)	653 (100)	845 (9.3)

Data are column % unless otherwise stated.
–, not applicable.
*Defined as undergoing endoscopy within 1 year of the iron deficiency test date.
†Including American Indians, Alaskan Natives, more than one racial groups and unknown.
LGI, lower gastrointestinal; UGI, upper gastrointestinal.

Gastric cancers were rare in all age cohorts, whereas colon cancer incidences increased with age (table 2). The overall incidence of GI malignancy was 3.32 cases per 1000 for those with ID and 3.17 for those without ID. The incidence of gastric cancer was similar with and without ID (0.60 (95% CI 0.23 to 1.55) and 0.63 (95% CI 0.17 to 2.31), respectively, p>0.99) as was the incidence of colon cancer (2.72 (95% CI 1.72 to 4.29) and 2.53 (95% CI 1.29 to 4.99), respectively, p=0.81).

When we examined those who had endoscopy in the first year, there was also no difference in cancer incidence in those with and without ID (table 3).

Table 2 Unadjusted incidence of gastric and colon cancers in women who were iron deficient compared with those who were not iron deficient

	Iron deficient			Non-iron deficient			
	Sample size (n)	Cancer* (n)	Incidence/1000 patients (95% CI)	Sample size (n)	Cancer* (n)	Incidence/1000 patients (95% CI)	P value
Anaemic women (n=9783)							
Gastric cancer							
Age 20–49 years	6627	4	0.60 (0.23 to 1.55)	3156	2	0.63 (0.17 to 2.31)	>0.99
20–29	379	0	–	269	0	–	–
30–39	1656	3	1.81 (0.62 to 5.31)	935	0	–	0.56
40–49	4592	1	0.22 (0.04 to 1.23)	1952	2	1.02 (0.28 to 3.73)	0.21
Colon cancer							
Age 20–49 years	6627	18	2.72 (1.72 to 4.29)	3156	8	2.53 (1.29 to 4.99)	0.87
20–29	379	1	2.64 (0.47 to 14.79)	269	0	–	>0.99
30–39	1656	5	3.02 (1.29 to 7.05)	935	2	2.14 (0.59 to 7.77)	>0.99
40–49	4592	12	2.61 (1.50 to 4.56)	1952	6	3.07 (1.41 to 6.69)	0.74
Non-anaemic women (n=22 657)							
Gastric cancer							
Age 20–49 years	6979	0	–	15 678	3	0.19 (0.07 to 0.56)	0.56
20–29	1010	0	–	2122	0	–	–
30–39	2068	0	–	5076	0	–	–
40–49	3901	0	–	8480	3	0.35 (0.12 to 1.04)	0.56
Colon cancer							
Age 20–49 years	6979	16	2.29 (1.41 to 3.72)	15 678	12	0.77 (0.44 to 1.34)	0.003
20–29	1010	0	–	2122	0	–	–
30–39	2068	1	0.48 (0.09 to 2.73)	5076	1	0.20 (0.03 to 1.12)	0.50
40–49	3901	15	3.85 (2.33 to 6.33)	8480	11	1.30 (0.72 to 2.32)	0.01

Comparisons were made using Fisher's exact tests.
–, not applicable.
*Within 5 years of the iron deficiency test date.

Symptoms and cancer

Dysphagia was present in 286 women, but no oesophageal cancers were diagnosed. Gastric cancer had significant associations with UGI symptoms, dysphagia and weight loss. Colon cancer was associated with rectal bleeding and LGI and UGI symptoms. (table 4). Notably, ID was not associated with any primary outcome.

In multivariable modelling, the adjusted odds for gastric cancer were significantly increased with dysphagia (adjusted OR (aOR) 6.41, 95% CI 1.69 to 24.27) and weight loss (aOR 24.38, 95% CI 7.05 to 84.31), while the odds for colon cancer were increased with LGI (aOR 3.02, 95% CI 1.44 to 6.36) or UGI (aOR 2.49, 95% CI 1.15 to 5.39) symptoms and rectal bleeding (aOR 7.15, 95% CI 3.44 to 14.85) (online supplemental etable 2). Of note, ID did not increase the odds of either cancer.

Odds of endoscopy

The adjusted odds of receiving endoscopy decreased with younger age and Asian, black or Hispanic race/ethnicity (online supplemental etable 3). The odds increased with ID, any symptoms and higher Charlson score. On examining the interaction of symptoms and ID with receiving endoscopy, the ID women who received endoscopy had fewer LGI symptoms than did the non-ID women who received endoscopy (34.9% compared with 53.2%, p<0.001), but the UGI/dysphagia symptoms were equal in the two groups (online supplemental etable 4).

Optimal endoscopy strategies

The numbers of endoscopies needed to detect one cancer according to ID status and symptoms are presented in table 4. Endoscopy for ID had similar yield to endoscopy without ID. A strategy of UGI endoscopies performed only for UGI or dysphagia symptoms would yield more

Table 3 Unadjusted incidence of gastric and colon cancer in women who underwent endoscopy procedure within 1 year of testing for iron deficiency*

	Iron deficient			Non-iron deficient			
	Sample size (n)	Cancer† (n)	Incidence/1000 patients (95% CI)	Sample size (n)	Cancer† (n)	Incidence/1000 patients (95% CI)	P value
Anaemic women (n=653)							
Gastric cancer							
Age 20–49 years	527	1	1.90 (0.34 to 10.67)	126	1	7.94 (1.40 to 43.59)	0.35
20–29	11	0	–	4	0	–	–
30–39	82	1	12.20 (2.16 to 65.89)	36	0	–	>0.99
40–49	434	0	–	86	1	11.63 (2.06 to 62.96)	0.17
Colon cancer							
Age 20–49 years	527	8	15.18 (7.71 to 29.67)	126	2	15.87 (4.36 to 56.03)	>0.99
20–29	11	0	–	4	0	–	–
30–39	82	4	48.78 (19.13 to 118.80)	36	1	27.78 (4.92 to 141.70)	>0.99
40–49	434	4	9.22 (3.59 to 23.46)	86	1	11.63 (2.06 to 62.96)	>0.99
Non†anaemic women (n=939)							
Gastric cancer							
Age 20–49 years	388	0	–	551	0	–	–
20–29	33	0	–	47	0	–	–
30–39	75	0	–	132	0	–	–
40–49	280	0	–	372	0	–	–
Colon cancer							
Age 20–49 years	388	7	18.04 (8.77 to 36.77)	551	3	5.44 (1.85 to 15.88)	0.10
20–29	33	0	–	47	0	–	–
30–39	75	1	13.33 (2.36 to 71.73)	132	1	7.58 (1.34 to 41.66)	>0.99
40–49	280	6	21.43 (9.86 to 45.95)	372	2	5.38 (1.48 to 19.39)	0.08

–, not applicable.
*No comparisons were significant due to small event size.
†Within 5 years of the iron deficiency test date.

gastric cancers than using ID as a criterion (n=5 and n=4, respectively), with 57.2% (=3793/6627) the number of UGI endoscopies. Performing colonoscopies only for LGI or rectal bleed symptoms instead of for ID would yield more colon cancers (n=19 and n=18, respectively), with 42.1% (=2793/6627) the number of colonoscopies. A detailed summary of the NND according to symptom and age subgroups is available in online supplemental etable 5.

A key question is that of yield of endoscopy in women with IDA but without gastrointestinal symptoms. In those with IDA without dysphagia or UGI symptoms, no gastric cancers were found in 4064 women aged 20–49 years. In those with IDA but without LGI symptoms or rectal bleeding, four colon cancers were found in 4778 women for a rate of 0.84 per 1000, far less than the rate of 2.66 per 1000 in the entire cohort.

Non-cancer findings

The numbers of oesophagitis, ulcers and IBD diagnosed both clinically and endoscopically over the subsequent 5 years is shown in table 5, and the numbers diagnosed by endoscopy within the first year are shown in online supplemental etable 6. There was no increase in these diagnoses with ID; if anything, the trend was towards more findings in those without ID. Because oesophagitis and ulcers would be diagnosed by UGI endoscopy, we investigated whether this trend was because a higher percentage of non-ID underwent UGI endoscopy for UGI symptoms, but we found that the rate of UGI symptoms was similar in those with and without ID (online supplemental etable 4).

Findings in non-anaemic women

The demographics of the women tested for ID and without anaemia were similar to those with anaemia (online supplemental etable 7). Of note, those with ID had more menorrhagia, and those who underwent endoscopy had more symptoms and a higher Charlson score.

The overall findings were similar to those of anaemic patients, although with generally lower rates of cancer and therefore wider CIs (table 2). The presence or absence of ID made no difference in the incidence of cancers, with the exception of more colon cancers in

Table 4 Unadjusted incidence of gastric and colon cancers stratified by iron deficiency and symptoms in 9783 anaemic women aged 20–49 years

	Sample size (n)	Cancer* (n)	NND one cancer (95% CI)	Incidence/1000 patients (95% CI)	P value
Gastric cancer, age 20–49 years					
Random	9783	6	1631 (748 to 3558)	0.61 (0.28 to 1.34)	–
Iron deficiency					
(+)	6627	4	1657 (645 to 4260)	0.60 (0.23 to 1.55)	>0.99
(–)	3156	2	1578 (434 to 5754)	0.63 (0.17 to 2.31)	
Any symptoms					
Yes	5078	6	847 (389 to 1847)	1.18 (0.54 to 2.58)	0.03
No	4705	0	–	–	
UGI symptoms					
Yes	3705	5	741 (317 to 1735)	1.35 (0.58 to 3.16)	0.03
No	6078	1	6078 (1074 to 34,431)	0.16 (0.03 to 0.93)	
Dysphagia					
Yes	286	2	143 (40 to 521)	6.99 (1.92 to 25.10)	0.01
No	9497	4	2375 (924 to 6105)	0.42 (0.16 to 1.08)	
Weight loss					
Yes	220	3	74 (26 to 216)	13.6 (4.65 to 39.3)	<0.001
No	9563	3	3188 (1085 to 9373)	0.31 (0.11 to 0.92)	
Any gastric symptoms: UGI and/or dysphagia					
All women					
Yes	3793	5	759 (325 to 1776)	1.32 (0.56 to 3.08)	0.04
No	5990	1	5990 (1059 to 33,933)	0.17 (0.03 to 0.95)	
Iron deficient (+) women (*n=6627*)					
Yes	2563	4	641 (250 to 1648)	1.56 (0.61 to 4.01)	0.02
No	4064	0	–	–	
Iron deficient (–) women (*n=3156*)					
Yes	1230	1	1230 (218 to 6968)	0.81 (0.14 to 4.59)	>0.99
No	1926	1	1926 (341 to 10,910)	0.52 (0.09 to 2.94)	
Colon cancer, age 20–49 years					
Random	9783	26	377 (257 to 552)	2.66 (1.81 to 3.89)	–
Iron deficiency					
(+)	6627	18	369 (234 to 582)	2.72 (1.72 to 4.29)	>0.99
(–)	3156	8	395 (201 to 779)	2.53 (1.29 to 4.99)	
Any symptoms					
Yes	5078	21	242 (159 to 370)	4.14 (2.71 to 6.31)	0.003
No	4705	5	941 (403 to 2203)	1.28 (0.45 to 2.49)	
LGI symptoms					
Yes	2471	16	155 (96 to 251)	6.48 (3.99 to 10.50)	<0.001
No	7312	10	732 (398 to 1346)	1.37 (0.74 to 2.52)	
Rectal bleed					
Yes	577	10	58 (32 to 106)	17.30 (9.44 to 31.60)	<0.001
No	9206	16	576 (355 to 935)	1.74 (1.07 to 2.82)	
Weight loss					
Yes	220	1	220 (40 to 1246)	4.55 (0.80 to 25.30)	0.48
No	9563	25	383 (260 to 565)	2.61 (1.77 to 3.86)	

Continued

Table 4 Continued

	Sample size (n)	Cancer* (n)	NND one cancer (95% CI)	Incidence/1000 patients (95% CI)	P value
Any colon symptoms: LGI and/or rectal bleed					
All women					
Yes	2793	19	147 (95 to 230)	6.80 (4.36 to 10.60)	<0.001
No	6990	7	999 (485 to 2062)	1.00 (0.49 to 2.07)	
Iron deficient (+) women (*n=6627*)					
Yes	1849	14	133 (79 to 222)	7.57 (4.52 to 12.70)	<0.001
No	4778	4	1195 (465 to 3072)	0.84 (0.33 to 2.15)	
Iron deficient (–) women (*n=3156*)					
Yes	944	5	189 (82 to 442)	5.30 (2.26 to 12.30)	0.02
No	2212	3	738 (252 to 2168)	1.36 (0.46 to 3.98)	

Comparisons were made using Fisher's exact tests.
*Within 5 years of the iron deficiency test date.
(–), negative; (+), positive; –, not applicable; LGI, lower gastrointestinal; NND, number needed to detect; UGI, upper gastrointestinal.

women aged 40–49 years with ID, which in turn led to significance in the differences in the combined 20–49 cohort. This 40–49 ID cohort was a further anomaly as the only age bracket where the incidence of cancer was higher in non-anaemic women than in anaemic women. In the subgroup with endoscopy, ID made no difference in cancer incidence (table 3).

The associations with specified symptoms were of lower frequencies than in anaemic women but again using symptoms rather than ID as a guide to endoscopy found equivalent number of cancers with fewer endoscopies (online supplemental etables 8). Notably, in women without UGI or dysphagia symptoms, no gastric cancers were found in 4178 women with ID nor in 9511 without ID. In those without rectal bleed or LGI symptoms, six colon cancers were found in 4747 women with ID for a rate of 1.26 per 1000, about the same rate as colon cancer in a random woman (1.24 per 1000) and below the rate of 2.03 in those with symptoms regardless of ID status.

For non-cancer findings, again, there was no significant difference with or without ID In those without anaemia (table 5).

DISCUSSION

Our study found that in women aged 20–49 years who were tested for ID and had anaemia, the incidence of gastrointestinal cancers was low and was not affected by the presence or absence of ID. Our incidences are lower than in older studies most likely because those study cohorts were small and included only patients who received endoscopy. Those studies are therefore comparable with our cohort who had IDA and endoscopy within a year. For example, when we summed the rates in eight prior case series in women aged 20–49 years, 8 out of 818 women (0.98%) had gastric cancers and 14 of 600 (2.33%) had colon cancer.[3–10] In our study, the incidence in those who had IDA and early endoscopy was 0.19% and 1.52%, respectively. When we included the entire population who tested positive for IDA regardless of endoscopy, our incidence was lower, 0.06% for gastric cancers and 0.30% for colon cancers. By comparison, this is similar to the general female population incidence of acquiring gastric cancer (0.1%) and colon cancer (0.4%) between the ages of 20 and 49 years.[14]

In reviewing the risk factors for early endoscopy, we showed a selection bias in that those who receive endoscopy were more likely to be ID and to have symptoms. This is important because those with ID but without symptoms had a much lower rate of cancer, lower even than the rate of cancer in anaemic women randomly endoscoped.

This suggests that primary care doctors and gastroenterologists were selective in referring patients and in performing endoscopies even within the IDA group.

We are aware of two other population studies in the 20–49 age group. A 2-year follow-up of the 1971–1974 National Health and Nutrition Examination Survey found that none of the 92 premenopausal women with IDA were diagnosed with gastrointestinal malignancy, nor were 350 ID without anaemia.[15] Second, in 2020, a large Veterans Administration study was published examining the rate of colon cancer in those with IDA and age 18–49 years.[11] Their 5-year cumulative incidence in women aged 18–49 years was 0.11%, lower than in our study. Unlike our study, their controls were all those without IDA without requirement for iron testing nor stratifying by anaemia status, nor did they examine the role of symptoms.

In agreement with other studies and the American Gastroenterological Association (AGA) recommendations, we found that those with symptoms had a higher incidence of malignancy than those without symptoms.[3 4 16] Indeed, we found that a strategy of UGI endoscopy in those with UGI or dysphagia symptoms

Table 5 Unadjusted incidence of oesophagitis, ulcers and IBD in women who were iron deficient compared with those who were not iron deficient

	Iron deficient			Non-iron deficient			
	Sample size (n)	Pathology* (n)	Incidence/1000 patients (95% CI)	Sample size (n)	Pathology* (n)	Incidence/1000 patients (95% CI)	P value
Anaemic women (n=9783)							
Oesophagitis							
Age 20–49 years	6627	100	15.09 (12.42 to 18.32)	3156	66	20.91 (16.47 to 26.52)	0.04
20–29	379	6	15.83 (7.28 to 34.10)	269	2	7.43 (2.04 to 26.70)	0.48
30–39	1656	28	16.91 (11.72 to 24.33)	935	24	25.67 (17.31 to 37.91)	0.13
40–49	4592	66	14.37 (11.31 to 18.24)	1952	40	20.49 (15.08 to 27.78)	0.07
Ulcer							
Age 20–49 years	6627	59	8.90 (6.91 to 11.47)	3156	41	12.99 (9.59 to 17.58)	0.06
20–29	379	1	2.64 (0.47 to 14.79)	269	3	11.15 (3.80 to 32.27)	0.31
30–39	1656	10	6.04 (3.28 to 11.08)	935	6	6.42 (2.94 to 13.93)	0.90
40–49	4592	48	10.45 (7.89 to 13.83)	1952	32	16.39 (11.64 to 23.05)	0.045
IBD							
Age 20–49 years	6627	24	3.62 (2.43 to 5.38)	3156	14	4.44 (2.64 to 7.43)	0.54
20–29	379	1	2.64 (0.47 to 14.79)	269	1	3.72 (0.66 to 20.75)	>0.99
30–39	1656	5	3.02 (1.29 to 7.05)	935	4	4.28 (1.66 to 10.95)	0.73
40–49	4592	18	3.92 (2.48 to 6.19)	1952	9	4.61 (2.43 to 8.74)	0.69
Non-anaemic women (n=22 657)							
Oesophagitis							
Age 20–49 years	6979	82	11.75 (9.48 to 14.56)	15678	221	14.10 (12.37 to 16.06)	0.16
20–29	1010	6	5.94 (2.73 to 12.90)	2122	17	8.01 (5.01 to 12.79)	0.53
30–39	2068	22	10.64 (7.04 to 16.06)	5076	56	11.03 (8.51 to 14.30)	0.88
40–49	3901	54	13.84 (10.63 to 18.02)	8480	148	17.45 (14.88 to 20.47)	0.14
Ulcer							
Age 20–49 years	6979	58	8.31 (6.43 to 10.73)	15678	97	6.19 (5.07 to 7.54)	0.07
20–29	1010	3	2.97 (1.01 to 8.70)	2122	8	3.77 (1.91 to 7.42)	>0.99
30–39	2068	17	8.22 (5.14 to 13.13)	5076	26	5.12 (3.50 to 7.49)	0.12
40–49	3901	38	9.74 (7.11 to 13.34)	8480	63	7.43 (5.81 to 9.49)	0.18
IBD							
Age 20–49 years	6979	30	4.30 (3.01 to 6.13)	15678	65	4.15 (3.25 to 5.28)	0.87

Continued

Table 5 Continued

	Iron deficient			Non-iron deficient			
	Sample size (n)	Pathology* (n)	Incidence/1000 patients (95% CI)	Sample size (n)	Pathology* (n)	Incidence/1000 patients (95% CI)	P value
20–29	1010	0	–	2122	7	3.30 (1.60 to 6.79)	0.10
30–39	2068	6	2.90 (1.33 to 6.32)	5076	15	2.96 (1.79 to 4.87)	0.97
40–49	3901	24	6.15 (4.14 to 9.14)	8480	43	4.95 (3.67 to 6.69)	0.45

Comparisons were made using Fisher's exact tests.
–, not applicable.
*Within 5 years of the iron deficiency test date.
IBD, inflammatory bowel disease.

and colonoscopy for those with rectal bleeding or LGI symptoms was overall superior to one of endoscopy for IDA in terms of yield of cancers and number of endoscopies needed to detect them. This calls into question the usefulness of routine bidirectional ('flip') procedures for ID done in order to discover asymptomatic cancers in these age groups. In particular, gastric cancers without UGI symptoms were extremely rare in this age group. In women without gastric symptoms, no gastric cancers were found in 4064 ID women with anaemia or 4178 without anaemia. If confirmed in other studies, this low yield would call into question routine UGI endoscopy for asymptomatic women in these age groups with ID and suggests instead targeting endoscopies at those with symptoms. For colon cancers, performing colonoscopies in asymptomatic women with ID is no more productive than targeting a random woman tested for ID. Equivalent number of cancers were found with far fewer procedures by using symptoms instead of ID as an indication for colonoscopy.

Our paper focuses on cancers, but we included the rates of selected non-cancer findings in order to give a rough estimate for those findings and to acknowledge that these findings may also be important and may justify endoscopy. Unlike cancers, these may remain asymptomatic during the follow-up period and thus their diagnosis without UGI endoscopy is less reliable. We did find that in those who underwent endoscopy in the first year the rate of findings did not differ by ID status. We reviewed whether this equivalence was due to a confounding by indication, whereby in non-ID women, more endoscopies were performed for symptoms, but we found that they had the same rate of UGI symptoms as did those with ID. This suggests that it is not a given that young women with ID have more of these findings, indeed the trend in our study was in the opposite direction. Our findings are hypothesis generating, as it would take a separate and larger study to fully account for all the confounders and biases in looking at this issue, including the role of asymptomatic findings in this age group.

Our findings support the British Society of Gastroenterology 2021 recommendation that per se 'IDA in young women is not an indication for endoscopic investigation' and should be reserved for the presence of red flag symptoms, major genetic risk, or recurrent or refractory anaemia disproportionate to other causes, or absence of menses.[17] Our findings support the AGA technical review recommendation that in patient who have gastrointestinal symptoms, evaluation should be site directed rather than routine bidectional endoscopy.[16] Our paper does not support the 2020 AGA recommendation for bidirectional endoscopy over iron replacement for asymptomatic premenopausal women with IDA and agrees with its conclusion that the pooled evidence overestimates the incidence of cancer due to inclusion of symptomatic

women.[18] We also found that symptoms were a more efficient indication for endoscopy than ID, as ID in the absence of symptoms did not increase the risk of cancer in women with anaemia. Finally, a subsequent published correspondence with the authors of the guideline noted that the AGA guideline did not address ID without anaemia in large part due to a 'paucity of data'.[12 19] Our findings help address this deficit. Whether (fecal immunochemical test (FIT)) testing can be used to further stratify who in this age group should undergo endoscopy, as has been shown to be the case in older age groups, can be tested in future studies.[20]

Strengths

Our study avoids referral bias by including all patients diagnosed with ID, not just those referred for endoscopic examination, and ensured adequate follow-up by its inclusion criteria.

Our definition of ID included a ferritin LLN as that report label highlighted a value that would trigger attention and action. What levels to choose as a cut-off depends on the values attached to sensitivity versus specificity and on the presence of 'inflammatory diseases',[21] many of which are components of the Charlson score.[22] In women of childbearing age, who are generally healthy,[23] a level <15 µg/L is recommended by the WHO and has been shown to have a specificity of 98% and sensitivity of 75% for ID as defined by no stainable bone marrow iron.[23 24] Our level was close to this, and the low Charlson score in our patients is consistent with their being generally healthy.

Limitations

An inherent limitation of our study is that endoscopy is the method most used to diagnose gastric and colon cancers, raising the possibility of underdiagnosis in the group without early endoscopy. We addressed this by including all cancers diagnosed in the first 5 years, expecting that cancers large enough to cause ID would become apparent within 5 years. This is similar to assumptions in other studies although they used 2 years of follow-up.[15 25] To control for the possibility that de novo cancers in the years after diagnosis of ID attenuated the difference between ID and non-ID, we examined the differences in those with endoscopy within a year, but here too found no difference.

We relied on symptoms as coded by physicians and we cannot rule out that uncoded diagnoses exist, despite the fact that a high percentage of our study group had symptoms. The symptom of rectal bleeding or haematochezia deserves special attention in formulating algorithms in light of population studies showing that 15%–18% of the population has some rectal bleeding every year.[26 27] Thus, the specificity and workload will vary greatly depending on how that symptom is defined.

Our cohorts included only those tested for ID, which was necessary in order to derive a comparison group without ID. We do not address the risk of cancer in those not tested for ID nor do we address why patients were tested for ID, whether as a routine screen or as a targeted test. In this, we address the problem as faced by the gastroenterologist.

The number of outcome events was low in our study, with wide CIs, so the results must be interpreted with caution and confirmed by other studies. However, the rarity of outcome events in those with IDA is in itself an important finding and perhaps not unexpected by clinicians.[28] The even lower rate of findings in those with ID without anaemia can help guide decisions on whether endoscopy should be offered to these women given the controversy provoked by the AGA guidelines.

CONCLUSION

Our population-wide study found that UGI and colon cancers were rare in women of menstruating age and that when controlled for the presence of anaemia, they were not more common in those who were ID than in those who were not. We also found that in this age group, a symptom-based strategy detected more cancers with fewer procedures than did a strategy of endoscopy for those with ID.

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Contributors J-LS was responsible for initial conception and first draft, L-YT for initial data analysis, and both contributed to further design, analysis and interpretation of the data, critical revision of the article for important intellectual content, and both gave final approval of the article. J-LS is the guarantor of the overall content of this article.

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