Dig Dis Sci (2014) 59:2249–2254
DOI 10.1007/s10620-014-3131-5

ORIGINAL ARTICLE

Duodenal Adenomas Coincide with Colorectal Neoplasia

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Received: 19 December 2013 / Accepted: 22 March 2014 / Published online: 6 April 2014

Abstract
Background and Aim Small case series have alluded to an association between sporadic duodenal adenomas and colorectal neoplasia. The strength of the association remains uncertain. This case–control study was designed to test this association in a large national pathology database.
Methods This study, performed at Miraca Life Sciences, a specialized pathology laboratory that receives gastrointestinal biopsy specimens from outpatient centers throughout the US, included all subjects who underwent a bidirectional endoscopy with biopsy results from both procedures between January 2008 and December 2011. The association between duodenal and colonic neoplasms was investigated using odds ratios (OR) and their 95 % confidence intervals (CIs) derived from univariate and multivariate analyses.
Results There were 203,277 patients who underwent bidirectional procedures within the study period (mean age 58 years, 58 % females). Duodenal adenomas were present in 537 patients (median age 65 years, 51 % females; OR for male sex 1.34, 95 % CI 1.13–1.59). Hyperplastic colon polyps were present in 30,205 and colon adenomas in 85,801 patients. Hyperplastic polyps were more common in patients with duodenal adenomas (1.45, 1.07–1.95). Patients with duodenal adenomas also had a significantly greater prevalence of all types of colonic adenomas (2.65, 2.16–3.25), particularly of advanced adenomas (4.30, 3.24–5.70) and colorectal cancer (3.13, 1.38–7.12). Duodenal adenomas were associated with an equally increased risk for left and right colon adenomas.
Conclusions Patients with duodenal adenomas harbor an increased risk for any type of colonic neoplasm. This association may provide new insights into the general mechanisms underlying mucosal proliferation in the gastrointestinal tract.

Keywords Colon polyps · Colorectal cancer · Duodenal adenoma · Familial adenomatous polyposis

Abbreviations

CI	Confidence interval
DA	Duodenal adenoma
EGD	Esophago-gastro-duodenoscopy
HG	High-grade
OR	Odds ratio

Introduction

Duodenal adenomas are uncommon lesions with a reported prevalence of less than 0.4 % in patients undergoing esophago-gastro-duodenoscopy (EGD) [1, 2]. Although patients with hereditary conditions causing germ line mutations in the *APC* gene, as well as patients with MYH-associated polyposis (MAP), have an increased risk for

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Table 1 Previous studies involving patients with sporadic duodenal adenoma (DA) and evaluation of the colon

Authors and year	DA and colonoscopy	Any colon adenoma (%)	Advanced colon adenoma[a] (%)	Colon adenocarcinoma (%)	Control patients with colon adenoma[b] (%)
Seifert et al. [9]	7	4 (57)	n.a.	n.a.	n.a.
Apel et al. [10]	22	16 (73)	n.a.	1 (5)	n.a.
Murray et al. [11]	34	12 (35)	6 (18)	7 (21)	26/102 (25)
Ford et al. [12]	11	4 (36)	3 (27)	0	n.a.
Schneider et al. [8]	19	4 (21)	1 (5)	1 (5)	27/104 (26)
Pequin et al. [13]	35	11 (31)	8 (23)	2 (6)	17/70 (24)
Ramsoekh et al. [14]	49	17 (35)	9 (18)	4 (8)	21/147 (14)
Lagarde et al. [15]	29	15 (52)	4 (14)	3 (10)	11/58 (19)
Dariusz et al. [16]	48	31 (65)	n.a.	5 (10)	35/144 (24)
Abbass et al. [17]	17	9 (53)	n.a.	n.a.	n.a.
Gonzalez-Ortiz et al. [18]	21	9 (43)	4 (19)	n.a.	38/84 (45)

n.a. Not available

[a] Advanced adenoma defined in previous studies as size ≥10 mm, villous component, and/or high-grade dysplasia

[b] Age- and sex-matched controls

duodenal adenomas [3–7], most of these neoplasms are diagnosed in patients without a known polyposis syndrome; [8] in this clinical context, they are referred to as sporadic duodenal adenomas.

During the last two decades, several studies have suggested an association between sporadic duodenal adenoma and colonic adenomas (Table 1) [8–18]. However, the small size of the series, the different methodologies, and the diverse origin of the study patients and controls have prevented reaching a clear consensus on the strength of this association. According to the American Society of Gastrointestinal Endoscopy (ASGE), the recommendation to offer a colonoscopy to patients without known polyposis syndrome in whom a duodenal adenoma is detected is supported by a low level of evidence (2C) [19]. This study was designed to test the hypothesis that the analysis of a large nationwide population of patients who underwent EGD and colonoscopy would reveal a significant association between the occurrences of duodenal adenomas and colonic neoplasia even in the absence of familial adenomatous polyposis.

Materials and Methods

Study Setting and Data Source

This study was conducted at Miraca Life Sciences, a specialized pathology laboratory receiving specimens from gastroenterologists operating in private outpatient endoscopy and surgery centers throughout the USA, the District of Columbia, and Puerto Rico. Biopsy interpretation is performed using a standardized approach to specimen handling and diagnostic criteria. Uniformity among pathologists is maximized through a standardized approach to specimen handling and a pre-determined set of diagnostic criteria and terminology for biopsy reading. Consensus is maintained and updated through daily multi-headed microscope conferences, frequent didactic conferences, a journal club, a terminology review committee, and ongoing comprehensive quality assurance review. Internal diagnostic codes are assigned to each case at the time of diagnosis by the pathologist. Miraca Life Sciences maintains a database of all endoscopic procedures from which a specimen was submitted to the laboratory. For every patient, the following information is available: gender and age of the patient, brief clinical history with indication for procedure and procedural findings, procedure date and location, and histopathologic findings. The study was approved by the Miraca Life Sciences Institutional Review Board. All data of the study were collected exclusively by reviewing pre-existing records, and no direct contact with either patients or providers was made. No information from any individual patient was revealed, and all patient records were de-identified before being included in the present analysis. For these reasons, the study protocol was exempted from the need for informed consent from its participants.

Selection of Patients

The study included patients who had an EGD and a colonoscopy between January 1, 2008 and December 31, 2011. The three most common indications for EGD in declining order were reflux disease (46 %), abdominal pain (39 %), and dyspepsia (16 %). The three most common indications for colonoscopy in declining order were abdominal pain (31 %), diarrhea (28 %), and colorectal cancer screening (23 %). A total of 257 patients identified by their provider as carriers of one of the familial polyposis

syndromes were excluded. To identify patients with duodenal adenoma (with or without high-grade dysplasia) and duodenal adenocarcinoma, we used internal diagnostic codes and identified additional cases by free-text searches using Boolean logic. For patients who underwent more than one examination during the study period, we used the first chronological examination as the index event. For the colon, we used the following histopathologic categories: hyperplastic polyp, tubular adenoma, tubulovillous adenoma, villous adenoma, adenoma with high-grade dysplasia (tubular, tubulovillous, or villous), and colonic adenocarcinoma. Polyps were grouped by number as follows: 1–2, 3–4, 5–6, and 7+. Adenomas were grouped by size (as assessed by the endoscopist) as 0–9, 10–19, 20–29, and 30+ mm. Adenomatous polyps that were greater than 9 mm or contained high-grade dysplasia or villous architecture were also grouped as "advanced adenoma" [20]. Polyps were assigned to the left colon, if they were located anywhere between the rectum and descending colon; polyps were assigned to the right colon, if they were located anywhere between the splenic flexure and cecum.

Histopathologic Criteria and Slide Review

Adenomas arising from duodenal surface epithelium have a histologic appearance closely resembling adenomatous lesions of the colon; therefore, these lesions rarely present a diagnostic challenge to the pathologist. In our laboratory, duodenal adenomas are diagnosed when villous, tubular, or tubulovillous lesions with a spectrum of architectural and cytologic atypia corresponding to low- or high-grade dysplasia are present in specimens from the duodenum [21]. For the purpose of this study, we reviewed slides from all patients with a diagnosis of high-grade dysplasia or adenocarcinoma in duodenal adenomas; 10 % of the duodenal adenomas with low-grade dysplasia; and all cases with diagnoses that appeared ambiguous for any reason, including (but not limited to) cases designated as "suspicious for," "consistent with," and similar phrases. Cases in which technical limitations either due to sampling (small or fragmented biopsies) or processing (poor orientation, staining, or microtome artifacts) interfered with evaluation were not included in this series.

Statistical Analysis

The statistical analysis was carried out using Excel® or Access® (from Microsoft, Redmond, WA) and the statistical software of SAS in Cary, NC. The analysis was focused on the prevalence of colonic neoplasms among patients with or without duodenal adenomas. Odds ratios and their 95 % confidence intervals were calculated to describe the strengths of the associations between individual types of colonic neoplasms and the presence of duodenal adenoma. We also used multivariate logistic regression to adjust the odds ratios for age, sex, and varying characteristics of the colonic neoplasms.

Results

There were 203,277 unique patients who met the inclusion criteria. Of these, a total of 537 patients harbored duodenal adenomas. The demographic characteristics of case and control subjects are summarized in Table 2. Case subjects with duodenal adenomas were older than controls without (mean age 65.3 ± 12.7 years vs. 57.8 ± 15.2, $p < 0.001$). They were also more likely to be male (OR 1.34, 95 % CI 1.13–1.59). Of the total population, 54,400 (26 %) patients were younger than 50 years, and 150,877 (74 %) patients were 50 years old and older. Figure 1 depicts the age distributions of subjects with duodenal or colonic neoplasms. The occurrences of colonic and duodenal adenomas were both characterized by a marked age-dependent rise. Patients with duodenal adenoma had a significantly greater prevalence of all types of colonic adenomas, particularly of advanced adenomas and colorectal cancer (Table 2).

Additional results from the univariate analyses are depicted in Table 3. Although the relationship between presence of duodenal and colonic neoplasia applied to individual subgroups of adenomatous colon polyps stratified by polyp size and number, the magnitude of the odds ratios remained largely unaffected by such polyp characteristics. Duodenal adenomas were equally associated with left- and right-sided colonic polyps.

Initially, all individual characteristics, such as age, gender, polyp type, size, number, and location were entered as predictor variables in a multivariate logistic regression analysis, with presence of duodenal adenoma serving as outcome variable. In the final model, age and colonic adenoma remained the only two statistically significant, independent variables to positively predict occurrence of duodenal adenoma (Table 4). Other variables that showed a significant association with duodenal adenoma in the univariate analyses no longer contributed to the overall model.

Discussion

The analysis of this large series of patients indicates that in community-based endoscopic practices throughout the USA, a duodenal adenoma is detected once in every 400 patients who undergo an EGD and a simultaneous colonoscopy. In our series, these rare lesions occurred mostly in the 6th and 7th decade, with a distinct male predominance.

Table 2 Associations of duodenal adenoma with colonic neoplasm

Parameter	Total	Duodenal adenoma		Odds ratio	95 % confidence interval
		Present	Absent		
Age (SD)	57.8	65.3 (12.7)	57.8 (15.2)	–	–
Total	203,277	537 (0.3 %)	202,740 (99.7 %)	–	–
Females	117,791	272 (0.2 %)	117,519 (99.8 %)	1	(Reference)
Males	85,486	265 (0.3 %)	85,221 (99.7 %)	1.34	(1.13–1.59)
No colon polyp	85,982	128 (0.1 %)	85,854 (99.9 %)	1	(Reference)
Hyperplastic polyp	30,205	65 (0.2 %)	30,140 (99.8 %)	1.45	(1.07–1.95)
Serrated adenoma	5,338	12 (0.2 %)	5,326 (99.8 %)	1.51	(0.84–2.73)
Any adenoma	85,801	338 (0.4 %)	85,463 (99.6 %)	2.65	(2.16–3.25)
Villous or HG dysplasia	6,735	37 (0.5 %)	6,698 (99.5 %)	3.71	(2.57–5.35)
Advanced adenoma	12,098	77 (0.6 %)	12,021 (99.4 %)	4.30	(3.24–5.70)
Adenocarcinoma	1,290	6 (0.5 %)	1,284 (99.5 %)	3.13	(1.38–7.12)

Percentage calculated as fraction of total, e.g. 537/203,277 = 0.3 %

Odds ratio calculated by comparison with reference group, e.g. (265 × 117,519)/(85,221 × 272) = 1.34

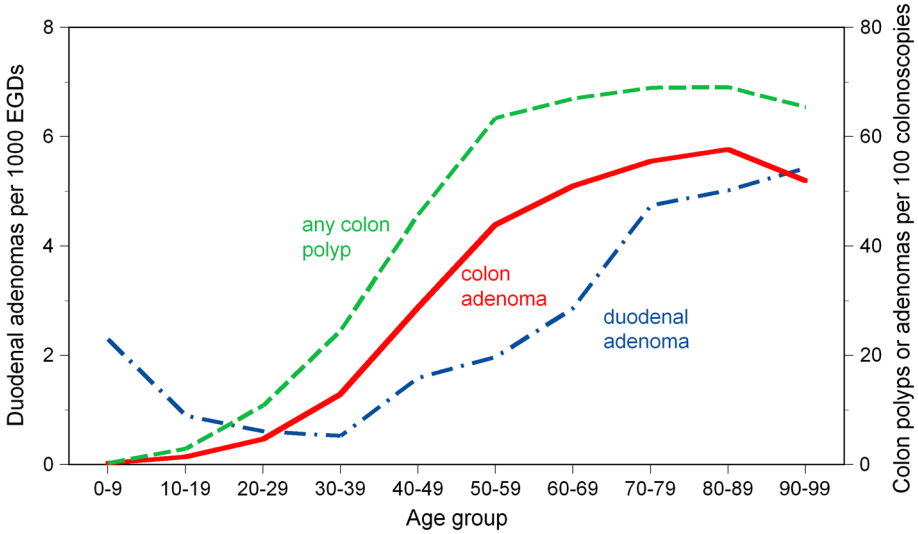

Fig. 1 Age distributions of subjects with duodenal or colonic neoplasms

Our most significant finding was the relatively strong association between sporadic duodenal adenoma and any type of colonic neoplasia. This association applied to any type of colonic neoplasia, ranging from hyperplastic polyps to colon cancer. It tended to be more pronounced in advanced lesions of the colon, such as villous adenomas or adenocarcinomas.

The wide methodological disparities and the different patient populations among the studies listed in Table 1 make it difficult to compare our findings with previous results. The overall percentage of patients with duodenal adenomas reported to have had colon adenomas varied between a minimum of 21 % (Schneider et al. in a series of 19 patients) and a maximum of 73 % (Apel et al. in 22 patients). In the two largest controlled series to date (Dariusz et al. [16] 48 patients and 144 controls; and Ramsoekh et al. [14] 49 patients and 147 controls), the combined OR (calculated from these authors' reported raw data) was 4.84 (95 % CI 2.93–8.00). Our odds ratio for the overall association between duodenal and colonic adenoma of OR = 2.65 (95 % CI 2.16–3.25) was somewhat lower, reflecting the outcomes in a much larger patient population, less likely to be influenced by a selection bias secondary to the underlying hypothesis.

This study has several limitations. Because the analysis was based on pathology database, only procedures that resulted in the acquisition of a biopsy sample were included. In spite of such limitation, however, we were able to recruit a large comparison group of over 85,000 subjects with bidirectional endoscopy but without any colon neoplasm. It is unknown how many patients (with or without duodenal adenomas) had colonoscopic examinations, during which no colonic polyps were detected or no biopsy specimens were taken from the upper gastrointestinal tract. Because such limitation applies to case and control subjects alike, it is unlikely to have significantly altered the associations revealed by the analysis. Because the database is limited to a 4-year time period, it is impossible to identify those patients

Table 3 Associations stratified by size, number, and location of colonic adenomas

Parameter	Total	Duodenal adenoma		Odds ratio	95 % confidence interval
		Present	Absent		
No colon polyp (control)	85,982	128 (0.1 %)	85,854 (99.9 %)	1	(Reference)
Adenoma size					
0–9	54,786	170 (0.3 %)	54,616 (99.7 %)	2.09	(1.66–2.63)
10–19	3,077	14 (0.5 %)	3,063 (99.5 %)	3.07	(1.76–5.33)
20–29	441	2 (0.5 %)	439 (99.5 %)	3.06	(0.75–12.39)
≥30	474	1 (0.2 %)	473 (99.8 %)	1.42	(0.20–10.17)
Adenoma number					
1–2	65,370	248 (0.4 %)	65,122 (99.6 %)	2.55	(2.06–3.16)
3–4	19,197	81 (0.4 %)	19,116 (99.6 %)	2.84	(2.15–3.76)
5–6	1,130	8 (0.7 %)	1,122 (99.3 %)	4.78	(2.34–9.79)
≥7	104	1 (1.0 %)	103 (99.0 %)	6.51	(0.90–47.03)
Polyp location					
Left colon	76,420	245 (0.3 %)	76,175 (99.7 %)	2.16	(1.74–2.67)
Right colon	139,895	392 (0.3 %)	139,503 (99.7 %)	1.88	(1.54–2.30)

Adenoma size known for only 67 % of patients. Patients with left- and right-sided adenomas are listed twice. Left colon = rectum to descending colon, right colon = splenic flexure to cecum

Table 4 Strength of associations in a multivariate model

Variable	Duodenal polyp		Chi-square	*p*
	OR	95 % CI		
Age	14.09	(7.41–26.83)	64.90	<0.0001
Adenoma	1.93	(1.62–2.30)	53.89	<0.0001

who had been previously cleared of any duodenal or colonic polyps and who were free of polyps at the time of the study period. Due to the particular nature of the database, we have also been limited in our ability to identify and account for potential confounders, such as patient selection for colonoscopy or EGD. Besides gender and age, little or no additional information was available regarding other patient characteristics, such as presence of comorbid conditions, socioeconomic status, or social habits.

In addition to its potential limitations, our study has several obvious strengths. The sample size was large and yielded a correspondingly large number of patients with duodenal adenomas, let alone colonic neoplasms, unmatched by any previous such investigation. All specimens were rigorously and carefully characterized, using standardized interpretation criteria with routinely performed quality checks. Because the data were directly derived from a pathology database, the diagnoses of both colonic and duodenal neoplasms were associated with high levels of accuracy. The data were collected by clinicians and pathologists who were unaware of any potential use of their diagnoses for future epidemiologic analysis. The recruitment of patients into the study was, therefore, unbiased by its underlying hypothesis.

The mechanisms underlying the relationship between duodenal and colonic adenoma are presently unknown and largely hypothetical. It is enticing to speculate that besides the major APC gene responsible for the familial adenomatous polyposis, there may be other lesser genes that promote mucosal proliferation. Although all patients with known familial adenomatous polyposis were carefully screened and excluded from the present analysis, the possibility remains that a small fraction of yet unknown patients harbored an attenuated form of the disease. It is interesting to note that the odds ratio for hyperplastic polyps was smaller than those of adenomatous polyps. The relative small odds ratio for serrated adenoma could also reflect on different genetic pathway or just on the influence of fewer cases. There is also the possibility that environmental factors stimulate neoplastic growth in the duodenum, as well as in the colon. The association between infection with *H. pylori* and colonic neoplasia, for instance, suggests that even moderately elevated gastrin levels may promote formation of colonic neoplasia [22, 23]. The relationship between *H. pylori* and duodenal adenoma has not been investigated as yet.

The occurrence of duodenal adenoma is rare and its attributable risk for colonic neoplasia is likely to be extremely small. The prevalence of duodenal adenoma increases with age in a fashion similar to the age-dependent rise in the prevalence of colon polyps. The majority of duodenal polyps occur among patients who should be referred to screening colonoscopy for age-dependent reasons alone. The incidental findings of duodenal adenoma during an EGD, however, could provide an additional incentive to schedule a screening colonoscopy. Although

with an OR = 2.65 the association between duodenal and colonic adenoma is only moderately elevated, it is of similar order of magnitude as any positive family history for non-hereditary colon cancer. Considering the infrequent occurrence of duodenal adenomas and their benign course outside the realm of familial adenomatous polyposis, there is probably also little reason to recommend any general screening for duodenal polyps in all patients with colonic adenomas. The main relevance of the association between duodenal and colonic adenomas may rest with its potential implications for the pathogenesis of intestinal polyps and the insights that it may provide about the underlying mechanisms.

In conclusion, our study of a large database of pathology specimens shows that patients with duodenal adenomas harbor an increased risk for any type of colonic neoplasms, ranging from hyperplastic polyps to tubular adenomas and colon cancer. This association may provide new insights about the general mechanisms underlying mucosal proliferation in the gastrointestinal tract. The relationships between duodenal and colonic neoplasm were found in an epidemiologic study that served primarily to generate new hypotheses. If confirmed by other clinical studies, in the future, any incidental finding of duodenal adenomas could provide an additional incentive to recommend a screening colonoscopy.

Conflict of interest Robert M. Genta is employed by Miraca Life Sciences, Irving, TX. No funding was obtained for this study.

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