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Original Article

Is Presence or History of Extracolonic Primary Malignancy a Risk for Colorectal Neoplasia? An Analysis of Patients Who Underwent Colonoscopy

Mitsuhiro Akita[a], Sakiko Hiraoka[a]*, Eisuke Kaji[a,b,c], Koji Takemoto[d], Yasuhiro Nagahara[e], Hiroshi Yamamoto[f], Kazuhide Yamamoto[a], and Jun Kato[g]

[a]Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan, [b]Japanese Red Cross Society Himeji Hospital, Hyogo 670–8540, Japan, [c]Mitoyo General Hospital, Kan'onji, Kagawa 769–1695, Japan, [d]Tsuyama Central Hospital, Tsuyama, Okayama 708–0841, Japan, [e]Nihon Kokan Fukuyama Hospital, Hiroshima 721–0927, Japan, [f]Kurashiki Central Hospital, Kurashiki, Okayama 710–8602, Japan, [g]Second Department of Internal Medicine, Wakayama Medical University, Wakayama 641–0012, Japan

Whether presence or history of extracolonic primary malignancy is a risk for colorectal neoplasia is not fully known. In this study, 26,452 first-time colonoscopy cases were examined using a colonoscopy database. Among the analyzed subjects, 3,026 (11%) subjects had history or concomitance of extracolonic primary malignancy, while the remaining 23,426 subjects did not. Colorectal neoplasia was observed in 39% of all the subjects. A crude comparison showed that the prevalence of any type of colorectal neoplasia was higher in subjects with extracolonic malignancy than in those without (42% vs. 39%, $p = 0.0012$). However, after adjusting for confounding factors, the odds ratios (ORs) of subjects with extracolonic malignancy for having colorectal neoplasia, advanced neoplasia, and cancer were all less than 1.0, and all significantly different from those of subjects without extracolonic malignancy. Analysis according to the type of extracolonic malignancy revealed that gastric cancer cases had a significantly lower risk for colorectal advanced neoplasia (OR: 0.81; 95% CI: 0.67–0.99). Among major malignancies, only esophageal squamous cell cancer cases had increased risk for colorectal neoplasia (OR: 1.66; 95% CI: 1.20–2.29). Patients with presence or history of extracolonic malignancy did not carry a higher risk of occurrence of colorectal neoplasia.

Key words: colorectal cancer, colonoscopy, risk factor, database

Colorectal cancer (CRC) is one of the leading causes of cancer deaths in many countries, and thus a plethora of reports exist regarding risk factors for CRC and colorectal premalignant lesions [1]. In particular, smoking and drinking habits [2, 3], red meat consumption [4], obesity [5], diabetes [6], and family history of CRC [7] have been shown to be definite clinical risk factors for CRC. However, although many of the risk factors such as smoking are common among cancers originating from various organs [8], it is largely unknown whether presence and history of extracolonic primary cancer/malignancy is a risk for colorectal neoplasia including CRC. If so, a specialized CRC screening strategy for the patients who have or had other primary malignancies may be required.

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*Corresponding author. Phone:+81–86–235–7219; Fax:+81–86–225–5991
E-mail:sakikoh@cc.okayama-u.ac.jp (S. Hiraoka)

In this study, we examined whether presence or history of extracolonic primary cancer is a risk for colorectal neoplasia using a large colonoscopy database registered in hospitals across Japan.

Materials and Methods

Study design. We have maintained a multicenter colonoscopy database since 2003. This database includes clinical data on all patients who underwent colonoscopy at Okayama University Hospital and 18 affiliated hospitals. The collected data included age, gender, indications for colonoscopy, past and family history of colorectal cancer, history or concomitance of primary malignancies of other organs, and the location, size, and histology of polyps or cancer found by colonoscopy. Data input was performed by the individual colonoscopist, or, at a few institutes, by nurses or assistants.

From June 2005 to May 2009, results from a total of 105,612 colonoscopies were registered into this database. Among these, 38,786 first-time colonoscopy cases were initially considered eligible for this study. The exclusion criteria included cases less than 20 years of age, with prior resection of any part of the colon, with familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer, with inflammatory bowel disease, and whose data lacked clinical information or histological information on polyps. After excluding these subjects, 26,452 cases were analyzed.

In this analysis, we examined colonoscopic findings according to the status of extracolonic malignancy. Subjects were divided into 2 groups: those with presence or history of extracolonic malignancy and those without. Prevalence of neoplasia was compared between the 2 groups. This database analysis was approved by the institutional review board of Okayama University Hospital and each affiliated hospital. Informed consent was obtained from each patient.

Colonoscopic findings. During the colonoscopy, the location and size of all polypoid lesions and cancers were determined. The size of the polyps resected with polypectomy or surgical resection was measured just after resection. The polyps that underwent biopsy alone were measured endoscopically using standard clinical practices, such as visual estimation and the open biopsy forceps method [9, 10].

Pathologic findings. Histologic studies were performed on all polyps and tumors taken by polypectomy or biopsy procedures by board certified pathologists at each participating hospital. CRCs included all invasive cancer and cancer in the Tis category (carcinoma *in situ* and intramucosal) of the TNM Clinical Classification [11]. Traditional tubular adenomas were classified as tubular, tubulovillous, or villous adenomas. They were also classified as low or high-grade according to the degree of dysplasia. Adenomas $\geq$10 mm, with a villous component, or with high-grade dysplasia or cancer were defined as advanced neoplasia.

Statistical analysis. We used the chi-square test or Fisher's exact test for univariate analysis and a logistic regression model in order to adjust for confounding factors. Results are shown as odds ratios (ORs) with 95% confidence intervals (CIs). These analyses were performed using the JMP program (version 8; SAS Institute, Cary, NC, USA). All p values are two-sided and considered significant when less than 0.05.

Results

Clinical characteristics of analyzed subjects. Of the 38,786 colonoscopy cases enrolled in this study, 26,452 cases were eligible for analysis. Those excluded had insufficient pathological data (n = 9,468), prior resection of any part of the colon (n = 273), familial adenomatous polyposis (n = 5), inflammatory bowel disease (n = 236), or insufficient clinical data (n = 2,117), or were less than 20 years of age (n = 235). Of these subjects, 3,026 (11%) subjects had history or concomitance of extracolonic primary malignancy, while the remaining 23,426 subjects did not. The characteristics of the subjects are shown in Table 1. The proportion of males was larger in the subjects with history or concomitance of extracolonic malignancy. In addition, they were older. The indications for colonoscopy were rather different between the 2 groups; screening was a major indication in subjects with extracolonic malignancy, while nearly half of the patients without extracolonic malignancy underwent colonoscopy due to a positive fecal occult blood test.

Colorectal neoplasia was observed in 39% of all the subjects. The prevalence of any type of neoplasia was higher in subjects with extracolonic malignancy

Table 1 Characteristics of the study population

	No. of patients (n=26,452)	%	Extracolonic primary malignancies (+) (n=3,026)	%	Extracolonic primary malignancies (−) (n=23,426)	%	*p* value
Sex							
Male	14,251	54	1,701	56	12,550	54	0.006
Female	12,201	46	1,325	44	10,876	46	
Age							
Mean ± SD, y			65.6 ± 11.5		58.5 ± 14.6		<0.0001
20–49	6,441	24	273	9	6,168	26	
50–69	12,790	48	1,484	49	11,306	48	
70 <	7,221	27	1,269	42	5,952	25	
Indication for colonoscopy							<0.0001
Screening	2,401	9	870	29	1,531	7	
Positive fecal occult blood test	11,740	44	782	26	10,958	47	
Abdominal symptoms	5,346	20	471	16	4,875	21	
Rectal bleeding	3,615	14	335	11	3,280	14	
Others	3,350	13	568	19	2,782	12	
Colorectal neoplasia							
No neoplasia	16,181	61	1,769	58	14,413	62	0.001
Neoplasia	10,271	39	1,258	42	9,013	39	
Adenoma < 9 mm	5,936	22	757	25	5,179	22	
Advanced neoplasia	4,337	16	501	17	3,836	15	NS
Adenoma > 10 mm	2,111	8	248	8	1,863	8	
Tubulovillous or villous adenoma	281	1	20	1	262	1	
High-grade dysplasia	271	1	37	1	234	1	
Cancer	1,672	6	196	7	1,476	6	NS

than in those without (42% vs. 39%, $p = 0.0012$). A crude comparison between the 2 groups revealed no differences in the prevalence of advanced neoplasia and cancer.

Prevalence of colorectal neoplasia according to type of extracolonic malignancy. The prevalence of colorectal neoplasia according to the type of extracolonic malignancy was examined (Table 2). The prevalence of all neoplasia, advanced neoplasia, or cancer varied to some extent among subjects with major malignancies. However, it should be noted that the difference in the prevalence was largely attributable to the gender and age of the patients. For example, the prevalence of neoplasia in subjects with breast or uterine cancer was lower than in those with other malignancies. The prevalence of neoplasia in patients with prostate cancer was relatively high, in part due to the older age of those patients.

Adjusted ORs for colorectal neoplasia in patients with extracolonic malignancy. Because the prevalence of colorectal neoplasia was affected by patient age and gender, ORs for occurrence of colorectal neoplasia in subjects with extracolonic malignancy were calculated with adjustments for age and gender (Table 3). Intriguingly, the occurrences of all neoplasia, advanced neoplasia, and cancer in subjects with extracolonic malignancy were shown to be significantly less than in the patients without this condition (OR (95% CIs): 0.87 (0.80–0.94), 0.78 (0.70–0.87), and 0.77 (0.66–0.90), respectively). Age stratification revealed that the trend was true and statistically significant (except for cancer in patients between 50–69 years of age) in subjects who were 50 years old or older.

In addition to age and gender, indication for colonoscopy could also be a bias for the prevalence of colorectal neoplasia. Therefore, ORs were calculated with indication for colonoscopy (screening, positive fecal occult blood test, abdominal symptoms, and rectal bleeding) as a confounding factor. This analysis

Table 2 Prevalence of colorectal neoplasia in patients with extracolonic primary malignancy

	Total	Age (Mean±SD, y)	All neoplasia	%	Advanced neoplasia	%	Colorectal cancer	%
Extracolonic primary malignancies (−)	23,426	58.5 ± 14.6	9,013	39	3,836	15	1,476	6
Extracolonic primary malignancies (+)	3,026	65.6 ± 11.5	1,258	42	501	17	196	6
Gastric cancer	842	67.4 ± 10.5	370	44	140	17	57	7
Breast cancer	346	61.8 ± 11.2	102	30	39	11	18	5
Uterine cancer	324	60.9 ± 13.3	90	28	38	12	14	4
Prostatic cancer	261	72.5 ± 6.7	133	51	58	22	22	8
Lung cancer	203	68.4 ± 9.7	90	44	40	20	15	7
Hepatoma	200	66.9 ± 10.1	96	48	34	17	12	6
Esophagial cancer	168	66.6 ± 8.9	99	59	33	20	8	5
others	814	64.3 ± 12.4	336	41	146	18	61	7

Table 3 Correlation between extracolonic primary malignancies and colorectal neoplasia

	All neoplaisa[c] Adjust OR (95%CI)[a]	Advanced neoplasia[d] Adjust OR (95%CI)[a]	Colorectal cancer Adjust OR (95%CI)[a]
All patients[b]	0.87 (0.80–0.94)***	0.78 (0.70–0.87)***	0.77 (0.66–0.90)***
	*0.91 (0.83–0.99)**	*0.83 (0.74–0.93)****	*0.82 (0.70–0.96)**
20–49 years[c]	1.27 (0.94–1.71)	1.22 (0.74–1.90)	1.61 (0.62–3.42)
	1.03 (0.74–1.40)	*1.00 (0.60–1.60)*	*1.31 (0.49–2.90)*
50–69 years[c]	0.88 (0.79–0.99)*	0.77 (0.66–0.90)***	0.81 (0.64–1.02)
	0.92 (0.82–1.04)	*0.81 (0.69–0.96)*	*0.80 (0.62–1.02)*
70 years< [c]	0.88 (0.77–0.99)*	0.82 (0.70–0.95)**	0.77 (0.62–0.94)*
	0.90 (0.79–1.02)	*0.86 (0.73–1.00)*	*0.82 (0.66–1.02)*

[a]Odds ratio and p value of extra colonic primary malignancies for colorectal neoplasia. [b]Relative risk adjusted for age and gender (upper), and with additional adjustment for indication for colonoscopy (lower, bold and italic letters). [c]Relative risk adjusted for gender (upper), and with additional adjustment for indication for colonoscopy (lower, bold and italic letters). [d]All neoplasia including all colorectal adenomas and cancers.
*$p < .05$, **$p < .01$, ***$p < .001$

yielded results similar to those described above: the occurrences of all neoplasia, advanced neoplasia, and cancer in patients with extracolonic malignancy were found to be significantly less than in those without extracolonic malignancy (OR (95% CIs): 0.91 (0.83–0.99), 0.83 (0.74–0.93), and 0.82 (0.70–0.96), respectively), although a majority of the findings were no longer statistically significant with age stratification. These results suggest that presence or history of extracolonic malignancy is not a risk factor for colorectal neoplasia, but instead, carries a lower risk of colorectal neoplasia.

Although there were differences in the frequency of extracolonic primary malignancy among institutes (*e.g.*, Okayama University Hospital vs. 5 major affiliated hospitals; 28% vs. 8.6–10.1%), the results were not much skewed in the analysis with adjustment of institutes (data not shown).

Adjusted ORs for colorectal neoplasia according to type of extracolonic malignancy. Finally, adjusted ORs for colorectal neoplasia were calculated according to the type of extracolonic malignancy. Although most of the 7 major extracolonic malignancies showed a trend towards lower risk of colorectal neoplasia, many of them did not reach statistical significance; negative associations were found

between prostatic cancer and all neoplasia (OR (95% CIs): 0.73 (0.58–0.95) and 0.76 (0.59–0.97) after adjusting for age/gender and indication for colonoscopy, respectively) and advanced neoplasia (OR (95% CIs): 0.73 (0.54–0.99) after adjusting for indication for colonoscopy) (Table 4). In particular, presence or history of gastric cancer was found to be associated with a significantly lower risk of all neoplasia, advanced neoplasia, and cancer (OR (95% CIs): 0.81 (0.70–0.94), 0.70 (0.58–0.84), and 0.75 (0.56–0.97), respectively). Even after adjustment for indication for colonoscopy, the lower risk for advanced neoplasia remained statistically significant (OR (95% CIs): 0.81 (0.67–0.99)).

Only in the case of esophageal squamous cell cancer did we find a higher risk of colorectal neoplasia (OR (95% CIs): 1.38 (1.01–1.90) after adjusting for age/gender). Although the trend was more pronounced after adjustment for indication for colonoscopy (OR (95% CIs): 1.66 (1.20–2.29)), no risks of advanced neoplasia and cancer were observed.

Discussion

Unexpectedly, we found that the presence or history of extracolonic primary malignancy was not a risk factor for colorectal neoplasia in this large population who underwent colonoscopy. Rather, those patients had a relatively lower risk of colorectal neoplasia than subjects without extracolonic malignancy.

To the best of our knowledge, there have been no reports that evaluated the risk association between extracolonic primary malignancy and colorectal neoplasia. There are common risk factors among cancers originating from various organs, such as alcohol, smoking, *etc*. Therefore, our hypothesis prior to the start of this study, which was that subjects with extracolonic malignancy would have a higher risk of colorectal neoplasia, seemed highly plausible. However, our unexpected results suggest that the presence of factors that are associated with suppression of colorectal neoplasia development override the effects of the common carcinogenic risk factors.

Although it seems highly unlikely that there are definite genetic or environmental factors that simulta-

Table 4 Type of extracolonic primary malignancies and risk of colorectal neoplasia

	No.	All neoplasia[a] Adjusted OR (95%CI)	Advanced neoplasia Adjusted OR (95%CI)	Colorectal cancer Adjusted OR (95%CI)
Gastric cancer[b]	842	0.81 (0.70–0.94)**	0.70 (0.58–0.84)***	0.75 (0.56–0.97)*
		0.88 (0.76–1.02)	*0.81 (0.67–0.99)**	*0.93 (0.69–1.23)*
Breast cancer (only female)[c]	346	0.92 (0.73–1.16)	0.89 (0.62–1.23)	0.91 (0.54–1.43)
		0.91 (0.72–1.16)	*0.86 (0.60–1.20)*	*0.86 (0.51–1.37)*
Uterine cancer (only female)[c]	324	0.86 (0.67–1.10)	0.94 (0.65–1.31)	0.74 (0.41–1.23)
		0.89 (0.69–1.14)	*0.93 (0.64–1.30)*	*0.86 (0.51–1.37)*
Prostatic cancer (only male)[c]	261	0.73 (0.58–0.95)*	0.75 (0.55–1.01)	0.75 (0.47–1.14)
		*0.76 (0.59–0.97)**	*0.73 (0.54–0.99)**	*0.69 (0.43–1.06)*
Lung cancer[b]	203	0.84 (0.63–1.11)	0.88 (0.61–1.23)	0.82 (0.46–1.34)
		0.77 (0.58–1.03)	*0.77 (0.53–1.09)*	*0.68 (0.38–1.13)*
Hepatoma[b]	200	1.01 (0.76–1.34)	0.75 (0.51–1.08)	0.69 (0.36–1.19)
		1.03 (0.77–1.38)	*0.77 (0.52–1.12)*	*0.70 (0.37–1.23)*
Esophagial cancer[b]	168	1.38 (1.01–1.90)*	0.81 (0.54–1.18)	0.52 (0.23–1.00)
		*1.66 (1.20–2.29)***	*1.12 (0.73–1.65)*	*0.79 (0.35–1.56)*

[a]All neoplasia including all colorectal adenomas and cancers. [b]Relative risk adjusted for age and gender (upper), and with additional adjustment for indication for colonoscopy (lower, bold and italic letters). [c]Relative risk adjusted for age (upper), and with additional adjustment for indication for colonoscopy (lower, bold and italic letters).

*$p < .05$, **$p < .01$, ***$p < .001$

neously suppress colon carcinogenesis and promote carcinogenesis of other types of cancer, those who are likely to develop colorectal neoplasia may have a predisposition to escape from development of other types of cancer. For example, there may be microorganisms in the gut flora that directly injure the colorectal epithelium, but may also indirectly prevent other types of cancer by activating the immune system. Further data and considerations are needed to resolve this issue.

Another explanation for our results is that the presence or experience of any type of cancer would render patients more health-conscious, such that they may take actions to improve of their health, including quitting or reducing smoking or drinking, increase in physical activity, or taking supplements. In fact, it has been reported that patients with head and neck cancer who stopped smoking and drinking after treatment were less likely to develop metachronous cancer than those who did not [12]. Moreover, once patients have suffered from any type of cancer, they will be more likely to seek medical examination in response to slight or marginal symptoms. And of course, subjects with only slight symptoms would be less likely to harbor colorectal neoplasia than those with pronounced symptoms. Thus, presence or history of malignancy could change the patients' attitude towards health care, possibly resulting in less prevalence of colorectal neoplasia.

In our study, CRC screening was a major indication for colonoscopy in subjects with extracolonic malignancy, although this was rather rare in those without extracolonic malignancy. There may be 2 reasons for this tendency. First, clinicians were likely to be anxious about concomitance of other malignancies following the discovery of one malignancy. Second, when patients with 1 type of cancer are scheduled to undergo surgery, particularly abdominal surgery, it is important to know whether colonic lesions are present so that they can dealt with simultaneously. It appears to be natural that asymptomatic subjects who underwent colonoscopy with indication of CRC screening were less likely to have colonic lesions than subjects who had abdominal symptoms or a positive fecal occult blood test result. To correct this bias, we adjusted for indications for colonoscopy as well as gender and age. In addition, we analyzed the subjects with each indication separately, to compare the results for each indication with the results of the analysis of all subjects (data not shown). The findings indicated that history or concomitance of extracolonic malignancy is definitely not a risk factor for colonic neoplasia.

Presence or history of gastric cancer, the most prevalent malignancy in Japan, also was not correlated with increased risk of colorectal neoplasia; in fact, it was correlated with a decreased risk of advanced colorectal neoplasia. The most potent risk factor of gastric cancer is *Helicobacter pylori* (*H. pylori*) infection. Several reports have indicated that *H. pylori* infection is correlated with increased risk of colorectal neoplasia, although this risk is not as great as that for gastric cancer [13, 14]. Long-term continuous *H. pylori* infection causes atrophic gastritis, from which gastric cancer develops. Inoue *et al.* reported that although *H. pylori* infection is a risk factor for colorectal adenoma, the presence of atrophic gastritis is not a particularly great risk for distal colorectal adenoma [15]. This suggests that the progression of gastric atrophy due to *H. pylori* infection lowers the risk of distal colorectal neoplasia. A subanalysis of our results on the location of colorectal neoplasia indicated that presence or history of gastric cancer significantly lowered the risk of distal colorectal neoplasia, but this trend was not observed in the risk of proximal colorectal neoplasia (distal neoplasia: OR = 0.78 (0.67–0.91), $p = 0.002$; proximal neoplasia: OR = 0.90 (0.76–1.05), $p = 0.19$). Those who are predisposed to gastric cancer occurrence usually have atrophic gastritis, irrespective of whether or not they currently have or previously had *H. pylori* infection. Therefore, subjects who developed gastric cancer might have lower risk for distal colorectal neoplasia.

In our analysis, esophageal squamous cell cancer was the only malignancy that carried a higher risk of colorectal neoplasia. The predominant risk factors of esophageal cancer are smoking and alcohol consumption [16], which are also those of various other cancers, including CRC. Although it is largely unknown why esophageal cancer alone was correlated with the occurrence of colorectal neoplasia, polymorphism of enzymes metabolizing alcohol may be partially responsible. The aldehyde dehydrogenase Glu504Lys polymorphism is correlated with increased risk of esophageal cancer [17]. This polymorphism is also correlated with occurrence of colorectal cancer, particularly

among alcoholics [18]. Because esophageal cancer is likely to develop in heavy drinkers, heavy drinking and the predisposing polymorphism may significantly affect the development of colorectal neoplasia in esophageal cancer patients.

There are limitations to this study. First, some of the enrolled patients may have had hereditary cancers, despite the fact that the family history was carefully investigated. In particular, patients with Lynch syndrome are known to have both colorectal and extracolonic cancers, particularly gastric cancer [19]. However, Lynch syndrome has been reported to account for only 0.4% of CRC cases in Japan [20]. Second, the prevalence of *H. pylori* infection in the general population in Japan, where this study was performed, tends to be higher than that of Western subjects [21]. In addition, the aldehyde dehydrogenase Glu504Lys polymorphism is much more common in Asian than in Caucasian populations [22]. The high prevalence of *H. pylori* infection and the predisposing polymorphism probably affected the results of our study with regard to gastric and esophageal cancers, respectively. Third, this study was based on analyses of colonoscopy database. To more accurately investigate the effect of extracolonic malignancy on the presence of colorectal neoplasia, a large scale population-based study is required. Moreover, information about extracolonic malignancy were collected from a questionnaire written by patients on the day of colonoscopy. Therefore, the presence of subclinical extracolonic malignancy could not be examined accurately. Finally, there may have been a bias because patients with a history of cancer are likely to pay more attention to their health. Despite these limitations, however, our findings will clearly be useful at the clinical level for sparing some patients from needless additional CRC screenings.

In conclusion, patients with presence or history of extracolonic malignancy did not carry a higher risk of occurrence of colorectal neoplasia; rather, those patients had a relatively lower risk of colorectal neoplasia. Therefore, those who currently have or previously had an extracolonic malignancy can be regarded as being at average-risk for CRC and do not need to receive any special CRC screening.

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