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## Risk factors for small intestinal adenocarcinomas that are common in the proximal small intestine

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### Abstract

The frequency of primary small intestinal adenocarcinoma is increasing but is still low. Its frequency is approximately 3% of that of colorectal adenocarcinoma. Considering that the small intestine occupies 90% of the surface area of the gastrointestinal tract, small intestinal adenocarcinoma is very rare. The main site of small intestinal adenocarcinoma is the proximal small intestine. Based on this characteristic, dietary animal proteins/lipids and bile concentrations are implicated and reported to be involved in carcinogenesis. Since most nutrients are absorbed in the proximal small intestine, the effect of absorbable intestinal content is a suitable explanation for why small intestinal adenocarcinoma is more common in the proximal small intestine. The proportion of aerobic bacteria is high in the proximal small intestine, but the absolute number of bacteria is low. In addition, the length and density of villi are greater in the proximal small intestine. However, the involvement of villi is considered to be low because the number of small intestinal adenocarcinomas is much smaller than that of colorectal adenocarcinomas. On the other hand, the reason for the low incidence of small intestinal adenocarcinoma in the distal small intestine may be that immune organs reside there. Genetic and disease factors increase the likelihood of small intestinal adenocarcinoma. In carcinogenesis experiments in which the positions of the small and large intestines were exchanged, tumors still occurred in the large intestinal mucosa more often. In other words, the influence of the intestinal contents is small, and there is a large difference in epithelial properties between the small intestine and the large intestine. In conclusion, small intestinal adenocar-

cinoma is rare compared to large intestinal adenocarcinoma due to the nature of the epithelium. It is reasonable to assume that diet is a trigger for small intestinal adenocarcinoma.

**Key Words:** Small intestine; Large intestine; Adenocarcinoma; Risk factor; Carcinogenesis

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**Core Tip:** When investigating the risk factors for small intestinal adenocarcinoma, an important point to note is that small intestinal adenocarcinoma is often found in the proximal small intestine. Intestinal contents remain in the ileum longer than in the jejunum, so poorly absorbed food is unlikely to be a carcinogenic factor. Animal proteins and lipids, bile concentrations, and aerobic bacteria, which are thought to be concentrated in the proximal small intestine, may be carcinogens in the small intestine. Since small intestinal adenocarcinoma is much rarer than colorectal adenocarcinoma, it is unlikely that small intestinal villi are involved in carcinogenesis.

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## INTRODUCTION

Although the small intestine occupies 75% of the gastrointestinal tract length and 90% of the mucosal surface area, primary small intestinal cancer accounts for less than 5% of gastrointestinal cancers[1]. During the last century, enteroscopy was a difficult procedure to perform, and thus, the elucidation of small intestinal cancer was delayed compared to that of other gastrointestinal cancers. However, in this century, capsule endoscopy and balloon-assisted endoscopy have made it easier than ever to examine the small intestine. The frequency of small intestinal cancer has been increasing since 2000 or earlier and continues to rise with the addition of improved diagnostic power *via* new endoscopes[2]. Especially in patients with anemia of unknown cause, cases of small intestinal cancer diagnosed as a bleeding source are increasing[3]. In addition, many cases are diagnosed by positron emission tomography or computed tomography. The frequency of small intestinal adenocarcinoma is still on the rise, partly due to the widespread performance of small intestinal examinations[4].

According to a 2006 French report, the incidence of primary small intestinal malignancies in both men and women was approximately four times that 30 years ago (1.2 males and 0.8 females per 100000 in 2006)[5]. Primary small intestinal malignancies include neuroendocrine tumors, sarcomas, and lymphomas in addition to adenocarcinomas. A report of 10946 primary malignancies of the small intestine, mainly in Europe, showed that adenocarcinomas accounted for 37% of cases, carcinoid tumors accounted for 37% of cases, sarcomas accounted for 12% of cases, and malignant lymphomas accounted for 4% of cases[6]. In the United States, 40% of primary malignancies of the small intestine are reported to be adenocarcinomas, and 36% are carcinoid tumors[7].

According to the cancer statistics published yearly by the American Cancer Society, 5420 small intestinal malignancies and 145290 colorectal malignancies were predicted to develop in the United States in 2005[8]. The frequency of small intestinal malignancies was only 3.7% of that of colorectal malignancies. In 2019, the predicted number of colorectal malignancies was almost 145600 cases. However, the number of small bowel malignancies was 10590, which is 7.3% of the number of colorectal malignancies. Additionally, this percentage is twofold higher than that reported in 2005[9]. In the United States, colorectal adenocarcinomas account for 98% of colorectal malignancies, but small intestinal adenocarcinomas account for only approximately 30%-40% of small intestinal malignancies [10]. Therefore, regarding adenocarcinoma at present, the number of cases of small intestinal adenocarcinoma is approximately 3% of that of large intestinal adenocarcinoma cases. Considering that the small intestinal villi and circular folds have even been reported to occupy 98% of the intestinal surface area [11], the frequency of small intestinal adenocarcinoma per surface area is extremely low compared to that of colorectal adenocarcinoma.

In the 1970s, an experiment was performed in which azoxymethane, a carcinogen, was intravascularly administered to rats. The results showed that adenocarcinomas appeared in the proximal small intestine, which corresponds to the duodenum, and the large intestine. However, no adenocarcinoma appeared in the jejunum/ileum[12]. It is worth noting that in this experiment, in rats in which a part of the small intestine or large intestine had been replaced, tumors still appeared in the large intestine and

not the small intestine, regardless of the position in the digestive tract. In other words, the content of the intestinal tract did not significantly influence the development of tumors in the intestinal tract, and this experiment showed that the properties of the intestinal tract are involved in the development of tumors. This azoxymethane administration experiment was conducted again recently, and the results did not show carcinogenicity in the small intestine[13]. In the 1980s, an experiment was conducted in which dimethylhydrazine was administered to rats to examine the reproducibility of the above experiment, and the results were similar[14]. Based on this fact, many tumors can develop in the proximal small intestine (probably in the papilla of Vater) and in the large intestine, regardless of the position in the digestive tract. However, tumor development is less common in the jejunum and ileum. In other words, there is a decisive difference between the small and large intestines.

Differences between the small and large intestines are mainly the presence or absence of villi, intestinal contents, intestinal content retention time, intestinal flora, intestinal epithelial turnover, mucosal properties, and genetic factors. There are very few adenocarcinomas in the small intestine compared to the large intestine, but small intestinal adenocarcinomas are more common in the jejunum than in the ileum, as shown below. Here, we would like to consider the risk factors for small intestinal adenocarcinoma.

## RISK FACTORS FOR SMALL INTESTINAL ADENOCARCINOMA IN THE PROXIMAL SMALL INTESTINE

**Table 1** summarizes the reports of small intestinal adenocarcinoma according to site, namely, the duodenum, jejunum, and ileum. The majority of reports show that adenocarcinoma is the most common malignancy in the duodenum. The oral side of the duodenum can usually be explored endoscopically, which is why many malignancies are diagnosed in this area. However, these reports may include cancer of the papilla of Vater. The only Chinese report on this topic does not show a high cancer incidence rate in the duodenum. In this report, 160 cases of cancer of the papilla of Vater were excluded from 202 cases of all small intestinal adenocarcinomas, and adenocarcinomas were more common in the jejunum than in other parts of the small intestine[15]. When we examined the adenocarcinomas of the small intestine that were diagnosed at our institution only in patients in whom a normal papilla of Vater was observed, the jejunum was the most common site. This finding is in agreement with that reported in China. Because the duodenum is short, this result may be appropriate in assessments of the small intestine alone. In recent years, the papilla of Vater has been suggested to have characteristics different from those of the duodenum[16,17]. A mixture of bile and pancreatic juice passes through the papilla of Vater, and the bile and pancreatic ducts themselves have different carcinogenic properties. It is natural to think that the carcinogenic origin in the papilla of Vater is different from that in the small intestinal mucosa. We did not examine cancer of the papilla of Vater here.

When comparing the jejunum and the ileum and excluding the duodenum, adenocarcinoma was more common in the jejunum than in the ileum in all reports. Based on these results, it seems clear that there are more small intestinal adenocarcinomas in the proximal small intestine than in the distal small intestine. According to a report summarizing small intestinal gastrointestinal stromal tumors (GISTs), the jejunum has more GISTs than the ileum[18]. In addition, reports of small intestinal neuroendocrine tumors are often reported in the jejunum within 1 m from the ileocecal valve[19]. Differences in the site of occurrence are observed depending on the type of tumor. Here, since small intestinal adenocarcinoma is more common in the proximal small intestine, we would like to determine the risk factors for adenocarcinoma of the small intestine by considering the difference between the proximal side of the small intestine and the distal side.

### Food

Most absorbable dietary components are absorbed in the duodenum and jejunum[20]. In other words, undegraded proteins and unabsorbed lipids flow in the proximal part of the small intestine. Diets containing high volumes of animal fat and protein have been reported to have a high risk of small intestinal adenocarcinoma, with correlation coefficients of 0.61 and 0.75, respectively[21]. Lipids and even small amounts of large peptides penetrate the cell membrane, which may be involved in carcinogenesis. Most proteins and lipids are absorbed in the proximal intestine and rarely reach the ileum, so there is no contradiction in this respect. Therefore, they may be involved in the carcinogenesis of the small intestine.

### Bile and pancreatic juice

The proximal part of the small intestine has higher levels of bile and pancreatic juice than the distal part. A review of the literature on the effects of bile and pancreatic juice reveals that bile may be converted to carcinogenic deoxycholic acid by bacteria and that cholecystectomy reduces the incidence of small intestinal cancer[22,23]. In other words, bile may be involved in small intestinal carcinogenesis. However, it is difficult to judge the validity of the results because there are few reports on the effects of

**Table 1** Regions where small intestinal adenocarcinoma was reported

Country	Year	Number <sup>1</sup>	Duodenum		Jejunum		Ileum		Ref.
France	2020	347	210	60.6%	72	20.7%	65	18.7%	[31]
China	2020	42	11 <sup>2</sup>	26.2%	29	69.0%	2	4.8%	[15]
Japan	2015	47	14	29.8%	21	44.7%	12	25.5%	[32]
United States	2010	421	230	54.6%	142	33.7%	49	11.7%	[33]
China	2010	197	108	54.8%	59	29.9%	30	15.3%	[34]
United States	2006	460	272	59.1%	98	21.3%	90	19.6%	[35]
United States	2005	195	113	57.9%	54	27.7%	28	14.4%	[7]
United States	1996	1404	777	55.3%	376	26.8%	251	17.9%	[2]
Japan	Our cases	50 <sup>3</sup>	20	40.0%	26	52.0%	4	8.0%	N/A

<sup>1</sup>Number excludes cases of unknown site.

<sup>2</sup>A total of 160 cases of primary cancer in the papilla of Vater were excluded.

<sup>3</sup>Only patients with a normal papilla of Vater were included.

N/A: Not applicable.

bile on the small intestine.

### **Intestinal chemicals**

The contents of the intestinal tract include chemicals contained in the diet and various chemical substances produced by bacteria. As mentioned above, chemical carcinogenesis occurs when the large intestine comes into contact with chemical substances. However, since the transit time of the intestinal contents into the small intestine is approximately 4 h, which is considerably shorter than that of the large intestine, the effect of chemical substances in the intestine is thought to be smaller than that of the large intestine. In addition, if carcinogenesis due to dietary or bacterial chemical substances is the main cause of adenocarcinoma, more adenocarcinomas would be likely to develop in the ileum, where the intestinal contents stagnate longer than in the jejunum. However, if the carcinogen is absorbed in the oral side of the small intestine, this is not inconceivable.

### **Intestinal flora**

Intestinal bacteria influence the intestinal tract through various means. Among the various chemicals produced by intestinal bacteria, those that not only cause inflammation but also have a direct carcinogenic effect and those that delay or prevent cell division of the intestinal epithelium have been reported[24]. Delaying epithelial turnover may be beneficial for bacteria directly involved in the epithelium. This delay in turnover is considered to be a factor that increases the possibility of cancer cell engraftment. There is a high possibility that intestinal bacteria are involved in carcinogenesis in the large intestine. However, it is difficult to explain why the number of jejunal adenocarcinomas is larger than that of ilial adenocarcinomas if intestinal bacteria are strongly associated with carcinogenesis in the small intestine. This is because it is difficult to explain why there are few bacteria in the proximal small intestine but many small intestinal adenocarcinomas in that area. However, the proximal small intestine is characterized by a relatively large number of aerobic bacteria, although the absolute number of bacteria is small. Therefore, given that small intestinal adenocarcinoma predominantly occurs in the proximal small intestine and aerobic bacteria are abundant in the proximal small intestine, the role of aerobic bacteria in small intestinal adenocarcinoma must be considered.

### **Immunity**

To absorb and excrete various substances, the cell membrane of the small intestine needs to have direct contact with the outside environment of the body. Therefore, the intestinal lumen needs to protect itself against bacteria, viruses, and many substances that invade the body using various types of immune mechanisms. The small intestine has the highest levels of immunity in the body. Additionally, the lymphatic system within the small intestine is stronger in the distal small intestine, where cancer may be strongly eliminated by immune mechanisms. Benzopyrene, for example, has been reported to suppress mouse immunity and thus, in the presence of carcinogens, lead to adenocarcinoma development in the proximal small intestine[25]. However, it remains unclear whether immunity can explain why cancer is overwhelmingly less common in the small intestine than in the large intestine because there are few reports on this topic.

**Table 2 Risk factors for small intestinal adenocarcinoma**

Factor	Disease	Risks of small intestinal adenocarcinoma	Ref.
Animal fat		Correlation coefficient of 0.61	[21]
Animal protein		Correlation coefficient of 0.75	[21]
		2-3-fold higher risk	[36]
Bile salts		Bile salts may transform into carcinogenic deoxycholic acid	[22]
Hereditary polyposis	FAP	APC mutation; 5% is small bowel adenocarcinoma and half is duodenal adenocarcinoma	[27]
		The incidence is 330 times higher than that in the general population	[28]
	HNPCC	MMR gene mutation; lifetime risk is at approximately 1% in a French registry	[29]
	PJS	STK11 mutation; incidence is 520 times higher than that in the general population	[30]
Disease	Crohn's disease	The incidence is 17.4 times higher than that in the general population	[37]
		The incidence is almost 3 times higher than that in the average American	[38]
	Celiac disease	It is implicated in 8%-13% of small bowel adenocarcinoma cases	[39,40]

FAP: Familial adenomatous polyposis; APC: Adenoma polyposis coli; HNPCC: Hereditary nonpolyposis colorectal cancer; MMR: Mismatch repair; PJS: Peutz-Jeghers syndrome; STK 11: Serine/threonine kinase 1.

### Villus length

The small intestine has villi and crypts, and the large intestine has only crypts and no villi. The lifespan of cells that have migrated to the villi is short, and the small intestinal epithelium is thought to be renewed every 3-5 d[26]. The proximal small intestine has longer and denser villi than the distal part. Therefore, the rate of epithelial turnover in the proximal small intestine may be longer than that in the distal part. This may be the reason why small intestinal adenocarcinoma is more common in the proximal small intestine. However, considering that many cancers develop in the large intestine, which has only crypts, it is unlikely that villi are significantly involved in cancer development.

## SUMMARY OF SMALL INTESTINAL ADENOCARCINOMA RISK FACTORS

Based on the above rationale and considering that the number of small intestinal adenocarcinomas in the proximal small intestine is larger than that in the distal small intestine, the possible causes of carcinogenesis are the effects of diet, bile concentration, aerobic bacteria, and intestinal immunity, in the order described. However, none of the above causes is definitive. Table 2 briefly summarizes the reported risk factors for small intestinal adenocarcinoma. In addition to the above causes, genetic factors and inflammatory diseases have been added to the table. Papillary carcinoma is increased in patients with familial adenomatous polyposis due to a mutation in adenoma polyposis coli, but it is less associated with the jejunum and ileum[27,28]. Small intestinal adenocarcinoma also occurs in hereditary nonpolyposis colorectal cancer patients due to mismatch repair mutations, but it is much less frequent than colorectal adenocarcinoma[29]. Small intestinal adenocarcinoma occurs 520-fold more often in patients with Peutz-Jeghers syndrome than in healthy individuals, but the population with small intestinal adenocarcinoma was originally small[30]. An increase in small intestinal adenocarcinoma is also observed in patients with Crohn's disease and celiac disease, which are thought to be related to inflammatory carcinogenesis. Therefore, it is understandable that genetic factors and disease factors are involved in small intestinal adenocarcinoma.

## CONCLUSION

Small intestinal adenocarcinoma is characterized by its predominance in the proximal small intestine. Animal proteins and lipids, bile concentrations, aerobic bacteria, and intestinal immunity were discussed as factors playing a role in small intestinal adenocarcinoma. Of these, it is highly possible that the dietary content absorbed in the proximal part of the small intestine is a risk factor for small intestinal adenocarcinoma. However, since the number of small intestinal adenocarcinomas is small, there are few reports, and none of the results are definitive. Moreover, in small intestine/large intestine replacement

experiments, at least in rats, the results show that the contents of the intestine are rarely involved in carcinogenesis. It seems that the nature of the organs is strongly related to susceptibility to carcinogenesis. Future studies are expected.

## FOOTNOTES

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