World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v3.i3.33

World J Gastrointest Oncol 2011 March 15; 3(3): 33-42
ISSN 1948-5204 (online)

EDITORIAL

Epidemiology of cancer of the small intestine

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Received: September 29, 2010 Revised: February 8, 2011
Accepted: February 15, 2011
Published online: March 15, 2011

Abstract

Cancer of the small intestine is very uncommon. There are 4 main histological subtypes: adenocarcinomas, carcinoid tumors, lymphoma and sarcoma. The incidence of small intestine cancer has increased over the past several decades with a four-fold increase for carcinoid tumors, less dramatic rises for adenocarcinoma and lymphoma and stable sarcoma rates. Very little is known about its etiology. An increased risk has been noted for individuals with Crohn's disease, celiac disease, adenoma, familial adenomatous polyposis and Peutz-Jeghers syndrome. Several behavioral risk factors including consumption of red or smoked meat, saturated fat, obesity and smoking have been suggested. The prognosis for carcinomas of the small intestine cancer is poor (5 years relative survival < 30%), better for lymphomas and sarcomas, and best for carcinoid tumors. There has been no significant change in long-term survival rates for any of the 4 histological subtypes. Currently, with the possible exceptions of obesity and cigarette smoking, there are no established modifiable risk factors which might provide the foundation for a prevention program aimed at reducing the incidence and mortality of cancers of the small intestine. More research with better quality and sufficient statistical power is needed to get better understanding of the etiology and biology of this cancer. In addition, more studies should be done to assess not only exposures of interest, but also host susceptibility.

Key words: Cancer of the small intestine; Histology; Incidence; Risk factors; Survival

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Pan SY, Morrison H. Epidemiology of cancer of the small intestine. *World J Gastrointest Oncol* 2011; 3(3): 33-42 Available from: URL: http://www.wjgnet.com/1948-5204/full/v3/i3/33.htm DOI: http://dx.doi.org/10.4251/wjgo.v3.i3.33

INTRODUCTION

The small intestine represents the longest part of the digestive tract, making up 75% of the length (about 6 m long and 4 times as long as the large intestine) and 90% of the absorptive surface area of the gastrointestinal tract. It has three sections: the duodenum, jejunum and ileum. Malignant tumors of the small intestine are rare all over the world[1], with a global incidence of less then 1.0 per 100 000 population[2]. Cancers of the small intestine or small bowel cancer (SBC) account for only 0.42% of total cancer cases and 2.3% of cancers of digestive system in the United States[3]; while in Canada, 0.37% and 1.78% respectively[4]. Mortality of the cancer is even lower, accounting for only 0.2% of the total cancer deaths in the United Sates and in Canada[3,4].

Because of its rarity and multiple histological subtypes, this cancer has been less studied and understanding of it is very limited. This paper will give a brief review of the

literature on its pathology, trends of incidence, mortality, international variation, risk factors and survival.

HISTOPATHOLOGY

There are around 40 different histological subtypes of small intestinal cancers; the most common types are adenocarcinoma, lymphoma, sarcoma and carcinoid tumor[5,6].

Adenocarcinomas

Approximately 30%-40% of the cancers observed in the small intestine are adenocarcinomas, a percentage much lower than the proportion in the colon where the overwhelming majority is adenocarcinomas. Most of the tumors located in the duodenum and the duodenal-jejunal junction are adenocarcinomas[5,7,8]. In the U.S. population, the average annual age-adjusted incidence rates per 100 000 population of carcinomas of the small intestine based on 1992-2006 data from the Surveillance, Epidemiology and End Results (SEER) were 1.45 and 1.00 for males and females respectively. Rates for blacks were more than twice those of whites (1.29 *vs* 0.63)[9].

Carcinoid tumors

This histological type accounts for some 35%-42% of neoplasms in the small intestine, most of which occur in the ileum and rarely in the duodenum[5,7,8]. Almost all neuroendocrine cancers of the small intestine are carcinoid tumors[1]. The average annual incidence rates per 100 000 population of neuroendocrine small intestine cancer in the U.S. for the period 1992 to 2006 were 1.00 and 0.70 for men and women respectively. Risks were higher for blacks [incidence rate ratio (IRR) = 1.63, 95% confidence intervals (CI) = 1.50-1.78)] and lower for Hispanics (IRR = 0.64, 95% CI: 0.56-0.72) and Asians/Pacific Islanders (IRR = 0.29, 95% CI: 0.24-0.34)[9].

Lymphomas

About 15%-20% of cancers of the small intestine are lymphomas with most occurring in the ileum and jejunum[7,8]. Primary lymphoma at this site include mucosa-associated lymphoid tissue (MALT) lymphoma, large B-cell lymphoma, Mantle cell lymphoma, immunoproliferative small intestinal disease (IPSID), Burkitt's lymphoma and enteropathy associated T-cell lymphoma, with MALT type as the most common lymphoma of the small intestine which accounts for 42.5% of the lymphomas as shown in one study[1,10]. Incidence rates in the US are low at 0.54 in males and 0.26 in females per 100 000 (age-adjusted) based on the SEER 1992-2006 data[9].

Sarcomas

Small intestinal sarcomas constitute only 10%-15% of the malignancies seen in the small intestine with a more even distribution throughout the small intestine compared to adenocarcinomas and carcinoid tumors[1,5,8,11]. There are various benign and malignant mesenchymal tumors arising in the small intestine. The most common type of sarcomas occurring in the small intestine is the gastrointestinal stromal tumors (GISTs) (representing over 90% of sarcomas)[12-15] which were classified as leiomyosarcomas or neurogenic tumors before the advent of KIT immunohistochemistry[1,12]. Other types are leiomyomas, leiomyosarcomas, lipoma, angiosarcoma and Kaposi's sarcoma[1]. According to the US SEER data (1992-2006), the average annual incidence rates per 100 000 population were 0.24 and 0.17 for males and females respectively. Risks were higher for Asians (IRR = 1.36, 95% CI: 1.13-1.62)[9].

DESCRIPTIVE EPIDEMIOLOGY

International variation and gender/racial difference

International data shows that the incidence is higher in North America, western Europe and Oceania than in Asia[2,8,16]. According to 1998-2002 data, the incidence rates were 1.4 per 100 000 for men and 1.0 for women in USA and Sweden, 1.1 (men) and 0.8 (women) in Canada, 1.4 (men) and 1.2 (women) in Norway, 1.2 (men) and 0.9 (women) in Australia and 0.7 (men) and 0.4 in Japan (women)[2]. The incidence rises after the age of 40 years for all histological subtypes with the increase much more rapid for carcinoma and carcinoid tumors than for lymphoma. Rates stabilize after the age of 70 years for carcinoid tumors whereas the incidence of sarcomas increases more slowly than other three types and stabilizes after the age of 60 years[8]. Men have higher incidence rates than women, overall and for all histological subtypes of small intestine cancer in most countries[2,5,7,8,17,18].

Of particular interest is the consistent finding of higher incidence rates in US black populations for both males and females compared to whites[2,8]. Furthermore, mortality rates among blacks of both genders are also elevated in comparison to whites, reflecting both their higher incidence rates and poorer overall 5 years survival[7]. Reasons for the differences in survival between US whites and blacks are largely unexplained. Examination of long-term surveillance data by histology subtype suggests that the incidence was higher in US blacks than in whites for adenocarcinomas and carcinoid tumors only while the incidence for lymphoma is higher in whites than in blacks with similar incidence for sarcoma between the two races[5,8,9].

A Finnish cohort study on 2.3 million people of 45-69 years of age during 1971-1995 revealed a higher incidence in the higher social classes, especially in males, with the differences more evident in the beginning of the follow-up period and absent by the end of the observation period[17]. However, another study on cancers of the small intestine in England, Scotland and Wales from 1975 to 2002 found no differences in survival by indices of social deprivation[18].

Temporal trends

The US SEER registries data of long-term surveillance show an increase in incidence rates of the small intestine from 1.18 in 1973 to 2.27 per 100 000 population in 2004, with the increase more than 4-fold for carcinoid tumors

(from 0.21 in 1973 to 0.93 in 2004) and less dramatic increases for adenocarcinomas (from 0.57 to 0.73) and lymphomas (from 0.22 to 0.44) and relatively stable for sarcomas (from 0.18 to 0.19)[7]. The increase occurred in both men and women and in both whites and blacks, but may be most pronounced among black males[8]. In addition, the UK study on cancers of the small intestine from 1975 to 2002 noticed increases in incidence but declines in mortality due to better survival[18]. The reason for the increase in incidence is largely unknown but it could be due to the increase in some risk factors such as the rising prevalence of obesity[8].

There is evidence of a geographical correlation between the incidence rates of small intestine and colon cancer[8], suggesting that the two cancers may share some risk factors. This geographical correlation and shared risk factors may partially account for the international variation in the incidence rate of small intestine cancer.

ETIOLOGY AND RISK FACTORS

The reason for the much lower incidence of small intestinal cancer than of colorectal cancer is largely unknown but has been hypothesized to be related to several mechanisms. The much quicker transit time of food in the small intestine than in the large intestine (because peristaltic ring contractions in the small intestine occur with greater frequency than in the colon) may result in shorter time of exposure of its mucosa to carcinogens. The small intestine has much lower bacterial load, thus has decreased concentration of potential carcinogens from bile acid breakdown[19]. High level of IgA expression in the small intestine may be protective against lymphoma[20]. Studies also demonstrate that the small intestine generates less endogenous reactive oxidative species (ROS) than the colon does, which may lead it to handle oxidative stress more effectively than the colon and results in less oxidative damage during times of exogenous oxidant stress in the small intestine than in the colon[21]. The differential response to DNA damage may explain the different cancer susceptibility between the small and large intestine[21,22].

Because of the rarity of SBC, relatively little is known about risk factors for SBC. However, the international correlation between rates of colon cancer and small intestine cancer suggests that some of the same factors which affect colon cancer incidence may be operative for small intestine cancers. For example, correlations between international per capita consumption of animal protein and fat and small intestine cancer rates are in the same direction as those seen for colorectal cancer[23], and coupled with what is known about bowel transit time in both the small and large intestine, suggest that a focus on factors found to be associated with colorectal cancer may be fruitful.

Predisposing diseases and medical conditions

Much of the knowledge generated to date on the origins and etiology of cancers of the small intestine comes from studies of gastrointestinal conditions. Small intestinal cancers have been observed to be more common in people with a number of inflammatory bowel diseases and conditions.

Inflammatory bowel diseases: Inflammatory bowel disease includes Crohn's disease and ulcerative colitis, two clinically related but histologically distinct diseases.

Crohn's disease is a long-term chronic condition of the gastrointestinal tract. It is characterized by transmural, granulomatous inflammation that occurs in a discontinuous pattern with a tendency to form fistulae. Crohn's disease is a recognized risk factor for cancer of the small intestine, with relative risks reported as high as 60[16,24-34]. A meta-analysis showed a relative risk of 33.2 (95% CI: 15.9-60.9) for small bowel cancer in patients with Crohn's disease[35]. Extended duration of the disease, distal jejunal and ileal location, male sex, small bowel bypass loops, strictures, chronic fistulous disease, young age of diagnosis and occupational hazards or exposure to halogenated aromatic compounds with aliphatic amines, asbestos and solvents are suggested to be associated with an increased risk of small bowel carcinoma in patients with Crohn's disease[6,24,29,31,36].

Ulcerative colitis has been shown to be associated with an increased risk of colorectal cancer, hepatobiliary cancer, nonmelanoma skin cancer and leukemia[37-42]. However, it is unclear whether patients with ulcerative colitis have an increased risk for cancers of the small intestine[34,38].

Celiac disease: Celiac disease is an inflammatory small intestinal disorder characterized by the inability of the small intestine to deal with the gluten fractions of cereals such as wheat, barley and rye; its prevalence is nearly 1% of general population[43-48]. Its prevalence has increased due to greater awareness, improved screening test and access to diagnostic facilities[49-53]. It occurs in genetically predisposed individuals *human leukocyte antigen-DQ2* or *DQ8* (*HLA-DQ2* or *DQ8*)[44,54]. There are indications that celiac disease is inheritable as there is evidence of familial aggregation[55,56]. In addition, homozygous twins have a 70% concordance for the disease[57]. Patients with celiac disease are at elevated risk of T-cell non-Hodgkin's lymphoma and also adenocarcinoma of the small intestine[58-62]. The risk of adenocarcinoma in patients with celiac disease is increased many-fold as compared with the risk in the general population[62] with reported relative risks between 60 and 80[58,59,63-65]. These carcinomas are most often located in the jejunum and are more likely to develop as an adenoma-carcinoma sequence than as dysplasia in flat mucosa[66].

Small intestine adenomas: Although the prevalence of adenomas in the small intestine is much lower than their prevalence in the colon, it is suggested that the adenoma-carcinoma sequence is as significant in the small intestine as in the large intestine[67,68]. As in the colon, adenoma in the small intestine appears to be a precursor of adenocarcinoma[20]. A large fraction of villous adenomas of the small intestine has been shown to progress to malignancy[69]. In a retrospective analysis of 192 villous adenomas

of the duodenum, the incidence of malignant changes at the time of presentation was 42%[70]. Most of the adenomas in the small bowel occur in the duodenum[68]. Villous histology, increasing size and a higher grade of dysplasia of the adenoma increase the risk of neoplastic transformation from adenoma to carcinoma[5,20].

Familial adenomatous polyposis: Familial adenomatous polyposis (FAP) is an autosomal dominant genetic disorder caused by mutations of the APC gene on the long arm of chromosome 5[71]. Most patients diagnosed with FAP have multiple adenomas in the small bowel, usually in the duodenum[72,73] and these patients are at increased risk of small intestinal cancer, especially duodenal cancer[70,74-76]. The prevalence of duodenal adenomatosis in FAP patients are 50%-90% and 3%-5% of these patients develop duodenal cancer; however, periampullary adenomas seem to have a high risk of malignant transformation[77].

Peutz-Jeghers syndrome: Peutz-Jeghers syndrome (PJS) is an autosomal dominant condition due to a mutation in the *serine/threonine kinase 11* (*STK11*) gene on the short arm of chromosome 19, characterized by melanin spots on lips and buccal mucosa and multiple gastrointestinal hamartomatous polyps[78-80]. Polyps in PJS subjects are usually found in the small intestine and are more common in the jejunum than the ileum, followed by the duodenum[81]. Patients with Peutz-Jeghers syndrome have been reported to be at elevated risk of both gastrointestinal and non-gastrointestinal cancers including breast and ovarian cancers in women, testicular tumors in males and cancers of the pancreas, esophagus, stomach and lung in both sexes[82-86]. PJS has been clearly demonstrated to be associated with an increased risk of small intestinal adenocarcinoma[20]. A meta-analysis of 210 PJS patients observed a statistically significant increase in relative risk for cancer of small bowel (RR = 520), stomach (RR = 213), colon (RR = 84), esophagus (RR = 57), pancreas (RR = 132), lung (RR = 17), breast (RR = 15.2), uterus (RR = 16.0) and ovary (RR = 27) respectively[82].

Associations with other cancers

Hereditary non-polyposis colorectal cancer: Hereditary non-polyposis colorectal cancer (HNPCC), or Lynch syndrome, is an autosomal dominant disorder related to a germline mutation in either the *Mut S homologue 2* (*hMSH2*) or *Mut L homologue 1* (*hMLH1*) mismatch repair gene[87,88]. HNPCC is associated with a substantially increased risk of cancers of the colorectum, endometrium, stomach, ovary, small intestine, urinary tract and brain[87,89-92]. The relative risk of small bowel cancer in patients with HNPCC has been estimated to be more than 100 compared with the general population, with a lifetime risk of 1%-7%[90,93]. The risk for SBC has been reported to be higher in *MLH1* mutation carriers than in *MSH2* mutation carriers[90]. HNPCC-associated SBC are mainly adenocarcinoma, occur at an earlier age and appear to have a better prognosis than those occurring in the general population[94,95].

Sporadic colorectal cancer: The demonstration of a geographical correlation between rates of SBC and colorectal cancer[8] suggest a common etiology. Various studies have shown that the risk of SBC following primary colorectal cancer were elevated; also, in those diagnosed with primary SBC, there was a 4 to 5-fold risk of developing colorectal cancer[96-101]. These studies suggest etiological similarities between cancers of the small intestine and colorectal cancers but, to date, potential common carcinogenic agents have not been elucidated in analytic epidemiological studies.

Other cancers: The risk of SBC has been reported to be elevated in patients with a diagnosis of non-Hodgkin's lymphoma and cancers of prostate, female genitalia, lung and skin, as well as others[102-106]. One study reported that SBC risk was increased (although not statistically significant) in patients diagnosed with merkel cell carcinoma of the skin[107].

Behavioral and environmental risk factors

Diet and alcohol consumption: Dietary factors have been suggested to be related to the risk of SBC. An ecological study of SBC mortality and food data by WHO showed correlations with per capital daily consumption of animal fat and animal protein (correlation coefficient were 0.61 and 0.75 respectively)[108]. A case-control study of 430 cases and 921 controls observed two-to three-fold increases in SBC risk with frequent intake of red meat and salt-cured/smoked foods but no association with alcohol consumption[23]. Another case-control study of 36 cases with small intestinal adenocarcinoma and 998 population controls also reported a significant increase in risk associated with frequent intake of foods rich in heterocyclic aromatic amines (based on the combined intake of fried bacon and ham, barbecued and/or smoked meat and smoked fish) in males only and with total sugar intake[109].

A hospital-based case-control study by Negri *et al*[110] found an increased risk of adenocarcinoma of the small intestine among the highest consumers of red meat and of refined carbohydrates, while a decreased risk was associated with consumption of fish and vegetables. However, the number of cases in this study was quite small (23 cases), leading to wide confidence intervals around point estimates of risk, and so these findings must be treated with caution. Moreover, the findings of this study apply only to adenocarcinomas of the small bowel and not necessarily to other histologies.

A prospective study of 494 000 men and women with up to 8 years of follow-up observed no clear relationship of red or processed meat with either adenocarcinoma or carcinoid tumors of the small intestine, but reported a significantly increased risk for carcinoid tumors with saturated fat intake, suggesting that saturated fat intake might account for the positive associations with meat intake found in previous studies[111]. Another prospective study of the same subjects reported an inverse association between intake of fiber from grains and from beans

and small intestinal cancer[112].

Negri *et al*[110] found no association between alcohol consumption and risk of adenocarcinoma of the small intestine. Two other studies also did not find a relationship between alcohol intake and SBC risk[23,113]. On the other hand, a few studies have observed a positive association between alcohol consumption and SBC, either adenocarcinoma[30,109] or carcinoid tumors[30]. Although a European case-control study did not find that the risk of small intestinal adenocarcinoma was associated with total alcohol and wine intake, it did show that a higher intake of beer or spirits was related to the risk of small intestinal adenocarcinoma[114].

Body mass index/obesity: A number of studies have examined the relationship between Body mass index (BMI), obesity and small intestine cancers, with varying results[5,110,115-118]. In a cohort of 28 129 hospital patients with a discharge diagnosis of obesity, the relative risk for cancer of the small intestine was 2.8 (95% CI: 1.6-4.5), with the increase seen in both men and women. However, the number of cases were small with only 9 cases in men and 8 cases in women observed[115]. A cohort study of two million Norwegians with 1 162 SBC cases (including 230 cases with cancer of the duodenum) demonstrated a moderately increased risk for SBC among overweight and obese men, and for cancer of the duodenum among obese women[116]. This is a large study with an average of 23 years of follow-up. Another cohort study of 362 552 Swedish construction workers (men) found that overweight (BMI 25.0-29.9) and obese (BMI $\geqslant$ 30.0) men had an elevated risk of small intestine cancer with a RR of 1.44 (95% CI: 1.01-2.04) and 1.16 (95% CI: 0.58-2.36) respectively[118]. The absence of a trend over the 2 groups of men argues against a causal relationship, although it must be noted that the study involved only 9 obese men with small bowel cancer. Moreover, Samanic *et al*[117] assessed cancer risk in a large cohort of U.S. white and black male veterans hospitalized with a diagnosis of obesity. This study demonstrated a 58% increase in risk of cancer of the small intestine in obese white veterans compared with the non-obese (RR = 1.58, 95% CI: 1.18-2.12), but no elevated risk in black men (RR = 1.07, 95% CI: 0.54-2.08). The finding of a significant relationship with obesity in whites but not in blacks again argues against causality; however, again, the number of black cases was small (9 cases).

Not all studies have shown an association with BMI or obesity. The case-control study by Chow *et al*[23] observed no association with BMI. The case-control investigation by Negri *et al*[110] actually observed an inverse relationship between BMI and risk of small intestine cancer, as did another hospital-based case-controls study of carcinoid tumors[113].

Thus, while analogy to risk factors known to be involved in colorectal cancer is an attractive model for investigation of risk factors for small intestine cancers, the data to date involving diet are too scanty to enable any conclusions to be drawn. The positive association seen between measures of obesity in several cohort studies requires confirmation before recommendations for prevention can be made.

Cigarette smoking: Cigarette smoking has been consistently shown to be associated with the risk of small intestine cancer[30,109,119] although the evidence is still limited. One study noted that cigarette smoking was associated with increased risk for both adenocarcinoma and carcinoid tumors[30], whereas a European case-control studies suggest a modest increase in risk for malignant carcinoid tumor[119] but no association with adenocarcinoma[114]. The study by Hassan *et al*[113]did not demonstrate a significant association for carcinoid tumors.

Other risk factors: Biliary tract diseases such as cholecystitis and gallstones have been suggested to be a risk factor or promoter of SBC. A Danish study of 42 098 patients diagnosed with gallstones[120] demonstrated an elevated risk for cancer of the small intestine associated with presence of gallstones. The association was mainly confined to carcinoid tumor but was observed both in early (1-4 years) and late (5-16 years) follow-up. A further investigation by Kaerlev *et al*[119] confirmed the gallstone association; however, the association may be due to enhanced medical surveillance during the early phase of the cancer disease. A small case-control study of 19 cases of adenocarcinoma and 17 cases of malignant carcinoid tumors suggested a significant association of cholecystectomy with both adenocarcinoma and malignant carcinoid tumors[30].

There are suggestions that infections of *Helicobacter pylori* and *Campylobacter jejuni* are related to the risk of developing lymphoma of the small intestine, especially IPSID[1,121-127]. But research on this area is scarce and the evidence is too limited.

Other evaluated medical histories in relation to small bowel carcinoid tumors[119] include hepatitis, cirrhosis of the liver, use of corticosteroids and exposure to ionizing radiation through medical treatment with radioactive substances, with no association observed; however, an association between carcinoid tumor and oophorectomy was noted, although it has not been explained or replicated in other studies.

In an analysis assessing the correlation between satellite-measured ground-level solar UV-B and cancer incidence (1998-2002) and mortality (1993-2002) in the United States, Boscoe *et al*[128] observed an inverse relationship, i.e. higher rates of small intestine cancer in the north than in the south. The authors suggest that the lower incidence and mortality in southern states than in the north may be related to higher levels of serum vitamin D in people in the south due to the increased levels of ambient UV-B.

In addition, several findings have emerged from occupational studies. Elevated risks of small bowel cancers have been seen in Australian nuclear industry workers[129]. A European population-based case-control study observed an elevated risk of carcinoid tumor of the small intestine among shoemakers, structural metal preparers, construction painters and other construction workers, bookkeepers, machine fitters and welders, as well as among people with regular occupational exposure to organic solvents and rust-preventive paint containing lead[130].

SURVIVAL AND PROGNOSIS

According to the data from US SEER data for the period 1992 to 2005, the 5 years relative survival was 80.7% for neuroendocrine (primarily carcinoid) cancers, 28.0% for carcinomas, 57.9% for sarcomas and 64.1% for lymphomas[9]; while for patients who underwent resection, the 5 years observed survival was 64.6% for carcinoid tumors, US SEER data for the period 1992 to 2005, 32.5% for adenocarcinomas, 39.9% for sarcomas and 49.6% for lymphomas based on 1985-2000 SEER data[7]. Although other cancer sites have demonstrated higher long-term survival rates due to novel adjuvant therapies over the last 2 decades, the US data from 1985 to 2000 showed no significant change in long-term survival rates for any of the 4 histological subtypes[7]. Another study observed an improvement in survival rates in England, Wales and Scotland over the time period of 1975 to 2002 but the changes were not statistically significant because of the small number of patients[18]. A Swedish study found 5 years survival rates of 39% for duodenal adenocarcinoma and 46% for jejuno-ileal adenocarcinoma[131].

Earlier tumor stages at diagnosis (stage Ⅰ and Ⅱ), small tumor size and curative resection have been identified as factors for favorable overall survival, whereas poorly differentiated tumors, lymph node involvement or metastasis and distant metastases as factors predicting poor prognosis[1,132-134]. For small intestinal lymphoma, the survival is largely determined by histological grade, stage and respectability[1] with a higher survival for B-cell lymphoma than for T-cell lymphoma[135]. For small intestinal sarcomas, the prognosis is mainly dependent on the mitotic count, size, depth of invasion and presence of metastasis[1]. As the US data demonstrates[7], age is suggested as a more powerful prognostic factor for carcinoid tumors compared with the other histology subtypes. In addition, being male and black is associated with a poorer prognosis.

Recent randomized controlled trials demonstrated that with the development of *imatinib* and *sunitinib*, the median overall survival of advanced GIST has improved from approximately 2 years to over 5 years[136]. A systematic review also suggested that *imatinib* used in the adjuvant setting improved recurrence-free survival of KIT-positive localized GIST[137]. Imatinib is a small molecule tyrosine kinase inhibitor active against KIT and platelet-derived growth factor-α, while sunitinib is a broad spectrum tyrosine kinase inhibitor[136].

CONCLUSION

Cancers of the small intestine are rare. They are comprised of 4 major histological types (adenocarcinomas, carcinoid tumors, lymphomas and sarcomas). The different tissues of origin suggest that each type may have a unique etiology, adding to the difficulties of obtaining adequate numbers for analysis.

The incidence of small intestine cancer has increased over the past several decades, with the increase more than 4-fold for carcinoid tumors and less profound for adenocarcinoma and lymphoma and relatively stable for sarcomas. There are excesses of small intestinal cancers in patients with Crohn's disease, celiac disease, adenoma, familial Adenomatous polyposis and Peutz-Jeghers syndrome. Although there are correlations between the incidence rates of small and large bowel cancers (at least on the adenocarcinomas), there are basically no well established hypotheses to test about etiology.

Currently, with the possible exceptions of obesity and cigarette smoking, there are no established modifiable risk factors which might provide the foundation for a prevention program aimed at reducing the incidence and mortality of cancers of the small intestine. More research with better quality and sufficient statistical power is needed to get better understanding of the etiology and biology of this cancer. In addition, more studies should be done to assess not only exposures of interest but also host susceptibility, for example, genes related to celiac disease, FAP, PJS and HNPCC could be the candidates for host susceptibility genes because of the excess of small intestinal cancers in patients with these conditions.

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