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Risk Factors of Small Intestine Cancer: An Epidemiological Analysis and Their Role in Early Diagnosis - A Literature Review

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ABSTRACT:
Introduction: Small intestinal cancer is a rare form of cancer affecting the duodenum, jejunum, or ileum. Its incidence is increasing, although it is less commonly diagnosed than colorectal cancers. Understanding risk factors is crucial for early detection and prevention. These factors include non-modifiable ones like sex, race, age, and genetic conditions, as well as modifiable factors like diet, alcohol, smoking, and obesity.
Materials and Methods: A search of PubMed with the keywords "small intestine cancer" and "risk factors" identified 928 articles. After review, 48 publications and one textbook, were included.
Results: Small intestine cancer is more common in men and African Americans. Genetic conditions such as Lynch syndrome, Familial Adenomatous Polyposis (FAP), Peutz-Jeghers syndrome (PJS), and Multiple Endocrine Neoplasia (MEN1) significantly increase the risk. Chronic conditions like Crohn's disease and celiac disease also increase risk. Diets high in red meats, processed foods, and animal fats, are linked to higher risk.

Discussion: Age and sex are key non-modifiable risk factors, with risk increasing with age, particularly over 60. Genetic conditions like Lynch syndrome, FAP, and PJS are major contributors. Chronic inflammatory diseases such as Crohn's and celiac disease raise risk. Diets rich in animal fats, processed meats, and smoking contribute to higher risks, as does obesity. Healthy diet, quitting smoking, and maintaining a healthy weight, may reduce risk.
Conclusion: Genetic mutations, such as those in Lynch syndrome, FAP, and PJS, are significant risk factors, while lifestyle factors like diet, smoking, and obesity also play a role. Increased surveillance for individuals with genetic predispositions or inflammatory conditions may allow for earlier detection. Despite limited data, a balanced diet, weight management, and avoiding smoking may help reduce risk. Further research is needed to improve prevention strategies.

Keywords: small intestine, risk factors, epidemiology, ileum cancer

INTRODUCTION

Small intestine cancer, though relatively rare compared to other gastrointestinal cancers, is a serious health condition that can significantly impact those affected. It refers to cancer that develops in the tissues of the small intestine, which is responsible for absorbing nutrients from food. This type of cancer includes various forms such as adenocarcinoma, carcinoid tumours, and lymphoma, each with different characteristics and treatment approaches.

Small intestine cancer is often challenging to diagnose due to its location and the non-specific nature of early symptoms, which may include abdominal pain, unexplained weight loss, and changes in bowel habits. By the time it is diagnosed, the cancer is frequently at an advanced stage, which complicates treatment. Factors that increase the risk of developing small intestine cancer include genetic predispositions (such as Lynch syndrome or familial adenomatous polyposis), chronic conditions like Crohn's disease and celiac disease, and certain lifestyle factors such as diet and smoking.

Despite its rarity, small intestine cancer can be aggressive, and its prognosis is heavily dependent on the stage at diagnosis. Treatment typically involves surgery, chemotherapy, or targeted therapies, depending on the type and extent of the cancer. Early detection remains crucial for improving outcomes, and ongoing research is essential to better understand the disease and identify more effective treatments.

LITERATURE REVIEW

1. Non-modifiable risk factors

1.1 Sex

Men are more frequently diagnosed and die from small intestinal cancer than women. In the United States, the frequency of small intestinal cancer for men in 2018 was 2.6, and 1.0 for women. The frequency for African American men was 4.2, and for African American women was 2.5. Studies conducted in the United Kingdom show that the incidence rate of small intestinal cancer is comparable for both sexes: 2.1/100,000 men and 2.2/100,000 women. The rate of small intestin cancer diagnoses for men in Scotland was 3.5/100,000, which is higher than average in the UK. The incidence rate for women in Scotland is lower, at 1.6/100,000.

According to statistics from the United States and Sweden covering the years 1998-2002, the incidence of small intestine cancer was 1.4 and 1.0 for men, and 1.0 for women in both the United States and Sweden. In Japan, the incidence rate was 0.7 for men and 0.4 for women. In the United States, the male-to-female mortality ratio is 1.6:1.0. In the United Kingdom, although men are diagnosed more often, the survival rate for men is higher than for women [1]. In the case of adenomas and carcinoids of the small intestine, men have an increased risk of developing these compared to women [2,3].

1.2 Race and ethnicity

The incidence of small intestine cancer for African Americans in the United States is 1.6-1.8 times higher than for White Americans. African Americans also have proportionally higher mortality rates. Based on data from 1998-2002, small intestine cancer was least common among residents of Asia, Pacific Islanders, Native Americans, and residents of Alaska, and most common in North America and Europe [1]. In a study published in 2013, non-Hispanic White individuals had an increased risk of malignant carcinoid tumors of the small intestine, while non-Hispanic Black women had an increased risk of adenocarcinoma [3].

1.3 Age

The average age of diagnosis is 60 years [4]. In the United States, the median age at diagnosis is 66 years. In the United Kingdom, the average age of diagnosis is 80-84 years. After the age of 40, the risk of developing the disease increases. The median age of death in the United States is 72 years, while the peak mortality in the United Kingdom occurs at 85-89 years, which is surprising information [1].

1.4 Inherited mutations

1.4.1 Lynch syndrome

Lynch syndrome is an inherited condition that predisposes individuals to colorectal cancer, but also to small intestine cancer, with the risk being 100 times higher than in the general population [4, 10]. A study conducted between 2006 and 2009 showed a 1% risk of small bowel adenocarcinoma (SBA) for individuals with Lynch syndrome [8]. A study published in 2018, which involved 3,119 patients, demonstrated that the risk of duodenal cancer in individuals with Lynch syndrome was 6.5% for mutations in the MLH1 gene and 2.0% for mutations in the MSH2 gene [9]. A French study found Lynch syndrome in 7% of patients with small bowel adenocarcinoma (SBA). In 61% of cases, the tumor was located in the duodenum, in 30% in the jejunum, and in 9% in the ileum [7]. In another study, the relative risk of SBA ranged from 25 in the early stages of Lynch syndrome to 291 in individuals with a mutation in MLH1. However, this risk is still low, and according to the French registry, it is 1% [1]. In patients with Lynch syndrome, small intestine cancer appears 10-20 years earlier than in the general population [10]. If a patient presents with abdominal pain, bleeding, or anemia, small bowel cancer should be considered in the diagnosis.

1.4.2 Familial adenomatous polyposis (FAP)

Familial adenomatous polyposis (FAP) is associated with a mutation in the APC gene, which leads to the formation of numerous colorectal polyps and colorectal cancer [2]. In a study involving 1,255 patients with familial adenomatous polyposis, it was reported that 57 patients (4.5%) developed adenocarcinoma of the upper gastrointestinal tract. The most common locations were the duodenum (12%), jejunum (8.5%), and ileum (1.7%) [5]. In another study, the relative risk of duodenal adenocarcinoma was 330, and for papillary duodenal adenocarcinoma, it was 123 in FAP patients compared to the general population [6]. A prospective French study published in 2020, which included 347 patients with small bowel adenocarcinoma (SBA), estimated that 1.7% of SBA cases occurred in conjunction with FAP [7]. The results confirm the increased risk of small intestine cancer in patients with familial adenomatous polyposis.

1.4.3 Peutz - Jeghers syndrome (PJS)

This is an autosomal dominant inherited disease, characterized by a mutation in the tumor suppressor gene LKB1. Small intestine cancer occurs frequently in this syndrome [4]. A study involving 210 individuals reports that the relative risk of small intestine cancer is 520 times higher than in the general population [11].

1.4.4 Multiple endocrine neoplasia syndrome type 1 (MEN1)

MEN1 is an inherited autosomal dominant disease caused by a mutation in the MEN1 gene. It is the most common hereditary syndrome associated with neuroendocrine tumors (NETs), including those in the upper gastrointestinal tract. Defects in MEN1 account for 5–10% of all GI NETs [1].

1.4.5 Neurofibromatosis type 1

Neurofibromatosis type 1 is an autosomal dominant inherited disorder. It occurs in the general population with a frequency ranging from 1 in 2,500 to 1 in 4,000. Patients with this condition have a 2-4 times higher risk of developing stromal and neuroendocrine tumors [12].

1.5 Crohn's disease (CD)

Crohn's disease is a proven risk factor for small intestine cancer. Patients with Crohn's disease have a 100 times higher risk than the general population. Small intestine cancer in these patients is located in the ileum in 83%, in the jejunum in 10%, and in the duodenum in 7%. As the disease duration increases, the risk of developing small intestine cancer also rises. The risk significantly increases after 10 years and peaks after 20 years. Protective factors in patients with Crohn's disease include the chronic use of salicylates and resection of the terminal ileum [4, 13]. A cohort study involving 11,759 patients with Crohn's disease of the small intestine estimated the standardized incidence ratio of small bowel adenocarcinoma (SBA). In all patients, it was 34.9, and 46.0 in patients with Crohn's disease for more than 8 years [13]. SBA occurring in Crohn's disease has an aggressive course with frequent metastases [7]. SBA in Crohn's disease differs from de novo SBA. In Crohn's disease, it develops as a result of long-term inflammatory processes in the ileum. This is likely the cause of premature death in patients with early-onset Crohn's disease [14].

In patients with Crohn's disease involving the small intestine, and in those with worsening symptoms or resistance to treatment, small intestine cancer should be excluded [1].

1.6 Celiac disease

Celiac disease is an autoimmune disorder triggered by the consumption of gluten. The autoimmune response leads to inflammation, damage to enterocytes, and an increased risk of precancerous changes, which can result in small intestine adenocarcinoma and small bowel lymphoma. The development of small intestine cancer in these patients is likely caused by a disruption in DNA repair mechanisms. Small intestine cancers diagnosed in celiac disease generally have a better prognosis and are detected at earlier stages compared to lymphomas [4]. In a study involving 259 individuals with celiac disease and histologically confirmed malignancy, 19 patients had small bowel adenocarcinoma, and 133 had malignant lymphoma, with 80% of lymphomas located in the small intestine [15]. A British study, including 295 patients with small intestine cancer, found that celiac disease was associated with 13% of small bowel adenocarcinoma cases, mainly located in the jejunum. According to a Swedish study, the relative risk of developing small bowel adenocarcinoma in celiac patients is 10 [16]. In another study from the same country, the risk ratio for small bowel adenocarcinoma was 3.05 [18]. An Italian study on celiac patients showed that 0.65% developed small bowel adenocarcinoma. A French study found that 1.5% of patients with small bowel adenocarcinoma had celiac disease [7]. In a Swedish study, the mortality risk was calculated using standardized mortality ratios (SMR), comparing mortality rates in celiac patients with those in the general Swedish population. The risk of death increased in cases of small bowel cancer (SMR-17.3) [17]. Since celiac disease can coexist with SBA, patients with small bowel adenocarcinoma should be screened for celiac disease.

1.7 Intellectual disability (ID)

A study conducted in Sweden included 3,531,305 individuals, of which 27,956 had been diagnosed with intellectual disability (ID). The study involved live-born children in Sweden whose mothers were born in Nordic countries. Patients were followed from birth until the diagnosis of cancer, emigration, death, or until they reached the age of 43, whichever came first. A total of 188 cases of cancer were identified among individuals with ID. A statistically significant increase in the risk of cancer was observed for all types of cancer. For small intestine cancer, the hazard ratio (HR) was 12.0. The risk of developing cancer was not modified by the severity of ID or sex but was higher in cases of syndromic ID [49].

2. Modifiable risk factors

2.1 Diet

Among the risk factors for small intestine cancer are a diet rich in animal fats, red and smoked meats, and salt [4]. Most nutrients are absorbed in the duodenum and jejunum, while in the ileum, the food content stays longer than in its proximal sections. Small bowel adenocarcinoma is typically located in its proximal part. It is suspected that lipids and large proteins that pass through the cell membrane in the proximal parts of the intestine may be involved in carcinogenesis [19].

When comparing the transit time in the small intestine and colon, dietary carcinogens have a shorter contact time with the cells of the small intestine than with those of the colon [7]. A case-control study showed that consuming large amounts of red and salted or smoked meat results in a 2-3 times higher risk of developing small intestine cancer [20]. Another case-control study found that consuming large amounts of smoked and fried meats rich in heterocyclic amines and aromatic hydrocarbons increases the risk of small intestine cancer in men, but not in women [21]. A further study showed an association between saturated fats found in meat and small intestine cancer [22]. In 2015, the International Agency for Research on Cancer (IARC) classified processed meat as a carcinogen and red meat as a probable carcinogen for small and large bowel cancers. Consumption of fiber from cereals and vegetables accelerates transit time and likely shortens exposure to carcinogens, which has been considered a protective factor against small intestine and colon cancer [23].

2.2 Alcohol

Studies analyzing the impact of alcohol on the risk of small intestine cancer are limited, and no association between alcohol and this cancer has been detected [20, 24, 25]. A European study showed that consuming beer and strong alcohols increases the risk of small intestine adenocarcinoma, while consuming red wine does not [26]. Another study shows that individuals with small intestine adenocarcinoma consumed more alcohol than the entire cohort. Alcohol consumption was not associated with the risk of malignant carcinoid tumors of the small intestine (overall or divided into wine, beer, and liquor) [3]. A study conducted in the United States suggests that alcohol consumption is a risk factor for small intestine neuroendocrine tumors (SINT), regardless of family history [27]. A study including a European population did not identify alcohol as a risk factor, regardless of the amount of alcohol in beer [28].

2.3 Smoking

A European study shows a significant impact of smoking on neuroendocrine tumors of the small intestine [26, 30]. A study conducted in the United States confirms that smoking is a risk factor for small intestine neuroendocrine tumors (SINT), regardless of family history [27]. Other studies suggest that smoking increases the risk of neuroendocrine tumors and small intestine adenocarcinoma [29-31]. A European study reports that the relative risk of small intestine cancer remained high among former smokers who quit more than 10 years ago, and this association was observed regardless of the number of cigarettes smoked. The tumor was located in 63% of cases in the ileum, 7% in the duodenum, 1% in the jejunum, and in the remaining cases, it was found in two or more regions [26]. In another study, the percentage of current smokers was lower among individuals with malignant carcinoid tumors of the small intestine and small intestine adenocarcinoma (regardless of gender) compared to the percentage of smokers in the entire cohort, and no associations were found between smoking and the risk of small intestine cancer [3]. The biological impact of tobacco smoke is probable, but the basis for its potential carcinogenic effect is unclear. The links between smoking and small intestine cancer are not strong. Smoking is considered a weak risk factor for small intestine cancer [26].

2.4 Obesity

Studies investigating the impact of obesity on the risk of small intestine cancer show conflicting results. One study estimated the relative risk at 2.8 for individuals diagnosed with obesity [32]. Another study set the relative risk at 1.1 for obese individuals and 1.44 for those with overweight [34]. Other studies have shown that obesity increases the risk of small intestine cancer in men, but not in women [33, 40]. Several studies found no impact of body mass index (BMI) on the risk of small intestine cancer [20, 24-26, 34]. A European study identified abdominal obesity as a potential risk factor for small intestine adenocarcinoma [35]. In a large Norwegian study, which included over two million patients, small intestine cancer was diagnosed in 1,162 individuals. 50% had carcinoid tumors, and 35% had adenocarcinomas. An increased risk of small intestine cancer was observed with rising BMI, regardless of gender [33]. The inconsistency of these findings may be due to the small sample size, given the rarity of the disease.

2.5 Gastric acid, bile, and pancreatic enzymes

The proximal part of the small intestine has higher concentrations of bile and pancreatic juice than the distal part. Bile can be converted by bacteria into deoxycholic acid, which is carcinogenic, potentially serving as a risk factor for adenocarcinoma. The reliability of this data is difficult to verify [19]. The frequency of duodenal adenocarcinoma can be explained by the constant irritation of the mucosa caused by gastric acid, bile, and pancreatic enzymes [7].

2.6 Gallstones and cholecystectomy

In the United States, the co-occurrence of gallstones or bile duct stones with small bowel cancer was analyzed in a population of 3.41 million military veterans. It was not found that gallstones are a risk factor for small bowel cancer [36]. In another study, an increased occurrence of small bowel adenocarcinoma (SBC) was observed in patients with gallstones and gallstone surgery that occurred within two years prior to the diagnosis of SBC. This association is likely due to detection bias, as both conditions may have been detected during the same medical examination [26]. Two case-control studies conducted in the United States showed a significant association between cholecystectomy and the development of small bowel neuroendocrine tumors (NETs) [37, 43]. Two population-based case-control studies found a significant association between gallstones and the development of small bowel NETs [28, 37]. Another study showed that cholecystectomy reduces the risk of small bowel cancer, whereas gallstones increase this risk [38]. A Danish study found that gallstones increase the risk of small bowel cancer, mainly for neuroendocrine tumors. This association may be caused by increased medical surveillance in individuals with gallstones. Another theory is that in the case of gallstones, more bile is produced, which may have carcinogenic effects. Another study shows that individuals who have undergone cholecystectomy have an increased risk of small bowel cancer [1].

2.7 Cholangitis

A study conducted in Denmark included 4,333 patients with cholangitis (including 178 individuals with primary sclerosing cholangitis). During the 17-year observation period, 477 gastrointestinal cancers were observed.

An increased risk was noted for small bowel cancer, with the standardized incidence ratio (SIR) being 18.2. Cholangitis was considered a marker of occult gastrointestinal cancer [39].

2.8 Triglycerides level

The study was conducted across six cohorts from Austria, Norway, and Sweden, including 807,485 individuals. During the observation period, 339 cases of small bowel cancer were diagnosed (54% were neuroendocrine tumors, 29% were adenocarcinomas, and 17% were other or unknown types). It was shown that triglycerides were positively and linearly associated with the risk of small bowel cancer in women. No such associations were observed in men. The cause may be the difference in hormone composition between men and women [40].

2.9 Colorectal cancer

The occurrence of colon cancer increases the risk of small bowel cancer and vice versa [4, 20]. In patients diagnosed with colon and rectal cancer, the risk of developing a second cancer was significantly elevated. Patients with colon cancer diagnosed before the age of 75 had a higher risk of developing small bowel cancer compared to the general population [41]. Another study involving 2,581 patients with small bowel cancer found that colorectal adenocarcinoma increases the risk of small bowel cancer, and vice versa, regardless of gender. This may be due to shared risk factors for both colon and small bowel cancers [42].

2.10 Family history of cancer

Studies conducted in the United States have shown that a family history of any type of cancer increases the risk of developing malignant carcinoid tumors of the small intestine. Research conducted in Sweden and Finland found that neuroendocrine tumors (NETs) of the small intestine in first-degree relatives increase the risk of developing this type of cancer. It was also shown that kidney cancer and polycythemia vera among first-degree relatives may be risk factors. A study conducted in Sweden revealed an increased risk of neuroendocrine tumors of the small intestine in individuals whose parents had carcinoid tumors. Another study found that the occurrence of oral cancer in siblings is a risk factor for neuroendocrine tumors of the small intestine. Another study conducted in the United States showed that the occurrence of colorectal cancer or prostate cancer in first-degree relatives is a risk factor for developing neuroendocrine tumors of the small intestine [43]. In a different study, borderline significantly increased risk of malignant carcinoid tumors of the small intestine was observed in individuals with a positive family history of any cancer, colorectal cancer, or personal history of colorectal polyps [3]. The risk of small bowel cancer was also studied in patients whose parents had pancreatic cancer. An increased risk of small bowel cancer was found, and this association may indicate the presence of Lynch syndrome in some families [44].

2.11 Hormone therapy during menopause

A prospective study conducted in the United States found a link between the use of menopausal hormone therapy and neuroendocrine tumors of the small intestine. The risk ratio for women who had previously used menopausal hormones was 2.29, and 1.94 for women currently using menopausal hormones, compared to women who had never used such therapy [43].

Another study showed that the use of hormonal therapy during menopause increases the risk of malignant carcinoid tumors [3].

2.12 Medicines

A study conducted in Denmark examined the long-term use of aspirin and its impact on cancer risk in Denmark. The study involved 1,909,531 people, and 422,778 cases of cancer were diagnosed during the average follow-up period of 18.2 years. Long-term aspirin use (≥5 or ≥10 years) was associated with at least a 10% reduction in the risk ratio for small bowel cancer [45]. Another Danish study investigated the impact of bisphosphonate use in patients with osteoporosis on the cause of death. Death due to small bowel cancer reached statistical significance for etidronates [46]. Long-term use of medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids does not lower the risk of small bowel cancer [1]. However, long-term use of salicylates in patients with Crohn's disease reduces the risk of small bowel adenocarcinoma [4, 13].

2.13 Vitamin C

A Mendelian randomization study conducted on Finnish and British populations found a potential protective effect of high vitamin C levels on the risk of developing small bowel cancer. The study included 676,796 participants. The findings regarding the impact of vitamin C on the risk of small bowel cancer require further investigation [47].

2.14 Occupational risks

Studies that have shown a connection between specific occupations and the risk of small bowel cancer require confirmation due to the rarity of the disease. One study found that Australian nuclear power plant workers have an increased risk of small bowel cancer, despite radiation exposure being regulated. Another study indicated that those at risk include workers exposed to organic solvents and anti-corrosive paints containing lead, welders, accountants, construction workers, metal fabricators, and shoemakers [1]. In another study, it was shown that mortality among Dutch miners with pneumoconiosis was statistically higher than expected, with small bowel cancer being one of the causes [48]. Another study suggests that the risk of adenocarcinoma of the small bowel was increased among building caretakers, housewives, farm workers, dry cleaning workers, textile industry workers, and welders. Identifying the actual risk factors is difficult due to the rarity of the disease [30].

2.15 Physical activity

A study conducted in the United States included 237 cases of small bowel cancer. The impact of physical activity was assessed through questions about exercise, sports, and activities such as lifting heavy loads. Intense physical activity was defined as activity that caused rapid breathing, increased heart rate, or sweating, and lasted for more than 20 minutes.

It was observed that individuals with small bowel adenocarcinoma were less active than the entire cohort. However, this finding did not establish a sufficient connection and was not considered a risk factor for small bowel cancer [3].

2.16 Intestinal flora

Chemicals produced by bacteria may have carcinogenic effects or disrupt the division of epithelial cells in the intestinal lining. This theory seems plausible in the case of colon cancer due to the high number of bacteria in that part of the digestive tract. However, the reason for the higher occurrence of adenocarcinomas in the jejunum rather than the ileum is difficult to explain. The proximal part of the small intestine contains fewer bacteria, yet it shows a higher incidence of adenocarcinomas than the distal part of the small intestine. This may be due to the difference in the number of aerobic bacteria, which are more abundant in the proximal part of the small intestine [19].

DISCUSSION

The findings of this study highlight the complex interplay between genetic, environmental, and lifestyle factors in the development of small intestine cancer. While the overall incidence remains relatively low, the risk is notably higher among specific populations, such as men and African Americans. The increased risk among individuals with Lynch syndrome, FAP, and PJS emphasizes the importance of genetic screening and early surveillance for those at higher genetic risk.

The role of inflammatory diseases like Crohn’s disease and celiac disease is another critical consideration. Long-term inflammation in Crohn's disease, particularly in the ileum, significantly elevates the risk of adenocarcinoma in the small intestine. Moreover, the autoimmune processes involved in celiac disease may disrupt DNA repair mechanisms, further increasing the risk of cancer development.

Dietary and lifestyle factors, such as the consumption of red meats, alcohol, and tobacco, are modifiable factors that contribute to an increased risk of small intestine cancer. While the evidence for alcohol remains limited, studies show that smoking and obesity are more consistently associated with small intestine cancer, particularly neuroendocrine tumors and adenocarcinoma. Given the rarity of the disease, however, the difficulty in establishing strong associations between these lifestyle factors and cancer risk remains a challenge.

In addition, the findings suggest the potential for preventive strategies, particularly for individuals with Crohn’s disease or genetic syndromes. Early screening and lifestyle modification could mitigate some of the risks, particularly for individuals who are genetically predisposed to this rare cancer.

CONCLUSION

Small intestinal cancer is a rare but complex disease influenced by a combination of non-modifiable and modifiable risk factors. Non-modifiable factors like sex, age, race, genetic mutations, and underlying medical conditions contribute significantly to the development of this cancer. Among modifiable factors, diet, smoking, obesity, and certain medications can influence the risk, but the relationship between these factors and the disease is often nuanced.

Understanding the role of these risk factors is crucial for identifying individuals at high risk, enabling earlier detection and personalized prevention strategies. Given the rarity of small intestine cancer, further research is needed to refine our understanding of its etiological factors, particularly in terms of modifiable lifestyle changes and their impact on disease development.

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