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Original article

Risk of cancer in patients with irritable bowel syndrome: a nationwide population-based study

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ABSTRACT

Purpose: The aim of our study was to evaluate the overall cancer risk among patients with the irritable bowel syndrome (IBS) by using a nationwide population-based data set.
Methods: We obtained data on newly diagnosed IBS patients (age ≥ 20 years) without antecedent cancer from the Taiwan National Health Insurance Research Database for the period between 2000 and 2010. Standardized incidence ratios (SIRs) were calculated for various types of cancer in the IBS patients.
Results: A total of 1,043 people among the 29,838 IBS patients had developed cancer, and the follow-up was 139,185 person-years (median, 4.56 years), leading to a significantly increased SIR (1.18; 95% confidence interval [CI]) = 1.11–1.26) among all cancer types. However, after excluding cancer that developed within the first year after IBS diagnosis, the increased SIR of overall cancer was nonsignificant. In particular, the IBS patients exhibited an increased risk of cancers of the colon and rectum (SIR = 1.51; 95% CI = 1.31–1.73), liver and biliary tract (SIR = 1.40; 95% CI = 1.21–1.62), pancreas (SIR = 1.56; 95% CI = 1.02–2.28), and kidney (SIR = 1.56; 95% CI = 1.10–2.15).
Conclusions: An increased SIR in IBS patients was observed only within the first year of IBS diagnosis. The findings of this study might have resulted from detection bias, localized symptoms, or paraneoplastic syndromes associated with IBS-like symptoms. Additional prospective studies are necessary to confirm these findings.

Introduction

Irritable bowel syndrome (IBS) is among the most common reasons for patients seeking medical advice from primary care doctors and gastroenterologists [1]. IBS is characterized by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits. Prevalence estimates for IBS vary widely among different geographic regions [2]. Epidemiologic studies have revealed that the estimated lifetime prevalence rate for the IBS ranges from 6% to 46% worldwide [3–5]. In Taiwan, the prevalence rate is between 17.5% and 22.1%, and nearly 50% of the patients with IBS symptoms consult physicians [6]. In the Chinese population, IBS patients account for 11.3% of gastroenterology outpatients [7]. Despite the availability of several treatment options, IBS remains a major public health concern. IBS exerts a detrimental effect on patients' work, education, social relationships, and quality of life [6,8], and it has consistently been associated with considerable disability and use of medical services [9,10]. IBS has been reported as the second leading cause, after the common cold, of absence from work or school.

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The etiology of IBS remains unclear. The disorder is often described as a functional disease, and functional gastrointestinal diseases are not caused by structural or biochemical abnormalities. Therefore, the diagnosis of IBS is based on the presence of typical symptoms and exclusion of specific organic diseases. According to the current diagnostic standard, the Rome III criteria, IBS is distinguished into the following three subtypes on the basis of typical features: IBS with constipation, IBS with diarrhea, and mixed IBS [11]. Identifying a patient's predominant gastrointestinal complaint is crucial in selecting the appropriate diagnostic test and treatment. Along with an assessment of symptom-based criteria, a test should be conducted for the presence of concerning features that identify patients requiring a more detailed evaluation to exclude organic disease. Such features include the onset of symptoms after the age of 55 years, progressively worsening symptoms, unexplained weight loss, gastrointestinal blood loss, family history of organic gastroenterological disease, and unexplained iron-deficiency anemia [12].

Because IBS is a symptom-based disorder, treatments can address abdominal symptoms such as pain, bloating, or bowel symptoms, including diarrhea and constipation. First-line IBS therapies primarily involve over-the-counter medications aimed at ameliorating diarrhea or constipation. However, compared with prescription medications, over-the-counter medications offer fewer benefits for relieving all IBS symptoms such as pain and bloating. During the past decade, lifestyle adjustment and dietary intervention have become critical first-line treatment options. Other prescription medications, such as antidepressants, prosecretory agents, and antibiotics, could be considered second-line IBS therapies. In addition, psychological treatments, including hypnotherapy, can be used [13].

In recent years, research into the concept of functional bowel disease has proliferated. Certain diseases that had initially been considered functional were ultimately determined to be associated with organic abnormalities and were then removed from the functional category. An example is *Helicobacter pylori* infection of the stomach. Numerous studies have addressed the possible pathophysiological mechanisms of functional bowel disorders, despite the unclear etiology of such disorders [14–16]. During the past 40 years, many factors that contribute to the pathophysiology of IBS have emerged. Such factors include abnormalities in gastrointestinal motility, visceral sensitivity [17], brain–gut axis interaction [18–20], and psychosocial distress [21,22]. Recent studies have focused on altered gut immune activation, intestinal permeability, and intestinal and colonic microbiomes [23,24]. Furthermore, the increased prevalence of IBS-like symptoms in inflammatory conditions, such as celiac disease [25], inflammatory bowel disease [26], and severe acute gastroenteritis [27–29], suggests that inflammation plays a role in the pathogenesis of IBS. However, it is worth emphasizing that although one or more of these mechanisms are evident in most IBS patients, none, including inflammation hypothesis, can account for the symptoms in all cases. However, studies exploring the possible role of inflammation in the pathogenesis of IBS continue to draw the attention of many researchers in the field [30].

Evidence of the relationship between inflammation and carcinogenesis is increasing [31–34], and, therefore, assuming that IBS is associated with cancer development is reasonable. Two previous studies in the United Kingdom and Denmark that examined whether IBS increases the risk of colorectal cancer reported negative results [35,36]. A similar finding was reported by Hsiao et al. in Taiwan [37]. However, because IBS diagnosis is typically a process of elimination, the validity of a physician's early diagnosis of IBS is likely questionable [36,37]. In addition, whether patients with IBS may increase the risk of other types of cancer remain unclear.

This study was conducted to determine whether IBS is associated with an increased risk of cancer. A population-based retrospective cohort design was applied using data from the National Health Insurance Research Database (NHIRD) in Taiwan.

Materials and methods

Data sources

The National Health Insurance (NHI) program, which was implemented in 1995, is a mandatory and universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents, and it has a coverage rate of 98%. The NHI program is contracted with over 99% of the hospitals and medical clinics in Taiwan [38]. Coverage is available for outpatient, inpatient, emergency, dental, and traditional Chinese medicine services, as well as for prescription drugs. In this study, data were obtained from the publicly accessible NHIRD, which is managed by the National Health Research Institutes of Taiwan. The NHIRD registry for catastrophic illnesses provides comprehensive enrollment information on all patients with severe diseases (e.g., cancer) who have received copayment exemption under the NHI program. The Institutional Review Board of Taipei Veterans General Hospital approved this study (2013-10-002CE). Written consent from the study patients was not obtained because the NHI data set consists of deidentified secondary data used for research purposes, and the Institutional Review Board of Taipei Veterans General Hospital issued a formal written waiver of the requirement for informed consent.

Study population

We conducted a retrospective cohort study of patients who were newly diagnosed with the IBS between January 1, 2000, and December 31, 2010. Patients were recruited if they were at least 20 years of age at the time of IBS diagnosis and if they had no prior malignancies. We identified IBS patients from the NHIRD according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) Code 561.4, and the criteria have been used in similar studies previously [36,37]. However, to enhance the validity of IBS diagnosis, we excluded data on patients who had fewer than three visits and those whose diagnosis was altered within 3 months of the index date [39]. We defined the date of the first IBS diagnosis in the database as the index date, and we excluded patients diagnosed with IBS before 2000 to ensure that the study population had no IBS diagnosis before enrollment.

Statistical analysis

The main dependent variable was cancer occurrence. The Registry for Catastrophic Illness was used to identify patients diagnosed with cancer. For a diagnosis of cancer to be reported in the Registry for Catastrophic Illness, histologic confirmation is required. Patients with IBS were followed until the development of cancer, death, withdrawal from the NHI program, or the end of 2010, whichever occurred first.

The risk of cancer among the IBS cohort was determined using the standardized incidence ratio (SIR), which is defined as the observed number of cancer occurrences divided by the expected number. The expected number of cancers was calculated by multiplying the national incidence rate of all types of cancer (stratified by sex, calendar year, and age in 5-year intervals) by the corresponding stratum-specific person-years accrued in the cohort. The incidence rates of cancer among the general population were obtained from the Taiwan Cancer Registry. The 95% confidence