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Lower Gastrointestinal Cancers (AB Benson, Section Editor)

Rectal Cancer in Asian vs. Western Countries: Why the Variation in Incidence?

Yanhong Deng, MD, PhD

Address
Department of Medical Oncology, Guangdong Institute of Gastroenterology, Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Disease, Supported by National Key Clinical Discipline, The Sixth Affiliated Hospital, Sun Yat-sen University , 26 Yuancun Er Heng Road, Guangzhou, 510655, China
Email: dengyanh@mail.sysu.edu.cn

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Opinion statement

Colorectal cancer (CRC) is the third most common cancer worldwide. CRC has been thought to be less common in Asia compared to Western countries. However, the incidence rates of CRC in Asia are high and there is an increasing trend in the Asian population. Furthermore, colorectal cancer accounts for the greatest number of all incidences of CRC in Asia. The increasing adoption of a Western lifestyle, particularly in dietary habits, is likely the most important factor contributing to the rapid increase in colon cancer incidence; it is noteworthy that trends for rectal cancer were flat. The etiology of colon and rectal cancer is a bit different. The risks of distal colon and rectal cancers are more likely to be related to environmental factors, such as polluted surface water sources, alcohol consumption, and habitual smoking. The lack of great change in the incidence of rectal cancer might be due to weaker associations with such lifestyle factors. Therefore, it has been hypothesized that proximal and distal sections of the colon and rectum are two different organs in terms of function and genetic background. It may mean differences in differential sensitivities and exposures to carcinogens. However, despite the decrease in whole incidence, the CRC incidence in young adults in Western countries are reversely increasing, especially in rectal cancer, due to reasons largely unknown. Although the treatment algorithm is different between Asia and western countries, globally, the survival rate for patients with rectal cancer has risen during the past 10 years. Screening contributes a great deal to reducing the incidence and improving survival. Most countries in Asia, such as China, need nationwide registration and screening systems to provide better data.

Introduction

Colorectal cancer (CRC) still ranks as the third most common cancer in the world [1]. It has been estimated that 1,360,300 cases of CRC occurred worldwide in 2012 and that 693,900 people died from the disease [2•]. CRC has been thought to be less common in Asia compared to Western countries [2•]. However, studies from Japan, Korea, Mainland China, and Hong Kong have shown that CRC not only has a high rate of incidence, but an increasing trend as well [3–6].

Multiple reasons contribute to the incidence increasing in Asia. The difference between colon and rectal cancer was also noted in terms of incidence, potential etiology, and geography treatment algorithms.

Reasons for incidence increasing in Asian countries

Taking China as an example of increasing incidence, in China, the most impressive increase in the incidence rates of CRC was observed from 1972–1974 to 1987–1989 (85% in men and 79% in women). The average rate of increase in incidence is 4.2% per year [7]. The incidence rates increased steadily from 1972 to 2005, with the age-adjusted incidence rates of colon cancer increasing from 6.09 and 5.70 to 14.70 and 14.35 per 100,000 in men and women, respectively. The rates of rectal cancer increased from 7.68 and 6.51 to 11.45 and 8.28 per 100,000 in men and females, respectively [8]. The incidence of CRC in China is now approximately 37.6 per 100,000, with a mortality rate of 19.1 per 100,000 [6]. CRC has become a substantial burden in China, particularly in the more developed provinces (Table 1).

Multiple risk factors have contributed to the increase in the incidence of CRC, including age, dietary habits, economic status, and geographic location [9–11]. The increasing adoption of a Western lifestyle, particularly in dietary habits, is likely the most important factor contributing to the rapid increase in colon cancer incidence. In China, per capital consumption of pork, eggs, and milk products has increased more than 100% during the past 3 decades [12]. Saturated fat-containing foods have been linked to colon cancer risk in several epidemiological investigations, including a large case-control study among Chinese people in North America and China [13]. Part of the trend may be due to decreased physical activity, which has been shown to elevate risk. Increases in diagnosis may have been greater for colon cancer than rectal cancer. Of course, improvements in cancer reporting during the study period also may be involved, although it is noteworthy that trends for rectal cancer were flat [9, 14••]. It was reported that sedentary behavior was significantly associated with colon cancer, but it did not have a statistically significant association with rectal cancer [15]. Accompanying the increase in the incidence of colon cancer is a parallel increase in the

Table 1. The incidence rates of colorectal cancer in China 1972 vs. 2005

	Colon-men	Colon-women	Rectal-men	Rectal-women
1972(/100,000)	6.09	5.7	7.68	6.51
2005(/100,000)	14.7	14.35	11.45	8.28

prevalence of obesity in this population [16]. Findings from a large, prospective study confirm a positive association between obesity and colon cancer in men. Furthermore, the study suggests that abdominal obesity plays a more important role in colon carcinogenesis than does general obesity [16].

Higher rates of rectal cancer in Asia likely changing because of etiology difference from colon cancer

In developing countries or low-risk areas such as Asia, rectal cancer accounts for the greatest number of all CRCs. The incidence of rectal cancer among all CRCs is generally less than 40% in Europe and North America, in contrast to the 50% or more in Asia [17].

In China, a proximal shift has been noted since the 1980s [18–20]. The proportion of rectal cancer in CRC has decreased significantly from 71.2% in the 1980s to 66.7% in the 1990s; however, the proportion of cancer of the transverse colon and ascending colon continues to increase significantly (10.9 vs 15.2%) [21]. The reason for this is still not fully known. Several factors contribute to it, such as improved diagnostic accuracy of lesions in the colon and varying etiologic factors.

Environmental factors are thought to be linked to the high incidence of rectal cancer. Studies have found that polluted surface water sources are risk factors for rectal cancer [22]. Drinking water chlorination by-products (e.g., chloroform and carbon tetrachloride) have been reported to be potential carcinogens [22, 23]. In China and in most low-risk areas in the agricultural district, chemical fertilizer and pesticide were widely used in 1970s–1980s. Organic phosphorus and chlorine degraded slowly, which may be one of the important reasons why the incidence of rectal cancer has increased. Hardness levels in Taiwan's drinking water were thought to relate to rectal cancer mortality in Yang's study [24]. In addition, a Chinese study found the people who drink well water have the highest incidence density of CRC, particularly rectal cancer [25].

High intake of dietary fat and animal foods and low physical activity are well-established risk factors for colon cancer in Western societies. In contrast, the lack of change in incidence of rectal cancer may be due to weaker associations with such lifestyle factors. In two case-control studies among Asians that separately examined cancers of the colon and rectum, no association was found between animal foods and total fat intake and rectal cancer [26]. In addition, in two other studies conducted among Asian populations, a protective effect of physical activity was associated only with the risk for colon cancer, not with the risk for rectal cancer [27]. Reasons for variations in subsite incidence rates of CRC by age and sex are unclear. Although it has been proposed that risks of distal colon and rectal cancers are more likely to be related to environmental factors [28], host factors, such as genetic susceptibility, hormonal factors, and other endogenous factors, are linked more strongly to proximal colon cancer. Limited studies have examined risk factors by subsite, but findings are largely inconsistent. Alcohol consumption appeared to influence the risk of rectal cancer more strongly than colon cancer [29]. Habitual smoking increased the risk of rectal cancer but not colon cancer [30] .The differences suggest that this risk factor does not contribute equally to colon and rectal cancers [16, 31].

Increasing incidence of CRC in young population in western countries is noted

Despite observed declines in overall CRC incidence, several recent studies have reported a concerning increase in CRC incidence among adults younger than 50 [32–35]. The largest increase was observed for rectal cancer, and the second largest increase was observed for distal colon cancer. The increase in proximal colon cancer was significantly smaller than that for distal colon and rectal cancers [32, 33]. The incidence of rectal cancer in patients younger than 40 years of age has quadrupled since 1980, and cancers in this group are 3.6 times more likely to have signet cell histology [33].

The majority of CRC in young adults is sporadic, and approximately 15% of the cases of CRC in this population are hereditary. The exact reasons for this increase are largely unknown. Multiple risk factors, such as genetic, lifestyle, and environmental factors, can contribute to the development of CRC in young populations. Studies have also suggested several other possible explanations, such as lack of screening in younger populations, delayed diagnosis due to lack of insurance, and a low index of suspicion from physicians. Dietary factors (e.g., intake of fats and red meats) and lifestyle factors (e.g., physical activity and obesity) have been shown to be associated with CRC risk [34]. Siegel et al. [32] suggested that the increased prevalence over the past 3 decades of obesity and type 2 diabetes may partially account for the increased CRC incidence rates in young adults. However, these statistics suggest that it can explain only approximately5% of the increased incidence rate of CRC. Therefore, an increasing prevalence of diabetes is likely not a cause of the increased rates of CRC in young adults. In addition, the increase is more obvious in rectal cancer; however, the observation suggests that diabetes is related to both colon and rectal cancer [36], and the effect of obesity is slightly stronger for the risk of colon versus rectal cancer [37]. This indicates that both diabetes and obesity contribute less to the increase risk in young patients. Other reasons should be taken into account, such as infection factors.

The difference among rectal, proximal, and distal colon cancer

People often regard colon cancer and rectal cancer as one disease because one is the continuation of the other, and they are similar in morphology and configuration. However, there are some differences between the colon and rectal cancer. The colon originates embryologically from the midgut and hindgut, whereas the rectum originates from the cloaca. According to the anatomy, the capillary networks of the ascending colon are honeycomb-like and multilayered, which decrease to the rectum. It is speculated that the multilayered capillary networks of the proximal colon may be closely related to the greater water absorption and electrolyte transport activities [38]. Otherwise, the colon and rectum have different functions. The colon is primarily involved with water absorption and

solidification and storage of fecal contents [17]. The rectum is normally empty, and its function is mainly that of temporary fecal storage. The morphologic features and histochemical reactions of the colon and rectum are also different. Neutral mucopolysaccharide is predominant in the ascending colon, whereas the rectum has acidic mucin predominantly or exclusively. Furthermore, the rectum shows an unusually high concentration of endocrine cells [39]. Short-chain fatty acid production by cecal contents is up to eightfold higher than contents from the sigmoid/rectum [40]. The metabolic pathways such as that of glucose, butyrate, and polyamines are also different. Therefore, it has been hypothesized that proximal and distal colons are two different organs [28]. This may mean differences in differential sensitivities and exposures to carcinogens for the proximal and distal sections of colon and rectum.

The proximal and distal sections of the colon and rectum are also different with regard to genetic level. According to the gene expression profiling, the consensus molecular subtype (CMS) of CRC has defined four subtypes: CMS1 (MSI Immune), CMS2 (Canonical), CMS3 (Metabolic), and CMS4 (Mesenchymal). CMS1 is characterized by increased expression of genes associated with a diffuse immune infiltrate, mainly composed of TH1 and cytotoxic T cells, along with strong activation of immune evasion pathways, an emerging feature of MSI CRC. CMS2 tumors display epithelial differentiation and strong upregulation of WNT and MYC downstream targets, classically implicated in CRC carcinogenesis. In contrast, enrichment for multiple metabolism signatures is pronounced in CMS3 epithelial CRCs, in line with the occurrence of KRAS-activating mutations, described as inducing prominent metabolic adaptation. Finally, CMS4 tumors show clear upregulation of genes implicated in epithelial mesenchymal transition (EMT) and signatures associated with the activation of transforming growth factor β (TGF β) signaling, angiogenesis, matrix remodeling pathways, and complement inflammatory system. CMS1 tumors are frequently diagnosed in women who have right-sided lesions and present with higher histopathological grade. Conversely, CMS2 tumors are mainly left-sided [41]. Thus far, there are no data from Asia reflecting the biology of CRC similar to CMS subtypes. We plan to study CMS subtypes using the samples collected from the Chinese rectal cancer study, the FOWARC trial [42•].

Microbiota has been identified to be associated with colorectal cancer carcinogenesis. Microbiota differences between patients with proximal colon cancer and distal colon cancer (including rectal) have been noted, both at the level of the whole community and for single operational taxonomic unit and genus. The abundances of *Alistipes*, *Akkermansia*, *Halomonas*, and *Shewanella* are significantly higher in patients who have rectal and distal cancers. Contrastingly, *Faecalibacterium*, *Blautia*, and *Clostridium* are significantly more abundant in patients who have proximal cancer. It seems likely that a CRC-distinctive microbiota is already present and possibly involved in the early stages of cancer development. The biological significance of differences in the microbiota in the proximal and distal colon is not currently clear but worthy of future exploration [43].

Recently, more and more studies have shown that tumors located in the right colon have poorer prognosis than those in the left colon and rectum [44]. They also have differences in drug sensitivity and genetic features [45].

Difference in treatment algorithm between Asian and Western countries

The treatment algorithm for locally advanced rectal cancer is quite different between Asia and Western countries. Especially in Japan, routinely lateral lymph node dissection is done and radiation is not routinely used [46]. In China, most of the surgeons do not use neoadjuvant treatment. During the past 10 years, more and more physicians have accepted the concept of neoadjuvant treatment, but they dislike the use of radiation because of its high postoperative complications and poor anal function. We have conducted a study to compare chemotherapy alone to chemoradiation and found that chemotherapy alone can be a substitute, in part, for radiation. However, long-term follow-up is needed [42•].

Despite the difference of incidence and treatment algorithms, the 5-year survival rate has increased for patients who have colon and rectal cancers in most developed countries and regions, including North America, Europe, Oceania, and parts of East Asia (South Korea and urban areas in China). Data for rectal cancer are now available for 1,413,861 patients in 46 countries between 1995 and 1999, in 57 countries between 2000 and 2004, and in 60 countries for 2005–2009. For patients diagnosed with rectal cancer between 2005 and 2009, age-standardized 5-year net survival increased to between 50.5% and 59.0% in many countries [47].

In some of the developed nations of North America and Northern Europe, the incidence rates of CRC are actually declining, due in part to the effect of CRC screening being performed. Through screening, CRC is being detected early, resulting in curative treatment and prevention through the removal of premalignant lesions, which contributes a great deal to improve survival [47] .However, the incidence of CRC in patients younger than 50 years of age has been increasing. It is estimated that the incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively, for patients between the ages of 20 and 34 years by 2030 [37]. In Asian countries such as China, nationwide CRC registration and screening system are lacking, which can result in low accuracy in terms of incidence. However, centers for disease control and prevention of most of the provinces in China have collected data. In the near future, nationwide data will be probably available in China.

Compliance with Ethical Standards

Conflict of Interest
Yanhong Deng declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Provide the fundamental reasons for why the difference of incidence change of rectal and colon cancer occurred.

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Provide the treatment algorithm in China. Physicians are more cautious about preoperative radiation being routinely done in locally advanced rectal cancer.

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