• COLORECTAL CANCER •

Racial differences in the anatomical distribution of colorectal cancer: a study of differences between American and Chinese patients

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Received: 2002-07-08   **Accepted:** 2002-08-02

Abstract

AIM: To compare the racial differences of anatomical distribution of colorectal cancer (CRC) and determine the association of age, gender and time with anatomical distribution between patients from America (white) and China (oriental).

METHODS: Data was collected from 690 consecutive patients in Cleveland Clinic Florida, U.S.A. and 870 consecutive patients in Nan Fang Hospital affiliated to the First Military Medical University, China over the past 11 years from 1990 to 2000. All patients had colorectal adenocarcinoma diagnosed by histology and underwent surgery.

RESULTS: The anatomical subsite distribution of tumor, age and gender were significantly different between white and oriental patients. Lesions in the proximal colon ($P<0.001$) were found in 36.3 % of white vs 26.0 % of oriental patients and cancers located in the distal colon and rectum in 63.7 % of white and 74 % of oriental patients ($P<0.001$). There was a trend towards the redistribution from distal colon and rectum to proximal colon in white males over time, especially in older patients (>80 years). No significant change of anatomical distribution occurred in white women and Oriental patients. The mean age at diagnosis was 69.0 years in white patients and 48.3 years in Oriental patients ($P<0.001$).

CONCLUSION: This is the first study comparing the anatomical distribution of colorectal cancers in whites and Chinese patients. White Americans have a higher risk of proximal CRC and this risk increased with time. The proportion of white males with CRC also increased with time. Chinese patients were more likely to have distal CRC and developed the disease at a significantly earlier age than white patients. These findings have enhanced our understanding of the disease process of colorectal cancer in these two races.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers in the world and the second leading cause of cancer death in the United States[1, 2]. It is estimated that 552 000 Americans died of cancer in the year 2000; about 55 000 of these cancer deaths were attributed to CRC. In recent years, the incidence of CRC has increased rapidly in China making it the fourth leading cause of cancer mortality in China[3]. In general, majority of these cancers are distally located. During the last two decades many investigators have noted that the incidence rate of CRC vary widely by race and gender and the location also has changed with time[4-15], with a trend towards redistribution of primary CRC from left to right[16, 17]. Proximal cancers have a tendency to present at a more advanced stage and are associated with a poor prognosis. Increasing age, female gender, black, non-Hispanic race and the presence of comorbid illnesses were factors associated with a greater likelihood of developing colorectal cancer in a proximal location. Black patients with colon cancer are more likely to have a poorer survival than white patients[13, 18-21]. However, it is not clear whether there are any differences in anatomical distribution of primary colorectal cancer between American (white) and Chinese (oriental) patients.

We hypothesized that there are significant differences of anatomical distribution of primary colorectal cancers between the white (American) and oriental (Chinese) patients. The purpose of this study is to compare the differences in anatomical distribution of colorectal cancers and to describe any association of age, gender and time with primary CRC in white and oriental patients.

MATERIALS AND METHODS

A retrospective study was undertaken. Data was collected from 690 consecutive white patients in Cleveland Clinic Florida U. S.A. and 870 consecutive Chinese patients in Nan Fang Hospital affiliated to the First Military Medical University in southern China over the past 11 years from 1990 to 2000. All the patients with CRC were diagnosed by histology and underwent surgery. Anatomical location of primary colorectal adenocarcinoma, race, age at diagnosis, gender and year of diagnosis were noted. Descriptive data on the type of treatment, patterns of recurrence and metastasis, survival, and the coexistence of disease were not the focus of our analysis. The Z-test and Fisher's Exact Test were performed to detect statistically significant differences in anatomical site distribution, age and gender over time between the white and oriental groups. In this study "proximal colon" includes the cecum, ascending colon, hepatic flexure, transverse colon and splenic flexure; "distal colon" includes the descending colon, sigmoid colon and rectum[22]

RESULTS

664 Consecutive white patients in Cleveland Clinic Florida and 816 consecutive oriental patients in Nan Fang Hospital in China had documented histological diagnosis of colorectal

adenocarcinomas (Table 1). Patients with a diagnosis of adenocarcinoma only were included in this study.

Table 1 Histological diagnosis of patients with colorectal cancer

	No of patients (%)	
	White	Oriental
Adenocarcinoma	664 (96.2)	816 (93.8)
Nonadenocarcinoma	26 (3.8)	54 (6.2)
Total	690 (100.0)	870 (100.0)

Anatomical subsite distribution

Data on the anatomical distribution, race and gender in the two groups are shown in Table 2. The anatomical distribution of the lesions was markedly different between the two races. Comparision showed that 36.3 % of whites *vs* 26.0 % of oriental patients ($P<0.001$) had lesions in the proximal colon and 63.7 % of whites *vs* 74 % of orientals ($P<0.001$) had cancers located in the distal colon. The proportions of cancers located in the cecum, ascending and descending colon in white patients were higher than those in the orientals ($P<0.01$). Rectal and hepatic flexure tumors were less frequent in whites than in the orientals ($P<0.001$). There was no significant difference between cancers located in the transverse colon, splenic flexure and sigmoid colon.

Gender

Analysis by gender conforms to the overall racial differences. The proportions of cecal tumors was higher in the white men ($P<0.001$) and women ($P<0.001$) compared with their Oriental counterparts. Ascending and descending colon cancers were also significantly more common in white men ($P<0.05$) but not in women ($P>0.05$). Rectal cancers were significantly more common in oriental men ($P<0.001$) and women ($P<0.001$). Oriental patients also had significantly more hepatic flexure cancers among men ($P<0.001$) and women ($P<0.001$). There was no significant difference in the rates of transverse colon, splenic flexure or sigmoid colon cancers.

There was a significant gender difference beteen the races (Table 3). The male: female ratio was slightly higher in whites (1.49:1) as compared with oriental patients (1.22:1). The gender ratio (m:f) in whites was 1.43:1 for proximal tumors and 1.52:1 for distal tumors; in oriental patients the ratio was 1.06:1 for proximal tumors and 1.29:1 for distal tumors.

Age

The mean age at diagnosis was 69.8 years (range 20-91) in white patients *vs* 48.3 years (range 13-84) years in oriental patients; oriental patients were therefore younger by twenty-one years ($P<0.001$). Incidence of CRC generally increased with age; it peaked between 70-79 years in white patients, whereas the highest incidence in oriental patients was observed between 50-59 years ($P<0.001$) (Figure 1).

We have further analyzed the age related distribution of proximal and distal tumors in the two racial groups (Figure 2). In white patients, the incidence of proximal tumors had an early peak by the age of 29 years; the incidence then declined significantly so that the lowest rates of proximal lesions were found in the 30-59 years; the incidence of proximal tumors then gradually rose to a peak at 70-79 years. There was a significant difference in the proportions of proximal tumors

Table 2 Anatomic subsite distribution of colorectal cancer by race

	Men				Women				Total			
	White		Oriental		White		Oriental		White		Oriental	
	n	%	n	%	n	%	n	%	n	%	n	%
Cecum	57	8.6	14	1.7[c]	50	7.5	16	2.0[c]	107	16.1	30	3.7[c]
Ascending	45	6.8	31	3.8[a]	32	4.8	29	3.6	77	11.6	60	7.4[b]
Hepatic flexure	5	0.8	27	3.3[c]	2	0.3	26	3.2[c]	7	1.1	53	6.5[c]
Transverse	27	4.1	20	2.5	13	1.9	25	3.0	40	6.0	45	5.5
Splenic flexure	8	1.2	17	2.1	2	0.3	7	0.8	10	1.5	24	2.9
Descending	20	3.0	9	1.1[a]	11	1.7	7	0.9	31	4.7	16	2.0[b]
Sigmoid	63	9.5	82	10.0	54	8.1	64	7.9	117	17.6	146	17.9
Rectum	172	25.9	249	30.5[c]	103	15.5	193	23.7[c]	275	41.4	442	54.2[c]
Proximal	142	21.4	109	13.6[c]	99	14.9	103	12.6[a]	241	36.3	212	26.0[c]
Distal	255	38.4	340	41.7[c]	168	25.3	264	32.3[a]	423	63.7	604	74.0[c]
Total	397	59.8	449	55.0	267	44.2	367	45.0	664	100.0	816	100.0

[a]$P<0.05$, [b]$P<0.01$, [c]$P<0.001$.

Table 3 Anatomic subsite distribution of colorectal cancer by race and time

		Proximal			Distal			Total		
Time		Man	Woman	Ratio	Man	Woman	Ratio	Man	Woman	Ratio
1990-1995	White	51	43	1.19	106	72	1.47	157	115	1.37
	Yellow	55	49	1.12	163[b]	128[a]	1.27	218[b]	177	1.23
1996-2000	White	91	56	1.63	149	96	1.55	240	152	1.58
	Yellow	54[c]	54[a]	1.00	177	136	1.30	231[b]	190	1.22
Total	White	142	99	1.43	255	168	1.52	397	267	1.49
	Yellow	109[c]	103[a]	1.06	340[c]	264[a]	1.29	449	367	1.22

[a]$P<0.05$, [b]$P<0.01$, [c]$P<0.001$.

between various age groups: 0-29 years *vs* 30-59 years as well as 30-59 years vs. 60 years and older (*P*<0.001). In oriental patients, the curve for incidence of proximal lesions was relatively flat. Young patients between 0-29 years had the lowest rate which was significantly lower than patients above 30 years (*P*<0.001). The curves for proximal cancers in White and Oriental patients diverge at the extremes of age and there were significant differences between the two races at 0-29 years as well as above 70 years (*P*<0.01). In White patients, there was a marked increase in the rates of proximal tumors whereas the frequency of distal tumors decreased with age. This trend was not observed in Oriental patients (Figure 2).
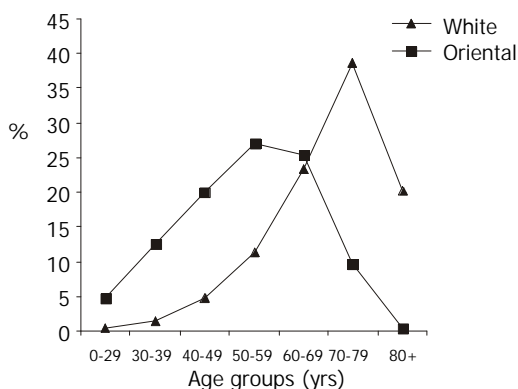
**Figure 1** Age related incidence of colorectal cancers in two races.
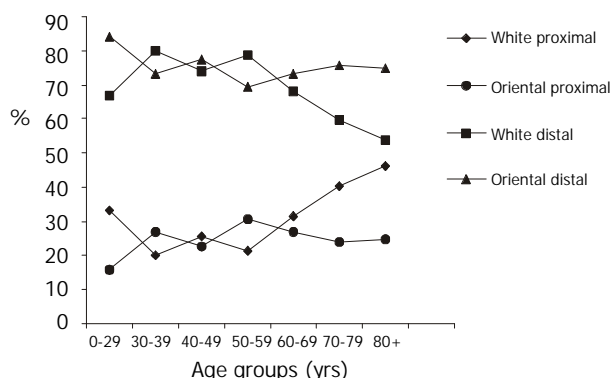
Figure 2 Age-related distribution of cancers.

Time
Generally, there was an increase in the proportion of white men with colorectal cancer from 1.37:1 during 90-95 to 1.58:1 during 96-2000 (*P*<0.05) (Table 3). This increase was especially seen in proximal cancers of whites which increased from 1.19:1 in 90-95 to 1.63:1 in 96-2000 (*P*<0.01); the gender ratio among whites for distal cancers changed from 1.47:1 in 90-95 to 1.55:1 in 96-2000 (*P*>0.05). There was no significant change in the gender distribution of oriental patients (*P*>0.05) between these two time periods.

Table 3 shows that in whites the proportion of proximal cancers increased from 34.6 % in 1990-1995 to 37.5 % between 1996-2000 and distal cancers decreased from 65.4 % to 62.5 % of all cancers between the same periods of time. There was a trend towards a redistribution of primary colorectal cancers from distal to proximal colon, but the difference was not significant. When we further compared the relationshiPbetween anatomical distribution and gender, a marked trend was found towards the redistribution of primary colorectal cancers from distal colorectum to proximal colon in white men with time, especially in the 80-99 years group, but this change was not significant (*P*>0.05) (Figure 3). No significant change of anatomical distribution of tumor occurred in Oriental patients

over time (*P*>0.05); in whom the proportion of cancers on the proximal side remained significantly higher. In addition, the proportion of proximal tumors remained significantly lower in white than in oriental patients.
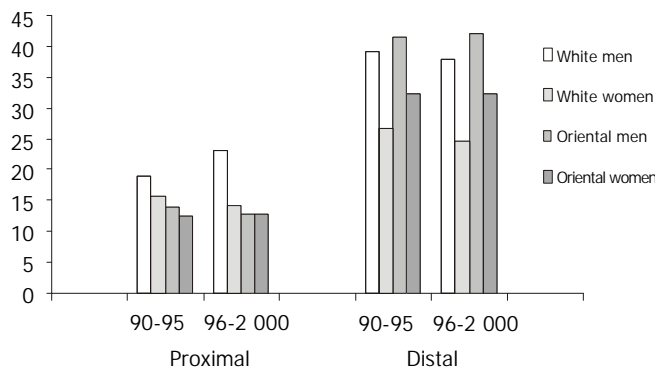
Figure 3 Gender and time based distribution of colorectal adenocarcinomas. The Y-axis shows percentage of tumors.

DISCUSSION

An important aspect of colorectal cancer is its anatomical site of origin, the majority of these cancers being diagnosed in the distal colon and rectum. Epidemiological characteristics of colorectal cancer differ by anatomical subsite, which suggests that other underlying subsite-specific differences may be present. There is evidence of a steady migration of colorectal cancer from distal to more proximal sites[17], although a decrease in proximal cancerswas reported[22]. This is the first study comparing the anatomical distribution of colorectal cancers in these two large racial groups - American and Chinese. The study demonstrates that the most frequent anatomical subsite of origin of primary colorectal adenocarcinomas is the same - the rectum and sigmoid colon, in American and Chinese patients. The proportion of cancers located in the cecum and ascending colon in whites are significantly higher than those in the oriental patients; the latter did have significantly more tumors in the rectum. The proportion of cancers located in the transverse and sigmoid colon was similar in the two groups. Overall, the frequency of lesions in the proximal colon of white patients (36.3 %) was markedly higher than that of oriental patients (26.0 %). Likewise, the proportion of tumors located in the distal colon of oriental patients (74 %) was significantly higher than that of whites (63.7 %). CRC is considerd a disease of western developed countries, which has an approximately 10 times greater incidence than developing countries of Africa[23]. In general, the developed countries have a predominance of left-sided cancers, whereas low-risk communities have a higher proportion of right-sided cancers[24]. Compared with America, China is a low risk community. The reasons for the significantly higher incidence of right-sided CRC in white patients are still not clear.

Many hypotheses have been developed based on histological differences between the left and right colon, differences in their functions, sex hormones, diet, and genetics. Proximal and distal sections of the colon also have different embryologic origins and morphology. The proximal colon is primarily involved with water absorption and solidification of fecal contents for storage. It is likely that there are differences in sensitivity and exposure to carcinogens for the proximal and distal sections of colon. There might even be differences in the etiologic agent between right-sided and left sided colorectal cancers; a study showed that different carcinogens produced cancers in different parts of the large bowel in experimental animals[20].

No specific carcinogen has been found to cause CRC in humans, but the differences in the epidemiological patterns of CRC among various populations suggest the role of an environmental or dietary etiologic agent[25]. The higher consumption of refined carbohydrates and fat and less dietary fiber may contribute to the increased incidence of colorectal cancers in the western countries[16, 26]. Increased dietary fat resulted in increased bile acids in the intestine, a possible mechanism for carcinogenesis[27]. High concentrations of fecal bile acids have been observed in people who eat a high fat diet. Bile acids in turn caused colonic bacteria to produce increased amounts of secondary bile acids and other metabolic by products, compounds that may be associated with the high risk of large bowel cancer[9, 28-30].

Dietary fiber may play an important protective role against colorectal cancer by diluting the fecal concentration of mutagens and bile acids, and by altering the colonic luminal environment[31]. Even the type of dietary fiber may be important in reducing the fecal mutagenic activity[31]. It is said that, it is imperative to point out that the evidence linking fiber and colorectal cancer is not conclusive. Dietary fiber probably protects against carcinogenesis, if it is present in the diet from an early age[32].

Another possible factor increasing the risk of rectal cancer is consumption of large amounts of alcoholic beverages, particularly beer. For example, alcohol has been shown to increase the relative risk for colon cancer by 1.71 when prospective study is made in black and white patients. In contrast, increased amount of vitamin C intake may be protective against rectal cancer[22, 24, 33-34].

We have observed a trend toward a redistribution of CRC from distal to proximal in white men, especially in the older men, a finding that is similar to others in the literature which showed a trend towards the redistribution of primary CRC from left to right with increasing time[35]. We found no significant change in the anatomical distribution of colorectal cancer in white women and oriental patients, the distribution remaining fairly stable in these two groups.

In recent years, the male:female ratio for CRC rose in many published reports[4, 36]. This study showed that overall rates of colorectal cancers were higher among men than women in both races, but the proportion of white men was greater than that of oriental men, especially for proximal cancers. Between the periods 1990-95 and 1996-2000, we found the male-female ratio in whites rose from 1.19:1 to 1.68:1 for proximal colon cancers and 1.47:1 to 1.55:1 for distal colon cancers; over the same periods, in Oriental patients, the male-female ratio declined from 1.12:1 to 1:1 for proximal and rose from 1.27:1 to 1.30:1 for distal cancers (Table 3). There was no significant change in the oriental race, a finding in agreement with others[9].

This gender-based disparity is largely unexplained. Recently it has been suggested that hormone replacement therapy may decrease the incidence of colorectal cancer in females. Female sex hormones are known to affect cholesterol metabolism which in turn affects bile acid production, a pathway linked to the development of colorectal cancer. Differences in bile acid metabolism between the proximal and distal colon may contribute to the gender-based disparity in colorectal cancer risk[24].

Age at diagnosis was significantly different between the races. The mean age was 69.8 years in whites and 48.3 years in oriental patients; oriental patients being diagnosed about twenty-one years earlier. The whites presented most commonly between 70-79 years, but the oriental patients had the highest rate of presentation between 50-59 years. The greater proportion of proximal tumors with increasing age in older white patients has also been noted by others[15,37-40]. This trend was not observed in oriental patients. There was a higher

incidence of CRC in younger oriental patients of both sexes, the reasons for which are unknown.

The explanation for differences among racial or ethnic groups may lie in host, environmental, or behavioral factors that act alone or in combination. Heredity plays only a small role. As for colorectal adenocarcinoma, patients in China share the epidemiological characteristics of developing countries. It seems that behavioral factors, such as the dietary habits of Americans and Chinese are more likely to contribute to the difference.

We found that white Americans have a higher risk of proximal CRC and this risk increased with time. The proportion of white males with CRC also increased with time. Chinese patients were more likely to have distal CRC and developed the disease at a significantly earlier age than white patients. As colorectal cancer is one of the most common cancers in the world, it is important to conduct further study to explain subsite differences between the races and sexes. Evaluation of such differences will improve our understanding of colorectal carcinogenesis and may help formulate preventive strategies and perhaps guide research on therapy.

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Edited by Ma JY