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Incidence Pattern of Colorectal Cancer in Korea by Subsite of Origin

It has been suggested that colorectal cancer might not be one homogenous disease entity, based on the distinctive characteristics of its subsite of origin. Incidence data on 4,987 colorectal cancer were obtained from the Seoul Cancer Registry between 1993 and 1995. Age, sex, and subsite-specific incidence rates were compared. The age-standardized annual incidence rates of total colorectal cancer were 26.1 and 18.0 per 100,000 for men and women, respectively. There were no appreciable difference in the rates of colon and rectal cancer for either sex (colon vs rectum: 12.8 vs 13.2 for men, 9.3 vs 8.6 for women). The incidence rate of right colon was slightly higher in men than in women, and this discrepancy became even greater in left colon (men vs women: 3.5 vs 3.0 for right colon, 4.7 vs 2.9 for left colon). When the incidence rate of right colon was compared with that of left colon, women had a higher rate in the right colon among the elderly, aged 60 yr and over and a lower rate at age 40 yr or less, while the opposite was observed for men. More analytic approaches are needed to identify which factors are related with these descriptive results in colorectal cancer incidence.

Key Words: *Colorectal Neoplasms; Epidemiology; Incidence; Registries*

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INTRODUCTION

Colorectal cancer has been rapidly increasing in Korea during the last decade, which was known as low risk area. The age-standardized mortality rates increased from 8.7 in 100,000 to 16.5 in 100,000 for men and from 6.3 in 100,000 to 14.3 in 100,000 for women between 1987 and 1996 (1). Based on the Central Cancer Registry Program (CCRP), which has been operated by the Korean government since 1980, the proportion of colorectal cancer among total registered cancers has increased from 5.8% and 5.8% in 1982 to 8.4% and 8.2% in 1996 for men and women, respectively (2).

Colorectal cancer is the fourth most common cancer and accounts for 8.5% of all malignancies worldwide. The age-standardized incidence rates, however, vary approximately 10-fold across countries (3). The highest rates are seen in Western societies such as North America, Western Europe, Australia, and New Zealand (30-50 per 100,000), while the rates were very low in most of the Asian and African countries (less than 10 per 100,000) in the late 1980s. But, recently the incidence has increased in some Asian countries such as Japan (4) and China (5). Studies on migrants have shown that those moving from low- to high-risk countries acquire an elevated risk of large bowel cancer even in the first-generation (6). It has been proposed that environmental factors, characterized by the western life style, including high fat/low fiber diets, may be closely related to the risk of colorectal cancer (7).

Colon to rectal cancer incidence rate ratios are higher in populations with a significant risk for colorectal cancer, while these ratios are correspondingly lower in most of the low risk countries (8). In addition, the ratios tend to increase as the overall incidence of colorectal cancer increases, and these are particularly obvious in Japan (4). Rectal cancer has been decreasing in both men and women in the United States over the past 50 yr (9). In terms of the colon cancer subsite, it was reported that left-sided cancer predominated in populations at high risk of colorectal cancer, while right-sided cancer predominated in low-risk countries (8). The increase of colorectal cancer observed in Japan was primarily due to the increase of left-sided cancer (10).

However, the proportional increase of right-sided over left-sided colon cancers has been observed in high-risk countries in several population-based cancer registries (11-15), and in hospital-based case studies (16, 17), especially in the elderly (11, 12, 15) and in women (11). It is also well documented that different colorectal cancer

subsites have different male to female incidence ratios and that the male excess is pronounced from the right colon to the rectum (5, 13).

These descriptive results suggest that colorectal cancer may not be one homogenous disease entity (18) and that environmental risk factors affect this organ differently by subsite (19). Therefore, we examined the epidemiologic characteristics of colorectal cancer incidence in Seoul, Korea between 1993 and 1995, based on the Seoul Cancer Registry (SCR), with special reference to age and sex distributions by subsite.

MATERIALS AND METHODS

We obtained data from the Seoul Cancer Registry (SCR), which is a population-based urban cancer registry in Korea. The overall results and methods of the program are described in detail elsewhere (20). Briefly, the SCR has collected data upon incident cancer cases diagnosed among Seoul residents since 1991. The SCR covers a population of 10.2 million, which corresponded to one quarter of the total population of Korea in 1995. This study was restricted to the time period 1993-1995. The primary source of incident data in the SCR was the registry file of the CCRP, which has nationwide records collected from the major training hospitals since 1980. The records of patients residing in the Seoul area were extracted from these files. Medical records of patients who were diagnosed in CCRP non-participating hospitals were reviewed by the SCR data collection team. Data was computerized and sorted using a system based on a nationwide personal identification number. In the case of duplicate records, only the record with the earlier date of diagnosis was kept unless it was a multiple primary case. The prevalent cases were identified by merging newly registered cases with existing CCRP and SCR files and deleted.

Cancer death statistics in Seoul during this period were obtained from the National Bureau of Statistics to calculate the cross-sectional age-sex specific mortality/incidence (M/I) ratio, which is one of the methods used for measuring the completeness of the registry (21). The validity of the information from the registry was assessed using indices such as the proportion of histologically verified cases (HV%) and the proportion of age unknown (Age UNK%). The overall completeness and validity of the SCR were found comparable to those of established cancer registries in other countries (20). A brief summary of these figures for colorectal cancer are shown in Table 1.

All cancers of the colorectum diagnosed between January 1, 1993 and December 31, 1995, were included in the analysis, and defined by primary site codes C18.0 to C20.9 according to the International Classification of Diseases for Oncology (22). Cancer cases were categorized into three groups by subsite, right (i.e., cancers in the cecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure), left (i.e., cancers in descending and sigmoid colon), and rectum (i.e., cancers in rectosigmoid junction and rectum). Tumors with site unspecified (C18.9) or overlapping sites (C18.8) were excluded from the subsite-specific analyses, but were included in the combined analyses. Average annual incidence rates per 100,000 were calculated using the 1994 mid-year population of Seoul as a denominator. Age-standardized rates were computed by the direct method using both the 1990 Korean population with both sexes combined and the world standard population as standards.

Table 1. The completeness and validity indices for colorectal cancer by sex in the Seoul Cancer Registry, 1993-1995

Men			Women		
M/I	HV	AgeUNK	M/I	HV	AgeUNK
33.9%	80.0%	0.2%	34.3%	73.7%	0.1%

M/I: mortality/incidence ratio, HV: histologically verified cases, AgeUNK: age unknown

RESULTS

A total of 4,987 incident colorectal cancer cases was accrued in the SCR between 1993 and 1995. The substite distribution pattern is summarized in Table 2. Cancers arising from the colon and rectum were equally distributed (colon vs rectum: 49.7% vs 50.3%). When examined by colon subsite, there appeared little difference in the proportions of right and left cancer (right vs left colon: 16.9% vs 17.0%). 15.8% of total colorectal cancer was classified as subsite unknown or as an overlapping site.

The age-specific and age-standardized annual incidence rates averaged over 3 yr are shown in Table 3. The crude incidence rates of colorectal cancer were 16.0 per 100,000 for men and 14.9 per 100,000 for women. The age-standardized rates (world standard population) were 26.1 and 18.0 per 100,000, for men and women, respectively. Age-specific incidence rates increased with age, with more than a two-fold increase in every decade for both sexes. There were no appreciable difference in the age-standardized rates of colon and rectal cancers for either sex (colon vs rectal: 12.8 vs 13.2 for men, 9.3 vs 8.6 for women). The age-adjusted male to female incidence rate ratios (IRRs) were 1.45 for colorectal cancer,

Table 2. Subsite distribution of colorectal cancer in Koreans based on the Seoul Cancer Registry, 1993-1995

Subsite	Male (%)	Female (%)	Total (%)	Sub-group (%)
Cecum and Appendix	85 (3.3)	107 (4.5)	192 (3.9)	
Ascending colon	192 (7.4)	189 (7.9)	381 (7.6)	
Transverse colon with both flexures	140 (5.4)	128 (5.4)	268 (5.4)	Right colon (16.9)
Descending colon	66 (2.5)	61 (2.6)	127 (2.5)	
Sigmoid colon	393 (15.1)	331 (13.9)	724 (14.5)	Left colon (17.0)
Colon, overlapping	29 (1.1)	29 (1.2)	58 (1.2)	
Colon, unspecified	352 (13.5)	377 (15.8)	729 (14.6)	Colon, total (49.7)
Rectosigmoid junction	186 (7.1)	132 (5.5)	318 (6.4)	
Rectum	1,165 (44.7)	1,025 (43.1)	2,190 (43.9)	Rectum, total (50.3)
Total	2,608 (100)	2,379 (100)	4,987 (100)	

Table 3. Age-specific and age-adjusted annual average incidence rates per 100,000 for colorectal cancer by sex, Seoul, Korea, 1993-1995

Age (yr) group	No. of population		Colorectal cancer		Colon cancer		Rectal cancer	
	Male	Female	Male	Female	Male	Female	Male	Female
<30	2,946,604	2,735,235	0.5	0.6	0.3	0.2	0.3	0.4
30-34	524,496	520,704	4.3	3.8	2.1	2.0	2.2	1.7
35-39	490,846	505,687	6.7	7.3	3.3	3.0	3.4	4.4
40-44	369,473	373,602	12.4	11.3	5.5	5.9	6.9	5.4
45-49	327,023	317,003	21.1	20.1	8.9	10.2	12.2	9.9
50-54	284,127	255,844	41.6	33.1	19.4	15.6	22.3	17.5
55-59	210,240	191,448	66.6	54.0	31.6	25.9	35.0	28.0
60-64	120,845	137,573	100.4	66.9	48.5	36.6	51.9	30.3
65-69	68,975	100,576	149.8	99.8	76.8	51.0	73.0	48.7
70-74	45,805	75,680	232.1	127.3	112.8	70.9	119.3	56.4
75 and over	35,642	89,434	260.0	152.8	137.5	84.2	122.5	68.6
Total population	5,424,07	5,302,786						
No. of cases*	62,604	2,376	2,604	2,376	1,255	1,220	1,349	1,156
Crude rate			16.0	14.9	7.7	7.7	8.3	7.3
Adjusted rate†			21.3	15.0	10.5	7.7	10.8	7.3
Adjusted rate‡			26.1	18.0	12.8	9.3	13.2	8.6
Age-adjusted sex ratio§			1.45		1.38		1.53	

*age unknown: 4 for male, 3 for female; †age-adjusted for the 1990 Korean population, both sexes; ‡age-adjusted for world standard population; §based on the rate adjusted for world standard population

1.38 for colon cancer, and 1.53 for rectal cancer.

Age-specific and adjusted incidence rates for subsites of colon cancer are shown in Table 4. Men had a higher age-adjusted rate in the left colon than the right colon, while there was little difference in women. The age-adjusted male:female IRR increased from 1.20 in the right colon to 1.60 in the left colon. The age-specific male:female IRRs did not appear to be greatly different across the age groups for the right colon, while the IRRs for the left colon were less than 1 by age 50 yr and increased gradually thereafter, from 1.23 in the age range 50-54 yr to 2.54 in the range 70-74 yr.

Fig. 1 shows the age-specific IRRs of right to left colon cancer by sex. For women, the righ:left IRRs appeared to increase to greater than 1 after age 60 yr, while IRRs higher than 1 were observed in men younger than 50 yr. When age was divided into three broad groups (≦49, 50-59, ≧60 yr), striking contrasts became apparent between the right:left IRRs by sex (Table 5). Women in the elderly age-group of 60 yr and over had an IRR of 1.23 and in those less than 40 yr of age the IRR was 0.89. Men on the other hand had corresponding IRRs of 0.69 in the elderly and 1.49 in the younger age group. Fig. 2 shows the proportion of cancer patients aged 60 yr and over by subsite. For men, the proportion was higher in the left colon than the right colon (right vs

Table 4. Age-specific and age-standardized average annual incidence rate per 100,000 and sex ratios for colon cancer by subsite, Seoul, Korea, 1993-1995

Age (yr) group	Right colon			Left colon		
	Male	Female	M:F	Male	Female	M:F
<30	0.1	0.1	1.86	0.1	0.1	1.30
30-34	1.0	0.6	1.49	0.4	0.8	0.50
35-39	1.5	1.1	1.33	1.0	1.3	0.81
40-44	2.5	2.5	1.01	1.7	2.1	0.84
45-49	3.2	3.0	1.04	2.4	4.3	0.57
50-54	6.0	4.0	1.48	7.5	6.1	1.23
55-59	8.9	6.4	1.38	13.5	10.4	1.29
60-64	15.7	12.8	1.22	19.3	10.2	1.90
65-69	17.9	15.9	1.12	34.3	17.2	1.99
70-74	29.8	30.4	0.98	45.8	18.1	2.54
75 and over	29.0	21.2	1.36	32.7	18.6	1.76
Crude rate	2.3	2.4		2.8	2.5	
Adjusted rate*	2.9	2.4		3.7	2.5	
Adjusted rate†	3.5	3.0		4.7	2.9	
Age-adjusted sex ratio‡	1.20			1.60		

*age-adjusted for the 1990 Korean population, both sexes; †age-adjusted for world standard population; ‡based on the rate adjusted for world standard population

Table 5. Annual average incidence rate of right and left colon cancer and their rate ratios by sex for three broad age-groups, Seoul, Korea, 1993-1995

Age (yr) group	Male			Female		
	Right colon (per 100,000)	Left colon (per 100,000)	Right to left ratio	Right colon (per 100,000)	Left colon (per 100,000)	Right to left ratio
≤49	0.76	0.51	1.49	0.67	0.75	0.89
50-59	7.21	10.05	0.72	5.07	7.97	0.64
≥60	20.40	29.37	0.69	18.76	15.29	1.23

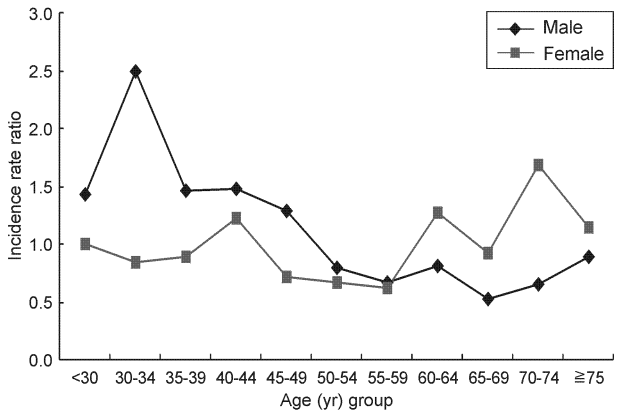

Fig. 1. Age and sex-specific incidence rate ratio of right to left colon cancer, Seoul, Korea, 1993-1995.

Fig. 2. Proportion of colorectal cancer patients aged 60 yr and over for substies of colorectal cancer by sex, Seoul, Korea, 1993-1995. *$p<0.05$, based on chi-square test.

left: 43.8% vs 52.1%, $p<0.05$), while the opposite was observed in women (right vs left: 59.1% vs 47.2%, $p<0.05$).

DISCUSSION

The colorectal cancer incidence rates obtained during

this study were much higher than those reported previously in Korea (23, 24). The differences could be due to the area of cancer registry. Seoul is the most affluent city in Korea, while the Kangwha is one small rural area (23) and the nationwide study by Park et al. (24) surveyed only those insured by the Korea Medical Insurance Corporation, though the company is one of the largest insurance organizations operated by the government. The indices that were used to evaluate the completeness of the registry (Table 1) give us some assurance of the veracity of the registry data. The incidence rates were comparable to those of Shanghai, China (22.1 for men, and 18.5 for women) during 1990-1994 (5) and lower than those in Japan (37.6 for men and 23.0 for women) in 1989 (25).

It was observed that men had higher rates of colorectal cancer than women and that the male:female sex ratios varied from 1.2 in the right colon to 1.6 in the left colon and were 1.53 for the rectum. Similar results were reported in other studies (5, 13). These findings raised the possibility that some male-related risk factors, such as alcohol and/or smoking, affect preferentially the left-sided colon and rectum rather than the right-sided colon. Giovannucci et al. (26) reported that high alcohol intake increased the risk of developing colon cancer, especially for the left colon.

The age-specific sex ratios of the left colon were interesting. Women in the 50 yr and under age group had higher rates than men, but thereafter, the rate of the men gradually increased and exceeded that of the women. However, in the right colon no appreciable differences in the age-specific sex ratios were observed. This reversal of incidence rates in women, at around the age of menopause, has been observed in other countries (5, 13, 27), and suggests that reproductive factors and/or other sex-related exposures are implicated in the risk of left colon cancer in women (28). Some studies have shown a protective effect of hormone replacement therapy (HRT) on colorectal cancer (29, 30), but the effects of HRT were found to be inconsistent in terms of the subsite of the large bowel, i.e., for distal colon only (29) or for proximal colon only (30). More analytic work using alternative approaches is required to elucidate the subsite specific association, and determine which factors are related to colorectal cancer incidence.

In our study, there appeared to be a higher risk in the right colon than the left colon among elderly women aged 60 yr or over and in men aged 50 yr or less. Consequently, the mean age at diagnosis in the right colon was found to be higher than that of the left colon among women (Fig. 2). Similar findings have been reported in other studies (31), but this rightwards shift with advancing age, described as 'aging gut' by Schub et al. (12), needs cautious interpretation to preclude potential possibilities of detection bias. Firstly, if a significant number of polyps in the left colon have been more removed through screening sigmoidoscopy, this would result in a lower incidence of left cancer as compared with right cancer. However, it is unlikely that such screening practices be offered preferentially to the older cohorts, especially to elderly women. Secondly, if right-sided colon cancer had been detected more frequently by full colonoscopy, we might observe a relative increase in right colon cancer. However, this is believed to be very unlikely because screening methods for colorectal cancer were very unpopular in this country until very recent times. In addition, there seems to be no reason for age/sex difference in such practices. Thirdly, if symptoms in cancers arising from the right colon could be more indolent than those of left colon (32), right colon cancer may be detected later in life resulting in a higher right to left ratio among the elderly women. However, several studies have reported no differences in stage distribution (33) or in the proportion of metastatic lesions (14) according to subsite of the colon affected, and it is difficult to explain why we can not observe the same patterns among elderly men.

One possible biologic mechanism for this phenomenon is that subsite specific environmental risk factors have a different latency period. Some endogenous factors, such as bile acid, were postulated to be more related to the right colon (34), and these may have a longer latency period than the environmental factors, which affect the left colon. Or perhaps the same factors have a longer latency in the right colon than the left colon. The large bowel is known to have embryologically distinct origins in terms of its proximal and distal parts. The proximal part, which accounts for up to two thirds of the transverse colon, originates from the midgut, while the distal part, including the descending and sigmoid colon is derived from the hindgut, and the rectum including the rectosigmoid junction from the cloaca. Therefore, differences in the embryologic origin of the colonic epithelium of the right and left part of this cancer may determine differences in the susceptibility of biogenetically dissimilar tissues to environmental carcinogens and/or in the time needed to develop clinical disease.

Bufill et al. (29) proposed that cancers arising from the right colon are a genetically stable form of the disease, while cancers in the left colon have greater genetic instability, and summarized by stating that colonic ontogeny and oncodevelopmental markers as well as hereditary components differ in the right colon and the left colon/rectum. More specifically, *K-ras* mutations were reported to be present more frequently in the left colon and amongst older men. Microsatellite instability, on the

other hand, was most frequent among younger men and older females and almost exclusively associated with the right colon, which suggests that different genetic pathways to colorectal cancer dominate in the right and left segments of the large bowel (35). These findings appears to be somewhat consistent phenotypically with our findings, which show a higher rate ratio of right to left colon cancer among younger men and older women.

In addition, some colorectal cancers were proposed to arise de novo out of flat mucosa without a prior adenomatous stage (36). Bedenne et al. (37) insisted that approximately 40% of all colorectal cancer cases would arise de novo and that right colon cancer showed consistently fewer adenomatous remnants than left colon or rectal cancer based on the cancer registry data. The importance of these two pathways seems to depend on the site in the bowel and may relate to different causative factors (37), and possibly to different latency periods.

So further studies, which incorporate genetic, pathologic, and environmental aspects are needed to fully explain this pattern of colorectal cancer incidence and to identify the nature of the underlying pathway.

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