White Blood Cell Count and the Risk of Colon Cancer

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and the Risk of Colon Cancer

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Table of Contents

List of Tables

List of Figures

ABSTRACT

Background

Increasing evidence suggests that inflammation may be linked to the pathogenesis of colorectal cancer. However, recently, two conflicting observational results were reported on the relationship between the inflammatory marker C-reactive protein (CRP) and the risk of colorectal cancer. Few epidemiologic studies have examined the association between inflammatory markers and the risk of colorectal cancer.

Purpose

We aimed to examine the association between WBC count and the risk of colon and rectal cancer in this prospective cohort study.

Methods

We prospectively examined the mortality and incidence risk for colon and rectal cancers among 424,419 Koreans (108,907 men and 315,512 women). The subjects were 40 to 95 years of age and from the Korean Cancer Prevention Study (KCPS) cohort. All subjects received medical examination from the National Health Insurance Corporation in 1993 and 1995. The maximum follow-up period was 10 years, from January 1, 1994 to December 31, 2003.

Results

An elevated WBC count was associated with a higher mortality risk of colon cancer (highest versus lowest quartile: men, 1.55, 95% CI 1.10-2.18, p for trend=0.0014; women,

1.51, 95% CI 1.12-2.03, p for trend=0.0049). Similarly, an elevated WBC count was associated with a higher incidence risk of colon cancer (highest versus lowest quartile: men, 1.38, 1.09-1.76, p for trend=0.0017; women, 1.46, 95% CI 1.20-1.78, p for trend=0.0003). A positive linear trend was also observed in non-smokers. There was no significant association between WBC count and the risk of rectal cancer.

Conclusion

Our findings demonstrate that an elevated WBC count is associated with an increase in both the mortality and incidence rates of colon cancer. These results support our hypothesis that inflammation increases the risk of colon cancer.

INTRODUCTION

The incidence of colorectal cancer has been increasing gradually during the past several decades in Korea. In 1980, when the Central Cancer Registry began, colorectal cancers accounted for 5.8% of the total cancers (National Cancer Institute. 2003). In 1990 and 2002, this figure increased to 6.9% and 11.2%, respectively. With estimates of 11,000 new cases annually, colorectal cancer is the fourth most common cancer and the fourth leading cause of cancer-related mortality in Korea (Korea National Statistical Office. 2003).

Considerable studies have examined factors that influence the development of colorectal cancer. Family histories of colorectal cancer (Durno, 2005), obesity (Moore, 2004), animal fat intake (Nagata, 2001), alcohol (Shimizu, 2003), cigarette smoking (Lüchtenborg, 2005), physical inactivity (Slattery, 2003), and insulin resistance (Jee, 2005) have been regarded as predisposing factors of colorectal cancer.

Increasing evidence suggests that inflammation may be linked to the pathogenesis of colorectal cancer. Many studies have suggested a relationship between colorectal cancer and chronic inflammation. The risk of colorectal cancer increases in patients with long-standing inflammatory bowel diseases (Levin, 1992). In addition, several studies have consistently shown a risk reduction for the incidence of colorectal adenoma and cancer among regular and prolonged users of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) (Giovannucci, 1994; Giardiello, 1993). However, recently, two conflicting observational results were reported on the relationship between the inflammatory marker C-reactive protein (CRP) and the risk of colorectal cancer. A nested case-control study showed that individuals with C-reactive protein (CRP) concentrations in the highest quartile had a significantly higher

risk for the incidence of colon cancer compared with individuals in the lowest quartile (Erlinger, 2004). On the contrary, conflicting results were shown in another prospective study in which an elevated plasma CRP level was not a predictor of colorectal cancer, rather it was shown to be merely increased after the onset of colorectal cancer (Zhang, 2005). Few epidemiologic studies have examined the association between inflammatory markers and the risk of colorectal cancer.

WBC count is also a marker of nonspecific inflammation. Hence, WBC was included and analyzed in this study to examine its relationship with the risk of colorectal cancer. We hypothesized that an elevated WBC count is associated with the risk of colorectal cancer. Further, we hypothesized that this association would be independent of smoking because WBC counts and CRP levels tend to be chronically elevated in smokers (Zalokar, 1981; Das, 1985). To examine these hypotheses, we determined the risk of colon and rectal cancer associated with WBC count in this prospective cohort study.

METHODS

Study Population

The Korean Cancer Prevention Study (KCPS) is a prospective cohort study that was designed to assess risk factors for mortality, incidence, and hospital admission for cancer. The KCPS cohort was composed of government employees, teachers, and their dependents insured by the Korea Medical Insurance Corporation from 1992 through 1995. The subjects had at least one medical examination and completed a questionnaire during that period. In brief, the KCPS cohort includes 1,329,525 Koreans (846,907 men and 482,618 women) from 30 to 95 years old who met the above selection criteria. The current analysis was limited to the 446,878 participants who were the insured workers' family dependents in 1993 and 1995. Insured workers were excluded from this study population because there was no WBC count record in their examinations. The 3,703 participants who reported a history of any cancer at enrollment and 1,483 participants who died of cancer before the start of follow-up were also excluded. Additionally, 17,273 participants with missing data on any covariate information were excluded from this study. After these exclusions, 424,419 participants (108,907 men and 315,512 women), who received medical examination in 1993 and 1995, were included in the analyses.

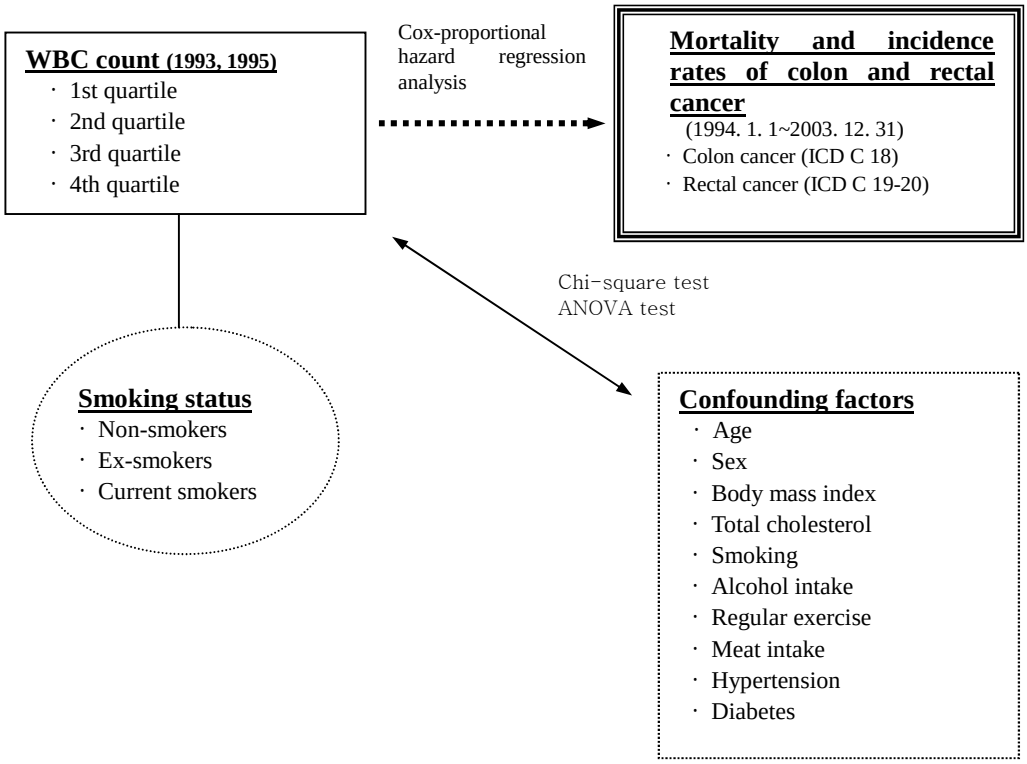

Figure 1. The framework of the current study

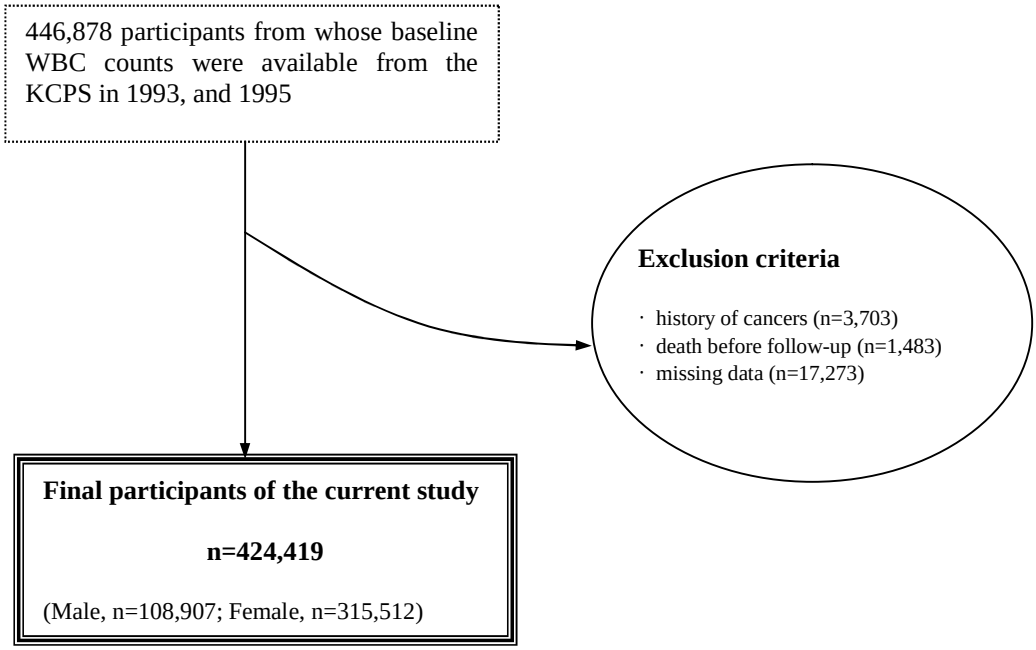

Figure 2. The selection procedure of the study population

Data Collection

The medical examinations were performed according to a standard procedure and conducted by the medical staffs at local hospitals. In the 1993 and 1995 questionnaires, participants were asked about smoking habits and other health behaviors. Participants were also asked if they were currently being treated for cancer or other diseases. If so, they were asked for the date of diagnosis. The completed questionnaires were reviewed by a trained staff and then entered into a database. The data were also checked and cleaned again during the analysis. Body mass index (BMI, kg/m^2) was calculated as the ratio of weight (kilograms) divided by height squared ($meters^2$). WBC count, fasting plasma glucose, and total cholesterol were measured under fasting conditions for routine clinical purposes. Each hospital had internal and external quality control procedures directed by the Korean Association of Laboratory Quality Control. Alcohol consumption per day was categorized as follows: not drinking (0 g), light drinking (1-29.9 g), and moderate to heavy drinking (30 g or more). Diabetes was defined as self-reported history of the disorder or when a fasting plasma glucose level was $\geq$126 mg/dL. Hypertension was defined as self-reported history of the disorder or when systolic blood pressure was $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg.

The maximum follow-up period was 10 years, from January 1, 1994 to December 31, 2003. The exact dates of completion of the survey form were not recorded in each year. Consequently, follow-up accrual began January 1 of the calendar year and ended in the year in which the survey form was completed. Subjects who completed a survey but died in the same calendar year were excluded.

Because the study involved routinely collected medical data, it was not necessary to obtain

individual participant consent. The study was approved by both Institutional Review Boards of Yonsei University and the Johns Hopkins Bloomberg School of Public Health.

Cancer Outcomes

The primary outcomes were the mortality and incidence risk of colon and rectal cancer based on the National Cancer Registry data and hospitalization records. Although Korea has a National Cancer Registry, reporting may not have been complete during the time of follow-up. Thus, hospital administration files were used to identify the first admission date for cancer. Therefore, incident cancer cases were coded as occurring upon either registration to the National Cancer Registry or on a hospital admission due to cancer diagnosis. Mortality was ascertained from the death certificates. A computerized search of death certificate data from the National Statistical Office in Korea was performed using the unique identification number assigned at birth. Causes of death were assigned at the hospitals by trained abstractors. The analysis was limited to those deaths assigned to the 10th revision of the International Classification of Diseases (ICD-10); C18, malignant neoplasm of colon; C19, malignant neoplasm of rectosigmoid junction; and C20, malignant neoplasm of rectum.

Statistical Analysis

The chi-square test and one-way analysis of variance were used to analyze the statistical differences among characteristics of the study participants according to WBC counts at enrollment. Categorization of WBC counts into quartiles was based on the distribution of WBC counts among the study participants aged 40 to 95 years at baseline. Therefore, WBC

counts (cells/μL) were categorized as ≤5500, 5501-6500, 6501-7600, and >7600. In all primary analyses, the WBC count category of ≤5500 cells/μL was the reference group.

Age-adjusted death and incidence rates were calculated for each category of WBC counts and were directly standardized to the age distribution of the Korean population in 1995. Cox proportional hazards regression models were used to compute hazard ratios (HRs) and its 95% confidence intervals (CIs), while adjusting for other potential risk factors. Cox models were also used to assess the trends in risk with quartiles of WBC count as a continuous variable. To exclude subclinical disease at baseline, we conducted analysis for the incidence of colon cancer after excluding cases that occurred within 2 years of follow-up. The association between WBC count and the incidence of colon cancer was also assessed by stratification according to smoking status in order to confirm that the association was independent of the effects of smoking on WBC count.

All analyses were conducted using SAS statistical software, version 8.1 (SAS Institute Inc, Cary, NC). All statistical tests were two-sided, and statistical significance was determined at $p<0.05$.

RESULTS

The baseline characteristics of the study population according to quartiles of WBC counts are shown in Tables 1 and 2. The mean BMI, systolic and diastolic blood pressure, fasting plasma glucose concentration, total cholesterol concentration, amount of daily alcohol consumption, smoking duration, and frequency of meat intake were increased with higher WBC count. The percentages of hypertension, diabetes, and current smoking were also increased with higher WBC count. Regular exercise was inversely associated with higher WBC count.

Table 1. Baseline characteristics of WBC counts in male participants by quartile [*]

	Quartiles of WBC count, cells/μL				p value
	≤5500 (n=18,616)	5501-6500 (n=24,567)	6501-7600 (n=28,018)	>7600 (n=37,711)	
Age, year	63.3 (8.8)	62.6 (8.7)	62.4 (8.5)	61.8 (8.5)	<0.0001
Body mass index, kg/m^2	22.2 (2.8)	22.6 (2.9)	22.7 (2.9)	22.8 (2.9)	<0.0001
Systolic blood pressure, mmHg	128.0 (20.5)	129.4 (21.0)	130.0 (21.0)	130.2 (21.1)	<0.0001
Diastolic blood pressure, mmHg	81.6 (13.0)	82.3 (13.1)	82.8 (13.3)	82.9 (13.2)	<0.0001
Fasting plasma glucose, mg/dL	95.9 (31.1)	96.5 (32.2)	96.6 (31.6)	97.6 (34.6)	<0.0001
Total cholesterol, mg/dL	183.5 (37.4)	188.8 (37.9)	191.3 (6.0)	194.0 (39.6)	<0.0001
Alcohol consumption, g/day	1.8 (6.9)	1.8 (6.9)	1.9 (6.0)	2.0 (6.1)	0.0379
Smoking duration	29.4 (18.2)	30.8 (1.6)	31.8 (17.2)	33.7 (16.1)	<0.0001
Smoking status, %					<0.0001
Non smoker	26.2	22.5	20.1	15.6	
Ex-smoker	31.0	29.0	26.7	22.5	
Current smoker	42.7	48.5	53.2	61.9	
Regular exercise, %	33.3	32.2	31.1	29.1	<0.0001
Meat intake, times /week, %					<0.0001
Nearly none	46.8	46.0	45.3	44.5	
1-2	30.0	29.4	29.4	29.2	
≥ 3	23.2	24.6	25.3	26.3	
Hypertension, %[†]	33.4	35.9	36.9	37.4	<0.0001
Diabetes, %[‡]	8.0	8.4	8.6	9.6	<0.0001

[*] Data are expressed as mean (SD) unless otherwise indicated.

[†] Hypertension was defined as SBP≥ 140 mmHg, DBP ≥ 90 mmHg, or history of the disorder.

[‡] Diabetes was defined as fasting plasma glucose level of at least 126 mg/dL (7.0 mmol/L) or history of the disorder.

Table 2. Baseline characteristics of WBC counts in female participants by quartile [*]

	Quartile of WBC count, cells/μL				p value
	≤5500 (n=90,790)	5501-6500 (n=84,260)	6501-7600 (n=73,364)	>7600 (n=67,098)	
Age, year	53.9 (9.7)	54.5 (9.9)	55.0 (10.0)	55.8 (10.4)	<0.0001
Body mass index, kg/m^2	23.5 (3.0)	23.9 (3.1)	24.2 (3.1)	24.4 (3.3)	<0.0001
Systolic blood pressure, mmHg	123.2 (19.9)	125.3 (20.7)	126.5 (21.1)	128.2 (21.7)	<0.0001
Diastolic blood pressure, mmHg	79.2 (12.9)	80.5 (13.3)	81.1 (13.4)	82.0 (13.6)	<0.0001
Fasting plasma glucose, mg/dL	90.7 (21.6)	92.4 (25.4)	93.8 (27.8)	96.3 (32.8)	<0.0001
Total cholesterol, mg/dL	194.5 (38.2)	199.2 (38.9)	201.7 (39.7)	205.6 (41.1)	<0.0001
Alcohol consumption, g/day	0.1 (0.6)	0.1 (0.7)	0.1 (1.1)	0.1 (0.6)	0.0379
Smoking duration	4.8 (9.5)	5.8 (10.8)	6.7 (11.7)	8.3 (13.2)	<0.0001
Smoking status, %					<0.0001
Non smoker	94.0	92.2	90.6	87.7	
Ex-smoker	2.3	2.8	3.1	3.6	
Current smoker	3.8	5.1	6.3	8.7	
Regular exercise, %	19.2	18.6	18.3	17.3	<0.0001
Meat intake, times /week, %					<0.0001
Nearly none	24.9	24.8	24.7	24.3	
1-2	60.3	60.3	60.2	60.0	
≥ 3	14.8	14.9	15.1	15.7	
Hypertension, %[†]	23.9	27.9	30.1	33.2	<0.0001
Diabetes, %[‡]	3.6	5.0	6.2	8.6	<0.0001

[*] Data are expressed as mean (SD) unless otherwise indicated.

[†] Hypertension was defined as SBP≥ 140 mmHg, DBP ≥ 90 mmHg, or history of the disorder.

[‡] Diabetes was defined as fasting plasma glucose level of at least 126 mg/dL (7.0 mmol/L) or history of the disorder.

Overall Patterns of All Cause Mortality

During the 10 year follow-up, 25,458 and 21,482 deaths occurred among men and women, respectively. As shown Figure 3, WBC level was positively associated with age adjusted all-cause mortality rates in women, whereas this figure seemed to be like U-shaped in men. The multivariate adjusted hazard ratios (HRs) for all cause mortality in the highest quartile of WBC count were 1.15 and 1.22 compared with the reference category in men (95% CI 1.11-1.20, p for trend <0.0001) and women (95% CI 1.18-1.27, p for trend <0.0001), respectively (Tables 3, 4).

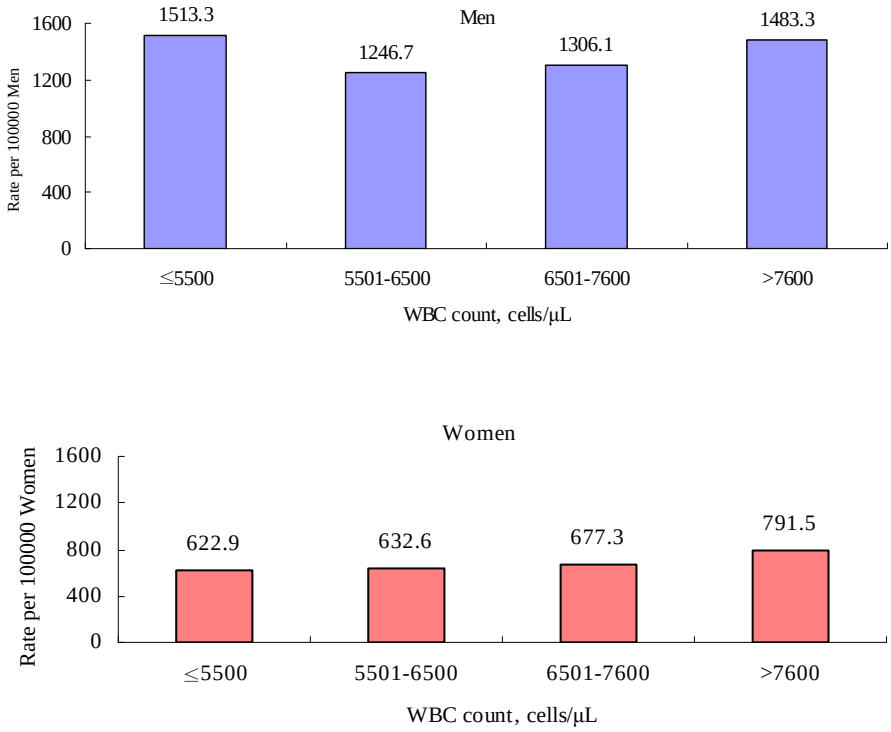

Figure 3. Age-adjusted mortality rate per 100,000 from all causes by quartile of WBC count in men and women, 1994-2003

Mortality Risk for Colon and Rectal Cancer

For men, there were 9,010 deaths from all cancers including 310 from colon cancer and 229 from rectal cancer during the 10 year follow-up. For women, there were 5,871 deaths from all cancers including 352 from colon cancer and 237 from rectal cancer. Tables 3 and 4 show that the HRs for mortality from colon cancer increase with higher quartiles of WBC count among men and women. The multivariate adjusted HRs for all-cause mortality in the highest quartile of WBC count were 1.33 (95% CI 1.03-1.72, p for trend=0.0031) for colorectal cancer and 1.55 (95% CI 1.10-2.18, p for trend=0.0014) for colon cancer, compared with the reference category in men (Table 3). The higher mortality risk associated with higher quartiles of WBC count was also observed for colon cancer in women (highest versus lowest quartile: HR 1.51, 95% CI 1.12-2.03, p for trend=0.0049) (Table 4). In contrast to colon cancer, there was no significant difference in mortality risk for rectal cancer between the highest quartile and the lowest quartile in men or women.

Table 3. Age-adjusted mortality rate per 100,000 person-years and hazard ratios for all causes, all cancers, and colon and rectal cancer by quartile of WBC count in men, 1994-2003[*]

	Quartile of WBC count, cells/μL				p value for trend
	≤5500 (n=18,616)	5501-6500 (n=24,567)	6501-7600 (n=28,018)	>7600 (n=37,711)	
All causes, n	4,307	5,499	6,377	9,275	
Death rate[†]	1513.3	1246.7	1306.1	1484.3	
HR[‡]	1.00	0.99(0.96-1.04)	1.02(0.98-1.06)	1.15(1.11-1.20)	<0.0001
All cancers, n	1,618	1,962	2,196	3,237	
Death rate[†]	572.1	466.6	459.6	514.8	
HR[‡]	1.00	0.93(0.87-0.99)	0.90(0.85-0.96)	1.01(0.95-1.07)	0.3820
Colorectal cancer, n	86	102	134	217	
Death rate[†]	28.6	20.3	24.5	31.3	
HR[‡]	1.00	0.91(0.68-1.21)	1.06(0.81-1.40)	1.33(1.03-1.72)	0.0031
Colon cancer, n	47	56	75	132	
Death rate[†]	19.7	8.6	12.6	20.3	
HR[‡]	1.00	0.94(0.64-1.40)	1.10(0.76-1.59)	1.55(1.10-2.18)	0.0014
Rectal cancer, n	39	46	59	85	
Death rate[†]	8.9	11.7	11.9	11.0	
HR[‡]	1.00	0.90(0.58-1.39)	1.07(0.71-1.61)	1.22(0.83-1.80)	0.1555

Abbreviations: CI, confidence interval; HR, hazard ratio.

[*]Participants with any of the following features at study entry were excluded: missing data on leukocyte count, existing cancer, and missing data on questionnaire.

[†]The rate per 100,000 person-years is given, standardized to the age distribution of men in the 1995 Korean national population.

[‡]The Cox proportional hazards model was adjusted for age, BMI, total cholesterol, smoking status, regular exercise, alcohol consumption per day (none, 0-29.9 g/day, ≥30 g/day), frequency of meat intake per week (nearly none, 1-2, ≥3), hypertension, and diabetes.

Table 4. Age-adjusted mortality rate per 100,000 person-years and hazard ratios for all causes, all cancers, colon and rectal cancer by quartile of WBC count in women, 1994-2003[*]

	Quartile of WBC count, cells/μL				p value for trend
	≤5500 (n=90,790)	5501-6500 (n=84,260)	6501-7600 (n=73,364)	>7600 (n=67,098)	
All causes, n	5,134	5,220	5,159	5,969	
Death rate[†]	622.9	632.6	677.3	791.5	
HR[‡]	1.00	1.01(0.98-1.05)	1.06(1.02-1.11)	1.22(1.18-1.27)	<.0001
All cancers, n	1,657	1,411	1,429	1,374	
Death rate[†]	191.5	165.7	185.0	183.7	
HR[‡]	1.00	0.91(0.85-0.98)	1.01(0.94-1.08)	0.99(0.93-1.07)	0.6429
Colorectal cancer, n	155	146	137	151	
Death rate[†]	18.2	17.0	17.8	19.6	
HR[‡]	1.00	0.95(0.75-1.19)	1.00(0.79-1.26)	1.11(0.88-1.40)	0.3408
Colon cancer, n	86	80	83	103	
Death rate[†]	10.1	9.4	10.9	13.2	
HR[‡]	1.00	1.03(0.76-1.41)	1.18(0.87-1.61)	1.51(1.12-2.03)	0.0049
Rectal cancer, n	69	66	54	48	
Death rate[†]	8.1	7.6	6.9	6.4	
HR[‡]	1.00	0.98(0.69-1.39)	0.92(0.64-1.32)	0.79(0.54-1.16)	0.2179

Abbreviations: CI, confidence interval; HR, hazard ratio.

[*]Participants with any of the following features at study entry were excluded: missing data on leukocyte count, existing cancer, and missing data on questionnaire.

[†]The rate per 100,000 person-years is given, standardized to the age distribution of women in the 1995 Korean national population.

[‡]The Cox proportional hazards model was adjusted for age, BMI, total cholesterol, smoking status, regular exercise, alcohol consumption per day (none, 0-29.9 g/day, ≥30 g/day), frequency of meat intake per week (nearly none, 1-2, ≥3), hypertension, and diabetes.

Incidence Risk for Colon and Rectal Cancer

The incidences of colon cancer during the 10 year follow-up were 604 among men and 838 among women. The trend of colorectal cancer incidence was generally similar to the mortality risk of colorectal cancer. Tables 5 and 6 show that the HRs for colon cancer incidence increase with the higher quartiles of WBC count. The multivariate adjusted HRs for incidence in the highest quartile of WBC count were 1.23 (95% CI 1.03-1.47, p for trend=0.0030) for colorectal cancer and 1.38 (95% CI 1.09-1.76, p for trend=0.0017) for colon cancer, compared with the reference category in men (Table 6). The higher incidence risk associated with an increased WBC count was also seen for colon cancer in women (highest versus lowest quartile: HR 1.46, 95% CI 1.20-1.78, p for trend=0.0003) (Table 6). There was no significant difference in incidence risk for rectal cancer between the highest quartile and the lowest quartile among men or women. A total 145 cases of colon cancer occurred within 2 years of follow-up, 61 cases for men and 84 cases for women. Even after excluding these cases that occurred within 2 years of follow-up, this association was sustained. The multivariate adjusted HRs for incidence of colon cancer in the highest quartile of WBC count were 1.34 (95% CI 1.04-1.73, p for trend=0.0058) in men and 1.41 (95% CI 1.14-1.73, p for trend=0.0058) in women.

Table 5. Age-adjusted incidence rate per 100,000 person-years and hazard ratios for all cancers, colon and rectal cancer by quartile of WBC count in men, 1994-2003[*]

	Quartile of WBC count, cells/μL				p value for trend
	≤5500 (n=18,616)	5501-6500 (n=24,567)	6501-7600 (n=28,018)	>7600 (n=37,711)	
All cancers, n	1,950	2,505	2,816	4,014	
Incidence rate[*]	857.8	752.4	744.7	817.1	
HR[‡]	1.00	0.98(0.92-1.04)	0.96(0.90-1.01)	1.02(0.97-1.08)	0.2861
Colorectal cancer n	183	228	276	435	
Incidence rate[*]	89.8	59.8	78.1	83.6	
HR[‡]	1.00	0.95(0.78-1.15)	1.02(0.84-1.23)	1.23(1.03-1.47)	0.0030
Colon cancer, n	94	123	149	238	
Incidence rate[*]	43.2	31.7	42.0	49.2	
HR[‡]	1.00	1.00(0.76-1.31)	1.07(0.83-1.39)	1.38(1.09-1.76)	0.0017
Rectal cancer, n	111	130	157	232	
Incidence rate[*]	58.7	34.5	44.2	40.5	
HR[‡]	1.00	0.91(0.71-1.18)	0.99(0.77-1.26)	1.16(0.91-1.45)	0.0985

Abbreviations: CI, confidence interval; HR, hazard ratio.

[*]Participants with any of the following features at study entry were excluded: missing data on leukocyte count, existing cancer, and missing data on questionnaire.

[†]The rate per 100,000 person-years is given, standardized to the age distribution of men in the 1995 Korean national population.

[‡]The Cox proportional hazards model was adjusted for age, BMI, total cholesterol, smoking status, regular exercise, alcohol consumption per day (none, 0-29.9 g/day, ≥30 g/day), frequency of meat intake per week (nearly none, 1-2, ≥3), hypertension, and diabetes.

Table 6. Age-adjusted incidence rate per 100,000 person-years and hazard ratios for all cancers, colon and rectal cancer by quartile of WBC count in women, 1994-2003[*]

	Quartile of WBC count, cells/μL				p value for trend
	≤5500 (n=90,790)	5501-6500 (n=84,260)	6501-7600 (n=73,364)	>7600 (n=67,098)	
All cancers, n	3,557	3,122	2,799	2,626	
Incidence rate[*]	458.9	423.8	431.9	435.8	
HR[‡]	1.00	0.99(0.94-1.04)	1.00(0.95-1.06)	1.02(0.97-1.08)	0.3789
Colorectal cancer, n	405	400	353	371	
Incidence rate[*]	52.1	53.1	52.8	58.4	
HR[‡]	1.00	1.03(0.90-1.19)	1.03(0.89-1.19)	1.15(0.99-1.33)	0.0812
Colon cancer, n	216	215	195	212	
Incidence rate[*]	27.7	28.5	29.6	33.3	
HR[‡]	1.00	1.27(1.02-1.50)	1.26(1.03-1.54)	1.46(1.20-1.78)	0.0003
Rectal cancer, n	228	222	183	189	
Incidence rate[*]	29.3	29.5	27.1	30.1	
HR[‡]	1.00	1.10(0.91-1.32)	1.04(0.85-1.27)	1.14(0.93-1.39)	0.2987

Abbreviations: CI, confidence interval; HR, hazard ratio

[*]Participants with any of the following features at study entry were excluded: missing data on leukocyte count, existing cancer, and missing data on questionnaire.

[†]The rate per 100,000 person-years is given, standardized to the age distribution of women in the 1995 Korean national population.

[‡]The Cox proportional hazards model was adjusted for age, BMI, total cholesterol, smoking status, regular exercise, alcohol consumption per day (none, 0-29.9 g/day, ≥30 g/day), frequency of meat intake per week (nearly none, 1-2, ≥3), hypertension, and diabetes.

Incidence Risk for Colon Cancer according to Smoking status

We also assessed the association between WBC count and incidence of colon cancer after stratification by smoking status (non-smokers, ex-smokers, and current smokers) in order to confirm that the associations were independent of the effects of smoking on WBC count.

Among men who reported never smoking, a positive linear trend was observed between the incidence of colon cancer and WBC count. The multivariate adjusted HRs for incidence of colon cancer were 1.56 (95% CI 0.83-2.95), 2.61 (95% CI 1.45-4.68), and 2.90 (95% CI 1.62-5.17) with increasing WBC count quartiles, compared with a reference quartile (p for trend <0.0001) (Figure 4). A similar positive linear trend was also observed in female non-smokers. The multivariate adjusted HRs for colon cancer incidence were 1.27 (95% CI 1.04-1.55), 1.26 (95% CI 1.02-1.55), 1.47 (95% CI 1.19-1.81) with increasing WBC count quartiles, compared with a reference quartile (p for trend=0.0006) (Figure 5). However, there was no significant difference in incidence of colon cancer among ex-smokers and current smokers (Figures 4, 5).

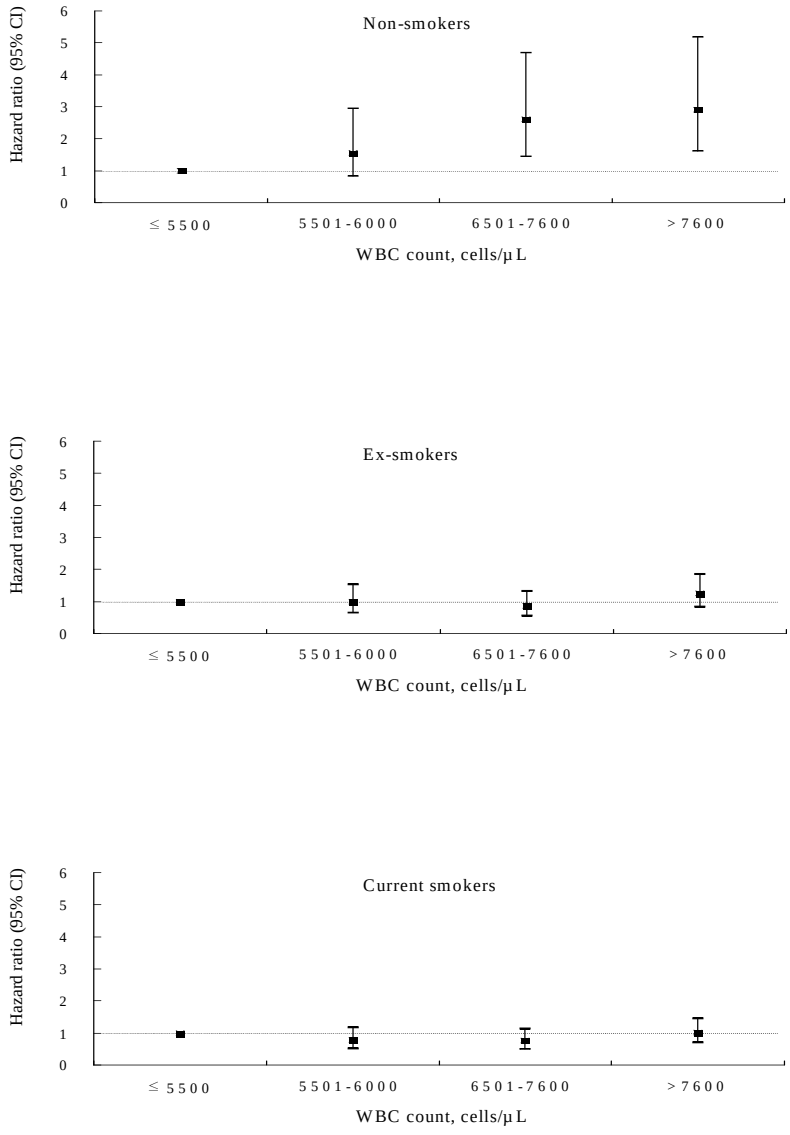

Figure 4. Hazard ratios[*] for colon cancer incidence by quartile of WBC count in men by smoking status, 1994-2003 (*The Cox proportional hazards model was adjusted for age, BMI, total cholesterol, regular exercise, alcohol consumption per day (none, 0-29.9 g/day, ≥30 g/day), frequency of meat intake per week (nearly none, 1-2, ≥3), hypertension, and diabetes.)

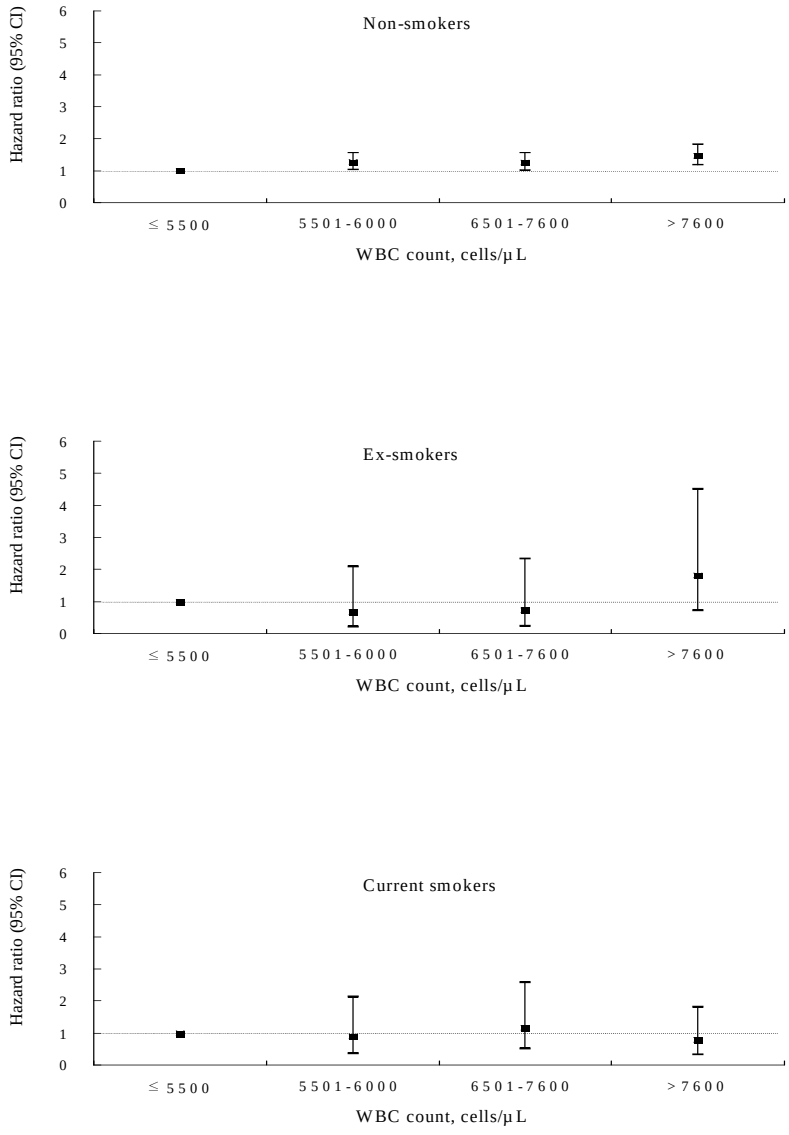

Figure 5. Hazard ratios[*] for colon cancer incidence by quartile of WBC count in women by smoking status, 1994-2003 ([*]The Cox proportional hazards model was adjusted for age, BMI, total cholesterol, regular exercise, alcohol consumption per day (none, 0-29.9 g/day, ≥30 g/day), frequency of meat intake per week (nearly none, 1-2, ≥3), hypertension, and diabetes

DISCUSSION

In this large prospective cohort study of Korean men and women, a positive association between WBC count and the risk of colon cancer was found. Our data suggest that an elevated WBC count increases the incidence risk and mortality of colon cancer in men and women. These findings are consistent with emerging evidence suggesting that inflammation increases the risk of colon cancer. Individuals with long-term inflammatory bowel disease, in particular ulcerative colitis, are at higher risk for developing colorectal cancer than ordinary individuals (Levin, 1992). A clinical trial demonstrates that regular use of anti-inflammatory agents can reduce the risk of colorectal adenoma, a well-known precancerous lesion (Baron, 2003). In a recent prospective cohort study examining the association between WBC count and the mortality risk of cancers, an elevated WBC count increased the mortality risk for all cancers. However, the study failed to show this association through subgroup analyses including colon, breast, and prostate cancer (Erlinger, 2004). This may be due to the lower number of deaths from the site-specific cancers mentioned.

There are two previous prospective studies with conflicting results on the relationship between inflammatory markers and the incidence of colorectal cancer. In a recent nested case-control study of 172 colorectal cases (131 colon cases, 41 rectal cases) within the CLUE II cohort in which 22,887 residents of Washington County, Maryland were studied prospectively, the incidence risk of colon cancer increased with higher CRP levels. However, this association was not found in rectal cancer (Erlinger, 2004). On the contrary, a different prospective study with 27,913 healthy women within the Women's Health Study showed that a high CRP level was not a predictive risk factor for the development of colorectal cancer (Zhang, 2005).

Despite a positive association between WBC count and the incidence risk and mortality of colon cancer, we did not find a similarly significant association with rectal cancer in the present study. A potential limitation of the CLUE II cohort study is a relatively smaller number of rectal cancer patients (n=41), which could have weakened the association between an elevated CRP level and the incidence of rectal cancer. Our study overcomes this weakness by conducting prospective follow-ups on a larger number of rectal cancer patients during a 10 year follow-up period. Accordingly, our findings implicate that the role of inflammation involved in the development of colon cancer may be different from that of rectal cancer. The biological mechanisms through which an elevated WBC count increases the risk of colon cancer have not yet been established. However, several plausible mechanisms between colon cancer and inflammation deserve consideration based on previous studies. Cyclooxygenase-2 (COX-2) may be linked to the pathogenesis of colon cancer development. COX-2 protein is over-expressed and the prostaglandin E_2 level is elevated in the portal vein and colonic mucosa in human colorectal cancers (Oka, 1994; Pugh, 1994). COX-2 protein may control angiogenesis by modulating production of the vascular endothelial growth factor (VEGF), which promotes sustained endothelial cell proliferation and vascular permeability in tumorogenesis (Yancopoulos, 2000; Tsujii, 1998). Many other studies also demonstrate that the carcinogenic effect of inflammation may be linked to DNA damage in proliferative cells (Maeda, et al. 1998), alteration of p53 tumor suppressor gene (Chen, 2005), inhibition of apoptosis (Sheng, 1998) during the various stages of carcinogenesis. Dietary and lifestyle risk factors for colon cancer, such as a diet high in calories, animal fat, and/or refined carbohydrates, physical inactivity, central obesity, and high body mass index are also related to inflammation and insulin resistance (Verdaet, 2004; Wolever, 1996). Insulin resistance may lead to tumor growth by elevating bioavailable insulin growth factor-1 (IGF-1) and decreasing

insulin growth factor binding protein-1 (IGFBP-1) (Ma, 2004). These inflammatory effects on colon cancer may not only be through systemic pathway mediated by cytokines and chemokines but also directly linked to the colon epithelium. A recent study shows that individuals with more risk factors for colorectal cancer have a higher level of calprotectin, which is a marker of bowel inflammation at the tissue level (Poullis, 2004).

Our study has several potential limitations to take into consideration. First, WBC counts during the 10 year follow-up were not available for our study. Thus, only one measurement of WBC count, at baseline examination, was included in the analysis. Therefore, it was not possible to determine whether an acute, brief episode of inflammation or chronic inflammation was responsible for the correlation found in the current study. Second, data on potentially confounding factors, such as past medical history of inflammatory bowel disease or colorectal polyps, medication history (aspirin, other NSAIDs or estrogen use) were unavailable in the baseline questionnaire. Thus, such variables are not fully adjusted in our Cox-proportional hazards regression model. Lastly, the study population in our cohort, particularly the older aged population, might not be representative of the general population in Korea.

Despite these potential limitations, the current study has several important strengths. First, the current study is a large prospective study with a relatively long period of follow-up, so we can be confident about the temporal relationship between inflammation and the risk of colon cancer. Second, this positive association was sustained even after excluding the cases of colon cancer that developed within the first 2 years of follow-up, thereby reducing the likelihood of a subclinical cancer at the baseline of the study. Consequently, the elevated WBC count was unlikely to be caused and biased by a subclinical colon cancer. Finally, similar positive trends observed in non-smokers suggest that the incidence risk of colon cancer associated with an elevated WBC count is independent of the effects of smoking on WBC count.

In conclusion, our findings demonstrate that an elevated WBC count is a predictor of the incidence risk and mortality of colon cancer. These results support our hypothesis that inflammation increases the risk of colon cancer. Further observational and experimental studies are needed to confirm these findings and to determine the role of inflammation in the carcinogenesis of colon and rectal cancer.

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국문 요약

연구배경

염증이 대장암, 직장암 발생과 관련있을 것이라는 가설이 꾸준히 제시되고 있으나, 최근 비특이적 염증지표인 C-reactive protein (CRP)가 대장암, 직장암의 발생위험을 높인다는 보고와 대장암, 직장암 발생과 관련이 없다는 상반된 역학 연구가 발표되었다.

연구목적

저자들은 전향적인 대규모 코호트 연구를 통해 비특이적 염증지표인 백혈구수와 대장암, 직장암 발생의 관계에 대해 알아보고자 한다.

연구방법

한국 암 예방 연구 코호트 (Korean Cancer Prevention Study : KCPS) 중에서 연구시작 당시 백혈구수 측정이 가능했던 40세 - 95세 사이의 424,319명 (남 : 108,907명, 여 : 315,512명)을 대상으로 백혈구수 구간을 4구간으로 구분한 후 1994년부터 2003년까지 대장암, 직장암의 발생률 및 사망률과 각각의 상대위험도를 구하였다. 또한, 흡연여부에 따른 대장암 발생의 상대위험도를 구하였다.

연구결과

10년의 추적관찰 기간 동안 제 4구간의 대장암으로 인한 사망위험이 기준집단에 비해 남성에서는 1.55배 높았으며 (95% 신뢰구간 1.10-2.18, p for trend=0.0014), 여성에서는 1.51배 높았다 (95% 신뢰구간 1.12-2.03, p for trend=0.0049).

대장암 발생도 대장암으로 인한 사망과 비슷한 양상이었다. 제 4구간의 대장암 발생 위험이 기준집단에 비해 남성에서는 1.38배 높았으며 (95% 신뢰구간 1.09-1.76, p for trend=0.0017), 여성에서는 1.46배 높았다 (1.20-1.78, p for trend=0.0003). 흡연여부에 따른 대장암 발생의 위험도 남성과 여성 모두 비흡연자에서 대장암 발생의 상대위험도가 높았다. 남성과 여성 모두 백혈구수 구간별 직장암 발생과 사망의 상대위험도는 유의한 차이가 없었다.

결론

비특이적 염증지표인 백혈구수가 높을수록 대장암 발생의 위험과 사망의 위험이 높아진다.