Association between fasting serum glucose levels and incidence of colorectal cancer

: The Korean Cancer Prevention Study-II

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The Master's Thesis submitted to the Department of Epidemiology

Then Graduate School of Public Health, Yonsei University

in partial fullfillment of the requirements for the degree of Master of Public Health

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June 2015

This certifies that the dissertation of Hyun-Young Shin is approved.

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July 2015

Acknowledgements

세브란스 병원에서 가정의학과 강사를 시작하면서 새로운 마음으로 보건대학원 에 입학한지 벌써 2-3 여년이 흘렀습니다. 당시에 야심찬 마음으로 새로운 보건분야를 공부하겠다는 의욕을 불사르며 바쁜 와중에도 수업을 꼬박꼬박 참여하기 위해 고군분투했던 기억이 아직도 선명합니다. 그동안에 저는 많이 성장하였습니다. 의과대학, 인턴, 레지던트 그리고 강사시절의 임상경험과 보건대학원에서의 축적한 보건의료에 대한 이론과 지식이 합쳐져 제 자신을 성숙시켰다고 생각합니다. 특히 제 전공인 역학부분에서의 배움은 소중한 제 성장의 밑거름이 될 것이라고 확신합니다. 고귀한 데이터를 얻어 스스로 통계를 돌려보고 결과물을 교수님들과 논의하던 그 한순간 한순간이 소중합니다. 또한 바쁜 와중에서도 낙오되지 않도록 잘 챙겨주었던 동기들까지 보건대학원에서의 추억과 인연은 소중한 자산이 되었습니다. 이 자리를 빌어서 지선하 교수님, 김희진 교수님, 박소희 교수님께 감사의 말씀 드립니다. 그리고 사랑하는 나의 가족들, 특히 부모님과 물심양면으로 고생 많았던 신랑, 그리고 사랑스런 도담이와 곧 태어날 우리 둘째 아가에게도 이 기쁨을 같이 나누고 싶습니다. 감사합니다.

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I. Introduction

Colorectal cancer(CRC) is the third and second most common cancer in men and women, respectively, worldwide (Ferlay, et al., 2010). In Korea, it is the third most common cancer overall, and the second most common cancer in men [2]. A Westernized life style and diet is thought to be one of the major reasons for the observed increase in incidence of CRC in Korea and in other developed countries (National Cancer Center, 2014, National Cancer Center, Shin, et al., 2012). Numerous studies have shown that colorectal carcinogenesis is associated with metabolic disorders, such as obesity, metabolic syndrome, and diabetes mellitus; however, the exact mechanisms are currently unclear (Jee, et al., 2008, Ishim, et al., 2013, Giovannucci, et al., 2010).

The incidence of diabetes mellitus has been increasing vastly in most countries, including Korea (Shaw, et al., 2010, Kim, 2011) and it undoubtedly represents one of the most challenging health issues of the 21st century (International Diabetes Federation, 2014). Many studies have reported that diabetes mellitus is related with the increasing incidence of CRC (Giovannucci, et al., 2010, Larsson et al., 2005, Deng et al., 2012, De Bruijn, et al., 2013, Yuhara et al., 2011, Zanders et al., 2014, Inoue et al., 2012). Recently, diabetes mellitus as well as impaired fasting glucose(IFG) as a marker of pre-diabetes, have been spotlighted as a way to minimize the medical and socio-economic burden of diabetes mellitus, by

permitting early detection and intervention. Several studies have reported that pre-diabetes is a possible risk factor of cardiovascular diseases (Barzilay et al., 1999, Kim et al., 2013); however, there is currently no consensus about the association of cancer incidence and IFG. As CRC is broadly known to be a metabolic-related cancer, studying the incidence of CRC and its correlation with fasting serum glucose(FSG) levels could be helpful to design better prevention strategies for controlling the progression and development of CRC.

Ⅱ. Material and Methods

This study was approved by the institutional review board of the Yonsei University, and all study participants provided written consent, according to the principles of the Declaration of Helsinki.

1. Study population

This is the Korean Metabolic Syndrome Research Initiative study in Seoul, initiated in 2005. The initial study population included 183,336 individuals who visited health promotion centers in university hospitals between 2004 and 2011. Among the total sample population, 278 participants who were diagnosed with colorectal cancer as well as 7132 patients with diabetes mellitus at the time of enrollment were excluded from the study. In addition, 249 subjects with an extremely low body mass index(BMI)<16 kg/m^2, weight$\leq$30 kg, or height$\leq$130 cm were excluded. Therefore, the final subject group consisted of 175,677 Korean men and women(men, n = 103,452; women, n = 72,225). The mean follow-up period was 4.7 years. A detailed description of the Korean Cancer Prevention Study-II design and methods of selection of participants has been published previously (Jee et al., 2010).

2. Questionnaire and anthropometric measurements

Each participant was interviewed by using a structured questionnaire to collect the following details: education level(<high school vs.≥high school), smoking history(never smoked, ex-smoker, or current smoker), alcohol drinking(non-drinker vs. consumer of any amount of alcohol on a regular basis), and regular exercise(yes or no). Participant height and weight were measured while the participants were wearing light clothing. BMI was calculated by dividing the weight(kg) by the square height(m^2). Systolic and diastolic blood pressures were measured after a rest period of at least 15 min.

3. Blood collection and biochemical analyses

For clinical chemistry assays, serum－separated from peripheral venous blood－was obtained from each participant after a minimum fasting period of 12h, and stored at －70°C until the time of analysis. Levels of FSG, total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured by using a COBAS INTEGRA 800 and a Hitachi-7600 analyzer(Hitachi, Tokyo, Japan).

4. Diagnosis of CRC

Data regarding the incidence of CRC was obtained from the records of

the National Cancer Registry and from the hospitals where the participants had been treated. Although Korea has a National Cancer Registry, reports were not complete during the time of follow-up; therefore, hospital admission files were used to identify the first admission events for CRC. An incident of CRC was considered to have occurred on the basis of a positive report either from the National Cancer Registry or upon hospital admission for a cancer diagnosis. According to the International Classification of Diseases, Tenth Revision(ICD-10), CRC was coded as C18-C20 (World Health Organization, 2011).

5. Statistical analysis

Person-years were calculated from the baseline enrollment to 2011, the date of CRC diagnosis, death, or loss of follow-up. Crude incidence rates(per 100,000 person-years) were calculated with the person-years and number of cases of CRC. Hazard ratios(HRs) were calculated by using the Cox proportional hazard model, after adjusting for age, sex, BMI, smoking status, alcohol consumption, and regular exercise. BMI as an indicator of obesity was adjusted in this study for the effect to be minimized. The analyses were performed separately for men and women. Subsequently, the same analyses were used after the FSG levels were divided into high(FSG$\geq$100 mg/dL) or low(FSG<100 mg/dL), and into 4 categories on the basis of the cut-offs of 100 mg/dL, 110 mg/dL, and

126mg/dL, in the total population, and in men and women separately. Kaplan-Meier survival analyses were used to evaluate the incidence probability of CRC in the four FSG groups. All statistical tests were two-sided, and statistical significance was determined as $P < 0.05$. SAS statistical software, version 9.2(SAS Institute Inc., Cary, NC) was used for all analyses.

Ⅲ. Results

The basic characteristics of the participants(103,452 men and 72,225 women) are summarized in Table 1. A total of 320 patients were newly diagnosed with CRC among the 175,677 participants over 816,143 total person-years(mean follow-up, 4.7 years). The crude incidence rates per 100,000 person-years were 39.21 overall, 47.73 for men, and 27.31 for women. The incident rate increased with age in both men and women(Table 2). The HR for developing CRC in subjects with high FSG was statistically significant(HR, 1.40; 95% confidence interval [CI], 1.10–1.78), and the association remained significant after adjusting for confounding variables(HR, 1.45; 95% CI, 1.10–1.90). When the same analysis was performed according to the sex of the subjects, the HR for developing CRC was relatively high in men(HR, 1.51; 95% CI, 1.11–2.05), whereas no association was observed in women (HR, 1.23; 95% CI, 0.67-2.26)(Table 3). When Cox proportional hazards regression models were applied to site-specific CRC, only the HR of rectal cancer was statistically significant in both the total population and men(HR, 1.49; 95% CI, 1.00–2.24; HR, 1.59; 95% CI, 1.01–2.48, respectively), whereas no significant associations were observed for proximal and distal colon cancers in all groups(Table 4). Increasing trends in the HR of CRC according to the increase of FSG levels were observed(P=0.006 in the total population[Supplementary Fig. 1], P=0.005 in men[Fig. 1], and P=

0.67 in women[data not shown]). When the obese and non-obese groups were sub-analyzed, interestingly, the incidence of distal colon cancer in men was found to be significantly associated with high serum glucose levels in the non-obese group(BMI<25), whereas the incidence of distal colon cancer in women was found to be significantly associated with high serum glucose levels in the obese group(BMI≥25). However, due to the low incidences of distal colorectal cancer in women during a relatively short follow-up period, the confidence interval was observed to be wide. [Supplementary Table 1].

Figure 2 illustrates the incidence trends of CRC during the follow-up period, as determined using the Kaplan-Meier method in the four FSG groups. The cumulative CRC incidence probabilities gradually increased over time, with a sharper increase observed in the high-level FSG groups compared to the low-level FSG groups.

Ⅳ. Discussion

In this prospective cohort study of a large Korean population, we found that the incidence of CRC was positively associated with FSG levels. Especially, hyperglycemia including IFG correlated with CRC incidence in men, indicating that pre-diabetes status might be related with colorectal carcinogenesis. This finding was consistent with several previous studies, although the specific classification and study designs differed between the studies. In the Framingham Heart Study-offspring cohort, the incidence of CRC was found to higher in subjects with IFG. The early exposure of high glucose levels displayed a strong association with CRC, and the HRs proportionally increased with the exposure period of IFG(IFG exposure 5–10 y: HR, 1.76; 95% CI, 1.09–2.84; 10–20y: HR, 2.55; 95% CI, 1.60–4.05;and ≥20y: HR, 3.26; 95% CI, 1.73–6.14) (Prekh et al., 2013). Another study in Korea, similar to ours, showed the association between IFG and incidence of CRC in men only(glucose, 90–109mg/dL: HR, 1.08; 95% CI, 1.01–1.15; glucose, 110–125mg/dL: HR, 1.14; 95% CI, 1.02–1.27), however, unlike in our study, the incidences of site-specific colorectal cancer were not examined (Jee et al., 2005). These two studies were commonly adjusted for age, sex, smoking, and alcohol use, however diet, calori intake or family history of colorectal cancer were not included.

On the other hand, a prospective cohort study in Austria found that

the association between IFG and the risk of CRC was higher in women(HR, 1.57; 95% CI, 1.08–2.28) than in men (HR, 1.37; 95% CI, 0.94–2.01) (Rapp el al., 2006). These inconsistent results between men and women might be explained by considering the interaction of sex hormones, inadequate control of confounding factors, and different sample sizes between the studies. Furthermore, a study in a Swedish cohort revealed that the association between hyperglycemia and colon cancer was not significant (Stattin et al., 2007).

There are many hypotheses about the mechanisms behind the potential association between hyperglycemia and CRC. Hyperinsulinemia through insulin-like growth factor signaling (Ish-Shalom et al., 1997, Khandwala et al., 2000, Cohen et al., 2012), chronic inflammation (Yu et al., 2009, Danel et al., 2013), delayed bowel transit time (Will et al., 1998), changes in bile acid (Stadler et al., 1988), and imbalanced microbiota in the bowels (Tlaskalová-Hogenová el at., 2011), have all been suggested. Recently, a study of Kannisto Vetvik et al. demonstrated that involvement of adiponectin-AMP-activated protein kinase α signaling in colorectal carcinogenesis was depending on the glucose levels (Katja et al., 2014). As IFG is an early stage of diabetes mellitus, similar mechanisms are likely responsible for the association between IFG and CRC as well. In addition, the common risk factors of diabetes mellitus and CRC, such as central obesity, high BMI, physical inactivity, and a high-calorie diet, have also been suggested to be the cause of the observed association.

However, the association persisted after controlling for these risk factors in our study, suggesting that this is not the only explanation.

In the present study, the incidence of rectal cancer was associated with elevated glucose levels in men but not in women. There have been several studies about the site-specific relative risks of CRC according to glucose levels, but the results are inconsistent with those of the present study. The Iowa Women's Health study reported that the incidence of proximal colon cancer was associated with diabetes mellitus (Limburg et al., 2005), whereas the study by He et al. and the Nurses' Health study found that the incidence of right and left colon cancer, but not rectal cancer, were significantly associated with diabetes mellitus (He et al., 2010, Hu et al., 1999). Moreover, a prospective study in Sweden demonstrated a slightly higher risk of cecum/ascending colon cancer compared to other sites of CRC in patients with diabetes mellitus (Weiderpass et al., 1997). Rectal cancer is known to be the most common subsite of colorectal cancer in Asian male (Shin et al., 2012), whereas proximal colon cancer is known to be the most common site of colorectal cancer for Asian womens,Whites and Blacks living in U.S. (Murphy et al., 2011, Wu et al., 2004). This might be the one of the contributing factors of the association. However, the mechanisms behind the site-specific incidence of CRC, and its association with hyperglycemia, have not yet been fully explained.

When the glucose levels were sub-classified into 4 categories in our study, the HR of each group displayed an increase in trend in the incidence of CRC; however, the HRs were not statistically significant in the group with fasting glucose levels of 110 to 126mg/dL. This might be owing to the sample size of patients with CRC and the study duration not being sufficient, leading to poor statistical power.

There are several limitations to our study. First, the participants in the cohort were followed-up for a relatively short period, and therefore it may not have been enough time to fully detect the cancer incidence. Second, no information about insulin levels, cancer stages, and comorbidities were available for this study, and may have been confounding factors, making the association between CRC and FSG levels more complicated to establish. Third, this cohort consisted of people who visited health screening centers at university hospitals, and, therefore, selection bias existed. Moreover, variability in the laboratory methods used at each center might have influenced the results. Lastly, the cases of colorectal cancer occurred during the first year, included in the analysis, may have little effect from glucose level during carcinogenesis. However, when those cases were excluded in the analysis, the association between elevated glucose level and rectal cancer incidence was observed to be attenuated. Despite the limitations, a major strength of this study is that it represents the largest cohort study performed to date, with 19 multi-centers in Korea tracking the nationwide incidence of cancer.

V. Conclusions

Our findings suggest that pre-diabetes and diabetes statuses are related with CRC development and progression in men. Based on these results, early detection and intervention aimed at controlling fasting serum glucose level may represent a novel way of preventing colorectal carcinogenesis. Further experimental studies and larger, longer prospective epidemiologic studies are needed to fully understand the biological and molecular mechanisms of hyperglycemia and its association with carcinogenesis and the incidence of site-specific CRC.

Acknowledgements/ Funding

This work was supported by an extramural grant from the Seoul R&BD program, Republic of Korea(10526); a grant from the National R&D Program for Cancer Control; Ministry for Health, Welfare and Family Affairs, Republic of Korea(0920330); the National Research Foundation of Korea(NRF) grant, funded by the Korea government(MEST) (No. 2011-0029348); and a grant from the National R&D Program for Cancer Control; Ministry for Health, Welfare and Family Affairs, Republic of Korea(1220180).

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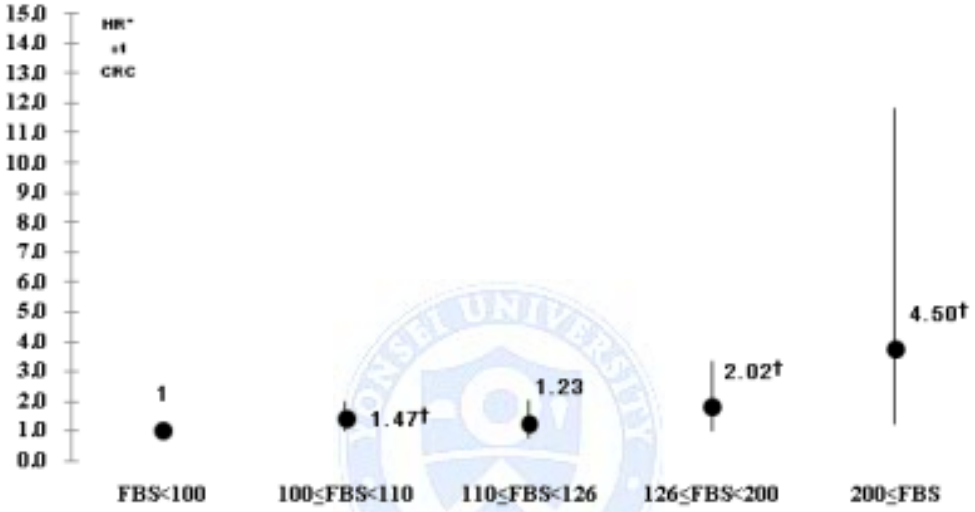
Figure 1. Hazard ratio and 95% confidence interval for colorectal cancer according to fasting serum glucose levels in men.

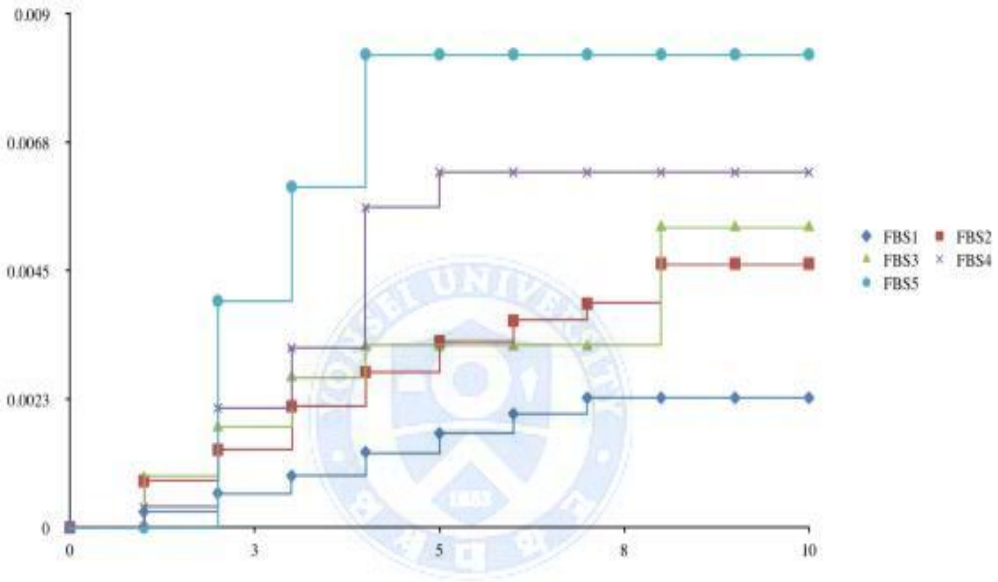


Abbreviations: HR, Hazard Ratio; FSG, fasting serum glucose

*HR from Cox proportional hazards regression analysis adjusted for age, sex, body mas index, smoking, alcohol drinking, and regular exercise. (P trend =0.03)

† P value<0.05

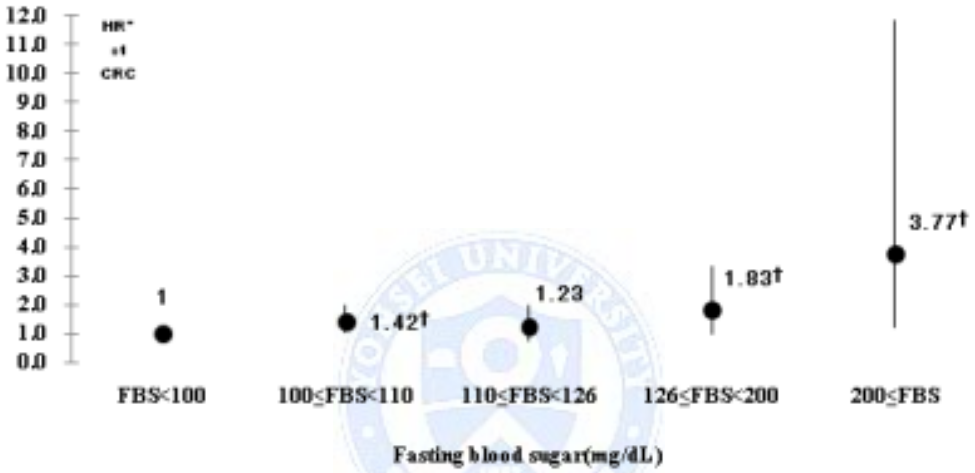
Figure 2. Culmulative colorectal cancer incidence probability according to fasting serum glucose levels.



Abbreviations: CRC, colorectal cancer; FSG, fasting serum glucose

*Cumulative CRC Incidence Probability, using Kaplan-Meier survival analysis.

Supplementary Figure 1. Hazard ratio and 95% confidence interval for colorectal cancer according to fasting serum glucose levels in men and women.



Abbreviations: HR, Hazard Ratio; FSG, fasting serum glucose

HR* from Cox proportional hazards regression analysis adjusted for age, sex, body mass index, smoking, alcohol drinking, and regular exercise. (P trend =0.04)

† P value<0.05

Table 1. Basic characteristics of study participants.

Total (n=175,677)	Men (n=103,452)	Women (n=72,225)
Variables	**Mean ± SD**	**Mean ± SD**
Age (years)	42.0 ± 9.8	41.5 ± 11.2
BMI (kg/m^2)	24.4 ± 2.9	22.3 ± 3.1
Systolic BP (mmHg)	121.4 ± 13.5	112.9 ± 15.1
Diastolic BP (mmHg)	76.6 ± 10.0	70.6 ± 10.1
FSG (mg/dL)	94.0 ± 16.7	87.9 ± 13.3
Total cholesterol (mmol/L)	192.7 ± 33.4	184.6 ± 33.3
Triglyceride (mmol/L)	158.0 ± 100.7	100.5 ± 60.4
HDL-cholesterol (mmol/L)	49.1 ± 9.7	57.7 ± 11.4
LDL-cholesterol (mmol/L)	115.8 ± 62.2	108.0 ± 30.8

Abbreviations: BMI, body mass index, BP, blood pressure; FSG, fasting serum glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein

Table 2. Person year, incident case, and crude incidence rate of colorectal cancer in men and women

	Men (n=103,452)			Women (n=72,225)		
	Person-year	**CRC**	**IR[a]**	**Person-year**	**CRC**	**IR[a]**
Overall	816142.7	320	39.21			
Sex	475625.3	227	47.73	340497.9	93	27.31
Duration of f/u (years)						
<1	87.8	23	26195.9	77.2	16	20725.4
1 - 2	841.4	27	3208.9	701.0	9	1283.9
2 - 3	1804.0	20	1108.6	1179.9	12	1017.0
3 - 4	127695.0	45	35.2	90426.5	19	21.0
4≤	345209.6	112	32.4	248120.3	37	14.9
Location of CRC						
Proximal	95.7	35	36572.6	61.9	24	38772.2
Distal	162.8	66	40540.5	45.8	25	54585.2
Rectal	287.1	113	39359.1	104.4	40	38314.2

Abbreviations: CRC, colorectal cancer; IR, incidence rate; PY, Person-year

[a] Incidence rate per 100,000 person-year

Table 3. Incidence rate and hazard ratio for developing colorectal cancer in individuals with high or low fasting serum glucose levels

	Person-year	CRC	IR[a]	HR[b]	95% CI	HR[c]	95% CI	HR [d]	95% CI
Fasting serum glucose[e] (Total)									
Low	677675.6	221	32.61	1.00		1.00		1.00	
High	138467.0	99	71.50	1.40	1.10-1.78	1.45	1.11-1.90	1.45	1.10-1.90
Fasting serum glucose[e] (Men)									
Low	375362.6	145	38.63	1.00		1.00		1.00	
High	100275.2	82	81.77	1.54	1.17-2.02	1.51	1.12-2.05	1.51	1.11-2.05
Fasting serum glucose[e] (Women)									
Low	302313.0	76	25.14	1.00		1.00		1.00	
High	38191.9	17	44.51	0.99	0.57-1.70	1.25	0.68-2.28	1.23	0.67-2.26

Abbreviations: CRC, colorectal cancer; IR, incidence rate, HR, hazard ratio; CI, confidence interval

[a] Incidence rate per 100,000 person-year

[b] Cox proportional hazards regression analysis adjusted for age and sex.

[c] Cox proportional hazards regression analysis adjusted for age, sex, and body mass index.

[d] Cox proportional hazards regression analysis adjusted for age, sex, body mass index, smoking, alcohol drinking, and regular exercise.

[e] Low <100 mg/dL, high≥100 mg/dL

Table 4. Incidence rate and hazard ratio for developing proximal colon, distal colon, and rectal cancers in individuals with high or low fasting serum glucose levels

	Proximal Colon Cancer		Distal Colon Cancer		Rectal Cancer	
	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI
Fasting serum glucose[b] (Total)						
Low	1.00		1.00		1.00	
High	1.42	0.77-2.62	1.60	0.99-2.61	1.49	1.00-2.24
Fasting serum glucose[b] (Men)						
Low	1.00		1.00		1.00	
High	1.69	0.81-3.53	1.53	0.88-2.64	1.59	1.01-2.48
Fasting serum glucose[b] (Women)						
Low	1.00		1.00		1.00	
High	1.11	1.06-1.15	1.94	0.66-5.66	1.12	0.41-3.06

Abbreviations: HR, hazard ratio; CI, confidence interval

a Cox proportional hazards regression analysis adjusted for age, sex, body mass index, smoking, alcohol drinking, and regular exercise.

[b] Low <100 mg/dL, high ≥100 mg/dL

Supplementary Table 1. Incidence rate and hazard ratio for developing proximal colon, distal colon, and rectal cancers in individuals with high or low fasting serum glucose levels

		Proximal Colon Cancer		Distal Colon Cancer		Rectal Cancer	
		HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI
BMI<25	**Fasting blood sugar[b] (Total)**						
	Low	1.00		1.00		1.00	
	High	1.74	0.79-3.84	1.69	0.95-3.02	2.04	1.21-3.46
	Fasting blood sugar[b] (Men)						
	Low	1.00		1.00		1.00	
	High	2.10	0.81-5.42	1.98	1.06-3.71	2.31	1.30-4.10
	Fasting blood sugar[b] (Women)						
	Low	1.00		1.00		1.00	
	High	1.03	0.22-4.84	0.56	0.07-4.41	1.08	0.24-4.83
BMI≥25	**Fasting blood sugar[b] (Total)**						
	Low	1.00		1.00		1.00	
	High	1.18	0.46-2.99	1.54	0.64-3.70	1.00	0.54-1.84
	Fasting blood sugar[b] (Men)						
	Low	1.00		1.00		1.00	
	High	1.31	0.42-4.08	0.89	0.31-2.59	1.00	0.50-2.00
	Fasting blood sugar[b] (Women)						
	Low	1.00		1.00		1.00	
	High	0.93	0.18-4.86	11.05	1.21-101.15	0.98	0.26-3.70

Abbreviations: BMI, body mass index; HR, hazard ratio; CI, confidence interval

[a] Cox proportional hazards regression analysis adjusted for age, sex, body mass index, smoking, alcohol drinking, and regular exercise.

[b] Low <100 mg/dL, high ≥100 mg/dL

Abstract

Association between fasting serum glucose levels and incidence of colorectal cancer : The Korean Cancer Prevention Study-II

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The incidence of colorectal cancer(CRC) is steadily increasing worldwide. Numerous studies have demonstrated that diabetes mellitus is related to an increased risk of CRC; however, the association between impaired fasting glucose and CRC is unclear. Therefore, we evaluated the correlation between the incidence of fasting serum glucose(FSG) levels and CRC, which can be used to develop novel methods for preventing CRC.

A total of 183,336 individuals from the Korean Metabolic Syndrome Research Initiative study were enrolled between 2004 and 2011. The incidence of CRC was assessed during a mean follow-up of 4.7 years. Hazard ratios(HR) for CRC according to FSG levels were calculated with

the Cox proportional hazard model adjusted for age, sex, body mass index, smoking status, alcohol consumption, and regular exercise.

The risk of developing CRC in subjects with high FSG was significant(HR, 1.45; 95% confidence interval [CI], 1.10–1.90) in total population, and the risk was higher in men(HR, 1.51; 95% CI, 1.11–2.05). The HR of rectal cancer was significantly higher in men in the high FSG group and the HR of proximal cancer was significantly higher in women in the high FSG group.

The incidence of CRC positively correlated with FSG levels in men. Therefore, early detection and intervention for controlling elevated glucose levels may be indicated as a way to prevent carcinogenesis. Further studies are needed to elucidate the biological and molecular mechanisms of hyperglycemia and its relationship with carcinogenesis and the site-specific incidence of CRC.

Key Words: colorectal cancer, fasting serum glucose, hyperglycemia, impaired fasting glucose, incidence, rectal cancer

Association between fasting serum glucose levels and incidence of colorectal cancer : The Korean Cancer Prevention Study-II

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Abstract (in Korean)

한국인에서의 공복혈당과 대장암 발생의 관련성 연구

: The Korean Cancer Prevention Study-II

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신현영

연구배경 : 전세계적으로 대장암 발병이 증가하고 있는 가운데, 수많은 연구를 통해 당뇨와 대장암의 연관성에대해 보고되어 왔다. 하지만 공복혈당과 대장암과의 관련성은 아직 명확하지 않은 상태이다. 본연구의 목적은 공복혈당과 대장암의 관련성을 확인하여, 대장암 예방에 기여할수 있을 위험인자를 확인하고자 한다.

방법 : 2004년부터 2011까지의 Korean Metabolic Syndrome Research Initiative study에서 183,336명의 참가자를 모집하고, 평균 4.7년동안의 추적관찰을 통하여 대장암의 발병사례를 수집한다. 나이, 성별, 비만도, 흡연여부, 음주여부 및 운동상태를 보정한 Cox proportional hazard model 을 통하여 대장암 발병의 Hazard ratios를 구한다.

결과 : 한국남성에서 대장암 발병과 공복혈당과의 양의 상관관계를 확인

하였다. 특히, 대장암 발병 위치에 따른 분석에서, 남성은 직장암에서, 여성은 근위부 대장암에서 높은 공복혈당과 관련성이 있음을 확인하였다. 그러므로 공복혈당을 조기에 발견하고 이를 낮추기 위한 노력이 대장암 형성과정을 예방할 수 있을 것으로 기대한다. 앞으로 높은 공복혈당과 암형성과정의 분자생물학적인 메커니즘과 대장암 발생위치와의 관련성을 밝혀내기 위한 추가적인 연구가 필요할 것으로 사료된다.

핵심되는 말 : 대장암, 공복혈당, 고혈당, 내당능장애, 발병, 직장암