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Population attributable fraction estimation for established colorectal cancer risk factors in Korea

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ABSTRACT

Population attributable fraction estimation for established colorectal cancer risk factors in Korea

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Background: Colorectal cancer incidence has increased in Korea in accordance with westernization. We estimated the population attributable fraction (PAF) of well-established risk factors for colorectal cancer, using both nationwide and worldwide risk estimates.

Materials and methods: We estimated the PAFs attributable to tobacco smoking, alcohol consumption, obesity, physical inactivity, and meat intake. Relative risks

(RRs) were estimated from the meta-analyses of the studies conducted in both Korean and worldwide populations. Worldwide RRs were obtained from previous studies that reported summary effect sizes of associations between colorectal cancer and each risk factor and included the largest number of studies or colorectal cancer cases. The prevalence of each exposure was calculated by using data from the 2001 Korean National Health Examination Survey. National cancer incidence data from the Korea Central Cancer Registry were used to estimate the number of colorectal cancer cases attributable to each risk factor.

Results: When using RRs estimated in the Korean population, the PAFs of all selected risk factors considered in this study were 44.5% for men and 22.7% for women. The most important risk factor for colorectal cancer among men was alcohol consumption (24.3%) and among women was meat intake (14.2%). When using RRs estimated in worldwide populations, the PAFs were 54.7% for men and 37.3% for women. The most important risk factor among both men and women was red meat intake (men, 23.1%; women, 23.0%). When global estimated RRs were applied to the risk factors from the limited numbers of Korean studies ($n > 3$), the PAFs for all selected risk factors were 55.8% for men and 38.3% for women.

Conclusions: Appropriate lifestyle modifications could decrease risk for colorectal cancer in the Korean population by 55.8% for men and 38.3% for women.
Keywords: Colorectal Neoplasms; Population attributable fraction; Risk Factors; Lifestyle; Republic of Korea

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Epidemiology of colorectal cancer

Colorectal cancer, the third-most common cancer among men and the second-most common cancer among women worldwide, varies with geography and ethnicity [1]. In Korea, the age-standardized incidence rate for colorectal cancer was 34.4 per 100,000 in 2013 and increased 4.6% annually from 1999 to 2013 [2]. The age-standardized incidence rates (ASR) for this cancer were higher among men (ASR, 45.6 per 100,000) than among women (ASR, 24.4 per 1 million) [2].

Established risk factors for colorectal cancer

Tobacco smoking

Tobacco smoking is defined as a group 1 carcinogen in humans [3], and there is sufficient evidence in humans to consider it a risk factor for colorectal cancer [4]. Several cohort studies [5 6] and meta-analyses [7-10] have reported increased risk for colorectal cancer among both men and women who smoke. Former smokers have higher risk than current smokers compared with never smokers [7 10]. A statistically significant dose-response relationship between increasing number of pack-years and cigarettes per day and increased colorectal cancer risk has also been reported [7]. Asian populations generally have lower risk than European or American populations [7 10].

The effect of smoking on colorectal cancer appears to be stronger for rectal cancer than for colon cancer [7 10].

Alcohol consumption

Alcohol is classified as group 1 carcinogen in humans [11] and is a known risk factor for colorectal cancer. There is significant difference between men and women in the colorectal cancer risk associated with alcohol consumption. The World Cancer Research Fund and American Institute of Cancer Research graded alcohol consumption as a "convincing" risk factor only among men, whereas among women it was graded as a "probable" risk factor [4]. Many studies support these associations. According to several studies, the effect of alcohol consumption on colorectal cancer risk has a dose-response relationship [12], and does not vary by alcoholic beverage type or anatomical site [13]. Fewer data are available for the association in women, although findings appear to be similar to those for men [4 14 15]. There are regional differences in risk for colorectal cancer associated with alcohol consumption, and it has been suggested that Asians have higher risk than European or American populations [12 16].

Obesity

Obesity is considered a major risk factor for colorectal cancer with convincing evidence for both men and women [4]. There are differences in the effect of obesity on colorectal cancer risk according to sex, region, and anatomical subsite, and effects appear to be larger among men than among women [4 17 18]. Asian populations have higher risk for colorectal cancer incidence compared with European populations [17].

For anatomical subsites, the association between obesity and colorectal cancer risk are stronger for colon cancer compared with rectal cancer [4 17]. Both general obesity, as defined by body mass index, and central obesity, as defined by waist circumference, are related to increased colorectal cancer risk [4 17].

Physical inactivity

The World Cancer Research Fund and American Institute of Cancer Research have reported that there is "convincing" evidence that physical activity is associated with decreased colon cancer risk [5]. One meta-analysis showed a statistically significant association between colorectal cancer risk and physical activity [19]. However, the effect of physical activity was statistically significant and strong only for colon cancer, not for rectal cancer [5 20], and it was stronger among men than women [20]. Physical inactivity due to insufficient participation in physical activity could be considered a risk factor for colorectal cancer. A recent meta-analysis on the association between sedentary behavior and increased colorectal cancer risk showed that the association was stronger for colon cancer than for rectal cancer [21]. Furthermore, this is in concordance with results from studies on the relationship between physical activity and decreased colorectal cancer risk.

Red and processed meat intake

The International Agency for Research on Cancer has classified consumption of processed meat and red meat as group 1 and 2A carcinogens in humans [22]. The World Cancer Research Fund and American Institute of Cancer Research have also reported that there is convincing evidence that consumption of red and processed meat is a cause of colorectal cancer [5]. The effect of red and processed meat intake on increased colorectal cancer risk was stronger among men than among women [23 24]. Additionally, the association was stronger in North American populations, including populations in the United States and Canada, than among European populations [24].

Previous studies on attributable fraction of risk for colorectal cancer risk factors

Table 1 and Table 2 show the most widely quoted estimates of risk attributable to alcohol consumption, tobacco smoking, meat intake, dietary fiber intake, obesity, physical inactivity, infections, and ionizing radiation, which are from a study in the United Kingdom (UK) [25]. The total PAFs of risk for the risk factors considered in the UK study were 56.5% for men and 51.9% for women. Among East Asian countries, Japan [26], China [27-29], and Korea [30-33] also have PAF estimates. Compared with the UK estimates, fewer risk factors were included in estimations from these three countries. For Korea, the PAFs were estimated using the fractions of colorectal cancer incidence and mortality in 2009 that were attributable to four lifestyle and environmental factors, including smoking, alcohol consumption, infectious agents, excess body weight, and physical activity. The total PAFs of risk for selected risk factors considered in Korea were 16.7% for men and 11.4% for women [33]. Reasons for these low PAFs include the limited number of previous studies available to estimate relative risk (RR) in the Korean population and the absence of PAFs for other established risk factors such as meat intake.

Table 1 Population attributable fractions of risk for colorectal cancer risk factors from previous studies of men, %.

Causes of Cancer	UK[25] 2010 (incidence)	Japan[26] 2005 (Incidence /mortality)	China 2005 (mortality)	Korea 2009 (incidence)
Alcohol consumption	15.5	32.9	2.06[27]	8.6[30]
Tobacco smoking	6.6	20.4		1.5[31]
Meat intake	24.8			
Dietary fiber intake	10.2			
Obesity	13.6	5.2*		6.8 [32]
Physical inactivity	3.0	3.2*	Urban: 23.7*[28] Rural: 7.43*[28]	0.8 [32]
Infections	1.5			
Ionizing radiation	1.1			
All above combined	56.5	Colon: 51.0 Rectum: 46.6	Colon: 19.7[29] Rectum: 2.5[29]	16.7[33]

* Colon

Table 2 Population attributable fractions of risk for colorectal cancer risk factors from previous studies of women, %.

Causes of Cancer	UK[25] 2010 (incidence)	Japan[26] 2005 (Incidence /mortality)	China 2005 (mortality)	Korea 2009 (incidence)
Alcohol consumption	6.9	2.1	0.15[27]	4.2[30]
Tobacco smoking	9.9	4.5		0.4[31]
Meat intake	16.4			
Dietary fiber intake	14.6			
Obesity	12.2	4.0*		6.6 [32]
Physical inactivity	3.6	2.9*	Urban: 11.0*[28] Rural: 3.59*[28]	0.9 [32]
Infections	3.1			
Ionizing radiation	2.2			
All above combined	51.9	Colon: 12.8 Rectum: 6.5	Colon: 8.3[29] Rectum: 1.7[29]	11.4[33]

* Colon

Burden of colorectal cancer in Korea

The mortality rate for colorectal cancer was quite low (ASR, 12.9 and 6.7 per 100,000 among men and women in 2013), compared with the incidence rate (ASR, 45.6 and 24.4 per 100,000 among men and women in 2013) [2]. As a consequence of cumulative impact, the age-standardized 5-year prevalence rates for colorectal cancer increased 5.0% annually from 109.2 per 100,000 in 2007 to 137.6 per 100,000 in 2013 [34]. In addition to the effects of an ageing population, the social and economic burden of colorectal cancer may worsen considerably in coming years. In fact, in several studies of the economic burden of cancer, the estimated socioeconomic burden of colorectal cancer has continually increased, and prevention of colorectal cancer was emphasized for reducing the burden [35-37].

Population attributable fraction of risk

There are many measures to quantify disease burden, including population attributable fraction (PAF) of risk. The PAF of risk presents the proportional reduction in average disease risk by eliminating certain causal factors from the population [38]. In other words, it is used to describe the excess disease associated with an exposure. Thus, it is valuable for estimates of the impact of established risk factors in a specific population.

Objectives

In this study, we aimed to estimate the population attributable risk of colorectal cancer incidence for well-established risk factors. Due to an insufficient number of

Korean studies on colorectal cancer and its risk factors, it was difficult to estimate stable summary RRs for some risk factors. Therefore, we used estimates of RR both Korean studies and worldwide studies to calculate PAFs and compare national and global risk estimates. Furthermore, due to the limited number of Korean studies, we present PAFs with pooled RRs obtained from meta-analyses of worldwide populations as a substitute for national estimates.

MATERIALS AND METHODS

Data selection

Literature search

A search was conducted in the PubMed, EMBase and KoreaMed databases for all publications up to March 24, 2016 with no restrictions on language. To identify additional studies, we searched the reference lists of the identified articles. Table 3 shows the search terms used by data source, target population, and each risk factor.

Table 3 Search terms used by data source, target population, and each risk factor.

Target population	Data source	Search term
Tobacco smoking		
Nationwide	Pubmed	"Colorectal Neoplasms"[Mesh] AND "Smoking"[Mesh] AND ("Korea"[Mesh] OR "Republic of Korea"[Mesh])
	EMBase	'colorectal cancer'/exp AND 'smoking'/exp AND 'korea'/exp
	KoreaMed	Colorectal cancer' [ALL] AND 'Smoking' [ALL]
Worldwide	Pubmed	"Colorectal Neoplasms"[Mesh] AND "Smoking"[Mesh] AND "Meta-Analysis"[Publication Type]
	EMBase	colorectal cancer'/exp AND 'smoking'/exp AND 'meta analysis'/exp
Alcohol consumption		
Nationwide	Pubmed	"Colorectal Neoplasms"[Mesh] AND "Alcohol Drinking"[Mesh] AND ("Korea"[Mesh] OR "Republic of Korea"[Mesh])
	EMBase	'colorectal cancer'/exp AND 'alcohol consumption'/exp AND 'korea'/exp
	KoreaMed	Colorectal cancer' [ALL] AND 'Alcohol' [ALL]

Table 3 Continued.

Target population	Data source	Search term
Alcohol consumption		
Worldwide	Pubmed	"Colorectal neoplasms"[MeSH Terms] AND "Alcohol Drinking"[Mesh] AND "Meta-Analysis"[Publication Type]
	EMBase	'colorectal cancer'/exp AND 'alcohol consumption'/exp AND 'meta analysis'/exp
Physical inactivity		
Nationwide	Pubmed	"Colorectal Neoplasms"[Mesh] AND "Motor Activity"[Mesh] AND ("Korea"[Mesh] OR "Republic of Korea"[Mesh])
	EMBase	'colorectal cancer'/exp AND ('physical activity'/exp OR 'physical inactivity'/exp OR 'exercise'/exp) AND 'korea'/exp
	KoreaMed	Colorectal cancer' [ALL] AND 'physical' [ALL]

Table 3 Continued.

Target population	Data source	Search term
Physical inactivity		
Worldwide	Pubmed	"Colorectal neoplasms"[MeSH Terms] AND "Motor Activity"[Mesh] AND "Meta-Analysis"[Publication Type]
	EMBase	'colorectal cancer'/exp AND ('physical activity'/exp OR 'physical inactivity'/exp OR 'exercise'/exp) AND 'meta analysis'/exp
Obesity		
Nationwide	Pubmed	Colorectal Neoplasms[Mesh] AND ("Obesity"[Mesh] OR "Overweight"[Mesh] OR "Body Weights and Measures"[Mesh]) AND ("Korea"[Mesh] OR "Republic of Korea"[Mesh])
	EMBase	'colorectal cancer'/exp AND ('obesity'/exp OR 'weight, mass and size'/exp) AND 'korea'/exp
	KoreaMed	‘Colorectal cancer' [ALL] AND 'Obesity' [ALL] ‘Colorectal cancer' [ALL] AND 'BMI' [ALL] ‘Colorectal cancer' [ALL] AND 'Overweight' [ALL] ‘Colorectal cancer' [ALL] AND 'Excess weight' [ALL]

Table 3 Continued.

Target population	Data source	Search term
Obesity		
Worldwide	Pubmed	"Colorectal neoplasms"[MeSH Terms] AND ("Obesity"[Mesh] OR "Overweight"[Mesh] OR "Body Weights and Measures"[Mesh]) AND "Meta-Analysis"[Publication Type]
	EMBase	'colorectal cancer'/exp AND ('obesity'/exp OR 'weight, mass and size'/exp) AND 'meta analysis'/exp
Meat intake		
Nationwide	Pubmed	"Colorectal Neoplasms"[Mesh] AND "meat"[Mesh] AND ("Korea"[Mesh] OR "Republic of Korea"[Mesh])
	EMBase	'colorectal cancer'/exp AND 'meat'/exp AND 'korea'/exp
	KoreaMed	‘Colorectal cancer' [ALL] AND 'meat' [ALL]
Worldwide	Pubmed	"colorectal neoplasms"[MeSH Terms] AND "Meat"[Mesh] AND "Meta-Analysis"[Publication Type]
	EMBase	‘Colorectal cancer'/exp AND 'meat'/exp AND 'meta analysis'/exp

Inclusion criteria

National estimates

Epidemiological studies with RR estimates or odds ratios, and corresponding 95% confidence intervals (CIs) were included. We also included studies that reported an effect size for each exposure level for which prevalence can be estimated in the Korean population. When there were multiple reports from the same study, we included only one report, either the most recently published report or the report including the most cases, to avoid bias in the meta-analysis.

Global estimates

For the global estimates, we included data on pooled RRs and corresponding 95% CIs in the pooled meta-analysis of worldwide populations. We then chose one study, either the study with the most cases or the study that included and conducted analyses separately for men and women.

Relative risks for colorectal cancer used to calculate population attributable fractions of risk

Meta-analyses were performed to evaluate pooled RRs and 95% CIs for each exposure level. When studies reported RR by cancer subsite, including proximal colon, distal colon and rectum, colorectal cancer risk was estimated by meta-analysis across subsites using a fixed-effect model and a single exposure level. When we summarized

RRs across studies, we used a random-effect model to deal with heterogeneity across studies. Publication bias was assessed by visual inspection of the funnel plots. Because large differences were found between sexes for prevalence or the effects of colorectal cancer risk factors, we abstracted RRs separately for men and women.

Studies reported RRs according to various ranges of alcohol consumption. We estimated an average risk, in terms of log (RR), per 1g/day increase of alcohol consumption from fitting a linear regression model to the log (RR) on the midpoint of each category. A meta-analysis was conducted to obtain pooled average risks of colorectal cancer per 1 g per day increase in alcohol consumption across studies.

Estimation of exposure prevalence

Assuming a latency period of more than 10 years, the prevalence of each exposure was estimated by using 2001 Korean National Health Examination Survey data [39]. The prevalence of smoking history was estimated using self-reported information. When survey participants responded to the question about smoking status that they had never smoked, they were classified as a ‘never smoker’. When they responded to the question about current smoking status that they had smoked in the past, they were classified as a ‘former smoker’. When they responded to the question about current smoking status that they smoked every day or smoked occasionally, they were classified as a ‘current smoker’. The prevalence of alcohol consumption was estimated based on the proportion of drinkers to non-drinkers, and average alcohol consumption was estimated according to the amount consumed among drinkers. When participants responded to the question about alcohol consumption status that they never drank or rarely drank, they were classified as a ‘never drinker’. Otherwise, they were classified as an ‘ever drinker’. Daily alcohol consumption amounts were calculated based on information reported for frequency and amount of usual alcohol consumption. Body mass index was calculated to assess obesity using measured height and weight. The prevalence of vigorous physical activity was estimated based on participants’ responses to questions about types of exercise that made them sweat or become out of breath. We calculated the proportion who participated in vigorous physical activity by scoring the intensity of each type of reported exercise by using metabolic equivalent values as defined by Ainsworth *et al* [40]. The prevalence of meat intake was estimated by using self-reported information on the frequency of meat intake. The questionnaire included questions about beef, pork, chicken, ham and sausage, and “red meat”, which included both beef and pork.

Cancer incidence in 2013

Cancer incidence data were obtained from the “Annual Report of Cancer Statistics in Korea in 2013 [34]” published by the National Cancer Center in Korea. Cancer cases were classified using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) [41]. We defined colorectal cancer using the ICD-10 codes C18 to C20.

Statistical analysis

Meta-analyses estimating pooled RRs were performed using the “metafor” package [42] in R [43]. Estimations of exposure prevalence were performed using the

SAS SURVEYMEANS and SURVEYFREQ procedures (version 9.3; SAS Institute Inc., Cary, NC) to account for the complex survey design and sample weights.

Calculation of population attributable fractions of risk

PAFs of risk were calculated by using the following formula for polytomous exposure as proposed by Hanley [44 45]:

$$\text{Population attributable fraction} = \frac{\sum_{i=1}^{k} P_i(RR_i - 1)}{1 + \sum_{i=1}^{k} P_i(RR_i - 1)} \quad , i \text{ refers to } i\text{st exposure level.}$$

Because estimated RRs were continuous variables, we derived the risk of exposure for colorectal cancer per unit of increase in exposure and estimated the average risk for the whole population based on the average level of exposure, assuming a log-linear relationship between exposure and risk, by means of the formulae [46]:

$$\text{Risk} = e^{[\ln(\text{risk per unit}) \times average\ \ level\ in\ population]}$$

$$\text{Population attributable fraction} = \frac{Prevelence(Risk - 1)}{1 + Prevalence(Risk - 1)}$$

For assumptions about independent exposures and their effects, we also calculated the PAF of risk accounting for interaction among multiple exposures, using following formula [26]:

$$\text{Population attributable fraction} = 1 - \prod_{i=1}^{n}(1 - PAF_i)_i \quad , i \text{ refers to } i\text{st exposure.}$$

RESULTS

Identification of Korean studies

Tobacco smoking

Figure 1 presents the process of literature selection for inclusion in the analysis. Forty-four studies were initially identified through database searches, and 6 additional studies were included from reviews of the references cited in the original 44 articles. Four duplicates were removed, and 37 studies that did not report on associations between tobacco smoking and colorectal cancer incidence were excluded by screening the article’s titles and abstracts. Nine studies [47-55] were additionally screened for the estimations of the RRs of tobacco smoking.

Table 4 shows information from studies reporting associations between tobacco smoking and colorectal cancer risk in the Korean population.

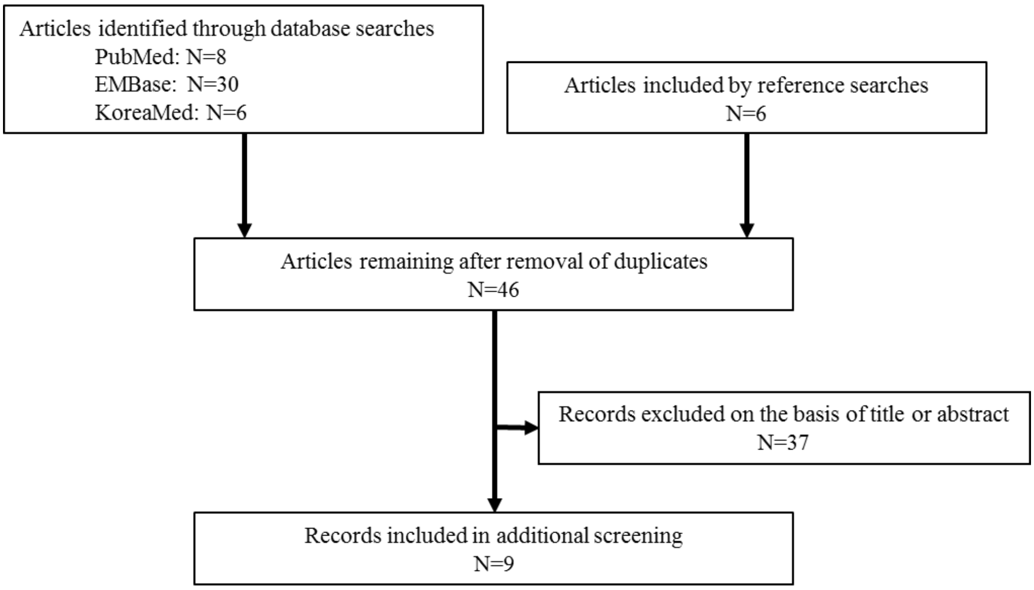


Figure 1 Flow chart for selection of studies on the association between tobacco smoking and colorectal cancer risk in the Korean population.

Table 4 Studies reporting associations between tobacco smoking and colorectal cancer risk in the Korean population.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Kim JI et al. (2003)	Case-control	Not specified	Both, combined	Colon	125	Smoking history	Never smoker	Ever smoker	[47]
Ahn EJ et al. (2006)	Case-control	2003 to 2005	Both, combined	Colorectum	80	Smoking history	Never smoker	Former smoker, current smoker	[48]
Kim HJ et al. (2006)	Cohort	1993 to 1998	Both, combined	Colorectum	97	Smoking history	Never smoker	Former smoker, current smoker	[49]
						Smoking duration	Never smoker	≤ 45 (year), > 45	

Table 4 Continued.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Kim HJ et al. (2006)	Cohort	1993 to 1998	Both, combined	Colorectum	97	Smoking amount	Never smoker	< 10 (pack-year), 10-19, ≥ 20	[49]
Lim HJ et al. (2008)	Cohort	1993 to 1998	Both, combined	Colorectum	111	Smoking history	Never smoker	Former smoker, current smoker	[50]
Kim J et al. (2009)	Case-control	2001 to 2004	Both, separately	Colorectum	597	Smoking history	Never smoker	Former smoker, current smoker	[51]

Table 4 Continued.

Author (year)	Study design	Study period	Sex	Outcome	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Shin A et al. (2011)	Cohort	1996 to 1997	Both, separately	Proximal colon, distal colon, rectum	3,834	Smoking history	Never smoker	Former smoker, current smoker	[52]
Jo J et al. (2012)	Case-control	2004 to 2007	Both, separately	Colorectum	187	Smoking history	Never smoker	Former smoker, current smoker	[53]
Kim J et al. (2012)	Case-control	1998 to 2004	Both, combined	Colorectum	783	Smoking history	Never smoker	Former smoker, current smoker	[55]

Table 4 Continued.

Author (year)	Study design	Study period	Sex	Outcome	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Cho S et al. (2015)	Cohort	1993 to 2005	Both, separately	Colorectum	220	Smoking history	Never smoker	Former smoker, current smoker	[54]
					198	Smoking duration	Never smoker	< 20 (year), 20-39, ≥ 40	
					196	Smoking amount	Never smoker	< 10 (pack-year), 10-19, ≥ 20	

Alcohol consumption

As shown in Figure 2, 35 studies were initially identified through database searches and 1 study was included through reference searches. Eighteen studies did not report associations between alcohol consumption and colorectal cancer incidence. Eight studies [47 50-52 54-59]were additionally screened for the estimations of RRs for alcohol consumption.

Table 5 shows information from studies reporting associations between alcohol consumption and colorectal cancer risk in the Korean population.

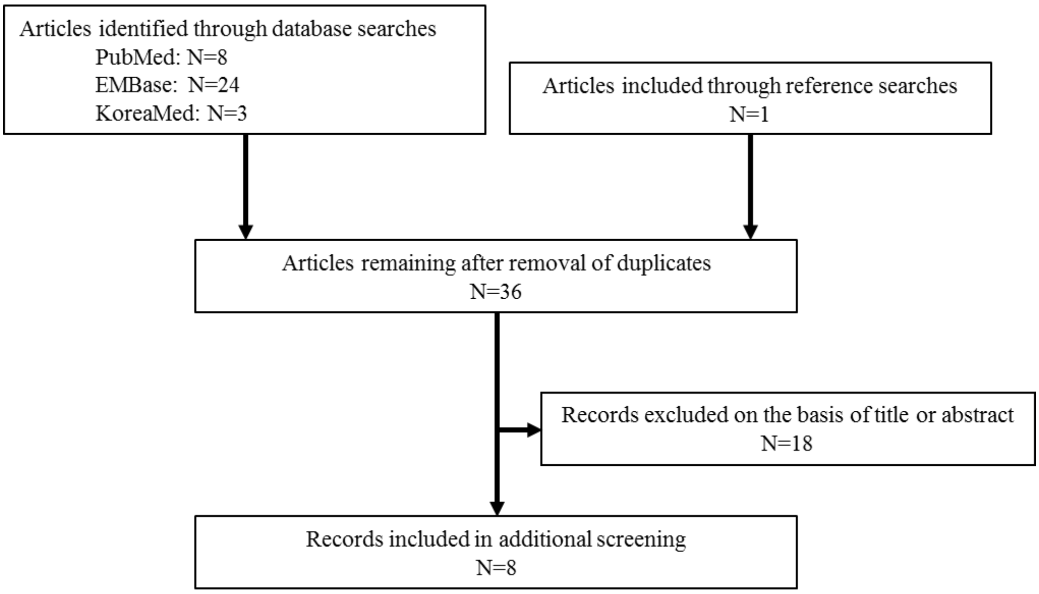


Figure 2 Flow chart for selection of studies reporting associations between alcohol consumption and colorectal cancer risk in the Korean population.

Table 5 Studies reporting associations between alcohol consumption and colorectal cancer risk in the Korean population.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Kim JI et al. (2003)	Case-control	Not specified	Both, combined	Colon	125	Alcohol consumption frequency	< 2 (times/week)	≥ 2 (times/week)	[47]
Hong YC et al. (2005)	Case-control	2001 to 2003	Both, combined	Colorectum	209	Alcohol consumption amount	< 80 (g/week)	≥ 80 (g/week)	[56]

Table 5 Continued.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Lim HJ et al. (2008)	Cohort	1993 to 1998	Both, combined	Colorectum	112	Alcohol consumption history	Never drinker	Former drinker, current drinker	[50]
					112	Alcohol consumption frequency	Never drinker	≤ 2 (times/month), 3-4, 5-8, 9-12, ≥ 30	
					106	consumption	Never drinker	≤ 24 (g/day), 25-48, 49-72, > 72	

Table 5 Continued.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Kim J et al. (2009)	Case-control	2001 to 2004	Both, separately	Colorectum	596	Alcohol consumption amount	< 5 (g/day)	5-29 (g/day), ≥30	[51]
Shin A et al. (2011)	Cohort	1996 to 1997	Both, separately	Proximal colon, distal colon, rectum	3,834	Alcohol consumption frequency	Never drinker	2-3 times/month, 1-2 times/week, 3-4 times/week, almost everyday	[52]

Table 5 Continued.

Author (year)	Study design	Study period	Sex	Outcome	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Shin A et al. (2011)	Cohort	1996 to 1997	Both, separately	Proximal colon, distal colon, rectum	3,832	Alcohol consumption amount	Never drinker	Never drinker, less than half bottle, one bottle of Korean distilled spirits, more than one bottle of Korean distilled spirits	[52]

Table 5 Continued.

Author (year)	Study design	Study period	Sex	Outcome	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Kim J et al. (2012)	Case-control	1998 to 2004	Both, combined	Colorectum, colon, rectum	1,480	Alcohol consumption amount	Never drinker	< 5 (g/day), 5-29, ≥ 30	[55]
Shin A et al. (2014)	Cohort	1996 to 1997	Men	Colorectum, proximal colon, distal colon, rectum	Not specified	Alcohol consumption amount	0 (g/day)	1-14.9 (g/day), 15-24.9, ≥ 25	[57]

Table 5 Continued.

Author (year)	Study design	Study period	Sex	Outcome	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Shin A et al. (2014)	Cohort	1996 to 1997	Women	Rectum	Not specified	Alcohol consumption amount	0 (g/day)	1-14.9 (g/day), 15-24.9, ≥ 25	[57]
Cho S et al. (2015)	Cohort	1993 to 2005	Both, separately	Colorectum	219	Alcohol consumption history	Never drinker	Former drinker, current drinker	[54]

Table 5 Continued.

Author (year)	Study design	Study period	Sex	Outcome	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Cho S et al. (2015)	Cohort	1993 to 2005	Both, separately	Colorectum	212	Alcohol consumption duration	Never drinker	< 15 (year), 15-29, ≥ 30	[54]
					206	Alcohol consumption amount	Never drinker	< 10 (g/day), 10-29, ≥ 30	

Obesity

Fifty-eight studies were initially identified through database searches and 3 additional studies were included through reference searches (Figure 3). After 2 duplicates were removed, the titles and abstracts of 59 studies were screened. We then excluded 45 studies that did not report associations between obesity and colorectal cancer incidence, 5 studies that were not original articles, and 3 studies did not report effect sizes, such as RR or odds ratios. Six studies [50 52 57 60-62] remained and were additionally screened for the estimation of pooled RRs.

Table 6 shows information on studies reporting associations between obesity and colorectal cancer risk in the Korean population. All studies defined obesity according to body mass index (BMI), although the ranges used to define BMI and upon which the RRs were based differed from each other.

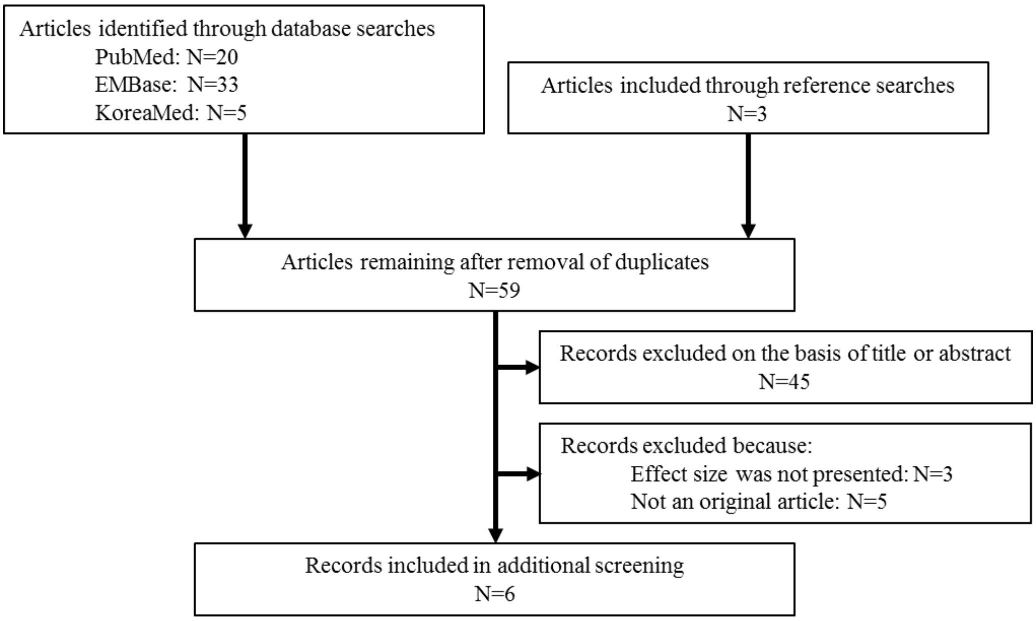


Figure 3 Flow chart for selection of studies reporting associations between obesity and colorectal cancer risk in the Korean population.

Table 6 Studies reporting associations between obesity and colorectal cancer risk in the Korean population.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Chung YW et al. (2006)	Case-control	2002 to 2004	Both, combined	Colorectum	105	Body mass index	< 23.0 (kg/m²)	23.0-24.9 (kg/m²), ≥ 25.0	[60]
Jee SH et al. (2008)	Cohort	1992 to 1995	Both, separately	Colon, rectum	12,343	Body mass index	23.0-24.9 (kg/m²)	< 20.0 (kg/m²), 20.0-22.9, 25.0-29.9, ≥ 30.0	[61]

Table 6 Continued.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Lim HJ et al. (2008)	Cohort	1993 to 1998	Both, combined	Colorectum	112	Body mass index	18.5-22.9 (kg/m^2)	< 18.5 (kg/m^2), 23.0-24.9, ≥ 25.0	[50]
Shin A et al. (2011)	Cohort	1996 to 1997	Both, separately	Proximal colon, distal colon, rectum	3,836	Body mass index	18.5-22.9 (kg/m^2)	< 18.5 (kg/m^2), 23.0-24.9, ≥ 25.0	[52]

Table 6 Continued.

Author (year)	Study design	Study period	Sex	Outcome	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Shin A et al. (2014)	Cohort	1996 to 1997	Men	Colorectum, colon, proximal colon, distal colon, rectum	Not specified	Body mass index	< 25.0 (kg/m^2)	≥ 25.0 (kg/m^2)	[57]
			Women	Proximal colon	Not specified	Body mass index	< 25.0 (kg/m^2)	≥ 25.0 (kg/m^2)	
Wie GA et al. (2014)	Cohort	2004 to 2008	Both, combined	Colorectum	53	Body mass index	< 25.0 (kg/m^2)	≥ 25.0 (kg/m^2)	[62]

Physical activity

Twenty-one studies were initially identified through database searches and an additional 4 studies were included through reference searches (Figure 4). After 2 duplicates were removed, 18 studies were additionally excluded for several reasons. Thirteen studies did not report associations between physical activity and colorectal cancer incidence. Three studies were not original articles. Two studies did not report effect sizes, such as RR or odds ratios. Five studies [47 50 51 63 64] were additionally screened for the estimation of RRs of alcohol consumption.

Table 7 shows information from studies reporting associations between physical activity and colorectal cancer risk in the Korean population.

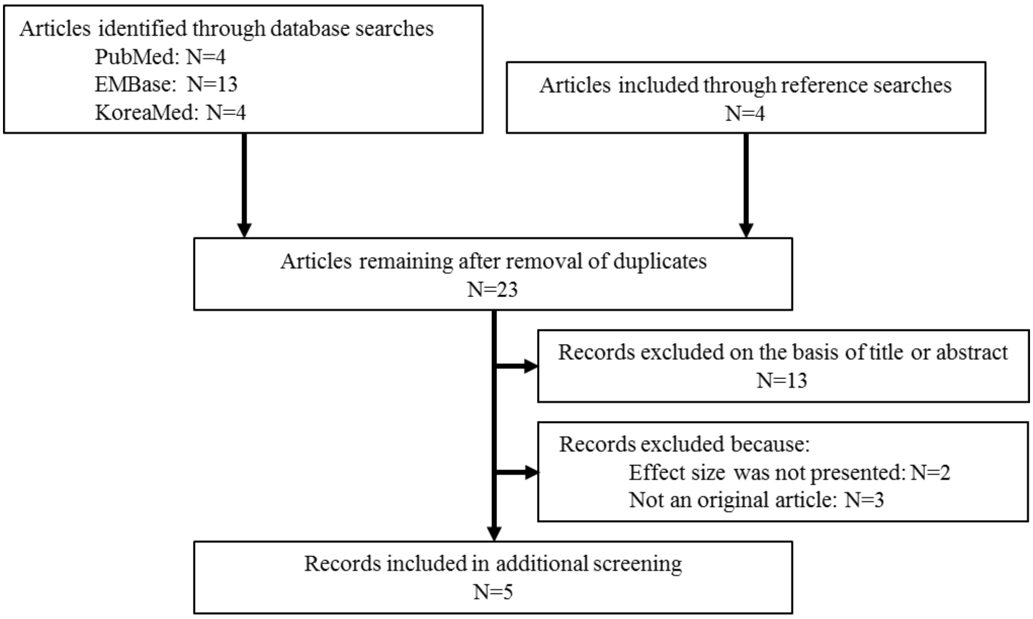


Figure 4 Flow chart for selection of studies reporting associations between physical activity and colorectal cancer risk in the Korean population.

Table 7 Studies reporting associations between physical activity and colorectal cancer risk in the Korean population.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Kim DH et al. (2002)	Case-control	1995 to 1996	Both, separately	Colorectum	235	Total energy expenditure (TEE)	Sedentary (TEE ≤ 170 (kcal/day))	Moderate (TEE: 170-330 (kcal/day)), active (TEE: > 330)	[63]
					235	Physical activity (leisure-time physical activity, LPTA) intensity	Never heavy LPTA (MET: ≥ 6)	Ever heavy LPTA (MET: ≥ 6)	
Kim JI et al. (2003)	Case-control	Not specified	Both, combined	Colon	125	Duration of weekly physical activity	< 4 (hours/week)	≥ 4 (hours/week)	[47]

Table 7 Continued.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Lim HJ et al. (2008)	Cohort	1993 to 1998	Both, combined	Colorectum	108	Physical activity frequency	Frequently	Sometimes, rarely	[50]
Yun YH et al. (2008)	Cohort	1996 to 2002	Men	Colorectum	1,827	Combination of frequency and duration with vigorous, sweat-producing leisure time physical activity	Low (≤ 4 times/week for < 30 min/time or ≤ 1 time/week for ≥ 30 min/time)	Moderate-High (high; ≥ 5 times/week for ≥ 30 min/time, moderate; 2–4 times/week for ≥ 30 min/time or ≥ 5 times/week for < 30 min/time)	[64]

Table 7 Continued.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Kim J et al. (2009)	Case-control	2001 to 2004	Both, separately	Colorectum	596	Physical activity (leisure-time physical activity, LPTA) intensity	Never heavy LPTA (MET: ≥ 6)	Ever heavy LPTA (MET: ≥ 6)	[51]

Meat intake

For national estimates, 23 studies were initially identified through database searches and 2 additional studies were included through reference searches. After 2 duplicates were removed, 17 studies were excluded for several reasons. Twelve studies did not report associations between meat intake and colorectal cancer incidence. Five studies were not original articles. Six studies [47 48 52 57 62 65] were included in additional screening for the estimation of RRs of meat intake.

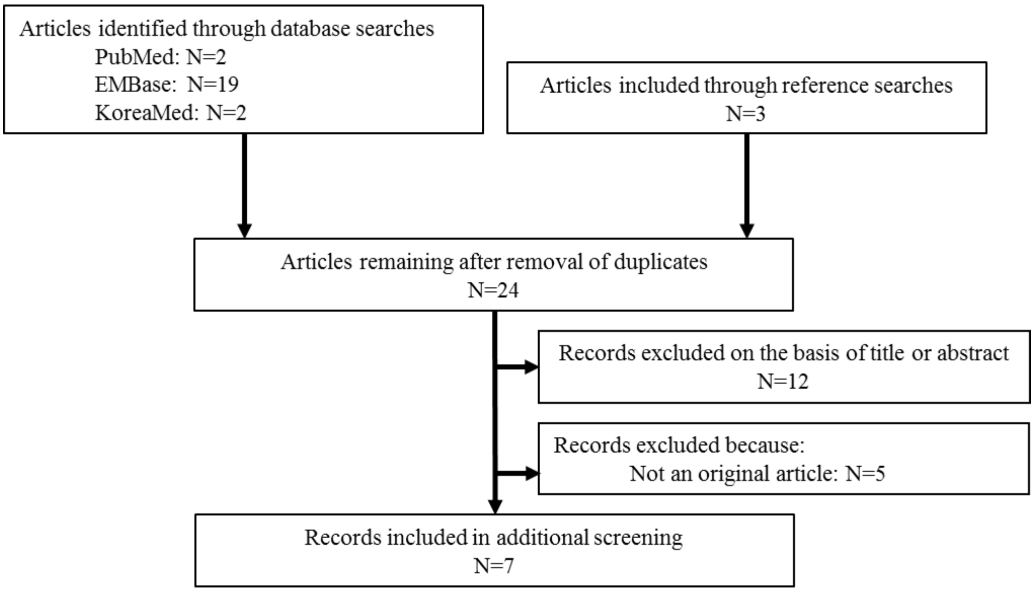


Figure 5 Flow chart for selection of studies reporting associations between meat intake and colorectal cancer risk in the Korean population.

Table 8 Studies reporting associations between meat intake and colorectal cancer risk in the Korean population.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Kim JI et al. (2003)	Case-control	Not specified	Both, combined	Colon	125	Meat intake frequency	< 2 times/week	≥ 2 times/week	[47]
Ahn EJ et al. (2006)	Case-control	2003 to 2005	Both, combined	Colorectum	80	Meat intake frequency	None	< 3, ≥ 3 times/week	[48]
Kim J et al. (2011)	Cohort	1996 to 1997	Both, separately	Colorectum	6,444	Meat intake frequency	≤ once a week	2-3, ≥ 4 times/week	[65]
Shin A et al. (2011)	Cohort	1996 to 1997	Both, separately	Proximal colon; distal colon; rectum	3,785	Meat intake frequency	≤ once a week	2-3, ≥ 4 times/week	[52]

Table 8 Continued.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Shin A et al. (2014)	Cohort	1996 to 1997	Men	Colorectum; colon; proximal colon	Not specified	Meat intake frequency	≤ once a week	2-3, ≥ 4 times/week	[57]
			Women	Colorectum; colon; distal colon; rectum	Not specified	Meat intake frequency	≤ once a week	2-3, ≥ 4 times/week	
Wie GA et al. (2014)	Cohort	2004 to 2008	Both, combined	Colorectum	53	Meat intake amount	< 43 g/day	≥ 43 g/day	[62]

Table 8 Continued.

Author (year)	Study design	Study period	Sex	Cancer subsite (Outcome)	Colorectal cancer cases	Exposure	Reference level	Risk level	Reference
Chun YJ et al. (2015)	Case-control	2010 to 2011	Both, combined	Colorectum	184	Red meat intake frequency	< 0.93 serving/week	0.93-2.7, > 2.7 serving/week	[66]

Definition of exposure

We screened articles that met our inclusion criteria to define “optimum” and “risk” levels of exposure. Exposure levels for each risk factor were defined according to the definitions found in the most studies. Table 9 shows the optimum level of exposure or the theoretical minimum risk exposure, and the risk level of exposure for each risk factor. We defined exposure to each risk factor as it was defined in the studies included in the final analysis. Exposures to tobacco smoking were assessed by smoking history (never, former and current smoker). Exposure to alcohol consumption was estimated as risk per 1g per day increase due to different cut-offs for alcohol consumption across the studies. Obesity was assessed using body mass index (BMI) as a weight-based measurement of general obesity. We defined “obese” as BMI greater than or equal to 25 $kg \cdot m^{-2}$, according to recommendations for Asian populations [67]. The current study focused on the carcinogenic effects of obesity with obesity defined as BMI $\geq$ 25.0 kg/m^2 compared with normal BMI = 18.5-22.9 kg/m^2. Physical inactivity was defined as not performing vigorous physical activity. The definition of “vigorous physical activity” was the same as that in each studies used to estimate national estimates, which generally was a metabolic equivalent (MET) value over 6 $kcal \cdot kg^{-1} \cdot hr^{-1}$. In addition, we considered physical activity defined as the combination of intensity and duration. Exposure to meat intake was defined differently for national and global estimates. Total meat intake including beef, pork, chicken, and ham and sausage were considered for national estimates, and red meat intake including beef and pork was considered for global estimates. We also used another definition of meat intake for national estimates in order to include most studies in the meta-analysis.

Table 9 Calculation of optimum level of exposure and risk level of exposure.

Exposure	Type of estimates	Optimum exposure level	Risk exposure level
Tobacco smoking	National and global	Never smoker	Former smoker, current smoker
Alcohol consumption	National and global	Never drinker	Ever drinker
Obesity	National	Normal weight: BMI between 18.5 and 23 kg/m^2	Obese: BMI of more than 25 kg/m^2
	Global	Normal weight **	Obese**

Table 9 Continued.

Exposure	Type of estimates	Optimum exposure level	Risk exposure level
Physical inactivity	National	Performing vigorous physical activity*	Not performing vigorous physical activity*
		Moderate-High (high; ≥ 5 times/week for ≥ 30 min, moderate; 2–4 times/week for ≥ 30 min or ≥ 5 times/week for < 30 min)	Low (≤ 4 times/week for < 30 min or ≤ 1 time/week for ≥ 30 min)
	Global	Highest activity level **	Lowest activity level **
Meat intake	National	Meat intake frequency of less than once per week	Meat intake frequency of more than twice per week
		No meat intake	Meat intake
	Global	No red meat intake	Red meat intake

* Defined as metabolic equivalent (MET) value over 6 $kcal \cdot kg^{-1} \cdot hr^{-1}$.

** Defined by each study included in the meta-analysis.

Relative risk estimates in the Korean population

Tobacco smoking

Table 10 and Figure 6, Figure 7 show the RRs (or ORs) used in the analysis of tobacco smoking and colorectal cancer risk. We conducted the meta-analysis across included studies to obtain pooled RRs by smoking history (never, former and current smoker). One [52] of the studies reported RRs by subsite; we combined those RRs into a single estimate across subsites based on the fixed effect model. When pooled RRs across the studies were estimated, the risk estimates from the random effect model were used. Although the pooled estimates did not show significant associations between colorectal cancer risk and current smoker status among men (pooled RR: 1.07, 95% CI: 0.87-1.32) or women (pooled RR: 1.03, 95% CI: 0.79-1.35), they showed significantly increased risk between colorectal cancer risk and former smoker status for both sexes (men, pooled RR: 1.12, 95% CI: 1.11-1.32; women, pooled RR: 1.31, 95% CI: 1.06-1.63). Figure 8 and Figure 9 show the funnel plots with pseudo 95% confidence limits. Evidence of publication bias was found for studies reporting on men who were former smokers.

Table 10 Relative risks or odds ratios reported in selected studies included in the meta-analysis and pooled relative risks for tobacco smoking.

		RR or OR (95% CI)			
Author (year)	Sex	Former smoker		Current smoker	
Ahn EJ et al. (2006)	Both sexes	1.50	(0.70-3.40)	0.90	(0.40-1.80)
Kim HJ et al. (2006)	Both sexes	2.03	(1.02-4.03)	1.36	(0.80-2.32)
Lim HJ et al. (2008)	Both sexes	1.34	(0.86-2.09)	0.82	(0.50-1.33)
Kim J et al. (2009)	Men	1.22	(0.75-1.98)	1.62	(1.00-2.63)
	Women	2.12	(0.44-10.32)	1.86	(0.38-9.03)
Shin A et al. (2011)*	Men	1.17	(1.06-1.28)	0.97	(0.90-1.05)
	Women	0.93	(0.59-1.46)	0.95	(0.74-1.22)
Jo J et al. (2012)	Men	1.59	(0.89-2.85)	0.64	(0.36-1.14)
	Women	0.69	(0.05-9.90)	0.56	(0.04-8.07)
Kim J et al. (2012)	Both sexes	1.40	(0.96-2.05)	1.53	(1.05-2.23)
Cho S et al. (2015)	Men	1.33	(0.76-2.32)	0.97	(0.58-1.62)
	Women	1.14	(0.35-3.67)	0.30	(0.10-0.97)
Pooled relative risk	Men	1.21	(1.11-1.32)	1.07	(0.87-1.32)
	Women	1.31	(1.06-1.63)	1.03	(0.79-1.35)

[*] Meta-analysis was performed for proximal colon, distal colon and rectum, using the fixed effect model.

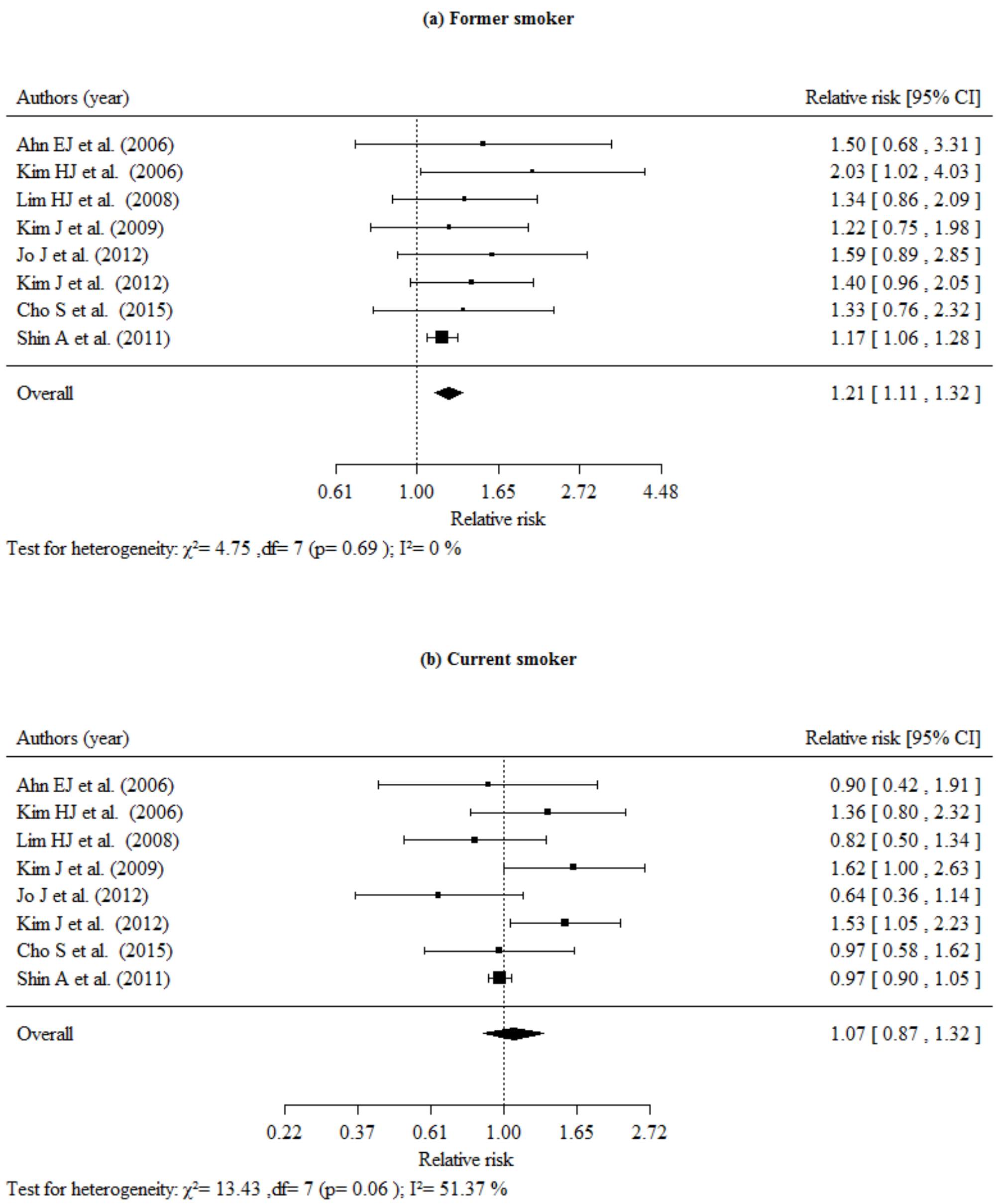


Figure 6 Forest plot of tobacco smoking and colorectal cancer among men. (a) former and (b) current smokers.

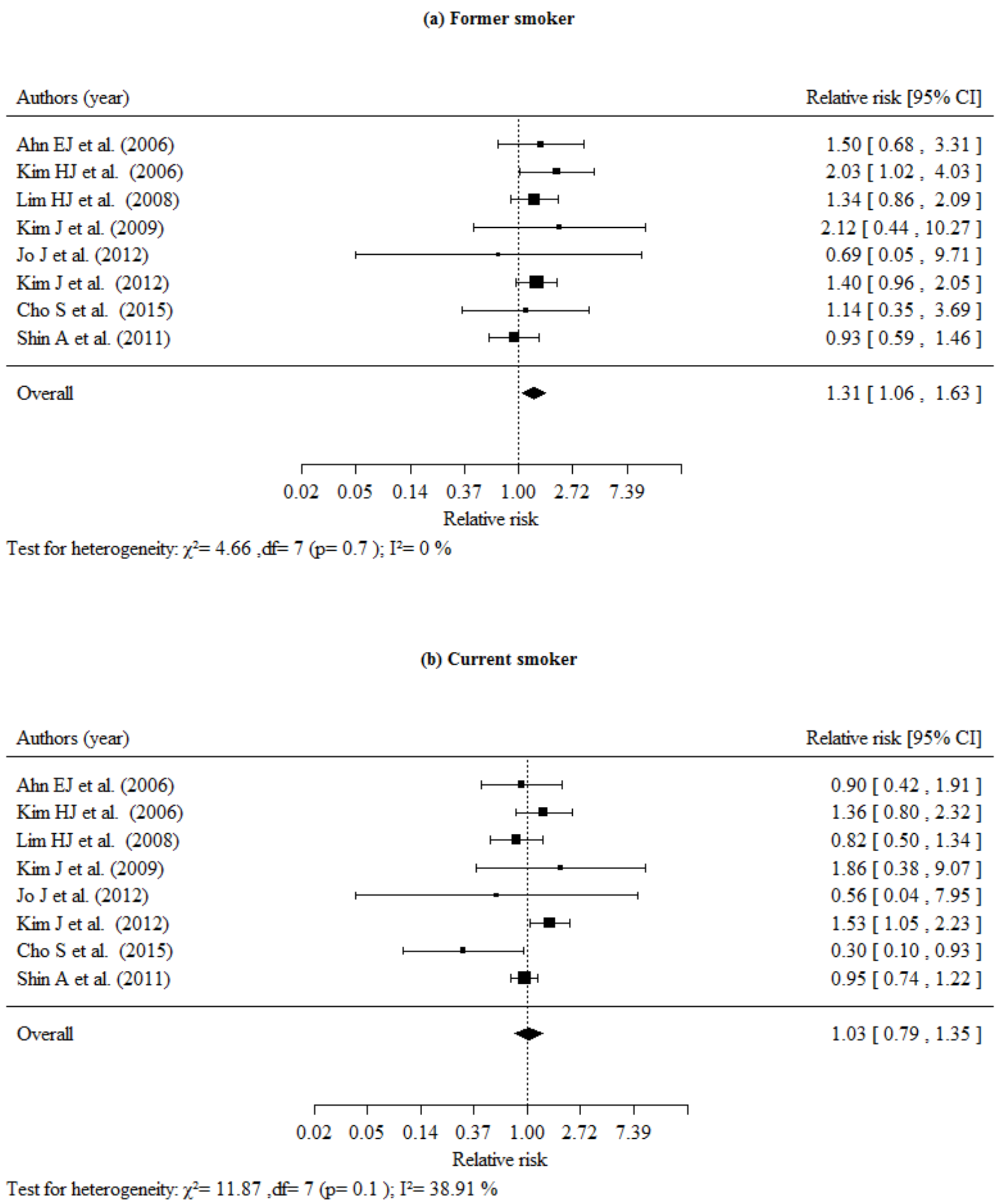
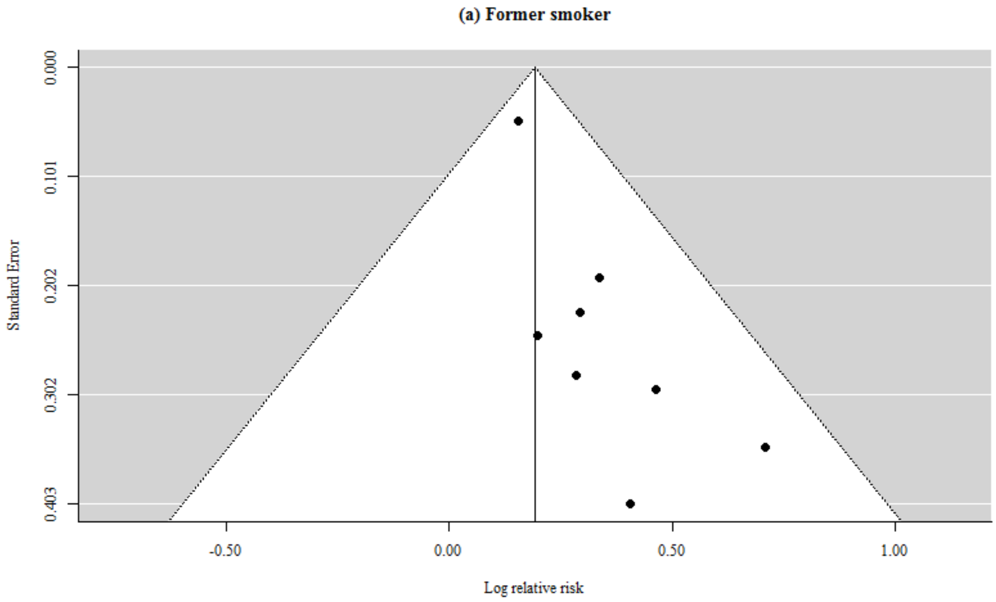


Figure 7 Forest plot of tobacco smoking and colorectal cancer among women.; (a) former and (b) current smokers.



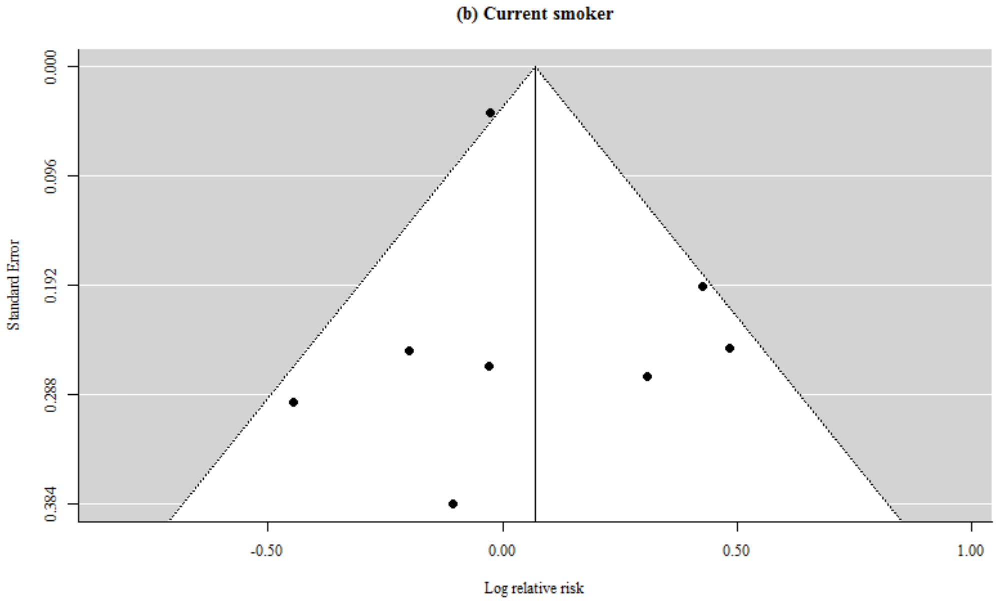
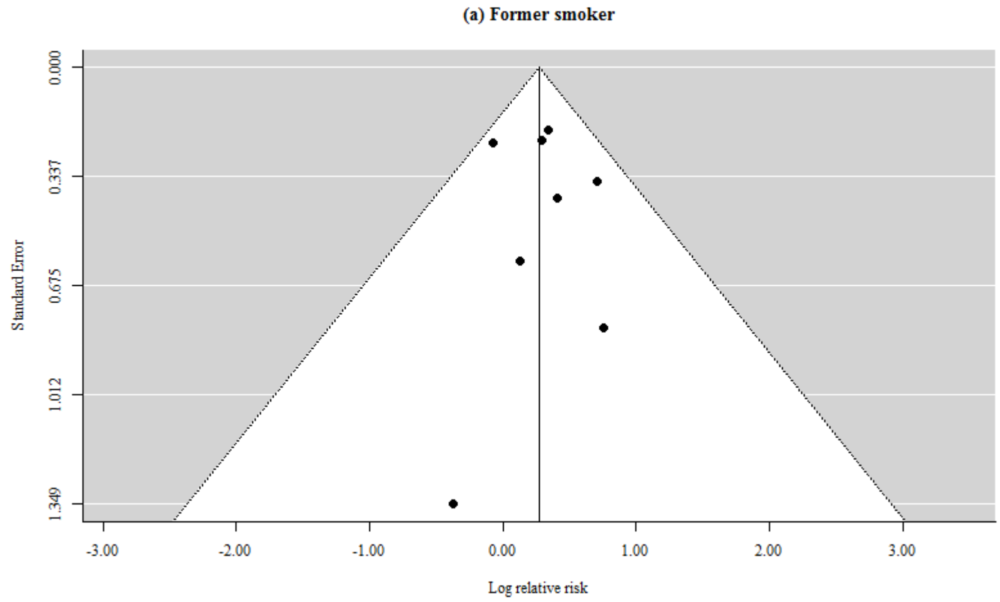


Figure 8 Funnel plot of tobacco smoking and colorectal cancer among men.; (a) former and (b) current smokers.



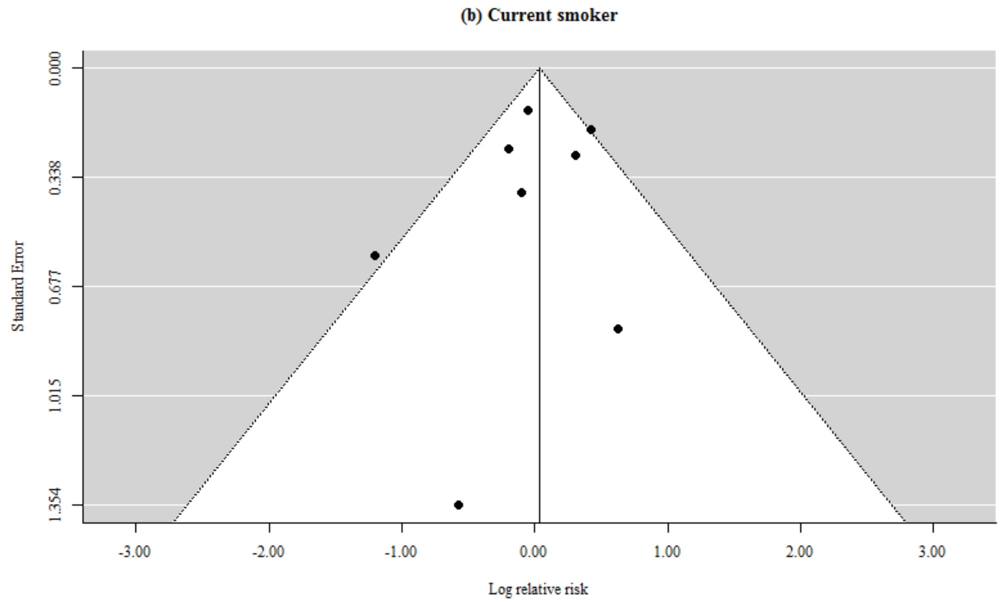


Figure 9 Funnel plot of tobacco smoking and colorectal cancer among men; (a) former and (b) current smokers.

Alcohol consumption

Table 11 and Figure 10 show the RRs (or ORs) used in the analysis of alcohol consumption and colorectal cancer risk by sex. Studies reported RRs according to various ranges of alcohol consumption. One [57] of the studies reported RRs by subsite; the RRs were combined into a single estimate across subsites based on the fixed effect model. The pooled estimates show increased risk for alcohol consumption with marginal significance (men, pooled RR: 1.02, 95% CI: 1.01-1.02; women, pooled RR: 1.02, 95% CI: 1.01-1.03). Figure 11 shows the funnel plot with pseudo 95% confidence limits according to sex. There was evidence of publication bias for studies reporting results for women.

Table 11 Relative risks or odds ratios reported from selected studies for meta-analysis and pooled relative risk for alcohol consumption.

Author (year)	Sex	Alcohol consumption level	RR or OR (95% CI)	Risk for 1 g of daily alcohol consumption increase
Hong YC et al. (2005)	Both sexes	< 80 (g/week)	1.00	1.18 (1.07-1.31)
		≥ 80	2.60 (1.46-4.62)	
Lim HJ et al. (2008)	Both sexes	Never drinker	1.00	1.00 (0.98-1.02)
		≤ 24 (g/day)	0.62 (0.35-1.12)	
		≤ 48	1.13 (0.52-2.45)	
		≤ 72	1.07 (0.26-4.48)	
		> 72	1.15 (0.28-4.72)	
Kim J et al. (2009)	Men	< 5 (g/day)	1.00	1.02 (1.00-1.04)
		5-29	1.12 (0.70-1.82)	
		≥30	1.68 (1.04-2.72)	
	Women	< 5 (g/day)	1.00	1.00 (0.93-1.08)
		5-29	1.87 (0.22-15.74)	
		≥ 30	1.05 (0.12-8.85)	
Kim J et al. (2012)	Both sexes	< 5 (g/day)	1.00	1.02 (1.01-1.03)
		5-29	1.22 (0.88-1.69)	
		≥ 30	1.76 (1.26-2.46)	

Table 11 Continued.

Author (year)	Sex	Alcohol consumption level	RR or OR (95% CI)	Risk for 1 g of daily alcohol consumption increase
Shin A et al.	Men	0 (g/day)	1.00	1.01 (1.01-1.01)
(2014)		1-14.9	1.11 (1.04-1.19)	
		15-24.9	1.23 (1.13-1.32)	
		≥ 25	1.26 (1.18-1.35)	
	Women	0 (g/day)	1.00	1.03 (1.01-1.05)
		1-14.9	1.00 (0.83-1.20)	
		≥ 15	1.48 (1.10-1.99)	
Cho S et al.	Men	Never drinker	1.00	1.03 (1.01-1.04)
(2015)		< 10 (g/day)	1.28 (0.71-2.31)	
		10-29	1.77 (0.96-3.26)	
		≥ 30	2.24 (1.31-3.84)	
	Women	Never drinker	1.00	0.99 (0.94-1.06)
		< 10 (g/day)	0.82 (0.41-1.63)	
		10-29	0.95 (0.23-3.87)	
		≥ 30	0.76 (0.11-5.44)	
Pooled	Men			1.02 (1.01-1.02)
relative risk	Women			1.02 (1.01-1.03)

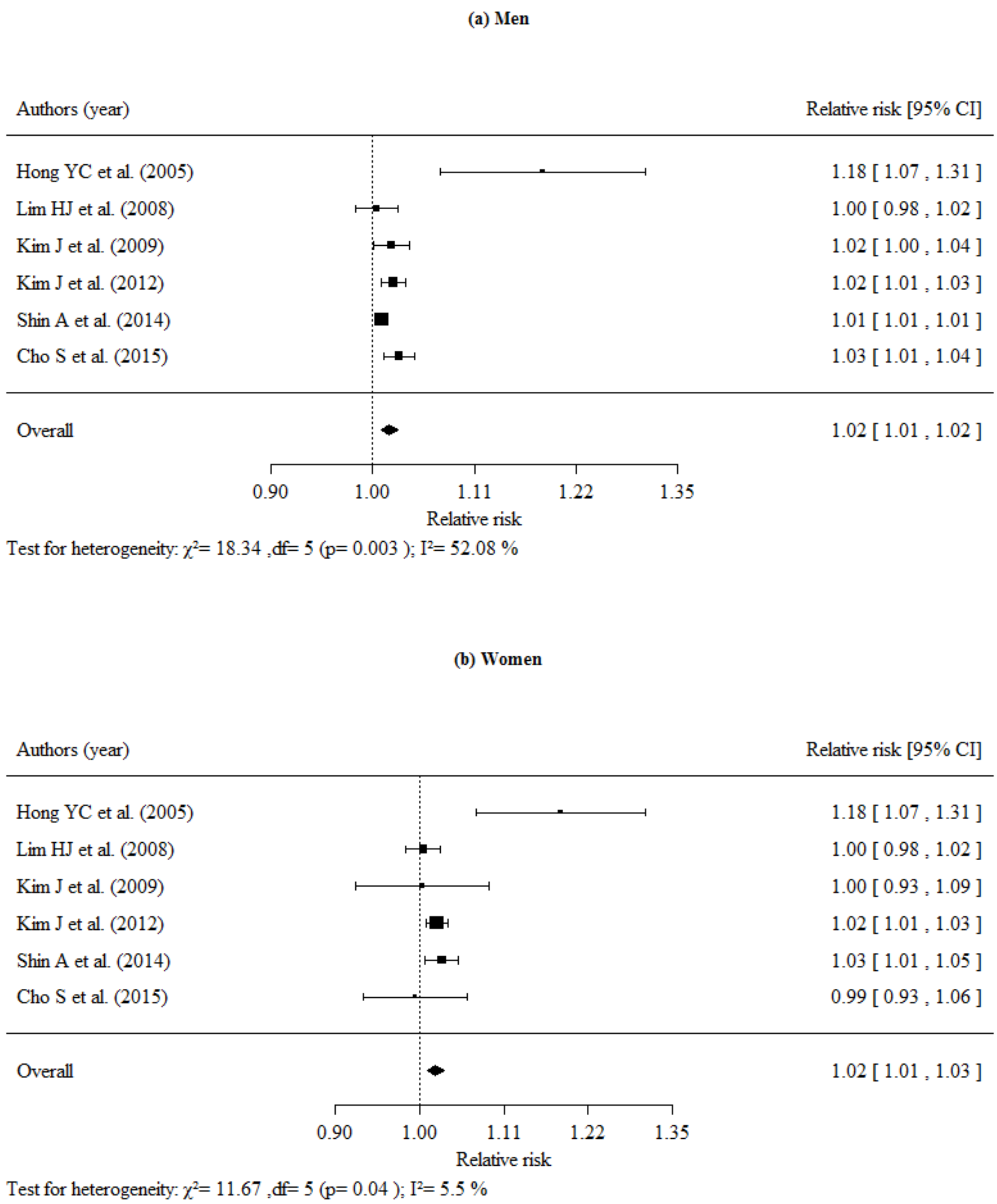


Figure 10 Forest plot of alcohol consumption and colorectal cancer among (a) men and (b) women.

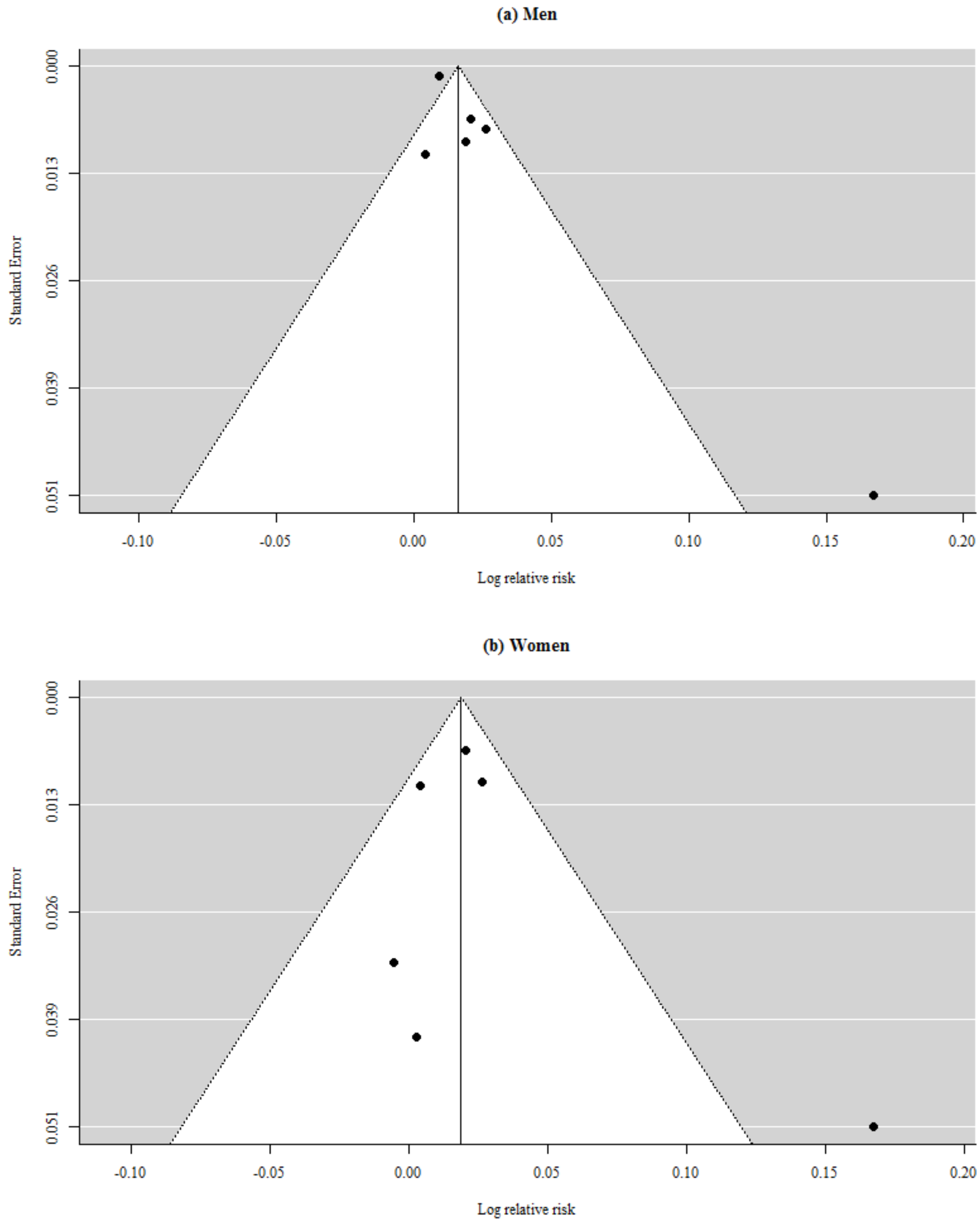


Figure 11 Funnel plot of alcohol consumption and colorectal cancer among (a) men and (b) women.

Obesity

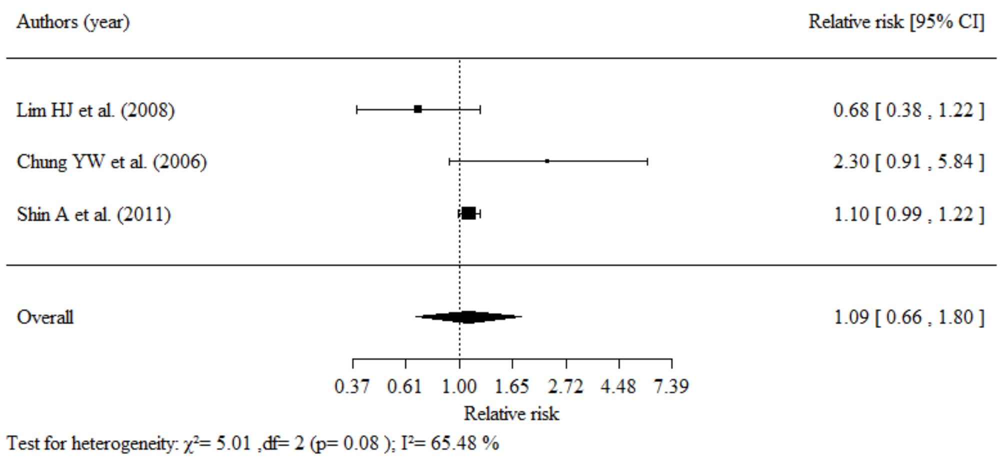
Table 12 and Figure 12 show the RRs (or ORs) used in the analysis of obesity and colorectal cancer risk by sex. One study [52] reported RRs by subsite; these RRs were combined into a single estimate across the subsites. Although the pooled estimates were not statistically significant, they show increased colorectal cancer risk associated with obesity in men (pooled RR: 1.09, 95% CI: 0.66-1.80), which was lower than the risk associated with obesity in women (pooled R: 1.15, 95% CI: 0.67-1.97).

Figure 13 shows the funnel plot with pseudo 95% confidence limits according to sex. There was no evidence of publication bias in the selected studies.

Table 12 Relative risks or odds ratios reported from selected studies for the meta-analysis and pooled relative risk for obesity.

		RR or OR (95% CI)
Author (year)	Sex	Obesity, compared with normal weight
Chung YW et al. (2006)	Both sexes	2.30 (0.90-5.80)
Lim HJ et al. (2008)	Both sexes	0.68 (0.38-1.22)
Shin A et al. (2011)	Men	1.10 (0.99-1.22)
	Women	1.21 (1.05-1.40)
Pooled relative risk	Men	1.09 (0.66-1.80)
	Women	1.15 (0.67-1.97)

(a) Men



(b) Women

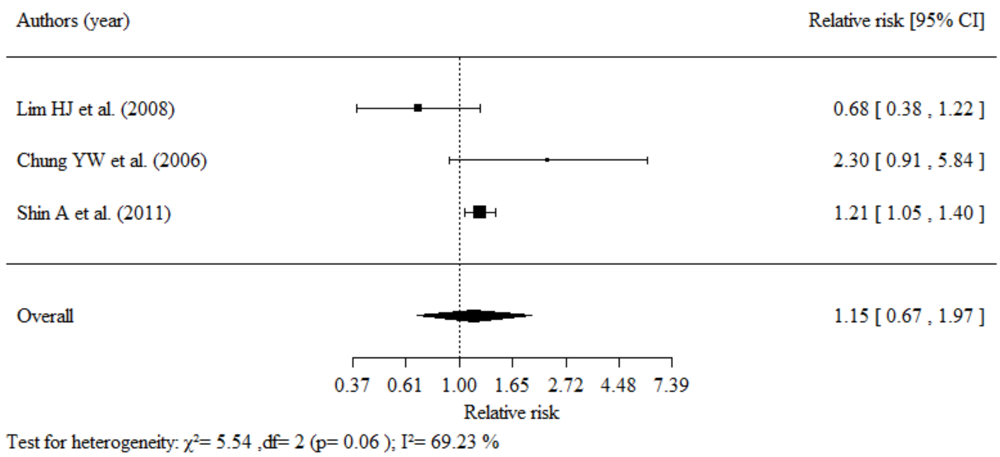


Figure 12 Forest plot of obesity and colorectal cancer among (a) men and (b) women.

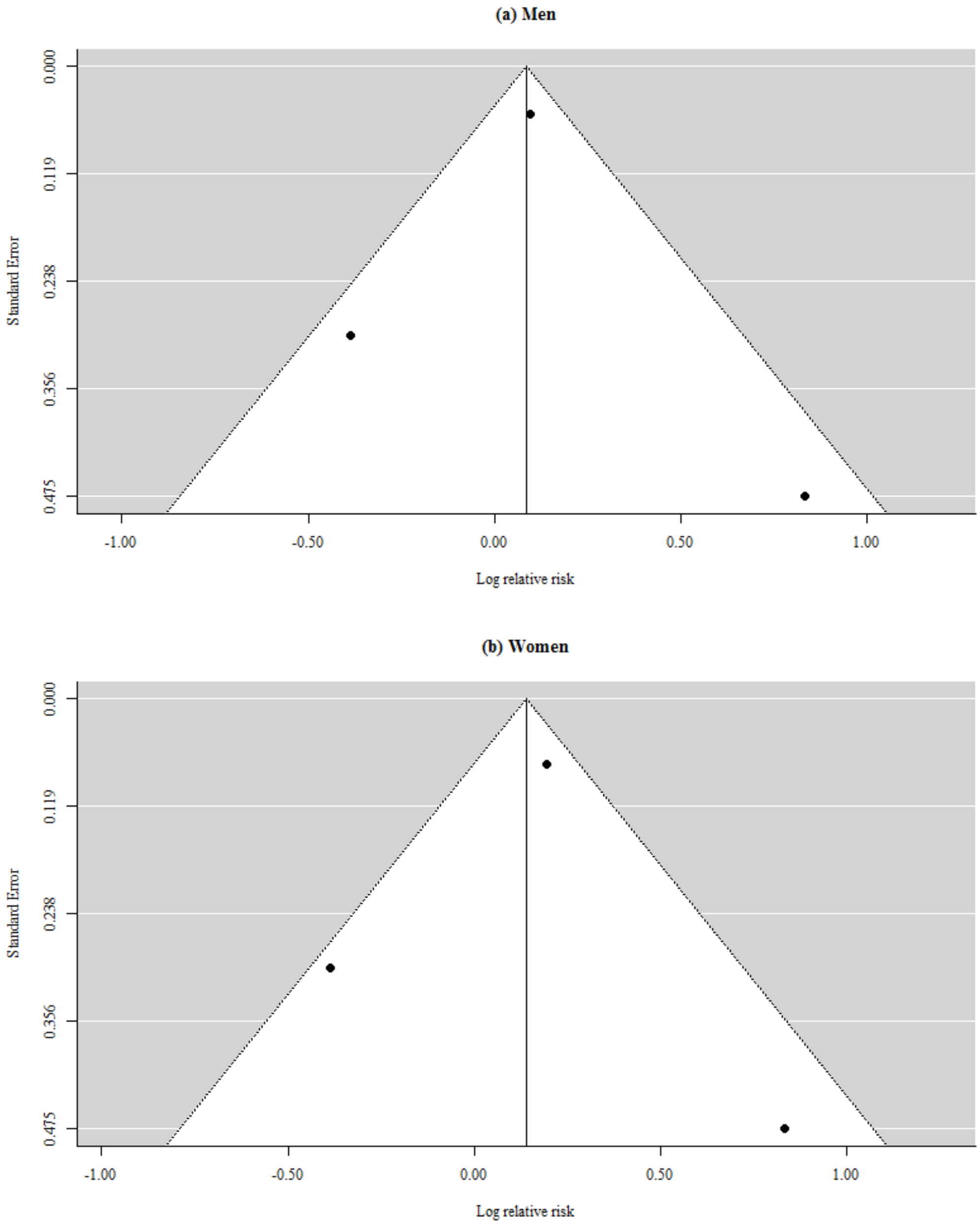


Figure 13 Funnel plot of obesity and colorectal cancer among (a) men and (b) women.

Physical activity

Table 13 and Figure 14 show the RRs (or ORs) used in the analysis of physical activity and colorectal cancer risk by sex. Two studies [51 63] were included in the meta-analysis. Although the pooled estimates were not statistically significant, they show decreased colorectal cancer risk associated with physical activity among both men (pooled RR: 0.68, 95% CI: 0.37-1.25) and among women (pooled RR: 0.91, 95% CI: 0.47-1.75). Figure 15 shows the funnel plot with pseudo 95% confidence limits according to sex. The number of studies included in the estimation of the pooled RRs for physical activity was too small to assess publication bias. The definition of exposure for physical activity defined by vigorous physical activity may have been too strict compared to recommendations for physical activity for cancer prevention

Table 14). Instead, we calculated an additional PAF by using RRs from a study that defined physical activity as the combination of frequency and duration of vigorous, sweat-producing leisure-time physical activity.

Table 13 Relative risks or odds ratios reported from studies selected for the meta-analysis and pooled relative risks for physical activity.

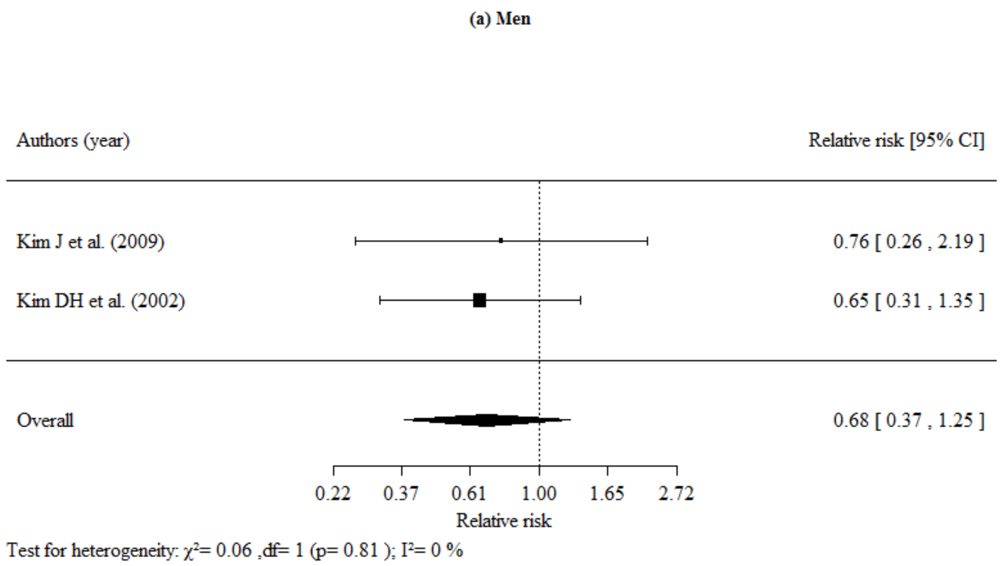
Author (year)	Sex	RR or OR (95% CI) Participation on vigorous activity (MET: ≥ 6)
Kim DH et al. (2002)	Men	0.76 (0.55-4.57)
	Women	0.65 (0.42-3.68)
Kim J et al. (2009)	Men	0.65 (0.30-1.30)
	Women	1.10 (0.50-2.60)
Pooled relative risk	Men	0.68 (0.37-1.25)
	Women	0.91 (0.47-1.75)

Table 14 Relative risk for physical activity; defined as the combination of frequency and duration of vigorous, sweat-producing leisure time physical activity

Author (year)	Sex	Physical activity level	RR or OR (95% CI)
Yun YH et al. (2008)	Men	Low*	1.00
		Moderate-High**	0.98 (0.90-1.08)

* Low (≤ 4 times/week for < 30 min/time or ≤ 1 time/week for ≥ 30 min/time)

** Moderate-High (high; ≥ 5 times/week for ≥ 30 min/time, moderate; 2–4 times/week for ≥ 30 min/time or ≥ 5 times/week for < 30 min/time)



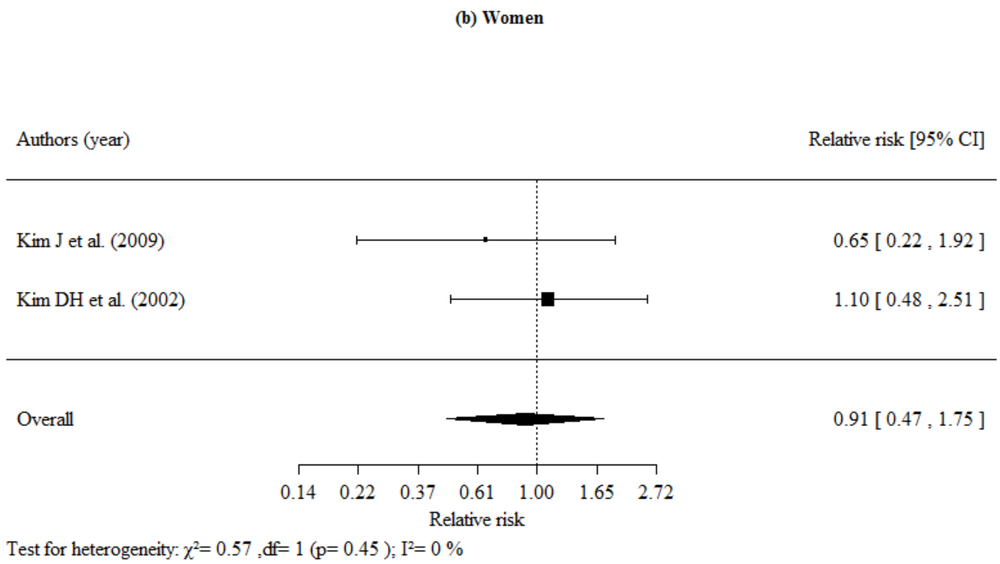


Figure 14 Forest plot of physical activity and colorectal cancer among (a) men and (b) women.

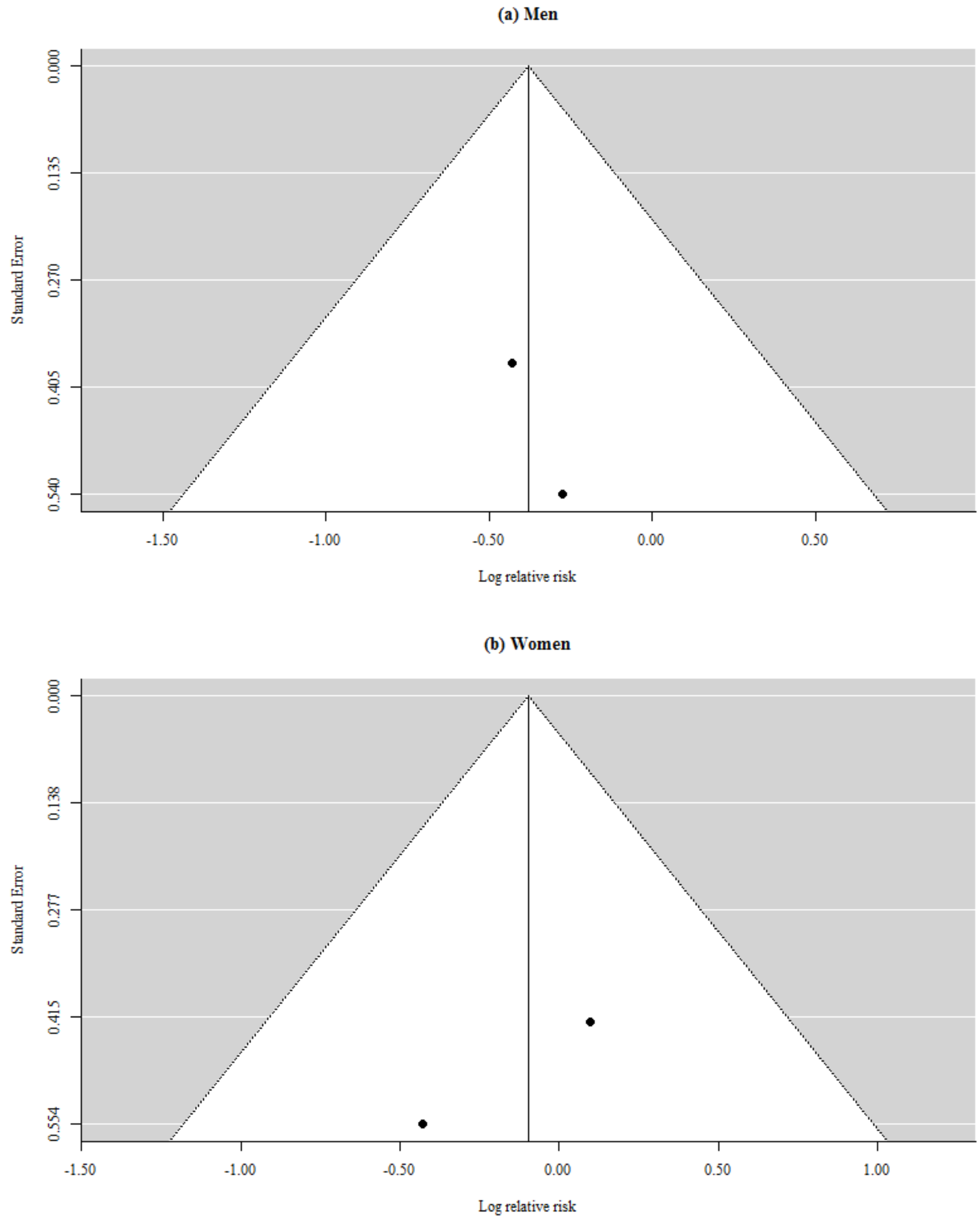


Figure 15 Funnel plot of physical activity and colorectal cancer among (a) men and (b) women.

Meat intake

Although the exposure to meat intake category that include the most studies was "meat intake" compared to "no meat intake", this was not an appropriate representation of circumstances in Korea. For this reason, we defined the meat intake exposure as weekly meat intake frequency. In addition, we performed a meta-analysis to estimate the risk of meat intake compared to no meat intake as a supplemental analysis (Table 16).

Table 15 Relative risks reported from selected studies of meat intake.

Author (year)	Sex	Meat intake level	RR or OR (95% CI)
Kim J et al. (2011)	Men	≤ once a week	1.00
		2-3 (times/week)	1.05 (0.99-1.12)
		≥ 4	1.13 (1.02-1.26)
	Women	≤ once a week	1.00
		2-3 (times/week)	1.07 (0.97-1.18)
		≥ 4	1.42 (1.21-1.66)

Table 16 Pooled relative risk for each increment of meat intake per week used to estimate population attributable risk of meat intake compared with never meat intake

Author (year)	Sex	Meat intake level	RR or OR (95% CI)	Risk for each increment of meat intake per week
Kim JI et al. (2003)	Both sexes	< 2 (times/week)	1.00	1.72 (1.12-2.76)
		≥ 2	1.72 (1.12-2.76)	
Ahn EJ et al. (2006)	Both sexes	None	1.00	1.19 (0.89-1.61)
		< 3 (times/week)	1.20 (0.50-2.80)	
		≥ 3	1.70 (0.70-4.20)	
Kim J et al. (2011)	Men	≤ once a week	1.00	1.04 (1.01-1.08)
		2-3 (times/week)	1.05 (0.99-1.12)	
		≥ 4	1.13 (1.02-1.26)	
	Women	≤ once a week	1.00	1.12 (1.06-1.18)
		2-3 (times/week)	1.07 (0.97-1.18)	
		≥ 4	1.42 (1.21-1.66)	

Table 16 Continued.

Author (year)	Sex	Meat intake level	RR or OR (95% CI)	Risk for each increment of meat intake per week
Chun YJ et al. (2015)	Both sexes	< 0.93 (serving/week)	1.00	3.08 (1.85-5.12)
		0.93-2.7	3.64 (1.67-7.94)	
		> 2.7	7.33 (2.98-18.06)	
Pooled relative risk	Men			1.53 (0.97-2.41)
	Women			1.56 (1.01-2.39)

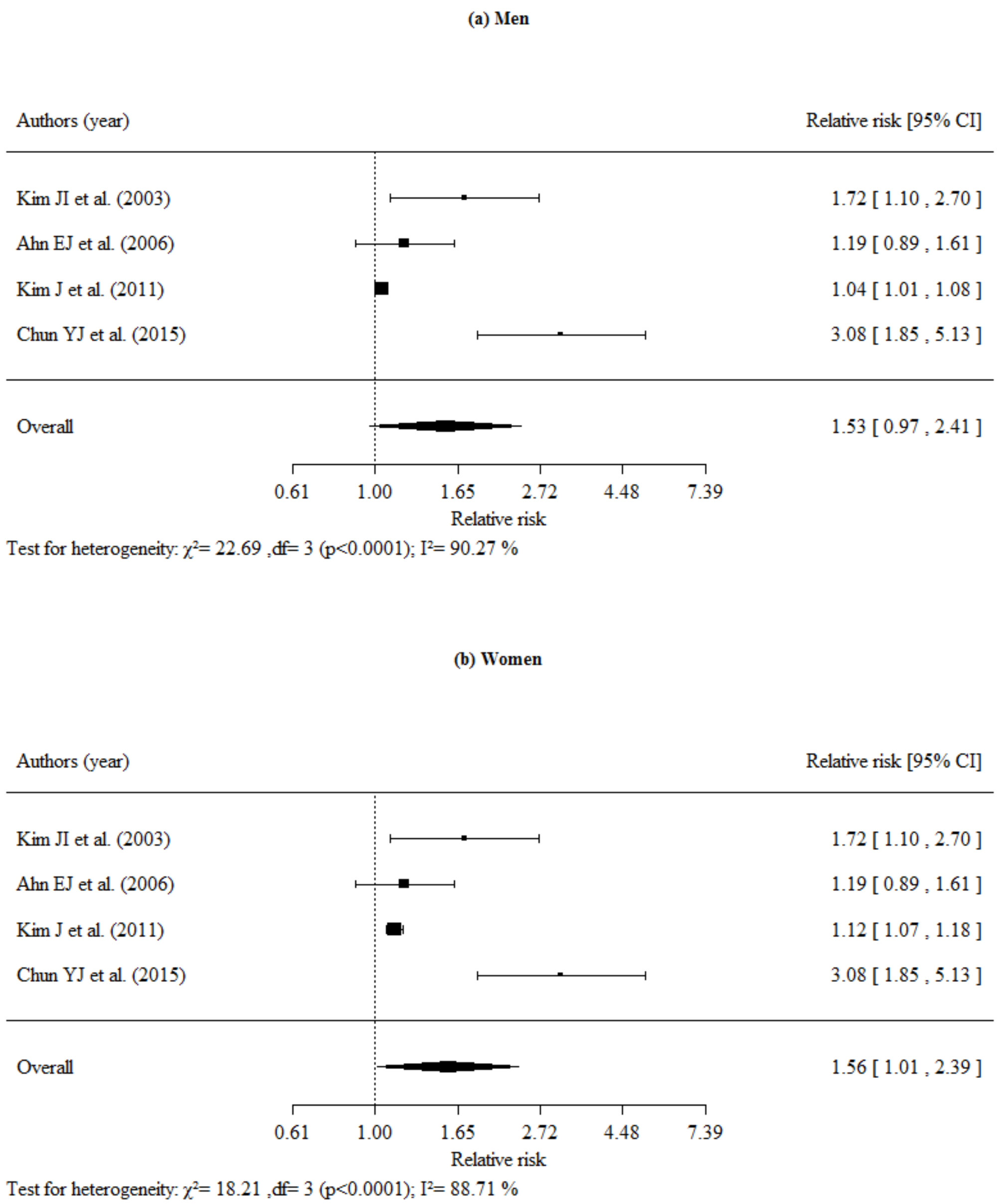


Figure 16 Forest plot of meat intake and colorectal cancer among (a) men and (b) women.

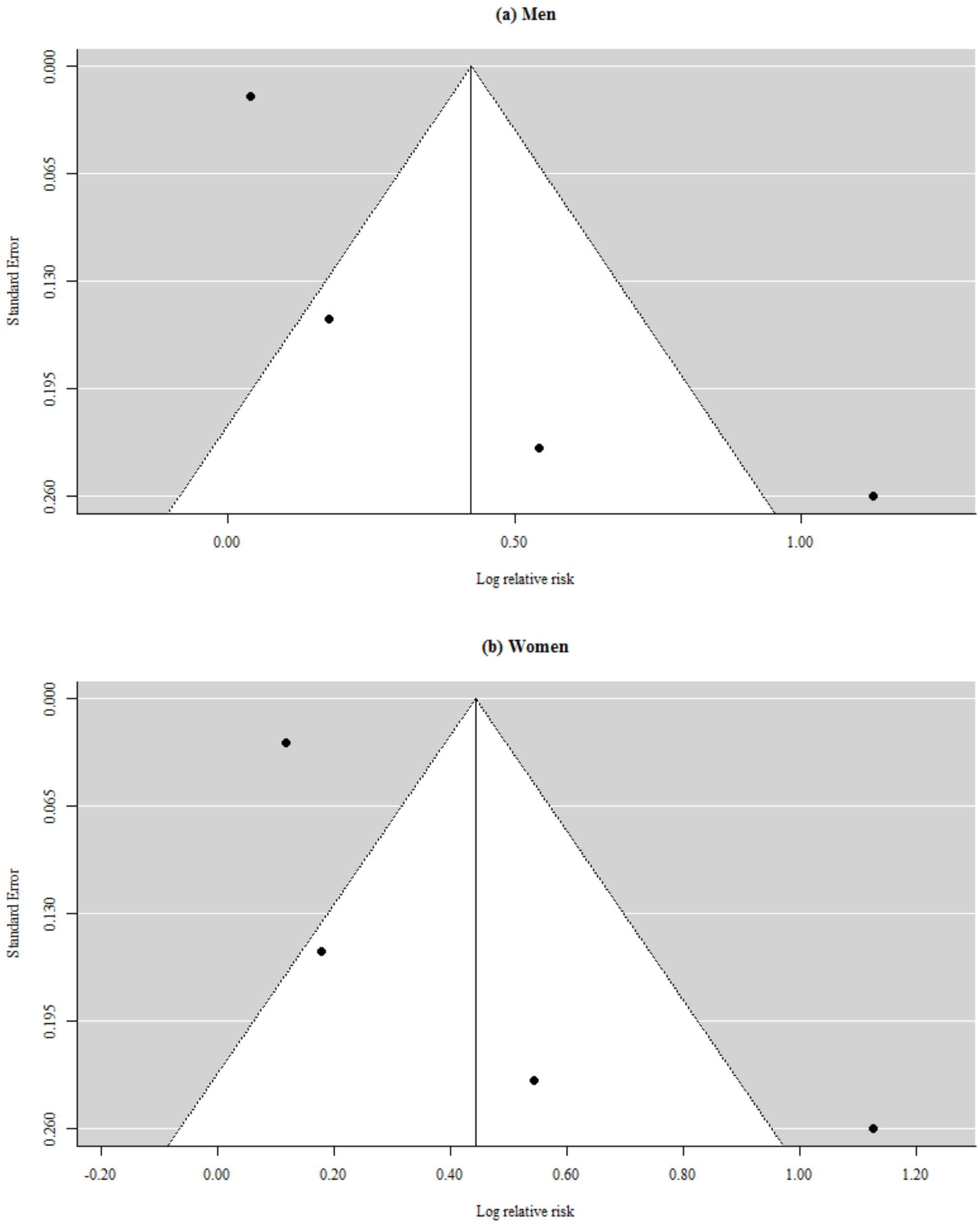


Figure 17 Funnel plot of meat intake and colorectal cancer among (a) men and (b) women.

Global relative risk estimates population

We screened articles that met inclusion criteria and selected one study for each risk that had the most cases or studies. Table 17 shows the pooled global RRs.

Table 17 Pooled global RR estimated for calculation of population attributable fraction.

Exposure	Men	Women	Source of pooled RR
Tobacco smoking			
Never smoker	1.00	1.00	[68]
Former smoker	1.18 (1.11 - 1.27)	1.20 (1.11 - 1.30)	
Current smoker	1.12 (1.02 - 1.25)	1.05 (0.94 - 1.18)	
Alcohol consumption; daily alcohol consumption amount, g			
Never drinker	1.00	1.00	[69]
≤ 12.5	1.05 (0.95 - 1.16)	0.95 (0.89-1.01)	
12.5-50	1.21 (1.11 - 1.32)	1.07 (0.99-1.16)	
> 50	1.53 (1.30 - 1.80)	1.24 (0.68-2.25)	
Obesity*			
Normal	1.00	1.00	[17]
Obese	1.47 (1.36 - 1.58)	1.15 (1.08 - 1.23)	
Physical activity**			
Low level	1.00	1.00	[70]
High level	0.82 (0.70-0.95)	0.87 (0.70-1.08)	

Table 17 Continued.

Exposure	Men	Women	Source of pooled RR
Red meat intake; weekly red meat consumption frequency			
Never	1.00	1.00	[71]
< once	1.31 (1.12 - 1.54)	0.92 (0.75-1.12)	
2-4 times	1.27 (1.04 - 1.56)	1.02 (0.91-1.15)	
5-7 times	1.29 (0.96 - 1.74)	1.14 (0.96-1.34)	
≥ 7 times	1.38 (0.97 - 1.96)	0.93 (0.72-1.20)	

* The study summarized the effect size for the "obese" category defined by each study included in the meta-analysis.

** Summary of effect sizes for the most active level in each study that was included in the meta-analysis.

Estimated prevalence of exposure

Table 18 and Table 19 show the prevalence of exposures for the national estimates. The prevalence of former (17.9%) and current (61.8%) smoker status among men was greater than among women (1.6% for former smokers and 5.4% for current smokers). More than half of men were ever drinkers (73.5%), whereas most women (70.7%) were never drinkers. The prevalence of obesity was higher than normal weight among women (42.7% for normal weight and 29.3% for obesity). The prevalence of participating in vigorous physical activity was lower than the prevalence of not participating in vigorous physical activity among both men (30.0% for vigorous physical activity and 70.0% for no vigorous physical activity) and women (17.0% for vigorous physical activity and 83.0% for no vigorous physical activity). The prevalence of those who participated in moderate-to-high levels of physical activity (men, 41.1%; women 37.5%) was lower than the prevalence of those participating in low levels of physical activity (men, 58.9%; women, 65.5%) for both sexes. The frequency of meat intake among men was higher than among women.

Table 18 Prevalence of exposures for national estimates, %.

	Men	Women
Tobacco smoking		
Never smoker	20.3	93.0
Former smoker	17.9	1.6
Current smoker	61.8	5.4
Alcohol consumption*		
Never drinker	26.5	70.7
Ever drinker	73.5	29.3
Obesity; body mass index, kg/m^2		
Underweight (< 18.5)	3.5	5.5
Normal (18.5-22.9)	39.1	42.7
Overweight (23.0-24.9)	24.9	22.5
Obese (≥ 25.0)	32.4	29.3
Physical activity; intensity**		
Participation in vigorous physical activity	70.0	83.0
No participation in vigorous physical activity	30.0	17.0
Physical activity; combination of frequency and duration***		
Moderate-High	41.1	37.5
Low	58.9	62.5

Table 18 Continued.

	Men	Women
Meat intake; weekly meat consumption frequency		
≤ once a week	11.3	18.9
2-3 times/week	49.9	49.9
≥ 4 times/week	38.8	31.2
Meat intake****		
No meat intake	1.1	2.2
Meat intake	98.9	97.8

* Average alcohol consumption: 22.1 g per day among men, 6.6 g per day among women (2001 National Health and Nutrition Examination Survey).

** Defined as metabolic equivalent (MET) value over 6 $kcal \cdot kg^{-1} \cdot hr^{-1}$.

*** Low (≤ 4 times/week for < 30 min/time or ≤ 1 time/week for ≥ 30 min/time), Moderate-High (high; ≥ 5 times/week for ≥ 30 min/time, moderate; 2–4 times/week for ≥ 30 min/time or ≥ 5 times/week for < 30 min/time).

**** Average weekly meat intake frequency: 4.4 times per week among men, 3.7 times per week among women (2001 National Health and Nutrition Examination Survey).

Table 19 Prevalence of exposures for global estimates, %.

	Men	Women
Tobacco smoking		
Never smoker	20.3	93.0
Former smoker	17.9	1.6
Current smoker	61.8	5.4
Alcohol consumption; daily alcohol consumption amount, g		
Never drinker	26.5	70.7
≤ 12.5	36.9	25.4
12.5-50	27.3	3.5
> 50	9.3	0.4
Obesity; body mass index, kg/m2		
Underweight(< 18.5)	3.5	5.5
Normal (18.5-22.9)	39.1	42.7
Overweight (23.0-24.9)	24.9	22.5
Obese (≥ 25.0)	32.4	29.3
Physical activity; intensity of physical activity in daily life		
Stable, light or moderate	83.4	96.0
Hard or very hard	16.6	4.0

Table 19 Continued.

	Men	Women
Red meat intake; weekly red meat consumption frequency		
Never	1.4	2.6
< once	56.4	64.5
2-4 times	20.6	17.0
5-7 times	13.4	9.3
≥ 7 times	8.2	6.6

Estimated population attributable fractions (PAFs) of risk

PAFs based on risk estimates in the Korean population

Table 20 presents PAFs for each level of selected risk factors in Korea. The PAF for ever smoker status, including former and current smokers, was 7.6% among men and 0.7% among women. Among men, the PAF for former smokers was 3.6% and for current smokers was 4.2%; among women, the PAF for former smokers was 0.5% and for current smokers was 0.2%. The PAF for alcohol consumption was 24.3% among men and 3.7% among women. The PAF for obesity was 2.8% among men and 4.2% among women. The PAF for physical inactivity when defined as participating in no vigorous physical activity was 12.2% among men and 1.7% among women. When defined by the combination of frequency and duration, the PAFs for physical inactivity were lower among both sexes, 1.2% among men and 1.3% among women. The PAF for meat intake of more than 2 times per week was 7.0% among men and 14.2% among women. The PAF for meat intake was 53.3% among men and 47.4% among women, compared with no meat intake.

Table 20 Population attributable fraction of risk using national estimates, %.

	Men	Women
Tobacco smoking		
Never smoker	Optimum level	
Former or current smoker*	7.6	0.7
Former smoker	3.6	0.5
Current smoker	4.2	0.2
Alcohol consumption**		
Never drinker	Optimum level	
Ever drinker	24.3	3.7
Obesity (body mass index, kg/m^2)		
Normal (18.5-22.9)	Optimum level	
Obese (≥ 25.0)	2.8	4.2
Physical activity; intensity***		
Participation in vigorous physical activity	Optimum level	
No participation in vigorous physical activity	12.2	1.7
Physical activity; combination of frequency and duration****		
Moderate-High	Optimum level	
Low	1.2	1.3

Table 20 Continued.

	Men	Women
Meat intake; weekly meat consumption frequency		
≤ once	Optimum level	
≥ 2 times *	7.0	14.2
2-3 times	2.4	3.4
≥ 4 times	4.8	11.6
Meat intake*****		
No meat intake	Optimum level	
Meat intake	84.2	80.6

* Calculated by a modified Levin's formula for multiple categories, proposed by Hanley.

** Average alcohol consumption: 22.1 g per day among men, 6.6 g per day among women (2001 National Health and Nutrition Examination Survey).

*** Defined as metabolic equivalent (MET) value over 6 $kcal \cdot kg^{-1} \cdot hr^{-1}$.

**** Low (≤ 4 times/week for < 30 min/time or ≤ 1 time/week for ≥ 30 min/time), Moderate-High (high; ≥ 5 times/week for ≥ 30 min/time, moderate; 2–4 times/week for ≥ 30 min/time or ≥ 5 times/week for < 30 min/time).

***** Average weekly meat intake frequency: 4.4 times per week among men, 3.7 times per week among women (2001 National Health and Nutrition Examination Survey).

Table 21 shows the PAFs and the number of colorectal cancer cases attributable to each risk factor using national estimates. The most modifiable factor for colorectal cancer was alcohol consumption (24.3%), followed by physical inactivity (12.2%), tobacco smoking (7.6%), meat intake (7.0%), and obesity (2.8) among men, and meat intake (14.2%), followed by obesity (4.2%), alcohol consumption (3.7%), physical inactivity (1.7%) and tobacco smoking (0.7%) among women. The PAFs for selected risk factors considered in this study were 44.5% for men and 22.7% for women, which accounted for 7,760 cases among men and 2,624 cases among women.

Table 21 Number of colorectal cancer cases attributable to risk factors in Korea in 2013, using national estimates.

	Men		Women	
	PAF (%)	Cases (N)	PAF (%)	Cases (N)
All cases		17,445		11,543
Tobacco smoking	7.6	1,326	0.7	122
Alcohol consumption	24.3	4,239	3.7	645
Obesity	2.8	488	4.2	733
Physical inactivity	12.2	2,128	1.7	297
Meat intake	7.0	1,221	14.2	2,477
All of the above risk factors	44.5	7,760	22.7	2,624

Global PAFs based on risk estimates for worldwide populations

Table 22 presents PAFs for each level of selected risk factors in Korea using the estimated risk for worldwide populations. The PAF for ever smokers, including former and current smokers, was 9.6% among men and 0.6% among women. Among men, the PAF for former smokers was 3.1% and for current smokers was 6.9%; among women, the PAF for former smokers was 0.3% and for current smokers was 0.3%. The PAF for alcohol consumption was 11.1% among men and 2.2% among women, and the levels of daily alcohol consumption with the highest PAFs were 12.5-50g among men and less than 12.5g among women. The PAF for obesity was 13.2% among men and 4.2% among women. The PAF for physical activity was 15.5% among men and 12.5% among women. The PAF for red meat intake was 23.1% among men and 23.0% among women. The levels of red meat intake frequency with the highest PAF were less than once per week among both men (14.9%) and women (16.7%).

Table 22 Population attributable risk using global estimates, %.

	Men	Women
Tobacco smoking		
Never smoker	Optimum level	
Former or current smoker*	9.6	0.6
Former smoker	3.1	0.3
Current smoker	6.9	0.3
Alcohol consumption; daily alcohol consumption amount, g**		
Never drinker	Optimum level	
Ever drinker*	11.1	2.2
≤ 12.5	1.8	1.3
12.5-50	5.4	0.7
> 50	4.7	0.2
Obesity (body mass index, kg/m2)		
Normal (18.5-22.9)	Optimum level	
Obese (≥ 25.0)	13.2	4.2
Physical activity ***		
High level	Optimum level	
Low level	15.5	12.5

Table 22 Continued.

	Men	Women
Red meat intake; weekly red meat consumption frequency**		
Never	Optimum level	
Ever*	23.1	23.0
< once	14.9	16.7
2-4 times	5.3	4.4
5-7 times	3.8	2.6
≥ 7 times	3.0	2.4

* Calculated by the modified Levin's formula for multiple categories, proposed by Hanley.

** Using relative risk among men.

*** Using reciprocal value of RR for low levels of physical activity, compared with high levels of physical activity.

Table 23 shows the PAFs and the number of colorectal cancer cases attributable to risk factors using global estimates. The most modifiable factor for colorectal cancer was red meat intake (23.1%), followed by physical inactivity (15.5%), obesity (13.2%), alcohol consumption (11.1%), and tobacco smoking (9.6%) among men, and red meat intake (23.0%), followed by physical inactivity (12.5%), obesity (4.2%), alcohol consumption (2.2%) and tobacco smoking (0.6%) among women. The PAFs for the selected risk factors considered in this study was 54.7% for men and 37.3% for women, which accounted for 9,537 cases among men and 4,300 cases among women.

Table 23 Number of colorectal cancer cases attributable to risk factors in Korea in 2013, using global estimates.

	Men		Women	
	PAF (%)	Cases (N)	PAF (%)	Cases (N)
All cases		17,445		11,543
Tobacco smoking	9.6	1,675	0.6	105
Alcohol consumption	11.1	1,936	2.2	384
Obesity	13.2	2,303	4.2	733
Physical inactivity	15.5	2,704	12.5	2,181
Red meat intake	23.1	4,030	23.0	4,012
All of the above risk factors	54.7	9,537	37.3	4,300

PAFs of colorectal cancer risk in the Korean population

Only a few studies were included in the estimation of pooled RRs in the Korean population for some exposures such as physical activity and meat intake. Therefore, the pooled estimates may not reasonably represent actual risk. In addition, although 'red meat intake' is considered a risk factor for colorectal cancer, the Korean studies assessed the association according to ''meat intake", which included white meat, to assess the association. Considering this, we substituted pooled RR for physical activity and meat intake that were estimated using fewer than 2 studies with RRs obtained from the meta-analysis of worldwide populations.

As shown in Table 24, the most modifiable factor for colorectal cancer was alcohol consumption (24.3%), followed by red meat intake (23.1%), physical inactivity (15.5%), tobacco smoking (7.6%), and obesity (2.8%) among men, and red meat intake (23.0%), followed by physical inactivity (12.5%), obesity (4.2%), alcohol consumption (3.7%), and tobacco smoking (0.7%) among women. The PAF for selected risk factors considered in this study was 55.8% for men and 38.8% for women, which accounted for 9,738 cases among men and 4,418 cases among women.

Table 24 Number of colorectal cancer cases attributable to risk factors in Korea in 2013.

	Men		Women	
	PAF (%)	Cases (N)	PAF (%)	Cases (N)
All cases		17,445		11,543
Tobacco smoking	7.6	1,326	0.7	122
Alcohol consumption	24.3	4,239	3.7	645
Obesity	2.8	488	4.2	733
Physical inactivity*	15.5	2,704	12.5	2,181
Red meat intake*	23.1	4,030	23.0	4,012
All of the above risk factors	55.8	9,738	38.3	4,418

* Substituted RRs calculated from Korean population data with RR from meta-analysis of worldwide populations.

DISCUSSION

The attributable fraction of risk varied according to sex and risk estimates. The two most important modifiable factors among men were alcohol consumption (24.3%) and physical inactivity (15.5%), when assessed using national estimates, and red meat intake (23.1%) and physical inactivity (15.5%), when assessed using global estimates. Among women, the two most important factors were meat intake (14.2%) and obesity (4.2%), when assessed using national estimates, and red meat intake (23.0%) and physical inactivity (12.5%), when assessed using global estimates. Regardless of risk estimates and sex, physical inactivity was an important lifestyle exposure. The PAF for physical inactivity was far higher than those found in other studies in Korea. This discrepancy could be explained by differences in the definition of physical inactivity. In previous studies in Korea, authors defined physical inactivity as weekly duration of physical activity, without regard to the intensity of the physical activity. One previous study on the association between physical activity and site-specific cancer risk reported that the effect size of physical activity on colorectal cancer risk differed by the intensity of the activity [72]. The PAF for alcohol consumption using national estimates was also higher than that found in other studies in Korea. High relative risk contributed to the high PAF in this study. The number of total cases included in our study (more than 802 cases; 1 study [58] did not indicate the number of cases) was greater than that in previous studies in Korea (622 cases), and we expect to give more reliable results. Otherwise, the PAFs for alcohol consumption using global estimates were rather similar to those of prior studies in Korea. However, there were regional differences in colorectal cancer risk attributed to alcohol consumption, and Asians have higher risk than other population [12 16]. Therefore, we suggest that the PAF for alcohol consumption using national estimates is close to the true value, compared with the PAF using global estimates. For meat intake, the PAFs using national estimates were lower than those calculated using global estimates among both men and women. These differences could be due to the definitions used for the optimum level of meat intake and the definition of meat itself. For the national estimates, the reference meat intake level was a meat intake frequency of less than once per week, which could cause increased hazards at the reference level, compared to no meat intake as the reference level. Additionally, the effect of total meat intake could be attenuated because of the risk of red meat.

Strengths of this study include the following. We used nationwide cancer incidence data and national representative data to estimate the prevalence of exposures. In addition, there are several limitations to the current study. We did not perform an evaluation of the quality of the studies included in our study. There were also only a limited number of published epidemiologic studies conducted in the Korea population, so we could not estimate PAFs for other risk factors, such as dietary fiber.

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요 약

대장암은 전세계 뿐만 아니라 국내에서도 발생률이 높은 암종이다. 본 연구에서는 대장암 발생과의 연관성이 잘 알려진 위험요인에 대해 한국에서의 인구집단 기여위험도를 산출하고자 한다. 본 연구에서 다루는 위험요인은 흡연, 음주, 비만, 신체활동, 육류 섭취이다. 기여위험도 산출을 위해 이용된 각 위험요인에 의한 대장암 발생 위험도는 한국 인구집단을 대상으로 보고된 연구들 을 메타분석을 통해 하나의 값으로 요약하여 이용하였으며, 전세계 인구를 대상으로 하는 해외 메타 문헌에서의 위험도도 기여위험도 산출에 이용하였다. 위험요인별 유병률은 2001 년 국민건강영양조사 자료로부터 추정되었으며, 대장암 발생 건수는 2013 년 중앙 암등록 통계자료를 참고하였다.

국내 연구에서의 위험도를 이용한 경우, 본 연구에서 다룬 전체 위험요인에 대한 인구집단 기여위험도는 남성에서 44.5%, 여성에서 22.7%였다. 대장암 발생에 가장 많이 기여하는 위험 요인으로는 남성에서 음주 (24.3%), 여성에서 육류 섭취 (14.2%)였다. 해외 메타 연구에서의 위험도를 이용한 경우, 전체 위험요인에 대한 인구집단 기여위험도는 남성에서 54.7%, 여성에서 37.3%였다. 가장 높은 기여위험도를 나타낸 요인은 남성 (23.1%)과 여성 (23.0%) 모두 적색육 섭취였다. 국내 연구 수가 제한적인 요인에 대해서 해외 문헌 결과를 적용한 경우, 인구집단 기여위험도는 남성에서 55.8%, 여성에서 38.3%였다. 결론적으로, 적절한 위험요인의 통제를 통해 남성에서는 55.8%, 여성에서는 38.3%의 대장암 위험 감소를 기대할 수 있었다.

주요어: 대장암; 인구집단 기여위험도; 생활 습관; 위험 요인

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