Visceral Fat Accumulation Is Associated with Colorectal Cancer in Postmenopausal Women

Jee-Yon Lee¹, Hye-Sun Lee², Duk-Chul Lee¹, Sang-Hui Chu³, Justin Y. Jeon⁴, Nam-Kyu Kim⁵*, Ji-Won Lee¹*,

¹Department of Family Medicine, Yonsei University, College of Medicine, Seodaemun-gu, Seoul, Republic of Korea, ²Department of Biostatistics, Yonsei University, College of Medicine, Seodaemun-gu, Seoul, Republic of Korea, ³Department of Clinical Nursing Science, Yonsei University, College of Nursing, Nursing Policy Research Institute, Biobehavioural Research Centre, Seodaemun-gu, Seoul, Republic of Korea, ⁴Department of Sport and Leisure Studies, Sports Medicine Laboratory, Yonsei University, Seodaemun-gu, Seoul, Republic of Korea, ⁵Department of General Surgery, Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea

Abstract

Background: Obesity is a known risk factor for colorectal cancer (CRC), and emerging data suggest that this association is mediated by visceral fat rather than total body fat. However, there is a lack of studies evaluating the association between visceral fat area and the prevalence of CRC.

Methods: To investigate the relationship between visceral adiposity and prevalence of CRC, data of 497 women diagnosed with CRC and 318 apparently healthy women were analysed and data of well-balanced 191 pairs of women with CRC and healthy women matched based on propensity scores were additionally analysed. Diagnosis of CRC was confirmed by colonoscopy and histology. Metabolic parameters were assessed, along with body composition, using computed tomography.

Results: The median visceral fat area was significantly higher in the CRC group compared with the control group before and after matching. The prevalence of CRC increased significantly with increasing visceral fat tertiles after matching (p for trend <0.01). A multivariate analysis showed that mean visceral fat area of individuals in the 67th percentile or greater group was associated with an increased prevalence of CRC (adjusted odds ratio: 1.80; 95% confidence interval: 1.12–2.91 before matching and adjusted odds ratio: 2.96; 95% confidence interval: 1.38–6.33) compared with that of individuals in the 33rd percentile or lower group.

Conclusion: Thus, we conclude that visceral fat area is positively associated with the prevalence of CRC. Although we could not determine the causality, visceral adiposity may be associated with the risk of CRC. Further prospective studies are required to determine the benefits of controlling visceral obesity for reducing CRC risk.

Citation: Lee J-Y, Lee H-S, Lee D-C, Chu S-H, Jeon JY, et al. (2014) Visceral Fat Accumulation Is Associated with Colorectal Cancer in Postmenopausal Women. PLoS ONE 9(11): e110587. doi:10.1371/journal.pone.0110587

Copyright: © 2014 Lee et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper.

Funding: This study was supported by a 2013 Faculty Research Grant from Yonsei University College of Medicine (6-2013-0021) and the Bio & Medical Technology Development Program, through the National Research Foundation of Korea funded by the Ministry of Science, ICT & Future Planning (NRF-2013M3A9B6046413). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Introduction

Obesity and cancer are emerging as two of the most serious health problems worldwide. Obesity is known to increase the risk of cardio-metabolic diseases including Type 2 diabetes mellitus (DM), cardiovascular disease, and metabolic syndrome [1,2]. Furthermore, the relationship between obesity and several types of cancer such as renal, oesophageal, colorectal, and breast cancer has also been reported [3,4]. The precise underlying mechanism that explains how obesity promotes these diseases is still unclear; however, recent evidence suggests that visceral adipose tissue may play a key role in this relationship. Visceral adipose tissue, largely distributed in the abdominal cavity, shows higher hormonal and metabolic activities than subcutaneous fat tissue [5]. Visceral adipocyte-secreted growth factors, proinflammatory cytokines, and adipokines are considered mediating factors associated with the carcinogenesis of obesity-related tumours [6].

Colorectal cancer (CRC) is well known as an ‘obesity-related’ cancer. Recent epidemiologic studies have shown that waist circumference or the waist-hip ratio, which reflect abdominal adiposity rather than total body mass index (BMI), showed greater association with increased risk of CRC [7–9]. These findings indicate that the regional distribution of adipose tissue, not overall adiposity, may contribute to the increased risk of CRC. Altered metabolic activity and systemic chronic inflammation induced by visceral adipose tissue are also considered to be related with colorectal carcinogenesis [10]. A few studies have assessed the
relationship between CRC risk and visceral obesity using a direct method to measure visceral fat area; however, the results were inconclusive [11–13]. Some studies showed increased CRC risk with higher visceral adipose tissue accumulation. However, no significant relationship, and even opposing results, have been reported.

Therefore, we investigated the relationship between the prevalence of CRC and visceral fat area by comparing a colorectal cancer group and a case-matched control group of Korean women.

Methods

Ethical statement

All subjects participated in the study voluntarily, and written informed consent was obtained from each participant. The study complied with the Declaration of Helsinki, and the Institutional Review Board of Yonsei University College of Medicine approved this study.

Study subjects

The study subjects consisted of 1920 postmenopausal women who visited the Department of Colorectal Surgery and were diagnosed with CRC during their visit and 670 postmenopausal women who visited the Health Promotion Centre and the Department of Family Medicine at Severance Hospital for routine health check-ups that included a screening colonoscopy between November 2010 and August 2012. Menopausal status was defined as having had no menstrual periods for 12 consecutive months without any biological or physiological cause. We excluded women who were taking medication for a diagnosis of hypertension, diabetes mellitus, chronic liver disease, chronic renal disease, coronary artery occlusive disease, or stroke. We also excluded women who underwent polyp removal procedures or who were diagnosed with CRC or other types of cancer prior to their participation in the study. After applying the exclusion criteria, a total of 497 women diagnosed with CRC were defined as the CRC group, and 318 apparently healthy women were defined as the control group. From the CRC and healthy groups, a well-balanced study population consisting of 199 pairs of women was selected by propensity score matching.

Measurement of clinical parameters

All subjects completed a questionnaire about their lifestyle, such as smoking, alcohol consumption, regular exercise, underlying medical conditions, and medications. Cigarette smoking was defined as current or past smokers, and alcohol consumption was defined as drinking alcohol more frequently than once per week or more than 70 grams per week during the previous year.

Blood pressure was measured in the sitting position after the subject was asked to rest for longer than 10 minutes. The mean blood pressure (mmHg) was calculated using the systolic blood pressure (SBP) and diastolic blood pressure (DBP) as follows: (SBP+2×DBP)/3. Body mass index (BMI) was defined as weight (kg) divided by height squared (m²).

Blood samples were collected after at least 8 hours of fasting. Fasting glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, and total cholesterol levels were measured by using the Hitachi 7600 Automatic analyzer (High-Technologies Corporation, Hitachi, Tokyo, Japan). White blood cell (WBC) counts were measured using an automated blood cell counter (ADVIA 120, Bayer, NY, USA). The biomarkers were part of the routine tests for patients who were planning to receive CRC surgery. The control group also have received the same blood tests as a part of their routine health check-ups.

Assessment of body composition

Abdominal fat tissue areas were measured by computed tomography (Tosmscan 350; Philips, Mahwah, NJ, USA) as described previously [14]. A single cross-sectional CT image of a 3-mm thick slice at the level of L4–L5 interspace was obtained with the subject in a supine position. The visceral and subcutaneous fat areas were calculated at this slice using a commercially available software program (TeraRecon Aquarius; TeraRecon, CA, USA), which determined the fat area electronically by setting the attenuation range from −150 to −50 Hounsfield units. Visceral adipose tissue areas were measured by delineating the intra-abdominal cavity at the internal aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body. The subcutaneous adipose tissue area was calculated by subtracting the VAT area from the total adipose tissue area. All measurements were performed by a skilled radiologist who was blinded to the patient data. The inter- and intra-coefficients of variation (CVs) for reproducibility were 1.4% and 0.5%, respectively.

Diagnosis of CRC

All participants received colonoscopic examinations performed by experienced gastroenterologists after bowel preparation with 4 litres of polyethylene glycol solution (Colyte; Taegu, Seoul, Korea). All procedures were performed by using a standard video colonoscope (CFQ240L, Olympus, Optical, Tokyo, Japan). Biopsies were taken from all detected suspicious lesions, and the final diagnosis of CRC was made by histopathological analysis. CRC was diagnosed if malignant cells were observed above the muscularis mucosae. The classification system recommended by the American Joint Committee on Cancer (AJCC) was used for tumour staging [15]. The locations of the tumours were recorded and divided into sigmoid, ascending, transverse, and descending colon, and rectum.

Statistical analyses

Data for demographic characteristics are represented as the mean ± standard deviation or number (%). To reduce the effect of confounding factors that may affect the relationship between CRC and visceral adiposity, we adjusted for differences in the clinical basal characteristics between the CRC and control groups using propensity score matching [16]. The demographic characteristics of the CRC and control groups before matching were compared using two-sample t-tests for continuous data and Chi-square tests or Fisher’s exact tests for categorical data. All variables constituting baseline demographic characteristics, such as age, BMI, smoking status, alcohol consumption, and regular exercise, were included as exact matching factors. A propensity score for the predicted probability of cancer in each woman was estimated using a logistic regression model fit with five factors. The controls were matched 1:1 with CRC patients. A nearest-neighbour-matching algorithm with a greedy heuristic was used to match patients for demographic characteristics. The matched demographic characteristics of the CRC and control groups were compared using paired t-tests for continuous data and McNemar tests for categorical data. The metabolic parameters were described as median and interquartile range, and differences between the two groups after matching were compared using Wilcoxon signed-rank tests.

Tertiles were categorized as follows based on visceral fat areas:

Q1: <67.98 cm², Q2: 67.98–91.67 cm², Q3: >91.67 cm². The
prevalence of CRC according to the visceral fat tertiles was compared using the Cochran-Armitage trend test. The odds ratio and 95% confidence intervals (CI) for CRC were calculated using conditional logistic regression analyses after adjusting for confounding factors across visceral fat tertiles.

All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

**Results**

**Characteristics of the study population**

The clinical characteristics of the CRC and control groups before and after propensity score matching are given in Table 1. Women with CRC showed a significantly higher age and lower BMI and lower incidence of regular exercise. After propensity score matching was completed, there were 199 matched pairs of participants. There were no significant differences in clinical characteristics between the two groups.

Table 2 shows the metabolic parameters of the CRC and control groups before and after matching. Visceral fat area, visceral/subcutaneous fat ratio, mean blood pressure, fasting glucose levels, WBC count, and creatinine levels were significantly higher in the CRC group compared to the control group before and after matching (p<0.05). The subcutaneous fat area was significantly lower in the CRC group compared to the control group before and after matching (p<0.05). ALT levels were significantly higher in the control group only before matching (p<0.01)

**Characteristics of colorectal neoplasms**

Table 3 describes the stage and location of the tumours in the CRC group before after matching. Categorization of patients according to cancer stage at first diagnosis revealed that 13.49% (n = 77) of patients were stage I, 24.55% (n = 122) were stage II, 25.15% (n = 125) were stage III, and 34.81% (n = 173) were stage IV before matching. After propensity score matching, 16.58% (n = 77) of patients were stage I, 24.55% (n = 122) were stage II, 23.12% (n = 46) were stage III, and 36.18% (n = 72) were stage IV.

Of these, 276 (55.53%) patients had a tumour in the colon and 221 (44.47%) had a tumour in the rectum before matching and 113 (56.70%) patients had a tumour in the colon, and 86 patients (43.22%) had a tumour in the rectum after matching.

**Table 1. Comparison of demographic characteristics between the control group and the colorectal cancer group before and after propensity score matching.**

|                | Unmatched                                                                 | Matched                                                                 |
|----------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------|
|                | Control (n = 318)                                                        | Cancer (n = 497)                                                         | P-value <sup>a</sup> | Control (n = 199)                                                        | Cancer (n = 199)                                                         | P-value <sup>b</sup> |
| Age (years)    | 58.38±9.84                                                               | 60.70±12.29                                                             | <0.01                  | 60.73±8.55                                                               | 60.73±8.55                                                               | >.99                   |
| BMI (kg/m2)    | 23.91±2.39                                                               | 23.4±3.55                                                               | 0.02                   | 23.84±2.42                                                               | 23.56±3.18                                                               | >.99                   |
| Smoking status | 113(46)                                                                  | 132(62)                                                                | 0.49                   | 2(1.01)                                                                  | 2(1.01)                                                                  | >.99                   |
| Alcohol consumption | 211(66.00)                                                   | 204(62)                                                                | 0.10                   | 2(1.01)                                                                  | 2(1.01)                                                                  | >.99                   |
| Regular exercise | 822(25.79)                                                            | 34(6.84)                                                                | <.001                  | 9(4.52)                                                                  | 9(4.52)                                                                  | >.99                   |

Normality was tested by the Kolmogorov-Smirnov test.
Data are the mean± standard deviation or percentage.
<sup>a</sup>P - values were derived from an independent-sample t-test for continuous data, and Chi-square test was performed for categorical data.
<sup>b</sup>P - values were derived from a paired t-test for parametric data or the McNemar test for categorical data.

Abbreviation: BMI, body mass index.

**Discussion**

Our cross-sectional study revealed a positive relationship between abdominal visceral obesity and CRC in Korean women. Visceral fat areas in the third tertile were associated with an approximately three times higher prevalence of CRC compared with areas in the first tertile after propensity score matching and adjusting for confounding factors (odds ratio: 2.96; 95% CI: 1.38–6.33). Furthermore, this association persisted even after separating the cancer sites and stages.

The prevalence of CRC has rapidly increased in the past 20 years in conjunction with the increasing prevalence of obesity worldwide [3]. Obesity is known to increase the risk of CRC significantly [10,17] and is also related with poor prognosis after treatment [18]. Recent studies have demonstrated the important role of visceral adiposity rather than general obesity in colorectal carcinogenesis [7–9]. However, these studies assessed CRC risk through direct measurement of visceral fat area using CT and provided conflicting results. Recent clinical studies have shown a significant association between CRC and visceral fat area. [11,12].
However, opposing results have also been reported. A small sample size, the confounding effect of unequal clinical characteristics of the participants, and the effect of tumour-related weight loss prior to the measurement of visceral fat are the factors that likely contributed to these unexpected results. In the present study, all of the participants underwent colonoscopy in the same hospital, and demographic characteristics between the control and CRC groups were carefully matched to reduce the effect of potential confounding factors. To our knowledge, this is the first study to compare the association between the prevalence of CRC and visceral fat area in confounding characteristics-matched cohorts.

### Table 2. Comparison of metabolic parameters between the control group and the colorectal cancer group before and after propensity score matching.

| Parameter                      | Unmatched       | Matched         |
|--------------------------------|-----------------|-----------------|
|                                | Control (n = 318) | Cancer (n = 497)| P-value | Control (n = 199) | Cancer (n = 199) | P-value |
| Visceral fat area (cm²)        | 74.02(24.58–246.04) | 88.2(19.3–256.2) | <0.01  | 73.47(24.58–246.04) | 87.2(19.3–231.3) | <0.01  |
| Subcutaneous fat area (cm²)    | 209.4(48.09–437.09) | 189.5(22.8–445.2)| <0.01  | 205.79(48.09–394.44) | 195.1(81.4–445.2) | 0.02   |
| Visceral/Subcutaneous Fat ratio (%) | 0.35(0.09–2.04) | 0.45(0.14–1.72) | <0.01  | 0.34(0.09–2.04) | 0.44(0.18–1.14) | <0.01  |
| Mean blood pressure (mmHg) b  | 86.67(67–117) | 89.33(65.67–136) | <0.01  | 86.67(67–117) | 90.33(68.33–121.67) | <0.01  |
| Fasting glucose (mg/dl)        | 90(64–170) | 98(69–384) | <0.01  | 90(64–170) | 100(69–326) | <0.01  |
| Total cholesterol (mg/dl)      | 183(100–270) | 182(76–333) | 0.57   | 178(100–270) | 188(80–285) | 0.36   |
| WBC (counts/L)                 | 5475(2760–9770) | 6405(1020–23940) | <0.01  | 5500(2760–9770) | 6350(1020–23940) | <0.01  |
| Creatinine (mg/dL)             | 0.73(0.41–7.01) | 0.75(0–2.6) | <0.01  | 0.73(0.41–6.73) | 0.74(0–1.56) | 0.04   |
| AST (U/L)                      | 18(8–75) | 18(4–166) | 0.14   | 18(8–75) | 18(4–94) | 0.14   |
| ALT (U/L)                      | 16(7–167) | 14(0–218) | <0.01  | 16(7–167) | 14(5–100) | 0.10   |

*P - values were derived using the Wilcoxon signed rank test.
Data are the median (25–75 percentile range).

The mean blood pressure (mmHg) was calculated using the systolic blood pressure (SBP) and diastolic blood pressure (DBP) as follows: (SBP+2XDBP)/3.

Abbreviation: WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

doi:10.1371/journal.pone.0110587.t002

### Table 3. Clinical features of the colorectal cancer patients after propensity score matching.

|                               | No. | %    |
|-------------------------------|-----|------|
| Before propensity score matching                        |
| Stage of tumour               |     |      |
| I                             | 77  | 15.49|
| II                            | 122 | 24.55|
| III                           | 125 | 25.15|
| IV                            | 173 | 34.81|
| Location                      |     |      |
| Colon                         | 276 | 55.53|
| Sigmoid                       | 138 | 27.77|
| Ascending                     | 87  | 17.51|
| Transverse                    | 20  | 4.02 |
| Descending                    | 31  | 6.24 |
| Rectum                        | 221 | 44.47|
| After propensity score matching                      |
| Stage of tumour               |     |      |
| I                             | 33  | 16.58|
| II                            | 48  | 24.12|
| III                           | 46  | 23.12|
| IV                            | 72  | 36.18|
| Location                      |     |      |
| Colon                         | 113 | 56.78|
| Sigmoid                       | 50  | 25.13|
| Ascending                     | 39  | 19.60|
| Transverse                    | 9   | 4.52 |
| Descending                    | 15  | 7.54 |
| Rectum                        | 86  | 43.22|

doi:10.1371/journal.pone.0110587.t003
The precise mechanisms that explain the relationship between visceral adiposity and CRC remain unclear. However, we suggest some possible mechanisms based on our results. First, visceral adipocyte-secreted proinflammatory cytokines and adipokines may induce a protumourigenic status. Chronic inflammation promotes carcinogenesis by several mechanisms, including the enhancement of cancer cell proliferation and angiogenesis [19]. Previous studies have shown that visceral adipocytes secrete higher levels of proinflammatory cytokines, including interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α) [20]. Increased levels of these cytokines induce a protumourigenic environment [21]. Altered adipokine secretion may also affect colorectal carcinogenesis. For example, adiponectin which exhibits anti-tumour characteristics through anti-inflammatory and proapoptotic actions [22] shows a negative correlation with visceral fat mass [23]. Furthermore, lower adiponectin levels have been reported in CRC patients [24,25]. Therefore, systemic chronic inflammation and altered metabolic function may serve as a link for the association between visceral obesity and CRC.

Insulin resistance is another factor that supports the association between visceral obesity and CRC. The correlation between visceral adipose tissue and insulin resistance is well established [26]. Lipolysis is more active in visceral adipose tissue than in subcutaneous adipose tissue, which results in the insulin resistance status being characterized as hyperinsulinemia [27]. Hyperinsulinemia is known to increase the risk of cancers, including CRC [28], and the prevalence of CRC is higher in Type II DM patients [29]. Insulin directly stimulates colorectal carcinogenesis by activating the anti-apoptotic and mitogenic cellular signalling pathways [22]. Furthermore, the role of insulin in regulating insulin-like growth factor (IGF) axis activity is also related with the tumourigenic effect of insulin. Chronic hyperinsulinemia inhibits the production of IGF-binding protein 1 (IGFBP-1) and IGFBP-2, which results in the increased bioavailability of IGF-1 [30]. IGF-1 acts as a procarcinogen by enhancing tumour cell proliferation and decreasing cell death [31]. These results collectively suggest that the increased insulin resistance induced by visceral adiposity may be associated with an increased risk of CRC.

**Figure 1.** Comparison of the prevalence of colorectal cancer according to visceral fat tertiles before propensity score matching (Figure 1-A). Comparison of the prevalence of colorectal cancer according to visceral fat tertiles after propensity score matching (Figure 1-B). P-value was derived using the Cochran-Armitage trend test. doi:10.1371/journal.pone.0110587.g001

The precise mechanisms that explain the relationship between visceral adiposity and CRC remain unclear. However, we suggest some possible mechanisms based on our results. First, visceral adipocyte-secreted proinflammatory cytokines and adipokines may induce a protumourigenic status. Chronic inflammation promotes carcinogenesis by several mechanisms, including the enhancement of cancer cell proliferation and angiogenesis [19]. Previous studies have shown that visceral adipocytes secrete higher levels of proinflammatory cytokines, including interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α) [20]. Increased levels of these cytokines induce a protumourigenic environment [21]. Altered adipokine secretion may also affect colorectal carcinogenesis. For example, adiponectin which exhibits anti-tumour characteristics through anti-inflammatory and proapoptotic actions [22] shows a negative correlation with visceral fat mass [23]. Furthermore, lower adiponectin levels have been reported in CRC patients [24,25]. Therefore, systemic chronic inflammation and altered metabolic function may serve as a link for the association between visceral obesity and CRC.

Insulin resistance is another factor that supports the association between visceral obesity and CRC. The correlation between visceral adipose tissue and insulin resistance is well established [26]. Lipolysis is more active in visceral adipose tissue than in subcutaneous adipose tissue, which results in the insulin resistance status being characterized as hyperinsulinemia [27]. Hyperinsulinemia is known to increase the risk of cancers, including CRC [28], and the prevalence of CRC is higher in Type II DM patients [29]. Insulin directly stimulates colorectal carcinogenesis by activating the anti-apoptotic and mitogenic cellular signalling pathways [22]. Furthermore, the role of insulin in regulating insulin-like growth factor (IGF) axis activity is also related with the tumourigenic effect of insulin. Chronic hyperinsulinemia inhibits the production of IGF-binding protein 1 (IGFBP-1) and IGFBP-2, which results in the increased bioavailability of IGF-1 [30]. IGF-1 acts as a procarcinogen by enhancing tumour cell proliferation and decreasing cell death [31]. These results collectively suggest that the increased insulin resistance induced by visceral adiposity may be associated with an increased risk of CRC.

**Table 4.** Odds ratios and 95% confidence intervals for the prevalence of colorectal cancer according to visceral fat area tertiles before propensity score matching.

| Visceral fat area tertiles, OR (95% CI) | Q1 (19.30–67.01) N = 271 | Q2 (67.10–96.26) N = 273 | Q3 (96.30–256.20) N = 271 |
|---------------------------------------|---------------------------|---------------------------|---------------------------|
| Colorectal cancer                     |                           |                           |                           |
| Model 1a                              | 1.00                      | 1.01 (0.71–1.40)          | 2.47 (1.72–3.55)          |
| Model 2b                              | 1.00                      | 0.82 (0.55–1.23)          | 1.80 (1.12–2.91)          |
| Colon cancer                          |                           |                           |                           |
| Model 1a                              | 1.00                      | 0.80 (0.54–1.19)          | 2.09 (1.39–3.13)          |
| Model 2b                              | 1.00                      | 0.66 (0.41–1.06)          | 1.46 (0.84–2.52)          |
| Rectal cancer                         |                           |                           |                           |
| Model 1a                              | 1.00                      | 1.34 (0.87–2.06)          | 3.13 (2.00–4.88)          |
| Model 2b                              | 1.00                      | 1.13 (0.68–1.88)          | 2.18 (1.22–3.91)          |
| Stage I, II                           |                           |                           |                           |
| Model 1a                              | 1.00                      | 0.88 (0.56–1.37)          | 2.58 (1.66–4.01)          |
| Model 2b                              | 1.00                      | 0.61 (0.37–1.04)          | 1.59 (0.89–2.83)          |
| Stage III, IV                         |                           |                           |                           |
| Model 1a                              | 1.00                      | 1.08 (0.74–1.59)          | 2.40 (1.60–3.59)          |
| Model 2b                              | 1.00                      | 1.04 (0.65–1.67)          | 1.85 (1.06–3.21)          |

doi:10.1371/journal.pone.0110587.t004
In addition, the direct effect of visceral adiposity on the development of CRC also should be considered. Recently, Huffman et al. demonstrated the effect of visceral fat on the development of intestinal tumours, independent of known metabolic mediators [32]. Surgical removal of the visceral fat mass significantly reduced the risk of intestinal cancer in female mice; however, it failed to increase the levels of adiponectin and reduce the level of glucose, leptin, chemokines, and total adiposity. This result suggests that visceral adiposity, at least in part, might directly affect carcinogenesis in the gastrointestinal (GI) tract, independent of insulin resistance or inflammatory adipocytokines. Further experimental studies are needed to elucidate the precise mechanism by which visceral adiposity affects the prevalence of CRC.

Our study demonstrated a significant relationship between visceral obesity and CRC in females in contrast to previous findings that showed relatively weak or no relationship between CRC and visceral obesity in female group [33–35]. However these studies have some limitations that most studies did not adjust the menopausal status and hormone replacement status that may affect the relationship between visceral obesity and CRC. For example Tobias et al [8], have reported a significant relationship between CRC risk and the waist-hip ratio only in postmenopausal women who had not used HRT compared to HRT users. Because our data were obtained from postmenopausal women without HRT, our results may reflect the association of visceral obesity and CRC after minimizing the countering beneficial effects of exogenous oestrogen replacement. Additionally, many previous studies have shown a significant association between the risk of CRC and body composition, including waist circumference and waist: hip ratio in males [8,36]. Therefore, although we only investigated the relationship between CRC and visceral obesity in females, it is possible that these significant relationships also exist in the male population. Large-scale prospective studies are required to examine the precise roles of gender in relation to cancer prevalence and visceral obesity.

Our study has several limitations. First, the cross-sectional design cannot establish a causal relationship between CRC and visceral fat area. Although our hypothesis suggested that visceral obesity might induce a higher risk of CRC, further prospective interventional studies are needed to elucidate this relationship. Second, we studied a small number of women who visited a single hospital. Therefore, our results do not allow for a generalization of the population at large. Third, we could not compare the levels of proinflammatory cytokines and adipokines that may act as important mediating factors because we used the data from the patients who visited the hospital for health check-up or for preoperative measurement. However, our results showed significantly higher WBC counts in the CRC group compared with the control group, which reflect the systemic inflammatory status of the CRC cells. Finally, due to the retrograde data collection method, clinically important variables, such as socio-economic status (including education and household income), could not be adjusted and may affect our results.

In conclusion, our results demonstrate that visceral adiposity is independently associated with the prevalence of CRC in Korean women. Although we could not determine causality, our results collectively suggest that visceral obesity, as well as total obesity, may be associated with the risk of CRC. Further interventional prospective studies with larger sample sizes are required to understand the causal relationship between visceral adiposity and the prevalence of CRC, as well as to determine the benefits of controlling visceral obesity for reducing CRC risk.

### Table 5. Odds ratios and 95% confidence intervals for the prevalence of colorectal cancer according to visceral fat area tertiles after propensity score matching.

| Visceral fat area tertiles, OR (95% CI) | Model Q1 (19.30–67.98) N = 132 | Q2 (68.00–93.23) N = 133 | Q3 (93.30–246.60) N = 133 |
| --- | --- | --- | --- |
| Colorectal cancer | Model 1a | 1.00 | 1.86 (1.10–3.13) | 3.47 (2.01–5.98) |
|  | Model 2b | 1.00 | 1.60 (0.81–3.14) | 2.96 (1.38–6.33) |
| Colon cancer | Model 1a | 1.00 | 1.43 (0.74–2.74) | 3.58 (1.71–7.50) |
|  | Model 2b | 1.00 | 1.09 (0.45–2.60) | 3.47 (1.24–9.68) |
| Rectal cancer | Model 1a | 1.00 | 2.90 (1.19–7.11) | 3.76 (1.60–8.83) |
|  | Model 2b | 1.00 | 3.54 (0.97–12.91) | 4.15 (1.05–16.34) |
| Stage I, II | Model 1a | 1.00 | 1.34 (0.40–4.41) | 2.70 (0.62–11.63) |
|  | Model 2b | 1.00 | 2.82 (1.19–6.67) | 3.64 (1.41–9.39) |
| Stage III, IV | Model 1a | 1.00 | 1.40 (0.71–2.74) | 3.32 (1.70–6.48) |
|  | Model 2b | 1.00 | 1.93 (0.77–4.89) | 3.80 (1.39–10.40) |

OR: odds ratio; CI: confidence interval.

|  |  |  |  |
| --- | --- | --- | --- |

aunadjusted.

1Adjusted for subcutaneous fat area, mean blood pressure, fasting glucose, total cholesterol, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) and white blood cell (WBC) counts.

OR (95% CI) were derived using conditional logistic regression test.

doi:10.1371/journal.pone.0110587.t005

Visceral Fat and Colorectal Cancer

PLOS ONE | www.plosone.org 6 November 2014 | Volume 9 | Issue 11 | e110587
Acknowledgments

We greatly appreciate the efforts of the participants and hospital staff during this study.

References

1. Feinleib M (1985) Epidemiology of obesity in relation to health hazards. Annals of Internal Medicine 103: 1019–1024.
2. Mann GV (1974) The influence of obesity on health (first of two parts). The New England journal of medicine 291: 178.
3. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. The Lancet 371: 569–578.
4. Marmot M, Atinmo T, Byers T, Chen J, Hirohata T, et al. (2007) Food, nutrition, physical activity, and the prevention of cancer: a global perspective.
5. Ibrahim MM (2010) Subcutaneous and visceral adipose tissue: structural and functional differences. Obesity reviews 11: 11–18.
6. Després JP, Lemieux I (2006) Abdominal obesity and metabolic syndrome. Nature 444: 881–887.
7. Schoen RE, Tangen CM, Kuller LH, Burke GL, Cushman M, et al. (1999) Increased blood glucose and insulin, body size, and incident colorectal cancer. Journal of the National Cancer Institute 91: 1147–1154.
8. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, et al. (2006) Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). Journal of the National Cancer Institute 98: 920–930.
9. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, et al. (1995) Physical activity, obesity, and risk for colon cancer and adenoma in men. Annals of internal medicine 122: 327–334.
10. Donohoe CL, Doyle SL, Reynolds JV (2011) Visceral adiposity, insulin resistance and cancer risk. Diabet Med 3: 12.
11. Oh TH, Byeon JS, Myung SJ, Yang SK, Choi KS, et al. (2008) Visceral obesity as a risk factor for colorectal neoplasm. Journal of gastroenterology and hepatology 23: 411–417.
12. Yamamoto S, Nakagawa T, Matsuhiya Y, Kusano S, Hayashi T, et al. (2010) Visceral fat area and markers of insulin resistance in relation to colorectal neoplasia. Diabetes Care 33: 104–109.
13. Eraslan E, Turkay C, Koktener A, Koca C, Uz B, et al. (2009) Association of visceral fat accumulation and adiponectin levels with colorectal neoplasia. Digestive diseases and sciences 54: 862–868.
14. Lee JW, Lee HR, Shim JY, Im JA, Kim SH, et al. (2007) Viscerally obese women with normal body weight have greater brachial-ankle pulse wave velocity than nonviscerally obese women with excess body weight. Clinical endocrinology 66: 572–578.
15. O’Connell JB, Maggard MA, Ko CY (2004) Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. Journal of the National Cancer Institute 96: 1420–1425.
16. d’Agostino RB (1980) Tutorial in biostatistics: propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 17: 2265–2281.
17. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. New England Journal of Medicine 348: 1625–1638.
18. Tsujinaka S, Korinsh F, Kawamura YJ, Saito M, Tajima N, et al. (2008) Visceral obesity predicts surgical outcomes after laparoscopic colectomy for sigmoid colon cancer. Diseases of the colon & rectum 51: 1757–1767.
19. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A (2009) Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis 30: 1073–1081.
20. Dussere E, Moulin P, Vidal H (2000) Differences in mRNA expression of the proteins secreted by the adipocytes in human subcutaneous and visceral adipose tissues. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 1500: 88–96.
21. Harvey AE, Lashinger LM, Hursting SD (2011) The growing challenge of obesity and cancer: an inflammatory issue. Annals of the New York Academy of Sciences 1229: 45–52.
22. Roberts DI, Deve C, Renshan AG (2010) Biological mechanisms linking obesity and cancer risk: new perspectives. Annual review of medicine 61: 301–316.
23. Kadawaki T, Yamauchi T (2005) Adiponectin and adiponectin receptors. Endocrine reviews 26: 439–451.
24. An W, Bai Y, Deng S-X, Gao J, Ben Q-W, et al. (2012) Adiponectin levels in patients with colorectal cancer and adenoma: a meta-analysis. European Journal of Cancer Prevention 21: 126–133.
25. Sugiyama M, Takahashi H, Hosono K, Endo H, Kato S, et al. (2009) Adiponectin inhibits colorectal cancer cell growth through the AMPK/mTOR pathway. International journal of oncology 34: 339.
26. Hardy OT, Czech MP, Conover S (2012) What causes the insulin resistance underlying obesity? Current Opinion in Endocrinology, Diabetes and Obesity 19: 81–87.
27. Wajchenberg BL (2000) Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocrine reviews 21: 697–738.
28. Colangelo LA, Gasparr SM, Gann PH, Dyer AR, Liu K (2002) Colorectal cancer mortality and factors related to the insulin resistance syndrome. Cancer Epidemiology Biomarkers & Prevention 11: 385–391.
29. Yang YX, Hennessey S, Lewis JD (2004) Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. GASTROENTEROLOGY-BALTIMORE THEN PHILADELPHIA-127: 1044–1050.
30. Blum WF, Schweizer R (2004) Insulin-like growth factors and their binding proteins.
31. Pollak M (2008) Insulin and insulin-like growth factor signalling in neoplasia. Nature Reviews Cancer 8: 913–920.
32. Huffman DM, Augenlicht LH, Zhang X, Lofrese JJ, Atzmon G, et al. (2013) Abdominal Obesity, Independent from Caloric Intake, Accounts for the Incidence of Cancer. Carcinogenesis 34: 872–880.
33. Hou L, Ji B-T, Blair A, Dai Q, Gao Y-T, et al. (2006) Obesity and colorectal cancer risk in Chinese people: menopause as an effect modifier. European Journal of Cancer Prevention Research 6: 177–187.
34. Terry P, Miller A, Rohan T (2002) Obesity and colorectal cancer risk in women. Gut 51: 191–194.
35. Shimizu N, Nagata C, Shimizu H, Kametani M, Takeyama N, et al. (2003) Height, weight, and alcohol consumption in relation to the risk of colorectal cancer in Japan: a prospective study. British journal of cancer 88: 1039–1043.
36. Larson SG, Wolk A (2007) Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. The American journal of clinical nutrition 86: 536–565.

Author Contributions

Conceived and designed the experiments: JYL NKK JWL DCL. Performed the experiments: JYL JWL. Analyzed the data: JYL HSL JWL. Contributed reagents/materials/analysis tools: NKK JWL HSL JYL. Wrote the manuscript: JYL JWL SHC JYJ DCL.