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Associations among Pericolonic Fat, Visceral Fat, and Colorectal Polyps on CT Colonography

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Abstract

OBJECTIVE—To determine the association between pericolonic fat and colorectal polyps using CT colonography (CTC).

METHODS—1169 patients who underwent CTC and same day optical colonoscopy were assessed. Pericolonic fat was measured on CTC in a band surrounding the colon. Visceral adipose tissue volume was measured at the L2-L3 levels. Student t-tests, odds ratio, logistic regression, binomial statistics and weighted-kappa were performed to ascertain associations with the incidence of colorectal polyps.

RESULTS—Pericolonic fat volume fractions (PFVF) were 61.5±11.0% versus 58.1±11.5%, 61.6 ±11.1% versus 58.7±11.5%, and 62.4±10.6% versus 58.8±11.5% for patients with and without any polyps, adenomatous polyps, and hyperplastic polyps, respectively ($p<0.0001$). Similar trends were observed when examining visceral fat volume fractions (VFVF). When patients were ordered by quintiles of PFVF or VFVF, there were 2.49, 2.19 and 2.39-fold increases in odds ratio for the presence of any polyp, adenomatous polyps, or hyperplastic polyps from the first to the fifth quintile for PFVF, and 1.92, 2.00 and 1.71-fold increases in odds ratio for VFVF. Polyps tended to occur more commonly in parts of the colon that had more PFVF than the spatially-adjusted average for patients in the highest quintile of VFVF.

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CONCLUSION—Pericolonic fat accumulations, like visceral fat, are correlated with an increased risk of adenomatous and hyperplastic polyps.

Keywords

CT, colon; CT, virtual imaging; pericolonic fat measurement, visceral fat measurement; colonic polyps

INTRODUCTION

Colorectal cancer (CRC), the third most prevalent cancer in the United States, is highly preventable by the removal of precancerous polyps [1]. There are a number of different risk factors for CRC, including age greater than 50 years, personal history of inflammatory bowel disease or colorectal polyps or cancers, family history of colorectal polyps or cancers and certain inherited syndromes [2].

One potential risk factor, accumulations of adipose tissue, has been the subject of prior research. The comorbidity of cancer and obesity sparked this focus, with traditional anthropometric measures of obesity, such as body mass index and waist circumference positively correlating with an increased risk of colon adenomas [3]. Moreover, the routine use of computed tomography allows one to focus on fatty accumulations in specific regions of the body. Patients with high visceral adipose tissue content as measured between the L2-L3 region of the body in CTC images, for instance, have a greater association with the presence of both adenomatous and hyperplastic polyps [4].

A question that emerges when considering these results is whether fatty accumulations themselves are inducing polyp formation either due to contact or by local cell-to-cell interactions. The theory is not without precedence. Visceral adipose tissue is more metabolically active than subcutaneous fat and produces adipokines and other cytokines that can lead to proinflammatory, procoagulant, and insulin resistant states which could be conducive to tumorigenesis in the local environment [5]. Upregulation of nuclear factor-κB from adipose tissue, for example, leads to an increase in nitric oxide that may lead to an increase in reactive oxygen species in the environment [5]. Moreover, adipose tissue surrounding organ tissues may generate a hypoxic environment, altering pathways involved in angiogenesis, cell proliferation, and apoptosis, which, in turn, could make the organ tissue more favorable for tumor invasion, metastasis, and survival [5].

Supporting evidence for this might be inferred from a stronger association between pericolonic fat and the presence of polyps than the previously studied association between all visceral fat within the internal body contour and polyp formation. This would be more suggestive of paracrine mechanisms involved in polyposis. In this study, we explore this possibility by measuring the pericolonic fat in our cohort as well as the visceral fat and examine how this data correlates with the presence or absence of polyps in the colons of the patients.

METHODS

Patient Population

The population of 1233 asymptomatic adults retrospectively examined in this study with permission from our institution's Office of Human Subjects Research was derived from an Institutional Review Board-approved project published elsewhere [6]. The patients underwent CT colonography and optical colonoscopy on the same day. The ages of the adults varied between 40 to 79 years, and 97.4% of the patients were of average risk of colorectal cancer based on family histories. The population had been previously evaluated to determine the relationships amongst the incidence of adenomatous and hyperplastic polyps and quantification of visceral adiposity and body mass index [7]. Forty-seven patients were excluded because of incomplete optical colonoscopy, inadequate prepararation or failure of the CTC system. Of the remaining 1186 patients, an additional 17 were excluded due to incomplete spine segmentation during the analysis of the CT images. Characteristics of the remaining 1169 patients are tabulated in Table 1.

Bowel Preparation

Patients underwent a 24-hour colonic preparation that consisted of oral administration of 90 ml sodium phosphate (Fleet 1 preparation, Fleet Pharmaceuticals), 10 mg bisacodyl, 500 ml of barium sulphate (2.1% by weight; Scan C, Lafayette Pharmaceuticals) and 120 ml of diatrizoate meglumine and diatrizoate sodium (Gastrografin, Bracco Diagnostics) given in divided doses.

CTC Scanning

The colon was distended with patient-controlled insufflation of room air. CT scanning occurred during one breathhold in each of the prone and supine positions using a four-or eight-channel CT scanner (General Electric LightSpeed or LightSpeed Ultra). CT scanning parameters included 1.25 – 2.5 mm section collimation, 15 mm per second table speed, 1 mm reconstruction interval, 100 mAs and 120 kVp.

Optical Colonoscopy

Patients underwent same-day optical colonoscopy by one of 17 colonoscopists. The colonoscopies were performed using segmental unblinding, wherein CTC results were revealed to the colonoscopists during the examination to create an enhanced reference standard. Polyp sizes were determined at optical colonoscopy using a calibrated guidewire. The polyp findings at optical colonoscopy after segmental unblinding served as the reference standard for polyps in this study.

Visceral fat measurement

Fully-automated visceral adipose tissue measurement software was used to measure each image in the L2-L3 region (65 ± 9 slices) on supine CTC scans [4]. Total volumes for this region were computed by summing the volumes computed in each image in the region. A corresponding visceral fat volume fraction (VFVF), or the fraction of fat voxels divided by

the voxels comprising the internal body volume, was evaluated. Validation of this protocol, involving automated measurements of adipose tissue, was performed in a previous study [4].

Pericolonic Fat Measurement

The entire colon was segmented by a level set algorithm [8]. The colon in the L2-L3 region was dilated by 9 voxels (approximately 6 mm). The dilated region, a volumetric "stripe" surrounding the colon, was defined as the pericolonic region. The pericolonic fat volume fraction (PFVF) was calculated by dividing the number of fat voxels within the pericolonic region by the total number of voxels in this region. Figure 1 illustrates the fully-automated method to measure the visceral and pericolonic adipose tissue.

Local pericolonic fat distribution along the entire colon was also measured. The colon centerline from rectum to cecum was extracted from the segmented colon [9]. For each point on the centerline, the "stripe" of soft tissue surrounding the colon in a plane orthogonal to the centerline was determined and defined as the pericolonic region. PFVF was reported approximately every 5 mm along the colon to finer detail than colonic segments would provide. Supplementary Figure 1 illustrates the pericolonic fat of an entire colon. 486 of 1169 patients had at least one polyp. In total, 971 polyps were confirmed by optical colonoscopy. 253 of 971 polyps had been identified on CTC and had coordinates at CTC as polyps smaller than 6 mm are generally not recorded at CTC. 44 polyps did not have centerline location information due to colon collapse. Among the remaining 209 polyps, 143 are adenomas and 66 are hyperplastics.

Statistical Analysis

The presence or absence of adenomatous or hyperplastic polyps was confirmed by segmental-unblinded optical colonoscopy. The PFVF and VFVF means, standard deviations and p-values (Student's unpaired t-test, using Microsoft Excel 2010) were calculated to compare patients with and without any polyps of any type, patients with and without adenomatous polyps, and for those with and without hyperplastic polyps. The correlation between PFVF and VFVF was calculated using the Pearson product-moment correlation (Microsoft Excel 2010).

The patient set, separated by sex, was divided into quintiles of VFVF and PFVF data. The male and female quintiles were then recombined. Odds ratios (OR) for the presence or absence of at least one polyp of any type were calculated using Matlab for each quintile by dividing the odds per quintile by the odds retrieved from the lowest quintile population. Similarly, ORs were calculated for the presence/absence of at least one adenomatous polyp and hyperplastic polyp.

To gauge the predictive value of pericolonic compared to visceral fat when incorporated into a probabilistic model that includes sex and age, several multiple logistic regression analyses (http://statpages.org/logistic.html) were performed. With the presence/absence of at least one polyp of any type, at least one adenomatous polyp, and at least one hyperplastic polyp serving as the dichotomous dependent variables, one set of analyses was performed with age, sex (coded as male=1 and female=0), and PFVF (0-100%) serving as independent variables. A second set was performed with age, sex, and VFVF (0-100%), and a third set

was performed with age, sex, PFVF, and VFVF. The estimated odds ratios, adjusted for the other variables in each analysis, indicate the amount by which the odds change when the value of the predictor is increased by one unit.

One-tailed binomial statistics [10] were performed to ascertain whether those colon locations harboring polyps had higher PFVF compared to the average PFVF at the same colon location in different patient populations. Each colon was normalized to 0 (rectum) to 1 (cecum) based on its length. Polyp locations were defined as their normalized distance to rectum [11]. PFVF at the polyp location was compared to the average PFVF computed from patients in the highest quintile of VFVF for the patients who had at least one polyp, at least one adenoma or at least one hyperplastic polyp.

P-values less than .05 were considered statistically significant.

Quadratic-weighted kappa statistics [12] were used to assess the agreement of VFVF and PFVF measurements. Kappa values between 0.61 and 0.80 [13] were considered as good agreement.

RESULTS

Visceral and pericolonic fat measurements were successfully calculated from the 1169 patients (Table 1). PFVF and VFVF are highly correlated with each other (Figure 2) (Pearson product-moment correlation coefficient: 0.941). The average PFVF and VFVF for patients with any polyps was, respectively, 3.4% and 3.3% higher than for patients without any polyps ($p < .0001$). The same trend was found when patients were divided into groups with/without adenomatous polyps (PFVF and VFVF: 2.9% difference) and with/without hyperplastic polyps (PFVF: 3.6% difference; VFVF: 3.4% difference).

The odds and ORs per quintile (organized by PFVF and VFVF), and probabilities for having at least one polyp of any type, at least one adenomatous polyp, or at least one hyperplastic polyp are reported in Tables 2 and 3. Notably, a 2.49-fold increase in OR is observed between the first quintile of PFVF values to the fifth quintile with respect to the presence/absence of any polyp, reflected as a 22% increase in probability, whereas only a 1.92-fold increase is observed when examining the first and fifth quintiles of patients sorted by VFVF, indicating an increase in probability of 15%. For both PFVF and VFVF quintiles, higher quintiles had statistically significant increases in OR values.

For PFVF, there was a 2.19-fold increase in ORs between the highest and lowest quintiles when testing for the presence/absence of adenomatous polyps, and a 2.39-fold increase between the quintiles when testing for hyperplastic polyps. For VFVF, there was a 2-fold increase in OR between the lowest to highest quintile for adenomatous polyps, and a 1.71 fold increase for hyperplastic polyps.

Multiregression analyses showed that all factors considered in the regression models were statistically significant predictors for the presence/absence of polyps ($p<0.05$). OR's for changes in age, gender, PFVF, and VFVF adjusted for other variables, calculated as the difference in odds (for presence/absence of polyps, adenomatous polyps, and hyperplastic

polyps) when increasing a single variable by one user-defined increment, are tabulated in Table 4. Note that the incremental changes recorded for age is a year, for gender is a transition from female to male, and for PFVF and VFVF values is a change of 1%. As such, only PFVF and VFVF factors are directly comparable. When adjusting only for age and gender, PFVF odds changed by a factor of 1.022 for presence/absence of polyps, 1.017 for presence/absence of adenomatous polyps, and 1.026 for presence/absence of hyperplastic polyps; VFVF odds changed by a factor of 1.019, 1.015, and 1.022.

The logistic regression model incorporating all factors (treating PFVF and VFVF as separate contributors) demonstrates that the VFVF value as a predictive variable is diluted when compared against PFVF. PFVF ORs were 1.02(any polyp),1.01 (adenomatous), and 1.02 (hyperplastic) adjusted for all other variables, similar to values reported in the 3 variable regression model, whereas VFVF ORs were 1.00,1.00,and 1.01. Given that a dramatic change in the coefficient of regression is reported for VFVF when adding the PFVF predictive variable to the model for presence/absence of polyps (0.0218 to 0.0020) an issue with collinearity of variables is also suspected, which complicates comparisons between the relative contributions of PFVF and VFVF in the four variable model.

The concordance of PFVF and VFVF per quintile is reported in Table 5. 572 of 1169 patients were highly concordant (in the same quintile of PFVF and VFVF). 963 of 1169 patients were concordant within ±1 quintile of PFVF and VFVF. None of the patients were extremely discordant (first quintile of one variable and fifth quintile of the other). Quadratic-weighted kappa and its 95% confidence interval for patients with polyps were 0.73 and [0.70, 0.77]. Quadratic-weighted kappa and its 95% confidence interval for all patients were 0.76 and [0.75, 0.77]. Concordant and discordant examples are shown in Figure 3.

The correlation of local pericolonic fat distribution of entire colon on patient populations and corresponding polyps are illustrated in supplementary Figures 2-4. The degree of PFVF from rectum to cecum is shown as a function of normalized distance along the colon. Supplementary Figures 2-4 illustrate the results from three patient populations which have top 20% visceral fat volume fraction and at least one polyp (supplementary Figure 2), at least one adenoma (supplementary Figure 3), and at least one hyperplastic (supplementary Figure 4). For a particular colon location, more polyps (122 of 209, $p = 0.009$) reported higher PFVF than the mean PFVF of the patient population at that location. The same trend was found for adenomas (82 of 143, $p = 0.047$) and hyperplastics (39 of 66, $p = 0.088$).

For each polyp, the percentage of PFVF of the entire colon less than the PFVF nearby the polyp is shown in supplementary Figure 5. Polyps tended to occur at the sites having greater PFVF in a particular colon ($p=0.019$).

DISCUSSION

We found that increasing accumulation of pericolonic fat was associated with an increasing risk of adenomatous and hyperplastic polyps. The highest quintile of patients segregated by PFVF had a 74%, 76%, 100% greater probability of having a polyp, adenomatous polyp, or hyperplastic polyp. Polyps also tended to occur more commonly in parts of the colon that

had more PFVF in a particular patient's colon and when compared to the spatially-adjusted average for patients in the highest quintile of VFVF.

The assessment of PFVF addresses the core question of the study, the predictive value of pericolonic fat deposits compared to the previously established value of visceral fat [4]. Unlike the PFVF measurements, visceral fat assessments are not colon location specific. Without colon location specific information, the collinearity between the two variables is an important issue. PFVF and VFVF are already highly correlated with each other. This is logical, as pericolonic fat accounts for a subset of adipose tissue voxels included within the L2-L3 internal body volume used to calculate visceral fat. Multiple regression performed with age and gender and one of the fat metrics (PVFV or VFVF) demonstrated that both had statistically significant odds ratios from 1.01-1.03 for a 1% increase in pericolonic fat and visceral fat content. PFVF odds ratios were higher than those of the VFVF variable for the presence/absence of any polyps, adenomatous polyps, and hyperplastic polyps, suggesting that pericolonic fat might serve as a marginally more significant risk factor than visceral accumulations in non-location specific assessments.

One surprising finding was the increased odds associated with the presence and absence of hyperplastic polyps when focusing on pericolonic fat. Hyperplastic polyps, generally distinguished as largely asymptomatic polyps with papillary infoldings giving a sawtooth or serrated appearance to the polyp surface, were traditionally believed to have no malignant potential and were characterized by a small increase in proliferative processes resulting in a hyperplasia [14]. By definition, these polyps are not expected to form adenocarcinomas. However, studies have been performed more recently that have contested the traditional assumption that hyperplastic polyps are harmless. In fact, the adenoma to adenocarcinoma conversion may account for only 70-80% of colorectal cancer cases [15]. An increased risk of colorectal cancer from hyperplastic polyps might arise through a serrated polyp pathway. The serrated polyp pathway, which begins with the transformation of hyperplastic polyps to atypical variants (sessile serrated adenomas), might result in serrated carcinomas [16]. One study of a small cohort of patients at the University of Vermont presenting with hyperplastic polyps concluded with the assertion that hyperplastic polyps still carry significant risk associated with colorectal cancer, again suggesting that a subset of the polyps may follow the serrated polyp pathway [17]. Extending the disparate serrated polyposis to this study might be an approach to better understand whether certain variants of colonic hyperplasia might account for an increased risk in cancer. For this study, however, we have not found any evidence in the literature supporting a mechanistic connection between the serrated polyp pathway and accumulations of adipose tissue, leaving us with an unanswered question.

As to the question of whether local (paracrine and contact-based) or systemic (endocrine) influences are to be implicated in the increased presence of neoplastic polyposis, namely adenomas, there is ample evidence in the literature to support both pathways if not a combination of the two. Adipose tissue has only recently received attention as a possible causative agent in the pathogenesis of cancers, largely due to the outdated view of the adipose cells as inert storage cells; however, they have now been recharacterized as highly metabolically active, with endocrine functions that could easily account for influences on

cancer formation [18]. Dysfunction of adipocytes is thought to release proinflammatory and potentially mitogenic factors that may lead to cancer [19]. The key question becomes whether the local release of these factors in a paracrine, vasculature-independent manner or the influences of a dysfunctional systemic state, such as metabolic syndrome, contribute significantly to the formation of neoplasms in the colon. Arguments in favor of the systemic effects of fat tissue include the notion that visceral adipose tissue accumulations may result in insulin resistance and hyperinsulinemia [20] or could lead to a global decrease in adiponectin levels associated with the development of colorectal adenomas [21].

The two major adipocyte-derived paracrine pathways involve extracellular matrix signaling and hypoxia-induced signaling, both of which are associated with insulin signaling, nuclear κ-light-chain-enhancer of activated B cells, and tissue growth factor β, among other cytokines, proinflammatory, and proangiogenic processes [19]. Additionally, dysfunctional adipose tissue may recruit adipose tissue macrophages associated with cancer cell function [22]. Lastly, direct contact of fat to tissue may serve as an energy buffer for malignant cells, nourishing their increased metabolic demand in the colon [19].

Unfortunately, the possible local effects of fat on the colon have not been thoroughly evaluated. Pericolonic fat, itself, has not appeared frequently in the literature as a factor contributing to *de novo* tumor or polyp formation. In the established clinical setting, inflammation of these fatty accumulations has been used to diagnose diverticulitis, among other disorders associated with abdominal pain [23]. In the context of cancer, abnormal fat distributions have been studied as a possible means of predicting extramuscular tumor infiltration, where a 91% positive predictive value was reported when examining histopathological findings in 63 colorectal carcinomas [24]. However, the authors of the study only highlight the potential use of pericolonic fat to provide a means of diagnosis or staging. By focusing on polyps, including those with potential for malignancy, we hope to expand the utility of pericolonic fat analysis to include prediction and prevention of carcinogenesis.

This study has several limitations. The patients were scanned at a single point in time. No information was available about chronicity of visceral adiposity. Therefore, variations in amount and distribution of adipose tissue over time, which would likely influence any paracrine effect, could not be evaluated. Pericolonic fat measurements have not been explicited validated. However, measurement of fat on abdominal CT scans is a standard procedure. Nevertheless, there could be partial volume effect related artifacts at the interface between the colon wall and the fat or dependency on colonic distension or configuration that affect the accuracy or reproducibility of PFVF measurements. Such artifacts or dependencies would not be expected to differ between patients with and without polyps, unless the polyps were very large, which was not the case in this study. We do not have information on the patients that would have permitted subgroup analyses by metabolic phenotype. We were not able to distinguish mesenteric from omental fat, which might shed light on the paracrine mechanism. On CT scans, there is no clear delineation between the mesenteric and omental fat although it may be possible in the future to estimate the contributions of each based on the locations of the tenia coli [25] and marginal artery [26].

As a final point of discussion, we note that the study was restricted to the examination of the L2-L3 levels of the colon for the comparison of PFVF and VFVF, a choice supported in the literature for the analysis of visceral adipose tissue [27]. Our choice to focus on this region for the analysis of pericolonic fat may be an important limitation of the study. The L2-L3 level will not consistently capture the same regions of the colon from patient to patient, and does not inform us about how polyp incidence and location might be associated with fat distributions along the colon.

In summary, pericolonic fat does appear to be correlated with increased risk of polyposis for both hyperplastic and adenomatous polyps. Even accounting for the collinearity of the variables of pericolonic fat volume fractions and visceral fat volume fractions, pericolonic fat appears to hold a slightly greater value as a predictor when adjusted against age and gender, a fact that might prove useful when weighed against advances in automated CT analyses. Measurements spatially localized to the colon indicated that polyps, particularly adenomas, tended to occur more frequently in colon areas with greater pericolonic fat than the average. What remains to be seen is if a mechanistic link between this increased correlation and local effects of adipose tissue on the colon can be identified to address the possibility that adipose tissue itself can have a spatially localized carcinogenic influence on the colon.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known about this subject?

1. Visceral fat is known to be associated with an increased risk of developing colonic polyps.
2. Visceral fat is thought to release humoral factors that might accelerate the growth of colonic polyps.

What does this study add?

1. This study shows that pericolonic fat deposits are associated with an increased risk of developing colonic polyps.
2. Both hyperplastic and adenomatous polyps were more likely to occur in patients having increased pericolonic fat.
3. Polyps tend to occur at colon locations having greater pericolonic fat than either the patient-specific average percentile or the location-adjusted average in patients in the highest quintile of visceral fat.

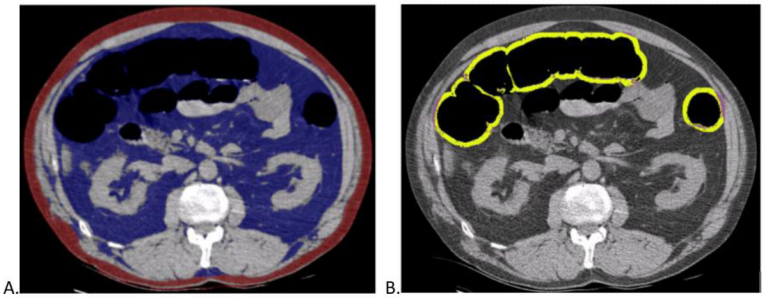

Fig. 1.

Illustration of fully-automated method to measure adipose tissue of a 66-year-old man. (A) Segmented subcutaneous (red) and visceral (dark blue) adipose tissue. (B) Segmented pericolonic adipose tissue (yellow) and soft tissue (purple).

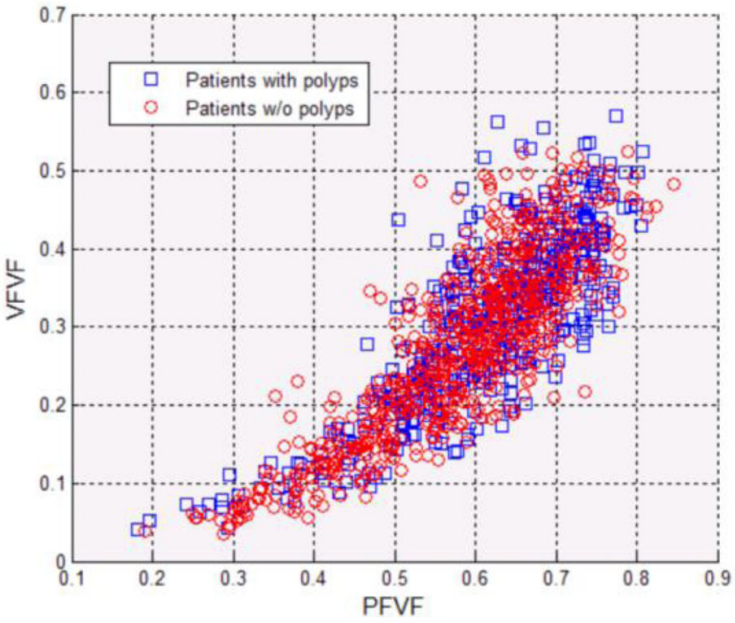

Fig. 2.
Scatterplot of PFVF and VFVF.

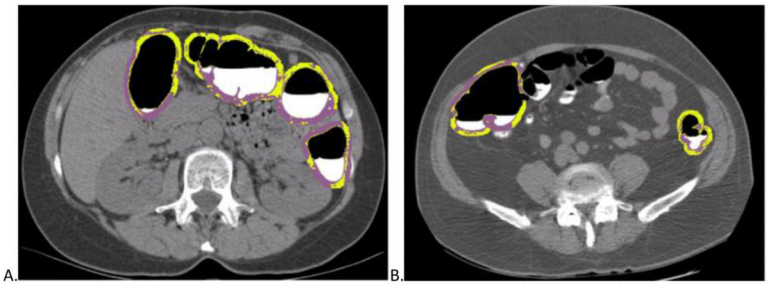

Fig. 3.

Illustration of concordant (A) and discordant (B) PFVF and VFVF measurements. (A) Both PFVF and VFVF are in 1st quintile. This patient does not have any polyps. (B) PFVF and VFVF are in 2nd and 5th quintile, respectively. This patient had 1 polyp. (Yellow: segmented pericolonic adipose tissue. Purple: non-adipose soft tissue).

Table 1

Patient characteristics, visceral fat volume fraction and pericolonic fat volume fraction

	Any Polyp	**Adenomatous**	**Hyperplastic**
Number (n=1169)	486/683	335/834	240/929
Male (n=686)	314/372	221/465	161/525
Age (mean ±s.d) p	58.8±7.1/57.1±7.3 <0.0001	59.2±7.0/57.2±7.3 0.002	58.5±7.1/57.6±7.3 0.043
PFVF (mean±s.d.) p	0.615±0.110/0.581±0.115 <0.001	0.616±0.111/0.587±0.115 <0.001	0.624±0.106/0.588±0.115 <0.001
VFVF (mean ±s.d) p	0.309±0.109/0.276±0.113 <0.001	0.311±0.108/0.282 ±0.113 <0.001	0.317±0.108/0.283±0.112 <0.001

Data are for groups with/without indicated polyp type.

Table 2

Odds ratios for having one or more polyps for different groupings of patients by PFVF.

Any polyps					
Quintiles	**Odds**	**Probability**	**OR**	**P**	**95% CI of OR**
1	**0.45**	**0.31**	**1.00**	-	-
2	**0.63**	**0.39**	**1.39**	**0.05**	**[0.95 2.03]**
3	**0.70**	**0.41**	**1.55**	**0.01**	**[1.06 2.27]**
4	**0.78**	**0.44**	**1.72**	**0.00**	**[1.18 2.51]**
5	**1.13**	**0.53**	**2.49**	**0.00**	**[1.70 3.63]**
Adenomatous polyps					
Quintiles	Odds	Probability	OR	P	95% CI of OR
1	**0.27**	**0.21**	**1.00**	-	-
2	**0.36**	**0.26**	**1.34**	**0.09**	**[0.87 2.06]**
3	**0.44**	**0.31**	**1.67**	**0.01**	**[1.10 2.54]**
4	**0.40**	**0.29**	**1.52**	**0.03**	**[1.00 2.33]**
5	**0.58**	**0.37**	**2.19**	**0.00**	**[1.45 3.31]**
Hyperplastic polyps					
Quintiles	Odds	Probability	OR	P	95% CI of OR
1	**0.16**	**0.14**	**1.00**	-	-
2	**0.22**	**0.18**	**1.34**	**0.13**	**[0.82 2.20]**
3	**0.23**	**0.19**	**1.40**	**0.09**	**[0.86 2.30]**
4	**0.31**	**0.24**	**1.88**	**0.01**	**[1.17 3.03]**
5	**0.39**	**0.28**	**2.39**	**0.00**	**[1.50 3.81]**

Subjects were divided into quintiles (separated by gender then recombined) based on the value of PFVF. For each quintile, odds, probability (fraction of patients in the quintile having one or more polyps of a given type), odds ratio (OR), P value and 95% confidence interval (CI) of odds ratio are shown for presence of at least one polyp (adenomatous or hyperplastic), adenomatous polyp, or hyperplastic polyp.

Table 3

Odds ratios for having one or more polyps for different groupings of patients by VFVF

Any polyps					
Quintiles	**Odds**	**Probability**	**OR**	**P**	**95% CI of OR**
1	**0.46**	**0.32**	**1.00**	-	-
2	**0.68**	**0.40**	**1.46**	**0.03**	**[1.00 2.14]**
3	**0.72**	**0.42**	**1.55**	**0.01**	**[1.06 2.26]**
4	**0.89**	**0.47**	**1.93**	**0.00**	**[1.33 2.82]**
5	**0.89**	**0.47**	**1.92**	**0.00**	**[1.32 2.80]**
Adenomatous polyps					
Quintiles	Odds	Probability	OR	P	95% CI of OR
1	**0.24**	**0.20**	**1.00**	-	-
2	**0.40**	**0.29**	**1.65**	**0.01**	**[1.07 2.53]**
3	**0.42**	**0.30**	**1.73**	**0.01**	**[1.13 2.66]**
4	**0.47**	**0.32**	**1.94**	**0.00**	**[1.27 2.96]**
5	**0.49**	**0.33**	**2.00**	**0.00**	**[1.31 3.06]**
Hyperplastic polyps					
Quintiles	Odds	Probability	OR	P	95% CI of OR
1	**0.19**	**0.16**	**1.00**	-	-
2	**0.19**	**0.16**	**1.04**	**0.44**	**[0.63 1.70]**
3	**0.26**	**0.21**	**1.40**	**0.08**	**[0.88 2.25]**
4	**0.34**	**0.25**	**1.81**	**0.01**	**[1.14 2.86]**
5	**0.32**	**0.24**	**1.71**	**0.01**	**[1.08 2.72]**

Subjects were divided into quintiles (separated by gender then recombined) based on the value of VFVF. For each quintile, odds, probability (fraction of patients in the quintile having one or more polyps of a given type), odds ratio (OR), P value and 95% confidence interval (CI) of odds ratio are shown for presence of at least one polyp (adenomatous or hyperplastic), adenomatous polyp, or hyperplastic polyp.

Table 4

Odds ratios for coefficients of multiple logistic regression

	Any Polyps	Adenomatous Polyps	Hyperplastic Polyps	Any Polyps	Adenomatous Polyps	Hyperplastic Polyps	Any Polyps	Adenomatous Polyps	Hyperplastic Polyps
Age	1.03 [1.01-1.05] p< 0.001	1.04 [1.02-1.06] p< 0.001	1.01 [1.00-1.03] p=0.145	1.03 [1.01-1.05] p< 0.001	1.03 [1.02-1.05] p< 0.001	1.01 [0.99-1.03] p=0.272	1.03 [1.01-1.05] p< 0.001	1.04 [1.02-1.06] p< 0.001	1.01 [0.99-1.03] p=0.186
Gender	1.31 [1.02-1.70] p=0.037	1.38 [1.04-1.83] p=0.025	1.30 [0.95-1.79] p=0.103	1.34 [1.03-1.73] p=0.028	1.39 [1.05-1.85] p=0.022	1.32 [0.96-1.82] p=0.088	1.31 [1.01-1.70] p=0.042	1.37 [1.03-1.83] p=0.030	1.29 [0.93-1.78] p=0.122
PFVF	1.022 [1.010-1.034] p<0.001	1.017 [1.004-1.030] p=0.009	1.026 [1.011-1.042] <0.001	-	-	-	1.021 [1.001-1.041] p=0.041	1.015 [0.993-1.036] p=0.182	1.022 [0.998-1.047] p=0.075
VFVF	-	-	-	1.019 [1.007-1.031] p=0.002	1.015 [1.002-1.028] p=0.022	1.023 [1.008-1.038] p=0.002	1.002 [0.982-1.022] p=0.847	1.003 [0.982-1.025] p=0.776	1.006 [0.982-1.030] p=0.650

Each column shows the results of one of nine multiple logistic regressions, each using either three or four dependent variables for calculation of the odds ratio of having any polyp, any adenomatous polyp, or any hyperplastic polyp. All regressions included both age and gender. As indicated, three regressions included PFVF, three included VFVF, and three included both PFVF and VFVF. Read odds ratio as increase in age of 1 yr, or increase in PFVF or VFVF by 1%, or change from male to female. Only PFVF and VFVF are directly comparable.

Table 5

Concordance of PFVF and VFVF.

Quintiles	VFVF_1st	VFVF_2nd	VFVF_3rd	VFVF_4th	VFVF_5th
PFVF_1st	52/178	17/44	3/11	1/1	0/0
PFVF_2nd	16/44	39/103	20/52	9/24	6/10
PFVF_3rd	6/11	27/55	34/81	18/56	12/32
PFVF_4th	0/1	6/25	27/67	43/79	26/61
PFVF_5th	0/0	5/6	14/24	39/73	66/131

Data are patients with polyps / all patients in that category.