Original Article

Myosteatosis mediates the link between specific dietary components and colorectal carcinogenesis: from PPLSS multi-center study

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Background and Objectives: We assumed the specific dietary components may impact colorectal carcinogenesis via ectopic fat accumulation. **Methods and Study Design:** The multi-center case-control study analyzed CT-derived body composition parameters and dietary intake in 163 colorectal cancer (CRC) patients and 144 non-CRC controls. Ectopic fat distribution was characterized by elevated low-attenuation muscle area (LAMA) and reduced skeletal muscle density (SMD, myosteatosis). We employed logistic regression to assess diet-body composition-CRC associations, mediation analysis to elucidate ectopic fat's role, and random forest modelling to evaluate variable importance in CRC risk prediction. **Results:** CRC patients exhibited obvious myosteatosis (68.1 vs. 31.9%, *p* <0.001), which promoted colorectal carcinogenesis (95%CI: 0.524, 0.935 in men, 95%CI: 0.425, 0.956 in women via reduced SMD). Linear regression revealed diet rich in animal-derived nutrients and carbohydrates increased LAMA ($\beta = 6.31$, 95%CI: 0.766, 11.858), but decreased SMD ($\beta = -3.14$, 95%CI: -5.173, -1.099) and normal attenuation muscle area (NAMA) in men, while these components elevated visceral adiposity index (VAI) in women ($\beta = 10.8$, 95%CI: 1.265, 20.347). Low bean protein consumption decreased NAMA ($\beta = -13.3$, 95%CI: -20.812, -5.860) and SMD ($\beta = -2.95$, 95%CI: -4.994, -0.908) in men, while increasing VAI ($\beta = 14.6$, 95%CI: 0.820, 28.451) in women. Mediation analysis confirmed NAMA (mediated proportion 11.0%, *p* = 0.026 in men; 7.24%, *p* = 0.030 in women), LAMA (11.0%, *p* = 0.040 in men; 14.6%, *p* = 0.002 in women) and SMD (17.5%, *p* = 0.004 in men; 15.4%, p = 0.004 in women) mediated the relationship between excessive consumption of animal-derived nutrients and colorectal carcinogenesis. **Conclusions:** Myosteatosis, an inconspicuous obesity phenotype, plays key role in colorectal carcinogenesis but can be mitigated by partial substitution of red meat with soy protein.

Key Words: myosteatosis, colorectal cancer, inconspicuous obesity, bean protein, animal-derived nutrients

INTRODUCTION

Colorectal cancer (CRC) ranks as the second most common cancer globally and a leading cause of cancer-related deaths, with notable sex-based disparities in incidence and clinical outcomes.[1] Among established risk factors, obesity has been identified as a key modifiable contributor to CRC development. Epidemiological studies indicate that men with obesity face a 30-70% higher risk of

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colon cancer, with a U-shaped relationship observed between body mass index (BMI) and colon cancer risk.[2] However, obesity is no longer solely defined by BMI, a traditional yet limited metric, but rather by abnormal fat deposition patterns, particularly in visceral and intramuscular compartments. These ectopic fat deposits drive metabolic dysregulation, including insulin resistance (IR) and chronic low-grade inflammation, which collectively promote hormone-related malignancies, like CRC.[3–9]

Ectopic fat accumulation serves as a critical link between obesity and its metabolic sequelae. Visceral obesity is associated with poorer CRC prognosis, likely mediated by obesity-induced mechanisms, like pro-inflammatory and angiogenic cytokines secretion.[10-12] Similarly, myosteatosis, marked by excessive intramuscular fat infiltration, induced lipotoxicity and IR, fostering a pro-inflammatory tumor microenvironment,[4,13] which is further increased the risk of metastatic progression.[14] Consequently, body composition analysis provides critical insights into nutritional deficits and metabolic disturbances stemming from chronic inflammation, offering potential avenues for targeted interventions to improve survival outcomes in patients with CRC.[15,16]

Although the precise mechanisms behind obesity-related tumor remain incompletely understood, emerging evidence suggests fat distribution patterns may play a key role. The rising incidence of CRC is likely driven by lifestyle changes, including sedentary behaviour and excessive energy-dense foods consumption, which promote pathological fat accumulation.[12,17,18] The geographic variability in CRC rates, and differences observed among migrant populations, further underscores the pivotal role of diet and lifestyle in carcinogenesis.[2] Notably, long-term dietary improvements reduced ectopic fat storage, with studies reporting 50cm^3 lower visceral adipose tissue (VAT) and 52cm^3 lower subcutaneous adipose tissue (SAT) per standard deviation increase in diet quality,[19] reinforcing the protective role of nutrition in attenuating obesity-associated CRC risk. Moreover, sex-specific lifestyle patterns promote disparities in CRC incidence. Compared to women, men exhibit higher consumption of red meat, alcohol, and tobacco, coupled with lower intake of fruits and vegetables and a more sedentary lifestyle.[20,21] These behavioral differences substantially influence CRC susceptibility and progression, highlighting the importance of investigating how lifestyle-mediated changes in body composition modulate CRC risk.

This study proposes a “Diet-Body Composition” axis as a key mechanism linking modern Western-style diets to CRC. Specifically, we hypothesize that diets high in saturated fatty acids (abundant in processed and red meats) or calories induced ectopic lipid deposition in skeletal muscle (myosteatosis) and visceral compartments, which promote colorectal carcinogenesis. We aim to explore the specific dietary components influence CRC risk via ectopic fat accumulation, especially myosteatosis, and evaluate sex-specific disparities in the cross-talk of diet and muscle-fat distribution in the CRC development.

METHODS

Participants

Participants were recruited, with written permission, from the Peking Union Medical College Hospital (PUMCH) multicenter Prospective Longitudinal Sarcopenia study (PPLSS). The study included CRC-related participants from the General Surgery department at Tianjin Union Medical Center (TUMC), which serves as one research site within PPLSS. PPLSS is a multi-center cross-sectional and cohort study, evaluating changes in body composition and clinical outcomes among persons with sarcopenia and sarcopenic obesity in China (NCT02873676), approved by the Human Ethics Committee of the PUMCH (No. HS889) and TUMC (No. I24PJ0189).

Prior to the baseline examination, all participants completed a medical screening to evaluate physical function. Those with heart, kidney, liver failure, communicable diseases, or conditions affecting study outcomes were disqualified. Eligible individuals aged ≥18 needed an abdominal CT scan within a month before enrollment, a thorough physical examination, and an independent questionnaire investigation. Based on the inclusive and exclusive criteria, cases were defined as patients with a confirmed stage III or IV CRC via pathology who had not received treatment, while controls were matched to the cases based on age, devoid of any history of cancer. We finally included 163 patients with CRC and 144 age-matched controls (approximately 1:1 ratio) in the final analysis.

Computed tomography image analysis for body composition phenotypes

CT images in DICOM format were acquired from the hospital's Picture Archiving and Communication System. The lumbar vertebra served as a reference for assessing muscle characteristics, radiodensity, and adiposity using Slice-O-Matic Version 6.0 software (Serial Number: 306F4FF2, Tomovision, Montreal, Quebec, Canada). A strong relationship emerged between muscle areas at the third lumbar vertebra (L3) and total body muscle mass ($r2 = 0.855$, $p < 0.010$), establishing L3 as a credible landmark.[22] If automated analysis was inadequate, a consultant radiologist performed manual segmentation with Slice-O-Matic. Inter-rater reliability, assessed by the intra-class correlation coefficient (ICC), indicated high values for skeletal muscle mass (0.984), intramuscular adipose tissue (IMAT, 0.954), SAT (0.998), and VAT (0.999).

The average of two consecutive L3 axial images was used for body composition analysis, including skeletal muscle area (SMA), which consists of normal attenuation muscle area (NAMA) and low attenuation muscle area (LAMA), fat-related metrics like skeletal muscle radiodensity (SMD), VAT, and SAT.[23] Tissue areas were quantified using anatomical features and Hounsfield unit (HU) ranges: LAMA (-29 to 29), NAMA (30 to 150), VAT (-150 to -50), and SAT (-190 to -30). The skeletal muscle index (SMI), visceral adipose index (VAI), and subcutaneous adipose index (SAI)[24] were derived from the cross-sectional area of adipose and muscle mass, normalized by height (cm^2/m^2). Sarcopenia was defined as SMI $\leq 52.4 cm^2/m^2$ for men and $\leq 38.5 cm^2/m^2$ for women,[25] while sarcopenic obesity (SO) required VAT ≥ 100 cm^2 alongside sarcopenia.[26] Visceral obesity (VO) guidelines varied by age and gender: for 17-39, men >120.5 cm^2, women >62.6 cm^2; for 40-59, men >134.4 cm^2, women >85.9 cm^2; for >60, men >131.7cm^2, women >115.6cm.[27] Myosteatosis, indicated by SMD <33HU in men and <28 HU in women, emerged as a significant finding.[28]

Assessment of covariates

Clinical data included demographics, tumor characteristics, comorbidity history, patient-reported health conditions, and biochemical evaluations. Lifestyle factors involved age, sex, race/ethnicity, and alcohol/tobacco consumption. Diagnosis of metabolic syndrome followed International Diabetes Federation criteria.[29] Tumor confirmation relied on histology, with staging as per the American Joint Committee on Cancer TNM Classification (8th edition).[30] Surgical factors encompassed tumor specifics, size, staging, pathology, and lymph node involvement. Dietary data was collected through a customized questionnaire based on the Korea National Health and Nutrition Examination Survey,[31] validated via expert review and previous testing to ensure accuracy in intake frequency and portion sizes, analyzing energy and nutrient content using Chinese Food Composition data. The reliability, validity and acceptability of the questionnaire were analyzed by a pilot study. The alpha coefficient was 0.6, the recovery was 96%, and the response rate was 95%. The time taken to complete the data collection ranged from 18.0 to 29.0 minutes depending on the participant's capacity to complete measurements, with an average of 15.0 ± 7.0 minutes across all subjects. This questionnaire collected data on dietary intake prior to the CRC diagnosis in each patient. All interviews were conducted face-to-face by trained nutritional data collector, utilizing standardized food atlases and physical models to facilitate accurate portion estimation. Prior to database entry, questionnaires underwent logical verification by a secondary researcher to identify potential anomalies, such as implausible energy values or missing data. Physical activity levels were assessed using the International Physical Activity Questionnaire.[32] Anthropometric measurements [height, weight, waist circumference (WC), calf circumference (CC), grip strength] were taken, averaging two readings.

Statistical analysis

The sample size was calculated using PASS15, which aimed to determine the minimum sample size needed to detect odds ratios of 2 with 0.9 power and 0.05 significance, referencing recent large-scale studies on dietary intake and CRC risk.[33-35] The control group's exposure probability in China was based on Zhang et al.'s study.[36] Finally, the minimum sample size was 117 each group.

Continuous data were reported as mean (± SD), while categorical data appeared as counts and percentages. Group comparisons applied the Mann-Whitney U-test for continuous variables and the Chi-squared or Fisher's exact test for categorical variables. Sex-stratified logistic regression models evaluated the relationship between dietary intake, body composition, and CRC risk: Model-1 was unadjusted, Model-2 adjusted for age, exercise, smoking, and drinking, and Model-3 further adjusted for BMI, metabolic syndrome, LDL, HDL, FFA, and TG. Sex-stratified multivariable linear regression analyzed dietary intake's relationship with body composition, adjusting for confounders. Causal mediation analysis assessed body composition's role in the link between dietary factors and CRC risk using the "mediation" R package. Variable importance was evaluated through deep learning algorithms, and correlation analysis assessed multicollinearity. The cohort (n = 154 men, n = 153 women) was divided into a training group (n = 123 men, n = 122 women, 80 %) and a validation group (n = 31 men, n = 32 women, 20 %). Models were built using random forest algorithms, with ROC analysis and 10-fold cross-validation for evaluation.

Principal component analysis (PCA) examines dietary intake's association with CRC risk. We utilized 9 nutrients from 10 food groups with daily intakes, as shown in Supplementary Table 1. The analysis, with varimax rotation, developed three dietary features based on eigenvalue (≥1.0) screen plots, and interpretability of factors. We calculated factor loadings for each food group across the three dietary features, and a factor score for each subject obtained for the 9 nutrients, in which intakes of food groups were weighted by their factor loadings and summed. Dietary features were named based on factor loadings (factor loading >|0.40|) that contributed the most to each component. We identified three dietary features in the overall population and male participants including principal component (PC)1 revealed relatively higher intakes of animal protein, total fat, and total protein with factor loadings greater than 0.400; PC2 exhibited higher carbohydrate (factor loading >0.800) intake, and PC3 was linked to lower bean protein (factor loading <-0.800) intake. In women, PC1 also indicated high animal protein, total fat, and total protein with factor loadings greater than 0.410. PC2 reflected low bean protein (factor loading -0.618) but high carbohydrate intake (factor loading 0.773), and PC3 indicated higher carbohydrate (factor loading 0.537) and bean protein (factor loading 0.693) intakes. Each dietary feature categorized participants into high (Q4) and low (Q1-Q3) groups based on dietary pattern scores. The higher score of dietary pattern means it aligns with dietary features; for example, in the case of low bean protein intake, a higher dietary pattern score means a lower consumption of bean protein. R (Version

4.3.1) and Python 3.0 processed the analysis, with p-value <0.05 indicating significance.

RESULTS

Baseline characteristics

A total of 722 participants were recruited from the PPLSS study between November 2021 and January 2024. Of these, 296 were CRC, while 426 were controls. After excluding those with missing CT-images or clinical data, 307 participants were deemed eligible for this study (Figure 1).

Subjects with CRC were younger (p = 0.015), with mean of 67.0(60.0-73.0)y, more likely to be man (57.1% vs 42.3%, p = 0.014), involved in smoking or with a history of smoking (p <0.001), drinking (p <0.001), physically inactive (p <0.001), and had metabolic syndrome (p <0.001) or dyslipidaemia characterized by higher FFA (p = 0.001), TG (p = 0.093), LDL (p <0.001), and LH ratio (p <0.001) , and lower HDL (p = 0.056). Similar patterns persisted when stratified by sex (Table 1).

The feature of body composition in colorectal cancer

Significant variations in body composition were noted in patients with CRC (Table 2), characterized by distinctive ectopic fat distribution patterns, with increased intramuscular and visceral fat accumulation (Figure 2a, b). They exhibited with higher LAMA (49.5 vs. 37.0 cm^2, p <0.001) and lower SMD (27.8 vs. 32.7 HU, p <0.001), indicative of significant myosteatosis (68.1% vs. 31.9 %, p <0.001). Meanwhile, they also displayed remarkable central fat accumulation, with higher WC (91.0 vs. 86.0 cm, p <0.001) and VAI (46.7 vs. 38.2 cm^2/m^2) levels, alongside with higher VO (56.4 % vs. 39.6 %. p = 0.005) rate. Remarkably, the muscle atrophy in patients with CRC was not obvious, exhibiting with similar sarcopenia rate and significantly higher SO rate (47.2 % vs. 34.0 %, p = 0.026) between CRC patients and controls, likely due to higher LAMA levels masking muscle loss. Notably, patients with CRC exhibited elevated visceral and intramuscular fat, linked to reduced strength and CC, as 35.1 % of men and 44.4 % of women had grip strength below sarcopenia thresholds.[37]

Table 2 also outlines sex-specific fat accumulation and muscle atrophy in patients with CRC. Men show increased ectopic fat within muscle tissues, alongside with higher LAMA (51.6 vs. 40.6 cm^2, p <0.001) and lower SMD (30.4 vs. 34.9 HU, p <0.001) statue, characterizing with significantly notable myosteatosis phenotype (61.3 % vs. 26.2 %, p <0.001, Figure 2a, c). Although the difference did not show significance, male patients with CRC shown lower SAT levels (104 vs. 113 cm^2, p = 0.410) and relatively higher central adiposity (136 vs. 119 cm^2, p = 0.909). Multivariate logistic regression further indicated lower SMD (OR = 0.781, 95%CI = 0.631, 0.950, p = 0.017, Supplementary Table 2) heighten the risk of CRC after adjusted for age, exercise, smoking, and drinking. Similarly, higher SAI level (OR = 0.964, 95%CI = 0.931, 0.994, p = 0.024) decreased the risk of CRC. Further adjustments for metabolic syndrome, BMI, and blood lipids, SMD still shown similar trend with CRC in the model-3. In women, except for significantly higher LAMA levels, lower SMD levels and significant myosteatosis (77.1% vs. 36.1%, p <0.001, Figure 2b, d), they exhibited remarkable central fat accumulation, with higher WC (90.0 vs. 80.2 cm, p = 0.001) and VAI (46.9vs. 36.1cm^2/m^2, p = 0.012) levels, alongside with higher VO (57.1% vs. 33.7%. p = 0.006) and SO (41.4% vs. 19.3%. p = 0.005) rate. Multivariate logistic regression did not indicate LAMA and VAI were significant risk factors, though only SMD (OR = 0.652, 95%CI = 0.425, 0.956, p = 0.035) maintained significance in the model-3. After stratification by sex, significant differences in muscle wasting and muscle strength were observed among patients with CRC (Table 2). These findings indicate ectopic fat distribution (myosteatosis via SMD defining) may contribute to CRC occurrence in both sexes, especially in male patients with CRC. Taken together, these figures suggested intramuscular fat may link the mechanism behind obesity-related tumor, distinct from muscle atrophy.

The feature of dietary intake in colorectal cancer

In patients with CRC, daily nutrient intake was significantly lower than controls (p <0.001), except for carbohydrates (p = 0.037, Supplementary Table 3). We used PCA to analyze dietary components and their interactions with the risk of CRC. The first three components accounted for 91.1% of variability in nutrient intake (Supplementary Table 4). Additionally, we compared high (Q4) and low (Q1-Q3) dietary feature intervals, revealing consistency with factor loading characteristics (Supplementary Table 5-7).

Subsequent analysis identified specific dietary components associated with an increased risk of CRC across multiple models. In Model-1, PC2 (OR = 3.66, 95%CI: 2.795, 4.784) and PC3 (OR = 2.34, 95%CI: 1.755, 3.123) were significantly associated with higher CRC risk, even after adjusting for lifestyle factors in Model-2. Further adjustment in Model-3 revealed that PC1 (OR = 1.80, 95%CI: 1.192, 2.703), PC2 (OR = 8.42, 95%CI: 3.808, 18.62), and PC3 (OR = 2.97, 95%CI: 1.912, 4.626) all exhibited a markedly elevated risk of CRC (Supplementary Table 8). These findings suggest that diets high in animal-derived nutrients, resembling Western dietary patterns, may elevate CRC risk, whereas bean protein appears to confer a protective effect.

Association of dietary intake and fat distribution in the occurrence of CRC

The relationship between nutrients intake and body composition in CRC, after adjusting for confounders, is depicted in Figure 3. Linear regression revealed men had an inverse relationship between SMI and PC3 (β = -2.62, 95%CI: -5.144, -0.099, Figure 3a), along with negative correlations of NAMA and SMD with PC1(β = -10.9, 95%CI: -18.316, -3.409, Figure 3b; β = -3.14, 95%CI: -5.173, -1.099, Figure 3c), PC2 (β = -17.3, 95%CI: -28.205, -6.360; β = -5.51, 95%CI: -8.041, -2.071) and PC3(β = -13.3, 95%CI: -20.812, -5.860; β = -2.95, 95%CI: -4.994, -0.908). Positively, LAMA correlated with PC1(β = 6.31, 95%CI: 0.766, 11.858, Figure 3d) and PC2(β = 11.0, 95%CI: 2.818, 19.071). In women, dietary intake primarily affected central fat distribution, with VAI positively correlating with PC1 (β = 10.8,

Table 1. General characteristics of participants[†]

	Total			Men		
	Control (n=144)	CRC (n=163)	*p*	Control (n=61)	CRC (n=93)	*p*
Age, median (IQR, y)	69.0 (65.0, 72.3)	67.0 (60.0, 73.0)	0.015	70.0 (65.0, 73.0)	66.0 (60.0, 71.0)	0.005
Sex, n (%)	61 (42.4)	93 (57.1)	0.014	NA	NA	NA
BMI median (IQR, kg/m^2)	23.3 (21.3, 25.5)	23.4 (21.5, 26.0)	0.541	23.5 (21.9, 25.4)	23.4 (21.3, 25.4)	0.773
Work, n (%)			0.054			0.177
Relatively high intensity	7 (4.86)	19 (11.7)		4 (6.56)	14 (15.1)	
Relatively low intensity	137 (95.1)	144 (88.3)		57 (93.4)	79 (85.0)	
Smoking, n (%)			<0.001			<0.001
Never	115 (79.9)	88 (54.0)		33 (54.1)	29 (31.2)	
Quit	21 (14.6)	27 (16.6)		20 (32.8)	24 (25.8)	
Current	8 (5.56)	48 (29.5)		8 (13.1)	40 (43.0)	
Drinking, n (%)	28 (19.4)	79 (48.5)	<0.001	20 (32.8)	74 (79.6)	<0.001
Physical inactivity, n (%)	15 (10.4)	64 (39.3)	<0.001	7 (11.5)	30 (32.3)	0.006
Metabolic syndrome, n (%)	21 (14.6)	59 (36.2)	<0.001	9 (14.8)	30 (32.3)	0.024
FFA, median (IQR, µmol/ml)	633 (531, 749)	690 (591, 876)	0.001	616 (517, 747)	662 (570, 812)	0.059
TG, median (IQR, mmol/L)	1.10 (0.71, 1.46)	1.17 (0.91, 1.41)	0.093	1.07 (0.71, 1.53)	1.07 (0.86, 1.35)	0.720
HDL, median (IQR, mmol/L)	1.38 (1.17, 1.68)	1.02 (0.89, 1.13)	0.056	1.28 (1.07, 1.54)	1.00 (0.86, 1.11)	0.205
LDL, median (IQR, mmol/L)	2.60 (2.20, 3.13)	2.75 (2.38, 3.20)	<0.001	2.47 (1.96, 2.88)	2.59 (2.20, 3.07)	<0.001
LH ratio, median (IQR)	1.91 (1.35, 2.43)	2.76 (2.20, 3.42)	<0.001	1.88 (1.33, 2.57)	2.65 (2.13, 3.34)	<0.001

	Women		
	Control (n=83)	CRC (n=70)	*p*
Age, median (IQR, y)	68.0 (64.5, 72.0)	68.5 (60.0, 74.0)	0.669
Sex, n (%)	NA	NA	NA
BMI median (IQR, kg/m^2)	22.9 (20.7, 25.6)	23.4 (21.8, 26.0)	0.276
Work, n (%)			0.540
Relatively high intensity	3 (3.61)	5 (7.14)	
Relatively low intensity	80 (96.4)	65 (92.9)	
Smoking, n (%)			0.003
Never	82 (98.8)	59 (84.3)	
Quit	1 (1.20)	3 (4.29)	
Current	0 (0.00)	8 (11.4)	
Drinking, n (%)	8 (9.64)	5 (7.14)	0.794
Physical inactivity, n (%)	8 (9.64)	34 (48.6)	<0.001
Metabolic syndrome, n (%)	12 (14.5)	29 (41.4)	<0.001
FFA, median (IQR, µmol/ml)	644 (576, 774)	728 (617, 984)	0.001
TG, median (IQR, mmol/L)	1.10 (0.70, 1.40)	1.25 (0.96, 1.51)	0.022
HDL, median (IQR, mmol/L)	1.42 (1.26, 1.73)	1.04 (0.92, 1.14)	0.033
LDL, median (IQR, mmol/L)	2.65 (2.28, 3.22)	2.95 (2.55, 3.45)	<0.001
LH ratio, median (IQR)	1.92 (1.41, 2.36)	2.98 (2.23, 3.44)	<0.001

FFA: Free fatty acid, TG: Triglyceride, LDL: Low density lipoprotein, HDL: High density lipoprotein, LH ratio: LDL HDH Ratio, NA: Not Applicable.

[†] Mann-Whitney test was used for continuous variables and Fisher's exact test was used for categorical variables

Table 2. Body composition features of participants[†]

	Total			Men		
	Control (n=144)	CRC (n=163)	*p*	Control (n=61)	CRC (n=93)	*p*
NAMA, cm^2	65.7 (50.7, 94.2)	63. 3 (45.8, 89.2)	0.153	95.1 (85.9, 104)	82.3 (65.6, 101)	0.010
NAMA, HU	46.8 (44.0, 49.3)	44.0 (41.8, 45.9)	<0.001	46.8 (44.0, 50.7)	44.3 (42.7, 46.1)	<0.001
LAMA, cm^2	37.0 (30.0, 46.9)	49.5 (38.7, 58.9)	<0.001	40.6 (30.5, 47.6)	51.6 (40.5, 61.1)	<0.001
LAMA, HU	5.44 (4.44, 6.84)	7.14 (5.75, 8.47)	<0.001	6.38 (4.98, 7.29)	7.54 (6.72, 8.78)	<0.001
SMD, HU	32.7 (27.8, 36.1)	27.8 (22.3, 33.0)	<0.001	34.9 (32.3, 38.7)	30.4 (24.7, 35.0)	<0.001
SMI, cm^2/m^2	40.5 (34.9, 46.5)	41.5 (36.1, 47.7)	0.178	35.9 (41.0, 49.7)	46.6 (41.2, 50.9)	0.900
SAT, cm^2	120 (91.2, 159)	121 (93.9, 167)	0.894	113 (83.9, 136)	104 (80.0, 132)	0.410
SAI, cm^2/m^2	45.3 (34.7, 62.2)	43.2 (33.1, 61.7)	0.507	38.3 (30.6, 47.2)	35.7 (27.2, 44.3)	0.320
SAT, HU	-101 (-105, -95.5)	-104 (-108, -98.0)	<0.001	-97.9 (-101, -93.0)	-103 (80.0, 132)	0.001
VAT, cm^2	103 (67.1, 171)	125 (88.3, 172.5)	0.055	119 (81.8, 191)	136 (28.2, 65.8)	0.909
VAI, cm^2/m^2	38.2 (26.4, 64.2)	46.5 (30.3, 63.1)	0.135	40.7 (30.6, 64.2)	44.6 (28.2, 65.8)	0.770
VAT, HU	-96.3 (-100, -89.6)	-96.2 (88.3, 173)	0.725	-94.5 (-99.6, -87.7)	-95.3 (85.7, 197)	0.934
WC, cm	86.0 (77.6, 94.0)	91.0 (83.5, 97.8)	<0.001	88.0 (84.0, 95.0)	91.0 (84.0, 96.5)	0.139
CC, cm	34.4 (33.0, 36.2)	33.3 (31.5, 35.4)	<0.001	35.0 (34.0, 37.0)	34.0 (32.0, 35.5)	<0.001
Strength, kg	22.7 (18.9, 31.3)	24.6 (16.7, 30.3)	0.608	32.5 (28.2, 35.9)	28.9 (25.3, 33.9)	0.035

	Women		
	Control (n=83)	CRC (n=70)	*p*
NAMA, cm^2	55.1 (44.4, 64.1)	46.2 (33.3, 57.5)	0.001
NAMA, HU	46.8 (43.9, 48.9)	43.4 (41.3, 45.4)	<0.001
LAMA, cm^2	35.9 (29.5, 45.3)	46.6 (38.2, 55.9)	<0.001
LAMA, HU	4.94 (3.66, 6.20)	6.44 (5.09, 7.57)	<0.001
SMD, HU	30.2 (26.2, 33.7)	23.5 (20.4, 28.1)	<0.001
SMI, cm^2/m^2	36.1 (32.3, 41.2)	37.1 (33.3, 39.9)	0.728
SAT, cm^2	132 (102, 185)	157 (119, 193)	0.083
SAI, cm^2/m^2	52.9 (38.8, 74.4)	63.4 (45.8, 76.8)	0.115
SAT, HU	-103 (-106, -99.5)	-106 (-110, -102)	<0.001
VAT, cm^2	88.3 (58.1, 146)	118 (92.7, 156)	0.009
VAI, cm^2/m^2	36.1 (22.6, 59.7)	46.9 (35.9, 60.1)	0.012
VAT, HU	-96.8 (-101, -90.6)	-97.2 (-101, -93.2)	0.406
WC, cm	80.2 (73.0, 93.5)	90.0 (82.0, 98.5)	0.001
CC, cm	33.9 (32.5, 35.5)	32.3 (31.0, 34.4)	0.008
Strength, kg	19.4 (16.4, 22.5)	16.9 (12.7, 21.3)	0.006

NAMA: Normal Attenuation Muscle Area, LAMA: Low Attenuation Muscle Area, SMD: Skeletal Muscle Density, SMI: Skeletal Muscle Index, SAT: Subcutaneous Adipose Tissue, SAI: Subcutaneous Adipose Index, VAT: Visceral adipose tissue, VAI: Visceral adipose index, WC: Waist Circumference, CC: Calf Circumference.

[†] Mann-Whitney test was used for continuous variables and Fisher's exact test was used for categorical variables.

Table 2. Body composition features of participants†

	Total			Men		
	Control (n=144)	CRC (n=163)	*p*	Control (n=61)	CRC (n=93)	*p*
Myosteatosis, n (%)	46 (31.9)	111 (68.1)	<0.001	16 (26.2)	57 (61.3)	<0.001
Visceral Obesity, n (%)	57 (39.6)	92 (56.4)	0.005	29 (47.5)	52 (55.9)	0.394
Sarcopenia, n (%)	103 (71.5)	122 (74.9)	0.598	52 (85.3)	78 (83.9)	0.998
Sarcopenic Obesity, n (%)	49 (34.0)	77 (47.2)	0.026	33 (54.1)	48 (51.6)	0.891

	Women		
	Control (n=83)	CRC (n=70)	*p*
Myosteatosis, n (%)	30 (36.1)	54 (77.1)	<0.001
Visceral Obesity, n (%)	28 (33.7)	40 (57.1)	0.006
Sarcopenia, n (%)	51 (61.5)	44 (62.9)	0.990
Sarcopenic Obesity, n (%)	16 (19.3)	29 (41.4)	0.005

NAMA: Normal Attenuation Muscle Area, LAMA: Low Attenuation Muscle Area, SMD: Skeletal Muscle Density, SMI: Skeletal Muscle Index, SAT: Subcutaneous Adipose Tissue, SAI: Subcutaneous Adipose Index, VAT: Visceral adipose tissue, VAI: Visceral adipose index, WC: Waist Circumference, CC: Calf Circumference.

†Mann-Whitney test was used for continuous variables and Fisher's exact test was used for categorical variables

Table 3. The mediation effect of the dietary factors and body composition for colorectal cancer

Variables	Total effect	Direct effect	Mediated effect	Proportion mediated (%)	p[¶]
Men					
PC1[†]					
NAMA, cm^2	-0.105 (-0.173, -0.063)	-0.093 (-0.159, -0.053)	-0.012 (-0.026, -0.001)	11.0	0.026
LAMA, cm^2	-0.106 (-0.172, -0.068)	-0.095 (-0.159, -0.062)	-0.012 (-0.028, -0.0004)	11.0	0.040
SMI, cm^2/m^2	-0.101 (-0.169, -0.062)	-0.099 (-0.167, -0.059)	-0.002 (-0.011, 0.002)	2.27	0.406
SMD, HU	-0.109 (-0.175, -0.067)	-0.090 (-0.147, -0.054)	-0.019 (-0.037, -0.005)	17.5	0.004
SAI, cm^2/m^2	-0.104 (-0.169, -0.064)	-0.103 (-0.168, -0.064)	-0.001 (-0.006, 0.003)	0.941	0.648
VAI, cm^2/m^2	-0.105 (-0.163, -0.063)	-0.106 (-0.163, -0.063)	0.0002 (-0.003, 0.004)	0.195	0.906
PC2[‡]					
NAMA, cm^2	-0.049 (-0.126, 0.008)	-0.045 (-0.116, 0.011)	-0.004 (-0.030, 0.017)	8.93	0.712
LAMA, cm^2	-0.055 (-0.124, 0.006)	-0.062 (-0.123, -0.004)	0.007 (-0.016, 0.030)	12.7	0.618
SMI, cm^2/m^2	-0.050 (-0.116, 0.013)	-0.047 (-0.110, 0.019)	-0.003 (-0.018, 0.008)	6.07	0.670
SMD, HU	-0.051 (-0.124, 0.011)	-0.046 (-0.115, 0.008)	-0.005 (-0.037, 0.024)	10.1	0.678
SAI, cm^2/m^2	-0.051 (-0.133, 0.013)	-0.054 (-0.141, 0.010)	0.004 (-0.004, 0.016)	7.08	0.450
VAI, cm^2/m^{2}SAI, cm^2/m^2	-0.051 (-0.127, 0.013)	-0.052 (-0.129, 0.013)	0.001 (-0.007, 0.012)	2.22	0.786
PC3[§]					
NAMA, cm^2	0.037 (-0.031, 0.114)	0.028 (-0.033, 0.106)	0.009 (-0.013, 0.033)	23.4	0.514
LAMA, cm^2	0.040 (-0.032, 0.112)	0.045 (-0.026, 0.116)	-0.004 (-0.027, 0.020)	10.9	0.868
SMI, cm^2/m^2	0.041 (-0.031, 0.119)	0.037 (-0.035, 0.115)	0.004 (-0.007, 0.020)	9.75	0.574
SMD, HU	0.040 (-0.038, 0.116)	0.046 (-0.018, 0.120)	-0.005 (-0.035, 0.027)	13.2	0.970
SAI, cm^2/m^2	0.044 (-0.035, 0.118)	0.053 (-0.026, 0.133)	-0.010 (-0.033, 0.003)	22.6	0.392
VAI, cm^2/m^2	0.043 (-0.034, 0.117)	0.044 (-0.034, 0.120)	-0.001 (-0.011, 0.009)	2.29	0.842
Women					
PC1[†]					
NAMA, cm^2	-0.104 (-0.148, -0.067)	-0.097 (-0.141, -0.058)	-0.008 (-0.020, -0.0004)	7.24	0.030
LAMA, cm^2	-0.107 (-0.145, -0.069)	-0.092 (-0.128, -0.055)	-0.016 (-0.032, -0.004)	14.6	0.002
SMI, cm^2/m^2	-0.105 (-0.147, -0.066)	-0.105 (-0.149, -0.067)	0.0002 (-0.003, 0.004)	0.177	0.960
SMD, HU	-0.109 (-0.150, -0.067)	-0.092 (-0.133, -0.051)	-0.017 (-0.031, -0.005)	15.4	0.004
SAI, cm^2/m^2	-0.105 (-0.147, -0.066)	-0.103 (-0.145, -0.064)	-0.002 (-0.008, 0.003)	1.73	0.552
VAI, cm^2/m^2	-0.105 (-0.148, -0.068)	-0.105 (-0.147, -0.066)	-0.001 (-0.006, 0.004)	0.677	0.728
PC2[‡]					
NAMA, cm^2	0.102 (0.032, 0.186)	0.101 (0.033, 0.180)	0.001 (-0.024, 0.021)	0.811	0.938
LAMA, cm^2	0.118 (0.041, 0.194)	0.115 (0.043, 0.187)	0.003 (-0.030, 0.033)	2.37	0.824
SMI, cm^2/m^2	0.103 (0.038, 0.181)	0.103 (0.035, 0.182)	-0.000001 (-0.007, 0.006)	0.001	0.998
SMD, HU	0.107 (0.038, 0.194)	0.096 (0.037, 0.178)	0.010 (-0.022, 0.044)	9.78	0.472
SAI, cm^2/m^2	0.102 (0.038, 0.176)	0.103 (0.038, 0.177)	-0.001 (-0.010, 0.008)	1.08	0.836
VAI, cm^2/m^2	0.103 (0.029, 0.189)	0.100 (0.026, 0.184)	0.003 (-0.005, 0.016)	2.57	0.552

NAMA: Normal Attenuation Muscle Area, LAMA: Low Attenuation Muscle Area, SMI: Skeletal Muscle Index, SMD: Skeletal Muscle Density, SAI: Subcutaneous Adipose Index, VAI: Visceral adipose index.

[†] PC1: Principal component 1 associated with high animal-derived nutrients intake

[‡] PC2: Principal component 2 related to low bean protein intake and high carbohydrate intake

[§] PC3: Principal component 3 linked to high carbohydrate and bean protein intake

[¶] *p* values of mediated effect for colorectal cancer adjusted for age, exercise, smoking, drinking, metabolic syndrome, and BMI

Table 3. The mediation effect of the dietary factors and body composition for colorectal cancer

Variables	Total effect	Direct effect	Mediated effect	Proportion mediated (%)	*p*[¶]
Women					
PC3[§]					
NAMA, cm^2	-0.037 (-0.113, -0.022)	-0.036 (-0.113, -0.031)	-0.001 (-0.023, 0.020)	3.03	0.850
LAMA, cm^2	-0.032 (-0.111, -0.043)	-0.036 (-0.110, -0.032)	0.004 (-0.022, 0.033)	12.3	0.994
SMI, cm^2/m^2	-0.040 (-0.116, -0.032)	-0.040 (-0.117, -0.032)	0.00005 (-0.007, 0.006)	0.013	0.908
SMD, HU	-0.035 (-0.115, -0.032)	-0.037 (-0.109, -0.030)	0.002 (-0.020, 0.031)	5.73	0.994
SAI, cm^2/m^2	-0.039 (-0.118, -0.033)	-0.035 (-0.115, -0.036)	-0.004 (-0.016, 0.005)	9.96	0.514
VAI, cm^2/m^2	-0.039 (-0.117, -0.029)	-0.043 (-0.122, -0.030)	0.004 (-0.007, 0.016)	9.66	0.564

NAMA: Normal Attenuation Muscle Area, LAMA: Low Attenuation Muscle Area, SMI: Skeletal Muscle Index, SMD: Skeletal Muscle Density, SAI: Subcutaneous Adipose Index, VAI: Visceral adipose index.

[†] PC1: Principal component 1 associated with high animal-derived nutrients intake

[‡] PC2: Principal component 2 related to low bean protein intake and high carbohydrate intake

[§] PC3: Principal component 3 linked to high carbohydrate and bean protein intake

[¶] *p* values of mediated effect for colorectal cancer adjusted for age, exercise, smoking, drinking, metabolic syndrome, and BMI

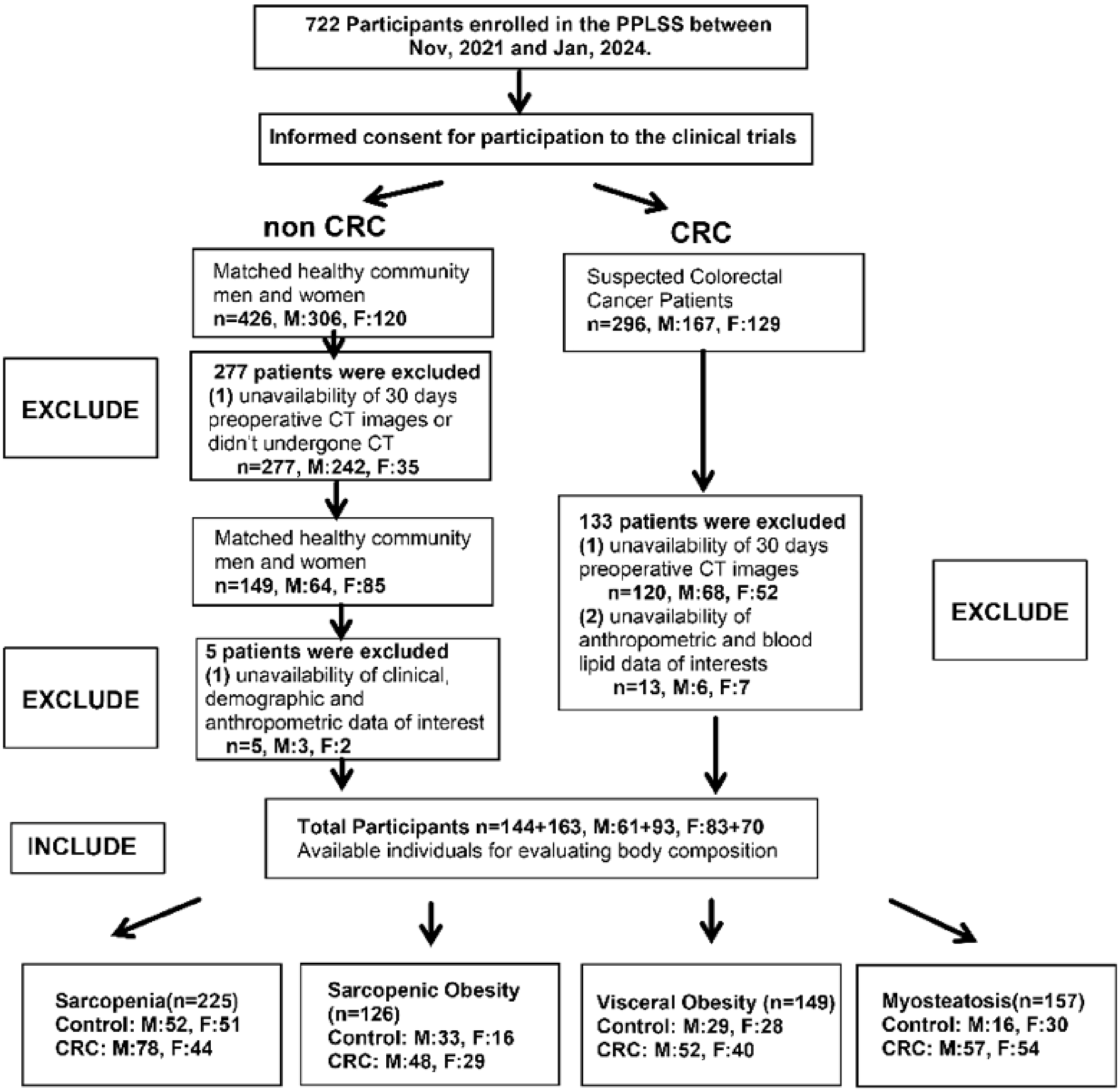

Figure 1. The flowchart of participants. Participants for this study were enrolled from the Peking Union Medical College Hospital (PUMCH) multicenter Prospective Longitudinal Sarcopenia Study (PPLSS). All participants selected were based on the relevant inclusion and exclusion criteria at every step.

95%CI: 1.265, 20.347, Figure 3e), PC2 (β = 14.6, 95%CI: 0.820, 28.451), and PC3 (β = 16.2, 95%CI: 4.055, 28.296). The three principal components favor SAI, but no significant differences were found. These results indicate high animal-derived saturated fats diets may harm muscle health and fat distribution in patients with CRC, while plant protein-based foods, especially beans, may provide anti-inflammatory benefits for male patients. Furthermore, gender disparities in the association between body composition changes and dietary components play significant role.

In the mediation analysis, we identified body composition parameters mediate the interaction between dietary components and colorectal carcinogenesis. SMD (p = 0.012, mediated proportion 9.70%) partially mediates the link between PC1 and the risk of CRC in men (Supplementary Table 7). Similarly, NAMA (p = 0.032, mediated proportion 6.05%), LAMA (p = 0.038, mediated proportion 9.782%), and SMD (p = 0.004, mediated proportion 11.9%) serve as partial mediators for women (Supplementary Table 9). After adjusting for confounders, NAMA (p = 0.026, mediated proportion 11.0%), LAMA (p = 0.040, mediated proportion 11.0%), and SMD (p = 0.004, mediated proportion 17.5%) partially mediate the link between PC1 and the risk of CRC for men (Table 3). For women, NAMA (p = 0.030, mediated proportion 7.24%), LAMA (p = 0.002, mediated proportion 14.6%), and SMD (p = 0.004, mediated proportion 15.4%) continue this mediation (Table 3). These findings established that SMD and LAMA act as key mediators bridging the influence of dietary factors on colorectal carcinogenesis.

To elucidate the impact of diet and obesity, key modifiable risk factors, on colorectal carcinogenesis, we leveraged deep learning to uncover novel molecular determinants. After eliminating redundant parameters by multicollinearity analyses, random forest models achieved high accuracies (AUC = 0.949, accuracy = 0.818 in men; AUC = 0.975, accuracy = 0.864 in women) (Figure 4a, d). Verification in the internal test set (31 men, 32 women) demonstrated satisfactory results (AUC = 0.863, accuracy=0.702 in men; AUC = 0.956, accuracy = 0.870 in women). (Figure 4b, e). To avoid overfitting, we employed 10-fold cross-validation, yielding consistent

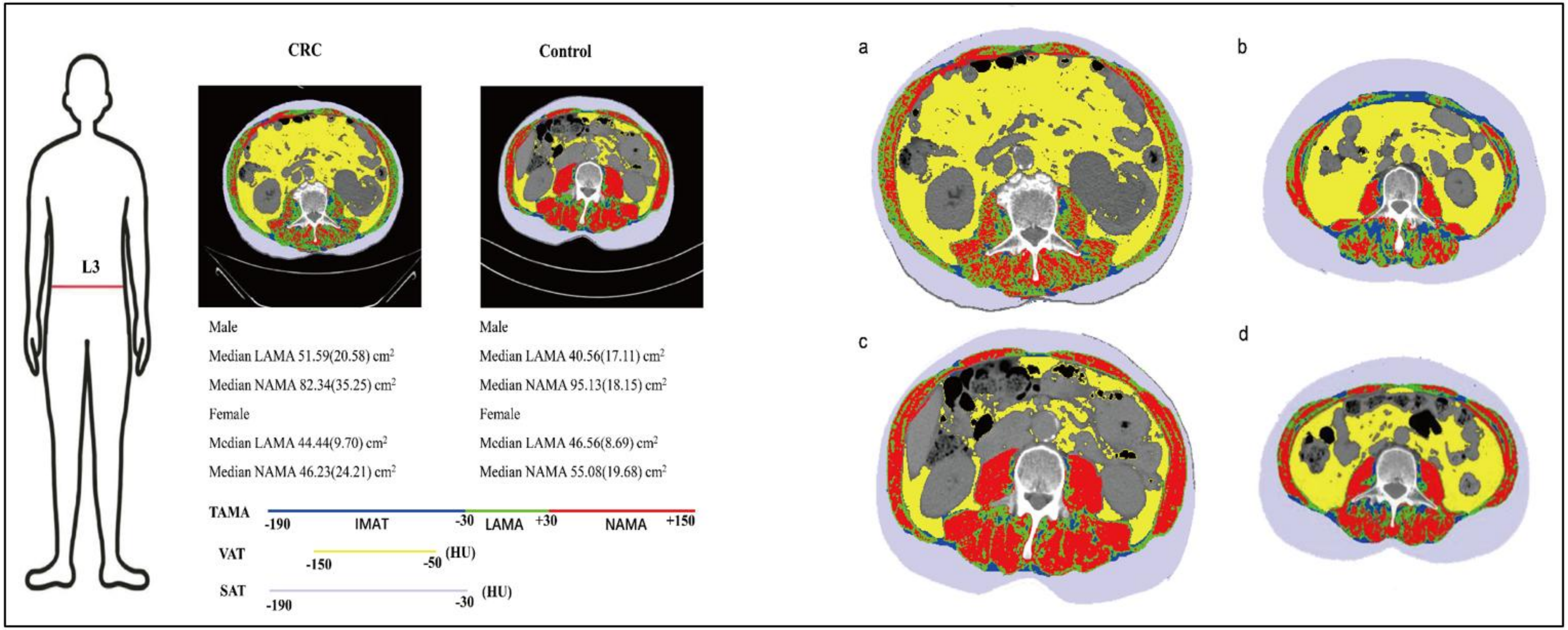

Figure 2. CT measurement images (at 3rd lumbar vertebra level) of body composition. (a) Male CRC patient, BMI 26.45 kg/m^2, aged 68y. SMA = 153.54cm^2; VAT = 212.1cm^2; SAT = 100.3cm^2; SMD = 22.97HU; NAMA = 68.15cm^2; LAMA = 85.39cm^2. (b) Female CRC patient, BMI 25.91 kg/m^2, aged 65y. SMA = 91.63cm^2; VAT = 120.4cm^2; SAT = 215.5 cm^2; SMD = 24.23HU; NAMA = 42.93 cm^2; LAMA = 48.70cm^2. (c) Male control individual, BMI 23.82 kg/m^2, aged 65y. SMA = 127.7 cm^2; VAT = 43.05cm^2; SAT = 105.7cm^2; SMD = 36.59HU; NAMA = 91.97cm^2; LAMA = 35.73cm^2. (d) Female control individual, BMI 25.28 kg/m^2, aged 64y. SMA = 90.29cm^2; VAT = 83.81cm^2; SAT=149cm^2; SMD = 37.02HU; NAMA = 62.64cm^2; LAMA = 27.65cm^2. SMA: Skeletal Muscle Area, VAT: Visceral Adipose Tissue, SAT: Subcutaneous Adipose Tissue, SMD: Skeletal Muscle Density, NAMA: Normal Attenuation Muscle Area, LAMA: Low Attenuation Muscle Area

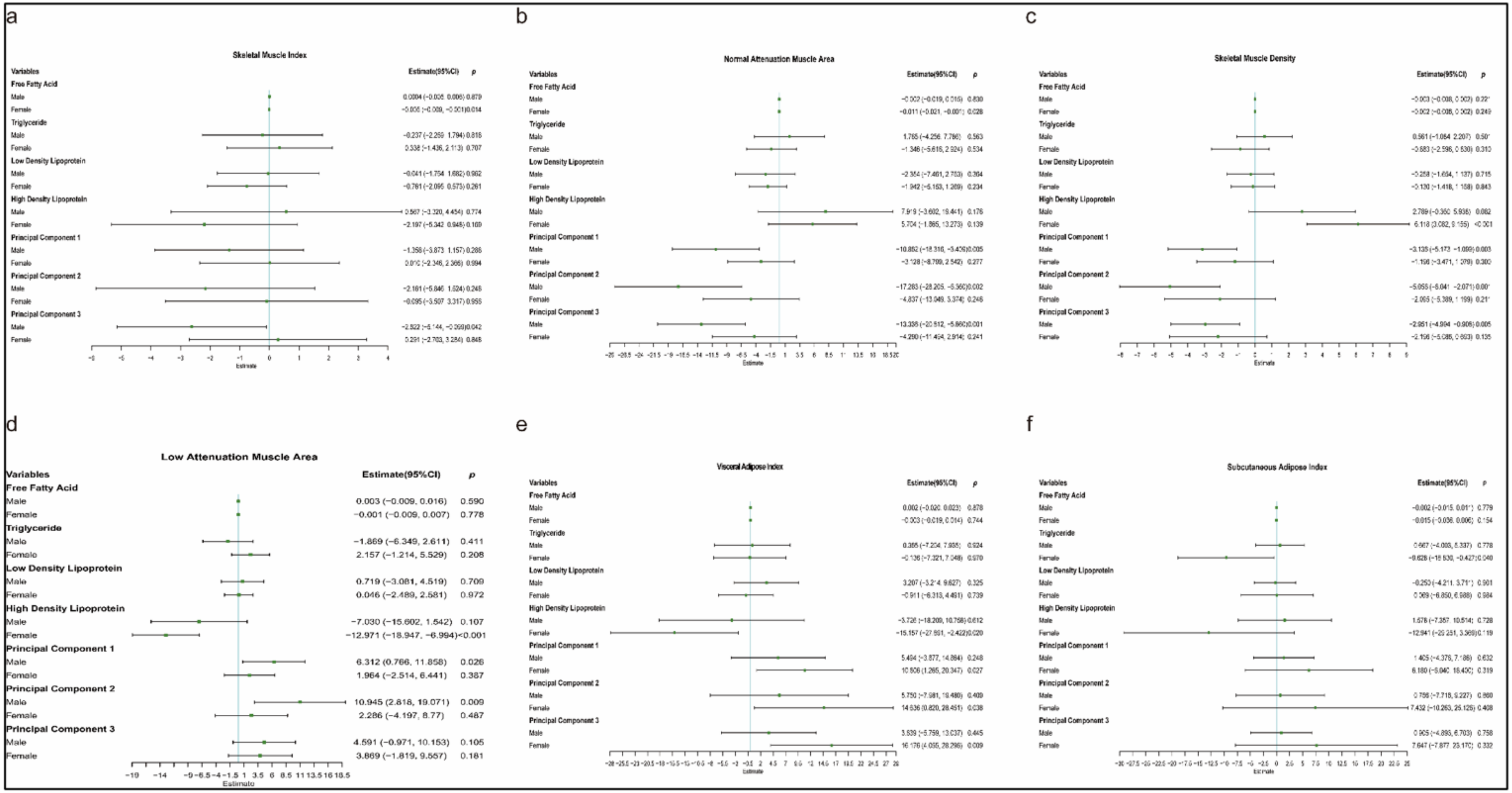

Figure 3. The forest plot of associations between nutrients intake pattern and body composition. Models were adjusted by age, exercise, metabolic syndrome, drinking, and total energy. (a) The association between nutrients intake pattern and skeletal muscle index. (b) The association between nutrients intake pattern and normal attenuation muscle area. (c) The association between nutrients intake pattern and skeletal muscle density. (d) The association between nutrients intake pattern and low attenuation muscle area. (e) The association between nutrients intake pattern and visceral adipose index. (f) The association between nutrients intake pattern and subcutaneous adipose index. The figures were generated with R software (Version 4.3.1). In men, PC1: Principal component 1 associated with high animal-derived nutrients intake, PC2: Principal component 2 linked to high carbohydrate intake, PC3: Principal component 3 related to low bean protein intake; In women, PC1: Principal component 1 associated with high animal-derived nutrients intake; PC2: Principal component 2 related to low bean protein intake and high carbohydrate intake; PC3: Principal component 3 linked to high carbohydrate and bean protein intake

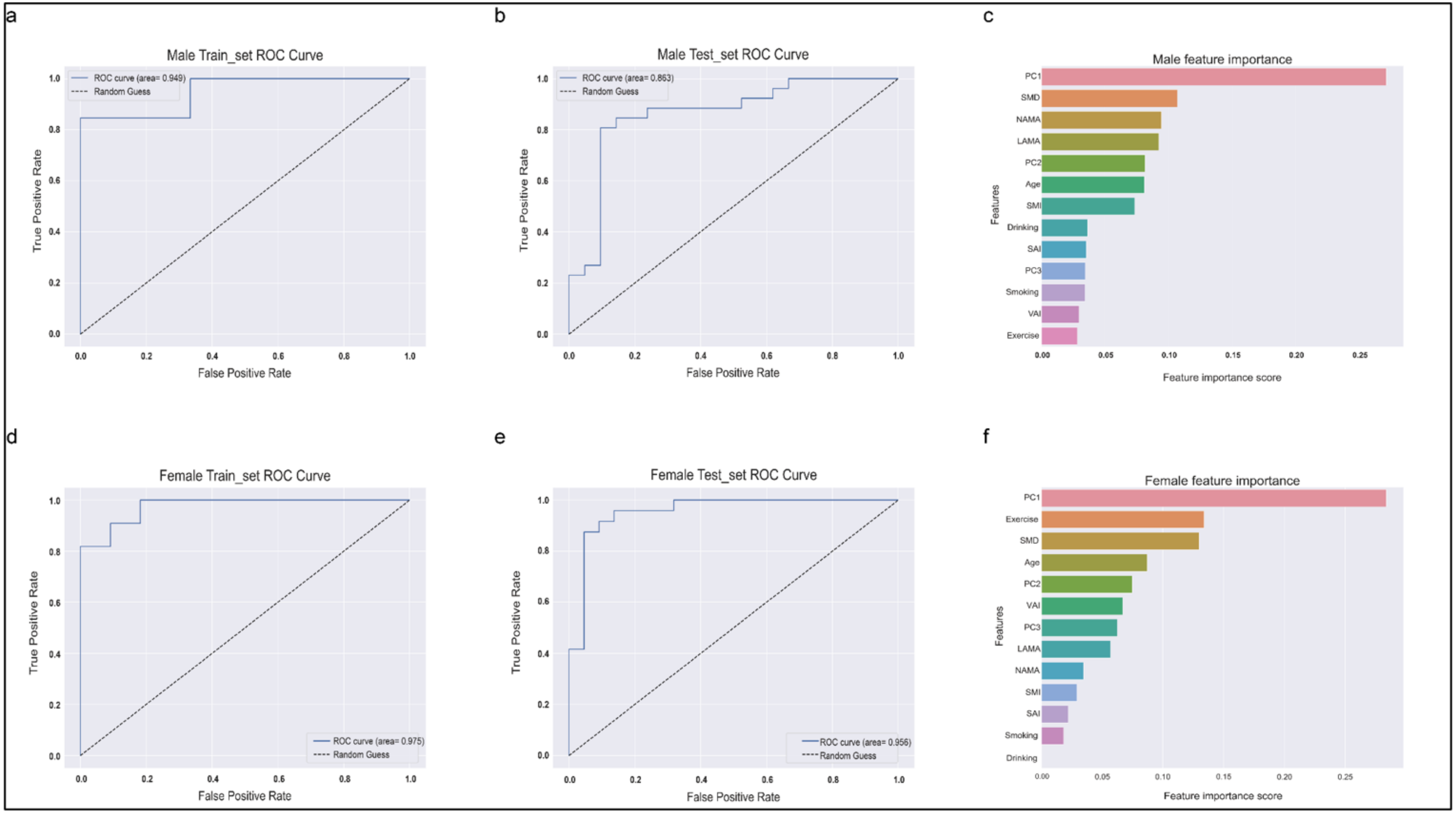

Figure 4. The feature importance score of nutrient intake pattern and body composition. The models were established based on the random forest. (a) Receiver operating characteristic (ROC) curve evaluates the train model for men. (b) ROC curve evaluates the test model for men. (c) The features importance score for men. (d) ROC curve evaluates the train model for women. (e) ROC curve evaluates the test model for women. (f) The features importance score for women. In men, PC1: Principal component 1 associated with high animal-derived nutrients intake, PC2: Principal component 2 linked to high carbohydrate intake, PC3: Principal component 3 related to low bean protein intake; In women, PC1: Principal component 1 associated with high animal-derived nutrients intake; PC2: Principal component 2 related to low bean protein intake and high carbohydrate intake; PC3: Principal component 3 linked to high carbohydrate and bean protein intake; NAMA: Normal Attenuation Muscle Area, LAMA: Low Attenuation Muscle Area, SMI: Skeletal Muscle Index, SMD: Skeletal Muscle Density, SAI: Subcutaneous Adipose Index, VAI: Visceral adipose index

performance (Supplementary Table 10). Through comprehensive computational assessment, model feature importance scoring (Figure 4c, f) demonstrated that SMD and PC1 served as critical factors for colorectal carcinogenesis risk stratification.

DISCUSSION

Our findings demonstrate dietary composition is significantly associated with colorectal carcinogenesis, primarily mediated by intramuscular fat deposition. CRC patients exhibited inconspicuous obesity patterns resulting from intramuscular lipid accumulation, which correlated with elevated LAMA and decreased SMD levels. These pathological changes were significantly associated with higher consumption of animal-derived nutrients and reduced legume protein intake. Epidemiological research has long established an association between red meat intake and colorectal carcinogenesis, yet the pathophysiological mechanisms involved remain inadequately characterized. Our study offers pioneering population-level evidence suggesting dietary factors may influence oncogenesis through detrimental modifications in body composition, specifically by inducing muscle quality, myosteatosis as a quantifiable intermediary phenotype. Sex-stratified analyses revealed differential patterns that myosteatosis-driven CRC risk was strongly associated with increased animal protein intake and decreased bean protein consumption in men, while in women elevated animal protein and total energy intake predominantly contributed to central adiposity accumulation.

Cancer development demonstrates significant associations with body composition alterations, particularly low SMD (myosteatosis) and reduced SMI (sarcopenia). In obesity-related malignancies, like CRC, patients may maintain a deceptively normal physique due to concealed adipose deposits, including intra- and intermuscular adipose tissue that masks muscle wasting.[38] Obesity promotes CRC development via adipose tissue redistribution, where lipid mobilization from subcutaneous stores meets energy demands while residual visceral and intramuscular lipid accumulation drives pathological fat partitioning.[39] Although tumor-specific fat redistribution mechanisms vary across cancer types, all malignancies depend on subcutaneous adipose-derived lipids for energy metabolism.[40] Our logistic regression analysis identified an inverse relationship between SAI and CRC risk, corroborating Brown et al.'s large-scale study (n = 3,262) establishing subcutaneous adipose tissue as a prognostic marker for CRC-specific mortality.[41] Importantly, when excess lipids from subcutaneous fat redistribute to skeletal muscles, a detrimental cycle (known as the "Metabaging Cycle"[4]) occurs locally at the deposition site, characterized mainly by chronic inflammation and IR, disrupting fatty acid β-oxidation, increasing ROS production, and causing mitochondrial dysfunction. The harmful cycle of local myosteatosis and muscle IR can initiate a broader negative loop leading to rising lipolysis and local FFA concentrations (the Metabaging Cycle), thus worsening and spreading local hyperlipidemia. The resulting local hyperlipidemia, lipotoxicity, and IR induced local inflammaging, exacerbating lipid dysfunction and IR in an expanding cycle that results in muscle atrophy (sarcopenia) and further fat accumulation, supporting the idea that the fundamental mechanism for myosteatosis is systemic in nature.[42] Our findings demonstrate myosteatosis increases CRC risk by 15.5-fold, while SAI shows a protective inverse association, underscoring subcutaneous fat loss as a mortality driver and ectopic fat redistribution to intra- and intermuscular space as a carcinogenesis promoter, independent of body weight.

Dietary components play a crucial role in modulating metabolic pathways that influence cancer development via their impact on body composition.[43] Our findings substantiate the association between a Western diet[44-46] and elevated CRC risk, particularly among men, with ectopic fat deposition patterns, myosteatosis, emerging as a potential mechanistic link, independent of conventional metabolic factors. Emerging evidence[47] highlights the differential effects of dietary fat subtypes on adipose tissue distribution, where saturated and animal-derived fats demonstrate positive correlations with hepatic lipid accumulation, intermuscular adipose tissue (IMAT) and VAT, whereas plant-based fats exhibit an inverse association with IMAT in women. The potential carcinogenic effects of animal-derived nutrients, including saturated fats, heme iron, and arginine present in red and processed meats, may be mediated through chronic inflammation compromised colonic barrier function, thereby elevating CRC susceptibility.[48,49] Current dietary recommendations advocate restricting red meat consumption to fewer than three weekly portions (350-500g cooked weight) and complete avoidance of processed meat products, especially those preserved through smoking or containing nitrites.[44] Notably, our analysis revealed a protective association between legume consumption and CRC risk, corroborating previous observations[50] that identified an inverse relationship between legume intake (less than weekly) and sarcopenia risk (OR = 1.419), with complete abstinence further amplifying this risk (OR = 2.536). Preclinical investigations[51] demonstrate incorporating legume-derived proteins and bioactive constituents into calorie-restricted regimens significantly reduces both overall adiposity and ectopic fat deposition. Legumes exert beneficial effects on body composition, particularly in obese populations,[52] while concurrently delivering anti-neoplastic benefits via multimodal mechanisms, including glycemic control, antioxidant activity, and anti-inflammatory effects,[53] potentially mediated by bioactive compounds, like spermidine.[54] These findings substantially expand the recognized health benefits associated with legume consumption in nutritional epidemiology. Clinical, these results support dietary counseling strategies that promote increased legume consumption frequency and quantity, while advocating for a paradigm shift in protein sourcing, specifically advocating for partial substitution of red meat with soy-based protein alternatives. Studies[55] have demonstrated that females predominantly exhibit a higher proportion of subcutaneous adipose tissue, particularly in the gluteofemoral region, whereas males tend to accumulate more visceral or muscular tissue, consistent with our current findings. Sex differences in dietary behaviors and nutritional quality[12, 50, 56] suggested that males are more inclined to consume red and processed meats, whereas females tend to favor higher intakes of vegetables, fruits, and low-fat dairy products. In response to unhealthy dietary patterns, males may demonstrate earlier or more pronounced adverse alterations in body composition, such as myosteatosis. Variations in dietary composition and caloric exposure may contribute directly to differences in body composition and metabolic outcomes, underscoring the importance of considering dietary quality in the analysis of sex-specific adipose tissue and muscle phenotypes.

While this study provides valuable insights, several methodological limitations must be acknowledged. As an observational investigation, our research shares the inherent constraints of all non-randomized studies, including potential residual confounding from unmeasured variables. The relatively modest sample size may affect the statistical power, potentially limiting the generalizability of certain findings. Due to limited sample size in early-stage (I/II) cohort and the inability to perform robust sensitivity analyses, only stage III and IV patients were enrolled. A notable limitation is the lack of an early-stage (I/II) cohort, precluding direct application of these results to early-stage CRC populations. The reliance on self-reported lifestyle and dietary data introduces possible measurement errors and recall bias, despite our use of validated assessment tools. These limitations might be partially offset via comprehensive adjustment for known confounders.

In conclusion, myosteatosis, the inconspicuous obesity phenotype, serves as a critical pathophysiological link mediating the association between pro-carcinogenic dietary patterns and elevated colorectal carcinogenesis, especially for advanced-stage patients. These pathological changes significantly correlated with dietary components characterized by excessive intake of animal-derived nutrients coupled with insufficient consumption of plant-based proteins, particularly from legumes. This provides a concrete mechanistic pathway supporting the "diet-induced carcinogenesis" model. Our findings underscore novel intervention opportunities beyond conventional risk factors; specifically, modulating body composition, particularly muscle quality, through targeted strategies, like resistance training and optimized protein intake involving the substitution of animal-based proteins with bean-derived alternatives could serve as a personalized preventive approach for mitigating ectopic fat deposition and potentially modifying CRC risk via improvements in body composition.

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DISCLOSURE ON THE USE OF AI AND AI-ASSISTED TECHNOLOGIES

The authors reviewed and edited the content and takes full responsibility for the content of the publication.

CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare no financial support or relationships that may pose a conflict of interest.

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REFERENCES

1. Abancens M, Bustos V, Harvey H, McBryan J, Harvey BJ. Sexual Dimorphism in Colon Cancer. Front Oncol. 2020; 10:607909. doi: 10.3389/fonc.2020.607909.
2. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. Gut. 2013; 62:933-47. doi: 10.1136/gutjnl-2013-304701.
3. Safizadeh F, Mandic M, Pulte D, Niedermaier T, Hoffmeister M, Brenner H. The underestimated impact of excess body weight on colorectal cancer risk: Evidence from the UK Biobank cohort. Br J Cancer. 2023; 129:829-37. doi: 10.1038/s41416-023-02351-6.
4. Li CW, Yu K, Shyh-Chang N, Jiang Z, Liu T, Ma S, et al. Pathogenesis of sarcopenia and the relationship with fat mass: descriptive review. J Cachexia Sarcopenia Muscle. 2022; 13:781-94. doi: 10.1002/jcsm.12901.
5. Jura M, Kozak LP. Obesity and related consequences to ageing. Age (Dordr). 2016; 38:23. doi: 10.1007/s11357-016-9884-3.
6. Nunan E, Wright CL, Semola OA, Subramanian M, Balasubramanian P, Lovern PC, et al. Obesity as a premature aging phenotype-implication for sarcopenic obesity. Geroscience. 2022; 44:1393-405. doi: 10.1007/s11357-022-00567-7.
7. Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: Emerging biological mechanisms and perspectives. Metabolism. 2019; 92:121-35. doi: 10.1016/j.metabol.2018.11.001.
8. Tarasiuk A, Mosińska P, Fichna J. The mechanisms linking obesity to colon cancer: An overview. Obes Res Clin Pract. 2018; 12:251-59. doi: 10.1016/j.orcp.2018.01.005.
9. van Dijk DPJ, Zhao J, Kemter K, Baracos VE, Dejong CHC, Rensen SS, et al. Ectopic fat in liver and skeletal muscle is associated with shorter overall survival in patients with colorectal liver metastases. J Cachexia Sarcopenia Muscle. 2021; 12:983-92. doi: 10.1002/jcsm.12723.
10. Malietzis G, Aziz O, Bagnall NM, Johns N, Fearon KC, Jenkins JT. The role of body composition evaluation by computerized tomography in determining colorectal cancer treatment outcomes: a systematic review. Eur J Surg Oncol. 2015; 41:186-96. doi: 10.1016/j.ejso.2014.10.056.
11. Hendifar A, Yang D, Lenz F, Lurje G, Pohl A, Lenz C, et al. Gender disparities in metastatic colorectal cancer survival. Clin Cancer Res. 2009; 15:6391-7. doi: 10.1158/1078-0432.CCR-09-0877.
12. Turesky RJ. Mechanistic Evidence for Red Meat and Processed Meat Intake and Cancer Risk: A Follow-up on the International Agency for Research on Cancer Evaluation of 2015. Chimia (Aarau). 2018; 72:718-24. doi: 10.2533/chimia.2018.718.
13. Kalinkovich A, Livshits G. Sarcopenic obesity or obese sarcopenia: A cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main

mechanism of the pathogenesis. Ageing Res Rev. 2017; 35:200-21. doi: 10.1016/j.arr.2016.09.008.

14. Pring ET, Malietzis G, Gould LE, Lung P, Drami I, Athanasiou T, et al. Tumour grade and stage are associated with specific body composition phenotypes with visceral obesity predisposing the host to a less aggressive tumour in colorectal cancer. Eur J Surg Oncol. 2022; 48:1664-70. doi: 10.1016/j.ejso.2022.03.012.
15. García Almeida JM, García García C, Vegas Aguilar IM, Bellido Castañeda V, Bellido Guerrero D. Morphofunctional assessment of patient´s nutritional status: a global approach. Nutr Hosp. 2021; 38:592-600. doi: 10.20960/nh.03378.
16. Xiao J, Caan BJ, Weltzien E, Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA, et al. Associations of pre-existing co-morbidities with skeletal muscle mass and radiodensity in patients with non-metastatic colorectal cancer. J Cachexia Sarcopenia Muscle. 2018; 9:654-63. doi: 10.1002/jcsm.12301.
17. Mandic M, Safizadeh F, Niedermaier T, Hoffmeister M, Brenner H. Association of Overweight, Obesity, and Recent Weight Loss With Colorectal Cancer Risk. JAMA Netw Open. 2023;6: e239556. doi: 10.1001/jamanetworkopen.
18. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016; 66:115-32. doi: 10.3322/caac.21338.
19. Hennein R, Liu C, McKeown NM, Hoffmann U, Long MT, Levy D, Ma JT. Increased Diet Quality is Associated with Long-Term Reduction of Abdominal and Pericardial Fat. Obesity (Silver Spring). 2019; 27:670-7. doi: 10.1002/oby.22427.
20. Conti L, Del Cornò M, Gessani S. Revisiting the impact of lifestyle on colorectal cancer risk in a gender perspective. Crit Rev Oncol Hematol. 2020; 145:102834. doi: 10.1016/j.critrevonc.2019.102834.
21. Carr PR, Weigl K, Jansen L, Walter V, Erben V, Chang-Claude J, et al. Healthy Lifestyle Factors Associated With Lower Risk of Colorectal Cancer Irrespective of Genetic Risk. Gastroenterology. 2018; 155:1805-1815.e5. doi: 10.1053/j.gastro.2018.08.044.
22. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol (1985). 2004; 97:2333-38. doi: 10.1152/japplphysiol.00744.2004.
23. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008; 9:629-35. doi: 10.1016/S1470-2045(08)70153-0.
24. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31:1539-47. doi: 10.1200/JCO.2012.45.2722.
25. Conti C, Turri G, Gecchele G, Conci S, Zamboni GA, Ruzzenente A, Guglielmi A, Pedrazzani C. Sarcobesity Index Predicts Poor Disease-Specific Survival After Resection for Colorectal Cancer. J Surg Res. 2022; 279:398-408. doi: 10.1016/j.jss.2022.06.029.
26. Nishigori T, Tsunoda S, Okabe H, Tanaka E, Hisamori S, Hosogi H, Shinohara H, Sakai Y. Impact of Sarcopenic Obesity on Surgical Site Infection after Laparoscopic Total Gastrectomy. Ann Surg Oncol. 2016; 23:524-31. doi: 10.1245/s10434-016-5385-y.
27. Lee A, Kim YJ, Oh SW, Lee CM, Choi HC, Joh HK, et al. Cut-Off Values for Visceral Fat Area Identifying Korean Adults at Risk for Metabolic Syndrome. Korean J Fam Med. 2018; 39:239-46. doi: 10.4082/kjfm.17.0099.
28. Ebadi M, Tsien C, Bhanji RA, Dunichand-Hoedl AR, Rider E, Motamedrad M, Mazurak VC, Baracos V, Montano-Loza AJ. Skeletal Muscle Pathological Fat Infiltration (Myosteatosis) Is Associated with Higher Mortality in Patients with Cirrhosis. Cells. 2022; 11:1345. doi: 10.3390/cells11081345.
29. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents-an IDF consensus report. Pediatr Diabetes. 2007;8:299-306. doi: 10.1111/j.1399-5448.2007.00271.x.
30. Pedrazzani C, Conti C, Zamboni GA, Chincarini M, Turri G, Valdegamberi A, Guglielmi A. Impact of visceral obesity and sarcobesity on surgical outcomes and recovery after laparoscopic resection for colorectal cancer. Clin Nutr. 2020; 39:3763-70. doi: 10.1016/j.clnu.2020.04.004.
31. 31. Kim EY, Kim K, Kim YS, Ahn HK, Jeong YM, Kim JH, Kim JH, Choi WJ. Prevalence of and Factors Associated with Sarcopenia in Korean Cancer Survivors: Based on Data Obtained by the Korea National Health and Nutrition Examination Survey (KNHANES) 2008-2011. Nutr Cancer. 2017; 69:394-401. doi: 10.1080/01635581.2017.1267776.
32. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003; 35:1381-95. doi: 10.1249/01.MSS.0000078924. 61453.FB.
33. Mint Sidi Deoula M, El Kinany K, Hatime Z, Boudouaya HA, El Rhazi K. Meat and colorectal cancer in Middle Eastern and North African countries: update of literature review. Public Health Rev. 2020; 41:7. doi: 10.1186/s40985-020-00127-4.
34. Ma T, Tu K, Ou Q, Fang Y, Zhang C. Comparing the Associations of Dietary Patterns Identified through Principal Component Analysis and Cluster Analysis with Colorectal Cancer Risk: A Large Case-Control Study in China. Nutrients. 2023; 16:147. doi: 10.3390/nu16010147.
35. Klusek J, Nasierowska-Guttmejer A, Kowalik A, Wawrzycka I, Chrapek M, Lewitowicz P, Radowicz-Chil A, Klusek J, Głuszek S. The Influence of Red Meat on Colorectal Cancer Occurrence Is Dependent on the Genetic Polymorphisms of S-Glutathione Transferase Genes. Nutrients. 2019; 11:1682. doi: 10.3390/nu11071682.
36. Zhang S, Wang L, Jia X, Zhang J, Jiang H, Li W, et al. A Comparison between Dietary Consumption Status and Healthy Dietary Pattern among Adults Aged 55 and Older in China. Nutrients. 2022; 14:2778. doi: 10.3390/nu14132778.
37. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J Am Med Dir Assoc. 2020; 21:300-07. doi: 10.1016/j.jamda.2019.12.012.
38. Ghaben AL, Scherer PE. Adipogenesis and metabolic health. Nat Rev Mol Cell Biol. 2019; 20:242-58. doi: 10.1038/s41580-018-0093-z.
39. Bimurzayeva A, Kim MJ, Ahn JS, Ku GY, Moon D, Choi J, et al. Three-dimensional body composition parameters using automatic volumetric segmentation allow accurate prediction of colorectal cancer outcomes. J Cachexia Sarcopenia Muscle. 2024; 15:281-91. doi: 10.1002/jcsm.13404.
40. Suriben R, Chen M, Higbee J, Oeffinger J, Ventura R, Li B, et al. Antibody-mediated inhibition of GDF15-GFRAL activity reverses cancer cachexia in mice. Nat Med. 2020; 26:1264-70. doi: 10.1038/s41591-020-0945-x.

41. Brown JC, Caan BJ, Prado CM, Cespedes Feliciano EM, Xiao J, Kroenke CH, Meyerhardt JA. The Association of Abdominal Adiposity With Mortality in Patients With Stage I-III Colorectal Cancer. J Natl Cancer Inst. 2020; 112:377-83. doi: 10.1093/jnci/djz150.
42. Armstrong V, Stretch C, Fitzgerald L, Gopaul A, McKinnon G, Koziak J, et al. Characterizing cancer-associated myosteatosis: anatomic distribution and cancer-specific variability of low radiodensity muscle. JCSM Rapid Communications. 2021; 4:197-206.
43. Obniski R, Sieber M, Spradling AC. Dietary Lipids Modulate Notch Signaling and Influence Adult Intestinal Development and Metabolism in Drosophila. Dev Cell. 2018; 47:98-111. doi: 10.1016/j.devcel.2018.08.013.
44. Vernia F, Longo S, Stefanelli G, Viscido A, Latella G. Dietary Factors Modulating Colorectal Carcinogenesis. Nutrients. 2021; 13:143. doi: 10.3390/nu13010143.
45. Wang P, Song M, Eliassen AH, Wang M, Giovannucci EL. Dietary patterns and risk of colorectal cancer: a comparative analysis. Int J Epidemiol. 2023; 52:96-106. doi: 10.1093/ije/dyac230.
46. Ma T, Tu K, Ou Q, Fang Y, Zhang C. Comparing the Associations of Dietary Patterns Identified through Principal Component Analysis and Cluster Analysis with Colorectal Cancer Risk: A Large Case-Control Study in China. Nutrients. 2023; 16:147. doi: 10.3390/nu16010147.
47. Friden M, Mora AM, Lind L, Riserus U, Kullberg J, Rosqvist F. Diet composition, nutrient substitutions and circulating fatty acids in relation to ectopic and visceral fat depots. Clin Nutr. 2023; 42:1922-31. doi: 10.1016/j.clnu.2023.08.013.
48. Cho YA, Lee J, Oh JH, Shin A, Kim J. Dietary Inflammatory Index and Risk of Colorectal Cancer: A Case-Control Study in Korea. Nutrients. 2016; 8:469. doi: 10.3390/nu8080469.
49. Gurjao C, Zhong R, Haruki K, Li YY, Spurr LF, Lee-Six H, et al. Discovery and Features of an Alkylating Signature in Colorectal Cancer. Cancer Discov. 2021; 11:2446-55. doi: 10.1158/2159-8290.CD-20-1656. doi: 10.1158/2159-8290.CD-20-1656.
50. Li CW, Yu K, Shyh-Chang N, Li GX, Yu SL, Liu HJ, et al. Sterol metabolism and protein metabolism are differentially correlated with sarcopenia in Asian Chinese men and women. Cell Prolif. 2021;54: e12989. doi: 10.1111/cpr.12989.
51. Beavers KM, Gordon MM, Easter L, Beavers DP, Hairston KG, Nicklas BJ, Vitolins MZ. Effect of protein source during weight loss on body composition, cardiometabolic risk and physical performance in abdominally obese, older adults: a pilot feeding study. J Nutr Health Aging. 2015; 19:87-95. doi: 10.1007/s12603-015-0438-7.
52. Mu Y, Kou T, Wei B, Lu X, Liu J, Tian H, et al. Soy Products Ameliorate Obesity-Related Anthropometric Indicators in Overweight or Obese Asian and Non-Menopausal Women: A Meta-Analysis of Randomized Controlled Trials. Nutrients. 2019; 11:2790. doi: 10.3390/nu11112790.
53. Chen JH, Song J, Chen Y, Ding Q, Peng A, Mao L. The Effect of Vegan Protein-Based Diets on Metabolic Parameters, Expressions of Adiponectin and Its Receptors in Wistar Rats. Nutrients. 2016; 8:643. doi: 10.3390/nu8100643.
54. Pankoke S, Pfarrer C, Glage S, Mühlfeld C, Schipke J. Oral Supplementation with the Polyamine Spermidine Affects Hepatic but Not Pulmonary Lipid Metabolism in Lean but Not Obese Mice. Nutrients. 2022; 14:4318. doi: 10.3390/nu14204318.
55. Zou Y, Pitchumoni CS. Obesity, obesities and gastrointestinal cancers. Dis Mon. 2023; 69 (12):101592. doi: 10.1016/j.disamonth.2023.101592.
56. Du C, Adjepong M, Zan MCH, Cho MJ, Fenton JI, Hsiao PY, et al. Gender Differences in the Relationships between Perceived Stress, Eating Behaviors, Sleep, Dietary Risk, and Body Mass Index. Nutrients, 2022;14(5):1045. doi: 10.3390/nu14051045.