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Total and regional fat-to-muscle mass ratio and risks of pan-cancer: a prospective cohort study

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Abstract

Background The fat-to-muscle mass ratio (FMR) has served as a marker for various diseases. This study aimed to explore sex-specific associations between FMR in different body regions (whole body, trunk, arm, and leg) and cancer incidence.

Methods We included 435,986 cancer-free participants (203,133 men and 232,853 women) from the UK Biobank at baseline. FMR was calculated as the ratio of fat mass to muscle mass in each body region. Multivariable Cox proportional hazards models, along with Cox models incorporating restricted cubic splines (RCS) function, were employed to examine both linear and non-linear associations between FMR and cancer risk in men and women. Additionally, a combined grouping of body mass index (BMI) and FMR was used to assess the joint impact of body composition on cancer incidence.

Results During the follow-up period, 62,060 new cancer cases were recorded. Our analysis showed significant associations between both total and regional FMR and the risk of several cancers. In men, higher whole body FMR was associated with an increased risk of esophagus, stomach, colorectal, liver, pancreas, and kidney cancers, while a decreased risk was observed for prostate and non-melanoma skin cancers (FDR < 0.05). In women, higher FMR was associated with a higher incidence of gallbladder, pancreas, kidney, thyroid, breast, and uterus cancers (FDR < 0.05). Non-linear associations were observed for several cancer types, with specific FMR cut-off points presented using RCS curves. The analysis by combining BMI and FMR suggested potential interaction patterns, revealing some masked risks; for example, a significant increase in cancer incidence was also observed in individuals exhibiting high FMRs despite having low BMI.

Conclusions Our findings suggested that both total and regional FMR may serve as potential biomarkers for assessing the risk of overall and site-specific cancers.

Keywords Fat-to-muscle mass ratio, Body mass index, Pan-cancer, UK Biobank

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Background

With the development of modern society and changes in people's lifestyles, cancer has become a leading cause of premature mortality globally [1]. Despite the huge breakthroughs we have made in cancer treatment, which have resulted in many cancer patients surviving longer and better, it still places a huge burden on society and economic development [2, 3]. This highlights the urgent need for identifying predictive markers that enable early detection and intervention. Overweight and obesity, defined as having a body mass index (BMI) of 25–29.9 kg/m^2 and ≥ 30 kg/m^2 respectively, were increasingly recognized as major risk factors for several common cancers [4–6]. The global cancer burden associated with obesity was expanding, affecting 11.9% of men and 13.1% of women. Previous researchers have identified a link between obesity and an increased risk of cancers at various anatomical sites, including the esophagus, kidney, pancreas, breast, and colorectal regions [7–10]. However, BMI alone as a measure of obesity has limitations. For example, individuals with a higher BMI may have a lower risk of mortality, a phenomenon known as the "obesity paradox" [11]. This discrepancy may be due to variations in body composition among individuals with similar BMI values, emphasizing the need for more accurate anthropometric measurements [12].

Previous studies have pointed out that muscle mass and strength played an important role in intervention for health and mortality and were also involved in the pathogenesis of many chronic diseases [13, 14]. Focusing on fat gain or loss alone was not enough when it came to obesity, and interpretation of muscle composition was essential to provide a comprehensive understanding of the physical condition. The fat-to-muscle mass ratio (FMR) was a combination of fat and muscle metrics, which provided more comprehensive insights compared with traditional measures such as BMI, waist circumference, and waist-to-hip ratio [15, 16]. Bioelectrical impedance analysis (BIA) was a widely used tool for assessing body composition, which could estimate fat and muscle mass based on whole body conductivity. It has been developed and refined over time, allowing for an accurate assessment of health risks [17, 18]. Despite some measurement limitations, including easily influenced by hydration status, food intake, and skin temperature, BIA offered a direct evaluation of body composition. And previous studies comparing BIA with other methods concluded that BIA was a reliable alternative for estimating body composition. Its broad applicability and accuracy enhanced the clinical feasibility of using FMR for health assessment and screening [19, 20].

As an indicator of the balance between muscle and fat in the body, FMR has become a noteworthy factor in disease risks. Notably, multiple cohort studies have demonstrated that elevated FMR values were associated with an increased risk of type 2 diabetes, cardiovascular disease, and metabolic dysfunction-associated steatotic liver disease (MASLD), all of which shared underlying metabolic or endocrinological mechanisms [21–24]. Cancers, often associated with metabolic alterations, are a complex syndrome influenced by multiple factors, including changes in body composition such as reduced skeletal muscle mass and potential change of fat mass [25]. However, FMR for cancer-related studies has mainly focused on the effect of FMR on postoperative survival and cancer complications, with limited exploration of its association with cancer mortality and incidence of specific cancer types [26, 27].

An intriguing hypothesis suggested that fat mass represents the body's metabolic load, while muscle mass reflects metabolic capacity [28, 29]. The balance between these components was crucial for determining metabolic risk, rather than focusing on their absolute quantities. Both adipose tissue and skeletal muscle acted as endocrine organs, secreting hormones involved in autocrine, paracrine, and endocrine signaling, influencing both local and systemic metabolic functions [30]. Increased fat mass was linked to higher risks of insulin resistance, chronic inflammation, and metabolic diseases [31]. Muscle, however, supported better metabolic outcomes by enhancing insulin sensitivity and regulating oxidation [32]. As mentioned earlier, many cancers were also metabolically related [33]. The balance between fat and muscle may provide more insights into metabolic risk than separate measurements, highlighting the potential of FMR as a marker of metabolic health and a predictor of site-specific cancer risk. Given the variability in muscle and fat distribution, examining the relationships between FMR in areas like the arms, legs, and trunk, and cancer types could improve our understanding of the clinical implications of regional body composition [34]. Previous studies using BMI have not adequately accounted for the distinct physiological characteristics of muscle and fat, despite both contributing equally to body weight. The association between obesity and cancer development may vary across FMR levels. Given the established links between BMI and variables such as fat mass, muscle mass, and cancer incidence, we hypothesized that BMI might moderate the relationship between FMR and cancer risk, prompting joint analyses.

In this context, we conducted a comprehensive analysis between FMR in various body regions and overall cancer risk in different sexes, along with 21 site-specific cancers using a large prospective cohort from the UK Biobank. Initially, we examined linear relationships between FMR and various cancer types using the Cox proportional

hazards model. Subsequently, we explored potential nonlinear relationships using the Cox model with RCS function. We also examined the influence of BMI on these associations by stratifying participants based on their BMI and FMR levels. In conclusion, this research supported integrating FMR assessments into clinical practices for early cancer detection and prevention, emphasizing its potential utility in improving patient outcomes through targeted preventive strategies.

Methods

Study population

All data used in this investigation were obtained from the UK Biobank database. UK Biobank is a prospective cohort study involving over 500,000 community-dwelling adults aged 37–73 years old. Participants were recruited from various locations across the UK between 2006 and 2010 and completed self-administered questionnaires and relevant physical examinations. Further details are available at https://www.ukbiobank.ac.uk/. During the baseline period, biological samples were collected at various centers under strict quality control. Detailed information about the UK Biobank has been published previously [35]. All participants provided informed consent, and formal approval was obtained from the ethics committee. All data were made publicly available in the UKB repositories. In this study, participants with cancer at baseline (n = 56,286) and missing body composition data (muscle mass and fat mass for the whole body, trunk, arms, and legs; n = 11,441) were excluded. The final sample size for the main analysis was 435,986 (203,133 men and 232,853 women). Detailed information about participant selection was demonstrated in Fig. 1.

Exposure assessments

At baseline, trained personnel followed a standardized protocol to collect anthropometric data from participants. Staff measured height (cm) using a SECA 240 height measure (SECA, Hamburg, Germany). Weight (kg), body composition data (muscle mass and fat mass), and BMI were measured using the Tanita BC418MA (Tanita, Japan). BIA was employed to determine fat mass and predicted muscle mass in the trunk, left arm, right arm, left leg, and right leg. This technique was a reliable method for determining body composition across various ages, sexes, and body shapes [36, 37]. The FMR was calculated as the ratio of fat mass to predicted muscle mass in the corresponding area [23]. The arm FMR was calculated by combining data from both arms (arm FMR = fat mass (left arm + right arm)/muscle mass (left arm + right arm)), and similarly for the legs (leg FMR = fat mass (left leg + right leg)/muscle mass (left leg + right leg)).

Outcome assessments

Cancer outcomes were defined using ICD-10 coding (Additional file 1: Table S1). These data were provided by the National Cancer Registry. Outcome events were defined as the first cancer diagnosis, loss to follow-up, or end of follow-up, whichever occurred first. Follow-up time was calculated as the duration from baseline enrollment to the occurrence of outcome events. Finally, this analysis included overall cancer and 21 site-specific cancers, comprising 28,539 female patients and 33,521 male patients [38]. The number of cases and person-years with cancer were presented in Additional file 1: Table S2.

Covariates assessments

The possible confounding variables listed below were taken into account: age (years), race (non-White or White), center (East Midlands, London, North Eastern England, North West England, Scotland, South East England, South west England, Wales, West Midlands England, and Yorkshire and the Humber), BMI (kg/m^2), Index of Multiple Deprivation (IMD), qualification (A levels/AS levels or equivalent, College or University degree, CSEs or equivalent, NVQ or HND or HNC or equivalent, O levels/GCSEs or equivalent, other professional qualifications, or none of the above), smoking status (never, previous, or current), alcohol intake frequency (never, special occasions only, one to three times a month, once or twice a week, three to four times a week, or daily or almost daily), physical activity (high or low) evaluated by the standard: ≥ 75 min/week of vigorous intensity, or ≥ 150 min/week of moderate intensity, or an equivalent combination, family cancer history (yes or no), fruit intake (pieces/day), vegetable intake (tablespoons/day), fish intake (times/week), processed meat intake (once or more daily, 5–6 times a week, 2–4 times a week, once a week, less than once a week, or never). The IMD incorporates seven factors in its evaluation, including income deprivation, employment deprivation, health and disability deprivation, educational skills and training deprivation, housing and service barriers, living environment deprivation, and crime. These factors were combined to form a composite multiple deprivation index using appropriate weights and it provided a more complex and detailed evaluation criterion for regional poverty levels. The analysis of the female also included oral contraceptive use, hormone replacement therapy, and menopausal status. At baseline, these factors were assessed by trained staff or collected using an interactive touchscreen questionnaire. A large number of missing cases existed in the UK Biobank database. Missing data for covariates were shown in Additional file 1: Table S3.

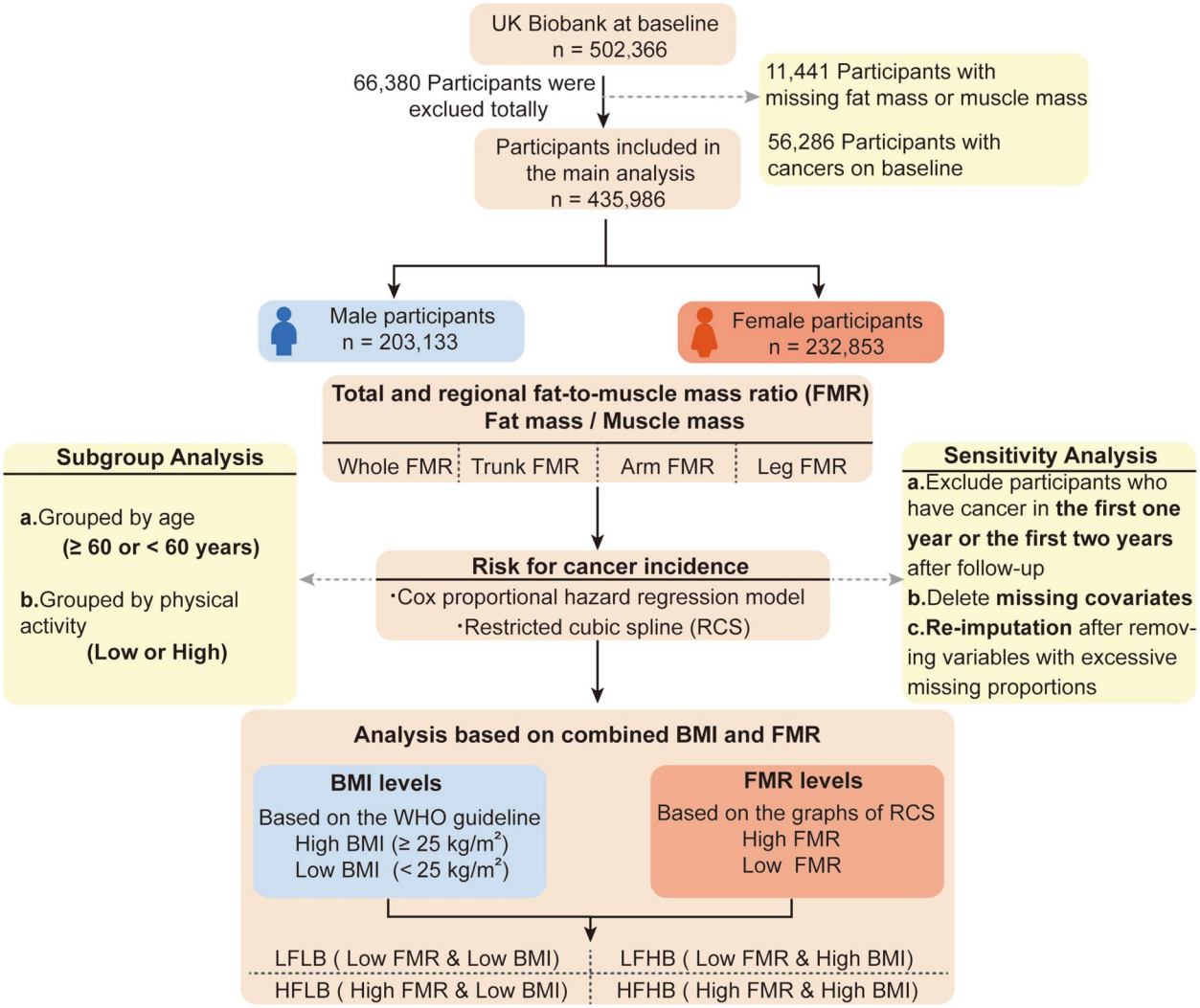

Fig. 1 Flowchart of the study

To maintain an adequate sample size, we used multiple imputations to handle missing covariates in the primary analysis. We performed multiple imputations using the mice package (version 3.16.0) in R software (version 4.4.1). The analysis employed the Fully Conditional Specification (FCS) method, which was formally equivalent to Multivariate Imputation by Chained Equations (MICE) and demonstrated high flexibility in handling mixed variable types [39]. FCS accommodates mixed variable types (continuous, binary, categorical) and iteratively imputes missing values on a variable-by-variable basis, applying variable type-specific regression models [40]. We generated 5 imputed datasets, following standard recommendations to ensure stable parameter estimates. Data comparisons before and after imputation were presented in Additional file 1: Table S4.

Statistical analyses

Since sexual differences in body composition were well-established, all analyses were categorized by gender. Baseline characteristics of individuals with and without cancer were reported. Continuous variables were presented as means and standard deviations (SDs). For categorical variables, we reported percentages relative to the total number of participants in each category. The study design was shown in Fig. 1. First, we analyzed the associations between total and regional FMR and various cancers in men and women using Cox proportional hazards regression models. Results were presented as hazard ratios (HR) and 95% confidence intervals (CI). We employed Cox regression models with RCS function to examine potential non-linear effects of FMR on the risk of incident cancer. Previous studies have shown that 3 to 5 knots are typically sufficient and the knot with the

lowest Akaike Information Criterion (AIC) was selected [41, 42]. In cases of multiple knots with the same AIC, the smallest number of knots was chosen to balance overfitting and optimal fit in cancer splines. In comparison, AIC at 4 knots was relatively smallest among 3 to 5 knots, supporting our choice of 4 knots. The median FMR value was used as a reference point for the RCS. Sensitivity analyses were conducted for the following scenarios: (1) exclusion of missing variables, (2) exclusion of individuals who experienced a cancer incident within 1 or 2 years to avoid reverse causation, and (3) exclusion of variable with a missing value proportion greater than 20%.

Considering the overall evaluation of BMI, we then explored the joint association between the FMR and BMI categories. Since BMI serves as an evaluation index of general body condition, we only performed combined analysis with the whole body FMR. BMI was categorized according to the World Health Organization (WHO) criteria, with a cut-off value of 25 kg/m^2 [21]. Individuals with BMI $\geq$25 kg/m^2 were considered to have a high BMI, while those with BMI $<$25 kg/m^2 were classified as low. We define the "cut-off point" as the threshold where the relationship between the independent and dependent variables changes significantly. The points intersecting the "HR = 1" line on the RCS curves were selected as the cut-off point [43–45]. We classified FMR as high or low using cutoff points of 0.36 for whole body FMR in men and 0.61 for whole body FMR in women.

Both BMI and FMR were categorized as high and low, resulting in four combinations: LFLB (low FMR and low BMI; reference group), LFHB (low FMR and high BMI), HFLB (high FMR and low BMI), and HFHB (high FMR and high BMI). We conducted subgroup analyses to investigate the relationship between FMR and pan-cancer, stratified by age ($<$ 60 or $\geq$60 years old) and physical activity (high or low). All analyses were conducted using R statistical software (version 4.4.1). Statistical significance was determined using a two-sided *P* value. We adjusted *P* values for the false discovery rate (FDR) in the primary analyses to control for false-positive results.

Results

Baseline characteristics

The baseline characteristics of participants were illustrated in Table 1. A total of 435,986 participants were included in the analyses, consisting of 203,133 men and 232,853 women. During the follow-up period, 62,060 new cancer cases were diagnosed among the participants. Participants who developed cancer at follow-up had relatively high FMR. In addition, these cancer patients tended to be older whites. From a socio-demographic perspective, they were relatively less educated, had lower IMD, and had higher rates of family history of cancer. From a lifestyle perspective, people with cancer were more likely to be or have been exposed to tobacco and to drink alcohol more often. For female participants, additional factors were examined, including menopausal status, use of oral contraceptives, and hormone therapy. Among the female participants, menopause and use of hormone therapy were more common, and the use of oral contraceptives was relatively low among those diagnosed with cancer at subsequent follow-up.

We also compared the baseline characteristics of included and excluded participants, and the results were shown in the Additional file 1: Table S5. Excluded participants tended to be older, had a higher proportion of White, higher BMI, lower educational level, higher IMD, and were more likely to engage in lifestyle habits such as smoking and drinking. They also tended to have lower physical activity, a relatively healthy diet, and a family history of cancer. Female participants excluded from the study were more likely to be postmenopausal, have more use of hormonal therapy, and have less frequent contraceptive use.

Linear relationship between total and regional FMR and cancer outcomes

The associations of FMR with the risk of different types of cancer were presented in Fig. 2. After adjusting for a wide range of covariates, we observed significant positive associations between whole body FMR and the risk of several cancers in men and women separately. The influence of whole body FMR varied across different cancer types. An elevated whole body FMR was significantly associated with an increased risk of overall cancer in female participants (HR = 1.13, 95% CI: 1.06–1.21, *FDR* < *0.001*); however, this relationship was reversed in male participants (HR = 0.89, 95% CI: 0.80–0.98, *FDR* = *0.021*). Consistently, for female participants, significant associations were observed for cancers of the bladder (HR = 2.65, 95% CI: 1.28–5.47, *FDR* = *0.021*), breast (HR = 1.64, 95% CI: 1.45–1.85, *FDR* < *0.001*), gallbladder (HR = 5.93, 95% CI: 2.44–14.44, *FDR* = *0.006*), kidney (HR = 3.39, 95% CI: 2.10–5.47, *FDR* < *0.001*), non-melanotic skin (HR = 0.54, 95% CI: 0.48–0.60, *FDR* < *0.001*), ovary (HR = 1.56, 95% CI: 1.09–2.23, *FDR* = *0.036*), pancreas (HR = 2.59, 95% CI: 1.63–4.12, *FDR* < *0.001*), thyroid (HR = 2.38, 95% CI: 1.30–4.37, *FDR* = *0.015*), and uterus (HR = 13.90, 95% CI:10.82–17.86, *FDR* < *0.001*). The observed associations predominantly involved cancers of the digestive, urinary, reproductive, and endocrine systems. In contrast, male participants demonstrated more significant associations with cancers of the digestive system, including esophagus (HR = 11.90, 95% CI: 6.19–22.88, *FDR* < *0.001*), stomach (HR = 2.66, 95% CI: 1.16–6.09, *FDR* = *0.047*), colorectal (HR = 3.16, 95% CI: 2.27–4.39, *FDR* < *0.001*), liver (HR

Table 1 Baseline characteristics of study participants ($n = 435,986$), stratified by cancer status at the end of follow-up

Characteristics	Female			Male		
	No cancer ***n = 204,314***	**Cancer** ***n = 28,539***	***P***	**No cancer** ***n = 169,612***	**Cancer** ***n = 33,521***	***P***
Whole FMR *(mean ± SD)*	0.63 ± 0.19	0.64 ± 0.19	*< 0.001*	0.36 ± 0.11	0.37 ± 0.11	*< 0.001*
Trunk FMR *(mean ± SD)*	0.56 ± 0.20	0.58 ± 0.20	*< 0.001*	0.41 ± 0.13	0.42 ± 0.13	*< 0.001*
Arm FMR *(mean ± SD)*	0.65 ± 0.26	0.66 ± 0.26	*< 0.001*	0.32 ± 0.11	0.32 ± 0.10	*< 0.001*
Leg FMR *(mean ± SD)*	0.73 ± 0.17	0.75 ± 0.17	*< 0.001*	0.30 ± 0.10	0.31 ± 0.10	*< 0.001*
Age, *years (mean ± SD)*	55.64 ± 8.02	58.86 ± 7.32	*< 0.001*	55.41 ± 8.23	60.66 ± 6.50	*< 0.001*
Center, *n (%)*			*< 0.001*			*< 0.001*
East Midlands	13,827 (6.77)	1936 (6.78)		11,287 (6.65)	2352 (7.02)	
London	24,629 (12.05)	2864 (10.04)		19,277 (11.37)	3226 (9.62)	
North Eastern England	23,378 (11.44)	3282 (11.50)		19,610 (11.56)	3980 (11.87)	
North West England	30,830 (15.09)	4645 (16.28)		26,783 (15.79)	5596 (16.69)	
Scotland	14,440 (7.07)	2416 (8.47)		11,272 (6.65)	2638 (7.87)	
South East England	17,718 (8.67)	2834 (9.93)		13,995 (8.25)	3132 (9.34)	
South West England	23,214 (11.36)	3391 (11.88)		18,402 (10.85)	3609 (10.77)	
Wales	8890 (4.35)	777 (2.72)		7621 (4.49)	882 (2.63)	
West Midlands England	17,191 (8.41)	2246 (7.87)		16,247 (9.58)	3084 (9.20)	
Yorkshire and the Humber	30,197 (14.78)	4148 (14.53)		25,118 (14.81)	5022 (14.98)	
Ethnic, *n (%)*			*< 0.001*			*< 0.001*
White	184,137 (90.12)	26,320 (92.22)		153,499 (90.50)	31,263 (93.26)	
Others	20,177 (9.88)	2219 (7.78)		16,113 (9.50)	2258 (6.74)	
Qualification, *n (%)*			*< 0.001*			*< 0.001*
A levels/AS levels or equivalent	24,689 (12.08)	3285 (11.51)		18,063 (10.65)	3259 (9.72)	
College or University degree	65,846 (32.23)	8429 (29.54)		59,348 (34.99)	10,613 (31.66)	
CSEs or equivalent	11,653 (5.70)	1287 (4.51)		10,394 (6.13)	1205 (3.59)	
Other professional qualifications	11,705 (5.73)	1753 (6.14)		7251 (4.28)	1772 (5.29)	
NVQ or HND or HNC or equivalent	9377 (4.59)	1262 (4.42)		15,104 (8.91)	3390 (10.11)	
O levels/GCSEs or equivalent	48,076 (23.53)	6686 (23.43)		32,267 (19.02)	6074 (18.12)	
None of the above	32,968 (16.14)	5837 (20.45)		27,185 (16.03)	7208 (21.50)	
IMD *(mean ± SD)*	17.10 ± 13.79	16.50 ± 13.50	*< 0.001*	17.87 ± 14.45	16.64 ± 13.85	*< 0.001*
BMI, *kg/m^2 (mean ± SD)*	27.07 ± 5.18	27.26 ± 5.20	*< 0.001*	27.86 ± 4.24	27.86 ± 4.10	*0.944*
Smoke, *n (%)*			*< 0.001*			*< 0.001*
Current	17,625 (8.63)	2777 (9.73)		21,386 (12.61)	4185 (12.49)	
Previous	62,174 (30.43)	9726 (34.08)		62,299 (36.73)	14,572 (43.47)	
Never	124,515 (60.94)	16,036 (56.19)		85,927 (50.66)	14,764 (44.04)	
Alcohol, *n (%)*			*< 0.001*			*< 0.001*
Daily or almost daily	32,103 (15.71)	5158 (18.07)		41,726 (24.60)	9640 (28.76)	
3 or 4 times a week	42,234 (20.67)	5810 (20.36)		44,359 (26.15)	8955 (26.71)	
1 or 2 times a week	53,046 (25.96)	7127 (24.97)		44,496 (26.23)	8258 (24.64)	
1 to 3 times a month	26,932 (13.18)	3582 (12.55)		15,595 (9.19)	2583 (7.71)	
Special occasions only	30,620 (14.99)	4301 (15.07)		12,533 (7.39)	2250 (6.71)	
Never	19,379 (9.48)	2561 (8.97)		10,903 (6.43)	1835 (5.47)	
Physical activity, *n (%)*			*0.009*			*0.416*
High	168,148 (82.30)	23,872 (83.65)		126,459 (74.56)	25,064 (74.77)	
Low	36,166 (17.70)	4667 (16.35)		43,153 (25.44)	8457 (25.23)	
Family history, *n (%)*			*< 0.001*			*< 0.001*
No	133,212 (65.20)	17,220 (60.34)		112,669 (66.43)	20,380 (60.80)	
Yes	71,102 (34.80)	11,319 (39.66)		56,943 (33.57)	13,141 (39.20)	
Fruit, *pieces/day (mean ± SD)*	3.34 ± 2.57	3.40 ± 2.57	*0.001*	2.75 ± 2.62	2.79 ± 2.50	*0.010*

Table 1 (continued)

Characteristics	Female			Male		
	No cancer ***n* = 204,314**	**Cancer** ***n* = 28,539**	***P***	**No cancer** ***n* = 169,612**	**Cancer** ***n*= 33,521**	***P***
Vegetable, *tablespoons/day (mean ± SD)*	5.11 ± 3.28	5.05 ± 3.06	*0.004*	4.68 ± 3.53	4.70 ± 3.20	*0.239*
Fish, *times/week (mean ± SD)*	3.44 ± 1.45	3.52 ± 1.39	*< 0.001*	3.36 ± 1.45	3.50 ± 1.38	*< 0.001*
Processed meat, *n (%)*			*< 0.001*			*< 0.001*
Once or more daily	785 (0.38)	96 (0.34)		2319 (1.37)	433 (1.29)	
5–6 times a week	3009 (1.47)	408 (1.43)		8908 (5.25)	1653 (4.93)	
2–4 times a week	38,568 (18.88)	5335 (18.69)		62,639 (36.93)	12,299 (36.69)	
Once a week	58,386 (28.58)	8331 (29.19)		50,039 (29.50)	10,391 (31.00)	
Less than once a week	77,364 (37.87)	11,150 (39.07)		36,049 (21.25)	7306 (21.80)	
Never	26,202 (12.82)	3219 (11.28)		9658 (5.69)	1439 (4.29)	
Menopausal, *n (%)*			*< 0.001*			
No	54,015 (26.44)	4374 (15.33)				
Yes	119,121 (58.30)	19,707 (69.05)				
Not sure (had a hysterectomy)	22,086 (10.81)	3503 (12.27)				
Not sure (other reason)	9092 (4.45)	955 (3.35)				
Oral contraceptive, *n (%)*			*< 0.001*			
No	37,444 (18.33)	6017 (21.08)				
Yes	166,870 (81.67)	22,522 (78.92)				
Hormone, *n (%)*			*< 0.001*			
No	130,296 (63.77)	15,450 (54.14)				
Yes	74,018 (36.23)	13,089 (45.86)				

Data were presented as mean ± SD for continuous variables and number (percentage) for categorical variables

FMR Fat-to-muscle mass ratio, *SD* Standard deviation, *BMI* Body mass index, *IMD* Index of multiple deprivation

= 37.57, 95% CI: 16.76–84.24, *FDR < 0.001*), and pancreas (HR = 3.32, 95% CI: 1.67–6.61, *FDR = 0.002*). Furthermore, for site-specific cancers in the systems mentioned above, whole body FMR was identified as a significant risk factor for kidney cancer (HR = 4.38, 95% CI: 2.40–8.01, FDR < *0.001*) and a protective factor for non-melanotic skin cancer (HR = 0.54, 95% CI: 0.45–0.64, *FDR < 0.001*). It's worth noting that whole body FMR was a significant protective factor for prostate cancer (HR = 0.56, 95% CI: 0.47–0.68, *FDR < 0.001*), which was part of the male reproductive system. Trends in whole body FMR and regional FMR (trunk, arm, and leg) were found to be similar, although some differences were noted (Additional file 1: Fig. S1, S2, and S3). There were some exceptional results where FMR did not show the same trend. In women, arm FMR and leg FMR lost significant association with ovary cancer. In men, trunk FMR and arm FMR, on the other hand, contributed to the development of gallbladder cancer.

Nonlinear relationship between total and regional FMR and cancer outcomes

We used the Cox model with RCS function to explore the non-linear relationship between FMR and cancer risk, as shown in Fig. 3. The curves were classified into several types based on their shape: concave upward, concave downward, positive U-shape, inverted U-shape, linear increase, and linear decrease. Moreover, the curves for specific cancer types intersected the horizontal line at "HR = 1" of different FMR types in women (0.61 for whole body FMR, 0.55 for trunk FMR, 0.60 for arm FMR, and 0.72 for leg FMR) and men (0.36 for whole body FMR, 0.40 for trunk FMR, 0.30 for arm FMR, and 0.29 for leg FMR). These threshold nodes were utilized for subsequent classification of groups. The detailed RCS result for site-specific cancers, categorized by gender, was provided in the supplementary materials (Additional file 1: Fig. S4, S5, S6, S7, S8, S9, S10, and S11).

The RCS function revealed a complex non-linear relationship between certain cancers and various FMR. In men, all four FMR demonstrated non-linear associations with the risk of lung, esophagus, and prostate cancers. The whole body FMR and the leg FMR also exhibited non-linear associations with the risk of bladder and head and neck cancers. In women, whole body FMR, arm FMR, and leg FMR exhibited significant non-linear associations with total cancer, breast cancer, chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma, and esophagus cancer. Trunk FMR only showed non-linear

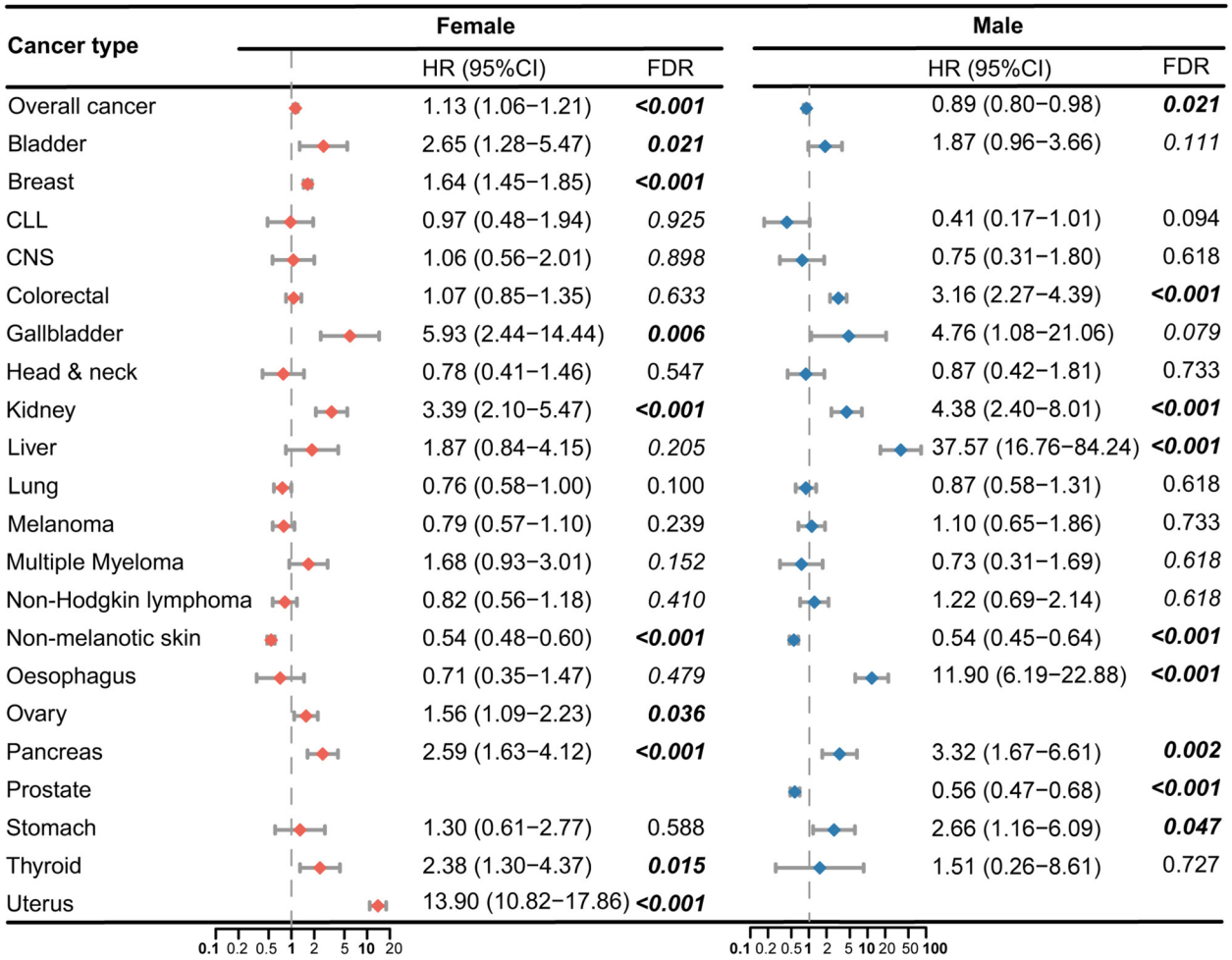

Fig. 2 Multivariable-adjusted HRs (95% CIs) for cancer outcomes by whole body FMR

To enhance the clarity of the figure, we opted to use logarithmic axes. Specifically, we adjusted the axis distances to reflect ratio values. Models were adjusted for age (years), race (non-White or White), center (East Mid-lands, London, North Eastern England, North West England, Scotland, South East England, South west England, Wales, West Midlands England, and Yorkshire and the Humber), BMI (kg/m2), Index of Multiple Deprivation (IMD), qualification (A levels/AS levels or equivalent, College or University degree, CSEs or equivalent, NVQ or HND or HNC or equivalent, O levels/GCSEs or equivalent, other professional qualifications, or none of the above), smoking status (never, previous, or current), alcohol intake frequency (never, special occasions only, one to three times a month, once or twice a week, three to four times a week, or daily or almost daily), physical activity (high or low), family cancer history (yes or no), fruit intake (pieces/ day), vegetable intake (tablespoons/day), fish intake (times/ week), processed meat intake (once or more daily, 5–6 times a week, 2–4 times a week, once a week, less than once a week, or never). We also incorporated menopausal, oral contraceptive use, and hormone replacement therapy in the analysis for females. HR, hazard ratio; CI, confidence interval; CNS, central nervous system; CLL, chronic lymphocytic leukemia

associations with breast cancer, CLL, and esophagus cancer.

Joint grouping of BMI and whole body FMR

As a well-established and extensively studied indicator, BMI was utilized to assess the degree of obesity. This indicator has been well-established, validated, and extensively studied [46]. In contrast, FMR focused on the health effects of the balance between muscle and fat mass in the body [47]. These two indices offered complementary value, as they assessed human health from different dimensions. We therefore investigated the combined effects of FMR and BMI on cancer risk. Since BMI was an index for assessing general body condition, we conducted a combined analysis with whole body FMR. Both BMI and FMR were categorized into "high" and "low" groups, resulting in four distinct categories: LFLB (reference category), LFHB, HFLB, and HFHB (Fig. 4). The effects of BMI and FMR across

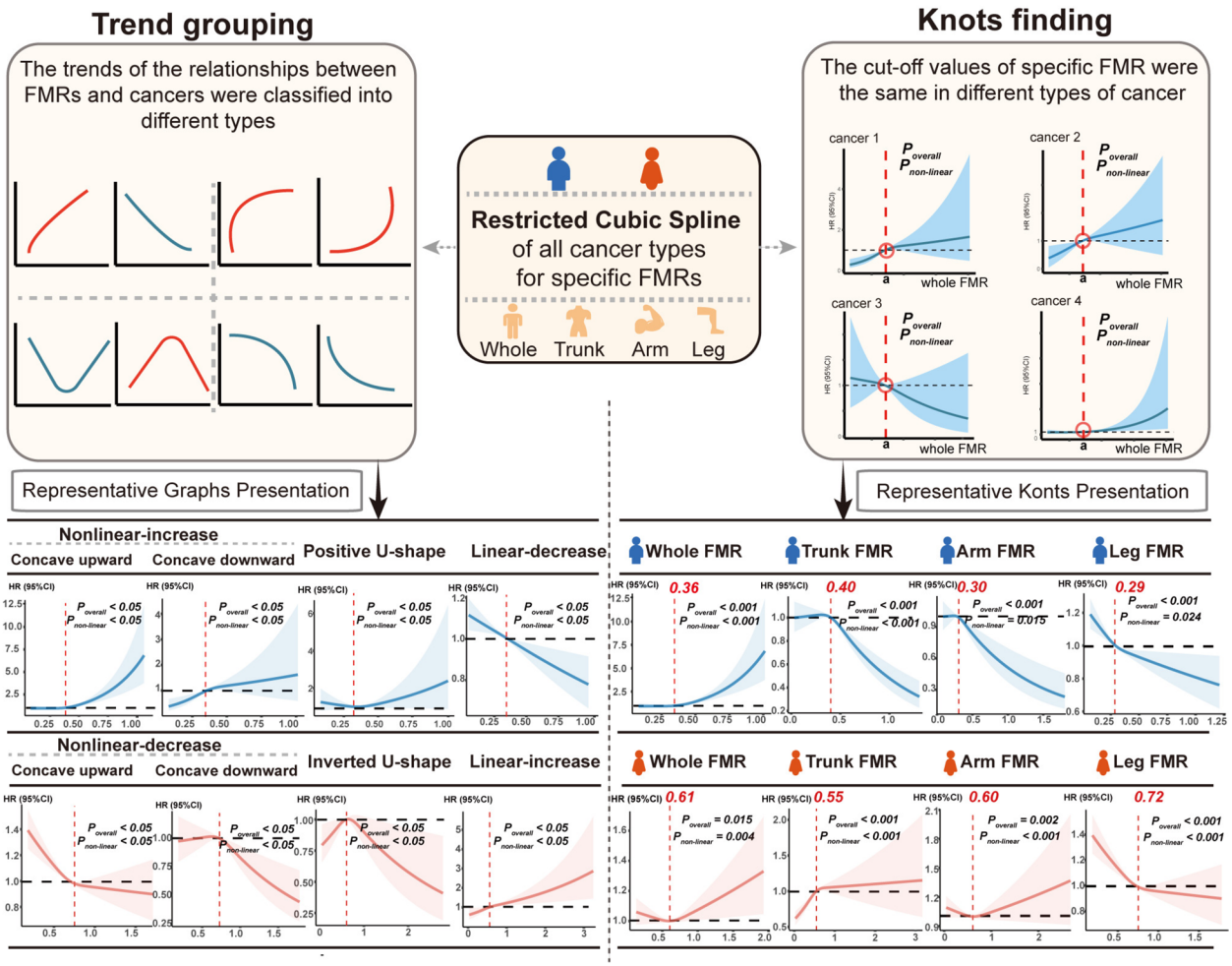

Fig. 3 Analysis of the shape of the relationship between FMR and cancer outcomes using the restricted cubic spline.

We presented key results achieved by RCS analysis, including the detection of nonlinear relationships and the identification of FMR thresholds. On the left, we presented some representative patterns of the mechanisms observed in all nonlinear relationships (nonlinear-increase, linear-increase, nonlinear-decrease, linear-decrease, positive U-shape, inverted U-shape). The reported *p*-values served to demonstrate the statistical significance of the RCS plots. Complete nonlinear analysis for all cancer types were presented in Additional file 1:Fig. S4–S11. On the right, we showed different FMR thresholds on the RCS plots. In each RCS plot, the first P represented the *P*-value for overall, and the second P represented the *P*-value of non-linear Models were adjusted for age (years), race (non-White or White), center (East Mid-lands, London, North Eastern England, North West England, Scotland, South East England, South west England, Wales, West Midlands England, and Yorkshire and the Humber), BMI (kg/m2), Index of Multiple Deprivation (IMD), qualification (A levels/AS levels or equivalent, College or University degree, CSEs or equivalent, NVQ or HND or HNC or equivalent, O levels/GCSEs or equivalent, other professional qualifications, or none of the above), smoking status (never, previous, or current), alcohol intake frequency (never, special occasions only, one to three times a month, once or twice a week, three to four times a week, or daily or almost daily), physical activity (high or low), family cancer history (yes or no), fruit intake (pieces/day), vegetable intake (tablespoons/day), fish intake (times/week), processed meat intake (once or more daily, 5–6 times a week, 2–4 times a week, once a week, less than once a week, or never). We also incorporated menopausal, oral contraceptive use, and hormone replacement therapy in the analysis for females

these categories were graphically represented, clearly delineating risk profiles.

Our study identified three interaction patterns between BMI and FMR regarding cancer outcomes. In women with lung cancer, only those with HFLB showed a significant association with the disease, with higher BMI not increasing the risk. In breast or uterus cancer, both the HFLB and LFHB groups exhibited a significant risk, which increased further when both BMI and FMR were elevated. Similarly, in non-melanoma skin cancer, LFHB acted as a protective factor, with this effect being stronger when both BMI and FMR were elevated. The final pattern was significantly associated with outcomes only when both BMI and FMR were high (HFHB), and this was observed in gallbladder, kidney, and thyroid cancers in women. In men, HFHB was found to amplify the effects

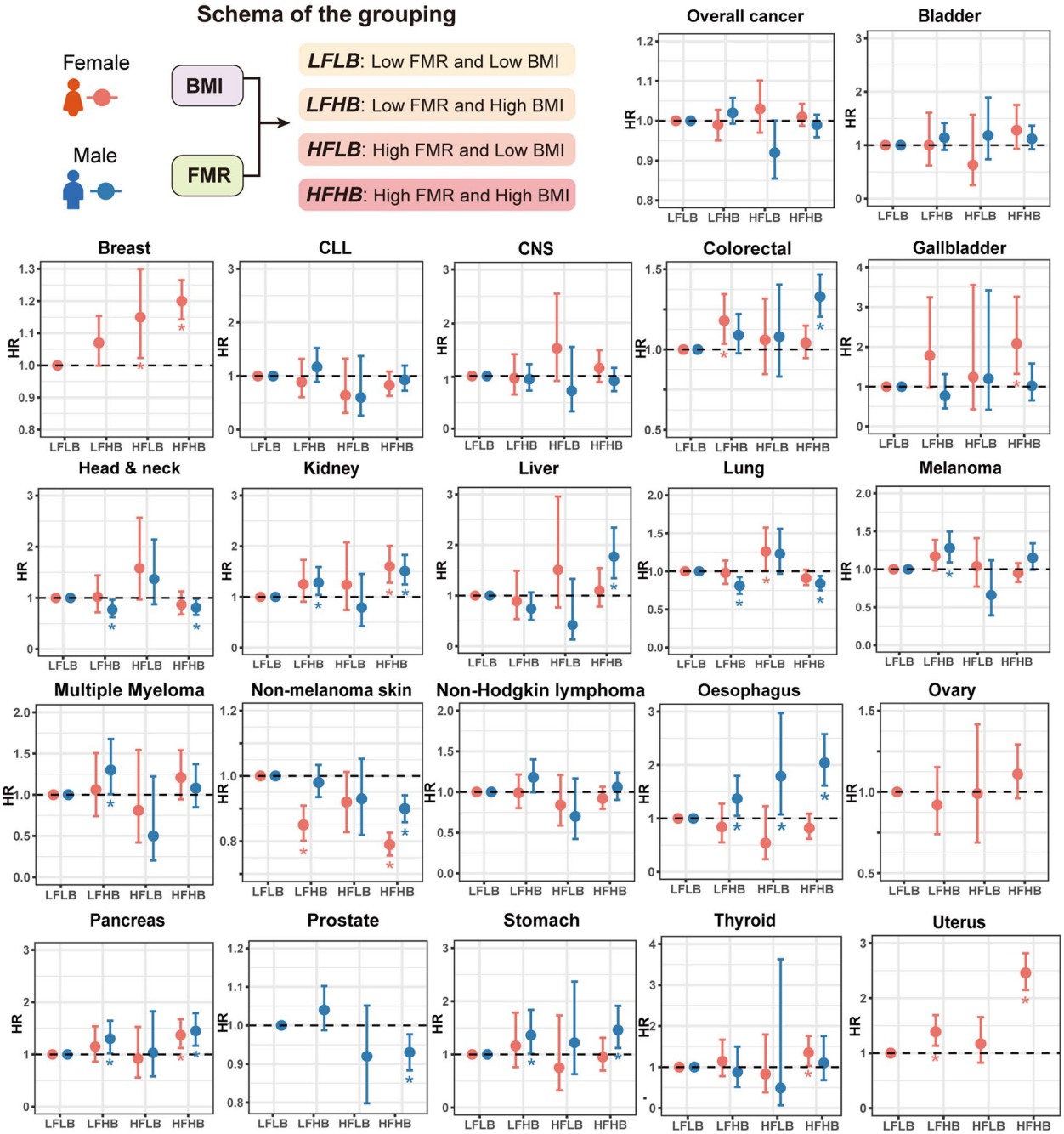

Fig. 4 Multivariable-adjusted HRs (95% CIs) for cancer outcomes by joint grouping of BMI and whole body FMR

Herein were the groupings based on the cut-off values of whole body FMR and BMI. Then we conducted Cox regression on the categorical variable, and models were adjusted for age (years), race (non-White or White), center (East Midlands, London, North Eastern England, North West England, Scotland, South East England, South west England, Wales, West Midlands England, and Yorkshire and the Humber), BMI (kg/m^2), Index of Multiple Deprivation (IMD), qualification (A levels/AS levels or equivalent, College or University degree, CSEs or equivalent, NVQ or HND or HNC or equivalent, O levels/GCSEs or equivalent, other professional qualifications, or none of the above), smoking status (never, previous, or current), alcohol intake frequency (never, special occasions only, one to three times a month, once or twice a week, three to four times a week, or daily or almost daily), physical activity (high or low), family cancer history (yes or no), fruit intake (pieces/day), vegetable intake (tablespoons/day), fish intake (times/week), processed meat intake (once or more daily, 5–6 times a week, 2–4 times a week, once a week, less than once a week, or never). We also incorporated menopausal, oral contraceptive use, and hormone replacement therapy in the analysis for females. FMR, fat-to-muscle ratio; BMI, body mass index; CNS, central nervous system; CLL, chronic lymphocytic leukemia

of individual BMI (LFHB) and FMR (HFLB) in head and neck, kidney, lung, esophagus, pancreas, and stomach cancers. However, in colorectal, liver, and prostate cancers, a significant impact on outcomes was observed only when both BMI and FMR were at high levels (HFHB). To simplify their relationship, we classified the potential patterns into several terms. These patterns were classified as "independent," where changes in FMR alone significantly impacted cancer risk; "synergistic," where changes in either BMI or FMR were significant, but the effect was stronger when both changed together; and "interactive," where the effect was significant only when both BMI and FMR changed simultaneously. This generalization may be incomplete, and further research could be helpful to clarify the interaction between the two.

Subgroup analyses

Subgroup analyses examined the relationships between various FMR levels and specific cancer types across different populations. Participants were categorized based on age and physical activity levels. Age was categorized into two groups: under 65 years and 65 years or older. Physical activity was classified as either high or low. Significant interaction between FMR and age or physical activity has not been observed in most cancers. In women with older age, whole body FMR was generally associated with a more increased risk of overall cancer, breast cancer, multiple myeloma, and non-melanoma skin cancer, but a decreased risk of pancreatic and stomach cancers. In women with physical inactivity, however, whole body FMR had a more detrimental effect on overall cancer, stomach cancer, and non-melanoma skin cancer. In addition to that, the risk of colorectal, kidney, liver, prostate, and non-melanoma skin cancers in men varied across different age groups. The risk of colorectal and kidney cancers was higher in younger age groups, while the risk for other types was higher in older age groups (Additional file 1: Table S6). The findings suggested that age-related and activity-related changes may influence cancer susceptibility. Results from subgroup analyses of the other three FMR types were presented in the additional file 1 (Additional file 1: Table S7, S8, and S9).

Sensitivity analyses

In the sensitivity analyses, three primary tests were performed to assess the robustness of the results. First, the analysis was repeated after excluding participants who had cancer disease within 1 year of the initial follow-up (Additional file 2: Fig. S1, S2, S3, and S4). The results were generally consistent with the primary analysis. For the male population, the correlation between whole body FMR and trunk FMR with overall cancer risk exhibited a loss of statistical significance. Next, the exclusion criteria were expanded to include participants who had cancer within 2 years of the initial follow-up, and the conclusions remained unchanged (Additional file 2: Fig. S5, S6, S7, and S8). This analysis included the association between whole body FMR and trunk FMR with overall cancer risk, which once again lost statistical significance in men. Besides, we re-imputed after removing variables with an excessive proportion of missing (physical activity), and the results remained consistent with retaining this variable (Additional file 2: Fig. S9, S10, S11, and S12). Finally, participants with missing data were excluded, resulting in more conservative findings, with weaker associations for bladder and uterus cancers in women, and for overall cancer, gallbladder, prostate, and stomach cancers in men (Additional file 2: Fig. S13, S14, S15, and S16). Sensitivity analysis confirmed that the main analysis results were generally robust.

Discussion

This comprehensive prospective cohort study revealed a significant association between FMR of various body regions and the incidence of different types of cancer. Gender-specific differences were observed, with men showing a stronger association between FMR and cancer risk in overall cancer, colorectal, kidney, liver, non-melanotic skin, esophagus, pancreas, prostate, and stomach. Conversely, women exhibited significant effects of FMR on overall cancer risk, as well as on cancers of the bladder, breast, gallbladder, kidney, non-melanotic skin, ovary, pancreas, thyroid, and uterus. Our primary focus was on examining the association between whole body FMR and various types of cancer, while also comparing the findings with those of specific FMR for the trunk, arm, and leg. We employed Cox model with RCS function to examine the non-linear relationships between FMR and cancer risk, which uncovered significant non-linear responses in certain cancers, occasionally reversing the direction of risk association. BMI was a widely utilized measure of overall body condition. The cohort was stratified into four groups according to the combinations of BMI and FMR, revealing that FMR significantly affected the incidence of certain cancers. These findings suggested that FMR could be a valuable body composition marker for cancer monitoring and prevention, though the varying impacts across different cancer types and between genders underscored the need for further refinement in its clinical application.

This was the first study that we are aware of that compared the impact of both total and regional FMR on the risk of different types of cancer. Prior research has primarily focused on traditional anthropometric measures,

such as BMI and waist circumference, to investigate the relationship between obesity and cancer risk. As the well-established and extensively studied indicators, numerous studies have demonstrated that BMI and waist circumference are significant risk predictors for cancer in multiple regions worldwide [48–51]. However, their limitations were becoming more pronounced with the development of personalized medicine [52]. Some reports have highlighted that BMI is not a direct measure of body fat, which means it can't reflect the distribution of fat in the body, and offer detailed insights into an individual's health or disease status. A low BMI might mask excess fat, while a high BMI could obscure high lean mass. Instead, studies suggested that obesity should be assessed using direct measurements of body fat or at least one anthropometric criterion alongside BMI [53]. Studies from diverse geographical regions have separately examined the impacts of fat and muscle on cancer risk. For instance, in a UK cohort study, visceral and subcutaneous adipose tissues, along with adiposity in different body regions, were implicated in influencing various cancers, including colorectal, stomach, pancreas, liver, esophagus, kidney, and bladder cancers [16]. Given that these previous studies demonstrated that conventional markers such as waist circumference and BMI may not adequately capture the complex relationship between body composition and cancer risk, FMR, which included both fat and muscle mass, could partially address this gap in this context [54, 55]. FMR offered a nuanced understanding by considering the relative balance between fat and muscle.

Generally, multiple studies have consistently identified the detrimental effects of excess fat and the protective role of skeletal muscle against the adverse impacts of excess adiposity [16, 56, 57]. However, the exact mechanisms linking fat and muscle tissues to cancer risk only remained partially understood. Inflammation and immunity stood out as key areas for exploring these connections. Obesity was recognized as a chronic, subclinical pro-inflammatory condition that is strongly associated with subsequent cancer development [58]. As an endocrine organ, adipose tissue secreted several adipokines, such as lipocalin, resistin, leptin, interleukin-6 (IL-6), and TNF-α (tumor necrosis factor-α) [59]. Adipokine secretion patterns were upset by the excessive growth of adipose tissue, which led to chronic inflammation and the development of several illnesses, including cancer. Furthermore, these variables complexly regulated the activities of different immune cells, such as macrophages and natural killer (NK) cells [60–62]. In contrast, skeletal muscle played a vital role in immune regulation and inflammatory responses through the secretion of myokines. Particularly, interleukin-15 (IL-15) became a key participant in modulating the development and function of immune cells, influencing NK cell proliferation, activation, and distribution [63, 64].

Oxidative stress emerged as another crucial mechanistic factor in the obesity-cancer relationship. It contributed to the transformation of cells into tumors by damaging cellular structures, such as DNA and proteins, through multiple pathways involving excessive production of reactive oxygen species (ROS) [65]. Adipose tissue, especially obesity-induced mast cells, could produce large amounts of ROS. These ROS directly damaged adipose tissue and promoted cancer by enhancing local inflammatory responses and altering hormone metabolism [66]. Muscle tissue, a metabolically active tissue, produced ROS during exercise and metabolism, where normal ROS levels were essential for its function [67]. However, in specific conditions, muscle secretion could indirectly influence cancer development by affecting the local redox state, impacting the tumor microenvironment [68]. Higher muscle mass could mitigate obesity-induced oxidative imbalance, while lower muscle mass resulted in local and systemic inflammation [56, 69]. Systemic inflammation, in turn, might cause persistent muscle loss and, to some extent, strengthened the association with disease [70]. A complex metabolic interaction existed between muscle and fat. Muscle loss could lead to fat imbalance, further promoting cancer development by increasing inflammatory responses and oxidative stress in adipose tissue [71].

We also observed that the predominant types of fat varied across different body sites. The trunk primarily consisted of abdominal fat, while the arms and legs mainly contained subcutaneous fat. Abdominal fat was partly classified as visceral fat, which had high metabolic activity and was linked to an increased risk of metabolic diseases, cardiovascular diseases, and certain cancers [72]. Fat in the arms and legs was generally considered subcutaneous fat, which had lower metabolic activity compared to visceral fat. Subcutaneous fat in the arms and legs is considered a "safer" fat deposit for metabolic health; however, a reduced ability to expand subcutaneous fat in certain body regions may also predict the incidence of these diseases [73]. Therefore, fat deposition in different body regions has varying impacts on health [74]. This partly accounted for the discrepancy observed in the results of different types of FMR.

The strengths of this study included the use of a large sample size, a prospective UKB cohort, and an extended follow-up period, with control for several variables. The impact of FMR was significantly enhanced by considering both muscle and fat mass, combining their effects to assess the association between FMR and pan-cancer outcomes, rather than focusing solely on the relationship between total fat mass and cancer outcomes. Additionally,

we assessed region-specific FMR alongside whole body FMR to identify potential differences and similarities.

We also acknowledged several limitations. First, as this was an observational study, causal relationships cannot be established. Additionally, we acknowledged that some cancers showed wide hazard ratios and confidence intervals, possibly due to the small sample size and measurement methods. A small proportion of results had limited statistical power and investigators should remain cautious and avoid using them as the sole basis for decision-making. Second, computed tomography and other techniques were not used to measure both the fat mass and muscle mass with high accuracy in the UK Biobank. A number of factors that affected bioimpedance results were necessary to control, thus reducing some of the bias in the results. Ethnic and gender differences were also observed when using BIA to assess muscle versus fat mass [75]. We recognized its limitations and recommend future studies using advanced imaging techniques to confirm our findings. Third, UKB participants were predominantly White British and healthier, which may have introduced selection bias and limited the generalizability of the results. Additionally, a large proportion of participants (> 10%) were excluded from the analysis. This may introduce selection bias. We examined and reported baseline characteristics of excluded individuals versus those in the analysis. Caution should be exercised when generalizing statistics to the general population and further analysis will be needed to generalize the findings to a wider population [76]. We also performed a subgroup analysis of age and exercise status. However, some results of hazard ratios and *P*-values indicated a higher risk in younger individuals or those who maintain ideal physical activity levels, which may seem counterintuitive. This may be limited by the total sample size and the number of people in a particular subgroup. We need a further investigation into the role of FMR in various cancer types and its validity as a metric for cancer prevention across diverse populations. Finally, reverse causality could be a concern, but the study adequately controlled for potential confounders by considering a wide range of known and suspected risk factors. Furthermore, our results remained unchanged after excluding patients who developed outcomes during the first 2 years of follow-up.

Conclusions

In summary, our study found a significant association between both total and regional FMR and cancer risk. Cox regression analysis revealed that in men, the risk of colorectal, kidney, liver, pancreas, and stomach cancers increased with higher FMR, while the risk of overall and non-melanoma skin cancers decreased. In women, the risk of bladder, gallbladder, kidney, ovary, pancreas, thyroid, and uterus cancers generally increased with higher FMR. The Cox model with RCS function indicated several non-linear relationships between FMRs and cancer risk. In men, FMR was non-linearly associated with the risk of lung, esophagus, prostate, bladder, and head and neck cancers. In women, FMR was significantly non-linearly associated with overall cancer, esophagus cancer, CLL, non-Hodgkin lymphoma, and breast cancer. By combining BMI and FMR, we gained new insights into managing their relationship effectively. These findings highlight the importance of early monitoring and management of FMR as a strategy to mitigate cancer risk. Given the correlation between FMR and cancer susceptibility, establishing an optimal FMR threshold to balance risks across cancer types is crucial. Further research is needed to refine our understanding of the complex interactions between muscle and adipose tissue in cancer pathogenesis.

Abbreviations

FMR	Fat-to-muscle mass ratio
RCS	Restricted cubic spline
BMI	Body mass index
BIA	Bioelectrical impedance assessment
MASLD	Metabolic dysfunction-associated steatotic liver disease
UKB	UK Biobank
SD	Standard deviation
IMD	Index of multiple deprivations
CI	Confidence interval
HR	Hazard ratio
AIC	Akaike information criterion
WHO	World Health Organization
FDR	False discovery rate
FCS	Fully Conditional Specification
MICE	Multivariate Imputation by Chained Equations
LFLB	Low FMR and low BMI
LFHB	Low FMR and high BMI
HFLB	High FMR and low BMI
HFHB	High FMR and high BMI
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor-α
NK	Natural killer cells
IL-15	Interleukin-15
ROS	Reactive oxygen species
DEXA	Dual-energy X-ray absorptiometry

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04102-1.

Additional File 1: Tables S1-S9 and Figures S1-S11. Table S1 – Diagnosis of cancer based on ICD10. Table S2 – The number of cases and person-years with cancer. Table S3 – The missing number and proportion of primary variables. Table S4 – Comparison of baseline characteristics of participants before and after multiple imputation. Table S5 – Comparison of baseline characteristics of included and excluded participants. Table S6 – Subgroup analysis of association between whole body FMR and cancer risk. Table S7 – Subgroup analysis of association between trunk FMR and cancer risk. Table S8 – Subgroup analysis of association between arm FMR and cancer risk. Table S9 – Subgroup analysis of association between leg FMR and cancer risk. Figure S1 – Multivariable-adjusted HRs for cancer outcomes by trunk FMR. Figure S2 – Multivariable-adjusted HRs for cancer outcomes by arm FMR. Figure S3 – Multivariable-adjusted HRs for cancer outcomes

by leg FMR. Figure S4 – RCS analysis of whole body FMR and all cancer outcomes in male participants. Figure S5 – RCS analysis of trunk FMR and all cancer outcomes in male participants. Figure S6 – RCS analysis of arm FMR and all cancer outcomes in male participants. Figure S7 – RCS analysis of leg FMR and all cancer outcomes in male participants. Figure S8 – RCS analysis of whole body FMR and all cancer outcomes in female participants. Figure S9 – RCS analysis of trunk FMR and all cancer outcomes in female participants. Figure S10 – RCS analysis of arm FMR and all cancer outcomes in female participants. Figure S11 – RCS analysis of leg FMR and all cancer outcomes in female participants

Additional File 2: Figures S1-S16. Figure S1 – Hazard ratios for cancer outcomes among whole body FMR based on the data by excluding patients diagnosed within one year of first follow-up. Figure S2 – Hazard ratios for cancer outcomes among trunk FMR based on the data by excluding patients diagnosed within one year of first follow-up. Figure S3 – Hazard ratios for cancer outcomes among arm FMR based on the data by excluding patients diagnosed within one year of first follow-up. Figure S4 – Hazard ratios for cancer outcomes among leg FMR based on the data by excluding patients diagnosed within one year of first follow-up. Figure S5 – Hazard ratios for cancer outcomes among whole body FMR based on the data by excluding patients diagnosed within two years of first follow-up. Figure S6 – Hazard ratios for cancer outcomes among trunk FMR based on the data by excluding patients diagnosed within two years of first follow-up. Figure S7 – Hazard ratios for cancer outcomes among arm FMR based on the data by excluding patients diagnosed within two years of first follow-up. Figure S8 – Hazard ratios for cancer outcomes among leg FMR based on the data by excluding patients diagnosed within two years of first follow-up. Figure S9 – Hazard ratios for cancer outcomes among whole body FMR based on the data by multiple imputed data after removing physical activity. Figure S10 – Hazard ratios for cancer outcomes among whole body FMR based on the data by multiple imputed data after removing physical activity. Figure S11 – Hazard ratios for cancer outcomes among arm FMR based on the data by multiple imputed data after removing physical activity. Figure S12 – Hazard ratios for cancer outcomes among leg FMR based on the data by multiple imputed data after removing physical activity. Figure S13 – Hazard ratios for cancer outcomes among whole body FMR based on the data by deleting missing covariates. Figure S14 – Hazard ratios for cancer outcomes among trunk FMR based on the data by deleting missing covariates. Figure S15 – Hazard ratios for cancer outcomes among arm FMR based on the data by deleting missing covariates. Figure S16 – Hazard ratios for cancer outcomes among leg FMR based on the data by deleting missing covariates

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Authors' contributions
Z.Q.L and X.W.H contributed supervision, paper revising, data analysis and editing. R.Z.W and Y.D.X contributed visualization, paper writing and paper revising. Y.S.W contributed guidance on biostatistics and paper revising. Y.Y.Z contributed visualization and paper revising. A.N.Z, S.T.L, Y.H.B, X.H, S.Y.W, Z.K.Z, H.X.M, P.L and Q.C contributed study design and paper revising. All authors read and approved the final manuscript.

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Data availability
This work has been conducted using the UK Biobank Resource (https://www.ukbiobank.ac.uk/). The UK Biobank is an open access resource and bona fide researchers can apply to use the UK Biobank dataset by registering and applying on the website. Further information is available from the corresponding author upon request. Resource data were obtained under Application Number 98680.

Declarations

Ethics approval and consent to participate
The UK Biobank study was approved by the National Research Ethics Service Committee North West-Haydock. And each participant gave their informed written consent. Resource data were obtained under Application Number 98680.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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