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Trabajo Original

Otros

Causal effect of sarcopenia-related traits on the occurrence and prognosis of breast cancer – A bidirectional and multivariable Mendelian randomization study

Efecto causal de los rasgos relacionados con la sarcopenia sobre la aparición y el pronóstico del cáncer de mama: estudio de aleatorización mendeliana bidireccional y multivariable

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Abstract

Background and aims: although sarcopenia is associated with several types of cancer, there is limited research regarding its effect on breast cancer. We aimed to explore the causality between sarcopenia-related traits and the incidence and prognosis of breast cancer.

Methods: two-sample bidirectional and multivariate Mendelian randomization (MR) analyses were utilized in this study. Genome-wide association studies were used to genetically identify sarcopenia-related traits, such as appendicular lean mass, grip strength of both hands, and walking pace. Data on the incidence and prognosis of breast cancer were collected from two extensive cohort studies. Multivariate MR analysis was used to adjust for body mass index, waist circumference, and whole-body fat mass. The primary method used for analysis was inverse-variance weighted analysis.

Results: a significant association was found between appendicular lean mass and ER- breast cancer (OR = 0.873, 95 % CI: 0.817-0.933, $p = 6.570 \times 10^{-5}$). Increased grip strength of the left hand was associated with a reduced risk of ER- breast cancer (OR = 0.744, 95 % CI: 0.579-0.958, p = 0.022). Stronger grip strength of the right hand was associated with prolonged survival time of ER+ breast cancer patients (OR = 0.463, 95 % CI: 0.242-0.882, $p = 0.019$). In the multivariable MR analysis, appendicular lean mass, grip strength of both hands, and walking pace were still genetically associated with the development of total breast cancer and ER-/+ breast cancer.

Conclusions: several sarcopenia-related traits were genetically associated with the occurrence and prognosis of breast cancer. It is crucial for elderly women to increase their strength and muscle mass to help prevent breast cancer.

Keywords:

Breast cancer. Sarcopenia-related traits. Risk factor. Causal relationship. Mendelian randomization.

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Consent to participate: informed consent was obtained from all individual participants included in the study.

Availability of data and materials: all GWAS summary statistics data in this study are publicly available for download by qualified researchers.

Author´s contributions: ZJH conceptualized and designed the study. LJZ, JH, and XWC collected the data. ZJH performed the analysis. All authors contributed to the interpretation of the results. LJZ, XYL, and JY offered professional suggestions and critical revisions to the article. ZJH and LJZ drafted the initial version of the manuscript. All authors critically reviewed many manuscript revisions and contributed important intellectual content. ZJH and JY had full access to all the data in the study and were responsible for the data's integrity, the accuracy of the analyses, and the final decision to submit the manuscript for publication.

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Resumen

Antecedentes y objetivos: aunque la sarcopenia se asocia a múltiples tipos de cáncer, los estudios sobre sus efectos sobre el cáncer de mama son limitados. Nuestro objetivo es explorar la relación causal entre las características relacionadas con la sarcopenia y la incidencia y el pronóstico del cáncer de mama.

Método: este estudio utilizó un análisis de aleatorización mendeliana (MR) bidireccional y multivariable de doble muestra. Los estudios de asociación genómica completa se utilizan para identificar genéticamente características relacionadas con la sarcopenia, como la masa magra apendicular, la fuerza de agarre de las manos y la velocidad al caminar. Los datos de incidencia y pronóstico del cáncer de mama provienen de dos amplios estudios de cohortes. El análisis de MR multivariable se utilizó para ajustar el índice de masa corporal, la circunferencia de la cintura y la masa grasa corporal total. El principal método de análisis fue el análisis ponderado por ANOVA inverso.

Resultados: la masa magra apendicular se asoció significativamente al cáncer de mama ER- (OR = 0,873, IC 95 %: 0,817-0,933, $p = 6{,}570 \times 10^{-5}$), el aumento de la fuerza de agarre del lado izquierdo se asoció a una disminución del riesgo de cáncer de mama ER- (OR = 0,744, IC 95 %: 0,579-0,958, $p = 0{,}022$) y el aumento de la fuerza de agarre del lado derecho se asoció a una mayor supervivencia de los pacientes con cáncer de mama ER+ (OR = 0,463, IC 95 %: 0,24-0,882, $P = 0{,}019$). En el análisis MR multivariable, la masa magra apendicular, la fuerza de agarre de ambas manos y la velocidad al caminar mantuvieron su asociación genética con la aparición del cáncer de mama total y del cáncer de mama ER-/+.

Conclusión: varios rasgos relacionados con la sarcopenia tienen correlación genética con la aparición y el pronóstico del cáncer. Mejorar la fuerza y la masa muscular de las mujeres mayores es fundamental para ayudar a prevenir el cáncer de mama.

Palabras clave:

Cáncer de mama. Rasgos relacionados con la sarcopenia. Factores de riesgo. Relación causal. Aleatorización mendeliana.

INTRODUCTION

Breast cancer is one of the three most common types of cancer worldwide, alongside lung and colon cancer (1). It has a high incidence, with approximately one in every eight to ten women developing breast cancer at some point in their lifetime (1). In 2020, the United States alone reported over 276,000 new cases of invasive breast cancer and over 48,000 cases of noninvasive breast cancer, according to data from the National Cancer Foundation (2). Despite numerous studies conducted on breast cancer, its incidence rate continues to rise, making it the leading cause of disease burden among women (3). Additionally, breast cancer is the second leading cause of death among females, underscoring the importance of further studying its risk factors (4). Various factors, including physical activity, hormones, and circulating lipids, have been proven to be associated with the occurrence and progression of breast cancer (5). Recent studies have indicated a potential association between sarcopenia and breast cancer, likely stemming from age-related muscle mass reduction, which is a significant risk factor in the elderly population (6,7).

Sarcopenia is a syndrome characterized by the progressive loss of skeletal muscle volume, strength, and function, which has been demonstrated to be associated with the development of various diseases (8). There is a strong association between sarcopenia and a higher risk of experiencing several detrimental health outcomes, including more severe postoperative complications, lower overall and progression-free survival rates, and extended hospital stays (9). In cancer patients, muscle mass is generally reduced, which is considered a crucial factor in predicting adverse clinical outcomes (10). Moreover, sarcopenia is closely linked to several types of cancer, such as esophageal, gastric, pancreatic, colorectal, and breast cancer (11). These studies highlight a significant correlation between sarcopenia and human diseases, particularly cancer.

Mendelian randomization (MR) is widely recognized as a credible method for elucidating causal relationships between exposures and outcomes, effectively controlling for confounding factors and avoiding reverse causation (12). By capitalizing on the natural randomness of alleles during meiosis, MR analysis can reveal the causal associations between exposures and outcomes. Single nucleotide polymorphisms (SNPs) serve as instrumental variables (IVs) in MR studies, as they are not influenced by potential environmental confounders or disease status (13). However, there remains a lack of MR investigations into the causal effects of sarcopenia-related traits on the incidence and prognosis of breast cancer. Therefore, we employed genetic variants strongly linked to sarcopenia-related traits to estimate the effects on breast cancer using two-sample bidirectional and multivariable MR analyses.

MATERIALS AND METHODS

STUDY DESIGN

Two-sample bidirectional and multivariate MR analyses were employed in this study based on the STROBE-MR statement (12). The MR analysis is based on the following three assumptions: a) assumption 1: the genetic IVs used in the analysis are strongly associated with the sarcopenia-related traits under investigation; b) assumption 2: the genetic IVs are not influenced by confounding factors that could introduce bias into the analysis; and c) Assumption 3: the genetic IVs solely affect the outcome through the exposure being studied and do not operate through other paths (14) (Fig. 1). The Mendelian randomization-Egger (MR-Egger), weighted median, heterogeneity test, pleiotropy test, and Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) methods were performed to assess the reliability of the associations and investigate the potential presence of horizontal pleiotropy in the IVs. Pleiotropy and heterogeneity tests were conducted to assess whether the genetic IVs exhibited pleiotropy or heterogeneity. By detecting and addressing outliers, the MR-PRESSO method helped improve the robustness and accuracy of the causal estimates obtained in the MR analysis (15). To assess the influence of outlying and pleiotropic SNPs on the

results, we conducted a leave-one-out sensitivity test. Since body mass index (BMI), waist circumference, and whole-body fat mass were the related confounding factors for sarcopenia-related traits and breast cancer, multivariate MR analysis was conducted to effectively control for possible confounding factors.

DATA SOURCE

Sarcopenia-related traits such as appendicular lean mass, hand grip strength (right and left), and walking pace were used as the exposures in this study. Appendicular lean mass is considered a reliable indicator of muscle mass (16). Appendicular lean mass data were calculated using bioelectrical impedance analysis with a large cohort of European individuals (n = 450,243), while also adjusting for appendicular fat mass and other covariates to account for potential confounding factors (16). Grip strength has been widely recognized as an important indicator of sarcopenia (17). The grip strength data were collected from 461,089 individuals of European descent for right-hand grip strength and 461,026 individuals for left-hand grip strength after adjusting for age and sex (18). Meanwhile, the data on walking pace were obtained from the summary-level statistic, which included 459,915 individuals of European ancestry (19). Genetic association summary statistics for breast cancer risk were obtained from two consortia: the Breast Cancer Association Consortium (BCAC), which consisted of 68 studies, and the Discovery, Biology, and Risk of Inherited Variants in Breast Cancer Consortium (DRIVE) (20). The study included data on the risk and survival time of breast cancer, including breast cancer (cases = 122,977, controls = 105,974), ER+ breast cancer (cases = 69,501, controls = 105,974), ER- breast cancer (cases = 21,468, controls = 105,974), survival time of breast cancer (cases = 2,900, controls = 35,054), ER+ breast cancer (cases = 1,333, controls = 21,726), and ER- breast cancer (cases = 920, controls = 5,961) (20,21). Detailed information about the data sources can be found in supplementary table I (https://www.nutricionhospitalaria.org/anexos/05139-01.pdf).

SELECTION OF GENETIC IVs

The IVs were selected based on rigorous criteria to ensure a strong correlation with sarcopenia-related traits. SNPs that showed a significant association ($p\text{-}value < 5 \times 10^{-8}$) with the traits were considered potential IVs. To avoid potential bias caused by linkage disequilibrium (LD), SNPs that might have existing LD were removed. The criteria for removal included a low possibility of LD ($R^2 < 0.001$) and a longer physical distance between the SNPs (≥ 10,000 kb) (22). The criterion of an F value ($F = Beta^2 / SE^2$) greater than 10 was used to validate the IVs in this study and avoid potential bias caused by weak instruments. Additionally, the IVs selected for this study underwent a thorough examination on the PhenoScanner website (http://www.phenoscanner.medschl.cam.ac.uk/) to account for any pleiotropic effects. The details of the IVs used in this study are presented in supplementary table II (https://www.nutricionhospitalaria.org/anexos/05139-01.pdf).

STATISTICAL ANALYSIS

All analyses were performed using the R software (Version 4.2.1). All analyses were based on the "TwoSampleMR" (Version 0.5.6) and "MR-PRESSO" (Version 1.0) R packages. The Bonferroni-corrected significance level of $p < 0.002$ (0.05 / 24) was utilized to avoid bias (23). A p-value between 0.002 and 0.05 was considered a suggestive association. A p-value larger than 0.05 indicated that there was no statistical association between the corresponding exposures and outcomes.

DATA AVAILABILITY STATEMENT

All GWAS summary statistics data in this study are publicly available for download by qualified researchers.

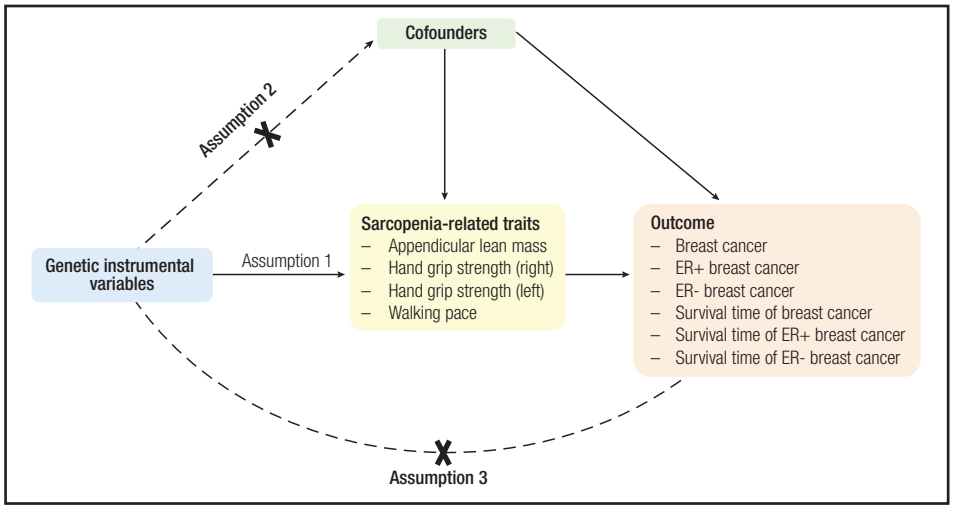

Figure 1.
Directed acyclic graph of this Mendelian randomization study.

Table I. Causal association between sarcopenia-related traits and breast cancer

Exposure	Outcome	Method	Number of IVs	OR (95 % CI)	*p*-value
Appendicular lean mass	Breast cancer	IVW	609	0.992 (0.942, 1.044)	0.751
		WM	609	1.000 (0.947, 1.056)	0.993
		MR Egger	609	1.019 (0.903, 1.148)	0.764
	ER+ breast cancer	IVW	609	1.023 (0.968, 1.082)	0.415
		WM	609	1.027 (0.964, 1.094)	0.410
		MR Egger	609	1.076 (0.945, 1.224)	0.269
	ER- breast cancer	IVW	609	0.873 (0.817, 0.933)	6.570×10^{-5}
		WM	609	0.845 (0.777, 0.920)	1.058×10^{-4}
		MR Egger	609	0.860 (0.735, 1.005)	5.811E-02
Hand grip strength (right)	Breast cancer	IVW	161	0.979 (0.811, 1.183)	0.826
		WM	161	0.917 (0.771, 1.091)	0.330
		MR Egger	161	0.673 (0.337, 1.347)	0.265
	ER+ breast cancer	IVW	161	1.013 (0.825, 1.244)	0.903
		WM	161	1.065 (0.879, 1.289)	0.522
		MR Egger	161	0.772 (0.362, 1.645)	0.503
	ER- breast cancer	IVW	161	0.843 (0.662, 1.074)	0.167
		WM	161	0.766 (0.584, 1.004)	0.054
		MR Egger	161	0.511 (0.210, 1.244)	0.141
Hand grip strength (left)	Breast cancer	IVW	145	0.936 (0.764, 1.146)	0.522
		WM	145	0.910 (0.762, 1.086)	0.296
		MR Egger	145	0.608 (0.277, 1.335)	0.217
	ER+ breast cancer	IVW	145	1.006 (0.809, 1.252)	0.955
		WM	145	1.028 (0.843, 1.255)	0.784
		MR Egger	145	0.791 (0.338, 1.848)	0.589
	ER- breast cancer	IVW	145	0.744 (0.579, 0.958)	*0.022*
		WM	145	0.751 (0.561, 1.003)	0.053
		MR Egger	145	0.368 (0.139, 0.973)	*0.046*
Walking pace	Breast cancer	IVW	53	0.731 (0.460, 1.161)	0.184
		WM	53	0.541 (0.381, 0.767)	*0.001*
		MR Egger	53	0.769 (0.116, 5.104)	0.786
	ER+ breast cancer	IVW	53	0.719 (0.440, 1.173)	0.186
		WM	53	0.491 (0.319, 0.754)	*0.001*
		MR Egger	53	0.898 (0.121, 6.646)	0.917
	ER- breast cancer	IVW	53	0.824 (0.410, 1.658)	0.588
		WM	53	0.927 (0.476, 1.803)	0.823
		MR Egger	53	0.786 (0.044, 13.921)	0.870

95 % CI: 95 % confidence interval; IV: instrumental variables; IVW: inverse-variance weighted; OR: odds ratio; WM: weighted median.

Table II. Causal association between sarcopenia-related traits and survival time of breast cancer

Exposure	Outcome	Method	Number of IVs	OR (95 % CI)	*p*-value
Appendicular lean mass	Survival time of breast cancer	IVW	597	0.971 (0.861, 1.096)	0.633
		WM	597	1.065 (0.874, 1.298)	0.534
		MR Egger	597	1.119 (0.849, 1.476)	0.425
	Survival time of ER+ breast cancer	IVW	596	0.918 (0.766, 1.099)	0.349
		WM	596	0.923 (0.695, 1.225)	0.578
		MR Egger	596	0.890 (0.589, 1.344)	0.578
	Survival time of ER- breast cancer	IVW	597	1.061 (0.855, 1.316)	0.592
		WM	597	1.383 (0.986, 1.941)	0.061
		MR Egger	597	1.206 (0.735, 1.981)	0.459
Hand grip strength (right)	Survival time of breast cancer	IVW	163	0.899 (0.584, 1.385)	0.630
		WM	163	0.812 (0.431, 1.528)	0.518
		MR Egger	163	1.738 (0.331, 9.127)	0.514
	Survival time of ER+ breast cancer	IVW	163	0.463 (0.242, 0.882)	*0.019*
		WM	163	0.577 (0.211, 1.579)	0.284
		MR Egger	163	3.308 (0.277, 39.553)	0.346
	Survival time of ER- breast cancer	IVW	163	1.099 (0.050, 24.044)	0.361
		WM	163	1.656 (0.545, 5.030)	0.373
		MR Egger	163	1.451 (0.653, 3.222)	0.952
Hand grip strength (left)	Survival time of breast cancer	IVW	149	0.879 (0.558, 1.383)	0.577
		WM	149	0.678 (0.341, 1.351)	0.269
		MR Egger	149	0.987 (0.164, 5.927)	0.989
	Survival time of ER+ breast cancer	IVW	149	0.525 (0.267, 1.033)	0.062
		WM	149	0.568 (0.207, 1.557)	0.271
		MR Egger	149	0.502 (0.034, 7.371)	0.616
	Survival time of ER- breast cancer	IVW	149	0.975 (0.404, 2.348)	0.954
		WM	149	1.498 (0.431, 5.214)	0.525
		MR Egger	149	3.818 (0.116, 126.131)	0.454
Walking pace	Survival time of breast cancer	IVW	55	0.651 (0.243, 1.746)	0.394
		WM	55	0.527 (0.137, 2.019)	0.350
		MR Egger	55	4.070 (0.045, 365.620)	0.543
	Survival time of ER+ breast cancer	IVW	55	1.311 (0.309, 5.565)	0.714
		WM	55	1.058 (0.120, 9.355)	0.959
		MR Egger	55	1.743 (0.002, 1400.155)	0.871
	Survival time of ER- breast cancer	IVW	56	0.284 (0.049, 1.629)	0.158
		WM	56	0.081 (0.007, 0.900)	*0.041*
		MR Egger	56	0.029 (1.219×10^{-5}, 70.757)	0.379

95 % CI: 95 % confidence interval; IV: instrumental variables; IVW: inverse-variance weighted; OR: odds ratio; WM: weighted median.

RESULTS

TWO-SAMPLE BIDIRECTIONAL MR ANALYSIS

The IVW results revealed associations between sarcopenia-related traits and breast cancer. Specifically, appendicular lean mass was found to be associated with the occurrence of ER- breast cancer (OR = 0.873, 95 % CI: 0.817-0.933, $p = 6.570 \times 10^{-5}$). Additionally, the grip strength of the right hand showed an effect on the survival time of ER+ breast cancer (OR = 0.463, 95 % CI: 0.242-0.882, $p = 0.019$), while the grip strength of the left hand was associated with the occurrence of ER- breast cancer (OR = 0.744, 95 % CI: 0.579-0.958, $p = 0.022$). However, no evidence was observed for other sarcopenia-related traits and breast cancer in the MR analysis. Reverse MR analysis revealed a significant association between the occurrence of breast cancer and lower grip strength in the right hand (OR = 0.990, 95 % CI: 0.980-1.000, $p = 0.043$). Furthermore, the survival time of ER-negative breast cancer was found to be significantly associated with walking pace (OR = 0.998, 95 % CI: 0.996-1.000, $p = 0.026$). There were no significant associations of the occurrence and prognosis of breast cancer with other sarcopenia-related traits. Tables I and II, supplementary table III (https://www.nutricionhospitalaria.org/anexos/05139-01.pdf), and figures 2 and 3 present the results of the two-sample bidirectional MR analysis.

Table III. Influence of sarcopenia-related traits on breast cancer and survival time of breast cancer after regulating BMI, waist circumference, and whole body fat mass by multivariate Mendelian randomization analysis

Exposure	Outcome	Method	Number of IVs	OR (95 % CI)	*p*-value
Appendicular lean mass	Breast cancer	IVW	453	0.968 (0.908, 1.031)	0.309
	ER+ breast cancer	IVW	453	0.989 (0.923, 1.059)	0.743
	ER- breast cancer	IVW	453	0.878 (0.810, 0.951)	*0.001*
	Survival time of breast cancer	IVW	481	0.979 (0.848, 1.130)	0.773
	Survival time of ER+ breast cancer	IVW	481	0.866 (0.696, 1.077)	0.195
	Survival time of ER- breast cancer	IVW	481	1.179 (0.908, 1.531)	0.216
Hand grip strength (right)	Breast cancer	IVW	49	0.740 (0.581, 0.943)	*0.015*
	ER+ breast cancer	IVW	49	0.799 (0.614, 1.041)	0.096
	ER- breast cancer	IVW	49	0.696 (0.502, 0.967)	*0.031*
	Survival time of breast cancer	IVW	55	0.822 (0.469, 1.442)	0.495
	Survival time of ER+ breast cancer	IVW	55	0.460 (0.190, 1.114)	0.085
	Survival time of ER- breast cancer	IVW	55	0.918 (0.314, 2.683)	0.875
Hand grip strength (left)	Breast cancer	IVW	46	0.695 (0.547, 0.883)	*0.003*
	ER+ breast cancer	IVW	46	0.732 (0.565, 0.948)	*0.018*
	ER- breast cancer	IVW	46	0.676 (0.488, 0.936)	*0.018*
	Survival time of breast cancer	IVW	51	0.653 (0.373, 1.145)	0.137
	Survival time of ER+ breast cancer	IVW	51	0.443 (0.183, 1.073)	0.071
	Survival time of ER- breast cancer	IVW	51	0.510 (0.172, 1.507)	0.223
Walking pace	Breast cancer	IVW	21	0.553 (0.342, 0.895)	*0.016*
	ER+ breast cancer	IVW	21	0.685 (0.406, 1.157)	0.158
	ER- breast cancer	IVW	21	0.491 (0.250, 0.965)	*0.039*
	Survival time of breast cancer	IVW	23	1.285 (0.395, 4.183)	0.677
	Survival time of ER+ breast cancer	IVW	23	4.586 (0.759, 27.728)	0.097
	Survival time of ER- breast cancer	IVW	23	0.206 (0.024, 1.802)	0.153

95 % CI: 95 % confidence interval; IV: instrumental variables; IVW: inverse-variance weighted; OR: odds ratio; WM: weighted median.

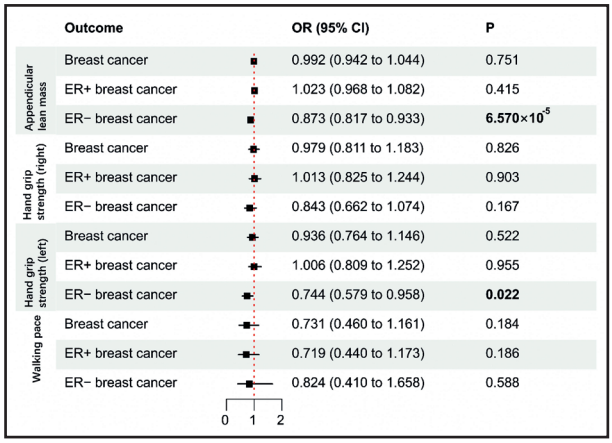

Figure 2.

Forest plot of two-sample bidirectional Mendelian randomization estimation of the causal association between sarcopenia-related traits and breast cancer (95 % CI: 95 % confidence interval; OR: odds ratio).

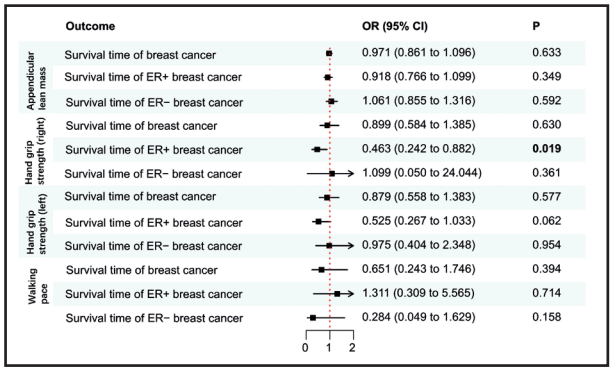

Figure 3.

Forest plot of two-sample bidirectional Mendelian randomization estimation of the causal association between sarcopenia-related traits and survival time of breast cancer (95 % CI: 95% confidence interval; OR: odds ratio).

MULTIVARIABLE MR ANALYSIS

After conducting multivariable MR analysis to control for BMI, waist circumference, and whole-body fat mass, we found a significant association between appendicular lean mass and the occurrence of ER- breast cancer (OR = 0.878, 95 % CI: 0.810-0.951, $p = 0.001$). Additionally, grip strength in the right hand was found to be related to the occurrence of breast cancer (OR = 0.740, 95 % CI: 0.581-0.943, $p = 0.015$), as well as ER- breast cancer (OR = 0.696, 95 % CI: 0.502-0.967, $p = 0.031$). Similarly, grip strength in the left hand was shown to be connected with the occurrence of breast cancer (OR = 0.695, 95 % CI: 0.547-0.883, $p = 0.003$), ER+ breast cancer (OR = 0.732, 95 % CI: 0.565-0.948, $p = 0.018$), and ER- breast cancer (OR = 0.676, 95 % CI: 0.488-0.936, $p = 0.018$). Furthermore, walking pace had a significant impact on the occurrence of both breast cancer (OR = 0.553, 95 % CI: 0.342-0.895, $p = 0.016$) and ER- breast cancer (OR = 0.491, 95 % CI: 0.250-0.965, $p = 0.039$). The results of the multivariable MR analysis are presented in table III.

SENSITIVITY ANALYSIS

To evaluate the credibility of the aforementioned findings, we conducted thorough sensitivity analyses. These entailed employing the heterogeneity test, pleiotropy test, MR-PRESSO test, and F statistics (Supplementary tables IV and V: https://www.nutricionhospitalaria.org/anexos/05139-01.pdf). The F values of all chosen IVs were higher than 10, indicating their effectiveness in minimizing potential bias. Additional information concerning the IVs can be found in supplementary table II. Furthermore, the scatter plot and funnel plot displayed the causal effect of appendicular lean mass on ER- breast cancer, grip strength of the left hand on ER- breast cancer, and grip strength of the right hand on survival time of ER+ breast cancer. These plots provide support for the reliability of the two-sample bidirectional MR results, as shown in supplementary figures 1-3 (https://www.nutricionhospitalaria.org/anexos/05139-01.pdf).

DISCUSSION

In this study, we evaluated the causal relationship between sarcopenia-related traits and the occurrence and prognosis of breast cancer. Appendicular lean mass was found to be connected with the occurrence of ER- breast cancer, the grip strength of the left hand was associated with ER- breast cancer, and higher grip strength of the right hand was connected with longer survival time of ER+ breast cancer in the two-sample bidirectional MR analysis. Multivariate MR analysis demonstrated that appendicular lean mass was related to ER- breast cancer; the grip strength of the right hand and walking pace were associated with the occurrence of total breast cancer and ER- breast cancer; and stronger grip strength of the left hand was connected with a lower risk of total breast cancer, ER+ breast cancer, and ER- breast cancer after adjusting for genetically predicted BMI, waist circumference, and whole-body fat mass.

Breast cancer is a prevalent malignancy among women. Its onset and progression are influenced by factors such as age, genetic factors including BRCA1 and BRCA2 gene mutations, and other significant contributors affecting women's health (24). In recent years, some studies have found that sarcopenia and other age-related metabolic diseases are related to the occurrence and development of breast cancer (25). Sarcopenia, commonly observed in cancer patients, could significantly impact their overall outcome (26). An observational study revealed a general decrease in muscle mass among breast cancer patients, highlighting the importance of early screening for sarcopenia symptoms (such as reduced muscle mass and grip strength) to effectively mitigate the risk of complications (27). A meta-analysis uncovered that sarcopenia significantly affected a wide

range of adverse health-related outcomes, particularly in patients with breast cancer (28). This observation aligns with the symptoms associated with sarcopenia observed in our study and the survival time of breast cancer patients. Similarly, myopenia plays a significant role in determining the prognosis of various types of cancer, such as resectable esophageal cancer, noninvasive bladder cancer, and pancreatic cancer (29-31). This finding aligned with the observed causal relationship between sarcopenia-related traits and survival time in breast cancer patients in our MR study. In recent years, several studies have highlighted a higher prevalence of sarcopenia in cancer patients, which significantly impacts their prognosis and quality of life (32,33). Furthermore, a study demonstrated a significant reduction in muscle mass among breast cancer patients undergoing chemotherapy (34). These findings supported the conclusion of our reverse-MR study, which revealed lower grip strength and walking speed in breast cancer patients. A randomized controlled trial assessed the associations of sarcopenia with poor performance status, increased mortality risk, and greater side effects in oncologic patients (35). Additionally, breast cancer patients exhibited markedly impaired muscle strength and joint dysfunctions both before and after anticancer treatment (35). In a 13-year cohort study by Betty Kane et al., which followed 3,241 women, it was discovered that muscular atrophy (low muscle mass) and poor muscle mass (low muscle radioactive density) were linked to higher mortality in patients with metastatic breast cancer and poor prognosis in patients with nonmetastatic breast cancer (36). Theresa Mader et al. conducted an experiment involving a physical exercise intervention on mice with breast cancer, which resulted in a significant improvement in muscle quality and the enhancement of their mitochondria and antioxidant status, suggesting a potential mechanism for myopenia affecting breast cancer (37). Moreover, a study employing deep-learning imageomics technology found that body muscle and fat content significantly impacted the distant metastasis and related prognosis of breast cancer patients (38). These findings aligned with our own observation that myopenia was closely related to the occurrence and development of breast cancer, even after adjusting for relevant confounding factors.

This study focused on identifying the causal effects of sarcopenia-related traits on the occurrence and prognosis of breast cancer. To enhance the interpretability of the results, we utilized multivariate MR analysis to eliminate the confounding effect of BMI, waist circumference, and whole-body fat mass. Additionally, to ensure accuracy, we employed Bonferroni correction to mitigate the risk of type-I error (23). Finally, the utilization of relevant phenotypic data derived from European cohorts for exposure and outcomes had the potential to significantly reduce population selection bias (39).

This study has several limitations. First, in the multivariate MR analysis, we considered only three vital risk factors for pancreatic cancer; other risk factors were not included due to data limitations. Second, the causal effects of sarcopenia-related traits on the occurrence and prognosis of breast cancer in populations of different races remain unknown due to the inclusion of predominantly European cohorts in this study. Third, future studies should explore in detail the potential mechanism of how sarcopenia-related traits affect the occurrence and prognosis of breast cancer.

CONCLUSION

In conclusion, our two-sample bidirectional and multivariable MR study revealed the genetic association between certain sarcopenia-related traits and the occurrence and prognosis of breast cancer. These findings suggested that older women should prioritize improving their muscle quality to effectively prevent the onset and progression of breast cancer.

REFERENCES

1. Harbeck N, Gnant M. Breast cancer. Lancet 2017;389(10074):1134-50. DOI: 10.1016/s0140-6736(16)31891-8
2. Nassif AB, Talib MA, Nasir Q, Afadar Y, Elgendy O. Breast cancer detection using artificial intelligence techniques: A systematic literature review. Artificial intelligence in medicine 2022;127:102276. DOI: 10.1016/j.artmed.2022.102276
3. Britt KL, Cuzick J, Phillips KA. Key steps for effective breast cancer prevention. Nature reviews Cancer 2020;20(8):417-36. DOI: 10.1038/s41568-020-0266-x
4. Torre LA, Siegel RL, Ward EM, Jemal A. Global Cancer Incidence and Mortality Rates and Trends--An Update. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2016;25(1):16-27. DOI: 10.1158/1055-9965.Epi-15-0578
5. Dixon-Suen SC, Lewis SJ, Martin RM, English DR, Boyle T, Giles GG, et al. Physical activity, sedentary time and breast cancer risk: a Mendelian randomisation study. British journal of sports medicine 2022;56(20):1157-70. DOI: 10.1136/bjsports-2021-105132
6. Burstein HJ, Curigliano G, Thürlimann B, Weber WP, Poortmans P, Regan MM, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol 2021;32(10):1216-35. DOI: 10.1016/j.annonc.2021.06.023
7. Petermann-Rocha F, Balntzi V, Gray SR, Lara J, Ho FK, Pell JP, et al. Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle 2022;13(1):86-99. DOI: 10.1002/jcsm.12783
8. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet 2019;393(10191):2636-46. DOI: 10.1016/s0140-6736(19)31138-9
9. Yuan S, Larsson SC. Epidemiology of sarcopenia: Prevalence, risk factors, and consequences. Metabolism: clinical and experimental 2023;144:155533. DOI: 10.1016/j.metabol.2023.155533
10. Prado CM, Orsso CE, Pereira SL, Atherton PJ, Deutz NEP. Effects of β-hydroxy β-methylbutyrate (HMB) supplementation on muscle mass, function, and other outcomes in patients with cancer: a systematic review. J Cachexia Sarcopenia Muscle 2022;13(3):1623-41. DOI: 10.1002/jcsm.12952
11. Williams GR, Dunne RF, Giri S, Shachar SS, Caan BJ. Sarcopenia in the Older Adult With Cancer. J Clin Oncol 2021;39(19):2068-78 DOI: 10.1200/jco.21.00102
12. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement. Jama 2021;326(16):1614-21. DOI: 10.1001/jama.2021.18236
13. Yao S, Zhang M, Dong SS, Wang JH, Zhang K, Guo J, et al. Bidirectional two-sample Mendelian randomization analysis identifies causal associations between relative carbohydrate intake and depression. Nature human behaviour 2022;6(11):1569-76. DOI: 10.1038/s41562-022-01412-9
14. Sekula P, Del Greco MF, Pattaro C, Köttgen A. Mendelian Randomization as an Approach to Assess Causality Using Observational Data. Journal of the American Society of Nephrology: JASN 2016;27(11):3253-65. DOI: 10.1681/asn.2016010098
15. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nature genetics 2018;50(5):693-8. DOI: 10.1038/s41588-018-0099-7
16. Pei YF, Liu YZ, Yang XL, Zhang H, Feng GJ, Wei XT, et al. The genetic architecture of appendicular lean mass characterized by association analysis in the

UK Biobank study. Communications biology 2020;3(1):608. DOI: 10.1038/s42003-020-01334-0
17. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48(1):16-31. DOI: 10.1093/ageing/afy169
18. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS medicine 2015;12(3):e1001779. DOI: 10.1371/journal.pmed.1001779
19. Liu C, Liu N, Zeng Y, Xiao B, Wang P, Zhou C, et al. COVID-19 and sarcopenia-related traits: a bidirectional Mendelian randomization study. Frontiers in endocrinology 2023;14:1162936. DOI: 10.3389/fendo.2023.1162936
20. Michailidou K, Lindström S, Dennis J, Beesley J, Hui S, Kar S, et al. Association analysis identifies 65 new breast cancer risk loci. Nature 2017;551(7678):92-4. DOI: 10.1038/nature24284
21. Guo Q, Schmidt MK, Kraft P, Canisius S, Chen C, Khan S, et al. Identification of novel genetic markers of breast cancer survival. Journal of the National Cancer Institute 2015;107(5). DOI: 10.1093/jnci/djv081
22. Chen X, Kong J, Pan J, Huang K, Zhou W, Diao X, et al. Kidney damage causally affects the brain cortical structure: A Mendelian randomization study. EBioMedicine 2021;72:103592. DOI: 10.1016/j.ebiom.2021.103592
23. Sedgwick P. Multiple hypothesis testing and Bonferroni's correction. BMJ (Clinical research ed) 2014;349:g6284. DOI: 10.1136/bmj.g6284
24. Nolan E, Lindeman GJ, Visvader JE. Deciphering breast cancer: from biology to the clinic. Cell 2023;186(8):1708-28. DOI: 10.1016/j.cell.2023.01.040
25. Escala-Garcia M, Morra A, Canisius S, Chang-Claude J, Kar S, Zheng W, et al. Breast cancer risk factors and their effects on survival: a Mendelian randomisation study. BMC Med 2020;18(1):327. DOI: 10.1186/s12916-020-01797-2
26. Gielen E, Dupont J, Dejaeger M, Laurent MR. Sarcopenia, osteoporosis and frailty. Metabolism: clinical and experimental 2023;145:155638. DOI: 10.1016/j.metabol.2023.155638
27. Morlino D, Marra M, Cioffi I, Santarpia L, De Placido P, Giuliano M, et al. Prevalence of Sarcopenia in Women with Breast Cancer. Nutrients 2022;14(9). DOI: 10.3390/nu14091839
28. Xia L, Zhao R, Wan Q, Wu Y, Zhou Y, Wang Y, et al. Sarcopenia and adverse health-related outcomes: An umbrella review of meta-analyses of observational studies. Cancer medicine 2020;9(21):7964-78. DOI: 10.1002/cam4.3428
29. Jogiat UM, Sasewich H, Turner SR, Baracos V, Eurich DT, Filafilo H, et al. Sarcopenia Determined by Skeletal Muscle Index Predicts Overall Survival, Disease-free Survival, and Postoperative Complications in Resectable Esophageal Cancer: A Systematic Review and Meta-analysis. Ann Surg 2022;276(5):e311-e8. DOI: 10.1097/sla.0000000000005452
30. Liu P, Chen S, Gao X, Liang H, Sun D, Shi B, et al. Preoperative sarcopenia and systemic immune-inflammation index can predict response to intravesical Bacillus Calmette-Guerin instillation in patients with non-muscle invasive bladder cancer. Front Immunol 2022;13:1032907. DOI: 10.3389/fimmu.2022.1032907
31. De Luca R, Gianotti L, Pedrazzoli P, Brunetti O, Rizzo A, Sandini M, et al. Immunonutrition and prehabilitation in pancreatic cancer surgery: A new concept in the era of ERAS® and neoadjuvant treatment. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2023;49(3):542-9. DOI: 10.1016/j.ejso.2022.12.006
32. Xie K, He D, Zhao T, Liu T, Tang M. Gastric Cancer with Sarcopenia: an Area Worth Focusing On. Current treatment options in oncology 2023;24(10):1305-27. DOI: 10.1007/s11864-023-01122-y
33. Ashton E, Arrondeau J, Jouinot A, Boudou-Rouquette P, Hirsch L, Huillard O, et al. Impact of sarcopenia indexes on survival and severe immune acute toxicity in metastatic non-small cell lung cancer patients treated with PD-1 immune checkpoint inhibitors. Clin Nutr 2023;42(6):944-53. DOI: 10.1016/j.clnu.2023.03.023
34. Jang MK, Park S, Park C, Doorenbos A, Go J, Kim S. Hematologic toxicities, sarcopenia, and body composition change in breast cancer patients undergoing neoadjuvant chemotherapy. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer 2023;31(7):419. DOI: 10.1007/s00520-023-07890-5
35. Klassen O, Schmidt ME, Ulrich CM, Schneeweiss A, Potthoff K, Steindorf K, et al. Muscle strength in breast cancer patients receiving different treatment regimes. J Cachexia Sarcopenia Muscle 2017;8(2):305-16. DOI: 10.1002/jcsm.12165
36. Caan BJ, Cespedes Feliciano EM, Prado CM, Alexeeff S, Kroenke CH, Bradshaw P, et al. Association of Muscle and Adiposity Measured by Computed Tomography With Survival in Patients With Nonmetastatic Breast Cancer. JAMA oncology 2018;4(6):798-804. DOI: 10.1001/jamaoncol.2018.0137
37. Mader T, Chaillou T, Alves ES, Jude B, Cheng AJ, Kenne E, et al. Exercise reduces intramuscular stress and counteracts muscle weakness in mice with breast cancer. J Cachexia Sarcopenia Muscle 2022;13(2):1151-63. DOI: 10.1002/jcsm.12944
38. Miao S, Jia H, Cheng K, Hu X, Li J, Huang W, et al. Deep learning radiomics under multimodality explore association between muscle/fat and metastasis and survival in breast cancer patients. Briefings in bioinformatics 2022;23(6). DOI: 10.1093/bib/bbac432
39. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. Genetic epidemiology 2016;40(7):597-608. DOI: 10.1002/gepi.21998