Central Obesity, Body Mass Index, Metabolic Syndrome and Mortality in Mediterranean Breast Cancer Patients

Anna Crispo
Istituto Nazionale Tumori-IRCCS “Fondazione G. Pascale”
Livia Silvia Augustin
Istituto Nazionale Tumori-IRCCS “Fondazione G. Pascale”
Assunta Luongo
Istituto Nazionale Tumori-IRCCS “Fondazione G. Pascale”
Claudia Calderaio
University of Naples Federico II
Joao Breda
WHO Athens Quality of Care Office
Sergio Coluccia
Istituto Nazionale Tumori-IRCCS “Fondazione G. Pascale”
Alessandra Calabrese
Istituto Nazionale Tumori - IRCCS, 'Fondazione Pascale'
Vittorio Marrazzo
University of Naples Federico II
Rosa Giannatiempo
Ospedale Evangelico Betania, Department of Pathology
Paola Trasacco
University of Naples Federico II
Elvira Palumbo
Istituto Nazionale Tumori-IRCCS “Fondazione G. Pascale”
Sara Vitale
Istituto Nazionale Tumori-IRCCS “Fondazione G. Pascale”
Giuseppe Porciello
Istituto Nazionale Tumori-IRCCS “Fondazione G. Pascale”
Piergiacomo Di Gennaro
Istituto Nazionale Tumori-IRCCS “Fondazione G. Pascale”
Roberta Caputo
Istituto Nazionale Tumori - IRCCS, 'Fondazione Pascale'
Giuseppe Buono
Istituto Nazionale Tumori - IRCCS, 'Fondazione Pascale'
Claudio Vernieri
IFOM ETS
Francesco Schettini
Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS
Maria Grimaldi
Istituto Nazionale Tumori-IRCCS “Fondazione G. Pascale”
Flavia Nocerino
Istituto Nazionale Tumori-IRCCS “Fondazione G. Pascale”
Egidio Celentano
Istituto Nazionale Tumori-IRCCS “Fondazione G. Pascale”
Alfonso Amore
Istituto Nazionale per lo Studio e la Cura dei Tumori, "Fondazione Pascale"-IRCCS
Mario Giuliano (mario.giuliano@unina.it)
University of Naples Federico II
Pietro De Placido
University of Naples Federico II
Carmine De Angelis
University of Naples Federico II
Roberto Bianco

University of Naples Federico II
Michelino De Laurentiis
Istituto Nazionale Tumori - IRCCS, 'Fondazione Pascale'
Carlo La Vecchia
Università degli Studi di Milano
Grazia Arpino
University of Naples Federico II

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Abstract

Background: Obesity and metabolic disorders have been associated with poorer outcomes in many cohorts

of breast cancer (BC) patients, with poor evidence from Mediterranean cohorts. The purpose of this study is to investigate the prognostic potential of anthropometric variables in early BC patients living in a Southern region of Italy.

Methods: This prospective cohort study enrolled 955 consecutive early BC patients treated at the Istituto Nazionale dei Tumori "G. Pascale" and at the University Hospital "Federico II", Naples, Italy, between January 2009 and December 2013. Median follow-up was 11.8 years and ended on June 15th 2022. Anthropometric measurements and indices namely body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), as well as Metabolic Syndrome (MetS) and its components, were collected. All-cause and BC-specific mortality were calculated.

Results: Mean age was 55.3 years (±12.5 years); 61% of patients were post-menopausal. At data cut-off, 208 (22%) patients had died, 131 (14%) of whom from BC. Obesity was found in 29% of patients. High WC or WHR and the presence of MetS were associated with a moderately increased risk of all-cause mortality (WC ≥ 88 cm, HR=1.39, 95%CI:1.00-1.94; WHR > 0.85, HR=1.62, 95%CI:1.12-2.37; MetS, HR=1.61, 95%CI:1.12-2.32). An increased BC-specific mortality risk was found in obese patients (HR=1.72, 95%CI:1.06-2.78), in those with WC ≥88 (HR=1.71, 95%CI:1.12-2.61)and in those with high WHR, both when evaluated as a categorical variable (WHR>0.85, HR=1.80, 95%CI:1.13-2.86) and as a continuous variable (for each 0.1-U increase in WHR, HR=1.33, 95%CI:1.08-1.63) as well as the presence of MetS (HR=1.81, 95%CI:1.51-2.85). These associations varied according to menopausal status and BC subtype.

Conclusions: Central obesity significantly increased total and BC-specific mortality particularly in pre-menopausal women, while in post-menopause the MetS was a stronger risk factor. These associations were significant mainly in luminal subtypes while no relevant findings were observed in TNBC. The magnitude of risk suggests that obesity and the presence of the MetS or its single components may nullify the benefit of effective BC therapies. Active lifestyle intervention studies should be encouraged for several expected beneficial effects.

Introduction

Breast cancer (BC) was the first cause of cancer incidence in women and the fifth cause of cancer mortality globally in 2020.[1] In Europe, the highest incidence rates were observed in Northern and Western Europe and the lowest in Southern Europe. However, 5-year survival rates have been increasing in all European countries, particularly in Northern and Western Europe.[2] These differences in cancer incidence and survival could be related to several risk factors, among which non-modifiable and modifiable risk factors.[2] Among modifiable risk factors, obesity was closely associated with an increased risk of cancer and with poorer outcomes in cancer patients, particularly BC patients.[3]

In most studies, obesity was defined on the basis of body mass index (BMI) which represents a surrogate of total body adiposity. The later approach is widely used in epidemiological studies as it can be simply calculated on the basis of patient weight and height.[4] However, other anthropometric measurements such as waist circumference (WC), and waist-to-hip ratio (WHR) are used to estimate the presence of central adiposity and they are considered more accurate indicators of cancer risk than body weight.[5]·[6] In a study of American BC survivors, high WC and WHR were associated with a worse overall and BC-specific survival.[7] However, American Black BC survivors may have a different body composition and fat distribution compared to European Caucasians. They may also have a different exposure to other modifiable risk factors such as food-related behaviors and the well-known negative features of Western U.S. diets that are associated with an increased overall mortality among BC survivors.[4]·[8]

Herein we investigated the prognostic potential of the anthropometric variables body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) together with a diagnosis of Metabolic Syndrome (MetS) and the presence of MetS components on clinical outcomes in women from Campania, a Southern Mediterranean region of Italy.

Materials and Methods

Study population and design

A total of 955 BC patients were enrolled in this study between January 2009 and December 2013 at the Istituto Nazionale dei Tumori, "G. Pascale" and at the University Hospital "Federico II", Naples, Italy. Anthropometric measurements (weight, height, waist and hip circumference), clinical data (age, menopausal status, type of adjuvant therapy, MetS components) and tumor characteristics were reported before starting systemic (neo) adjuvant therapy. Median (min, max) time of follow-up calculated up to June 15, 2022 was 11.8 years (8.9, 14.5). The follow-up was performed via telephone surveys in which operators collected data on vital health status. A detailed description of the study population and design can be found in an earlier study.[9]

The study was approved by the Institutional Review Board of the University of Naples Federico II (IRB approval number 75/15) and participants provided written informed consent to participate. The patients' records and data were anonymized and de-identified prior to analysis.

Body fat measurements

Body mass index (BMI) information was available for 933 patients and categorized according to canonical BMI ranges.[10] Hip circumference and waist circumference (WC) measurements (in cm) were collected from 901 and 900 patients, respectively. WC was also categorized according to NCEP-ATP III criteria.[11] Waist-to-hip ratio (WHR) was calculated as the ratio between waist and hip circumferences, and categorized as ≤ 0.85 or > 0.85.

Metabolic syndrome and its components

MetS was defined according to NCEP-ATP III criteria.[11] Complete data to assess MetS were available for 718 patients (75%), and for 626 of them (66%) we were able to collect information about the specific number of MetS components (0, 1–2, ≥ 3), while for the remaining 92 patients (10%) we did not have sufficient information to attribute a score of MetS component of 0, 1 or 2 (Table 1).

Table 1
Patients and tumor characteristics, all-cause and BC-specific deaths, overall and by menopausal-status. Naples, Italy, 2009–2022.

	All			Pre-menopausal			Post-menopausal		
Variables	**N (%)**	**Deaths from all-causes**	**Deaths from breast cancer**	**N (%)**	**Deaths from all-causes**	**Deaths from breast cancer**	**N (%)**	**Deaths from all-causes**	**Deaths from breast cancer**
	955	208	131	369	34	31	586	174	100
Center									
IRCCS G. Pascale	526 (55)	137	87	196 (53)	20	19	330 (56)	117	68
Policlinico Federico II	429 (45)	71	44	173 (47)	14	12	256 (44)	57	32
Age (years)									
< 40	93 (10)	15	14	92 (25)	15	14	1 (0)	0	0
40–49	249 (26)	21	17	232 (63)	16	14	17 (3)	5	3
50–59	257 (27)	52	41	45 (12)	3	3	212 (36)	49	38
≥ 60	356 (37)	120	59	0	0	0	356 (61)	120	59
ER									
Negative (0)	172 (18)	49	36	57 (15)	10	9	115 (20)	39	27
Positive (> 0)	781 (82)	159	95	311 (84)	24	22	470 (80)	135	73
PGR									
Negative (0)	217 (23)	65	47	68 (18)	13	12	149 (25)	52	35
Positive (> 0)	736 (77)	143	84	300 (81)	21	19	436 (74)	122	65
Ki67 > 20									
Negative (< 20%)	547 (58)	95	53	172 (47)	11	11	295 (50)	84	42
Positive (≥ 20%)	398 (42)	112	77	194 (53)	22	19	287 (49)	90	58
Surrogate molecular Subtypes									
Luminal A-like	310 (33)	59	30	110 (30)	3	3	200 (34)	56	27
Luminal B-like/HER2-	341 (37)	75	50	141 (38)	15	13	200 (34)	60	37
HER2+	152 (16)	34	23	67 (18)	6	6	85 (15)	28	17
Triple Negative	123 (13)	33	26	40 (11)	9	8	83 (14)	24	18
HR status									
HR-	158 (17)	48	36	49 (13)	9	9	109 (19)	39	27
HR+	795 (83)	160	95	319 (86)	25	22	476 (81)	135	73
Cancer stage									
I-IIA	614 (64)	110	57	244 (66)	18	16	370 (63)	92	41

	All			Pre-menopausal			Post-menopausal		
Variables	**N (%)**	**Deaths from all-causes**	**Deaths from breast cancer**	**N (%)**	**Deaths from all-causes**	**Deaths from breast cancer**	**N (%)**	**Deaths from all-causes**	**Deaths from breast cancer**
IIB	125 (13)	30	19	46 (13)	7	7	79 (14)	23	12
IIIA-IIIC	174 (18)	56	45	68 (18)	8	7	106 (18)	48	38
Tumor dimension (T)									
T1	530 (56)	96	54	215 (58)	15	13	315 (54)	81	41
T2	352 (37)	89	60	125 (34)	16	15	227 (39)	73	45
T3-T4	49 (5)	17	13	22 (6)	3	3	27 (5)	14	10
Axillary Nodal status (N)									
N0	513 (54)	92	42	193 (52)	15	13	320 (55)	77	29
N+	413 (43)	107	82	169 (46)	18	17	244 (42)	89	65
Histological grade									
G1	57 (6)	7	1	26 (7)	0	0	31 (5)	7	1
G2	386 (40)	85	48	140 (38)	10	10	246 (42)	75	38
G3	490 (51)	105	73	197 (53)	21	18	293 (50)	84	55
Cancer type									
Invasive ductal carcinoma	710 (74)	158	106	281 (76)	31	28	429 (73)	127	78
Invasive lobular carcinoma	149 (16)	32	16	52 (14)	1	1	97 (17)	31	15
Tubular carcinoma	31 (3)	4	2	15 (4)	0	0	16 (3)	4	2
Other	65 (7)	14	7	21 (6)	2	2	44 (8)	12	5
Treatments									
No therapy	59 (7)	7	3	19 (5)	2	1	40 (7)	5	2
Adjuvant/Neoadjuvant	120 (14)	31	22	50 (14)	9	9	70 (12)	22	13
Hormone	678 (79)	118	65	266 (72)	13	12	412 (70)	105	53
Body Mass Index, kg/m^2									
N	933	202	127	359 (97)	33	30	574 (98)	169	97
< 25	341 (37)	57	36	194 (53)	15	12	147 (25)	42	24
25–30	317 (34)	67	36	112 (30)	12	12	205 (35)	55	24
≥ 30	275 (29)	78	55	53 (14)	6	6	222 (38)	72	49
Waist circumference, cm									

	All			Pre-menopausal			Post-menopausal		
Variables	N (%)	Deaths from all-causes	Deaths from breast cancer	N (%)	Deaths from all-causes	Deaths from breast cancer	N (%)	Deaths from all-causes	Deaths from breast cancer
N	900	192	124	347 (94)	31	29	553 (94)	162	95
< 88	410 (46)	64	41	225 (61)	15	14	185 (32)	49	27
≥ 88	490 (54)	129	83	122 (33)	16	15	368 (63)	113	68
Waist-to-hip ratio, u									
N	899	192	124	348 (94)	31	29	551 (94)	161	95
≤ 0.85	322 (36)	46	32	184 (50)	13	12	138 (24)	33	20
> 0.85	577 (64)	146	92	164 (44)	18	17	413 (71)	128	75
Metabolic syndrome (MetS)[2]									
No	545 (76)	95	65	271 (93)	24	23	274 (64)	71	42
Yes	173 (24)	64	42	21 (7)	2	2	152 (36)	62	40
MetS components									
None	122 (19)	11	10	81 (36)	6	6	41 (10)	5	4
1–2	331 (53)	75	48	125 (55)	15	14	206 (52)	60	34
≥ 3	173 (28)	64	42	21 (69)	2	2	152 (38)	62	40

[1] For some variables the sum does not add up to the total due to missing values. [2] MetS was defined by the presence of 3 to 5 of the following criteria: WC > 88 cm, blood pressure ≥ 130/ ≥ 85 mmHg, fasting (at least 8-hour fasting) concentration of serum triglycerides ≥ 150 mg/dL, high-density protein cholesterol (HDL-C) < 50 mg/dL and fasting plasma glucose concentration ≥ 110 mg/dL,

Abbreviations: ER, estrogen receptor; PGR, progesterone receptor; HER2, human epidermal growth factor receptor-2; HR, hormone receptor.

Tumor characteristics

IHC-based surrogates of molecular BC subtypes were assigned based on the criteria established by the 13th St Gallen International Breast Cancer Conference (2013) Expert Panel.[12, 13]

Statistical analyses

Survival time was calculated from the date of BC diagnosis to the date of patient death or to the end of the follow-up period (June 15th 2022), which ever occurred first. The calculation of all-cause and BC-specific mortality in patients lost to follow-up was censored on the last day in which the patient was considered free from the event.

The corresponding adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using adjusted Cox multivariable proportional hazards regression models, and a stepwise approach if necessary. Adjustments variables included terms for age (≤ 40, 41–60, > 60), center, tumor stage (I-IIA; IIB; IIIA-IIIC) and molecular subtypes (HR+/HER2-, HER2+, TN). The HRs were calculated for BMI, WC and WHR as categorical variables; moreover, the HRs for an increase of 5 units (U) (kg/m^2) of BMI, 10-U (cm) of WC and 0.1-U of WHR were also estimated when these variables were evaluated as continuous ones in the models. A stratified analysis was also performed by normalizing for molecular subtypes and by luminal status to investigate the association between anthropometric and metabolic measurements and all-cause or BC-specific mortality. All statistical analyses were performed using R version 4.1.3.

Results

This study enrolled 955 women with early BC. Mean age 55.3 ± 12.5 years, and 61% of patients were post-menopausal. Of 955 patients enrolled, 208 patients died from any cause (34 in pre- and 174 in post-menopausal status), and 131 of them died from BC (31 in pre- and 100 in post-menopausal status). The characteristics of patients and their tumors, as well as the number of patients undergoing death events, are summarized in Table 1. Regarding BC subtypes, 33% and 37% of patients had Luminal A-like and Luminal B-like BC, respectively, 16% of patients had HER2 + BC (either HR + or HR-), and 13% of patients had

triple-negative BC (TNBC). Overall, 83% of all patients had HR + tumors. Two-thirds (64%) had stage I-IIA disease. The most frequent histological tumor grades were G2 and G3 (40% and 51%, respectively). Invasive ductal carcinoma (IDC) was the main histological type (74%). Regarding pharmacologic treatments, most patients (79%) received endocrine therapy, while 14% received (neo) adjuvant chemotherapy (CT), thus reflecting a population of patients with relatively low clinical risk of tumor recurrence. Similar distributions of tumor characteristics were observed in pre-and post-menopausal women.

Obesity (BMI ≥ 30 kg/m^2) was found in 29% of the whole study cohort, 14% in pre- and 38% in post-menopausal women. Approximately 24% of patients met the criteria for a diagnosis of MetS, 7% in pre- and 36% in post-menopausal status, while the presence of 1–2 criteria was found in 53% of patients overall, 55% in pre- and 52% in post-menopause.

All-cause and BC-specific mortality were 78% and 85%, respectively (Additional Fig. 1). Table 2 summarizes anthropometric/metabolic variables and their association with all-cause or BC-specific mortality, overall or according to menopausal status. Although obese patients had a higher risk of death compared to normal weight/overweight patients (Additional Fig. 2), multivariable analysis did not show an independent association between BMI, as evaluated as a categorical variable, and all-cause mortality. However, each 5.0-U increase in BMI was associated with an increased risk of all-cause mortality (HR = 1.17, 95% CI: 1.02–1.34, p = 0.030). Unlike BMI, a high WC and WHR were associated with a moderately increased risk of all-cause mortality also when evaluated as dichotomic variables (WC ≥ 88 cm, HR = 1.39, 95%CI: 1.00-1.94; WHR > 0.85, HR = 1.62, 95%CI: 1.12–2.37), and this association retained statistical significance when WC and WHR were evaluated as continuous variables (HRs = 1.16, 95%CI: 1.05–1.29) and HR = 1.27, 95%CI: 1.07–1.50 respectively). Lastly, we found an association between MetS components and the risk of all-cause mortality (HR = 1.61, 95%CI: 1.12–2.32). In particular, patients with ≥ 3 MetS components had almost quadrupled the risk of death versus patients without MetS (HR = 3.94, 95%CI: 1.88–8.26).

Table 2
Association of anthropometric measures and MetS with all-cause and BC-specific mortality, overall and by menopausal status, Naples, Italy, 2009–2022.

	All				Pre-menopausal				Post-menopausal			
	Deaths from all-causes		Deaths from breast cancer		Deaths from all-causes		Deaths from breast cancer		Deaths from all-causes		Deaths from breast cancer	
	HR* (95%CI)	p**	HR* (95%CI)	p**	HR* (95%CI)	p**	HR (95%CI)	p**	HR* (95%CI)	p**	HR (95%CI)	p**
Body Mass Index, *kg/m²*		**0.345**		**0.029**		0.291		0.090		0.277		**0.032**
< 25	1		1		1		1		1		1	
25–30	0.99 (0.67–1.47)		1.03 (0.62–1.73)		1.79 (0.77–4.13)		2.44 (1.00-5.95)		0.73 (0.48–1.12)		0.52 (0.28–0.98)	
≥ 30	1.25 (0.85–1.84)		1.72 (1.06–2.78)		1.91 (0.70–5.26)		2.60 (0.90–7.48)		0.95 (0.63–1.41)		1.06 (0.62–1.79)	
Per 5 U	**1.17 (1.02–1.34)**	**0.030**	**1.31 (1.11–1.55)**	**0.002**	**1.43 (1.04–1.96)**	**0.028**	**1.58 (1.15–2.18)**	**0.005**	1.06 (0.91–1.23)	0.457	1.15 (0.94–1.41)	0.189
Waist circumference, cm		**0.053**		**0.014**		**0.007**		**0.006**		0.926		0.536
≤ 88	1		1		1		1		1		1	
> 88	1.39 (1.00-1.94)		1.71 (1.12–2.61)		**2.94 (1.35–6.42)**		**3.09 (1.37–6.94)**		1.02 (0.71–1.46)		1.17 (0.72–1.89)	
Per + 10 cm	**1.16 (1.05–1.29)**	**0.005**	**1.24 (1.10–1.40)**	**0.001**	**1.33 (1.01–1.76)**	**0.046**	**1.39 (1.05–1.86)**	**0.023**	1.09 (0.97–1.23)	0.141	1.15 (0.99–1.34)	0.065
Waist-to-hip ratio, u		**0.011**		**0.014**		**0.036**		**0.035**		0.367		0.395
≤ 0.85	1		1		1		1		1		1	
> 0.85	1.62 (1.12–2.37)		1.80 (1.13–2.86)		**2.38 (1.06–5.33)**		**2.46 (1.06–5.71)**		1.21 (0.80–1.84)		1.27 (0.73–2.20)	
Per 0.1 U	**1.27 (1.07–1.50)**	**0.005**	**1.33 (1.08–1.63)**	**0.007**	1.54 (0.91–2.60)	0.105	1.61 (0.93–2.77)	0.089	1.12 (0.92–1.36)	0.246	1.15 (0.90–1.47)	0.254
Metabolic syndrome (MetS)		**0.010**		**0.010**		0.463		0.476		0.193		0.103
No	1		1		1		1		1		1	
Yes	1.61 (1.12–2.32)		1.81 (1.51–2.85)		1.79 (0.38–8.47)		1.76 (0.37–8.38)		1.29 (0.88–1.89)		1.50 (0.92–2.45)	
MetS components		**0.001**		**0.008**		0.170		0.218		0.099		0.150
None	1		1		1		1		1		1	
1–2	2.92 (1.44–5.91)		2.45 (1.15–5.25)		2.99 (0.95–9.44)		2.79 (0.87–8.91)		2.39 (0.95–6.01)		2.09 (0.73–5.95)	
≥ 3	3.94 (1.88–8.26)		3.60 (1.60–8.11)		2.76 (0.45–16.89)		2.55 (0.42–15.63)		**2.77 (1.09–7.06)**		2.73 (0.95–7.84)	

*Cox proportional hazard ratio (HR) adjusted by terms of: age (≤ 40, 41–60, > 60), center (IRCCS G. Pascale, Policlinico Federico II), cancer stage (I-IIA, IIB, IIIA-IIIC) and molecular subtypes (Luminal A, Luminal B, HER 2+, TN); **For the entire variable the p-value refers to Wald Test, for numerical variable z-Test p-value was reported. Significant results are shown in bold.

Regarding BC-specific mortality risk, it was higher in obese patients (BMI ≥ 30 kg/m^2, HR = 1.72, 95%CI: 1.06–2.78) and for each 5.0-U increase in BMI (HR = 1.31, 95%CI: 1.11–1.55). In addition, patients with a WC ≥ 88 cm had a 71% increased risk of BC-specific mortality (HR = 1.71, 95%CI: 1.12–2.61). These results were confirmed for each 10-U increase in WC (HR = 1.24, 95%CI: 1.10–1.40, p = 0.001). We also found an independent association between higher WHR and an increased risk of BC-specific mortality, both when WHR was evaluated as a categorical variable (for WHR > 0.85, HR = 1.80, 95%CI: 1.13–2.86) and

when it was considered as a continuous one (for each 0.1-U increase in WHR, HR = 1.33, 95%CI: 1.08–1.63). The presence of MetS was associated with an 81% increased risk of BC-specific mortality (HR = 1.81, 95%CI: 1.51–2.85). In addition, the presence of 1–2 or ≥ 3 MetS criteria was associated with significantly higher risk of BC-specific mortality (HR = 2.45, 95%CI: 1.15–5.25 and HR = 3.60, 95%CI: 1.60–8.11, respectively).

Among pre-menopausal patients, a 5-U increase in BMI was associated with an increased risk for all-cause or BC-specific mortality (HR = 1.43, 95%CI: 1.04–1.96 and HR = 1.58, 95%CI: 1.15–2.18, respectively). A high WC was independently associated with an increased risk of all-cause and BC-specific mortality both as a categorical variable (WC > 88, HR = 2.94, 95%CI: 1.35–6.42 and HR = 3.09, 95%CI: 1.37–6.94, respectively) and as a continuous variable (HR = 1.33, 95%CI: 1.01–1.76 and HR = 1.39, 95%CI: 1.05–1.86 respectively). Similarly, BC patients with WHR > 0.85 had a 2-fold increased risk of all-cause and BC-specific mortality (HR = 2.38, 95%CI: 1.06–5.33 and HR = 2.46, 95%CI: 1.06–5.71 respectively). Among post-menopausal women we only found an increased risk of all-cause mortality in the presence of ≥ 3 MetS components (HR = 2.77, 95%CI: 1.09–7.06).

Then, we moved to study the prognostic impact of anthropometric and metabolic variables according to tumor biology. Table 3 shows the results of multivariable models according to surrogate molecular subtypes. In patients with HR+/HER2- disease, we found a slightly increased risk in all-cause mortality and BC-related death for every 5-U increase in BMI (HR = 1.21, 95%CI: 1.01–1.44, and HR = 1.58, 95%CI: 1.11–1.72, respectively). We also found a borderline significant increase in BC-specific mortality risk in patients with WC ≥ 88 cm (HR = 1.75, 95%CI: 0.99–3.06), as well as a statistically significantly increased risk in either all-cause or BC-specific mortality for each 10-U increase in WC (HR = 1.19, 95%CI: 1.06–1.34 and HR = 1.28, 95%CI: 1.11–1.48, respectively). Patients with high WHR also had higher risk of all-cause mortality, both when WHR was considered as a dichotomous (WHR > 0.85, HR = 1.85, 95%CI: 1.14–2.99) and as a continuous variable (HR = 1.26, 95% CI: 1.04–1.53). Moreover, an increased risk of death (all-cause and BC-specific) was observed for each 0.1-U increase in WHR (HR = 1.26, 95%CI: 1.04–1.53 and HR = 1.32, 95%CI: 1.03–1.68, respectively). Finally, we found significantly increased risk of all-cause or BC-specific mortality in patients with 1–2 MetS components (HR = 3.86, 95%CI: 1.37–10.84 and HR = 3.68, 95%CI: 1.11–12.22, respectively) and ≥ 3 MetS components (HR = 4.65, 95%CI: 1.59–13.57 and HR = 4.62, 95%CI: 1.30-16.46, respectively).

Table 3
Association of anthropometric measures and MetS with all-cause and BC-specific mortality by molecular subtypes, Naples, Italy, 2009–2022.

	HR+				HER 2+				TN			
	Deaths from all-causes		Deaths from breast cancer		Deaths from all-causes		Deaths from breast cancer		Deaths from all-causes		Deaths fro breast can	
	HR*(95%CI)	p**	HR*(95%CI)	p**	HR*(95%CI)	p**	HR*(95%CI)	p**	HR*(95%CI)	p**	HR*(95%CI)	p**
Body Mass Index, *kg/m²*		0.433		0.087		0.501		0.183		0.835		0.8
< 25	1		1		1		1		1		1	
25–30	1.10 (0.68–1.78)		1.03 (0.53–1.99)		0.93 (0.36–2.42)		1.03 (0.29–3.61)		0.76 (0.26–2.17)		1.25 (0.38–4.04)	
≥ 30	1.35 (0.82–2.21)		1.78 (0.94–3.37)		1.53 (0.64–3.68)		2.47 (0.84–7.27)		0.77 (0.28–2.15)		0.88 (0.25–3.12)	
Per 5 U	**1.21 (1.01–1.44)**	**0.035**	**1.58 (1.11–1.72)**	**0.004**	1.23 (0.89–1.68)	0.207	1.42 (0.94–2.16)	0.096	1.11 (0.75–1.14)	0.616	1.16 (0.74–1.84)	0.5
Waist circumference, cm		0.088		0.052		0.245		0.087		0.999		0.9
≤ 88	1		1		1		1		1		1	
> 88	1.44 (0.95–2.18)		1.75 (0.99–3.06)		1.59 (0.73–3.49)		2.30 (0.89–5.99)		1.00 (0.42–2.41)		0.99 (0.37–2.68)	
Per 10 U	**1.19 (1.06–1.34)**	**0.004**	**1.28 (1.11–1.48)**	**0.001**	**1.36 (1.04–2.77)**	**0.024**	**1.62 (1.10–2.37)**	**0.014**	0.94 (0.70–1.27)	0.696	0.94 (0.70–1.34)	0.8
Waist-to-hip ratio		**0.013**		0.087		0.735		0.176		0.357		0.2
≤ 0.85	1		1		1		1		1		1	
> 0.85	**1.85 (1.14–2.99)**		1.67 (0.93-3.00)		1.14 (0.53–2.44)		1.97 (0.74–5.27)		1.75 (0.53–5.78)		2.27 (0.59–8.71)	
Per 0.1 U	**1.26 (1.04–1.53)**	**0.019**	**1.32 (1.03–1.68)**	**0.028**	1.42 (0.91–2.21)	0.124	1.49 (0.86–2.59)	0.154	1.30 (0.69–2.42)	0.417	1.32 (0.67–2.61)	0.4
Metabolic syndrome (MetS)		**0.125**		0.169		**0.005**		**0.002**		0.766		0.9
No	1		1		1		1		1		1	
Yes	1.42 (0.91–2.23)		1.52 (0.84–2.76)		**3.45 (1.45–8.22)**		**5.05 (1.80–14.20)**		1.18 (0.41–3.44)		1.08 (0.33–3.51)	
MetS components		**0.019**		0.061		**0.034**		**0.016**		0.198		0.2
None	1		1		1		1		1		1	
1–2	**3.86 (1.37–10.84)**		**3.68 (1.11–12.22)**		0.96 (0.29–3.21)		0.55 (0.14–2.14)		6.99 (0.84–58.08)		6.15 (0.73–52.10)	
≥ 3	**4.65 (1.59–13.57)**		**4.62 (1.30-16.46)**		3.03 (0.83–11.03)		2.94 (0.75–11.56)		5.69 (0.59–54.77)		4.72 (0.47–47.87)	

* Cox proportional hazard ratio (HR) adjusted by terms of: age (≤ 40, 41–60, > 60), center (IRCCS G. Pascale, Policlinico Federico II), cancer stage (I-IIA, IIB, IIIA IIIC);

**For the entire variable the p-value refers to Wald Test, for numerical variable z-Test p-value was reported. Significant results are shown in bold.

Abbreviations: HR, hormone receptor, HER2, human epidermal growth factor receptor-2; TN, triple negative

In patients with HER2 + BC, each 10-U increase of WC was associated with an increased risk of all-cause or BC-specific mortality (HR = 1.36, 95%CI: 1.04–2.77; HR = 1.62, 95%CI: 1.10–2.37, respectively). HER2 + BC patients meeting the criteria of a MetS diagnosis also had an increased risk of all-cause and BC-specific mortality (HR = 3.45 95%CI: 1.45–8.22 and HR = 5.05, 95%CI: 1.80–14.20, respectively). Similarly, the presence of at least 3 components of MetS was associated with a trend towards increased mortality (all-cause p = 0.005 and BC-specific p = 0.002).

Lastly, in patients with TNBC we did not find an independent association between BMI, WC, WHR, or MetS categories, and all-cause and BC-specific mortality (Table 3 and Fig. 1).

Luminal BC is a highly heterogenous group of diseases, which includes more and less clinically aggressive forms, such as Luminal B-like and Luminal A-like patients. For this reason, among HR+/HER2- BC patients we separately evaluated the association between anthropometric/metabolic variables and all-cause or BC-specific mortality in patients with Luminal A-like and Luminal B-like disease (Table 4). BMI and WC were not associated with either all-cause nor BC-specific mortality in Luminal A-like patients. However, an increased risk in BC-specific mortality for each 5-U increase in BMI (HR = 1.43, 95%CI: 1.02-2.00). When WC was considered as a continuous variable there was an increased risk for each 10-U increase of all-cause and BC-specific mortality (HR = 1.28, 95%CI: 1.05–1.55 and HR = 1.41, 95%CI: 1.07–1.86, respectively). Similarly, high WHR was associated with an increased risk of all-cause and BC-specific mortality for each 0.1-U increase in WHR (HR = 1.74, 95%CI: 1.28–2.39 and HR = 1.92, 95%CI: 1.27–2.90, respectively). The presence of MetS was associated with an increased risk of all-cause and BC-specific mortality (HR = 2.84, 95%CI: 1.47–5.48 and HR = 2.81, 95%CI: 1.15–6.86, respectively). In addition, the presence of ≥ 3 MetS components was associated with a significantly higher risk of all-cause and BC-specific mortality (HR = 2.98, 95%CI: 1.52–5.88 and HR = 2.80, 95%CI: 1.14–6.88, respectively). In Luminal B-like BC patients there was a significantly higher risk of mortality (all-cause and BC-specific) for each 10-U increase in WC (HR = 1.18, 95%CI: 1.01–1.38 and HR = 1.22, 95%CI: 1.01–1.46, respectively). Regarding MetS, the presence of 1–2 MetS components was associated with a significantly higher risk of all-cause mortality compared with 0 MetS components (HR = 3.07, 95%CI: 1.0-8.81) (Table 4).

Table 4
Association of anthropometric or MetS variables and all-cause or BC-specific mortality by Luminal subtypes (A vs. B).

	Luminal A					Luminal B				
		Deaths from all-causes		Deaths from breast cancer			Deaths from all-causes		Deaths from breast cancer	
Variable	Deaths/N total cases	HR*(95%CI)	p**	HR (95%CI)	p**	Deaths/N total cases	HR*(95%CI)	p**	HR (95%CI)	p**
Body mass index, *kg/m²*			0.247		0.090			0.675		0.386
< 25	11/103	1		1		19/117	1		1	
25–30	21/110	1.28 (0.61–2.69)		0.75 (0.23–2.49)		29/127	0.98 (0.52–1.87)		1.05 (0.47–2.36)	
≥ 30	27/91	1.79 (0.87–3.67)		2.05 (0.78–5.36)		26/92	1.24 (0.64–2.40)		1.59 (0.71–3.56)	
Per 5.0 U	59/304	1.24 (0.97–1.58)	0.084	**1.43 (1.02-2.00)**	**0.038**	74/336	1.18 (0.93–1.49)	0.169	1.28 (0.97–1.68)	0.083
Waist circumference, cm			0.099		0.147			0.073		0.221
≤ 88	15/136	1		1		19/137	1		1	
> 88	43/166	1.66 (0.89–3.10)		2.00 (0.79–5.09)		50/185	1.66 (0.94–2.95)		1.51 (0.77–2.97)	
Per 10 U	58/302	**1.28 (1.05–1.55)**	**0.013**	**1.41 (1.07–1.86)**	**0.016**	69/322	**1.18 (1. 01-1.38)**	**0.034**	**1.22 (1.01–1.46)**	**0.036**
Waist-to-hip ratio			0.058		0.318			0.104		0.301
≤ 0.85	9/103	1		1		15/108	1		1	
> 0.85	49/198	2.10 (0.97–4.52)		1.62 (0.60–4.39)		54/194	1.63 (0.89-3.00)		1.44 (0.71–2.91)	
Per 0.1 U	58/301	**1.74 (1.28–2.39)**	**0.001**	**1.92 (1.27–2.90)**	**0.002**	69/322	1.13 (0.86–1.48)	0.388	1.08 (0.77–1.53)	0.654
Metabolic syndrome (MetS)			**0.002**		**0.023**			0.885		0.890
No	18/164	1		1		36/193	1		1	
Yes	25/58	**2.84 (1.47–5.48)**		**2.81 (1.15–6.86)**		19/60	1.04 (0.58–1.89)		1.05 (0.50–2.23)	
MetS components			**0.036**	+	0.193			0.059		0.158
None	0/37					4/44	1		1	
None + 1–2	15/135	1		1		30/121	**3.07 (1.07–8.81)**		2.91 (0.85–9.90)	
≥ 3	25/58	**2.98 (1.52–5.88)**	**0.002**	**2.80 (1.14–6.88)**	**0.03**	19/60	1.02 (0.56–1.86)	0.9	2.44 (0.66–9.04)	

*HR adjusted by terms of: age (≤ 40, 41–60, > 60), center (Pascale, Policlinico), Stage (I-IIA, IIB, IIIA-IIIC).

**For the entire variable the p-value refers to Wald Test, for numerical variable z-Test p-value was reported. +model was not implemented due to absence of events in reference category. Significant results are shown in bold.

MetS components may not impact mortality to the same extent. Then, we investigated the impact of each MetS component on all-cause and BC-specific mortality across BMI categories (Additional Table 1).

Finally, we investigated the impact of adiposity through BMI categories in conjunction with MetS on BC-specific mortality (Additional Fig. 3).

Discussion

Our data show that high BMI, central obesity and MetS are independently associated with an increased risk of all-cause and BC-specific mortality BC survivors. The impact of anthropometric and metabolic parameters on long-term clinical outcomes varies depending on menopausal status and BC molecular subtype, with the most significant associations being found in pre-menopausal patients and in women with Luminal A-like malignancies. To the best of our knowledge, this is the first prospective study that evaluated the prognostic significance anthropometric measurements and MetS components on mortality outcomes in a large cohort of BC survivors living in a Southern Mediterranean region.

In BC patients, obesity has been associated with more aggressive tumor characteristics, such as larger tumor size and higher grade, as well as with higher patient comorbidities[14], reduced disease-free, overall and BC-specific survival.[15]-[16–18] A prognostic role of obesity, as evaluated according to BMI categories, has been reported both at baseline and after BC diagnosis[19], and regardless of menopausal status, with an indication of stronger association between obesity and higher mortality risk in pre-menopausal patients.[19] In our study, each 5.0-U increase in BMI increased all-cause and BC-specific mortality in the overall study population. However, the magnitude of the effect on survival mostly resulted from the prognostic impact of obesity among pre-menopausal women. BMI is commonly used as a proxy of obesity because of easy accessibility of patient height and weight in retrospective studies; on the other hand, anthropometric measures, such as WC and WHR, are not routinely collected in clinical practice. However, BMI may not fully capture or distinguish several anthropometric and metabolic alterations that are associated with obesity in cancer patients. In addition, BMI does not take into account absolute and relative lean body mass.[20] On the other hand, WC and WHR more reliably reflect body fat distribution and the presence of central obesity. In a population of Black BC survivors, Bandera et al.[7] found that high WC and WHR are associated with a significantly increased risk of death after a BC diagnosis, with less substantial results for BMI.[7] In the present study, adiposity was evaluated using 3 measurements methods, namely BMI, WC and WHR. However, our data also confirms the relevance of central obesity on all-cause and BC-specific mortality. In detail, each 10-U increase in WC and every 0.1-U increase in WHR were associated with increased all-cause and BC-specific mortality in the overall study population, and particularly in pre-menopausal setting. Together, these results suggest that central obesity may be especially detrimental in younger BC survivors, and that lifestyle interventions aimed at preventing or reversing central obesity are a clinical priority in these patients.

We previously showed that MetS is associated with an increased risk of BC recurrence and mortality.[21] In fact, BC patients with 1–2 MetS components had an higher risk of all-cause and BC-mortality when compared to patients without MetS components.[21] Herein we confirm the later findings and we also show that even the presence of a single MetS component is associated with higher all-cause and BC-specific mortality. MetS affected survival outcomes regardless of menopausal status and independent of body weight. However, each MetS component may not impact survival to the same extent (Additional Table 3). In fact, hypertriglyceridemia was the component that most affected mortality, even in women with a normal BMI. On the contrary, hyperglycemia could determine worse outcomes particularly among obese patients. If confirmed by future studies, these observations may be of particular clinical relevance because they suggest that a close monitoring of patient plasma triglycerides or glucose concentration, as well as prompt correction of dysregulated plasma triglyceride of glucose levels through the use of physical activity, lifestyle or pharmacologic interventions, may improve the prognosis of patients with surgically resected, early BC

There is evidence that the association between obesity or metabolic disorders and BC patient prognosis varies according to BC subtype, with fairly consistent results for ER-positive BCs, but not for other BCsubtypes.[14] Herein, we found that central obesity is associated with higher risk of all-cause and BC-specific mortality among HR + BC patients, especially Luminal A-like patients, while we found no clear associations in HER2 + and TN BC patients. Because obesity is associated with elevated aromatase activity and serum estrogen levels in post-menopausal women, it is possible that obesity modulates responses to endocrine therapy as shown in several studies.[22]-[23] In pre-menopausal patients, a similar pattern was seen in the Austrian Breast and Colorectal Cancer Study Group 12 trial, in which anastrozole plus goserelin was associated with higher risk of tumor recurrence and death in both overweight and obese women when compared with tamoxifen plus goserelin, whereas disease-free survival (DFS) and overall survival (OS) were similar in the two treatment cohorts among normal-weight women.[24] The association between BMI and clinical outcomes has been also evaluated in the Tamoxifen and Exemestane Trial (TEXT) and Suppression of Ovarian Function Trial (SOFT) trials, which investigated exemestane versus tamoxifen plus ovarian suppression; however, these data have not been reported [25, 26] although it has been reported that higher BMI is associated with a higher likelihood of elevated estradiol during treatment.[27] In contrast, a recent meta-analysis reported that general obesity was associated higher all-cause mortality in HR+/ HER2-, HER2 + and TN BC patients.[28] Similar to our findings, a more recent meta-analysis showed that general obesity was associated with all-cause and BC-specific mortality in HR+/HER2-, and HER2 + BC, while no clear associations were observed in TN BC patients.[29] In our study MetS was associated with all-cause and BC-specific mortality in HR + and HER2 + BC patients and to a lesser extent in TN patients. Biologic factors involved in MetS, namely insulin resistance, hyperinsulinemia, hyperglycemia, altered adipokines and inflammation are potentially relevant across BC subtypes, regardless of endogenous estrogen levels.[30]

Our study has several strengths. Firstly, it centers on a large, high quality, multicenter cohort of BC survivors. The data were prospectively collected, and the clinical and tumor features were annotated and for whom complete information on MetS components, anthropometric indices and measurements, subsequent treatment and clinical outcomes are available. Main limitations of this study are: a) limited information on existing comorbidities and concomitant therapies; b) nutritional and antropometric status, and in particular the presence/absence of obesity before diagnosis was not evaluated; c) although anthropometric measurements (body weight, WC, WHR) are low cost, easy-to-collect and to use in daily clinical practive, their use can be problematic due to their vulnerability to measurement errors and lack of reliability. Nevertheless, the consistency between BC-specific mortality and all-cause mortality results are pressuring in this perspective.

In conclusion, our data confirm and expand previous data showing an association between central obesity and an increased risk of death. The magnitude of this effect (35–40% increased risk) suggests that obesity may nullify the benefit of our best BC therapies. Based on our findings, future prospective trials should investigate if lifestyle changes, such as nutritional or physical activity interventions, which are capable of positively modifying anthropometric and metabolic parameters, are also associated with improved clinical outcomes. In this respect, the multicentric, randomized, phase III trial BWEL (NCT02750826)

investigated if promoting weight loss interventions in surgically-resected, overweight or obese BC patients results in a reduction of BC recurrences. Results of this trial are highly expected.

Abbreviations

breast cancer (BC), body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), metabolic syndrome (MetS)

Declarations

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Competing interests

MG reports Consulting fees from Honoraria Lilly, Celgene, Novartis, Pfizer, Astra Zeneca, Daiichi-Sankyo, MSD, Honoraria from Lilly, Celgene, Novartis, Pfizer, Istituto Gentili, Eisai Europe Ltd, Roche, Astra Zeneca, Daiichi-Sankyo, MSD, Gilead, travel accomodations from Novartis, Pfizer, Roche; LSA is a founding member of the International Carbohydrate Quality Consortium (ICQC, www.carbquality.com), has received honoraria from the Nutrition Foundation of Italy (NFI, Milan), research grants for lifestyle studies from Lega Italiana per la Lotta contro i Tumori (LILT, Rome) a non-profit organization for the fight against cancer, and in-kind study support from Abiogen Pharma (Pisa, Italy), Barilla Spa (Parma, Italy), Roberto Alimentare (Treviso, Italy), Panificio Giacomo Luongo (Napoli, Italy), Consorzio Mandorle di Avola (Siracusa, Italy), SunRice (Australia) and Almond Board of California (USA); JB …; RC reports Honoraria from Novartis, Lilly, Astra Zeneca, Daichii Sankyo, Veracyte, Pfizer, has been Consulting/Advisor for Roche, Astra Zeneca, Lilly, Daichii Sankyo, Novartis, Seagen, MSD, Gilead, received research funding from Gilead, and travel accommodation from Lilly, Novartis; GB reports Honoraria or speakers' fee from Novartis, GSK, Eli-Lilly, Pfizer, AstraZeneca, Roche, Daiichi Sankyo, Exact Science, Genetic.Spa; CV reports Advisory role for Novartis, Pfizer, Eli Lilly, Daiichi Sankyo, Consultancy for Eli Lilly, Honoraria as a speaker from Novartis, Pfizer, Eli Lilly, Istituto Gentili, Accademia di Medicina, Research grants from Roche; FS reports honoraria from Novartis, Gilead and Daiichy-Sankyo for educational events/materials and travel expenses from Novartis, Gilead and Daiichy-Sankyo; PDP reports Speaker's Honoraria from Lilly, Gilead, MSD, Roche, Exact Sciences, Novartis, travel accommodations from Gilead, Lilly, Istituto Gentili, Roche; CDA reports Honoraria from Novartis, Lilly, Seagen, Pfizer, Astra Zeneca, Advisory role for Lilly, GSK, Novartis, travel accomodations from Gilead and Pfizer, research grants from Novartis; RB reports Honoraria from Roche, Astra Zeneca, Novartis, Lilly, BMS, MSD, Pfizer, Advisory role for Roche, Astra Zeneca, Novartis, Lilly, BMS, MSD, Pfizer, research Investigator Grant from AIRC; MDL reports personal fees as Speaker's and Advisory Board Honoraria from Pfizer, Novartis, Roche, Astra Zeneca, Eisai, Eli Lilly, MSD, Pierre Fabre; GA reports Consulting fees from Roche, Astra Zeneca, Novartis, Lilly, MSD, Pfizer, Honoraria from Roche, Astra Zeneca, Novartis, Lilly, MSD, Pfizer, travel accomodations from Roche, Astra Zeneca, Novartis, Lilly, MSD, Pfizer all outside the submitted work. AC, AL, CC, SC, AC, VM, RG, PT, EP, SV, GP, PDG, MG, FN, EC, AA, CLV report no COI to disclose.

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Authors' contributions

Conceptualization: AC, EC, MG, GA

Data Curation: all the authors

Formal Analysis: AC, SC, PDG, CLV

Investigation: AC, RC, GB, MG, FN, MG, PDP, CDA, RB, MDL, GA

Methodology: AC, SC, PDG, CLV

Resources: RC, GB, MG, RB, MDL, GA

Software: AC, SC, PDG

Visualization: AC, LSA, AL, SC PDG, MG, PDP, CLV, GA

Writing-original draft: AC, LSA, AL, CC, SC, VM, RG, PT, EP, SV, GP, CV, FS, EC, MG, PDP, CLV, GA

Writing-review and editing: AC, LSA, AL, JB, EP, SV, GP, CV, FS, EC, AA, MG, PDP, CLV, GA

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Figures

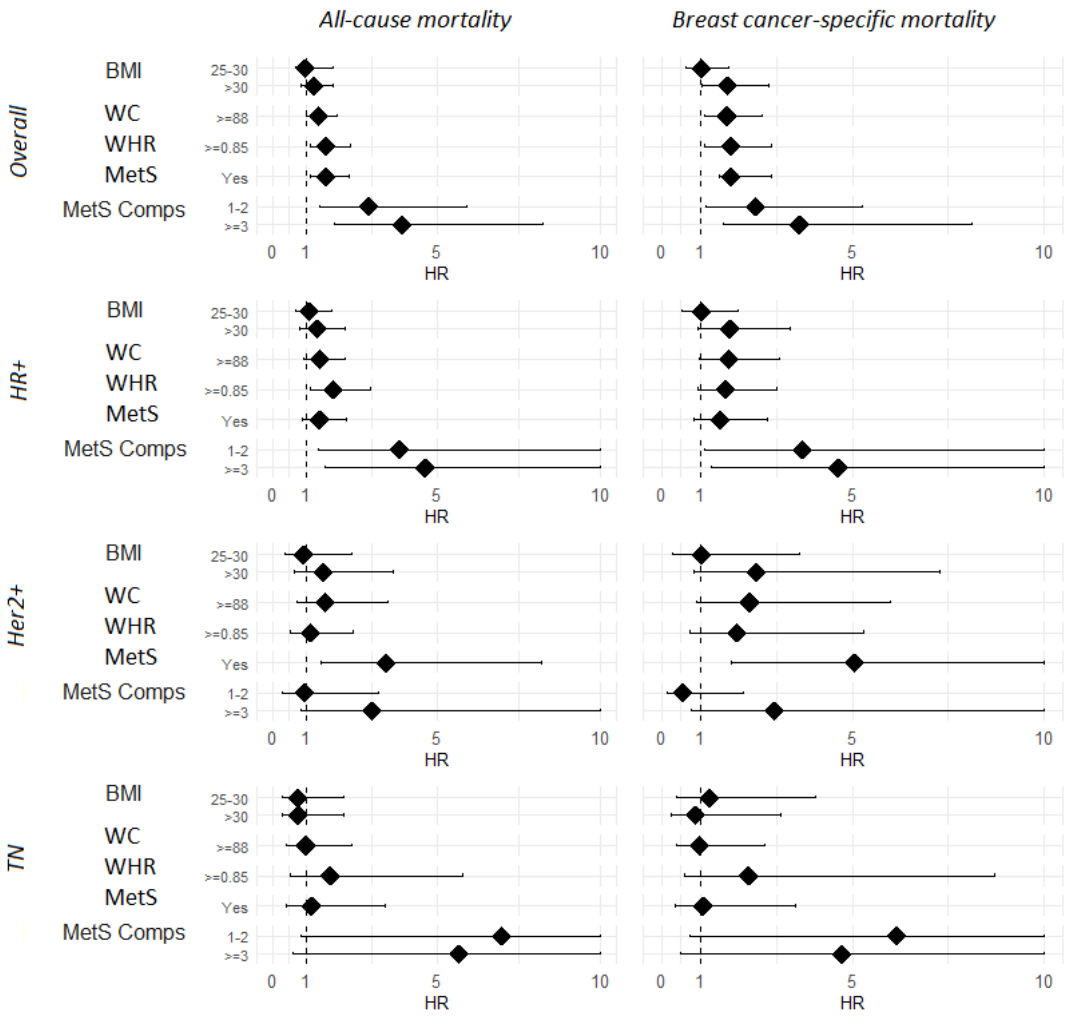

Figure 1

Forest plot for BMI, WC, WHR, MetS, MetS components of all-cause and BC-specific mortality.

Forest plot of the HRs and 95% CI of All-cause and BC-specific mortality for BMI, WC, WHR, MetS, MetS components and Molecular Subtypes: Overall and by Molecular Subtypes.

Abbreviations: HR+, hormone receptor positive; HER2+, Human epidermal growth factor receptor-2 positive; TN, triple negative; BMI, Body Mass Index (BMI is calculated as weight in kilograms divided by height in meters squared); WC, Waist Circumference (in centimeters); WHR, Waist-to-hip Ratio (WHR calculated as the ratio between waist and hip circumferences); MetS, Metabolic Syndrome (defined according to NCEP-ATP III criteria); MetS Comps, Metabolic Syndrome Components (1-2 criteria, >= 3 criteria).

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