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Original article

BMI is an independent prognostic factor for late outcome in patients diagnosed with early breast cancer: A landmark survival analysis

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1. Introduction

Breast cancer (BC) is the most common malignancy in women all over the world. Early detection combined to progress in cancer treatment has considerably improved BC outcome [1]. However, still some patients experience disease recurrence. Timing of disease relapse varies according to molecular subtypes, with triple negative and HER2-positive tumors showing the highest rate within the first 3–5 years after diagnosis. In contrast, for patients with hormone-receptor (HR) positive tumors, the risk of recurrence may persist longer [2,3]. The excess of weight is a major public health problem in industrialized countries, with 39% of the world's adult population being overweight and about 13% obese in 2016 (15% of adult women) [4]. Obesity in the general population is related to high mortality and it represents a risk factor for many diseases, as cardiovascular illness, diabetes and cancer, including BC [5–8]. Indeed, the relative risk for BC is 1.1 (95% Confidence Interval (CI) 1.1–1.2) in postmenopausal women for each 5 body mass index (BMI) units increase [9]. The biological mechanisms underlying the association between increased BMI and BC incidence are not well established but may be related to endocrine and metabolic alterations [10]. Hyper-adiposity may intensify estrogen production and cause a chronic subclinical inflammation with elevated circulating levels of pro-inflammatory proteins related to cancer development [11]. Another potential mechanism may involve the prolonged hyperinsulinemia that can increase the synthesis of adipokines and cytokines involved in breast tumorigenesis [12]. Moreover, insulin has important effect on AKT/mTOR signaling, an important pathway often involved in tumor growth [13]. The same mechanisms may explain the association between increased BMI and worse prognosis after the diagnosis of BC described in literature. However, in the majority of these studies, the follow-up period was not sufficiently long to permit an accurate evaluation of events occurring later than 10–15 years from diagnosis [10–15]. Considering the rising obesity rates and its association with pathological conditions with a potential impact on life expectancy, a better understanding of the association between BMI and long-term prognosis in BC patients is needed. In this study, we aimed at evaluating the association between BMI and outcome in a population of BC patients with a long follow up allowing to focus on late events.

2. Materials and methods

2.1. Population

All patients with early BC diagnosed at Istituto Oncologico Veneto (Padua, Italy) between 2000 and 2007 that underwent primary surgery and with available information on body weight and height at the time of diagnosis were retrospectively identified. Body weight and height were measured after surgery and BMI was calculated as weight in kilograms divided by height in square meters. According to WHO standard, the following BMI categories were identified [16]:

- Underweight: BMI<18.5 kg/m2

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- Normal: BMI 18.5–24.9 kg/m2
- Overweight: BMI 25–29.9 kg/m2
- Obese: BMI ≥ 30 kg/m2
  Obese class I: 30.0–34.9 kg/m2
  Obese class II: 35.0–39.9 kg/m2
  Obese class III: ≥ 40.0 kg/m2

Length of follow up was not considered as inclusion criteria. However, in the final cohort of patients included in this study, <1% had follow up data up to 1 year after diagnosis and 96% had follow up > 36 months after diagnosis.

The following data were collected: age, menopausal status, largest pathological tumor diameter, nodal status, pathological stage according to AJCC 7th edition [17], hormone receptors (HR) and HER2 status, type of surgical and systemic treatment, type and date of survival events (if any), date of last follow up or death [18].

HR status was defined by immunohistochemistry. HR positivity was defined as ≥1% of tumor cells positively stained for estrogen and/or progesterone receptor.

HER2 was evaluated by immunohistochemistry and in situ hybridization in case of a 2 + score by immunohistochemistry. HER2 was defined positive if immunohistochemistry score 3 + and/or ISH amplified. Immunohistochemistry scoring and ISH evaluation were performed according to the guidelines in force at the time of analysis [19].

2.2. Statistical analysis

2.2.1. Statistical analyses were conducted with SPSS version 25

Descriptive statistics for tumor clinicopathological features and treatment data in terms of absolute and relative values were provided. The chi-square tests for the association with BMI category were calculated. Survival endpoints were: invasive-Disease Free Survival (iDFS, defined as the time from diagnosis to: local/distant relapse, contralateral invasive BC, second-primary invasive BC, second-primary non-BC or death without any event) and Overall Survival (OS, defined as the time from BC diagnosis to death from any cause). Late-iDFS was calculated from the landmark of 10 years after diagnosis. All patients who were alive and free from iDFS-event at 10 years from diagnosis were included in late-iDFS analysis. Log-rank test was used to compare survival between groups. Hazard ratios (HRs) and the 95% CI were calculated by cox regression models. Threshold for statistical significance was established at $p < 0.05$. All tests were two-sided.

3. Results

3.1. Characteristics of the study population

A total of 992 patients diagnosed with early BC between January 2000 and December 2007 were identified. The characteristics of study population stratified by BMI classes are shown in Table 1. According to BMI, 30 patients (3%) were underweight, 482 (49%) were normal weight, 319 (32%) were overweight and 161 were obese (respectively 11% grade I, 4% grade II and 1% grade III obesity). Due to the low number of underweight patients, we considered the following categories: underweight/normal weight, overweight, obese (any grade, BMI≥30 kg/m2). Higher BMI was found to be statistically associated with older age at diagnosis with a median age of 60 years (range 48–71) for obese patients, 58 years (range 47–70) for overweight patients and 50 years (range 43–62) for underweight/normal weight patients ($p < 0.001$). Consistently, overweight and obese patients were more frequently post-menopausal (77.4% and 81.1% respectively) as compared to underweight/normal patients (51.5%). More advanced stages (II and III) and nodal involvement were also significantly associated with higher BMI categories (both with $p < 0.001$). No significant difference was observed according to histological grade ($p = 0.903$), HR status ($p = 0.398$), HER2 status ($p = 0.662$), type of surgical treatment (breast conservative surgery or mastectomy, $p = 0.700$), receipt of chemotherapy ($p = 0.463$) and endocrine-therapy ($p = 0.064$).

3.2. Association of BMI with iDFS and OS

With a median follow up of 152 months (95% CI 149–155 months), a total of 358 iDFS and 212 OS events have occurred. Fig. 1A shows Kaplan-Meier iDFS curves according to BMI categories. Rates of iDFS at 15 years were 61%, 54% and 34% for underweight/normal, overweight and obese patients, respectively (log-rank $p = 0.003$). Univariate cox-regression model (Table 2) showed a significant worse iDFS for obese as compared to underweight/normal patients (HR 1.56, 95% CI 1.19–2.03, $p = 0.001$), whereas there was no significant difference between overweight and underweight/normal weight patients (HR 1.04, 95% CI 0.82–1.32, $p = 0.767$). With regards to OS, rates at 15 years were 78%, 70% and 61% for underweight/normal, overweight and obese patients, respectively (log-rank $p = 0.075$), as shown in Fig. 1B. Univariate cox-regression model (Table 2) showed a significantly worse outcome for obese patients compared to underweight/normal weight patients (HR 1.49; 95% CI 1.04–2.12, $p = 0.029$) and no significant difference between overweight and underweight/normal weight patients (HR 1.23, 95% CI 0.91–1.68, $p = 0.182$).

In multivariate models for iDFS and OS including the other factors that resulted significantly associated with survival in univariate analysis, BMI was not an independent predictor of outcome, as shown in Table 2.

3.3. Association of BMI with late-iDFS

At 10 years from diagnosis, 612 patients were alive and free from iDFS event. At a median follow up of 39 months (95% CI 37–41 months), a total of 87 late-iDFS events have occurred.

At 5 years after the 10-years landmark, late-iDFS rates were 85%, 74% and 50% for underweight/normal, overweight and obese patients, respectively (log-rank $p < 0.0001$), as shown in Fig. 2A. Univariate cox-regression model (Table 2) evidenced a significantly worse outcome not only for obese, but also for overweight patients as compared to underweight/normal weight patients (HR 3.73; CI 2.25–6.20, $p < 0.001$ and HR 1.69; 95% CI 1.01–2.83, $p = 0.047$, respectively). In a multivariate analysis including other variables that resulted significantly associated with late-iDFS, BMI category maintained an independent prognostic value for the comparison between obese and underweight/normal patients (HR 2.81; 95% CI 1.64–4.83, $p < 0.001$; Table 2). Table 3 shows type of late-iDFS events distribution stratified by BMI. Event type distribution was significantly different according to BMI categories ($p < 0.0001$), with distant relapse, second breast cancer, second non-breast cancer and death from any cause more frequently occurring among obese patients.

3.4. Association between BMI and prognosis according to hormone receptor status

We examined the impact of BMI on outcome according to HR status by using a definition of HR-positivity of ≥1% of cells positive for estrogen and/or progesterone receptor.

In the subgroup of HR positive patients, rates of iDFS at 15 years from diagnosis were: 61%, 55% and 34% for underweight/normal, overweight and obese patients, respectively (log-rank $p < 0.001$).

Table 1
Baseline patients' characteristics according to BMI category.

		Underweight/Normal N (%)	*Overweight N (%)*	*Obese N (%)*	*Total N (%)*	*P*
All		512 (52)	319 (32)	161 (16)	992 (100)	
Age median (yrs), Q1-Q3						<0.001
		50 (43–62)	58 (47–70)	60 (48–71)	53 (45–67)	
Menopausal Status	*POST*	262 (51)	246 (77)	129 (81)	637 (65)	<0.001
	PRE	247 (49)	72 (23)	30 (19)	349 (35)	
Stage	*I*	262 (54)	125 (40)	48 (30)	435 (46)	<0.001
	II	182 (37)	143 (47)	79 (50)	404 (42)	
	III	45 (9)	39 (13)	31 (20)	115 (12)	
Nodal status	*Negative*	321 (65)	182 (59)	75 (47)	578 (60)	<0.001
	Positive	172 (35)	127 (41)	84 (53)	383 (40)	
Grade	*1/2*	343 (71)	208 (69)	105 (71)	656 (70)	0.903
	3	143 (29)	93 (31)	44 (29)	280 (30)	
HR	*Negative*	50 (10)	41 (13)	18 (11)	109 (11)	0.398
	Positive	457 (90)	277 (87)	139 (89)	873 (89)	
HER2	*Negative*	297 (82)	181 (85)	95 (83)	573 (83)	0.662
	Positive	65 (18)	32 (15)	19 (17)	116 (17)	
Type of surgery	*BCS*	352 (69)	216 (68)	115 (72)	683 (69)	0.700
	Mast	158 (31)	101 (32)	45 (28)	304 (31)	
CT	*No*	157 (31)	103 (32)	43 (27)	303 (31)	0.463
	Yes	350 (69)	215 (68)	117 (73)	682 (69)	
ET	*No*	93 (18)	80 (25)	35 (22)	208 (21)	0.064
	Yes	409 (82)	235 (75)	124 (78)	768 (79)	
Type of ET	*Tam*	151 (38)	64 (28)	38 (31)	253 (33)	0.090
	AI	82 (20)	62 (27)	35 (28)	179 (24)	
	Other/switch	170 (42)	106 (45)	50 (41)	326 (43)	
Duration of ET	*Up to* 5 yrs	199 (62)	100 (54)	61 (61)	360 (69)	0.189
	>5 yrs	121 (38)	85 (46)	39 (39)	245 (40)	

Abbreviations: BMI, Body Mass Index; yrs, years; Q1, first quartile; Q3, third quartile; HR, hormone receptors; HER2, human epidermal growth factor 2; BCS, Breast Conservative Surgery; Mast, mastectomy; CT, chemotherapy; ET, Endocrine Therapy.

Cox regression analysis showed a HR of 1.04 (95% CI 0.80–1.35, $p = 0.754$) for overweight vs underweight/normal weight and a HR of 1.72 (95% CI 1.30–2.28, $p < 0.001$) for obese vs underweight/normal weight patients.

For HR positive patients, rates of late-iDFS at 5 years after the 10-years landmark were 84%, 76% and 50% for underweight/normal, overweight and obese patients, respectively (log-rank $p < 0.0001$, Fig. 2B). Cox regression analysis showed a HR of 1.61 (95% CI 0.92–2.81, $p = 0.097$) for overweight vs underweight/normal weight and a HR of 3.86 (95% CI 2.25–6.62, $p < 0.001$) for obese vs underweight/normal weight patients.

In this subgroup of patients we also analyzed the impact of type and duration of endocrine therapy on late-iDFS, overall and according to BMI category. We observed no association between type of ET with late outcome. There was a numerical difference favoring a better outcome with longer duration of ET, however this was not statistically significant. More details can be found as Supplementary Table S1.

In the subgroup of HR-negative patients, with only 107 patients included, we observed no impact of BMI on iDFS (15-year rates 63%, 54%, 43% for underweight/normal weight, overweight and obese, $p = 0.662$). The sample size was too limited and did not allow for late-iDFS analysis ($n = 65$ patients, $n = 10$ events).

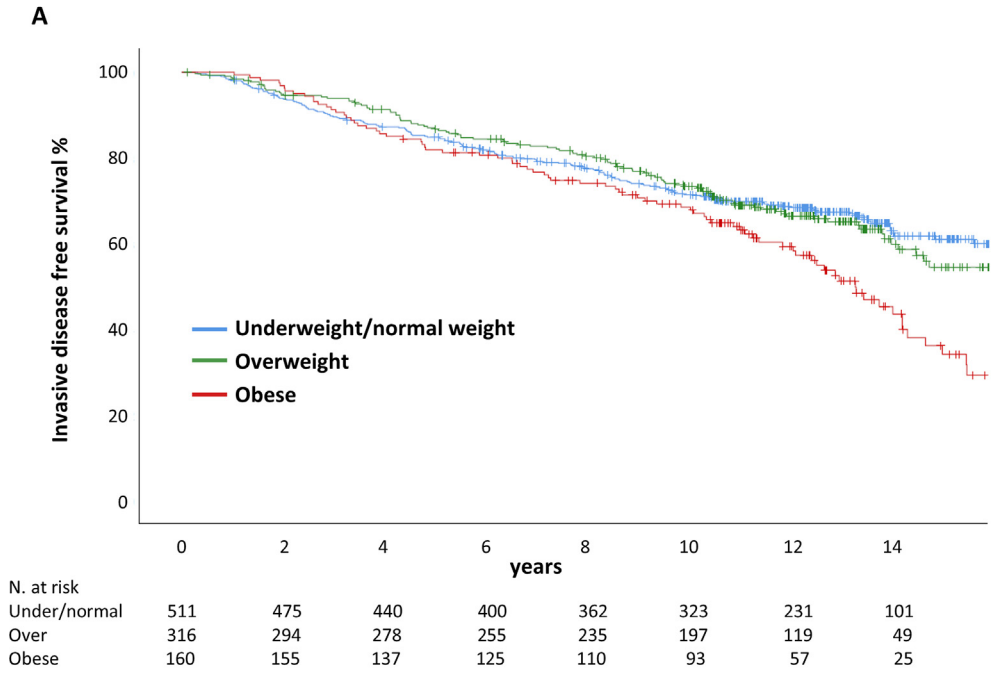
3.5. Association between BMI and prognosis in HER2-positive patients

Supplementary Fig. S1 shows the impact of BMI on iDFS and late-iDFS in HER2-positive patients ($n = 116$ cases of 689 patients with available HER2 status). BMI was not significantly associated with iDFS (log-rank $p = 0.537$). In late-iDFS analysis, 67 HER2-positive patients were included. Obesity was significantly associated with worse late outcome (log-rank $p = 0.006$).

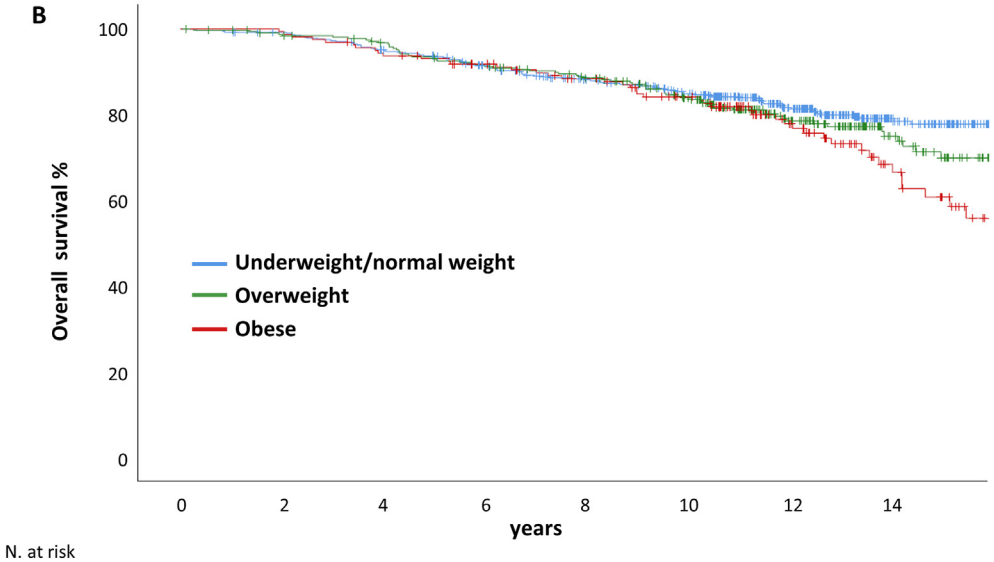
4. Discussion

This study examined the impact of BMI on outcome, focusing on late events, in a large cohort of early BC patients. Obesity conferred a poor prognosis in term of both iDFS and OS. The added value of this work is the long follow-up, allowing to specifically assess the impact of BMI on late outcome. We demonstrated that obesity was independently associated with worse late-iDFS.

In our cohort, a higher BMI was correlated with advanced stage and nodal involvement at diagnosis. These findings are supported by literature [20–22] and could be related to a more difficult breast examination, especially self-exam, in obese women, which may lead to a delay in breast lumps diagnosis [23–25]. In this population, the delay in medical consultation could also depend from psychological perception of self and low socioeconomic status, as previously reported [26]. Our results are consistent with main literature with regards to the association between BMI and BC patients' prognosis. Two large meta-analyses, respectively of 43 and 82 international studies, showed a poorer outcome for obese BC patients vs non-obese, independently from menopausal and HR status [27,28]. Our cohort was composed for the vast majority of HR-positive patients. Most of the existing data show the strongest association of BMI and outcome in patients with HR-positive tumors. Data from a National Surgical Adjuvant Breast and Bowel Project (NSABP) trial of among 4077 HR positive, node-negative patients showed an increased risk of overall mortality, second tumors and contralateral breast cancer, but not of recurrence, among obese patients; no difference in breast cancer-specific survival was found [29]. Similarly, Sparano et al. showed an association between high BMI at diagnosis and higher risk of recurrence and death in HR-positive and HER2-negative patients included in 3 adjuvant trials [30]. Several mechanisms have been proposed to explain the correlation between HR-positive BC and adipose tissue: accumulation of adipose tissue induces high circulating levels of sex



N. at risk								
Under/normal	511	475	440	400	362	323	231	101
Over	316	294	278	255	235	197	119	49
Obese	160	155	137	125	110	93	57	25



N. at risk								
Under/normal	511	503	478	446	410	379	269	129
Over	316	306	295	276	259	226	137	65
Obese	160	158	148	139	127	112	72	36

Fig. 1. 15-years iDFS (**A**) and OS (**B**) according to BMI. Number of at-risk individual is reported under the graphs.

hormones, as estrone and free estradiol, that may stimulate residual neoplastic cell to grow [31]. Moreover, hyper-adiposity is related to a chronic hyperinsulinemia which reduces production of insulin-like growth factors (IGF) binding proteins, causing elevated levels of free IGF which can stimulate the synthesis of sex steroid hormones [12,32]. The worst prognosis among obese patients could also be influenced by treatment-related factors. In fact, the use of ideal body surface area (or a maximum of 2 kg/mq) to calculate chemotherapy dose could lead to an under-estimation of drugs. Furthermore, it has been observed that many physicians tend to reduce drugs' doses in heavy patients concerning of adverse effects [33]. With regards to endocrine therapy, some evidences suggested a lower benefit in obese patients treated with aromatase inhibitors (letrozole and anastrozole) in both advanced and adjuvant setting. The lack of complete suppression of the aromatization process of androgens to estrogens in adipose tissue in obese women with standard doses of aromatase inhibitors could be a possible explanation of this phenomenon [34,35]. A number of studies [13,36,37] have also tested the role of obesity on outcome in TNBC patients. Even if a recent genomic analysis revealed molecular networks and biological pathways associating obesity with TNBC [38], a recent meta-analysis with 4412 TNBC patients showed no significant

Table 2
Univariate and Multivariate Cox proportional Hazard Models for 15-years iDFS, 15-years OS and Late iDFS at 5 years after the landmark of 10 years.

iDFS					
		Univariate Hazard Ratio (95%CI)	p	Multivariate Hazard Ratio (95%CI)	p
Age (continuous)		1.02 (1.01–1.03)	<0.001	1.01 (1.00–1.02)	0.027
Menopause	PRE	Ref	<0.001	Ref	0.014
	POST	1.89 (1.48–2.41)		1.47 (1.08–2.00)	
Stage	I	Ref	0.007	Ref	0.014
	II	1.38 (1.09–1.75)	<0.001	1.35 (1.06–1.71)	<0.001
	III	2.59 (1.90–3.51)		2.46 (1.79–3.37)	
Grade	1/2	Ref	0.188	NA	
	3	1.17 (0.93–1.47)			
BMI	Under/Normal	Ref	0.767	Ref	0.177
	Over	1.04 (0.82–1.32)	0.001	0.84 (0.65–1.08)	0.307
	Obese	1.56 (1.19–2.03)		1.16 (0.87–1.55)	
OS					
		Univariate Hazard Ratio (95%CI)	**p**	**Multivariate Hazard Ratio (95%CI)**	**p**
Age (continuous)		1.04 (1.03–1.05)	<0.001	1.03 (1.02–1.05)	<0.001
Menopause	PRE	Ref		Ref	
	POST	2.91 (2.03–4.17)	<0.001	1.54 (0.98–2.41)	0.062
Stage	I	Ref		Ref	
	II	1.65 (1.19–2.28)	0.003	1.63 (1.17-2-26)	0.004
	III	3.31 (2.32–4.90)	<0.001	3.25 (2.16–4.89)	<0.001
Grade	1/2	Ref	0.042	Ref	0.015
	3	1.35 (1.01–1.80)		1.45 (1.07–1.95)	
BMI	Under/Normal	Ref	0.182	Ref	
	Over	1.23 (0.91–1.68)	0.029	0.94 (0.68–1.30)	0.706
	Obese	1.49 (1.04–2.12)		0.96 (0.65–1.41)	0.820
Late iDFS					
		Univariate Hazard Ratio (95%CI)	**p**	**Multivariate Hazard Ratio (95%CI)**	**p**
Age (continuous)		1.02 (1.00–1.04)	0.025	1.00 (0.98-1-02)	0.972
Menopause	PRE	Ref		Ref	
	POST	2.25 (1.36–3.71)	0.002	1.87 (1.04–3.37)	0.036
Stage	I	Ref			
	II	1.18 (0.74–1.88)	0.479	1.07 (0.67–1.70)	0.793
	III	2.31 (1.17–4.56)	0.016	1.58 (0.76–3.26)	0.223
Grade	1/2	Ref	0.062	NA	
	3	0.59 (0.34–1.03)			
BMI	Under/Normal	Ref		Ref	
	Over	1.69 (1.01–2.83)	0.047	1.34 (0.78–2.31)	0.286
	Obese	3.73 (2.25–6.20)	<0.001	2.81 (1.64–4.83)	<0.001

Abbreviations: yrs, years; iDFS, Invasive Disease Free Survival; CI, Confidence Interval; Ref, reference; BMI, Body Mass Index; OS, Overall Survival.

association between obesity and DFS ($p = 0.60$) or OS ($p = 0.71$) [39]. In our analysis, the sample size of hormone receptor-negative subgroup was underpowered to allow any subgroup analysis difference (only 11% of total population).

Our paper focused specifically on late outcome, with a landmark analysis after 10 years from diagnosis. In the last decades survival rates have constantly increased in women with BC [40,41]. However, the risk of late relapse still represents a challenge. Indeed, it has been recently demonstrated that the risk of BC recurrence continues steadily after 5–20 years from diagnosis especially for HR-positive BC patients [3]. Therefore, the identification of factors associated with late relapse in BC survivors is essential in order to offer individualized treatment strategies (i.e. extended adjuvant endocrine therapy) and plan life style-related preventive measures. Moreover, the pool of long-term BC survivors is expected to further increase, thus calling for a particular attention on competing causes of mortality/morbidity (as cardiovascular disease, chronic illness and second cancers). In this perspective, the control of modifiable risk factors such as obesity should be encouraged.

In an exploratory analysis we also showed the association between obesity and increased risk of late-iDFS event in HER2-positive patients. Most of the HER2-positive patients in our cohort were also HR-positive (89%). Our results are somehow in contrast with previous data in HER2-positive patients, showing a prognostic impact of BMI and in particular of obesity for HER2-positve/HR-negative patients and not for HER2-positve/HR-positive patients [42,43]. However, only 21% of HER2-positive patients in our study received trastuzumab and the sample size is very limited. Therefore these data should be interpreted with caution.

We observed an association between obesity and risk of developing a second primary cancer. The long exposure to a status of chronic subclinical inflammation and the increased levels of free IGF-1 connected with excess weight could explain the excess of second primary tumors in patients with high BMI. Our finding is consistent with previously reported data [44] and also with the special report of the International Agency for Research on Cancer (IARC) which concluded that there is sufficient evidence for a cancer-preventive effect of avoidance of weight gain for cancers of the colon, esophagus, renal-cell, postmenopausal BC and corpus uteri [9].

Because of its retrospective nature, our database lacked information on change in body weight after diagnosis, and this could be a limitation. In fact, during and after adjuvant therapy for BC, gaining weight represents a frequent condition, especially due to alteration in metabolism and changing in dietary habits and lifestyle [45]. Chan et al. described the impact of weight gain in a cohort of more than 200.000 patients. In this meta-analysis, for each 5 kg/m2 increase of BMI before, <12 months after, and >12

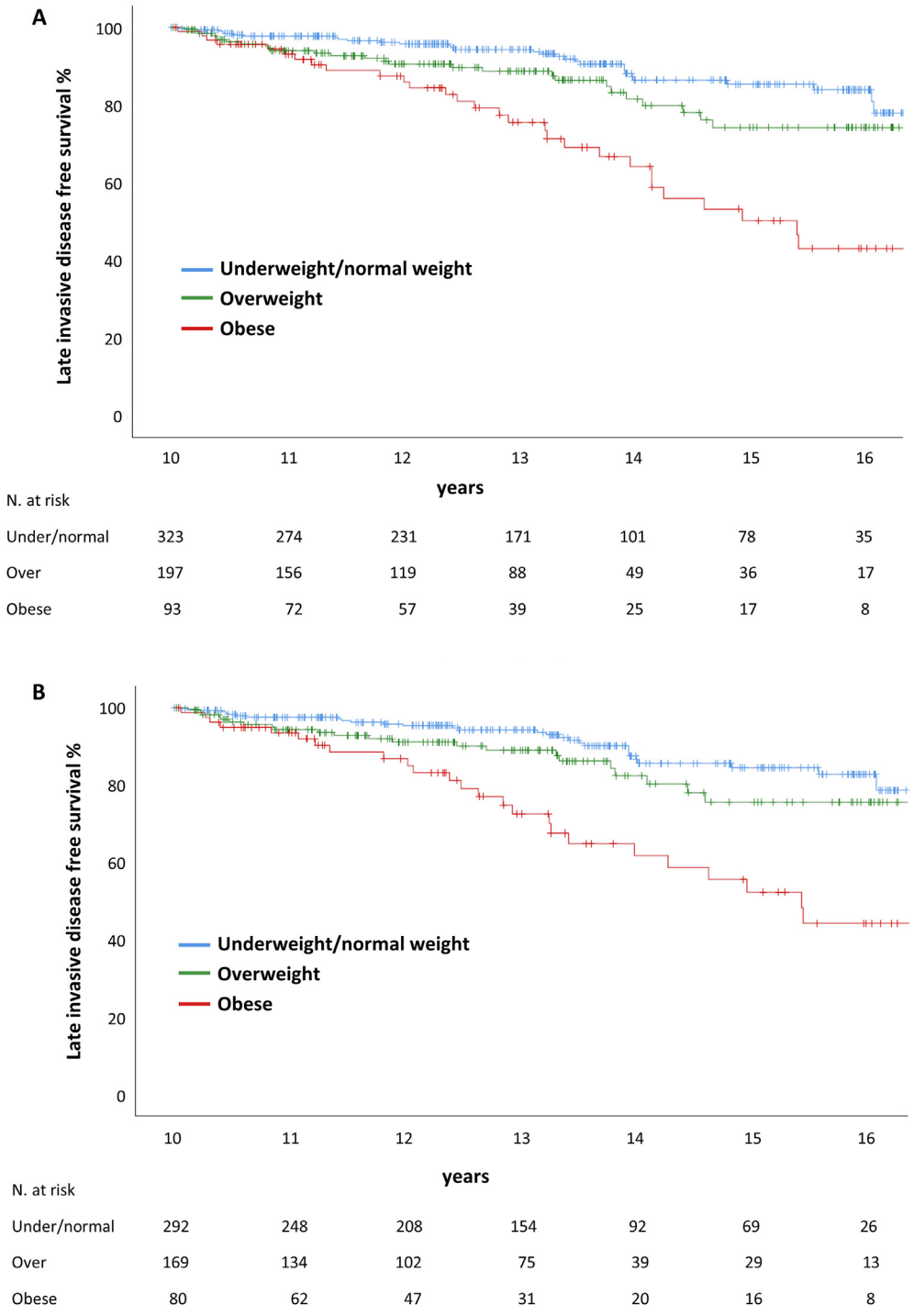


Fig. 2. Late iDFS at 5 years from the landmark of 10 years after diagnosis according to BMI in the whole population (A) and in HR + patients (B). Number of at-risk individuals is reported under the graphs.

months after diagnosis, an increased risk of total mortality and BC specific mortality was demonstrated [28]. Similarly, Bradshaw et al. showed a poor prognosis among women who gained more than 10% weight after diagnosis of BC compared with those who maintained their weight [46].

Another limitation of our study is the lack of body composition measure. Indeed, BMI definition is only related to weight and height, not necessary to fatness, and definition of obesity or leanness may not be accurate by using this index. New aspects as sarcopenia and waist-to-hip ratio could be more precise in describing body composition. In particular, sarcopenia has been shown to be associated with an increased risk of recurrence and death in early and metastatic setting [45] and a high waist-to-hip ratio seems to be correlated with poor prognosis in postmenopausal women [47]. However, BMI remains a simple and totally reproducible index. Further studies are needed to understand how to integrate these indexes.

Table 3
Late iDFS events distribution across BMI classes.

	Underweight/Normal N (%)	Overweight N (%)	Obese N (%)	p
Local relapse	7 (2)	4 (2)	3 (3)	<0.0001
Distant relapse	3 (1)	1 (1)	6 (7)	
Second BC	6 (2)	1 (1)	5 (5)	
Second non-BC	7 (2)	8 (4)	5 (5)	
Death w/o event	8 (3)	12 (6)	10 (11)	
No Events	291 (90)	171 (86)	64 (69)	
Total	322 (100)	197 (100)	93 (100)	

Abbreviations: iDFS, Invasive Disease Free Survival; BMI, Body mass Index; BC, Breast Cancer.

5. Conclusions

Our cohort represents a large mono-institutional database about impact of BMI in early BC patients. We confirmed the negative impact of being obese on BC prognosis. With a long follow-up, a high BMI was associated with increased rates of relapse, second primary tumors and death occurring in the period that started from 10 years after BC diagnosis. Considering the increasing number of women living after a BC diagnosis and the progressively growing prevalence of overweight and obesity among adults, understanding the link between BC and body size is crucial. As BMI is a modifiable risk factor, interventions to control body weight should be pursued.

Ethical approval

All authors declare that the work has been carried out in accordance with The Code of Ethics of the World medical Association (Declaration of Helsinki). The study protocol has been approved by the Ethics Committee of Istituto Oncologico Veneto IRCCS of Padova.

Declaration of interest

No competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.07.003.

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