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Senescent obesity signature in breast cancer: a paradigm of reverse cardio-oncology

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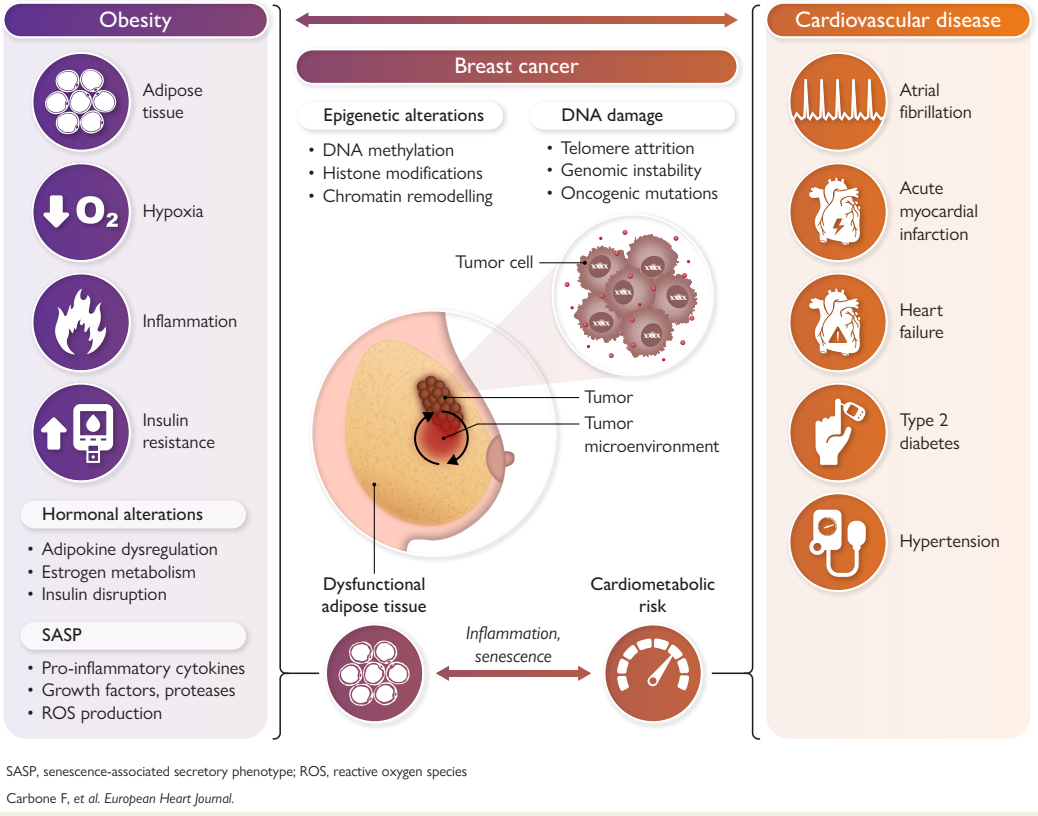
Graphical Abstract



Links between obesity and cardiovascular disease underlying the reverse cardio-oncology paradigm in breast cancer

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Abstract

The field of reverse cardio-oncology examines how subclinical and overt cardiometabolic dysfunction—such as obesity—fuels breast cancer (BCa) risk and altered tumour biology through shared mechanisms such as chronic inflammation, hormonal dysregulation, and cellular senescence. Limitations of body mass index (BMI) have prompted the development of refined obesity phenotypes, including metabolically healthy vs unhealthy obesity and sarcopenic obesity that more accurately stratify BCa risk. Reverse cardio-oncology is conceptually distinguished from traditional cardio-oncology by focusing on how cardiometabolic impairment—even in the absence of manifest cardiovascular disease—increases BCa incidence and worsens prognosis. Within a common-soil framework, senescent adipose tissue is recognized as a key driver of breast tumour microenvironment remodelling through senescence-associated secretory phenotype (SASP), epigenetic reprogramming, and immunosenescence. Emerging translational strategies—including lifestyle modification, cardiometabolic therapies such as GLP-1 receptor agonists and SGLT2 inhibitors, and senolytic approaches—highlight opportunities to integrate cardiovascular and oncologic prevention and treatment in women with or at risk for BCa. Overall, this review synthesizes current knowledge on obesity's mechanistic links to BCa within a reverse cardio-oncology paradigm and provides a conceptual foundation for improved risk stratification and interdisciplinary clinical management.

Keywords Obesity • Cancer • Adiposity • Adipobiology • Senescence • Inflammation • Cardio-oncology • Insulin resistance

Introduction

Reverse cardio-oncology is an emerging framework describing how cardiovascular (CV) risk factors and cardiometabolic dysfunction influence cancer initiation, progression, and outcomes.[1] Unlike traditional cardio-oncology—which focuses on CV toxicity from cancer therapies—reverse cardio-oncology examines how metabolic derangements, chronic inflammation, endocrine alterations, and clonal haematopoiesis create a biological substrate that predisposes to malignancy, including breast cancer (BCa).[2,3]

The global rise in obesity has intensified interest in how cardiometabolic factors contribute to cancer risk, yet body mass index (BMI) alone insufficiently captures obesity-related metabolic heterogeneity.[4] Refined phenotypes—including metabolically healthy obesity (MHO), metabolically unhealthy obesity (MUO), metabolically unhealthy normal weight (MUNW), and sarcopenic obesity (SO) have been proposed to improve clinical and prognostic accuracy[5,6] (see Supplementary data online, *Glossary*). Epidemiologic and meta-analytic data indicate that cardiometabolic impairment—even without overt CV disease—elevates BCa incidence and influences prognosis, reinforcing the relevance of incorporating obesity and metabolic phenotypes within the reverse cardio-oncology lens (see Supplementary data online, *Table S1*). Obesity affects BCa at two non-overlapping levels: by increasing proliferative pressure, mutational opportunity and malignant initiation, and by remodelling the tumour–host interface to accelerate progression, resistance, and metastatic spread. Beyond these processes, cellular senescence has emerged as a common soil linking obesity, ageing biology, and BCa.[6,7] Senescence is a stress–response programme characterized by stable cell-cycle arrest and a senescent-associated secretory phenotype (SASP), which profoundly influences tissue homeostasis, chronic inflammation, and cancer-related remodelling.[8,9] Whether obesity synergistically fuels BCa through a premature or accelerated senescence remains a fascinating, albeit unaddressed, issue. This review critically synthesizes current knowledge to clarify: (i) how obesity subtypes and cardiometabolic profiles shape BCa incidence and prognosis; (ii) the relevance of reverse cardio-oncology within the obesity–BCa axis; (iii) mechanistic links between adipose-tissue senescence and tumour-microenvironment remodelling; (iv) the contribution of systemic inflammation, hormonal dysregulation, and epigenetic reprogramming; and (v) knowledge gaps and translational opportunities for prevention and therapy. Through this integrative approach, we aim to support improved risk stratification and more personalized management of individuals with obesity at risk for or living with BCa.

The epidemiology of breast cancer and excess weight: a paradigm for 'reverse cardio-oncology'?

Incidence and risk: adiposity as an etiologic driver

BCa still remains the most common malignancy among women, accounting for nearly 30% of all new female cancers annually.[10] Global incidence patterns are shaped by demographic transitions, socioeconomic development, and changes in lifestyle and reproductive factors. The correlation between BCa incidence and the Human Development Index (HDI) underscores how life expectancy, education, and living standards influence population-level exposure to risk factors.[11,12] Low- and middle-income countries show rising incidence with persistently high mortality, often due to later-stage diagnosis and a fragmented health system.[13–15] Even in high-income countries, socioeconomic disparities continue to influence stage at diagnosis, genomic testing utilization, and survival, with variables such as race, insurance status, and geographic setting remaining strong predictors of unequal outcomes.[16–18]

Within this broader epidemiologic framework, adiposity has emerged as a major etiologic driver of BCa, particularly after menopause. Obesity patterns vary by ethnicity, socioeconomic position, and developmental status, with global trends reflecting

an 'obesity transition' characterized by narrowing sex differences and reversal of socioeconomic gradients.[19,20] These dynamics mirror persistent food insecurity and the widespread adoption of ultra-processed, energy-dense dietary patterns.[21,22] Such trends interact with demographic ageing and behavioural risk factors to progressively increase the burden of cardiometabolic disturbances that predispose to BCa. Translational data support a shared risk burden between CV disease and BCa, consistent with a common-soil hypothesis.[23–25] Observational and mechanistic work further supports this interplay: patients with heart failure show increased non-cardiac mortality including cancer,[26] while experimental models demonstrate that CV injury and remodeling—including IL (interleukin)-1β–dependent inflammation, post-myocardial infarction monocyte reprogramming, and macrophage-derived mediators—can promote tumour growth and metastatic traits[4,27–36] Although these links appear weaker for BCa than for other malignancies, hormonal pathways may partially modulate the CV–BCa relationship.[29,31,37] Because most shared risk factors between CV disease and BCa are modifiable, adherence to ideal CV health would consistently associate with lower BCa incidence. More recently, addressing social determinants of health has been emphasized as a strategy to reduce both CV disease and BCa burdens and advance health equity.[23]

Exploring the link between BCa and adiposity remains challenging. Associations between obesity, metabolic health, and BCa are well described,[38] and lifestyle patterns such as regular physical activity and the Mediterranean diet show consistent protective effects.[39,40] Because cardiometabolic risk is not fully captured by BMI alone, there is a progressive shift towards incorporating additional anthropometric measures—including waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio, and body-shape indices—and phenotype-based stratification.[5,41–44] Accordingly, relatively few studies have examined BCa risk across obesity phenotypes rather than BMI categories *per se*[45–52] (*Table 1*).

Key takeaways from *Table 1*

- Metabolic unhealthiness raises risk across sizes: Metabolically unhealthy status increases BCa risk in both normal-weight and overweight groups (e.g. HOMA-IR/MetS), with MU-obesity (MUO) showing the highest risk[49,50,52]
- Central adiposity and glycaemia matter: Among MetS components, fasting glucose and waist circumference show the strongest independent associations with BCa risk[52]
- Beyond BMI: Weight can outperform BMI for risk prediction,[51] and WC change around the menopausal transition signals risk even when weight change does not.[50]
- Phenotypic paradoxes exist: Some cohorts report lower risk in metabolically healthy overweight and selected severe-obesity phenotype[50,53] underscoring phenotype instability and the need for longitudinal assessment.[54,55]
- Research gap: Combined anthropometric + metabolic index models are scarce but promising and should be prioritized in future long-term studies.[55]

Metabolic health appears to be a major driver of BCa risk—often outweighing the impact of adiposity itself—particularly among people with overweight, while evidence among people living with obesity remains more heterogeneous, with paradoxical risk reductions noted in some metabolically healthy or severe-obesity phenotypes.[53] Because BMI and WC reflect different aspects of adiposity, their wide variability across and within BMI categories highlights the limitations of using either measure alone, and yet they are rarely combined in BCa risk estimation. The definition of 'metabolic health' also remains problematic: not meeting ≥3 MetS (metabolic syndrome) criteria does not reliably identify truly healthy individuals, and this phenotype is increasingly recognized as a transitional state along a continuum that shifts across the life course.[54,56] Emerging metabolic indices—such as visceral adiposity markers, triglyceride-to-glucose ratio, lipid-accumulation products, and composite cardiometabolic scores—may help refine obesity phenotyping and BCa risk assessment, although they have been evaluated in only a few studies and seldom integrated with anthropometric measures.[55]

Prognosis and disease course: adiposity as an outcome modifier

Beyond incidence, the obesity signature on the BCa genomic landscape would broadly influence progression-free and overall survival (PFS and OS, respectively). Standardized genomic phenotyping (PAM50 gene analyses) and the risk of recurrence score significantly differ by waist-to-hip ratio,[57] while heterogeneous—but discrete—DNA methylation regions with potentially functional differentially methylated positions/regions offer a promising substrate for prognostic stratification and therapy selection in triple negative (TN) BCa.[58] Preclinical work further shows that obesity promotes the escape from tumour dormancy towards aggressive growth, marked by a switch to the vascular phenotype with increased neovascularization.[59] In TNBCa models of obesity, deep metabolic reprogramming underlines the metastatic potential,[60] alongside remodelling in extracellular matrix[61] and altered monocyte trajectories with enhanced neutrophil activation and extracellular trap formation.[62] Consistently, individuals with obesity and BCa display distinct morphological and immunophenotyping features in axillary lymph nodes.[63] Since 2019, meta-analyses have reported a modest worsening of disease-free survival (DFS) and OS across BCa subtypes. In most recent studies, adiposity is repeatedly—but not uniformly—associated with poorer DFS and OS, sometimes with a 'U-shaped' pattern in which underweight is equally detrimental (*Table 2*).[8,64–97]

Key takeaways from *Table 2*

- Overall pattern: Higher adiposity is often linked to poorer outcomes (DFS/OS), but findings are heterogeneous across cohorts and endpoints.[64–67,78,88] Several studies show a U-shaped association, with both underweight and obesity conferring risk.[65,79,90]
- Central adiposity > BMI: WHR and WC predict all-cause and BCa-specific mortality more consistently than BMI in multiple cohorts.[77,87,94]
- Metabolic health matters: MetS and glycemic dysregulation carry independent prognostic weight; in WHI, a higher MetS score predicted post-BCa and BCa-specific mortality even after BMI adjustment.[95] Lipids (e.g. low HDL-c) and

Table 1 Summary of the studies describing the risk of breast cancer according to the obesity phenotype

Authors	Year	Study design and time frame	Population size and anthropometric/ metabolic status	Statistical adjustment	Results
Gunter *et al.*[45]	2015	Longitudinal analysis from WHI Mean follow-up 8.2 y	2893/497 cohort/case 50 to 79-y post-menopausal women MH/MU vs OW/NW defined by BMI ± HOMA-IR	Age; BMI; HOMA-IR (or fasting insulin quartile); menopausal status; hormone therapy use; family history of BCa; smoking; alcohol; physical activity	Metabolically unhealthy status (HOMA-IR) significantly increases BCa risk in both NW (HR 2.06 [95% CI 1.01–4.22]) and OW (HR 2.01 [95% CI 1.35–2.99]).
Park *et al.*[46]	2017	Longitudinal analysis from the Sister Study Mean follow-up 6.4 y	50 884/1388 cohort/case in 35 to 74-y-old women MetS criteria and BMI MHNW, MUNW, MHOW/OB, NWCO Pre and post-menopausal status	Age; race/ethnicity; education; age at menarche; parity; breastfeeding; hormone-replacement therapy; oral contraceptive use; family history; smoking; alcohol; physical activity	MUNW (≥1 MetS criteria) (HR 1.26 [95% CI 1.01–1.56]) and MUOW/O (HR 1.24 [95% CI 0.99–1.55]) have an increased risk of post-menopausal BCa than healthy phenotypes. An excess BCa risk is also observed in NWCO (HR 1.58 [95% CI 1.02–2.46]), whereas a 'paradoxical' risk reduction characterizes MHOW/OB (HR 0.71 [95% CI 0.52–0.97])
Kabat *et al.*[47]	2017	Longitudinal analysis from WHI 15-y follow-up	21 000/1176 control/case 50 to 79-y post-menopausal women MH/MU and NW/OW/OB	Age; BMI; MetS components (waist circumference, blood lipids, blood pressure, glucose); plus smoking; alcohol; physical activity; hormone therapy; family history; education; race	Both BMI and the MetS, considered individually, are positively associated with BCa, even after mutual adjustment. MUO has the highest risk of BCa with HR of 1.62 [95% CI 1.33–1.96].
Soltani *et al.*[48]	2021	Systematic review of 3 studies	43 352/839 cohort/case 18 to 90-y-old women with diabetes BMI	Age; diabetes duration/severity; smoking; alcohol; BMI; plus any cohort-specific covariates originally adjusted	Each 5-unit increase in BMI increases the BCa risk by 12% (RR 1.12 [95% CI 1.05–1.20]). The increased risk is steeper for BMI around 35 kg/m^2.
Park *et al.*[49]	2021	Longitudinal analysis from NHIS of South Korea 9-y follow-up	3 095 336 of 40 to 79 y-old post-menopausal women BMI and/or MetS to define MH/MU and NW/OB (OB defined by BMI (≥25.0 kg/m^2)	Age; age at menarche; age at menopause; parity; breastfeeding; hormone therapy; oral contraceptive use; family history; smoking; alcohol; vigorous and moderate physical activity	Both OB and MetS are associated with BCa risk, with an HR of 1.30 (95% CI 1.26–1.33) and 1.16 (95% CI 1.13–1.19), respectively. The association slightly weakens after mutual adjustment. MetS criteria all increase BCa risk, but the effect is greater for FPG (HR 1.08 [95% CI 1.05–1.11]) and WC (1.06 [95% CI 1.03–1.10]). When combined into obesity phenotypes, BCa risk increases in MUNW and MHO, with the highest risk in MUO.

Continued

Table 1 *Continued*

Authors	Year	Study design and time frame	Population size and anthropometric/ metabolic status	Statistical adjustment	Results
Park *et al.*[50]	2022	Longitudinal study 6-y follow-up	184 931 women 40 to 59-year-old in pre-post-menopausal transition BMI and WC change	Age; baseline BMI or WC; change in BMI/WC; smoking; alcohol; physical activity; education; hormone therapy; parity; family history; other standard BCa covariates	WC ≥5 cm but not weight gain was related to an increased BCa risk (HR 1.15 [95% CI 1.01–1.30]). In women with normal BMI or WC in pre-menopause WC change during transition was not associated with BCa risk.
Ye *et al.*[51]	2022	Longitudinal analysis of the Prospective Family Study Cohort Follow-up 11.5-year	6761/416 cohort/case <79-y old post-menopausal women BMI and weight	Age; baseline BMI; baseline weight; weight change; smoking; alcohol; physical activity; hormone therapy; family history; race/ ethnicity; education	Weight was more informative than BMI for predicting BCa risk with a log risk gradient 1.23 times that for BMI.
Mahamat-Saleh *et al.*[52]	2023	Longitudinal analysis of EPIC registry 8-y follow-up	1130/610 control/case 35–75-y old pre- and post-menopausal women MHNW, MH OW/OB, MUNW, and MUOW/OB based on BMI/WC and MetS criteria	Age; assay batch; center; education; BMI (if not defining phenotype); smoking; alcohol; physical activity; menopausal status; hormone therapy; dietary factors	MU OW/OB were at higher risk of post-menopausal BCa compared to MHNW according with both BMI (OR 1.58 [95% CI 1.14–2.19]) and WC (OR 1.51 [95% CI 1.09–2.08]). Conversely, MHOW/OB and MUNW did not show an excess risk of BCa.

PubMed search ((healthy obes* [Title/abstract]) OR (unhealthy [Title/abstract]) OR (overweight [Title/abstract])) AND (('breast cancer risk' [Title/abstract]) OR ('risk of breast cancer' [Title/abstract])) from 2015 to present. BCa, breast cancer; BMI, body mass index; central obesity; CI, confidence interval; circumference; EPIC, European prospective investigation into cancer and nutrition; FPG, fasting plasma glucose; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; MetS, metabolic syndrome; MH, metabolically healthy; MHNW, metabolically healthy normal weight; MHOW/OB, metabolically healthy overweight/obesity; MU, metabolically unhealthy; MUNW, metabolically unhealthy normal weight; NHIS, National Health Insurance Service (South Korea); NW, normal weight; NWCO, normal weight; OB, obesity; OR, odds ratio.; OW, overweight; RR, relative risk; WC, waist;WHI, Women's Health Initiative.

Table 2 List of the studies summarizing the link between the adipose/metabolic status and BCa outcome

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Kim *et al.*[64]	2019	Retrospective 2000–2015	5919 patients, with different receptor ER, PR, and HER profiles	Multivariable Cox models stratified by menopausal status and tumour subtype; adjusted for BMI category; age; ER/PR/HER2 status; treatment (surgery type, chemo, radiation, endocrine); and clinical factors (tumour size, node status) in relapse-free and OS analyses.	OB prevalence was higher in over 50 y old, in post-menopausal state, and in higher tumour stage. Postoperation radiation therapy was less likely to be received in UW patients. ER, PR, and HER2 status were similar across groups.
Wang K *et al.*[65]	2019	Retrospective Multicentre 2005–2015	18 600 BCa patients 8394 invasive BCa 4462 (53.2%) were premenopausal	Multivariable logistic and Cox models adjusted for age; menopausal status; BMI category; tumour size; grade; node status; ER/PR/HER2 status; surgery type; adjuvant therapy (chemo, radio, endocrine); and centre-level clustering via robust variance estimation.	In the premenopausal group, OW and OB frequently have larger tumour size (>5 cm) (OR, 1.30; $P < .01$) and TNBCa (OR 1.31; $P = .01$). In this group, UW had significantly higher risk of HER2 positive BCa (OR 1.71; $P = .02$) and distant metastasis (OR 2.59; $P = .01$). In the post-menopausal group, OW showed higher risks of large tumour size (OR, 1.46; $P = .01$) and lympho-vascular invasion (OR 1.46; $P = .01$). A U-shaped relationship between BMI and DFS was found for UW vs NW HRadj 2.80 ($P < .001$); OW vs NW, HRadj 1.40 ($P = .02$).
Blair *et al.*[66]	2019	Case-control Median FU in the sub-cohort was 94 months (range 2–205 months)	697 BCa deaths	Cox multivariate models adjusted for age; race/ethnicity, physical activity; AJCC stage; tumour grade; subtype-specific variables; treatment modality; and comorbidities, with mediation analysis treating tumour characteristics (stage/grade) as potential intermediates.	Mortality risk in luminal A- and luminal B-like BCa was 1.8 (95% CI 1.3–2.5) and 2.2 (95% CI 0.9–5.0) times more likely in women with OB. OB was not associated with BCa-specific mortality in HER2 and TNBCa.
Cantini *et al.*[67]	2020	Retrospective 2006–2016	279 women with early (Stage I–III) invasive BCa	Cox proportional-hazards models adjusted for HR status; BMI category (<25 vs ≥25 kg/m^2); tumour stage; size; nodal status; adjuvant chemotherapy type; trastuzumab duration; and hormone therapy in multivariate analyses of 3-y DDFS.	3DFS for patients with ER- and PR− was lower for BMI ≥25 kg/m^2 (HR 87% [95% CI 75%–98%] vs 98% [95% CI 95%–100%]; $P = .003$), also in multivariate analysis (HRadj 1.79 [95% CI 1.04–3.07]; $P = .03$).
Oudanonh *et al.*[68]	2020	Longitudinal 1995–2010	3747 women diagnosed with nonmetastatic ER + invasive BCa	Multivariable Cox regression adjusted for age; BMI category, PR status; ER status; stage; grade; tumour size; node status; treatment (surgery, chemo, radiation, endocrine); plus tests for additive/multiplicative interaction between BMI and PR status on mortality.	All-cause mortality in PR-tumours increases in UW (HR 2.76 [95% CI 1.40–4.91]), OW (HR 2.02 [95% CI 1.43–2.81]), or OB (HR 2.51 [95% CI 1.67–3.65]), when compared to PR + NW. Especially PR + BCa shows a similar risk profile regardless of BMI.

Continued

Table 2 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Rasmy *et al.*[69]	2020	Cohort 2010–2013	80 early invasive BCa	Logistic models for pCR and Cox for PFS/OS adjusted for BMI group (<25 vs ≥25 kg/m²); menopausal status; tumour grade; subtype; stage; lymphovascular invasion; treatment regimen; and demographic factors (age, comorbidities) in both univariable and multivariable frameworks.	In the survival analysis, DFS does not differ between the BMI categories 25–29.9 and >30 kg/m² ($P = .19$). Conversely, patients with normal BMI have significantly better OS than patients with OB ($P = .029$), with a lower mortality rate (2.3% vs 16.7%; $P = .037$).
Engkakul *et al.*[70]	2020	Retrospective 2004–2011	400 Stage I, II and III (pT1–4, pN0-3 and M0) BCa	Retrospective cohort Cox models adjusted for age, comorbidities, menopausal status, family history, hormone use, tumour stage, treatment modalities (surgery, radiation, chemotherapy, hormonal therapy), plus mutual adjustment for BMI category in survival analyses.	5-y DFS do not differ in OB and non-OB groups (82% vs 82.3%; HR 0.94 [95% CI 0.61–1.44]; $P = .779$). Similarly, 5-y survival does not differ among groups (89.4% and 90%; HR 1.11 [95% CI 0.64–1.92]; $P = .703$)
Tong *et al.*[71]	2020	Longitudinal 2012–2017	679 HER2+ IDC (94.6%) BCa patients. Treatment with mastectomy (77.91%), SLNB (58.76%)	Multivariable Cox models adjusted for IGF-1 level; BMI category (≥24 kg/m²); MetS components (per AHA/NHLBI); hormone therapy; tumour size; nodal status; treatment regimen; plus interaction term for BMI × IGF-1 in stratified RFS and OS analyses.	Circulating IGF-1 and IGFBP-3 increase in pre/perimenopausal women ($P < .001$ for both). IGF-1 alone does not associate with RFS ($P = .620$), but its combination with BMI does ($P = .009$). While high IGF-1 increases 4-y RFS in NW (91% vs 85%; HR .53 [95% CI 0.27–1.00], $P = .049$), an opposite effect occurs in OW (88.3 vs 95.7%; HR 3.20 [95% CI 1.00–10.21]; $P = .038$). High IGF-1 levels are also independently associated with better OS (HR 0.26 [95% CI 0.08–0.82]; $P = .044$).
Franzoi *et al.*[72]	2020	Longitudinal 2019–2020	1138 patients in endocrine therapy, 757 also received abemaciclib, and 381 placebo	Cox proportional hazards regression (multivariate analysis) adjusted for age, Eastern Cooperative Oncology Group ECOG performance scale, prior endocrine therapy (ET), prior aromatase inhibitor use, menopausal status, number of metastatic sites, and type of ET. Interaction tests for BMI and treatment groups.	Overall response rate to abemaciclib is higher in UW/NW when compared with OW/OB (49.4% vs 41.6%; OR 0.73 [95% CI 0.54–0.99]) to 5.01). Abemaciclib generally increases PFS regardless of BMI.

Continued

Table 2 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Konishi *et al.*[73]	2020	Longitudinal 2010–2017	397 548 BCa treated with mastectomy (total or partial). BMI-based UW/NW/OW/OB groups 9.7%, 64.8%, 28.4%, 5.5%, respectively. 9.3%, 64.3%, 20.6%, 5.8%, respectively	Multinomial logistic regression (adjusted for age); binary logistic regression for side of breast cancer (adjusted for age); subgroup analyses by presumed menopausal status (age <45 vs ≥55 y).	Postsurgical complications, length of stay, and hospitalization costs show a U-shaped distribution according to BMI. Especially, OB is associated with a higher rate of greater postsurgical complications, 30-day readmission, duration of anaesthesia, length of stay, and hospitalization costs. BMI-based groups differ for the quadrant distribution of BCa
Saleh *et al.*[75]	2021	Longitudinal 2008–2016	12 999 metastatic BCa BMI	Multivariable models for OS and PFS adjusted for BMI category; underweight; age; performance status; time to MBC; metastatic site(s); number of metastatic sites; BC subtype; (first-line) chemotherapy; endocrine therapy; targeted therapy, with variables selected via stepwise backward elimination ($P < .10$) and inclusion of known prognostic factors.	While the rate of BCa was higher in OB, UW—but not OW/OB—associates with a more aggressive biology. Median OS and PFS worsen in UW (HR 1.14 [95%CI 1.02–1.27] and HR 1.11 [95% CI 1.01–1.22], respectively).
Ko *et al.*[76]	2021	Longitudinal 2009–2015	1225 invasive BCa patients and 35 991 healthy females	Multi-variable Cox regression was used to adjust for BMI, ALC, NLR, histologic grade, hormone receptor status (ER/PR/HER2), Ki-67 labelling index, tumour size, and lymph node involvement when assessing DFS and OS. KM analysis with log-rank tests compared survival outcomes between BMI and ALC risk groups. Subgroup analyses evaluated interactions by age, breast cancer subtype (ER+/HER2−, HER2+, TNBC), and disease stage (I-III). Confounding control was applied by excluding patients who received neoadjuvant chemotherapy or had stage IV disease.	While both OW and OB experience worse DFS, having high ALC improves DFS (HR 0.43 [95% CI 0.29–0.65]; $P < .001$). The combination of high BMI/low ALC defines a high-risk group for poor DFS (HR 2.48 [95% CI 1.70–3.62]; $P < .001$).

Continued

Table 2 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Bandera *et al.*[77]	2021	Longitudinal median FU of 5.9y (range, 0.5–14.8 y)	1891 BCa. 68.3% prevalence of central OB total of 1060 women (56.1%) had obesity, and 1291 women (68.3%) had central obesity	Multivariable Cox models for all-cause and breast-cancer-specific mortality adjusted for age, income, smoking status, tumour stage, tumour subtype, and type of surgery.	Q4 for WHR has 61% increased risk of all-cause death (HR 1.61 [95% CI 1.12–2.33]) and a 68% increased risk of BCa-specific death (HR 1.68 [95% CI 1.04–2.71]). Both all-cause and BCa-specific death are similarly higher in Q4 for WC (HR 1.74 [95% CI 1.26–2.41] and 1.64 [95% CI, 1.08–2.48], respectively), % body fat (HR 1.53 [95% CI, 1.09–2.15] and 1.81 [95% CI, 1.17–2.80], respectively), and fat mass index (HR 1.57 [95% CI, 1.11–2.22] and 1.74 [95% CI, 1.10–2.75], respectively), but not BMI (HR 1.26 [95% CI 0.89–1.79] and 1.33 [95% CI 0.84–2.10], respectively). When stratified for ER and menopausal status, and age, WHR retains the higher risk prediction for all-cause death in ER- BCa (HR 2.24 [95% CI 1.14–4.41]), post-menopausal status (HR 2.15 [95% CI 1.28–3.61]), and >60-y-old patients (HR 1.76 [95% CI 1.37–2.26]).
Lin *et al.*[78]	2021	Longitudinal 1990–2005	5000 patients with Stage I–III BCa candidate to surgery	Cox regression model (multivariate analysis) adjusted for tumour size, nodal status, oestrogen receptor (ER) status, HER2 status, and nuclear grade. Subgroup analyses by age (<50 vs ≥50 years).	OB is associated with advanced stage, higher nuclear grade, and higher percentages of ER + cells. OB is an independent prognostic factor of OS ($P < .001$), but not DFS ($P = .067$), especially in < 50-y-old BCa.
Kim *et. al.*[79]	2021	Retrospective 2007–2012	907 pT1-2 and pN0-1 BCa candidate to surgery	Competing-risk regression for local recurrence adjusted for variables with univariate $P < .20$: including age (<35 y); final margin status; and intrinsic subtype (other covariates not listed, model built via Gray's method)	5-yr cumulative incidence rate of LR was 3.2% with greater risk in both UW luminal A BCa (RR 3.33; $P = .041$) and severe OB (RR 3.81; $P = .048$).
Orlandini *et al.*[80]	2021	Retrospective 1999–2013	1664 Stage I–III BCa	Retrospective Cox and logistic models adjusted for BMI category; NLR (or PLR); stage; subtype; and standard clinicopathologic factors (tumour size, nodal status) when testing combined BMI + NLR prognostic groups	Higher BMI is associated with larger tumour, relapse risk, and worse survival, but is limited to stage I BCa. Once categorized, NLRhigh (NLR >4) is an independent prognostic factor for recurrence and mortality. When combined, the NLRhigh and BMIhigh subgroup shows the worst DFS ($P = .046$), BCa-specific and OS ($P < .001$ and $P = .006$, respectively).

Continued

Table 2 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Takada *et al.*[81]	2021	Longitudinal 2007–2019	421 BCa candidate to POC	Multivariable Cox regression adjusted for age; tumour size; skin infiltration; lymph node status; Ki67 index; objective response rate (ORR); pathological complete response (pCR); tumour-infiltrating lymphocyte (TIL) density; and BMI category (UW, NW, OW, OB)	OB associates with lower TIL density than NW/OW (P = .001 and .003, respectively), better OS in the TNBCa subgroup (P-value for Log Rank .031).
Yang *et al.*[82]	2022	Longitudinal 2010–2020	438 stage I to III BCa	Multivariate Cox proportional-hazards models adjusted for age (≥ 40, 41–59, ≥ 60 year); menopausal status; TNM Stages (I, II, III); type of surgery (mastectomy vs lumpectomy); lymph-node status; ER status; PR status; HER2 status; plus, depending on model, BMI category (at diagnosis or post-chemotherapy), weight-change category, and number/indicators of metabolic disorders.	BMI categories and weight change have no effect on the OS. Rather, baseline HDL-c and late-developed metabolic disorders associate with poor prognosis (OR 2.20 [95% CI 0.99–4.86] and 1.51 [95% CI 1.05–2.19, respectively.
Chung *et al.*[83]	2022	Retrospective 2011–2014	1460 Chinese BCa	Cox models stratified by follow-up period (18–48 m vs > 48 m) and adjusted for baseline socio-demographics (marital status, education); comorbidity status; lifestyle (smoking, physical activity, diet); tumour characteristics (AJCC stage, ER/PR/HER2 subtype); and treatments (hormonal therapy, chemotherapy, radiotherapy).	While a decrease in WHR ≥5% reduces all-cause death risk (HR 0.21 [95% CI 0.06–0.75]) and BCa-specific mortality (HR 0.21 [95% CI 0.06–0.77]), any WHR increase enhances the risks of all-cause mortality (2.67 [95% CI 1.22–5.85]). Contrariwise, BMI fails to predict any outcome.
Xie *et al.*[84]	2022	Cross-sectional 1999–2017	4 136 123 BCa cases with 782 454 deaths	Cross-sectional ecological correlations using Pearson's r; no multivariable adjustment. State-level trends were described unadjusted	OB significantly associates with BCa incidence (r = 0.316; P = .020) and mortality (r = 0.400; P = .004), whereas physical activity shows an opposite effect in ≥55 y BCa patients (r = –0.577; P < .001)
Somashekhar *et al.*[85]	2022	Retrospective 2017–2021	184 BCa candidate to POC	Multivariable logistic regression for pCR included menopausal status; BMI category (<22.9, 23–27.4, ≥ 27.5 kg/m²); type of surgery (BCS + SLNB, MRM, BCS + ALND); and molecular subtype (luminal A/B, HER2-enriched, TNBC). Variables with P < .25 in univariate analysis were entered, then forward-stepwise selection retained these four.	NW has the highest rate of pathological complete response (75%) with the lowest observed in OB (33.8%). This effect was greater in ER/HER2+ and TNBCa with OR of 3.46 and 2.21, respectively.

Continued

Table 2 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Zhang *et al.*[8]	2022	Longitudinal 2014–2016	40 post-menopausal TNBCa	Log-rank tests for DFS; no multivariable adjustments reported in survival curves. For clinical associations, BMI and insulin resistance were compared by Mann–Whitney U tests; no additional covariate adjustments specified.	In TNBCa the worse DFS was observed in OB (HR 4.39 [95% CI 1.07–18.02], $P < .05$).
Pezo *et al.*[86]	2022	Retrospective 2007–2017	11 601 women with Stage I–III BCa, NW (33.5%), OW (31.9%) and OB (33.1%)	Multivariable Cox models for OS adjusted for BMI category; age; tumour stage; number of positive nodes; grade; ER status; and HER2 status, separately in AC-paclitaxel and FEC-docetaxel arms (full list of covariates in *Table 3* of the paper).	OS does not change with BMI ($P = .66$) also after adjustment
Taroeno-Hariadi *et al.*[87]	2022	Retrospective 2010–2019	223 BCa OB prevalence 38.1% Abdominal obesity (WHR ≥0.85) prevalence 48.9%	Multivariate Cox regression adjusted for age; BMI; waist-to-hip ratio (WHR); metabolic-syndrome components; with inclusion of time to metastasis/death, stratification by menopausal status and hormone receptor subtype; and mutual adjustment for obesity markers in disease-free and OS analyses.	OB does not associate with DFS nor OS, while WHR does (HR 1.54, $P = .083$ and HR 3.12; $P = .019$, respectively). WHR ≥0.85 was independently associated with unfavorable DFS (HR 1.907; $P = .027$). with greater accuracy than MetS.
Acevedo *et al.*[88]	2022	Longitudinal 2011–2020	5191 BCa, mainly at stage I-III ($n = 4791$; 92.3%) 20% of them received POC	Multivariate Cox models for OS, IDFS, DDFS, BCSS adjusted for BMI; clinical stage; treatment regimen; and standard demographic covariates (age, insurance/hospital type, comorbidities)	OB is a predictor of early recurrence and poorer survival ($P = .005$ and .045, respectively). Alongside age ($P = .019$) and advanced stage at diagnosis ($P = .006$).
Luis *et al.*[89]	2022	Retrospective 2012–2016	2246 BCa	Binary logistic models adjusted for age at diagnosis and family history of breast cancer (when examining receptor status); and for age at diagnosis, family history, laterality, topographic localization, histological type; and receptor status (when modelling bilateral vs unilateral disease and differentiation grade).	OW and OB are associated with worse outcomes in BCa patients. Especially people with OB present larger (OR 1.42 [95% CI 1.13–1.78]; *P*-value: .002) and more poorly differentiated tumours (OR 1.48 [95% CI 1.15–1.90]; *P*-value: .002) and a trend towards a worse OS (OR 1.31 [95% CI .93–1.83]; *P*-value: 0.117). OW was more likely associated with bilateral BCa (OR 3.08 [95% CI 1.23–7.72]; *P*-value: .017) than OB, but with a lower risk of metastasis at diagnosis (OR 0.53 [95%CI 0.30–0.92]; *P*-value: .024).

Continued

Table 2 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Wei *et al.*[90]	2023	Retrospective median of 4.87 (IQR:3.26–6.84)y of FU period	1049 BCa	Restricted cubic-spline Cox models adjusted for age; education, occupation, age at menarche, menopausal status, parity/history of livebirth, smoking, and alcohol consumption, with spline terms for BMI to capture nonlinear (U-shaped) associations with OS and BCSS.	A 'U-shaped' relationship of BMI levels with OS and BCa-specific survival was observed at a turning point of 23 kg/m^2. To the left side of the HR was 0.83 (95% CI 0.70–0.98) for OS and 0.80 (95% CI 0.65–0.98) for BCa-specific survival. Conversely, to the right of the turning point, the HR was 1.22 (95% CI 1.10–1.37 for OS and 1.28 (95% CI, 1.13–1.46) for BCa-specific survival.
Van Baelen *et al.*[91]	2023	Longitudinal 2000–2020	2856 patients with Invasive lobular BCa	Linear and multinomial logistic regression ('Model 2') adjusted for centre plus age, grade; tumour size; nodal involvement, multifocality, and PR expression; Cox models for DFS/OS further adjusted for these clinicopathological variables and treatment covariates, stratified by centre.	Older age at diagnosis, higher tumour grade, larger tumour size, nodal involvement, and multifocality are all associated with high BMI. BMI is also associated with worse outcomes for different DFS, DRFS, and OS but only at univariate analysis.
Lipsyc-Sharf *et al.*[92]	2023	Longitudinal 1997–2010	9479 non-Hispanic black/Hispanic vs non-Hispanic white BCa	Cox models for RFS/OS adjusted for age, race/ethnicity, BMI category, tumour subtype, and trial arm, within subgroups defined by age, BMI, and subtype (no additional lifestyle or clinical covariates reported beyond trial design factors).	Ethnicity influences 5-y OS in < 50-y-old (P = .008) with poorer prognosis in young non-Hispanic black (HR 1.34 [95% CI 1.04–1.71]) and Hispanic participants (HR 1.62 [95% CI 1.16–2.29]). Ethnicity also influences RFS in OW, with worse outcomes in Hispanic people (HR 1.81 [95% CI 1.23–2.68]).
Lammers *et al.*[93]	2023	Longitudinal median FU of 13.1y	1860 post-menopausal ER/PR + BCa	Multivariable Cox regression for DFS adjusted for BMI category, age, intrinsic subtype, and in predictive models, additionally for treatment arm (3 vs 6 y of anastrozole	OW and OB identify negative prognostic groups for DFS (HR 1.16 [95% CI 0.97–1.38] and 1.26 [95% CI 1.03–1.54], respectively).
Crispo *et al.*[94]	2023	Retrospective 2009–2013	955 early BCa	Multivariable Cox models adjusted for age; BMI; waist circumference (WC); waist-to-hip ratio (WHR); MetS; plus menopausal status and breast-cancer subtype in subtype-specific analyses	High WC (≥88 cm), WHR (>0.85) and MetS were significantly associated with all-cause mortality (HR1.39, 1.62, and 1.61, respectively). A significantly increased risk in BCa-specific mortality characterizes OB, high WHR, and MetS (HR 1.72, 1.71, 1.80, and 1.81, respectively). Central obesity significantly increased total and BCa-specific mortality in premenopausal and luminal BCa subtypes, while in post-menopause MetS it the strongest risk factor.

Continued

Table 2 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Chelbowski *et al.*[95]	2024	Longitudinal 20y FU for mortality	63 330 post-menopausal BCa and MetS scoring	Cox models adjusted for BMI; MetS score; and, when examining each in turn, mutually adjusted for the other plus standard WHI covariates (age; race/ethnicity; education; smoking; alcohol; physical activity; family history; hormone-therapy use; prior oestrogen/progestin duration; comorbidity index)	Once adjusted for BMI, a high MetS score (3–4) was associated with ER+/PR- BCa (P = 0.03), a 53% higher risk of death after BCa (P < .001), and a 44% higher risk of BCa-specific mortality (P = .03). Contrariwise, OB adjusted for MetS score was associated with ER+/PR + BCa but with higher BCa incidence, overall and BCa-specific deaths (P < .001 for all).
Schindler *et al.*[96]	2024	Longitudinal 13y FU	1110 postsurgical BCa patients scheduled to adjuvant RT	Multivariable Cox regression adjusted for race/ethnicity, BMI; tumour stage; clinical tumour stage, and included interaction terms for race × BMI stratified by menopausal status; PFS and OS models controlled for standard clinical covariates (size, nodal status) alongside obesity and race.	At multivariate analysis, an association between African Americans and worse PFS covers both OB (HR 2.19 [95% CI 1.06–4.51]) and non-OB (HR 2.11 [95% CI 1.05–4.21]) staged 0-II BCa. Contrariwise, OB alone is not associated with PFS or OS.
Holm *et al.*[97]	2024	Longitudinal 2010–2020	2673 stage I-III BCa	Cox models for DFS/OS adjusted for age; race/ethnicity; education; Charlson Comorbidity Index; tumour stage; grade; ER status; and C-reactive protein quartiles, stratified by BMI category.	In BMI-stratified analyses, event risk in NW/OW groups was highly dependent on CRP with HRadj of 1.70 (95% CI 1.09–2.66) and 1.75 (95% CI = 1.08–2.86). This relationship is lost in OB. High CRP levels increased death risk (HRadj 2.47 [95% CI = 1.62–3.76]) with a stronger association in NW/OB (HRadj 3.66 [95% CI 1.95–6.87] and 1.92 [95% CI 1.06–3.46]) but not in people with OB.

Pubmed search ((obes* [Title]) OR (metabolically healthy [Title]) OR (metabolically unhealthy [Title]) OR (sarcopenic obes* [Title]) OR (body mass index [Title])) AND (BCa [Title]) AND ((mortality [Title/abstract]) OR (outcome [Title/abstract]) OR (progression [Title/abstract]) OR (prognos* [Title/abstract])) NOT review from 2015 to present.

AJCC, American Joint Committee on Cancer; ALC, absolute lymphocyte count; ALND, axillary lymph node dissection;BCa, breast cancer; BCS, breast-conserving surgery; BCSS, breast cancer–specific survival; BMI, body mass index; CI, confidence interval; CMD, cardiometabolic disease(s).; CRP, C-reactive protein; DDFS, distant disease-free survival; DFS, disease-free survival; DRFS, distant recurrence-free survival; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; ET, endocrine therapy; HDL-c, high-density lipoprotein cholesterol; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IDFS, invasive disease-free survival; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor–binding protein; KM, Kaplan-Meier; MBC, metastatic breast cancer; MRM, modified radical mastectomy; NLR, neutrophil-to-lymphocyte ratio; NW, normal weight; OB, obesity; OR, odds ratio; OS, overall survival; OW, overweight; pCR, pathological complete response; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio; POC, postoperative chemotherapy; PR, progesterone receptor; RFS, recurrence-free survival; RT, radiotherapy; SLNB, sentinel lymph node biopsy; TIL, tumour-infiltrating lymphocyte; TNBCa, triple-negative breast cancer; UW, underweight; WC, waist circumference; WHR, waist-to-hip ratio

Table 3 Comparison of senescent signatures in BCa patients with normal weight and obesity

Axis/component	Normal weight	Obesity
Total senescent cell burden (tumour/stroma)[101–104]	Mostly localized to tumour cells; lower systemic inflammation	Increased burden in mammary adipose and stroma, plus systemic senescence
SASP (IL-6, IL-8, chemokines, MMPs)[105–110]	More 'focal' SASP	Amplified, pro-angiogenic SASP (↑ IL-6/IL-8, TNF-α, MMPs)
Adipokines (L/A ratio)[111–117]	Lower leptin; more favourable L/A ratio	Elevated leptin; unfavourable L/A ratio promoting tumour signalling
Immune senescence[110,118–120]	Less prominent	Stronger immunosenescent phenotype
Angiogenesis[121,122]	Lower endothelial dysfunction	Enhanced endothelial senescence; impaired VEGF response
Transcriptomic senescence scores[98,123–125]	Lower predicted senescence scores	Higher enrichment of senescence/SASP pathways

IL, interleukin; L/A ratio, leptin/adiponectin ratio; MMPs, matrix metalloproteinases; SASP, senescence-associated secretory phenotype; TNF-α, tumour necrosis factor alpha; VEGF, vascular endothelial growth factor.

incident metabolic disorders also associate with worse prognosis.[82]

- Inflammation/immune tone modifies risk: Lower absolute lymphocyte count and higher neutrophil to lymphocyte ratio worsen outcomes and interact with BMI[76,80] high CRP strongly predicts events and mortality, particularly in strata without obesity. TILs are lower in obesity (worse immune contexture).[81]
- Subtype nuances: (i) luminal disease: Obesity is repeatedly associated with higher mortality in luminal A/B 68, and worse DFS in ER-/PR- early disease when BMI ≥25 kg/m²[67]; (ii) HER2+/IGF-1 interaction: High IGF-1 improves RFS in normal-weight but worsens RFS in HER2+ patients with overweight (BMI × IGF-1 interaction)[71]; (iii) TNBC: Several reports show poorer DFS/OS with obesity[8]; however, signals are not uniform across all studies; (iv) treatment/complications: Response to abemaciclib was lower in under/normal-weight vs overweight/obesity overall response rates (but PFS benefit persisted across BMI)[72]; surgical complications, LOS, and costs show a U-shaped across BMI.[73,74]
- Life-course and demographics: Menopausal status, age, race/ethnicity, and PR status modulate BMI-outcome links (e.g. PR– tumours in UW/OW/OB with higher mortality[68]; race × BMI effects on PFS 100; age-specific risks.[78,92]
- Mechanistic bridge to outcomes: Preclinical data support obesity-driven dormancy escape, angiogenic switching, ECM remodelling, and myeloid/neutrophil reprogramming.[59–62]

Within the wealth of studies, heterogeneity across cohorts is substantial, including differences in sample size, disease stage, hormone-receptor profile, HER2 expression, and treatment strategy. Adiposity is assessed mostly—but not exclusively—by BMI, with intriguing findings emerging from the use of the waist-to-hip ratio and the association with inflammatory biomarkers (e.g. neutrophil-to-lymphocyte ratio and C-reactive protein). Given these limitations, future works– including meta-analysis—should harmonize cohort features and adiposity measures to clarify prognostic effects. In addition, serial assessment of cardiometabolic health across the care continuum of BCa (i.e. from diagnosis to surgery, treatment, and long-term follow-up) may capture critical inflection points in the adipose tissue–breast axis and improve risk stratification.

Remodelling of the tumour microenvironment by senescent adipocytes: a key driver of breast cancer development and progression

Adipose tissue senescence: a feed-forward loop fuelling tumour initiation

Emerging preclinical and translational evidence shows that obesity profoundly reshapes senescence dynamics both systemically and within the tumour microenvironment (TME). Senescence signatures in BCa appear signatures appear predominantly in non-tumoural compartments—tumour-associated adipose tissue, fibroblasts, and infiltrating immune cells—rather than in BCa cells themselves. While chemotherapy amplifies senescence-related programmes in individuals with normal weight, obesity intensifies multiple layers of senescence-associated dysfunction, including immune exhaustion, expanded effector-memory T-cell clones, and reduced naïve T-cell reservoirs.[50,98,99] A recent spatial atlas of human adipose tissue identified senescence-prone metabolic, progenitor, and vascular subtypes that are further enriched in obesity.[100] Although partly reversible with weight loss, senescence persists in key compartments, indicating a persistent adipose 'ageing field effect' that heightens vulnerability to malignant initiation. (*Table 3*).[98,101–125] Disturbances associated with obesity increasingly appear causal—not merely correlative—in BCa initiation[126] (*Figure 1*). Insulin resistance and hyperinsulinemia activate IR/IGF-1→PI3 K/Akt/mTOR, while mediators derived from senescent adipose tissue amplify proliferative pressure.[127,128] Obesity also increases aromatase expression,[129] raising local oestrogen levels and establishing a feed-forward link between adipocyte senescence, oestrogen production,

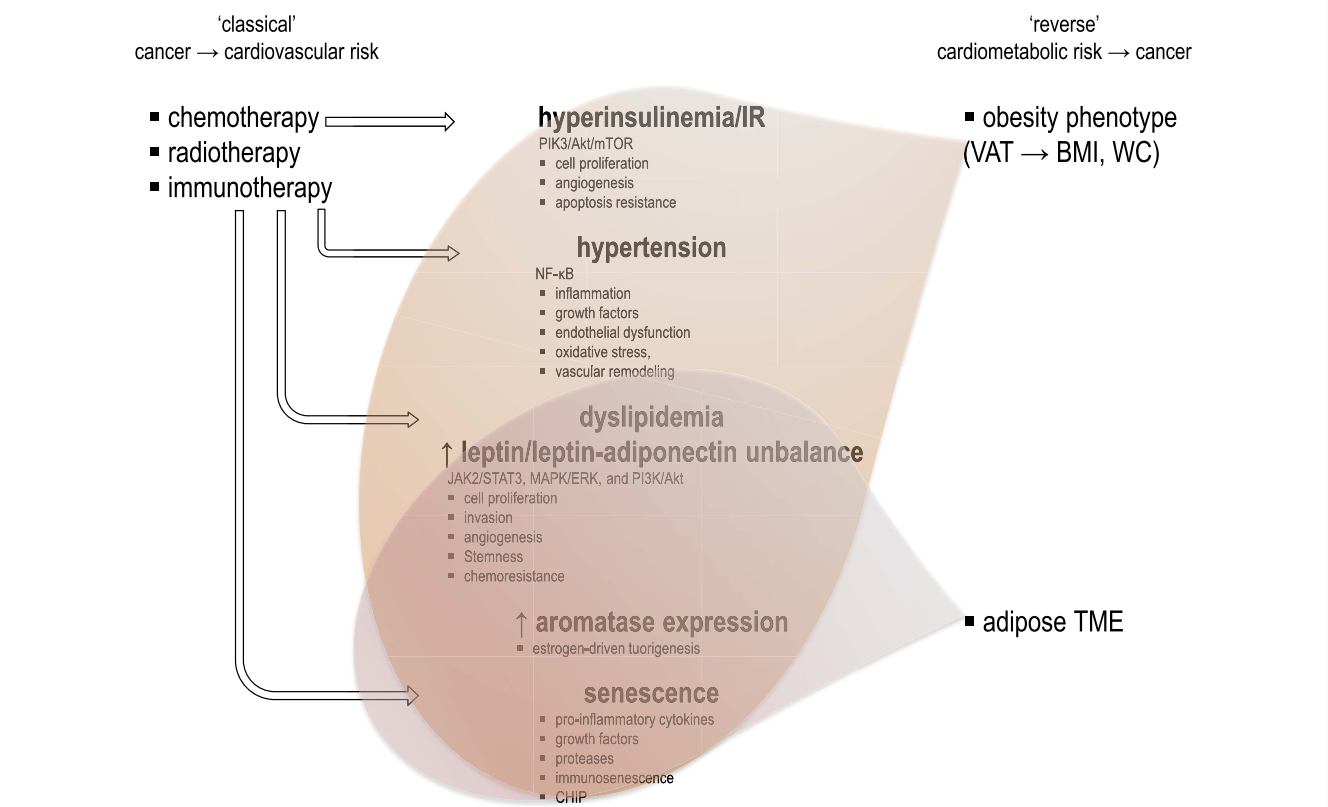

Figure 1 Intersecting pathways in classical vs reverse cardio-oncology: a shared mechanistic landscape with diverging clinical outcomes. This conceptual diagram illustrates the layered mechanisms by which obesity-associated cardiometabolic alterations contribute to breast cancer development—partially mirroring the pathophysiological drivers of cardiovascular disease in classical cardio-oncology. Shared mediators such as insulin resistance (IR), inflammation, endothelial dysfunction, and senescence underpin both cancer progression ('reverse cardio-oncology') and cardiotoxicity induced by cancer therapies ('classical cardio-oncology'). However, while classical cardio-oncology focuses on tumour-triggered cardiac damage, reverse cardio-oncology highlights how systemic metabolic dysfunction fosters a tumour-permissive environment triggered by both visceral and BCa-associated adipose tissues (VAT and adipose TME, respectively). Understanding these intersecting yet directionally distinct pathways may support integrated prevention strategies in patients with obesity with cancer or cardiovascular risk. CHIP: clonal haematopoiesis of undetermined potential

and outgrowth of oestrogen receptor (ER)-positive clones.[130] Population differences such as the menopausal-obesity paradox likely reflect varying oestrogenic contexts and adiposopathy-related traits.[131] Additional metabolic cues—including 27-hydroxycholesterol[132] and angiotensin II–NF-κB signalling—further promote epithelial turnover and mutational opportunity, accelerating the progression of subclinical lesions.[133]

Obesity also drives profound epigenetic remodelling. Hypertrophic adipocytes adopt a senescence-like phenotype characterized by hyperinsulinemia-driven G2 arrest and SASP polarization,[7,128] while visceral adipose tissue (VAT) macrophages acquire a p16INK4a-driven senescent-like phenotype, predominantly driven by osteopontin (OPN).[134] These changes align with accelerated biological ageing, as shown by transcriptomic overlap between diet-induced obesity and chronological ageing and by human estimates of epigenetic age acceleration (~2.3 years per 10 BMI units).[135,136] Methylation maps in adipose and breast tissues reveal alterations across tumour suppressors, oncogenes, cytokines, and DNA repair pathways.[137–139] Extracellular vesicles (EVs) derived from VAT or breast adipose tissue in obesity carry distinct miRNA cargo that enhances tumour development and metastatic potential[140–147]; similar patterns are seen in EVs derived from breast adipose tissue of women living with obesity.[148] Broad omics signatures have been recently interrogated in obesity medicine, from vulnerability to food addiction[149] to the interference with weight loss and diabetes remission.[150,151] Single-cell sequencing further demonstrates obesity-induced 'immune memory' with persistent signatures of antigen presentation, T-cell exhaustion, inflammation, and lipid dysregulation.[152] Together, these multi-omic signals suggest that obesity confers a specific mutational and epigenetic landscape consistent with a causal role in carcinogenesis.

Senescence also intersects with trained immunity, in which the epigenetic rewiring of myeloid progenitors represents a canonical maladaptive form characterized by persistent inflammatory memory and exaggerated cytokine output. Clonal haematopoiesis of indeterminate potential (CHIP)—common in ageing, chronic inflammation, and cardiometabolic disease—generates precisely such epigenetically reprogrammed myeloid progenitors with heightened cytokine production and accelerated athero-inflammation.[153–156] The most commonly mutated

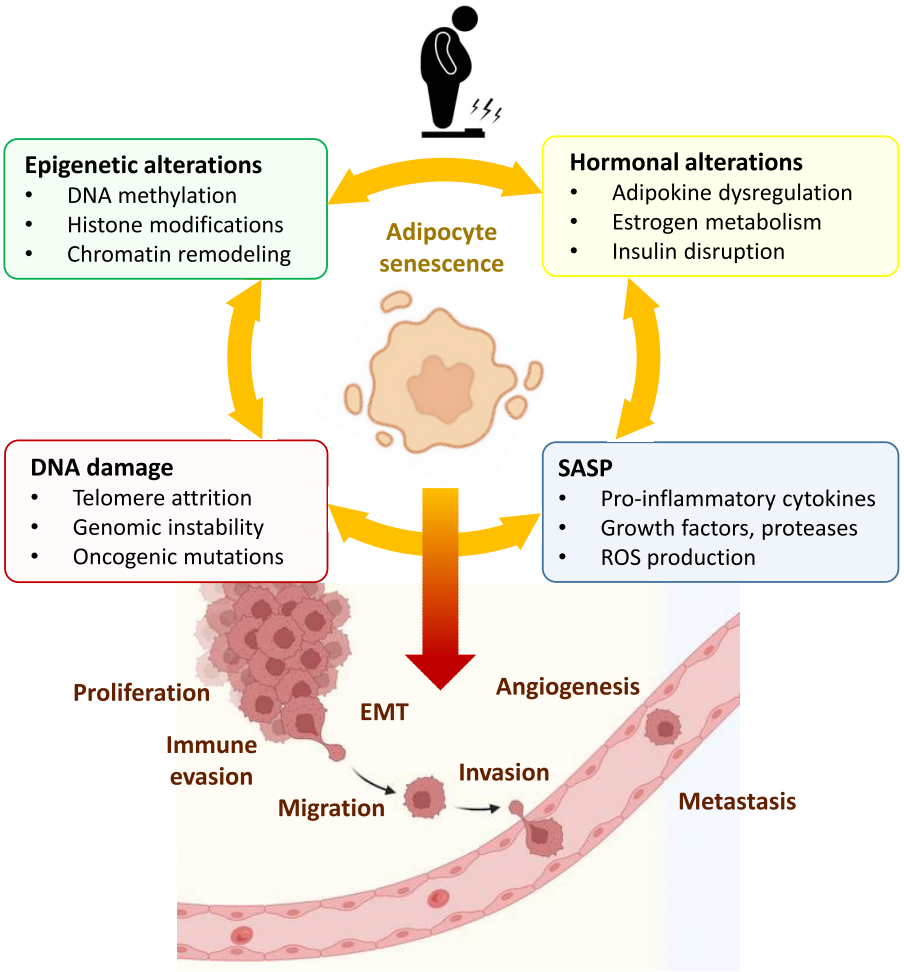

Figure 2 Adipocyte senescence as a central node linking obesity to breast cancer progression. This schematic illustrates the multifaceted contributions of adipocyte senescence to the establishment of a tumour-permissive microenvironment in obesity. Adipocyte senescence, triggered by metabolic stress and chronic inflammation, is characterized by persistent DNA damage (e.g. telomere attrition, genomic instability), epigenetic remodelling (e.g. DNA methylation, histone modifications), hormonal imbalances (e.g. increased aromatase activity, adipokine dysregulation), and the secretion of a senescence-associated secretory phenotype (SASP). These alterations collectively fuel cancer hallmarks such as proliferation, angiogenesis, migration, immune evasion, and metastasis—mainly through paracrine signalling within the tumour microenvironment. Notably, these processes establish a feed-forward loop whereby senescent adipocytes perpetuate local and systemic inflammation, disrupt immune surveillance, and enhance endocrine-driven tumour growth. This integrative framework highlights the role of senescent adipose tissue as both a source and amplifier of oncogenic signalling in breast cancer associated with obesity

driver genes in *de novo* CHIP cases encode epigenetic regulators involved in DNA hypo- and hypermethylation.[157] CHIP prevalence increases sharply with age, is associated with coronary disease and early-onset MI[158,159] and may be linked to visceral adiposity.[155,156] Among women of older age with BCa, CHIP reaches ~44% at diagnosis and increases during treatment, correlating with advanced stage and worse survival,[160,161] while remaining less relevant in younger patients.

Senescence-driven inflammation and molecular instability in breast cancer progression

Once BCa is established, the same endocrine axes fuel its progression (*Figure 2*). Insulin/IGF-1, activates PI3 K/Akt/mTOR to promote proliferation, angiogenesis, and resistance to apoptosis,[127,128] obesity-enhanced aromatase drives ER-positive tumourigenesis,[162] and leptin signalling promotes EMT, angiogenesis, stemness, and chemoresistance[163]; whereas adiponectin counteracts these processes.[164] Lipid-derived cues such as 27-hydroxycholesterol and angiotensin II–NF-κB signalling further remodel the TME towards metastatic competence. Obesity enriches the TME with senescent adipocytes producing a SASP (IL-1β, IL-6, IL-8, chemokines, growth factors, and MMPs), which enhances proliferation, angiogenesis, survival, and extracellular matrix remodelling.[4,165–170]

Senescence-driven genomic instability adds additional momentum. Persistent DNA damage and chromosomal instability in adipocytes propagate bystander senescence, altering DNA methylation and histone landscapes in adjacent epithelial cells

and promoting malignant transformation.[84,171] Within epithelial/tumour cells, SASP cytokines (IL-6, IL-8, TNF-α) activate STAT3 and NF-κB, leptin activates PI3 K/AKT/mTOR, and EVs from obesity-derived adipose tissue reprogramme tumour metabolism and enhance metastatic behaviour via hypoxia inducible factor (HIF)-1α.[172–178] Adipose senescence feeds into a broader immunosenescent phenotype. Obesity impairs neutrophil, macrophage, NK-cell, and T-cell function; expands anergic memory T cells; reduces naïve T-cell pools; and exhausts $CD4^+/CD8^+$ compartments.[50] SASP-rich niches suppress immune surveillance, while obesity-associated upregulation of PD-1/PD-L1 further blunts antitumour immunity.[102,179] ER-specific differences in TME immune composition may underlie additional heterogeneity.[180–183] Ultimately, obesity accelerates systemic epigenetic ageing across BCa subtypes, reinforcing the need for deeper characterization of the BCa–adipose axis beyond BMI-based epidemiology (*Table 4*).[184,185]

Key takeaways from *Table 4*

- ER status and menopausal context: Multiple cohorts show stronger associations of higher BMI with ER+/luminal risk—particularly in post-menopausal women (e.g. higher ER+/PR + incidence with BMI ≥35 kg/m²; larger tumours, nodal positivity, and advanced stage).[138,151,208] Signals for TNBC are more nuanced: higher BMI relates to increased TNBC risk in premenopausal women in some studies, but reduced odds post-menopause in others.[134,137]
- Beyond BMI: central adiposity matters. WC/WHR often track BCa risk or phenotype more closely than BMI, including subtype distributions and metastasis risk (e.g. higher WHR associated with metastasis; central obesity linked to ER+/PR+ tumours).[57,136,139,143]
- Epigenetics/omics links: BMI associates with methylation changes in ER+ tumours (DNMT-related, IGF-binding, repair genes)[209]; recurrence biology can be heavier in higher-BMI groups (e.g. higher 21-gene RS > 20 in ER+/HER2− under 45 y)[146]; obesity-related gene signatures can refine recurrence prediction (LOG-CPI).[196]
- Metabolic health as a driver: MetS and related biomarkers (insulin, leptin/CRP) mediate a substantial fraction of BMI's effect on BCa risk[142]; circulating oestrogens and oestrogen-metabolite profiles rise with higher BMI and WHR post-menopause[190]; cardiometabolic diseases relate to mortality risk.[203]
- Population heterogeneity: Associations vary by ancestry/region and study design; some cohorts report paradoxical or inverse relations (e.g. reduced odds with higher BMI in specific African cohorts or phenotypes).[140,141]
- Life-course BMI trajectories: Early-life BMI patterns and adult weight gain shape later ER+ risk, emphasizing timing of adiposity exposure.[149,150]

Current clinical evidence has not yet clarified whether, and through which mechanisms, obesity influences the development of different BCa histotypes. Moreover, BMI-based stratification is intrinsically limited and may yield misleading or apparently paradoxical associations.[210] The interplay between BCa cells, their microenvironment, and remote adipose tissues, thus, requires a deeper characterization that moves beyond—or integrates with—epidemiological evidence.

Obesity fingerprints on breast cancer cells' genomics

While increasing efforts have focused on the VAT secretome, largely limited to adipocytokine imbalance, chronic inflammation, and oestrogen/insulin signalling,[211] only a few studies have probed adiposity-associated changes in human BCa at the transcriptomic level, and fewer still at the genomic level.[123,124] In contrast, BCa genomics is an active field of research, with some alterations already informing clinical practice as treatment targets or markers of resistance to treatment.[212] A recent seminal paper led by Christine Desmedt was the first to interrogate the correlation between adiposity and BCa mutational signatures, extending the analysis to the TME and cross-compartment interaction.[98] Using an atlas of genes known to harbour driver genomic alterations in BCa, the authors pooled cohorts (METABRIC, ICGC, ELBC, MINDACT, Biokey) stratified by BMI and BCa subtypes. At bulk resolution, PIK3CA mutations were less frequent in ER+/HER2- BCa, whereas CCND1 and CCNE1 amplification—implicating CDK4/6—were more common in people living with obesity and ER+/TNBCa. These patterns point to an obesity-associated mutation landscape that confers selective proliferative advantage,[213] supporting the hypothesis of a specific mutagenesis—rather than mere accumulation of somatic mutations—in obesity carcinogenesis.

The effects of interventional approaches to obesity on BCa risk

The obesity dilemma finds further room in BCa when interventions are considered.[214,215] The Mediterranean diet still represents the prototype of a healthy diet, with established benefits on 'adiposopathy'.[216,217] lower cancer incidence (including BCa),[218,219] and longer survival.[220] More recently, intermittent fasting has gained relevance from the cardiometabolic health perspective in relation to its potential effects on BCa biology.[221] Short-term fasting and fasting mimicking diets can sensitize cancer cells to therapy,[222] while protecting normal tissues from treatment-related toxicity.[223] Seminal work shows that reductions in circulating IGF-1, insulin, and glucose drive metabolic shifts that delay or reverse drug resistance, yielding tumour regression and improved outcomes in mice and humans.[224] These effects extend to the TME.[225,226] A healthy lifestyle includes regular physical activity to improve body composition by increasing lean mass and reducing VAT inflammation.[227–229] Through decreased leptin release and better sex-hormone regulation, physical activity lowers BCa risk and recurrence.[230–232] Multimodal exercise and diet programmes appear most effective for improving body composition in women diagnosed with or at high risk for BCa.[229]Unfortunately, unhealthy diet and physical inactivity remain the true pandemic of the current century, fuelling the current obesity surge. Driven by the consequent health and economic burden, many efforts are now addressed to developing pharmacological interventions. Observational cohorts and meta-analyses link the use of

Table 4 List of the studies summarizing the link between breast cancer phenotyping and the adipose/metabolic status

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Neuhouser *et al.*[186]	2015	Longitudinal analysis from WHI Extended FU 13 y	67 142 US women aged 50 to 79-y post menopause, weight BMI	Cox models stratified by age group, randomization arm, hysterectomy status, and study phase; adjusted for age (continuous); race/ethnicity; education; parity; age at first birth; bilateral oophorectomy; family history of breast cancer; prior oestrogen use and duration; prior oestrogen + progestin use and duration; smoking; diabetes; alcohol consumption.	Besides an increases BCa risk in grade 2/3 OB (HR 1.58 [95% CI 1.40–1.79]), a BMI greater than 35 kg/m^2 associates with a higher risk of ER+/PR + BCa (HR 1.86 [95% CI 1.60–2.17]), larger tumour size at diagnosis (HR 1.89 [95% CI 1.46–2.45]), positive lymph nodes (HR 1.89 [95% CI 1.46–2.45]), and regional and/or distant stage (HR 1.94 [95% CI 1.52–2.47]).
Miyagawa *et al.*[187]	2015	Case-control 2009–2011	1297 Japanese women, 615 BCa/682 healthy women from BCa screening program) mean 58-y old pre and post-menopause BMI	Logistic regression adjusted for age (continuous); age at menarche (continuous); parity (yes/no); family history of breast cancer (yes/no); and, for post-menopausal women, age at menopause (continuous).	While a 1-unit increase in BMI reduces the risk of BCa in pre-menopause (ORadj 0.82 [95% CI 0.71–0.95]), the risk increases in post-menopause (ORadj 1.09 [95% CI 1.04–1.15]) and associates with a luminal A subtype (ORadj 1.18 [95% CI 1.10–1.26]).
Hair *et al.*[181]	2015	Cross-sectional from the Carolina Breast Cancer Study 1993–1996	492 samples mean 47-y old pre and post-menopause methylation BMI	Linear models (Limma empirical Bayes) adjusted *a priori* for age and race, plus any variable associated with both BMI and methylation at $P < .05$ (only menopausal status met that criterion).	In analyses restricted to ER + tumours (n = 208), 21 methylation probes are significantly associated with BMI, mainly on sites coding for DNA methyltransferase, IGF-binding protein, and an excision/repair gene.
Kwan *et al.*[188]	2015	Cross-sectional 1997–2000	1676 early-stage BCa >21-y old ER1, PR, ERBB2, and 10 proliferation genes	All regression models (multinomial logistic for subtype; linear for gene expression) were adjusted for age at diagnosis; race/ethnicity; moderate–vigorous physical activity, AJCC tumour stage; and cohort (LACE vs pathways). Models were stratified by menopausal status when testing effect modification.	Severe OB associates with higher expression of proliferation genes compared with NW (adjusted mean difference 0.44 [95% CI 0.18–0.71]). This association was stronger in post-menopausal women (P for interaction .06). However, severe OB is inversely associated with ER1 expression and more likely associated with Basal-like and Luminal B BCa subtypes.
Chen *et al.*[189]	2016	Case-control 2004–2012	2659 20–69-y old pre and post-menopause BMI	Polytomous logistic regression (TN, H2E, luminal B vs luminal A) adjusted for age; height; weight quartile; menopausal status; plus in sensitivity analyses for OC use; HRT use; parity; family history; physical activity.	While the risk of TNBCa is 82% higher in OB premenopausal women (95% I 1.32–2.51), the risk of TNBCa (OR 0.75 [95% CI 0.54–1.00]) and ER–/HER2 (OR 0.47 [95% CI 0.32–0.69]) BCa decreases in post-menopause.

Continued

Table 4 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Wang *et al.*[190]	2017	Cross-sectional 2012–2013	1439 Chinese women, 25–70-y old pre and post-menopause BMI, WC, and WHR	Polytomous unconditional logistic regression adjusted for height, weight, waist circumference, hip circumference, physical activity (yes/no), menopausal status, and in trend tests further for BMI category.	Besides an overall higher BCa risk with the increase of BMI, WC, and WHR ($P < .001$ for all), weight >62 Kg increases by 21% and 34% risk of ER+/PR + and ER−/PR- BCa, respectively. While any association in post-menopause, in premenopausal, the risk increases by 121% and 105% for ER+/PR + ER−/PR−, respectively. WC measure provides similar results.
Sahin *et al.*[191]	2017	Retrospective analysis Mean FU 48.6 months for pre-menopausal group FU 47.7 months for post-menopausal group	3767 Turkish women Mean 48.6-y old pre and post-menopause BMI Luminal A-like, Luminal B-like, HER2-enriched, and TNBCa	Retrospective models did not explicitly list multivariable adjustments in the main text, implying analyses were unadjusted for covariates beyond stratification by menopausal status and BMI group.	OB post-menopausal women were more likely to present TNBCa if compared with women with BMI <25 ($P = .001$); no additional findings relating to other BCa subtypes were observed among this group. Concerning premenopausal patients with OB, there was an increased risk of TNBCa ($P = .007$) and a lower incidence of luminal-like BCa ($P = .033$); this group also displayed higher tumour stage and grade at presentation compared with NW women.
Gershuni *et al.*[192]	2017	Retrospective study 2000–2013	848 women with primary operable BCa Mean age at diagnosis 64-y old BMI A-like, Luminal B-like, HER2-enriched, and TNBCa	Comparative subtype distribution analysis across BMI groups relied on χ^2 tests and did not adjust for potential confounders (age, race, comorbidities) beyond the stratified descriptive comparisons.	The BCa subtype distribution among the three BMI subgroups (NW/OW/OB) showed a higher incidence of luminal A in women with OB (58.1%) and of HER2-like in NW women (36.6%) ($P < .008$). Women with OW were also associated with poorer disease-free survival outcomes.
Brouckaert O *et al.*[193]	2018	Cross-sectional 2000–2013	337 women mean 58 years old pre- and post-menopause BMI	Logistic regression of subtype probability as a function of continuous BMI, corrected for age at diagnosis. Subtype analyses were further conditioned on menopausal status; no additional covariates were included.	While a lower BMI delays the age at diagnosis in pre-menopause, an opposite effect was observed in post-menopause. In post-menopause age-adjusted BMI is also associated with ER positivity ($P = .031$]), luminal B (1.02 [95% CI.1.01–1.04]) and HER2-like (0.95 [95% CI.0.92–0.98]) BCa.

Continued

Table 4 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Lubián López DM, *et al.*[194]	2021	Cross-sectional	347 Caucasian women. Mean age 59-y old pre-and post-menopause large breast volume BMI, WHR	Comparisons of prognostic factors by BMI/WHR used χ^2 and *t*-tests; multivariable logistic models were not specified, implying unadjusted descriptive analyses	Patients with central obesity (WHR 0.85) were associated with increased risk of ER + and PR + tumours (P = .48 and .29, respectively) with lower rate of Ki67 (P = .42). In addition, women with larger breast volume were more likely to have an ER positive BCa rather than the group with small breast volume (P = .04). No additional findings concerning menopausal status.
Akinyemiju *et al.*	2021	Case control study 2 y FU	705 African women (419 final cases; 286 final controls) BMI	Multivariable logistic models adjusted for BMI, height, weight, age, and then stratified by menopausal status. Further adjustment sets included self-reported diabetes history when evaluating weight/BMI associations, but molecular subtype analyses did not list additional covariates.	Higher BMI (ORadj: 0.79; 95% CI: 0.67, 0.95) and weight (ORadj: 0.83; 95% CI: 0.69, 0.98) were associated with reduced odds of BCa in adjusted models. Higher BMI was associated with reduced odds of Luminal A, Luminal B, and HER2-enriched BCa among pre/perimenopausal women, and reduced odds of triple-negative BCa among post-menopausal women
Akinyemiju *et al.*[195]	2022	Cohort study from MEND study with 4 y FU	296 BCa and 259 controls) Luminal A/B, TNBCa, HER2	Model 1: unadjusted; Model 2: adjusted for age; Model 3: additionally adjusted for age at menarche, number of pregnancies, number of births, menopausal status, and prior diabetes and hypertension status; Model 4: additionally adjusted for BMI	Compared to controls, cases were more likely to have metabolic syndrome (30% vs 17%, P < .001). They were also less likely to report prior diagnosis of diabetes (1% vs 15%, P < .001), hypertension (19% vs 48%, P < .001), and ever having used HRT (.7% vs 15% P < .001) compared with controls.
Dashti *et al.*[196]	2022	Longitudinal Analysis from WHI observational study	188 breast cancer, ER + BMI	Causal mediation (case-cohort) analyses: BMI (categorical) models adjusted for pre-exposure confounders: age, education, alcohol intake, smoking, physical activity, NSAID use, age at menarche, parity, OC use, HRT use and duration, age at menopause; family history, biomarker-cancer models additionally adjust for exposure and prior mediators.	For breast cancer, the total effect RR for BMI ≥30 vs ≥18.5–<25 kg/m^2 was 1.87 (95%CI 1.11–3.13). The indirect effect RRs were 1.38 (0.79–2.33) through leptin and CRP, 1.58 (95%CI 1.17–2.43) through insulin, and 1.11 (95%CI 0.98–1.30) through estradiol. The direct effect RR was 0.82 (95% CI 0.39–1.68).

Continued

Table 4 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Geczik *et al.*[197]	2022	Longitudinal Analysis of the Ghana Breast Health Study	585 post-menopausal women's BMI, WHR	Age at blood draw; blood draw year; smoking status; time since menopause, ever-use of oral contraceptives, and additional adjustment for unconjugated oestradiol in secondary analyses.	Measured BMI (≥ 30 vs 18.5–24.9 kg/m^2) was positively associated with parent oestrogens (multivariable adjusted GM for unconjugated estrone: 78.90 (66.57–93.53) vs 50.89 (43.47–59.59), $P < .001$; and unconjugated oestradiol: 27.83 (21.47–36.07) vs 13.26 (10.37–16.95), $P < .001$). Independent of unconjugated oestradiol, measured BMI was associated with lower levels of 2-pathway metabolites and higher levels of 16-ketoestradriol. Similar patterns of association were found with WHR
Kohls *et al.*[198]	2022	Longitudinal Analysis of European Prospective Investigation into Cancer and Nutrition study 8 y FU	1620 BC patients Weight, BMI, CMD	Multivariable Cox proportional-hazards models stratified by age at diagnosis (50–69 y, ≥70 y), country, and sex (for CRC); adjusted for smoking status; physical activity; alcohol consumption; and educational level at recruitment	In BCa patients, a higher BMI was associated with a 4% increase in risk of death (95% CI 1.00–1.08). CMDs were associated with a 46% increase in risk of death (95% CI 1.01–2.09).
Olsson *et al.*[57]	2022	Prospective Cohort study 3.7 y median FU	2767 women with Stage I-III BC BMI, WHR	Kaplan–Meier and GLM for WHR/BMI→metastasis adjusted for age; grade; stage; race; ER status; metastasis frequency models also for genomic risk (risk of recurrence score) in stratified analyses.	High-WHR was associated with a higher risk of metastasis (5-y risk difference, RD, 4.3%; 95% confidence interval, 2.2–6.5)
Menikdiwela *et al.*[199]	2022	Cross-sectional 2018–2020	1928/1610 Luminal A and B BCa 61y old pre and post-menopause BMI	Logistic models for luminal B vs A adjusted for Black/African-American race; BMI; menopausal status in multivariable frameworks; exact covariate list not fully enumerated beyond those three factors.	Luminal B phenotype is prevalent in patients with higher mean BMI ($P = .010$) and African American patients, while post-menopausal status is associated with a decreased risk ($P = .028$).
Lee *et al.*[200]	2022	Longitudinal 2010–2020	776 patients with ER + HER− Korean BCa, younger 45 years (pre-menopause); 45 months FU BMI 21-gene recurrence score	Multivariable logistic model for high 21-gene recurrence score adjusted for age, BMI; correlation analyses by age group, but the multivariable recurrence score vs BMI model includes only BMI and age, no other covariates specified.	The proportion of recurrence score >20 is higher in patients with BMI ≥25.0 kg/m^2. This association is confirmed in the adjusted analysis with an OR of 2.06 (95% CI 1.28–3.32).

Continued

Table 4 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Alshamsan *et al.*[201]	2022	Retrospective study 2002–2014 FU 39 months	2212 Saudi women Mean age 45 y old Median BMI 30 kg/m^2 Non-metastatic BCa A-like, Luminal B-like, HER2-enriched, and TNBCa	Retrospective regression of clinical features vs BMI categories, adjusted for age; menopausal status; OC history; stage; screening detection; radiation therapy (implicit in multivariable models), and for HER2 analyses, also for tumour biology details; the paper reports BMI associations 'independently' but does not list a formal covariate set.	The analysis found a higher incidence of TNBCa among premenopausal women (OR 1.30; 95% CI 1.01–1.69; *P* = .04); on the other hand, more advanced-stage tumours (stage III [OR 1.45; 95% CI 1.05–2.01; *P* = .02]) were associated with post-menopausal women, without a substantial difference in the prevalence of breast cancer subtypes. Moreover, a higher percentage of hormone receptor-positive tumours among post-menopausal women with BMI 30 kg/m^2, compared with women with a lower BMI and the same menopausal status (49% vs 53.5%) were found.
Pedersen *et al.*[202]	2023	Longitudinal from the Diet, Cancer, and Health cohort born from 1930 to 1996	6698 Danish patients are a mean of 56 years old, post-menopausal BMI	Cox models for BMI trajectories: crude adjusted for year of birth; fully adjusted for year of birth; age at menarche; parity; breastfeeding duration; education; HRT use; smoking; alcohol; physical activity.	Among the BMI trajectories identified, the risk of post-menopausal ER + BCa is lower in patients with steep increases in BMI during childhood (HR 0.67 [95% CI 0.47–0.95]) and adolescence (HR 0.68 [95% CI 0.46–1.01]) that thereafter largely stabilized. The risk of ER + BCa was instead higher in patients who experienced low gain in BMI during childhood and adolescence, followed by a subsequent steep increase during adulthood (HR 1.28 [95% CI 0.98–1.67])
Busund *et al.*[208]	2023	Prospective study mean FU of 14.9 y	148 866 Norwegian post-menopausal women (7223 cases of breast cancer) Age 30–70 years BMI Luminal A-like, Luminal B-like, HER2-enriched, and TNBCa	Cox models for BMI trajectory-subtype: adjusted for age, race, education, physical activity, smoking, alcohol, HRT, BMI at baseline (via trajectory latent class membership), with heterogeneity tests across subtypes.	Women with OW or OB in the post-menopausal period have shown an increased risk of developing luminal A-like cancer (10-y HR 1.04) and a reduced risk of developing luminal B-like cancer (10 y HR 0.93). The % risk further increases among older patients and those with a history of elevated BMI over a long-life period (HR 1.09 for OW women and HR 1.20 for OB women). The association with HER2-positive and TNBCa subtypes did not yield notable results.

Continued

Table 4 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Christakoudi *et al.*[203]	2023	Cohort Study mean FU of 14.0 y	218 276 women (9011 incident breast cancers) Luminal A and B BMI, HIP index, body shape index	Multivariable Cox models adjusted for height, smoking status and intensity; alcohol consumption; physical activity; attained education; HRT use; oral contraceptive use; age at menarche; parity and age at first live birth; breastfeeding duration; log energy intake; plus stratification by age, country, and detailed menopausal status categories.	Despite a poor association of ABSI with overall BCa risk (HR 0.98 [95% CI 0.96–1.01]), a borderline inverse association was found in post-menopausal women (HR 0.97 [95% CI 0.94–1.00]; *n* = 5268 cases), BCa diagnosed at age ≥55 y (HR 0.98 [95% CI 0.95–1.00] *n* = 7043), ER + PR- subtypes (HR 0.89 [95% CI 0.82–0.97] *n* = 726), and ER-PR- subtypes (HR 0.91 [95% CI 0.84–0.98] *n* = 759). BMI associated strongly with overall BCa risk (HR 1.07 [95% CI 1.05–1.10]), in post-menopausal women (HR 1.12 [95% CI 1.09–1.15]), and those diagnosed at age ≥ 55 year (HR 1.10 [95% CI 1.08–1.13]) and ER + PR + subtypes (HR = 1.12 [95% CI 1.08–1.17]; *n* = 3101), but not PR- subtypes.
Harborg *et al.*[204]	2023	Longitudinal Analysis of Malmö Diet and Cancer Study patients, median FU of 11.1 y	17 035 Swedish women with invasive breast cancer BMI, WC, body fat percentage	Random-effects meta-analysis of prognosis by subtype used subgroup and sensitivity analyses, but did not list additional covariates—analyses were stratified by menopausal status and BMI group only, with no further multivariable adjustment reported	The increased risk of BCa risk characterizes BMI-defined OB (HR 1.44 [95% CI 1.00–2.07]), WC (HR 1.31 [95%CI 0.98–1.77]), and body fat percentage (HR 1.41 [95% CI 1.02–1.98]). OB-related BCa risk is associated with low socio-economic status (HR 2.55 [95% CI 1.08–6.02]), larger tumours >20 mm (HR 2.68 [95%CI 1.42–5.06]), and ER-BCa (HR 3.13 [95% CI 1.09–8.97]).
Hao *et al.*[205]	2023	Longitudinal study 3-y FU	442 Chinese women Inflammatory biomarkers related di BCa BMI	Linear mixed-effects models adjusted for age, education, occupation, age at menarche, menopausal status, history of livebirth, smoking status, and alcohol consumption. Effect modification was tested by baseline BMI group, menopausal status, and metabolic-syndrome status (NCEP-ATP III definition).	Increasing BMI significantly is associated with an average 3-y increase in resistin (β 0.019 [95% CI 0.004 to 0.034]), soluble leptin receptor (β 0.022 [95% CI 0.009 to 0.035]), and negatively with adiponectin (β −0.006 [95% CI −0.012 to 0.001]).

Continued

Table 4 *Continued*

Authors	Year	Study design and time frame	Population size and characteristics	Statistical adjustment	Results
Nag *et al.*[206]	2023	Prospective case-control study 3-y FU	912 women (266 TNBCa cases, 646 non-TNBCa controls) BMI, WC, WHR	Unconditional logistic regression models adjusted for the same set of covariates in both univariable and multivariable analyses; however, 'No factor was significant after adjustment for covariates,' implying the fully adjusted model included at least age, menopausal status, BMI, waist circumference, waist-to-hip ratio, socio-economic status, and other questionnaire-based risk factors.	Not high BMI (>vs ≤24.9) but WC and WHR associate with TNBCa (OR 0.64 [95% CI 0.45–0.90]; *P* = .012 and OR 0.72 [95% CI 0.51–1.0]; *P* = .056).
Zhang *et al.*[207]	2024	Longitudinal from TCGA, GEO, and METABRIC	1278 luminal BCa samples RNA-seq on 4150 differentially expressed genes	Multivariate Cox model for the LOG-CPI prognostic index, adjusted for RiskScore (7-gene signature), AJCC stage, and patient age-variables selected via lowest AIC.	Extracting molecular prognostic indicators related to obesity or BMI significantly contributes to the development of a robust and precise clinical predictive signature (LOG-CPI score) for recurrence risk.

PubMed search ((obes* [Title]) OR (metabolically healthy [Title]) OR (metabolically unhealthy [Title]) OR (sarcopenic obes* [Title]) OR (body mass index [Title])) AND ((breast cancer [Title]) AND (phenotype [Title]) OR (luminal [Title]) OR (oestrogen [Title]) OR (HER [Title])) NOT review from 2015 to present.

ABSI, A Body Shape Index; AJCC, American Joint Committee on Cancer (staging system); BCa, breast cancer; BMI, body mass index; CI, confidence interval; CMD, cardiometabolic diseases; ER, oestrogen receptor; ERBB2/HER2, human epidermal growth factor receptor 2; FU, follow-up; HR, hazard ratio; HRT, hormone replacement therapy; IGF/IGFBP, insulin-like growth factor/IGF-binding protein; MetS, metabolic syndrome; NW/OW, normal weight/overweight; OB, obesity; OC, oral contraceptives; OR, odds ratio; PR, progesterone receptor; RR, relative risk; TCGA/GEO/METABRIC, The Cancer Genome Atlas/Gene Expression Omnibus/Molecular Taxonomy of Breast Cancer International Consortium; TNBCa, triple-negative breast cancer (typo 'tripe' fixed); WC/WHR, waist circumference/waist-to-hip ratio; WHI, Women's Health Initiative.

Table 5 Summary of the interventional approaches to obesity in BCa risk

Agent	Mechanisms of action	Evidence
Metformin	Activates AMPK → inhibits mTOR; lowers hepatic gluconeogenesis; reduces systemic insulin/IGF 1	
GLP1-receptor agonist	Enhances insulin sensitivity and weight loss; direct anti-tumour effects via miRNA modulation and DNA methyltransferase activity in BCa cells	Liraglutide ↓ BCa cell viability/migration *in vitro*; GLP1R expression in tumours correlates with better outcomes
SGLT2 inhibitors	Inhibit tumour glucose uptake; induce glycosuria → weight loss and ↓ insulin/inflammation	Empagliflozin and canagliflozin slow BCa xenograft growth; diabetic patients on SGLT2is show lower BCa incidence and mortality
Senolytics	Selectively clear senescent cells → reduce SASP (IL-6, MMPs); restore adipose homeostasis	D + Q in obese mice improves insulin sensitivity and adipose inflammation; pilot in diabetics shows ↓ senescence markers

AMPK, AMP-activated protein kinase; BCa, breast cancer; D + Q, dasatinib + quercetin (senolytic cocktail); GLP-1R, glucagon-like peptide-1 receptor; IGF-1, insulin-like growth factor 1; mTOR, mechanistic target of rapamycin; SASP, senescence-associated secretory phenotype; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

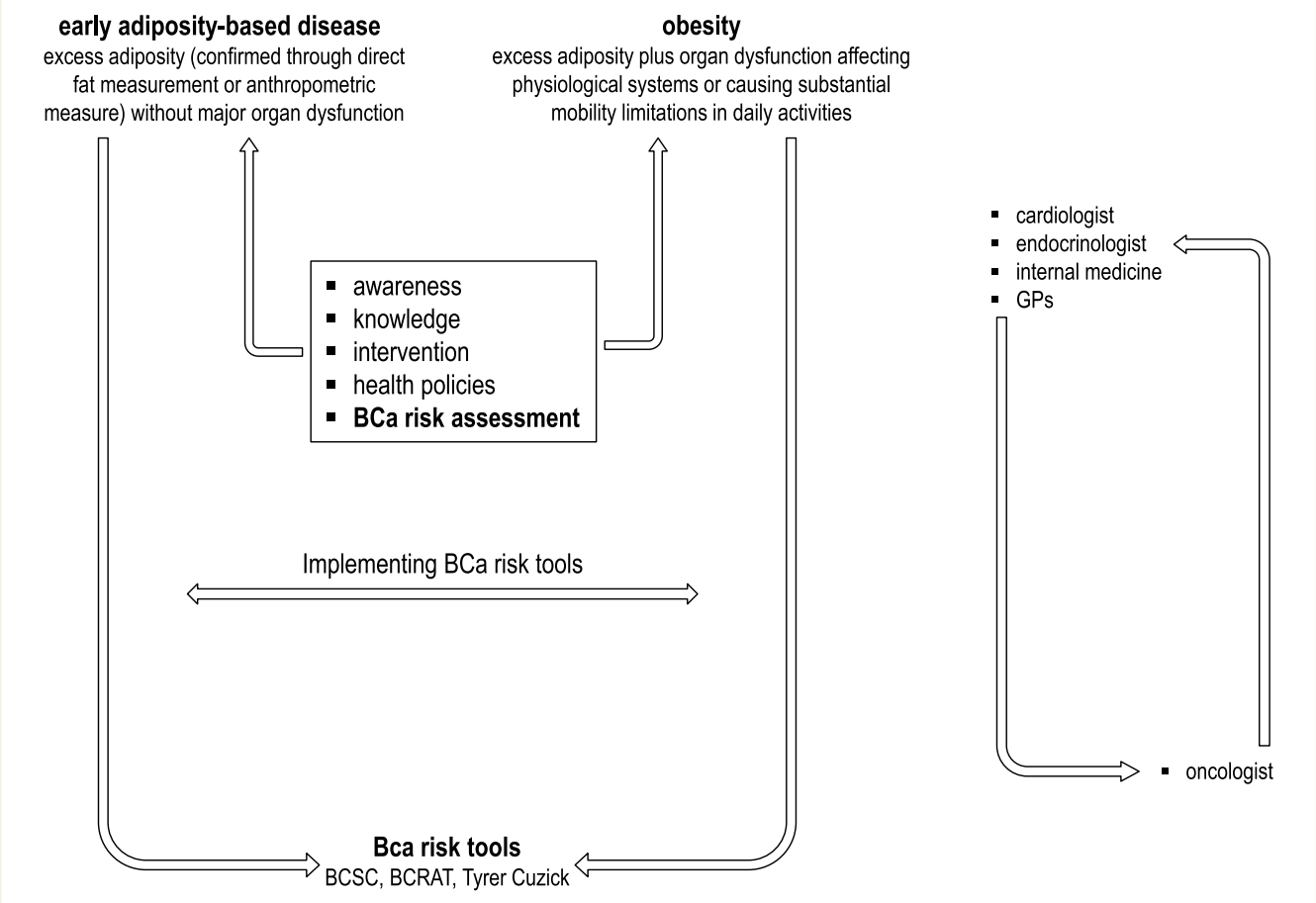

Figure 3 Clinical flowchart for obesity-integrated breast cancer risk stratification. Current BCa risk tools (e.g. BCRAT, Tyrer–Cuzick) do not formally include obesity metrics, yet this framework highlights a potential clinical pathway for incorporating obesity screening into BCa risk stratification

metformin with a roughly 20%–25% reduction in BCa incidence and improved DFS survival among women, with diabetes though questions remain given its pleiotropic actions.[233,234] Recent metabolomic profiling identifies metformin-related pathway changes—CYP1A2 activation, altered fatty-acid desaturase activity, and shifts in amino-acid metabolism (including impaired branched-chain amino-acid catabolism)—that may contribute to lower recurrence risk in survivors with overweight.[235] These

Table 6 Summary of actionable insights in reverse cardio-oncology

Key takeaways

- Obesity phenotyping enhances risk stratification beyond BMI.
- Adipose senescence and its SASP remodel the tumour microenvironment, linking metabolic dysfunction to tumour initiation and progression.
- AI and multi-omics enable deep phenotyping of cardiometabolic signatures, though robust clinical validation remains necessary.

Clinical translation: holistic prevention and treatment

- Lifestyle modification: adherence to healthful dietary patterns (e.g. Mediterranean diet) and regular physical activity remains foundational, improving body composition and reducing both breast cancer risk and recurrence.
- Pharmacotherapy: GLP-1 receptor agonists and SGLT2 inhibitors demonstrate substantial weight loss and cardiometabolic benefits, positioning them as promising adjuncts for breast cancer prevention and supportive care.
- Metabolic surgery: bariatric procedures confer sustained weight reduction and amelioration of obesity-associated comorbidities, including a lower incidence of breast cancer.

Clinical implications

- Risk stratification based on senescent and metabolic signatures may improve prognostic accuracy.
- Adipose tissue senescence contributes to immune ageing and therapy resistance in BCa patients with obesity.
- Integrating obesity-related biomarkers (e.g. SASP factors, L/A ratio) into clinical workflows could guide personalized treatment.
- Weight loss strategies may reverse pro-tumourigenic features in the tumour microenvironment.

Future Directions

- Standardization: develop and adopt uniform definitions, measurements, and terminology in obesity–breast cancer research (e.g. reproducible imaging protocols for fat depots).
- Longitudinal cohorts and RCTs: prioritize long-term observational studies and well-designed randomized trials to establish causality and track dynamic obesity phenotypes' impact on breast cancer outcomes.
- Emerging technologies: expand AI/ML integration with multi-omics (metabolomics, epigenetics, microbiome) to refine predictive models and ensuring rigorous validation in diverse, real-world cohorts to mitigate bias and safeguard privacy.
- Interdisciplinary collaboration: foster concerted efforts among clinicians, researchers, policymakers, and patients to address gaps, promote non-stigmatizing obesity care, and translate findings into equitable, data-driven strategies.

AI, artificial intelligence; BMI, body mass index; GLP, glucagon-like peptide-1; ML, machine learning; RCTs, randomized clinical trials; SASP, senescence-associated secretory pattern; SGLT, sodium-glucose cotransporters.

add to known AMPK-activating/mTOR-inhibitory effects and systemic reductions in insulin/IGF-1 signalling that can blunt initiation and progression. For sodium–glucose cotransporter pathways, experimental work suggests SGLT1 promotes BCa cell survival/proliferation[236] and inducer of tamoxifen resistance,[237] while pharmacologic SGLT2 inhibition (SGLT2i) counters these effects in BCa cells[238–240] and mouse models.[241] SGLT2i have shown cardiotoxicity-preventive signals in preclinical settings,[242,243] and clinical trials are ongoing (https://clinicaltrials.gov/search?cond=Breast%20Cancer&intr=SGLT2%20inhibitor); however, no definite clinical trial translation in BCa exists to date[244] and dose/safety questions in women without diabetes remain. Concerns about cancer risk with glucagon-like peptide-1 receptor agonists (GLP-1RA) arose from numerically higher BCa events in early trials, but long-term observational studies and meta-analyses have not confirmed increased BCa risk,[245] and even suggest lower colorectal cancer risk in drug-naïve type 2 diabetes, independent of BMI.[246] Furthermore, the recent finding of GLP-1R within BCa tissue suggests potential benefits in this setting. GLP-1R expression in BCa tissue further supports potential benefit: liraglutide reduces BCa cell viability and migration via epigenetic modulation (miRNAs, DNA methyltransferase activity),[247] with apparent synergy alongside chemotherapy—but a diminished effect at higher doses.[248] In severe obesity, bariatric surgery lowers BCa incidence and stage at diagnosis compared with BMI-matched controls, approximating outcomes seen in women with BMI <25 kg/m^2.[249,250] Effects are strongest in hyperinsulinemia[251] and appear regardless of menopausal status and hormonal profile.[252] While contemporary procedures are minimally invasive and yield faster cardiometabolic gains than drugs,[253] surgical risks, cost, and coverage barriers persist. In a murine model of obesity-driven TNBCa, caloric restriction matched—or outperformed—bariatric surgery, suppressing tumour growth and producing shared/distinct changes in transcripts, epigenetics, secretome, microbiota, and antitumour immunity.[254] Whether directly targeting senescence could be an option for obesity and BCa is an exciting—albeit unexplored—horizon. So far, targeting senescence in solid tumours using senolytics, alone or combined with chemotherapy, has proven to be limited in effectiveness or associated with intolerable toxicity.[255] While a deeper understanding of senescence hallmarks is needed to produce the next generation of senolytic strategies, advances in nanomedicine may partially overcome toxicity issues.[256] On the other hand, evidence rather supports the use of senolytic agents to counteract obesity-driven metabolic dysfunction. In diet-induced obese mice, intermittent clearance of p16^{Ink4a}+ senescent cells—using dasatinib plus quercetin—dramatically improved insulin sensitivity, glucose tolerance, and adipose tissue homeostasis, by reducing pro-inflammatory SASP factors and restoring adipogenic capacity.[104] These preclinical findings have spurred early human studies: a small pilot trial of senolytic therapy in adults with diabetic kidney disease demonstrated reduced circulating markers of senescence and inflammation, along with modest improvements in adipose insulin signalling.[257] While safety, optimal dosing, and long-term effects need rigorous evaluation, these data suggest that targeted removal of senescent adipose and stromal cells could become a novel adjunct in obesity medicine—potentially synergizing with diet, exercise, and metabolic drugs to ameliorate insulin resistance, curb low-grade chronic inflammation, and ultimately reduce BCa risk and progression in high-risk, populations with obesity (*Table 5*; *Figure 3*).

Conclusion

The epidemiologic link between cardiometabolic risk and cancer, including BCa, is established, and mechanistic understanding is increasingly growing. As the field evolves towards a 'reverse cardio-oncology' paradigm, cardiometabolic health emerges as a key modifier of cancer development and prognosis and remains central to ongoing scientific progress. Obesity phenotyping can refine patient stratification, but transitions between metabolically healthy and unhealthy states (and *vice versa*) need clearer characterization. A key takeaway is to move beyond BMI: comprehensive phenotyping should combine anthropometrics like WC (whose association with cardiovascular risk is fully realized when adjusted for BMI) with metabolic indices. Clarifying phenotype dynamics over time will help resolve paradoxes and strengthen risk prediction, including for BCa. Substantial heterogeneity remains across studies in terms of design (retrospective *vs.* prospective), population size and selection, BMI categorization, BCa subtype stratification, and outcome definitions (e.g. DFS, OS, BCa-specific survival). Furthermore, not all studies consistently adjusted for key confounders such as menopausal status, comorbidities, or treatment modality. Some heterogeneity also arose from different cutoff values for central adiposity (WC, WHR) or MetS definitions, which may limit direct comparability. These differences, while reflecting real-world diversity, should be carefully considered when interpreting pooled patterns and prognostic implications.

At the same time, broad omics signatures in BCa are opening opportunities to map the 'obesity landscape' and connect seemingly distant diseases.[258] As many obesity hallmarks are now brought under the umbrella of senescence, reducing obesity and cardiometabolic burden is likely to become a complementary pillar in BCa prevention and treatment.[207,259] Finally, the scale and complexity of omics data call for a more extensive use of artificial intelligence (AI). AI is just about everywhere in the fields of obesity and BCa right now, mainly at an early stage, but the pace of change is undeniable.[260–263] Thus, AI appears critical to further pursue an increasingly appropriate reverse cardio-oncology approach with exciting scenarios on the horizon. Articulating these actionable insights—spanning prevention, diagnosis, and therapeutic innovation—would provide a comprehensive framework to contextualize current evidence, support interdisciplinary collaboration, and accelerate the translation of reverse cardio-oncology concepts into improved outcomes for women with or at risk for BCa (*Table 6*; *Figure 3*).[264–266]

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

Luca Liberale is co-inventor on the international patent WO/2020/226993 filed in April 2020. The patent relates to the use of antibodies specifically binding IL-1α to reduce various sequelae of ischemia-reperfusion injury to the central nervous system. Luca Liberale reports speaker fees from Daiichi-Sankyo outside the submitted work and has received funding from the Novartis Foundation for Medical-biological Research (unrelated to this work). Gema Frühbeck reports research grants paid to her Institution from Spanish Institute of Health ISCIII. Gema Frühbeck reports payment of honoraria from Eli Lilly, Novo Nordisk, Regeneron, Astra Zeneca, Boehringer Ingelheim and Marabou Foundation as speaker and/or member of advisory boards, and payment of honoraria as member of the OPEN Spain Initiative. Gema Frühbeck is Co-chair of the Scientific Advisory Board of the European Society for the Study of Obesity - unpaid position.

Data Availability

No data were generated or analysed for or in support of this paper.

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