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SPECIAL REPORT

Postdiagnosis body fatness, weight change and breast cancer prognosis: Global Cancer Update Program (CUP global) systematic literature review and meta-analysis

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Abstract

Previous evidence on postdiagnosis body fatness and mortality after breast cancer was graded as limited-suggestive. To evaluate the evidence on body mass index (BMI), waist circumference, waist-hip-ratio and weight change in relation to breast cancer prognosis, an updated systematic review was conducted. PubMed and Embase were searched for relevant studies published up to 31 October, 2021. Random-effects meta-analyses were conducted to estimate summary relative risks (RRs). The evidence was judged by an independent Expert Panel using pre-defined grading criteria. One randomized controlled trial and 225 observational studies were reviewed (220 publications). There was strong evidence (likelihood of causality: probable) that higher postdiagnosis BMI was associated with increased all-cause mortality (64 studies, 32 507 deaths), breast cancer-specific mortality (39 studies, 14 106 deaths) and second primary breast cancer (11 studies, 5248 events). The respective summary RRs and 95% confidence intervals per 5 kg/m^2 BMI were 1.07 (1.05-1.10), 1.10 (1.06-1.14) and 1.14 (1.04-1.26), with high between-study heterogeneity (I^2 = 56%, 60%, 66%), but generally consistent positive associations. Positive associations were also observed for waist circumference, waist-hip-ratio and all-cause and breast cancer-specific mortality. There was limited-suggestive evidence that

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; CIs, confidence intervals; CUP Global, Global Cancer Update Program; CUP, Continuous Update Project; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; RCT, randomized controlled trial; RR, relative risk; WCRF, World Cancer Research Fund.

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postdiagnosis BMI was associated with higher risk of recurrence, nonbreast cancer deaths and cardiovascular deaths. The evidence for postdiagnosis (unexplained) weight or BMI change and all outcomes was graded as limited-no conclusion. The RCT showed potential beneficial effect of intentional weight loss on disease-free-survival, but more intervention trials and well-designed observational studies in diverse populations are needed to elucidate the impact of body composition and their changes on breast cancer outcomes.

KEYWORDS
Body fatness, breast cancer survival, evidence grading, systematic review, weight change

What's new?

Greater body fatness and adult weight gain are established risk factors for postmenopausal breast cancer, but the impact of excess body weight on breast cancer outcomes remains unclear. In this systematic review and meta-analysis of the Global Cancer Update Program, the independent expert panel concluded that there was strong evidence (likelihood of causality: probable) that postdiagnosis body fatness increases the risks of all-cause mortality, breast cancer-specific mortality and second primary breast cancer in women diagnosed with breast cancer. The findings support the development of lifestyle recommendations for breast cancer survivors to avoid obesity and be physically active, within the limits of their ability and specific medical advice.

1 | INTRODUCTION

In 2020, breast cancer was the most common cancer and the leading cause of cancer death in women globally, with 2.3 million incident cases and 0.7 million deaths estimated.[1] As of the end of 2020, there were 7.8 million women worldwide who had survived at least 5 years after a breast cancer diagnosis.[1]

Higher body fatness and adult weight gain have been established as risk factors for postmenopausal breast cancer, in particular hormone-sensitive breast cancers.[2,3] With the increasing global prevalence of overweight and obesity,[4] it is expected that many women diagnosed with breast cancer will have excess body weight, but the impact on breast cancer outcomes has been less clear than for incidence.

Previous meta-analyses of epidemiologic studies published up to 30 June, 2012 included in the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Third Export Report showed increased risks of all-cause mortality and breast cancer-specific mortality with higher postdiagnosis BMI.[5] In addition, women of normal body weight (BMI of 18.5-24.9 kg/m^2) after a breast cancer diagnosis were shown to have a more favorable overall survival than women of other weight statuses.[6]

Despite these statistically significant associations, the evidence was judged as limited-suggestive because of limitations in the design or conduct of the observational studies. In particular, the potential for residual confounding and reverse causation limited the confidence to determine causality.[5] Women with obesity may have more treatment complications and may receive less effective treatment compared with women without obesity.[7] Furthermore, cancer treatments may alter body weight and composition and could lead to adverse metabolic consequences.[8] Not all studies included in the meta-analyses reported information on breast cancer subtypes; although the association appeared to be similar in women with hormone receptor-positive or -negative breast cancers,[6,9] the relationship was less clear in women with aggressive tumors, such as triple-negative breast cancers.[10,11]

Breast cancer patients can have a long survival time and remain at risk of recurrence long after diagnosis.[12] Therefore, understanding the impact of postdiagnosis body fatness on breast cancer outcomes is important for identifying potentially actionable lifestyle targets for the growing number of women living with and beyond breast cancer.[13,14] We conducted updated systematic literature reviews and meta-analyses to summarize the evidence published until and after 30 June 2012 of the previous report[5] and an independent Expert Panel evaluated the accumulated evidence. This paper presents the evidence on body fatness, weight change and breast cancer outcomes, whereas evidence on physical activity, diet and the overall summary is presented in the accompanied papers.[15-17]

2 | MATERIALS AND METHODS

The present review forms part of the on-going Global Cancer Update Program (CUP Global), formally known as the WCRF/AICR Continuous Update Project (CUP).[18] The peer-reviewed protocol is available online.[19] Full details on the methods and search strategies are provided in Text S1. The PRISMA checklist is available in Table S1.

2.1 | Search strategy, selection criteria and data extraction

PubMed and Embase were searched for relevant publications through 31st October, 2021. The reference lists of identified articles were screened for any additional publications not identified in the primary searches.

Inclusion criteria were (1) Randomized controlled trials (RCTs), longitudinal observational studies, or pooled analyses of individual data of these studies; (2) With at least 100 women diagnosed with first primary breast cancer during adulthood; (3) Reported results on postdiagnosis BMI, waist circumference or waist-hip-ratio, and changes in weight or BMI in relation to all-cause mortality, breast and nonbreast cancer-specific mortality, breast cancer recurrence (or "recurrence/relapse-free survival", "disease-free survival", "event-free survival", "progression-free survival" and "additional breast cancer events"), any second primary cancers, or cardiovascular mortality.

In the case of multiple publications from the same or overlapping populations, the publication with the largest number of events was selected for inclusion in the meta-analysis. Study and participants' characteristics and results were extracted into the CUP Global database. Study selection and data extraction was checked by a second reviewer. Any disagreements were resolved by consensus. The quality of individual studies was not graded using a specific tool. Instead, relevant study characteristics that could be used to explore potential sources of bias were included into the CUP Global database. For all the included studies, information on potential for selection bias, information bias of exposure and outcome assessment, and residual confounding by cancer stage and treatment was retrieved after identifying the most likely influential sources of bias in cancer survival studies.[20,21] The potential influence of measurement error, length of follow-up and loss to follow-up, and adjustment for confounding factors on results was tested in subgroup meta-analyses and meta-regression analyses. Details on how the study authors addressed the potential biases were also included. In the Expert Panel meeting, whether the studies had serious quality issues were discussed when judging the evidence for each exposure-outcome association.

2.2 | Statistical methods for meta-analysis

The summary relative risk (RR) estimates and their 95% confidence intervals (CIs) were calculated using the inverse variance random-effects model.[22] When at least three (additional) studies were identified in the updated search, a linear dose-response meta-analysis was conducted (or updated if reviewed previously with evidence up to 30 June, 2012[5]) if the studies reported sufficient information for analysis, otherwise the studies were descriptively synthesized. The multivariable adjusted RR estimates per exposure increment unit were pooled in a dose-response meta-analysis either with estimates provided in the original publications or estimated by us using the generalized weighted least-squares regression model.[23,24] Standard imputations were conducted to calculate the required information when missing (0-57% across analyses)[25,26] (Text S1).

In the linear dose-response meta-analysis, the underweight group (BMI <18.5 kg/m^2 or as defined by studies) was excluded to avoid possible impact on the risk estimation. Pre- to postdiagnosis (≥1 year) weight change was grouped into moderate (5-10%), or high (>10%) weight loss or gain.[27,28] The RR estimates for the weight change vs stable weight (±5% or as defined by studies) groups were pooled in categorical meta-analyses.

Between-study heterogeneity was assessed by the Cochran's Q test and I^2 statistic,[29] accompanied by visual inspection of the forest plots for consistency of associations, which contributes towards evidence grading. Pre-defined subgroup meta-analyses and random-effects meta-regression analyses were conducted to explore if a certain disease or study characteristics or aspect of risk of bias explain between-study heterogeneity.[30] This included the exploration of the potential influence of changes in treatment regimens, over time, on the associations, by grouping the studies according to the diagnosis or treatment period: before 2000 or after 2000 for the shift to include doxorubicin/cyclophosphamide in chemotherapy,[31] and before 2005 or after 2005 for the reduced anthracycline use and the introduction of taxanes,[32] and human epidermal growth factor receptor 2 (HER2) targeted therapy—trastuzumab.[33]

Small study effects such as publication bias was examined using Egger's test and visual inspection of the funnel plots for asymmetry, when there were more than 10 studies.[34] Individual studies may potentially influence the summary RR estimate and was examined by leave-one-out analysis.[35]

Restricted cubic spline regression with three knots at 10th, 50th and 90th percentiles of distribution of the exposure was conducted and pooled in random-effects meta-analysis when five or more studies, each with data for at least three exposure categories, including the underweight group if presented, were available.[36,37] The linear and nonlinear models were compared using a likelihood ratio test.[38]

A two-tailed *P* value of <.1 was considered as evidence for small study effects or between-study heterogeneity in the generally low-powered Egger's test and meta-regression analyses.

2.3 | Evidence grading criteria

An independent Expert Panel (ELG, MJG, AAJ, EK, VL, SKC and AMT) graded the quality of the evidence into strong (subgrades evaluating likelihood of causality: convincing, probable, or substantial effect on risk unlikely) or limited (subgrades evaluating likelihood of causality: limited-suggestive or limited-no conclusion) level, using pre-defined evidence grading criteria (Table S2).

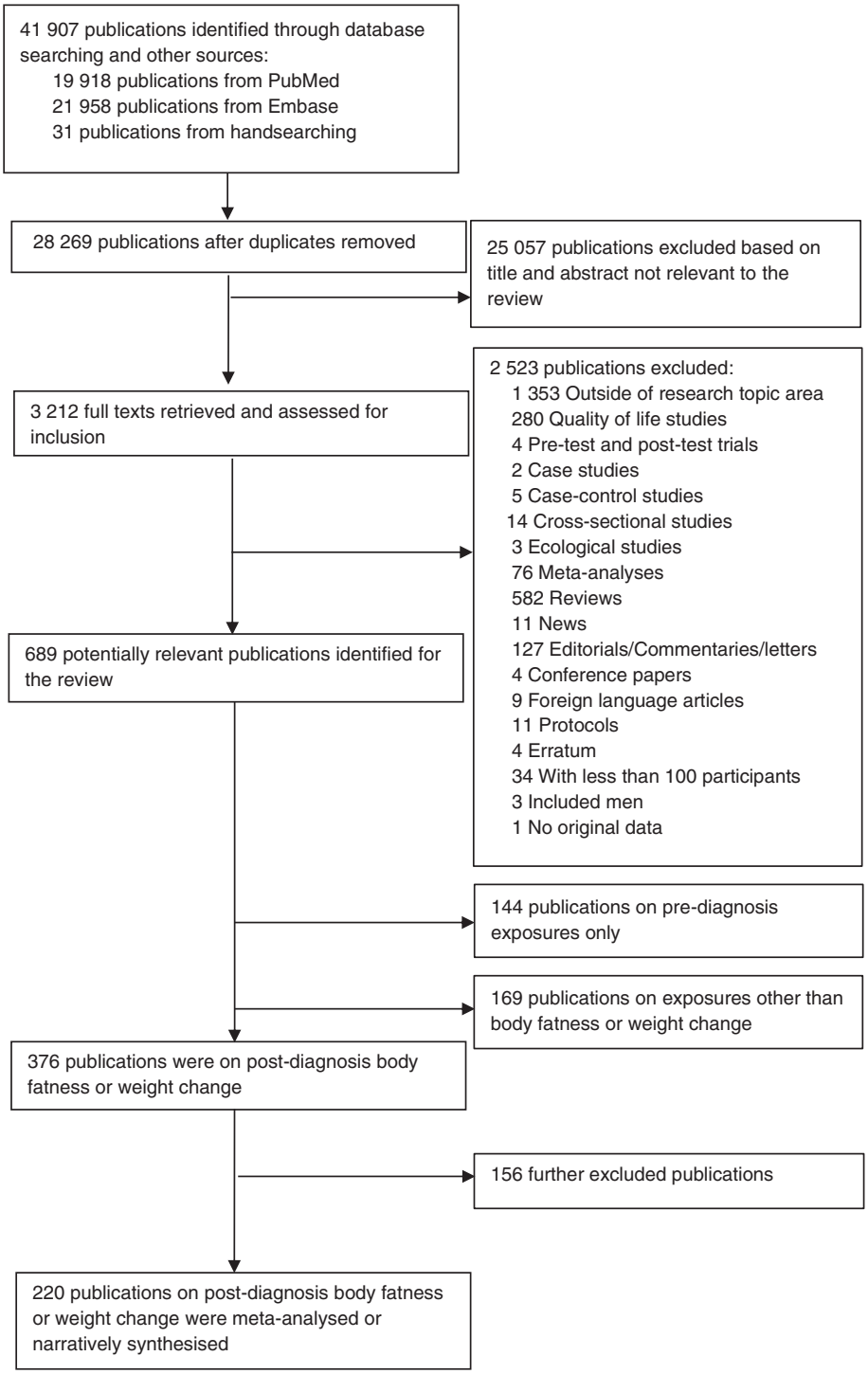
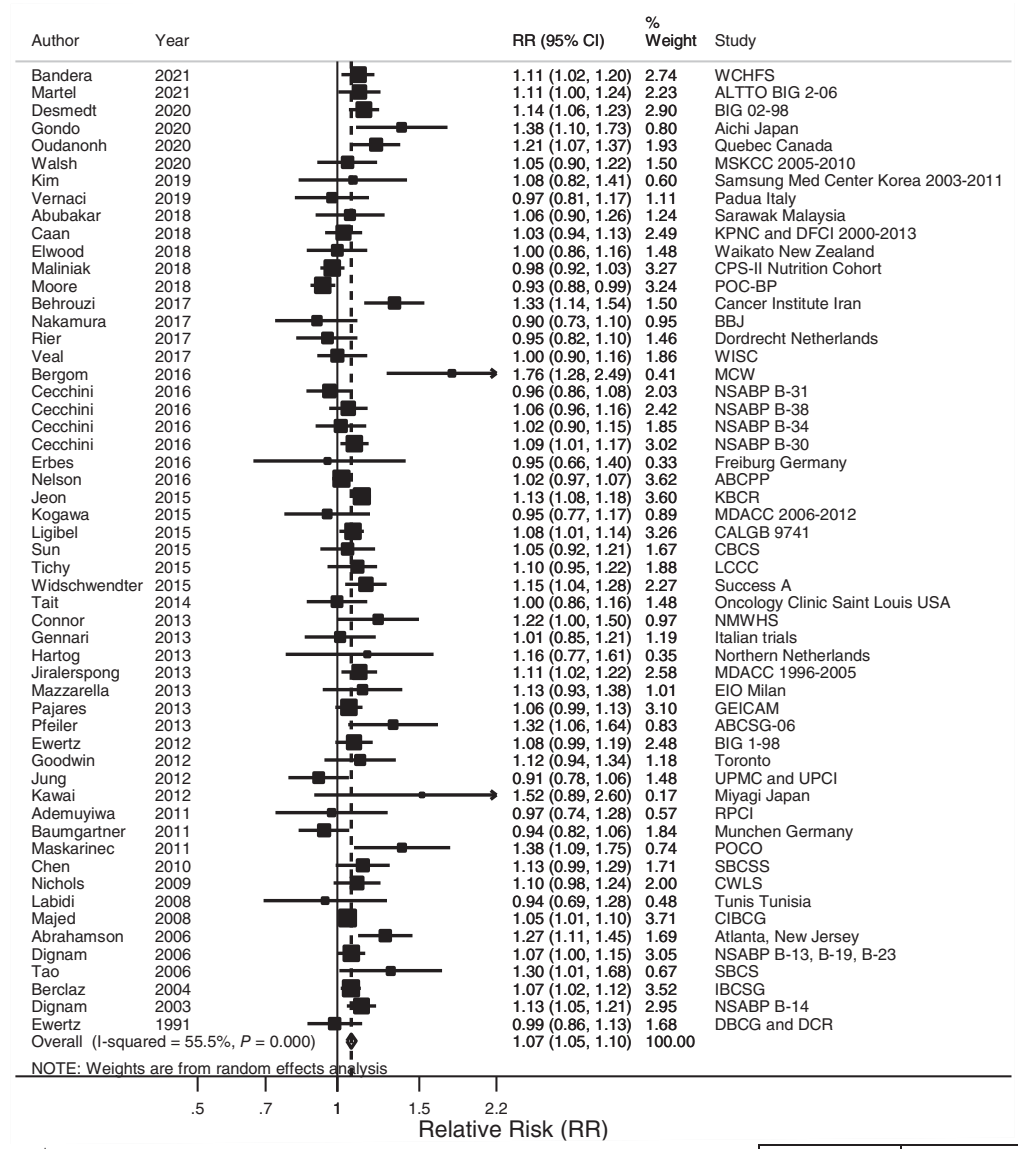


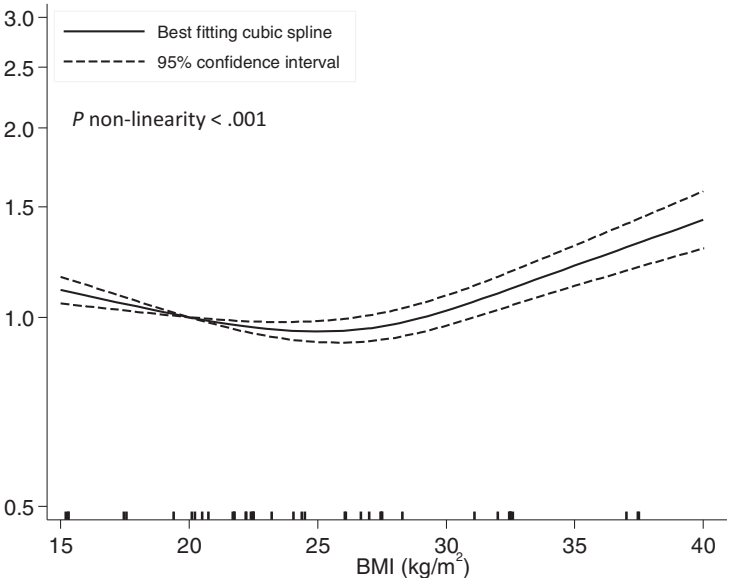
FIGURE 1 Flow chart of study selection process

TABLE 1 Evidence grades and main findings from the meta-analyses and narrative syntheses

	Diet, nutrition, physical activity and survival in women with breast cancer					
		Increases risk				
		Exposure		Outcome	Summary of findings RR (95% confidence interval)	Conclusions
Strong evidence	Convincing	—		—	—	—
	Probable	Postdiagnosis greater body fatness	BMI	All-cause mortality	64 studies, 32 507 deaths 1.07 (1.05-1.10) per 5 kg/m^2 I^2 56%, *P* Egger .16	The evidence is substantial, generally consistent, and shows evidence of a dose-response relationship. The observed associations are unlikely to be caused solely by chance or bias. More RCT evidence is required for the evidence to be judged "convincing."
			WC		5 studies, 983 deaths 1.18 (1.07-1.31) per 10 cm I^2 = 55%	
			WHR		8 studies, 2443 deaths 1.30 (1.20-1.40) per 0.1 unit I^2 0%	
			BMI	Breast cancer-specific mortality	39 studies, 14 106 deaths 1.10 (1.06-1.14) per 5 kg/m^2 I^2 60%, *P* Egger <.001	
			WC		3 studies, 262 deaths 1.12 (1.03-1.22) per 10 cm I^2 0%	
			WHR		6 studies, 1307 deaths 1.21 (1.08-1.35) per 0.1 unit I^2 6%	
			BMI	Second primary breast cancer (BMI)	11 studies, 5248 events 1.14 (1.04-1.26) per 5 kg/m^2 I^2 66%	
Limited evidence	Limited suggestive	Postdiagnosis greater body fatness	BMI	Recurrence	63 studies, 29 749 deaths 1.05 (1.03-1.08) per 5 kg/m^2 I^2 54%, *P* Egger .46	The evidence is substantial, generally consistent and shows evidence of a dose-response relationship, but is limited in methodological quality relating to outcome assessment.
			WC		RRs ranged from 1.18 to 1.70 for the highest vs lowest WC in 5 out of the 6 studies, 2 of the 95% CIs did not include one	
			WHR		2 studies, no association	
			BMI	Nonbreast cancer related mortality (BMI)	10 studies, 2307 deaths 1.06 (0.94-1.19) per 5 kg/m^2 I^2 78%, *P* Egger .30	The evidence is substantial, but there is inconsistency.
			BMI	CVD mortality (BMI)	2 studies, 124 deaths 1.16 (0.96-1.41) per 5 kg/m^2 I^2 0%	The evidence is sparse but is suggestive of a positive association.
	Limited—no conclusion	Postdiagnosis BMI or weight change (gain or loss)	Pre- to postdiagnosis weight/BMI change Any period postdiagnosis weight/BMI change Weight/BMI change during cancer treatment			The evidence is sparse and inconsistent and is limited in methodological quality. Relating to exposure assessment.

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; WC, waist circumference; WHR, waist-hip-ratio.





BMI (kg/m^2)	RR estimates (95% CI)
16	1.08 (1.04-1.13)
18	1.04 (1.02-1.06)
20	1.00
22	0.97 (0.95-0.99)
25	0.95 (0.91-0.99)
27	0.96 (0.92-1.01)
30	1.02 (0.97-1.08)
32	1.09 (1.03-1.16)
35	1.21 (1.12-1.30)
37	1.29 (1.19-1.41)

FIGURE 2 Legend on next page.

3 | RESULTS

Overall, 376 publications were identified reporting results on postdiagnosis body fatness and weight or BMI change and selected outcomes in breast cancer survivors; Figure 1 shows the flowchart of the search process. The meta-analyses included 101 publications reporting postdiagnosis BMI (assessed from at-diagnosis to on average 5.8 years postdiagnosis), waist circumference (at-diagnosis to 7.9 years postdiagnosis), waist-to-hip ratio (at-diagnosis to 2.5 years postdiagnosis) and pre- to postdiagnosis weight gain or loss (from 1 year before to 1 year or more after diagnosis).[27,39-138] In addition, 119 publications were descriptively synthesized[139-257] and 156 publications were excluded.[258-413]

The 220 included publications comprised 226 studies and included over 456 000 women diagnosed with breast cancer, of whom over 36 000 died of any causes, approximately 21 000 died of breast cancer and approximately 30 000 experienced an additional breast cancer event. Geographically, 79 publications were from North America,[27,39,41,46,47,49-51,53,54,56-58,61-64,69,71-74,77,79-81,84,87,88,91,93,95,98-100,107,109,111,113-115,117,118,124,126-128,132,140,146,147,149,150,154,165,166,168,170,171,174,175,177-179,183,184,190,192,200,201,203,211,217,225,235,248,253,256,257] 64 from Europe,[43,48,60,66,67,70,76,89,90,92,94,101,103-105,108,116,130,133,135-137,141-145,148,155-162,164,173,181,182,186,187,191,193-195,198,199,204,207,208,212,218,219,224,229,230,232,237,240,243,245,246,255] 50 from East or Southeast Asia[40,42,55,75,78,82,83,86,96,97,110,112,119,122,125,129,131,134,151-153,163,167,169,172,176,180,189,202,205,209,210,213,214,216,220,222,226-228,231,236,239,241,242,244,247,250,251,254] and 27 from international locations[45,52,59,68,102,106,120,121,123,138,221,238,252] or elsewhere.[44,65,85,139,185,188,196,197,206,215,223,233,234,249] One RCT was identified.[256] All others were observational studies. The publications included or excluded in each specific meta-analysis or descriptive synthesis and the reasons for exclusion, and the corresponding study description and participants' characteristics are provided in Tables S3 and S4-S8.

Below is an overview of the findings. Table 1 shows the summary findings and the judgment of the Expert Panel.

3.1 | Postdiagnosis body mass index

The respective linear dose-response meta-analyses included 64 studies that reported all-cause mortality (52 publications, 32 507 deaths),[39-41,43-46,53-55,57,63-68,70,72,78,79,81,82,84,85,88,89,91,93-95,97,98,100,102,104,105,109,111-114,116,118,120,123,125-127,129,130,135] 39 studies that reported breast cancer-specific mortality (31 publications, 14 106 deaths),[57,63-65,74,75,77-79,82,86,91,93,95,96,98-103,106,109,110,117,118,122,125,126,128,137] 63 studies that reported breast cancer recurrence (49 publications, 29 749 events),[40,41,43-46,48,51,54-56,59,63-66,68-70,72-74,76,79,83-85,88,89,92,94,96,102,104,106,110,112,115,116,120-125,127,130,131,136] 11 studies that reported second primary breast cancer (eight publications, 5248 events),[58,63,64,87,90,108,132,138] 10 studies that reported nonbreast cancer-related mortality (seven publications, 2307 deaths),[57,63-65,77,95,106] and two studies that reported cardiovascular mortality (two publications, 124 deaths).[100,114]

Higher postdiagnosis BMI was associated with higher risks of all-cause mortality (summary RR per 5 kg/m^2: 1.07, 95% CI: 1.05-1.10; Figure 2), breast cancer-specific mortality (1.10, 95% CI: 1.06-1.14; Figure 3), breast cancer recurrence (1.05, 95% CI: 1.03-1.08; Figure S1) and second primary breast cancer (1.14, 95% CI: 1.04-1.26; Figure S2). There was evidence of between-study heterogeneity for all outcomes. The I^2 was 56%, 60%, 54% and 66% (all P heterogeneity <.001), respectively. There was suggestion of positive associations between BMI (per 5 kg/m^2) and nonbreast cancer-related mortality (1.06, 95% CI: 0.94-1.19; I^2 78%, P heterogeneity <.001) and cardiovascular mortality (1.16, 95% CI: 0.96-1.41; I^2 0%, P heterogeneity = .38; Figures S3 and S4).

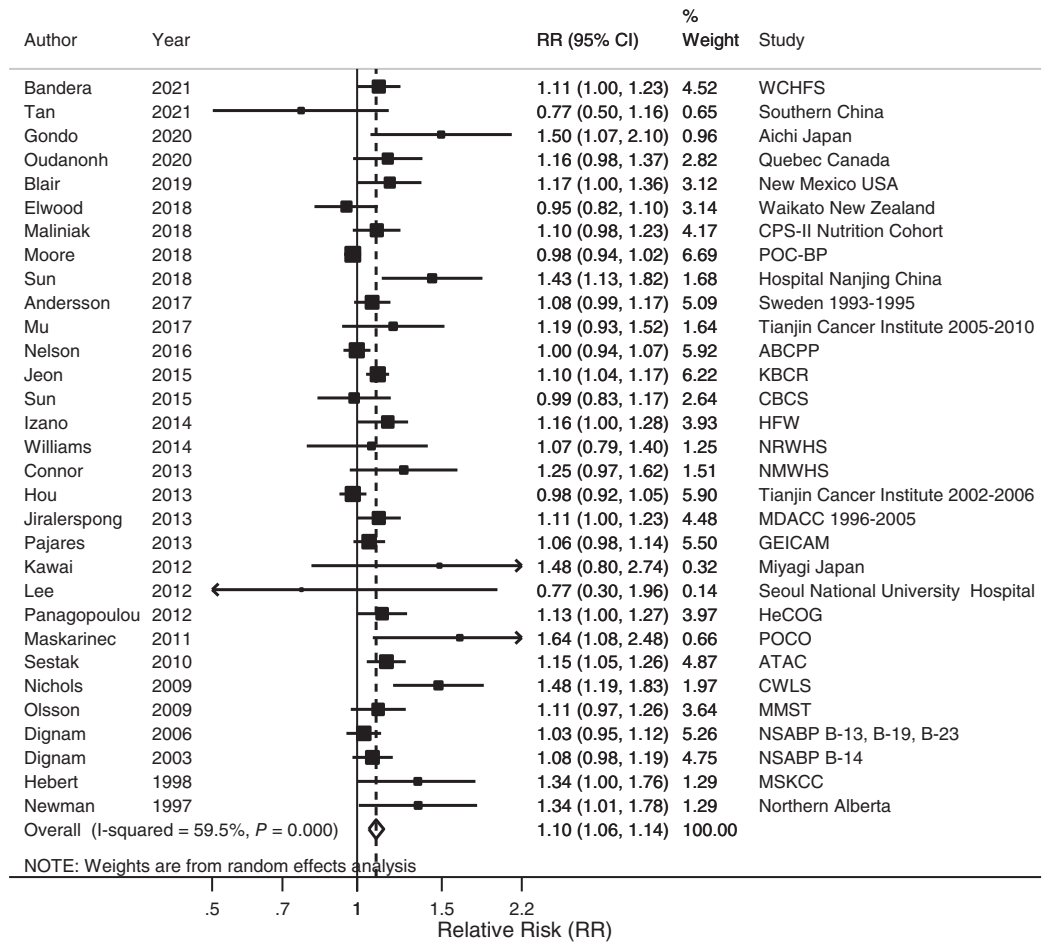
Nonlinear dose-response analysis detected a J-shaped relationship with all-cause mortality (P nonlinearity <.001; 52 studies, 27 478 deaths; 40 publications).[39-41,45,53-55,57,63-65,67,68,70,72,78,79,81,82,85,91,93-95,97,98,100,102,104,109,111,112,116,118,120,123,125,126,129,130] Compared with BMI arbitrary chosen at 20 kg/m^2, increased all-cause mortality risks were observed for BMI below 18 kg/m^2 and above 32 kg/m^2 with the most favorable survival in the upper normal to low overweight range (24-26 kg/m^2). Increased risk of breast cancer-specific mortality was evident for BMI above 29 kg/m^2 (P nonlinearity = .02; 34 studies, 13 324 deaths; 27 publications)[57,63-65,75,78,79,82,86,91,93,95,96,98-103,106,109,110,118,125,126,128,137] (Figures 2 and 3). The curves for breast cancer recurrence (P nonlinearity = .71; 47 studies, 28 165 events; 37 publications)[40,41,45,48,51,54,55,59,63-65,68-70,72,73,79,83,85,89,94,96,102,104,106,110,112,115,116,119,120,123-125,130,131,133] and second primary breast cancer (P nonlinearity = .19; nine studies, 2925 events; seven publications)[58,63,64,87,108,132,138] appeared linear (Figures S1 and S2).

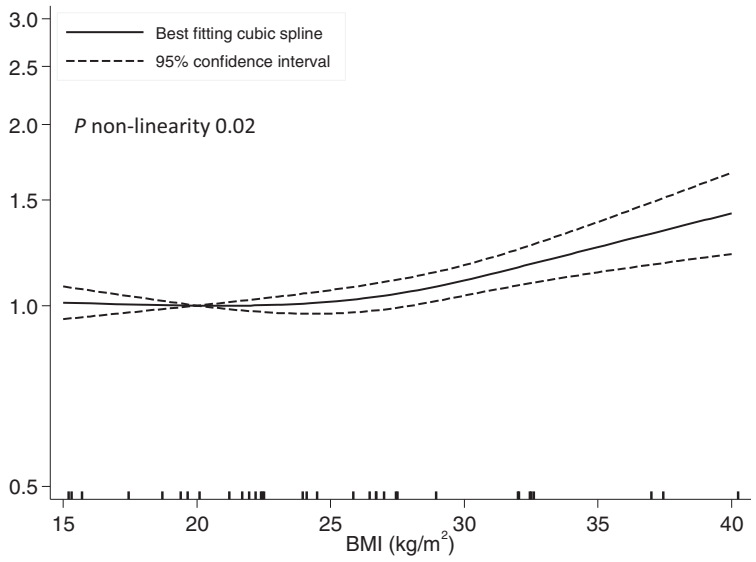
Figures S5-S7 show the RR estimates for the analyses comparing the highest to lowest BMI category, including the studies that were not available in the dose-response meta-analyses (Table S3). Most studies showed that higher BMI was associated with poorer survival after breast cancer.

3.2 | Subgroup dose-response meta-analyses and meta-regression analyses of postdiagnosis BMI

The results from the subgroup dose-response meta-analyses (by menopausal status, hormone receptor subtype, nodal status, geographic

FIGURE 2 Linear and nonlinear dose-response meta-analyses of postdiagnosis body mass index and all-cause mortality. Forest plot shows the linear dose-response results for postdiagnosis body mass index (BMI) and all-cause mortality from the inverse variance DerSimonian-Laird random-effects model. Diamond represents the summary relative risk (RR) estimate and its width as the 95% confidence interval (CI). Each square represents the RR estimate of each study and the horizontal line across each square represents the 95% CI of the RR estimate. The increment unit was per 5 kg/m^2. Nonlinear curve was estimated using restricted cubic spline regression with three knots at 10th, 50th and 90th percentiles of distribution of the exposure and pooled in random-effects meta-analysis. BMI at 20 kg/m^2 was selected as reference. The table shows selected BMI values and their corresponding RR (95% CI) estimated in the nonlinear dose-response meta-analysis.





BMI (kg/m^2)	RR estimates (95% CI)
16	1.01 (0.96-1.06)
18	1.00 (0.98-1.03)
20	1.00
22	1.00 (0.98-1.02)
25	1.01 (0.97-1.06)
27	1.04 (0.98-1.09)
29	1.08 (1.02-1.14)
32	1.16 (1.08-1.24)
35	1.25 (1.13-1.39)
37	1.32 (1.16-1.50)

FIGURE 3 Linear and nonlinear dose-response meta-analyses of postdiagnosis body mass index and breast cancer-specific mortality. Forest plot shows the linear dose-response results for postdiagnosis body mass index (BMI) and breast cancer-specific mortality from the inverse variance DerSimonian-Laird random-effects model. Diamond represents the summary relative risk (RR) estimate and its width as the 95% confidence interval (CI). Each square represents the RR estimate of each study and the horizontal line across each square represents the 95% CI of the RR estimate. The increment unit was per 5 kg/m^2. Nonlinear curve was estimated using restricted cubic spline regression with three knots at 10th, 50th and 90th percentiles of distribution of the exposure and pooled in random-effects meta-analysis. BMI at 20 kg/m^2 was selected as reference. The table shows selected BMI values and their corresponding RR (95% CI) estimated in the nonlinear dose-response meta-analysis.

TABLE 2 Subgroup meta-analyses of postdiagnosis body mass index and breast cancer outcomes by disease characteristics

Subgroup by disease characteristics[a]	All-cause mortality Summary RR (95% CI) I^2, *P* heterogeneity	Breast cancer mortality Summary RR (95% CI) I^2, *P* heterogeneity	Breast cancer recurrence Summary RR (95% CI) I^2, *P* heterogeneity
Menopausal status			
Premenopausal	5 studies, 1812 deaths 1.10 (1.02-1.20) 27%, 0.24	4 studies, 193 deaths 1.35 (1.08-1.70) 21%, 0.29	6 studies, 2575 events 1.23 (1.06-1.42) 77%, 0.001
Postmenopausal	10 studies, 4924 deaths 1.06 (0.99-1.13) 68%, 0.001 *P* meta-regression .52	6 studies, 1329 deaths 1.12 (1.07-1.18) 0%, 0.45 *P* meta-regression .14	9 studies, 5059 events 1.06 (1.02-1.11) 23%, 0.24 *P* meta-regression .17
Hormone receptor subtype			
ER+ and/or PR+	5 studies, 1048 deaths 1.10 (0.96-1.26) 67%, 0.02	2 studies, 520 deaths 1.70 (0.57-5.06) 65%, 0.09	5 studies, 2557 events 1.06 (1.01-1.11) 0%, 0.51
ER+	8 studies, 4640 deaths 1.11 (1.07-1.15) 0%, 0.45	3 studies, 925 deaths 1.09 (1.01-1.18) 0%, 0.75	7 studies, 4097 events 1.06 (1.02-1.11) 25%, 0.24
ER+/PR+	2 studies, 433 deaths 1.03 (0.90-1.17) 2%, 0.31	—	—
ER−	6 studies, 2005 deaths 1.09 (1.04-1.14) 0%, 0.55	4 studies, 700 deaths 1.05 (0.97-1.13) 1%, 0.32 *P* meta-regression .50	6 studies, 2989 events 1.06 (1.02-1.11) 0%, 0.91
ER−/PR−	3 studies, 235 deaths 1.20 (1.00-1.42) 35%, 0.22 *P* meta-regression .18	—	2 studies, 189 events 1.22 (1.06-1.40) 0%, 0.48 *P* meta-regression .60
Molecular subtype			
ER+ and/or PR+/ HER2−	2 studies, 1491 deaths 1.24 (1.14-1.33) 0%, 0.66	2 studies, 973 deaths 1.01 (0.78-1.31) 86%, 0.008	—
ER+ and/or PR+/ HER2+	3 studies, 794 deaths 1.04 (0.94-1.16) 0%, 0.79	—	2 studies, 691 events 1.01 (0.92-1.11) 0%, 0.65
Triple negative/basal-like	7 studies, 2364 deaths 1.03 (0.98-1.09) 0%, 0.42	2 studies, 726 deaths 1.03 (0.88-1.20) 13%, 0.28	5 studies, 1174 events 0.97 (0.83-1.13) 46%, 0.12
HER2+	4 studies, 1566 deaths 1.03 (0.96-1.11) 19%, 0.30 *P* meta-regression .12	—	5 studies, 2056 events 1.06 (1.00-1.11) 4%, 0.38 *P* meta-regression .59
Invasiveness of tumor			
Invasive	55 studies, 30 735 deaths 1.07 (1.04-1.09) 58%, <0.001	32 studies, 13 160 deaths 1.08 (1.04-1.13) 62%, <0.001	50 studies, 27 035 events 1.05 (1.03-1.07) 38%, 0.007
Invasive and in situ	8 studies, 1576 deaths 1.12 (1.04-1.22) 34%, 0.16 *P* meta-regression .41	5 studies, 631 deaths 1.26 (1.09-1.46) 41%, 0.15 *P* meta-regression .21	5 studies, 1377 events 1.19 (1.08-1.30) 34%, 0.20 *P* meta-regression .02
Nodal status			
Node+	6 studies, 5556 deaths 1.06 (1.03-1.10) 0%, 0.48	—	6 studies, 6504 events 1.06 (1.03-1.09) 0%, 0.68

TABLE 2 (Continued)

Subgroup by disease characteristics[a]	All-cause mortality Summary RR (95% CI) I^2, *P* heterogeneity	Breast cancer mortality Summary RR (95% CI) I^2, *P* heterogeneity	Breast cancer recurrence Summary RR (95% CI) I^2, *P* heterogeneity
Node-	6 studies, 2168 deaths 1.09 (1.04-1.15) 0%, 0.78 *P* meta-regression .35	5 studies, 1292 deaths 1.08 (0.98-1.19) 45%, 0.17	5 studies, 2618 events 1.04 (1.00-1.09) 0%, 0.46 *P* meta-regression .50
Cancer stage			
Early stage/stage 0-III/ nonmetastatic	30 studies, 20 393 deaths 1.08 (1.04-1.12) 67%, <0.001	16 studies, 7856 deaths 1.11 (1.05-1.17) 72%, <0.001	27 studies, 15 677 events 1.06 (1.04-1.07) 0%, 0.54
Stage 0-II	2 studies, 438 deaths 1.20 (1.02-1.40) 22%, 0.26	—	3 studies, 659 events 1.06 (0.77-1.45) 80%, 0.002
Locally advanced/ stage III	4 studies, 411 deaths 0.98 (0.88-1.09) 35%, 0.21	—	3 studies, 396 events 1.02 (0.87-1.20) 52%, 0.13
Stage IV/distant/ metastatic	5 studies, 761 deaths 0.95 (0.87-1.04) 0%, 0.66 *P* meta-regression .14	—	8 studies, 1057 events 0.91 (0.86-0.96) 0%, 0.74 *P* meta-regression .003

Abbreviations: CI, Confidence interval; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; RR, relative risk.

[a]Results not shown for the strata with only one study or the few studies with unknown information.

location, study type, exposure time, treatment period, length of follow-up, loss to follow-up, BMI assessment and covariate adjustment) largely resembled those of the main analyses, with few exceptions (Tables 2 and 3). However, few studies were included in some subgroups leading to wide 95% CIs and limiting the ability to assess/explain heterogeneity. Meta-regression analyses indicated that tumor invasiveness or stage may partly explain the heterogeneity observed for breast cancer recurrence (I^2 = 54%), with the studies of invasive and in situ breast cancers showing a higher average positive association (five studies/publications)[55,96,110,112,127] compared with studies with only invasive cancers (50 studies, 41 publications),[40,41,43-46,48,51,54,56,59,63-66,68-70,72,74,79,84,85,88,89,92,94,102,104,106,115,116,120-125,130,131,136] and the studies of metastatic breast cancers showing inverse associations (eight studies, two publications)[70,121] compared with the positive associations observed for early stage disease cases (27 studies/publications)[41,43,44,46,48,51,54,56,59,63,66,68,69,72,74,79,88,89,94,106,116,120,122-124,127,130] (*P* meta-regression = .02 and .003, respectively). A similar pattern by tumor stage was observed for all-cause mortality (30 studies, 28 publications on early stage diseases[41,43,44,46,54,63,66-68,72,78,79,88,89,91,94,95,98,100,111,116,120,123,125-127,129,130]; five studies, three publications on metastatic disease[70,81,105]; *P* meta-regression .14; Table 2). The studies with fewer breast cancer deaths (four studies/publications with <100 events[74,86,93,117]; 16 studies, 15 publications with 100-500 events[57,65,77,82,91,96,99,100,106,109,110,118,125,126,137]) observed stronger positive associations compared with the studies with more breast cancer deaths (18 studies, 11 publications with >500 events[63,64,75,78,79,95,98,101-103,128]), which may have contributed to the heterogeneity observed for breast cancer-specific mortality (I^2 = 60%; *P* meta-regression = .04; Table 3).

3.3 | Postdiagnosis waist circumference and waist-to-hip ratio

The respective linear dose-response meta-analyses of postdiagnosis waist circumference included five studies reporting on all-cause mortality (983 deaths)[39,71,72,112,118] and three on breast cancer-specific mortality (262 deaths),[71,117,118] and of postdiagnosis waist-to-hip ratio included eight studies reporting on all-cause mortality (2443 deaths)[39,55,60,71,107,109,112,118] and six on breast cancer-specific mortality (1307 deaths).[49,60,71,107,109,118]

Higher waist circumference and waist-to-hip ratio were associated with higher risks of all-cause mortality and breast cancer-specific mortality. The summary RRs per 10 cm increase in waist circumference were 1.18 (95% CI: 1.07-1.31; I^2 = 55%) and 1.12 (95% CI: 1.03-1.22; I^2 = 0%), and per 0.1 unit increase in waist-to-hip ratio were 1.30 (95% CI: 1.20-1.40; I^2 = 0%) and 1.21 (95% CI: 1.08-1.35; I^2 = 6%), respectively.

Nonlinear dose-response meta-analyses including the same studies showed linear relationships (*P* nonlinearity = .47, .08 and .73, respectively; Figures S8-S11).

Both studies with[39,49,55,71,107] and without[39,60,72,109,112,118] BMI adjustment on average showed a positive association (Figures S12-S14). No further subgroup and sensitivity analyses were conducted because of the low number of included studies.

TABLE 3 Subgroup meta-analyses of postdiagnosis body mass index and breast cancer outcomes by study characteristics

Subgroup by study characteristics[a]	All-cause mortality Summary RR (95% CI) I^2, *P* heterogeneity	Breast cancer mortality Summary RR (95% CI) I^2, *P* heterogeneity	Breast cancer recurrence Summary RR (95% CI) I^2, *P* heterogeneity
Geographic location			
East or Southeast Asia	8 studies, 6375 deaths 1.13 (1.05-1.21) 33%, 0.17	8 studies, 4847 deaths 1.12 (1.00-1.26) 69%, 0.002	9 studies, 3406 events 1.13 (1.00-1.27) 78%, <0.001
Europe	13 studies, 5555 deaths 1.04 (0.99-1.10) 32%, 0.14	3 studies, 1593 deaths 1.10 (1.03-1.17) 0%, 0.82	14 studies, 7498 events 1.05 (1.00-1.10) 45%, 0.04
Multi-national	8 studies, 5460 deaths 1.08 (1.05-1.12) 0%, 0.59	5 studies, 1145 deaths 1.10 (1.01-1.19) 44%, 0.18	15 studies, 9913 events 1.04 (1.00-1.08) 68%, 0.003
North America	32 studies, 14 435 deaths 1.06 (1.03-1.10) 62%, <0.001 *P* meta-regression .22	22 studies, 6204 deaths 1.11 (1.05-1.16) 64%, <0.001 *P* meta-regression .81	22 studies, 8163 events 1.05 (1.03-1.08) 13%, 0.29 *P* meta-regression .73
Study type			
Secondary analysis of clinical trials	22 studies, 11 069 deaths 1.08 (1.06-1.11) 2%, 0.43	10 studies, 2871 deaths 1.08 (1.04-1.12) 0%, 0.46	30 studies, 17 098 events 1.05 (1.03-1.08) 51%, 0.01
Prospective cohort studies	12 studies, 10 840 deaths 1.07 (1.02-1.12) 40%, 0.07	8 studies, 3932 deaths 1.15 (1.04-1.27) 50%, 0.06	9 studies, 6798 events 1.05 (1.02-1.09) 0%, 0.67
Retrospective cohort studies	20 studies, 5199 deaths 1.06 (1.00-1.12) 67%, <0.001	9 studies, 3336 deaths 1.08 (1.00-1.18) 69%, 0.001	22 studies, 5044 events 1.04 (0.98-1.11) 62%, <0.001 *P* meta-regression .67
Follow-up of cases from case-control studies	5 studies, 1565 deaths 1.16 (1.07-1.26) 27%, 0.25	4 studies, 775 deaths 1.16 (0.99-1.35) 69%, 0.02	—
Population-based studies/ Follow-up of cases from a noncancer cohort	2 studies, 1622 deaths 1.04 (0.91-1.18) 84%, 0.012	3 studies, 547 deaths 1.10 (1.02-1.19) 0%, 0.97	—
Pooled analyses	3 studies (1 publication), 2212 deaths 1.02 (0.97-1.07) *P* meta-regression .43	3 studies (1 publication), 1131 deaths 1.00 (0.94-1.07) *P* meta-regression .91	—
Exposure time[b]			
Before chemotherapy	40 studies, 22 641 deaths 1.06 (1.03-1.09) 56%, <0.001	24 studies, 8213 deaths 1.09 (1.04-1.15) 61%, 0.001	40 studies, 21 643 events 1.06 (1.03-1.08) 52%, <0.001
During chemotherapy	2 studies, 723 deaths 1.16 (0.99-1.37) 68%, 0.08	—	—
After chemotherapy	6 studies, 3345 deaths 1.04 (0.96-1.12) 63%, 0.05	4 studies, 1072 deaths 1.12 (1.06-1.19) 0%, 0.93 *P* meta-regression .50	3 studies, 1572 events 1.05 (1.00-1.11) 0%, 0.69
Before hormonal therapy	2 studies, 991 deaths 1.16 (0.97-1.40) 60%, 0.11 *P* meta-regression .41		7 studies, 2375 events 1.02 (0.89-1.17) 86%, 0.001 *P* meta-regression .50
Treatment period			
≤2000	16 studies, 11 045 deaths 1.09 (1.05-1.12) 43%, 0.05	12 studies, 2956 deaths 1.18 (1.08-1.28) 55%, 0.02	17 studies, 13 519 events 1.05 (1.02-1.08) 33%, 0.10

TABLE 3 (Continued)

Subgroup by study characteristics[a]	All-cause mortality Summary RR (95% CI) I^2, *P* heterogeneity	Breast cancer mortality Summary RR (95% CI) I^2, *P* heterogeneity	Breast cancer recurrence Summary RR (95% CI) I^2, *P* heterogeneity
>2000	16 studies, 4761 deaths 1.08 (1.01-1.14) 66%, <0.001 *P* meta-regression .63	7 studies, 2555 deaths 1.08 (0.98-1.18) 74%, 0.01 *P* meta-regression .28	16 studies, 4041 events 1.09 (1.03-1.16) 41%, 0.04 *P* meta-regression .10
≤2005	26 studies, 15 404 deaths 1.08 (1.06-1.11) 21%, 0.19	16 studies, 4487 deaths 1.14 (1.08-1.21) 43%, 0.05	27 studies, 19 817 events 1.05 (1.03-1.07) 23%, 0.16
>2005	2 studies, 154 deaths 0.98 (0.87-1.11) 0%, 0.71 *P* meta-regression .20	—	3 studies, 365 events 0.97 (0.86-1.09) 0%, 0.78 *P* meta-regression .23
Length of follow-up			
≤5 years	13 studies, 2820 deaths 1.07 (1.00-1.14) 35%, 0.12	5 studies, 1254 deaths 1.14 (0.97-1.34) 57%, 0.05	19 studies, 4326 events 1.02 (0.95-1.10) 62%, 0.002
5-10 years	35 studies, 20 706 deaths 1.07 (1.03-1.10) 65%, <0.001	21 studies, 9478 deaths 1.11 (1.06-1.16) 67%, <0.001	30 studies, 16 409 events 1.06 (1.03-1.09) 57%, <0.001
>10 years	12 studies, 8123 deaths 1.09 (1.04-1.13) 45%, 0.06 *P* meta-regression .91	10 studies, 2750 deaths 1.08 (1.01-1.15) 50%, 0.07 *P* meta-regression .87	8 studies, 6983 events 1.05 (1.04-1.07) 0%, 0.65 *P* meta-regression .65
Loss to follow-up			
Complete/<10% loss	18 studies, 7171 deaths 1.05 (1.00-1.11) 64%, <0.001	10 studies, 3676 deaths 1.11 (1.03-1.19) 70%, <0.001	17 studies, 5944 events 1.08 (1.03-1.13) 41%, 0.04
≥10% loss	1 study, 189 deaths 1.38 (1.10-1.73)	2 studies, 137 deaths 1.08 (0.56-2.09) 83%, 0.02	2 studies, 329 events 1.14 (0.82-1.58) 55%, 0.14
No description	45 studies, 25 147 deaths 1.08 (1.05–1.10) 42%, 0.005 *P* meta-regression .10	27 studies, 10 293 deaths 1.09 (1.05-1.13) 40%, 0.04 *P* meta-regression .96	44 studies, 23 476 events 1.04 (1.02-1.07) 57%, <0.001 *P* meta-regression .20
Number of events			
<100	5 studies, 329 deaths 1.06 (0.96-1.17) 0%, 0.75	4 studies, 211 deaths 1.25 (1.01-1.56) 24%, 0.27	5 studies, 364 events 0.92 (0.74-1.15) 61%, 0.04
100-500	30 studies, 7759 deaths 1.09 (1.05-1.14) 50%, 0.001	16 studies, 3425 deaths 1.15 (1.09-1.21) 43%, 0.04	23 studies, 5971 events 1.09 (1.04-1.15) 35%, 0.06
>500	22 studies, 24 419 deaths 1.06 (1.03-1.09) 63%, <0.001 *P* meta-regression .61	18 studies, 10 470 deaths 1.05 (1.01-1.09) 58%, 0.008 *P* meta-regression .04	28 studies, 23 414 events 1.04 (1.02-1.07) 64%, <0.001 *P* meta-regression .21
BMI assessment			
Measured	23 studies, 12 539 deaths 1.07 (1.03-1.10) 54%, 0.002	9 studies, 1719 deaths 1.08 (0.99-1.18) 66%, 0.01	25 studies, 13 911 events 1.04 (1.01-1.08) 45%, 0.02
Self-reported	9 studies, 3710 deaths 1.08 (1.01-1.16) 58%, 0.02	10 studies, 2050 deaths 1.14 (1.08-1.20) 11%, 0.34	5 studies, 1048 events 1.09 (1.01-1.19) 21%, 0.28
From records	22 studies, 11 879 deaths 1.07 (1.03-1.11) 53%, 0.003	14 studies, 8582 deaths 1.10 (1.04-1.16) 59%, 0.002	25 studies, 10 948 events 1.04 (1.00-1.08) 62%, <0.001

(Continues)

TABLE 3 (Continued)

Subgroup by study characteristics[a]	All-cause mortality Summary RR (95% CI) I^2, *P* heterogeneity	Breast cancer mortality Summary RR (95% CI) I^2, *P* heterogeneity	Breast cancer recurrence Summary RR (95% CI) I^2, *P* heterogeneity
	P meta-regression .48	*P* meta-regression .44	*P* meta-regression .32
Covariate adjustment			
Age, disease, treatment, comorbidity, smoking, alcohol or physical activity	6 studies, 4030 deaths 1.02 (0.97-1.08) 53%, 0.09	5 studies, 1632 deaths 1.06 (0.98-1.14) 49%, 0.14	-
Age, disease, treatment, comorbidity or smoking	10 studies, 4727 deaths 1.11 (1.06-1.17) 26%, 0.21	8 studies, 1818 deaths 1.13 (1.04-1.24) 38%, 0.14	6 studies, 4422 events 1.06 (1.02-1.10) 0%, 0.90
Age, disease, treatment	30 studies, 12 336 deaths 1.07 (1.04-1.11) 32%, 0.07	16 studies, 7830 deaths 1.09 (1.04-1.14) 55%, 0.01	38 studies, 12 754 events 1.06 (1.02-1.10) 68%, <0.001
Not adjusted for age, disease characteristics, or treatment	18 studies, 11 414 deaths 1.06 (1.02-1.11) 70%, <0.001 *P* meta-regression .31	10 studies, 2826 deaths 1.12 (1.00-1.24) 69%, 0.001 *P* meta-regression .84	19 studies, 12 573 events 1.05 (1.02-1.08) 24%, 0.16 *P* meta-regression .93

Abbreviations: CI, Confidence interval; RR, relative risk.

[a]Results not shown for the strata with only one study or the few studies with unknown information, except for loss to follow-up that was mostly not described in the studies.

[b]Exposure time relative to cancer treatment was defined according to when the exposure assessment was conducted in the studies. Some study participants might not have received the treatment.

Five[112,143,151,207,255] out of six studies reported higher breast cancer recurrence with higher waist circumference[72,112,143,151,207,255] (Hazard ratios for the highest vs lowest category ranged from 1.18 to 1.76; Figure S15). No clear trend of association with breast cancer recurrence was observed for waist-to-hip ratio (two studies and four publications).[42,55,112,214]

3.4 | Postdiagnosis weight and BMI change

One weight loss intervention trial, of 338 postmenopausal, stage I-IIIa, hormone receptor-positive breast cancer survivors receiving adjuvant letrozole and with BMI at least 24 kg/m^2, was identified.[256] The results suggested improved survival (but the CIs were wide) in women randomized into the 24-month lifestyle intervention group compared with the education group (HRs 0.71, 95% CI: 0.41-1.24 for disease-free survival; 0.86, 0.35-2.14 for overall survival; 52 breast cancer events, 19 deaths, 8 years median follow-up). Weight loss in the intervention group was not sustainable (−5.5% vs −0.6% at 12 months; −3.7% vs −0.4% at 24 months; −2.0% vs −1.6% at 36 months). Additional landmark analysis of weight loss up to 24 months in disease-free participants showed attenuated results.[256]

In observational studies, postdiagnosis weight or BMI change were evaluated for the timeframes from before diagnosis to one or more years after diagnosis (pre- to postdiagnosis; 10[27,39,42,50-52,55,100,107,146] and 2[178,225] publications, respectively), for any period postdiagnosis (7[120,132,138,149,172,218,240] and 1[211] publications, respectively), or specifically during cancer treatment (5[39,147,191,204,257] and 7[84,132,160,177,200,236,254] publications, respectively), and these exposures were separately reviewed.

Categorical meta-analyses of percentage weight change from before to after diagnosis were possible in seven studies reporting results on all-cause and breast cancer-specific mortality (three publications, 2784 total deaths, 1752 breast cancer deaths),[50,52,107] but substantial between-study heterogeneity was present in some analyses. There was a suggestion that weight loss (unknown causes) across the investigated timeframes, was associated with higher all-cause mortality compared with stable weight (RRs: 1.15-5.29; Figures S16-S18).

Meta-analysis was not possible for BMI change. There was a suggestion that, compared with stable BMI, pre- to postdiagnosis BMI gain[178,225] was associated with higher all-cause mortality, breast cancer-specific mortality and breast cancer recurrence, and that BMI gain after neoadjuvant chemotherapy was associated with higher all-cause mortality among nonmetastatic survivors.[177,236] Only two studies each reported results (Figure S19).

No clear trend of association was observed for other investigated postdiagnosis changes of weight or BMI and breast cancer outcomes (Figures S16-S20).

3.5 | Sensitivity analyses and tests of publication bias

The overall summary RR estimates remained materially unchanged in leave-one-out sensitivity analyses. There was evidence of small study effects in the analysis of BMI and breast cancer-specific mortality

(Egger $P = .001$; Figure S21), with the average positive associations being stronger in studies of fewer compared with more events (Table 3). No evidence of publication bias was detected in analyses of other pre-specified outcomes (Egger P values ≥.19).

3.6 | Evidence grading

Table 1 shows the summary of findings and the corresponding evidence grades (Table S2).

The evidence on body fatness (BMI, waist circumference, waist-to-hip ratio) and all-cause mortality, breast cancer-specific mortality and second primary breast cancer (BMI only) was substantial, consistent in general and across different study designs and populations and showed evidence of a dose-response relationship, which was unlikely to be caused by chance or bias. This evidence was graded as strong (subgrade: probable), but not convincing, as more supporting evidence from RCTs is needed.

The evidence for body fatness and breast cancer recurrence was limited in quality relating to outcome assessment but suggestive of a positive dose-response relationship. The evidence suggesting an increased risk of nonbreast cancer-related mortality (BMI only) and cardiovascular mortality (BMI only) with greater body fatness was also limited suggestive.

The evidence on weight or BMI change was sparse and inconsistent and was limited in quality relating to exposure assessment and no conclusions could be made.

4 | DISCUSSION

The epidemiologic evidence on body fatness, weight change and breast cancer prognosis was systematically synthesized and independently evaluated. The estimated increase in risk per 5 kg/m^2 higher postdiagnosis BMI was 7% for all-cause mortality, 10% for breast cancer-specific mortality and 14% for second primary breast cancer. There was high, partially explained, between-study heterogeneity, but the positive associations were generally consistent across several study and disease subgroups. However, most subgroups included a low number of studies and will require further analyses in the future.

Plausible biological mechanisms underpinning the observed associations of increased body fatness with poorer survival have been widely studied.[414-417] Increased conversion of androgens to oestrogens by aromatase in adipose fat, decreased levels of sex-hormone binding globulin and the resulting increased circulating oestrogen levels may drive breast cancer progression in postmenopausal women with obesity.[418] Other potential mediators include insulin resistance and associated increased insulin levels[419]; chronic sub-clinical inflammation[420]; and altered adipokine levels,[421] including increased leptin that is pro-inflammatory and decreased adiponectin and the consequent reduced anti-inflammatory and insulin-sensitising effects.[422] These inter-connected signaling pathways could promote tumor growth and proliferation in women with obesity. In the present review, there was evidence that the association with breast cancer recurrence were, on average, inverse among women with metastatic disease but positive among women with early-stage diseases. The results may reflect disease characteristics (tumor biology and treatment responses) rather than host factors (obesity and its metabolic consequences) may have greater impact on recurrence and survival in these distinctive survivors. Further studies are needed to elucidate such findings.

The present nonlinear analysis of postdiagnosis BMI and all-cause mortality revealed a J-shaped relationship suggesting a more favorable survival in women of high normal to low overweight (24-26 kg/m^2) compared with women of low normal weight (arbitrary chosen at 20 kg/m^2). This observation relates somewhat to the phenomenon of the "obesity paradox" that has been reported in other cancer patients.[423] The exact causes are unclear but could include metabolic advantage, collider stratification bias (selection bias), confounding and/or reverse causation bias.[424] In addition, BMI does not reflect fat distribution and cannot distinguish lean from fat mass.[425,426] Analyses conducted for waist circumference and waist-to-hip ratio in the present review showed positive associations with all-cause and breast cancer-specific mortality, which may be independent of BMI. Sarcopenia and sarcopenic obesity may also be independent prognostic factors for breast cancer,[427] but further investigations are needed to study in more detail associations with body shape and composition.[428]

Taken together, the evidence was graded as strong (subgrade: probable) for body fatness and all-cause mortality, breast cancer-specific mortality and second primary breast cancer. The evidence for BMI and higher risk of breast cancer recurrence was graded as limited-suggestive since the outcomes were inconsistently defined across the studies,[429] and could be misclassified and/or incompletely ascertained in observational studies that used participants' reported or registry record linkage data.[430,431] The evidence for BMI and higher risks of nonbreast cancer-related mortality and cardiovascular mortality was also graded as limited-suggestive. There was a paucity of data on cardiovascular mortality, despite cardiovascular deaths being the most common cause of nonbreast cancer deaths in breast cancer patients,[432,433] and high BMI may increase cardiovascular events in general.[434] More research is needed to investigate these important outcomes.

Relatively few numbers of studies investigated weight or BMI change and the results were substantially heterogeneous. Weight loss after cancer diagnosis may be associated with higher all-cause mortality, but the intentionality of weight loss was unclear and could be related to cancer cachexia.[435] In the pooling project, the positive association with large weight loss was only restricted to the under or normal weight individuals, those with comorbidities, and who ever smoked,[52] hence the overall results could be affected by reverse causation. In addition, we found no apparent associations between weight or BMI gain and breast cancer outcomes across the timeframes, unlike a recent published meta-analysis that reported negative prognostic impact with large weight gain overall.[436] The association may be distorted, as chemotherapy may cause weight gain particularly in patients treated with older regimens that often incorporated high doses of corticosteroids.[437] The evidence was judged as limited-no conclusion.

We only identified one small weight loss intervention trial publishing results on survival outcomes, which suggested beneficial effects of intervention through diet, physical activity and behavioral change compared with education.[256] Whether sustainable, intentional weight loss can reverse the adverse pathological sequelae and improve survival outcomes in breast cancer patients with overweight and obesity requires elucidation. Findings on the combined influence of body fatness and physical activity could provide important lifestyle and cancer care information.

The substantial body of evidence (226 studies with over 456 000 women) accumulated over the years was comprehensively and systematically synthesized, and independently graded using standardized criteria. All postdiagnosis data were pooled, and subgroup analyses were conducted by timeframe relative to cancer treatment to better account for any influence from treatment on body measurements. Other subgroup analyses were conducted, however, individual studies may not report enough, comparable information required for inclusion in a dose-response meta-analysis. For the analyses by breast cancer subtype, the low numbers of studies, coupled with the low numbers of the less common breast cancers, that were differently assessed and classified in the studies, had hindered definitive conclusions on these associations. As shown, recent published meta-analyses with largely the same included studies reported conflicting results,[436,438,439] suggesting further investigation in studies using comparable classification is warranted.

Several limitations in relation to the evidence require discussion. First, survival benefit may present in studies that recruited participants who were well enough to survive the cancer years after diagnosis. Second, most studies did not have repeated body measurements to account for postdiagnosis weight change[440,441] or changes in muscle and fat mass[442] perhaps because of chemotherapy or changes in lifestyle or hormonal metabolism.[443] Third, reverse causation because of undetected disease outcome that leads to changes in exposure was possible, but most studies included only early stage (I-III) breast cancer survivors, who on average showed positive associations that were not observed among metastatic breast cancer survivors in the present subgroup meta-analyses across the outcomes. Fourth, uncontrolled or residual confounding, from lifestyle factors for which information were often missing, tumor stage and treatment that could lack details and pre-diagnosis body fatness that may drive the development of aggressive tumors,[444] was possible. However, studies adjusted at least for age, tumor stage, cancer treatment, and either comorbidities or smoking, on average, showed positive associations. Consistent positive associations were also observed among the secondary analysis of clinical trials[45,48,54,59,63,64,68,70,88,102-104,106,116,120,121,123,147,159,161,162,164,181,191,193,199,203,211,221,222,238,252,253,283] which were expected to have better treatment protocols and management. The evidence of greater body fatness causing increased mortality was unlikely to be caused solely by chance or bias, and was graded as strong probable evidence. To reach the strong convincing grade, more definitive evidence from RCTs (body composition, weight control or weight loss trials[445]) is needed.

The present review supports the advice for women who have completed primary treatment for breast cancer to follow the WCRF/AICR Cancer Prevention Recommendations to eat a healthy diet, be physically active and maintain a healthy weight if it fits with the specific medical advice given by their cancer management team.[5] Adherence to such lifestyle recommendations, in line with the recently released American Cancer Society Guideline on Diet and Activity for Cancer Survivors 2022,[446] has shown to lower all-cause mortality.[447]

Continual research effort is needed to inform whether specific recommendations are needed for different breast cancer survivors.

5 | CONCLUSIONS

There was strong probable evidence that higher postdiagnosis body fatness increases risks of all-cause mortality, breast cancer-specific mortality and second primary breast cancer in women diagnosed with breast cancer. The evidence for breast cancer recurrence, nonbreast cancer-related mortality and cardiovascular mortality was limited suggestive. For postdiagnosis weight or BMI change, the evidence was limited-no conclusion. Intervention trials, well-designed observational studies and biological mechanistic studies in diverse populations are needed to elucidate the impact of body composition and distribution and their changes on outcomes across the cancer continuum.

AUTHOR CONTRIBUTIONS

Konstantinos K. Tsilidis and Doris S. M. Chan are co-principal investigators of CUP Global at Imperial College London. Konstantinos K. Tsilidis was part of the Expert Panel but was not involved with judging the evidence after becoming a co-principal investigator of CUP Global. Teresa Norat and Doris S. M. Chan wrote the protocol based on the advice from the Protocol Expertise Group and implemented the study with Konstantinos K. Tsilidis. Doris S. M. Chan and Neesha Nanu did the literature search. Rita Vieira, Leila Abar, Katia Balducci, Margarita Cariolou and Neesha Nanu did the study selections and data extraction. Nerea Becerra-Tomas did the study selections, data extraction and checked the data. Doris S. M. Chan and Rita Vieira checked, analyzed and interpreted the data. Dagfinn Aune and Georgios Markozannes were CUP Global team members who revised the manuscript. Darren C. Greenwood was statistical adviser. Anne McTiernan (AMcT), Steven K. Clinton (SC), Edward L. Giovannucci (EG), Ellen Kampman (EK), Alan A. Jackson (AJ), Konstantinos K. Tsilidis (KT), Marc J. Gunter (MG) and Vivien Lund (VL) (lay member) were the Expert Panel members who provided judgments on the evidence and advised on the interpretation of the review. Elio Riboli and Amanda J. Cross were Expert Panel observers. Kate Allen, Nigel T. Brockton, Helen Croker, Daphne Katsikioti, Deirdre McGinley-Gieser, Panagiota Mitrou and Martin Wiseman were the CUP Global Secretariat members who provided overall coordination for the work and convened and facilitated discussions with the Expert Panel.

Doris S. M. Chan drafted the original manuscript. All authors reviewed and provided comments on the manuscript. Doris S. M. Chan is the guarantor and has full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in our study. Data sources and handling of these data are described in the Materials and Methods section. Further details are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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