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REVIEW ARTICLE

World Cancer Research Fund International: Continuous Update Project—systematic literature review and meta-analysis of observational cohort studies on physical activity, sedentary behavior, adiposity, and weight change and breast cancer risk

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Abstract

Purpose The purpose of the present study was to systematically review the complex associations between energy balance-related factors and breast cancer risk, for which previous evidence has suggested different associations in the life course of women and by hormone receptor (HR) status of the tumor.

Methods Relevant publications on adulthood physical activity, sedentary behavior, body mass index (BMI), waist and hip circumferences, waist-to-hip ratio, and weight change and pre- and postmenopausal breast cancer risk were identified in PubMed up to 30 April 2017. Random-effects meta-analyses were conducted to summarize the relative risks across studies.

Results One hundred and twenty-six observational cohort studies comprising over 22,900 premenopausal and 103,000 postmenopausal breast cancer cases were meta-analyzed. Higher physical activity was inversely associated with both pre- and postmenopausal breast cancers, whereas increased sitting time was positively associated with postmenopausal breast cancer. Although higher early adult BMI (ages 18–30 years) was inversely associated with pre- and postmenopausal breast cancers, adult weight gain and greater body adiposity increased breast cancer risk in postmenopausal women, and the increased risk was evident for HR+ but not HR− breast cancers, and among never but not current users of postmenopausal hormones. The evidence was less consistent in premenopausal women. There were no associations with adult weight gain, inverse associations with adult BMI (study baseline) and hip circumference, and non-significant associations with waist circumference and waist-to-hip ratio that were reverted to positive associations on average in studies accounting for BMI. No significant associations were observed for HR-defined premenopausal breast cancers.

Conclusion Better understanding on the impact of these factors on pre- and postmenopausal breast cancers and their subtypes along the life course is needed.

Keywords Systematic literature review · Breast cancer · Life course · Adiposity · Weight change · Physical activity

Introduction

Globally, breast cancer is the most frequent cancer and the leading cause of cancer death in women. There were an estimated 2.09 million incident cases and 0.63 million deaths from breast cancer worldwide in 2018 [1], which imposes

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a considerable burden on public health. While mammography screening reduces breast cancer mortality by up to 40 percent [2], cancer prevention via lifestyle modifications is clearly needed [3]. Overweight and obesity—globally prevalent conditions [4, 5]—manifested by chronic excessive energy intake and inadequate energy expenditure through low physical activity and increased sedentary behavior [6] could be one such target. Physical activity is also an important focus, as it may influence breast cancer risk through mechanisms in addition to body weight modulation [7].

The Third Expert Report published by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concluded that there is strong evidence that vigorous physical activity protects against premenopausal breast cancer, moderate or vigorous physical activity protects against postmenopausal breast cancer, and greater body fatness and weight gain in adult life causes postmenopausal breast cancer (https://www.wcrf.org/dietandcancer) [8]. These conclusions supported the recommendations for cancer prevention which promote healthy body weight (World Health Organisation definition: 18.5 to 24.9 kg/m^2) and adequate energy balance throughout life (be physically active, eat a diet rich in wholegrains, vegetables, fruit and beans, limit consumption of 'fast foods' and other processed foods high in fat, starches or sugars, and sugar sweetened drinks). Previous studies have shown that adherence to the 2007 WCRF/AICR recommendations [9] is associated with reduced breast cancer risk [10–17], breast cancer mortality [18] and total mortality [19], and improved cancer survival [20]; signifying the importance of healthy lifestyles.

As part of the on-going WCRF International Continuous Update Project (CUP) [21], we conducted a comprehensive systematic review and meta-analysis of the associations between adulthood physical activity, sedentary behavior, body mass index (BMI), waist and hip circumferences, waist-to-hip ratio, and weight change and the risk of overall and estrogen receptor (ER) and/or progesterone receptor (PR)-defined pre- and postmenopausal breast cancer, for which previous evidence has suggested complex differential associations [22–24]. These data contributed to the scientific evidence for the development of cancer prevention recommendations in the WCRF/AICR Third Expert Report [8]. Here, we describe the current knowledge and our findings.

Materials and methods

Full details of the methods used in the present review are available online in the supplementary material.

Literature search

Relevant publications were searched in PubMed up to 30th April 2017, using a tested search strategy with no language restriction. Reference lists of related articles were screened.

Study selection

Inclusion criteria were (1) randomized controlled trials, cohort studies, case–cohort studies, case–control studies within a cohort, or pooled analyses of individual data from studies of these designs; (2) studies that investigated the associations of interest; and (3) studies reporting relative risk, hazard ratio, or odds ratio and its measure of variability.

The publication with more number of cases was selected from multiple publications of the same study or studies of overlapping populations. Pooled analyses that combined case–control studies with cohort studies were excluded [25, 26].

Data extraction

Study characteristics, participant characteristics, exposure factors and breast cancer outcomes, numbers of cases and non-cases per exposure category, relative risk estimates (RR) with their 95% confidence intervals (CI) or *p*-values, and covariate adjustment in the analysis were extracted into the CUP database.

Study quality evaluation

The risk of bias of the included studies was assessed for various aspects relating to menopausal status classification, exposure and outcome ascertainment, and confounding factors adjustment. Supplementary Table S1 shows the scoring criteria.

Statistical methods

The primary analysis was linear dose–response meta-analysis, conducted when at least three studies report the required information on an association. A summary RR was calculated using a random-effects model, which allows for possible variations of associations across the studies [27].

The procedures to pool the results from individual studies were in accordance with other published meta-analyses [28–31]. This involved the pooling of dose–response estimates that were either directly reported in the studies or calculated by us for the studies reporting RR estimates for at least three exposure levels using the generalized weighted least-squares regression model [32, 33]. In this method,

numbers of cases and non-cases or population at risk and exposure values (mean or midpoint of range) per category are needed. If the required information was not available, standard methods were used to impute these [34, 35]; if this could not be done, the study was excluded from the meta-analysis (insufficient data).

For physical activity (any domains) and adulthood weight loss, because the required data for dose–response trend estimation were not reported in most studies, random-effects categorical meta-analyses that compared the highest with the lowest level were also conducted.

Multivariable adjusted estimates were selected for the meta-analyses. Between-study heterogeneity was assessed by the Cochran Q test, and I^2 statistic [36], and potential heterogeneity sources were explored in pre-defined subgroup meta-analyses and univariate meta-regression analyses [37]. Small study bias such as publication bias was assessed by Egger's test and visual inspection of the funnel plots when there were more than ten studies [38]. Influence analysis was conducted by omitting each study in turn from the meta-analysis. Exploratory non-linear dose–response meta-analysis was conducted when there were five or more studies with at least four exposure categories, using restricted cubic spline regression with three knots [39, 40].

A two-tailed p-value of < 0.05 was considered as statistical significant, except for the p-value of < 0.10 in the generally low-powered Egger's test [38]. Statistical package Stata 13.1 (StataCorp, College Station, TX, USA) was used.

Results

Figure 1 shows the PRISMA flowchart. Overall, 142 publications from 126 observational cohort studies, comprising over 22,900 premenopausal and 103,000 postmenopausal breast cancer cases among 8.53 million women, mostly from North America and Europe, and some from Australia and New Zealand, China, Korea, and Japan were meta-analyzed [14, 41–181]. No randomized controlled trials were identified.

Figures 2, 3, 4, and 5 show the results of the meta-analyses. Supplementary materials: Table S2 is the list of studies included and excluded with exclusion reason from the meta-analyses, Table S3 shows the main characteristics of the included studies, Table S4 is the PRISMA checklist, Tables S5 to S17 show the results of the subgroup meta-analyses, and Figs. S1 to S52 are the graphical results of the analyses.

Physical activity and premenopausal breast cancer

Vigorous physical activity was statistically significantly inversely associated with premenopausal breast cancer risk when comparing the highest with the lowest level. The summary RR was 0.79 (95% CI 0.69–0.91), with low between-study heterogeneity ($I^2 = 6\%$, p heterogeneity $= 0.37$) (5 studies) (Fig. S1). The associations were inverse but not significant for total physical activity (recreational, household, occupational physical activity combined) (5 studies), recreational (12 studies), and occupational physical activity (8 studies). There was no association with walking (2 studies) (Figs. 2 and S2–S5).

The associations were not significantly different in the subgroup meta-analyses (p-values for meta-regression ≥ 0.10) (Tables S5 and S6). Dose–response meta-analyses were possible for vigorous and recreational physical activity (3 studies each). The results were not significant (Figs. 3 and S6–S7). In influence analyses, the association became non-significant for vigorous physical activity but remained unchanged for the other domains. There was no indication of small study bias (Egger's test $p = 0.89$).

Physical activity and postmenopausal breast cancer

Significant inverse associations for physical activity and postmenopausal breast cancer risk were observed across all domains in the highest versus the lowest meta-analyses, except for walking (Fig. 2). The summary RRs were 0.90 (95% CI 0.85–0.95; $I^2 = 0\%$, p heterogeneity $= 0.96$) (11 studies) for vigorous, 0.86 (0.78–0.94; $I^2 = 9\%$, p heterogeneity $= 0.35$) (6 studies) for total, 0.88 (0.82–0.94; $I^2 = 35\%$, p heterogeneity $= 0.06$) (21 studies) for recreational, 0.90 (0.85–0.96; $I^2 = 0\%$, p heterogeneity $= 0.89$) (9 studies) for occupational physical activity, and 0.95 (0.86–1.04; $I^2 = 0\%$, p heterogeneity $= 0.98$) (4 studies) for walking (Figs. S1–S5).

In the subgroup meta-analyses by BMI, recreational physical activity was non-significantly inversely associated with postmenopausal breast cancer among women of normal weight (summary RR 0.85, 95% CI 0.72–1.01) (5,946 cases), and weaker or no associations were observed among women who were overweight (0.95, 0.85–1.06) (3,548 cases) or obese (1.00, 0.86–1.15) (1,803 cases) (p for meta-regression $= 0.53$) (5 studies [67, 122, 128, 138, 160]) (Fig. S9). The inverse associations were more evident among postmenopausal hormone never users [56, 92, 128, 138, 139] than ever users [56, 92, 128, 138, 139, 164]; and for vigorous physical activity, stronger for postmenopausal ER− [110, 139] than ER+ [108, 110, 139, 141] breast cancers (Figs. S10–S13). Meta-analyses of the other subgroups mostly confirmed the inverse associations (p-values for meta-regression ≥ 0.05) (Tables S5–S7).

Limited numbers of studies could be included in the dose–response meta-analyses (Fig. 3). The summary RR was 0.98 (95% CI 0.97–0.99) per 10 metabolic equivalent of task (MET)-hour/week of recreational physical activity (6 studies). Non-significant associations of similar magnitude

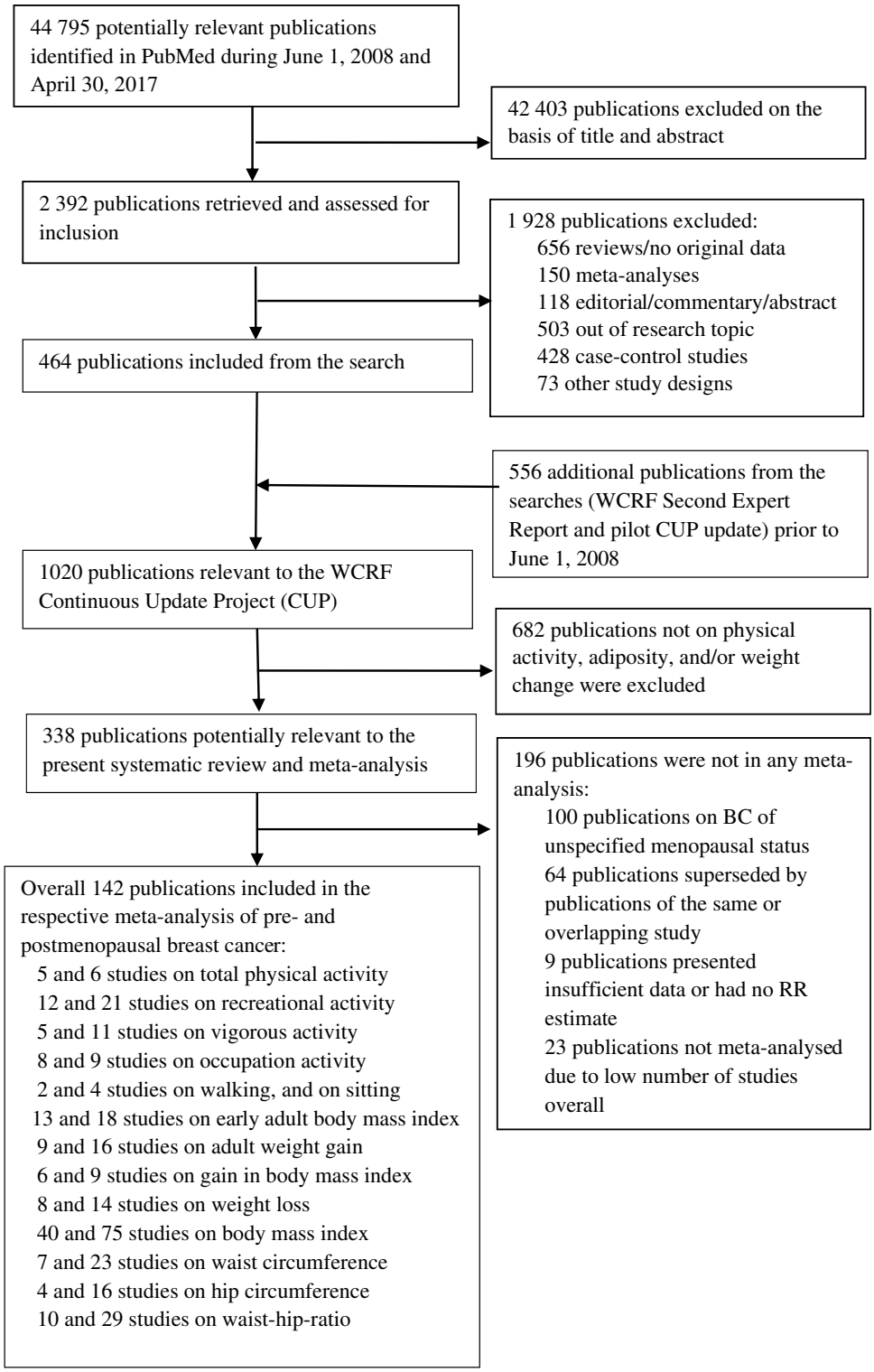

Fig. 1 PRISMA flowchart: studies of physical activity, sedentary behavior, adiposity, and weight change and breast cancer risk

were observed for total and vigorous physical activity (3 studies each) (Figs. S6-S8).

Non-linear analysis showed no departure from linearity ($p = 0.68$) (Fig. S14). The association with total physical activity became non-significant but the summary estimate was unchanged (RR for highest versus lowest level 0.86, 95% CI 0.74–1.00) when one study [160] was omitted from influence analysis. Small study bias was detected in the analysis of recreational physical activity (Egger's test $p = 0.01$). Smaller studies with a stronger than the average inverse association [42, 133, 155, 182] and one study with

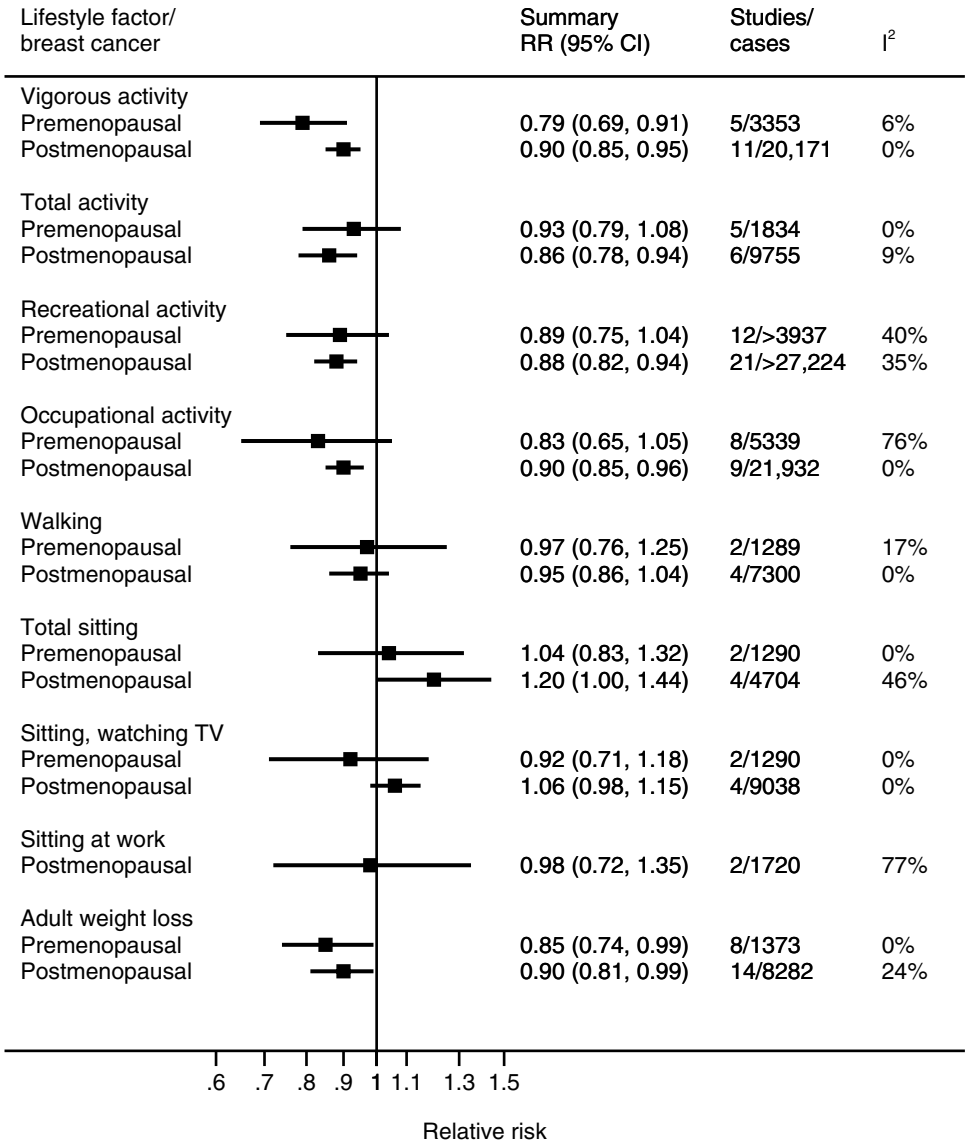

Fig. 2 Summary risk estimates of pre- and postmenopausal breast cancer for the highest versus the lowest categories of physical activity, adiposity, and weight change

a weaker association [160] may have driven the asymmetry in the funnel plot.

Sedentary behavior and premenopausal and postmenopausal breast cancer

Increased total sitting time was not associated with premenopausal breast cancer (2 studies) (Fig. 2). However, it was positively associated with postmenopausal breast cancer. The summary RRs were 1.20 (95% CI 1.00–1.44) for the highest versus the lowest level ($I^2 = 46\%$, p heterogeneity = 0.13) (4 studies) (Fig. 2) and 1.07 (95% CI 1.01–1.14) per 5 h/day ($I^2 = 0\%$, p heterogeneity = 0.55) (3 studies) (Fig. 3). The associations were not observed for sitting while watching television or at work (Figs. S15–S17) and did not persist in influence analyses.

Early adult body mass index and premenopausal and postmenopausal breast cancer

Greater early adult BMI (ages 18–30 years) was significantly inversely associated with premenopausal breast cancer. The summary RR was 0.86 (95% CI 0.78–0.96) per 5 kg/m^2 ($I^2 = 47\%$, p heterogeneity = 0.05) (13 studies) (Figs. 3 and S18).

Inverse association of similar magnitude was observed for postmenopausal breast cancer (0.81, 0.75–0.87) (Figs. 3 and S18). There was significant between-study heterogeneity ($I^2 = 50\%$, p heterogeneity = 0.01) (18 studies). Subgroup meta-analyses showed that studies that adjusted for adult BMI or weight gain [68, 87, 99, 136, 154, 162] on average observed a stronger inverse association compared with unadjusted studies [54, 56, 102, 111, 113, 130, 167, 170, 178], and may partially explain the observed heterogeneity

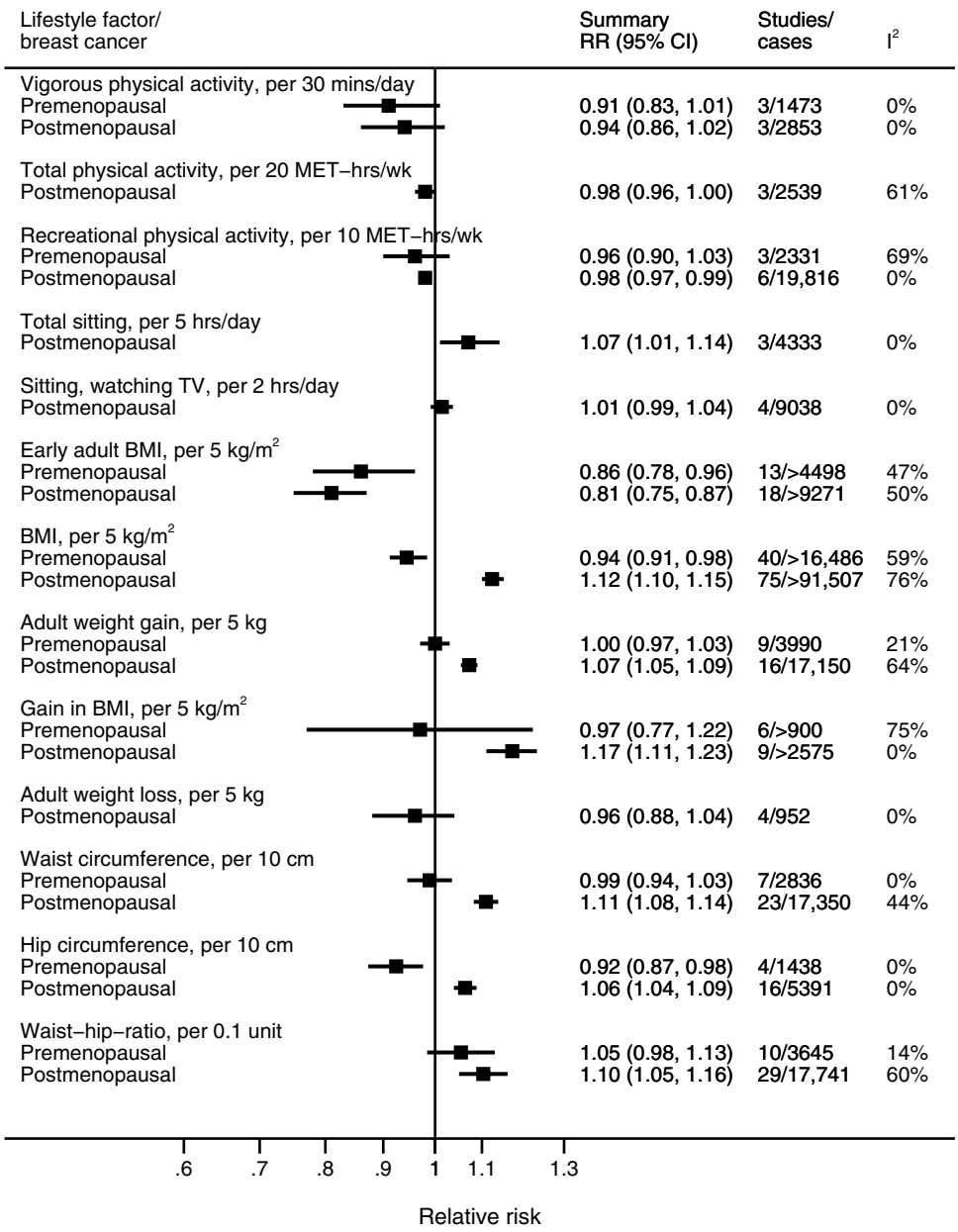

Fig. 3 Summary risk estimates of pre- and postmenopausal breast cancer per unit increment of physical activity, adiposity, and weight change

(p-value for meta-regression = 0.009). Inverse associations persisted across most other subgroups (p-values for meta-regression ≥ 0.08) (Table S8).

There were no indications of non-linear relationships ($p \geq 0.29$) (Figs. S19–S20) or small study bias ($p \geq 0.13$).

Body mass index and premenopausal breast cancer

Greater BMI (study baseline) was significantly inversely associated with premenopausal breast cancer. The summary RR was 0.94 (95% CI 0.91–0.98) per 5 kg/m^2 ($I^2 = 59\%$, p heterogeneity < 0.001) (40 studies) (Figs. 3 and S21).

The observed heterogeneity may partially be explained by study location (p for meta-regression = 0.004). On average, the association was significant and inverse in European studies [47, 49, 66, 97, 106, 114, 115, 119, 120, 143, 168, 169, 171, 173, 175], non-significant and inverse in North American studies [56, 57, 80, 136, 144, 159, 171, 180], but non-significant and positive in Asian studies (8 Japanese studies [174] and 1 Chinese study [112]) (Table S9).

BMI was not significantly associated with premenopausal ER+ and ER− breast cancers (5 studies, 4 publications [57, 65, 95, 127]) (Fig. S22).

There was no indication of departure from linearity ($p = 0.31$) (Fig. S23). The funnel plot showed asymmetry, probably driven by study heterogeneity ($p = 0.06$). BMI was not associated with premenopausal breast cancer mortality (36 studies, 2 publications [143, 179]) (Fig. S24).

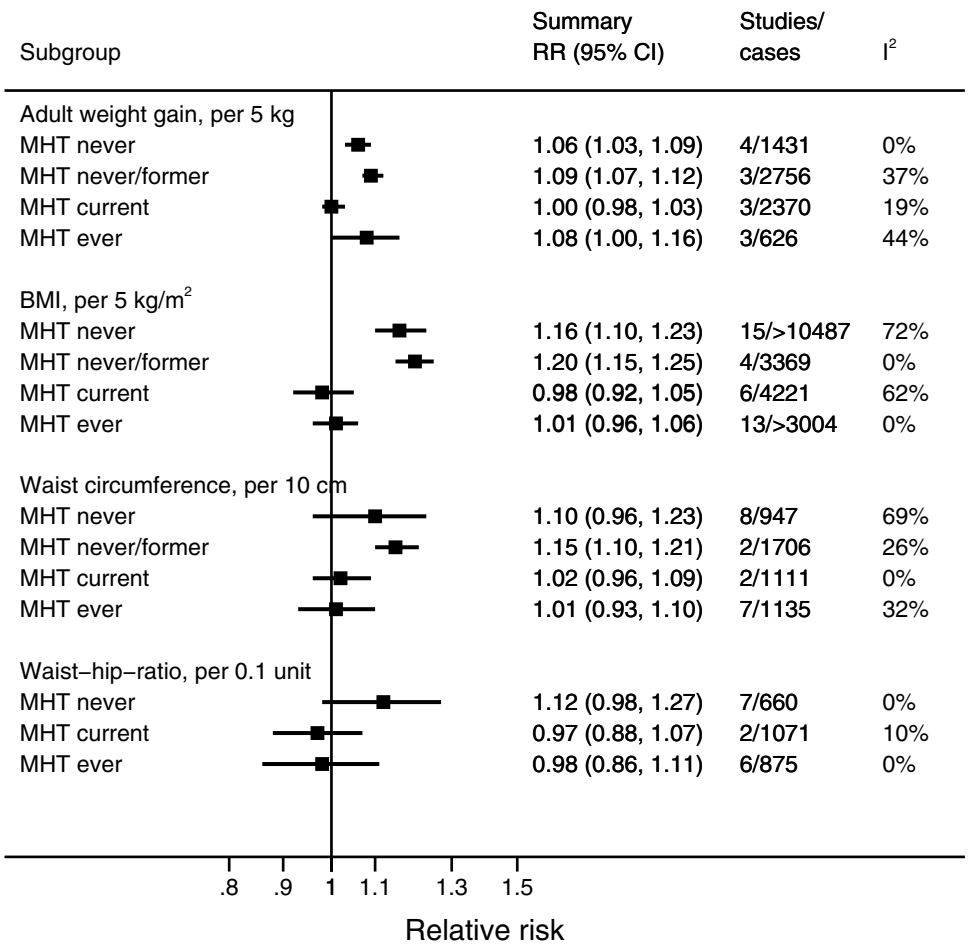

Fig. 4 Summary risk estimates of effect modification by postmenopausal hormone use in the associations of adiposity and weight change with postmenopausal breast cancer

Body mass index and postmenopausal breast cancer

Greater BMI was significantly positively associated with postmenopausal breast cancer. The summary RR was 1.12 (95% CI 1.10–1.15) per 5 kg/m^2 ($I^2 = 76\%$, p heterogeneity < 0.001) (75 studies) (Figs. 3 and S21).

Study location may partially explain between-study heterogeneity (p for meta-regression < 0.001). Asian studies [59, 86, 112, 158, 174] showed an average stronger positive association than studies from Europe [46, 47, 49, 63, 66, 72, 79, 88, 91, 96, 97, 115, 120, 125, 143, 153, 168, 169, 171, 172], North America [44, 51, 56, 57, 75, 80, 81, 98, 100, 101, 136, 152, 159, 167, 171, 178], and Australia and New Zealand [68, 135] (Table S9). Positive associations were evident among never [56, 72, 130, 136, 143, 162, 171, 178], former [178], and never/former [41, 75, 85, 106] postmenopausal hormone users but not current [41, 75, 85, 106, 177, 178] or ever [56, 72, 102, 130, 162, 171] postmenopausal hormone users (p for meta-regression = 0.002) (Figs. 4 and S25).

The associations were different between the HR subtypes, with positive associations observed for postmenopausal ER+ [57, 65, 82, 84, 95, 100, 102, 141, 154], PR+ [50, 95, 102, 154], and ER+PR+ [41, 55, 95, 102, 132, 136, 148, 156, 161, 177] breast cancers, and non-significant associations for ER− [57, 60, 65, 82, 95, 100, 102, 154], PR- [50, 95, 102, 154], ER−PR− [41, 55, 95, 102, 132, 136, 148, 156, 161, 177], ER+PR− [41, 55, 73, 102, 132, 156, 161], and ER−PR+ [73] breast cancers (Figs. 5 and S26–S27).

In non-linear analysis, the estimated RRs for women who were overweight (27.5 kg/m^2) and obese (32.5 kg/m^2) were 1.16 (95% CI 1.10–1.22) and 1.29 (1.19–1.39), respectively, compared with women who were normal weight (21.7 kg/m^2) ($p = 0.31$) (Fig. S28). Small study bias was detected ($p = 0.04$). Asymmetry in the funnel plot was driven by a few studies reporting stronger than the average positive association [79, 80, 86, 112, 158, 159, 174]. BMI was positively associated with postmenopausal breast cancer mortality (1.21, 1.15–1.28) (39 studies [48, 132, 140, 143, 179]) (Fig. S29).

Adult weight gain and BMI gain and premenopausal and postmenopausal breast cancer

Adult weight gain and BMI gain (from aged 18 years to study baseline) were not associated with premenopausal breast cancer (9 studies and 6 studies, respectively) (Figs. 3

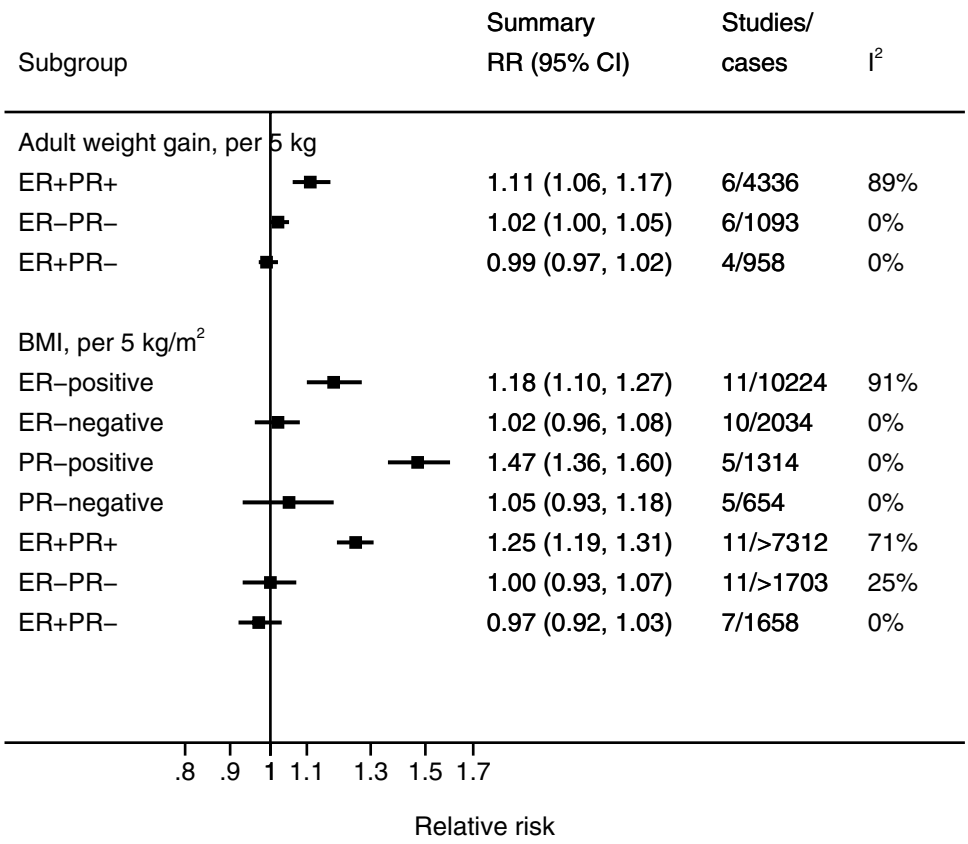

Fig. 5 Summary risk estimates of hormone receptor-defined postmenopausal breast cancer per unit increment of adiposity and weight change

and S30-S31). There was statistical evidence of non-linearity ($p = 0.03$), but no significant association was observed along the curve (Fig. S32).

Positive associations were observed for postmenopausal breast cancer. The summary RRs were 1.07 (95% CI 1.05–1.09) per 5 kg ($I^2 = 64\%$, p heterogeneity < 0.001) (16 studies) and 1.17 (1.11–1.23) per 5 kg/m^2 ($I^2 = 0\%$, p heterogeneity $= 0.81$) (9 studies) (Figs. 3 and S30–S31).

None of the subgroup analyses could clearly explain the observed heterogeneity (Tables S10 and S11). Asian studies [99, 133, 183] on average showed a stronger, but not significantly different, positive association than Australian [102], European [43, 107, 170], or American studies [41, 52, 56, 75, 77, 136, 142, 178, 181] (p for meta-regression $= 0.06$). Different associations by postmenopausal hormone use were observed (p for meta-regression $= 0.01$), but the status used in the studies overlapped (positive associations among never [56, 102, 136, 142], never/former [41, 75, 107], and ever users [56, 102, 142]; null association among current users [41, 75, 107]) (Figs. 4 and S33).

Adult weight gain was significantly positively associated with ER+ PR+ breast cancers [41, 55, 74, 102, 136, 150] but not with ER+ /PR− [41, 55, 102, 150] or ER-/PR- [41, 55, 74, 102, 136, 150] breast cancers in postmenopausal women (Figs. 5 and S34).

No deviation from linearity was detected ($p = 0.75$) (Fig. S35), but there was evidence of small study bias ($p = 0.04$). Asymmetry in the funnel plot was possibly driven by a small study [52] and Asian studies [99, 133] showing stronger positive associations.

Adult weight loss and BMI loss and premenopausal and postmenopausal breast cancer

Inverse associations were observed for both pre- and postmenopausal breast cancers when comparing any weight loss (of unknown intention, from aged 18 years to study baseline) with stable weight. The summary RRs were 0.85 (95% CI 0.74–0.99; $I^2 = 0\%$, p heterogeneity $= 0.93$) (8 studies) and 0.90 (0.81–0.99; $I^2 = 24\%$, p heterogeneity $= 0.20$) (14 studies), respectively (Figs. 2 and S36). There was no clear pattern of differences between the subgroups (Table S12). Dose–response meta-analysis was possible for postmenopausal breast cancer (4 studies). The result was not significant (Fig. S37). Results similar to the main findings were observed in influence analyses, but the statistical significance was lost. There was no evidence of small study bias (Egger's test $p = 0.26$).

Waist and hip circumferences, and waist-to-hip ratio and premenopausal breast cancer

Higher waist circumference was not associated with premenopausal breast cancer. The per 10-cm increase summary RR was 0.99 (95% CI 0.94–1.03; $I^2 = 0\%$, p heterogeneity = 0.88) (7 studies) (Fig. 3); however, in studies further adjusted for BMI (4 studies [89, 94, 106, 177]), there was an average positive association (1.15, 1.05–1.26) (Fig. S38).

For hip circumference, there was a significant inverse association (0.92, 0.87–0.98 per 10 cm; $I^2 = 0\%$, p heterogeneity = 0.50) (4 studies) (Fig. 3); but a non-significant association in BMI adjusted studies (1.05, 0.80–1.36) (3 studies [89, 94, 106]) (Fig. S39).

For waist-to-hip ratio, there was a non-significant association (1.05, 0.98–1.13 per 0.1 unit; $I^2 = 14\%$, p heterogeneity = 0.31) (10 studies) (Fig. 3); and a borderline positive association in BMI adjusted studies (1.14, 1.00–1.29) (7 studies [89, 94, 106, 112, 131, 159, 177]) (Fig. S40).

Results were similar across the subgroups (Tables S13–S15). Non-linear analyses showed no departure from linearity, but the 95% CIs were wide because of little data ($p \geq 0.07$) (Figs. S41–S43). There was no indication of small study bias ($p = 0.25$).

Waist and hip circumferences, and waist-to-hip ratio and postmenopausal breast cancer

Postmenopausal breast cancer risk was significantly positively associated with all adiposity measures evaluated. The summary RRs were 1.11 (95% CI 1.08–1.14; $I^2 = 44\%$, p heterogeneity = 0.04) per 10 cm of waist circumference (23 studies), 1.06 (1.04–1.09; $I^2 = 0\%$, p heterogeneity = 0.48) per 10 cm of hip circumference (16 studies), and 1.10 (1.05–1.16; $I^2 = 60\%$, p heterogeneity < 0.001) per 0.1 unit of waist-to-hip ratio (29 studies) (Fig. 3). In BMI adjusted studies, the association was attenuated for waist circumference (1.07, 1.01–1.13) (7 studies [79, 82, 94, 98, 106, 154, 177]), lost statistical significance for hip circumference (1.12, 0.95–1.32) (3 studies [79, 94, 106]), and waist-to-hip ratio (1.05, 0.98–1.13) (8 studies [79, 94, 106, 112, 131, 154, 159, 177]) (Figs. S44-S46).

The positive association was stronger in European [46, 79, 97, 145] and North American studies [41, 56, 76, 82, 94, 98, 101, 136] than Australian and New Zealand studies (10 studies, 1 publication [135]) (p for meta-regression = 0.04) (Table S13); and was more evident among never or former users [41, 56, 79, 82, 130, 136] than current or ever users [41, 56, 79, 130, 177] of postmenopausal hormones (p-values for meta-regression ≥ 0.06) (Figs. 4 and S47–S48). There were no indications of non-linear relationship (p-values ≥ 0.06) (Figs. S49–S52) or small study bias (p-values ≥ 0.25).

Quality of studies included in the meta-analyses

Most studies used record linkage to ascertain cancer cases and met the required quality aspects (Figs. S53–56), and were considered average to good quality. Higher or lower risk of bias studies on average did not found significantly different associations in the subgroup meta-analyses (Tables S5–S17).

Discussion

Summary of findings

The present systematic literature review and meta-analysis demonstrates the complex associations between adulthood energy balance-related factors and breast cancer risk in pre- and postmenopausal women.

Higher physical activity, in particular recreational physical activity, was associated with reduced risk of pre- and postmenopausal breast cancer, although there were less data on premenopausal women. The risk reduction was observed at high levels similar to the prolonged moderate physical activity of 45 to 60 min daily suggested for weight maintenance [184]. Physical activity may operate through obesity-related biological pathways or mechanisms that involve immunity and defense [7, 185], which could explain the observed inverse associations for both postmenopausal ER+ and ER− breast cancers. Strenuous physical activity before menarche may delay the onset of menstruation and increase anovulatory cycles in young women [186]. In the present meta-analysis, significant inverse association was observed among normal weight women. It is unclear if the lack of association in overweight or obese women is due to low number of women with the required physical activity level or if any independent effect of physical activity is masked by excessive body adiposity. Previously, the National Cancer Institute Cohort Consortium (35,178 breast cancer cases overall) reported inverse associations in women of BMI < 25 and ≥ 25 kg/m^2, with no effect modification [187]. Confirmation is needed in pre- and postmenopausal women. Sedentary behavior, represented by sitting time, was associated with an increased risk of postmenopausal breast cancer. Excessive sitting reduces overall energy expenditure and contributes to obesity [188, 189], but could also be an independent risk factor for breast cancer [190].

Higher early adult BMI (ages 18–30 years) was inversely associated with both pre- and postmenopausal breast cancers. The results corroborate with the inverse association published recently by the Premenopausal Breast Cancer Collaborative Group of 19 cohort studies [191] (5 studies are in common with the present meta-analysis [56, 113, 136, 175, 180]). The study also reported risk reductions for ER+ and

ER− breast cancers in premenopausal women [191], which are potentially driven by estrogen-induced early breast differentiation [192] and slower pubertal growth [193] that may reduce the susceptibility to carcinogens in the breast tissue of young girls with higher adiposity.

Weight loss was inversely associated with pre- and postmenopausal breast cancer. The results were not robust, and the intentionality of weight loss and potential weight regain were largely not known in the studies. The present findings require further confirmations, although studies of stable weight loss and bariatric surgery have shown postmenopausal breast cancer risk reduction [70, 194, 195], and participants who lost weight or body fat in randomized controlled trials have demonstrated favorable changes in hormonal and metabolic profiles [196–198].

Weight gain (from aged 18 years to study baseline) and subsequent excessive body adiposity (total adiposity, assessed by BMI at study baseline; abdominal adiposity, assessed by waist circumference, and waist-to-hip ratio; and gluteo-femoral adiposity, assessed by hip circumference) consistently increased the risk of breast cancer in postmenopausal women. Non-linear analyses did not reveal any threshold, indicating any weight gain after early adult years may lead to increased risk. The associations were more evident for HR+ but not HR- postmenopausal breast cancers; and among never but not current users of postmenopausal hormones, probably because exogenous estrogens, a strong risk factor of postmenopausal breast cancer [199], have masked the effect of the hormones synthesized in adipose tissue. Recent publications reported largely supportive results. These included the different age-specific associations with baseline BMI for the risk of luminal-like and triple-negative breast cancers reported by the National Cancer Institute Cohort Consortium (9 cohorts) [200], and the strong positive associations between different adiposity measures and breast cancer risk in long-term postmenopausal women reported by the UK Biobank Prospective Cohort Study [201].

The evidence was less consistent in premenopausal women. In the present meta-analysis, we observed no association with adult weight gain, but weight gain between 40 and 50 years has been reported to increase premenopausal breast cancer risk [72]. Since middle age is a period when more fat is deposited viscerally [202], it is possible that timing, duration, as well as location of fat deposition are important factors for breast cancer development. Higher adult BMI (study baseline) was inversely associated with breast cancer risk in premenopausal women, although there was a lack of consistency across the study results. One possible explanation is the positive association observed in Asian studies [112, 174]. Asian women tend to be more prone to visceral fat accumulation than their Western counterparts [203], but further replication of the result is needed. In terms of abdominal obesity, we observed non-significant associations that were reverted to positive associations in studies accounting for total adiposity; since total and abdominal adiposity are highly correlated [41, 145, 159, 165], the suggested independent effect requires confirmation. There were no significant associations for HR-defined premenopausal breast cancers, but the meta-analyses included few studies.

Mechanistically, increased expression of aromatase in adipose tissue of postmenopausal women with obesity increases conversion of androgens to estrogens that induce tumor cell proliferation and inhibit apoptosis [204, 205]; whereas lowered concentrations of progesterone in premenopausal women with obesity mitigate estrogen-induced proliferation in breast epithelial cells [206], albeit inconsistent findings on progesterone and breast cancer [207–209]. Studies on gene expression patterns in breast tissue have shown that as body weight increases, there is increased breast cancer cell proliferation in postmenopausal women but decreased proliferation in premenopausal women [210]. Abdominal obesity is frequently associated with insulin resistance and hyperinsulinemia [211, 212]. Insulin and insulin-like growth factor-I are mitogenic. Insulin also inhibits sex hormone-binding globulin synthesis, leading to higher concentrations of free oestradiol [205]. Other proposed mechanisms that link obesity to breast cancer include increased concentrations of proinflammatory cytokines and leptin that induce aromatization and reduced concentrations of adiponectin that has anti-inflammatory and insulin-sensitizing ability [205, 213–215].

Our findings are generally in agreement with those of published umbrella reviews of the literature evidence on physical activity and adiposity with cancer risk [216–218], but are opposite to the results of Mendelian randomization (MR) studies. Recent publications from large-sized MR studies reported inverse associations with genetically predicted adiposity for the risk of breast cancer, overall [219] and in premenopausal [220–222] and postmenopausal women [220, 222], which were not shown in an earlier small study [47]. One possible explanation is that genetically predicted adiposity may be more closely related to early life adiposity than later life adiposity that is largely influenced by the environment. One MR study provided causal evidence that higher childhood adiposity reduces breast cancer risk [219].

Study limitations

Several limitations in the present review require discussion. There may be some level of misclassification of cancer as pre- or postmenopausal depending on whether the required information was taken at study baseline or cancer diagnosis; however, subgroup meta-analyses by timing of classification mostly did not show significantly different associations.

Premenopausal breast cancer studies that used baseline information on average found an inverse association with adult BMI, opposite to the positive association in postmenopausal studies.

The association with physical activity may have been underestimated due to measurement error, as frequency, intensity, and type of activity were poorly characterized in most studies. Attenuation of the associations due to regression dilution is possible as most studies had long follow-up (≥ 10 years) and collected information at baseline. Recall or other biases in weight change and weight at early age are also possible. While BMI—a practical measure of total adiposity—is predictive of health outcomes on a population level, it does not reflect fat distribution or differentiates lean from fat mass that varies across women of different age and ethnicity [223].

Data on pre- and postmenopausal hormone receptor-defined breast cancers were limited. Information on type of postmenopausal hormone use was not available for meta-analysis. A few studies did not report data sufficient for the meta-analysis [224–230]; nevertheless, most excluded studies reported concordant findings with the meta-analyses.

Strength of the study and future research

The present systematic literature review is extensive and comprehensive, in that all known existing scientific evidence from observational cohort studies—a design that is less prone to recall and selection biases than case–control studies [9]—on different domains of physical activity, sedentary behavior, adiposity measures, and weight change in different periods of adulthood in relation to breast cancer risk by menopausal status and hormone receptor subtype were summarized. Most meta-analyses comprised more than 900 breast cancer cases from at least three cohort studies that were of average to good quality.

With the accumulated evidence, we were able to explore the magnitude and the shape of the associations. Nevertheless, more longitudinal studies with repeated exposure assessments along the life course are needed, in women across all age range, and from different ethnic/racial groups who may have different risk patterns. Improved assessments for better quantification and characterization of exposure factors are needed, to evaluate their independent and joint effects on breast cancer development. Also, more studies are needed to clarify the different associations in molecular and clinical breast cancer subgroups. Randomized controlled trials, in particular weight loss trials and physical activity trials, are needed to provide definitive evidence for effective interventions to prevent breast cancer.

In conclusion, physical activity reduces breast cancer risk in both pre- and postmenopausal women, whereas factors reflecting energy imbalance influence the risk differently along the life course of the women. Although higher adiposity at early adulthood may reduce pre- and postmenopausal breast cancer risk, weight gain and excessive adiposity later in life increase the risk, consistently in postmenopausal women and evidently for HR+ but not for HR− postmenopausal breast cancers. Under precautionary principle, women should aim to be physically active (at least 150 min/week) and follow a lifestyle that leads to healthy body weight (BMI 18.5–24.9 kg/m^2) for breast cancer prevention. Only about 25% of the public recognize the link between obesity and cancer [231]. Therefore, collective effort—driven by public health policies [232]—is needed to promote healthy lifestyles for cancer prevention.

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Author contributions TN is the principal investigator of the Continuous Update Project at Imperial College London and wrote the protocol and implemented the study. RV and CS developed and managed the database for the Continuous Update Project. DSMC, RV, and LA did the literature search and study selections. DSMC, RV, LA, SV, NN, MC, DNR, JS, LA, RL, DA, and EP did the data extraction. DSMC checked, analyzed, and interpreted the data. DCG was statistical adviser. AMT and EVB were panel members of the Continuous Update Project and advised on the interpretation of the review. DSMC drafted the original manuscript and all authors revised the manuscript. DSMC 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.

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Compliance with ethical standards

Conflict of interest Teresa Norat, Doris S.M. Chan, Leila Abar; Margarita Cariolou, and Neesha Nanu are supported by the World Cancer Research Fund International. Anne McTiernan has received research grant from the Breast Cancer Research Foundation. Darren C. Greenwood and Elisa V. Bandera declare that they have no conflicts of interest.

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