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Linking Physical Activity to Breast Cancer Risk via the Insulin/Insulin-like Growth Factor Signaling System, Part 2

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Linking Physical Activity to Breast Cancer Risk via the Insulin/Insulin-like Growth Factor Signaling System, Part 2: The Effect of Insulin/Insulin-like Growth Factor Signaling on Breast Cancer Risk

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ABSTRACT

Perturbation of the insulin/insulin-like growth factor (IGF) signaling system is often cited as a mechanism driving breast cancer risk. A systematic review identified prospective cohort studies and Mendelian randomization studies that examined the effects of insulin/IGF signaling (IGF, their binding proteins (IGFBP), and markers of insulin resistance] on breast cancer risk. Meta-analyses generated effect estimates; risk of bias was assessed and the Grading of Recommendations Assessment, Development and Evaluation system applied to evaluate the overall quality of the evidence. Four Mendelian randomization and 19 prospective cohort studies met our inclusion criteria. Meta-analysis of cohort studies confirmed that higher IGF-1 increased risk of breast cancer; this finding was supported by the Mendelian randomization studies. IGFBP-3 did not affect breast cancer. Meta analyses for connecting-peptide and fasting insulin showed small risk increases, but confidence intervals were wide and crossed the null. The quality of evidence obtained ranged from 'very low' to 'moderate'. There were insufficient studies to examine other markers of insulin/IGF signaling. These findings do not strongly support the biological plausibility of the second part of the physical activity—insulin/IGF signaling system—breast cancer pathway. Robust conclusions cannot be drawn due to the dearth of high quality studies.

See related article by Swain et al., p. 2106

Introduction

Physical activity is associated with a reduced risk of breast cancer (1–3). However, the mechanisms on the causal pathway underlying the physical activity–breast cancer relationship are not well understood. Physical activity has been shown to decrease fasting insulin levels (4–6) and insulin/IGF signaling has been implicated in the development of a range of malignancies, including breast cancer (7–9). In healthy individuals, blood glucose levels are regulated by insulin but when this process is disrupted, either due to insulin resistance or inadequate production of insulin by the pancreas, glucose levels rise allowing adverse metabolic conditions to manifest. Elevated levels of both glucose and insulin have been implicated in breast cancer development (10–13). Blood glucose levels can be measured directly, or a 3 month average glucose level determined by measurement of glycated hemoglobin or hemoglobin A1c (HbA1c); a complex of glucose bound to hemoglobin, (a protein in red blood cells).

The insulin/insulin-like growth factor (IGF) signaling system consists of three ligands (insulin, IGF-1, IGF-2), six ligand binding proteins (IGFBP 1–6), and 2 transmembrane tyrosine kinase receptors, insulin receptor and type I IGF receptor (IGF-1R). Functional receptors exist as either homo- or hetero-dimers with both forms capable of transducing a signal. Insulin/IGF ligands circulate bound to IGFBPs; the most abundant of these being IGFBP-3 (14). In addition to facilitating transport, IGFBPs regulate ligand bioavailability. Breast cancer risk could be modulated by any component of the insulin/IGF signaling system.

Insulin is derived from proinsulin, cleavage of which gives rise to equimolar concentrations of insulin and connecting-peptide (C-peptide; ref. 15). While insulin is metabolized by the liver, C-peptide remains intact and therefore reflects the production of insulin by the pancreas (specifically the beta cells). Due to its longer half-life and increased stability in serum (15, 16), C-peptide is often measured as a marker of insulin in preference to measuring insulin directly. Insulin may affect cancer risk directly, through its mitogenic properties or by increasing growth-promoting signaling (12). It can also enhance activation of the IGF-1 system, which is involved in cell differentiation, proliferation, and apoptosis (17). Both IGF-1 and IGF-2 have been shown to stimulate proliferation of breast cancer cells prepared from excised tissue and established cell lines (13, 18–21). High levels of insulin have also been shown to suppress hepatic synthesis of sex hormone binding globulin (22), a glycoprotein which regulates the bioavailability of estrogens

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and androgens (23), hormones implicated in breast cancer development. The cross-talk between the insulin-IGF and steroid hormone signaling pathways is well established (24–32). We have recently published systematic reviews appraising the role of physical activity on sex hormone production (33) and the impact of these hormones on breast cancer risk (34).

The World Cancer Research Fund (WCRF) International and University of Bristol developed a causal evidence synthesis framework for conducting systematic reviews of biological mechanisms that may explain exposure–cancer associations (35, 36). We outlined this framework, and how the related Text Mining for Mechanism Prioritisation (TeMMPo) tool (35) was used to identify and prioritize biomarkers of the insulin signaling pathways in our protocol paper (37). The first part of our systematic review of the physical activity–insulin/IGF signaling system–breast cancer risk pathway examined the evidence for the effect of physical activity on insulin/IGF signaling (38). Here, we synthesize and appraise the evidence to determine whether the insulin/IGF signaling system (IGFs, their binding proteins and markers of insulin resistance) affects breast cancer risk in women.

Material and Methods

The methods used in this systematic review have been previously reported (37). The current review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (39) and has been registered on PROSPERO (CRD42020146736). In brief, systematic searches of Medline (Ovid) and Embase were performed up to March 2021. Search terminology is provided in Supplementary Table S1. Studies were eligible for inclusion if they were written in the English language, prospective cohort studies (including nested case–control and case–cohort studies) and Mendelian randomization studies, that examined associations of circulating IGF-1, IGF-2, IGFBP-1, IGFBP-3, insulin, C-peptide, fasting glucose, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), Homeostatic Model Assessment for Insulin Sensitivity (HOMA-S), HbA1c, or quantitative insulin-sensitivity check index (QUICKI) with breast cancer risk. Studies that included participants taking medication that could influence study outcomes, e.g., insulin, were excluded from this review. Similarly, studies including women taking oral contraceptives or hormone replacement therapy were excluded given that steroid hormone–insulin/IGF cross-talk may well give rise to confounding.

Following duplicate removal in EndNote X9 (Clarivate), two reviewers independently screened all titles, abstracts and full text papers for inclusion in the review using Covidence software (40). Where consensus on inclusion of a paper could not be met, a third investigator was consulted and a two-third majority determined the outcome. Data were extracted and entered into pre-piloted tables. Risk of bias in prospective cohort studies was assessed using the Risk of Bias in Non-randomized Studies-of Exposures (ROBINS-E) tool (41). Confounders such as body composition, alcohol intake, physical activity or smoking impacted the risk of bias. To rate the overall strength of the evidence for each biomarker of the insulin/IGF signaling system–breast cancer pathway, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used (42). Random effects meta-analyses were used to estimate breast cancer risk for women with the highest levels compared with the lowest of the reported categories of insulin/IGF signaling biomarkers. Where possible, subgroup analyses were performed to examine whether effect estimates differed between pre- and postmenopausal women. The 'drmeta' Stata package was used to perform a one-stage random-effects dose–response meta-analysis of summarized data using restricted cubic splines, to graphically represent the shape of associations for each biomarker of the insulin/IGF signaling system and breast cancer risk (43–45).

Sensitivity analyses excluded studies with serious overall risk of bias or moderate risk of bias for exposure classification (i.e., biomarker measurement). All effect estimates generated by the meta-analyses were presented as relative risks (RR; highest compared with the lowest level) and 95% confidence intervals (CI), although these have been derived from studies that present a mix of RR, ORs, and HRs. Where there were multiple publications based on a single cohort that examined the insulin/IGF signaling system biomarkers–breast cancer pathway, we extracted data from the publication with the greatest number of cases. All statistical analyses were performed using Stata version 16 (Stata Corporation, College Station, Texas).

Results

Search results

A PRISMA flow diagram (**Fig. 1**) provides details of the screening process for papers, the number excluded (and reasons for exclusion) at each stage, for selected insulin/IGF signaling system biomarkers. Of the 2,504 results identified by systematic searches, 23 publications met our inclusion criteria; 19 were prospective cohort studies (46–64), 3 were Mendelian randomization studies (65–67), and 1 paper reported data from both prospective cohort and Mendelian randomization studies (68). Our stringent inclusion criteria meant that a number of studies that might reasonably have been expected to be included on the basis of study design, were in fact excluded because participants were taking exogenous hormones (Supplementary Table S2).

Study characteristics

Study characteristics are provided in Supplementary Tables S3A and S3B. The smallest of the four Mendelian randomization studies (65–68) contained 589 cases and 10,520 controls, the largest contained 122,977 cases and 105,974 controls. Biomarkers examined included fasting glucose ($n = 3$), 2 hour glucose ($n = 1$), fasting insulin ($n = 2$), HOMA-IR ($n = 1$), HbA1c ($n = 1$), IGF-1 ($n = 1$), and IGFBP-3 ($n = 1$). Of the 20 prospective cohort publications (46–64, 68), six included premenopausal women (range 279 to 51,712), 18 included postmenopausal women (range 188 to 148,529) and two contained women of a defined age rather than menopausal status (range 3,179 to 3,345). Biomarkers examined in these publications included IGF-1 ($n = 13$), IGFBP-3 ($n = 8$), insulin ($n = 7$), C-peptide ($n = 5$), glucose ($n = 3$), free IGF-1 ($n = 2$), IGFBP-1 ($n = 2$), HbA1c ($n = 2$), HOMA-IR ($n = 2$), and IGF-2 ($n = 1$). It should be noted that of the 20 prospective cohort publications, four papers used data from participants in the European Prospective Investigation into Cancer and nutrition (EPIC) cohort (51–54), three papers used data from participants in the UK Biobank cohort (47, 61, 68) and four papers used data from participants in the Women's Health Initiative (WHI) cohort (55–57, 62); data was extracted from the paper reporting the greatest number of cases in instances where the same biomarker was measured. Data reported by Jernstrom and Barret-Connor (63) could not be included in the meta-analyses because it was not provided in a compatible format. Details were not always provided, but where they were, it was clear a breast cancer diagnosis within the first year (up to 3 years in some studies) of study

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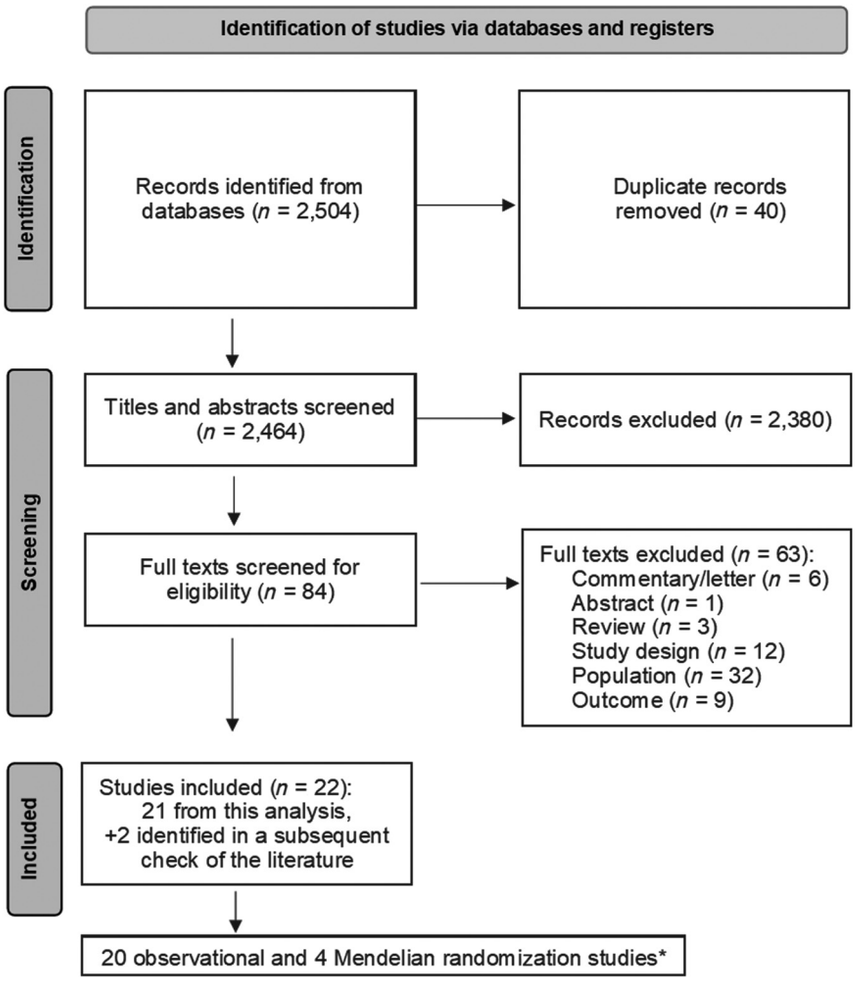

Figure 1.
PRISMA flow diagram. This figure incorporates literature search, screening, and study selection.

recruitment led to the participant being excluded (by the investigators) from analyses.

Risk of bias

Assessments of risk of bias are presented in Supplementary Table S4. The overall risk of bias was assessed as moderate in 14 studies and serious in six studies using ROBINS-E. All cohort studies were judged to have at least moderate levels of bias owing to potential confounding effects on breast cancer risk. Six studies were judged to have serious bias due to confounding as they did not adjust for measures of body composition, alcohol intake, physical activity, or smoking (46, 49–52, 58). All of the studies used medical or health insurance records to verify breast cancer incidence. A number of specific tools have been designed for assessing the strength/quality of Mendelian randomization studies, but none have been validated or tested for general use in the appraisal of bias (69). The strength of Mendelian randomization arises from the 'fixed' nature of germline genotypes, but there are core assumptions, which must be met to provide unbiased effect estimates (70). Each of the four Mendelian randomization studies (65–68) included in this systematic review assessed the quality of the genetic instruments employed and the potential for pleiotropy.

Effects of the insulin/IGF signaling system on breast cancer risk

Forest plots, comparing breast cancer risk for women with the highest quantile compared with the lowest quantile of insulin/IGF biomarkers, are presented in **Fig. 2**. Dose–response curves for IGF-1 are presented in **Fig. 3**. Funnel plots are presented in the Supplementary Fig. S1.

Insulin

Three prospective cohorts reported circulating insulin levels in controls and breast cancer cases (49, 55, 57, 58, 62). Evidence for an association of insulin with breast cancer risk was weak (RR = 1.12; 95% Cl, 0.30–1.94) with substantial heterogeneity existing between the data sets (I^2 = 66.67%). Of these three cohorts, premenopausal (49), or postmenopausal women (62) were used exclusively in two and the third used both pre- and postmenopausal women, the data (58) from which were analyzed separately. Data from two Mendelian randomization studies (65, 66) indicated that breast cancer risk increased with higher levels of insulin (OR = 1.71 per SD increase; 95% CI, 1.26–2.31 and HR = 1.80 per μIU/mL; 95% Cl, 0.18–18.06) although the second study lacked precision and incorporated the null. Participants of these two studies were not differentiated on the basis of menopausal status.

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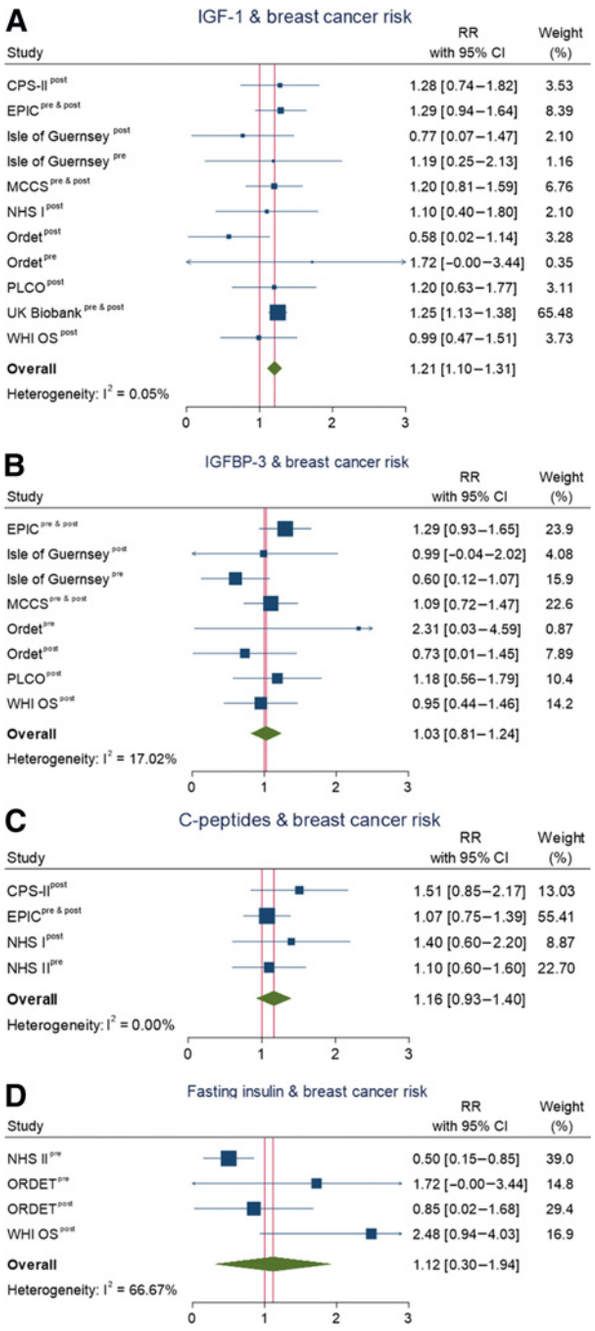

Figure 2.

Forest plots for effects of insulin/IGF signaling system biomarkers on breast cancer risk. Forest plot for (**A**) IGF-1, (**B**) IGFBP-3, (**C**) C-peptid, and (**D**) fasting insulin.

C-peptide

Four prospective cohort studies (49–51, 54, 64) assessed the impact of C-peptide on breast cancer risk; weak evidence of an association was observed (RR = 1.16; 95% CI, 0.93–1.37; $I^2 = 0.0\%$), in the absence of heterogeneity. Women from the three studies were either exclusively pre- (49) or postmenopausal (50, 64), or not differentiated on the basis of menopausal status (54).

Igf-1

A meta-analysis of eligible prospective cohort studies ($n = 9$; refs. 46, 48, 50–53, 55, 58, 60, 64, 68), found that IGF-1 was associated with an increased breast cancer risk (RR = 1.21; 95% CI, 1.10–1.31; $I^2 = 0\%$; **Fig. 2**) which was dose-dependent (**Fig. 3**). The cohorts consisted of postmenopausal women exclusively (50, 55, 60), pre- and postmenopausal women, with the data analyzed according to status (46, 58) and women not differentiated on the basis of menopausal status (48, 52, 68). Heterogeneity between the data sets was low. This result was driven by the inclusion of data from the UK Biobank study, which accounted for 56% of the overall outcome; it was the only study of the six that were eligible, to find IGF-1 increased breast cancer risk (**Fig. 2**). Three of these studies used models adjusting for IGFBP-3; individually, none of the three studies showed an association of IGF-1 on breast cancer risk prior to, or following the adjustment for IGFBP-3 (Supplementary Fig. S2; RR = 0.97; 95% CI, 0.70–1.24; $I^2 = 0.0\%$). When the data were stratified by menopausal status, there was little evidence of an impact of IGF-1 on breast cancer risk (RR for premenopausal = 1.02; 95% CI, 0.71–1.24; $I^2 = 0\%$; RR for postmenopausal = 1.10; 95% CI, 0.90–1.31; $I^2 = 3\%$; Supplementary Fig. S3). The stratified analyses of the data did not include data from the UK Biobank study because the risk estimates were reported per 5-nmol/L increment rather than by highest versus lowest quintile, as per the remaining studies. A Mendelian randomization study undertaken by Murphy and colleagues (68), supported the association of IGF-1 with breast cancer risk (OR per 5-nmol/L increment = 1.05; 95% CI, 1.01–1.10) and linked it to estrogen receptor–positive tumors (OR per 5-nmol/L increment = 1.06; 95% CI, 1.01–1.11), but not estrogen receptor–negative tumors (OR per 5-nmol/L increment = 1.02; 95% CI, 0.96–1.08; ref. 68). Sensitivity analyses found these results to be robust.

IGFBPs

Six prospective cohort studies investigated the impact of circulating IGFBP-3 levels on breast cancer risk (46, 48, 51–53, 55, 58, 60). The cohorts consisted of postmenopausal women exclusively (55, 60), pre- and postmenopausal women, data analyzed according to status (46, 58) and women not differentiated on the basis of menopausal status (48, 52).There was little evidence that IGFBP-3 had any impact on breast cancer risk overall (RR = 1.03; 95% CI, 0.81–1.24; $I^2 = 17.02\%$). When the data were stratified by menopausal status, IGFBP-3 appeared to reduce the risk of breast cancer for premenopausal women (RR = 0.77; 95% CI, 0.51–1.04; $I^2 = 0.0\%$) while postmenopausal women's risk of breast cancer increased (RR = 1.16; 95% CI, 0.90–1.41; $I^2 = 0.0\%$), although the CIs for the two subgroups were overlapping (Supplementary Fig. S4). There was little evidence that genetically predicted IGFBP-3 concentrations influenced breast cancer risk (OR per SD of IGFBP-3 = 1.00; 95% CI, 0.97–1.04; ref. 68). The limited numbers of eligible studies meant it was not possible to conduct meta-analyses for IGFBP-1, however, neither of the prospective cohort studies reported an association of IGFBP-1 with breast cancer risk (51, 58).

Glucose

There was little evidence of an association between fasting glucose levels and breast cancer risk in prospective cohort studies of postmenopausal women (WHI: HR = 1.14 per mg/dL; 95% CI, 0.60–2.16; ORDET: RR = 1.6 per ng/mL; 95% CI, 0.59–4.46, highest versus the lowest quartile; refs. 57, 58). However, in premenopausal women, glucose levels were associated with breast cancer risk (RR =

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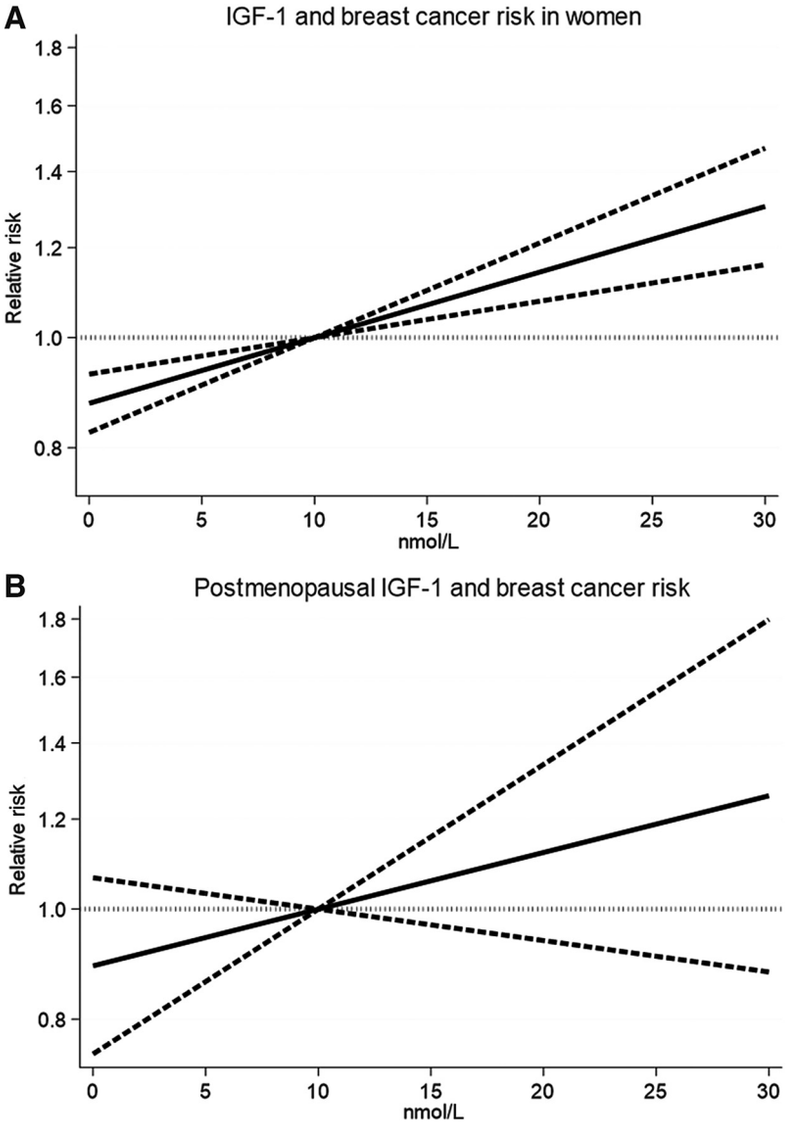

Figure 3.
Dose–response meta-analysis for IGF-1 and IGFBP-3 (nmol/L) and breast cancer risk. Dose–response plot for (**A**) IGF-1 and (**B**) IGFBP-3.

2.76 per mg/dL; 95% CI, 1.18–6.46); additional analyses showing that breast cancer in these women was more likely to arise after the age of 48 (58). Three Mendelian randomization studies investigated the impact of genetically predicted glucose levels on breast cancer risk with differing outcomes. Participants were not stratified according to menopausal status in two of the three studies. Fasting glucose levels were reported to either have no effect in two studies (OR = 1.03 per mmol/L; 95% CI, 0.85–1.25; ref. 67); OR per mmol/L = 1.06; 95% CI, 0.95–1.17; ref. 65), or to reduce breast cancer risk in postmenopausal women (HR = 0.59; 95% CI, 0.35–0.99; ref. 66); 2-hour glucose measurements were associated with an increased risk of breast cancer (OR per SD increase in 2 hour glucose = 1.80; 95% CI, 1.30–2.49; ref. 65).

Other biomarkers

Data were available from prospective cohort studies for HbA1c (47, 59), HOMA-IR (57, 66), free IGF (55, 58), and IGF-2 (46) however, there was insufficient data for these outcomes to perform meta-analyses examining breast cancer risk. HbA1c and HOMA-IR were also the subject of Mendelian randomization studies. HbA1c was not associated with breast cancer risk in either the prospective cohorts or Mendelian randomization study (47, 59, 67), although a weak inverse association was observed in a prospective cohort of postmenopausal women which appeared to be confined to women who had never used hormone replacement therapy (RR = 0.53; 95% CI, 0.30–0.93; ref. 59). Findings from prospective cohort and Mendelian randomization studies investigating the association between HOMA-IR and breast cancer risk in postmenopausal women were contradictory, with a positive association (HR = 2.99; 95% CI, 1.56–5.73; P_{trend} = 0.0008; ref. 57) and no association reported (HR = 0.94; 95% CI, 0.81–1.08), respectively (66).

Grade

Results of the GRADE appraisal are presented in **Table 1**. The GRADE criteria initially classifies evidence from prospective cohort studies as 'low' (71). However, where a large effect estimate is reported and/or dose–response data are provided, reclassification to a higher level (moderate or high) may be warranted. Where there is a high risk

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Table 1. GRADE appraisal for insulin/IGF signaling system–breast cancer risk pathways.

Outcome, menopausal status	Study type, number, participant numbers (*n*)	Effect estimates (RR, 95% CI)	Quality of evidence determination					Quality of evidence final
				Criteria for downgrading				
			ROB	Inconsistency	Imprecision	Pub bias	Criteria for upgrading	
Insulin								
All women	Observational[b], 3 (2,139)	1.12 [0.30–1.94]	Serious	No	Yes	?	None	**Very low**
All women	Mendelian randomization, 2 (193,415)	1.80 [0.18–8.06][63]1.16 [0.96–1.41][62]	–	No	Yes	–		
IGF-1								
All women	Observational, 9 (215,500)	1.21 [1.10–1.31] *	Moderate	No	No	Yes	Dose–response	**Moderate**
IGFBP-3 adjusted	Observational, 3 (3,650)	0.97 [0.70–1.24]	–	–	No	–		
All women	Mendelian randomization, 1 (228,951)	1.05 [1.01–1.10][65]						
IGFBP3								
All women	Observational, 6 (6,692)	1.03 [0.81–1.24]	Moderate	No	No	No	None	**Moderate**
All women	Mendelian randomization, 1 (228,951)	1.00 [0.97–1.04][65]	–	–	No	–		
C-peptide								
All women	Observational, 4 (5,452)	1.16 [0.93–1.40]	Serious	No	No	?	None	**Very low**
Glucose[a]								
Premenopausal	Observational, 1 (334)	2.8 [1.2–6.5][56]*	Serious	Yes	Yes	–	None	**Very low**
Postmenopausal		1.63 [0.59–4.46][56]	–	No	Yes	–		
Postmenopausal	Observational, 1 (5,450)	1.14 [0.60–2.16][55]	–	–	Yes	–		
All women	Mendelian	1.03 [0.85–1.25][64]						
All women	randomization, 2 (411,257)	1.06 [0.95–1.17][62]						
Post- menopausal		0.63 [0.50–0.79][63]						
All women: 2hr glucose	Mendelian randomization, 1 (11,109)	1.50 [1.21–1.86][62]*						
HbA1c								
Premenopausal	Observational, 1 (7,442)	1.08 [0.65–1.79][57]	Moderate	No	Yes	–	None	**Very low**
Postmenopausal	Observational, 1 (27,110)	0.73 [0.54–0.98][45]	–	–	Yes	–		
All women	Mendelian randomization, 1 (228,951)	1.02 [0.73–1.45][64]						
HOMA-IR								
Postmenopausal	Observational, 1 (5,450)	2.99 [1.56–5.73][55]*	Moderate	Yes	Yes	–	None	**Very low**
Postmenopausal	Mendelian randomization, 1 (11,109)	0.94 [0.81–1.08][63]	–	–	No	–		
IGF-2								
Premenopausal	Observational, 1 (279)	0.86 (0.42–1.76)[44]	Serious	No	Yes	–	None	**Very low**
Postmenopausal	Observational, 1 (188)	0.87 (0.37–2.05)[44]						

Note: Data from published studies are acknowledged with reference numbers in superscript.

*Increased breast cancer risk.

[a]All glucose measures except those specified, relate to fasting glucose.

[b]Observational, prospective cohort studies are classified as 'low' quality at the start of quality assessment.

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of bias, evidence of imprecision or inconsistency, downgrading the classification to 'very low' may be appropriate (71). Randomized control trials (RCT) are the gold standard with quality of evidence starting at 'high'. A Mendelian randomization study that satisfies the three core assumptions (1. genetic variants are robustly associated with the exposure, 2. no confounding of the variants and 3. variants influence the outcome only through the exposure) can be seen as equivalent to RCTs (72). Evidence that IGF-1 increases breast cancer risk came from both prospective cohort and Mendelian randomization studies with large numbers of participants. Dose–response relationships for pre- and postmenopausal women were demonstrated and there was consistency in outcomes between prospective cohorts and Mendelian randomization studies. It is important to note however, that effect estimates for IGF-1 were small and largely driven by data from the UK Biobank study (68). The IGF-1 funnel plot (Supplementary Fig. S1) suggested publication bias and individual studies assessed collectively, were found to have a moderate risk of bias, largely due to the presence of confounders (Supplementary Table S4). Taking these factors into account, the quality of evidence for IGF-1 was upgraded to 'moderate' (**Table 1**). The quality of evidence for IGFBP-3 was upgraded to moderate given the precision of the effect estimates and consistency of the outcome between study types. The quality of evidence for C-peptide, glucose, insulin, HbA1c, HOMA-IR and IGF-2, was downgraded to 'very low' due to either serious risk of bias, imprecision of the data and/or inconsistent outcomes (**Table 1**; Supplementary Table S4). The small number of studies for C-peptide and insulin prevented a definitive assessment of publication bias (Supplementary Fig. S1). The contribution of Mendelian randomization studies to the quality of data sets is not clear; much depends on the quality of the genetic instruments employed and the strength of their association with the outcome. Where the outcome is consistent across study types, Mendelian randomization studies clearly add to the quality of evidence; usually large numbers of participants, genetically randomized. However, when outcomes are not in accord, either within and/or across study types, determining the impact Mendelian randomization studies have on the quality of evidence becomes dependent on the specificity of the instrument-outcome association and the ability to interpret its strength.

Discussion

Given that the insulin/IGF signaling system (including IGFs, their binding proteins and markers of insulin resistance) may be important for breast cancer development (7, 9), we conducted a systematic review of the literature to determine whether the insulin/IGF signaling system affects breast cancer risk in women. We found that IGF-1 contributes to breast cancer risk, but there was little evidence that other biomarkers of the insulin/IGF signaling system play a part. Our systematic review and meta-analysis does not support a role for insulin, IGFBP-3 or C-peptide in the aetiology of breast cancer. However, our findings are limited by the dearth of high quality studies in this area; we were unable to conduct meta-analyses for HbA1c, HOMA-IR, IGF-2 or IGFBP-1 on this basis. A definitive conclusion could not be drawn for glucose given a lack of consistency between study outcomes.

Despite a large amount of literature on the insulin/IGF signaling system and breast cancer, the number of studies eligible for inclusion in this systematic review was fewer than what might have been anticipated. This was mainly due to the exclusion of study cohorts that allowed women to take oral contraceptives or hormone replacement therapy; bias may have been introduced given the established interplay between IGF/insulin and steroid hormone signaling pathways (24–32). As a consequence, only a small number of studies that met our stringent selection criteria were included in this systematic review. In designing future studies in this area, investigators should either incorporate appropriate control groups to ensure the effects of exogenous sex hormones can be isolated, or carefully consider their inclusion criteria to avoid reporting confounded outcomes. Large-scale, collaborative efforts are more likely to further our understanding of biological processes than numerous, small, potentially under powered studies.

The Mendelian randomization studies included in this systematic review investigated the impact of insulin (65, 66), IGF-1 (68), IGFBP-3 (68), glucose (65–67), HbA1c (47, 59) and HOMA-IR (57, 66) on breast cancer risk. Where RCTs are not feasible/available, Mendelian randomization studies are an alternative provided they are sufficiently powered and appropriate sensitivity analyses to test the assumptions of the randomization have been performed. Genetically predicted outcomes are less prone to confounding and the potential for reverse causation is eliminated; if core assumptions are satisfied, causal conclusions can be drawn (69). While there are guidelines to assist in assessing Mendelian randomization studies (MR-STROBE: Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization; ref. 73), validated tools to assess risk of bias and quality of the evidence are not currently available. Within our systematic review, three Mendelian randomization studies investigated the impact of glucose on breast cancer risk, and three different outcomes were reported: no change (fasting glucose) (65, 67); a decrease (fasting glucose; ref. 66) and an increase (2-hour glucose; ref. 65). One of the three studies investigated postmenopausal women exclusively (66), the other two included women spanning pre- and postmenopausal states (65, 67). Two of these studies used summary genetic associations from the same genome-wide association study (GWAS) of women enrolled in the Breast Cancer Association Consortium (65, 67) but with different genetic instruments employed in the analyses, the third used harmonized and imputed data from GWASs of women enrolled in the WHI (66). Glucose was measured in either the fasting state or 2 hours following a glucose challenge. These measures of glucose, while correlated (74), reflect different biological processes which may explain the findings reported by Shu and colleagues (65), of a positive association of 2-hour glucose but not fasting glucose, with breast cancer risk. Methodologic differences between studies make direct comparisons difficult.

Similar results reported between prospective cohort studies and Mendelian randomization studies strengthen causal inference (75). Results for IGF-1, IGFBP-3, and HbA1c reported here were consistent across study types and in line with other reports in the literature (46–48, 51–53, 58–60, 67, 68, 76–78). In contrast to the conflicting results reported for glucose in Mendelian randomization studies, two prospective cohort studies of postmenopausal women reported no association between glucose and breast cancer risk (57, 58). This result was consistent with the outcomes of both prospective cohort and Mendelian randomization studies which found no association of HbA1c with breast cancer risk (59, 67).

An effect of insulin on breast cancer risk was not observed in our meta-analysis of prospective cohort studies. Significant heterogeneity was noted between data sets and the quality of the evidence as assessed by GRADE, was categorized as 'low'. The outcome, however, was consistent with the results for C-peptide (which were homogeneous and more precise). C-peptide and insulin are

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produced in equimolar concentrations from the cleavage of proinsulin. Given that C-peptide is more stable than insulin, it may be preferable in some circumstances to measure C-peptide as a proxy for insulin. In contrast, two Mendelian randomization studies reported that insulin increased breast cancer risk, although one lacked precision and crossed the null (66).

A strength of this review is the use of the WCRF International/University of Bristol framework (35) which incorporates a risk of bias assessment and a quality assessment, to synthesize the evidence for the insulin/IGF signaling system and its impact on breast cancer risk. Only prospective cohort and Mendelian randomization studies met the criteria for inclusion. We used the text-mining program TeMMPo to prioritize potential biomarkers for these systematic reviews. TeMMPo ranked potential biomarkers based on the quantity of evidence available for exposure–biomarker and biomarker–outcome relationships. While this ensured that biomarkers with the most published evidence were reviewed, consideration of only the top 20 biomarkers might mean that some novel or less extensively studied biomarkers were overlooked. We restricted study populations to apparently 'healthy' women at baseline, excluding those with pre-existing menstrual or metabolic disorders and those taking medication, which might influence study outcomes, e.g., insulin. While we excluded studies where participants were using oral contraceptives or hormone replacement therapy at study recruitment and during follow-up, we were unable to account for past exogenous hormone use. The limited number of studies and pooling of pre- and postmenopausal data in some, prevented conclusions being drawn about breast cancer risk in response to insulin/IGF signaling during the different phases of the reproductive cycle. Similarly, the impact of breast cancer type and/or hormone receptor status could not be evaluated.

The overarching aim of this two-part series of reviews was to determine whether the insulin/IGF signaling system mediates the reduction in breast cancer risk observed with higher levels of physical activity. Part 1 of this review addressed whether physical activity affects the insulin/IGF signaling system in women (38). Decreases in fasting glucose, fasting insulin, and insulin resistance were reported in response to physical activity, whereas IGF-1 levels increased in the absence of a change in IGFBP-3 (38). In part 2, presented here, we examined whether the insulin/IGF signaling system could reduce a women's risk of breast cancer. No association between insulin, C-peptide, IGFBP-3, and breast cancer risk were identified, but IGF-1 was found to increase breast cancer risk. IGF-1 exerts autocrine and paracrine actions on growth and apoptosis and has been implicated in the development of solid tumors (31, 79). The finding that physical activity increased IGF-1 levels, which in turn, has the potential to increase breast cancer risk, makes it unlikely that insulin/IGF signaling is the mechanism by which the protective effect of physical activity on breast cancer risk is mediated.

Our findings are consistent with new evidence about the efficacy of metformin and breast cancer prevention and progression. Metformin is an insulin sensitizer that is commonly prescribed to treat diabetes. On the basis of evidence from epidemiologic studies and preclinical studies demonstrating an antiproliferative effect in animal models and cell lines, a number of randomized clinical trials have been conducted to test the effect of metformin (80). However, the majority of observational studies have been retrospective, the results of which may be affected by selection and recall biases. Immortal time bias may also have resulted in the apparent protective effect of metformin being exaggerated (81). A number of randomized clinical trials are currently evaluating the preventive effect of metformin in women at high risk of breast cancer (80). A recent meta-analysis combined the results of five small, phase II randomized trials (a total of 396 participants) and showed that metformin was not associated with improved survival outcomes in nondiabetic women with breast cancer (81). Definitive results were recently published from a large randomized clinical trial (MA.32; that included over 2,500 nondabetic women with high-risk, operable breast cancer in the primary analysis); the addition of metformin to standard treatment did not improve invasive disease-free survival (82). Nevertheless, interim analysis of MA.32 indicated that metformin was associated with decreased levels of insulin, hs-CRP and leptin in nondiabetic patients, and decreased estradiol levels in women with ER-negative disease (83, 84). This highlights the difficulties associated with interpreting the impact of interventions provided in addition to best practice. Additional prospective studies are therefore required to determine whether metformin will show benefit in a risk reduction setting.

There are significant challenges in infering specific downstream signaling in both breast cancer and untransformed breast epithelial cells in relation to circulating levels of insulin and IGF-1. Because these cells can express both insulin and IGF-1 receptors, and that these can act as homodimers and heterodimers eliciting different downstream signaling, the biological effects of insulin and IGF-1 can be context-dependent (85). This is compounded in breast cancer cells, where driver mutations can affect these pathways directly, in PIK3CA mutant cells for example. There are also a number of challenges associated with blood collections and IGF-1 measurements themselves. There are currently no standardized methods to measure blood levels of IGF-1, and levels of both IGF-1 and insulin are substantially altered with feeding. Hence, without accounting for time since last meal, a non-negligeable amount of variation can be introduced, thereby confounding the results.

Although we found no convincing evidence that the insulin/IGF signaling system mediates the effect of physical activity on breast cancer risk, robust conclusions cannot be drawn due to the dearth of high quality studies. Additional large scale epidemiologic studies, appropriately controlled for confounders, and further Mendelian randomization studies using GWAS data from more diverse populations would help to clarify the observations of our systematic reviews and meta-analyses.

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Note

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