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1 **Linking physical activity to breast cancer: text mining results and a protocol for**
2 **systematically reviewing three potential mechanistic pathways**

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46 **ABSTRACT**

47 Epidemiological research suggests that physical activity is associated with a reduced risk of
48 breast cancer, but the causal nature of this link is not clear. Investigating mechanistic
49 pathways can provide evidence of biological plausibility and improve causal inference. This
50 project will examine three putative pathways (sex steroid hormones, insulin signalling, and
51 inflammation) in a series of two-stage systematic reviews. Stage 1 used Text Mining for
52 Mechanism Prioritisation (TeMMPo) to identify and prioritise relevant biological
53 intermediates. Stage 2 will systematically review the findings from studies of (i) physical
54 activity and intermediates; and (ii) intermediates and breast cancer. Ovid MEDLINE,
55 EMBASE, and SPORTDiscus will be searched using a combination of subject headings and
56 free-text terms. Human intervention and prospective, observational studies will be eligible for
57 inclusion. Meta-analysis will be performed where possible. Risk of bias will be assessed
58 using the Cochrane Collaboration tool, the ROBINS-I or ROBINS-E tool, depending on
59 study type. Strength of evidence will be assessed using the GRADE system. In addition to
60 synthesising the mechanistic evidence that links physical activity with breast cancer risk, this
61 project may also identify priority areas for future research and help inform the design and
62 implementation of physical activity interventions.

63 **Systematic review registration:** These reviews have been prospectively registered on
64 PROSPERO: 2020 CRD42020146736; CRD42020165696; CRD42020165689.

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Background

Breast cancer accounts for around one-quarter of all female cancers and is the leading cause of cancer-related death among women globally.[1] Epidemiological research suggests physical activity may protect against the development of breast cancer. Engaging in moderate physical activity is associated with a reduction in the risk of post-menopausal breast cancer of approximately 13%, while vigorous physical activity has been associated with risk reductions of 9 and 17% for pre- and post-menopausal breast cancer, respectively.[2] Although the evidence in support of these associations has been described as strong, the observational design, typically with one exposure assessment, of studies included in the Continuous Update Project Report make it difficult to draw firm conclusions regarding causality.[2]

Several mechanistic pathways underpinning the association between physical activity and breast cancer have been proposed.[3] Increased exposure to sex steroid hormones increases breast cancer risk.[4-7] The expression of oestrogen and progesterone receptors in a tumour are positive prognostic indicators, and breast cancer treatments that target these pathways remain the most effective.[4] Further, androgens can stimulate the growth of breast cancers, either by a direct action or following aromatisation to estrogen.[8] Physical activity may therefore reduce breast cancer risk via its effect on female sex hormones.[3] In premenopausal women, there is some evidence to suggest that vigorous physical activity can disrupt regular menstrual function,[9] and, when combined with energy restriction, may result in delayed onset of menarche.[10, 11] Intervention studies suggest that vigorous physical activity results in small reductions in total and free oestrogen and oestradiol levels in healthy pre-menopausal women, changes that are not completely explained by anthropometric change.[9, 12] Amongst postmenopausal women, numerous randomised controlled trials (RCTs) have demonstrated that moderate or vigorous aerobic physical activity reduces both total oestradiol and free oestradiol, and increases sex hormone binding globulin (SHBG).[12]

It has also been proposed that insulin resistance increases breast cancer risk.[13-15] Insulin resistance necessitates an increase in production of insulin by pancreatic beta cells in order to maintain normal glucose levels.[15] Insulin can enhance tumour development directly through stimulating cellular proliferation and via activation of the insulin like growth factor (IGF-I) system, which mediates cellular differentiation, proliferation, and apoptosis.[15-17] Insulin can also regulate the synthesis and availability of sex hormones.[18] Increased insulin sensitivity is an adaptive response to physical activity.[19] An acute bout of physical activity precedes an

98   increase in insulin-stimulated glucose uptake in the exercised skeletal muscle that lasts for up

99   to 48 hours.[19, 20] Regular physical activity leads to improvements in whole body as well as

100   skeletal muscle insulin sensitivity via increases in GLUT4 receptor number and function,

101   muscle capillarisation, and blood flow.[19, 21, 22] Physical activity has also been associated with

102   lower levels of IGF-I and increased levels of insulin-like growth factor-binding protein 3,

103   which binds to IGF-I, reducing its bioavailability.[23]

104   Inflammation has been implicated in the aetiology of most cancers.[3, 24] Inflammation

105   stimulates cell proliferation, tumour micro-environmental changes and oxidative stress,

106   which can deregulate normal cell growth and promote malignant conversion and

107   progression.[25] Adipose tissue secretes multiple biologically active polypeptides, many of

108   which are pro-inflammatory cytokines (referred to as adipokines).[26, 27] Adipokines may play a

109   role in the development of insulin resistance, as leptin and adiponectin enhance insulin

110   sensitivity through activation of adenosine monophosphate protein kinase.[26] Adipokines

111   might also increase breast cancer risk by affecting oestrogen biosynthesis and activity.[28]

112   Observational research supports an association between lower levels of physical activity and

113   an adverse, chronic inflammatory profile.[29, 30] Physical activity interventions demonstrate that

114   regular activity induces expression of anti-inflammatory cytokines and suppresses the

115   expression of pro-inflammatory cytokines in the general population, as well as elderly and

116   obese populations.[31, 32]

117   This brief summary of these putative mechanisms is based on narrative reviews that are

118   common in the literature, and a small number of human trials and experimental studies.

119   Narrative reviews may be biased, and lead to erroneous conclusions being drawn.[33] Thus,

120   there is a strong need for more rigorous reviews of the total body of mechanistic evidence.

121   Systematic review, synthesis of data subject to quality appraisal, and where possible, meta-

122   analysis, will provide greater insight into the plausibility and strength of evidence that

123   supports these pathways. The World Cancer Research Fund (WCRF) International and the

124   University of Bristol have developed a novel framework for generating an overview of

125   biological pathways and undertaking systematic reviews of mechanistic research relating to

126   exposure-outcome associations.[33] The framework, which has been independently validated,[34]

127   provides a protocol for synthesising mechanistic research.

128   Our aim is to use the WCRF International/University of Bristol framework to synthesise key

129   putative mechanistic pathways underlying the association of physical activity with reduced

130   breast cancer risk. We will take a targeted approach, focussing on the molecular pathways
131   most frequently discussed in the literature, namely: (i) sex steroid hormones; (ii) insulin
132   signalling; and (iii) inflammation (pro- and anti-inflammatory markers).

133   **Methods**

134   Our series of systematic reviews to examine three intermediate pathways (sex steroid
135   hormones, insulin signalling, and inflammation) that may connect physical activity and breast
136   cancer risk will each contain two stages. While it is understood that there is interplay between
137   these three pathways, for the purpose of the systematic reviews we treat these as separate
138   etiological functions.

139   Stage 1 (completed; results are presented below) used an automated process, "Text Mining
140   for Mechanism Prioritisation" (TeMMPo),[35] to quantify and visualise the amount of evidence
141   for specific intermediate phenotypes within the three intermediate pathways. As the quantity
142   of evidence available may not reflect more recent and less researched developments in the
143   scientific literature, TeMMPo results were combined with expert input to ensure all key
144   pathways were identified.

145   Stage 2 comprises systematic reviews of intermediate phenotypes identified in Stage 1. The
146   protocol for Stage 2 is structured in accordance with the Preferred Reporting Items for
147   Systematic Reviews and Meta-Analyses (PRISMA) statement,[36] and is presented in this
148   paper. The reviews have been registered with PROSPERO (International prospective register
149   of systematic reviews: CRD42020146736; CRD42020165696; CRD42020165689).

150   **Stage 1 - Prioritisation of intermediates**

151   Medical subject headings (MeSH) for exposure, intermediate and outcome, relevant to each
152   pathway were entered into TeMMPo (Supplementary Table 1) and used to generate a
153   comprehensive list of intermediate phenotypes for each pathway and produce a graphical
154   representation (Sankey plot)[33] of intermediate phenotypes potentially mediating the physical
155   activity - breast cancer association. The top scoring intermediates for each pathway were
156   reviewed by study investigators for relevance and biological plausibility, according to a
157   predefined inclusion and exclusion criteria (Supplementary Tables 2-4). Expert input was
158   also sourced to identify potentially relevant intermediates not identified by TeMMPo.
159   Intermediates were identified via the text mining process and those added based on expert
160   review are clearly demarcated in the results. The prioritised intermediates were then grouped

161 into categories based on type (e.g. oestrogens or androgens), before moving on to systematic
162 review.

163 Table 1 presents the final list of steroid sex hormones selected for systematic review; after
164 review of the intermediates prioritised by TeMMPo, the investigator team decided that
165 glucocorticoids should be added to the list. Although not a sex hormone, glucocorticoids
166 belong to the same steroid superfamily as estrogen, androgens and progestogens. Table 2
167 presents the final list of insulin signalling biomarkers for inclusion in the systematic reviews
168 (HOMA-IR, HOMA-S, HbA1c and QUICKI were added based on expert input), and Table 3
169 presents the final list of inflammatory biomarkers for systematic review (the investigator
170 team decided that interferon-gamma and chemokine ligand 2 should be added to the
171 intermediates prioritised by TeMMPo).

172 **Stage 2 – Systematic review of mechanistic pathways**

173 Using the WCRF International/University of Bristol framework, we will systematically
174 review the published research relating to (i) physical activity and prioritised intermediates,
175 and (ii) prioritised intermediates and breast cancer risk. These systematic reviews will help to
176 clarify the causal pathways by which physical activity helps prevent breast cancer.

177 **Inclusion and exclusion criteria**

178 Intervention trials, Mendelian randomization studies and prospective cohort studies will be
179 eligible for inclusion. Neither cross-sectional nor case-control studies will be eligible due to
180 the likely serious bias arising from timing of exposure and outcome collection. Participants
181 will include human post-pubescent (i.e. has experienced menarche) and pre- and post-
182 menopausal women with no prior history of cancer. Studies of women with conditions that
183 may confound exposure – outcome associations (e.g. type 2 diabetes, polycystic ovarian
184 syndrome) will be excluded. Studies of elite athletes will also be excluded due to the inability
185 to account for the likely effect of diet, as well as the relatively high prevalence of menstrual
186 dysfunction. For the physical activity – intermediate component, the exposure must be
187 physical activity or exercise only (e.g. not an intervention combining exercise and caloric
188 restriction). For the intermediate – breast cancer component, the outcome must be cancer
189 incidence. Studies examining carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS)
190 will be excluded as they are both pre-cancerous and non-invasive. Only studies in English
191 will be eligible for inclusion.

192 **Search strategy**

193 Relevant publications will be identified through a systematic search of the following
194 electronic databases: PubMed/Ovid MEDLINE (1946- present), Ovid EMBASE (1980-
195 present) and SPORTDiscus (1930- present). Two sets of searches will be undertaken: (i)
196 studies linking physical activity (exposure) to prioritised intermediates, and (ii) studies
197 linking the intermediate phenotypes to reduced breast cancer risk (outcome). For the
198 exposure – intermediate pathway search, exposures will include any type, duration, and
199 frequency of physical activity. The prioritised biological markers related to sex steroid
200 hormones (Table 1), insulin signalling (Table 2), and inflammation (Table 3), were identified
201 in Stage 1. For the intermediate – outcome search, outcomes will include any incident,
202 invasive breast cancer. Standard controlled vocabulary (MeSH), text words and keywords
203 will be used in the searches. The developed search strategy will be used for all databases;
204 syntax modifications will be made to conform to individual database requirements. Reference
205 lists of reviews will be hand searched for articles which may not have been retrieved in the
206 search process.

207 **Data management**

208 References will be downloaded to Endnote X9 (Philadelphia PA, Clarivate) for curation and
209 duplicates will be removed. Covidence software (Melbourne VIC, Covidence) will facilitate
210 the review/assessment of articles by independent researchers. Stata 16 (College Station TX,
211 StataCorp) will be used for meta-analysis and meta-regression where appropriate.

212 **Selection of studies**
213 Titles and abstracts of articles yielded by the searches will be screened for eligibility by two
214 independent reviewers against the inclusion/exclusion criteria. Where consensus is not
215 reached on eligibility, a third reviewer will be available for adjudication. The full text of
216 articles deemed appropriate for inclusion will be reviewed by two independent reviewers for
217 eligibility.

218 **Data Extraction**
219 Data extraction will be performed independently by two reviewers using a pre-piloted
220 system. Extracted data will include information on:

221 • Study design (e.g. authors, year, setting)

222 • Population (e.g. demographic information, health status)

223   • Exposure (e.g. self-reported or accelerometer-assessed physical activity) or
224   intervention (e.g. exercise duration, frequency, intensity, time, type)

225   • Outcome (e.g. definition, assessment method)

226   • Statistical measures (e.g. analysis performed, confounders, effect estimates,
227   confidence intervals).

228 **Risk of bias assessment**

229 Three separate tools will be used to assess the risk of bias (ROB) in individual studies. The
230 Cochrane Collaboration tool, which assesses potential bias related to design, conduct, and
231 reporting, will be applied to human RCTs.[37] For non-randomised human studies, the Risk Of
232 Bias In Non-randomized Studies – of Interventions (ROBINS-I) or of Exposures (ROBINS-
233 E) tool, which assesses bias due to confounding, participant selection, measurement of
234 exposures and outcomes, and reporting, will be used.[38] A minimal set of confounding factors
235 needed to be adjusted for in studies in order to avoid a 'serious' rating for confounding when
236 using the ROBINS-I or ROBINS-E tools (Supplementary Methods and Materials 1).

237 **Data synthesis and analysis**

238 Intervention and observational studies will be analysed separately. Random effects meta-
239 analysis of continuous outcomes (physical activity – intermediate pathways) and binary
240 outcomes (intermediate – breast cancer pathways) will be performed for studies when the
241 exposure, intermediate and outcome are consistently defined in $\geq$ 3 studies. Statistical
242 heterogeneity among effect estimates will be quantified using the I^2 statistic. Meta-regression
243 and subgroup analyses will be used, where possible, to assess whether there is heterogeneity
244 within overall results due to differences in the study populations (e.g. exercise type, lean vs
245 obese participants, menopausal status, menstrual cycle stage and breast cancer subtype). In
246 addition, to graphically represent the dose-response effect of intermediates on breast cancer, a
247 one-stage random-effects dose-response meta-analysis will be performed using restricted
248 cubic splines. This method has been recently outlined and utilises quantities and effect
249 estimates for each category of biomarker concentrations presented in individual studies.[39]
250 Publication bias will be assessed by visual inspection of funnel plots. When meta-analysis is
251 not possible, we may use the albatross plot[40] or a narrative synthesis will be undertaken.

252 **Quality assessment**

253 To rate the quality of evidence, and the strength of any findings generated, the Grading of

254 Recommendations Assessment, Development, and Evaluation (GRADE) system will be

255 employed.[41] This system rates the quality of evidence for a particular exposure-variable

256 relationship, providing a score between very low to high based on the type of studies

257 available, as well as their ROB, the consistency and precision of findings, directness,

258 publication bias, effect estimates, dose-response relationships, and influence of confounding

259 factors.[41]

Discussion

261 The overarching aims of these systematic reviews of mechanisms are to clarify which

262 intermediate phenotypes mediate the association between physical activity and breast cancer

263 risk, and to appraise the strength of evidence for these pathways. The comprehensive nature

264 of these reviews will provide robust evidence of biological plausibility, and thus strengthen

265 causal inference.

266 To date, insight into potential pathways linking physical activity and breast cancer has come

267 predominantly from narrative reviews, a small number of single-stage systematic reviews,

268 and from individual studies.[3, 9, 12, 42] Narrative reviews may be biased, and can lead to

269 erroneous conclusions being drawn. Single stage reviews synthesise only one part of the

270 pathway from exposure to outcome, focussing on either physical activity and intermediates

271 (and inferring that these are robust markers of breast cancer risk) or on intermediates and

272 breast cancer risk (with limited evidence relating to the exposures that are hypothesised to

273 affect intermediate levels). The current two-stage reviews are distinct as they appraise the

274 strength of evidence for both physical activity to intermediate and intermediate to breast

275 cancer pathways. The strengths of the current approach include the use of the WCRF

276 International and Bristol University framework for identifying and prioritising biological

277 intermediates, as well as the systematic synthesis (incorporating meta-analysis where

278 possible) and appraisal of available evidence. The dose-response meta-analyses we propose

279 represent a novel contribution to the literature. The framework has been independently

280 validated and facilitates a two-stage review process to examine intermediates.[34] Systematic

281 review offers a rigorous scientific method for identifying and synthesising evidence, while

282 the GRADE system provides a structured process for appraisal the quality and strength of a

283 body of evidence.[41]

284   Physical activity is unlikely to affect cancer risk via a singular pathway in isolation, and it is

285   acknowledged that the molecular pathways we focus on are interrelated.[43] However, it is not

286   within the scope of our protocol to investigate synergistic effects across multiple pathways,

287   despite the potential for these to produce clinically meaningful risk reductions. The complex

288   interplay between different pathways does not lend itself to systematic review.

289   The knowledge generated by these reviews will help to strengthen causal inference from

290   epidemiological data linking physical activity with a reduced risk of breast cancer.

291   Elucidation of the mechanistic pathways may inform the optimal design of physical activity

292   interventions to best target key intermediates in at-risk populations. Greater insight into

293   breast cancer aetiology may also facilitate the development of targeted treatment modalities

294   and give rise to novel drug candidates. Systematic review and appraisal of these intermediate

295   pathways will identify priority areas for future breast cancer research, and potentially divert

296   resources away from pathways that are not supported by evidence.

297

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399

400 **Table 1: Intermediates for sex steroid hormones included in systematic reviews**

Steroid Type	Prioritised intermediate
Oestrogen	Oestradiol
	Hydroxyestrones
	Oestrogens, Catechol
	Oestradiol Congeners
	Oestrone
	Oestriol
Progesterone	Progesterone
	Pregnanediol
	Progesterone Congeners
	17-alpha- Hydroxyprogesterone
	Pregnenolone
Androgens	Testosterone
	Dehydroepiandrosterone
	Androstenedione
	Dihydrotestosterone
	Testosterone Congeners
	Androstenediol
	Etiocholanolone
	Androsterone
	Androstane-3,17-diol
	Epitestosterone
Glucocorticoids	Cortisol[a]
Other	Sex Hormone-Binding Globulin

401 [a] Intermediates added based on expert review

402

403 **Table 2: Intermediates for insulin signalling included for systematic review**

	Prioritised intermediate
IGFs	Insulin-Like Growth Factor I
	Insulin-Like Growth Factor II
	Insulin-Like Growth Factor Binding Protein 1
	Insulin-Like Growth Factor Binding Protein 3
Insulin resistance	Insulin
	Pro-insulin
	C-Peptide
	Fasting glucose
	HOMA-IR[a]
	HOMA-S[a]
	HbA1c[a]
	QUICKI[a]

404   [a] Intermediates added based on expert review

405

406 **Table 3: Intermediates for inflammation included for systematic review**

	Prioritised intermediate
Cytokines	Tumour-necrosis factor-alpha
	Interleukin-1
	Interleukin-6
	Interleukin-8
	Interleukin-10
	Interleukin-13
	Interleukin 1 beta
	Interferon-gamma[a]
	Chemokine ligand 2[a]
Adipokines	Adiponectin
	Leptin
Other	C-Reactive protein

407   [a] Intermediates added based on expert review

408

Cancer Epidemiology, Biomarkers & Prevention

Linking physical activity to breast cancer: text mining results and a protocol for systematically reviewing three potential mechanistic pathways

Brigid M Lynch, Roger L Milne, Dallas R English, et al.

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