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Lichamelijke activiteit bij jonge *BRCA*- dragers en een lager risico op borstkanker

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Abstract

Invoering:

Er werd een systematisch literatuuronderzoek uitgevoerd om te bepalen of de mate van fysieke activiteit (PA) tijdens de adolescentie en de jonge volwassenheid (AYA) verband hield met een verlaagd levenslang risico op borstkanker bij dragers van schadelijke mutaties in *de BRCA1- en BRCA2* -genen.

Methoden:

Ovid/MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science en CINAHL werden doorzocht naar artikelen met informatie over AYA PA en de incidentie van borstkanker bij vrouwen met schadelijke *BRCA1*- en *BRCA2* -genmutaties (zoekopdracht gestart in oktober 2019; laatste update en volledige analyses in maart 2021). Onafhankelijke reviewers screenden artikelen op titel/abstract en full text-niveau en losten verschillen op in overleg met de hoofdauteurs. De NIH Quality Assessment Tools werden gebruikt om bronnen van bias te beoordelen.

Resultaten:

In totaal werden 1957 unieke artikelen geïdentificeerd; vijf voldeden aan de inclusiecriteria. De steekproefgrootte varieerde van 68 tot 1185. Alle studies waren gebaseerd op zelfgerapporteerde AYA PA. Eén studie mat sportbetrokkenheid; de andere maten recreatieve activiteit. Eén grote studie was nul, terwijl vier andere een vermindering van de incidentie van borstkanker op latere leeftijd lieten zien met een hogere AYA PA ($p \leq 0,05$). De bescherming

was echter beperkt tot premenopauzale borstkanker in één van de studies (OR = 0,62, 95% BI 0,40-0,96; *P* -trend = 0,01). Bovendien werd AYA PA in één studie geassocieerd met een hogere leeftijd bij de diagnose van borstkanker (p = 0,03).

Conclusie:

Uit een beperkt aantal onderzoeken blijkt dat AYA PA het risico op borstkanker kan verminderen of vertragen bij dragers van schadelijke mutaties in *de BRCA1- en BRCA2* -genen.

Trefwoorden: Lichamelijke activiteit, *BRCA1* , *BRCA2* , AYA

Invoering

Borstkanker is de meest voorkomende vorm van kanker bij vrouwen. [1] Fysieke activiteit (PA) tijdens de volwassenheid, [2-5], evenals in de adolescentie en jongvolwassenheid (AYA), [6-8], is omgekeerd evenredig met de incidentie van borstkanker bij vrouwen met een gemiddeld risico. De risicoreductie kan worden bereikt door middel van lichaamsbeweging in vet, insuline, ontstekingen en hormoonverlagende middelen. [3] ’ [9-11]

Het dragen van schadelijke *BCRA1*- en *BCRA2* -genmutaties verhoogt het risico op borstkanker aanzienlijk. [12] Toch is er beperkt onderzoek gedaan naar het PA- en borstkankerrisico onder *BRCA*- mutatiedragers. [1] Gezien de hogere niveaus van circulerende geslachtshormonen onder *BRCA* -mutatiedragers, [13] kan het afzwakken van de beschikbaarheid van oestrogeen door regelmatige lichaamsbeweging bijzonder gunstig zijn voor de mutatiedragers. [14] ’ [15]

To reduce chronic disease risks moderate to vigorous PA is recommended for 60 minutes/day most days per week for all youth (approximately ≥ 20 MET-hours/week), 30–60 minutes/day for adults.[16] However, PA drops precipitously in adolescence and does not rebound, especially among girls.[17] This behavioral shift combined with earlier onset of breast cancer among *BRCA* mutation carriers[18–21] highlights the need to examine AYA exercise and breast cancer risk in this population specifically.

Methods

The systematic review was performed using PICOT as a structural guide and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement as the reporting guide.[22]

Eligibility Criteria

Studies that included data on PA during AYA years (with or without age stratification) among women, breast cancer incidence, and carriage of deleterious *BRCA1* or *BRCA2* gene mutations were eligible. Studies not focused on PA, only looking at adult or post-diagnosis PA, or not specific to or stratified for *BRCA* mutation status, and studies without breast cancer incidence data were not included. Also excluded were: animal studies, clinical trials without published data, conference abstracts, case reports, protocol papers, reviews, systematic reviews, meta-analyses, opinion pieces, letters to the editor, dissertations, book chapters, and studies not available in English.

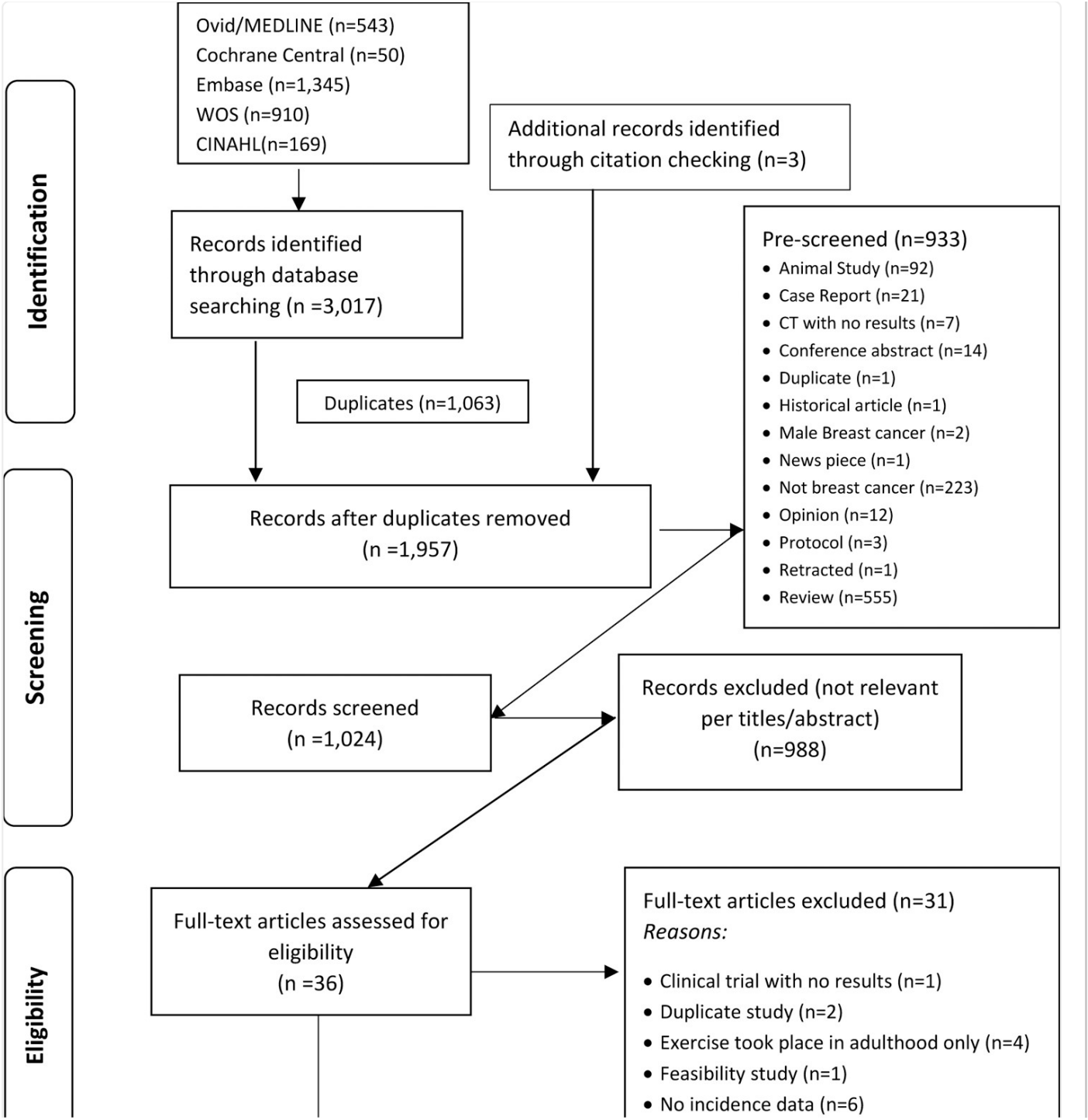
Search Strategy

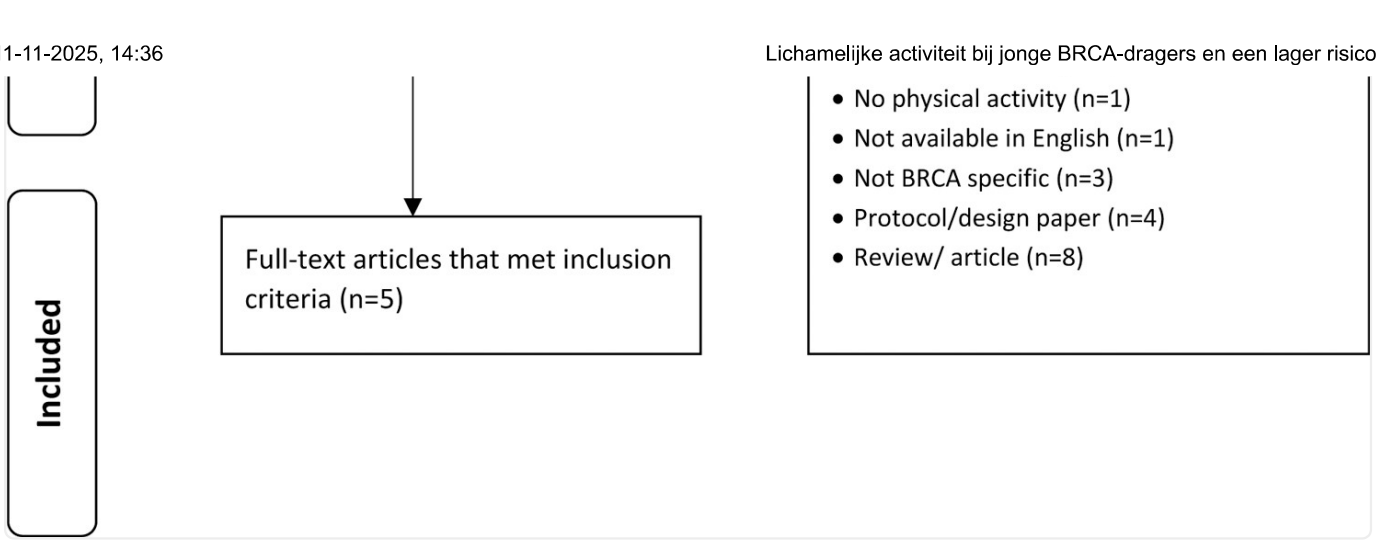
A medical librarian initially searched the following databases using controlled vocabulary terms (e.g. MeSH, Emtree) and keywords from the dates of their inception to October 21–22, 2019: Ovid/ MEDLINE; Elsevier/Embase; Cochrane Wiley/Cochrane Central Register of Controlled Trials (CENTRAL); Clarivate/ Web of Science (WOS); and EBSCO/Cumulative Index of Nursing and Allied Health Literature (CINAHL). Searches in WOS were updated on December 21, 2020, in anticipation of institutional loss of database access; the others were updated on March 29, 2021. Search strategies are available in Appendix A. Reference lists of review articles were also examined. Records were exported to EndNote Version X9 (Clarivate Analytics, Philadelphia, PA, USA).

Study Selection

The medical librarian pre-screened initial search results to exclude animal studies, case reports, clinical trials with no published results, conference abstracts, obvious opinion pieces, studies about cancers other than breast cancers and those limited to breast cancer in males, protocols, retracted articles, and reviews, including other systematic reviews and meta-analyses (Figure 1). Search results were then equally divided among reviewer pairs for title/abstract and full text review phases. For both phases, each article was screened by each member of the pair independently according to standard procedures. Disagreements were resolved by consensus of reviewers in consultation with the lead authors.

Figure 1. Study Flow Diagram.


Identification
Screening
Eligibility
Ovid/MEDLINE (n=543)
Cochrane Central (n=50)
Embase (n=1,345)
WOS (n=910)
CINAHL(n=169)
Additional records identified through citation checking (n=3)
Records identified through database searching (n =3,017)
Duplicates (n=1,063)
Pre-screened (n=933)
Animal Study (n=92)
Case Report (n=21)
CT with no results (n=7)
Conference abstract (n=14)
Duplicate (n=1)
Historical article (n=1)
Male Breast cancer (n=2)
News piece (n=1)
Not breast cancer (n=223)
Opinion (n=12)
Protocol (n=3)
Retracted (n=1)
Review (n=555)
Records after duplicates removed (n =1,957)
Records screened (n =1,024)
Records excluded (not relevant per titles/abstract) (n=988)
Full-text articles assessed for eligibility (n =36)
Full-text articles excluded (n=31)
Reasons:
Clinical trial with no results (n=1)
Duplicate study (n=2)
Exercise took place in adulthood only (n=4)
Feasibility study (n=1)
No incidence data (n=6)



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Study flowchart of the process of literature search and selection of studies meeting the inclusion criteria

Quality Assessment

Two independent reviewers assessed potential risks for bias using design specific NIH Quality Assessment Tools (Table 1). Similar categories between tools were placed together in the summary; differences in study type or scoring categories were indicated in parentheses.

Table 1.

Bias assessment of studies related to AYA physical activity, carriage of deleterious BRCA mutations, and breast cancer incidence using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (OS) and the NIH Quality Assessment of Case-Control Study (CC) criteria

NIH Bias Categories	Kehm 2020 (OS)	King 2003 (OS)	Pijpe 2010 (OS)	Lammert 2018 (CC)	Grill 2017 (OS)
Research question clear	+	+	+	+	+
Study population defined	+	+	+	+	+
Eligible participation ≥50% (OS); randomly selected from eligible if <100% (CC)	+	+	+	−	+
Similar populations recruited (across cohort and cases and controls; Inclusion/ exclusion prespecified	+	+	+	+	+
Processes to select cases/controls valid, reliable, consistent (CC only)	NA	NA	NA	+	NA
Sample size justification [a]	−	−	−	−	−

NIH Bias Categories	Kehm 2020 (OS)	King 2003 (OS)	Pijpe 2010 (OS)	Lammert 2018 (CC)	Grill 2017 (OS)
Exposure(s) measured occurred prior to outcome(s)	+	+	+	+	+
Follow-up timeframe sufficient (OS only) [b]	+	+	+	NA	+
Different levels of the exposure related to outcome assessed (OS only)	+	+	+	NA	−
Exposure measures clearly defined, valid, reliable, consistent	+	+	+	+	+
Exposure(s) assessed ≥1 time (cohort); concurrent controls (CC)	−	−	+	+	−
Outcome measures clearly defined, valid, reliable (OS); case-control status differentiation clear (CC)	+	+	+	+	+
Outcome assessors blinded to exposure status (OS); Exposure assessors blinded to case/control status (CC)	−	−	−	−	−
Loss to follow-up after baseline ≤20% (OS only)	+	+	+	NA	+

NIH Bias Categories	Kehm 2020 (OS)	King 2003 (OS)	Pijpe 2010 (OS)	Lammert 2018 (CC)	Grill 2017 (OS)
Key confounders measured and adjusted	+	+	+	+	–

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Medium grey + means present; near black – means not present or requirements not met; light grey NA means not applicable/bias category limited to study type indicated in parentheses, not present in the bias instrument for the other study type.
[a.] *Power* – while authors all considered power, none provided sample size justification, necessary effect size, or equations;
[b.] sufficient time from exposure to outcome is not applicable because of the retrospective AYA PA questionnaire, but in the observational studies, Grill, Pipje, Kehm, King, there were approximately 28 yrs between the AYA years and breast cancer diagnosis.

Data Extraction

Standard extraction forms were developed and pilot-tested for this systematic review. The following information was extracted: population characteristics, PA assessment, duration of follow-up, risk statistics, and, if available, PA associations with age of diagnosis. Data related to age groups outside AYA were not analyzed.

Results

Figure 1 demonstrates the process of the literature search and study selection. Five studies of the initially identified 3020 met full inclusion criteria: two cohort studies,[23, 24] two cross sectional analyses,[25, 26] and one case-control study.[27] All studies presented clearly defined research questions, objectives, and population descriptions. Sample size justification and blinding were lacking across studies. Retrospective assessment of AYA PA by self-report was a source of bias across studies but ameliorated potential loss to follow-up. Four studies statistically adjusted for potential confounders, such as BMI; one study was underpowered to do so.[26]

Study and sample characteristics

Study characteristics are presented in Table 2. Countries of origin varied by study, with race/ethnicity specified in only two studies, described as predominantly white[23] and Ashkenazi Jewish.[25] Mean age at enrollment ranged from 40.0–46.3 across studies, while the AYA period assessed ranged from 10–34 years of age. The majority of the articles assessed PA frequency, intensity, and duration,[23, 24, 26, 27] and computed metabolic equivalent values (METs)[23, 24, 27] using standard procedures.[28] The cut-points for MET comparisons varied across studies. Two studies classified individuals as active versus less- or not active.[25, 26]

Table 2.

Population characteristics and study designs across studies of AYA physical activity among *BRCA1* and *BRCA2* deleterious mutation carriers and non-carriers

Citation	Design & Data Source	Baseline Population Characteristics	PA Assessment	AYA PA Timeframe	Follow-up	Ana
Lammert et al, Breast Cancer Res Treat, 2018	Case-control N=886 (Cases 443; Controls 443) Multi-national (80 centers; 17 countries)	Female, *BRCA1* (77.4%) & *BRCA2* (22.6%) mutation; Single control/case, matched by mutation, country of residence, birth yr (± 3 yrs); average age controls 50.9 +/− 11.6 years, cases 51.6 +/− 10.9 years; % premenopausal	Questionnaire: MVPA, hrs/wk. Converted to METs: moderate (4.5); vigorous (7.0)	Ages 12–13, 14–17, 18–22, 23–29, 30–34 years	NA	Back Step Logi Regr Cova parit base toba OCP oopl

Citation	Design & Data Source	Baseline Population Characteristics	PA Assessment	AYA PA Timeframe	Follow-up	Anal
		controls 26.6%; cases 8.8%				
Kehm, Cancer Research, 2020[a]	Prospective Cohort N=1185 Multi-national (US, Canada, Australia, New Zealand, & kConFab consortium)	Female, *BRCA1* (55.61%) & *BRCA2* (44.39%) mutations, aged >18 years, and no risk-reducing surgery; included retrospective and prospective cases; % pre-menopausal 59%	Questionnaire: any PA, hrs/wk, during AYA. Converted to METs.	Ages 12–17 years	annual follow up for a median 10.3 years	Mult Cox Prop Haza Cova race, educ parit brea toba HRT alcol BMI

Citation	Design & Data Source	Baseline Population Characteristics	PA Assessment	AYA PA Timeframe	Follow-up	Anal
King, Science, 2003[a]	Cross-sectional; breast cancer survivor cohort; *BRCA1/2* mutation carriers N=104 United States	Females (Ashkenazi Jewish), *BRCA1* (65%) & *BRCA2* (35%) mutation, aged > 18 years, diagnosed with breast cancer between September 1996 and December 2000; % pre-menopausal NA; 42% diagnosed <50years of age (differed by birth cohort)	Questionnaire: categorized as active vs inactive during AYA	"Teenage years"	NA	Mult Cox Prop Haza Cova deca birth
Pijpe, Breast Cancer Res	Retrospective Cohort (with prospective follow-up)	Female, *BRCA1* (77%) & *BRCA2* (23%) mutation, no	Questionnaire: any PA, hrs/wk, converted to	Before age 30 years	Up to date of breast cancer	Time Mult Cox Prop

Citation	Design & Data Source	Baseline Population Characteristics	PA Assessment	AYA PA Timeframe	Follow-up	Ana
Treat, 2010[b]	N=725 Netherlands	prior breast cancer history, aged > 18 years; % pre-menopausal cohort 42%, cases 71%	METs; number of years active		incidence; Median age at end of follow-up 45.5 +/− 13.3 yrs	Haza Cova OCP. alcol parit men statu age spec grou occu activ
Grill, Arch Gynecol Obstet, 2017[b]	Cross-sectional at RCT baseline N=68 Germany	Female, *BRCA1* (61.8%) & *BRCA2* (32.2%) mutation, >18 yrs old, enrolled in LIBRE-1; %pre-menopausal NA.	Interviews and Questionnaire: any PA, hrs/wk and sports	Ages 10–19 and 20–29 years	None	Chi S Test

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HRT, hormonal replacement therapy; hrs, hours; MVPA, moderate to vigorous physical activity; OCP, oral contraceptive pill; RCT, randomized controlled trial; wk, week.
[a.]Total population of Kehm study 15,550 and King, 1008. The populations listed in table are the stratified groupings of *BRCA 1 & 2 deleterious mutations*;
[b.]Additional age groups outside the AYA timeframe of interest not presented.

AYA Physical Activity Associations with Breast Cancer Incidence

Four of five studies showed a significant reduction in breast cancer risk, up to 40%, with higher AYA PA[24–27] (N=3 lifetime risk;[24–26] N=1 limited to pre-menopausal breast cancer and adolescent activity[27]). A dose-response relationship was not demonstrated. In contrast, the largest study was null,[23] though the direction of AYA PA effect for *BRCA2* mutation carriers alone was protective.[23] One study additionally demonstrated an association between AYA PA and older age at breast cancer diagnosis among *BRCA* mutation carriers (p = 0.03).[25]

Discussion

The majority of the studies reviewed support a potential role for AYA PA in reducing or delaying breast cancer incidence among deleterious *BRCA* variant carriers, which expands upon previous breast cancer risk reductions associated with adult[2–5] and AYA PA[8] among average risk women. Importantly, effect sizes herein align with the breast cancer risk reduction estimates with AYA PA in the average risk population.[8] Taken together, these data suggest that beneficial effects of AYA PA may not be overwhelmed by genetic predisposition to breast cancer, though the dose of PA required has yet to be established.

While one may posit that the data are equivocal, based on the null study sample size versus sample in the remaining studies showing benefit, it is important to factor in the value of replication across sites. The collective data also suggest that the relation between AYA PA and breast cancer risk among *BRCA* mutation carriers may be nuanced and potentially more evident for *BRCA*2, adolescent versus young adult PA, and pre- versus postmenopausal cancers. Lower age of diagnosis and higher risk rates among *BRCA* 2 mutation carriers[18–21] emphasize the need to stratify along these lines. Additionally, all studies utilized retrospective self-report PA, which is prone to bias that may vary across regions and contribute to inconsistent results. Lastly, study designs and PA cut-points varied and limited studies were identified with the following: prospective follow-up;[23, 24] alignment of AYA age groups;[23, 27] stratification by age groups,[26, 27] pre- versus postmenopausal cancer,[27] and *BRCA* mutation type;[23] and adequate accounting of confounders, like BMI and hormone use,[23, 24, 27] which may differentially impact pre- versus postmenopausal risk.

Future studies with prospective, standardized, and repeated AYA PA assessment and more diverse populations among *BRCA* mutation carriers are needed. Nevertheless, the benefits of PA far outweigh risks of sedentarism across chronic conditions,[16] so a physically active lifestyle across the lifespan is recommended regardless of *BRCA* status.

Supplementary Material

Appendix A. Search Terms

NIHMS1867419-supplement-Appendix_A__Search_Terms.docx (34KB, docx)

Table 3.

Adolescent and young adult physical activity and risk of breast cancer among *BRCA1* and *BRCA2* deleterious mutation carriers versus non-carriers

Author	N	PA Age	Mutation	PA	Pre-men Dx	95% CI	Post-men Dx	95% CI	Li
Odds Ratios, 95% CIs									
				MVPA					
Lammert, 2018[a]	443	12yr – 17yr	*BRCA1/2*	Q1	1		1		
				Q2	1.04	0.70–1.53	1.25	0.71–2.18	
				Q3	1.48	0.94–2.32	1.39	0.71–2.73	
				Q4	**0.62**	**0.40–0.96**	1.53	0.87–2.71	
		18yr – 34yr	*BRCA1/2*	Q1	1		1		
				Q2	1.53	0.99–2.37	0.94	0.51–1.74	
				Q3	1.11	0.70–1.74	0.70	0.36–1.36	

Author	N	PA Age	Mutation	PA	Pre-men Dx	95% CI	Post-men Dx	95% CI	Li
				Q4	0.99	0.65–1.49	1.15	0.67–1.98	
				TOTAL					
		12yr – 17yr	*BRCA1/2*	Q1	1		1		
				Q2	0.83	0.53–1.31	0.89	0.48–1.67	
				Q3	1.4	0.92–2.12	1.18	0.65–2.14	
				Q4	0.89	0.59–1.33	1.1	0.63–1.91	
		18yr – 34yr	*BRCA1/2*	Q1	1		1		
				Q2	1.57	0.99–2.49	0.94	0.48–1.84	
				Q3	1.41	0.89–2.24	1.55	0.84–2.87	
				Q4	1.08	0.71–1.66	0.99	0.55–1.78	
Hazards Ratios, 95% CIs									
Kehm, 2020[b]	1185	12yr – 17yr	*BRCA1*	MVPA Q2–Q5 vs. Q1	NA		NA		

Author	N	PA Age	Mutation	PA	Pre-men Dx	95% CI	Post-men Dx	95% CI	Li
			BRCA2	Q2–Q5 vs. Q1	NA		NA		
King, 2003[c]	104	12yr – 17yr	*BRCA1/2*	Active /very active vs. inactive	NA		NA		
Pijpe, 2010[d]	725	<30yr	*BRCA1/2*	Low	NA		NA		
				Med	NA		NA		
				High	NA		NA		
Chi Squared Test									**Ca**
Grill, 2017[e]	68	10yr – 19yr	BRCA1/2	Active	NA		NA		**27**
				Less Active	NA		NA		**3**

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[Boldface indicates statistical significance (p<0.05).]

[a.]MVPA adolescent Q1 ≤6.75, Q2 >8.55 and ≤15.75, Q3 >15.75 and ≤27.56, Q4 > 25.88 MET-hrs/wk and young adult Q1 ≤6.75, Q2 >8.55 and ≤15.75, Q3 15.75 and ≤ 29.25, Q4 .29.25. Total recreational adolescent PA Q1≤24.25, Q2 >24.25 ≤ 40.25, Q3 >40.25 and ≤69.25, Q4 >69.25 and young adult Q1 ≤20.33, Q2 >20.33 and ≤ 38.58, Q3 38.58 and ≤ 63, >63 MET-hrs/wk;

[b.]MVPA Q1 0–14 METs/wk vs combined Q2 to Q5 ranging 15–121 METs/wk, reported prospective and retrospective combined data – all adolescent PA was retrospective report regardless of f/u for cases;

[c.]active or very active in recreational, dance, and sports activities versus inactive;

[d.]low <10.6, medium 10.6–21.7, high ≥ 21.7 MET-hrs/wk presented;

[e.]active versus less active compared to peers at age 10–19 years.

Samples presented are *BRCA* mutation carriers only; Data presented herein for Grill 2017 were obtained via personal communication with the lead author (original article presented the data as Figure 1). King and Kehm also included non-carriers and total sample was 1,008 and 15,550 respectively (total sample data not presented); The outcome for cox proportional hazards analyses were breast cancer incidence for Kehm and Pijpe studies, but age of diagnosis for King et al. CI, confidence interval; hrs, hours; MET, metabolic equivalents; MVPA, moderate to vigorous physical activity; PA, physical activity; pre-men, premenopausal cancer; post-men, postmenopausal cancer; Q; quantile.

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Conflict of Interest

The results from this review are presented as clear, honest without fabrication or manipulation of results and do not constitute endorsement by AJPM. There are no conflicts of interest or financial disclosures at this point of time for authors (AB, TL, CK, CV, CLH, EA, SV). The corresponding author would like to disclose receipt of funding from Disarm Therapeutics for another study in breast cancer patients. Disarm Therapeutics was not involved in the concept, writing, or interpretation of this manuscript in any way.

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Gekoppelde gegevens

In deze sectie worden alle gegevenscitaten, verklaringen over de beschikbaarheid van gegevens en aanvullend materiaal uit dit artikel verzameld.

Aanvullende materialen

Bijlage A. Zoektermen

NIHMS1867419-supplement-Appendix_A__Zoektermen.docx (34KB, docx)