Physical Activity, Reproductive Factors, and Breast Cancer Risk: A Prospective Cohort Study using data from the UK Biobank

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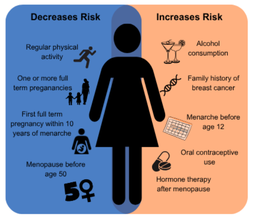
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Abstract

Introduction: Reproductive factors such as early menarche, late menopause, nulliparity, and exogenous hormone use are well-established risk factors for breast cancer. Physical activity is associated with a lower risk of breast cancer, but whether this protective effect varies across reproductive risk factors is not well characterized.
Objective: To investigate whether reproductive risk factors modify the association between physical activity and breast cancer risk.
Methods: Females ≥40 years without a history of cancer from UK Biobank provided self-reported data on moderate-to-vigorous intensity physical activity and reproductive factors (2007-2010). Physical activity levels were categorized based on reported metabolic equivalent hours per week (MET-hrs/week), with high levels of physical activity defined as ≥50 MET-hrs/week, moderate levels of physical activity as 10 to <50 MET-hrs/week, and low levels of physical activity as <10 MET-hrs/week. Incident cancers were ascertained to 13 May 2022. Multivariable Cox regressions were used to examine the association between baseline physical activity and breast cancer risk, adjusting for sociodemographic variables, lifestyle factors, and reproductive risk factors. Reproductive risk strata were defined by age at menarche (≤ vs. >12 years), parity (number of live births [<2 vs. 2+ live births]; age at first birth [within vs. more than 10 years from menarche]), age at menopause (≤ vs. >50 years), use of oral contraceptive and use of menopausal hormone therapy (ever use vs. never use). Multiplicative and additive interactions were assessed using interaction terms within Cox regression and Relative Excess Risk due to Interaction (RERI), respectively. Subgroup analyses were conducted for pre-menopausal and post-menopausal breast cancer risk.
Results: The study followed 242 721 participants for a mean of 12.53 years (SD: 2.55). During the study period, 8397 breast cancer cases were identified, including 748 pre-menopausal cases. Participants with high level of physical activity had significantly lower breast cancer risk (HR=0.87, 95%CI=0.82-0.93) compared to those with low level of physical activity. This association was observed for both pre- and post-menopausal breast cancer (HR [95% CI] = 0.78 [0.62-0.97] & 0.88 [0.83-0.94], respectively). The association between increased physical activity and decreased breast cancer risk was consistent across reproductive risk strata defined by age at menarche, parity, age at menopause, and use of oral contraceptive or menopausal hormone therapy (all p-values>0.05 for interaction terms and RERI estimates).
Conclusions: Physical activity is a useful breast cancer risk reduction strategy for women, regardless of their reproductive history.

Introduction

- Physical activity is associated with about 25–30% reduction in the risk of breast cancer[1]
- Differences in reproductive patterns and hormone exposures also shape breast cancer risk[2]
  - These patterns have changed across generations[3-5]



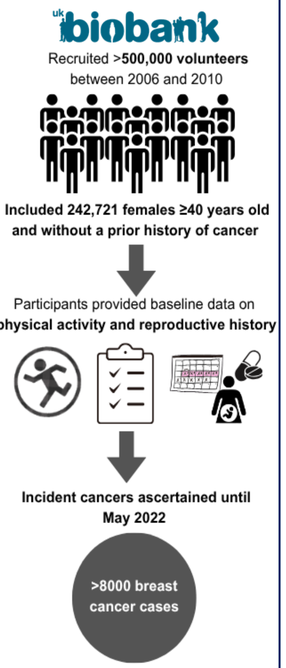
Research Question: **Is physical activity equally effective for women with reproductive histories that put them at a higher risk of breast cancer?**

Objective: **To investigate whether reproductive risk factors modify the association between physical activity and breast cancer risk.**

Methods and Materials

Study population

- Women ≥40 years without a history of cancer from UK Biobank[6]



Exposure and Outcome Variables

- Physical activity categorized as high (≥50), moderate (10-50) or low (<10) levels based on reported MET-hours per week
- Reproductive risk strata defined by:
  - Age at menarche ≤ vs. >12 yrs
  - Number of live births <2 vs. ≥2
  - Age at first live birth ≤ vs. >10 years from menarche
  - Age at menopause ≤ vs. > 50 years)
  - Use of oral contraceptive (ever use vs. never use)
  - Use of menopausal hormone therapy (ever use vs. never use)
- Participants were followed until cancer diagnosis, death, or date of most recent follow-up on May 13, 2022

Statistical Analyses

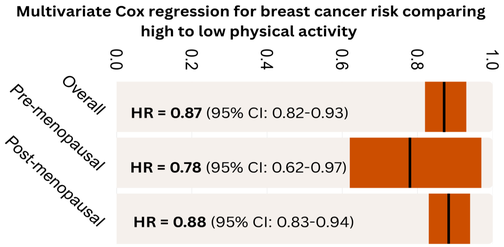
- Cox regression adjusting for sociodemographic, reproductive, & lifestyle factors to examine the association between baseline physical activity and breast cancer risk
- Multiplicative interactions assessed using interaction terms within bivariate Cox regression (physical activity x reproductive risk factor)
- Additive interactions assessed using Relative Excess Risk due to Interaction (RERI) estimates
- Subgroup analyses for pre- and post-menopausal breast cancer

Results

Physical Activity and Breast Cancer Risk

Participants with **high levels of physical activity had a significantly lower risk of breast cancer** compared to those with low levels of physical activity

- There was a significant protective effect for both pre- and post-menopausal breast cancer



Interactions with Reproductive Factors

- **The association between physical activity and overall breast cancer risk was consistent across reproductive risk strata**
- Oral contraceptive use was found to modify the association between physical activity and pre-menopausal breast cancer

Reproductive Risk Factors	Muliplicative interaction p-value	Additive interaction p-value
Age at menarche	0.72 (pre: 0.43, post: 0.90)	0.63 (pre: 0.41, post: 0.80)
Number of births	0.81 (pre: 0.52, post: 0.69)	0.90 (pre: 0.50, post: 0.76)
Age at first birth	0.37 (pre: 0.87, post: 0.32)	0.29 (pre: 0.95, post: 0.26)
Age at menopause	0.68 (post-menopausal only)	0.66 (post-menopausal only)
Menopausal hormone therapy	0.70 (post-menopausal only)	0.51 (post-menopausal only)
Oral contraceptives	0.87 (pre: **0.03****, post: 0.72)	0.84 (pre: 0.08, post: 0.76)

Conclusions

Physical activity is a useful population-level strategy for reducing the risk of breast cancer among women with different reproductive risk profiles

The **observed interaction between contraceptive use, physical activity, & pre-menopausal breast cancer risk is particularly significant** as:

- The incidence of breast cancer among pre-menopausal women in the United States is rising[7]
- The use of oral contraceptives is very common and is particularly relevant for younger women[6]

Our findings require further investigation, particularly exploring potential confounding factors and generalizability to other populations

Further investigation of the causal factors and potential biological mechanism underlying this interaction may be useful to inform precision prevention

Contact

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