Adolescent physical activity in relation to breast cancer risk

Published in final edited form as:
Breast Cancer Res Treat. 2014 June ; 145(3): 715–724. doi:10.1007/s10549-014-2919-5.

Adolescent physical activity in relation to breast cancer risk

Caroline E. Boeke,
Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA

A. Heather Eliassen,
Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA; Department of Medicine, Harvard Medical School, Boston, MA, USA

Hannah Oh,
Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA; Department of Nutrition, Harvard School of Public Health, Boston, MA, USA

Donna Spiegelman,
Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; Department of Nutrition, Harvard School of Public Health, Boston, MA, USA; Department of Biostatistics, Harvard School of Public Health, Boston, MA, USA

Walter C. Willett, and
Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA; Department of Medicine, Harvard Medical School, Boston, MA, USA; Department of Nutrition, Harvard School of Public Health, Boston, MA, USA

Rulla M. Tamimi
Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA; Department of Medicine, Harvard Medical School, Boston, MA, USA

Abstract

Adolescent physical activity may protect against premenopausal breast cancer. Whether it also prevents postmenopausal breast cancer, and whether associations are independent of adult activity, is unclear. We evaluated this association among 75,669 women in the Nurses' Health Study II. In

---

caroline.boeke@mail.harvard.edu.
Disclosures None.

1997, participants reported strenuous, moderate, and walking activity (hours/week) at ages 12–13, 14–17, 18–22, and 23–29 years. We estimated metabolic equivalent task hours (MET-h)/week. Participants also reported current physical activity over follow-up. Breast cancer diagnoses (n = 2,697; premenopausal = 1,351; postmenopausal = 965) through 2011 were reported by participants and confirmed with medical records. We additionally stratified analyses by median age at diagnosis. In Cox proportional hazards models adjusted for adolescent characteristics, physical activity from ages 14–22 was modestly inversely associated with premenopausal breast cancer [e.g., hazard ratio (HR) comparing 72+ to <21 MET-h/week 0.81 (95 % confidence interval (CI) 0.69–0.95; p-trend = 0.10) for ages 14–17 and 0.85 (95 % CI 0.71–1.02; p-trend = 0.06 for ages 18–22]. However, adjustment for adult activity and additional breast cancer risk factors attenuated the associations [ages 14–17: 0.85 (95 % CI 0.73–1.00; p-trend = 0.33)]. Associations were stronger among women diagnosed at younger ages [e.g., ages 18–22, HR 0.77 (95 % CI 0.60–0.99; p-trend = 0.05) for women diagnosed before 46.9 years; HR 1.02 (95 % CI 0.79–1.32; p-trend = 0.94) for those diagnosed at/after 46.9 years]. Early life physical activity was not associated with postmenopausal breast cancer. Overall, adolescent physical activity was not associated with breast cancer risk. However, we observed a suggestive inverse association of physical activity at ages 14–22 years with premenopausal breast cancer.

Keywords

Adolescence; Physical activity; Exercise; Breast cancer; Early life

Introduction

Adult physical activity appears to reduce breast cancer risk. In a recent meta-analysis of 31 prospective cohort studies comprising 63,786 breast cancer cases, a 12 % lower risk [relative risk (RR) 0.88; 95 % confidence interval (CI) 0.85–0.91] was observed for women in the highest category of activity compared with the lowest [1]. An estimated ten percent of breast cancers worldwide are attributable to adult inactivity [2]. Physical activity may reduce risk through several mechanisms, including changing menstruation patterns, increasing insulin sensitivity, and reducing fat mass, inflammation, and production of adipokines and sex hormones [3]. Previous studies in adults suggest a stronger association with estrogen receptor (ER)-negative cancers [4, 5].

Adolescence is a time of heightened susceptibility to breast cancer risk factors because breast tissue is still developing [6, 7]. In the Nurses' Health Study II (NHSII), greater lifetime physical activity was associated with a lower premenopausal breast cancer risk [hazard ratio (HR): 0.77 (95 % CI 0.64–0.93) comparing 39+ metabolic equivalent task hours (MET-h)/week of average lifetime activity to less activity], and physical activity during ages 12–22 years contributed most to this association [8]. However, this prior study included only 550 cases over limited follow-up (6 years). Additionally, authors of a recent meta-analysis did not find that physical activity during early life was more protective of breast cancer risk than adult activity [1]. Finally, whether adolescent physical activity protects against postmenopausal breast cancer, and whether associations are independent of adult physical activity, is not clear.

We assessed whether early life physical activity is associated with breast cancer risk, independent of adult activity, in the NHSII. We hypothesized that adolescent physical activity is protective for premenopausal and postmenopausal breast cancer, even after adjustment for adult activity, and that associations are strongest in women with ER-negative tumors.

Methods

Study population

In 1989, 116,430 US female registered nurses ages 25–42 years completed the initial NHSII questionnaire. Information is collected biennially through mailed questionnaires.

Follow-up for this analysis began in 1997, when adolescent physical activity was assessed. From 78,733 women with complete information about adolescent and adult physical activity on this questionnaire, we excluded women with a previous cancer diagnosis (except non-melanoma skin cancer) or an unknown date of breast cancer diagnosis, leaving 75,669 participants. The cumulative follow-up was over 90 % of the total possible person-years of follow-up from baseline.

Physical Activity Assessment

Women reported the average time per week (in seven categories ranging from 0 to ≥11 h) spent in (1) walking to/from school/work, (2) moderate recreational activity (e.g., hiking, walking for exercise, casual cycling, or yard work), and (3) strenuous recreational activity causing increased breathing, heart-rate, or sweating (e.g., running, aerobics, or lap swimming) at/in grades 7–8 in school (ages 12–13), grades 9–12 (ages 14–17), ages 18–22, and ages 23–29. To create a total activity score weighted by intensity, MET-h/week [9] were assigned using the following formula: (3.0 * hours of walking) + (4.5 * hours of moderate activity) + (7.0 * hours of strenuous activity). We grouped activity into categories used previously [8].

In 1989, 1991, 1997, 2001, and 2009, women reported average time per week (in 10 categories ranging from none 0 to ≥11 h) during the preceding year spent in walking or hiking outdoors, jogging, running, bicycling, lap swimming, tennis, calisthenics/aerobics/aerobic dance/rowing machine, and squash/racquetball. To calculate adult activity, MET scores for walking were assigned using reported pace (average: 3.0 METs); an intensity score was selected for the other activities, as described previously [10]. We calculated updated cumulative average physical activity at each cycle during follow-up for each participant using all available adult data (e.g., 1997 and 1999 used mean activity in 1989, 1991, and 1997; 2001 and 2003 used mean activity in 1989, 1991, 1997, and 2001; etc.). We grouped adult activity into categories used previously [8]. In a validation study in 151 NHSII participants, the adult activity questionnaire under-estimated moderate/vigorous activity compared with four 7-day activity diaries, but the correlation for moderate/vigorous activity (MET-h/week) was relatively strong ($r = 0.62$), suggesting that the questionnaire is reasonably valid for ranking participants [11].

Breast cancer case ascertainment

Women reported incident cancer diagnoses on biennial questionnaires through 2011. We reviewed medical records to confirm diagnoses and classify invasiveness and hormone receptor status. To identify cancers in non-respondents who died, death certificates and medical records were obtained.

Covariate assessment

At each cycle, we calculated participant age using birth date and questionnaire return date. In 1989, participants reported height, age at menarche, oral contraceptive (OC) history, reproductive history, alcohol intake at ages 15–17, 18–22, and 23–39 years, and body size at ages 10 and 20 years (using a nine category figure drawing developed by Stunkard et al. [12], as described previously [13]). Biennially, women reported weight, new pregnancies, breastfeeding duration (through 2003), OC and postmenopausal hormone use, menopausal status, age at menopause, and benign breast disease diagnosis. Women missing menopausal status were considered postmenopausal after a hysterectomy/bilateral oophorectomy or if a non-smoker over age 56 years/current smoker over 54 years, and premenopausal if a non-smoker under age 48 years/current smoker under 46 years. Every four years, women reported family history of breast cancer and alcohol consumption was measured with a semi-quantitative food frequency questionnaire. We calculated updated cumulative average alcohol consumption.

Statistical analysis

Person-time for each participant was calculated from the 1997 questionnaire return date to date of cancer diagnosis, death from any cause, loss to follow-up, or June 1, 2011, whichever came first. We used Cox proportional hazards models stratified on calendar year and age in months to estimate HRs and 95 % CIs. Covariates were updated every two years where possible. We examined categories of physical activity to allow for non-linearity and minimize the influence of outliers. We used the median values in each category as a continuous variable to test for linear trend. The associations appeared to be linear when we ran restricted cubic splines.

We adjusted for adolescent breast cancer risk factors including alcohol intake, height, age at menarche, and body size (MV_1 in tables). We ran a model additionally adjusted for adult predictors of breast cancer ($MV_{1+\text{adult factors}}$), including possible confounders or mediators. Adjusting for OC use and adolescent menstrual cycle characteristics did not change the associations; we did not include these variables in final models.

Results were similar for invasive and in situ cases; our primary analysis included both.

We assessed premenopausal associations by age at diagnosis (above versus below median age 46.9 years), adolescent OC use, adolescent alcohol consumption, and adult BMI. We assessed interactions using likelihood ratio tests with a continuous interaction term. To determine whether associations differed by ER status, we used cause-specific hazard Cox models [14, 15]. The data augmentation method described by Lunn and McNeil [16] was used to create a separate observation for each subject for each outcome type; we then stratified on event type in the Cox model analysis, allowing for estimation of separate associations of each risk factor with the relative hazard of each outcome. We used likelihood ratio tests to compare models assuming different associations of exposures with each tumor type to models assuming the same association with all types.

We assessed quintiles of “lifetime” [defined as mean adolescent (mean of 14–17 and 18–22 years) and adult] physical activity and breast cancer. We also categorized adolescent (ages 14–22) and adult activity into two groups roughly based on the median physical activity at each time period and cross-classified activity into four combinations of low/high adolescent/adult activity. We calculated a *p* value for interaction using a likelihood ratio test comparing a model with the main effects of adolescent and adult activity (continuous variables based on the median of the 5 categories), to a model with main effects and an interaction term.

Finally, we assessed whether substituting moderate or strenuous physical activity during adolescence in place of walking was associated with breast cancer. We created an isotemporal substitution model [17] adjusting for hours/week of moderate, strenuous, and total activity. The coefficients for moderate and strenuous activity can be interpreted as the apparent effect of substituting that type of activity for walking, while keeping total physical activity constant.

Analyses were conducted with SAS version 9.2 (SAS, Cary, USA). Statistical tests were two sided, and *p* values <0.05 were considered statistically significant. This study was approved by the Committee on the Use of Human Subjects in Research at Brigham and Women’s Hospital. Questionnaire completion was considered to imply informed consent.

Results

Over 975,258 person-years of follow-up, 2,697 breast cancers developed (premenopausal = 1,351; postmenopausal = 965). On average, women with higher physical activity between ages 14 and 17 had a lower BMI at age 18 (21.1 versus 21.6 comparing those with 72+ vs. <21 MET-h/week), were taller (65.1 versus 64.7 inches), were younger at first childbirth (26.1 versus 26.6 years), and had higher adult physical activity (47.5 versus 36.4 MET-h/week at baseline) compared to women with low adolescent physical activity (Table 1). More women in the highest category of activity consumed alcohol at ages 14–17 (24.7 vs. 20.6 %) and fewer experienced menarche before age 12 (23.2 vs. 26.2 %).

Women in the highest category of physical activity between ages 14 and 17 had a lower breast cancer risk [HR for 72+ versus <21 MET-h/week 0.85 (95 % CI 0.76–0.95; *p*-trend = 0.04)] in a model adjusted for adolescent characteristics. Adjustment for adult characteristics, especially adult BMI, modestly attenuated the association [HR 0.88 (95 % CI 0.78–0.98; *p*-trend = 0.16]; see Table 2]. The borderline inverse association appeared to be driven by premenopausal cases. For ages 14–17, the HR adjusted for adolescent factors was 0.81 (95 % CI 0.69–0.95; *p*-trend = 0.10) for premenopausal breast cancer; after additionally adjusting for adult factors the HR was 0.85 (95 % CI 0.73–1.00; *p*-trend = 0.33). Physical activity before age 14 and after 22 years was not associated with premenopausal breast cancer. High average physical activity between ages 14–22 (C72 MET-h/week) was associated with a modestly lower breast cancer risk [HR: 0.88 (95 % CI 0.78–0.99); *p*-trend = 0.04 in models adjusted for adolescent characteristics]. Early life physical activity was not associated with postmenopausal breast cancer risk.

Adolescent physical activity appeared to be more strongly related to ER-negative premenopausal breast cancer (Table 3), although case numbers were small (697 ER-positive and 170 ER-negative cases) and values were not statistically significant. For example, in the model adjusted for adolescent and adult characteristics, the women who were most physically active at ages 18–22 had a 16 % lower risk of ER-negative premenopausal breast cancer [HR 0.84 (95 % CI 0.50–1.41; *p*-trend = 0.55)] compared to those with little activity, versus no association with ER-positive cancer. In general, we did not observe differences by ER status for postmenopausal breast cancer (data not shown). However, there was a suggestive association between physical activity at ages 18–22 and ER-positive cancer [*n* = 536 cases; top versus bottom category HR 0.72 (95 % CI 0.54–0.97; *p*-trend = 0.01) in the fully adjusted model], whereas for ER-negative cancer (*n* = 117 cases), the association was not linear and the relative risk in the top versus bottom category was 0.88 (95 % CI 0.47–1.64; *p*-trend = 0.86; *p*-heterogeneity = 0.20).

Associations of physical activity between ages 14 and 22 with premenopausal breast cancer appeared slightly stronger among women who were younger at diagnosis (Table 4). For example, the fully adjusted association between activity at 18–22 years and premenopausal breast cancer was 0.77 (95 % CI 0.60–0.99; *p*-trend = 0.05) in women diagnosed before age 46.9 years (*n* = 677) and 1.02 (95 % CI 0.79–1.32; *p*-trend = 0.94) in women diagnosed at or after age 46.9 years (*n* = 674). However, the interactions were not statistically significant.

Adolescent alcohol consumption and OC use did not modify the associations examined. Substituting adolescent moderate or strenuous physical activity for walking was not associated with breast cancer risk. Having high lifetime physical activity was associated with a modestly lower breast cancer risk [HR 0.89 (95 % CI 0.78–1.00) for 55+ vs. <18 MET-h/week; *p*-trend = 0.05]. Having both high (above the median) adolescent and adult physical activity was associated with a slightly lower risk compared to both low adolescent and adult physical activity but the interaction was non-significant [HR 0.87 (95 % CI 0.79–0.97; *p*-interaction = 0.11)].

Discussion

In this study, physical activity between ages 14 and 22 years appeared to be modestly protective for premenopausal breast cancer, but adjusting for adult physical activity and other characteristics attenuated the association. The association appeared to be slightly stronger in women with ER-negative tumors and in younger premenopausal women, although the differences were not statistically significant. Early life physical activity was not associated with postmenopausal breast cancer risk.

In our study, the most frequent exercisers at ages 14–22 had a ~10–15 % lower risk of breast cancer. This finding is similar, although more modest, than was previously reported in this cohort with limited follow-up; [8] in that study, the most frequent exercisers at ages 12–22 had a 25 % lower premenopausal breast cancer risk [HR 0.75 (95 % CI 0.57–0.99; *p*-trend = 0.05)]. The present analysis has more than twice the number of premenopausal breast cancer cases (1,351 vs. 550 cases) and follow-up time (14 vs. 6 years). The attenuation observed could be explained by differences in etiology between younger and older cases of premenopausal cancer; the additional premenopausal cases included in this analysis tended to be older. When we separated premenopausal cases by age at diagnosis, the physical activity association was stronger among younger cases than older cases. Younger cases were more likely to have ER-negative tumors than older cases (20.8 vs. 15.9 %), and associations appeared to be strongest for ER-negative cancers. Thus, the more modest associations in this study could be due to a smaller proportion of total cases being ER-negative.

Being highly active in adolescence may be protective simply because physical activity at any age protects against breast cancer, and early life activity is correlated with adult activity (e.g., Spearman correlation of physical activity at ages 18–22 with current activity reported in 1997: $r \sim 0.2$). Still, among high adolescent exercisers, a suggestive association with premenopausal breast cancer remained, even after adjustment for adult activity, weight gain, and other characteristics that may be mechanisms through which adolescent physical activity influences breast cancer risk. Women who are active as adolescents are more likely to be active as adults and less likely to gain weight as they age, which could have independent effects on hormone levels/inflammatory pathways. Overall, physical activity at earlier (12–13 years) and later (23–29 years) ages was not associated with breast cancer. The model of breast cancer risk proposed by Pike et al. [6] suggests that risk factors are most influential between menarche and first pregnancy and more recent analysis supports this idea [7]. This time period roughly coincides with the ages where the association was strongest in our study (ages 14–22).

We did not find associations between early life physical activity and postmenopausal breast cancer. Our finding contrasts with a previous case–control study reporting a strong inverse association [18], but prospective cohort studies have shown modest or null associations. In the Women’s Health Initiative Observational Study, participation in physical activity at age 18 was associated with a slightly lower, though non-significant postmenopausal breast cancer risk [RR 0.94 (95 % CI 0.85–1.04)] [19], and in a prospective cohort of mostly postmenopausal Chinese women, no association was observed for physical activity between ages 13 and 19 years and breast cancer [20]. In the Nurses’ Health Study, we found that recent physical activity was more relevant for postmenopausal breast cancer than long-term average physical activity [10], and in 118,899 women in the prospective NIH-AARP Diet and Health Study, recent, but not early life, physical activity was associated with postmenopausal breast cancer risk [21]. In our study, women who went on to develop premenopausal breast cancer were on average 4 years younger when completing the adolescent activity questionnaire than women who went on to develop postmenopausal breast cancer; their recall may have been more accurate. Alternatively, by the time women are postmenopausal, other stronger factors may dominate and “wash out” any modest effects of adolescent activity on breast cancer. Taken together, these findings suggest that early life physical activity does not strongly protect against postmenopausal breast cancer, although activity later in life is probably beneficial [22].

Several mechanisms may mediate a reduction in breast cancer risk by physical activity, particularly activity occurring during early life when breast tissue is still developing. Adolescent athletes often experience delays in menarche and reduced menstrual cycles/ anovulation, which changes sex hormone exposure profiles. High levels of endogenous hormones like estrogens, androgens, and prolactin increase breast cancer risk [23]. Physical activity also can reduce fat mass and thereby change adipokine exposure. However, early life body fat appears to be protective against breast cancer risk; thus, weight change may not be a primary mechanism [24, 25]. Finally, exercise increases insulin sensitivity, reduces IGF-1, and reduces inflammation, which may help to protect against breast cancer [3, 23]. Given that in our population, the associations appeared to be strongest for ER-negative breast cancer, these non-hormonal mechanisms may be most likely to explain the observed association [26].

Study strengths include the large sample size, comprehensive case follow-up, and detailed prospective information on adult physical activity and other covariates. This study is limited by the fact that women recalled their early life physical activity at the mean age of 42 years, which likely introduced some exposure misclassification. However, these measurements should discriminate between women with very high and very low physical activity as adolescents, and breast cancers occurred after this assessment; therefore, any misclassification is likely non-differential [8]. Non-differential misclassification would likely attenuate the associations examined, and therefore, the true associations may be stronger than those reported here. Unmeasured factors may confound the associations. However, adjustment for breast cancer risk factors did not have a large impact on the associations examined, suggesting that any additional confounding is likely small.

In this cohort study, early life physical activity was not strongly associated with breast cancer risk. Physical activity between ages 14–22 appeared to be modestly protective for premenopausal breast cancer, but associations were attenuated when adjusted for adult physical activity and other adult factors. Early life physical activity was not associated with reduced postmenopausal breast cancer risk. However, given that few behaviors are known to prevent premenopausal breast cancer, the possible protective effect of adolescent physical is encouraging. Physical activity in early life and throughout adulthood should be promoted in all girls and women to prevent chronic diseases and possibly breast cancer.

Acknowledgments

We would like to thank the participants and staff of the Nurses' Health Study II for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. In addition, this study was approved by the Connecticut Department of Public Health (DPH) Human Investigations Committee. Certain data used in this publication were obtained from the DPH. The authors assume full responsibility for analyses and interpretation of these data. This work was supported by the Breast Cancer Research Foundation and the National Institutes of Health (grant numbers UM1 CA 176726, CA 050385). Caroline Boeke and Hannah Oh were funded by T32 CA 09001.

Abbreviations

NHSII	Nurses' Health Study II

MET-h	Metabolic equivalent task hours
HR	Hazard ratio
CI	Confidence interval
ER	Estrogen receptor
OC	Oral contraceptive
BMI	Body mass index

References

1. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. Breast Cancer Res Treat. 2013; 137(3):869–882. doi:10.1007/s10549-012-2396-7. [PubMed: 23274845]
2. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012; 380(9838):219–229. doi:10.1016/S0140-6736(12)61031-9. [PubMed: 22818936]
3. Friedenreich CM. Physical activity and breast cancer: review of the epidemiologic evidence and biologic mechanisms. Recent Results Cancer Res. 2011; 188:125–139. doi: 10.1007/978-3-642-10858-7_11. [PubMed: 21253795]
4. Peters TM, Schatzkin A, Gierach GL, Moore SC, Lacey JV Jr, Wareham NJ, Ekelund U, Hollenbeck AR, Leitzmann MF. Physical activity and postmenopausal breast cancer risk in the NIH-AARP diet and health study. Cancer Epidemiol Biomarkers Prev. 2009; 18(1):289–296. doi: 10.1158/1055-9965.EPI-08-0768. [PubMed: 19124511]
5. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. Br J Sports Med. 2008; 42(8):636–647. doi:10.1136/bjsm.2006.029132. [PubMed: 18487249]
6. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. Nature. 1983; 303(5920):767–770. [PubMed: 6866078]
7. Colditz GA, Frazier AL. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. Cancer Epidemiol Biomarkers Prev. 1995; 4(5):567–571. [PubMed: 7549816]
8. Maruti SS, Willett WC, Feskanich D, Rosner B, Colditz GA. A prospective study of age-specific physical activity and premenopausal breast cancer. J Natl Cancer Inst. 2008; 100(10):728–737. doi: 10.1093/jnci/djn135. [PubMed: 18477801]
9. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, Paffenbarger RS Jr. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc. 1993; 25(1):71–80. [PubMed: 8292105]
10. Eliassen AH, Hankinson SE, Rosner B, Holmes MD, Willett WC. Physical activity and risk of breast cancer among postmenopausal women. Arch Intern Med. 2010; 170(19):1758–1764. doi: 10.1001/archinternmed.2010.363. [PubMed: 20975025]
11. Wolf AM, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Corsano KA, Rosner B, Kriska A, Willett WC. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol. 1994; 23(5):991–999. [PubMed: 7860180]
12. Stunkard, AJ.; Sørensen, T.; Schulsinger, F., editors. The genetics of neurological and psychiatric disorders. Raven Press; New York: 1983. Use of the Danish Adoption Register for the study of obesity and thinness.
13. Baer HJ, Schnitt SJ, Connolly JL, Byrne C, Willett WC, Rosner B, Colditz GA. Early life factors and incidence of proliferative benign breast disease. Cancer Epidemiol Biomarkers Prev. 2005; 14(12):2889–2897. doi:10.1158/1055-9965.EPI-05-0525. [PubMed: 16365006]

14. Rosner B, Glynn RJ, Tamimi RM, Chen WY, Colditz GA, Willett WC, Hankinson SE. Breast cancer risk prediction with heterogeneous risk profiles according to breast cancer tumor markers. Am J Epidemiol. 2013 doi:10.1093/aje/kws457.
15. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. Am J Epidemiol. 2005; 162(10):975–982. doi:10.1093/aje/kwi309. [PubMed: 16207808]
16. Lunn M, McNeil D. Applying Cox regression to competing risks. Biometrics. 1995; 51(2):524–532. [PubMed: 7662841]
17. Mekary RA, Willett WC, Hu FB, Ding EL. Isotemporal substitution paradigm for physical activity epidemiology and weight change. Am J Epidemiol. 2009; 170(4):519–527. doi:10.1093/aje/kwp163. [PubMed: 19584129]
18. Shoff SM, Newcomb PA, Trentham-Dietz A, Remington PL, Mittendorf R, Greenberg ER, Willett WC. Early-life physical activity and postmenopausal breast cancer: effect of body size and weight change. Cancer Epidemiol Biomarkers Prev. 2000; 9(6):591–595. [PubMed: 10868694]
19. McTiernan A, Kooperberg C, White E, Wilcox S, Coates R, Adams-Campbell LL, Woods N, Ockene J. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. JAMA. 2003; 290(10):1331–1336. doi:10.1001/jama.290.10.1331. [PubMed: 12966124]
20. Pronk A, Ji BT, Shu XO, Chow WH, Xue S, Yang G, Li HL, Rothman N, Gao YT, Zheng W, Matthews CE. Physical activity and breast cancer risk in Chinese women. Br J Cancer. 2011; 105(9):1443–1450. doi:10.1038/bjc.2011.370. [PubMed: 21934685]
21. Peters TM, Moore SC, Gierach GL, Wareham NJ, Ekelund U, Hollenbeck AR, Schatzkin A, Leitzmann MF. Intensity and timing of physical activity in relation to postmenopausal breast cancer risk: the prospective NIH-AARP diet and health study. BMC Cancer. 2009; 9:349. doi:10.1186/1471-2407-9-349. [PubMed: 19796379]
22. Goncalves AK, Florencio G, Maisonnette MJ, Cobucci R, Giraldo P, Cote N. Effects of physical activity on breast cancer prevention: a systematic review. J Phys Act Health. 2013; 11(2):445–454. [PubMed: 23416687]
23. Tworoger SS, Rosner BA, Willett WC, Hankinson SE. The combined influence of multiple sex and growth hormones on risk of postmenopausal breast cancer: a nested case-control study. Breast Cancer Res. 2011; 13(5):R99. doi:10.1186/bcr3040. [PubMed: 22017816]
24. Harris HR, Tamimi RM, Willett WC, Hankinson SE, Michels KB. Body size across the life course, mammographic density, and risk of breast cancer. Am J Epidemiol. 2011; 174(8):909–918. doi:10.1093/aje/kwr225. [PubMed: 21911827]
25. Samimi G, Colditz GA, Baer HJ, Tamimi RM. Measures of energy balance and mammographic density in the Nurses' Health Study. Breast Cancer Res Treat. 2008; 109(1):113–122. doi:10.1007/s10549-007-9631-7. [PubMed: 17592770]
26. Neilson HK, Friedenreich CM, Brockton NT, Millikan RC. Physical activity and postmenopausal breast cancer: proposed biologic mechanisms and areas for future research. Cancer Epidemiol Biomarkers Prev. 2009; 18(1):11–27. doi:10.1158/1055-9965.EPI-08-0756. [PubMed: 19124476]

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Characteristics of 75,669 women in the Nurses' Health Study II in 1997 according to categories of physical activity between ages 14 and 17

	MET-h/week				
N	**<21** **15,393**	**21 to <36** **14,860**	**36 to <48** **10,288** **Mean (SD)/%**	**48 to <72** **15,932**	**72+** **19,196**
Family history of breast cancer	8.9 %	9.3 %	9.1 %	9.3 %	9.1 %
Height, inches	64.7 (2.6)	64.8 (2.6)	64.9 (2.6)	65.0 (2.6)	65.1 (2.6)
Adolescent characteristics					
BMI at 18 (kg/m^2)	21.6 (3.7)	21.3 (3.3)	21.2 (3.2)	21.1 (3.1)	21.0 (3.0)
Body size category >4[a]	18.2 %	14.8 %	13.4 %	12.3 %	10.5 %
Age at menarche < 12 years	26.2 %	24.5 %	23.3 %	24.0 %	23.2 %
Alcohol drinker	20.6 %	22.4 %	23.4 %	23.5 %	24.7 %
Adult characteristics					
Age (years)	43.1 (4.6)	42.9 (4.6)	42.6 (4.6)	42.5 (4.7)	42.0 (4.7)
Physical activity (MET-hours per week)	36.4 (80.2)	38.0 (79.8)	41.0 (83.1)	42.8 (83.7)	47.5 (84.9)
BMI	26.0 (6.1)	25.9 (6.0)	26.0 (6.0)	26.0 (5.9)	26.2 (6.0)
Alcohol consumption (g/day)	3.0 (5.6)	3.1 (5.7)	3.3 (5.8)	3.2 (5.5)	3.3 (6.0)
Current oral contraceptive user	9.0 %	8.4 %	8.4 %	8.3 %	8.0 %
Past oral contraceptive user	76.1 %	77.7 %	77.8 %	78.3 %	78.9 %
History of biopsy-confirmed benign breast disease	15.6 %	16.0 %	15.6 %	15.6 %	16.6 %
Nulliparous	20.9 %	20.0 %	19.9 %	19.1 %	19.0 %
Parity[b]	2.2 (0.9)	2.3 (0.9)	2.2 (0.9)	2.3 (0.9)	2.3 (1.0)
Age at first birth (years)[b]	26.6 (4.5)	26.6 (4.6)	26.5 (4.6)	26.4 (4.6)	26.1 (4.6)
Ever breastfed[b]	79.0 %	79.5 %	80.1 %	80.1 %	79.6 %
Postmenopausal	10.5 %	9.9 %	10.9 %	10.9 %	12.2 %

Values are standardized to the age distribution of the study population

[a] Based on a 9 point pictogram scale [12]. Average body size between ages 10 and 20 was calculated. Highest categories were categories 5–9

[b] Among parous women

Table 2

MET-hours per week of adolescent physical activity in relation to breast cancer risk in the Nurses' Health Study II, 1997–2011

	MET-hours per week					*p*-trend
	<21	**21 to <36**	**36 to <48**	**48 to <72**	**72+**	
	Hazard Ratio (95 % confidence interval)					
12–13 years						
All						
Person Years	209,638	204,936	135,383	202,606	222,695	
Cases	616	544	390	527	620	
MV_1	1.00	0.89 (0.79–1.00)	0.97 (0.86–1.11)	0.87 (0.77, 0.98)	0.93 (0.83–1.04)	0.38
$MV_{1+\text{adult factors}}$	1.00	0.90 (0.80–1.01)	0.99 (0.87–1.13)	0.89 (0.79–1.00)	0.97 (0.86–1.09)	0.84
Premenopausal						
PY	115,225	113,318	75,183	112,162	121,795	
Cases	312	282	190	261	306	
MV_1	1.00	0.89 (0.76–1.05)	0.92 (0.77–1.11)	0.84 (0.71–0.99)	0.92 (0.79–1.08)	0.41
$MV_{1+\text{adult factors}}$	1.00	0.91 (0.77–1.07)	0.94 (0.79–1.13)	0.86 (0.73–1.02)	0.97 (0.82–1.14)	0.80
Postmenopausal						
Person years	69,652	67,310	43,839	66,197	72,345	
Cases	218	190	146	192	219	
MV_1	1.00	0.88 (0.72–1.07)	1.04 (0.84–1.28)	0.90 (0.74–1.09)	0.93 (0.77–1.12)	0.58
$MV_{1+\text{adult factors}}$	1.00	0.88 (0.72–1.07)	1.05 (0.85–1.30)	0.92 (0.75–1.12)	0.95 (0.79–1.16)	0.84
						P-int = 0.83
14–17 years						
All						
Person Years	198,566	192,452	132,970	205,103	246,167	
Cases	609	508	367	579	634	
MV_1	1.00	0.85 (0.75–0.95)	0.90 (0.79–1.03)	0.91 (0.81–1.02)	0.85 (0.76–0.95)	0.04
$MV_{1+\text{adult factors}}$	1.00	0.86 (0.76–0.96)	0.92 (0.81–1.05)	0.93 (0.83–1.05)	0.88 (0.78–0.98)	0.16
Premenopausal						
PY	105,952	104,393	74,107	113,667	139,565	
Cases	309	241	185	291	325	
MV_1	1.00	0.77 (0.65–0.92)	0.86 (0.71–1.03)	0.87 (0.74–1.02)	0.81 (0.69–0.95)	0.10
$MV_{1+\text{adult factors}}$	1.00	0.78 (0.66–0.93)	0.88 (0.73–1.06)	0.90 (0.76–1.05)	0.85 (0.73–1.00)	0.33
Postmenopausal						
Person years	69,341	64,517	43,333	66,227	75,925	
Cases	221	192	132	203	217	
MV_1	1.00	0.92 (0.75–1.11)	0.95 (0.76–1.18)	0.94 (0.78–1.14)	0.87 (0.72–1.06)	0.23
$MV_{1+\text{adult factors}}$	1.00	0.92 (0.76–1.12)	0.96 (0.77–1.19)	0.96 (0.79–1.17)	0.90 (0.74–1.09)	0.37
						P-int = 0.58
18–22 years						

	MET-hours per week					*p*-trend
	<21	**21 to <36**	**36 to <48**	**48 to <72**	**72+**	
	Hazard Ratio (95 % confidence interval)					
All						
Person years	281,436	218,537	133,527	180,224	161,535	
Cases	808	630	376	493	390	
MV_1	1.00	1.03 (0.93–1.14)	1.02 (0.90–1.16)	0.99 (0.89–1.11)	0.89 (0.78–1.00)	0.05
$MV_{1+adult}$	1.00	1.04 (0.93–1.15)	1.05 (0.92–1.18)	1.01 (0.90–1.14)	0.91 (0.81–1.03)	0.15
Premenopausal						
Person Years	142,718	120,456	76,083	103,873	94,552	
Cases	371	322	197	263	198	
MV_1	1.00	1.07 (0.92–1.24)	1.04 (0.87–1.23)	1.02 (0.87–1.20)	0.85 (0.71–1.02)	0.06
$MV_{1+adult\ factors}$	1.00	1.07 (0.92–1.25)	1.06 (0.89, −1.26)	1.05 (0.89–1.24)	0.89 (0.74–1.06)	0.17
Postmenopausal						
Person Years	103,970	72,041	41,526	54,631	47,174	
Cases	323	229	123	165	125	
MV_1	1.00	1.03 (0.86–1.22)	0.97 (0.79–1.20)	0.98 (0.81–1.18)	0.88 (0.71–1.08)	0.21
$MV_{1+adult\ factors}$	1.00	1.03 (0.87–1.22)	0.99 (0.80–1.23)	0.99 (0.81–1.20)	0.89 (0.72–1.10)	0.28
						P-int = 0.94

	MET-hours per week					*p*-trend
	<15	**15 to <27**	**27 to <39**	**39 to <57**	**57+**	
	Hazard ratio (95 % confidence interval)					
23–29 years						
All						
Person years	184,479	217,759	148,232	213,528	211,261	
Cases	494	654	442	546	561	
MV_1	1.00	1.14 (1.01–1.28)	1.14 (1.00–1.29)	0.99 (0.87–1.12)	1.02 (0.90–1.15)	0.28
$MV_{1+adult\ factors}$	1.00	1.16 (1.03–1.30)	1.17 (1.02–1.33)	1.02 (0.90–1.15)	1.05 (0.93–1.20)	0.60
Premenopausal						
Person years	92,756	118,102	84,206	122,726	119,893	
Cases	221	334	237	280	279	
MV_1	1.00	1.19 (1.01–1.42)	1.20 (1.00–1.45)	0.98 (0.82–1.17)	1.00 (0.84–1.19)	0.15
$MV_{1+adult\ factors}$	1.00	1.22 (1.02–1.45)	1.24 (1.03–1.50)	1.02 (0.85–1.22)	1.05 (0.87–1.27)	0.39
Postmenopausal						
Person years	68,289	73,273	46,712	65,083	65,986	
Cases	200	227	142	202	194	
MV_1	1.00	1.07 (0.88–1.29)	1.05 (0.84–1.30)	1.07 (0.88–1.31)	1.02 (0.84–1.25)	0.97
$MV_{1+adult\ factors}$	1.00	1.09 (0.90–1.32)	1.07 (0.86–1.34)	1.09 (0.89–1.34)	1.04 (0.84–1.28)	0.87
						P-int = 0.62

MV_1: Stratified on calendar year and age in months and adjusted for family history of breast cancer (yes, no), height (continuous), age at menarche (< 12, 12+ years), adolescent body size (somatotype pictogram category 1, >1–2, >2–3, >3–4, >4–5, 5+, missing), and adolescent alcohol consumption (some, none, missing). $MV_{1+adult\ factors}$: Additionally adjusted for adult cumulative average physical activity (<9, 9 to <15, 15 to

<21, 21 to <33, 33+ MET-h/week), history of benign breast disease (biopsy confirmed, not biopsy confirmed, no), parity and age at first birth (nulliparous, 1–2 children and <25 years, 1–2 children and 25+ years, 3+ children and <25 years, 3+ children and 25+ years, missing), breastfeeding (none, ≤6 months, >6 months, missing), weight change since age 18 (continuous, missing indicator), adult alcohol intake (0, 0 to <5, 5 to <15, 15+ grams/day, missing). Models for all breast cancer additionally adjusted for menopausal status (premenopausal, postmenopausal, dubious). For models from ages 12 to 22 years, we adjusted for average somatotype pictogram category at ages 10 and 20 years; for models from 23 to 29 years we adjusted for somatotype at age 20. In the postmenopausal breast cancer models, $MV_{1+\text{adult factors}}$ additionally adjusted for age at menopause (continuous, missing) and hormone therapy use (current, past, never, missing). *P* value, test for interaction (*P*-int) based on MV_1

Table 3

MET-hours per week of adolescent physical activity in relation to ER-positive and ER-negative premenopausal breast cancer risk in the Nurses' Health Study II, 1997–2011

	MET-hours per week					*p*-trend
	<21	**21 to <36**	**36 to <48**	**48 to <72**	**72+**	
	Hazard Ratio (95 % confidence interval)					
12–13 years						
ER positive						
MV_1	1.00	0.89 (0.71–1.11)	0.87 (0.67–1.12)	0.89 (0.71–1.12)	0.93 (0.75–1.16)	0.74
$MV_{1+adult\ factors}$	1.00	0.90 (0.72–1.13)	0.89 (0.69–1.15)	0.91 (0.73–1.14)	0.96 (0.77–1.20)	0.98
ER negative						
MV_1	1.00	0.97 (0.62–1.51)	0.83 (0.49–1.40)	0.83 (0.52–1.31)	0.83 (0.53–1.30)	0.36
$MV_{1+adult\ factors}$	1.00	0.98 (0.63–1.53)	0.85 (0.50–1.43)	0.84 (0.53–1.34)	0.86 (0.55–1.35)	0.44
						P-het = 0.49
14–17 years						
ER positive						
MV_1	1.00	0.79 (0.62–0.99)	0.82 (0.64–1.06)	0.93 (0.75–1.16)	0.77 (0.61–0.96)	0.10
$MV_{1+adult\ factors}$	1.00	0.79 (0.62–1.00)	0.84 (0.65–1.08)	0.95 (0.76–1.19)	0.79 (0.63–0.99)	0.20
ER negative						
MV_1	1.00	0.89 (0.56–1.41)	0.78 (0.46–1.34)	0.82 (0.52–1.31)	0.86 (0.55–1.33)	0.59
$MV_{1+adult\ factors}$	1.00	0.89 (0.56–1.42)	0.80 (0.47–1.36)	0.84 (0.53–1.33)	0.89 (0.57–1.38)	0.71
						P-het = 0.81
18–22 years						
ER positive						
MV_1	1.00	1.04 (0.84–1.28)	0.99 (0.77–1.26)	1.03 (0.82–1.28)	0.90 (0.71–1.15)	0.40
$MV_{1+adult\ factors}$	1.00	1.05 (0.85–1.29)	1.01 (0.79–1.29)	1.06 (0.85–1.32)	0.94 (0.74–1.20)	0.65
ER negative						
MV_1	1.00	1.23 (0.81–1.88)	1.04 (0.62–1.72)	1.27 (0.82–1.96)	0.80 (0.48–1.35)	0.44
$MV_{1+adult\ factors}$	1.00	1.24 (0.82–1.90)	1.06 (0.64–1.76)	1.30 (0.84–2.02)	0.84 (0.50–1.41)	0.55
						P-het = 0.74

	<15	**15–26.9**	**27–38.9**	**39–56.9**	**57+**	***p*-trend**
	Hazard Ratio (95 % Confidence Interval)					
23–29 years						
ER positive						
MV_1	1.00	1.12 (0.88–1.41)	1.13 (0.88–1.46)	0.99 (0.77–1.26)	0.93 (0.72–1.18)	0.18
$MV_{1+adult\ factors}$	1.00	1.13 (0.90–1.44)	1.16 (0.90–1.50)	1.02 (0.79–1.30)	0.97 (0.75–1.25)	0.35
ER negative						
MV_1	1.00	1.44 (0.89–2.32)	1.38 (0.82–2.32)	1.12 (0.68–1.85)	0.85 (0.50–1.46)	0.14
$MV_{1+adult\ factors}$	1.00	1.46 (0.90–2.36)	1.42 (0.84–2.39)	1.15 (0.69–1.91)	0.89 (0.52–1.54)	0.19
						P-het = 0.44

Adjusted for the same variables listed in Table 2. However, to reduce the number of covariates given limited power in ER-stratified models, some variables coded differently [history of biopsy-confirmed benign breast disease (yes, no), birth index variable incorporating parity and age at first birth (continuous, missing), breastfeeding (ever, never), and adult alcohol intake (continuous)]. 697 women had ER-positive cancer and 170 had ER-negative cancer. *P* value, test for heterogeneity (*P*-het) based on MV_1

Table 4

MET-hours per week of adolescent physical activity in relation to premenopausal breast cancer by age at diagnosis in the Nurses' Health Study II, 1997–2011

	MET-hours per week					*p*-trend
	<21	**21 to <36**	**36 to <48**	**48 to <72**	**72+**	
	Hazard Ratio (95 % Confidence Interval)					
12–13 years						
Age at diagnosis <46.9 years						
MV_1	1.00	0.99 (0.78–1.25)	1.00 (0.77–1.30)	0.93 (0.73–1.18)	1.01 (0.80–1.27)	0.99
$MV_{1+\text{adult factors}}$	1.00	1.01 (0.80–1.28)	1.03 (0.79–1.34)	0.96 (0.76–1.22)	1.06 (0.85–1.34)	0.64
Age at diagnosis ≥46.9 years						
MV_1	1.00	0.82 (0.65–1.02)	0.86 (0.67–1.11)	0.76 (0.61–0.96)	0.85 (0.68–1.06)	0.23
$MV_{1+\text{adult factors}}$	1.00	0.82 (0.66–1.03)	0.88 (0.68–1.13)	0.78 (0.62–0.99)	0.89 (0.70–1.11)	0.42
						P-int = 0.87
14–17 years						
Age at diagnosis <46.9 years						
MV_1	1.00	0.77 (0.60–0.99)	0.87 (0.67–1.13)	0.90 (0.72–1.13)	0.77 (0.61–0.96)	0.10
$MV_{1+\text{adult factors}}$	1.00	0.78 (0.61–1.00)	0.89 (0.69–1.16)	0.93 (0.74–1.17)	0.81 (0.64–1.01)	0.24
Age at diagnosis ≥ 46.9 years						
MV_1	1.00	0.78 (0.61–0.98)	0.84 (0.64–1.09)	0.83 (0.66–1.05)	0.86 (0.69–1.08)	0.51
$MV_{1+\text{adult factors}}$	1.00	0.79 (0.62–1.00)	0.86 (0.66–1.12)	0.86 (0.68–1.09)	0.91 (0.73–1.14)	0.88
						P-int = 0.76
18–22 years						
Age at diagnosis < 46.9 years						
MV_1	1.00	0.99 (0.80–1.23)	0.96 (0.75–1.23)	0.98 (0.79–1.23)	0.76 (0.59–0.97)	0.03
$MV_{1+\text{adult factors}}$	1.00	0.99 (0.80–1.23)	0.96 (0.75–1.24)	1.00 (0.79–1.25)	0.77 (0.60–0.99)	0.05
Age at diagnosis ≥ 46.9 years						
MV_1	1.00	1.14 (0.93–1.41)	1.12 (0.87–1.43)	1.06 (0.84–1.34)	0.96 (0.75–1.24)	0.65
$MV_{1+\text{adult factors}}$	1.00	1.15 (0.93–1.42)	1.15 (0.90–1.48)	1.11 (0.88–1.40)	1.02 (0.79–1.32)	0.94
						P-int = 0.22

	<15	**15 to <27**	**27 to <39**	**39 to <57**	**57+**	***p*-trend**
	Hazard Ratio (95 % Confidence Interval)					
23–29 years						
Age at diagnosis <46.9 years						
MV_1	1.00	1.36 (1.06–1.74)	1.12 (0.85–1.48)	0.99 (0.76–1.28)	1.04 (0.80–1.34)	0.21
$MV_{1+\text{adult factors}}$	1.00	1.38 (1.07–1.77)	1.14 (0.86–1.51)	1.00 (0.76–1.31)	1.06 (0.80–1.39)	0.27
Age at diagnosis ≥46.9 years						
MV_1	1.00	1.04 (0.82–1.33)	1.28 (1.00–1.65)	0.98 (0.77–1.26)	0.96 (0.75–1.24)	0.44
$MV_{1+\text{adult factors}}$	1.00	1.07 (0.84–1.36)	1.34 (1.04–1.73)	1.03 (0.80–1.33)	1.04 (0.80–1.35)	0.87
						P-int = 0.63

Adjusted for the same variables listed in Table 2. Median age at diagnosis of premenopausal breast cancer was 46.9 years; women with a younger age at diagnosis were diagnosed before age 46.9 years (n = 677); women with an older age at diagnosis were diagnosed at age 46.9 years or greater (*n* = 674). *P* value, test for interaction (*P*-int) based on MV_1