Published in final edited form as:

Cancer Causes Control. 2011 March ; 22(3): 515–522. doi:10.1007/s10552-010-9719-y.

Does Hormone Therapy Counter the Beneficial Effects of Physical Activity on Breast Cancer Risk in Postmenopausal Women?

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Abstract

Objective—Studies consistently demonstrate that physical activity is inversely associated with postmenopausal breast cancer. Whether this association is stronger among non-hormone users or former users of menopausal hormone therapy (HT) is of interest given the marked decline in HT use since 2002.

Methods—The Women's Contraceptive and Reproductive Experiences Study, a population-based case-control study of invasive breast cancer, recruited white women and black women ages 35–64 years, and collected histories of lifetime recreational physical activity and HT use including estrogen-alone therapy (ET) and estrogen plus progestin therapy (EPT).

Results—Among postmenopausal women (1908 cases, 2013 control participants), breast cancer risk declined with increasing levels of lifetime physical activity among never HT users; among short-term HT users (fewer than 5 years); and current ET users; P_{trend} values ranged from 0.004 to 0.016. In contrast, physical activity had no significant association with risk among long-term and past HT users and among current EPT users. No statistical evidence of heterogeneity was demonstrated for duration or currency of HT use.

Conclusion—Breast cancer risk decreases with increasing lifetime physical activity levels among postmenopausal women who have not used HT, have used HT for less than 5 years, or are current ET users yet this study was unable to demonstrate statistically that HT use modifies the relationship between physical activity and breast cancer. With profound changes in HT use occurring since 2002, it will be important in future studies to learn whether or not any association

between physical activity and breast cancer among former HT users is a function of time since last HT use.

Keywords

Hormone therapy; physical activity; breast cancer

Physical inactivity is considered a well-established risk factor for breast cancer, particularly among postmenopausal women^{1–3}. The proposed biological mechanisms accounting for this relationship include alterations in hormone profiles, insulin resistance, and chronic inflammation⁴. Physical activity may directly influence circulating hormone or protein levels, or may indirectly influence risk by reducing body mass resulting in lower levels of circulating sex hormones⁵, or in greater insulin sensitivity, both of which may reduce breast cancer risk.

Whether the associations between physical activity and breast cancer vary according to patterns of hormone therapy (HT) use among postmenopausal women is of interest given the declining prevalence of use of both estrogen-alone therapy (ET) and estrogen-plus-progestin therapy (EPT)^{6–8}. HT use, and particularly EPT use, increases breast cancer risk^{9–10}, and could possibly counter the long-term beneficial effects of physical activity on breast cancer risk. Previous investigations have observed the interaction of hormone therapy use by postmenopausal women on the relationship between breast cancer risk and physical activity, some of which indicated no effect modification by HT use^{2–3, 12, 18–24} while few observed a lower breast cancer risk among active versus sedentary women who had never used HT^{13, 25}. These findings prompted the present investigation, which examines associations between physical activity and breast cancer risk according to women's use of HT, using data from the Women's Contraceptive and Reproductive Experiences (CARE) Study.

Materials and Methods

Study population

The Women's CARE Study is a population-based case-control study of invasive breast cancer risk among white (including Hispanic) women and black women, who were English speaking, born in the United States and living within one of 5 areas in the United States (Atlanta, Detroit, Los Angeles, Philadelphia and Seattle). Cases were diagnosed with histologically confirmed invasive breast cancer (International Classification of Diseases for Oncology codes C50.0–C50.9¹⁴) between July 1, 1994 and April 30, 1998, were 35–64 years of age at diagnosis, and had no previous diagnosis of *in situ* or invasive breast cancer. The date of diagnosis served as a case's reference date. The same demographic and health eligibility requirements were imposed during control subject identification by study site-specific random digit dialing, with the date of first household contact serving as the control subject's reference date. A complete description of study methods, including subject identification, recruitment, and participation rates, has been published¹⁵.

All participants provided written informed consent before completing an in-person interview. The study was approved by the institutional review board at each collaborating institution. Information was collected during the interview up to the participant's reference date. Interview response rates for cases and controls were 76.5% and 78.6%, respectively. A woman was considered postmenopausal if, before her reference date, 1) she had experienced a final menstrual period followed by 12-months with no menstrual period and no hormonal therapy (natural menopause), 2) she reported a bilateral oophorectomy causing cessation of menstruation (surgical menopause), or 3) her menstrual periods stopped because of radiation or chemotherapy at least 12 months before her reference date. Additionally, if a

woman was 55 years of age or older, she was considered postmenopausal if she had an unclear menopausal status (e.g., hysterectomy without bilateral oophorectomy before natural menopause), or if she experienced a final menstrual period followed by 12-months with no menstrual period despite using HT. Inclusion of women who had initiated hormone therapy prior to menopause did not alter the result or conclusions and were therefore were not included in the analyses.

A total of 1908 cases and 2013 control participants were eligible for analysis following exclusions, in order, of 9 cases and 3 control participants who were missing information on physical activity; 28 cases and 29 control participants who were missing information for at least one of the following: age at menarche, age at first term pregnancy (>26 weeks), total number of term pregnancies, total months of breast feeding, or body mass index 5 years before the reference date; 2102 cases and 2045 control participants who were premenopausal; 526 cases and 586 control participants with unknown menopausal status; and 2 cases and 5 control participants with missing information on duration of HT pill or patch use.

Assessment of recreational physical activity

Each participant reported details of all recreational physical activities in which she engaged throughout her life up to her reference date after completing a detailed calendar of life events with the interviewer¹⁶. The average number of hours of physical activity per week was calculated for each year from age 10 years through the reference age. A woman was considered inactive at any given age if her average hours of activity per week for that age was less than 0.67 hour¹⁶. Using the Compendium of Physical Activities¹⁷, each activity was assigned a metabolic equivalents of energy expenditure (MET) rating and MET-hours per week were estimated for each age. The lifetime activity measures (in hrs/wk/yr and MET-hrs/wk/yr) represent the average of these annual physical activity measures.

Assessment of HT use

Women provided detailed information on their use of ET, menopausal progestin alone therapy, and EPT. HT use, as defined here, included that used in oral form (pills) or as patches. Duration of HT pill/patch use was based on the total months of use of menopausal estrogen or progestin. HT users were classified users for less than 5 years or users for 5 or more years, and as current ET users, current EPT users, or former HT users.

Statistical analyses

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated using unconditional logistic regression models and represent the association between lifetime recreational physical activity measures and breast cancer risk. Women who were classified as inactive at all ages were used as the referent group. Multivariable models included design variables: age (continuous), study site (Atlanta, Detroit, Los Angeles, Philadelphia, or Seattle), and questionnaire version (original or modified) as well as the following potential confounding factors: family history of breast cancer in mother, sisters, or daughters (first-degree family history: yes, no, unknown/adopted); age at menarche (continuous); age at menopause (<35, 35–39, 40–44, 45–49, 50–54, or ≥55 years); age at first term pregnancy (<20, 20–24, 25–29, 30–34, ≥35 years or nulliparous); number of term pregnancies (continuous); body mass index at 5 years before the reference date (continuous); and total number of months breast feeding (continuous). For models stratified by current HT-use status, duration of HT pill use (never used, <5, or ≥5 years; ordinal) was included as a covariate. Trend tests for each physical activity variable were performed by fitting the median value of physical activity within each of the categories as a continuous variable. A likelihood ratio test for effect modification by HT duration or by current HT formulation

was constructed to assess homogeneity of trends across hormone exposures; this test compared two multivariable models, one with a single physical activity variable and the second with separate physical activity variable fit for each HT exposure category.

Results

The average reference ages were 57.3 ± 4.9 years for cases and 56.4 ± 5.5 years for control participants. The distributions of covariates included in the multivariable logistic regression models are shown in Table 1. Breast cancer risk was inversely associated with measures of lifetime average annual physical activity among postmenopausal women who had never used HT and among those who had used HT for less than 5 years (Hrs/wk/yr: $P_{\text{trend}}=0.016$ and $P_{\text{trend}}=0.004$, respectively; and MET-hrs/wk/yr: $P_{\text{trend}}=0.011$; $P_{\text{trend}}=0.008$, respectively, Table 2). Although the inverse associations between lifetime physical activity and breast cancer risk were not statistically significant among women with 5 or more years of HT use, the tests for homogeneity of trends across the three HT exposure categories did not differ statistically (Hrs/wk/yr: $P_{\text{homogeneity}}=0.12$; MET-hrs/wk/yr: $P_{\text{homogeneity}}=0.10$). Breast cancer risk also decreased as lifetime physical activity increased among current ET users, but not among current EPT users or past HT users (Hrs/wk/yr: $P_{\text{trend}}=0.011$, $P_{\text{trend}}=0.75$ and $P_{\text{trend}}=0.21$, respectively; and MET-hrs/wk/yr: $P_{\text{trend}}=0.019$, $P_{\text{trend}}=0.65$, and $P_{\text{trend}}=0.46$ respectively); however the trends in risk for non-users, current E users, current EPT users, and past users, did not differ statistically (Hrs/wk/yr, $P=0.44$; MET-hrs/wk/yr, $P=0.47$; Table 3). Despite the unique demographics of our population included 35% blacks, race (white vs. black) did not further modify these results (data not shown).

Discussion

A previous report examining physical activity and breast cancer risk among participants in the Women's CARE Study showed a modest inverse association (increasing physical activity associated with decreasing risk of invasive breast cancer) among black women and among white women¹⁶. Here, analyses were limited to postmenopausal women to determine whether this inverse association differed according to a women's history of HT use. Although statistically significant inverse associations were observed for women who never used HT, had used HT for a relatively short time (<5 yrs), or who were current ET users (with adjustment for duration of HT use), such associations were not observed for longer-term HT users, former HT users or current EPT users. Despite these differences, none of the tests for homogeneity of trends was statistically significant.

The present study examines physical activity and breast cancer risk according to a woman's history of HT use in greater detail than was done in two prior publications^{11–12}. A number of previous investigations observed the interaction of hormone therapy on the relationship between breast cancer risk and physical activity, some of which indicated no effect modification by HT use^{2–3, 12, 18–24} while few observed a lower breast cancer risk among active versus sedentary women who had never used HT^{13, 25}. However we limited our discussion to the studies most relevant to our methodology and findings which includes cohort studies by Howard et al.¹¹ and Patel et al.¹².

Cohort studies by Howard et al.¹¹ and Patel et al.¹² observed that breast cancer risk was inversely associated with physical activity among postmenopausal women who had never used HT, findings similar to the results presented here. However, the first of these studies compared postmenopausal women who had ever used HT to those who had never used HT¹¹; the second study compared current, former, and never users of HT¹². The current investigation subdivided HT users according to duration of use and formulation of current use. An analysis comparing never to ever HT users did not demonstrate any effect

modification by HT use of the association between lifetime physical activity and breast cancer risk (data not shown).

Important differences in the extent of physical activity assessment exist between the Women's CARE Study and the two cohort studies. Howard et al. limited physical activity to that performed in the year prior to study entry¹¹. Patel et al. assessed physical activity at 3 different time points, during the year before recruitment, in the year that was 10-years before recruitment and at age 40 years¹². Although Patel's study was a more comprehensive assessment than Howard et al., only physical activity during the year before recruitment was associated with breast cancer risk¹². The current study obtained extensive detail on lifetime (age 10 to reference date) physical activity assessed through in-person interviews during which a calendar of life events was completed to facilitate recall of activity levels throughout life.

In a case-control study of *in situ* and invasive breast cancer by Slattery et al. (2007), analyses were restricted to postmenopausal non-Hispanic white and Hispanic/American Indian women whose ages ranged through 79 years; physical activity data were obtained during in-person interviews using a computerized questionnaire to assess activities for the reference year, and at ages 15, 30, and 50 years¹³. Contrary to results from the current study, HT use modified the physical activity-breast cancer risk association with the greatest reduction in breast cancer risk observed among women who had not used HT within the past 2 years¹³. Notably, this category combined never users with past users of HT. The demographic profiles of Slattery's study and the current study differ in that the Women's CARE Study restricted age (35–64 years) and birthplace (US-born), included black women and had few Hispanic women (n=96) due to the birthplace restriction. The Women's CARE study also limited case eligibility to women with invasive breast cancer.

In summary, results from the Women's CARE Study show that breast cancer risk decreases with increasing lifetime physical activity levels among postmenopausal women who have not used HT, have used HT for less than 5 years, or are current ET users, but no trend is observed among longer duration HT users, current EPT users or past HT users. Despite these differences, this study was unable to demonstrate statistically that HT use modifies the relationship between physical activity and breast cancer. In light of the profound changes in HT use occurring since 2002, it will be important in future studies conducted after 2002, to learn whether or not any association between physical activity and breast cancer among former HT users is a function of time since last HT use.

Acknowledgments

Funding

This work was supported by the National Institute of Child Health and Human Development, with additional support from the National Cancer Institute (NCI), through contracts with Emory University (N01 HD 3–3168), the Fred Hutchinson Cancer Research Center (N01 HD 2–3166), the Karmanos Cancer Institute at Wayne State University (N01 HD 3–3174), the University of Pennsylvania (N01 HD 3–3176) and the University of Southern California (N01 HD 3–3175), and through an intra agency agreement with the Centers for Disease Control and Prevention (Y01 HD 7022). Additional support was provided by K05 CA136967 (to LB). General support through SEER contract numbers N01-PC-67006 (Atlanta), N01-CN-65064 (Detroit), N01-CN-67010 (Los Angeles), and N01-CN-0532 (Seattle) is also acknowledged. The collection of cancer incidence data for Los Angeles County used in this publication was supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by the California Health and Safety Code Section 103885. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the State of California, Department of Health Services.

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Table 1

Distribution of Covariates by Case (n=1908) and Control (n=2013) Status.

Covariate	No. cases (%)	No. control participants (%)
Reference age		
35–39 y	9 (0.5)	22 (1.1)
40–44 y	30 (1.6)	50 (2.5)
45–49 y	95 (4.9)	149 (7.4)
50–54 y	336 (17.6)	358 (17.8)
55–59 y	729 (38.2)	757 (37.6)
60–64 y	709 (37.2)	677 (33.6)
Race		
White	1263 (66.2)	1298 (64.5)
Black	645 (33.8)	715 (35.5)
Study site		
Atlanta	358 (18.8)	387 (19.2)
Seattle	479 (25.1)	449 (22.3)
Detroit	265 (13.9)	322 (16.0)
Philadelphia	300 (15.7)	347 (17.3)
Los Angeles	506 (26.5)	508 (25.2)
Physical activity questionnaire ^a		
Original	170 (8.9)	208 (10.3)
Modified	1738 (91.1)	1805 (89.7)
First degree family history of breast cancer ^b		
No	1451 (76.1)	1686 (83.8)
Yes	363 (19.0)	233 (11.6)
Adopted/unknown	94 (4.9)	94 (4.6)
Age at menarche		
≤11 y	477 (25.0)	568 (28.2)
12 y	538 (28.2)	475 (23.6)
13 y	512 (26.8)	552 (27.4)
≥14 y	381 (20.0)	418 (20.8)
Age at menopause		
<35 y	117 (6.1)	180 (8.9)
35–39 y	148 (7.8)	225 (11.2)
40–44 y	289 (15.1)	370 (18.4)
45–49 y	617 (32.3)	583 (29.0)
50–54 y	608 (31.9)	534 (26.5)
≥55	129 (6.8)	121 (6.0)
Age at first term pregnancy (>26 wk)		
<20 y	490 (25.7)	596 (29.6)
20–24 y	700 (36.7)	772 (38.3)
25–29 y	319 (16.7)	276 (13.7)

Covariate	No. cases (%)	No. control participants (%)
30–34 y	101 (5.3)	96 (4.8)
≥35	298 (15.6)	273 (13.6)
No. of term pregnancies (>26 wk)		
0	267 (14.0)	248 (12.3)
1	273 (14.3)	239 (11.9)
2	512 (26.8)	524 (26.0)
3	401 (21.0)	427 (21.2)
4	230 (12.1)	260 (12.9)
≥5	225 (11.8)	315 (15.7)
No. of months breast-feeding		
Never breast-fed	1073 (56.2)	1056 (52.5)
≤6 mo	474 (24.8)	543 (27.0)
7–15 mo	194 (10.2)	216 (10.7)
≥16 mo	167 (8.8)	198 (9.8)
Duration of HT use		
Never used	694 (36.4)	696 (34.6)
<5 y	538 (28.2)	632 (31.4)
≥5 y	676 (35.4)	685 (34.0)
Status of HT use		
Never used	694 (36.4)	696 (34.6)
Current use	948 (49.7)	955 (47.4)
Past use	266 (13.9)	362 (18.0)
Length of HT use (months) ^c		
Current ET use	105.01 (82.50)	117.18 (90.11)
Current E + P use	77.42 (51.76)	70.41 (51.76)
Past HT use	29.38 (36.13)	33.48 (46.18)
Body mass index at 5 years before reference date ^d		
<22.5 kg/m ²	466 (24.4)	472 (23.4)
22.5–24.9 kg/m ²	434 (22.8)	440 (21.9)
25–27.4 kg/m ²	399 (20.9)	420 (20.9)
≥27.5 kg/m ²	609 (31.9)	681 (33.8)

Abbreviation: HT = hormone therapy

^aOriginal physical activity questionnaire includes exercise activities performed at least 2 hours/week for at least 4 months at any given age; the modified version includes activities performed at least 1 hour/week for at least 4 months at any given age.

^bMother, sister, or daughter.

^cExpressed as mean (standard deviation).

^dReference date is the case's date of diagnosis or the date of first contact with the household during the random digit dialing screening process for control participants.

Table 2

Lifetime Physical Activity and Relative Odds of Invasive Breast Cancer Stratified by Duration of HT Use ^{*,a}

Lifetime average physical activity	No HT Use			<5 years HT Use			>5 years HT Use		
	# cases/controls	OR ^b	95% CI	# cases/controls	OR ^b	95% CI	# cases/controls	OR ^b	95% CI
Annual hrs/wk									
Inactive	262/248	1.0 (reference)		146/177	1.0 (reference)		161/145	1.0 (reference)	
≤0.4	142/133	0.94	0.70, 1.27	130/104	1.40	0.99, 1.97	146/157	0.81	0.59, 1.12
.5–1.2	111/104	0.90	0.65, 1.25	96/117	0.89	0.62, 1.27	136/137	0.82	0.59, 1.14
1.3–2.9	95/105	0.75	0.53, 1.05	88/111	0.86	0.59, 1.23	117/136	0.70	0.49, 0.98
≥3.0	84/106	0.67	0.48, 0.95	78/123	0.69	0.48, 0.99	116/110	0.88	0.62, 1.25
<i>P</i> _{trend}			0.016			0.004			0.76
Annual MET-hrs/wk									
Inactive	262/248	1.0 (reference)		146/177	1.0 (reference)		161/145	1.0 (reference)	
≤2.2	143/134	0.95	0.70, 1.28	131/110	1.33	0.95, 1.88	156/167	0.82	0.60, 1.13
2.3–6.6	121/116	0.88	0.64, 1.20	105/110	1.00	0.70, 1.43	134/140	0.77	0.55, 1.08
6.7–15.1	97/103	0.76	0.54, 1.06	83/125	0.72	0.50, 1.03	111/124	0.72	0.51, 1.02
≥15.2	71/95	0.64	0.45, 0.92	73/110	0.74	0.50, 1.07	114/109	0.89	0.62, 1.26
<i>P</i> _{trend}			0.011			0.008			0.87

Abbreviations: HT = hormone therapy; OR = odds ratio; CI = confidence interval; MET = metabolic equivalent of energy expenditure.

* Overall test for homogeneity of trends for average annual hrs/week, *P* = 0.12; for average annual MET-hrs/wk, *P* = 0.10.

^a Lifetime activity was defined as activity from age 10 years to reference date; reference date is the case patient's diagnosis date or the date of first contact with the household during the random digit dialing screening process for control participants. *P*_{trend} values were derived from the Wald test. *P* values for homogeneity of trends were derived from the likelihood ratio test. All *P* values are two-sided.

^b Adjusted for age; study site; race; questionnaire version (1 vs. 2); first degree family history of breast cancer; age at menarche; age at first term pregnancy (>26 weeks); total number of >26 week pregnancies; duration of HT use; body mass index at 5 years before reference data; and number of months breast feeding.

Table 3
Lifetime Physical Activity and Relative Odds of Invasive Breast Cancer Stratified by Recency and Formulation of HT Use^{*,a}

Lifetime average physical activity	No HT Use			Current ET Use			Current E + P Use			Past HT Use		
	# cases/controls	OR ^b	95% CI	# cases/Controls	OR ^b	95% CI	# cases/controls	OR ^b	95% CI	# cases/controls	OR ^b	95% CI
Annual hrs/wk												
Inactive	262/248	1.0 (reference)		121/121	1.0 (reference)		100/77	1.0 (reference)		84/124	1.0 (reference)	
≤0.4	142/133	0.95	0.71, 1.29	101/128	0.77	0.53, 1.11	108/79	1.00	0.65, 1.52	67/53	1.76	1.10, 2.79
.5–1.2	111/104	0.91	0.66, 1.26	83/101	0.78	0.53, 1.16	112/89	0.88	0.58, 1.33	38/64	0.79	0.48, 1.30
1.3–2.9	95/105	0.77	0.55, 1.08	71/112	0.58	0.39, 0.86	93/74	0.88	0.57, 1.35	40/61	0.91	0.55, 1.49
≥3.0	84/106	0.69	0.49, 0.97	63/104	0.57	0.38, 0.86	92/69	0.92	0.59, 1.43	37/60	0.88	0.53, 1.45
<i>P</i> _{trend}			0.022			0.011			0.75			0.21
Annual MET-hrs/wk												
Inactive	262/248	1.0 (reference)		121/121	1.0 (reference)		100/77	1.0 (reference)		84/124	1.0 (reference)	
≤2.2	143/134	0.96	0.71, 1.29	110/132	0.81	0.57, 1.17	104/81	0.93	0.61, 1.42	73/63	1.62	1.04, 2.53
2.3–6.6	121/116	0.89	0.65, 1.23	76/102	0.70	0.47, 1.04	126/95	0.91	0.61, 1.37	38/53	0.93	0.56, 1.55
6.7–15.1	97/103	0.78	0.56, 1.10	71/111	0.57	0.38, 0.85	89/67	0.94	0.60, 1.46	33/71	0.64	0.39, 1.06
≥15.2	71/95	0.66	0.46, 0.94	61/100	0.60	0.39, 0.91	86/68	0.87	0.56, 1.36	38/51	1.09	0.65, 1.81
<i>P</i> _{trend}			0.016			0.019			0.65			0.46

Abbreviations: HT = Hormone therapy; ET = estrogen therapy; E+P = estrogen plus progestin therapy; OR = odds ratio; CI = confidence interval; MET = metabolic equivalent of energy expenditure.

^{*} Overall test for homogeneity of trends for average annual hrs/week, *P* = 0.44; for average annual MET-hrs/wk, *P* = 0.47.

^a Lifetime activity was defined as activity from age 10 years to reference date; reference date is the case patient’s diagnosis date or the date of first contact with the household during the random digit dialing screening process for control participants. *P*_{trend} values were derived from the Wald test. *P* values for homogeneity of trends were derived from the likelihood ratio test. All *P* values are two-sided.

^b Adjusted for age; study site; race; questionnaire version (1 vs. 2); first degree family history of breast cancer; age at menarche; age at menopause; age at first term pregnancy (>26 weeks); total number of >26 week pregnancies; type of HT use; body mass index at 5 years before reference data; and number of months breast feeding.