Title

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Journal

Cancer Causes & Control, 28(12)

ISSN

0957-5243

Authors

Nomura, Sarah JO
Dash, Chiranjeev
Sheppard, Vanessa B
et al.

Publication Date

2017-12-01

DOI

10.1007/s10552-017-0968-x

Peer reviewed

Published in final edited form as:

Cancer Causes Control. 2017 December ; 28(12): 1405–1416. doi:10.1007/s10552-017-0968-x.

Sedentary Time and Postmenopausal Breast Cancer Incidence

Sarah J.O. Nomura[1], **Chiranjeev Dash**[1], **Vanessa Sheppard**[2], **Deborah Bowen**[3], **Matthew Allison**[4], **Wendy Barrington**[5], **Rowan Chlebowski**[6], **Mace Coday**[7], **Lifang Hou**[8], **Barbara Howard**[9], **Michael LaMonte**[10], **JoAnn Manson**[11,12], **Marian Neuhouser**[13], **Electra Paskett**[14], **Maryam Sattari**[15], **Marcia Stefanick**[16], **Jean Wactawski-Wende**[10], and **Lucile L. Adams-Campbell**[1]

[1]Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, 1000 New Jersey Ave SE, Washington, DC, 20003, USA

[2]Department of Health Behavior and Policy, School of Medicine, Virginia Commonwealth University, 830 East Main Street, Richmond, VA 23219, USA

[3]Department of Bioethics and Humanities, University of Washington, Health Sciences Building, 1959 NE Pacific Street, Seattle, WA 98195, USA

[4]Department of Family Medicine and Public Health, University of California-San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA

[5]Department of Epidemiology, School of Public Health, University of Washington, Health Sciences Building, 1959 NE Pacific Street, Seattle, WA 98195, USA

[6]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA 90502, USA

[7]Department of Preventive Medicine, The University of Tennessee Health Science Center, Doctors Office Building, 66 North Pauline Street, Memphis TN 38163, USA

[8]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, 680 North Lake Shore Drive, Chicago, IL 60611

[9]MedStar Health Research Institute, 6525 Belcrest Road, Hyattsville, Maryland 20782, USA

[10]Department of Epidemiology and Environmental Health, University at Buffalo, 401 Kimball Tower, Buffalo, New York 14214, USA

[11]Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, 900 Commonwealth Avenue, Boston, MA 02215, USA

[12]Department of Epidemiology, Harvard T. H. Chan School of Public Health, 677 Huntington Ave, Boston, MA 02115, USA

[13]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Seattle, WA 98109, USA

CORRESPONDING AUTHOR: Sarah J. O. Nomura, Georgetown-Lombardi Comprehensive Cancer Center, 1000 New Jersey Ave SE, Washington, DC 20003, Phone: 202-687-3957, Fax: 202-687-1368, sjo36@georgetown.edu.

[14]Division of Cancer Prevention and Control, College of Medicine, The Ohio State University, 370 W 9th Ave, Columbus, OH 43210, USA

[15]Deprtment of Internal Medicine, University of Florida College of Medicine, 2000 SW Archer Rd, Gainesville, FL 3260, USA

[16]Department of Medicine, Stanford Prevention Research Center, Stanford University, Stanford, California. 1265 Welch Rd, Palo Alto, CA 94305, USA

Abstract

PURPOSE—The objective of this study was to evaluate the prospective association between sedentary time and postmenopausal breast cancer incidence, and whether associations differ by race/ethnicity, physical activity levels and body measurements.

METHODS—The Women's Health Initiative Observational Study (WHI-OS) is a prospective cohort among women ages 50–79 years at baseline (1994–1998) (analytic cohort=70,233). Baseline questionnaire data was used to estimate time spent sitting and total sedentary time. Associations between time spent sitting and invasive breast cancer incidence overall (N= 4,115 cases through September 2015), and by hormone receptor subtypes, were investigated using Cox proportional hazards regression. Analyses were replicated stratified by race/ethnicity, body measurements, and physical activity.

RESULTS—Among women in this study, 34.5% reported ≤5 hours/day sitting, 40.9% reported 6–9 hours/day and 24.7% reported ≥10 hours/day. Time spent sitting (≥10 vs. ≤5 hours/day adjusted HR=1.00, 95% CI: 0.92–1.09) was not associated with breast cancer incidence, regardless of hormone receptor subtype. Associations did not differ by race/ethnicity, physical activity or body measurements.

CONCLUSIONS—Results from this study do not support an association between sedentary time and breast cancer incidence.

Keywords

Breast Cancer; Sedentary; Sitting Time; Body Composition; Physical Activity

INTRODUCTION

Breast cancer is the most common cancer type reported among women in the United States, regardless of race or ethnicity [1]. In 2016, an estimated 246,660 new breast cancer cases were diagnosed among U.S. women with approximately 78% diagnosed in women older than 55 years of age [2]. Modifiable lifestyle factors have been shown to influence breast cancer risk, particularly alcohol consumption, adiposity, and physical activity [3].

Recent research indicates that sedentary time (behaviors that require little to no additional energy expenditure beyond basal metabolic rate) may be associated with increased breast cancer risk [4,5]. Previous research suggests the impact of sedentary behavior on health outcomes may not be due only to the absence of regular recreational physical activity [6–8]. This may be due to the fact that a person can meet recreational physical activity

recommendations and still spend a large proportion of their time sedentary. Current recreational physical activity recommendations are for 150-minutes moderate intensity aerobic activity per week or 75-minutes vigorous physical activity per week for general health [9]. Cancer prevention recommendations from the World Cancer Research Fund/ American Institute for Cancer Research WCRF/AICR) recommend 30 minutes each day of moderate physical activity (e.g. brisk walking) [10]. Sedentary time accounts for a large proportion of time per day in the United States [11,12]. Data are limited, but research suggests sedentary time is high, regardless of race/ethnicity, but may be higher among certain racial/ethnic populations [12,13].

A recently published systematic review and meta-analysis observed a modest (~8% increase), but statistically significant, association between sedentary time and breast cancer [5]. In addition to breast cancer risk, sedentary time has also been shown to be associated with biomarkers linked with an increased risk for breast cancer, such as c-reactive protein (CRP, and interleukin-6 (IL-6) [14,15]. Breast cancer encompasses as many as 21 different histological subtypes and 4 primary molecular subtypes [16]. Evidence suggests that associations between lifestyle factors and breast cancer may differ by breast tumor subtype and race/ethnicity, but research for several lifestyle exposures in relation to subtypes remains limited and results are inconsistent [17–19]. Few studies have evaluated whether sedentary behavior is differentially associated with breast cancer hormone receptor subtypes, and results are conflicting, but suggestive of possible heterogeneity by hormone receptor subtypes [20,21]. Among the proposed biological mechanisms by which sedentary behavior could influence breast cancer risk include adiposity-mediated pathways, the IGF-insulin pathway and inflammation-related pathways [4].

Previous publications from the Women's Health Initiative Observational Study (WHI-OS) suggest a relationship between sedentary time and disease outcomes [22,23]. For example, sedentary time was shown to be associated with increased mortality in the WHI-OS, but has not been investigated in relation to breast cancer incidence [22]. In an ancillary study of the WHI, time spent sitting was evaluated in relation to several cancer-related biomarkers, including insulin-like growth factor-1 (IGF-1), IGF-binding protein-3 (IGFBP-3), CRP, and IL-6 [24]. In this cross-sectional analysis, there were no clear patterns of association, but results indicated that associations may differ by race/ethnicity and physical activity levels. Further research is needed to clarify the relationship between sedentary time and breast cancer risk, including whether there are differences by tumor subtypes or race/ethnicity and the role of obesity and recreational physical activity. To address these research gaps, we evaluated the prospective association between sedentary time and breast cancer incidence and whether associations differed by race/ethnicity, hormone receptor subtypes, physical activity levels and body measurements, in postmenopausal women in the WHI-OS.

MATERIALS AND METHODS

Study Population

The WHI-OS is a prospective cohort of 93,676 postmenopausal women between the ages of 50–79 years at study entry (1994–1998). Women were enrolled at 40 U.S. clinical centers throughout the county. Details about the study design, recruitment, enrollment and data

collection procedures have been outlined in depth in a previously published report [25]. All women provided written and informed consent and the study protocol was approved by the institutional review boards at each study center.

Data Collection

At the baseline clinic visit, participants completed self-administered questionnaires on demographics, medical history, medication usage, smoking habits, recreational physical activity, sedentary time, diet and other lifestyle-related factors. Height, weight, waist circumference (WC) and hip circumference were also measured at this visit using a standardized protocol. Measured height and weight were used to calculate body mass index (BMI) (kg/m^2). Waist to hip ratio (WHR) was calculated from waist and hip circumference measurements. Weight gain since age 18 was computed by subtracting current weight from weight at age 18.

Sedentary time was assessed at baseline by the following two questions: (1) “During a usual day or night about how many hours to you spend sitting? Be sure to include the time you spend sitting at work, sitting at the table eating, driving or riding in a car or bus, and sitting up watching TV or talking.” and (2) “During a usual day or night, about how many hours do you spend sleeping or laying down with your feet up? Be sure to include the time you spend sleeping or trying to sleep at night, resting, napping, and lying down watching TV.”. Participants had eight time categories to choose, ranging from <4 hours/day to ≥ 16 hours/day and were not asked about a specific timeframe for these behaviors, but were prompted they were being asked “about some of your usual activities”. In addition to time spent lying down, women were queried about how many hours of sleep they had on a typical night over the previous four weeks. To calculate total sedentary time, hours spent sleeping were subtracted from hours spent lying down. The intra-class correlation coefficient (ICC) for time spent sitting, lying and sleeping combined is 0.60; however, the individual measures (e.g. sitting time only) have not been evaluated separately [25,26].

Physical activity was collected via a series of questions on recreational time spent walking and engaged in mild, moderate and strenuous physical activity. Metabolic equivalents (MET) were estimated based on energy expenditure (intensity of activity) for each activity. Participants’ MET-hours/week were calculated by summing activity frequency*(minutes per session/60 min. per hour)*MET for activity (kcal per kg*hour). Total recreational physical activity METs were summed from calculated METs for each activity type (walking, mild, moderate, and strenuous). Recreational moderate and strenuous physical activity levels (defined as MET ≥4.0) were categorized into a four-level variable as follows: no activity= no moderate or strenuous recreational physical activity; Low=some moderate or strenuous recreational physical activity of limited duration, frequency or intensity; 3=moderate or strenuous activity of at least 20 minutes duration 2 – <4 times per week; high=moderate or strenuous activity of a least 20 minutes duration ≥4 times per week. In addition to recreational physical activity, time spent doing heavy indoor chores (examples: scrubbing floors, sweeping, vacuuming) and yard work (examples: mowing, raking, gardening, shoveling snow) was ascertained. MET-hours/week were estimated for these activities and summed with recreational physical activity levels to compute combined physical activity.

ICC for physical activity measures range from 0.51 for mild recreational activity to 0.77 for moderate to strenuous physical activity [25,26].

Questionnaire data were additionally collected on potential covariates including race/ethnicity, education, family history of breast cancer, non-steroidal anti-inflammatory drugs (NSAIDS), parity, age at menarche, mammogram frequency, smoking, alcohol intake, menopausal hormone therapy usage and diet. Healthy Eating Index 2005 scores (HEI 2005 Score) for participants were calculated using data from a 122-item food frequency questionnaire developed for WHI [27]. Daily individual nutrient and food servings were estimated using the Nutrition Data Systems for Research (2005 version, University of Minnesota, Minneapolis, MN). MyPyramid Equivalents were then calculated using the MyPyramid Equivalents Database (version 2.0, U.S. Department of Agriculture, Beltsville, Maryland). Diet quality scores were then generated as previously described with a higher score indicating better diet quality (maximum score=100) [28,29].

Analytic Cohort

Women with a previous history of breast cancer or other cancer (excluding non-melanoma skin cancer) or missing data on cancer history at baseline were excluded from the present analysis (N=13,037). Women with missing data on exposures of interest, including time spent sitting, time spent lying down, and time spent sleeping were also excluded (N=1,034). Additionally, women missing data on race/ethnicity (N=214), follow-up time (N=388) or covariates (N=8,770) used in final models were excluded for a final analytic sample size of 70,233. The majority of the women excluded for missing covariate data were missing either family history of breast cancer or pack-years of smoking.

Case Ascertainment

Invasive breast cancer cases in the WHI-OS were identified via an annual health status questionnaire or by cause of death reports [30]. Medical records were then collected and reviewed by trained WHI physician outcome adjudicators to verify self-reported primary breast cancer diagnoses. Records were reviewed for primary cancer site, sub-site, date of diagnosis, extent of disease (e.g. stage, tumor size), tumor morphology (e.g. grade, histology) and hormone receptor status and were then coded using SEER coding guidelines [31]. In this analytic cohort, 4,115 adjudicated invasive breast cancer cases were identified from baseline through September 30, 2015. In hormone receptor analyses, hormone receptor positive (HR+) is defined as breast tumors that were estrogen receptor and/or progesterone receptor positive (N=3,333) while women negative for both estrogen and progesterone receptors were classified as hormone receptor negative (HR−) (N=782). There were 265 cases with missing or unknown/not tested hormone receptor status. A total of 299 triple negative breast cancer cases were identified among women with HR− tumors. HER2/neu status was not ascertained in early study years, as a result, there were 1,060 breast cancer cases with missing or unknown/not tested HER2/neu status.

Statistical Analysis

Univariate associations between time spent sitting, total sedentary time and potential confounding and stratifying variables were evaluated using Wald χ^2 tests. Unadjusted and

adjusted associations between time spent sitting, total sedentary time and breast cancer incidence were evaluated using Cox proportional hazards regression. Person-time accrued from baseline until breast cancer occurrence, loss to follow-up, death or until end of follow-up (2015).

Time spent sitting and total sedentary time were evaluated continuously and categorically (≤5, 6–9, ≥10 hours/day). These cut-points were chosen for consistency with previous WHI-OS analyses and to allow sufficient numbers per category for stratified analyses [23]. More than 10% (N=15,925) of the analytic cohort reported fewer total hours lying down (which included time spent sleeping) than actual hours slept per night resulting in negative total sedentary time for 1,881 women. Analyses were run excluding these women and including these women with an assigned value of 0. Results did not differ, so presented results are from analyses in which women were assigned a value of 0. We evaluated both time spent sitting and total sedentary time to be consistent with previous WHI-OS reports that investigated total sedentary time [24,22,23,32]. However, results did not differ when using total sitting time compared to estimated total sedentary time as the measure of sedentary time exposure. Given the similar results and the limitations of the estimated total sedentary time only results for total sitting time are presented.

Confounding variables included in adjusted models were selected based on associations with both sedentary time and breast cancer risk. All adjusted models included the following covariates: age (continuous), region (Northeast, South, Midwest, West), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, Other), education (≤high school/GED, some college/associate degree, ≥college graduate), NSAID usage (yes/no), BMI (≤18.5, >18.5–<25, ≥25–<30, ≥30–<35, ≥35–<40, ≥40 kg/m^2), parity (nulliparous, 1–2, ≥3 children), recreational physical activity (no activity, low, moderate, high), mammogram frequency over past 5 years (none, 1, 2, 3, 4, ≥5), pack years smoking (never, <5, 5–<20, ≥20), alcohol intake (non-drinker, <1/week, 1–<7/week, ≥7 drinks/week), unopposed estrogen (never, past, current user), estrogen + progestin (never, past, current user), HEI 2005 Score (Quartiles).

To assess whether associations varied by hormone receptor subtype, analyses were replicated with breast cancer subtype as the outcome [hormone receptor positive (HR+), hormone receptor negative (HR−), triple negative]. Analyses were also replicated stratified by race/ethnicity to investigate possible racial or ethnic differences in observed associations. In analyses stratified by race/ethnicity, groups evaluated were non-Hispanic White, non-Hispanic Black, Hispanic and Asian. Sample size was too small to evaluate other racial/ethnic groups. Women who listed another race/ethnicity were excluded from the stratified analysis (N=1,052). Tests for multiplicative interaction between time spent sitting or total sedentary time and race/ethnicity were evaluated by including a cross-products term in Cox proportional hazards regression models.

Sedentary time, physical activity levels and body measurements are interrelated, which complicates interpretations of relative contributions for each individual factor on breast cancer risk [4,9,33]. It is also possible that exposure to the combination of more than one of factors could interact to differential influence breast cancer risk. To assess possible

interactions between sitting time, physical activity levels and body measurements analyses evaluating time spent sitting and breast cancer incidence were replicated stratified by physical activity levels and body measurements. Physical activity was evaluated as moderate and strenuous recreational physical activity (no activity, low, moderate, high), total recreational physical activity (no activity, >0–10, >10–20, >20 MET-hours/week), walking (no activity, >0–3.75, >3.75–7.5, >7.5 MET-hours/week), and combined physical activity (≤13.5, >13.5–25.85, >25.85–43.1, >43.1 MET-hours/week). Chosen cut-points for MET-hours/week were based on 25th, 50th and 75th percentiles. The reference groups from both recreational physical activity and walking were participants who reported no activity. The reference group for combined physical activity differs because no women reported no activity, so the lower 25th percentile was chosen as the reference. Body measurements evaluated were current BMI (<25, 25–<30, ≥30 kg/m^2), weight gain since age 18 (<10, 10–<25, ≥25 kg), WHR (<0.77, 0.75–<0.85, ≥ 0.85), and WC (<80, 80–88, ≥88 cm). Standard health cut-points were used for BMI, WHR and WC [23,34,35]. Due to the limitations with total sedentary time, overall similarities in assigned categories for total sitting time compared to total sedentary time, and lack of difference in study conclusions we present results stratified by physical activity and body measurements for total sitting time only. Tests for interaction between time spent sitting/total sedentary and race/ethnicity, physical activity or body measurements were evaluated by including a cross-products term in Cox proportional hazards regression models.

In an ancillary study in the WHI-OS, associations between time spent sitting and cancer-related biomarkers differed by menopausal hormone therapy usage [24]. Therefore, additional analyses were conducted to evaluate associations between sitting time and breast cancer incidence by estrogen and combined estrogen + progestin hormone therapy usage. Associations did not differ and results are not presented. Excluding invasive breast cancer cases diagnosed within the first two years of baseline did not change study results, so presented analyses include all cases diagnosed after baseline. All analyses were conducted using SAS 9.3 (SAS Institute, Inc. Cary, NC). Two-sided p-values are reported and a p-value <0.05 was considered statistically significant.

RESULTS

Population characteristics by total sitting time are presented on Table 1. The largest number of women reported typically sitting between 6–9 hours per day (40.9%), follow by ≤5 hours/day (34.5%) and ≥10 hour/day (24.7%). In the overall population, total time spent sitting (≥10 vs. ≤5 hours/day adjusted HR=1.00, 95% CI: 0.92–1.09) was not associated with postmenopausal breast cancer risk (Table 2). When stratified by race/ethnicity, total sitting time was not associated with breast cancer risk among non-Hispanic White (≥10 vs. ≤5 hours/day adjusted HR=1.01, 95% CI: 0.93–1.11), non-Hispanic Black (≥10 vs. ≤5 hours/day adjusted HR=0.91, 95% CI: 0.62–1.31) or Hispanic (≥10 vs. ≤5 hours/day adjusted HR=0.82, 95% CI: 0.47–1.43) women evaluated categorically or continuously. Among Asian women there was a suggestive inverse association between sedentary time and breast cancer incidence (≥10 vs. ≤5 hours/day adjusted HR=0.60, 95% CI: 0.33–1.07), which was statistically significant when evaluated continuously (per-unit increase, adjusted HR=0.86, 95% CI: 0.75–0.98). However, numbers in the strata for Hispanic and Asian

women were small and should be interpreted with caution. Additionally, when accounting for multiple comparisons, results would no longer be considered statistically significant. Tests for statistical interaction were by race/ethnicity were not statistically significant (data not presented). Time spent sitting was also evaluated in relation to breast cancer tumor subtypes and was not associated with breast cancer incidence, regardless of hormone receptor (HR+, HR−, triple negative) subtype (Table 3).

Associations between time spent sitting and breast cancer incidence were additionally evaluated across levels of physical activity (Table 4) and measures of body composition (Supplementary Table 1). When stratified by typical MET-hours/week spent walking (p-interaction=0.98) or total physical activity MET-hours/week (p-interaction=0.30) total time spent sitting and breast cancer incidence were not associated and did not differ by activity category. However, when evaluating levels of moderate and strenuous recreational physical activity total sitting time was positively associated with breast cancer risk among women with the highest reported levels of activity (≥10 vs. ≤5 hours/day adjusted HR=1.24, 95% CI: 1.07–1.44) (p-interaction=0.009). Similarly, total sitting time was positively associated with breast cancer incidence among women who reported engaging in >20 MET-hours/week of total recreational physical activity (≥10 vs. ≤5 hours/day adjusted HR=1.32, 95% CI: 1.12–1.56) (p-interaction=0.002). When adjusted for multiple comparisons the tests for interaction are no longer statistically significant. There was not a statistically significant relationship between total sitting time and breast cancer incidence, regardless of current BMI (p-interaction=0.31), weight gain since age 18 (p-interaction=0.94), WHR (p-interaction=0.60) or WC (p-interaction=0.95) category (available online in Supplementary Materials).

DISCUSSION

In this large prospective cohort of postmenopausal women sedentary time was not associated with overall invasive breast cancer risk or hormone receptor-specific breast cancer subtypes. In general, associations between sedentary time and breast cancer incidence did not differ by race/ethnicity, physical activity levels or body measurements.

Results from the present study differ from the findings in a recent meta-analysis that found a modest positive association between sedentary time and breast cancer [5]. Most studies in this review evaluated either occupational sitting or time spent watching television and not combined activities. In the present study, sedentary time was estimated from two general questions about time spent sitting or lying down with no differences in observed associations when sitting time was evaluated alone or when adding time spent lying down to sitting time. This differences between the present result and previous results could be related to differences in study populations or the data collection approach for ascertaining sedentary time.

As noted previously, sedentary time is not necessarily indicative of lack of physical activity. A person may meet recreational physical activity recommendations, but still engage in high levels of sedentary time. Current research suggests that sedentary behavior is associated with an increased risk for chronic disease, including breast cancer, independent of recreational

physical activity [21,6,36,7,8]. In our study, time spent sitting was generally unassociated with breast cancer incidence regardless of physical activity levels, however, among women who reported the highest levels of physical activity, time spent sitting was positively associated with breast cancer incidence and tests for interaction were statistically significant. Reasons for this observed association may be due to chance, residual confounding or that women who engage in high levels of recreational physical activity counter these activities by also engaging in prolonged sedentary time. Additionally, this may be a chance association due to multiple comparisons.

Sedentary time may be associated with metabolic dysfunction and inflammation both independently and through its role in weight gain, which could increase risk for breast cancer [37,38,4,14,15]. Hypothesized mechanisms are similar to those for lack of physical activity, and increasing recreational physical activity levels is often targeted to compensate for the increased time spent engaged in sedentary activities and to counteract the prevalence of obesity [33,9]. Sedentary time is associated with greater fat mass, but it remains unclear whether sedentary behavior influence breast cancer risk independently or via body composition only [4]. In the present analysis sitting time was not associated with breast cancer incidence and interactions between sitting time and body measurements were not observed. Associations between sedentary time and metabolic dysfunction [39,40,15,4] and inflammation-associated biomarkers [4,14] have been reported. A recent study also reported sedentary behavior was associated with higher urinary levels of estrogens and methylated catechols [41].

Previous analyses in the WHI-OS suggest sedentary time may be associated with chronic disease outcomes [24,22,23,32]. Time spent sitting was reported to be associated with all-cause, cardiovascular disease, coronary heart disease and cancer mortality, independent of recreational physical activity [23]. In another analysis, total sedentary time was associated with increased cardiovascular disease, coronary heart disease and cancer mortality [22]. In a sub-sample of the WHI-OS (N=755) time spent sitting per day was associated with cancer-related biomarkers, but patterns of associations were not clear and varied by race/ethnicity, levels of physical activity and estrogen hormone use [24]. In the only previous study to evaluated associations between sedentary time and cancer risk in the WHI-OS, sitting time was not associated with lung cancer risk [32].

This study had several strengths, including the prospective design and the large, multiethnic and geographically diverse study population. The study had sufficient sample size and numbers of breast cancer cases to evaluate associations between sedentary activities by hormone receptor subtypes, by race/ethnicity and across levels of physical activity and body measurements. While hormone receptor data was available for most invasive breast cancer cases, HER2/neu status was not ascertained in the early years, so this data is missing for a large number of cases. Although we had sufficient numbers to evaluate in several racial/ethnic groups, numbers were limited for some groups, which may result in spurious associations and may have contributed to the observed inverse associations in Hispanics and Asians. Additional limitations of this study include the collection of data using self-report questionnaires and the two broad questions used to ascertain sedentary time rather than objective measures or more detailed questions regarding sedentary behaviors. Recent

research suggests that it may be the pattern of sedentary time rather than only overall sedentary time that may influence health outcomes [36]. For example, prolonged sitting for a 4-hour time period compared to sitting for most of a 4-hour time period, but getting up to walk for 10 minutes each hour. In this study, sedentary time was estimated from reported time spent sleeping was subtracted from time spent lying down, however, several participants reported more time sleeping than lying down, which suggests possible misreporting for one or both of these variables. In this study population reliability for self-reported levels of physical activity and combined time spent sitting and lying down have previously been reported, but validity has not been assessed [25,26]. However, validity for recreational physical activity has been assessed in breast cancer patients with a correlation of 0.73 with accelerometer data [42] and physical activity measures and time spent sitting have been associated with other outcomes in expected directions [23,22]. Repeatability of sedentary questions tends to be high, but research suggests that current methods likely underestimate sedentary time, either because participants underreport inactivity and/or current assessment methods do not fully capture all types of sedentary activities [4]. However, research using objective measures, such as accelerometer data, have generally reached similar conclusions, that sedentary time is associated with increased chronic disease risk [43,14,36].

Results from this study do not support an association between sedentary time and breast cancer incidence. Given findings from previous research, however, this possible risk factor for breast cancer risk warrants further research. Studies evaluating objectively measured sedentary time in relation to breast cancer risk, breast tumor subtypes and breast cancer associated biomarkers could help clarify this relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C.

Authors would like to acknowledge the WHI Program Office, including (National Heart, Lung, and Blood Institute, Bethesda Maryland), Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller, Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg; Investigators and Academic Centers including (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner; (University of Minnesota, Minneapolis, MN) Karen L. Margolis; And Women's Health Initiative Memory Study (Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland.

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Table 1

Baseline Characteristics by Category of Time Spent Sitting

	Time Spent Sitting (hours/day)[a]		
	≤5	6–9	≥10
Overall (N, %)	24,205 (34.5)	28,696 (40.9)	17,332 (24.7)
Age (years) (mean, SD)[b]	64.0 (7.1)	64.0 (7.2)	61.3 (7.3)
Education (N, %)			
≤ High school graduate	6,018 (40.6)	5,899 (39.8)	2,905 (19.6)
Some college	9,061 (35.5)	10,256 (40.2)	6,179 (24.3)
≥College graduate	9,126 (30.5)	12,541 (41.9)	8,248 (27.6)
Race/ethnicity[b]			
Non-Hispanic White	19,666 (33.3)	24,735 (41.9)	14,677 (24.8)
Non-Hispanic Black	2,144 (40.0)	1,857 (34.7)	1,358 (25.3)
Hispanic	1,274 (50.5)	790 (31.3)	460 (18.2)
Asian	711 (32.0)	892 (40.2)	617 (27.8)
Other[c]	410 (39.0)	422 (40.1)	220 (20.9)
Physical activity (N, %)[d]			
No activity	2,706 (28.9)	3,537 (37.7)	3,126 (33.4)
Low	8,932 (33.3)	11,116 (41.4)	6,809 (25.3)
Moderate	4,450 (34.2)	5,405 (41.6)	3,145 (24.2)
High	8,117 (38.6)	8,638 (41.1)	4,252 (20.2)
Body mass index (kg/m^2) (mean, SD)[b]	26.6 (5.3)	27.1 (5.7)	28.1 (6.5)
Weight gain since 18yrs.(kg) (mean, SD)[b]	14.6 (13.4)	15.7 (14.0)	18.1 (15.6)
Waist circumference (cm) (mean, SD)[b]	83.2 (12.6)	84.5 (13.2)	86.3 (14.7)
Waist to hip ratio (mean, SD)[b]	0.80 (0.08)	0.81 (0.08)	0.81 (0.08)
HEI 2005 Score (mean, SD)[b]	70.0 (10.3)	69.6 (10.4)	68.1 (10.8)
Energy Intake (kilocalories) (mean, SD)[b]	1,488 (711)	1,556 (644)	1,619 (709)
Fruit & vegetable intake (N, %)			
<2 servings/day	5,928 (35.4)	6, 513 (38.9)	4,311 (25.7)
2–4 servings/day	15,196 (33.4)	18,970 (41.8)	11,273 (24.8)
≥5 servings/day	3,070 (38.3)	3,208 (40.0)	1,743 (21.7)
Alcohol Intake (N, %)			
Non-drinker	7,945 (38.2)	8,110 (39.0)	4,766 (22.9)
<1 drink/week	7,321 (32.5)	9,224 (41.0)	5,960 (26.5)
1–<7 drinks/week	6,066 (33.4)	7,676 (42.2)	4,435 (24.4)
≥7 drinks/week	2,873 (32.9)	3,686 (42.2)	2,1171 (24.9)
Smoking (N, %)			
Never	13,342 (36.3)	15,080 (41.0)	8,334 (22.7)
<5 pack-years	3,783 (36.1)	4,208 (40.2)	2,488 (23.7)
5 – <20 pack-years	3,426 (33.8)	4,163 (41.1)	2,548 (25.1)

	Time Spent Sitting (hours/day)[a]		
	≤5	6–9	≥10
≥20 pack-years	3,654 (28.4)	5,245 (40.8)	3,962 (30.8)
NSAID usage (N, %)			
No	19,953 (34.9)	23,258 (40.7)	13,915 (24.4)
Yes	4,252 (32.4)	5,438 (41.5)	3,417 (26.1)
Estrogen + progestin usage (N, %)			
Never used	17,221 (35.2)	20,227 (41.3)	11,520 (23.5)
Past user	2,061 (34.6)	2,370 (39.8)	1,531 (25.7)
Current user	4,923 (32.2)	6,099 (39.9)	4,281 (28.0)
Parity (N, %)			
Nulliparous	2,525 (28.7)	3,587 (40.7)	2,696 (30.6)
1–2 children	8,333 (33.6)	9,931 (40.0)	6,570 (26.5)
≥3 children	13,347 (36.5)	15,178 (41.5)	8,066 (22.0)
Mammogram within 5yrs.(N, %)			
No	1,582 (39.4)	1,555 (38.7)	880 (21.9)
Yes	22,623 (34.2)	27,141 (41.0)	16,452 (24.9)

[a] Time spent sitting at work, driving or riding in car/bus, watching TV, and sitting while talking.

[b] SD=standard deviation.

[c] Includes American Indian or Alaskan native.

[d] No activity= no moderate or strenuous recreational physical activity; Low=some moderate or strenuous recreational physical activity of limited duration, frequency or intensity; 3=moderate or strenuous activity of at least 20 minutes duration 2 – <4 times per week; high=moderate or strenuous activity of a least 20 minutes duration ≥4 times per week.

Table 2

Time spent sitting and postmenopausal breast cancer incidence overall and by race/ethnicity in the Women's Health Initiative Observational Study

	Cases/Person-years	Crude[b] HR (95%CI)	P-trend	Adjusted[c] HR (95% CI)	P-trend
Time Spent Sitting[a]					
Overall					
≤5 hours/day	1,302/331,680	Reference	0.53	Reference	0.88
6–9 hours/day	1,748/403,678	1.06 (0.98–1.13)		1.03 (0.96, 1.11)	
≥10 hours/day	1,065/250,694	0.97 (0.89–1.05)		1.00 (0.92–1.09)	
Continuous (hrs/d)	4,115/986,052	0.99 (0.97–1.01)	0.33	1.00 (0.98–1.02)	0.72
Non-Hispanic White[d]					
≤5 hours/day	1,135/279,897	Reference	0.71	Reference	0.67
6–9 hours/day	1,582/356,001	1.07 (0.99–1.15)		1.04 (0.96–1.12)	
≥10 hours/day	958/218,442	0.98 (0.90–1.07)		1.01 (0.93–1.11)	
Continuous (hrs/d)	3,675/854,340	0.99 (0.97–1.01)	0.46	1.00 (0.98–1.02)	0.93
Non-Hispanic Black[d]					
≤5 hours/day	77/24,331	Reference	0.49	Reference	0.63
6–9 hours/day	80/22,138	1.04 (0.76–1.43)		1.01 (0.73–1.40)	
≥10 hours/day	51/16,297	0.87 (0.61–1.24)		0.91 (0.62–1.31)	
Continuous (hrs/d)	208/62,766	0.98 (0.91–1.06)	0.67	0.99 (0.91–1.07)	0.80
Hispanic[d]					
≤ 5 hours/day	44/14,151	Reference	0.84	Reference	0.49
6–9 hours/day	29/9,340	0.95 (0.60–1.52)		0.94 (0.58–1.52)	
≥10 hours/day	19/5,518	0.95 (0.56–1.63)		0.82 (0.47–1.43)	
Continuous (hrs/d)	92/29,009	0.98 (0.87–1.11)	0.79	0.95 (0.84–1.08)	0.60
Asian[d]					
≤5 hours/day	31/8,296	Reference	0.11	Reference	0.09
6–9 hours/day	39/10,643	0.95 (0.59–1.52)		0.93 (0.57–1.53)	
≥10 hours/day	23/7,573	0.63 (0.36–1.11)		0.60 (0.33–1.07)	
Continuous (hrs/d)	93/26,512	0.88 (0.77–1.00)	0.04	0.86 (0.75–0.98)	0.03

[a] Time spent sitting, including at work, driving or riding in car/bus, watching TV, and sitting while talking.

[b] Cox proportional hazards regression, unadjusted.

[c] Cox proportional hazards regression, covariates: age, region (Northeast, South, Midwest, West), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, Other), education (≤high school/GED, some college/associate degree, ≥college graduate), NSAID usage (yes/no), BMI (≤18.5, >18.5–<25, ≥25–<30, ≥30–<35, ≥35–<40, ≥40 kg/m^2), parity (nulliparous, 1–2, ≥3 children), recreational physical activity (no activity, low, moderate, high), mammogram frequency over past 5 years (none, 1, 2, 3, 4, ≥5), pack years smoking (never, <5, 5–<20, ≥20), alcohol intake (non-drinker, <1/week, 1–<7/week, ≥7 drinks/week), unopposed estrogen (never, past, current user), estrogen + progestin (never, past, current user), HEI 2005 Score (Quartiles).

[d] Cox proportional hazards regression, stratified by race/ethnicity, adjusted model includes all covariates except race/ethnicity.

Table 3

Time spent sitting and breast cancer incidence by hormone receptor status in the Women's Health Initiative Observational Study

	Cases/Person-years	Crude[b] HR (95% CI)	P-trend	Adjusted[c] HR (95% CI)	P-trend
Hormone Receptor Positive					
Time Spent Sitting[a]					
≤5 hours/day	1,043/331,680	Reference	0.77	Reference	0.81
6–9 hours/day	1,424/403,678	1.07 (0.99–1.16)		1.04 (0.96–1.13)	
≥10 hours/day	866/250,694	0.98 (0.90–1.07)		1.01 (0.92–1.11)	
Continuous (hrs/d)	3,333/986,052	0.99 (0.97–1.02)	0.59	1.00 (0.98–1.02)	0.91
Hormone Receptor Negative					
Time Spent Sitting[a]					
≤5 hours/day	166/331,680	Reference	0.72	Reference	0.84
6–9 hours/day	211/403,678	1.00 (0.82–1.23)		1.01 (0.82–1.24)	
≥10 hours/day	133/250,694	0.96 (0.76–1.20)		1.03 (0.81–1.30)	
Continuous (hrs/d)	510/986,052	0.99 (0.94–1.04)	0.60	1.00 (0.94–1.06)	0.94
Triple Negative					
Time Spent Sitting[a]					
≤5 hours/day	106/331,680	Reference	0.16	Reference	0.34
6–9 hours/day	121/403,678	0.90 (0.69–1.17)		0.91 (0.70–1.19)	
≥10 hours/day	72/250,694	0.81 (0.60–1.09)		0.86 (0.63–1.18)	
Continuous (hrs/d)	299/986,052	0.95 (0.89–1.02)	0.15	0.96 (0.89–1.04)	0.30

[a]Time spent sitting, including at work, driving or riding in car/bus, watching TV, and sitting while talking.

[b]Cox proportional hazards regression, unadjusted.

[c]Cox proportional hazards regression, covariates: age, region (Northeast, South, Midwest, West), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, Other), education (≤high school/GED, some college/associate degree, ≥college graduate), NSAID usage (yes/no), BMI (≤18.5, >18.5–<25, ≥25–<30, ≥30–<35, ≥35–<40, ≥40 kg/m^2), parity (nulliparous, 1–2, ≥3 children), age at menarche (≤11, 12–13, ≥14 years), physical activity (no activity, low, moderate, high), mammogram frequency over past 5 years (none, 1, 2, 3, 4, ≥5), pack years smoking (never, <5, 5–<20, ≥20), alcohol intake (non-drinker, <1/week, 1–<7/week, ≥7 drinks/week), unopposed estrogen (never, past, current user), estrogen + progestin (never, past, current user), HEI 2005 Score (Quartiles).

Table 4

Time spent sitting and breast cancer incidence across levels of physical activity

Total sitting time	Cases/Non-Cases	Adjusted[f] HR (95% CI)	Cases/Non-Cases	Adjusted[f] HR (95% CI)	Cases/Non-Cases	Adjusted[f] HR (95% CI)	Cases/Non-Cases	Adjusted[f] HR (95% CI)	P_{int}[g]
	Moderate and Strenuous Recreational Physical Activity[a]								
	No Activity		Low		Moderate		High		
≤5 hours/day	127/2,579	Reference	474/8,458	Reference	264/4,186	Reference	437/7,680	Reference	0.009
6–9 hours/day	187/3,350	1.07 (0.85–1.35)	680/10,436	1.04 (0.92–1.17)	359/5,046	0.96 (0.82–1.13)	522/8,116	1.03 (0.91–1.17)	
≥10 hours/day	174/2,952	1.03 (0.81–1.31)	390/6,419	0.92 (0.80–1.05)	184/2,961	0.82 (0.67–0.99)	317/3,935	1.24 (1.07–1.44)	
Continuous (hrs/d)	488/8,881	0.99 (0.94–1.04)	1,544/25,313	0.98 (0.95–1.01)	807/12,193	0.95 (0.91–0.99)	1,276/19,731	1.05 (1.01–1.09)	
	Total Recreational Physical Activity (MET hours/week)[b, c]								
	No Activity		>0 – 10 MET hours/week		>10 – 20 MET hours/week		>20 MET hours/week		
≤5 hours/day	127/2,579	Reference	431/7,836	Reference	365/5,635	Reference	379/6,853	Reference	0.002
6–9 hours/day	187/3,350	1.07 (0.85–1.35)	638/10,041	1.03 (0.91–1.17)	500/6,922	0.97 (0.85–1.11)	423/6,635	1.05 (0.92–1.21)	
≥10 hours/day	174/2,952	1.03 (0.81–1.31)	429/6,739	0.95 (0.83–1.09)	231/3,712	0.84 (0.71–0.99)	231/2,864	1.32 (1.12–1.56)	
Continuous (hrs/d)	488/8,881	0.99 (0.94–1.04)	1,498/24,616	0.99 (0.95–1.02)	1,096/16,269	0.97 (0.93–1.01)	1,033/16,352	1.05 (1.01–1.09)	
	Walking (MET-hours/week)[b, d]								
	No Activity		>0 – 3.75 MET hours/week		>3.75 – 7.5 MET hours/week		>7.5 MET hours/week		
≤5 hours/day	329/5,897	Reference	385/6,694	Reference	221/3,992	Reference	367/6,320	Reference	0.97
6–9 hours/day	459/7,758	1.03 (0.89–1.19)	549/8,332	1.02 (0.90–1.17)	319/4,499	1.10 (0.92–1.31)	421/6,359	1.00 (0.87–1.15)	
≥10 hours/day	375/5,978	1.06 (0.91–1.23)	328/4,819	0.96 (0.82–1.12)	163/2,493	1.05 (0.85–1.29)	199/2,977	0.97 (0.81–1.16)	
Continuous (hrs/d)	1,163/19,633	1.00 (0.96–1.04)	1,262/19,845	0.99 (0.95–1.03)	703/10,984	1.02 (0.97–1.07)	987/15,656	0.99 (0.95–1.03)	
	Combined Physical Activity (MET-hours/week)[b, e]								
	≤13.5 MET hours/week		>13.5–25.85 MET hours/week		>25.85–43.1 MET hours/week		>43.1 MET hours/week		
≤5 hours/day	252/4,630	Reference	313/5,212	Reference	337/5,831	Reference	400/7,230	Reference	0.32

Total sitting time	Cases/Non-Cases	Adjusted[f] HR (95% CI)	Cases/Non-Cases	Adjusted[f] HR (95% CI)	Cases/Non-Cases	Adjusted[f] HR (95% CI)	Cases/Non-Cases	Adjusted[f] HR (95% CI)	P_{int}[g]
6–9 hours/day	394/6,319	1.05 (0.90–1.24)	461/6,809	1.02 (0.88–1.18)	475/7,079	0.97 (0.84–1.12)	418/6,741	1.05 (0.91–1.20)	
≥10 hours/day	396/5,897	0.99 (0.84–1.17)	267/4,391	0.89 (0.75–1.05)	242/3,524	0.98 (0.83–1.16)	160/2,455	1.14 (0.95–1.38)	
Continuous (hrs/d)	1,042/16,846	0.99 (0.95–1.02)	1,041/16,412	0.97 (0.93–1.01)	1,054/16,434	1.00 (0.96–1.04)	978/16,426	1.02 (0.97–1.06)	

[a] No activity= no moderate or strenuous recreational physical activity; Low=some moderate or strenuous recreational physical activity of limited duration, frequency or intensity; 3=moderate or strenuous activity of at least 20 minutes duration 2 – <4 times per week; high=moderate or strenuous activity of a least 20 minutes duration ≥4 times per week.

[b] Quartiles.

[c] All energy expenditure from recreational physical activity, including walking, mild, moderate and strenuous.

[d] Energy expenditure from walking only.

[e] Energy expenditure from recreational physical activity + yard work + household chores.

[f] Cox proportional hazards regression, covariates: age, region (Northeast, South, Midwest, West), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, Other), education (≤high school/GED, some college/associate degree, ≥college graduate), NSAID usage (yes/no), BMI (≤18.5, >18.5–<25, ≥25–<30, ≥30–<35, ≥35–<40, ≥40 kg/m^2), parity (nulliparous, 1–2, ≥3 children), mammogram frequency over past 5 years (none, 1, 2, 3, 4, ≥5), pack years smoking (never, <5, 5–<20, ≥20), alcohol intake (non-drinker, <1/week, 1–<7/week, ≥7 drinks/week), unopposed estrogen (never, past, current user), estrogen + progestin (never, past, current user), HEI 2005 Score (Quartiles).

[g] P-value from interaction term included in fully adjusted model with sitting time and activity variables modeled as categorical.