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Cohort Profile: The Women's Health Accelerometry Collaboration

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Title: Cohort Profile: The Women's Health Accelerometry Collaboration

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Abstract

Purpose: This paper describes the Women's Health Accelerometry Collaboration, a consortium of two prospective cohort studies of women age 62 years or older, harmonized to explore the association of accelerometer-assessed physical activity and sedentary behavior with cancer incidence and mortality.

Participants: A total of 23,443 women were included in the study; 17,061 from the Women's Health Study (WHS) and 6382 from the Women's Health Initiative Objective Physical Activity and Cardiovascular Health (WHI/OPACH) Study.

Findings to Date: Accelerometry, cancer outcomes, and covariate harmonization was conducted to align the two cohort studies. Physical activity and sedentary behavior were measured using similar procedures with an ActiGraph GT3X+ accelerometer, worn at the hip for one week, during 2011-2014 for WHS and 2012-2014 for WHI/OPACH. Cancer outcomes were ascertained via ongoing surveillance using physician adjudicated cancer diagnosis. Relevant covariates were measured using questionnaire or physical assessments. Among 23,443 women who wore the accelerometer for at least 10 hours on a single day, 22,868 women wore the accelerometer at least 10 hours/day on >=4 of 7 days. The analytic sample (n=22,852) averaged 4976 (standard deviation (SD) 2669) steps/day and engaged in an average of 80.8 (SD 46.5) minutes/day of moderate-to-vigorous, 105.5 (SD 33.3) minutes/day of light high, and 182.1 (SD 46.1) minutes/day of light low physical activity. A mean of 8.7 (SD 1.7) hours/day were spent in sedentary behavior. Overall, 11.8% of the cohort had a cancer diagnosis (other than non-melanoma skin cancer) at the time of accelerometry measurement.

Future Plans: Using the harmonized cohort, we will access ongoing cancer surveillance to quantify the associations of physical activity and sedentary behavior with cancer incidence and mortality.

Keywords: accelerometry; cancer; cohort study; physical activity; sedentary behavior

Strengths and limitations of this study

- The combined prospective cohort will address research questions pertaining to accelerometer-assessed physical activity and sedentary behavior with cancer outcomes due to similar measurement protocols for the exposures, outcomes, and important covariates.
- A variety of sociodemographic, behavioral, and medical history were collected over many years prior to accelerometry measurement that allows for control of important confounders.
- Accelerometry was assessed for one week and may not represent behavior during the entire follow-up period.
- This cohort is limited to women age 62 years and older, and thus may not be generalizable to men or to younger adults.

Introduction

Cancer is the second leading cause of death in the United States for women, with an estimated 289,150 cancer-related deaths and 927,910 new cancer cases predicted to occur among women in 2021.[1] The leading types of new cancer cases for women include breast (30%), lung and bronchus (13%), colon and rectum (8%), uterine corpus (7%), skin melanoma (5%), and non-Hodgkin lymphoma (4%).[1] Cancer risk increases with age; however, certain screening tests are not recommended for adults 75 years or older since the harms outweigh the benefits. [2] This results in cancer that is often diagnosed at a more advanced stage among women 75 years or older than among women under the age of 75 years.

With a rapidly growing older population, there will be an increased demand for cancer-related health care. Among women at age 85 years without a history of cancer, the probability of cancer diagnosis in their remaining lifetime is 12.8% and the probability of cancer death is 9.6%.[2] Focusing on risk factors that are modifiable in later life that can help reduce cancer burden, such as physical activity and sedentary behavior, should be a public health priority.

Observational studies consistently report associations between lower self-reported moderate-to-vigorous leisure-time physical activity and increased risk of several cancer types.[3] In support of this, the 2018 United States' Physical Activity Guidelines Advisory Committee (PAGAC),[4] updated in 2019,[5] identified strong favorable associations comparing the highest to the lowest levels of physical activity on the risk of developing bladder, breast, colon, endometrium, esophageal adenocarcinoma, renal, and gastric cancers, and moderately favorable associations for lung cancer. However, there was a limited dose response gradient for esophageal adenocarcinoma, renal, and lung cancers. The review indicated limited evidence on physical activity occurring outside of leisure-time, and a lack of associations with physical activity by population subgroups, such as by age, socioeconomic status, or race/ethnicity.

The PAGAC also reported limited evidence on the relationship of sedentary behavior with cancer incidence and mortality.[4,6] Evidence supporting the PAGAC statements were primarily based on self-reported physical activity and sedentary behavior data. Self-reported light activity is especially difficult to recall, and is the most common intensity level older adults participate in.[7,8] To date, few studies of older adults have explored accelerometer-assessed physical activity and sedentary behavior with cancer incidence and mortality.[9-12] The scarcity of evidence is likely due to the need for larger studies with longer follow-up time to investigate cancer outcomes, particular for the less common tumor sites.

The Women's Health Accelerometry Collaboration will explore the associations of accelerometer-assessed physical activity and sedentary behavior with cancer outcomes by combining data from two large prospective studies: the Women's Health Study (WHS) and the Women's Health Initiative Objective Physical Activity and Cardiovascular Health (WHI/OPACH) Study. This endeavor requires harmonization of accelerometry, cancer outcomes, and covariates. The study will provide important insights on cancer incidence and mortality among women 62 years and older. The specific aim for this paper is to describe the rationale, methodology, proposed analysis plan, and characteristics of the cohort.

Cohort Description

In order to address the scientific gaps, we harmonized two cohort studies of women 62 years and older using similar data collection methodologies to quantify the associations between physical activity and sedentary behavior with multiple site-specific incident cancers and overall fatal cancers. Patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this research.

WHS: The WHS is a completed randomized trial (1992–2004) testing aspirin, beta-carotene, and vitamin E for preventing cardiovascular disease and cancer among 39,876 healthy United States women at least 45 years of age.[13-15] When the trial ended, women were invited to continue in an observational study. Of the 33,682 alive, 89% of women consented, reporting on their health habits and medical history annually on questionnaires. From 2011-2014, an ancillary study was conducted to collect accelerometry among participants.[16] In 2011, 29,494 women were alive and 18,289 agreed to participate and were sent an accelerometer, 6931 declined participation, 1456 were ineligible because they were unable to walk outside of the home, and the remaining 2818 did not respond to the invitation. Overall, 17,466 women returned the accelerometers for downloading. All study protocols were approved by the Brigham and Women's Hospital Institutional Review Board, and all women gave written informed consent.

WHI/OPACH: The WHI/OPACH Study[17] is an ancillary study to the WHI Long Life Study.[18] The ancillary study was designed to collect physical activity and sedentary behavior measured by accelerometry and self-report, and to collect detailed data on incident falls using daily falls calendars collected for up to 13 months. The primary outcomes of the original study included mortality,[19] falls,[20] and cardiovascular disease.[21,22] From 2012-2014, 9252 women consented to the WHI Long Life Study. Among those participants, 8618 consented to participate in the WHI/OPACH ancillary study collecting accelerometry. From this sample, 58 died before recruitment, 10 died before receiving the materials, 141 were ineligible (e.g., dementia, residing in a nursing home, not ambulatory), 765 could not be contacted, and 596 refused to participate. In summary, 7048 women were sent the accelerometer, a sleep log, the OPACH physical activity questionnaire (available in this paper[17]), and 13 falls calendars. Overall, 6489 women returned the accelerometers for downloading. All study protocols were approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and all women gave informed consent.

Accelerometry Data Collection: Both cohorts utilized the same accelerometer (ActiGraph GT3X+ accelerometer (Pensacola, Florida). The triaxial accelerometer was small (4.6x3.3x1.5 cm) and light weight (19 grams), with a dynamic range of +/-6 G. The WHS women were asked to wear the accelerometer on their right hip, removing it only during sleep, for 7 days. They were also asked to keep a log documenting wear and non-wear days.[16] The accelerometer and log were mailed to participants, with a mailer for return.

The WHI/OPACH women were asked to wear the accelerometer on their right hip for 7 days, including night time. The WHI/OPACH women were asked to keep a sleep log for in- and out-of-bed wear.[23] For women with missing sleep log data, their in-bed and out-of-bed times were imputed using person-specific means, if available, or the sample mean. Using the sleep log, the in-bed wear was removed to make the data congruent across the two cohorts. The accelerometer and log were given to most women at their study visit and were mailed back after completion.

The accelerometer recorded 3-dimensional raw acceleration signals at 30 Hz, which were aggregated using ActiLife software (version 6) to counts per 15-second epochs with the normal filter setting. To better detect movement from all directions, vector magnitude (VM) counts were derived by taking the square root of the sum of the three axes squared. Non-wear time was assessed using the validated Choi et al. algorithm,[24,25] defined as an interval of at least 90 consecutive minutes of zero VM counts/minute, with allowance of up to one 2-minute period of nonzero VM counts and requiring that no counts were detected during the 30 minutes upstream and downstream from that period.

Several metrics were used to describe physical activity and sedentary behavior from the accelerometer. First, average intensity per day was summarized as average VM/15-seconds. Second, using WHI/OPACH calibration-study derived accelerometry cutpoints, we defined sedentary behavior and physical activity from receiver operating characteristic curve analyses that balanced the number of false positives and false negatives.[26] VM/15-second cutpoints were defined as follows: sedentary 0-18, light low 19-225, light high 226-518, and moderate-to-vigorous physical activity >=519. Third, a moderate-to-vigorous bout was defined as >=10 minutes of consecutive moderate-to-vigorous minutes with allowance for interruptions for up to 20% of the time below the threshold and <5 consecutive minutes below the threshold. The bout must start and end with moderate-to-vigorous physical activity. Fourth, average steps per day was explored, derived from ActiGraph's proprietary algorithm.

Cancer Incidence and Mortality Outcomes: WHS participants received annual mailed questionnaires which asked about health history, including a diagnosis of cancer. Relevant medical records were obtained for all self-reported cancers (except for non-melanoma skin cancer).

As part of WHI, OPACH participants also received annual mailed questionnaires which asked about physician diagnosis of new cancer or malignant tumors, hospitalizations, and other health history. Medical records were obtained for all self-reported cancers except non-melanoma skin cancer.[27]

For both studies, physician adjudicators coded cancer using medical record documents such as the pathology report, hospital face sheet, operative report, hospital discharge summary, oncology consultation, radiology report, and tumor registry abstract. The date of cancer diagnosis is based on one of the following: microscopically-confirmed based on date the tissue

that resulted in a positive pathology was removed, not microscopically-confirmed based on the date of first hospitalization for cancer, self-report only based on date reported by participant, and both autopsy-only and death certificate-only based on death date.

For WHS, an Endpoints Committee of physicians blinded to questionnaire exposure data reviewed all medical records using pre-specified criteria. A cancer diagnosis was confirmed with histological or cytological evidence. In the absence of these diagnostic tests, strong clinical evidence accompanied by radiologic evidence or laboratory markers was used to confirm cancer occurrence. The histological type, grade, and stage of cancer were recorded. The date of cancer diagnosis was based on the earliest date of the relevant evidence (e.g., date of histological confirmation). For cancers diagnosed only on death certificates without prior medical records, the date of death was used.

Coding of cancer type was based on the Surveillance, Epidemiology, and End Results (SEER) program. Using the International Classification of Diseases for Oncology (ICD-O-3), the morphology code details the type and behavior of a tumor.[28] The code contained three parts: histology or cell type (4 digits), behavior or the way it acts in the body (1 digit), and grade, differentiation or phenotype (1 digit). Histology of the primary tumor was ascertained and its behavior code were ascertained. A behavior code is defined as 0: benign; 1: uncertain whether benign or malignant; 2: carcinoma in situ; and 3 or higher: malignant (invasive) primary site. These codes were applied identically across both cohorts; the final classification of cancer by site was limited to behavior code 3 and is summarized in **Supplemental Table 1.**[3]

Cancer surveillance is currently ongoing in both cohorts. Additionally, we ascertained if women had been diagnosed with a cancer prior to the accelerometer data collection, including type of cancer and time since diagnosis. For both cohorts, deaths were reported by family members or

postal authorities, with medical records, interviews with next of kin, and death certificates obtained to confirm the event. The National Death Index was searched periodically for cohort members. The underlying cause of death was classified on the basis of the death certificate, medical records, and other records such as an autopsy report using the ICD 10th edition. The death certificate diagnosis was used when no other records are available. In this paper, we report on cancer diagnosed from study enrollment to the date of accelerometry measurement.

Other Measurements: Sociodemographics, including age, race/ethnicity, and education were collected at study enrollment. Participants from both cohorts regularly completed mailed questionnaires regarding their health history and health behaviors and we used the measure closest to the time of accelerometer wear. Women reported general health, smoking status, alcohol intake, and average walking speed. They also reported on postmenopausal hormone use and history of diabetes, confirmed coronary heart disease, bilateral oophorectomy, and hysterectomy. Height and weight were self-reported in WHS and measured in WHI/OPACH. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and defined as underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), or obese (>=30.0).

Proposed Statistical Analysis: We will explore the association of physical activity and sedentary behavior with cancer incidence and mortality. For site-specific cancer analyses, if participants have a history of the cancer under analysis then they will be excluded. For example, if we analyze lung cancer incidence then we will exclude women who already have a lung cancer diagnosis prior to the accelerometer measurement. For composite cancer (a subset of cancer types combined) and total cancer analyses, we will include women who have a history of cancer prior to accelerometry measurement. For these analyses, we can further explore whether excluding those with cancer impacts the results or whether having prior cancer is a moderator.

Women with a hysterectomy prior to accelerometry measurement will be excluded from investigation of incident endometrial cancer. Similarly, women with bilateral oopherectomy prior to accelerometry measurement will be excluded from investigation of incident ovarian cancer. We will use stratified Cox regression models to estimate hazard ratios and 95% confidence intervals for various measures of physical activity and sedentary behavior with cancer incidence and mortality. The stratified model allows the baseline hazards for the two cohorts to differ.[29] However, the hazards of the exposure groups are assumed to be proportional, which will be tested using Schoenfeld residuals. We will censor follow-up time on the date of the cancer diagnosis, the date of death, or the date of last contact.

Analytic Sample: In total, 25,337 women were sent an accelerometer, with 18,289 contributing from the WHS cohort and 7048 from the WHI/OPACH cohort (**Table 1**). After excluding those that did not return the accelerometer, did not wear the accelerometer, or experienced accelerometer malfunction, 23,443 (92.5%) and 22,868 (90.3%) women contributed at least one and four adherent days of accelerometry wear, respectively, defined as wearing the device for at least 10 hours during a day while awake. WHS began as a trial for the primary prevention of cancer and cardiovascular disease; however, post-randomization, 16 women were subsequently found to have prevalent cancer and are excluded from the present study. The final sample size for the analyses was 22,852.

Findings To Date

At the time of accelerometry measurement, both cohorts had a mean age above 70 years (71.5 WHS, 78.7 WHI/OPACH), with a range of 62-89 years for WHS and 63-97 for WHI. Both cohorts had a mean BMI in the overweight category (26.2 WHS, 28.1 WHI/OPACH). WHS women compared to WHI/OPACH women had a higher proportion with at least some college

education (100% vs. 79.7%), very good or excellent general health (74.7% vs. 50.6%), drank alcohol daily (15.9% vs. 5.7%), used postmenopausal hormones (9.9% vs. 2.5%), and walked at least 3 mph (27.5% vs. 7.8%) (**Table 2**). At the time of accelerometry measurement, the WHI/OPACH women compared to WHS women included a higher proportion of Black (33.4% vs. 1.5%) and Hispanic (16.9% vs. 0.9%) women and had a higher proportion with diabetes (20.3% vs. 9.0%). The two cohorts were more similar with regards to never smoking (54.7% WHI/OPACH, 50.5% WHS), coronary heart disease (10.1% WHI/OPACH, 4.3% WHS), and cancer (11.7% WHI/OPACH, 11.9% WHS), or who reported a bilateral oophorectomy (19.2% WHI/OPACH, 22.2% WHS) or a hysterectomy (42.6% WHI/OPACH, 41.6% WHS).

Most women provided at least four days of adherent data (defined as 10 hours/day), with 14.9 hours/day of average awake wear time (**Table 3**). The WHS women engaged in a higher mean total volume of physical activity (146 vs. 101 average daily VM/15-seconds) and accumulated more mean steps per day (5489 vs. 3573) than WHI/OPACH women. WHS women engaged in approximately 2-3 times more mean moderate-to-vigorous physical activity (91.9 vs. 50.4 minutes/day) and bouts (18.2 vs. 6.4 minutes/day) than WHI/OPACH women. In contrast, mean light high and light low activity were similar. Sedentary behavior was higher among WHI/OPACH women compared to WHS women (555.6 vs. 510.6 minutes/day). It is important to note that some of the differences between cohorts may be due to age or other potential confounders, since all analyses were unadjusted for age differences.

We examined the number of incident and fatal cancers in the cohort, with cancer outcomes documented through December 31, 2019 for WHS and through March 30, 2020 for WHI/OPACH. During an average of 5.9 (SD 1.6) years of follow-up thus far, there have been 1378 cancer events among which 414 were fatal. The most common cancers were breast (459) and lung (146) cancer.

Strengths and Limitations

The Women's Health Accelerometry Collaboration cohort's primary strength is the statistical power to be able to address research questions regarding physical activity and sedentary behavior among older women in a cost-efficient manner by using data from existing studies. Cancer outcomes continue to be assessed annually by similar methods, adjudicated, and combined systematically across cohorts. Accelerometry was collected by the same device using similar procedures. A WHI/OPACH substudy of 200 women participated in a variety of laboratory-based activities while wearing the accelerometer and having oxygen uptake measured. Using these data, accelerometer cutpoints were developed specifically for women 60 years and older.[26] Raw accelerometry data will allow the research team to develop further measures of physical activity and sedentary behavior, such as using the activity index[30] and latent class analysis on accelerometry.[31] Using the raw data, we can apply two machine-learned algorithms developed specifically for older women; one designed to distinguish sitting, riding in a vehicle, standing still, standing moving, and walking,[32] while the other was designed to accurately quantify sitting bouts,[33] which, without the algorithm, are measured with substantial error.[34]

The Women's Health Accelerometry Collaboration cohort has several limitations. First, the accelerometer was worn once by participants for one week. It is possible that physical activity and sedentary behavior could change seasonally and over the course of follow-up, and thus not be represented by the measurement week. To address this concern, the question was explored in a subset of WHS participants that wore the accelerometer up to 3 times over a 2-3 year period, the initial measures of physical activity and sedentary behavior provided a reproducible measure at repeated time points.[35] Adjusting for age, season, and BMI, the intraclass correlation coefficients between women indicated moderate to high reproducibility for average

VM counts/day (0.83; 95% confidence interval 0.78, 0.87), sedentary behavior (0.73; 0.66, 0.80), light activity (0.67; 0.59,0.74), and moderate-to-vigorous physical activity (0.83; 0.78,0.87). This indicated that metrics derived from one week of accelerometer administration can estimate longer-term patterns of behavior among women of similar ages.

Second, there will need to be a longer follow-up period or other cohorts to address the relationships of accelerometry-assessed behaviors with rare cancers. Third, women that could not walk without assistance outside of their home were excluded due to the development of existing accelerometer algorithms on ambulation. More effort is needed to understand how to interpret accelerometry from non-ambulatory individuals in order to include them in studies of this kind.[36] Fourth, while WHS initially mailed accelerometers and used an awake only protocol, in contrast WHI/OPACH provided most of the accelerometers in-person at the home visit and used a 24-hour wear protocol. Despite these differences, there did not appear to be differential impact on accelerometer awake wear time between the cohorts.

Collaboration

Data are accessible through the established data sharing policies for the Women's Health Study at https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001964.v1.p1 and http://whs.bwh.harvard.edu/ . Similarly, data are accessible through the established data sharing policies for the Women's Health Initiative at https://www.whi.org/page/working-with-whi-data. Interested researchers can write to the study to clarify data access. Due to data sharing agreements, the Women's Health Accelerometry Collaboration data are not directly available.

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investigators listed at the following link: https://www-whi-org.s3.us-west-2.amazonaws.com/wp-content/uploads/WHI-Investigator-Short-List.pdf.

Contributors: IL, EJS, and RD were involved in study design, accelerometry acquisition, and/or analysis of the WHS. AL, KRE, IL, CD, and JB were involved in the study design, accelerometry acquisition, and/or analysis for the WHI/OPACH Study. KRE, along with the research team, secured funding for this project. KRE conceived of and drafted the manuscript, and GW helped with data analysis. All authors reviewed the manuscript critically and approved the final version.

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Data availability statement: Data are available for the Women's Health Study at https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001964.v1.p1 and for the Women's Health Initiative OPACH Study at https://www.whi.org/page/working-with-whi-data. Researchers using the data are required to follow the terms designed to protect the privacy of the participants.

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Table 1: Accelerometer wear overall and by cohort

	Total	WHS n	WHI/OPACH n
Sample invited to sub-study	38,746	29,494	9252
Agreed to participate and sent the accelerometer	25,337	18,289	7048
Returned accelerometer	24,429	17,708	6721
Data were downloaded	23,955	17,466	6489
At least one adherent day of wear (>=10 hours)	23,443	17,061	6382
Adherent wear >=4 days of >=10 hours/day	22,868	16,742	6126
Removed those with cancer at trial inception*	22,852	16,726	6126

*WHS began as a trial for the primary prevention of cancer and cardiovascular disease; however, post-randomization, 16 of the 16,742 women were subsequently found to have prevalent cancer and were excluded from the present study.

Table 2: Description of sample overall and by cohort

	Overall (n=22,852)		WHS (n=16,726)		Missing	WHI/OPACH (n=6126)		Missing
	Mean	SD	Mean	SD		Mean	SD	
Age, years	73.4	6.8	71.5	5.7	0	78.7	6.7	0
Body mass index, kg/m^2	26.7	5.3	26.2	5.0	3	28.1	5.7	386
	Percent	n	Percent	n	Missing	Percent	n	Missing
Sociodemographic								
Age categories								
60-69	35.1	8019	44.2	7392		10.2	627	0
70-79	43.8	10013	45.2	7565		40.0	2448	
80-89	20.0	4563	10.6	1769		45.6	2794	
>=90	1.1	257	0.0	0		4.2	257	
Race/ethnicity					0			0
White	83.1	18984	95.3	15938		49.7	3046	
Black	10.1	2300	1.5	253		33.4	2047	
Hispanic	5.2	1184	0.9	151		16.9	1033	
Unknown or other	1.7	384	2.3	384		0.0	0	
Education					269			41
High school or less	5.5	1237	0.0	0		20.3	1237	
Some college	46.7	10531	49.7	8182		38.6	2349	
College graduate or more	47.8	10774	50.3	8275		41.1	2499	
Self-reported or measured near accelerometry measurement								
General health					5			21
Excellent	20.7	4730	24.6	4115		10.1	615	

Very good	47.5	10842	50.1	8371		40.5	2471	
Good	27.3	6230	22.8	3804		39.7	2426	
Fair or poor	4.5	1024	2.6	431		9.7	593	
Body mass index					3			386
<18.5	1.8	415	2.0	334		1.3	81	
18.5-24.9	39.2	8953	43.1	7215		28.4	1738	
25.0-29.9	33.6	7672	33.6	5624		33.4	2048	
30.0-34.9	14.7	3356	13.5	2263		17.8	1093	
35.0-39.9	5.0	1145	4.1	692		7.4	453	
>=40	2.1	486	1.6	261		3.7	225	
Smoking					1			582
Current	3.4	749	3.5	590		2.9	159	
Former	45.1	10046	46.0	7695		42.4	2351	
Never	51.5	11474	50.5	8440		54.7	3034	
Alcohol					7			536
Never or rarely	37.9	8445	38.0	6356		37.4	2089	
Monthly	15.9	3558	9.8	1646		34.2	1912	
Weekly	32.9	7340	36.3	6069		22.7	1271	
Daily	13.3	2966	15.9	2648		5.7	318	
Walking speed					4			261
<2 mph	21.5	4906	17.5	2931		32.2	1975	
2-2.9 mph	40.2	9185	42.7	7143		33.3	2042	
3-3.9 mph	20.7	4728	25.5	4271		7.5	457	
>=4 mph	1.5	350	2.0	332		0.3	18	
Unsure or does not walk regularly	15.0	3418	12.2	2045		22.4	1373	

Medical history near accelerometry measurement								
Using postmenopausal hormones					6			0
Yes	7.9	1812	9.9	1657		2.5	155	
Diabetes history					0			0
Yes	12.0	2747	9.0	1501		20.3	1246	
Coronary heart disease					0			0
Yes	5.8	1328	4.3	712		10.1	616	
Oopherectomy, bilateral					0			94
Yes	21.4	4873	22.2	3718		19.2	1155	
Hysterectomy					0			0
Yes	41.9	9568	41.6	6957		42.6	2611	
Cancer at accelerometry measurement					0			0
Yes	11.8	2696	11.9	1982		11.7	714	

Table 3: Description of accelerometry measures overall and by cohort

	Overall (n=22,852)		WHS (n=16,726)		WHI/OPACH (n=6126)	
	Mean	SD	Mean	SD	Mean	SD
Wear time on adherent days, hours/day	14.9	1.3	14.9	1.3	14.9	1.3
Average daily vector magnitude per 15-seconds	134.0	53.9	146.0	52.8	101.2	42.1
Average daily steps/day	4975.9	2668.8	5489.4	2658.2	3573.1	2142.3
Average minutes/day using vector magnitude:						
Sedentary behavior	522.7	101.0	510.6	98.8	555.6	99.4
Light low	182.1	46.1	179.6	44.2	188.9	50.2
Light high	105.5	33.3	108.2	32.1	98.0	35.5
Moderate to vigorous	80.8	46.5	91.9	45.4	50.4	34.4
Moderate to vigorous bouts	15.0	22.8	18.2	24.6	6.4	13.6

Supplemental Table 1: International Classification of Diseases for Oncology, 3rd Ed. Codes for each cancer site used in ascertainment of primary incident invasive cancers across cohorts. This coding was developed from Moore et al.[3]

Cancer site	ICD-O-3 codes and, if applicable, ICD-O-3 histology‡
Esophageal adenocarcinoma	C150-159& histologies: 8140, 8142, 8144, 8261, 8310, 8480, 8481, 8570
Gallbladder	C239
Liver*	C220 and C221
Lung	C340-C349
Kidney	C649 and C659
Small intestine	C170-179
Gastric cardia	C160
Endometrial	C540-C549 and C559
Esophageal squamous	C150-159 and histologies 8041, 8070-8072, 8074
Myeloid leukemia	Acute myeloid leukemia: any histology of 9840, 9861, 9865-9867, 9869, 9871-9874, 9895-9898, 9910-9911, 9920 Acute monocytic leukemia: any histology of 9891 Chronic myeloid leukemia: any histology of 9863, 9875-9876, 9945-9946 Other myeloid/monocytic leukemia: any histology of 9860, 9930
Myeloma	Any histology of 9731-9732, 9734
Colon	C180-C189, C260
Head and neck	Lip: C000-C009 Tongue: C019-C029 Salivary gland: C079-C089 Floor of mouth: C040-C049 Gum and other mouth:C030-C039, C050-C059, C060-C069 Nasopharynx: C110-C119 Tonsil: C090-C099 Oropharynx: C100-C109 Hypopharynx: C129, C30-C139 Other oral cavity and pharynx: C140, C142, C148 Larynx: C320-C329
Rectum	C199, C209
Bladder	C670-C679
Breast	C500-C509
Non-Hodgkin's Lymphoma (NHL)	NHL-nodal: C024, C098, C099, C111, C142, C379, C422, C770-C779 and histologies: 9590-9597, 9670-9671, 9673, 9675, 9678-9680, 9684,

	9687-9691, 9695, 9698-9702, 9705, 9708, 9709, 9712, 9714-9719, 9724-9729, 9735, 9737, 9738, 9811-9818, 9823, 9827, 9837 NHL-extranodal, definition 1: All sites except C024, C098-C099, C111, C142, C379, C422, C770-C779 and histologies of: 9590-9597, 9670-9671, 9673, 9675, 9678-9680, 9684, 9687, 9688, 9689-9691, 9695, 9698-9702, 9705, 9708, 9709, 9712, 9714-9719, 9724-9729, 9735, 9737, 9738 NHL-extranodal, definition 2: All sites except C024, C098, C099, C111, C142, C379, C420-C422, C424, C770-C779 and histologies of: 9811-9818, 9823, 9827, 9837
Thyroid	C739
Gastric non-cardia	C161-169
Soft tissue	C380, C470-C479, C490-C499
Pancreas	C250-C259
Lymphocytic leukemia	Acute lymphocytic leukemia, definition 1: Any histology of 9826, 9835-9836 Acute lymphocytic leukemia, definition 2: C420, C421, C424 and histologies: 9811-9818, 9837 Chronic lymphocytic leukemia: C420, C421, C424 and histology 9823 Other lymphocytic leukemia: Any histology of 9820, 9832-9834, 9940.
Ovary	C569
Brain	C710-C719
Prostate‡	C619
Skin cancer, excluding basal and squamous	Melanoma: C440-C449 and histologies 8720-8790 Other non-epithelial skin: C440-C449, excluding histologies 8000-8005, 8010-8046, 8050-8084, 8090-8110, 8720-8790, 9050-9055, 9140, 9590-9992

* A small proportion of the liver cancer classification consists of intrahepatic bile duct cancer cases.

† A small proportion of the kidney cancer classification consists of renal pelvis cancer cases.

‡ Unless otherwise stated, cancer definitions exclude the histologies 9050-9055, 9140, and 9590-9992.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	10-11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	na

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	na
Discussion			
Key results	18	Summarise key results with reference to study objectives	na
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15-16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Title: Cohort Profile: The Women's Health Accelerometry Collaboration

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Abstract

Purpose: This paper describes the Women's Health Accelerometry Collaboration, a consortium of two prospective cohort studies of women age 62 years or older, harmonized to explore the association of accelerometer-assessed physical activity and sedentary behavior with cancer incidence and mortality.

Participants: A total of 23,443 women (age mean 73.4, SD 6.8) living in the United States and participating in an observational study were included; 17,061 from the Women's Health Study (WHS) and 6382 from the Women's Health Initiative Objective Physical Activity and Cardiovascular Health (WHI/OPACH) Study.

Findings to Date: Accelerometry, cancer outcomes, and covariate harmonization was conducted to align the two cohort studies. Physical activity and sedentary behavior were measured using similar procedures with an ActiGraph GT3X+ accelerometer, worn at the hip for one week, during 2011-2014 for WHS and 2012-2014 for WHI/OPACH. Cancer outcomes were ascertained via ongoing surveillance using physician adjudicated cancer diagnosis. Relevant covariates were measured using questionnaire or physical assessments. Among 23,443 women who wore the accelerometer for at least 10 hours on a single day, 22,868 women wore the accelerometer at least 10 hours/day on >=4 of 7 days. The analytic sample (n=22,852) averaged 4976 (standard deviation (SD) 2669) steps/day and engaged in an average of 80.8 (SD 46.5) minutes/day of moderate-to-vigorous, 105.5 (SD 33.3) minutes/day of light high, and 182.1 (SD 46.1) minutes/day of light low physical activity. A mean of 8.7 (SD 1.7) hours/day were spent in sedentary behavior. Overall, 11.8% of the cohort had a cancer diagnosis (other than non-melanoma skin cancer) at the time of accelerometry measurement. During an average of 5.9 (SD 1.6) years of follow-up, 1378 cancer events among which 414 were fatal have occurred.

Future Plans: Using the harmonized cohort, we will access ongoing cancer surveillance to quantify the associations of physical activity and sedentary behavior with cancer incidence and mortality.

Keywords: accelerometry; cancer; cohort study; physical activity; sedentary behavior

Strengths and limitations of this study

- The combined prospective cohort will address research questions pertaining to accelerometer-assessed physical activity and sedentary behavior with cancer outcomes due to similar measurement protocols for the exposures, outcomes, and important covariates.
- A variety of sociodemographic, behavioral, and medical history were collected over many years prior to accelerometry measurement that allows for control of important confounders.
- Accelerometry was assessed for one week and may not represent behavior during the entire follow-up period.
- A longer follow-up period will be needed to explore the relationships of accelerometry-assessed behaviors with rare cancers.

Introduction

Cancer is the second leading cause of death in the United States for women, with an estimated 289,150 cancer-related deaths and 927,910 new cancer cases predicted to occur among women in 2021.[1] The leading types of new cancer cases for women include breast (30%), lung and bronchus (13%), colon and rectum (8%), uterine corpus (7%), skin melanoma (5%), and non-Hodgkin lymphoma (4%).[1] Cancer risk increases with age; however, certain screening tests are not recommended for adults 75 years or older since the harms outweigh the benefits. [2] This results in cancer that is often diagnosed at a more advanced stage among women 75 years or older than among women under the age of 75 years.

With a rapidly growing older population, there will be an increased demand for cancer-related health care. Among women at age 85 years without a history of cancer, the probability of cancer diagnosis in their remaining lifetime is 12.8% and the probability of cancer death is 9.6%.[2] Focusing on risk factors that are modifiable in later life that can help reduce cancer burden, such as physical activity and sedentary behavior, should be a public health priority.

Observational studies consistently report associations between lower self-reported moderate-to-vigorous leisure-time physical activity and increased risk of several cancer types.[3] In support of this, the 2018 United States' Physical Activity Guidelines Advisory Committee (PAGAC),[4] updated in 2019,[5] identified an overall evidence grade of "strong" comparing the highest to the lowest levels of physical activity on the risk of developing bladder, breast, colon, endometrial, esophageal adenocarcinoma, renal, and gastric cancers, and an overall evidence grade of "moderate" for lung cancer. However, there was a limited dose response gradient for esophageal adenocarcinoma, lung, and renal cancers. The review indicated limited evidence on physical activity occurring outside of leisure-time, such as transportation, occupational, or household activities. The review also found that few studies reported on associations between

physical activity and cancer by population subgroups, such as by age, socioeconomic status, or race/ethnicity.

The PAGAC also reported limited evidence on the relationship of sedentary behavior with cancer incidence and mortality.[4,6] Evidence supporting the PAGAC statements were primarily based on self-reported physical activity and sedentary behavior data. Self-reported light activity is especially difficult to recall, and is the most common intensity level older adults participate in.[7,8] To date, few studies of older adults have explored accelerometer-assessed physical activity and sedentary behavior with cancer incidence and mortality.[9-12] The scarcity of evidence is likely due to the need for larger studies with longer follow-up time to investigate cancer outcomes, particularly for the less common tumor sites.

The Women's Health Accelerometry Collaboration will explore the associations of accelerometer-assessed physical activity and sedentary behavior with cancer outcomes by combining data from two large prospective studies: the Women's Health Study (WHS) and the Women's Health Initiative Objective Physical Activity and Cardiovascular Health (WHI/OPACH) Study. This endeavor requires harmonization of accelerometry, cancer outcomes, and covariates. The study will provide important insights on cancer incidence and mortality among women 62 years and older. The specific aim for this paper is to describe the rationale, methodology, proposed analysis plan, and characteristics of the cohort.

Cohort Description

In order to address the scientific gaps, we harmonized two cohort studies of women 62 years and older using similar data collection methodologies to quantify the associations between physical activity and sedentary behavior with multiple site-specific incident cancers and overall fatal cancers.

Patient and public involvement: Patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this research.

WHS: The WHS is a completed randomized trial (1992–2004) testing aspirin, beta-carotene, and vitamin E for preventing cardiovascular disease and cancer among 39,876 healthy United States women at least 45 years of age.[13-15] When the trial ended, women were invited to continue in an observational study. Of the 33,682 alive, 89% of women consented, reporting on their health habits and medical history annually on questionnaires. From 2011-2014, an ancillary study was conducted to collect accelerometry among participants.[16] In 2011, 29,494 women were alive and 18,289 agreed to participate and were sent an accelerometer, 6931 declined participation, 1456 were ineligible because they were unable to walk outside of the home, and the remaining 2818 did not respond to the invitation. Overall, 17,466 women returned the accelerometers for downloading. All study protocols were approved by the Brigham and Women's Hospital Institutional Review Board, and all women gave written informed consent.

All of the women in the accelerometer substudy were previously in the pharmacotherapy intervention arms (either active or placebo).[13-15] The pharmacotherapy intervention did not impact cancer incidence or mortality.[13-14] Thus, the interventions are unlikely to impact the associations we seek to investigate, namely the associations of physical activity and sedentary behavior with cancer outcomes.

WHI/OPACH: From 1993 to 1998, the WHI study initially recruited women 50-79 years for either a clinical trial(s) or an observational study from 40 clinical sites throughout the United States. The WHI/OPACH Study[17] is an ancillary study to the WHI Long Life Study,[18] which was a sub-study to WHI. The sampling frame of the WHI Long Life Study were all surviving and actively participating women from the hormone therapy trials with age >=63 years and all Hispanic and

African American women in WHI. The WHI/OPACH ancillary study was designed to collect physical activity and sedentary behavior measured by accelerometry and self-report, and to collect detailed data on incident falls using daily falls calendars collected for up to 13 months. The primary outcomes of the original study included mortality,[19] falls,[20] and cardiovascular disease.[21,22] From 2012-2014, 9252 United States women consented to the WHI Long Life Study. Among those participants, 8618 consented by mail or phone to participate in the WHI/OPACH ancillary study collecting accelerometry. From those who consented, 58 women died before they could be contacted to begin participation, 10 died before receiving the materials, 141 were determined to be ineligible (e.g., dementia, residing in a nursing home, not ambulatory), 765 could not be contacted, and 596 declined to participate when contacted. In summary, 7048 women were sent the accelerometer, a sleep log, the OPACH physical activity questionnaire (available in this paper[17]), and 13 falls calendars. Overall, 6489 women returned the accelerometers for downloading. All study protocols were approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and all women gave informed consent.

Accelerometry Data Collection: Both cohorts utilized the same accelerometer (ActiGraph GT3X+ accelerometer (Pensacola, Florida). The triaxial accelerometer was small (4.6x3.3x1.5 cm) and light weight (19 grams), with a dynamic range of +/-6 G. The WHS women were asked to wear the accelerometer on their right hip, removing it only during sleep, for 7 days. They were also asked to keep a log documenting wear and non-wear days.[16] The accelerometer and log were mailed to participants, with a mailer for return.

The WHI/OPACH women were asked to wear the accelerometer on their right hip for 7 days, including night time. The WHI/OPACH women were asked to keep a sleep log for in- and out-of-bed wear.[23] For women with missing sleep log data, their in-bed and out-of-bed times were imputed using person-specific means, if available, or the sample mean. Using the sleep log, the

in-bed wear was removed to make the data congruent across the two cohorts. The accelerometer and log were given to most women at their study visit and were mailed back after completion.

The accelerometer recorded 3-dimensional raw acceleration signals at 30 Hz, which were aggregated using ActiLife software (version 6) to counts per 15-second epochs with the normal filter setting. To better detect movement from all directions, vector magnitude (VM) counts were derived by taking the square root of the sum of the three axes squared. Non-wear time was assessed using the validated Choi et al. algorithm,[24,25] defined as an interval of at least 90 consecutive minutes of zero VM counts/minute, with allowance of up to one 2-minute period of nonzero VM counts and requiring that no counts were detected during the 30 minutes upstream and downstream from that period.

Several metrics were used to describe physical activity and sedentary behavior from the accelerometer. First, average intensity per day was summarized as average VM/15-seconds. Second, using WHI/OPACH calibration-study derived accelerometry cutpoints, we defined sedentary behavior and physical activity from receiver operating characteristic curve analyses that balanced the number of false positives and false negatives.[26] VM/15-second cutpoints were defined as follows: sedentary 0-18, light low 19-225, light high 226-518, and moderate-to-vigorous physical activity >=519. Third, a moderate-to-vigorous bout was defined as >=10 minutes of consecutive moderate-to-vigorous minutes, with allowance for interruptions for up to 20% of the time below the threshold and <5 consecutive minutes below the threshold (to set a maximum time when bouts occur >=25 minutes). The bout must start and end with moderate-to-vigorous physical activity.[27,28] Fourth, average steps per day was explored, derived from ActiGraph's proprietary algorithm.

Cancer Incidence and Mortality Outcomes: WHS participants received annual mailed questionnaires which asked about health history, including a diagnosis of cancer. Relevant medical records were obtained for all self-reported cancers (except for non-melanoma skin cancer).

As part of WHI, participants received annual mailed questionnaires which asked about physician diagnosis of new cancer or malignant tumors, hospitalizations, and other health history. Medical records were obtained for all self-reported cancers except non-melanoma skin cancer.[29]

For both studies, physician adjudicators coded cancer using medical record documents such as the pathology report, hospital face sheet, operative report, hospital discharge summary, oncology consultation, radiology report, and tumor registry abstract. The date of cancer diagnosis is based on one of the following: microscopically-confirmed based on date the tissue that resulted in a positive pathology was removed, not microscopically-confirmed based on the date of first hospitalization for cancer, self-report only based on date reported by participant, and both autopsy-only and death certificate-only based on death date.

For WHS, an Endpoints Committee of physicians blinded to questionnaire exposure data reviewed all medical records using pre-specified criteria. A cancer diagnosis was confirmed with histological or cytological evidence. In the absence of these diagnostic tests, strong clinical evidence accompanied by radiologic evidence or laboratory markers was used to confirm cancer occurrence. The histological type, grade, and stage of cancer were recorded. The date of cancer diagnosis was based on the earliest date of the relevant evidence (e.g., date of histological confirmation). For cancers diagnosed only on death certificates without prior medical records, the date of death was used.

Coding of cancer type was based on the Surveillance, Epidemiology, and End Results (SEER) program. Using the International Classification of Diseases for Oncology (ICD-O-3), the morphology code details the type and behavior of a tumor.[30] The code contained three parts: histology or cell type (4 digits), behavior or the way it acts in the body (1 digit), and grade, differentiation or phenotype (1 digit). Histology of the primary tumor was ascertained and its behavior code were ascertained. A behavior code is defined as 0: benign; 1: uncertain whether benign or malignant; 2: carcinoma in situ; and 3 or higher: malignant (invasive) primary site. These codes were applied identically across both cohorts; the final classification of cancer by site was limited to behavior code 3 and is summarized in **Supplemental Table 1.**[3]

Cancer surveillance is currently ongoing in both cohorts. Additionally, we ascertained if women had been diagnosed with a cancer prior to the accelerometer data collection, including type of cancer and time since diagnosis. For both cohorts, deaths were reported by family members or postal authorities, with medical records, interviews with next of kin, and death certificates obtained to confirm the event. The National Death Index was searched periodically for cohort members. The underlying cause of death was classified on the basis of the death certificate, medical records, and other records such as an autopsy report using the ICD 10th edition. The death certificate diagnosis was used when no other records are available. In this paper, we report on cancer diagnosed from study enrollment to the date of accelerometry measurement.

Covariates: Sociodemographics, including age, race/ethnicity, and education were collected at study enrollment. Participants from both cohorts regularly completed mailed questionnaires regarding their health history and health behaviors and we used the measure closest to the time of accelerometer wear. Women identified their general health by answering the question, “In general, would you say your health is excellent, very good, good, fair, or poor?” Women also reported on smoking status, alcohol intake, postmenopausal hormone use, and history of

diabetes, confirmed coronary heart disease, bilateral oophorectomy, and hysterectomy. Height and weight were self-reported in WHS and measured in WHI/OPACH. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and defined as underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), or obese (>=30.0).

Walking speed was collected from self-administered questionnaires. WHS women were asked, "What is your usual walking pace outdoors?" WHI/OPACH women were asked, "When you walk at home for more than 10 minutes without stopping, what is your usual speed?" We harmonized the response options as follows:

(1) <2 mph: easy, casual, <2 mph (WHS); casual strolling or walking <2 mph (WHI/OPACH)
(2) 2-2.9 mph: normal, average, 2-2.9 mph (WHS); average or normal, 2-3 mph (WHI/OPACH)
(3) 3-3.9 mph: brisk pace, 3-3.9 mph (WHS); fairly fast, 3-4 mph (WHI/OPACH)
(4) 4 mph or more: very brisk, striding, >4 mph (WHS); very fast, >4 mph (WHI/OPACH)
(5) Unknown or does not walk regularly: don't walk regularly (WHS); don't know, rarely or never walks >10 minutes (WHI/OPACH)

Proposed Statistical Analysis: We will explore the association of physical activity and sedentary behavior with cancer incidence and mortality. For site-specific cancer analyses, if participants have a history of the cancer under analysis then they will be excluded. For example, if we analyze lung cancer incidence then we will exclude women who already have a lung cancer diagnosis prior to the accelerometer measurement. For composite cancer (a subset of cancer types combined) and total cancer analyses, we will include women who have a history of cancer prior to accelerometry measurement. For these analyses, we can further explore whether excluding those with cancer impacts the results or whether having prior cancer is a moderator.

Women with a hysterectomy prior to accelerometry measurement will be excluded from investigation of incident endometrial cancer. Similarly, women with bilateral oopherectomy prior to accelerometry measurement will be excluded from investigation of incident ovarian cancer.

We will use stratified Cox regression models to estimate hazard ratios and 95% confidence intervals for various measures of physical activity and sedentary behavior with cancer incidence and mortality. The stratified model allows the baseline hazards for the two cohorts to differ.[31] However, the hazards of the exposure groups are assumed to be proportional, which will be tested using Schoenfeld residuals. We will censor follow-up time on the date of the cancer diagnosis, the date of death, or the date of last contact. Potential confounders will be the harmonized covariates described in the "Covariates" section.

Analytic Sample: In total, 25,337 women were sent an accelerometer, with 18,289 contributing from the WHS cohort and 7048 from the WHI/OPACH cohort (**Table 1**). After excluding those that did not return the accelerometer, did not wear the accelerometer, or experienced accelerometer malfunction, 23,443 (92.5%) and 22,868 (90.3%) women contributed at least one and four adherent days of accelerometry wear, respectively, defined as wearing the device for at least 10 hours during a day while awake. WHS began as a trial for the primary prevention of cancer and cardiovascular disease; however, post-randomization, 16 women were subsequently found to have prevalent cancer and are excluded from the present study. The final sample size for the analyses was 22,852.

Findings To Date

At the time of accelerometry measurement, both cohorts had a mean age above 70 years (78.7 (SD 6.7) WHI/OPACH, 71.5 (SD 5.7) WHS), with a range of 63-97 for WHI/OPACH and 62-89 years for WHS. Both cohorts had a mean BMI in the overweight category (28.1 kg/m^2 (SD 5.7)

WHI/OPACH, 26.2 kg/m^2 (SD 5.0) WHS). WHI/OPACH women compared to WHS women had a lower proportion with at least some college education (79.7% vs. 100%), very good or excellent general health (50.6% vs. 74.7%), drank alcohol daily (5.7% vs. 15.9%), used postmenopausal hormones (2.5% vs. 9.9%), and walked at least 3 mph (7.8% vs. 27.5%) (**Table 2**). At the time of accelerometry measurement, the WHI/OPACH women compared to WHS women included a higher proportion of Black (33.4% WHI/OPACH vs. 1.5% WHS) and Hispanic (16.9% vs. 0.9%) women and had a higher proportion with diabetes (20.3% vs. 9.0%) and coronary heart disease (10.1% vs. 4.3%). The two cohorts were more similar with regards to never smoking (54.7% WHI/OPACH, 50.5% WHS), cancer (11.7%, 11.9%), and receipt of a bilateral oophorectomy (19.2%, 22.2%) or a hysterectomy (42.6%, 41.6%).

Most women provided at least four days of adherent data (defined as 10 hours/day), with 14.9 hours/day of average awake wear time (**Table 3**). The WHS women engaged in a higher mean total volume of physical activity (146 vs. 101 average daily VM/15-seconds) and accumulated more mean steps per day (5489 vs. 3573) than WHI/OPACH women. WHS women engaged in approximately 2-3 times more mean moderate-to-vigorous physical activity (91.9 vs. 50.4 minutes/day) and bouts (18.2 vs. 6.4 minutes/day) than WHI/OPACH women. In contrast, mean light high and light low activity were similar. Sedentary behavior was lower among WHS women compared to WHI/OPACH women (510.6 vs. 555.6 minutes/day). It is important to note that some of the differences in accelerometry measures between cohorts may be due to age, such as indicated in **Table 4**, or due to other potential confounders.

We examined the number of incident and fatal cancers in the cohort, with cancer outcomes documented through December 31, 2019 for WHS and through March 30, 2020 for WHI/OPACH. During an average of 5.9 (SD 1.6) years of follow-up thus far, 1378 cancer events

occurred among which 414 were fatal. The most common cancers were breast (459) and lung (146) cancer.

Strengths and Limitations

The Women's Health Accelerometry Collaboration cohort's primary strength is the statistical power to be able to address research questions regarding physical activity and sedentary behavior with cancer among older women in a cost-efficient manner by using data from existing studies. Cancer outcomes continue to be assessed annually by similar methods, adjudicated, and combined systematically across cohorts. Accelerometry was collected by the same device using similar procedures and excellent adherence.

A WHI/OPACH substudy of 200 women participated in a variety of laboratory-based activities while wearing the accelerometer and having oxygen uptake measured. Using these data, accelerometer cutpoints were developed specifically for women 60 years and older.[26] The cutpoint was calibrated to estimate moderate to vigorous activity among older women, which is why the number of minutes may be higher than those reported from other studies that utilize calibration equations developed in younger samples of adults (i.e., what might be a "light" activity in a younger woman may actually require moderate or higher effort in an older woman).

Raw accelerometry data will allow the research team to develop further measures of physical activity and sedentary behavior, such as using the activity index[32] and latent class analysis on accelerometry.[33] Using the raw data, we can also apply two machine-learned algorithms developed specifically for older women; one designed to distinguish sitting, riding in a vehicle, standing still, standing moving, and walking,[34] while the other was designed to accurately quantify sitting bouts,[35] which, without the algorithm, are measured with substantial error.[36]

While studies investigating the associations between less common cancer subtypes and physical activity or sedentary behavior among older women have been limited due to smaller sample sizes and few cancer events, the combined cohorts provide improvement in statistical power, allowing researchers to be better equipped to investigate these associations. In addition to increasing power for the less common cancer outcomes, by including both cohorts we capture more diversity in the population of women in this age range which allows us to better understand these associations in a more heterogenous population.

The Women's Health Accelerometry Collaboration cohort has several limitations. First, the accelerometer was worn once by participants for one week. It is possible that physical activity and sedentary behavior could change seasonally and over the course of follow-up, and thus not be represented by the measurement week. To address this concern, the question was explored in a subset of WHS participants that wore the accelerometer up to 3 times over a 2-3 year period, the initial measures of physical activity and sedentary behavior provided a reproducible measure at repeated time points.[37] Adjusting for age, season, and BMI, the intraclass correlation coefficients between women indicated moderate to high reproducibility for average VM counts/day (0.83; 95% confidence interval 0.78, 0.87), sedentary behavior (0.73; 0.66, 0.80), light activity (0.67; 0.59,0.74), and moderate-to-vigorous physical activity (0.83; 0.78,0.87). This indicated that metrics derived from one week of accelerometer administration can estimate longer-term patterns of behavior among women of similar ages.

Second, there will need to be a longer follow-up period or other cohorts to address the relationships of accelerometry-assessed behaviors with rare cancers. Third, women that could not walk without assistance outside of their home were excluded due to the development of existing accelerometer algorithms on ambulation. More effort is needed to understand how to interpret accelerometry from non-ambulatory individuals in order to include them in studies of

this kind.[38] Fourth, while WHS initially mailed accelerometers and used an awake only protocol, in contrast WHI/OPACH provided most of the accelerometers in-person at the home visit and used a 24-hour wear protocol. Despite these differences, there did not appear to be differential impact on accelerometer awake wear time between the cohorts (**Table 3**). Fifth, most potential confounders were similarly measured across the two cohorts. However, height and weight assessed near the time of accelerometry measurement were self-reported in WHS and measured in WHI/OPACH.

Collaboration

Data are accessible through the established data sharing policies for the Women's Health Study at https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001964.v1.p1 and http://whs.bwh.harvard.edu/ . Similarly, data are accessible through the established data sharing policies for the Women's Health Initiative at https://www.whi.org/page/working-with-whi-data. Interested researchers can write to the study to clarify data access. Due to data sharing agreements, the Women's Health Accelerometry Collaboration data are not directly available.

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Contributors: KRE conceived of and drafted the manuscript and GW conducted the data analysis. IL, EJS, and RD were involved in study design, accelerometry acquisition, and/or analysis of the WHS. AZL, KRE, IL, CD, BTS, and JB were involved in the study design, accelerometry acquisition, and/or analysis for the WHI/OPACH Study. In addition, CCC, AGH, HP, and GW provided critical interpretation of the data harmonization and analysis for this work.

All authors (KRE, JB, CCC, CD, RD, AGH, HP, BTS, EJS, GW, IL, AZL) reviewed the manuscript critically and approved the final version.

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Table 1: Accelerometer wear overall and by cohort

	Total	Retained %	WHS n	Retained %	WHI/OPACH n	Retained %
Sample invited to sub-study	38,746	100	29,494	100	9252	100
Agreed to participate and sent the accelerometer	25,337	65.4	18,289	62.0	7048	76.2
Returned accelerometer	24,429	63.0	17,708	60.0	6721	72.6
Data were downloaded	23,955	61.8	17,466	59.2	6489	70.1
At least one adherent day of wear (>=10 hours)	23,443	60.5	17,061	57.8	6382	69.0
Adherent wear >=4 days of >=10 hours/day	22,868	59.0	16,742	56.8	6126	66.2
Removed those with cancer at trial inception*	22,852	59.0	16,726	56.7	6126	66.2

Abbreviations: n, sample size; WHI/OPACH, Women's Health Initiative Objective Physical Activity and Cardiovascular Health; WHS, Women's Health Study

*WHS began as a trial for the primary prevention of cancer and cardiovascular disease; however, post-randomization, 16 of the 16,742 women were subsequently found to have prevalent cancer and were excluded from the present study.

Table 2: Description of sample overall and by cohort

	Overall (n=22,852)		WHS (n=16,726)		Missing	WHI/OPACH (n=6126)		Missing
	Percent	n	Percent	n	Missing	Percent	n	Missing
Age categories								
60-69	35.1	8019	44.2	7392		10.2	627	0
70-79	43.8	10013	45.2	7565		40.0	2448	
80-89	20.0	4563	10.6	1769		45.6	2794	
>=90	1.1	257	0.0	0		4.2	257	
Race/ethnicity					0			0
White	83.1	18984	95.3	15938		49.7	3046	
Black	10.1	2300	1.5	253		33.4	2047	
Hispanic	5.2	1184	0.9	151		16.9	1033	
Unknown or other	1.7	384	2.3	384		0.0	0	
Education					269			41
High school or less	5.5	1237	0.0	0		20.3	1237	
Some college	46.7	10531	49.7	8182		38.6	2349	
College graduate or more	47.8	10774	50.3	8275		41.1	2499	
Self-reported or measured near accelerometry measurement								
General health					5			21
Excellent	20.7	4730	24.6	4115		10.1	615	
Very good	47.5	10842	50.1	8371		40.5	2471	
Good	27.3	6230	22.8	3804		39.7	2426	
Fair or poor	4.5	1024	2.6	431		9.7	593	
Body mass index					3			386
<18.5	1.8	415	2.0	334		1.3	81	
18.5-24.9	39.2	8953	43.1	7215		28.4	1738	
25.0-29.9	33.6	7672	33.6	5624		33.4	2048	

30.0-34.9	14.7	3356	13.5	2263		17.8	1093	
35.0-39.9	5.0	1145	4.1	692		7.4	453	
>=40	2.1	486	1.6	261		3.7	225	
Smoking					1			582
Current	3.4	749	3.5	590		2.9	159	
Former	45.1	10046	46.0	7695		42.4	2351	
Never	51.5	11474	50.5	8440		54.7	3034	
Alcohol					7			536
Never or rarely	37.9	8445	38.0	6356		37.4	2089	
Monthly	15.9	3558	9.8	1646		34.2	1912	
Weekly	32.9	7340	36.3	6069		22.7	1271	
Daily	13.3	2966	15.9	2648		5.7	318	
Walking speed					4			261
<2 mph	21.5	4906	17.5	2931		32.2	1975	
2-2.9 mph	40.2	9185	42.7	7143		33.3	2042	
3-3.9 mph	20.7	4728	25.5	4271		7.5	457	
>=4 mph	1.5	350	2.0	332		0.3	18	
Unknown or does not walk regularly	15.0	3418	12.2	2045		22.4	1373	
Medical history near accelerometry measurement								
Using postmenopausal hormones	7.9	1812	9.9	1657	6	2.5	155	0
Diabetes history	12.0	2747	9.0	1501	0	20.3	1246	0
Coronary heart disease	5.8	1328	4.3	712	0	10.1	616	0
Oopherectomy, bilateral	21.4	4873	22.2	3718	0	19.2	1155	94
Hysterectomy	41.9	9568	41.6	6957	0	42.6	2611	0
Cancer at accelerometry measurement	11.8	2696	11.9	1982	0	11.7	714	0

Abbreviations: n, sample size; SD, standard deviation; WHI/OPACH, Women's Health Initiative Objective Physical Activity and Cardiovascular Health; WHS, Women's Health Study

*WHS and WHI/OPACH categories were compared using chi-square tests. All associations were significant at p<0.0001.

Table 3: Description of accelerometry measures overall and by cohort

	Overall (n=22,852)		WHS (n=16,726)		WHI/OPACH (n=6126)	
	Percent		Percent		Percent	
Number of adherent days						
4 days	2.0		1.6		2.9	
5 days	4.4		3.6		6.6	
6 days	18.0		15.0		26.2	
7 days	75.6		79.8		64.3	
Number of weekend days						
0 days	1.2		1.0		1.6	
1 day	8.5		7.4		11.3	
2 or more	90.4		91.6		87.0	
	Mean	SD	Mean	SD	Mean	SD
Wear time on adherent days, hours/day	14.9	1.3	14.9	1.3	14.9	1.3
Average daily vector magnitude per 15-seconds	134.0	53.9	146.0	52.8	101.2	42.1
Average daily steps/day	4975.9	2668.8	5489.4	2658.2	3573.1	2142.3
Average minutes/day using vector magnitude:						
Sedentary behavior	522.7	101.0	510.6	98.8	555.6	99.4
Light low	182.1	46.1	179.6	44.2	188.9	50.2
Light high	105.5	33.3	108.2	32.1	98.0	35.5
Moderate to vigorous	80.8	46.5	91.9	45.4	50.4	34.4
Moderate to vigorous bouts	15.0	22.8	18.2	24.6	6.4	13.6

Abbreviations: n, sample size; SD, standard deviation; WHI/OPACH, Women's Health Initiative Objective Physical Activity and Cardiovascular Health; WHS, Women's Health Study

Table 4: Description of accelerometry measures by cohort stratified by age tertiles*

	Age 60-69 years				Age 70-76 years				Age 77+ years			
	WHS (n=7392)		WHI/OPACH (n=627)		WHS (n=6168)		WHI/OPACH (n=1781)		WHS (n=3166)		WHI/OPACH (n=3718)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Wear time on adherent days, hours/day	15.0	1.2	15.1	1.3	14.8	1.2	15.0	1.3	14.7	1.3	14.8	1.3
Average daily vector magnitude per 15-seconds	159.7	53.6	125.5	43.7	142.5	50.1	113.8	43.9	120.4	44.6	91.1	37.4
Average daily steps/day	6268.2	2693.7	5045.9	2477.3	5308.5	2499.4	4245.0	2211.0	4023.5	2142.9	3003.2	1811.7
Average minutes/day using vector magnitude:												
Sedentary behavior	499.9	99.1	527.8	99.2	512.9	98.0	538.2	101.3	531.4	96.0	568.6	96.3
Light low	182.7	44.2	200.7	47.2	177.8	43.3	193.9	49.3	176.0	45.6	184.5	50.5
Light high	109.0	31.3	107.5	34.1	108.7	32.4	103.7	34.8	105.8	33.1	93.7	35.5
Moderate to vigorous	105.0	44.9	72.7	36.8	88.8	43.1	61.2	36.3	67.4	39.4	41.4	29.5
Moderate to vigorous bouts	22.3	26.9	11.0	16.8	17.1	23.0	8.8	16.2	10.6	19.5	4.5	11.0

Abbreviations: n, sample size; SD, standard deviation; WHI/OPACH, Women's Health Initiative Objective Physical Activity and Cardiovascular Health; WHS, Women's Health Study

* Age was categorized based on WHAC-specific tertiles: 60-69 years, 70-76 years, and 77+ years.

Supplemental Table 1: International Classification of Diseases for Oncology, 3rd Ed. Codes for each cancer site used in ascertainment of primary incident invasive cancers across cohorts. This coding was developed from Moore et al.[3]

Cancer site	ICD-O-3 codes and, if applicable, ICD-O-3 histology‡
Esophageal adenocarcinoma	C150-159& histologies: 8140, 8142, 8144, 8261, 8310, 8480, 8481, 8570
Gallbladder	C239
Liver*	C220 and C221
Lung	C340-C349
Kidney	C649 and C659
Small intestine	C170-179
Gastric cardia	C160
Endometrial	C540-C549 and C559
Esophageal squamous	C150-159 and histologies 8041, 8070-8072, 8074
Myeloid leukemia	Acute myeloid leukemia: any histology of 9840, 9861, 9865-9867, 9869, 9871-9874, 9895-9898, 9910-9911, 9920 Acute monocytic leukemia: any histology of 9891 Chronic myeloid leukemia: any histology of 9863, 9875-9876, 9945-9946 Other myeloid/monocytic leukemia: any histology of 9860, 9930
Myeloma	Any histology of 9731-9732, 9734
Colon	C180-C189, C260
Head and neck	Lip: C000-C009 Tongue: C019-C029 Salivary gland: C079-C089 Floor of mouth: C040-C049 Gum and other mouth:C030-C039, C050-C059, C060-C069 Nasopharynx: C110-C119 Tonsil: C090-C099 Oropharynx: C100-C109 Hypopharynx: C129, C30-C139 Other oral cavity and pharynx: C140, C142, C148 Larynx: C320-C329
Rectum	C199, C209
Bladder	C670-C679
Breast	C500-C509
Non-Hodgkin's Lymphoma (NHL)	NHL-nodal: C024, C098, C099, C111, C142, C379, C422, C770-C779 and histologies: 9590-9597, 9670-9671, 9673, 9675, 9678-9680, 9684,

	9687-9691, 9695, 9698-9702, 9705, 9708, 9709, 9712, 9714-9719, 9724-9729, 9735, 9737, 9738, 9811-9818, 9823, 9827, 9837 NHL-extranodal, definition 1: All sites except C024, C098-C099, C111, C142, C379, C422, C770-C779 and histologies of: 9590-9597, 9670-9671, 9673, 9675, 9678-9680, 9684, 9687, 9688, 9689-9691, 9695, 9698-9702, 9705, 9708, 9709, 9712, 9714-9719, 9724-9729, 9735, 9737, 9738 NHL-extranodal, definition 2: All sites except C024, C098, C099, C111, C142, C379, C420-C422, C424, C770-C779 and histologies of: 9811-9818, 9823, 9827, 9837
Thyroid	C739
Gastric non-cardia	C161-169
Soft tissue	C380, C470-C479, C490-C499
Pancreas	C250-C259
Lymphocytic leukemia	Acute lymphocytic leukemia, definition 1: Any histology of 9826, 9835-9836 Acute lymphocytic leukemia, definition 2: C420, C421, C424 and histologies: 9811-9818, 9837 Chronic lymphocytic leukemia: C420, C421, C424 and histology 9823 Other lymphocytic leukemia: Any histology of 9820, 9832-9834, 9940.
Ovary	C569
Brain	C710-C719
Prostate‡	C619
Skin cancer, excluding basal and squamous	Melanoma: C440-C449 and histologies 8720-8790 Other non-epithelial skin: C440-C449, excluding histologies 8000-8005, 8010-8046, 8050-8084, 8090-8110, 8720-8790, 9050-9055, 9140, 9590-9992

* A small proportion of the liver cancer classification consists of intrahepatic bile duct cancer cases.

† A small proportion of the kidney cancer classification consists of renal pelvis cancer cases.

‡ Unless otherwise stated, cancer definitions exclude the histologies 9050-9055, 9140, and 9590-9992.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	10-11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	na

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	na
Discussion			
Key results	18	Summarise key results with reference to study objectives	na
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15-16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.