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Research Article

Longitudinal Associations of Leisure-Time Physical Activity and Cancer Mortality in the Third National Health and Nutrition Examination Survey (1986–2006)

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Longitudinal associations between leisure-time physical activity (LTPA) and overall cancer mortality were evaluated within the Third National Health and Nutrition Examination Survey (NHANES III; 1988–2006; $n = 15{,}535$). Mortality status was ascertained using the National Death Index. Self-reported LTPA was divided into inactive, regular low-to-moderate and vigorous activity. A frequency-weighted metabolic equivalents (METS/week) variable was also computed. Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated for overall cancer mortality in the whole sample, by body mass index categories and insulin resistance (IR) status. Nonsignificant protective associations were observed for regular low-to-moderate and vigorous activity, and for the highest quartile of METS/week (HRs range: 0.66–0.95). Individuals without IR engaging in regular vigorous activity had a 48% decreased risk of cancer mortality (HR: 0.52; 95% CI: 0.28–0.98) in multivariate analyses. Conversely, nonsignificant positive associations were observed in people with IR. In conclusion, regular vigorous activity may reduce risk of cancer mortality among persons with normal insulin-glucose metabolism in this national sample.

1. Introduction

Cancer is a major public health concern in the United States with approximately 25% of total deaths attributed to cancer [1]. The projected number of cancer deaths in 2010 alone was 1500 deaths per day, corresponding to a total of over 560,000 deaths. Therefore, investigations into modifiable risk factors that may reduce the rates of cancer mortality continue to be of significant importance. Physical activity has been hypothesized to protect against cancer through obesity reduction, improved insulin sensitivity and sex hormone profiles, and lowered inflammation [2]. The World Cancer Research Fund/American Institute for Cancer Research Expert Panel Report concluded that physical activity likely reduces the risk of some cancers and suggested an active lifestyle for protection against cancer progression and mortality [3]. However, concrete recommendations for physical activity to prevent cancer mortality are lacking, in part, due to inconsistencies in the existing evidence, and due to varying methodology and differing definitions of physical activity used [4]. Furthermore, at this time associations with physical activity are better established for cancer incidence as compared to mortality [4, 5].

A greater understanding of the protective effects of physical activity may enhance existing cancer control strategies and potentially reduce cancer mortality. The present study strengthens the evidence in the current literature by examining longitudinal associations between leisure-time physical activity (LTPA) in the Third National Health and Nutrition Examination Survey (NHANES III: 1988–1994) linked to mortality data through 2006. Excess adiposity and aberrations in the insulin-glucose axis are hypothesized to promote

carcinogenesis [6, 7] and may offset the protective potential of physical activity. It is noteworthy that research in the area of cancer mortality has typically focused on a single risk factor. Less attention has been devoted to the combined effects of body weight, insulin resistance (IR), physical activity, and cancer mortality [8–11], and the interrelationships of these risk factors warrant investigation. Therefore the current study is designed to expand the physical activity-cancer hypothesis by assessing whether body mass index (BMI) and IR modify the relationships of physical activity and cancer mortality. Existing data available from this national sample on body weight, laboratory values, self-reported physical activity data, and cancer mortality ($N = 863$) provides a unique opportunity to conduct these analyses. The results of this study provide data to guide clinical trials that may ultimately contribute to individualized physical activity recommendations for cancer control.

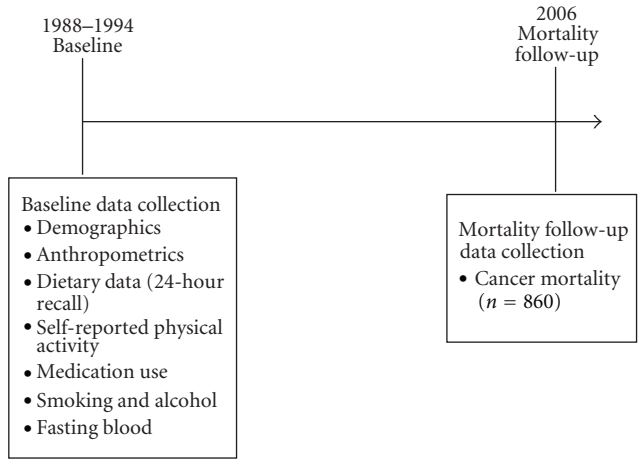

Figure 1: NHANES III data collection timeline.

2. Materials and Methods

2.1. Study Population. The NHANES III (1988–1994) population, a national sample of civilian noninstitutionalized individuals, was selected through a complex, multistage probability design [12]. Persons who were 17+ or older were eligible for the mortality follow-up from the date of participation (1988–1994) through December 31, 2006. This represents the last NHANES III mortality update. The current analyses included adults 20–89 years. Per the Adult Treatment Panel (ATP) definition, individuals were considered to be adults if they were at least 20 years old [13]. NHANES participants 89+ years were assigned an arbitrary age of 90 years for confidentiality purposes and were excluded from the analyses. Pregnant women were excluded because their baseline physical activity and BMI may not be an accurate reflection of their usual activity or body weight. Additionally, persons with missing values for the pertinent variables were also excluded, resulting in a final sample of 15,535 individuals.

2.2. Data Collection. The NHANES III survey consisted of a structured household interview and a standardized physical examination in a mobile examination center at entry into the study. Participants self-reported their age, race/ethnicity, level of education, leisure-time physical activity, dietary intakes, alcohol use, current prescription medication, and presence of doctor-diagnosed cancer in a personal interview. Race/ethnicity were categorized into (1) non-Hispanic whites, (2) non-Hispanic Blacks, (3) Mexican-Americans and (4) "other." Trained personnel measured height, weight and waist circumference during the in-person examination [12]. The measured height and weight were used to compute BMI. Smoking status was assessed during the in-person interview, in which participants reported the use of cigarettes, pipes, and cigars. A fasting blood sample was obtained during the physical examination that was used to measure fasting plasma glucose concentrations. Details of the NHANES III protocols have been previously published [14]. Figure 1 describes the data collection strategy in NHANES III.

2.3. Exposure: Leisure-Time Physical Activity. A questionnaire consisting leisure-time physical activity questions including type of activity and frequency of the activity in the past month was queried in the Household Adult Ques tionnaire administered once at baseline. There was no additional follow-up information on physical activity and other variables after time of entry into the study until the end of mortality follow-up (Figure 1). At baseline, participants were asked for example, if "In the past month, did you run or jog?" and "In the past month, how often did you jog or run?" Similarly, questions were asked on walking, bicycling, swimming, aerobics and/or aerobic dancing, other dancing, calisthenics, yard work, lifting weights, and engagement in up to four other activities that were not mentioned in the survey. Frequency of engagement in activities over the past 30 days was reported. These responses were standardized to weekly frequency by using the conversion factors of 4.3 weeks/month and 30.4 days/month per NHANES III [15]. A validated intensity rating in metabolic equivalents (MET) was provided by NHANES III for each activity as defined in the Compendium of Physical Activities [16]. For example, jogging/running was assigned an intensity rating of "8 METS." For this study, LTPA was classified as "low intensity," "moderate" and "vigorous" using the standard cut-offs established by Pate et al. [17]. Activities requiring <3 METS were classified as "low-intensity," activities requiring 3–6 METS were classified as "moderate" and >6 METS were classified as "vigorous" [17]. Participants who did not report engagement in any of the activities, were classified as "inactive." Because individuals engaging in "low intensity" activities represented <0.05% ($n = 7$) of the population, they were combined into the "moderate" activity group.

Next, participants were categorized as performing "regular low-to-moderate" exercises if they reported performing the activity at least 5 times per week and "regular vigorous" if they reported performing vigorous activities at least 3 times per week. These categories were mutually exclusive (so that if an individual performed vigorous and low-to-moderate activities, he/she was included in the vigorous activity group and not in both groups). Additionally, a frequency-weighted

LTPA variable was calculated by multiplying the frequency of each activity by its corresponding intensity value and summed. This variable was divided into quartiles in the regression models. The NHANES III survey did not collect information for duration of each bout of exercise, which limits more precise estimation of physical activity. The physical activity definitions used in this study are consistent with previously published studies using the NHANES III population [18–21].

2.4. Cancer Mortality Ascertainment. Mortality information was obtained from the updated NHANES III Linked Mortality Files that provide mortality follow-up data from the date of participation in the survey (1988–1994) through December 31, 2006 (Figure 1). Mortality was ascertained based upon either death certificates or from a probabilistic match between NHANES III and the National Center for Health Statistics, National Death Index (NDI) records. Cancer mortality was identified using the *International Classification of Diseases, Tenth Revision* (ICD-10; NCHS 2006; ICD-10 codes C00–C97). Persons were considered alive at the end of the follow-up period if they were not matched to a death record. Details of the mortality files are described elsewhere [22].

2.5. Statistical Methods. Descriptive statistics were generated to assess demographic, lifestyle and dietary attributes related with cancer mortality, and to identify potential confounders. Next, unadjusted univariate hazard ratio (HR) and 95% confidence intervals (95% CI) of overall cancer mortality and level of LTPA were computed using Cox proportional hazard models, using age as the time scale. Persons who died from causes other than cancer were censored at the age of death and persons who were considered alive were censored at the end of the study follow-up period.

We tested demographic, lifestyle, physiological, and dietary factors as potential confounders of the associations of LTPA and cancer mortality, by entering these additional variables singly into the Cox proportional hazards models. If the addition of the variable singly in the model changed the HR for cancer mortality by 10% or more, the variable was added to the final regression model. Potential variables tested were age (continuous and years), race or ethnicity (categorical: white, black, Mexican, and other), cardiovascular disease (categorical: yes/no), BMI (categorical: normal weight, overweight and obese), smoking (categorical: never, current, past), alcohol consumption (continuous: number of drinks/day), education (categorical: <12 and ≥ 12 years), aspirin use (yes/no) total dietary proteins (continuous: grams/day), total dietary fats (continuous: grams/day) total dietary carbohydrates (continuous: grams/day), and total calories (continuous: kilocalories/day). We tested for potential effect modification (considered significant for the purpose of these analyses at alpha value of 0.10 or less) by race, age, gender, BMI, and IR status for the relationships of physical activity and cancer mortality. A significance level of 0.05 was used for all the other tests. Sensitivity analyses were conducted by reanalyzing the associations after excluding persons with a baseline report of doctor-diagnosed cancer ($n = 588$). For exploratory purposes, we repeated analyses in adults 40+ years at baseline ($n = 9348$). The statistical analyses were performed using SAS v.9.1 and SUDAAN v.10.0.1 Sample weights provided by NHANES III were applied to all the analyses.

3. Results

3.1. Participant Characteristics. Baseline characteristics of NHANES III sample are expressed as either weighted frequencies for categorical variables or weighted means with their corresponding standard errors (SEs), and minimum and maximum values for continuous variables (Table 1). The population consisted of 76.8% non-Hispanic Whites, 10.4% non-Hispanic blacks, 5.2% Mexican-Americans, and 7.8% "other" ethnicities. The mean population age was 45 years. Approximately 85% of the participants reported engaging in any physical activity, with half (53.3%) of the population being moderately and 16.9% being vigorously active on a regular basis. About 15% of the sample was "inactive." Furthermore, 33% of the participants reported being more active, 21% reported being less active, and 44% estimated about the same level of activity as compared to their peers of the same sex and similar age. Over half the population was obese or overweight (BMI > 25), with a mean waist circumference of 92 cm. Twenty-two percent of the population had the insulin resistance syndrome, defined per the ATP III criteria as having at least three of the following five criteria: abdominal obesity (waist circumference >102 cm in men or >88 cm in women), insulin resistance (blood glucose >110 mg/dL), low high density lipoprotein (HDL) (<40 in men or <50 in women), high serum triglycerides concentration (>150 mg/dL), and hypertension (systolic blood pressure >130 mm Hg or diastolic blood pressure >85 mm Hg.) and 10.67% were insulin resistant (defined as blood glucose levels >110 mg/dL) [13]. In this dataset 5.5% ($n = 863$) of the population had died from cancer at the end of the follow-up period till 2006. Approximately 15% of the patients who had died of cancer had reported doctor-diagnosed cancer during their in-person baseline interview.

3.2. Associations between Leisure-Time Physical Activity and Overall Cancer Mortality. Overall, nonsignificant inverse associations were observed for overall cancer mortality among persons engaging in any activity, regular low-to-mod- erate or regular vigorous activity in the whole population (Table 2). Individuals who engaged in any activity were 8% and 5% less likely to die of cancer as compared to individuals who were "inactive," after adjusting for age (HR: 0.92; 95% CI: 0.71–1.19) and additional variables (HR: 0.95; 95% CI: 0.72–1.26), respectively. Associations were in a similar direction for regular low-to-moderate activity (HR: 0.92; 95% CI: 0.69–1.21), regular vigorous activity (HR: 0.66; 95% CI: 0.39–1.13), and for the highest versus lowest quartile of frequency-weighted METS per week (HR: 0.89; 95% CI: 0.68–1.16) after adjusting for age, race, sex, and smoking status, albeit not statistically significant. Additional adjustment for BMI did not change the associations.

Table 1: Characteristics of the NHANES III study participants at baseline ($N = 15,535$)[1].

	Percent (%)	Mean (SE)	Minimum	Maximum
Demographic information				
Non-Hispanic Whites	76.8			
Non-Hispanic Blacks	10.4			
Mexican Americans	5.2			
Other races/ethnicities	7.8			
Sex (men)	48.7			
Age (years)		45.0 (0.14)	20.0	89.0
Anthropometric measurements				
Body mass index (wt (kgs)/ht^2(meter)		26.5 (0.04)	14.4	62.1
Waist circumference (cm)		92.0 (0.12)	57.5	174.1
Physical activity				
Inactive	14.8			
Any activity	85.2			
Regular low to moderate intensity activity	53.3			
Regular vigorous activity	16.9			
METS/week[2]		3.67 (0.03)	0	53.5
Activity level compared to peers of same age				
More active	33			
Less active	21			
About the same	44			
Blood analyses				
Fasting glucose (mg/dL)		99.0 (0.24)	35.4	642.6
Insulin resistance[3]	10.67			
Insulin resistance syndrome[4]	22.2			
Dietary intake				
Percent kilocalories from carbohydrate		49.71 (0.09)	1.3	96.5
Percent kilocalories from total fat		33.52 (0.08)	1.2	76.20
Percent kilocalories from protein		15.42 (0.04)	2.0	62.8
Total calories[5]		2069.41 (8.37)	401.0	9,769.0
Cancer	% (n)[6]			
Overall cancer mortality	5.5 (863)			
Self-report of doctor-diagnosed cancer at baseline	3.82 (588)			
Individuals with self-reported doctor-diagnosed cancer at baseline who died of cancer	15 (128)			

[1] Data is presented as weighted frequencies (percentages) for categorical variables and as weighted means (SE), minimum, and maximum values for continuous variables.
[2] METS were only reported for documented leisure time physical activities in the self-report questionnaire.
[3] Insulin resistance was defined as blood glucose >110 mg/dL and includes individuals who consumed oral hypoglycemic agents or insulin users.
[4] Insulin resistance syndrome was defined as the presence of at least 3 of 5 criteria per the ATP III criteria.
[5] Only individuals who reported energy intake between 400–10,000 kcal were included in these analyses.
[6] n represent actual unweighted frequencies in the analyses dataset.

Analyses were repeated after excluding self-reported history of cancer at baseline ($n = 588$) to assess whether the observed nonsignificant associations persisted. The HRs among individuals with no history of cancer at baseline ranged from 0.82 to 1.09 for all levels of regular LTPA; however, the HRs were not statistically significant after adjusting for age and additional covariates in the whole population and the conclusions remained unchanged (Table 2). Restricting analyses to adults 40+ years at baseline yielded similar results (data not shown).

Table 2: Hazard ratio (HR) (95% CI) for cancer mortality and measures of leisure-time physical activity in NHANES III (1988–2006) participants 20–89 years ($n = 15,535$).

	Whole population	After excluding persons with existing cancer ($n = 588$)
Cancer deaths/number at risk	*860/15,535*	*733/14,951*
Any activity		
Age-Adjusted	0.92 (0.71–1.19)	1.04 (0.78–1.37)
Adjusted for additional variables[1]	0.95 (0.72–1.26)	1.10 (0.82–1.48)
Additional adjustment for BMI[2]	0.97 (0.73–1.29)	1.12 (0.83–1.50)
Regular low-moderate activity		
Age-Adjusted	0.89 (0.69–1.17)	1.01 (0.76–1.34)
Adjusted for additional variables[1]	0.92 (0.69–1.21)	1.07 (0.80–1.43)
Additional adjustment for BMI[2]	0.93 (0.70–1.24)	1.09 (0.81–1.48)
Regular vigorous activity		
Age-adjusted	0.62 (0.37–1.06)	0.73 (0.42–1.26)
Adjusted for additional variables[1]	0.66 (0.39–1.13)	0.82 (0.48–1.39)
Additional adjustment for BMI[2]	0.69 (0.40–1.19)	0.85 (0.50–1.44)
Frequency-weighted METS/week[3]		
Age-adjusted		
Quartile 1	1.00	1.00
Quartile 2	0.84 (0.67–1.05)	0.92 (0.71–1.18)
Quartile 3	0.72 (0.54–0.96)	0.80 (0.59–1.08)
Quartile 4	0.86 (0.68–1.10)	0.97 (0.78–1.26)
P value[4]	0.120	0.353
Adjusted for additional variables[1]		
Quartile 1	1.00	1.00
Quartile 2	0.85 (0.67–1.08)	0.95 (0.73–1.23)
Quartile 3	0.74 (0.56–0.98)	0.85 (0.64–1.14)
Quartile 4	0.89 (0.68–1.16)	1.04 (0.79–1.36)
P value[4]	0.139	0.422
Additional adjustment for BMI[2]		
Quartile 1	1.00	1.00
Quartile 2	0.85 (0.67–1.09)	0.95 (0.73–1.24)
Quartile 3	0.75 (0.57–1.00)	0.87 (0.65–1.15)
Quartile 4	0.91 (0.69–1.30)	1.06 (0.79–1.41)
P value[4]	0.132	0.426

[1] Adjusted for age, race, sex, and smoking.
[2] Adjusted for age, race, sex, smoking, and BMI.
[3] Quartile cutoffs (METS/week) quartile 1 <1.16; quartile 2: 1.16–10.47; quartile 3: 10.48–32; quartile 4: >48.33.
[4] P value for difference between quartiles.

Previous research has reported that BMI and IR are associated with cancer mortality [6, 23, 24]. Significant effect modification (a priori considered significant if $P < 0.1$) by IR in the relationships of physical activity and overall cancer mortality were noted ($P = 0.07$). Therefore, the analyses were stratified by IR status (yes/no) as shown in Table 3. Among individuals who were not insulin resistant, significant 54% (HR: 0.46; 95% CI: 0.24–0.87) and 49% (HR: 0.51; 95% CI: 0.27–0.97) decreased risk were observed between engagement in regular vigorous activity and overall cancer mortality, after adjusting for age and additional variables, respectively. Among individuals who were insulin resistant, an 82% increased risk of cancer mortality was observed (HR: 1.82; 95% CI: 0.71–4.65), albeit this finding was not statistically significant and therefore cannot be considered definitive. These associations persisted when the relationships were reevaluated in a sample after excluding persons with a cancer diagnosis at baseline, in sensitivity analyses (data not shown).

Although there was no significant effect modification by BMI ($P = 0.355$), for exploratory purposes only, the analyses were stratified by BMI < 25 (normal weight) and >25 (obese or overweight). Among persons with a lower

Table 3: Hazard ratio (HR) (95% CI) for cancer mortality and leisure-time physical activity in NHANES III (1988–1994) participants 20–89 years, by categories of body mass index and insulin resistance status

	By High and low BMI[1]		Insulin resistance status[2]	
Cancer deaths/number at risk	*521/9279*	*321/5991*	*228/2300*	*628/13,166*
	High BMI	Low BMI	IR	No IR
Any activity				
Age adjusted	1.02 (0.73–1.42)	0.82 (0.55–1.22)	0.89 (0.56–1.41)	0.94 (0.72–1.23)
Adjusted for additional variables[3]	1.03 (0.73–1.46)	0.90 (0.61–1.35)	0.88 (0.54–1.44)	0.99 (0.75–1.32)
Additional adjustment for BMI[4]	—	—	0.89 (0.54–1.48)	1.00 (0.76–1.32)
Regular low-moderate activity				
Age adjusted	1.00 (0.70–1.41)	0.80 (0.53–1.20)	0.84 (0.53–1.34)	0.93 (0.69–1.24)
Adjusted for additional variables[3]	1.00 (0.70–1.42)	0.88 (0.58–1.35)	0.84 (0.51–1.38)	0.97 (0.72–1.31)
Additional adjustment for BMI[4]	—	—	0.86 (0.51–1.43)	0.98 (0.73–1.32)
Regular Vigorous Activity				
Age-Adjusted	0.68 (0.33–1.39)	0.59 (0.28–1.27)	1.82 (0.71–4.65)	0.46 (0.24–0.87)
Adjusted for additional variables[3]	0.74 (0.36–1.52)	0.68 (0.32–1.45)	1.79 (0.67–4.87)	0.51(0.27–0.97)
Additional adjustment for BMI[4]	—	—	1.83 (0.66–5.04)	0.52 (0.28–0.98)
Frequency-weighted METS/week[5]				
Age-adjusted				
Quartile 1	1.00	1.00	1.00	1.00
Quartile 2	1.00 (0.08–1.46)	0.92 (0.64–1.34)	0.85 (0.43–1.67)	0.82 (0.63–1.05)
Quartile 3	0.96 (0.66–1.38)	0.61 (0.36–1.02)	0.67 (0.42–1.07)	0.76 (0.53–1.09)
Quartile 4	1.01 (0.69–1.48)	0.78 (0.51–1.18)	1.11 (0.65–1.09)	0.79 (0.6–1.03)
P value[6]	0.987	0.226	0.145	0.294
Adjusted for additional variables[3]				
Quartile 1	1.00	1.00	1.00	1.00
Quartile 2	0.99 (0.65–1.49)	0.99 (0.68–1.44)	0.82 (0.41–1.66)	0.83 (0.65–1.07)
Quartile 3	0.97 (0.69-1. 37)	0.68 (0.41–1.13)	0.69 (0.42–1.13)	0.80 (0.57–1.12)
Quartile 4	1.02 (0.69–1.52)	0.91 (0.58–1.45)	1.08 (0.62–1.89)	0.83 (0.62–1.12)
P value[6]	0.991	0.315	0.262	0.465
Additional adjustment for BMI[4]	—	—		
Quartile 1			1.00	1.00
Quartile 2			0.82 (0.41–1.66)	0.83 (0.65–1.07)
Quartile 3			0.69 (0.42–1.13)	0.80 (0.57–1.12)
Quartile 4			1.08 (0.62–1.89)	0.83 (0.62–1.12)
P value[6]			0.262	0.465

[1] BMI < 25 and ≥ 25.
[2] IR was considered to be present if blood glucose concentrations were >110 mg/dL.
[3] Adjusted for age, race, sex, and smoking.
[4] Adjusted for age, race, sex, smoking, and BMI.
[5] Quartile cutoffs (METS/week) quartile 1: <2.33; quartile 2: 1.24–13.60; quartile 3: 13.61–35.35 quartile 4: >35.36 for "low BMI" group quartile 1: <1.05; quartile 2: 1.06–9.65; quartile 3: 9.66–30.70; quartile 4: >30.72 for "High BMI" group; quartile 1: <1.63; quartile 2: 1.64–11.40; quartile 3: 11.41 to 34.65; quartile 4: >34.65 for "No IR"; quartile 1: 0; quartile 2: 0.1–6.28; quartile 3: 6.29–26.05; quartile 4: >26.05 for IR "Yes".
[6] *P* value for difference between quartiles.

BMI, the observed inverse associations were more protective for any activity and overall cancer mortality, albeit non-significant after adjusting for age (HR: 0.82; 95% CI: 0.55–1.22) and additional variables (HR: 0.90; 95% CI: 0.61–1.35) as compared to individuals with a BMI > 25 ((age-adjusted HR: 1.02; 95% CI: 0.73–1.42) and (adjusted for additional variables HR: 1.03; 95% CI: 0.73–1.46)). The HR were similarly <1 but remained non-significant among persons with a normal BMI engaging in regular low-to-moderate or regular vigorous LTPA. The direction of the associations persisted when reevaluated after excluding persons with no cancer diagnosis at baseline (data not shown).

Next, the frequency-weighted METS/week variable was divided into quartiles in the Cox proportional regression

models. Quartile 1 was the referent group and represented participants with the lowest level of METs expended, and quartile 4 represented the individuals with the highest level of METs expended. Although not significant, the HRs for quartiles 2, 3, and 4 were <1 as compared to quartile 1. These associations persisted among persons without insulin resistance and among participants with a BMI<25. The non-significant decreased risk for cancer mortality persisted after excluding persons with a cancer diagnosis at baseline (data not shown). Furthermore, HRs were similar when analyses were repeated among individuals who were 40 years or older at baseline.

4. Discussion

The current study was undertaken to elucidate the relationships between LTPA and cancer mortality in a nationally representative dataset and its linkage to mortality status (1988–2006). The comprehensive data available in the NHANES III sample on obesity, insulin resistance, and physical activity history provided a unique opportunity to evaluate the *combined* impact of these factors on longitudinally ascertained cancer mortality, an approach that has typically not been used in the previous studies.

Although the results of the current study are not statistically significant in the whole population, they are suggestive of protection against overall cancer mortality, specifically for vigorous activity (HR < 1). This study is similar to previous studies that have evaluated physical activity in relation to overall cancer mortality of site-specific cancer mortality. For example, a recent prospective cohort study among elder Japanese adults noted that high levels of physical activity (5 or more days per week) were associated with a 23% decreased risk of overall cancer mortality (P for trend = 0.02) [25]. Previous studies have shown that physical activity protects against mortality from some common cancers including lung [3], prostate [10, 26], breast [27–29], and colon cancer [11]. We observed a slight attenuation of the non-significant associations in the sensitivity analyses after excluding persons with self-reported cancer at baseline. This could perhaps be due to lifestyle changes among the cancer cases after diagnosis, or due to reverse causality. However, unavailability of follow-up measures of physical activity in the NHANES III survey limits the complete understanding of this phenomenon. Furthermore, the current study suggests that the protection afforded by LTPA may be realized in the absence of aberrations in the insulin-glucose axis. We note that the protective associations of LTPA and cancer mortality were more pronounced among non-insulin-resistant individuals who engaged in vigorous LTPA.

Several biological mechanisms may explain the potential protective role of physical activity against cancer mortality. With respect to this study, IR-related mechanisms seem particularly relevant. Insulin, an anabolic hormone, is hypothesized to promote cell proliferation, inhibit apoptosis, and support cancer progression [30–32]. Regular LTPA has been associated with improved insulin sensitivity [33–36]. Studies have demonstrated that the benefits of physical activity are apparent even in the absence of changes in body weight [2, 35]. IR is associated with increased levels of sex hormones and increased levels of inflammation [35], that may affect cancer risk [35, 37]. LTPA may also improve hormonal profiles [38, 39], reduce systemic inflammation [2], and ultimately delay cancer mortality.

Despite the potential biological mechanisms of physical activity in cancer biology, associations were not significant for all levels of LTPA in the whole population in this study. Some inherent limitations of the NHANES III survey design and assessment methods for physical activity could have contributed to measurement error and the quantitatively weak findings. It has been hypothesized that the time course of risk factors along the continuum of the cancer process is important [40] and previous studies suggest that physical activity after the diagnosis of cancer influences cancer mortality [29, 41]. LTPA information was collected once during the in-person interview at baseline. Changes in LTPA patterns over time and engagement in LTPA after cancer diagnosis during the follow-up period were not captured, potentially biasing the results towards the null. Next, physical activity was self-reported and was therefore vulnerable to recall bias due to under- or overreporting their level of LTPA [42]. Further, the NHANES III dataset was not well powered to investigate site-specific cancer mortality. Lastly, the results of this study might be an underestimation of the associations, because the exposure data were collected in 1988–1994 and the prevalence of IR as well as the proportion of physically inactive persons have increased in the past two decades [43–45], emphasizing the importance of physical activity in the current context.

5. Conclusion

In conclusion, this study uniquely utilizes a large, nationally representative sample of US adults and assesses the interrelationship between LTPA, obesity, and IR, two hypothesized risk factors of cancer mortality in the previous literature. The results suggest that the protective effects offered by physical activity against cancer mortality may be realized through the maintenance of normal metabolic function and may thereby serve a potential cancer control tool. If confirmed in additional epidemiologic studies, these findings may have important public health implications in the context of the high rates of insulin resistance and cancer mortality and a large proportion of persons with sedentary lifestyles in the USA. Further research is also required to determine the *critical periods of exposure* to physical activity during the life course with exposure measures before and after cancer diagnosis in relation to cancer outcomes in prospective studies.

Abbreviations

ATP III: Adult Treatment Panel III
BMI: Body mass index
CI: Confidence interval
HDL: High-density lipoprotein
HR: Hazard ratio

ICD-10: International Classification of Diseases, Tenth Revision
IR: Insulin resistance
LTPA: Leisure-time physical activity
METS: Metabolic equivalents
NDI: National Death Index
NHANES III: Third National Health and Nutrition Examination Survey
SE: Standard error.

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References

[1] A. Jemal, R. Siegel, J. Xu, and E. Ward, "Cancer statistics, 2010," *CA Cancer Journal for Clinicians*, vol. 60, no. 5, pp. 277–300, 2010.

[2] A. McTiernan, "Mechanisms linking physical activity with cancer," *Nature Reviews Cancer*, vol. 8, no. 3, pp. 205–211, 2008.

[3] World Cancer Research Fund/American Institute for Cancer Research, *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*, AICR, Washington, DC, USA, 2007.

[4] M. Barbaric, E. Brooks, L. Moore, and O. Cheifetz, "Effects of physical activity on cancer survival: a systematic review," *Physiotherapy Canada*, vol. 62, no. 1, pp. 25–34, 2010.

[5] A. E. Speed-Andrews and K. S. Courneya, "Effects of exercise on quality of life and prognosis in cancer survivors," *Current Sports Medicine Reports*, vol. 8, no. 4, pp. 176–181, 2009.

[6] N. Parekh, Y. Lin, R. B. Hayes, J. B. Albu, and G. L. Lu-Yao, "Longitudinal associations of blood markers of insulin and glucose metabolism and cancer mortality in the third National Health and Nutrition Examination Survey," *Cancer Causes and Control*, vol. 21, no. 4, pp. 631–642, 2010.

[7] E. Giovannucci, "Insulin and colon cancer," *Cancer Causes and Control*, vol. 6, no. 2, pp. 164–179, 1995.

[8] M. J. Borugian, S. B. Sheps, C. Kim-Sing et al., "Insulin, macronutrient intake, and physical activity: are potential indicators of insulin resistance associated with mortality from breast cancer?" *Cancer Epidemiology Biomarkers and Prevention*, vol. 13, no. 7, pp. 1163–1172, 2004.

[9] E. L. Richman, S. A. Kenfield, M. J. Stampfer, A. Paciorek, P. R. Carroll, and J. M. Chan, "Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor," *Cancer Research*, vol. 71, no. 11, pp. 3889–3895, 2011.

[10] S. A. Kenfield, M. J. Stampfer, E. Giovannucci, and J. M. Chan, "Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study," *Journal of Clinical Oncology*, vol. 29, no. 6, pp. 726–732, 2011.

[11] K. Y. Wolin, A. V. Patel, P. T. Campbell et al., "Change in physical activity and colon cancer incidence and mortality," *Cancer Epidemiology Biomarkers and Prevention*, vol. 19, no. 12, pp. 3000–3004, 2010.

[12] National Center of Health Statistics, *Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–1994*, National Center of Health Statistics, Hyattsville, Md, USA, 1995.

[13] "Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III)," *Journal of the American Medical Association*, vol. 285, no. 19, pp. 2486–2497, 2001.

[14] E. W. Gunter, B. G. Lewis, and S. M. Koncikowski, *Laboratory Procedures Used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994*, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Hyattsville, Md, USA, 1996.

[15] National Health and Nutrition Examination Survey: NHANES III Household Adult Data File Documentation, http://www.cdc.gov/nchs/nhanes/nh3data.htm.

[16] B. E. Ainsworth, W. L. Haskell, A. S. Leon et al., "Compendium of physical activities: classification of energy costs of human physical activities," *Medicine and Science in Sports and Exercise*, vol. 25, no. 1, pp. 71–80, 1993.

[17] R. R. Pate, M. Pratt, S. N. Blair et al., "Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine," *Journal of the American Medical Association*, vol. 273, no. 5, pp. 402–407, 1995.

[18] G. A. King, E. C. Fitzhugh, D. R. Bassett Jr. et al., "Relationship of leisure-time physical activity and occupational activity to the prevalence of obesity," *International Journal of Obesity*, vol. 25, no. 5, pp. 606–612, 2001.

[19] S. Liangpunsakul, D. W. Crabb, and R. Qi, "Relationship among alcohol intake, body fat, and physical activity: a population-based study," *Annals of Epidemiology*, vol. 20, no. 9, pp. 670–675, 2010.

[20] K. H. Schmitz, D. Xie, V. Teal, R. Ballard-Barbash, and D. Berrigan, "Association of IGF axis hormones with waist-to-hip ratio varies by physical activity," *In Vivo*, vol. 25, no. 2, pp. 245–250, 2011.

[21] D. R. Bassett Jr., E. C. Fitzhugh, C. J. Crespo, G. A. King, and J. E. McLaughlin, "Physical activity and ethnic differences in hypertension prevalence in the United States," *Preventive Medicine*, vol. 34, no. 2, pp. 179–186, 2002.

[22] NHANES III Linked Mortality File, http://www.cdc.gov/nchs/data_access/data_linkage/mortality/nhanes3_linkage.htm.

[23] J. R. Jaggers, X. Sui, S. P. Hooker et al., "Metabolic syndrome and risk of cancer mortality in men," *European Journal of Cancer*, vol. 45, no. 10, pp. 1831–1838, 2009.

[24] J. S. Lee, S. I. Cho, and H. S. Park, "Metabolic syndrome and cancer-related mortality among Korean men and women," *Annals of Oncology*, vol. 21, no. 3, Article ID mdp344, pp. 640–645, 2009.

[25] K. Ueshima, K. Ishikawa-Takata, T. Yorifuji et al., "Physical activity and mortality risk in the japanese elderly. a cohort study," *American Journal of Preventive Medicine*, vol. 38, no. 4, pp. 410–418, 2010.

[26] N. Orsini, R. Bellocco, M. Bottai et al., "A prospective study of lifetime physical activity and prostate cancer incidence and mortality," *British Journal of Cancer*, vol. 101, no. 11, pp. 1932–1938, 2009.

[27] A. Emaus, M. B. Veierød, S. Tretli et al., "Metabolic profile, physical activity, and mortality in breast cancer patients," *Breast Cancer Research and Treatment*, vol. 121, no. 3, pp. 651–660, 2010.

[28] M. D. Holmes, W. Y. Chen, D. Feskanich, C. H. Kroenke, and G. A. Colditz, "Physical activity and survival after breast cancer diagnosis," *Journal of the American Medical Association*, vol. 293, no. 20, pp. 2479–2486, 2005.

[29] R. E. Patterson, L. A. Cadmus, J. A. Emond, and J. P. Pierce, "Physical activity, diet, adiposity and female breast cancer prognosis: a review of the epidemiologic literature," *Maturitas*, vol. 66, no. 1, pp. 5–15, 2010.

[30] M. G. Vander Heiden, D. R. Plas, J. C. Rathmell, C. J. Fox, M. H. Harris, and C. B. Thompson, "Growth factors can influence cell growth and survival through effects on glucose metabolism," *Molecular and Cellular Biology*, vol. 21, no. 17, pp. 5899–5912, 2001.

[31] V. Ganapathy, M. Thangaraju, and P. D. Prasad, "Nutrient transporters in cancer: relevance to Warburg hypothesis and beyond," *Pharmacology and Therapeutics*, vol. 121, no. 1, pp. 29–40, 2009.

[32] M. Okumura, M. Yamamoto, H. Sakuma et al., "Leptin and high glucose stimulate cell proliferation in MCF-7 human breast cancer cells: reciprocal involvement of PKC-α and PPAR expression," *Biochimica et Biophysica Acta*, vol. 1592, no. 2, pp. 107–116, 2002.

[33] R. K. Dishman, R. A. Washburn, and G. W. Heath, *Physical Activity and Diabetes*, Human Kinetics, Champaign, Ill, USA, 2004.

[34] J. L. Ivy, "Role of exercise training in the prevention and treatment of insulin resistance and non-insulin-dependent diabetes mellitus," *Sports Medicine*, vol. 24, no. 5, pp. 321–336, 1997.

[35] H. K. Neilson, C. M. Friedenreich, N. T. Brockton, and R. C. Millikan, "Physical activity and postmenopausal breast cancer: proposed biologic mechanisms and areas for future research," *Cancer Epidemiology Biomarkers and Prevention*, vol. 18, no. 1, pp. 11–27, 2009.

[36] R. J. Sigal, G. P. Kenny, D. H. Wasserman, and C. Castaneda-Sceppa, "Physical activity/exercise and type 2 diabetes," *Diabetes Care*, vol. 27, no. 10, pp. 2518–2539, 2004.

[37] B. N. Díaz-Chico, F. G. Rodríguez, A. González et al., "Androgens and androgen receptors in breast cancer," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 105, no. 1–5, pp. 1–15, 2007.

[38] E. R. Bertone-Johnson, S. S. Tworoger, and S. E. Hankinson, "Recreational physical activity and steroid hormone levels in postmenopausal women," *American Journal of Epidemiology*, vol. 170, no. 9, pp. 1095–1104, 2009.

[39] A. McTiernan, S. S. Tworoger, K. B. Rajan et al., "Effect of exercise on serum androgens in postmenopausal women: a 12-month randomized clinical trial," *Cancer Epidemiology Biomarkers and Prevention*, vol. 13, no. 7, pp. 1099–1105, 2004.

[40] E. K. Wei, K. Y. Wolin, and G. A. Colditz, "Time course of risk factors in cancer etiology and progression," *Journal of Clinical Oncology*, vol. 28, no. 26, pp. 4052–4057, 2010.

[41] A. Vrieling and E. Kampman, "The role of body mass index, physical activity, and diet in colorectal cancer recurrence and survival: a review of the literature," *The American Journal of Clinical Nutrition*, vol. 92, no. 3, pp. 471–490, 2010.

[42] S. A. Prince, K. B. Adamo, M. E. Hamel, J. Hardt, S. C. Gorber, and M. Tremblay, "A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review," *International Journal of Behavioral Nutrition and Physical Activity*, vol. 5, article no. 55, 2008.

[43] E. W. Gregg, Y. J. Cheng, K. M. V. Narayan, T. J. Thompson, and D. F. Williamson, "The relative contributions of different levels of overweight and obesity to the increased prevalence of diabetes in the United States: 1976–2004," *Preventive Medicine*, vol. 45, no. 5, pp. 348–352, 2007.

[44] D. E. King, A. G. Mainous III, M. Carnemolla, and C. J. Everett, "Adherence to Healthy Lifestyle Habits in US Adults, 1988–2006," *American Journal of Medicine*, vol. 122, no. 6, pp. 528–534, 2009.

[45] Q. Zhang, Y. Wang, and E. S. Huang, "Changes in racial/ethnic disparities in the prevalence of type 2 diabetes by obesity level among US adults," *Ethnicity and Health*, vol. 14, no. 5, pp. 439–457, 2009.