Body Mass and Physical Activity and Risk of Gastric Cancer in a Population-Based Cohort Study in Norway

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Abstract

There is a relation between excess body mass index and overall cancer incidence and mortality, but the relation to noncardia gastric cancer is inconsistent. A high physical activity level decreases the risk of several cancers, but few studies have focused on gastric cancer. We conducted a population-based, prospective cohort study in Nord-Trondelag county in Norway. During 1984 to 1986, all adult residents were invited to participate in a health survey, where body height and weight were measured, and frequency, duration, and intensity of recreational physical activity, together with potential confounding factors, were assessed by questionnaires. New gastric cancers occurring during follow-up in 1984 to 2002 were identified by linkage to the Cancer Registry of Norway. Cox proportional hazards regression models were used to calculate hazard ratios with 95% confidence intervals, adjusted for age, sex, occupation, salt intake, smoking, and alcohol drinking. Follow-up of 73,133 cohort members (88% of all inhabitants) revealed 313 gastric cancers, including 264 noncardia cancers. No statistically significant associations were revealed between different levels of body mass index and risk of noncardia gastric cancer. A statistically significant 50% risk reduction among persons reporting at least a moderate level of recreational physical activity, based on a summary score of physical activity (hazard ratio, 0.5; 95% confidence interval, 0.3-0.9), and a dose-response relation was indicated (*P* for trend = 0.01). It is concluded that recreational physical activity might have a protective effect against gastric cancer. The sedentary lifestyle gaining ground in western societies might counteract the ongoing decrease in incidence of gastric cancer. (Cancer Epidemiol Biomarkers Prev 2008;17(1):135–40)

Introduction

Gastric cancer is a major health concern. With its combination of high incidence and poor survival, it holds the position as the second leading cause of cancer death worldwide (1). Despite declining incidence rates in many western countries, it is predicted that the number of affected patients globally will increase up to the year 2050 (2). Any factors that are related to the risk of developing this cancer and can be used for preventive actions should therefore be of great value. The prevalence of obesity in affluent societies is increasing, and there is a relation between excess body weight and overall cancer incidence and mortality (3). Further studies are important for the understanding of the etiology of different cancer forms and for estimating what health effects of preventive measures, if successful, might be expected in different populations. Whereas evidence for a positive association between obesity and risk of gastric cardia cancer has accumulated over recent years (4-6), epidemiologic findings concerning the relation between body mass index (BMI) and risk of noncardia gastric cancer have been inconsistent (2). There are indications of an inverse association between BMI and noncardia gastric cancer, but prospective studies have been sparse, and there is an obvious risk of bias in studies where mortality data are being used or where weight is reported retrospectively or with too short a latency interval between exposure and the gastric cancer (7-14). A high physical activity level has been shown to be protective against several cancers, but the small number of investigations of the relation between physical activity and risk of gastric cancer has prevented any firm conclusions from being drawn for this particular tumor. A recent review emphasized the urgent need of further and better studies addressing the role of BMI and physical activity in the etiology of gastric cancer (2). We therefore conducted a population-based, prospective cohort study to investigate the effect of BMI and recreational physical activity on gastric cancer risk.

Materials and Methods

Study Design. Between 1984 and 1986, all inhabitants in the county of Nord-Trondelag, Norway ages 20 years old or more were invited to participate in the Nord-Trondelag Health (HUNT) Study. Among 85,100 eligible

Received 8/1/07; revised 10/28/07; accepted 11/1/07.

Grant support: Swedish Cancer Society, Swedish Research Council, and European Cancer Union.

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doi:10.1158/1055-9965.EPI-07-0704

individuals, 75,058 (88%) accepted the invitation. They filled in a questionnaire that was included with the invitation, and attended a clinical examination at their local health centre. Body height and weight were measured objectively by trained nurses. At the examination, the participants received a second questionnaire to complete at home and return in a prestamped envelope. Briefly, information was collected on a range of lifestyle and health-related factors, including measures of physical activity, smoking, alcohol consumption, and education.

Exposure Assessment. At baseline, all participants attended a clinical examination at their local health centre and were asked to fill in a questionnaire. Body height and weight were measured objectively by trained study personnel. The questionnaire contained questions on average recreational physical exercise during a week (that is, walking, skiing, swimming, or other sports without further specification) with five response alternatives (0, 0-1, 1, 2-3, and ≥4 times), was filled in at home, and returned in the prestamped envelope. The average duration per occasion (<15, 15-30, 30-60, or ≥60 min) and intensity (light, average, and vigorous) of any such activities were given by participants who reported exercising at least once a week. In addition to exposure information on body dimensions and physical activity, questions were also asked about defined disorders and diseases, lifestyle factors such as use of alcohol and tobacco, behavioral habits, work and employment information, use of medications, and aspects of psychosocial well-being.

Follow-up. The unique 11-digit identity number of Norwegian citizens was used to link individuals from the HUNT Study to information on cancer incidence at the Cancer Registry of Norway (15, 16) where stomach cancer was registered according to the *International Classification of Diseases, Seventh Edition* codes 151.0, 151.8, and 151.9. Reporting to the Cancer Registry is mandatory, and since 1953, all new cancers diagnosed in Norway have been registered with information on affected organ, subsite within the organ, and histologic type (17). In the current study, we included patients diagnosed with gastric adenocarcinoma, the dominating type of malignancy in the stomach. Virtually all gastric cancers (>98%) are histologically confirmed, and the few cases without adenocarcinoma were not included in this study. The classification of gastroesophageal junction cases was made by the physicians and pathologists who reported the case to the Cancer Registry. For accurate censoring, we did register linkages with the Norwegian Central Person Registry, which provided information on vital status and emigration.

Study Variables. The participants were asked about their average frequency of recreational physical exercise during a week (that is, walking, skiing, swimming, or other sports) with five response options (0, <1, 1, 2-3, and ≥4 times, coded 1-5). Participants who reported exercising at least once a week were also asked about the average duration (<15, 15-30, 30-60, or >60 min, coded 1-4) and intensity (light, moderate, or vigorous, coded 1-3) of the activity. Frequency of physical exercise was recategorized into three levels (<1, 1, or ≥2 times a week), but for duration and intensity of physical activity we kept the original categorization. We did not code participants as missing on duration or intensity if they did not report exercising at least once a week. Among people who exercised once a week or more, we constructed a summary score of frequency, duration, and intensity. The score summarized each participant's responses to give equal weight to each measure according to the following equation: $1/5 \times$ frequency + $1/4 \times$ duration + $1/3 \times$ intensity. This resulted in a score variable with four categories: no activity, low, moderate, and high activity. A summary score below the median was classified as moderate activity, whereas a score at the median or above was classified as high activity. For the summary score variable, information on all aspects of physical activity had to be known to include the study participant in that analysis, with exception for the category ''low activity.'' Participants reporting exercising less than once a week were classified as having low activity. The study population was categorized into four groups according to their BMI at entry into the cohort (<18.5 corresponds to underweight, 18.5-24.9 corresponds to normal weight, 25.0-29.9 corresponds to overweight, and ≥30.0 corresponds to obesity).

Statistical Analyses. For the analyses of gastric cancer incidence, each participant contributed person-time from the date 3 years after the health survey examination to the date of a cancer diagnosis (all sites) or to the date of death, emigration, or end of follow-up (December 31, 2002). Hazard ratios (HR) and 95% confidence intervals (95% CI) of gastric cancer between categories of BMI and physical activity were estimated by a Cox proportional hazards regression model. Proportional hazards assumption was tested by Schoenfeld's method (18). In multivariable models, adjustments were made for attained age, gender, smoking status (never, former, and current), alcohol use (frequency during the last 2 weeks: never, not been drinking, 1-4 times, and ≥5 times), salt intake (consumption of highly salted foods: 0-1 time per month, >1-2 times per month, up to once per week, and ≥2 times per week), and occupation (higher-level employees or employers and professionals, intermediate employees, lower-level employees, other self-employed or farmers, skilled laborers, and unskilled laborers; ref. 19). Trend tests for the different exposures were made by introducing the categories as ordinal variables into the Cox model. For BMI, the trend test was based on the median value in each category. Interaction terms were constructed to determine whether multiplicative interaction modified the associations of BMI and physical activity with risk of gastric cancer. To avoid selection bias caused by influence of a yet undetected cancer on the exposure prevalence, we excluded 3,163 members of the study cohort whose follow-up time after participation in the health survey was less than 3 years (20). Among these excluded persons, 62 developed gastric cancer within the study period. We also did the analyses stratified for gender. Furthermore, the analysis of the risk of overall gastric cancer was stratified for BMI (<25 and ≥25 kg/m^2). The statistical tests were two sided. Stata (version 9.0) was used for all analyses.

Results

Study Participants. The 73,133 study cohort members were followed up for an average of 15.4 years,

Table 1. Distribution of overall gastric cancer and noncardia gastric cancer among members of the study cohort (men and women participating in the Nord-Trondelag Health Survey, 1984-1986) by baseline cohort characteristics

Characteristic	Cohort members, *n* (%)	Overall gastric cancer, *n* (%)	Noncardia gastric cancer, *n* (%)
No. participants	73,133 (100)	313 (100)	264 (100)
Females	37,178 (51)	126 (40)	106 (40)
Males	35,955 (49)	187 (60)	158 (60)
BMI (kg/m^2)			
<18.5	1,006 (1)	3 (1)	2 (1)
18.5-24.9	38,244 (52)	138 (44)	115 (43)
≥30.0	7,633 (10)	39 (12)	34 (13)
Missing	646 (1)	4 (1)	4 (2)
Smoking			
Never	27,568 (38)	118 (38)	98 (37)
Ever	12,748 (17)	66 (21)	55 (21)
Current	20,107 (27)	83 (27)	73 (28)
Missing	12,710 (17)	46 (15)	38 (14)
Alcohol (drinking in last 2 wk)	25,588 (35)	89 (28)	76 (29)
Education (y)			
≤10	50,251 (69)	254 (81)	217 (82)
≥13	5,859 (8)	14 (4)	12 (5)
Missing	13,463 (18)	40 (13)	33 (13)
Frequency of physical activity*			
<1	24,601 (34)	124 (40)	109 (41)
1	14,574 (20)	49 (16)	40 (15)
≥2	20,922 (29)	95 (30)	78 (30)
Missing	13,036 (18)	45 (14)	37 (14)
Duration of physical activity †			
<15	4,693 (6)	38 (12)	33 (13)
15-30	13,757 (19)	58 (19)	45 (17)
30-60	16,161 (22)	47 (15)	39 (15)
≥60	6,881 (9)	27 (9)	23 (9)
Missing	31,641 (43)	143 (46)	124 (47)
Intensity of physical activity			
Light	23,894 (33)	140 (45)	116 (44)
Moderate	15,892 (22)	36 (12)	30 (11)
Vigorous	1,344 (2)	3 (1)	2 (1)
Missing	32,003 (44)	134 (43)	116 (44)

*Average number of occasions of recreational physical activity in a week.
† Average duration of each occasion of physical exercise in minutes.

contributing a total of 1,122,765 person-years at risk. During this follow-up, we identified 313 new cases of gastric cancer, of which 264 (84%) were noncardia gastric cancer and 49 were gastric cardia cancer. Some characteristics of the study participants are presented in Table 1. There was a male predominance among the gastric cancer patients (60%). The mean age at baseline for cohort members was 49 years, and for gastric cancer patients it was 65 years. Approximately 10% of the study cohort members were obese (BMI > 30 kg/m^2), with a mean BMI of 25.2 kg/m^2, which was similar to that in the gastric cancer cases. Current smoking was reported by 27% of the cohort participants and by the same proportion of the gastric cancer cases, whereas formal education was lower among the patients with gastric cancer (Table 1). The mean physical activity score was 1.85 and 1.72 among cohort members and gastric cancer patients, respectively.

Table 2. BMI and HRs of incident gastric cancer and specifically noncardia gastric cancer among 73,133 Norwegians during 15.4 years of follow-up

BMI*	Overall gastric cancer				Noncardia gastric cancer			
	Person-years	*n*	HR †	HR ‡ (95% CI)	Person-years	*n*	HR †	HR ‡ (95% CI)
<18.5	11,838	3	1.4	0.7 (0.1-5.2)	11,834	2	1.2	0.9 (0.1-6.7)
18.5-24.9§	498,065	104	1.0	1.0	497,872	84	1.0	1.0
25.0-29.9	309,502	110	1.0	1.0 (0.7-1.4)	309,368	92	1.0	1.1 (0.7-1.6)
≥30.0	86,340	32	0.8	1.1 (0.7-1.8)	86,318	29	0.9	1.2 (0.7-2.1)
P for trend‖			0.38	0.74			0.77	0.42

NOTE: Both sexes combined.
*Normal weight used as reference. BMI calculated as body weight (kg) divided by the square of body height (m^2).
† Results adjusted only for age.
‡ Adjusted for age, recreational physical activity level, smoking, alcohol drinking, salt intake, and occupation.
§Reference category.
‖Physical activity score calculated from a weighted sum of frequency, intensity, and duration among participants who reported a physical activity frequency of once a week or more.

Table 3. Physical activity and HRs of incident gastric cancer and specifically noncardia gastric cancer among 73,133 Norwegians during 15.4 years of follow-up

Physical activity	Overall gastric cancer				Noncardia gastric cancer			
	Person-years	*n*	HR*	HR† (95% CI)	Person-years	*n*	HR*	HR† (95% CI)
Frequency/wk								
<1‡	300,441	93	1.00	1.0	300,381	83	1.0	1.0
1	192,168	43	0.8	0.6 (0.4-0.9)	192,094	34	0.7	0.6 (0.4-1.0)
>2	256,730	79	0.8	0.7 (0.5-1.0)	256,550	62	0.7	0.7 (0.5-1.0)
P for trend			0.09	0.08			0.02	0.06
Duration per episode of exercise (min)								
<15‡	51,014	26	1.0	1.0	50,978	22	1.0	1.0
15-30	170,700	49	0.8	0.8 (0.4-1.4)	170,573	37	0.7	0.7 (0.4-1.4)
31-60	214,759	40	0.7	0.6 (0.3-1.1)	214,697	32	0.6	0.6 (0.3-1.2)
>60	89,102	22	0.8	0.8 (0.4-1.6)	89,058	18	0.8	0.8 (0.4-1.6)
P for trend			0.32	0.32			0.38	0.43
Intensity								
Low‡	279,555	112	1.0	1.0	279,330	90	1.0	1.0
Moderate	219,883	29	0.8	0.9 (0.6-1.5)	219,832	23	0.8	0.9 (0.5-1.6)
High	19,235	3	1.9	1.7 (0.4-7.2)	19,232	2	1.6	2.2 (0.5-9.4)
P for trend			0.72	0.99			0.64	0.83
Summary score§								
No activity‡	87,538	46	1.00	1.0	87,523	42	1.0	1.0
Low	212,903	47	0.8	0.7 (0.4-1.1)	212,858	41	0.7	0.7 (0.4-1.1)
Moderate	202,835	64	0.7	0.6 (0.4-0.9)	202,688	50	0.6	0.5 (0.3-0.9)
High	226,442	45	0.6	0.5 (0.3-0.9)	226,352	36	0.5	0.5 (0.3-0.9)
P for trend			0.01	0.01			<0.01	0.01

NOTE: Both sexes combined.
*Results adjusted only for age.
† Adjusted for age, BMI, smoking, alcohol drinking, salt intake, and occupation.
‡ Reference category.
§Physical activity score calculated from a weighted sum of frequency, intensity, and duration among participants who reported a physical activity frequency of once a week or more.

BMI and Risk of Gastric Cancer. No statistically significant associations were found between different levels of BMI and risk of gastric cancer, and the point estimates were close to unity and did not change materially in the fully adjusted model (Table 2). Persons with obesity (BMI $\geq$ 30 kg/m^2) had an adjusted HR of 1.1 (95% CI, 0.7-1.8) for gastric cancer compared with those classified as having normal weight (BMI 25-29 kg/m^2), and no indications of any dose-response effects were revealed (*P* for trend = 0.74). The HRs for noncardia gastric cancer were similar to those for the risk of overall gastric cancer (Table 2). On stratification for gender, no gender-specific effects were seen (data not shown). The proportion of missing values for BMI among the study participants was <1%.

Table 4. Summary score of physical activity and risk of overall gastric cancer, stratified for BMI

Summary score*	BMI $\leq$ 25		BMI $\geq$ 25	
	Person-years	HR† (95% CI)	Person-years	HR (95 % CI)
No activity‡	42,554	1.0	44,983	1.0
Low	118,057	0.7 (0.3-1.4)	94,839	0.7 (0.4-1.3)
Moderate	108,391	0.6 (0.3-1.1)	94,427	0.6 (0.3-1.0)
High	141,912	0.4 (0.2-0.8)	84,525	0.7 (0.4-1.3)
P for trend		0.01		0.19

NOTE: BMI calculated as body weight (kg) divided by the square of body height (m^2).
*Physical activity score calculated from a weighted sum of frequency, intensity, and duration among participants who reported a physical activity frequency of once a week or more.
† Adjusted for age, BMI, smoking, alcohol drinking, salt intake, and occupation.
‡ Reference category.

Physical Activity and Risk of Gastric Cancer. A statistically significant 40% to 50% decrease in the risk of gastric cancer was seen among persons who had at least a moderate level of recreational physical activity based on the summary score compared with persons who reported no activity (HR, 0.5; 95% CI, 0.3-0.9; Table 3), and a dose-response relation was indicated (*P* for trend = 0.01). A statistically significant 40% risk reduction was associated with exercising once a week (HR, 0.6; 95% CI, 0.4-0.9). There was only one gender-specific effect: in the multivariable model, we identified a 50% to 60% risk reduction for both overall and noncardia gastric cancer among men who reported exercising for at least 15 min on each exercise occasion, whereas no evidence of such an effect was found among women (data not shown). The age-adjusted risk estimates regarding physical activity were not materially altered after adjustment for the potentially confounding variables listed in Materials and Methods, including BMI. Stratification for BMI did not indicate differences in effects of physical activity between heavier and leaner persons (Table 4). Thus, no strong confounding effects of the listed covariates were identified. There was a considerable amount of missing information on the physical activity variables as shown in Table 1. No evidence of any interaction between BMI and different measures of physical activity was identified (data not shown).

Discussion

This study indicates that at least a moderate level of recreational physical activity is associated with a halved risk of gastric cancer, whereas BMI is not associated with risk of this malignancy.

Strengths of this study include the prospective exposure assessment, the population-based design, the long and complete follow-up, the availability of ample information on BMI, physical activity, and several potentially important confounders, and information on the anatomical subsite of the tumor. The objective and uniform measurements of height and length by trained personnel reduced the risk of differential misclassification of BMI (21, 22). Furthermore, we used the incidence rate of gastric cancer as the outcome variable rather than the mortality rate, thus eliminating potential adiposity-related differences in the diagnosis or treatment of gastric cancer and potential real biological effects of weight on survival.

There are several limitations of our study. The measurement of physical activities used in this study is limited to recreational physical activity, and missing data might have affected our results. There were more missing information on the duration and intensity variables than for the frequency variable, and it was less common that study participants answered the questions related to the two former variables if they did not give information regarding their frequency of recreational physical activity. The results for physical activity were only statistically significant for the frequency variable and the summary score. We cannot exclude the possibility that potential effects of duration of physical activity and intensity of physical activity are obscured because of the pattern of missing data. However, by using the summary score variable, we used the information on these aspects of physical activity in a different way. Because the results for frequency of physical activity and the summary score of physical activity did not differ to any considerable extent, it is possible that the frequency of physical activity is driving the results also for the summary score variable. Yet, because the data collection took place long before the occurrence of any cancer, it should probably not materially bias our results. Other limitations of the study include lack of information on infection with *Helicobacter pylori*, a potentially confounding factor (23). However, our previous analyses in a random sample of 9,732 cohort members did not show any associations between BMI or physical activity and the occurrence of *H. pylori* infection.[5] It is therefore unlikely that *H. pylori* infection should have confounded our results to any material extent. Moreover, no detailed information on nutritional factors was available (e.g., intake of antioxidative vitamins, which may have a protective effect against gastric cancer; refs. 24-26). It is plausible that such dietary factors could be associated with weight and level of physical activity, and obese persons tend to have lower blood levels of antioxidants (27, 28). It may be argued that persons with a high recreational physical activity level stand out in different ways, making them a special group in terms of exposure to potential carcinogens and activities affecting the cancer risk. However, we had data that allowed adjustment for several potentially confounding factors (that is, age, sex, smoking, alcohol, salt intake, and occupation). Gastric cancer has a potentially long latency time, and exposures occurring late should not influence malignant development. To avoid this error, we excluded the first 3 years of follow-up. Patients with prediagnostic weight loss may have biased estimates of weight, a methodologic problem that is largely circumvented by using a prospective study design with exclusion of initial person-time. This also holds true for the prevalence of other potentially confounding variables; for example, it is plausible that a person stops smoking before a gastric cancer diagnosis because of the disease under study (reverse causality; ref. 20).

The number of previous studies addressing the effect of BMI or physical activity on the risk of gastric cancer risk is sparse. Although BMI is linked with an overall increase in the risk of cancer in general, results from case-control studies have indicated, rather, that a low BMI is associated with an increased risk of gastric cancer (7, 8, 29-31), whereas results from prospective studies have yielded contradictory results (3, 6, 9-14, 32). The lack of association between overweight or obesity and the risk of noncardia gastric cancer found in our study is in sharp contrast to the strong link that has been established between BMI and gastric cardia and esophageal adenocarcinoma (4-6). Regarding physical activity, one prospective study has shown a positive association between physical activity and stomach cancer risk (33). Severson et al. followed a cohort of 8,006 Japanese middle-aged men living in Hawaii. Study subjects contributed person-time from initial examination, and 343 cases were identified. Both recreational physical activity and physical activity at work were estimated, and relative risks of 1.45 and 1.74 were calculated, respectively. Differences between populations might be one explanation for the contradictory findings. Two previous investigations have in contrast failed to show any association (34, 35). In the study by Wannamethee et al., frequency, duration, and intensity of recreational physical activity were considered (34). Only 59 cases of stomach cancer were identified in this cohort of middle-aged British men, and no exclusion of initial person-time was done. The investigation made by Davey Smith et al. only considered the association of two measures of physical activity (leisure time activity and usual walking pace; ref. 35) Also in this investigation, a study population of middle-aged men was followed prospectively. During follow-up, 72 cases were identified. Mortality data were used, and analyses with exclusion of deaths in the first 5 and 10 years of follow-up did not materially alter the associations.

A biological mechanism clearly linking physical activity to gastric cancer risk is lacking, and this study provides no evidence of a link through obesity. Potential mechanisms include a genetic predisposition of habitually active persons, possibly influencing interest in exercise and susceptibility to cancer (36). Enhancing effects on the immune system have been proposed, including increases both in levels of circulating tumor-inhibiting natural killer cells and in their cancer inhibitory abilities (37). Physical exertion up-regulates the activity of free scavenger systems and oxidant levels. Decreases in insulin and insulin-like growth factors are

[5] Unpublished data.

also plausible ways in which a protective effect could be mediated.

In conclusion, this large population-based cohort study provides evidence that BMI is not associated with risk of stomach cancer, but it lends support to the hypothesis that exercise is protective. Statements about causality should be made with great caution and only after valid results from multiple studies have become available, but if our finding is true, physical exercise can be recommended in the prevention of gastric cancer. The ongoing decrease in the incidence of this cancer might be counteracted by the sedentary lifestyle gaining ground in western societies.

Acknowledgments

We thank the Norwegian Institute of Public Health and the HUNT Research Centre (Verdal, Norway) for performing the HUNT survey and the HUNT Research Centre and the medical faculty of the Norwegian University of Science and Technology (Trondheim, Norway) for allowing access to the database.

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