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Cancer Prevention Research

Research Article

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Physical Activity Is Associated with Reduced Risk of Gastric Cancer: A Systematic Review and Meta-analysis

Siddharth Singh[1], Jithinraj Edakkanambeth Varayil[1], Swapna Devanna[1], Mohammad Hassan Murad[2,3], and Prasad G. Iyer[1]

Abstract

Physical activity may be associated with reduced risk of gastric cancer. We performed a systematic review and meta-analysis to evaluate the magnitude of the association and the quality of supporting evidence. After a comprehensive search of bibliographic databases and conference proceedings through February 2013 for observational studies that examined associations between recreational and/or occupational physical activity and gastric cancer risk, we identified 16 studies (seven cohort, nine case control) reporting 11,111 cases of gastric cancer among 1,606,760 patients. Summary adjusted-OR estimates with 95% confidence intervals (CI) were estimated using the random-effects model. Meta-analysis demonstrated that the risk of gastric cancer was 21% lower among the most physically active people as compared with the least physically active people (OR = 0.79; 95% CI, 0.71–0.87) with moderate heterogeneity among studies (I^2 = 55%). This protective effect was seen for gastric cancers in the cardia (four studies; OR = 0.80; 95% CI, 0.63–1.00) and distal stomach (five studies; OR = 0.63; 95% CI, 0.52–0.76). The effect size was significantly smaller in high-quality studies (six studies; OR = 0.86; 95% CI, 0.75–0.99), as compared with low-quality studies (10 studies; OR = 0.74; 95% CI, 0.69–0.81). The results were consistent across sex, study quality, study design, and geographic location. In conclusion, meta-analysis of published observational studies indicates that physical activity is associated with reduced risk of gastric cancer. Lifestyle interventions focusing on increasing physical activity may decrease the global burden of gastric cancer, in addition to a myriad of other health benefits. *Cancer Prev Res; 7(1); 12–22. ©2013 AACR.*

Introduction

Gastric cancer is the fourth most common cancer worldwide, and the second leading cause of cancer-related mortality, causing more than 700,000 deaths annually (1). Unfortunately, almost half of the patients present with advanced, inoperable disease with a 5-year survival rate of less than 5% (2). Even in patients with resectable disease, prognosis is poor with 5-year survival rates in the order of 25% to 35% (3). Early endoscopic detection of gastric cancer is feasible and could potentially improve outcomes, but is cost prohibitive (4). Chemopreventive strategies aimed at treating *Helicobacter pylori* infection (5), use of aspirin (6) or statins (7) require a large number of patients be treated to prevent a single cancer, and hence, make it difficult to ascertain risk-benefit ratio and cost-effectiveness.

For nontobacco users, diet and physical activity are the most important modifiable determinants of cancer risk (8). Physical activity has been associated with a reduced incidence and mortality from certain cancers, particularly proximal and distal colorectal cancer (9), breast, and endometrial cancers (8, 10). The protective effect of physical activity against cancer is possibly mediated by counteracting the adverse carcinogenic effects of obesity, improving insulin sensitivity, and decreasing systemic inflammation leading to favorable immunomodulation (11, 12). There have been several studies reporting an inverse association between physical activity and risk of gastric cancer (13, 14), but results have been inconsistent (15, 16). Several systematic reviews on physical activity and cancer prevention have not addressed gastric cancer risk (8, 17).

To better understand the relationship between physical activity and gastric cancer risk, we performed a systematic review with meta-analysis of observational studies that investigated the association between physical activity and risk of gastric cancer.

Materials and Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic reviews and

Authors' Affiliations: [1]Division of Gastroenterology and Hepatology, Department of Internal Medicine; and [2]Department of Preventive Medicine; and [3]Knowledge and Evaluation Research Unit, Mayo Clinic, Rochester, Minnesota

Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

Corresponding Author: Prasad G. Iyer, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Phone: 507-255-6930; Fax: 507-255-7612; E-mail: iyer.prasad@mayo.edu

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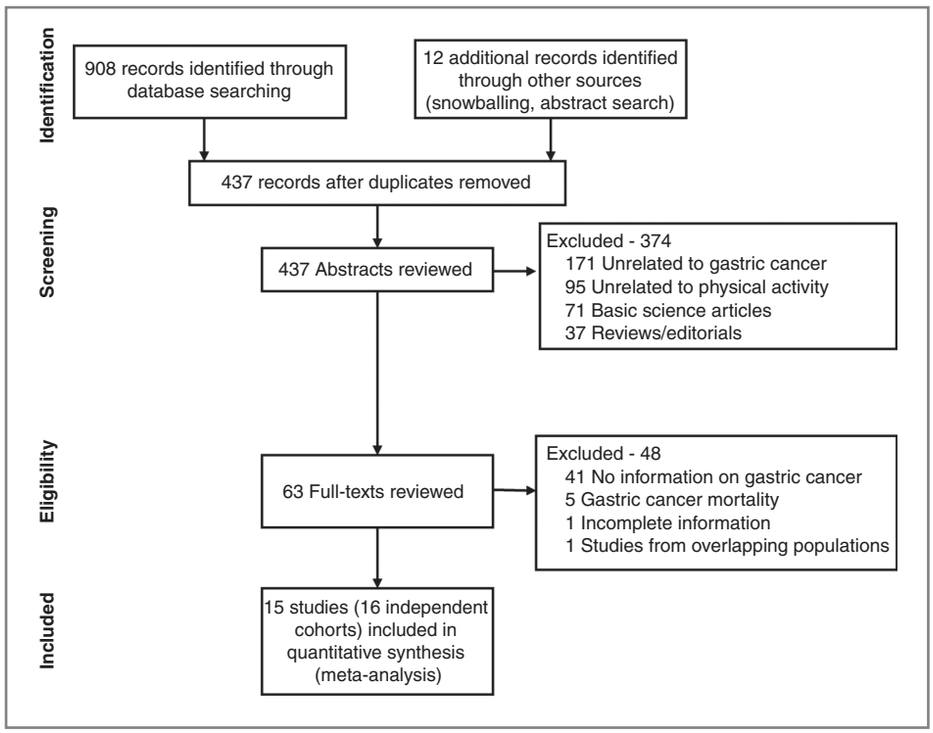

Figure 1. Flow sheet summarizing study identification and selection process.

Meta-Analyses (PRISMA) guidelines (18). The process followed *a priori* established protocol.

Search strategy and selection criteria

A systematic literature search of PubMed (1966 through February 1, 2013), Embase (1988 through February 1, 2013), and Web of Science (1993 through February 1, 2013) databases was conducted to identify all relevant observational studies on the relationship between physical activity and risk of gastric cancer. Studies considered in this meta-analysis were observational studies that met the following inclusion criteria: (i) evaluated and clearly defined physical activity (recreational or occupational), (ii) reported risk of gastric cancer, and (iii) reported relative risk (RR) or OR with 95% confidence intervals (CI) of the association between physical activity and gastric cancer risk, or provided data for their calculation. A combination of keywords was used in the search: (exercise OR physical activity OR walking OR motor activity) AND (gastric OR stomach) AND (cancer OR neoplasm OR carcinoma). The results were exported to a common EndNote (reference manager) file. After this, duplicates were removed, and a total of 422 unique studies were identified. Then, as per the protocol-defined study inclusion and exclusion criteria, two authors (S. Singh and J.E. Varayil), independently reviewed the title and abstract of studies identified in the search to exclude studies that did not investigate the association between physical activity and the risk of gastric cancer. The full text of the remaining articles was examined to determine whether it contained relevant information. Next, the bibliographies of the selected articles, as well as review articles on the topics, were manually searched for additional articles. We also searched conference proceedings of major gastroenterology (Digestive Diseases Week, United European Gastroenterology Week, and American College of Gastroenterology annual meeting) and oncology conferences (American Society of Clinical Oncology annual meeting and Gastrointestinal Research Forum, European Society of Medical Oncology annual meeting, and World Congress on GI Cancer) from 2005–2012 for studies that had been published only in the abstract form. Inclusion was not otherwise restricted by study size, language, or publication type. Studies that examined only the association between physical activity and mortality from gastric cancer were excluded. When there were multiple publications from the same population, only data from the most comprehensive report were included. The flow diagram summarizing study identification and selection is shown in Fig. 1.

Data abstraction

After study identification, data on study and patient characteristics, exposure and outcome assessment, potential confounding variables, and estimates of association, were independently abstracted onto a standardized form by two authors (S. Singh and S. Devanna). Details of data abstraction are reported in Supplementary Appendix. To estimate the dose–response relationship, using the least active group as reference, we measured the association between the middle tertile/quartile and reference as well as the association between the highest tertile/quartile and reference, and analyzed whether the difference between

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these estimates was significantly different. Conflicts in data abstraction were resolved by consensus, referring back to the original article.

Quality assessment

The risk of bias in included studies was assessed by two authors independently (S. Singh and J.E. Varayil), using the methodology suggested by Boyle and colleagues (9). Briefly, we used a three-item checklist to identify whether studies were at low or high risk of bias, based on: (i) study design—low risk of bias if studies were cohort or population based case control, and high risk of bias if hospital based case control or exclusively cancer registry based; (c) instrument used to measure physical activity—low risk of bias if instrument was reliable as shown in index study or related study, and high risk of bias if not reported; and (iii) key variables adjusted or accounted for age, sex, and obesity. If a study adjusted, matched, or accounted for the potential confounding effect of age, sex, and obesity in their analysis, then those studies were considered to be at low risk of bias, otherwise they were considered to be at high risk of bias. Overall, if a study was deemed to be at low risk of bias across all these domains, then it was considered a high-quality study; if the study was at high risk of bias across one or more of the three domains, then it was considered low-quality study (9). The overall agreement between the two reviewers for the final determination of each study was excellent (Cohen $\kappa = 0.92$), and disagreements were resolved by consensus.

Outcomes assessed

The primary analysis focused on assessing the association between physical activity and the risk of gastric cancer. *A priori* hypotheses to examine robustness of association and explain potential heterogeneity in the direction and magnitude of effect among different observational studies included location of study (Western population vs. Asian population), study design (case control vs. cohort), and study quality (high vs. low). Given the significant differences in pathophysiology of cardia and noncardia gastric cancer, we assessed subsite-specific impact of physical activity on gastric cancer. In additional subgroup analyses, we measured the impact of recreational and occupational activity domains separately, because the former is the modifiable aspect of energy expenditure, as well as sex-specific effects of physical activity.

Statistical analysis

We used the random-effects model described by DerSimonian and Laird to calculate pooled OR and 95% CI (19). Because outcomes were relatively rare, ORs were considered approximations of RR. Adjusted OR reported in studies was used for analysis to account for confounding variables. We assessed heterogeneity between study-specific estimates using two methods (20). First, the Cochran Q statistical test for heterogeneity, which tests the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect, was measured. Because this test is underpowered to detect moderate degrees of heterogeneity, a P of <0.10 was considered suggestive of significant heterogeneity. Second, to estimate what proportion of total variation across studies was due to heterogeneity rather than chance, I^2 statistic was calculated. In this, a value of <30%, 30%–60%, 61%–75%, and >75% was suggestive of low, moderate, substantial, and considerable heterogeneity, respectively (21). Once heterogeneity was noted, between-study sources of heterogeneity were investigated using subgroup analyses by stratifying original estimates according to study characteristics (as described above). In this analysis also, a P value for differences between subgroups of <0.10 was considered statistically significant (i.e., a value of $P < 0.10$ suggested that stratifying based on that particular study characteristic partly explained the heterogeneity observed in the analysis).

We assessed for publication bias quantitatively using Begg and Mazumdar rank correlation test (publication bias considered present if $P \leq 0.10$; ref. 22), and qualitatively, by visual inspection of funnel plots of the logarithmic OR versus their SE (23). All P values were two tailed. For all tests (except for heterogeneity and publication bias), $P < 0.05$ was considered statistically significant. All calculations and graphs were performed using Comprehensive Meta-Analysis version 2 (Biostat).

Results

From 422 unique studies identified using the search strategy, 15 studies met the inclusion criteria (13–16, 24–34). One population-based case–control study by Campbell and colleagues, using the Canadian National Enhanced Cancer Surveillance Study, reported and analyzed data from Ontario and seven other Canadian provinces separately using different physical activity measurement modality, and hence, these were analyzed as two separate studies (25). Hence, a total of 16 observational studies (seven cohort, nine case control), reporting on the association between physical activity and 11,111 cases of gastric cancer among 1,606,760 patients were included in the analysis. The coefficient of agreement between the two reviewers for study selection was very good (Cohen $\kappa = 0.78$). Three studies reported the association between physical activity and mortality from gastric cancer and were excluded (35–37). There were two studies from the same Japan-Hawaii Cancer Study cohort (33, 38) and hence, only the most comprehensive report from these was included (33).

Characteristics of included studies

The characteristics of these studies are shown in Table 1. The earliest cohort study recruited patients starting in 1965 and latest completed recruitment in 2000, with mean reported follow-up ranging from 6 to 18.8 years (13, 14, 16, 29, 30, 32, 33). Five studies were performed in Asian populations (16, 26, 27, 31, 32) and 10 studies were performed in Western populations (six in North America; refs. 13, 15, 25, 28, 33, 34) and 4 in Europe) (14, 24, 29, 30). Six studies were performed exclusively in men (27,

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Table 1. Baseline characteristics of the included studies

First author, reference	Study setting; location	Time period; follow-up	Total no. of participants	No. of gastric cancer (cardia/ noncardia)	Physical activity domain	Physical activity measurement; valid/reliable	Outcome measurement	Variables adjusted for
Cohort studies								
Huerta et al. (14)	Population; Europe (European Prospective Investigation into Cancer and Nutrition); 25- to 70-y-old men and women	Recruitment: 1992–2000; F/U: 8.8y	420,449	410; cardia 123, noncardia 188, unspecified 99	Recreational + occupational (separate also)	Self-administered questionnaire; yes	Central Cancer Registries; health insurance records, cancer and pathology hospital registries, active F/U	1, 2, 3, 5, 6, 7, 8, 10
Leitzmann et al. (13)	Population; USA (NIH-AARP Diet and Health Study); 50- to 71-y-old men and women	Recruitment: 1995–1996; F/U: 8y	487,732	642; cardia 313, noncardia 329	Recreational	Self-administered questionnaire; yes	Central Cancer Registry	1, 2, 3, 4, 5, 6, 7, 8, 9
Wannamethee et al. (30)	Population; England (British Regional Heart Study); 40- to 59-y-old men	Recruitment: 1978–1980; F/U 18.8y	7,588	59	Recreational	Self-administered questionnaire; yes	Central Cancer Registry, death certificates, postal follow-up	1, 2, 3, 5, 6, 9
Yun et al. (32)	Population; Korea (National Health Examination Program); >40-y-old men	Recruitment: 1996; F/U 6y	444,963	3,633	Recreational	Self-administered questionnaire; yes	Central Cancer registry	1, 2, 3, 4, 5, 6, 7, 11
Inoue et al. (16)	Population; Japan (Japan Public Health Center); 40 to 69-y-men and women	Recruitment: 1990–1994; F/U 7.5y	79,771	853	Recreational + occupational	Self-administered questionnaire; yes	Central Cancer Registries; Death certificate	1, 2, 3, 4, 5, 6, 7, 11
Sjodahl et al. (29)	Population; Norway (Nord-Trondelag Health Study); >20-y-men and women	Recruitment: 1984–1986; F/U 15.4y	73,133	313; cardia 49, noncardia 264	Recreational	Self-administered questionnaire; no	Central Cancer Registry	1, 2, 3, 4, 5, 6, 7, 9
Severson et al. (33)	Population; Hawaii (Japan-Hawaii Cancer Study); 46–68y old men	Recruitment: 1965–1968; F/U	8,006	172	Recreational (household) + occupational (separate also)	Self-administered questionnaire; yes	Central Cancer Registry	1, 2, 3, 5
Case–control studies								
Boccia et al. (24)	Hospital based; Turkey	1999–2005	329	74	Recreational	Interviewer-administered questionnaire; no	Medical records	None

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Table 1. Baseline characteristics of the included studies (Cont'd)

First author, reference	Study setting; location	Time period; follow-up	Total no. of participants	No. of gastric cancer (cardia/noncardia)	Physical activity domain	Physical activity measurement; valid/reliable	Outcome measurement	Variables adjusted for
Brownson et al. (34)	Cancer Registry; USA; >20-y-men	1984–1989	17,147 (all cancer patients)	358	Occupational	Job title based; no	Central Cancer Registry	1, 2, 3, 5
Campbell et al. (25)	Population; Canada (Canadian National Enhanced Cancer Surveillance Study—only Ontario); 20- to 74-y-old men and women	1995–1997	1,932	545; cardia 144, noncardia 401	Recreational (lifetime strenuous)	Self-administered questionnaire; no	Central Cancer Registry with independent validation	1, 2, 3, 4, 5, 7, 9
Campbell 2 et al. (25)	Population; Canada (Canadian National Enhanced Cancer Surveillance Study—seven provinces, not Ontario); 20 to 74-y-old men and women	1995–1997	3,736	636	Recreational (recent strenuous)	Self-administered questionnaire; no	Central Cancer Registry with independent validation	1, 2, 3, 5, 7, 9
Dosemeci et al. (26)	Hospital based; Turkey; men (no females with cancers)	1979–1984	5,613 (90% controls with nongastric cancers)	224	Occupational	Job-title based; no	Medical records	1, 2, 5, 9
Huang et al. (27)	Hospital based; Japan (hospital-based Epidemiological Research Program at Aichi Cancer Center); >18-y-old men	1988–1998	52,694	1988	Recreational	Interviewer-administered questionnaire; no	Medical records	1, 2, 8
Parent et al. (28)	Population; Canada; 35 to 70-y-old men	1979–1985	784	251	Recreational + occupational (separate also)	Interviewer-administered questionnaire; no	Central Cancer Registry, with independent validation	1, 2, 3, 4, 5, 6, 7, 9
Vigen et al. (15)	Population; USA; 30 to 74-y-old men and women	1992–1997	1,983	653; cardia 264, noncardia 389	Occupational	Job title based; no	Central Cancer Surveillance Program	1, 2, 3, 4, 5, 9
Wen et al. (31)	Hospital based; China	2008–2010	900	300	Recreational	Interviewer-administered questionnaire; no	Medical records	1, 2, 3, 5, 6, 7, 8

NOTE: 1, age; 2, sex; 3 obesity (body mass index, weight), 4, race/ethnicity; 5, smoking; 6, alcohol, 7, dietary factors; 8, family history of gastric cancer; 9, education and socioeconomic status; 10, *H. pylori*; 11, diabetes.

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Table 2. Quality assessment of included studies

	Bias in study design	Bias in instrument to measure physical activity	Bias in accounting for confounding variables	Overall quality of study
Cohort studies				
Huarta et al. (14)	Low	Low	Low	High
Leitzmann et al. (13)	Low	Low	Low	High
Wannamethee et al. (30)	Low	Low	Low	High
Yun et al. (32)	Low	Low	Low	High
Inoue et al. (16)	Low	Low	Low	High
Sjodahl et al. (29)	Low	High	Low	Low
Severson et al. (33)	Low	Low	Low	High
Case–control studies				
Boccia et al. (24)	High	High	High	Low
Brownson et al. (34)	High	High	Low	Low
Campbell et al. (25)	Low	High	Low	Low
Campbell 2 et al. (25)	Low	High	Low	Low
Dosemeci et al. (26)	High	High	High	Low
Huang et al. (27)	High	High	High	Low
Parent et al. (28)	Low	High	Low	Low
Vigen et al. (15)	Low	High	Low	Low
Wen et al. (31)	High	High	Low	Low

NOTE: Briefly, we used a three-item checklist to identify whether studies were at low or high risk of bias, based on: (i) study design—low risk of bias if cohort or population-based case–control studies, and high risk of bias if hospital-based case control or exclusively cancer registry based; (ii) instrument used to measure physical activity—low risk of bias if instrument valid and reliable as shown in index study or related study, and high risk of bias if not reported; (iii) key variables adjusted or accounted for: if a study adjusted, matched or accounted for the potential confounding effect of age, sex, and obesity in their analysis, then those studies were considered to be at low risk of bias, otherwise they were considered to be at high risk of bias. Overall, if a study was deemed to be at low risk of bias across all these domains, then it was considered a high-quality study, otherwise it was considered a low-quality study.

28, 30, 32–34); in one case–control study from Turkey (26), no cases of gastric cancer were observed in females, who formed <10% of entire study population. In eight studies, recreational (with or without household) physical activity was the only measured domain (13, 24, 25, 27, 29–32); in three studies, only occupational physical activity was inferred on the basis of the job title (15, 26, 34); four other studies reported combined recreational and occupational activity in estimating the lifetime physical activity (14, 16, 28, 33). In four studies, cases and controls were recruited from hospitals (24, 26, 27, 31); one study obtained data on cases and controls exclusively based on the state cancer registry, with no direct patient contact (34).

Quality of included studies

Six observational studies were at low risk of bias based on study design, exposure ascertainment, and adjusting for key confounding variables, and were deemed to be of high quality (Table 2; refs. 13, 14, 16, 30, 32, 33). The included studies variably accounted for other potential confounders: smoking (14/16), alcohol use (8/16), dietary patterns (9/16), and family history of gastric cancer (4/16). Socioeconomic status, which seems to have inverse association with physical activity, was accounted for in eight of 16 studies. Only one study adjusted for *H. pylori* infection (14). For outcome ascertainment, most studies relied on record linkage through the cancer registry (with or without review of death certificates and pathology databases), or review of medical records. In all these studies, a temporal relation between exposure and outcomes was established—physical activity preceded gastric cancer by at least 1 year and usually longer periods.

Risk of gastric cancer

Nine of the 16 studies reported an inverse association between physical activity and gastric cancer risk. On meta-analysis, risk of gastric cancer was 21% lower among the most physically active people as compared with the least physically active people (OR = 0.79; 95% CI, 0.72–0.87; Fig. 2). There was moderate heterogeneity observed across studies (I^2 = 57%, Cochran Q test $P < 0.01$). On subgroup analysis, consistent results were observed in both case–control and cohort studies, and across Asian and Western populations (Table 3). Subsite-specific data were available in five studies (13–15, 25, 29); as compared with the least physically active people, the most physically active people were 20% less likely to develop cardiac cancer (four studies; OR = 0.80; 95% CI, 0.63–1.00) and 37% less likely to develop noncardia gastric cancer (five studies; OR = 0.63; 95% CI, 0.52–0.76).

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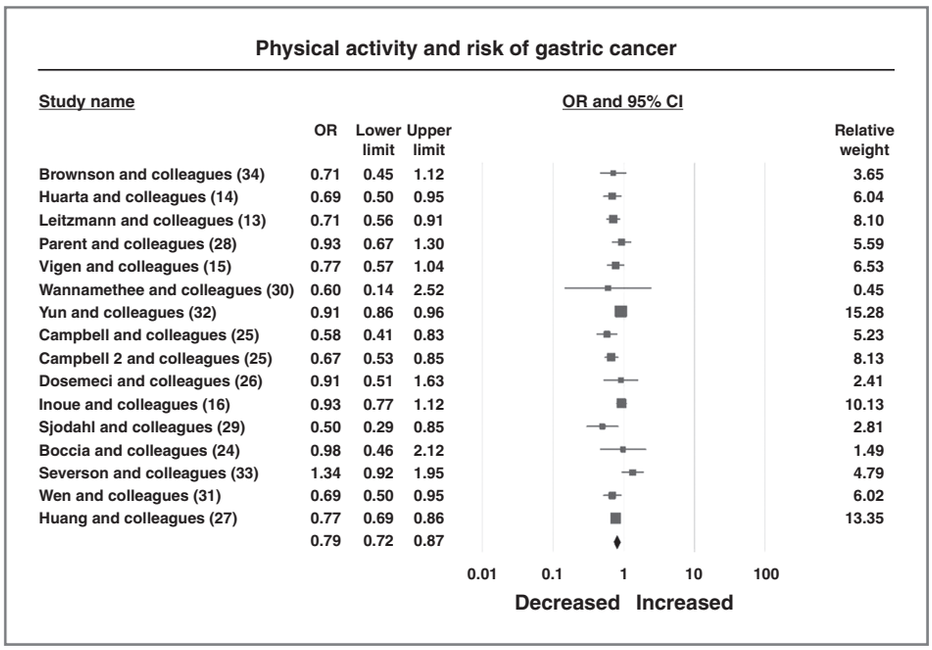

Figure 2. Summary of adjusted ORs assessing the risk of gastric cancer among the most physically active people as compared with the least physically active people (no consistent units across studies). Moderate heterogeneity was observed in the overall analysis ($I^2 = 55\%$). Please note that in the study by Severson and colleagues (33), the overall "physical activity index" was used for primary analysis.

Subgroup analysis

Sex-specific data were available for 10 studies (seven studies restricted to males; refs. 26–28, 30, 32–34); three studies provided sufficient data for sex-specific analysis; refs. 13, 15, 16). Increasing physical activity was associated with a reduced risk of gastric cancer in both men (10 studies; OR = 0.86; 95% CI, 0.75–0.99) and women (three studies; OR = 0.72; 95% CI, 0.55–0.94).

In 12 studies that reported recreational physical activity, an 18% reduction in gastric cancer risk was observed with increasing recreational activity (OR = 0.82; 95% CI, 0.72–0.94). Such an association was not observed between occupational physical activity and gastric cancer risk (six studies; OR = 0.90; 95% CI, 0.69–1.18; Fig. 3). A trend toward an inverse dose–response relationship between physical activity and gastric cancer risk was observed. Using the least active group as reference, people in the middle tertile or second quartile of physical activity had a nonstatistically significant 9% lower risk of gastric cancer (11 studies; OR = 0.91; 95% CI, 0.82–1.02). In comparison, the most physically active people (highest tertile of physical activity or fourth quartile) had a 22% lower risk of gastric cancer (11 studies; OR = 0.78; 95% CI, 0.68–0.90; *P* for difference between groups = 0.08).

Table 3. Subgroup analyses, as well as dose–response relationship, on the association of physical activity and gastric cancer risk

Groups	Categories	No. of studies	Adjusted OR	95% CI	Heterogeneity within groups (I^2; *P*)	*P* difference between groups
Site specific	Cardia	4	0.80	0.63–1.00	0; 0.59	0.12
	Noncardia	5	0.63	0.52–0.76	3; 0.39	
Sex specific	Males	10	0.86	0.75–0.99	63; <0.01	0.27
	Females	3	0.72	0.55–0.94	0; 0.59	
Study design	Case–control	9	0.75	0.69–0.82	0; 0.66	0.27
	Cohort	7	0.83	0.71–0.97	59; 0.02	
Study location	Asian	5	0.79	0.63–0.99	59; 0.05	0.11
	Western	11	0.74	0.64–0.84	27; 0.19	
Study quality	High	6	0.86	0.75–0.99	51; 0.07	0.07
	Low	10	0.74	0.69–0.81	0; 0.52	
Dose response	Middle tertile[a]	11	0.91	0.82–1.02	27; 0.18	0.08
	Highest tertile[a]	11	0.78	0.68–0.90	43; 0.06	

[a]Using least active people as reference category.

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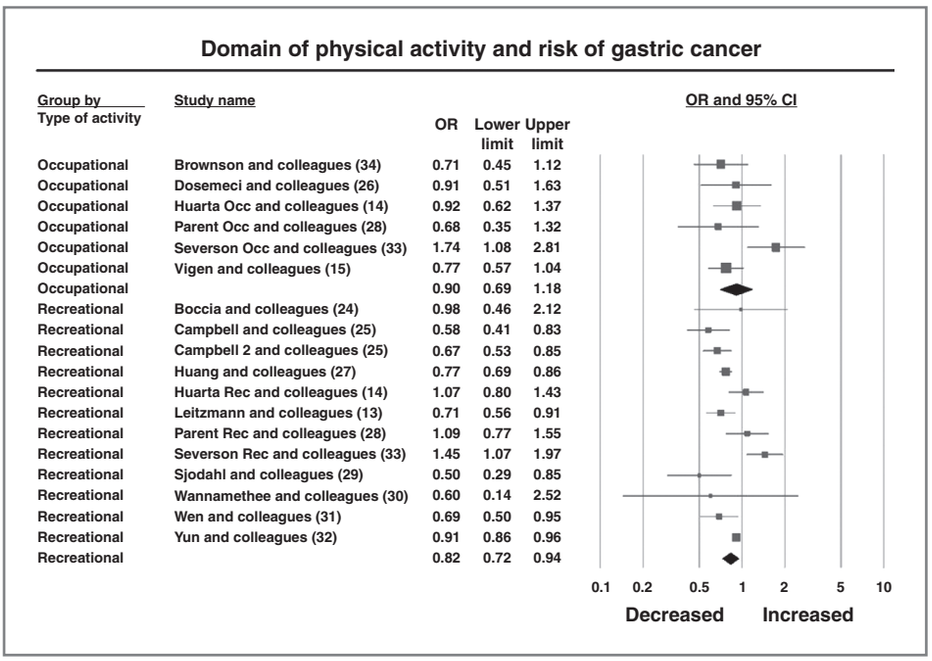

Figure 3. Gastric Cancer risk by domain of physical activity.

Sensitivity analysis and publication bias

On restricting analysis to six high-quality studies (13, 14, 16, 30, 32, 33), physical activity continued to have a significant inverse association with gastric cancer risk (OR = 0.86; 95% CI, 0.75–0.99), with moderate heterogeneity (I^2 = 51%, Cochran Q test P = 0.07). After excluding two studies in which the control population was composed of patients with nongastric cancer, a stable association was persistent between physical activity and gastric cancer (14 studies; 0.78; 95% CI, 0.71–0.87; refs. 26, 34). Campbell and colleagues reported the relationship between strenuous and moderate physical activity and risk of gastric cancer, separately; for the primary analysis, we used data for strenuous exercise (25). On using the data for moderate exercise instead of strenuous activity, the association between physical activity and gastric cancer risk persisted (OR = 0.84; 95% CI, 0.77–0.92). To assess whether any one study had a dominant effect on the summary OR, each study was excluded and its effect on the main summary estimate was evaluated. No study markedly affected the summary estimate or P value for heterogeneity among the other summary estimates, and the pooled point estimate remained statistically significant (range, 0.77–0.80), with the corresponding 95% CI bounds remaining below 0.9. Sufficient data were not available to perform stratified analyses based on histologic type of gastric cancer.

There was no evidence of publication bias, both quantitatively (Begg and Mazumdar rank correlation test, P = 0.62) and qualitatively, on visual inspection of the funnel plot (Supplementary Fig. S1).

Discussion

With the high incidence and poor prognosis associated with gastric cancer, cost-effective strategies aimed at preventing gastric cancer are highly desirable. Although chemopreventive strategies are attractive, currently, their cost-effectiveness and risk-benefit ratio is difficult to ascertain. In this systematic review and meta-analysis of 16 observational studies in 1.6 million patients with 11,111 gastric cancer cases, we found that the risk of gastric cancer was 21% lower among the most physically active people as compared with the least physically active people, after adjustment for important confounders, including age, obesity, and other risk factors for gastric cancer (smoking, alcohol, dietary patterns, and socioeconomic status). The results were stable across cohort and case–control studies in both Asian and Western populations. The risk reduction was seen independently for both cardia and noncardia gastric cancers, in both men and women. Importantly, recreational physical activity, the potentially modifiable component of energy expenditure, was independently associated with reduced risk of gastric cancer, in a dose-dependent manner. This gastric cancer risk modification is comparable with the 22% risk reduction seen with aspirin/NSAID use (with the inherent confounding by indication; ref. 6), and 16% risk reduction observed with statin use (7). Moreover, this point estimate for gastric cancer risk reduction with physical activity is comparable with the more established 12%, 24%, and 27% reduction in risk for breast (39), colorectal (40), and endometrial cancer (10), respectively. A previous systematic review by Wolin and Tuchman summarized the evidence from epidemiologic studies on the association between physical activity and gastrointestinal cancer prevention and mortality. However, in that review, only a single electronic database (PubMed) was searched resulting in some missed studies; there was no quality appraisal of current literature on this topic. A quantitative synthesis of the literature to calculate a summary estimate was not performed for the

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overall association or for subgroups (41). In its 2007 report on the role food, nutrition, and physical activity, the World Cancer Research Fund and American Institute of Cancer Research (Washington, DC) did not make any statement on the role of physical activity in decreasing gastric cancer risk (8).

Mechanism of action

Physical activity can modify the risk of cancer through several proposed mechanisms. Metabolic syndrome and insulin resistance have been associated with increased risk of cancer, including cardia gastric cancers (42, 43). This is mediated by adipokines and cytokines released by metabolically active visceral fat, which result in chronic hyperinsulinemia and increase risk of insulin-like growth factor-mediated carcinonogenesis (44). Exercise decreases visceral fat, lowering the level of carcinogenic adipocytokines, improves insulin sensitivity and reduces fasting insulin and C-peptide levels, and may decrease insulin-like growth factor-I (12). Physical activity has been shown to decrease chronic inflammation in intervention trials decreasing interleukin-6 and tumor necrosis factor-α, partly through fat loss (12). In addition, exercise has been shown to have immunomodulatory effects, improving innate and acquired immune response, promoting tumor surveillance (12, 45). Studies have also shown that aerobic exercise can decrease oxidative stress and enhance DNA repair mechanisms, decreasing carcinogenesis (45). Physically active individuals also have higher sunlight exposure and consequently, increased vitamin D levels, which may modify cell proliferation cascades (46).

In contrast with gastric cardia cancers in which adiposity plays a pathogenic role, distal, or noncardia, gastric cancers are primarily attributable to chronic inflammation due to *H. pylori* infection (47). Hence, although it is conceivable that physical activity may decrease risk of gastric cardia cancers directly, it is unclear how physical activity may contribute to decreased risk of noncardia *H. pylori*–mediated gastric cancer as was observed in our analysis. It is probable that unmeasured confounders relating to socioeconomic status that are associated with risk of *H. pylori* exposure and high recreational physical activity may have been responsible for this observation. Only one study adjusted for *H. pylori* infection (14); in this study, a decreased risk of gastric cancer was observed with increasing physical activity in both *H. pylori*–positive and *H. pylori*–negative cancers. Recent evidence suggests that obesity may potentiate gastric carcinogenesis in *H. felis*-infected mice by enhancing immature myeloid cell trafficking and TH17 response (48). Hence, it is possible that physical activity may also favorably modify obesity-accelerated gastric carcinogenesis in noncardia gastric cancer.

Strengths and limitations

The strengths of this analysis include (i) comprehensive assessment of the association between physical activity and overall and site-specific risk of incident gastric cancer; (ii) accounting for the effect of potential confounders particularly age, obesity, and other risk factors for gastric cancer such as smoking and alcohol use, in summarizing risk estimates by using the maximally adjusted point estimates from each study; (iii) incorporating the effect of both recreational and occupational physical activity, independently on gastric cancer risk; (iv) assessment of a dose–response relationship; (v) subgroup analyses that allowed assessment of sex-specific and location-specific (Asian and Western populations) effects of physical activity; (vi) sensitivity analyses based on study quality; and (vii) inclusion of all available studies and not restricting analysis based on study design, publication type, or language, and hence, being at low risk for selection or publication bias.

There are several limitations in our study. First, the meta-analysis included only observational studies. No randomized controlled trials have been performed to explore this association. Observational studies lack the experimental random allocation of the intervention necessary to test exposure-outcome hypotheses optimally. Despite adjusting for numerous covariates, it is not possible to eliminate the potential of residual confounding. It is possible that the observed decreased risk of gastric cancer seen in more physically active people users may relate to a "healthy user" bias (49). Physically active people may be more compliant with preventive health measures, as compared with patients who are not physically active. Physically inactive, and potentially poorly compliant, patients may have other unhealthy lifestyle practices predisposing them to gastric cancer. Although most of the studies accounted for some such lifestyle factors such as obesity, smoking and alcohol use, socioeconomic status was not consistently accounted for. Socioeconomic status interacts with both exposure (level of physical activity) and outcome (risk of gastric cancer, through *H. pylori* infection), and may have contributed to unmeasured confounding. We observed significant differences in the observed effect size in high-quality studies (OR = 0.86) as compared with low-quality studies (OR = 0.74); the former adjusted for key confounding variables, whereas the latter did not. Hence, what is perceived as a physical activity-mediated effect may indeed represent a sum of events and interactions, which modify gastric cancer risk in these physically active people. That said, an independent protective association was also observed on restricting analysis to high-quality studies. Second, moderate heterogeneity was observed in the overall analysis. This could not be explained through predetermined subgroup analyses, based on study location and design. This heterogeneity could be related to methodologic differences on the measurement of physical activity in the individual studies. The timing, intensity, and domain of physical activity may influence its association with health outcomes, but a detailed assessment of all these factors was not reported in individual studies. Third, the included studies did not provide data based on histologic subtypes of gastric, which are associated with different pathogenesis and prognosis. Another potential limitation that particularly applies to case–control studies evaluating cancer risk is recall bias, especially because most of these

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studies used a self-administered questionnaire to measure physical activity. However, on subgroup analysis, pooled analysis of prospective cohort studies reported a similar association between physical activity and gastric cancer risk, and there was no significant difference in risk estimates between case–control and cohort studies.

Conclusions

On the basis of this systematic review and meta-analysis of all observational studies, the risk of overall and site-specific gastric cancer is lower among the most physically active people as compared with the least physically active people. Hence, gastric cancer risk reduction may be an additional benefit to a myriad of health benefits with being physically active, which include cardiovascular, metabolic, and psychologic wellbeing. Currently, it is unclear what is the ideal type, intensity, frequency, and time period of physical activity that may modify cancer risk. For now, in the absence of interventional studies of physical activity on cancer risk, the American Cancer Society recommends "adopting a physically active lifestyle" and suggests that "adults engage in at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week, or an equivalent combination, preferably spread throughout the week" (50).

Disclosure of Potential Conflicts of Interest

P.G. Iyer has commercial research grant from Takeda Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: S. Singh, M.H. Murad, P.G. Iyer
Development of methodology: S. Singh, J.E. Varayil, M.H. Murad, P.G. Iyer
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Singh, J.E. Varayil, S. Devanna
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Singh, M.H. Murad, P.G. Iyer
Writing, review, and/or revision of the manuscript: S. Singh, J.E. Varayil, M.H. Murad, P.G. Iyer
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.H. Murad
Study supervision: M.H. Murad, P.G. Iyer

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Cancer Prevention Research

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