REVIEW

The association between physical activity and gastroesophageal cancer: systematic review and meta-analysis

Gundula Behrens · Carmen Jochem · Marlen Keimling · Cristian Ricci · Daniela Schmid · Michael Fred Leitzmann

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Abstract Physical activity may decrease gastroesophageal cancer risk through a reduction of oxidative stress and decreased chronic inflammation, yet few epidemiologic studies have been able to report a clear inverse association between physical activity and gastroesophageal cancer. Because no meta-analysis has investigated the relation of physical activity to gastroesophageal cancer, we conducted a comprehensive systematic review and meta-analysis according to the PRISMA guidelines based on 24 studies with a total of 15,745 cases. When we compared high versus low physical activity levels and summarized associations according to anatomic site and tumor histology, risk reductions were evident for esophageal adenocarcinoma [relative risk (RR) = 0.79, 95 % confidence interval (CI) = 0.66-0.94], adenocarcinoma (RR = 0.83, gastric cardia 95 % CI = 0.69-0.99) and gastric non-cardia adenocarcinoma (RR = 0.72, 95 % CI = 0.62-0.84). The risk reduction for esophageal squamous cell carcinoma (RR = 0.94, 95 % CI = 0.41-2.16) became statistically significant (RR = 0.66, 95 % CI = 0.46-0.96) after excluding an influential study. The test for heterogeneity by gastroesophageal cancer subtype was statistically non-significant (*p*-difference = 0.71). The RR of total gastroesophageal cancer for high versus low physical activity was 0.82 (95 % CI = 0.74-0.90). A doseresponse analysis of frequency of physical activity and total

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gastroesophageal cancer risk revealed that the greatest risk reduction was achieved among those engaging in moderate to vigorous physical activity five times per week (RR = 0.67, 95 % CI = 0.58–0.79). Our results provide support for an inverse relation of physical activity, in particular exercise frequency, to gastroesophageal cancer risk.

Keywords Physical activity \cdot Esophageal cancer \cdot Gastric cancer \cdot Meta-analysis

Introduction

Gastroesophageal cancers occur at a rate of approximately one million cases of gastric cancer and half a million cases of esophageal cancer each year and they represent the fourth and sixth leading cancer sites, respectively [1]. Gastric and esophageal cancers show poor 5-year survival rates of 28 and 17 %, respectively [2]. Esophageal adenocarcinoma is one of the most rapidly growing cancers in the United States [3–5], Europe [5], and Australia [5]. The poor prognosis of gastroesophageal cancers and the rapid increase in esophageal adenocarcinomas emphasize the need to identify potential measures for the primary prevention of gastroesophageal cancers, in particular esophageal adenocarcinomas.

Recent studies concluded that smoking cessation [6, 7], alcohol avoidance [8, 9], a healthy diet [10-13], and obesity and diabetes prevention [14-16] may prevent gastroesophageal cancer. Because physical activity is closely associated with those lifestyle factors, particularly with obesity and diabetes, physical activity may plausibly be linked to decreased risk of gastroesophageal cancer. However, the epidemiologic literature regarding a protective effect of physical activity is mixed, with five [17-21]

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of twelve studies [17–28] showing an inverse association between physical activity and esophageal cancer and eight [17, 23, 24, 27, 29–32] of 21 studies [17–19, 22–27, 29–40] yielding an inverse relation to gastric cancer.

Gastroesophageal cancers show distinct etiologies according to their anatomic site and tumor histologic type [41, 42], suggesting potential differences in their relations with physical activity. However, the associations between physical activity and gastroesophageal cancers according to anatomic site and tumor histologic type have not been comprehensively quantified in a meta-analysis. We therefore conducted a systematic review and meta-analysis of physical activity in relation to gastroesophageal cancers, examining potential variation by anatomic site and tumor histology. A further goal was to perform an exploratory dose–response meta-analysis in a first attempt to produce a physical activity recommendation for the primary prevention of gastroesophageal cancers.

Methods

Literature search

Our systematic review and meta-analysis followed the guidelines concerning preferred reporting items for systematic reviews and meta-analyses (PRISMA) [43]. Two authors (G.B. and M.F.L.) comprehensively searched the literature using PubMed (see Supplemental Material for PubMed search options) and Web of Science to identify published non-ecologic epidemiologic studies quantifying the relation between physical activity and gastroesophageal cancer incidence or mortality. We disregarded studies of cancer survivors. Our search was complemented by a scan of the reference lists of the identified studies. We considered all human research articles published in English through mid December 2013 not classified as review, meta-analysis, editorial, comment, letter, practice guideline, or news. Articles were eligible if they reported a relative risk estimate with a corresponding 95 % confidence interval (CI) or sufficient data to calculate them and if they accounted for age and, if applicable, for sex as potential confounding factors. Our search strategy included the terms physical activity, exercise, cardiorespiratory fitness, cardiovascular fitness, lifestyle, stomach cancer, stomach carcinoma, gastric cancer, gastric carcinoma, esophageal cancer, esophageal carcinoma, cancer, risk, incidence, and mortality (see Supplemental Material for Boolean PubMed search terms). That search yielded 2,209 articles. Ineligible articles were eliminated after screening titles and abstracts (n = 2,139) or full manuscripts (n = 47). Of the 23 remaining studies [17-19, 22-27, 29, 31-40, 44-46], two [44, 45] were removed because they were updated in a subsequent analysis [33] and one mortality study [46] was excluded because incidence data [24] from the same cohort were available. Three additional studies were found by manual search in the Web of Science [20, 21, 28] and one study [30] was found in the reference lists of the identified studies. Thus, a total of 24 studies [17–40] were included in the meta-analysis.

Data extraction

To assess potential differences in physical activity relations according to tumor histologic type and cancer anatomic site, we preferably extracted risk estimates for gastroesophageal cancer subtypes even if that meant that not all cancer cases could be considered. Specifically, we were unable to include 99 gastric cancers with an unspecified subsite from one study [23], for which no relative risks were reported. Also, we did not include the 49 gastric cardia cancers from another study [38] because risk estimates were unavailable for those cases. We extracted risk estimates for men and women separately whenever possible because men and women were considered independent samples. If studies reported on more than one physical activity domain, estimates for all domains were collected. With respect to different types of physical activity assessments, preference was given for assessments of lifelong physical activity, for assessments of vigorous physical activity, for the most comprehensive physical activity assessment, and for quantitative physical activity assessments. When there was a choice among quantitative physical activity assessments, we used frequency of physical activity because that was the most common quantitative physical activity component measured.

Study quality score

Two previous systematic reviews on physical activity and cancer [47, 48] found that the study quality as assessed by a score proposed by Monninkhof et al. [47] affected the summary risk estimates. Thus, we employed that quality score to assess whether selection bias, misclassification, or confounding affected the summary risk estimates. In addition, we rated the degree of control for confounding by awarding points for including smoking, adiposity, and alcohol intake as major adjustment factors in the multivariate models of the underlying studies.

Random effects meta-analysis

The odds ratios and hazard ratios presented in individual studies were interpreted as relative risk estimates (RR_i). These were log-transformed to log(RR_i) and their corresponding standard errors were computed as $s_i = d_i/1.96$, with d_i representing the

maximum of [log(upper 95 % CI bound of RR_i) – log(RR_i)] and [(log(RR_i) – log(lower 95 % CI bound of RR_i)] to take into account that the log-transformed 95 % confidence interval from one study [21] was not centred at the corresponding logtransformed relative risk. We employed a random effects model using the weighted average of the log(RR_i) expressed as $w_i = 1/(s_i^2 + t^2)$, where s_i represented the standard error of log(RR_i) and t^2 represented the restricted maximum likelihood estimate of the overall variance. Heterogeneity of the risk estimates was assessed using the Q- and the I²-statistics [49]. Publication bias was tested using funnel plot diagnostics, Begg's test [50], and Egger's test [51].

Stratified analyses

We investigated whether the summary risk estimate was affected by cancer major anatomic site (esophageal cancer, gastric cancer), histologic type (esophageal squamous cell carcinoma, esophageal adenocarcinoma), and anatomic subsite (gastric cardia adenocarcinoma, gastric non-cardia adenocarcinoma). We also examined potential differences according to study design (cohort, case-control), study quality score (tertiles), gender (men, women), study geographic region (North America, Europe, Australia, Asia), physical activity domain (recreational, occupational), timing in life of physical activity (recent past physical activity, distant past physical activity, consistent physical activity over time), physical activity assessment (assessment of energy expenditure, assessment of activity duration, assessment of activity frequency, and qualitative physical activity assessments using descriptive categories such as 'sedentary', 'light', 'moderate', or 'high' physical activity), and adjustments for smoking (yes, no), adiposity (yes, no), and alcohol intake (yes, no).

Sensitivity analyses

In order to investigate whether our summary risk estimate was affected by the inclusion of multiple risk estimates from a given study, we conducted a sensitivity analysis that included only one risk estimate per gender from each study, choosing the risk estimate with the highest quality score and the gastroesophageal cancer endpoint with the largest number of cases. We conducted a further sensitivity analysis in which we omitted one study at a time from the analysis to examine whether results were affected by an individual study. Because studies used heterogeneous definitions of exposure and reference levels of physical activity, we investigated whether the summary risk estimate changed if the meta-analysis was restricted to studies with comparable definitions of exposure and reference categories. We also tested whether restriction to studies of gastroesophageal cancer incidence changed the summary risk estimate.

Non-linear dose-response meta-analysis

Most studies [17, 19, 24, 29, 30, 32, 34, 38–40] based on quantitative physical activity assessments examined the association between frequency of moderate to vigorous recreational physical activity and gastroesophageal cancer risk. Five of those studies [24, 29, 32, 34, 38] provided sufficient information to be included in a non-linear dose–response meta-analysis [52].

All statistical analyses were performed in R [53] using the R-packages 'metafor' [54] and 'mvmeta' [55]. Risk estimates are reported with 95 % confidence intervals. Statistical significance was based on the 5 % significance level.

Results

Study characteristics

Table 1 presents the main characteristics of the nine cohort and 15 (non-nested) case–control studies of physical activity and gastroesophageal cancer included in the metaanalysis. Those studies comprised a total of 15,745 cases. Ten studies [17–19, 22–27, 29] examined more than one gastroesophageal endpoint, four studies [19, 23, 37, 39] investigated more than one physical activity domain, four studies [17, 20, 25, 31] presented results stratified by gender, one study [29] presented results stratified by geographic region, and one study [30] reported results stratified by family history of gastric cancer. Thus, the 24 studies reported 61 individual risk estimates.

All cohort studies examining recent past physical activity in relation to gastroesophageal cancer assessed the usual level of physical activity at baseline [23, 24, 26, 27, 31, 33, 37, 38], whereas case–control studies queried about physical activity performed at cancer incidence [18, 21, 22, 28, 34, 35, 39, 40], one year [32] or 2 years [29] before cancer incidence or before symptoms appeared [30]. By comparison, studies investigating distant past physical activity inquired about the level of physical activity ten or more years prior to baseline [36] (cohort study) or cancer incidence [17, 19, 20] (case–control studies).

Main analysis

We summarized associations according to gastroesophageal cancer anatomic site and histology (Fig. 1). High levels of physical activity showed statistically significant inverse

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Cohort sti	ıdies									
Authors, year, gender	Study geo- graphic region	Participants	Cases	Esophageal and gastric cancer site and type	Physical activity domain, timing in life	Relative risk (95 % CI), high versus low physical activity	Low physical activity defined by	High physical activity defined by	Adjustment factors (excluding age, sex)	Study quality score (%)
Batty et a	l. 2010 [33]									
Men	Europe	6,715	101	Gastric adenocarcinoma, subsite unspecified, fatal	Recreational, recent	0.65 (0.38, 1.14)	Not engaging in MVPA	Engaging in VPA	Forced expiratory volume in 1 s, obesity (BMI), SES (employment grade), smoking	67
Huerta et	al. 2010 [23	[
Men and women	Europe	420,449	80	Esophageal adenocarcinoma, non-fatal	Total, recent	0.98 (0.48, 2.01)	Physically inactive	Physically active	Alcohol intake, height, energy intake, fruit intake, meat intake (red/processed),	79
					Recreational, recent	0.72 (0.36, 1.42)	No VPA	More than 2 h of VPA per week	obesity (weight), SES (education), smoking	78
					Occupational, recent	0.95 (0.41, 2.20)	Sedentary occupation	Manual work		73
			123	Gastric cardia adenocarcinoma, non-fatal	Total, recent	1.05 (0.59, 1.86)	See above	See above		79
					Recreational, recent	1.14 (0.68, 1.91)	See above	See above		78
					Occupational, recent	0.70 (0.33, 1.48)	See above	See above		73
			188	Gastric non-cardia adenocarcinoma, non-fatal	Total, recent	0.44 (0.26, 0.74)	See above	See above		79
					Recreational, recent	0.98 (0.60, 1.60)	See above	See above		78
					Occupational, recent	0.82 (0.44, 1.52)	See above	See above		73
Inoue et c	ıl. 2008 [31]									
Men	Asia	37,898	621	Gastric adenocarcinoma, subsite unspecified, non- fatal or fatal	Total, recent	1.04 (0.84, 1.29)	Less than 27 METs per day	More than 36 METs per day	Alcohol intake, energy intake, history of type 2 diabetes mellitus, obesity (BMI), recreational physical activity	79
Women		41,873	232	Gastric adenocarcinoma, subsite unspecified, non- fatal or fatal	Total, recent	0.63 (0.42, 0.94)			(frequency), smoking, study center	79

Table 1 Characteristics of the 9 cohort studies and 15 case–control studies on physical activity and esophageal and gastric cancer risk included in the meta-analysis grouped by study design

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Table 1	continued									
Cohort stu	ıdies									
Authors, year, gender	Study geo- graphic region	Participants	Cases	Esophageal and gastric cancer site and type	Physical activity domain, timing in life	Relative risk (95 % CI), high versus low physical activity	Low physical activity defined by	High physical activity defined by	Adjustment factors (excluding age, sex)	Study quality score (%)
Leitzmann	et al. 2009 [.24]								
Men and women	North America	487,732	149	Esophageal squamous cell carcinoma, non- fatal	Recreational, recent	1.05 (0.64, 1.74)	Never/rarely engaging in VPA	Engaging in VPA 5 times per week or more (for 20 min or more)	Alcohol intake, family history of cancer, fruit and vegetable intake, meat intake (red meat), marital	72
			374	Esophageal adenocarcinoma, non-fatal	Recreational, recent	0.75 (0.53, 1.06)			status, obesity (BMI), race/ethnicity, SES (education), smoking	72
			313	Gastric cardia adenocarcinoma, non-fatal	Recreational, recent	0.83 (0.58, 1.19)				72
			329	Gastric non-cardia adenocarcinoma, non-fatal	Recreational, recent	0.62 (0.44, 0.87)				72
Paffenbar	ger et al. 198	7 [36]								
Men	North America	56,683	41	Gastric adenocarcinoma, subsite unspecified, non- fatal or fatal	Recreational, past	1.05 (0.50, 2.21)	Less than 5 h of VPA per week	5 h of VPA per week or more	Birth year	61
Severson	et al. 1989 [3	17								
Men	North America	7,925	172	Gastric adenocarcinoma, subsite unspecified, non- fatal	Total, recent	1.34 (0.92, 1.95)	Lower tertile of daily energy- expenditure index	Upper tertile of daily energy- expenditure index	Obesity (BMI), smoking	70
					Recreational, recent	1.45 (1.07, 1.97)	Sedentary occupation	Moderate to heavy work		59
					Occupational, recent	1.74 (1.08, 2.81)	Sedentary occupation	Moderate to heavy work		59
Sjödahl ei	t al. 2008 [38	1								
Men and women	Europe	73,133	264	Gastric non-cardia adenocarcinoma, non-fatal	Recreational, recent	0.70 (0.50, 1.00)	Engaging in MVPA less than once per week	Engaging in MVPA more than twice per week	Alcohol intake, obesity (BMI), salt intake, SES (job), smoking	70

Cohort st	udies									
Authors, year, gender	Study geo- graphic region	Participants	Cases	Esophageal and gastric cancer site and type	Physical activity domain, timing in life	Relative risk (95 % CI), high versus low physical activity	Low physical activity defined by	High physical activity defined by	Adjustment factors (excluding age, sex)	Study quality score (%)
Wanname Men	<i>thee et al.</i> 2 Europe	001 [26] 7.588	65	Esophageal cancer.	Recreational.	0.46 (0.11, 1.90)	No or moderate PA	High PA	Alcohol intake, obesity	74
	- 1			type unspecified, non-fatal or fatal	recent			þ	(BMI), SES (job), smoking	
			59	Gastric adenocarcinoma, subsite unspecified, non- fatal or fatal	Recreational, recent	0.60 (0.14, 2.47)				74
Yun et al.	2008 [27]									
Men	Asia	444,963	293	Esophageal cancer, type unspecified, non-fatal	Recreational, recent	0.84 (0.66, 1.06)	Combination of MVPA frequency and duration: MVPA less than 4 times per week and less than 30 min per session	Combination of MVPA frequency and duration: MVPA at least 2 times per week for at least 30 min per session or, alternatively, at least 5 times per week for less than 30 min per session	Alcohol intake, fruit and vegetable intake (healthy dietary pattern), history of diabetes (fasting glucose level), obesity (BMI), SES (employment), smoking	67
			3,633	Gastric adenocarcinoma, subsite unspecified, non- fatal	Recreational, recent	0.91 (0.86, 0.98)				67



Table 1	continued								
Case-cont	rol studies								
Authors, year, gender	Study geo- graphic region	Controls	Cases	Esophageal and gastric cancer site and type	Physical activity domain, timing in life	Relative risk (95 % CI), high versus low physical activity	Low physical activity defined by	High physical activity defined by	Adjustment factors (excluding age, sex)
Boccia et	al. 2005 [34 ₁	1							
Men and women	Europe	255	74	Gastric adenocarcinoma, subsite unspecified, non- fatal	Recreational, recent	0.97 (0.45, 2.09)	Never engaging in physical activity	Engaging in physical activity 5 or more times per week	I
Brownson 1991 [22	et al. 2J								
Men	North America	16,910	237	Esophageal cancer, type unspecified, non-fatal	Occupational, recent	1.43 (0.71, 3.33)	Low PA	High PA	Smoking
		16,789	358	Gastric adenocarcinoma, subsite unspecified, non- fatal	Occupational, recent	0.71 (0.45, 1.11)			
Campbell 2007, no sample [et al. m-Ontario 1 <mark>29</mark>]								
Men and women	North America	3100	636	Gastric adenocarcinoma, subsite	Recreational, recent	0.67 (0.53, 0.86)	Lowest VPA quartile	Highest VPA quartile	Meat intake (Western dietary pattern), obesity (BMI), SES (education), smoking

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49

Study quality score (%)

53

89

Meat intake (Western dictary pattern), obesity (BMI), SES (education), smoking

Highest lifetime VPA quartile

0.60 (0.34, Lowest lifetime VPA 1.07) quartile

Recreational, consistent

adenocarcinoma,

Gastric cardia non-fatal

144

1,387

Men and women

America North

Campbell et al. 2007, Ontario sample [29]

unspecified, non-fatal

0.73 (0.50, 1.07)

Recreational, consistent

Gastric non-cardia

401

adenocarcinoma, non-fatal

68

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Mather, Balling and Statistic and statistic and statistic and statistic and statistic and statistic and statistic and statistic and statistic and statistic and statistic and statistic and statistic and statistic and and statistic and and and and and and and and and and	Case-cont	rol studies									
Due of old 2013 (23) Institution (2013 (23)) Another of a state	Authors, year, gender	Study geo- graphic region	Controls	Cases	Esophageal and gastric cancer site and type	Physical activity domain, timing in life	Relative risk (95 % CI), high versus low physical activity	Low physical activity defined by	High physical activity defined by	Adjustment factors (excluding age, sex)	Study quality score (%)
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	<i>Dar et al.</i> Men and women	2013 [28] Asia	1,663	703	Esophageal squamous cell carcinoma, non- fatal	Occupational, recent	5.65 (3.49, 9.12)	Sedentary	Very active	Alcohol intake, fruit and vegetable intake, place of residence, race/ ethnicity, religion, SES (education), smoking (cigarettes, hookah, bidi), tobacco chewing (nass ontka)	61
Men Europe 2.127 2.4 Gastric admocarcinom, subsistion admocarcinom, subsistion admocarcinom, subsistion admocarcinom, subsistion minicipated Cerptationel (1.67) Description (1.67) Regy construction (1.67) Energy construction (1.67) Subsistion (1.67) Subsistion (1.67) <	Dosemeci	et al. 1993 [35]							(mas) Europ	
Ermadi et al. 2012 [20]MeinMiddle278150Econation0.53 (0.26, bast)SedentaryVery activeAge of first adut tooh loss family49MeinMiddle278150Econationa, non- carcinona, non- fatalCoupational, 0.21 (0.26, bast)SedentaryVery activeAge of first adut tooh loss family49Women2931500.30 (0.12, 0.7)0.30 (0.12, 0.7)Participani use, SES (cateaction), motion in use, SES (cateaction), <td>Men</td> <td>Europe</td> <td>2,127</td> <td>224</td> <td>Gastric adenocarcinoma, subsite unspecified, non- fatal</td> <td>Occupational, recent</td> <td>0.91 (0.59, 1.67)</td> <td>Energy expenditure < 8 kJ/min</td> <td>Energy expenditure > 12 kJ/ min</td> <td>Smoking, SES (occupation)</td> <td>47</td>	Men	Europe	2,127	224	Gastric adenocarcinoma, subsite unspecified, non- fatal	Occupational, recent	0.91 (0.59, 1.67)	Energy expenditure < 8 kJ/min	Energy expenditure > 12 kJ/ min	Smoking, SES (occupation)	47
	Etemadi e.	t al. 2012 [2	0]								
Women293150 0.30 (0.12 , 0.77) 0.30 (0.12 , 0.79) 0.30 (0.70 , 0.79) 0.30 (0.70 , 0.79) 0.30 (0.70 , 0.70) 0.79 ($0.$	Men	Middle East	278	150	Esophageal squamous cell carcinoma, non- fatal	Occupational, past	0.53 (0.26, 1.11)	Sedentary	Very active	Age of first adult tooth loss, family history of esophageal cancer, obesity (BMI at age 15 years), opium use, SES (education), smoking, use of piped water	49
Huang et al. 2004, family history of gastric cancer [30]Recreational, or 10, 57, less than 3 times per month or of physical-45Men and Asia 6,310 464 Gastric cancer (30)Recreational, or 11, 0.57, less than 3 times per month or of physical45womenadenocarcinoma, subsite0.89)month of physicalmore of physicalmore of physical-45womensubsite0.89)activityactivityactivity-45Huang et al. 2004, no family history of gastric cancer [30]Recreational, or 70, less than 3 times per month or subsite45Men and Asia44,3961,524GastricRecreational, or 70, less than 3 times per month or recent45womensubsite.0.89)month of physicalmore of physical45inspecified, non-fatal0.89)month of physical45	Women		293	150			0.30 (0.12, 0.77)			- - -	49
	Huang et v	al. 2004, fan	ily history ϵ	of gastric	cancer [30]						
Huang et al. 2004, no family history of gastric cancer [30] Men and Asia 44,396 1,524 Gastric Recreational, 0.79 (0.70, Less than 3 times per 3 times per month or – 45 women adenocarcinoma, recent 0.89) month of physical more of physical women subsite unspecified, non- fatal	Men and women	Asia	6,310	464	Gastric adenocarcinoma, subsite unspecified, non- fatal	Recreational, recent	0.71 (0.57, 0.89)	Less than 3 times per month of physical activity	3 times per month or more of physical activity	1	45
Men and Asia 44,396 1,524 Gastric Recreational, 0.79 (0.70 , Less than 3 times per 3 times per month or – 45 women adenocarcinoma, recent 0.89) month of physical more of physical subsite unspecified, non- fatal	Huang et	al. 2004, no	family histo	ry of gas	stric cancer [30]						!
	Men and women	Asia	44,396	1,524	Gastric adenocarcinoma, subsite unspecified, non- fatal	Recreational, recent	0.79 (0.70, 0.89)	Less than 3 times per month of physical activity	3 times per month or more of physical activity	I	45

Table 1 continued

Case-contr	ol studies									
Authors, year, gender	Study geo- graphic region	Controls	Cases	Esophageal and gastric cancer site and type	Physical activity domain, timing in life	Relative risk (95 % CI), high versus low physical activity	Low physical activity defined by	High physical activity defined by	Adjustment factors (excluding age, sex)	Study quality score (%)
Ibiebele et	al. 2012 [18	1								
Men and women	Australia	1,507	245	Esophageal squamous cell carcinoma, non- fatal	Recreational, recent	0.65 (0.47, 0.91)	Low PA	High PA	I	49
			299	Esophageal adenocarcinoma, non-fatal	Recreational, recent	0.81 (0.58, 1.12)				49
			336	Esophago-gastric junction adenocarcinoma, non-fatal	Recreational, recent	0.92 (0.67, 1.26)				49
Jessri et al	2011 [21]									
Men and women	Middle East	96	47	Esophageal squamous cell carcinoma, non- fatal	Total, recent	0.93 (0.25, 0.96)	Low PA	High PA	Energy intake, history of gastroesophageal reflux, medication, obesity (BMI), SES (education), smoking	49
Lam et al.	2004 [17]									
Men	Asia	3,918	235	Esophageal cancer, type unspecified, fatal	Recreational, past	0.57 (0.41, 0.80)	Engaging in MVPA less than once per month	Engaging in MVPA at least once per month	Alcohol intake, occupational physical activity, SES (education), smoking	60
			369	Gastric adenocarcinoma, subsite unspecified, fatal	Recreational, past	0.76 (0.60, 0.96)				60
Women		9,136	54	Esophageal cancer, type unspecified, fatal	Recreational, past	0.52 (0.28, 0.97)				60
			200	Gastric adenocarcinoma, subsite unspecified, fatal	Recreational, past	0.57 (0.41, 0.78)				60

Case-cont.	rol studies									
Authors, year, gender	Study geo- graphic region	Controls	Cases	Esophageal and gastric cancer site and type	Physical activity domain, timing in life	Relative risk (95 % CI), high versus low physical activity	Low physical activity defined by	High physical activity defined by	Adjustment factors (excluding age, sex)	Study quality score (%)
Parent et d	n. 2011 [19]	-								
Men	North America	533	66	Esophageal cancer, type unspecified, non-fatal	Total, consistent	0.54 (0.31, 0.93)	Less than 1.5 METs at work independent of leisure time PA or 1.5–3.9 METs at work and less than once per week engaged in leisure time MVPA	Energy expenditure of 4 METs per day or more at work independent of leisure time PA or 1.6–3.9 METs per day at work and at least once per week engaged in leisure time MVPA	Alcohol intake, beta-carotene intake, coffee intake (in models of esophageal cancer only), obesity (BMI), proxy respondent, race/ ethnicity, recreational/ occupational activity (mutual adjustment), SES (socio-economic status, education), smoking, tea intake (in models of esophageal cancer only)	73
					Recreational, past	0.54 (0.30, 0.97)	MVPA less than once per week	MVPA at least once per week		70
					Occupational, consistent	0.66 (0.23, 1.88)	1.5 METs or less of energy expenditure	Energy expenditure of 4 METs or more		69
			251	Gastric adenocarcinoma, subsite	Total, consistent	0.93 (0.67, 1.31)	See above	See above		73
				fatal						
					Recreational, past	1.09 (0.76, 1.54)	See above	See above		70
					Occupational, consistent	0.68 (0.35, 1.32)	See above	See above		69
Suwanrunz	gruang et al.	2008 [39]								
Men and women	Asia	202	101	Gastric adenocarcinoma, subsite unspecified, non- fatal	Recreational, recent	0.70 (0.33, 1.33)	Exercising less than 3 times per week	Exercising 3 times or more per week	1	49
					Occupational, recent	0.52 (0.23, 1.17)	Sedentary occupation	Heavy work		42

Table 1 continued

Case-con	trol studies									
Authors, year, gender	Study geo- graphic region	Controls	Cases	Esophageal and gastric cancer site and type	Physical activity domain, timing in life	Relative risk (95 % CI), high versus low physical activity	Low physical activity defined by	High physical activity defined by	Adjustment factors (excluding age, sex)	Study quality score (%)
Vigen et u	ıl. 2006 [25]									
Men	North America	988	192	Esophageal adenocarcinoma, non-fatal	Occupational, consistent	0.77 (0.54, 1.08)	Lifetime occupational PA averaged over years worked prior to age 65 years less than median	Lifetime occupational PA averaged over years worked prior to age 65 years equal to or greater than median	Birth place, obesity (BMI), race/ ethnicity, SES (education), smoking status	58
			221	Gastric cardia adenocarcinoma, non-fatal	Occupational, consistent	$\begin{array}{c} 0.81 \ (0.58, \ 1.11) \end{array}$		1		58
			235	Gastric non-cardia adenocarcinoma, non-fatal	Occupational, consistent	0.77 (0.55, 1.07)				58
Women		342	20	Esophageal adenocarcinoma, non-fatal	Occupational, consistent	0.35 (0.04, 3.15)				58
			43	Gastric cardia adenocarcinoma, non-fatal	Occupational, consistent	0.30 (0.07, 1.40)				58
			154	Gastric non-cardia adenocarcinoma, non-fatal	Occupational, consistent	1.07 (0.59, 1.91)				58
Watabe e	t al. 1998 [40	1								
Men and women	Asia	484	242	Gastric adenocarcinoma, subsite unspecified, non- fatal	Recreational, recent	0.94 (0.68, 1.32)	Engaging in MVPA less than once per week	Engaging in MVPA at least once per week	Place of residence	48
Wen et al	. 2010 [32]									
Men and women	Asia	600	300	Gastric adenocarcinoma, subsite unspecified, non- fatal	Recreational, recent	0.69 (0.51, 0.99)	Not engaging in MVPA	Engaging in MVPA at least 4 times per week	Alcohol intake, family history of cancer, fruit and vegetable intake, obesity (BMI), smoking	58
The bold RR relativ	risk estimates e risk, <i>CI</i> con	(N = 30) fidence int	represen erval, PA	nt those risk estimates. A physical activity, MV	included in the ri <i>PA</i> moderate to v	igorous sub-an /igorous physic	alysis allowing just one estin cal activity, VPA vigorous ph	nate per study and gender ysical activity, MET metaboli	c equivalent of task, BMI body mass in	ndex, SES
SOCIO-eCO	nomic status									

relations to gastric non-cardia adenocarcinoma (RR = 0.72). 95 % CI = 0.62-0.84), gastric cardia adenocarcinoma (RR = 0.83, 95 % CI = 0.69-0.99), and esophageal adenocarcinoma (RR = 0.79, 95 % CI = 0.66-0.94). No statistically significant association was observed for esophageal squamous cell carcinoma (RR = 0.94,95 % CI = 0.41-2.16). No overall differences in the relations of physical activity to esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma were observed (pdifference = 0.71). Similarly, comparing the relation of physical activity to esophageal adenocarcinoma with that to esophageal squamous cell carcinoma (p-difference = 0.61) and comparing the relation of physical activity to gastric noncardia adenocarcinoma with that to gastric cardia adenocarcinoma (p-difference = 0.26) revealed no statistically significant differences.

Combining all 61 risk estimates in a random effects model, we observed a statistically significant 18 % reduction in gastroesophageal cancer risk when comparing high versus low levels of physical activity (RR = 0.82, 95 % CI = 0.74–0.90). A funnel plot (supplementary Figure S1), Begg's test (p = 0.95), and Egger's test (p = 0.19) suggested no publication bias. The funnel plot, though, identified one extreme risk estimate [28]. We detected statistically significant heterogeneity between studies ($I^2 = 76$ %, p-heterogeneity < 0.001).

Stratified analyses

The relation of physical activity to gastroesophageal cancer was statistically significantly inverse in case–control studies (RR = 0.77, 95 % CI = 0.67–0.89), whereas it was statistically non-significant in cohort studies (RR = 0.89, 95 % CI = 0.78–1.01; *p*-difference = 0.18, Fig. 2).

A direct comparison between women and men revealed a stronger inverse association between physical activity and gastroesophageal cancer in women (RR = 0.60, 95 % CI = 0.48–0.73) than men (RR = 0.87, 95 % CI = 0.77–0.98; *p*-difference = 0.01) (Fig. 3), but modelling the effect of gender did not materially attenuate between-study heterogeneity ($I^2 = 72$ %, *p*-heterogeneity < 0.001). In contrast, no statistically significant differences in relations were observed for study quality score, study geographic region, physical activity domain, timing in life of physical activity, physical activity assessment, and adjustments for smoking, adiposity, or alcohol intake (all *p*-difference > 0.05) (Table 2).

In sub-analyses of total esophageal cancer (supplementary Table S1), the relations of distant past physical activity (RR = 0.53, 95 % CI = 0.42–0.67) and consistent physical activity over time (RR = 0.68, 95 % CI = 0.51–0.91) were statistically significant inverse, while that of recent

past physical activity was not (RR = 1.01, 95 % CI = 0.70-1.47; *p*-difference = 0.04).

Sub-analyses examining the relation of physical activity to total gastric cancer (supplementary Table S2) revealed that the inverse association was statistically significant in case–control studies (RR = 0.77, 95 % CI = 0.72–0.82) but not in cohort studies (RR = 0.90, 95 % CI = 0.76–1.06; *p*-difference = 0.04). Similarly, the inverse association of physical activity to gastric cancer was statistically non-significant in men (RR = 0.95, 95 % CI = 0.84–1.08) but it was statistically significant in women (RR = 0.64, 95 % CI = 0.50–0.84; *p*-difference = 0.02).

Sensitivity analyses

In a sensitivity analysis, we generated a summary risk estimate that included only one risk estimate per study and gender, using the risk estimate with the highest quality score for the gastroesophageal cancer endpoint with the largest number of cases. The 30 selected risk estimates are printed in bold in Table 1. We found no difference between that summary risk estimate (RR = 0.82, 95 % CI = 0.70–0.95) and our summary risk estimate from the main analysis (RR = 0.82, 95 % CI = 0.74–0.90; *p*-difference = 0.96).

We tested for influential studies by removing one study at a time from the meta-analysis and observed no material differences in the summary risk estimates for total gastroesophageal cancer, for total esophageal cancer or for total gastric cancer. Similarly, we observed no material changes in the modifying effects of study design and gender on the physical activity and gastroesophageal cancer relation. After excluding the study by Dar et al. [28] from the main analysis, the previously observed between-study heterogeneity was attenuated $(I^2 = 51 \%, p$ -heterogenesubstantially ity < 0.001) and the inverse association between physical activity and esophageal squamous cell carcinoma became statistically significant (RR = 0.66, 95 % CI = 0.46-0.96). After additionally including terms for study design and gender in the model, the heterogeneity between studies was no longer apparent ($I^2 = 0 \%$, *p*-heterogeneity = 0.08).

We identified four studies [23, 24, 32, 34] of recreational physical activity and gastroesophageal cancer whose exposure and reference levels could be considered comparable. Those studies compared participants engaging in 2 h per week or more of recreational physical activity with those not regularly engaging in recreational physical activity. The summary risk estimate combining those studies (RR = 0.79, 95 % CI = 0.69–0.91) did not statistically significantly differ from the risk estimate that was based on all studies of recreational physical activity (RR = 0.78, 95 % CI = 0.72–0.85; *p*-difference = 0.97) or from the risk estimate from our main analysis (RR = 0.82, 95 % CI = 0.74–0.90; *p*-difference = 0.80).

Authors, year, physical activity domain, gender RR (95% CI) Esophageal cance Esophageal squamous cell carcinoma Etemadi et al., 2012, occupational activity, women 0.30 (0.12, 0.77) Etemadi et al., 2012, occupational activity, men Ibiebele et al., 2012, recreational activity, men and women 0.53 (0.26, 1.11) 0.65 (0.47, 0.91) Jessri et al., 2011, total activity, men and women 0.93 (0.25, 0.96) Leitzmann et al., 2009, recreational activity, men and won 1.05 (0.64, 1.74) Dar et al., 2013, occupational activity, men and women 5.65 (3.49, 9.12) Random effects model for esophageal squamous cell carcinoma 0.94 (0.41, 2.16) Esophageal adenocarcinoma Vigen et al., 2006, occupational activity, women Huerta et al., 2010, recreational activity, men and women 0.35 (0.04, 3.15) 0.72 (0.36, 1.42) Leitzmann et al., 2009, recreational activity, men and women 0.75 (0.53, 1.06) Vigen et al., 2006, occupational activity, men 0.77 (0.54, 1.08) 0.81 (0.58, 1.12) Ibiebele et al., 2012, recreational activity, men and women 0.95 (0.41, 2.20) 0.98 (0.48, 2.01) Huerta et al., 2010, occupational activity, men and women Huerta et al., 2010, total activity, men and women Random effects model for esophageal adenocarcinoma 0.79 (0.66, 0.94) Esophageal cancer, type unspecified Wannamethee et al., 2001, recreational activity, men Lam et al., 2004, recreational activity, women 0.46 (0.11 1.90) 0.52 (0.28, 0.97) Parent et al., 2011, recreational activity, men 0.54 (0.30, 0.97) Parent et al., 2011, total activity, men Lam et al., 2004, recreational activity, men 0.54 (0.31, 0.93) 0.57 (0.41, 0.80) Parent et al., 2011, occupational activity, men Yun et al., 2008, recreational activity, men 0.66 (0.23, 1.88) 0.84 (0.66, 1.06) Brownson et al., 1991, occupational activity, men 1.43 (0.71, 3.33) Random effects model for esophageal cancer, type unspecified 0.67 (0.53, 0.85) Random effects model for total esophageal cancer 0.79 (0.60, 1.02) Esophago-gastric junction adenocarcinoma 0.92 (0.67, 1.26) Ibiebele et al., 2012, recreational activity, men and women Gastric cancer Gastric cardia adenocarcinoma Vigen et al., 2006, occupational activity, women 0.30 (0.07, 1.40) Campbell et al., 2007, Ontario sample, recreational activity, men and women Huerta et al., 2010, occupational activity, men and women 0.60 (0.34, 1.07) 0.70 (0.33, 1.48) Vigen et al., 2006, occupational activity, men 0.81 (0.58, 1.11) Leitzmann et al., 2009, recreational activity, men and women 0.83 (0.58, 1.19) 1.05 (0.59, 1.86) Huerta et al., 2010, total activity, men and women Huerta et al., 2010, recreational activity, men and women Random effects model for gastric cardia adenocarcinoma 1.14 (0.68, 1.91) 0.83 (0.69, 0.99) Gastric non-cardia adenocarcinoma Huerta et al., 2010, total activity, men and women 0.44 (0.26, 0.74) Leitzmann et al., 2009, recreational activity, men and women Sjödahl et al., 2008, recreational activity, men and women 0.62 (0.44, 0.87) 0.70 (0.50, 1.00) Campbell et al., 2007. Ontario sample, recreational activity, men and women 0.73 (0.50, 1.07) 0.77 (0.55, 1.07) 0.82 (0.44, 1.52) Vigen et al., 2006, occupational activity, men Huerta et al., 2010, occupational activity, men and women Huerta et al., 2010, recreational activity, men and women Vigen et al., 2006, occupational activity, women 0.98 (0.60, 1.60) 1.07 (0.59, 1.91) Random effects model for gastric non-cardia adenocarcinoma 0.72 (0.62, 0.84) Gastric adenocarcinoma, subsite unspecified Suwanrungruang et al., 2008, occupational activity, men and women 0.52 (0.23, 1.17) 0.57 (0.41, 0.78) 0.60 (0.14, 2.47) Lam et al., 2004, recreational activity, women Wannamethee et al., 2001, recreational activity, mer Inoue et al., 2008, total activity, women Batty et al., 2010, recreational activity, mer 0.63 (0.42, 0.94) 0.65 (0.38, 1.14) Campbell et al., 2007, non-Ontario sample, recreational activity, men and women Parent et al., 2011, occupational activity, men 0.67 (0.53, 0.86) 0.68 (0.35, 1.32) 0.69 (0.51, 0.99) Wen et al., 2010, recreational activity, men and womer 0.70 (0.33, 1.33) 0.71 (0.45, 1.11) Suwanrungruang et al., 2008, recreational activity, men and womer Brownson et al., 1991, occupational activity, men Huang et al., 2004, family history of gastric cancer, recreational activity, men and women Lam et al., 2004, recreational activity, men 0.71 (0.57, 0.89) 0.76 (0.60, 0.96) Huang et al., 2004, no family history of gastric cancer, recreational activity, men and women 0.79 (0.70, 0.89) Dosemeci et al., 1993, occupational activity, men 0.91 (0.59, 1.67) Yun et al., 2008, recreational activity, men 0.91 (0.86, 0.98) Parent et al., 2011, total activity, men Watabe et al., 1998, recreational activity, men and women 0.93 (0.67, 1.31) 0.94 (0.68, 1.32) Boccia et al., 2005, recreational activity, men and women Inoue et al., 2008, total activity, men 0.97 (0.45, 2.09) 1.04 (0.84, 1.29) Paffenbarger et al., 1987, recreational activity, men 1.05 (0.50, 2.21) Parent et al., 2011, recreational activity, mer Severson et al., 1989, total activity, men 1.09 (0.76, 1.54) 1.34 (0.92, 1.95) Severson et al., 1989, recreational activity, men Severson et al., 1989, occupational activity, men 1.45 (1.07, 1.97) 1.74 (1.08, 2.81) Random effects model for gastric adenocarcinoma, subsite unspecified 0.86 (0.76, 0.96) Random effects model for total gastric cancer 0.82 (0.76, 0.90) Random effects model for total gastroesophageal cancer 0.82 (0.74, 0.90) 0.1 0.5 1.0 2.0 10.0 Relative risk (log scale)

Fig. 1 Forest plot of a random effects meta-analysis including 61 risk estimates of gastroesophageal cancer for a high versus low level of physical activity, grouped by anatomic site and histologic type. *RR* relative risk, *CI* confidence interval

Authors, year, cancer site and type, physical activity domain, gender

RR (95% CI)

Cohort studies	
Huerta et al., 2010, GNCA, total activity, men and women	
Wannamethee et al., 2001, EC, type unspecified, recreational activity, men	0.46 (0.11, 1.90)
Wannamethee et al., 2001, GA, subsite unspecified, recreational activity, men	0.60 (0.14, 2.47)
Leitzmann et al., 2009, GNCA, recreational activity, men and women	0.62 (0.44, 0.87)
Inoue et al., 2008, GA, subsite unspecified, total activity, women	0.63 (0.42, 0.94)
Batty et al., 2010, GA, subsite unspecified, recreational activity, men	0.65 (0.38, 1.14)
Huerta et al., 2010, GCA, occupational activity, men and women	0.70 (0.33, 1.48)
Sjödahl et al., 2008, GNCA, recreational activity, men and women	0.70 (0.50, 1.00)
Huerta et al., 2010, EA, recreational activity, men and women	0.72 (0.36, 1.42)
Leitzmann et al., 2009, EA, recreational activity, men and women	0.75 (0.53, 1.06)
Huerta et al., 2010, GNCA, occupational activity, men and women	0.82 (0.44, 1.52)
Leitzmann et al., 2009, GCA, recreational activity, men and women	
Yun et al., 2008, EC, type unspecified, recreational activity, men	
Huerta et al., 2010, EA, occupational activity, men and women	0.95 (0.41, 2.20)
Huerta et al., 2010, GNCA, recreational activity, men and women	0.98 (0.60, 1.60)
Huerta et al., 2010, EA, total activity, men and women	0.98 (0.48, 2.01)
Inoue et al., 2008, GA, subsite unspecified, total activity, men	1.04 (0.84, 1.29)
Huerta et al., 2010, GCA, total activity, men and women	1.05 (0.59, 1.86)
Leitzmann et al., 2009, ESCC, recreational activity, men and women	1.05 (0.64, 1.74)
Paffenbarger et al., 1987, GA, subsite unspecified, recreational activity, men	1.05 (0.50, 2.21)
Huerta et al., 2010, GCA, recreational activity, men and women	1.14 (0.68, 1.91)
Severson et al., 1989, GA, subsite unspecified, total activity, men	1.34 (0.92, 1.95)
Severson et al., 1989, GA, subsite unspecified, recreational activity, men	1.45 (1.07, 1.97)
Severson et al., 1989, GA, subsite unspecified, occupational activity, men	1.74 (1.08, 2.81)
Random effects model for RRs from cohort studies	• 0.89 (0.78, 1.01)
Case-control studies	
Etemadi et al., 2012, ESCC, occupational activity, women	0.30 (0.12, 0.77)
Vigen et al., 2006, GCA, occupational activity, women	0.30 (0.07, 1.40)
Vigen et al., 2006, EA, occupational activity, women	0.35 (0.04, 3.15)
Lam et al., 2004, EC, type unspecified, recreational activity, women	0.52 (0.28, 0.97)
Suwanrungruang et al., 2008, GA, subsite unspecified, occupational activity, men and worr	nen 0.52 (0.23, 1.17)
Etemadi et al., 2012, ESCC, occupational activity, men	
Parent et al., 2011, EC, type unspecified, total activity, men	
Lam et al. 2004. EC, type unspecified, recreational activity, men	
Lam et al., 2004, GA, subsite unspecified, recreational activity, men	0.57 (0.41, 0.38)
Campbell et al., 2007, Ontario sample, GCA, recreational activity, men and women	0.60 (0.34, 1.07)
Ibiebele et al., 2012, ESCC, recreational activity, men and women	0.65 (0.47, 0.91)
Parent et al., 2011, EC, type unspecified, occupational activity, men	0.66 (0.23, 1.88)
Campbell et al., 2007, non-Ontario sample, GA, subsite unspecified, recreational activity, r	men and women - 0.67 (0.53, 0.86)
Parent et al., 2011, GA, subsite unspecified, occupational activity, men	0.68 (0.35, 1.32)
Wen et al., 2010, GA, subsite unspecified, recreational activity, men and women	0.69 (0.51, 0.99)
Suwanrungruang et al., 2008, GA, subsite unspecified, recreational activity, men and wom	en 0.70 (0.33, 1.33)
Brownson et al., 1991, GA, subsite unspecified, occupational activity, men	0.71 (0.45, 1.11)
Huang et al., 2004, family history of gastric cancer, GA, subsite unspecified, recreational a	ctivity, men and women - 0.71 (0.57, 0.89)
Campbell et al., 2007, Ontario sample, GNCA, recreational activity, men and women	0.73 (0.50, 1.07)
Lam et al., 2004, GA, subsite unspecified, recreational activity, men	
Vigen et al., 2006, EA, occupational activity, men	0.77 (0.54, 1.08)
Huang et al. 2000, GNOA, occupational activity, men	0.77 (0.35, 1.07)
Initiality et al., 2004, no family instory of gastric cancer, GA, subside unspecified, recreational	a activity, men and women F
Vigen et al. 2006 GCA occupational activity men	
Dosemeci et al., 1993, GA, subsite unspecified, occupational activity, men	0.91 (0.59, 1.67)
Ibiebele et al., 2012, EGJA, recreational activity, men and women	0.92 (0.67, 1.26)
Jessri et al., 2011, ESCC, total activity, men and women	0.93 (0.25, 0.96)
Parent et al., 2011, GA, subsite unspecified, total activity, men	0.93 (0.67, 1.31)
Watabe et al., 1998, GA, subsite unspecified, recreational activity, men and women	0.94 (0.68, 1.32)
Boccia et al., 2005, GA, subsite unspecified, recreational activity, men and women	0.97 (0.45, 2.09)
Vigen et al., 2006, GNCA, occupational activity, women	1.07 (0.59, 1.91)
Parent et al., 2011, GA, subsite unspecified, recreational activity, men	1.09 (0.76, 1.54)
Brownson et al., 1991, EC, type unspecified, occupational activity, men	1.43 (0.71, 3.33)
Dar et al., 2013, ESCC, occupational activity, men and women	5.65 (3.49, 9.12)
Random effects model for RRs from case-control studies	• 0.77 (0.67, 0.89)
	;
C	0.1 0.5 1.0 2.0 10.0
	Relative risk (log scale)



Fig. 2 Forest plot of a random effects meta-analysis including 61 risk estimates of total gastroesophageal cancer for a high versus low level of physical activity, grouped by study design. *RR* relative risk, *CI* confidence interval, *ESCC* esophageal squamous cell carcinoma, *EA*

RR (95% CI)

	•	
Men	i i i	
Wannamethee et al., 2001, EC, type unspecified, recreational activity		46 (0.11, 1.90
Etemadi et al., 2012, ESCC, occupational activity	0.	53 (0.26, 1.11
Parent et al., 2011, EC, type unspecified, recreational activity		54 (0.30, 0.97
Parent et al., 2011, EC, type unspecified, total activity		54 (0.31, 0.93
Lam et al., 2004, EC, type unspecified, recreational activity	0.	57 (0.41, 0.80
Wannamethee et al., 2001, GA, subsite unspecified, recreational activity	0.	60 (0.14, 2.47
Batty et al., 2010, GA, subsite unspecified, recreational activity	⊢ −− <u>−</u>	65 (0.38, 1.14
Parent et al., 2011, EC, type unspecified, occupational activity		66 (0.23, 1.88
Parent et al., 2011, GA, subsite unspecified, occupational activity	⊢ − − − − − − − − − −	68 (0.35, 1.32
Brownson et al., 1991, GA, subsite unspecified, occupational activity	⊢ = <u>−</u> − − − − − − − − − − − − − − − − − −	71 (0.45, 1.11
Lam et al., 2004, GA, subsite unspecified, recreational activity	⊢ ↓; 0.	76 (0.60, 0.96
Vigen et al., 2006, EA, occupational activity	<u>⊢ - :</u> 0.	77 (0.54, 1.08
Vigen et al., 2006, GNCA, occupational activity		77 (0.55, 1.07
Vigen et al., 2006, GCA, occupational activity	⊢−−−−	81 (0.58, 1.11
Yun et al., 2008, EC, type unspecified, recreational activity	⊢ ; 0.	34 (0.66, 1.06
Dosemeci et al., 1993, GA, subsite unspecified, occupational activity	0.	91 (0.59, 1.67
Yun et al., 2008, GA, subsite unspecified, recreational activity	. 0.	91 (0.86, 0.98
Parent et al., 2011, GA, subsite unspecified, total activity	<u>⊢_</u> , 0.	93 (0.67, 1.31
Inoue et al., 2008, GA, subsite unspecified, total activity	1.	04 (0.84, 1.29
Paffenbarger et al., 1987, GA, subsite unspecified, recreational activity	<u>⊢</u>	05 (0.50, 2.21
Parent et al., 2011, GA, subsite unspecified, recreational activity	· · · · · · · · · · · · · · · · · · ·	09 (0.76, 1.54
Severson et al., 1989, GA, subsite unspecified, total activity	1.	34 (0.92, 1.95
Brownson et al., 1991, EC, type unspecified, occupational activity	1.	43 (0.71, 3.33
Severson et al., 1989, GA, subsite unspecified, recreational activity	· · · · · · · · · · · · · · · · · · ·	45 (1.07, 1.97
Severson et al., 1989. GA, subsite unspecified, occupational activity		74 (1.08, 2.81
Den dem effecte medel fer DDe from studies errors men		(0.77.0.00
Random enects model for RRs from studies among men	0.87	(0.77, 0.90
Women		
Etemadi et al. 2012 ESCC occupational activity		30 (0 12 0 77
Vigen et al. 2006 GCA occupational activity		30 (0.07, 1.40
Vigen et al. 2006 EA occupational activity		35 (0.04, 3.15
Lam et al. 2004 EC type unspecified recreational activity		52 (0.28, 0.97
Lam et al. 2004, GA subsite unspecified, recreational activity		57 (0.41 0.78
Inoue et al. 2008. GA subsite unspecified total activity		33 (0.42 0.04
Vigen et al. 2006 GNCA occupational activity		17 (0 50 1 01
Pendem effects model for PBs from studies among women		(0.00, 1.01
Random effects model for RHS from studies among women	- : 0.60	(0.48, 0.73
	•	
Men and women		
Men and women		14 (0 26 0 74
Men and women Huerta et al., 2010, GNCA, total activity Suwannungruang et al. 2008, GA subsite unspecified, occupational activity		44 (0.26, 0.74 52 (0.23, 1.17
Men and women Huerta et al., 2010, GNCA, total activity Suwanrungruang et al., 2008, GA, subsite unspecified, occupational activity Camphelle et al. 2007. Ontario sample GCA recreational activity		44 (0.26, 0.74 52 (0.23, 1.17 50 (0.34 1.07
Men and women Huerta et al., 2010, GNCA, total activity Suwanrungruang et al., 2008, GA, subsite unspecified, occupational activity Campbell et al., 2007, Ontario sample, GCA, recreational activity Laitzmann et al. 2009, GNCA recreational activity		44 (0.26, 0.74 52 (0.23, 1.17 50 (0.34, 1.07
Men and women Huerta et al., 2010, GNCA, total activity Suwanrungruang et al., 2008, GA, subsite unspecified, occupational activity Campbell et al., 2007, Ontario sample, GCA, recreational activity Leizmann et al., 2009, GNCA, recreational activity Ibidele et al., 2012, ESCC, recreational activity		44 (0.26, 0.74 52 (0.23, 1.17 50 (0.34, 1.07 52 (0.44, 0.87
Men and women Huerta et al., 2010, GNCA, total activity Suwanrungruang et al., 2008, GA, subsite unspecified, occupational activity Campbell et al., 2007, Ontario sample, GCA, recreational activity Leitzmann et al., 2009, GNCA, recreational activity Ibiebele et al., 2012, ESCC, recreational activity Compbell et al., 2007, on Outrigo composed for uppercified, recreational activity		44 (0.26, 0.74 52 (0.23, 1.17 50 (0.34, 1.07 52 (0.44, 0.87 55 (0.47, 0.91
Men and women Huerta et al., 2010, GNCA, total activity Suwanrungruang et al., 2008, GA, subsite unspecified, occupational activity Campbell et al., 2007, Ontario sample, GCA, recreational activity Leitzmann et al., 2009, GNCA, recreational activity Ibiebele et al., 2012, ESCC, recreational activity Campbell et al., 2010, non-Ontario sample, GA, subsite unspecified, recreational activity Mono tel. al. 2010, GA, united unspecified recreational activity		44 (0.26, 0.74 52 (0.23, 1.17 60 (0.34, 1.07 52 (0.44, 0.87 55 (0.47, 0.91 57 (0.53, 0.86
Men and women Huerta et al., 2010, GNCA, total activity Suwanrungruang et al., 2008, GA, subsite unspecified, occupational activity Campbell et al., 2007, Ontario sample, GCA, recreational activity Leitzmann et al., 2009, GNCA, recreational activity Ibibebel et al., 2012, ESCC, recreational activity Campbell et al., 2007, non–Ontario sample, GA, subsite unspecified, recreational activity Wen et al., 2010, GCA, seupraticnal Activity Wurdt et al., 2010, GCA, exemptional Activity		44 (0.26, 0.74 52 (0.23, 1.17 50 (0.34, 1.07 52 (0.44, 0.87 55 (0.47, 0.91 57 (0.53, 0.86 59 (0.51, 0.99 70 (0.22, 1.48
Men and women Huerta et al., 2010, GNCA, total activity Suwanrungruang et al., 2008, GA, subsite unspecified, occupational activity Campbell et al., 2007, Ontario sample, GCA, recreational activity Leitzmann et al., 2009, GNCA, recreational activity Ibiebele et al., 2012, ESCC, recreational activity Campbell et al., 2007, non–Ontario sample, GA, subsite unspecified, recreational activity Wen et al., 2010, GA, subsite unspecified, recreational activity Huerta et al., 2010, GCA, occupational activity Campbell et al., 2007, Onc-Ontario sample, GA, subsite unspecified, recreational activity Huerta et al., 2010, GCA, occupational activity		44 (0.26, 0.74 52 (0.23, 1.17 50 (0.34, 1.07 52 (0.44, 0.87 55 (0.47, 0.91 57 (0.53, 0.86 59 (0.51, 0.99 70 (0.33, 1.48
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Fig. 3 Forest plot of a random effects meta-analysis including 61 risk estimates of total gastroesophageal cancer for a high versus low level of physical activity, grouped by gender. *RR* relative risk, *CI GA* gastr

confidence interval, ESCC esophageal squamous cell carcinoma, EA

esophageal adenocarcinoma, *EC* esophageal cancer, *GCA* gastric cardia adenocarcinoma, *GNCA* gastric non-cardia adenocarcinoma, *GA* gastric adenocarcinoma

Table 2 Random effects summary estimates of total gastroesophageal cancer risk for a high versus low level of physical activity by selected study characteristics

Table 2 continued

Stratification criterion	Number of included RRs	RR ^a (95 % CI)	<i>p</i> -difference
Physical activity assessment			
Assessment of energy expenditure	10	0.91 (0.86, 0.96)	
Assessment of activity duration	4	0.98 (0.74, 1.32)	
Assessment of activity frequency	19	0.74 (0.69, 0.80)	
Qualitative physical activity assessment	28	0.85 (0.68, 1.05)	0.33
Adjustment for smoking			
Adjusted for smoking	51	0.82 (0.73, 0.92)	
Not adjusted for smoking	10	0.79 (0.72, 0.86)	0.78
Adjustment for adiposity			
Adjusted for adiposity	43	0.82 (0.74, 0.90)	
Not adjusted for adiposity	18	0.85 (0.67, 1.08)	0.67
Adjustment for alcohol intake			
Adjusted for alcohol intake	32	0.81 (0.69, 0.94)	
Not adjusted for alcohol intake	29	0.83 (0.74, 0.93)	0.87

RR relative risk, CI confidence interval, MVPA moderate to vigorous physical activity

^a RR comparing highest versus lowest physical activity level

^b The *p*-difference values were obtained using meta-regression comparing the model including the stratification variable as explanatory variable with the null model not including any explanatory variables

^c Comparing risk estimates of total esophageal cancer with risk estimates of total gastric cancer disregarding risk estimates of esophago-gastric junction adenocarcinoma

^d Comparing risk estimates of esophageal squamous cell carcinoma with risk estimates of esophageal adenocarcinoma and disregarding risk estimates of esophageal cancers with unspecified histologic type

^e Comparing risk estimates of gastric cardia adenocarcinoma with risk estimates of gastric non-cardia adenocarcinoma and disregarding risk estimates of gastric adenocarcinoma with unspecified anatomic subsite

^f The quality score ranged from 42 to 79 percentage points (out of 100 percentage points), with lower and upper tertile cut-offs of 58 percentage points and 70 percentage points, respectively

^g Comparing risk estimates of men with risk estimates of women and disregarding risk estimates of men and women combined

^h Comparing risk estimates of recreational activity with risk estimates of occupational activity and disregarding risk estimates of total activity

When we excluded two studies on gastroesophageal cancer mortality [17, 33] and three studies using fatal and non-fatal gastroesophageal cancers as a combined endpoint [26, 31, 36], we obtained a summary risk estimate of RR = 0.83 (95 % CI = 0.77–0.89), which was comparable to that of the main analysis (*p*-difference = 0.62).

Dose-response meta-analysis

We conducted a random-effects dose-response meta-analysis to further explore the relation between frequency of moderate

Stratification criterion	Number of included	RR ^a (95 % CI)	<i>p</i> -difference ^b
	RRs		
Fotal gastroesophageal cancer risk	61	0.82 (0.74, 0.90)	
Cancer major anatomic site			
Esophageal cancer	21	0.79 (0.60, 1.02)	
Esophago-gastric junction adenocarcinoma	1	0.92 (0.67, 1.26)	
Gastric cancer	39	0.82 (0.76, 0.90)	0.92 ^c
Cancer anatomic subsite and h	istologic ty	pe	
Esophageal squamous cell carcinoma	6	0.94 (0.41, 2.16)	
Esophageal adenocarcinoma	7	0.79 (0.66, 0.94)	0.61 ^d
Esophageal cancer, type unspecified	8	0.67 (0.53, 0.85)	
Esophago-gastric junction adenocarcinoma	1	0.92 (0.67, 1.26)	
Gastric cardia adenocarcinoma	7	0.83 (0.69, 0.99)	
Gastric non-cardia adenocarcinoma	8	0.72 (0.62, 0.84)	0.26 ^e
Gastric adenocarcinoma, subsite unspecified	24	0.86 (0.76, 0.96)	
Study design			
Cohort	25	0.89 (0.78, 1.01)	
Case-control	36	0.77 (0.67, 0.89)	0.18
Study quality score ^f			
Upper tertile of quality score	19	0.81 (0.71, 0.92)	
Intermediate tertile of quality score	19	0.90 (0.70, 1.16)	
Lower tertile of quality score <i>Gender</i>	23	0.77 (0.72, 0.82)	0.32
Men	25	0.87 (0.77, 0.98)	
Women	7	0.60 (0.48, 0.73)	0.01 ^g
Men and women	29	0.83 (0.71, 0.97)	
Study geographic region			
North America	25	0.85 (0.75, 0.97)	
Europe	15	0.80 (0.68, 0.93)	
Australia	3	0.79 (0.64, 0.96)	
Middle East	3	0.48 (0.29, 0.81)	
Asia	15	0.82 (0.63, 1.08)	0.58
Physical activity domain			
Total activity	9	0.84 (0.65, 1.08)	
Recreational activity	33	0.78 (0.72, 0.85)	
Occupational activity	19	0.86 (0.64, 1.16)	0.19 ^h
Timing in life of physical activ	ity		
Recent past physical activity	40	0.88 (0.78, 1.00)	
Distant past physical activity	9	0.66 (0.53, 0.82)	
Consistent physical activity over time	12	0.77 (0.67, 0.88)	0.06

to vigorous physical activity and gastroesophageal cancer (Fig. 4). The best fitting dose–response model was given by

$$RR = \exp(a_1 dose^2 + a_2 dose^3)$$

where $a_1 = -0.051$, $a_2 = 0.007$, $var(a_1) = 1 \times 10^{-4}$, $cov(a_1, a_2) = -2 \times 10^{-5}$, and $var(a_2) = 3 \times 10^{-6}$, and no heterogeneity between studies was observed ($I^2 = 8$ %, *p*heterogeneity = 0.36). The J-shaped dose-response relation indicated that a maximal reduction in gastroesophageal cancer risk of 33 % was attained by engaging in moderate to vigorous physical activity at a frequency of five times per week (RR = 0.67, 95 % CI = 0.58-0.79) as compared to not engaging in moderate or vigorous physical activity.

Discussion

We conducted a random effects meta-analysis of physical activity in relation to gastroesophageal cancer and found that high versus low physical activity was associated with risk decreases of 17–28 % for esophageal adenocarcinoma, gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma, whereas no relation was detected for esophageal squamous cell carcinoma. However, apparent differences in risk across tumor subtypes were not statistically significant. When combining gastroesophageal cancer subsites, we observed a statistically significant 18 % reduction in total gastroesophageal cancer risk with high versus low levels of physical activity. Our dose–response meta-analysis showed that the greatest risk reduction of 33 % was achieved by engaging in moderate to vigorous activity at a frequency of five times per week.

We initially observed substantial between-study heterogeneity, which was no longer apparent after removing an influential study [28] and additionally including terms for study design and gender in the model. The authors of that influential, large hospital-based case–control study from Kashmir, India [28] compared high versus low levels of occupational physical activity and reported an odds ratio of 5.65 (95 % CI = 3.49–9.12) for esophageal squamous cell carcinoma but speculated about the possibility of residual confounding by socioeconomic status. After excluding that study [28], we found that physical activity was related to a substantial risk reduction of 34 % for esophageal squamous cell carcinoma.

Numerous biologic mechanisms potentially mediate the observed inverse association between physical activity and gastroesophageal cancer. For example, chronic inflammatory processes, such as *Helicobacter pylori* infection [56], gastroesophageal reflux [57], Barrett's esophagus [58], obesity [14] and type 2 diabetes mellitus [15, 16] support gastroesophageal carcinogenesis, while factors that reduce chronic inflammation, such as regular aspirin use [59, 60]



Fig. 4 Dose-response analysis of frequency of moderate to vigorous physical activity in relation to total gastroesophageal cancer

and dietary fiber intake [10, 11] are associated with reduced gastroesophageal cancer risk. In a similar vein, physical activity may inhibit gastroesophageal carcinogenesis by reducing chronic inflammation [61] and alleviating metabolic disorders associated both with chronic inflammation and gastroesophageal cancer, such as insulin resistance [62] and elevated insulin-like growth factor 1 levels [63, 64]. Physical activity may also prevent gastroesophageal carcinogenesis by decreasing oxidative stress [65] and improving DNA repair [66].

The observed consistency in risk reduction with physical activity across gastroesophageal cancer subtypes suggests that physical activity represents a shared protective factor for these cancers. That gastroesophageal cancers show common risk factors despite distinct etiologies is supported by observations of quite similar risk increases across gastroesophageal cancer subtypes of 7–16 % for each increment of 10 pack-years of smoking [67] and risk decreases of about 35–45 % for regular aspirin use [59, 60] and intakes of dietary fiber [10, 11]. Also, exposure to alcohol intake [8, 9, 68] and pickled foods [69, 70] has been positively related to all gastroesophageal cancer subtypes.

We examined whether obesity mediated the inverse relation of physical activity to risk of gastroesophageal cancer by comparing risk estimates that were adjusted for adiposity with those that were not. We noted that the inverse association between physical activity and gastroesophageal cancer was only modestly attenuated when the meta-analysis was restricted to datasets that were adjusted for adiposity. This suggests that the biologic mechanisms by which physical activity decreases risk for gastroesophageal cancer are only partly mediated through its effects on weight control. That the etiologic pathways linking increased physical activity to decreased risk of gastroesophageal cancer are distinct from those associated with weight control is supported by widely divergent associations between obesity and gastroesophageal cancer histologic types. Notably, obesity shows an approximate 30–50 % reduced risk for esophageal squamous cell carcinoma [71], whereas it exhibits a substantial increased risk for esophageal and gastric cardia adenocarcinomas in the order of 100 % [14].

The inverse association between physical activity and gastroesophageal cancer was more pronounced in case– control studies than cohort studies. Possible explanations for this particular constellation of findings are preferential selection of physically active controls, physical activity under-reporting among cases, or superior physical activity assessment in case–control studies than cohort studies. The gastroesophageal cancer risk reduction of 11 % with high versus low physical activity obtained from cohort studies likely represents the more conservative risk estimate than the 23 % risk reduction generated by case–control studies.

We observed a stronger inverse association between physical activity and gastroesophageal cancer in women than men. The modifying effect of gender was statistically significant for total gastroesophageal cancer and for total gastric cancer but not for total esophageal cancer, for which case numbers were limited. Apart from chance, one possible explanation for this finding is inhibitory effects of estrogen on gastroesophageal cancer growth [72, 73]. Support for a protective role of circulating estrogen levels also comes from observational studies showing an inverse association between hormone replacement therapy and gastroesophageal cancer [74].

We noted that distant past physical activity and consistent physical activity over time showed stronger inverse relations with total esophageal cancer than recent past physical activity. Other than chance, one possible explanation for this observation is that distant past or long-term consistent physical activity may better capture the relation of physical activity to gastroesophageal cancer, if one exists. Future studies should confirm whether distant past or consistent physical activity has greater potential for esophageal cancer prevention than recent past physical activity.

One potential limitation of the present meta-analysis is that a causal relation for the observed inverse association between physical activity and gastroesophageal cancer could not be established because no intervention study was available for inclusion. In addition, the investigation of the relation of physical activity to gastroesophageal cancer by anatomic subsite and histologic type was limited because only nine [18, 20, 21, 23–25, 28, 29, 38] of the 24 studies provided relevant data on cancer anatomic subsite and histologic type. Information on esophageal squamous cell carcinoma was provided by only five studies [18, 20, 21, 24, 28], which may partly explain the observed statistically non-significant inverse association with physical activity in the main analysis. Furthermore, we lacked sufficient information to assess whether the relation of physical activity to gastric cancer was modified by *H. pylori* infection status. One previous study [23] found no effect modification of the association between physical activity and gastric cancer by *H. pylori* infection status.

This first meta-analysis of physical activity and gastroesophageal cancer also has a number of important strengths. We included a large number of studies, which yielded a substantial number of cases and enabled us to evaluate different subtypes of gastroesophageal cancers according to anatomic site and tumor histologic type. We used standardized criteria for identifying pertinent studies and abstracting key information. Our meta-analysis differs from a previous meta-analysis of physical activity and gastric cancer [75] in that we (1) included five additional gastric cancer studies with 1,054 additional cases of gastric cancer [17, 33, 36, 39, 40]; (2) examined physical activity in relation to esophageal cancer and assessed differences according to gastroesophageal cancer histologic types; (3) generated a quantitative physical activity recommendation for the primary prevention of gastroesophageal cancers based on an exploratory dose-response meta-analysis; (4) used random effects meta-regression to identify and remove the sources of between-study heterogeneity in the published data; (5) explored for potential differences between studies of gastroesophageal cancer incidence and those of gastroesophageal cancer mortality; and (6) summarized risk estimates using comparable exposure and reference categories in a sensitivity analysis, thereby confirming the robustness of our primary findings.

In conclusion, our comprehensive meta-analysis provides support for an inverse relation of physical activity to risk of gastroesophageal cancer. We estimate that high versus low physical activity decreases the risk of gastroesophageal cancer by approximately 18 %. Our doseresponse meta-analysis suggests that engaging in any amount of moderate to vigorous physical activity is beneficial and that a frequency of five times per week of physical activity is associated with a risk reduction of 33 %. Future research is required to discern which specific types and durations of physical activity are needed for gastroesophageal cancer risk reduction. High-quality epidemiologic studies that employ standardized physical activity assessments and uniform definitions of high versus low physical activity levels are warranted.

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