

*Review*

## Physical Activity and Gastrointestinal Cancers: Primary and Tertiary Preventive Effects and Possible Biological Mechanisms

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**Abstract:** Gastrointestinal cancers account for 37% of all cancer deaths worldwide, underlining the need to further investigate modifiable factors for gastrointestinal cancer risk and prognosis. This review summarizes the corresponding evidence for physical activity (PA), including, briefly, possible biological mechanisms. Despite high public health relevance, there is still a scarcity of studies, especially for tertiary prevention. Besides the convincing evidence of beneficial effects of PA on colon cancer risk, clear risk reduction for gastroesophageal cancer was identified, as well as weak indications for pancreatic cancer. Inverse associations were observed for liver cancer, yet based on few studies. Only for rectal cancer, PA appeared to be not associated with cancer risk. With regard to cancer-specific mortality of the general population, published data were rare but indicated suggestive evidence of protective effects for colon and liver cancer, and to a lesser extent for rectal and gastroesophageal cancer. Studies in cancer patients on cancer-specific and total mortality were published for colorectal cancer only, providing good evidence of inverse associations with post-diagnosis PA. Overall, evidence of associations of PA with gastrointestinal cancer risk and progression is promising but still limited. However, the already available knowledge further underlines the importance of PA to combat cancer.

**Keywords:** physical activity; gastrointestinal cancer; prevention; cancer risk; epidemiology

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## 1. Introduction

Gastrointestinal cancers, including esophageal, gastric, pancreatic, liver, gallbladder, colon, and rectal cancers, are frequent cancers worldwide. In 2012, almost 30% of all incident cases were attributable to gastrointestinal cancers [1]. Colorectal cancer contributed nearly 1.4 million new cases, equivalent to about 10% of all cancer cases. With regard to mortality, 37.0% of all cancer deaths were related to gastrointestinal cancers. With 9.1%, 8.8%, and 8.5%, respectively, liver, gastric, and colorectal cancers contributed, after lung cancer, most to the total number of 8.2 million annual cancer deaths worldwide [1].

These numbers clearly indicate that a better understanding of the associations of modifiable risk and protective factors, such as physical activity (PA), with gastrointestinal cancer risk and prognosis is of high relevance in the global battle against cancer. Epidemiologic evidence generated over more than 30 years in more than 200 studies suggests that one third of cancer deaths may be attributable to dietary intake and PA habits [2]. This article provides a critical review concerning the impact of PA specifically on gastrointestinal cancers over the cancer continuum. Three fields are covered: (1) the evidence on possible reductions of cancer risks and mortality through a physically active lifestyle; as well as (2) the effects of exercise and PA in cancer patients on cancer progression and mortality; in addition, (3) insights into possible underlying biological mechanisms are briefly summarized.

## 2. Methods

Diseases or death outcomes considered in this review were all digestive cancers, covered by the topography codes C15–C25 of International Classification of Diseases, Tenth Revision, including esophagus (C15), gastric (C16), small intestine (C17), colon (C18), rectum (C19–C21), liver (C22), gallbladder and intra- and extrahepatic bile ducts (C23–C24), and pancreatic cancer (C25).

Whenever possible, we relied on previous qualitative and quantitative reviews of the available evidence, including reviews that covered several cancer sites and updated the evidence based on more recent publications [2–5]. Reported risk changes in percent refer to the relative rather than the absolute risk scale. Primary and tertiary preventive effects of PA were considered separately and were reviewed by cancer site. Cancer-specific gastrointestinal cancer mortality was reviewed as an outcome separately from cancer incidence, as the associations and underlying mechanisms may differ. Studies focusing on disease or treatment related side effects, such as cancer-related fatigue or quality of life, were outside the scope of this review.

## 3. Evidence of Primary Preventive Effects of Physical Activity

In the following, the evidence of primary preventive effects of increased PA levels on decreased risks and mortality of gastrointestinal cancers is reviewed. Major results are summarized in Table 1.

### 3.1. Physical Activity and Colon and Rectal Cancer Risk

The association between PA and colorectal cancer risk has been intensively studied in epidemiologic research. After evidence emerged that colon and rectal cancer have different etiologies [9], especially more recent studies reported results for these two sites separately. In 2007, an expert group summarized

the evidence [2]. This has been updated in 2011 by further 15 cohort studies, so that, overall, results from 21 prospective studies on total PA, 19 on occupational PA, and 39 on recreational PA were considered [6]. Some studies were classified as unsuitable for meta-analysis due to the assessment of PA. In parallel, another meta-analysis based on 24 case-control and 28 cohort studies investigated this association [7,8].

Most studies consistently observed an inverse association between PA and the risk of colon cancer: Thus, the reviews concluded that PA, within the range studied, convincingly protects against colon cancer [2,6]. The meta-analysis reported an estimated risk reduction of 24%, comparing the most versus least active individuals across all studies [8]. In studies that observed an inverse association, risk reductions ranged from 20% to 70%, and were found for all types of PA (e.g., recreational, occupational, total PA). With an average risk reduction of 31%, case-control studies reported larger overall risk reductions than cohort studies (average risk reduction 17%) [8]. Concerning the impact of sedentary behavior, characterized by prolonged sitting time and, thus, being distinctive from low PA, a recent meta-analysis on colon cancer reported statistically significant risk increases of 54% for TV viewing time, 24% for occupational sitting time, and 24% for total sitting time [10]. All other gastrointestinal cancers were unrelated to sedentary behavior.

The majority of studies that examined dose–response relations between increasing activity and decreasing risk reported statistically significant inverse trends [4]. Meta-analyses performed by the Expert panel of the Continuous Update Project of the World Cancer Research Fund on the continuous scale showed statistically significant summary risk reductions for colon and colorectal cancer for total PA but not for recreational [6]. Particularly the most recent studies reported results from models adjusted for other risk factors.

Effect modification had also been examined in several studies. There were no indications of modifying effects of body mass index (BMI) [8]. Concerning gender-effects, one meta-analysis reported similar risk reductions of 24% and 21% for men and women, respectively [8], whereas the World Cancer Research Fund's panel recently concluded that the effect was strong and consistent in men, but less strong in women [6]. The periods of life that may be most relevant for a potentially protective effect of a physically active lifestyle were not yet clearly established. There was some evidence that sustained activity over lifetime and activity done during adolescence were associated with the greatest reductions in colon cancer risk [7].

In contrast to colon cancer, scientific evidence indicates that there is no association between PA and the risk of developing rectal cancer. A summary of 31 studies reported a pooled relative risk for rectal cancer close to unity in the prospective cohort studies [7]. The pooled relative risk for case-control studies was less close to unity, but did not indicate a significant inverse association. The null association was consistent for men and women and across all types and doses of PA. This is in agreement with the World Cancer Research Fund panel that concluded that there is no evidence of risk reduction for rectal cancer by leading a physically active lifestyle [6].

In summary, there is abundant and convincing epidemiological evidence from prospective studies showing strong risk reductions through higher overall levels of PA for colon but not for rectal cancer, with evidence of a monotone dose-response relationship. In comparison with other lifestyle factors, PA is the only modifiable factor for colon cancer for which the evidence has been classified as convincing.

Due to the high incidence of colon cancer this indicates a major potential of PA in primary cancer prevention.

### 3.2. Physical Activity and Gastric and Esophageal Cancer Risk

In 2007, an expert panel stated that there was insufficient evidence to evaluate the association between PA and gastric cancer [2]. In 2014, three different groups published updated meta-analyses [11–13], with Behrens *et al.* being the most comprehensive one [13]. Their systematic review revealed 24 studies with a total of 15,745 cases and supported an inverse relation of PA to gastroesophageal cancer risk. The risk reduction of total gastroesophageal cancer for high versus low PA was 18% and statistically significant. A dose–response analysis of frequency of PA and total gastroesophageal cancer risk revealed that with 23% the greatest risk reduction was achieved among those engaging in moderate to vigorous PA five times per week. Comparing high versus low PA levels according to anatomic site and cancer histology, statistically significant risk reductions of 21% were evident for esophageal adenocarcinoma, of 17% for gastric cardia adenocarcinoma, and 28% for gastric non-cardia adenocarcinoma. The risk reduction for esophageal squamous cell carcinoma ranged between 6% and 34%, depending on the inclusion of one influential study. Few studies evaluated the effects of different types of PA. In general, studies that used more detailed PA assessment methods tended to observe significant risk reductions, whereas studies with a more general assessment resulted in null associations [7].

### 3.3. Physical Activity and Pancreatic Cancer Risk

The relation between PA and pancreatic cancer risk was examined in a recent systematic review and meta-analysis published in 2015 [14]. A total of 30 distinct studies, 22 prospective, and 8 retrospective studies, were reviewed. Thus, only 2 case-control studies were published since the last meta-analyses appeared in 2012 [15,16]. The WCRF panel stated in 2012 that the evidence for PA is not consistent and that no conclusions could be drawn. However, in the most recent review, combining the findings of all types/domains of PA from the cohort studies resulted in a weak, but statistically significant risk reduction of 7%, comparing the highest and lowest categories [14]. The pooled estimated risk reduction for case-control studies yielded a stronger, statistically significant risk reduction of 22%. Stratified analyses by timing in life of PA revealed statistically significant risk reductions for consistent activity during lifetime within cohort studies (risk reduction: 14%) and case-control studies (26%). Summary risk estimates did not differ by gender, smoking, BMI, geographic region, or type of PA. Thus, overall findings were weak but there was some suggestion for risk reductions for pancreatic cancer if PA was performed consistently over time.

### 3.4. Physical Activity and Liver, Gallbladder, and Bile Duct Cancer Risk

Given the restricted number of studies, neither a qualitative nor a quantitative review for these cancers has been published. To our knowledge, only four studies investigated the associations between PA and disease risk for liver, gallbladder and intra- or extra-hepatic bile duct cancers. All studies were prospective cohort studies. Most recently, the prospective NIH-AARP Diet and Health study

on 507,897 men and women with a median follow-up time of 10 years reported results based on 628 incident cases of liver cancer and 317 cases of extrahepatic biliary tract cancer [17]. Comparing the highest with the lowest level of vigorous PA revealed a statistically significant decreased risk for liver cancer by 36%, particularly hepatocellular carcinoma with a risk reduction of 44%. The associations were independent of BMI. Risk estimates for extrahepatic bile duct cancer and gallbladder cancer were reduced by 14% and 37%, respectively, but these reductions were not statistically significant [17]. These results are consistent with those from a large prospective study among 444,963 Korean men [18], which compared more than two versus less than two sessions of leisure-time PA per week in multivariable adjusted models. The study showed a statistically significant risk reduction of 12% for liver cancer. Risk reductions for gallbladder cancer were not significant. Similarly, a prospective study among 79,771 Japanese men and women compared the highest with the lowest quartile of total PA per day and reported a statistically significant risk reduction of 38% for liver cancer [19]. No risk estimates were reported for biliary tract cancers. In a large Taiwanese cohort of 416,175 men and women, researchers reported on 11,802 incident cancer cases after an average follow-up of 8 years [20]. Based on 1,676 cases, a significant risk reduction of incident liver cancer by 19% was found, when individuals with higher leisure time PA were compared to inactive ones. Results for gallbladder or biliary tract cancers were not reported. Thus, overall, there are only few studies on PA and its associations with these cancer sites. All four studies observed statistically significant risk reductions for liver cancer, with some potential for publication bias, whereas for gallbladder and bile duct cancer so far only two studies reported weak indications (Table 1).

**Table 1.** Associations of physical activity with gastrointestinal cancer risk and cancer-specific mortality based on epidemiologic studies in healthy populations.

Cancer site	Cancer risk	Cancer-specific mortality
Colorectal	++ (Colon)	+
	-- (Rectum)	(+)
Gastric	+	(+)
Esophagus	+	(+)
Pancreas	(+)	(-)
Gallbladder, Biliary Tract	(+)	0
Liver	+	(+)

No data published: 0; Evidence of a protective effect of physical activity: ++ convincing, + good, (+) limited; Evidence of no association with physical activity: -- convincing, - good, (-) limited; Evidence classification was performed qualitatively along the Bradford and Hill criteria.

### 3.5. Physical Activity and Gastrointestinal Cancer-Specific Mortality

Data on long-term effects of mostly pre-diagnosis PA on cancer-specific mortality for gastrointestinal cancers were rare, most reports on PA and mortality dealt primarily with all-cause or total cancer mortality, whereas more specific analyses were seldom reported and might be hampered by low case numbers. In the following, results are presented by study. A cancer-specific summary is presented in Table 1.

Recently, the prospective NIH-AARP Diet and Health study on 293,511 men and women with a median follow-up time of 12.1 years reported data on cancer-specific and overall cancer mortality [21]. For all causes of death taken together, inactive persons had a more than 50% greater mortality risk than the most active persons in this cohort. Statistically significant mortality risk reductions per one hour increase in pre-diagnosis leisure time PA per week were reported for all cancers (number of events:  $n = 15,001$ , risk reduction: 1%), of colon cancer ( $n = 1,036$ , 3%), and liver cancer ( $n = 397$ , 4%). For liver and colon cancer, participants who reported more than 7 hours of moderate or vigorous pre-diagnosis leisure time PA per week had about a 30% lower risk of cancer-specific death compared to physically inactive persons. Mortality risk reductions were statistically non-significant for esophagus cancer ( $n = 491$ , 2%), for gastric cancer ( $n = 304$ , 1%), and for pancreatic cancer ( $n = 1,239$ , risk increase: 2%).

Results after 40 years of follow-up from the U.K. Whitehall cohort study, which recruited 19,019 male, nonindustrial government employees, revealed no clear associations between PA variables and mortality from gastrointestinal cancers. Only in rectal cancer, mortality risk reduction was significantly associated with walking pace, but not with leisure time PA [22,23].

The Aerobics Center Longitudinal study investigated the association of cardiorespiratory fitness, a potential surrogate for maintained levels of total PA, with cancer-specific deaths. For gastrointestinal cancers, the results from the cohort study of 38,801 men from the U.S. were similar to those of the NIH-AARP project. In a mean length of 17 years of follow-up and 661,169 person-years of observation, 283 total digestive cancer deaths were identified. Statistically significant risk reductions were observed for colon cancer mortality (39%), for colorectal cancer mortality (42%), and liver cancer mortality (72%), with high versus low cardiorespiratory fitness [24]. The associations between fitness and small intestine, gallbladder, and pancreatic cancer were suggestive of a reduced risk, but did not reach statistical significance. For all digestive system cancers combined, the adjusted mortality risk reduction associated with being fit was statistically significant at 38%.

One further study, the Harvard Alumni Cohort Study, reported results on pancreatic cancer death only. Comprising 32,687 subjects with 212 deaths from pancreatic cancer, PA was not associated with pancreatic cancer mortality [25].

A large Taiwanese cohort of 416,175 men and women with an average follow-up of 8 years reported a significant 17% reduced overall cancer mortality risk based on 4,272 cancer death, when those with higher leisure time PA were compared to inactive individuals [20]. In this study, significant inverse associations were observed for deaths due to colorectal cancer (Number of events:  $n = 421$ , risk reduction: 25%) and liver cancer ( $n = 421$ , 15%). Specific results for other gastrointestinal cancers were not reported.

Overall, with only five studies, there is a scarcity of data on long-term effects of PA on cancer-specific mortality for gastrointestinal cancers. For colon and liver cancer, there is some suggestive evidence that cancer-specific mortality is related to higher amounts of PA.

### *3.6. Biological Mechanisms for Primary Preventive Effects*

There are several plausible biologic pathways and some evidence of mechanisms of sustained PA in gastrointestinal cancer development [6,26–28]. Many of these mechanisms are interlinked and vary in

their importance by cancer site. Performed regularly and in the long term, PA increases the body's metabolic efficiency and capacity. Other potential mechanisms include decreases in gut transit time, reductions in insulin levels and insulin resistance, increases in insulin stimulated synthesis of glycogen in muscles, changes in bile acid metabolism, increases in chronic anti-inflammatory processes, decreases in prostaglandin E2 expression, elevated tolerance to oxidative stress, maintenance of telomere length, and decreases in liver fat stores, in abdominal fat mass, partly triggered by effects on endogenous steroid hormones, and in obesity, with some of these pathways being established risk factors for various solid gastrointestinal cancers [2,29–34].

#### **4. Evidence of Tertiary Preventive Effects of Physical Activity**

##### *4.1. Associations between Physical Activity and Risk of Recurrence and Mortality in Cancer Patients*

After being diagnosed with cancer, the primary interest of patients lies on their chances of recovery and the risks of recurrence, and cancer-specific and overall mortality. These tertiary preventive effects have been studied much less than the effects of PA on cancer risk. Data were collected for the association with pre- and post-diagnosis PA behavior. The current evidence relies solely on observational data as randomized trials would need large sample sizes and long follow-up periods. However, this observational approach is prone to residual confounding, *i.e.*, that patients with a worse prognosis might tend to engage less in exercise, which could lead to an overestimation of a protective effect of PA. As shown in Table 2, research on tertiary preventive effects of PA for patients with gastrointestinal cancer types is restricted to a few studies on colorectal cancer.

For colorectal cancer, a recently published meta-analysis summarized seven prospective studies with follow-up times between 3.8 to 11.9 years [5]. A total of 5,299 colorectal cancer patients provided information on pre-diagnosis PA, and 6,348 patients on post-diagnosis PA. For colorectal cancer-specific mortality, participating in some pre-diagnosis PA, compared to not participating in any activity, yielded significant pooled risk reductions of 25%, higher activity levels resulted in a 30% risk reduction. The corresponding risk reductions for post-diagnosis PA were 26% and 35%, respectively. Results for all-cause mortality were similar, and the authors concluded that both pre-diagnosis and post-diagnosis PA were associated with reduced colorectal cancer-specific mortality and all-cause mortality. Whereas early studies indicated that an energy expenditure of 5–6 hours walking per week was needed to induce these benefits, the meta-analysis suggested that even relatively low amounts of PA reduced all-cause mortality in patients [5]. Based on the three studies that reported change in PA, a recent meta-analysis reported that increased PA from pre- to post-diagnosis was associated with a 30% reduced colorectal cancer-specific mortality risk and 25% reduced overall mortality risk [35].

**Table 2.** Associations of physical activity with cancer outcomes for tertiary prevention (risk of recurrence, cancer-specific and overall mortality) based on studies in gastrointestinal cancer patients.

Timing of physical activity	Studied cancer site	Recurrence risk	Cancer-specific mortality	Total mortality
Pre-diagnosis	Colorectal	0	(+)	(+)
	All other GI cancers	0	0	0
Post-diagnosis	Colorectal	(+)	(+)	(+)
	All other GI cancers	0	0	0
Changes from pre- to post-diagnosis	Colorectal	0	(+)	(+)
	All other GI cancers	0	0	0

No data published: 0; Evidence of a protective effect of physical activity: ++ convincing, + good, (+) limited; Evidence of no association with physical activity: -- convincing, - good, (-) limited; Evidence classification was performed qualitatively along the Bradford and Hill criteria.

In addition to this meta-analysis, the prospective NIH-AARP Diet and Health study recently reported results from 3,797 colorectal cancer patients with pre-diagnosis and 1,759 with post-diagnosis leisure-time PA. Cancer survivors reporting more than 7 hours per week of pre-diagnosis PA had a 20% lower all-cause mortality risk compared to those reporting no activity. For cancer-specific mortality an inverse, but not statistically significant, association of 16% was observed. The corresponding results for post-diagnosis physical activity were a 31% lower risk of all-cause mortality and a statistically non-significant 47% lower risk of colorectal cancer-specific mortality [36].

For all-cause mortality, an association of similar magnitude was observed in 237 patients with recurrent colon cancer for the level of post-diagnosis PA (risk reduction of 29% in favor of the physically most active group compared with the least active group) [37]. The benefit was not significantly modified by gender, BMI, number of positive lymph nodes, age, baseline performance status, adjuvant chemotherapy regimen, or recurrence-free survival period. In general, these findings are in line with those of the meta-analysis, indicating a beneficial effect of pre- and post-diagnosis PA on cancer-specific and overall mortality for colorectal cancer patients (Table 2).

Only one study reported results for recurrence-free survival from a prospective cohort of 832 stage III colon cancer patients [38]. Post-diagnosis PA conferred a significant risk reduction of 50% for patients who reported PA equivalent to 6 or more hours per week of walking at an average pace compared to patients with lower activity levels.

#### 4.2. Biological Mechanisms for Tertiary Preventive Effects

Many of the hypothesized or studied pathways mentioned in section 3.6 for the primary preventive effects of PA are assumed to be also relevant for the tertiary preventive effects of PA in cancer patients [39]. However, very few studies specifically investigated these hypotheses in cancer patients. A

systematic literature review on PA/exercise and biomarker research for all cancer types has recently been published by our group [40] and was updated to March 2015 for this manuscript. Only five publications out of a total of 25 for all cancers reported some results on blood-based biomarkers in gastrointestinal cancer patients from either observational or exercise intervention studies (Table 3). Each dealt with a different mechanism. The studies are summarized by site, study type, studied pathway and major results in Table 3.

**Table 3.** Studied biological mechanisms and pathways for the effects of exercise training in gastrointestinal cancer patients.

Gastrointestinal cancer site	First author and year of publication, study type, population size	Studied Pathway	Results
Colorectal Cancer	Allgayer 2004 [41], randomized trial, <i>n</i> = 23	Inflammatory parameters	Reductions of the IL-1ra/IL6 and IL-1ra/IL-1 $\beta$ ratio after two weeks of training with moderate intensity
	Allgayer 2008 [42], randomized trial, <i>n</i> = 48 after adjuvant therapy	DNA repair and oxidative stress	Significant decrease of 8-oxo-2'-deoxyguanosine excretion, a marker of oxidative DNA-damage, in the moderate training group and a non-significant increase in the high-intensity group after a 2-week training
Gastric Cancer	Na 2000 [43], randomized trial, <i>n</i> = 35	Immune response	Endurance training was associated with a significant change in function in vitro of isolated natural killer cells
	Yuasa 2009 [44], observational study, <i>n</i> = 106	Direct effects on cancer biology; epigenetic silencing of genes	More physical activity was correlated with a lower methylation frequency of the calcium channel-related gene CACNA2D3
Hepatocellular Cancer	Kaibori, 2013 [45], randomized trial, <i>n</i> = 51	Insulin-related metabolic factors, IGF signal transduction	Significantly reduced homeostasis model assessment (HOMA) score for the exercise group compared to the controls at 6 months postoperatively, as well as some improvements on insulin resistance

Overall, results on any of the hypothesized biological mechanisms for the tertiary preventive effects of PA are rare for gastrointestinal cancers and no conclusions can currently be drawn. Further well-designed exercise intervention trials of adequate size are needed in cancer patients that, whenever feasible, incorporate high-quality and hypothesis-driven translational and interdisciplinary components for further biomarker research in this field. Other study concepts and research disciplines could also make essential contributions, such as experimental animal studies, and overarching research incorporating these disciplines may result in major progress.

## 5. Discussion

This review summarized the evidence of beneficial effects of PA for gastrointestinal cancers over the cancer continuum, covering 30% of all incident cancers and 37% of all cancer deaths. For primary preventive associations with cancer incidence, a solid number of studies for quantitative summary evaluations were available for colon, rectal, pancreatic and gastroesophageal cancers. Only for colon cancer, there was convincing evidence for beneficial effects on cancer risk in the order of 20%–30%. Indications for risk reductions were observed weakly in pancreatic cancer and clearly in gastroesophageal cancer. In addition, liver cancer risk showed a clear inverse association and the other sites weak associations with PA, however, these observations were based on a small number of studies. Rectal cancer was the only cancer site with convincing evidence that PA was not associated with cancer risk. With regard to cancer-specific mortality for the considered cancers, published data were rare but indicated some suggestive evidence of protective effects for colon and liver cancer, and to a lesser extent for rectal and gastroesophageal cancer. Studies on tertiary preventive effects of pre- and post-diagnosis levels of PA on cancer prognosis were published for colorectal cancer only, providing good evidence of inverse associations with cancer-specific and total mortality. For recurrence risk, only one study was published. It yielded promising results. Several plausible biological pathways to explain the observed associations were studied but further investigations, particularly in cancer patients, are needed.

Despite the relevance of the topic, this review showed that many aspects of possible associations are still understudied. The level of evidence of the considered outcomes and cancers was completely defined by observational studies performed in mixed populations in different countries, where PA exposure assessment was mostly based on questionnaires. The instruments varied considerably in the quality and detail of data captured on timing, type, and dose of PA, making direct comparisons of the data across these studies difficult. Evidence from randomized controlled exercise intervention trials was not available, but corresponding trials are currently ongoing [46].

This review was restricted to the beneficial potential of PA on gastrointestinal cancers with regard to cancer risk reductions and improvements of cancer prognosis. There were no indications of harmful effects of PA for any of the considered outcomes. In contrast, further positive effects of PA exist that were not covered. Specifically for cancer patients, there is increasing evidence of a wide range of beneficial effects of PA and exercise on many relevant factors that are related with the disease and the therapy, as well as with quality of life including the reduction of cancer-related fatigue [47,48]. In addition, the primary preventive effects of PA with regard to other cancers and chronic diseases, such as postmenopausal breast cancer for women, cardiovascular diseases, metabolic diseases, osteoporosis and depression that were observed in healthy populations are relevant for all cancer survivors too. Furthermore, there are more general beneficial effects of PA on the gastrointestinal system that were not covered by this review, such as on gastroesophageal reflux disease, peptic ulcer disease, nonalcoholic fatty liver disease, cholelithiasis, diverticular disease, irritable bowel syndrome, and constipation [49]. Overall and given the high incidence of gastrointestinal cancers worldwide, the available evidence as summarized within this review further underlines the importance of a sufficient level of regular PA for healthy individuals and cancer patients to combat the cancer burden.

## Author Contributions

Karen Steindorf conceived and designed the review; all authors contributed to the conduction of the review and preparation of the manuscript. All authors read the final version.

## Conflicts of Interest

The authors declare no conflict of interest.

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