

Methodological issues when analysing the role of physical activity in gastric cancer prevention: a critical review

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Abstract The beneficial effect of physical activity (PA) has been confirmed in several types of cancer (especially colon and breast tumours). However, the role of PA as a risk factor directly related to the incidence of gastric cancer is still open to doubt. This is in part due to the fact that most studies have not considered gastric sub-site or histology of oesophageal cancer, as well as the different approaches used in order to measure PA. Indeed, some studies have tried to link gastric cancer to PA intensity and timing, whereas others have focused on a specific PA type such as recreational, occupational or sporting activity. Furthermore, most of them do not use validated questionnaires, and others create a PA index and employ different unit measures (metabolic equivalents, hours/week, times per week, etc.), which makes it difficult to compare its findings. Under these circumstances, this brief critical review aims to explore and show all the methodological issues that need to be taken into account in order to objectify the link between PA and gastric cancer, as well as provide alternative solutions to these matters.

Keywords Gastric cancer · Physical activity · Elderly · Epidemiology

Introduction

Gastric cancer is the fourth common type of cancer worldwide, and due to its high incidence and poor survival, it is the second leading cause of cancer death worldwide [8]. In the European Union, it is the fifth cancer in incidence and the fourth in mortality [21]. Most of the factors involved in the pathogenesis of this tumour act on the gastric mucosal microenvironment over a prolonged period of time and are responsible for the well-known Correa's precancerous cascade, which precedes the development of invasive cancer [12, 14]. Several environmental risk factors for these malignancies have been proposed, including tobacco or alcohol consumption, diet and medication [15]. The *Helicobacter pylori* is also considered as the strongest singular risk factor for this cancer, basically mediated by the interaction of its genetic characteristics and those of the guest [39].

Although the incidence of gastric cancer has declined among the general population, this is not the case for the elderly people due to the higher life expectancy [31]. A sedentary lifestyle has been associated with increased risk of cancer among the elderly population [23]. Therefore, it has been stated that elderly people should lead an active lifestyle in order to reduce its incidence [22]. In this regard, it is worth mentioning that although the beneficial effects of physical activity (PA) have been confirmed in several types of cancer (especially in colon and breast cancer), the role of PA as a risk factor directly related to the incidence of gastric cancer is still open to doubt [26, 49].

Several biological mechanisms, which can be classified as localised (specifically related to the anatomic location) or systemic [11], have been proposed in order to explain the relation between PA and gastric cancer. In the first case, it has been suggested that physical activity can reduce the circulating levels of several inflammatory markers such as C-reactive protein, interleukin-6 and tumour necrosis factor

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alpha [13]. Thus, exercise could reduce the inflammation of the stomach of epithelium, as it has been previously proposed in other chronic inflammatory digestive disorders [2]. In the same line, the concentration of prostaglandin E₂, a marker of inflammation that has been associated with gastric cancer risk [17], could be reduced due to the performance of endurance exercise [34]. Regarding the systemic effects, the evidence is based on the influence that the exercise performance seems to have on the immune system, mainly by improving its innate and acquired immune responses when recognising and eliminating cancerous cells [24]. Besides, PA may reduce oxidative stress, increase antioxidant enzymes and enhance DNA repair systems [35]. Finally, the effects of exercise on lipid metabolism should be taken into account. Indeed, obesity and PA may promote tumour development through various metabolic and endocrine pathways, involving insulin, insulin-like growth factor, leptin and various adipokines [3]. In this regard, findings from observational studies support a positive association between high body mass index and the risk for oesophageal and cardia adenocarcinoma [29].

In spite of all this, evidence from epidemiological studies linking gastric cancer and PA is inconsistent. This is partly due to the different approaches used in order to measure it and to the fact that its association with gastric cancer is not generally analysed by location and histological type.

Under these circumstances, this brief critical review has a double objective. First, it focuses on all methodological issues that need to be dealt with in order to objectify the link between PA and gastric cancer. Second, it tries to provide methodological alternatives which could help to improve the consistence of future studies of this kind.

The importance of considering gastric cancer sub-site and histology

From a histological point of view, gastric cancer must be classified according to its sub-site distribution. However, several studies on the protective role of PA in this malignancy have considered it as a single unit. For instance, Brownson et al. [9] found an excess of oesophageal malignancy in people whose occupation involved moderate PA. However, the authors did not include a histological analysis. Similarly, both a Chinese- and an Italian-matched hospital-based case-control studies [6, 52] showed that frequently PA had a protective effect on gastric cancer, but the authors considered it as a whole entity. Similarly, cohort studies found a statistically significant increased cancer risk associated with higher levels of PA. However, no information regarding the relationship of PA with oesophageal and gastric carcinoma according to histology and anatomical site was reported [36]. This lack of information can be observed in prospective studies with similar findings [26].

On the other hand, some studies have taken into account histological sub-site when analysing the effect of PA on gastric cancer risk, but no definitive conclusions can be extracted from them. For instance, Sjö Dahl et al. [43] observed that people who performed at least moderate PA showed a decrease in gastric cancer risk. Although the authors distinguished between cardia and non-cardia cases, they did not include cardia tumours in their final analysis. Similarly, in a case-control study which found an inverse association between an active lifestyle and stomach cancer incidence risk, the authors collected data on histological sub-site. However, stratified analyses were not conducted due to insufficient statistical power [11].

Hence, from an epidemiological point of view, future studies of this kind should distinguish among distal tumours (non-cardia), tumours of the proximal region of the stomach (cardia) and those of the gastro-oesophageal junction. Besides, they should analyse separately oesophageal adenocarcinoma (strongly related to gastro-oesophageal reflux disease) and oesophageal squamous cell carcinoma cancers.

The problem of measuring physical activity on gastric cancer: methodological clues

In order to assess the relationship between PA and gastric cancer, there are several questions which must be taken into account. Firstly, the subjects under study must be classified in a particular and specific category according to their PA level. Therefore, the three PA components (i.e. frequency, duration and intensity) must be examined within each category. Besides, it should be clearly specified the sort of PA which is being assessed, according to the domains where it is usually carried out. Finally, since PA practice varies in a lifetime, it is necessary to try to gather information about this habit at different age stages.

Classification according to PA level

Some epidemiological studies have failed to accurately identify the level of PA performed by the gastric cancer patients included in their samples. For instance, Leitzman et al. [32] followed during 8 years a cohort of 487,732 US men and women and found a strong inverse relationship between PA and risk for gastric (cardia and non-cardia) adenocarcinoma, but not for esophageal squamous cell. Increased PA was associated with a reduced risk for oesophageal adenocarcinoma. However, the measuring of PA was strictly related to the performance of continuous activities of certain intensity. Thus, lower intensity activities, such as walking, and physical efforts shorter than 20 min were omitted. In a similar line, Yuasa et al. [57] suggested some protective effect of PA on gastric carcinoma after

interviewing 106 patients suffering from this malignancy. However, the activity level of the sample was obtained by simply separating those who never exercised from the ones who performed PA at least 1 h per week. Finally, some studies have not explained in depth how PA level was assessed and analysed. Therefore, no further discussion in this regard can be made.

Thus, Sundelöf et al. [46] observed that PA level did not affect the risk of mortality in oesophageal adenocarcinoma, oesophageal squamous cell carcinoma or gastric cardia carcinoma. Nevertheless, information about how the intensity or the frequency of the PA performed was measured was not shown. Similarly, Lagergren et al. [30] did not find any association between PA and the risk of oesophageal adenocarcinomas. Physical activity was measured and divided into quartiles according to 12 variables including the usual ones, but the emphasis of the paper was on body mass index as a risk factor, so little mention was made of PA methods or results.

In order to be able to relate and identify the level of PA, it is advisable to avoid dichotomous variables (sedentary yes/no; active/inactive) which limit the information and the assessment of the PA impact. In this regard, some authors have suggested the use of objective data, such as oxygen consumption and basal heart rate measurements [41]. Moreover, it is essential to have a unit of measure able to rate the individual physical performance and properly classify it, according to frequency, duration and intensity. In this regard, it seems useful to follow the five units proposed in the 2008 physical activity guidelines (inactive, low, medium, high or very high) [38] expressed in metabolic equivalents (MET)/hour/week [53].

In order to categorise the activities carried out according to MET, the Compendium of Physical Activity, which has recently been updated [1], is generally used as a reference framework [25, 26]. However, the values in the Compendium do not take into account specific variables such as age, sex or body mass among others. Given all that, it is advisable for further studies to adjust the obtained MET values by following the guidelines proposed by some authors [10, 28].

Other actions that must be carried out in order to accurately measure patients' PA level are finding out the amount of time (in minutes) that they spend doing PA in a typical week (including, therefore, the weekend), as well as taking into account the weather influence on the sport habits. Therefore, it is interesting to distinguish at least between cold (fall–winter) and warm seasons (spring–summer) [42].

Finally, with the aim of identifying the intensity of the PA carried out by the patients, some studies have tried to gather information about the physiological response related to PA performance (appearance of sweat, shortness of breath, fatigue level, etc.) [25, 32]. However, since the capacity of

effort is different in each person and given that the physiological organic response strongly depends on the fitness level of each individual, the aforementioned criteria can be misleading. Therefore, it seems more accurate to obtain data about the intensity of the performed PA by taking into account, whenever possible, objective variables related to it, such as speed, heart rate or amount of load. This methodological resource can help to improve the validity of the PA total score and the PA index that are used in some studies to calculate the PA level of each patient [25, 26, 50].

Selecting PA domains

Usually, PA domains are divided into four categories: occupational, household, transport and leisure time; the last with either a recreational or competitive aim. However, this methodological key point when measuring the amount of PA performed by gastric cancer patients is too often ignored. Thus, De Jonge et al. [15] interviewed 126 patients with either esophageal, cardia or squamous cell adenocarcinoma, but only collecting information about PA levels at work and during spare time. Besides, the authors did not report about the influence of this risk factor in any case. A similar approach was used in the Nova Scotia Barret Esophagus Study [3], where, after interviewing patients with oesophageal adenocarcinoma, leading an active lifestyle was identified as a key factor capable of reducing the potential of progression to invasive malignancy at an early stage. However, PA assessment was restricted to calculate the amount of hours per week spent on low, medium and high intensity leisure and work activities. In a similar line, Watabe et al. [51], who found no evidence of PA as a risk factor, only informed about the relationship between recreational activity and stomach cancer, whereas in other studies, some degree of association between the performance of PA and the risk of gastric cancer was observed, but again only the recreational type was measured [11, 43]. Finally, in the Whitehall study [4], a protective effect of travel activity on stomach cancer was found among men, but no other type of PA was measured.

Occupational factors have been regarded as playing an important role in the aetiology of several types of cancer. Thus, different studies have investigated the relationship between occupational PA and gastric cancer, and whereas some of them observed an increased risk of this malignancy in people who were presumed to be less physically active at work [9, 20, 45], others did not find any degree of association [18]. On the contrary, Wannamethee et al. [50], who reported that the risks of esophageal and gastric cancer were inverse related to PA, did not include PA at work in the total PA index score used to assess patients' activity levels.

From the revised studies, it seems that the most accurate way of measuring the level of activity that an occupation

involves is assigning a PA score to every job title. For instance, Vigen et al. [49], classified job activity into sedentary (e.g. secretary), moderate (e.g. sale worker) and high jobs (e.g. gardener) and obtained a total lifetime occupational physical activity index. However, using job titles as proxies for work-related PA might be prone to misclassification [11]. Besides, these kinds of investigations do not take into account PA patterns outside the workplace. Thus, any conclusion should be considered as indirect evidence. A possible solution to this matter could be the application of the regulation ISO 8996:1990 [27] to the reported occupational activity. This seems to be an interesting strategy, as it allows classifying the effort demand according to the energetic cost in METs/hour/week. Thus, just by knowing the profession of the patient and the total amount of time spent on it, it is possible to obtain a specific value of occupational PA level.

In closing, there are several methodological clues that should be taken into account when analysing PA domains. For instance, housework can be perfectly considered as work/occupational activity. The same happens with agricultural work, which is a need for some whereas an amusement for others. Thus, it seems important to design and devote a part of the PA questionnaire to the occupational aspect, and another to the performance of PA in general. This section should include all kinds of PA the patient can carry out during the off-hours. Given the difficulty that implies to remember and enumerate all the activities carried out during a typical week, the questions must be properly contextualised and show examples. In this regard, it is advisable to include sections referring to housework (including minor farm work and gardening), PA as a means of health or movement (walking, cycling, climbing up or down stairs) and recreational sport (distinguishing between individual and team sports) or competitive practice (monitoring training and aimed at high performance).

Measurement of PA over lifetime

When analysing the association between gastric cancer and activity level, variations in changes in PA over lifetime are not always taken into account, thereby potentially missing a true association between them. Even longitudinal studies have shown some methodological flaws in this regard, such as trying to measure the activity level of the patients by merely including common definitions of PA in global questionnaires about lifestyle factors [54, 56], instead of using specific longitudinal ones.

The measuring PA throughout lifetime relies on the self-report of PA, which is known to be subject to measuring error. This error becomes compounded when the measures are combined with an indicator of change of PA over time. Thus, since the questionnaire is the only realistic approach that can be used to measure lifetime PA in epidemiological

studies, it should be properly tested, validated and designed. For instance, Inoue et al. [26] did use a quantitative approach for assessment using a common scale to estimate the effect PA on total cancer risk (including stomach cancer), by means of METs. Moreover, they assessed the validity of the proposed METs/day score among patients from their sample in two different seasons. However, the study focused on daily total PA level, and it is not clear if variation in changes in PA over lifetime was measured. In this line, Huerta et al. [25] conducted a prospective study in over half a million participants across ten European countries, in order to confirm the putative protection of PA on gastric cancer. Physical activity was measured by means of an overall index, which had been previously validated. Nevertheless, the transcultural validation might not be entirely appropriate. The authors combined time spent in sport and cycling, but it is not clear if this variable could be an accurate indicator of PA involvement. Indeed in some countries, cycling depends on several cultural and environmental factors and it is not as common as walking, which could be a more appropriate indicator. Besides, after revising the literature concerning the design and the previous administration of the questionnaire, it seems that patients were only asked about the performance of PA during the previous year. Again, it is not clear enough if changes on lifetime PA were controlled.

As it was previously noted, PA level is not kept constant in people across the lifespan. Overall, the volume of PA decreases over successive age groups, and there is an even greater age-related reduction in participation in vigorous sporting and fitness activities [47]. Thus, it is fundamental to know the PA level behaviour at least till the cancer onset. In this regard, one of the finest examples of how lifetime PA should be measured can be found in a Canadian nationwide case-control study, in which information on participants' PA during mid-teens, early 30s, early 50s and the period about 2 years prior to interview/diagnosis was gathered [11]. Nevertheless, it is not clear if these age stages were organised according to established criteria or to the sample size and amount of information available, with the aim of getting as much statistical power as possible. In this regard, a clear pattern of PA performance has been observed among these four categories of age: <25, 25 to 39, 40 to 54 and ≥ 55 years [33]. On the other hand, historical questionnaires tend to examine PA separately at ages 12–18, 19–34, 35–49 and ≥ 50 years [38]. Nevertheless, PA energy expenditure is notoriously difficult to measure in free-living situations, and retrospective measurement poses an even greater challenge, given the difficulty in validating such measurements. In this regard, it has been proposed to divide the questionnaires into discrete time periods, starting with the most recent 15 years in three 5-year sections. Following this, questions regarding PA from the age of 20 years until the most recent 15 years should be asked in 10-year sections [5].

Possibilities to objectively quantify PA

As it has been previously stated, PA is a complex multidimensional behaviour very difficult to assess objectively in epidemiologic studies. Particularly challenging is the estimation of PA energy expenditure (PAEE). The gold standard for measuring PAEE during free-living conditions is the doubly labelled water method, combined with an assessment of resting metabolic rate. However, this approach is expensive and does not provide any information on intensity and frequency patterns [7]. In this regard, motion sensors are emerging as a viable alternative. Three classes of motion sensors are being used increasingly in chronic disease populations, pedometers, accelerometers and integrated multisensory systems, each of them showing important limitations [48]. Pedometers are limited in their ability to detect certain PA patterns, while accelerometers have shown limitations in estimating moderate-intensity activities as well as for several lifestyle static and dynamic activities, especially water exercise [44]. Integrated multisensory systems combine accelerometry with other sensors that capture body responses to exercise and have several advantages such as providing contextual information in real time, as well as classifying activities into different types and converting them into an estimate of oxygen consumption. However, they are known for underestimating or overestimating energy expenditure under free-living conditions [19, 55]. Besides, these devices have been used infrequently in patients with chronic disease [48].

Regarding cancer studies, pedometers and accelerometers are basically used to motivate and assess PA adherence [40]. Nevertheless, proof exists that motor devices can be used in cancer epidemiology research, as is in the case of The Norwegian Women and Cancer Study [7]. Taken into account the methodology used in this cohort study, as well as the information provided in a similar one [16], some basic guidelines can be established for future investigations aimed at measuring gastric cancer patients PA levels by means of motion sensors. For instance, it is advisable to use a combined sensor that provides estimates of PAEE using accelerometry and heart rate monitoring data. This will allow to overcome some of the limitations regarding the under and overestimation of PAEE, previously stated. In this line, it seems important to attach the device to the thigh, since it allows for the differentiation of sedentary and active periods. Besides, the device will always remain in the leg for the intended period of time unlike other monitors that are integrated in a belt. Finally, in order to accurately measure PA, cancer patients should wear the device during 24 h for at least 4 days of a typical week, every 4–6 months. Nevertheless, this is an interval time which should be tested in different cancer populations, since it might be that PA patterns were not relatively stable over this period of time in every sample tested.

Study limitations

Critical reviews of this kind are justified when providing information to guide future epidemiological studies. There are two main methodological considerations derived from this study that should be considered in that respect.

First, the search for information was carried out in the English language and mainly through great databases. This is the reason why articles published in other languages, congress abstracts and other grey literature may have not been taken into account. And secondly, the quantity and quality of the information about the assessment of the PA is poor in some articles. As it has been impossible to contact the authors so that the information could be appropriately expanded, the depth of the analysis has been limited.

Future implications

With the aim of improving the methodology of future investigations designed to assess the relationship between PA and gastric cancer, some methodological considerations should be taken into account. First, it is advisable to suggest the use of blinding in the data collection in order to avoid any information bias in case-control studies. Secondly, an appropriate training of the interviewers must be ensured, as well as a good cultural adaptation, and a correct structuring of the PA assessment questionnaire.

Thirdly, the questionnaire should provide information about the PA carried out throughout lifetime; assessing the four PA domains (i.e. occupation, household, recreational and transport) with the same level of accuracy, so that none of them becomes under- or overmeasured. This would prevent the appearance of bias which could be associated with other variables. Finally, according to the authors, this study is based on the PA analysis in observational studies. Consequently, the approach to systems of randomization and allocation to treatment procedures lies beyond the scope of this research.

Conclusions

Research into the effects of PA on gastric cancer shows a series of methodological weaknesses which hinder us from reaching a firm conclusion. In this regard, the lack of attention paid to gastric cancer sub-site and histology, the difficulty in assessing the intensity of the performed PA, the necessity of taking into account all the areas where the former takes place, as well as the lack of an effective way to carry out a longitudinal assessment of the PA are the most remarkable aspects. Consequently, the relationship between both variables should be studied by means of lifetime PA

questionnaires which have been previously validated and organised in consistently defined age intervals. The information obtained from such questionnaires should take into account the four-category classification into which the PA domains are generally classified, as well as its three components. Finally, the level of reported PA should be categorised in MET/hours/week.

Conflict of interest The authors have no conflict of interest to disclose.

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