

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.ejcancer.com](http://www.ejcancer.com)

## Review

# Cardiorespiratory fitness and site-specific risk of cancer in men: A systematic review and meta-analysis



D.P. Pozuelo-Carrascosa<sup>a</sup>, C. Alvarez-Bueno<sup>a,\*</sup>, I. Cavero-Redondo<sup>a</sup>,  
S. Morais<sup>b</sup>, I.M. Lee<sup>c,d</sup>, V. Martínez-Vizcaíno<sup>a,e</sup>

<sup>a</sup> Universidad de Castilla-La Mancha, Health and Social Care Research Center, Cuenca, Spain

<sup>b</sup> EPIUnit – Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas 135, 4050-600, Porto, Portugal

<sup>c</sup> Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

<sup>d</sup> Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

<sup>e</sup> Universidad Autónoma de Chile, Faculty of Health Sciences, Talca, Chile

Received 19 December 2018; received in revised form 6 March 2019; accepted 14 March 2019

Available online 11 April 2019

## KEYWORDS

Risk of cancer;  
Site-specific cancer;  
Cardiorespiratory  
fitness;  
Meta-analysis

**Abstract Background:** Cardiorespiratory fitness is a strong predictor of all-cause morbidity and mortality; nevertheless, the association between cardiorespiratory fitness and the risk of cancer remains unclear. Thus, the aim of this study was to synthesize the evidence on the relationship between cardiorespiratory fitness and the risk of several sites of cancer in men.

**Methods:** A computerised search in MEDLINE, EMBASE and Web of Science databases from their inception to 13th February 2019 was performed. Both fixed and random-effects models were used to calculate the pooled hazard ratio (HR) estimates and their 95% confidence intervals (CIs) to examine the effect of high and moderate versus low cardiorespiratory fitness on site-specific cancer (lung, colon/rectum, prostate) and all-sites cancer.

**Results:** Ten studies were included in the qualitative review, and seven of them were included in the meta-analysis. Using low cardiorespiratory fitness as the reference group, moderate and high levels of cardiorespiratory fitness were associated with a lower risk (HRs) of lung cancer, 0.53 (95% confidence interval [CI], 0.39 to 0.68) and 0.52 (95% CI, 0.42 to 0.61); colorectal cancer, 0.74 (95% CI, 0.55 to 0.93) and 0.77 (95% CI, 0.62 to 0.92) and all cancer sites, 0.86 (95% CI, 0.79 to 0.93) and 0.81 (95% CI, 0.75 to 0.87), respectively.

**Conclusions:** Among men, cardiorespiratory fitness plays an important role in protecting against the risk of lung and colorectal cancer. Additionally, this protective effect was observed for all-sites cancer risk. These results show the importance of good cardiorespiratory fitness as a potential factor in cancer prevention.

© 2019 Elsevier Ltd. All rights reserved.

\* Corresponding author: University of Castilla-La Mancha, Health and Social Care Research Center, Cuenca, 16071, Spain.  
E-mail address: [Celia.AlvarezBueno@uclm.es](mailto:Celia.AlvarezBueno@uclm.es) (C. Alvarez-Bueno).

## 1. Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide, and it is the second cause of death globally. In Europe, it has been estimated that in 2018, there were over 3.9 million new cancer cases diagnosed and 1.93 million cancer-related deaths [1,2].

Although genetic factors play an important role in the aetiology of cancer, some environmental and lifestyle risk factors, such as obesity, tobacco use, diet, and physical activity, are associated with the incidence of cancer [3]. Physical activity along with dietary intake and tobacco smoking are among the main modifiable risk factors for cancer through lifestyle changes [4]. In fact, regular physical activity has been associated with the prevention of cancer at various sites [5].

Until recently, cancer epidemiological research has mostly focused on the influence of physical activity on the risk of cancer; nevertheless, evidence for the relationship between cardiorespiratory fitness and cancer incidence has been growing in such a way that it has been established that cardiorespiratory fitness is as strong a predictor of all-cause morbidity and mortality as physical activity is [6]. The preventive role of cardiorespiratory fitness is partially explained by its attenuating role in the relationship between adiposity and cancer mortality [7]; furthermore, higher cardiorespiratory fitness is related to a lower incidence of cardiovascular diseases, diabetes and chronic obstructive pulmonary disease, among others, and people suffering from these diseases have a worse prognosis in the development of cancer [8–10].

A recent umbrella review including 19 reviews addressed the relationship between higher levels of physical activity and a lower risk of cancer at various sites, especially colon and breast cancers [11]; however, the association between cardiorespiratory fitness and the risk of cancer remains unclear. A meta-analysis supported the relationship between higher cardiorespiratory fitness levels and a decrease in total cancer mortality risk [12]; nevertheless, not all cancer cases are fatal. Therefore, this systematic review and meta-analysis aims to synthesize the evidence regarding the relationship between cardiorespiratory fitness and the risk of cancer at several sites.

## 2. Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [13] and Meta-Analysis of Observational Studies in Epidemiology [14], and following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [15]. This systematic review and meta-analysis were registered through PROSPERO (CRD42018088733).

### 2.1. Search strategy

The MEDLINE (via PubMed), EMBASE and Web of Science databases were searched from their inception to 13th February 2019. The search strategy applied included “cardiorespiratory fitness” OR “CRF” OR “maximal oxygen uptake” OR “physical fitness” OR “exercise testing” OR “aerobic capacity” OR “exercise capacity” OR “VO<sub>2</sub>max”) AND (“cancer” OR “carcinoma” OR “neoplasm” OR “site-specific cancer” OR “cancer morbidity”) AND (risk OR incidence\* OR “follow up study” OR cohort). Articles included were prospective studies that analysed the risk of different site-specific cancers. Additionally, the reference lists of the full texts retrieved and pertinent systematic reviews were screened for relevant studies.

### 2.2. Selection criteria

Two reviewers (D.P.P.-C. and C.A.-B.) independently conducted a systematic literature search, and disagreements were solved by consensus or involving a third researcher (V.M.-V.) when necessary. Reviewers were not blinded to authors, journals, or institutions. The criteria for the exclusion of studies were as follows: (i) papers not written in English, French, Portuguese or Spanish; (ii) studies including subjects who had been diagnosed with cancer; (iii) studies not reporting the risk of cancer and/or the level of cardiorespiratory fitness; and (iv) nonprospective studies, such as review articles, editorials, comments, guidelines, or case reports. For the meta-analysis, when a study had multiple published reports, the study providing more detailed data and with the largest sample size was used. Nevertheless, any of the reports could be used to obtain information on the study characteristics.

### 2.3. Search and data extraction

Data extraction was performed independently by two authors (D.P.P.-C. and C.A.-B.) using a standardised data collection form. The following data were collected from each included study: (i) the name of the first author and year of publication; (ii) country; (iii) study name; (iv) period of data collection; (v) sample size; (vi) mean age and (vii) data concerning cardiorespiratory fitness (test used and cardiorespiratory fitness values) and cancer (site, number of events, and hazard ratio [HR] and the respective 95% confidence intervals [95% CIs]).

### 2.4. Risk of bias assessment

The validated Newcastle–Ottawa scale [16] was used for cohort studies to assess the quality of the included studies. In this scale, four points are assigned for the quality of selection, two points for comparability and

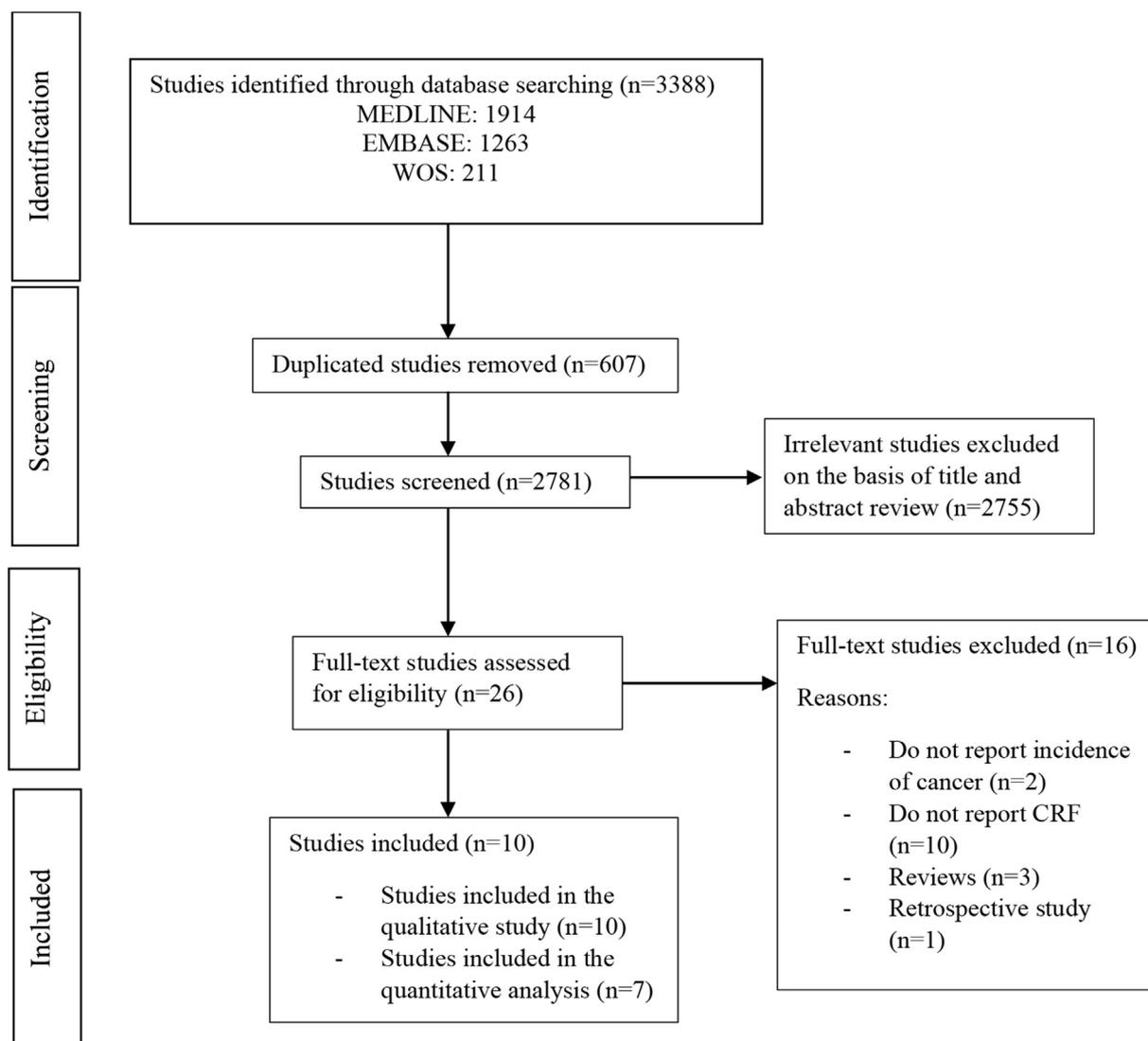


Fig. 1. Literature search: Preferred Reporting Items for Systematic Reviews and Meta-Analyses consort diagram. CRF, cardiorespiratory fitness; WOS, Web of Science.

three points for the quality of outcome and the adequacy of follow-up, for a maximum of nine points. Since no explicit guidelines exist [12,17], for these scores, each study was rated as “good”, “fair” or “poor” quality according to whether it scored six or more points, five or less than five, respectively.

### 2.5. Statistical analysis

The highest, medium, and lowest categories of cardiorespiratory fitness reported in the included studies as “high”, “moderate” and “low” cardiorespiratory fitness equivalents, respectively, and calculated the HR for each study separately by comparing the risk of cancer between the high or moderate cardiorespiratory fitness category and the lowest one. The estimated HR was calculated by comparing risk or protective factors to a reference value.

The Mantel-Haenszel fixed-effects model [18] and the DerSimonian and Laird random-effects model [19] were used to calculate the pooled HR estimates and the corresponding 95% CIs, which were used to examine the effect of high and moderate cardiorespiratory fitness on site-specific cancer (lung, colorectal, prostate) and all-site cancer, using low cardiorespiratory fitness as the reference category. Heterogeneity was assessed by the  $I^2$  statistic [20], using the following values for its interpretation: low (0%–40%), moderate (30%–60%), substantial (50%–90%) and considerable (75%–100%). The corresponding  $p$ -values were also considered [15].

The sensitivity analysis was conducted by calculating the pooled estimates after removing studies one by one to assess the influence of each study on the overall HR.

Statistical analyses were performed using STATA<sup>®</sup> SE software, version 14 (StataCorp, College Station, TX, USA).

### 3. Results

As shown in Fig. 1, of the 3388 potentially eligible references retrieved in the searches, after removing duplicates and screening by the title and abstract, ten studies were ultimately selected. All these studies were included in the qualitative review [21–30], and because some studies reported data from the same sample, only seven studies were included in the meta-analysis [21–25,28,30].

The percentage of agreement between reviewers estimated by the kappa statistic during the title-abstract stage was 91%, and during the full-text stage, the percentage agreement was 90%, and any discrepancies between reviewers in either stage were solved by consensus.

#### 3.1. Studies retrieved and characteristics

The ten studies in this systematic review included 62,899 participants, with sample sizes varying between 2268 and 13,949 participants (Table 1). The mean age of participants ranged from 40.2 to 59.2 years. No studies included women. The length of follow-up ranged from five to 40 years. Studies were conducted in the United States of America [22,25,27,29], Finland [23,26,28], Denmark [30] and Norway [21,24].

Seven studies reported the relationship between cardiorespiratory fitness and the incidence of prostate cancer [21,24,25,27–30], six studies reported the relationship between cardiorespiratory fitness and the incidence of lung cancer [21–23,25,26,28], and five studies described the association between cardiorespiratory fitness and gastrointestinal tract [28,30] or colon cancer [21,22,25]. Finally, two studies reported the relationship between cardiorespiratory fitness and skin cancer [21,22], oral/digestive cancer [21,30] and cancer of other sites such as the liver/bile duct/pancreas or kidney [21,22]; however, the data necessary to calculate the HRs were not available; thus, it was not possible to include these in the meta-analysis.

Regarding the test used for assessing cardiorespiratory fitness levels, four studies used a treadmill for maximal exercise tests [22,25,27,29], two used cycloergometer maximal exercise tests [21,24], one used the submaximal cycloergometer work test [30] and the other three used the maximal treadmill test but limited the tests by symptoms because patients had ischaemic heart disease [23,26,28].

Regarding the primary outcome, the incidence of site-specific cancer was as follows: for prostate cancer, the incidence ranged from 0.7% to 26.6%, for a total of 3012 prostate cancer cases; for skin cancer, a total of 416 cases were diagnosed, and the incidence ranged from 4.1 to 23.1%; 538 cases of lung cancer occurred, ranging in incidence from 1.8% to 4.2% and for colon cancer, 873 cases occurred with the incidence varying from 1.3% to 16.9%. The incidence of kidney cancer ranged from 1.5% to 2.5%, and that of liver/bile duct/pancreas cancer ranged from 1.8% to 3.8%.

#### 3.2. Meta-analysis

Among the seven studies included in the meta-analysis, four reported a relationship between cardiorespiratory fitness and the risk of prostate cancer [21,22,25,30], four studies reported a relationship with the risk of lung cancer [21,23,25,30] and four studies reported a relationship with colon cancer [21,22,25,30]. Additionally, five studies reported data on cardiorespiratory fitness levels and overall cancer risk [22,24,25,28,30]. The study of Nunez *et al.* [30] provided the necessary data to calculate the HR of cancer risk for individuals with high versus low cardiorespiratory fitness but not for moderate versus low cardiorespiratory fitness.

The data extracted from the studies included in the meta-analysis were adjusted for several covariates (see Table 1).

#### 3.3. Risk of bias assessment

All studies included received more than six points based on the Newcastle–Ottawa scale; thus, these studies were of high quality (see online Supplemental Table S1).

#### 3.4. Pooled estimates

Fig. 2 shows a forest plot of cancer risk comparing individuals with moderate versus low cardiorespiratory fitness. A moderate cardiorespiratory fitness level was associated with a lower risk of lung cancer ( $HR_{\text{Mantel-Haenszel}(M+H)} = 0.53$ ; 95% CI, 0.39 to 0.68;  $I^2 = 53.5\%$ ), colorectal cancer ( $HR_{M+H} = 0.74$ ; 95% CI, 0.55 to 0.93;  $I^2 = 48.7\%$ ) and all cancer sites ( $HR_{M+H} = 0.86$ ; 95% CI, 0.79 to 0.93;  $I^2 = 0.0\%$ ). A moderate cardiorespiratory fitness level was not associated with the risk of prostate cancer ( $HR_{M+H} = 1.07$ ; 95% CI, 0.92 to 1.21;  $I^2 = 0.0\%$ ). Also, because only two studies reported data on skin cancer, it was not possible to calculate pooled estimates for this site [21,22].

Fig. 3 shows the pooled estimates of cancer risk for individuals with high versus low cardiorespiratory fitness. High cardiorespiratory fitness was associated with a lower risk of lung cancer ( $HR_{M+H} = 0.52$ ; 95% CI, 0.42 to 0.61;  $I^2 = 62.3\%$ ), colorectal cancer ( $HR_{M+H} = 0.77$ ; 95% CI, 0.62 to 0.92;  $I^2 = 49\%$ ) and all cancer sites ( $HR_{M+H} = 0.81$ ; 95% CI, 0.75 to 0.87;  $I^2 = 0.0\%$ ). No association was found between high cardiorespiratory fitness and prostate cancer ( $HR_{M+H} = 1.15$ ; 95% CI, 1.0 to 1.30;  $I^2 = 0.0\%$ ). Pooled HR estimates for skin, genitourinary and oral/digestive cancers were not calculated because of the scarcity of studies.

#### 3.5. Publication bias and sensitivity analysis

Publication bias was not assessed because fewer than 10 articles were included in each site-specific cancer

Table 1  
Characteristics of studies included in the meta-analysis.

Reference	Country/ Study name	Period of data collection	Sample size	Age mean $\pm$ SD	CRF assessment/ values	Site and incidence of Cancer	Covariates	Risk of bias assessment score <sup>b</sup>
Nunez <i>et al.</i> 2018 [30]	Denmark/ Copenhagen Male Study	1970–2017	5128	48.8 (range 39–61)	Submaximal bicycle work High: 36–78 ml/ kg/min Moderate: 30 –35 ml/kg/min Low: 15–29 ml/ kg/min	Prostate: 7.6% Colorectal: 5.8% Oral/digestive: 10.6% Respiratory/ intrathoracic: 8.9% Genitourinary: 11.1% Other cancers: 6.3% All-cancers: 31.9%	Birth decades, smoking, grams of tobacco a day, alcohol, socioeconomic status, systolic blood pressure, diastolic blood pressure, previous acute myocardial infarction, diabetes, physical activity, BMI and interaction between BMI-CRF	6 points
Robsaahm <i>et al.</i> 2016 [24] and 2017 [21]	Norway/Oslo Ischemia Cohort	1972–2012	1997	<118.9 kJ/ kg: 52.4 $\pm$ 5.2 119 –161.4 kJ/ kg: 49.9 $\pm$ 5.0 >161.4 kJ/ kg: 46.9 $\pm$ 4.8	Total work by bicycle test T1: <118.9 kJ/kg T2: 119 –161.4 kJ/kg T3: >161.4 kJ/kg	All sites: 44.9% Mouth/ pharynx: 1.0% Oesophagus/ stomach: 1.8% Colon: 3.7% Rectum: 1.9% Liver/ gallbladder/bile duct: 0.6% Pancreas: 1.2% Lung: 4.7% Prostate: 9.1% Kidney: 1.5% Bladder: 3.2% Skin: 4.1% Lymphoma: 1.3% Leukaemia: 1.6% Central nervous system: 0.8%	Age, BMI and smoking	9 points (both)
Vainshelboim <i>et al.</i> 2017 [22]	USA/ Veterans Exercise Testing Study	1987–2012	4920	59.2 $\pm$ 11.4	Maximal treadmill exercise test Low: <5.0 METs Moderate: 5.0 –10.0 METs High: >10.0 METs	All sites: 25.8% Skin: 23.1% Prostate: 26.6% Colon/rectum: 16.9% Lung: 8.2% Head/neck: 4.3% Liver/bile duct/ pancreas: 3.8% Kidney: 2.5% Lung: 3.2%	Age, smoking status, history of drug and alcohol abuse, presence of diabetes and BMI	7 points
Pletnikoff <i>et al.</i> 2015 <sup>26</sup> and <sup>a</sup> 2016 [23]	Finland/ Kuopio Ischemic Heart Disease (KIHD)	1984–1989	2276	Without cancer: 52.8 $\pm$ 5.1 Lung cancer: 54.3 $\pm$ 4.5	Maximal symptom-limited exercise tolerance test Q1: 5.8 (1.8–7.2) Q2: 7.9 (7.2–8.6) Q3: 9.3 (8.6 –10.0) Q4: 11.6 (10.0 –18.7)	Lung: 3.2%	Age, date of examination year, cancer in family, smoking (cig/years), education and alcohol and fruits and vegetables intake	9 points (both)
Lakoski <i>et al.</i> 2015 [25]	USA/Cooper Center Longitudinal Study	1971–2009	13949	Low fit: 46.0 $\pm$ 8.0 Moderate fit:	Maximal treadmill exercise test Low: 8.4 $\pm$ 1.2	All sites: 12.1% Lung: 1.4% Colon: 1.3% Prostate: 9.4%	Age, visit date, BMI, smoking, systolic blood pressure, cholesterol, diabetes and fasting	8 points

Table 1 (continued)

Reference	Country/ Study name	Period of data collection	Sample size	Age mean $\pm$ SD	CRF assessment/ values	Site and incidence of Cancer	Covariates	Risk of bias assessment score <sup>b</sup>
	(CCLS)			49.0 $\pm$ 8.0 High fit: 51.0 $\pm$ 8.0	METs Moderate: 10.4 $\pm$ 1.2 METs High: 13.0 $\pm$ 1.8 METs		glucose	
<sup>a</sup> Byun et al. 2011 [27]	USA/ Aerobics Center Longitudinal Study (ACLS)	1976–2003	19042	Low fit: 44.4 $\pm$ 9.3 Moderate fit: 45.4 $\pm$ 9.5 High fit: 45.9 $\pm$ 9.9	Maximal treadmill exercise test Low: 8.6 $\pm$ 1.2 METs Moderate: 10.7 $\pm$ 1.2 METs High: 13.6 $\pm$ 2.0 METs	Prostate: 3.3%	Age, examination year, physical activity, current smoking, alcohol intake, family history of prostate cancer, diabetes, hypertension, hypercholesterolaemia, waist circumference and BMI	7 points
Laukkanen et al. 2010 [28]	Finland/ Kuopio Ischemic Heart Disease (KIHD)	1984–1989	2268	Low fit: 52.8 $\pm$ 5.1 Moderate fit: 55.0 $\pm$ 4.1 High fit: 52.7 $\pm$ 4.8	Maximal symptom-limited exercise tolerance test Low: <8.3 METs Moderate: 8.3 –9.5 METs High: >9.5 METs	All sites: 17.1% Lung: 2.3% GI tract: 4.1% Prostate: 5.6%	Age, examination year, cigarette smoking, alcohol consumption, waist-to-hip ratio, socioeconomic status and total caloric, fibre and fat intake	9 points
<sup>a</sup> Oliveria et al. 1996 [29]	USA/Cooper Clinic	1971–1989	12975	<13.7 min: 50.0 $\pm$ 10.0 13.7 –17.0 min: 44.9 $\pm$ 9.4 17.0 –21.0 min: 42.5 $\pm$ 8.9 >21.0 min: 40.2 $\pm$ 8.6	Maximal treadmill exercise test Q1: <13.7 min Q2: 13.7 –17.0 min Q3: 17.0 –21.0 min Q4: >21.0 min	Prostate: 0.7%	Age, BMI and smoking status	7 points

SD, standard deviation; CRF, cardiorespiratory fitness; METs, metabolic equivalents; BMI, body mass index.

<sup>a</sup> Study not included in the meta-analysis.

<sup>b</sup> Scores obtained based on the Newcastle–Ottawa scale [16]. According to these scores, each study was rated as “good”, “fair” or “poor” quality based on whether it scored six or more points, five or less than five, respectively.

subgroup [31]. In the sensitivity analysis, when the impact of individual studies was examined by removing studies from the analysis one at a time, none of these studies modified the pooled HR estimate.

#### 4. Discussion

To date, no study has synthesised the relationship between cardiorespiratory fitness and the risk of site-specific cancer. Our meta-analysis showed a significant reduction in the risk of lung cancer (47%), colorectal cancer (26%) and all cancer sites (14%) when comparing males with moderate versus low cardiorespiratory fitness levels. Additionally, a decrease in the risk of lung cancer (48%), colorectal cancer (23%) and all cancer sites (19%) was observed among males with high versus low cardiorespiratory fitness levels.

A previous meta-analysis reported an inverse relationship between cardiorespiratory fitness and all cancer

sites mortality [12]. Because not all cancer cases are fatal, the ability of cardiorespiratory fitness to prevent the incidence of cancer was examined in this review. As reported with mortality, our study demonstrates that aerobic capacity represents a strong negative predictor for the risk of developing cancer. Since each cancer site could have several etiological mechanisms, the influence of cardiorespiratory fitness on the risk of a specific-site of cancer may substantially differ for each cancer. However, to a greater or lesser extent, the preventive impact of cardiorespiratory fitness on cancer risk is conveyed through several potential mechanisms such as chronic inflammation [32], innate immunity [33], DNA repair ability [34], apoptosis and cell proliferation [35] and steroid hormone levels [36].

Most lung cancer cases are attributable to tobacco smoking [37,38], even with secondhand smoke exposure [39]. To a lesser extent, the relationship between cardiorespiratory fitness and lung cancer has been

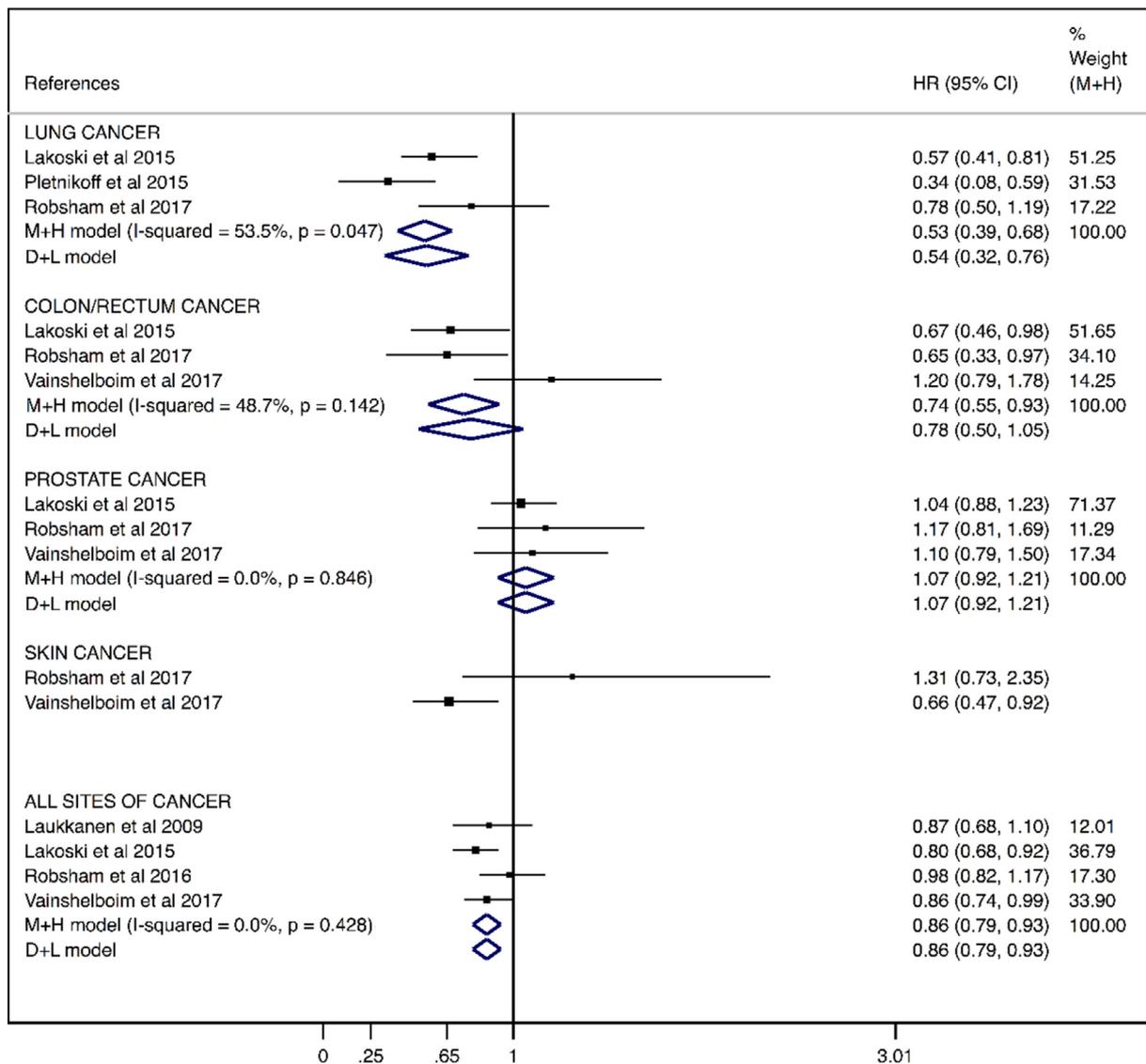


Fig. 2. Forest plot of site-specific risk of cancer for individuals with moderate versus low cardiorespiratory fitness. HR, hazard ratio; CI, confidence interval; M + H, Mantel-Haenszel method; D + L, DerSimonian and Laird method.

suggested by previous studies [40,41]. In the same way, smoking poses an additional risk for lung cancer because of its negative effect on cardiorespiratory fitness [42]. Our findings support that both moderate and high cardiorespiratory fitness play a protective role in lung cancer risk, even after controlling for smoking habits, since in all the included studies, this behaviour was adjusted for. Several of the mechanisms mentioned previously have been argued to link cardiorespiratory fitness and cancer; among them, the ability of cardiorespiratory fitness to inhibit tumour initiation and progression by decreasing circulating steroid hormone levels [36] plays a pivotal role. In addition, high aerobic capacity improves immune system function by increasing the number of natural killer cells [43], as well as the anti-inflammatory effect [36].

Higher levels of physical activity are inversely related to the risk of colon cancer [44,45]; however, although cardiorespiratory fitness reflects the functional consequences of the physical activity habits of the person [44], there are few studies assessing the relationship between cardiorespiratory fitness and the risk of colon cancer. Our study showed a lower risk of colorectal cancer in men with moderate and high versus low cardiorespiratory fitness. However, these results should be interpreted cautiously because information on alcohol consumption and dietary factors is lacking, and these are important risk factors associated with both exercise-related behaviours and colon cancer [46,47].

Surprisingly, our meta-analysis did not find any association between cardiorespiratory fitness and prostate

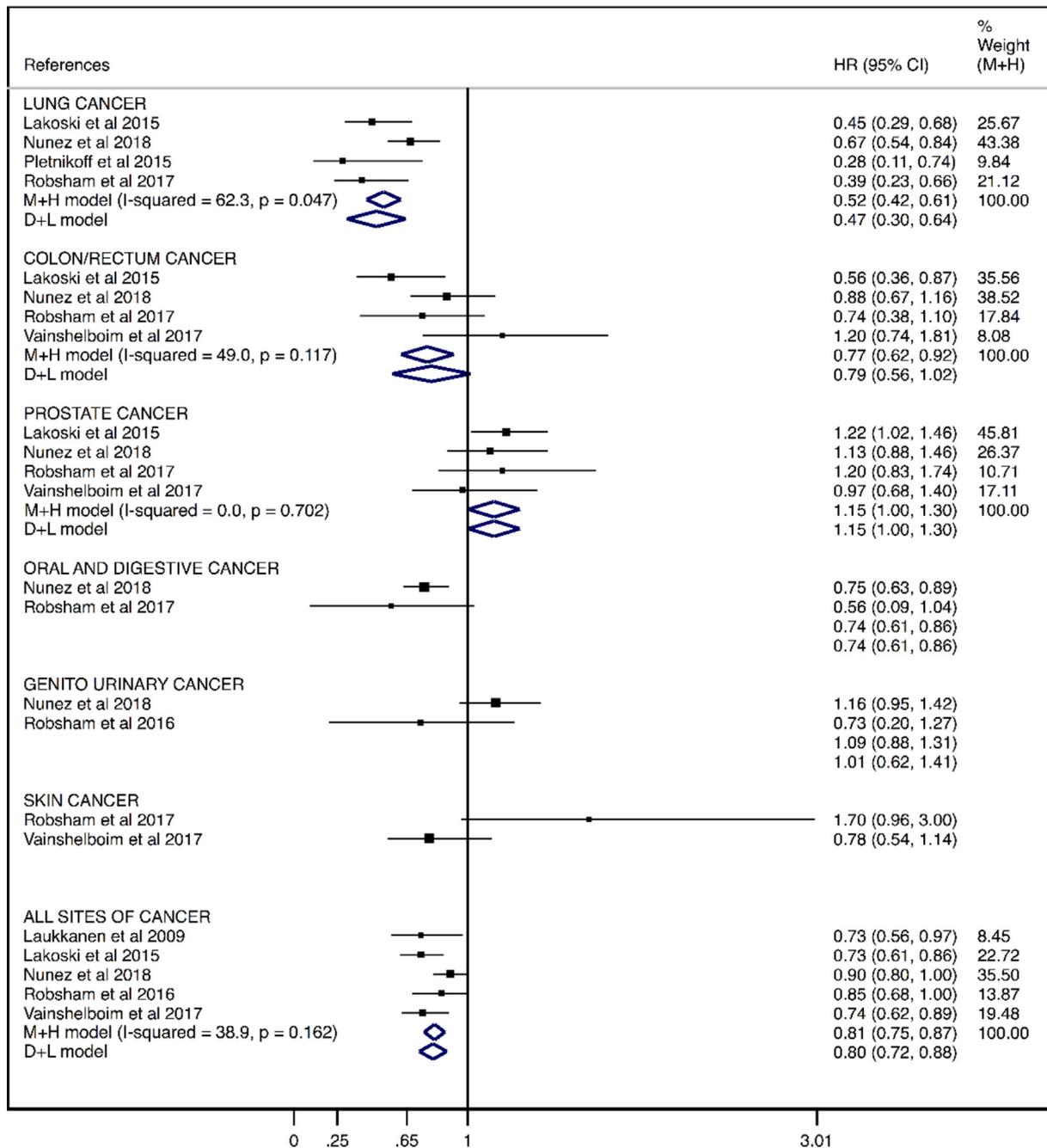


Fig. 3. Forest plot of site-specific risk of cancer for individuals with high versus low cardiorespiratory fitness. HR, hazard ratio; CI, confidence interval; M + H, Mantel-Haenszel method; D + L, DerSimonian and Laird method.

cancer risk. This could be because the included studies involved white (Caucasian) and high socioeconomic status men, and it has been argued that people with high socioeconomic level are usually more physically active and aware of their health status. As a consequence, a possible selection bias due to a higher number of small prostate tumours diagnosed could be the reason behind this lack of association [21].

A pooled HR was not calculated for the results between cardiorespiratory fitness level and risk of skin cancer because only two studies [21,22] provided data on

this cancer. They reported conflicting results; in one study, a direct relationship between cardiorespiratory fitness and skin cancer incidence was found [21], and in the other, there was an inverse relationship between higher categories of cardiorespiratory fitness and skin cancer incidence, and this association was statistically significant for moderate versus low cardiorespiratory fitness [22]. A potential explanation behind the former positive association could be that physically active people spend more time outdoors than sedentary people, and therefore, the former are more exposed to

ultraviolet radiation from the sun, which is the main risk factor for skin cancer [48].

Likewise, a pooled HR was not calculated for the results between cardiorespiratory fitness level and risk of genitourinary [24,30] and oral/digestive [21,30] cancers because only two studies provided data on these cancers.

Finally, when site-specific cancer was not taken into account, our study revealed that individuals with moderate and/or high levels of cardiorespiratory fitness levels had a lower risk of cancer (all-cancers combined) compared those with low levels of cardiorespiratory fitness.

#### 4.1. Strengths and limitations

This meta-analysis has several limitations that should be highlighted. First, a limited number of studies were included because the relationship between cardiorespiratory fitness and the risk of cancer has not been frequently studied. Second, all participants in the included studies were white and high socioeconomic status men, which limits the generalisability and the external validity of these results. Also related to this gender limitation, it is surprising that although a negative relationship has been found between cardiorespiratory fitness and breast cancer mortality [49], no studies have established the relationship between cardiorespiratory fitness and the risk of breast cancer since, fortunately, most of these cancers are not lethal. Third, cancer risk is related to several lifestyle habits such as smoking, physical activity and a healthy diet [50]; although the studies included adjustments for many of these risk factors, it would have been interesting to analyse the influence of these risk factors on the relationship between cardiorespiratory fitness and cancer risk.

The first strength of our study is that it is the first quantitative synthesis of the relationship between cardiorespiratory fitness and cancer risk. Additionally, this meta-analysis included high-quality studies, with a large number of participants and long periods of follow-up. Another important strength is that cardiorespiratory fitness was measured with objective, validated and reproducible tests.

## 5. Conclusions

In conclusion, our findings suggest that cardiorespiratory fitness in men may be associated with a lower risk of lung and colorectal cancer but not prostate cancer. Because exercise programs have demonstrated their ability to increase cardiorespiratory fitness in no more than 12–14 weeks [51,52]; our results, along with those previous studies relating cardiorespiratory fitness with cancer mortality, provided evidence to encourage people to engage in exercise programs to prevent lung and

colorectal cancer. However, these findings are based on a limited number of studies carried out in white and high socioeconomic status men; further high-quality studies including both men and women and other cancer sites are needed.

## Conflict of interest statement

None declared.

## Funding source

Diana P. Pozuelo-Carrascosa (FPU14/01370) is supported by a grant from the Spanish Ministry of Education, Culture and Sport (FPU13/03137). Iván Caverro-Redondo is supported by a grant from the Universidad de Castilla-La Mancha (FPU13/01582). Samantha Morais is supported by FEDER through the Operational Programme Competitiveness and Internationalization and national funding from the Foundation for Science and Technology – FCT (Portuguese Ministry of Science, Technology and Higher Education) under the Unidade de Investigação em Epidemiologia and Instituto de Saúde Pública da Universidade do Porto (EPI-Unit) (POCI-01-0145-FEDER-006862; Ref. UID/DTP/04750/2013) and under the scope of the project “NEON-PC - Neuro-oncological complications of prostate cancer: longitudinal study of cognitive decline” (POCI-01-0145-FEDER-032358; Ref. PTDC/SAU-EPI/32358/2017).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2019.03.008>.

## References

- [1] Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 2018;103:356–87.
- [2] Global cancer observatory: cancer today. International Agency for Research on Cancer; 2018. <https://gco.iarc.fr/today>.
- [3] Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. *Lancet Oncol* 2017;18:e457–71.
- [4] Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. *J Nutr* 2002;132:3456s–64s.
- [5] Winzer BM, Whiteman DC, Reeves MM, Paratz JD. Physical activity and cancer prevention: a systematic review of clinical trials. *Cancer Causes Control* 2011;22:811–26.
- [6] Lee IM, Shiroma EJ, Evenson KR, et al. Accelerometer-measured physical activity and sedentary behavior in relation to all-cause mortality: the women’s health study. *Circulation* 2018;137:203–5.
- [7] Farrell SW, Cortese GM, LaMonte MJ, Blair SN. Cardiorespiratory fitness, different measures of adiposity, and cancer mortality in men. *Obesity (Silver Spring)* 2007;15:3140–9.

- [8] Janssen-Heijnen ML, Szerencsi K, van de Schans SA, Maas HA, Widdershoven JW, Coebergh JW. Cancer patients with cardiovascular disease have survival rates comparable to cancer patients within the age-cohort of 10 years older without cardiovascular morbidity. *Crit Rev Oncol Hematol* 2010;76:196–207.
- [9] Janssen-Heijnen ML, Maas HA, Houterman S, Lemmens VE, Rutten HJ, Coebergh JW. Comorbidity in older surgical cancer patients: influence on patient care and outcome. *Eur J Cancer* 2007;43:2179–93.
- [10] van de Schans SA, Janssen-Heijnen ML, Biesma B, Smeenk FW, van de Poll-Franse LV, Seynaeve C, et al. COPD in cancer patients: higher prevalence in the elderly, a different treatment strategy in case of primary tumours above the diaphragm, and a worse overall survival in the elderly patient. *Eur J Cancer* 2007;43:2194–202.
- [11] Rezende LFM, Sa TH, Markozannes G, et al. Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases. *Br J Sports Med* 2018;52:826–33.
- [12] Schmid D, Leitzmann MF. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. *Ann Oncol* 2015;26:272–8.
- [13] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
- [14] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *J Am Med Assoc* 2000;283:2008–12.
- [15] Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions* version 5.1. 0. The Cochrane Collaboration; 2011. p. 5.
- [16] Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2018. . [Accessed 19 April 2018].
- [17] Penson D, Krishnaswami S, Jules A, McPheeters ML. Effectiveness of hormonal and surgical therapies for cryptorchidism: a systematic review. *Pediatrics* 2013;131:e1897–907.
- [18] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719–48.
- [19] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials* 1986;7:177–88.
- [20] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- [21] Robsahm TE, Falk RS, Heir T, et al. Cardiorespiratory fitness and risk of site-specific cancers: a long-term prospective cohort study. *Cancer Med* 2017;6:865–73.
- [22] Vainshelboim B, Muller J, Lima RM, et al. Cardiorespiratory fitness and cancer incidence in men. *Ann Epidemiol* 2017;27:442–7.
- [23] Pletnikoff PP, Tuomainen TP, Laukkanen JA, et al. Cardiorespiratory fitness and lung cancer risk: a prospective population-based cohort study. *J Sci Med Sport* 2016;19:98–102.
- [24] Robsahm TE, Falk RS, Heir T, et al. Measured cardiorespiratory fitness and self-reported physical activity: associations with cancer risk and death in a long-term prospective cohort study. *Cancer Med* 2016;5:2136–44.
- [25] Lakoski SG, Willis BL, Barlow CE, et al. Midlife cardiorespiratory fitness, incident cancer, and survival after cancer in men: the cooper center longitudinal study. *JAMA Oncol* 2015;1:231–7.
- [26] Pletnikoff PP, Laukkanen JA, Tuomainen TP, et al. Cardiorespiratory fitness, C-reactive protein and lung cancer risk: a prospective population-based cohort study. *Eur J Cancer* 2015;51:1365–70.
- [27] Byun W, Sui X, Hebert JR, et al. Cardiorespiratory fitness and risk of prostate cancer: findings from the Aerobics Center Longitudinal Study. *Cancer Epidemiol* 2011;35:59–65.
- [28] Laukkanen JA, Pukkala E, Rauramaa R, et al. Cardiorespiratory fitness, lifestyle factors and cancer risk and mortality in Finnish men. *Eur J Cancer* 2010;46:355–63.
- [29] Oliveria SA, Kohl III HW, Trichopoulos D, Blair SN. The association between cardiorespiratory fitness and prostate cancer. *Med Sci Sports Exerc* 1996;28:97–104.
- [30] Nunez C, Clausen J, Jensen MT, et al. Main and interactive effects of physical activity, fitness and body mass in the prevention of cancer from the Copenhagen Male Study. *Sci Rep* 2018;8:11780.
- [31] Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
- [32] Martinez-Gomez D, Eisenmann JC, Gomez-Martinez S, et al. Associations of physical activity and fitness with adipocytokines in adolescents: the AFINOS Study. *Nutr Metabol Cardiovasc Dis* 2012;22:252–9.
- [33] Nieman DC, Henson DA, Gusewitch G, et al. Physical activity and immune function in elderly women. *Med Sci Sports Exerc* 1993;25:823–31.
- [34] Pittaluga M, Parisi P, Sabatini S, et al. Cellular and biochemical parameters of exercise-induced oxidative stress: relationship with training levels. *Free Radic Res* 2006;40:607–14.
- [35] Campbell KL, McTiernan A, Li SS, et al. Effect of a 12-month exercise intervention on the apoptotic regulating proteins Bax and Bcl-2 in colon crypts: a randomized controlled trial. *Cancer Epidemiol Biomark Prev* 2007;16:1767–74.
- [36] Koelwyn GJ, Wennerberg E, Demaria S, Jones LW. Exercise in regulation of inflammation-immune Axis function in cancer initiation and progression. *Oncology (Williston Park)* 2015;29:908–20. 922.
- [37] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics. *CA Cancer J Clin* 2002;55:74–108. 2005.
- [38] Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. *Lung Canc* 2001;31:139–48.
- [39] Hori M, Tanaka H, Wakai K, et al. Secondhand smoke exposure and risk of lung cancer in Japan: a systematic review and meta-analysis of epidemiologic studies. *Jpn J Clin Oncol* 2016;46:942–51.
- [40] Sui X, Lee DC, Matthews CE, et al. Influence of cardiorespiratory fitness on lung cancer mortality. *Med Sci Sports Exerc* 2010;42:872–8.
- [41] Jones LW, Watson D, Herndon 2nd JE, et al. Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer. *Cancer* 2010;116:4825–32.
- [42] Misigoj-Durakovic M, Bok D, Soric M, et al. The effect of cigarette smoking history on muscular and cardiorespiratory endurance. *J Addict Dis* 2012;31:389–96.
- [43] Shephard RJ, Shek PN. Associations between physical activity and susceptibility to cancer: possible mechanisms. *Sports Med* 1998;26:293–315.
- [44] Peel JB, Sui X, Matthews CE, et al. Cardiorespiratory fitness and digestive cancer mortality: findings from the aerobics center longitudinal study. *Cancer Epidemiol Biomark Prev* 2009;18:1111–7.
- [45] Friedenreich CM. Physical activity and cancer prevention: from observational to intervention research. *Cancer Epidemiol Biomark Prev* 2001;10:287–301.
- [46] Pan P, Yu J, Wang LS. Colon cancer: what we eat. *Surg Oncol Clin N Am* 2018;27:243–67.
- [47] Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Canc* 2015;112:580–93.
- [48] Coglianò VJ, Baan R, Straif K, et al. Preventable exposures associated with human cancers. *J Natl Cancer Inst* 2011;103:1827–39.
- [49] Peel JB, Sui X, Adams SA, et al. A prospective study of cardiorespiratory fitness and breast cancer mortality. *Med Sci Sports Exerc* 2009;41:742–8.

- [50] Dartois L, Fagherazzi G, Boutron-Ruault MC, et al. Association between five lifestyle habits and cancer risk: results from the E3N cohort. *Cancer Prev Res (Phila)* 2014;7:516–25.
- [51] Batacan RB, Duncan MJ, Dalbo VJ, et al. Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. *Br J Sports Med* 2016;0:1–12.
- [52] Gillen JB, Martin BJ, MacInnis MJ, et al. Twelve weeks of sprint interval training improves indices of cardiometabolic health similar to traditional endurance training despite a five-fold lower exercise volume and time commitment. *PLoS One* 2016;11: e0154075.