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Association between physical activity and colorectal cancer risk and prognosis: A meta-analysis

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ABSTRACT

Reverse correlation has been frequently reported between physical activity (PA) and colorectal cancer (CRC) risk and mortality in numerous prospective studies. But the contradictive results make the conclusion elusive. Here we aim to cover the effects of pre-diagnosis in CRC incidence, pre- and post-diagnosis with CRC prognosis and overall mortality. With the eligible prospective studies up to 2015, the associations of pre-diagnosis or post-diagnosis PA with CRC risk, CRC prognosis, or all-cause mortality in the modes of exerciser Vs. non-exerciser and highest PA Vs. lowest PA were investigated by combing the hazard ratios (HRs) in random effects. We also tested the effect of single study on the summary estimates using influence-analysis. Publication bias was evaluated by Egger's and Begg's test. Compared with low pre-diagnosis PA group, the high PA group displayed a reduced risk (HR: 0.78 0.66–0.92) to develop CRC. Our findings also showed that both pre- and post-diagnosis PA were significantly associated with better CRC-specific prognosis and reduced risk of overall mortality in both exerciser Vs. non-exerciser and high PA Vs. low PA modes. With the most updated prospective studies, our systematic meta-analysis confirmed the beneficial effects of PA to CRC incidence and prognosis.

1. Introduction

Cancer is a global leading cause of morbidity and mortality, with about 14 million new cases and 8.2 million cancer related deaths (14.6% of all human deaths) in 2012 [1]. Physical inactivity, together with high body mass index (BMI), unhealthy diet, smoking and alcohol use are the 5 main risk factors causing about one third of cancer deaths. The effect of physical activity (PA) has been discovered in many cancers such as breast cancer, colorectal cancer (CRC), pancreatic cancer, prostate cancer, esophageal and gastric cardia cancer, head and neck cancer and endometrial cancer [2–8]. Recent meta-analysis supports that moderate PA reduces cancer mortality in both the general population and cancer survivors [9]. However, PA levels in populations especially cancer survivors are insufficient [10,11], so further investigations on the importance of PA in cancer are still needed.

CRC is the third commonly diagnosed cancer and the fourth leading cause of cancer death worldwide [1]. The benefit of PA in reducing CRC risk was first discovered early in 1980' [12,13]. Since 2006, several influential studies analyzed the relationships of PA with CRC recurrence and mortality [14–16]. But the subsequent studies showed inconsistent results which made the effect of PA in CRC elusive, especially whether pre-diagnosis PA reduced the risk of death [17–19]. More studies have been published in recent years for corroborating the overall benefit of PA in CRC prognosis further. To systematically analyze the association of PA with CRC, we carried out a meta-analysis combing studies up to 2015, covering the effect of pre-diagnosis in CRC incidence, pre- and post-diagnosis with CRC prognosis and overall mortality.

2. Materials and methods

2.1. Literature searching strategy

This meta-analysis was conducted following the guidelines of Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) [20]. An extensive literature search with no language restriction was performed in PubMed, Medline, and Embase (through 2015 Oct.) for studies focusing on the association between PA and CRC cancer risk or prognosis using key terms of

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"physical activity" with all the possible combination of "colorectal", "colon", or "rectal" and "tumor", "neoplasm", or "cancer". We also searched additional studies from reference lists of selected articles or review papers.

2.2. Inclusion criteria

The following inclusion criteria were used to identify the eligibility of each retrieved study: a full-published cohort study; the outcomes should be CRC risk, CRC specific prognosis, or all-cause mortality; specified PA exposure: pre- or post-diagnosis PA; at least two PA categories with information about the number of cases and personyears or participants, or it at least provided sufficient information to calculate these values; Hazard Ratio (HR) and its 95% CIs should be provided. The inclusion analysis was performed independently by three investigators (XYZ, JW, and LLW).

2.3. Data extraction

Data extraction was conducted by JW followed by two rounds of quality assessments by XYZ and LY. The following information was extracted: author and publication year, gender, population, population size, study duration, mean age of participants, mean time period between diagnosis and PA assessment, PA types (total PA, recreational PA, leisure-time PA or occupational PA) outcomes (association of pre- or post-diagnosis PA with CRC risk, CRC prognosis, or all-cause mortality), and most adjusted risk estimates and their 95% CIs with the corresponding PA categories.

2.4. Statistical analysis

Two comparison modes were applied in this meta-analysis: exerciser Vs. non-exerciser and highest PA Vs. lowest PA. In exerciser Vs. non-exerciser mode, the first PA category (reference group) was designated as "non-exerciser group", while the rest categories above the reference group were pooled as "exerciser group". The first and last PA category were designated as "lowest PA" and "highest PA" group, respectively. The meta-analysis was performed to combine the HRs in random effect. We compared the results between the random-effects and fixed-effects model to analyze the sensitivity. I-squared statistic was used to indicate the proportion of heterogeneity between studies in total variation; the cut-off points for low, moderate, and high degrees of heterogeneity were 25%, 50%, and 75%, respectively. We also tested the effect of single study on the summary estimates using influence-analysis [21]. Publication bias was evaluated by Egger's and Begg's test [22]. Software Stata 12.0 was used for all of the statistical analyses. All reported p values were two-sided and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of included datasets

After rigorous screening procedures, we obtained 16 eligible prospective studies that reported the association between levels of pre- or/and post-diagnosis PA and CRC risk, or/and CRC-specific prognosis, or/and all-cause mortality [10,14–19,23–32] (Fig. 1). For better investigating the effects of PA on CRC, we extracted all datasets available from these 17 studies and divided into five subgroups: pre-diagnosis-PA and CRC risk (I), pre-diagnosis-PA and CRC-specific prognosis(II), pre-diagnosis-PA and all-cause mortality(III), post-diagnosis-PA and CRC-specific prognosis(IV), and post-diagnosis-PA and all-cause mortality(V). Initially, there were

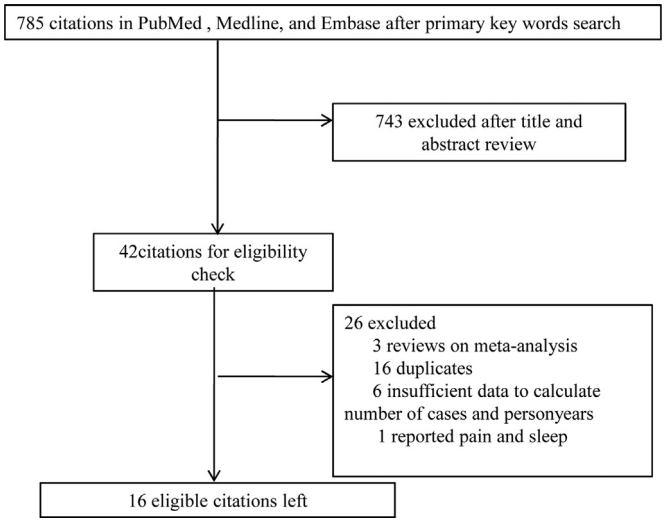

Fig. 1. Flow diagram of searching and selection strategy.

6 [23,24,31], 8 [15,16,19,27–29,32], 8 [15,16,19,27–29,32], 9 [14,16–19,25,26,28,30], and 8 [14,16–19,26,28,30] datasets for group I-V, respectively. In group IV, there were 4 [16,17,26,30] and 2 [14,25] datasets reported association of post-diagnosis-PA and CRC-specific mortality utilizing the same cohorts as NHS/ HPFS and GALGB/89803, respectively. We kept most updated datasets by excluding duplication, eventually 7 datasets were left in group IV. Similarly, 3 datasets were excluded from group V. So the final lists for group I-V are 6 [23,24,31], 8 [15,16,19,27–29,32], 8 [15,16,19,27–29,32], 5 [18,19,25,26,28], and 5 [14,18,19,26,28], respectively.

All the selected articles were published in English. There are 3 Australian and 3 European epidemiological studies, the rest were performed in American. Three studies distinguished colon and rectal cancer when reporting association with PA. The average age of participants ranges from 51.8–70.0 years old. The number of accumulated participants is 1,323,328. The rang of mean follow-up years and time period between diagnosis and assessment are 3.8–13 years and 4–36 months, respectively. Most of PA data were obtained by self-administered questionnaires, while 4 studies applied interview-administered questionnaires. The characteristics of included studies are listed in Table 1.

3.2. Association of pre-diagnosis PA with CRC risk

Six datasets on pre-diagnosis PA and CRC risk were available for meta-analysis (Suppl. Fig. 1). Compared with non-exercisers, the exercisers showed combined HR of 0.93 (95% CI: 0.82–1.05) to develop CRC. In highest Vs. lowest PA mode, the high PA group displayed a HR of 0.78 (0.66–0.92). The heterogeneities among the studies were moderate (exerciser Vs. non-exerciser: I-squared 68.7%, $p = 0.007$; highest PA Vs. lowest PA: I-squared 55.8%, $p = 0.045$).

3.3. Association of pre-diagnosis PA with CRC-specific prognosis and all-cause mortality

There were 8 datasets which reported association of pre-diagnosis PA with CRC-specific prognosis (Suppl. Fig. 2). The combined HRs in exerciser Vs. non-exerciser and highest PA Vs. lowest PA mode are 0.65(0.56–0.76) and 0.83(0.70–0.98), respectively. A moderate heterogeneity among studies was observed in exerciser Vs. non-exerciser mode (I-squared 65.3%, $p = 0.005$), while there was no significant heterogeneity in the mode of highest PA Vs. lowest PA ($p > 0.11$).