Physical activity and the risk of proximal colon and distal colon cancers: A meta-analysis

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Abbreviations: CI, Confidence Interval; RR, Relative Risk; RRR, Ratio of Risk Ratios

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ABSTRACT

Background: Although there is convincing evidence that physical activity reduces the risk of colon cancer, it is unclear whether it has a different effect on the risk of proximal colon and distal colon cancers. We conducted a systematic review and meta-analysis to investigate this issue.

Methods: Medline and EMBASE were used to search the literature for studies that have investigated the association between physical activity and the risk of proximal colon and distal colon cancers. A random-effects meta-analysis was conducted to estimate the summary relative risk (RR) of physical activity on the risk of cancers at the two sites.

Results: A total of 19 studies met the inclusion criteria. The summary relative risk of the main results from these studies indicated that the risk of proximal colon cancer was 27% lower among the most physically active people compared with the least active people (RR=0.73, 95% Confidence Interval =0.66-0.81). An almost identical result was found for distal colon cancer (RR=0.74, 95% Confidence Interval=0.68-0.80).

Conclusion: The results of this systematic review and meta-analysis suggest that there is strong and consistent evidence that physical activity is associated with a reduced risk of proximal colon and distal colon cancers, and that the association does not differ by subsite. Given this finding, future research on physical activity and colon cancer should focus on other aspects of the association that remain unclear, such as whether the intensity of physical activity matters, the effect of sedentary behaviour, and the effect of non-aerobic physical activity.

INTRODUCTION

The association between physical activity and the risk of colon cancer is well established, with the majority of studies finding that the most active individuals have a significantly lower risk of colon cancer compared to the least active (1, 2). A recent meta-analysis estimated that this risk reduction is approximately 24% for both males and females (3). Despite the extensive research that has been conducted in this area, there are several elements of the association between physical activity and colon cancer that remain unclear (4).

One of these issues is whether physical activity has a different effect on the risk of proximal colon and distal colon cancers. It has been proposed that proximal colon and distal colon cancers may be two distinct types of cancers with different genetic and environmental risk factors (5). There are embryologic, morphologic, physiologic and biochemical differences between the proximal colon and the distal colon, and morphologic, molecular and genetic differences between cancers arising in the proximal colon and the distal colon (5). There are also epidemiologic differences: older people and females are more likely to develop proximal colon cancer while distal colon cancers are more common in younger people and males, and while there has been an increase in the incidence of proximal colon cancer in Western countries, the incidence of distal colon cancer has decreased (5).

Examining whether physical activity has a different effect on proximal colon and distal colon cancers is important for several reasons. It may lead to a better understanding of the etiology of colon cancer. There may also be implications for future research in this area, especially if physical activity has a greater effect on distal colon cancer. Adenomas, which are known precursors to carcinomas, are more likely to be removed during flexible sigmoidoscopy and colonoscopy procedures when they are distally rather than proximally located (6, 7), and colonoscopy has been shown to confer a greater risk reduction for advanced neoplasms in the distal colorectum than those in the proximal colorectum (8). As such, the association between physical activity and colon cancer may attenuate as colorectal cancer screening programs become more widespread (1). The results of studies that have examined this issue have been inconsistent, and it remains unclear whether physical activity has a different effect on the risk of proximal colon and distal colon cancers (9). We conducted a systematic review and meta-analysis to investigate this issue. This review follows the PRISMA guidelines (10).

METHODOLOGY

Eligibility criteria and search strategy

We used Medline (from 1946 to January 16, 2012) and EMBASE (from 1947 to January 16, 2012) to search the literature for all cohort or case-control studies, published in English, that investigated the association between physical activity and the risk of incident proximal colon and distal colon cancers in humans. Note that 'right colon', 'right-sided colon' and 'proximal colon' were considered to be analogous terms, as were 'left colon', left-sided colon' and 'distal colon'.

To be included a study must have classified colon cancer into no more than two outcomes (i.e. proximal colon cancer and distal colon cancer), and the study must have defined the proximal colon as including at least the cecum, the ascending colon and the transverse colon, but no anatomic sites distal to the splenic flexure, and the distal colon as including at least the descending and sigmoid colons, but not the rectosigmoid junction or the rectum, and no anatomic sites proximal to the splenic flexure. We also included studies that investigated the effect of physical activity on anatomic-specific sites within the colon (i.e. cecum, ascending colon, and so on) and reported sufficient information for us to combine the results from these anatomic sites and calculate an effect size for our desired definitions of proximal colon and distal colon.

The following search strategy was used: (exercise or physical activity or walking or motor activity) and (colon or colorectal or rectum or rectal or bowel) and (cancer or neoplasm or carcinoma). We also manually searched the reference list of all the included original studies, as well as several recent review articles (1-3). After removal of duplicates, all the articles obtained from the searches of the database and reference lists were screened by one author (TB) to identify papers that investigated the effect of physical activity on the risk of colon cancer or colorectal cancer. Two authors (TB and TK) then independently read the full text of all these articles to determine whether the study met the eligibility criteria outlined above. Differences were resolved by discussion.

Data extraction

Data were extracted by one author (TB) using a data extraction form and entered into a database. A second author (TK) independently checked these data, and all differences were resolved by discussion. For each study, we extracted the estimated effect (relative risk or odds ratio), and its associated 95% confidence interval, of physical activity on the risk of proximal colon and distal colon cancers. If a study combined two or more physical activity domains (such as recreational, household and occupational) to make a single measure of physical activity this result was used for the primary meta-analysis. If a study reported the effect of two or more domains of physical activity but did not combine them, the recreational physical activity result was used. Recreational physical activity is the most commonly measured domain in observational studies of physical activity and cancer, and it has been suggested that it is main modifiable aspect of energy expenditure (11). If a study reported the effect of physical activity at multiple time periods or ages and over the lifetime, the lifetime result was used. In all studies, the result that compared the most active group with the least active group was used. The effect size and confidence intervals were inverted for studies in which the most active group was used as the reference group.

Other data extracted included study type, the sex of the participants, the country in which the study took place, the definitions of proximal colon and distal colon, the total number of colon cancer cases, the number of proximal colon cancer and distal colon cancer cases, and the validity and/or reliability of the questionnaire used to measure physical activity. We also extracted: the physical activity domain(s) that the main result was based on; the description of the highest and lowest physical activity categories used in the main result; any confounders controlled for in the analysis; any other variable whose confounding effect was assessed but which was not included in the final model; whether dose-response analyses were conducted; and, if applicable, the results of the dose-response analyses. Finally, we also extracted the highest versus lowest results of any domain-specific analyses that were not the main result.

If a study reported insufficient data (i.e. no risk estimates and/or confidence intervals) to include in the meta-analysis the corresponding author was contacted via email and asked if it was possible to supply the missing data. If a study did not provide definitions of proximal colon and distal colon we searched the literature for another publication from the same cohort or case-control study that did supply definitions.

Risk of bias in individual studies

A simple three item checklist was used to categorise studies as having either a lower risk of bias or a higher risk of bias. The first item concerned the study setting: cohort studies and population-based case-control studies were considered to have a lower risk of bias, while case-control studies that were not population-based (e.g. hospital-based or cancer registry-based) were considered to have a higher risk of bias. The second item concerned whether the validity and/or reliability of the instrument used to measure physical activity. Studies that reported that the instrument they used to measure physical activity was valid and/or reliable, or was similar to another questionnaire with known validity and/or reliability, were considered to have a lower risk of bias. Studies that did not report this information were considered to have a higher risk of bias. The third item concerned whether a study matched on, controlled for or considered the confounding effect (i.e. did not include these variables in the final model but reported that adjusting for them did not affect the results) of age and obesity (e.g. body mass index, body weight or waist circumference). Age and obesity were considered to be the main potential confounders of the association between physical activity and proximal colon and distal colon cancers. Studies that met all of the three items were classified as having a lower risk of bias than studies that did not meet all three criteria. We performed a subgroup analysis to determine whether the results differed between studies with a lower risk of bias and a higher risk of bias.

Statistical analysis

Random-effects meta-analyses were used to estimate the summary relative risk (RR) of physical activity on the risk of proximal colon and distal colon cancers. Case-control and cohort studies were combined in the primary analysis, as odds ratios and rate ratios provide similar estimates of risk when the outcome is rare (12). If a study reported results for males and females separately, both risk estimates were included in the primary analysis. Heterogeneity was assessed using I^2, while meta-regression was used to determine whether there was a statistically significant difference between the summary effect sizes for the effect of physical activity on proximal colon cancer and distal colon cancer. Publication bias was assessed by visual inspection of funnel plots, as well as statistically with the Egger test. We also performed sensitivity analyses to assess the impact of any possible publication bias by using the 'trim and fill' method (13).

We also examined whether smaller studies were more likely than larger studies to find that physical activity had a different effect on the risk of proximal colon and distal colon cancers, given the lower precision found in small studies. To investigate this, for each study we calculated the ratio (and 95% confidence interval) between the risk ratios found for the association between physical activity and proximal colon and distal colon cancers (as above, if the same study reported risk estimates for males and females both results were used). The ratio of risk ratios (RRRs) and associated 95% confidence intervals and standard errors were calculated using the formula outlined by Altman and Bland (14). A forest plot of the RRRs, with studies sorted by standard error, was visually inspected to investigate whether study size influenced the likelihood that a study found that physical activity had a different effect on the risk of proximal colon and distal colon cancers.

Subgroup analyses

Four *a priori* subgroup analyses were conducted: sex (males and females); study type (cohort and case-control); risk of bias (lower and higher risk of bias); and physical activity domain (occupational, recreational, household, or two or more of these domains combined). One *post hoc* sub-group analysis of studies with different definitions of proximal colon and distal colon was also conducted. For this analysis, studies that included the splenic flexure as part of the proximal colon were classified as having used ‘Definition One’, studies that included the splenic flexure as part of the distal colon were classified as having used ‘Definition Two’, while studies that did not include the splenic flexure in their definition of proximal colon or distal colon were classified as having used ‘Definition Three’. Meta-regression was used to calculate a ratio of risk estimates to determine whether there was a statistically significant difference between the summary risk estimates for males and females, from cohort and case-control studies, from studies with a lower risk of bias and a higher risk of bias, from studies with different definitions of proximal colon and distal colon, and from different physical activity domains. In each subgroup category, meta-regression was used to determine whether there was a statistically significant difference between the summary effect sizes for the effect of physical activity on proximal colon cancer and distal colon cancer.

All analyses were conducted in Stata 11.2 (StataCorp, College Station, TX), using the metan, metareg, metafunnel, metabias and metatrim commands (15).

RESULTS

Study selection

A total of 2588 articles were identified in the literature search (Figure One). A further two papers were obtained after manual searching of reference lists. After removal of duplicates a total of 1763 unique articles remained. After excluding articles that were not relevant to the current review, as well as letters, editorials and review articles, a total of 101 papers that investigated the effect of physical activity on the risk of colon cancer or colorectal cancer remained. After reviewing the full text of these articles, 49 articles were excluded as they did not include analyses of colorectal subsites., and a further 11 studies were excluded as there was another article from the same parent study with either longer follow-up or a more complete measure of physical activity (although one of these studies was included in the occupational physical activity meta-analysis (16)). Finally, six studies were excluded as they did not meet the required definition of proximal colon and distal colon, and a further 10 studies that reported results for specific anatomic sites with the colon were excluded as it was not possible to combine the results from these anatomic sites to calculate an effect size for our desired definitions of proximal colon and distal colon. Three studies did not provide a definition of proximal colon and distal colon (17-19), but a definition was obtained from other publications based on the same cohort or case-control study. This left 25 papers, but five did not report sufficient data to include in the meta-analysis (20-24). Contacting the authors of these studies resulted in the requested data being obtained for one study (20). This left a total of 21 studies in the primary meta-analysis (9, 17-20, 25-40).

Study characteristics

The main characteristics of the 21 studies included in the primary meta-analysis are displayed in Table One, and additional study characteristics are available as Supplementary Material (available online). More than 9,512 people with proximal colon cancer and 8,171 people with distal colon cancer participated in the studies included in the meta-analysis (three studies did not report the number of cases by subsite (28, 33, 37)). Twelve of the studies were cohort studies (18, 20, 25, 26, 28, 29, 31, 32, 34-36, 38) and nine were case-control studies (9, 17, 19, 27, 30, 33, 37, 39, 40). Eleven studies used 'Definition One' to classify anatomic sites as proximal colon or distal colon (18, 25-28, 32-36, 38), six used 'Definition Two' (9, 17, 20, 29, 31, 37), and four used 'Definition Three' (19, 30, 39, 40). Eight of the studies were conducted in Europe (one in multiple European countries (26), three in Sweden (27, 31, 35), and one in each of Finland (20), France (17), Norway (36) and Switzerland

(33)), nine were conducted in the United States (18, 25, 28, 29, 34, 37-40), three were conducted in Japan (19, 30, 32) and one was conducted in Australia (9). Five studies involved males only (20, 28, 31, 39, 40), three involved females only (18, 34, 38), five involved both males and females but did not report sex-specific results (17, 20, 26, 33, 36), and eight involved both males and females and did report sex-specific results (9, 19, 27, 29, 30, 32, 35, 37). In total, 29 sets of results were included in the primary analysis (13 sets of results for males (9, 19, 20, 27-32, 35, 37, 39, 40), 11 sets of results for females (9, 18, 19, 28-30, 32, 34, 35, 37, 38) and five sets of results for both sexes combined (17, 25, 26, 33, 36)). The main results of four studies were based on occupational activity (33, 35, 39, 40), nine studies on recreational activity (9, 20, 25, 28-30, 34, 36, 38), three studies on recreational and occupational activity combined (17, 27, 32), one on recreational and household activity combined (37), three on recreational, occupational and household activity combined (20, 26, 31), and one on recreational, occupational and transport-related activity combined (19).

For the sub-group meta-analyses of physical activity domains, 10 studies reported results for occupational activity (16, 19, 20, 26, 29, 31, 33, 35, 39, 40), 11 reported results for recreational activity (9, 19, 20, 25, 26, 28, 29, 31, 34, 36, 38), two reported results for household activity (26, 31), and eight reported results from a combination of two or more domains (17-19, 26, 27, 31, 32, 37).

Risk of bias

Four (30, 33, 39, 40) of the 21 studies were not cohort or population-based case-control studies. Eleven studies reported that the questionnaire used to measure physical activity was valid and/or reliable, or similar to other valid and/or reliable questionnaires (9, 18, 19, 26, 28, 29, 31, 32, 36-38). Sixteen studies matched on, adjusted for, or considered the confounding effect of age and obesity (9, 18-20, 25-29, 31-34, 36-38). Eleven studies (eight cohort, three case-control) met all three of the criteria and were classified as having a lower risk of bias (9, 18, 19, 26, 28, 29, 31, 32, 36-38), while 10 studies (four cohort, six case-control) failed to meet all three items and were classified as having a higher risk of bias (17, 20, 25, 27, 30, 33-35, 39, 40).

Dose-response

A total of 18 dose-response analyses (six in males, eight in females, and four in males and females combined) were conducted in the 13 studies that examined whether there was a dose-response relationship between physical activity and proximal colon and distal colon cancers (9, 19, 20, 25-27, 29, 31-35, 38). Seven (three in males, one in females, and three in male and females combined) of the 17 analyses of physical activity and the risk of proximal colon cancer found a significant ($p<0.05$) dose-response relationship (25, 26, 29, 32, 33, 35), while four (one in males, one in females, and two in males and females combined) of the 17 analyses of physical activity and the risk of distal colon cancer found a significant dose-response relationship (27, 33, 35, 38).

Ratio of risk ratios

Of the 29 sets of main results, one found that physical activity was associated with a significantly greater risk reduction for proximal colon cancer (32), while one found the opposite (38) (Figure Two). None of the remaining sets of main results were significantly different, although 10 found a non-significant greater risk reduction for proximal colon cancer (defined by an arbitrary RRR cut-off of equal to or less than 0.8) (17, 18, 20, 25, 26, 30, 32, 33, 39, 40), seven found a non-significant greater risk reduction for distal colon cancer (defined by an arbitrary RRR cut-off of equal to or greater than 1.25) (9, 19, 27, 28, 36, 38), and 10 found similar results for proximal colon and distal colon cancers (defined by a RRR between 0.81 and 1.24) (9, 29-31, 34, 35, 37).

Meta-analyses

Primary meta-analysis

The summary relative risk of the main results from the 21 studies indicates that the risk of proximal colon cancer is 27% lower among the most physically active people compared with the least active people (RR=0.73, 95% CI=0.66-0.81) (Figure Three). There was low heterogeneity (I^2=31.3%; P=0.057). An almost identical result was found for distal colon cancer (RR=0.74, 95% CI=0.68-0.80), again with low heterogeneity (I^2=0.0%; P=0.473). There was essentially no difference between the summary risk estimates for the effect of physical activity on proximal colon cancers and distal colon cancers (ratio of risk estimates=0.98, 95% CI=0.87-1.11).

Publication bias and small study effects

Visual inspection of the funnel plots revealed a small degree of asymmetry, primarily due to one to two studies, in both the proximal colon cancer and distal colon cancer results. The p-values from the Egger tests were 0.053 and 0.344 for the proximal colon cancer and distal colon cancer studies respectively. Using trim and fill methods to assess the impact of any potential publication bias, four studies and three studies were 'filled' to the proximal colon cancer and distal colon cancer meta-analyses respectively. The summary relative risks from the filled random-effects meta-analyses were 0.77 (95% CI=0.68-0.87) and 0.75 (95% CI=0.69-0.82) respectively (compared with 0.73 and 0.74 in the 'non-filled' meta-analyses). The filled funnel plots are available as Supplementary Material (available online).

Visual inspection of the forest plot of the ratio of risk ratios from each study indicated that smaller studies were more likely than larger studies to find that physical activity has a different effect on proximal colon and distal colon cancers (Figure Two).

Subgroup Analyses

The results from the subgroup analyses revealed no meaningful or statistically significant differences between the risk estimates for proximal colon and distal colon cancers (Table Two). Subgroup analyses also showed no statistically significant differences between the results for males and females, from studies with a higher or lower risk of bias, from studies with different definitions of proximal colon and distal colon, or from studies based on different physical activity domains. However risk estimates from case-control studies were, on average, significantly lower than those from cohort studies (ratio of risk estimates=0.86, 95% CI 0.76-0.98). All subgroup forest plots (study design, sex, risk of bias, proximal colon/distal colon definition, physical activity domain) are available as Supplementary Material (available online).

DISCUSSION

The results of this systematic review and meta-analysis suggest that the association between physical activity and colon cancer does not differ by subsite. The summary risk estimates from the 21 studies indicate that the risk of both proximal colon cancer and distal colon cancer is approximately 25% lower among the most active people than the least active people. There was no strong evidence that the results differed between males and females, between studies with a higher or lower risk of bias, or between studies between studies with different definitions of proximal colon and distal colon. However, the results from case-control studies were, on average, further from the null than those from cohort studies, which may be due to the influence of selection and recall biases in case-control studies (3). Sensitivity analyses suggested that any publication bias present had minimal effect on the summary relative risks.

Although the results of this meta-analysis suggest physical activity has a similar effect on the risk of proximal colon and distal colon cancer, several studies have found different but inconsistent results. From the 29 sets of results in this meta-analysis, eleven found a larger risk reduction for proximal colon cancer (17-19, 26, 27, 31, 32, 37, 39, 40), eight found a larger risk reduction for distal colon cancer (17-19, 26, 27, 31, 32, 37), and 10 found no difference (17-19, 26, 27, 31, 32, 37). Only two of the 29 RRRs were statistically significant (32, 38). It has been suggested that the inconsistent results from studies that have investigated the effect of physical activity on the risk of proximal colon and distal colon cancers may be due to methodological differences between the studies (20). For example, several different definitions of proximal colon and distal colon were used in the different studies. However subgroup analyses revealed no meaningful differences between the results from studies that used different definitions of proximal colon and distal colon.

Another methodological difference is the measurement of physical activity, which has been measured in a variety of time periods, at different intensities, and in different domains. The timing, intensity and domain of physical activity may influence the effect that it has on colon cancer risk (4), and there is interest in how these components influence health outcomes (41). Although there were too few studies to investigate timing and intensity of physical activity separately in this meta-analysis, it was possible to examine separate physical activity domains. The results across these domains differed. While the summary relative risks from studies that looked at occupational physical activity were similar for proximal colon cancers and distal colon cancers (0.72 and 0.75 respectively), the summary relative risk from studies that looked at recreational physical activity was higher for proximal colon cancer than for distal colon cancer (0.84 and 0.74 respectively). Conversely, the summary relative risks from studies that looked at household physical activity (0.65 and 0.97 for proximal colon and distal colon cancers respectively) or at physical activity performed in multiple domains were lower for proximal colon cancer than for distal colon cancer (0.65 and 0.75). The results do indicate, however, that physical activity in any domain reduces the risk of colon cancer.

It is also possible that physical activity has been found to have a different association by colon subsite due to chance, as many of these studies have had small numbers of participants with proximal colon and distal colon cancers (42). We assessed this by investigating whether smaller studies were more likely than larger studies to find that physical activity has a different effect on the risk of proximal colon and distal colon cancers, and found that was indeed the case (Figure Two). This suggests that at least some of the inconsistency may be due to imprecise estimates of risk caused by low statistical power.

A number of biological reasons for why physical activity may have a different effect on the risk of proximal colon and distal colon cancers have been put forth. Several authors have suggested that physical activity may affect gut motility more extensively in the proximal colon (26, 32, 43). It has also been argued that the effect of physical activity on gastrointestinal transit time and constipation would have a greater impact on the risk of distal colon cancer, as the distal colon has a strong storage function (19, 27). It has been proposed that the effect of physical activity on metabolic hormone levels and growth factors may influence proximal colon cancer more than distal colon cancer (32). Finally, the effect of physical activity on obesity and vitamin D have been suggested as reasons for a greater risk reduction for distal colon cancer (9).

This systematic review and meta-analysis had some limitations. Although we found low statistical heterogeneity in the primary meta-analysis and in the sub-group analyses, as with most meta-analyses of observational studies, the studies included in this review were conducted on different population groups, and the measurement and categorization of the exposure (physical activity) was highly heterogeneous. As such, the results of this meta-analysis should only be interpreted as showing that the research conducted to date indicates that the 'most active' individuals have a 25% lower risk of colon cancer than the 'least active', and that the risk reduction is virtually identical for cancers of the proximal colon and distal colon. The results do not provide any information about the duration, frequency, intensity or timing of physical activity required to optimally reduce the risk of colon cancer.

A further limitation is the exclusion of four studies that investigated the effect of physical activity on proximal colon and distal colon cancers but did not report sufficient data to include in the meta-analysis, and we were not able to obtain the information from the authors. Three of these studies reported that physical activity had a similar effect on the risk of proximal colon and distal colon cancers (21, 23, 24), while the fourth reported identical risk estimates (but no confidence intervals) for the association between lifetime recreational physical activity and the risk of proximal colon and distal colon cancers (22). It is therefore unlikely that inclusion of these studies would have had an effect on the results of the present meta-analysis. There have also been dozens of other published studies that have investigated the association between physical activity and colon cancer but have not reported the results of proximal colon and distal colon cancers separately. However our results are very similar to a recent meta-analysis that estimated the effect of physical activity on colon cancer (but did not look at subsite-specific colon cancer) (3). That meta-analysis, which included 17 of the 21 studies in the present meta-analysis, found a summary risk estimate of 0.76 for colon cancer, compared with summary relative risks of 0.73 for proximal colon cancer and 0.74 for distal colon cancer in the present meta-analysis. This suggests that the studies included in the current meta-analysis are a representative sample of the published studies that have investigated the effect of physical activity on colon cancer risk.

In conclusion, the results of this systematic review and meta-analysis indicate that there is strong and consistent evidence that physical activity is associated with a reduced risk of both proximal colon and distal colon cancers, and that the association does not differ by subsite. This suggests that future research on physical activity and colon cancer should focus on other aspects of the association that remain unclear, such as whether the intensity of physical activity matters, the effect of sedentary behaviour, the effect of non-aerobic physical activity such as resistance training, and whether obesity, diet and/or ethnicity modify the effect of physical activity on colon cancer (3, 4).

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Table One: Main characteristics of the studies included in the primary meta-analysis of studies that have investigated the effect of physical activity on the risk of proximal colon cancer (PCC) and distal colon cancer (DCC)

First Author, Year, Country	Sex	Study Setting	Number of Cases	Physical Activity Domain in Main Result (Subgroup Analyses)	Physical Activity Measurement Mode, Validity, Reliability	Confounding effect of age and obesity considered?	Main Result Risk Ratio/Odds Ratio (95% Confidence Interval)	Dose-response p-value
COHORT STUDIES								
Giovanucci, 1995, United States (28)	Males	Health Professionals	CC=203 PCC=NR DCC=NR	Recreational (REC)	Self-administered, Yes, Yes	Age: Yes Obesity: Yes	PCC: 0.75 (0.36-1.55) DCC: 0.50 (0.25-1.00)	Not Reported (NR)
Colbert, 2001, Finland (20)	Males	Participants in a randomised controlled trial	CC=152 PCC=69 DCC=81	REC (Occupational (OCC) in subgroup analyses)	Self-administered, No, No	Age: Yes Obesity: Yes	PCC: 0.73 (0.47-1.14) DCC: 0.94 (0.58-1.53)	NR
Chao, 2004, United States (25)	Both, combined	Population	CC=940 PCC=505 DCC=339	REC	Self-administered, No, No	Age: Yes Obesity: Yes	PCC: 0.63 (0.45-0.88) DCC: 0.82 (0.55-1.24)	PCC=0.008 DCC=0.15
Calton, 2006, United States (18)	Females	Breast Cancer Screening Project	CC=243 PCC=103 DCC=68	REC, OCC & Household (HH)	Self-administered, Yes, No	Age: Yes Obesity: Yes	PCC: 0.87 (0.46-1.62) DCC: 1.36 (0.75-2.46)	PCC=0.84 DCC=0.34
Friedenreich, 2006, Europe (26)	Both, combined	Population	CC=1094 PCC=429 DCC=491	REC, OCC & HH (All looked at separately in subgroup analyses)	Self-administered/Interview, Yes, Yes	Age: Yes Obesity: Yes	PCC: 0.65 (0.43-1.00) DCC: 0.96 (0.64-1.45)	PCC=0.004 DCC=0.83
Larsson, 2006, Sweden (31)	Males	Population	CC=309 PCC=133 DCC=138	REC, OCC & HH (All looked at separately in subgroup analyses)	Self-administered, Yes, No	Age: Yes Obesity: Yes	PCC: 0.71 (0.39-1.29) DCC: 0.70 (0.38-1.27)	PCC=0.32 DCC=0.47
Lee, 2007, Japan (32)	Both, separate	Population	CC=337 PCC=154 DCC=166	REC, OCC	Self-administered, Yes, No	Age: Yes Obesity: Yes	Females: PCC: 0.55 (0.24-1.26) DCC: 1.37 (0.66-2.85) Males: PCC: 0.29 (0.14-0.60)	Females: PCC=0.151 DCC=0.401 Males: PCC<0.001

							DCC: 0.89 (0.53-1.51)	DCC=0.685
Mai, 2007, United States (34)	Females	Teachers	CC=395 PCC=272 DCC=107	REC	Self-administered, No, No	Age: Yes Obesity: Yes	PCC: 0.77 (0.54-1.08) DCC: 0.63 (0.37-1.09)	PCC=0.24 DCC==0.49
Wolin, 2007, United States (38)	Females	Nurses	CC=547 PCC=302 DCC=245	REC	Self-administered, Yes, Yes	Age: Yes Obesity: Yes	PCC: 0.97 (0.68-1.38) DCC: 0.54 (0.34-0.84)	PCC=0.77 DCC=0.004
Howard,2008, United States (29)	Both, separate	Population (Retirees)	CC: 3410 PCC: 1860 DCC: 1360	REC (OCC in subgroup analyses)	Self-administered, Yes, Yes	Age: Yes Obesity: Yes	Females: PCC: 0.91 (0.70-1.17) DCC: 0.82 (0.58-1.14) Males: PCC: 0.83 (0.68-1.02) DCC: 0.83 (0.67-1.03)	Females: PCC=0.969 DCC=0.336 Males: PCC=0.033 DCC=0.285
Moradi, 2008, Sweden (35)	Both, separate	Census Records	CC=7900 PCC=3720 DCC=3074	OCC	Job-title based, No, No	Age: Yes Obesity: No	Females: PCC: 0.71 (0.50-0.91) DCC: 0.83 (0.59-1.25) Males: PCC: 0.83 (0.67-1.00) DCC: 0.71 (0.59-0.83)	Females: PCC=0.029 DCC >0.05 Males: PCC=0.004 DCC<0.001
Nilsen, 2008, Norway (36)	Both, combined	Population	CC=736 PCC=391 DCC=264	REC	Self-administered, Yes, No	Age: Yes Obesity: Yes	PCC: 0.81 (0.59-1.10) DCC: 0.56 (0.37-0.83)	NR
CASE-CONTROL STUDIES								
Vena, 1985, United States (40)	Males	Hospital	CC=210 PCC=70 DCC=98	OCC	Job-title based, No, No	Age: No Obesity: No	PCC: 0.39 (0.21-0.71) DCC: 0.72 (0.44-1.16)	NR
Brownson, 1989, United States (39)	Males	Cancer Registry	CC=1993 PCC=779 DCC=939	OCC	Job-title based, No, No	Age: No Obesity: No	PCC: 0.60 (0.39-0.94) DCC: 0.83 (0.57-1.21)	NR

Gerhardsson, 1990, Sweden (27)	Both, separate	Population	CC=452 PCC=181 DCC=147	REC, OCC	Self-administered, No, No	Age: Yes Obesity: Yes	Females: PCC: 0.71 (0.20-2.50) DCC: 0.24 (0.07-0.83) Males: PCC: 1.25 (0.33-5.00) DCC: 0.30 (0.09-1.00)	Combined: PCC=0.863 DCC=0.002
Inoue, 1995, Japan (30)	Both, separate	Hospital	CC=432 PCC=42 DCC=61	REC	Self-administered, No, No	Age: Yes Obesity: No	Females: PCC: 0.50 (0.20-1.50) DCC: 1.00 (0.50-2.00) Males: PCC: 0.70 (0.40-1.50) DCC: 0.70 (0.40-1.30)	NR
Slattery, 1995, United States (37)	Both, separate	Population	CC=1993 PCC=NR DCC=NR	REC, HH	Interview, No, Yes	Age: Yes Obesity: Yes	Females: PCC: 0.63 (0.44-0.89) DCC: 0.62 (0.44-0.88) Males: PCC: 0.56 (0.40-0.78) DCC: 0.65 (0.47-0.90)	NR
Levi, 1999, Switzerland (33)	Both, combined	Hospital	CC=119 PCC=NR DCC=NR	OCC	Interview, No, No	Age: Yes Obesity: Yes	PCC: 0.28 (0.11-0.67) DCC: 0.53 (0.24-1.16)	PCC=0.01 DCC=0.01
Boutron-Ruault, 2001, France (17)	Both, combined	Population	CC=106 PCC=43 DCC=63	REC, OCC	Self-administered, No, No	Age: Yes Obesity: No	PCC: 0.09 (0.01-0.70) DCC: 0.50 (0.20-1.00)	NR
Isomura, 2006, Japan (19)	Both, separate	Population	CC=438 PCC=175 DCC=262	REC, HH, Commuting (COM) (OCC in subgroup analyses)	Self-administered, No, Yes	Age: Yes Obesity: Yes	Females: PCC: 1.60 (0.70-3.60) DCC: 0.60 (0.30-1.10) Males: PCC: 0.90 (0.50-1.70) DCC: 0.70 (0.40-1.10)	Females: PCC=0.41 DCC=0.12 Males: PCC=0.69 DCC=0.19

Boyle, 2011, Australia (9)	Both, separate	Population	CC=552 PCC=284 DCC=268	REC (OCC in subgroup analyses, from (16))	Self-administered, No, Yes	Age: Yes Obesity: Yes	Females: PCC: 0.90 (0.52-1.54) DCC: 0.84 (0.47-1.50) Males: PCC: 1.11 (0.68-1.83) DCC: 0.66 (0.41-1.07)	Females: PCC=0.794 DCC=0.713 Males: PCC=0.577 DCC=0.227

Abbreviations: CC, Colon Cancer; COM, Commuting (Transport-Related) Physical Activity; DCC, Distal Colon Cancer; HH, Household Physical Activity; NR, Not Reported; OCC, Occupational Physical Activity; PCC, Proximal Colon Cancer; REC, Recreational Physical Activity.

Table Two: Summary of results from the primary random-effects meta-analysis and the sub-group random-effects meta-analyses

	Proximal Colon Cancer		Distal Colon Cancer		Meta-Regression	
	Relative Risk (95% CI)	**Heterogeneity (I^2, p-value)**	**Relative Risk (95% CI)**	**Heterogeneity (I^2, p-value)**	**Ratio of Relative Risks (95% CI)[*]**	**Within-group Ratio of Results (95% CI)**
All Studies (Primary Analysis)	0.73 (0.66, 0.81)	31.3%, p=0.057	0.74 (0.68, 0.80)	0.0%, p=0.473	0.98 (0.87, 1.11)	-
SUB-GROUP ANALYSES						
Study Design						
Cohort Studies	0.78 (0.72, 0.86)	2.6%, p=0.423	0.78 (0.70, 0.87)	15.4%, p=0.281	0.98 (0.86, 1.13)	1 (reference)
Case-Control Studies	0.67 (0.54, 0.85)	43.5%, p=0.041	0.67 (0.59, 0.77)	0.0%, p=0.789	1.01 (0.80, 1.29)	0.86 (0.76, 0.98)
Sex						
Males	0.71(0.60, 0.83)	40.7%, p=0.063	0.74 (0.67, 0.82)	0.0%, p=0.828	1.00 (0.84, 1.19)	1 (reference)
Females	0.81 (0.71, 0.92)	0.0%, p=0.516	0.76 (0.63, 0.92)	33.9%, p=0.128	0.94 (0.74, 1.18)	1.06 (0.92, 1.21)
Risk of Bias						
Lower Risk of Bias	0.78 (0.68, 0.89)	33.4%, p=0.095	0.74 (0.66, 0.84)	14.9%, p=0.282	0.95 (0.79, 1.14)	1 (reference)
Higher Risk of Bias	0.67 (0.57, 0.79)	25.7%, p=0.184	0.73 (0.65, 0.82)	0.0%, p=0.603	1.04 (0.87, 1.24)	0.94 (0.87, 1.06)
Proximal/Distal Colon Definition[†]						
Definition One	0.73 (0.64, 0.84)	24.8%, p=0.186	0.73 (0.62, 0.86)	37.6%, p=0.076	0.98 (0.80, 1.19)	1 (reference)
Definition Two	0.77 (0.65, 0.91)	39.9%, p=0.102	0.75 (0.66, 0.85)	0.0%, p=0.725	0.96 (0.78, 1.18)	1.04 (0.91, 1.18)
Definition Three	0.68 (0.48, 0.97)	43.5%, p=0.115	0.75 (0.61, 0.93)	0.0%, p=0.908	1.14 (0.77, 1.67)	0.97 (0.79, 1.19)
Physical Activity Domain						
Two or More Domains	0.66 (0.53, 0.83)	33.5%, p=0.122	0.74 (0.60, 0.90)	35.8%, p=0.104	1.13 (0.83, 1.54)	1 (reference)
Recreational Physical Activity	0.84 (0.76, 0.92)	0.0%, p=0.766	0.74 (0.66, 0.83)	10.9%, p=0.334	0.89 (0.77, 1.04)	1.14 (0.98, 1.33)
Occupational Physical Activity	0.72 (0.61, 0.85)	41.9%, p=0.056	0.75 (0.63, 0.88)	45.6%, p=0.037	1.03 (0.80, 1.34)	1.05 (0.89, 1.24)
Household Physical Activity[‡]	0.65 (0.46, 0.93)	29.6%, p=0.233	0.97 (0.75, 1.25)	0.0%, p=0.587	1.44 (0.63, 3.29)	-

[*] Reference is relative risk of proximal colon cancer
[†] Proximal colon/distal colon definitions outlined in text
[‡] Omitted from within-group meta-regression due to collinearity

Figure One: Flow Chart of Study Selection

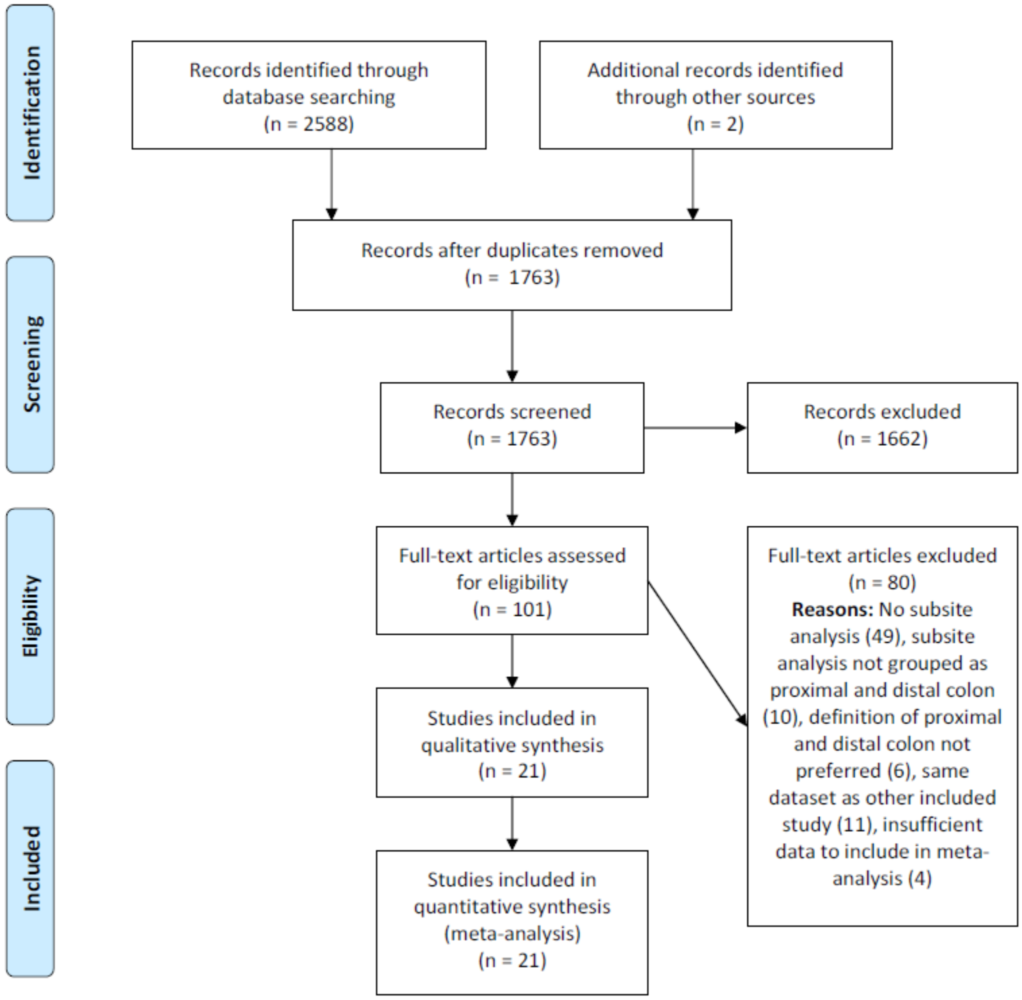

Figure Two: Forest Plot of Ratio of Risk Ratios (RRR) found for the association between physical activity and proximal colon cancer (PCC) and distal colon cancer (DCC) in each study (sorted by the standard error of the RRR)

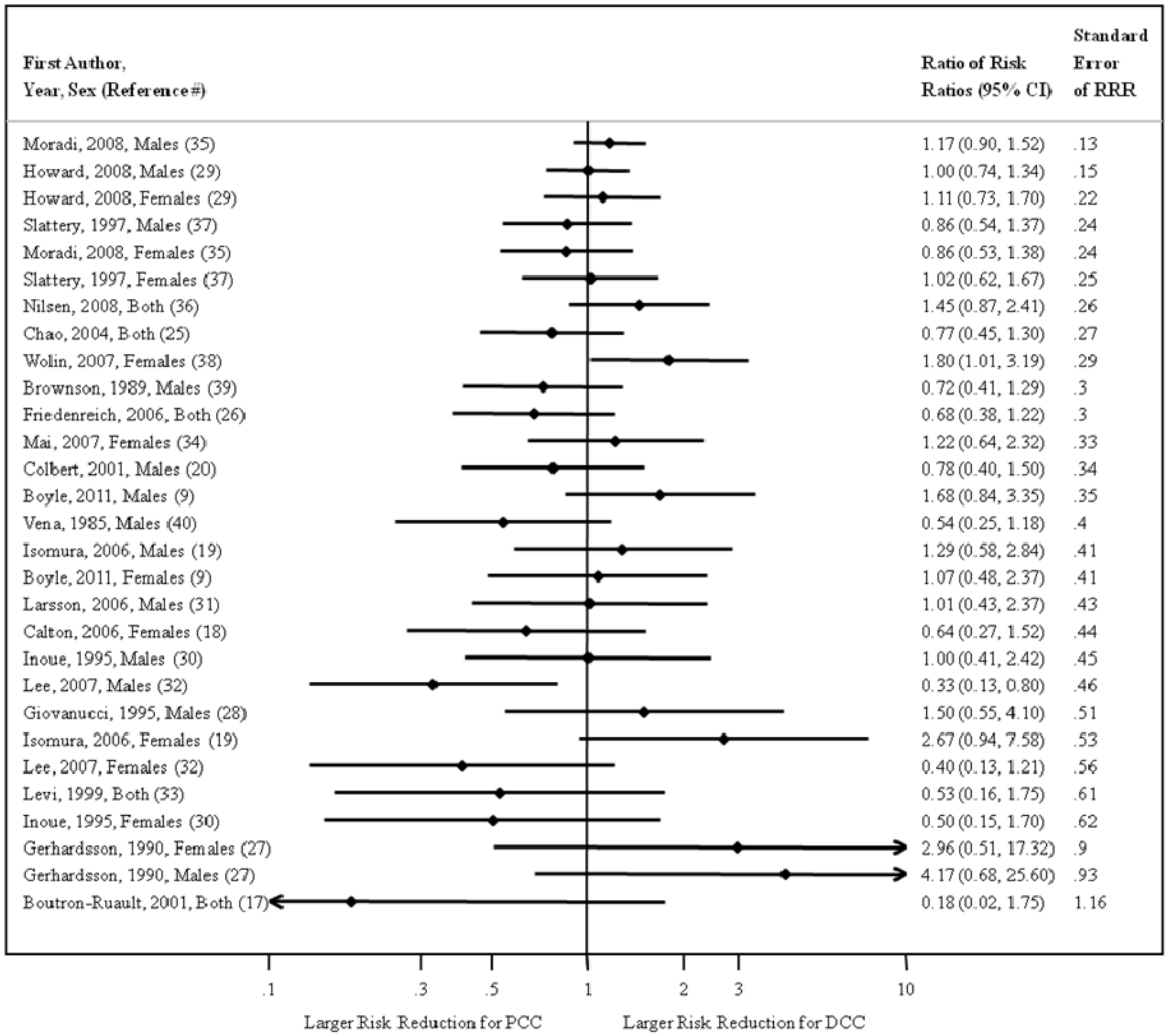

Figure Three: Random effects meta-analysis of the main result from studies that have investigated the effect of physical activity on the risk of proximal colon and distal colon cancers