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Kathleen Yaus Wolin
*Washington University School of Medicine in St. Louis*

Yan Yan
*Washington University School of Medicine in St. Louis*

Graham A. Colditz
*Washington University School of Medicine in St. Louis*

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Physical activity and risk of colon adenoma: a meta-analysis

KY Wolin*,1, Y Yan1 and GA Colditz1
1Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine in St Louis and Alvin J Siteman Cancer Center, 660 S Euclid Avenue, Box 8100, St Louis, MO 63110, USA

BACKGROUND: Little evidence is available on the relation of physical activity with colon adenomas, a colon cancer precursor.

METHODS: We conducted a systematic literature review and meta-analysis of published studies (in English) through April 2010, examining physical activity or exercise and risk or prevalence of colon adenoma or polyp. Random effects models were used to estimate relative risks (RRs) and corresponding confidence intervals (CIs). A total of 20 studies were identified that examined the association and provided RRs and corresponding 95% CIs.

RESULTS: A significant inverse association between physical activity and colon adenomas was found with an overall RR of 0.84 (CI: 0.77–0.92). The association was similar in men (RR = 0.81, CI: 0.67–0.98) and women (RR = 0.87, CI: 0.74–1.02). The association appeared slightly stronger in large/advanced polyps (RR = 0.70, CI: 0.56–0.88).

CONCLUSION: This study confirms previous reports of a significant inverse association of physical activity and colon adenoma, and suggests that physical activity can have an important role in colon cancer prevention.

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MATERIALS AND METHODS

We searched the literature using PubMed, CINAHL and Scopus for all studies on physical activity or exercise and colon polyps through April 2010. We employed the terms exercise and physical activity in combination with colon polyps using the terms colon polyp, colon adenoma, colorectal polyp, colorectal adenoma and adenomatous polyp. We also utilised a previous review of the data (Samad et al, 2005; Lee and Oguma, 2006; World Cancer Research Fund/American Institute for Cancer Research, 2007a) and manual searches of the reference lists of identified manuscripts. We included recurrent, incident and prevalent cases of colon polyps. We did not limit studies by type of physical activity or study sample demographics.

Our search yielded 89 potential articles. We excluded reviews, non-human studies, editorials/comments/letters to the editor, studies without colon polyps as an outcome, studies where physical activity was only included as a covariate (and thus no measure of association was presented), and where no metric for effect estimate precision (P-value, s.e., confidence interval (CI)) was provided. Combined with searches from the reference sections of manuscripts and previous reviews, this yielded 20 manuscripts. From each manuscript, we abstracted the sample size (including number of cases), gender, years of follow-up or type of control sample, case definition, physical activity domain, adenoma detection method, sample definition criteria and results. We also abstracted the variables that each study used in its most adjusted analysis. Data extraction was performed by a single investigator (KYW). Where studies included more than one type of physical activity without a summary measure, we included only leisure time physical activity, which is the major modifiable component of energy.
Previous meta-analyses have suggested that results for adenomatous polyps need to be presented separately from hyperplastic or malignant polyps. (Botteri et al., 2008) Although we did not restrict our analysis to studies where data was limited to adenomatous polyps, we did consider those results separately. Specifically, we excluded results for hyperplastic polyps where feasible. We also identified studies considered to be the ‘best approach’ using criteria similar to those used in a previous meta-analysis (Botteri et al., 2008), namely, studies that met all of the following: (1) limited the outcome to only adenomatous polyps; (2) all individuals received a full colonoscopy; and (3) the study population excluded anyone with inherited colorectal cancer syndromes, inflammatory bowel disease, a history of colon polyps or cancer, or a previous colon resection.

Data analysis

Meta-analysis of random effects was used to allow for the heterogeneity of results across studies. (Mosteller and Colditz, 1996) Data were processed in SAS, and the analyses were performed using R-package ‘meta’ (SAS Institute Inc., Cary, NC, USA). A summary forest plot was generated in Stata (StataCorp LP, College Station, TX, USA). As most studies reported RRs or odds ratios (ORs) and their associated 95 percent CIs, we used these data as summary statistics for each study. First, we derived the s.e. of log (RR or OR) using the 95 percent CI, with the expression: (log (upper limit) – log (lower limit))/2*1.96. These s.es were used as weights for summary effect estimates in the meta-analysis. We visually examined publication bias using Funnel plots, and employed the rank correlation method to formally test for bias. (Begg and Mazumdar, 1994) Where studies reported results separately for men and women, we included both estimates when reporting the overall association. To evaluate the potential effects of limiting results to only adenomatous polyps, we conducted exploratory analysis in the subset of those studies. We also included results separately for large/advanced adenomas, if the data were presented as such in the original manuscript. We also conducted exploratory analyses limited to those studies defined as the ‘best approach’. To test sub-analysis differences (large vs all adenomas; best approach vs all studies), we partitioned ‘total heterogeneity’ into between-group and within-group heterogeneity, and used the ‘between-group’ heterogeneity index as the test statistic against $\chi^2$ distribution with 1 degree of freedom. (Cooper and Hedges, 1994).

Results

We identified 20 studies of physical activity and colon adenomas (Table 1). (Kono et al., 1991, 1999; Little et al., 1993; Shinchi et al., 1994; Giovannucci et al., 1995, 1996; Sandler et al., 1995; Neugut et al., 1996; Enger et al., 1997; Lubin et al., 1997; Kahn et al., 1998; Enger et al., 1999, 2001; Lieberman et al., 2000; Tiemersma et al., 2001; Hauret et al., 2004; Wallace et al., 2005; Larsen et al., 2006; Rosenberg et al., 2006; Hermann et al., 2009) Most collected physical activity information via questionnaire, with nine studies only collecting information on leisure activity. Studies often did not specify or query the reasons participants underwent colonoscopy or sigmoidoscopy, thus, cases included are all adenomas; best approach vs all studies.

| Author and Year | Gender | Number of studies | Number of Cases | Relative Risk | Lower Confidence Interval | Upper Confidence Interval | Type of Physical Activity | Case definition | Non-case/comparison definition |
|----------------|--------|------------------|----------------|--------------|---------------------------|---------------------------|--------------------------|----------------|-------------------------------|
| Kono et al., 1991 | Both   | 1148             | 80             | 0.44         | 0.22                      | 0.87                      | Leisure                  | Adenoma         | None                          |
| Little et al., 1993 | Both   | 300              | 147            | 0.46         | 0.17                      | 1.29                      | Leisure                  | Adenoma         | FOBt negative                 |
| Shinchi et al., 1994 | Both   | 1712             | 228            | 1.2          | 0.8                       | 2                         | Leisure                  | Adenoma         | None                          |
| Giovannucci et al., 1995 | Men    | 12,879           | 455            | 0.79         | 0.57                      | 1.09                      | Leisure                  | Distal Adenoma   | No polyp                      |
| Sandler, 1995 | Men    | 234              | 86             | 0.92         | 0.36                      | 2.31                      | Leisure                  | Hyperplastic/none | Hyperplastic/none             |
| Sandler, 1995 | Women  | 350              | 114            | 0.64         | 0.35                      | 1.19                      | Leisure                  | Distal Adenoma   | None                          |
| Giovannucci et al., 1996 | Women | 1,057            | 330            | 0.58         | 0.4                       | 0.86                      | Leisure                  | Distal Adenoma   | None                          |
| Neugut, 1996   | Men    | 400              | 225            | 0.6          | 0.4                       | 1                         | Total                    | Adenoma         | None                          |
| Neugut, 1996   | Women  | 411              | 283            | 1.3          | 0.7                       | 2.3                       | Total                    | Adenoma         | None                          |
| Enger et al., 1997 | Both   | 920              | 460            | 1            | 0.7                       | 1.5                       | Total                    | Adenoma         | None                          |
| Lubin et al., 1997 | Both   | 392              | 196            | 0.6          | 0.3                       | 0.9                       | Total                    | Large/advanced Adenoma | Hyperplastic/None            |
| Kahn et al., 1998 | Men    | 72,686           | 7504           | 0.83         | 0.76                      | 0.91                      | Total                    | All polyps       | None                          |
| Kahn et al., 1998 | Women | 81,356           | 5,111          | 0.9          | 0.78                      | 1.03                      | Total                    | All polyps       | None                          |
| Kono et al., 1999 | Both   | 415              | 189            | 0.6          | 0.3                       | 1.3                       | Leisure                  | Adenoma         | Normal                        |
| Bourtou-Ruault et al., 2001 | Both | 581              | 154            | 1.3          | 0.7                       | 2.5                       | Total                    | Small adenoma    | None                          |
| Bourtou-Ruault et al., 2001 | Both | 635              | 208            | 0.8          | 0.4                       | 1.5                       | Total                    | Large/advanced adenoma | None                          |
| Colbert et al., 2002 | Both   | 1,839            | 733            | 1.2          | 0.9                       | 1.6                       | Total                    | Adenoma or cancer  | None                          |
| Lieberman et al., 2003 | Both   | 2,082            | 312            | 0.94         | 0.86                      | 1.02                      | Total                    | Large/advanced adenoma | None                          |
| Tiemersma et al., 2003 | Women | 471              | 196            | 1.05         | 0.72                      | 1.54                      | Total                    | Not specified      | Adenoma                        |
| Tiemersma et al., 2003 | Men    | 398              | 237            | 0.69         | 0.43                      | 1.1                       | Total                    | Not specified      | Adenoma                        |
| Hauret et al., 2004 | Both   | 405              | 177            | 0.63         | 0.34                      | 1.17                      | Total                    | Adenoma         | Hyperplastic/none             |
| Wallace et al., 2005 | Men   | 787              | 539            | 0.35         | 0.17                      | 0.72                      | Total                    | Large/advanced adenoma | None                          |
| Wallace et al., 2005 | Women | 787              | 205            | 1.21         | 0.36                      | 4.03                      | Total                    | Large/advanced adenoma | None                          |
| Larsen et al., 2006 | Both   | 3696             | 426            | 0.96         | 0.74                      | 1.25                      | Total                    | Low risk adenoma   | None                          |
| Larsen et al., 2006 | Both   | 3376             | 106            | 0.56         | 0.34                      | 0.92                      | Total                    | Large/advanced adenoma | None                          |
| Rosenberg et al., 2006 | Women | 45,400           | 1,390          | 0.72         | 0.57                      | 0.91                      | Leisure                  | All polyps       | None                          |
| Hermann et al., 2009 | Both   | 45,100           | 1,02           | 0.74         | 1.42                      | Total                    | Adenoma                  | None                          |

Abbreviation: FOBt = Fecal occult blood test.
Colbert et al., 2002; Lieberman et al., 2003; Wallace et al., 2005; Larsen et al., 2006) reported results separately for large or advanced adenomas.

We found significant heterogeneity in the results ($P<0.01$) and thus, focus our report on the random effects analysis (Figure 1). Overall, there was a significant inverse association between physical activity and colon polyps (fixed effect $RR = 0.87$, 95% CI: 0.83–0.91; random effects $RR = 0.84$, 95% CI: 0.77–0.92) when comparing the most to least active individuals in each study. The summary $RR$ was significant and similar in men ($RR = 0.81$, 95% CI: 0.67–0.98) and women ($RR = 0.87$, 95% CI: 0.74–1.02).

There was a tendency for the effect of physical activity to be restricted to large or advanced adenomas and not low grade ones. Similarly, physical activity was associated with large ($>1$ cm) (RR = 0.63, 95% CI: 0.36–1.10), but not with small adenomas in a sample of US male health professionals (Giovannucci et al., 1995). In a cohort of US female nurses, a significant overall risk reduction (RR = 0.58, 95% CI: 0.40–0.86) was reported, which was also stronger for larger than smaller adenomas (Giovannucci et al., 1996). Our meta-analysis found the effect was stronger, though not significantly so ($P = 0.16$), for large or advanced (RR = 0.70, 95% CI: 0.56–0.88) adenomas than for the overall effect. In analyses limited to the 18 studies where results for adenomatous polyps were separated from all polyps (i.e., hyperplastic, malignant polyps), the meta-analysis estimate for the association between physical activity and risk of polyps was largely unchanged ($RR = 0.83$, 95% CI: 0.73–0.93). In analysis limited to the six studies(Kono et al., 1991; Sandler et al., 1995; Colbert et al., 2002; Lieberman et al., 2003; Tiemersma et al., 2003: not specified; Hauret et al., 2004: > 40 MET h per wk vs < 17.1 MET h per wk; Wallace et al., 2005: high vs low tertile; Larsen et al., 2006: high vs low quartile; Rosenberg et al., 2006: > 40 MET h per wk vs none; Hermann et al., 2009: active vs inactive). ES = effect size; MET = metabolic equivalent.

**Figure 1**  Meta-analysis of physical activity and colon adenoma. Study physical activity level comparisons are as follows: Kono et al., 1991: $\geq 120$ vs 0 min per week; Little et al., 1993: $\geq 30$ min vs none; Shinchi et al., 1994: daily vs none; Giovannucci et al., 1995: highest vs lowest quintile; Sandler, 1995: highest vs lowest quartile; Giovannucci et al., 1996: highest vs lowest quintile; Neugut et al., 1996: any vs none; Neugut et al., 1996: $> 5.5$ h per day vs $< 4$ h per day; Enger et al., 1997: highest vs lowest quartile; Kahn et al., 1998: high vs low; Kono et al., 1999: high vs low; Colbert et al., 2001: high vs low; Colbert et al., 2002: high vs low quartile; Lieberman et al., 2003: per 5 unit change in physical activity index; Tiemersma et al., 2003: not specified; Hauret et al., 2004: > 40 MET h per wk vs < 17.1 MET h per wk; Wallace et al., 2005: high vs low tertile; Larsen et al., 2006: high vs low quartile; Rosenberg et al., 2006: > 40 MET h per wk vs none; Hermann et al., 2009: active vs inactive. ES = effect size; MET = metabolic equivalent.

### DISCUSSION

Previous, though limited, reviews have indicated physical activity is associated with a significant reduction in colon polyp risk. (World Cancer Research Fund/American Institute for Cancer Research, 2007a) Our comprehensive meta-analysis supports this conclusion, showing a significant 16% risk reduction when comparing the most to the least active. Risk reductions were similar for men and women, and held when limited to studies designated as the best approach. We found the association was notably stronger when analyses were limited to advanced or large polyps, with a risk reduction of 35%.
These results support the previously documented role of physical activity in colon cancer prevention (International Agency for Research on Cancer WHO, 2002; World Cancer Research Fund/American Institute for Cancer Research, 2007a and 2007b; Wolin et al, 2009). Earlier reports that failed to find an association between physical activity and colon polyps had suggested that physical activity may be more important in the adenoma to carcinoma sequence than in adenoma development (Colbert et al, 2002). Our meta-analysis, combined with the above-mentioned data demonstrating physical activity’s role in colon cancer prevention, suggests that physical activity has a role across the carcinogenic process. Several mechanisms have been proposed for such effects, including enhanced immune function, decreased inflammation, reduced insulin levels and insulin resistance, and higher vitamin D levels (Wolin et al, 2009). Hyperinsulinemia has also been directly related to colon polyp risk (Wei et al, 2006).

This comprehensive meta-analysis provides support for an inverse association between physical activity and colon polyps, and also for the role of physical activity in colon cancer carcinogenesis. Physical activity may reduce the risk of colon polyps by 15% and may provide a substantially larger reduction in risk of large and advanced polyps.

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