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REVIEW

Exercise in the prevention and treatment of colorectal neoplasms: effects and mechanisms.

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Abstract

Objective: This review examines factors that influence the widely varying estimates of protection against colorectal adenomas and cancers associated with occupational and leisure activity, and it seeks a realistic value for use in the formulation of public policy. Attention is also directed to underlying mechanisms, and brief consideration is given to the merits of exercise programmes after the treatment of colorectal tumours. *Methods:* The Ovid/Medline database was searched systematically from January 1996 to November 2015. The terms exercise therapy, physical education/training, athletes, physical fitness and physical activity/motor activity together yielded 205,142 hits, and a combination of the terms colon cancer, rectal cancer, colon adenoma and colon diverticulitis identified 52, 622 unique articles. Combining the 2 searches with a restriction to human subjects identified 286 papers. A review of the abstracts to these articles yielded 3 papers on colorectal adenomas and physical activity, and 41 studies of leisure or occupational activity in relation to colorectal cancer. A further 19 articles examined various aspects of the association between colorectal neoplasia and habitual physical activity. This database was supplemented extensively by articles gleaned from PubMed, Google Scholar and personal files, with a particular emphasis upon occupational studies conducted prior to 1996. *Results:* Almost all published research has found an association between physical activity and a reduced risk of colorectal adenomas. Risk ratios for sedentary behaviour have varied widely between studies, with a weighted average of 1.64 for 6 occupational studies, and 1.26 for 27 leisure studies; the relationship is apparently stronger in men than in women. A substantial association with an inactive lifestyle has also been reported for colon cancers, with a weighted average risk ratio of 1.27 in 39 occupational studies, and of 1.59 in 46 leisure studies. Likewise, for rectal cancers, risk ratios average 1.17 in 27 occupational studies and 1.24 in 20 leisure studies. For both colon and rectal cancers, risk ratios associated with a lack of physical activity were at least as great in women as in men. Inter-study differences in the reported risk-ratios reflect, among other variables, sample size, age, sex and race of subjects, choice of covariates, and the method and timing of activity measurements. Underlying mechanisms of benefit probably vary with the pattern of exercise adopted, but may include a reduced formation of colorectal adenomas, increased colonic motility, increased prostaglandin secretion, an increased use of NSAIDs, dietary changes and avoidance of obesity, a reduced risk of diabetes mellitus and a healthy overall lifestyle. There is growing evidence that an active lifestyle also improves the immediate outcome of colorectal surgery, and that subsequent involvement in an exercise programme enhances functional capacity and quality of life, with a reduced risk of tumour recurrence. *Conclusions:* There is now overwhelming evidence that vigorous habitual activity, either at work or in leisure, is associated with a reduced risk of adenomas and cancers of the colon and rectum. However, the reported benefits are based upon very high levels of weekly energy expenditure, and in terms of public policy the general sedentary population seems unlikely either to attain or to maintain such levels of effort; regular moderate physical activity seems unlikely to yield benefits >20% for colon tumours and >10% for rectal tumours. **Health & Fitness Journal of Canada 2015;8(4):52-89.**

Keywords: Adenoma, Cancer, Colon, Leisure activity, Lifestyle, Motility, Occupation, Prostaglandins, Rectum.

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Introduction

Colorectal cancer is a widely prevalent problem of our aging society, with over a million new cases per year worldwide. In the U.S., the year 2006 saw 108,000 new cases of colonic cancer, and 41,000 cases of rectal cancer, with some 50,000 deaths associated with these 2 diagnoses (Haggar and Boushey, 2009). A substantial impact upon health economics has been imputed. Based on a 2-fold increase in the risk of colorectal cancers in those subscribers who were totally inactive and a 40% increase of risk in subscribers who were irregularly active, the added direct annual cost to Blue Shield/Blue Cross of Minnesota (serving about 1.5 million adult residents of that State) was estimated at US$ 2.9 million (Garrett et al., 2004). Katzmarzyk et al. (2000) adopted a more cautious and probably more realistic risk ratio (1.39) for those who were inactive, attributing a total direct cost of colorectal cancers (hospital and physician care, drugs and research) of Cdn$66M to physical inactivity in the 1999 Canadian population of 30.5M, while Janssen (2012) estimated that by 2009 the costs of colorectal cancer to 33.6 M Canadians had risen to a direct annual expenditure of Cdn$61M and an indirect expenditures of Cdn$283 for a total annual cost of Cdn$344 M (Janssen, 2012). Another analysis for the Province of Ontario, with a population of almost 13 M, set the direct costs at Cdn$31.7 M, and the indirect costs at Cdn$151 M, for a total of Cdn$183 M in 2009 (Katzmarzyk, 2011).

Most colorectal carcinomas arise from adenomas, with up to 10% of adenomas becoming malignant. There is thus widespread practical interest in the potential of habitual physical activity to reduce the risk not only of colorectal cancers, but also of adenomas. It is now widely acknowledged that the lower incidence of both types of tumour in active individuals is not only statistically significant, but also has practical clinical importance (Boyle et al., 2012; Harriss et al., 2009; Lee, 2003; Shephard and Futcher, 1997; Slattery, 2004; Trojian et al., 2007; Wolin et al., 2011). However, analyses of the public health impact of an increase in habitual physical activity in the general population have been hampered by large inter-study differences in the estimates of risk for those who are sedentary. Perhaps the most striking example of this uncertainty is provided by two analyses of data for Harvard Alumni. A 2-fold increase in the risk of colorectal cancer was reported for sedentary subjects in a 1991 text (Lee et al., 1991), but just three years later a second report with a differing follow-up period and differing covariates decreased the estimated risk to 1.08 for essentially the same group of participants (Lee and Paffenbarger, 1994).

The main objective of the present report is to examine the factors that influence estimates of risk in studies of occupational and leisure behaviour, and to arrive at realistic average values for the formulation of public policy. Possible issues modifying the estimates of risk include sample size, choice of covariates, the method adopted when classifying habitual physical activity, and the timing of observations. Attention is also directed to mechanisms whereby exercise might reduce the risks of colorectal neoplasia, and brief consideration is given to the benefits of initiating exercise programmes after surgical treatment,

Methods

The Ovid/Medline database was searched systematically from January 1996 to November 2015. The terms exercise therapy (23,675 hits), physical education/training (6,084 hits), athletes (4,669 hits), physical fitness (14,709 hits) and physical activity/motor activity (180,302 hits) yielded a total of 205,142 entries. The terms colon cancer (36,803 hits), rectal cancer (18,518 hits), colon adenoma (199 hits) and colon diverticulitis (562 hits) identified 52,622 unique articles. Combining the two searches and restricting to human subjects yielded 286 papers. A review of the corresponding abstracts identified 3 papers on colorectal adenomas and physical activity, 36 articles describing epidemiological studies of leisure activity and five epidemiological studies of occupation in relation to colorectal cancer. A further 19 articles reviewed various aspects of the association between colorectal neoplasms and habitual physical activity. This database was supplemented extensively by other articles gleaned from PubMed, Google Scholar and personal files, with a particular emphasis upon occupational studies prior to 1996.

Results

Habitual physical activity and colorectal adenomas

The prevalence of colorectal adenomas in the general population has been set as high as 30%, although this may reflect in part the fact that data have been collected mainly on elderly people. If polyps are removed surgically, there is also a high recurrence rate (around 20%/yr). Although most colorectal carcinomas arise from adenomas, only 1-10% of adenomas progress to cancers. The risk of progression to a malignant tumour is increased if the adenoma is large, the histology is villous rather than tubular, and the lesion contains many abnormal cells. Given the high prevalence of colorectal adenomas, the appreciable risk of their progression to colorectal cancer and the strong likelihood of their recurrence after surgery, there is considerable interest in the potential of regular physical activity to reduce the risk of developing such tumours.

At least 33 human studies have examined associations between habitual physical activity and the risk of colorectal adenomas (Table 1); six were based upon differences of occupational activity, and 27 on assessments of leisure or total physical activity. Although most reports have shown a positive trend, this has not always reached statistical significance. The extent of the benefit reported in published articles may have been attenuated by imprecision in the measurement of habitual physical activity, although in studies that have not included such covariates as age, sex and body mass index, linkages between these risk-influencing factors and the amount of regular physical activity could also have exaggerated apparent associations between a lack of physical activity and the formation of adenomas.

Only one study found no effect from occupational activity (Sandler et al., 1995), and these investigators nevertheless noted that a substantial benefit was associated with leisure activity. Pooling data from the occupational studies, the weighted risk of adenomas for inactive individuals was a substantial 1.84 relative to those who had active or highly active occupations. However, the estimate of benefit was biased by a risk ratio of 5 derived from a single pair of active men (Neugut et al., 1996); ignoring this outlier, the risk ratio for those with sedentary occupations dropped to a weighted average of 1.50. One report further noted that the risk of sedentary work was greater for large adenomas (risk ratio 1.67) than for small ones (risk ratio 1.20) (Boutron-Rualt et al., 2001).

Table 1: Inactive/sedentary lifestyle and the risk of developing colorectal adenomas.

Author	Sample	Physical activity	Risk ratios	Covariates & comments
Occupational Studies				
Boutron-Rualt et al. (2001)	154 small, 208 large adenomas vs. 426 controls	Low vs. high occupational activity	Small adenomas 1.2 Large adenomas 1.67 Weighted 1.47	Age, sex
Kato et al. (1990)	525 adenomas, 578 controls	Sedentary occupation	1.69	Age, marital status, alcohol, smoking, family history
Klaus (1993)	170 colorectal adenomas, 245 controls	Work activity (none vs. > 4.2 MJ/wk)	1.19	Smoking, alcohol, use of NSAIDs
Little et al. (1993)	147 cases, 153 controls	Work activity below median, none vs. above	None 2.08, below median 1.50	Age, sex, social class
Neugut et al. (1996)	Colonoscopies: 506 normal, 298 with adenomas, 345 with past adenomas,197 with metachronous adenomas	Questionnaire & occupational title; moderate or low vs. very active occupation	Male moderate 3.00, low 5.00; Female inactive 1.11	Age, education, BMI, total energy intake, fibre, fat intake, smoking
Sandler et al. (1995)	86 M, 114 F colorectal adenomas, 384 controls	Job activity questionnaire	M 0.91 F 1.04	Benefit seen with leisure activity
Leisure or total physical activity				
Boutron-Rualt et al. (2001)	151 small, 204 large adenomas vs. 426 controls	Low vs. high leisure activity	Small adenomas 0.56 Large adenomas 1.11 Weighted risk 0.88	Age, sex
Colbert et al. (2002)	1905 adults in 3-yr prospective study of adenoma recurrences, 530 M, 203 F	Least active vs. estimated time spent on vigorous activity	Men 1.11 Women 1.43	Age
Enger et al. (1997)	488 colo-rectal adenomas and matched pairs, aged 50-74 yr	Questionnaire on *recent* physical activity (none vs. >4 or > 6 METs	None vs. > 6 METs 1.43 >4 METS 1.25	BMI, smoking, alcohol, diet
Giovanucci et al. (1995)	586 adenomas in 47,223 health professionals over 6 yr	Inactive vs. active	1.59	Age, parental history, endoscopy
Giovanucci et al. (1996)	439 adenomas in 13,057 nurses over 6 yr period	Low vs. high quintiles of leisure activity	1.75	Age, parental history, endoscopy
Guilera et al. (2005)	226 adenomas, 494 controls	Low or medium vs. high activity	Normal BMI 0.8 High BMI 0.96	Age, sex
Hauret et al. (2004)	177 cases, 228 controls	MET-hr/day of moderate to vigorous activity	Non-significantly higher in controls (30.2 vs. 27.6)	Age, sex, use of NSAIDs
Hermann et al. (2009)	536 colorectal adenomas in 4 yr follow-up of 25,540 subjects	4-level classification of habitual activity	1.07 (not significant relationship)	Age, sex, energy intake, diet, smoking, alcohol
Kahn et al. (1998)	10 yr follow-up of 72,868 men, 81,356 women. Cases 7504 M, 5111 F	3-level classification of physical activity (none/slight vs. high)	Men 1.20 Women 1.11	Age, diet, smoking, alcohol, aspirin use, family history & other factors

Table 1 Continued

Author	Sample	Physical activity	Risk ratios	Covariates & comments
Kato et al. (1990)	525 adenomas, 578 controls	Sport < 1 h/week vs. >1-2 h/wk	1.75	Age, area of residence, smoking, alcohol, family history
Klaus (1993)	170 colorectal adenomas, 245 controls	Physical activity questionnaire	No effect of activity	Smoking, alcohol, use of NSAIDs
Kono et al. (1991)	80 adenomatous polyps, 1148 normal subjects	Interview, active 2-3 h/wk vs. 1-2 or 0-1 or 0 h/week	1-2 h/wk 1.43 0-1 h/wk 1.14 0 h/wk 2.27	Smoking, alcohol, BMI, military rank
Larsen et al. (2006)	443 adenomas, 3447 controls	4-category exercise scale	No relationship to physical activity	
Lieberman et al. (2003)	391 hyperplastic polyps vs. 1441 controls	Framingham activity index score 24-28 vs. >36	1.22	
Little et al. (1993)	147 colorectal adenomas, 153 controls	None vs. run or cycle >30 min 1/wk	2.17	Age, sex, social class
Lubin et al. (1997)	196 patients, matched controls	Lowest vs. highest tertile of physical activity	1.67	Age, smoking, fibre intake
Neugut et al. (1996)	Colonoscopies: 506 normal, 298 adenomas, 345 past adenomas, 197 metachronous adenomas	No leisure activities vs. active	0.71 (M) 0.77 (F)	Age, education, BMI, total energy intake, fibre, fat intake, smoking
Rosenberg et al. (2006)	45,500 Black women, 6 yr follow-up; 1390 developed polyps	Walking & vigorous exercise <5 MET-hr/wk vs. >40 MET-hr/wk	1.31	Age, BMI, family history, smoking, education
Rozen et al. (1994)	243 colorectal adenomas, matched controls	Weekly activity report	Adenomas associated with low physical activity	Diet, weight gain, BMI, smoking, alcohol
Sandler et al. (1995)	200 adenomas, 384 controls	Lowest vs. highest activity quartile	M 1.09 F 1.56	
Shinchi et al. (1994)	228 adenomas, 1484 controls	No exercise vs. daily exercise	All adenomas 1.00 Large adenomas 2.00	Smoking, alcohol, waist-hip ratio, military rank
Stemmeman et al. (1988)	79 adenomas, 84 controls	Risk vs. 1st (most active quartile)	2nd 1.13 3rd 1.06 4th 1.15	Diet, cholesterol, smoking, alcohol
Terry et al. (2002)	441 non-advanced adenomas, 1866 controls	None vs. activity > 2h/wk	M 1.25 F 0.91	Age, sex, BMI, diet, hormone replacement therapy in women
Tiemersma et al. (2003)	237 M, 196 F 436 controls	Sedentary vs. "high" activity	M 1.45 F 0.95	?
Wallace et al. (2005)	4 yr follow-up of 930 patients with previously resected colorectal adenomas	Weekday and weekend MET-hr of activity	No association with tubular adenomas 0.97) or hyperplastic polyps (1.04)	Age, sex, BMI treatment time
Wolin et al. (2011)	Meta-analysis of 20 studies	Risk associated with no physical activity	Men 1.23 Women 1.15 (Large adenomas 1.43)	

Several of the studies found no significant protection against colorectal adenomas in the more active members of their sample, although the exercisers generally showed a reduced risk of colorectal cancers in these same studies (Hermann et al., 2009; Klaus, 1993; Larsen et al., 2006; Wallace et al., 2005). The weighted average risk ratio associated with inactive leisure behaviour was 1.26 in the 27 reports with numerical values; this estimate was heavily weighted by the largest study (12,615 cases), and the average risk ratio for the remaining 26 reports was 1.37. Most investigators found a somewhat greater protection against the development of adenomas in men than in women (possibly because more of the men engaged in vigorous exercise). Six studies provided sex comparisons, with the average risk of inactive leisure being about twice as great for men (1.21) as for women (1.12). In some (Giovannucci et al., 1995; Giovannucci et al., 1996) but not all (Enger et al., 1997) reports, the benefit associated with regular physical activity was greater for large than for small adenomas.

Data from controlled animal experiments have partially confirmed findings from the human epidemiological investigations. For example, a study of mice found 29% fewer polyps and 38% fewer large polyps in male animals that took 60 minutes per day of treadmill running for a period of 9 weeks, although no change was seen in female animals, and no benefit was found from the lighter activity of voluntary wheel-running in mice of either sex (Mehl et al., 2005).

Colorectal Cancer

Evidence of rectal cancer has been found in an Egyptian mummy dating from the era of Ptolomy. The incidence of colorectal tumours now varies some 20-fold between different countries, with rates being highest in developed societies. Migrants to North America quickly develop higher rates, suggesting the importance of a "western" lifestyle to the risk of developing such tumours. The factors involved probably include not only the lower levels of physical activity in developed societies, but also changes of diet, smoking and alcohol consumption.

Almost all colorectal tumours are adeno-carcinomas. They are characterized by expression of the cyclooxygenase-2 (COX-2) enzyme, which is not present in healthy colonic tissue. The survival rate depends greatly upon tumour stage when it is first diagnosed. For Stage I tumours, the 5-yr survival is around 90%, for Stage III it is 60-85%, and for tumours that have spread to other parts of the body it drops to around 12%; hence, the importance not only of preventive measures, but also of the early detection of colorectal tumours.

As with the adenomas, observations on associations between habitual physical activity and the risk of colorectal cancer have been based on the comparison of individuals with differing physical demands at work and on reports of leisure activity. Several authors have measured both of these variables, and in general they have found a closer association of cancer risk with occupational coding than with reported leisure activity (Albanes et al., 1989; Markowitz et al., 1992; Slattery et al., 2003; Tavani et al., 1999). Heavy occupational work is usually characterized by its duration rather than its intensity, and it may be that in terms of countering bowel cancer prolonged periods of moderate physical activity are a more effective measure than shorter periods of more intensive leisure activity. Also, inter-individual differences of occupational activity may be more stable and easier to ascertain than differences of leisure activity.

Regular vigorous physical activity has a substantial association with a reduced risk of colon cancer, but many investigators have found a lesser impact upon cancer rates for the rectum. Probably for this reason, benefit has been less apparent in a number of studies when colon and rectal tumours have been considered jointly (Albanes et al., 1989; Levi et al., 1999; Markowitz et al., 1992; Paffenbarger et al., 1987; Peters et al., 1999;

Steenland et al., 1995; Wei et al., 2004; Zhang, 1992).

Occupational studies

Occupational studies have typically attempted to categorize energy expenditures on the job, or have noted the hours of sitting, standing and more active forms of work. Occupational classifications have the advantage that a given activity pattern is typically sustained over many years, but the findings are sometimes confounded by other factors that influence cancer risk, particularly exposure to industrial toxins, differences in socio-economic status, smoking habits and the prevalence of an excessive consumption of alcohol. Moreover, because of progressive mechanization and automation, the physical demands of industrial work have declined sharply over the past 3 decades, and most occupational studies are based on data that was collected prior to 2000. (Stang et al., 2007) suggested that the decreasing physical demands at the worksite may have contributed to a secular increase in the ratio of colon to rectal tumours in Eastern Germany, Some studies simply made ratings of work-place activity at the time of the survey, but other investigators (Longnecker et al., 1995; Moradi et al., 2008; Slattery et al., 2003) attempted to capture workplace energy expenditures over periods of 10 yr or longer. Risk ratios have included a wide range of covariates, such as age, sex, smoking and alcohol consumption, diet, BMI and family history. A few studies (Boyle et al., 2011; Isomura et al., 2006; Johnsen et al., 2006; Markowitz et al., 1992) also co-varied for inter-individual differences in recreational activity.

In terms of colon cancer (Table 2), 39 studies have examined the risks associated with sedentary employment. When comparing sedentary workers with small groups of the most active employees, some reports have shown risk ratios as high as 2 (Boyle et al., 2011; Colbert et al., 2001; Fredriksson et al., 1989; Moradi et al., 2008) or even 3 (Peters et al., 1989; Tavani et al., 1999). Among the few reports that found no disadvantage to sedentary workers, the analysis of (Paffenbarger et al., 1987) was based on a very limited number of colon cancer deaths in longshore workers, and (Persky et al., 1981) found no relationship between resting heart rate (a rather indirect surrogate of physical activity) and the likelihood of death from colon cancer. (Pukkala et al., 1993) assumed that language teachers were less active than physical education teachers, but they included no covariates in their analysis. One study of 298 cases admitted the sample may have been too small to demonstrate benefit from physical activity (Johnsen et al., 2006). Another small study (Jarebinski et al., 1988; Vlajinac et al., 1987) found no protection from a high level of occupational activity. The weighted risk ratio for all 39 reports was 1.27. Benefit has sometimes been thought larger in men than in women (Vetter et al., 1992), perhaps because the physical demands and frequency of active employment are commonly greater for men. However, a formal sex comparison in 13 studies found respective risk ratios of 1.31 for men and 1.39 for women.

Table 2: Low level of physical activity at work and the risk of colonic cancer.

Author	Subjects	Physical activity	Risk ratio	Co-variates
Arbman et al. (1993)	98 cancer, 370 + 430 controls	Years of sedentary work, >20 vs. 0	Men 1.5 Women 1.0	Age, sex
Boyle et al. (2011)	320 M, 332 F cases, 996 controls	Sedentary vs. heavy/v. heavy work	2.40 (2.04 proximal, 2.74 distal colon)	Age, sex, recreational activity, smoking, alcohol, BMI, diabetes, socio-economic status
Brownson et al. (1989;1991)	1830 colon cancer, 15,309 cancers at other sites	Low vs. high occupational activity	All colon 1.2 Descending colon 1.9	Age, smoking
Chow et al. (1993;1994)	13,940 women, 4892 men cases 1293 M, 936 F	Sedentary vs. active job, low vs. high energy expenditure	Men 1.29, 1.48 Women 0.99, 1.36	Age, occupation, area of residence
Colbert et al. (2001)	73 cases	Sedentary vs. moderate/heavy work	2.22	Age, BMI, smoking
Dosemeci et al. (1993)	623 cases, 5613 controls	<8 vs >12 kJ/min; >6 vs < 2 hours sitting at work	1.8, 1.4	Age, smoking, socio-economic status
Fraser and Pearce (1993)	1651 male cases	Low energy expenditure based on occupational registry	1.2	Age
Fredriksson et al. (1989)	329 cases, 658 controls	Self-reported low vs. high activity	2.04	Age, sex
Friedenreich et al. (2006)	561 cases	Sedentary vs. manual/heavy work	1.10	Age, energy intake, smoking, height, weight, diet
Garabrant et al. (1984)	2950 cases	Sedentary vs. high activity on job classification	1.6 (2.7 descending colon, 2.0 transverse colon, 1.5 sigmoid colon)	Age, race, socio-economic status
Gerhardsson et al. (1986)	19-yr incidence in 1.1 million Swedish men 352 cases	Sedentary vs. active job classification	1.8	Age, marital & socioeconomic status, population density, area of residence
Gerhardsson et al. (1988)	14-yr incidence in Swedish twins, 102 cases	Self-reported moderate vs. highly active job	1.6	Age, sex, meat & coffee intake, area of residence
Hou et al. (2004)	464 M, 467 F	Low vs. high activity at work	1.23 M 1.56 F	Age, education, income, diet, marital status, pregnancies, menopause
Isomura et al. (2006)	778 cases, 767 controls	Sedentary vs. hard work	Colon 1.43 Proximal 1.43 Distal 1.67	Age, smoking, alcohol, area of residence, BMI, leisure activities
Jarebinski et al. (1988)	186 cases, 372 controls	Job activity	No effect	Smoking, alcohol, education, profession
Jedrychowski et al. (2002)	180 cases	Sedentary vs. physically active work	1.79	Age, sex, diet, BMI, education, NSAIDs
Johnsen et al. (2006)	157 M, 140 F	Sitting vs. manual work	0.85 M, 0.75 F	Smoking, alcohol, leisure activity, diet, hormone replacement therapy
Kato et al. (1990)	756 cases, 16,600 controls	Sedentary vs. physically active work	1.05	Age, marital status, smoking, alcohol, family history

Table 2 Continued

Author	Subjects	Physical activity	Risk ratio	Co-variates
Larsson et al. (2006)	299 cases	Light vs. heavy work	0.97 all sites 0.79 proximal, 1.27 distal colon	Age, BMI, smoking, education, family history, diabetes, NSAIDs
Le Marchand et al. (1997)	Cases 467 M, 358 F, 1192 controls	Sedentary work vs. most active tertile	1.51 M, 1.50 F R colon M 1.8 F 2.1; L colon M 1.3 F 1.0	Age, alcohol, smoking, diet, family history
Levi et al. (1999)	222 cases, 489 controls	Lowest vs. highest work, age 30-39 yr (max. effect at this age)	(Colorectal) 2.44	Age, sex, alcohol, education
Longnecker et al. (1995)	163 cases R. colon, 703 controls	Lifetime sedentary vs. > light occupation	1.47	Smoking, diet, BMI, family history, income race
Lynge and Thygesen (1988)	10-year incidence in 2 million+ people, cases 39 M, 20 F	Sedentary vs. non-sedentary work	Male 1.38 Female 1.73	Age, sex
Markowitz et al. (1992)	307 men vs. 1164 controls	Low vs. high activity at work	2.00	Age, race, area of residence, recreational activity
Marti and Minder (1989)	1995 cases	Low vs. high activity at work	1.30	Age
Moradi et al. (2008)	18-year follow-up of 2 million Swedes, activity classified for 10 years; 5900 M, 2000 F	Sedentary vs. high or very high activity at work	M 1.3 F 1.2 Proximal colon 1.2/1.4 Transverse colon 1.0/2.0 Distal colon 1.4/1.2 Descending colon 2.4/1.1	
Paffenbarger et al. (1987;1992)	6351 longshoremen, 22-year mortality, 21 colorectal cases	Light vs. heavy activity at work	0.85	Age, "heavy" smoking, blood pressure
Persky et al. (1981)	3132 cases, 5784 controls	Resting heart rate	No relation to cancer	
Peters et al. (1989)	147 cases, 147 controls	Low physical activity in longest held job	Transverse & descending colon 3.75 All colon 3.0	Age, diet, BMI, area of residence, occupational exposures to toxins
Pukkala et al. (1993)	26/8619 language teachers vs. 9/1499 phys ed. teachers,	Job type (assumed phys. ed. teachers more active)	0.78	Age
Simons et al. (2013)	1033 cases	Work energy expenditure <8 kJ/min vs. > 12 kJ/min	1.35 proximal colon 1.28, distal colon 1.41	Age, BMI, smoking, alcohol, diet, family history, energy intake
Steindorf et al. (2005)	98 incident cases, 193 controls	0 vs. > 147 MET-hr/wk at work	2.56	BMI, smoking, alcohol, fibre intake, calcium intake
Tavani et al. (1999)	451 M, 356 F cases, 4154 controls	Low to high occupational activity for M & F	M 1.96, F 2.22 Ascending colon 1.27, 2.33 transverse & desc. colon 2.02, 3.14 sigmoid colon 1.85, 1.72	

Table 2 Continued

Thune and Lund (1996)	16 yr follow-up of 53,242 M, 28,274 F; cases: 228 M, 98 F	Sedentary vs. heavy manual work	Male 1.22 Female 1.45	Age, smoking, diet, BMI, height, marital status
Vena et al. (1985)	Analysis of 455,000 deaths, cases 6459 M, 604 F	Low vs. highly active work	Male 1.35 Female 1.41	Age
Vena et al. (1985)	210 male cases, 431 controls	> 20 years of sedentary work	1.97	Age
Vena et al. (1985)	Analysis of 455,000 deaths, cases 6459 M, 604 F	Low vs. highly active work	Male 1.35 Female 1.41	Age
Vetter et al. (1992)	87 M, 13 F cases, 371 controls	High vs. low sitting time, low vs. high energy expenditure at work	1.5, 1.6 (effect largest in men, = 1.9)	Age, smoking
Vineis et al. (1993)	131 cases, 463 controls	Intensity of work <8 kJ/min vs. > 12 kJ/min	Male 1.40 Female 1.10	Age, social class, area of residence
Whittemore et al. (1990)	Chinese, 466 cases, 2448 matched controls	Self-reported inactive vs. active job	1.60	Age, sex, diet, body size, time since migration to Canada
Zhang et al. (2006)	155 cases, 593 controls	Low vs. high activity at work 10, 20 & 30 yrs prior to diagnosis	1.25 (1.43 R colon, 1.11 L. colon)	Age, sex, education, diet, family history

Whittemore et al. (1990) found that the benefit associated with active employment was larger in North Americans residents than in Chinese, possibly in part because of dietary differences or lower levels of non-occupational physical activity in the North Americans. Another study eliminated the effect of genetic susceptibility by comparing responses in twin pairs; using this model, they still showed a substantial risk of 1.6 for those in sedentary employment (Gerhardsson et al., 1988).

In contrast to colon cancer, the association between rectal cancer and a high level of occupational activity is inconsistent, with some reports suggesting a substantial benefit, and others finding either no effect or even an adverse response (Table 3). The weighted mean risk ratio in 27 studies was 1.17 for those with sedentary work; seven studies allowed a sex comparison, with weighted risk ratios of 1.17 for men, and 0.98 for women.

Leisure activity

A total of 46 studies have evaluated the association between a low level of leisure activity and the risk of colon cancer. The weighted risk ratio for these studies is 1.59 (Table 4). Sometimes, findings have been quite inconsistent; thus Lee and colleagues (1991) reported a risk ratio of 2.00, but three years later, an analysis of data for almost the same sample of Harvard alumni reported a risk ratio of only 1.08 (Lee and Paffenbarger, 1994). Sixteen studies compared colon cancer data between men and women, finding respective risk ratios of 1.34 and 1.36 for those with a sedentary lifestyle.

In terms of leisure activity and rectal cancer, 20 studies have shown a weighted risk ratio of 1.24 for individuals with a sedentary lifestyle (Table 5). Nine of these reports compared effects in men and

Table 3: Low levels of physical activity at work and the risk of rectal cancer.

Author	Subjects	Physical activity	Risk ratio	Co-variates
Arbman et al. (1993)	79 cases, 801 controls	0 vs. > 20 yr in a physically active occupation	M 3.33 F 0.59	Age, sex
Boyle et al. (2011)	318 cases, 996 controls	Sedentary vs. heavy/v. heavy work	1.52	Age, sex, recreational activity, smoking, alcohol, BMI, diabetes, socio-economic status
Brownson et al. (1989;1991)	812 cases, 15,309 cancers at other sites	Low vs. high occupational activity	1.2	Age, smoking
Colbert et al. (2001)	52 cases	Sedentary vs. moderate/heavy work	2.00	Age, supplement group
Dosemeci et al. (1993)	120 male cases, F not listed 5613 controls	Job activity < 8 kJ/min vs. > 12 kJ/min	M 1.50 F 1.10	Age, smoking, socio-economic status
Fraser and Pearce (1993)	1046 cases	Low vs. high occupational activity	1.3 (effect greatest at ages 45-54 years)	Age
Friedenreich et al. (2006)	322 cases	Sedentary vs. manual/heavy work	1.03	Age, energy intake, smoking, height, weight, diet
Garabrant et al. (1984)	1213 cases aged 20-64 yr.	Low vs. high occupational activity	1.03	Age, race, socio-economic status
Gerhardsson et al. (1986)	19-year incidence, 1.1 million Swedish men, 217 cases	Sedentary vs. active job	1.10	Age, marital & socioeconomic status, population density, area of residence
Huseman et al. (1980)	105 cases vs. 99 gall stones	Sedentary occupation	1.40	
Isomura et al. (2006)	208 M, 120 F cases, 470 controls	Sedentary vs. hard	1.67, 0.91	Age, smoking, alcohol, area of residence, BMI, leisure activities
Jarebinski et al. (1988)	98 cases, 196 controls	Job activity	No effect	Smoking, alcohol, education, profession
Kato et al. (1990)	753 cases, 16600 controls	Sedentary vs. active work	0.92	Age, marital status, smoking, alcohol, family history
Larsson et al. (2006)	186 cases	Light vs. heavy work	0.86	Age, BMI, smoking, education, family history, diabetes, NSAIDs
Le Marchand et al. (1997)	221 M, 129 F cases, 1192 controls	Sedentary work vs. most active tertile	M 1.2 F 0.6	Age, alcohol, smoking, diet, family history
Longnecker et al. (1995)	242 cases, 703 controls	Lifetime sedentary vs. > light occupation	1.01	Smoking, diet, BMI, family history, income race
Lynge and Thygesen (1988)	25 M, 4 F cases relative to general population	Sedentary vs. non-sedentary work	Male 0.96 Female 0.61	Age, sex
Markowitz et al. (1992)	123 men vs. 1164 controls	Low vs. high activity at work	1.67	Age, race, area of residence, recreational activity
Marti and Minder (1989)	1066 cases	Low vs. high activity at work	1.30	Age

Table 3 Continued

Author	Subjects	Physical activity	Risk ratio	Co-variates
Moradi et al. (2008)	18-year follow-up of 2 million Swedes, activity classified for 10 years, 4206 M, 1122 F	Sedentary vs. high or very high activity at work	M 1.1 F 1.0	
Pukkala et al. (1993)	15/8619 language teachers vs. 1/1499 phys ed. teachers,	Job type	4.07	Age
Simons et al. (2013)	422 M cases	Work energy expenditure <8 kJ/min vs. > 12 kJ/min	0.76	Age, BMI, smoking, alcohol, diet, family history, energy intake
Tavani et al. (1999)	350 M, 214 F cases, 4154 controls	Low to high occupational activity for M & F	M 0.76 F 1.14	
Thune and Lund (1996)	16 yr follow-up of 53,242 M, 28,274 F (168M, 55F cases)	Sedentary vs. heavy manual work	Male 1.00 Female 1.14	Age, smoking, diet, BMI, height, marital status
Vena et al. (1985)	276 male cases, 431 controls	> 20 years of sedentary work	1.13	Age
Vena et al. (1987)	Analysis of 455,000 deaths; cases 2617 M, 118 F	Low vs. highly active work	Male 1.30 Female 1.00	Age
Whittemore et al. (1990)	Chinese, 439 cases, 2448 matched controls	Self-reported inactive vs. active job	1.60	Age, sex, diet, body size, time since migration to Canada

Table 4: Low levels of leisure activity or combined leisure + occupational activity and an increased risk of colon cancer.

Author	Subjects	Physical activity	Risk ratio	Co-variates
Ballard-Barbash et al. (1990)	73 M, 79 F with large bowel cancer from 1906 M & 2308 F	Least active vs. most active tertile	M 1.8 F 1.1	Age, BMI
Bostik et al. (1994)	210 cases in prospective study of 35,215 women	3-level classification of physical activity	1.05	Multiple co-variates
Calton et al. (2006)	243 cases, prospective study of 31,783 women	Self-administered questionnaire, lowest vs. top quintile of activity over past 12/12	0.87	Age, BMI, education, family history, smoking, alcohol, calcium, red meat, use of HRT & aspirin
Chao et al. (2004)	536 M, 404 F cases in 70,403 M, 80,771 F	Self-reported 0 vs. > 8 hrs/wk and 0 vs. > 30 MET-hrs/wk leisure activity	0 vs. 8 h/wk M 1.72 F 1.47 MET-hrs/wk M 1.67 F 1.30	Age, education, prior exercise level, smoking, alcohol, red meat, folate, fibre, multivitamins and hormones in women
Colbert et al. (2001)	83 cases	Sedentary vs. active leisure	1.22	Age, BMI, smoking
Friedenreich et al. (2006)	1094 cases	Leisure activity <12 vs. >42.8 MET-h/wk	1.18	Age, energy intake, smoking, height, weight, diet
Gerhardsson et al. (1986)	19-yr incidence in 1.1 million Swedish men, 102 cases	Least vs. most active leisure	1.6 (combined)	Age, marital & socioeconomic status, population density, area of residence
Gerhardsson de Verdier et al. (1990)	352 cases, 512 controls	Sedentary vs. very active leisure	1.8 (combined); L. colon 3.2, R. colon 1.1	Age, sex, BMI, diet, energy intake
Giovanucci et al. (1995)	201 cases in 47,723 health professionals over 6 yr	0.9 vs. 46.8 MET-h/wk leisure	1.89	
Hou et al. (2004)	177 M, 179 F	Low vs. high leisure activity	1.39 M 1.19 F	Age, education, income, diet, marital status, pregnancies, menopause
Howard et al. (2008)	2257 M, 1090 F	Never vs. exercise > 5/wk	1.22 M 1.15 F	Age, smoking, alcohol, education, race, family history, energy intake, diet
Isomura et al. (2006)	248 cases, 468 controls	0 vs. > 16 MET-h/wk leisure activity	All colon 1.25 Proximal 1.12 Distal 1.43	Age, smoking, alcohol, area of residence, BMI,
Jedrychowski et al. (2002)	180 cases	Sedentary vs. active leisure	1.79	Age, sex, diet
Johnsen et al. (2006)	157 M, 140 F	Sedentary vs. decrease of risk per reported leisure activity	1.11 M, 1.12 F	Smoking, alcohol, leisure activity, diet, hormone replacement therapy
Kato et al. (1990)	221 cases, 578 controls	Sport < 1 h/wk	1.67	Age, marital status, smoking, alcohol, family history

Table 4 continued

Author	Subjects	Physical activity	Risk ratio	Co-variates
Larsson et al. (2006)	307 cases	<10 vs. > 60 min/day leisure activity	1.79 all colon 1.39 proximal, 2.5 distal colon	Age, BMI, smoking, education, family history, diabetes, NSAIDs
La Vecchia et al. (1999)	687 M, 537 F cases, 4145 controls	Low vs. high leisure activity	1.46 M, 1.58 F	Age, sex, diet, energy intake, area of residence, education, family history
Le Marchand et al. (1997)	8467 M, 358 F cases, 1192 controls	Least vs. largest tertile of lifetime leisure activity	R colon M 1.43 F 1.67; L colon M 1.43, F 1.67	Age, alcohol, smoking, diet, family history
Lee et al. (1991)	17,148 Harvard alumni, 225 cases over 23 yr follow-up	Leisure activity < 4 MJ/wk vs. > 10 MJ/wk	2.00	Age
Lee and Paffenbarger (1994)	17,607 Harvard alumni, 280 cases	Leisure activity < 4 MJ/wk vs. > 10 MJ/wk	1.08	Age, BMI, parental history
Lee et al. (1997)	21,807 physicians, 217 cases	No vigorous exercise vs. > 5/wk	0.9	Age, obesity, alcohol
Levi et al. (1999)	222 cases, 489 controls	Lowest vs. highest activity at age 30-39 (maximum effect)	(Colorectal) 1.89	Age, sex, alcohol, education
Longnecker et al. (1995)	163 cases R. colon, 703 controls	None vs. vigorous activity > 2/wk	1.75	Smoking, diet, BMI, family history, income race
Lund-Nielsen et al. (2001)	213 M, 179 F	Low vs. high physical activity index	(Colorectal) 1.85 M, 1.23 F	?
Mai et al. (2007)	395 F	0-0.5 vs. >4 h/wk moderate or strenuous leisure activity	1.33 all colon 1.30 proximal 1.35 distal colon	Age, BMI, smoking, hormone use, folate intake
Marcus et al. (1994)	536 F cases, 2315 controls	Active 0-1 vs. >7 times/wk	2.11	
Martinez et al. (1997)	396 cases colon cancer in F	Self-reported <2 vs. > 20 MET-h/wk leisure activities	1.85; no difference by colonic site	Age, smoking, family history, BMI, HRT, red meat & alcohol
Morrison et al. (2013)	455 cases	Sedentary vs. any leisure activity	1.69	Age, sex, smoking, alcohol, BMI, cholesterol, diabetes, study site
Nilsen et al. (2008)	197 M, 205 F	Low vs. high (frequency, duration & intensity) leisure activity	1.45 M All colon 1.39 F All colon Ascending 1.04 Transverse 3.00 Descending 1.18 Sigmoid 3.45	BMI, smoking, alcohol, education, marital status
Polednak (1976)	107 cases in 8393 men	Sedentary vs. major university athletes	0.94	Body size
Schnohr et al. (2005)	14-yr follow-up of 13,216 F and 18,718 M; 180 (F), 215 (M) cases	Self-reported leisure activity, sedentary vs. most active	M 1.39 F No effect	Age, smoking, alcohol, education, birth cohort, BMI

Table 4 continued

Author	Subjects	Physical activity	Risk ratio	Co-variates
Larsson et al. (2006)	307 cases	<10 vs. > 60 min/day leisure activity	1.79 all colon 1.39 proximal, 2.5 distal colon	Age, BMI, smoking, education, family history, diabetes, NSAIDs
La Vecchia et al. (1999)	687 M, 537 F cases, 4145 controls	Low vs. high leisure activity	1.46 M, 1.58 F	Age, sex, diet, energy intake, area of residence, education, family history
Le Marchand et al. (1997)	8467 M, 358 F cases, 1192 controls	Least vs. largest tertile of lifetime leisure activity	R colon M 1.43 F 1.67; L colon M 1.43, F 1.67	Age, alcohol, smoking, diet, family history
Lee et al. (1991)	17,148 Harvard alumni, 225 cases over 23 yr follow-up	Leisure activity < 4 MJ/wk vs. > 10 MJ/wk	2.00	Age
Lee and Paffenbarger (1994)	17,607 Harvard alumni, 280 cases	Leisure activity < 4 MJ/wk vs. > 10 MJ/wk	1.08	Age, BMI, parental history
Lee et al. (1997)	21,807 physicians, 217 cases	No vigorous exercise vs. > 5/wk	0.9	Age, obesity, alcohol
Levi et al. (1999)	222 cases, 489 controls	Lowest vs. highest activity at age 30-39 (maximum effect)	(Colorectal) 1.89	Age, sex, alcohol, education
Longnecker et al. (1995)	163 cases R. colon, 703 controls	None vs. vigorous activity > 2/wk	1.75	Smoking, diet, BMI, family history, income race
Lund-Nielsen et al. (2001)	213 M, 179 F	Low vs. high physical activity index	(Colorectal) 1.85 M, 1.23 F	?
Mai et al. (2007)	395 F	0-0.5 vs. >4 h/wk moderate or strenuous leisure activity	1.33 all colon 1.30 proximal 1.35 distal colon	Age, BMI, smoking, hormone use, folate intake
Marcus et al. (1994)	536 F cases, 2315 controls	Active 0-1 vs. >7 times/wk	2.11	
Martinez et al. (1997)	396 cases colon cancer in F	Self-reported <2 vs. > 20 MET-h/wk leisure activities	1.85; no difference by colonic site	Age, smoking, family history, BMI, HRT, red meat & alcohol
Morrison et al. (2013)	455 cases	Sedentary vs. any leisure activity	1.69	Age, sex, smoking, alcohol, BMI, cholesterol, diabetes, study site
Nilsen et al. (2008)	197 M, 205 F	Low vs. high (frequency, duration & intensity) leisure activity	1.45 M All colon 1.39 F All colon Ascending 1.04 Transverse 3.00 Descending 1.18 Sigmoid 3.45	BMI, smoking, alcohol, education, marital status
Polednak (1976)	107 cases in 8393 men	Sedentary vs. major university athletes	0.94	Body size
Schnohr et al. (2005)	14-yr follow-up of 13,216 F and 18,718 M; 180 (F), 215 (M) cases	Self-reported leisure activity, sedentary vs. most active	M 1.39 F No effect	Age, smoking, alcohol, education, birth cohort, BMI

Table 4 Continued

Author	Subjects	Physical activity	Risk ratio	Co-variates
Severson et al. (1989)	172 cases in 7925 Hawaian-Japanese	Low vs. high leisure activity	1.41	Age, smoking, BMI
Simons et al. (2013)	1107 M, 924 F	<30 vs. > 90 min/day leisure activity	All colon 0.94 M, 1.43 F proximal colon 1.09 M, 1.41 F distal colon 0.85 M, 1.45 F	Age, BMI, smoking, alcohol, diet, family history, energy intake
Slattery et al. (1988;1990)	229 cases, 384 controls	No activity vs. high leisure activity 2 yr before diagnosis	3.70	Age, sex, BMI, smoking , education, area of residence
Slattery (1997)	2073 cases, 2466 matched controls	Lowest vs. highest lifetime leisure activity	1.63	Age, BMI, tumour site
Steindorf et al. (2005)	98 incident cases, 193 controls	< 23 v s. > 764 MET-hr/wk leisure activity	1.22	BMI, smoking, alcohol, fibre intake, calcium intake
Tang et al. (1999)	42 M, 27 F cases, 70 controls	Sedentary vs. activity > 20 MET-h/wk	5.26 M 1.59 F	Smoking, alcohol, diet, water intake
Thun et al. (1992)	1150 cases in 764,343 patients over 6 yr	Low vs. high leisure activity	Male 1.92 Female 1.11	Age, smoking, diet, BMI, height, marital status
Thune and Lund (1996)	230 M, 99 F cases in 80,616 people over 16 yr	Sedentary vs. regular training	M 0.75 F 1.19	Age, smoking, BMI, lipids, height, marital status
Wei et al. (2009)	2040 F	2 vs. 21 MET-h/wk leisure activity	2.0	Multivariate model
White et al. (1996)	444 cases, 427 controls	None vs. 2/wk leisure activity > 4.5 METs	1.43	Age, sex, BMI, health behaviours
Whittemore et al. (1990)	274 M, 192 F cases, 2448 matched controls	Sedentary	M (N.Am) 1.6 M (China) 0.85 F (N Am) 2.0 F (China) 2.5	Diet, BMI, time in N. America
Wolin et al. (2007)	282 F	0 vs. > 4 h/wk moderate or vigorous leisure activity	1.79 All colon proximal colon 1.89, distal colon 1.96	Age, BMI, smoking, alcohol, diet, multivitamins, NSAIDs, family history
Wolin et al. (2010)	1863 cases, 826 deaths	Change in physical activity over 10 & 15 yr	15 yr incidence 1.05 15 yr deaths 1.09	Sex, BMI, diet, energy intake, smoking, education, NSAIDs, hormones
Wu et al. (1987)	11,578 cases	< 1 h/day vs. > 2 h/day leisure activity	(Colorectal) 2.50 M, 1.12 F	Smoking, alcohol, Quetelet index, coffee, laxatives
Yang et al. (1994)	267 L, 247 R-sided colon cancer		Physical activity related more to L-sided cancer.	
Zhang et al. (2006)	585 cases, 2172 controls	Physical activity <1/month vs. > 2/wk	1.43 M & F, R colon 1.67, L colon 1.25	Age, sex, education, diet, family history

Table 5: Low levels of leisure activity or combined leisure + occupational activity and the risk of rectal cancer.

Author	Subjects	Physical activity	Risk ratio	Co-variates
Chao et al. (2004)	390 cases in 70,403 M, 80,771 F	Self-reported 0 vs. > 8 hr/wk leisure activity	1.20	Age, education, prior exercise level, smoking, alcohol, red meat, folate, fibre, multivitamins and hormone replacement
Colbert et al. (2001)	105 cases	Sedentary vs. active	1.08	Age, supplement group
Friedenreich et al. (2006)	599 cases	<12 vs. > 42.8 MET-h/wk leisure activity	0.83	Age, energy intake, smoking, height, weight, diet
Gerhardsson et al. (1998)	14-yr incidence in 16,447 Swedes,	Recreational activity	1.2	Age, sex, diet
Gerhardsson de Verdier et al. (1990)	Cases 107 M, 110 F, 512 controls	Sedentary vs. very active leisure	0.90 M 1.40 F	Age, sex, BMI, diet, energy intake
Isomura et al. (2006)	198 M, 132 F cases, 470 controls	0 vs. > 16 MET-h/wk leisure activity	2.00 M 1.11 F	Age, smoking, alcohol, area of residence, BMI
Kato et al. (1990)	221 cases, 578 controls	Sport < 1 h/wk	1.75	Age, marital status, smoking, area of residence
Larsson et al. (2006)	187 cases	<10 vs. > 60 min/day leisure activity	1.69	Age, BMI, smoking, education, family history, diabetes, NSAIDs
Le Marchand et al. (1997)	221 M, 129 F cases, 1192 controls	Least vs. greatest tertile of lifetime recreation	M 2.0 F 1.25	Age, alcohol, smoking, diet, family history
Lee et al. (1991)	17,148 Harvard alumni, 44 cases over 23 yr	Leisure activity < 4 MJ/wk vs. > 10 MJ/wk	0.58	Age
Lee and Paffenbarger (1994)	17,607 Harvard alumni, 53 cases	Leisure activity < 4 MJ/wk vs. > 10 MJ/wk	0.28	Age, BMI, parental history
Lee et al. (1997)	21,807 physicians, 217 cases	No vigorous exercise vs. > 5 d/wk	0.9	Age, obesity, alcohol
Longnecker et al. (1995)	242 cases, 703 controls	None vs. vigorous activity > 2/wk	0.85	Smoking, diet, BMI, family history, income race
Mao et al. (2003)	838 M, 589 F	<6 vs. >31 MET-h/wk leisure activity	0.87 M 1.14 F	Age, BMI, smoking, alcohol, education, diet, energy intake, multivitamins
Morrison et al. (2013)	455 cases	Sedentary vs. any activity	1.47	Age, sex, smoking, alcohol, BMI, cholesterol, diabetes, study site
Severson et al. (1989)	172 cases in 7925 Hawaiian-Japanese	Low vs. high leisure activity	0.71	Age, smoking, BMI
Simons et al. (2013)	402 M, 227 F	Leisure energy expenditure <8 kJ/min vs. > 12 kJ/min	0.91 M, 1.69, F	Age, BMI, smoking, alcohol, diet, family history, energy intake
Slattery et al. (2003)	559 M, 393 F, 1295 controls	Long-term low vs. high leisure activity	1.67 M 2.00 F	Age, BMI, smoking, NSAIDs, fibre, calcium
Tang et al. (1999)	48 M, 43 F cases, 92 controls	Sedentary vs. active > 20 MET-h/wk	2.27 M 1.19 F	Smoking, alcohol, diet, water intake
Thune and Lund (1996)	228 cases in 80,616 people over 16 yr study	Sedentary vs. regular training	M 1.02 F 0.67	Age, smoking, BMI, lipids, height, marital status
Waterbor et al. (1988)	985 baseball players	Sedentary controls vs. players	0.95	Playing position, waist/height ratio

women, finding weighted average risk ratios of 1.26 for men and 1.42 for women.

Conclusions

Associations between habitual physical activity and colorectal neoplasia have now been studied in a very large number of patients (Table 6). For reasons discussed below the findings are far from consistent, but it is at least clear that a higher level of physical activity is associated with a reduced risk of adenomas, colon and rectal cancers; further, the association is possibly somewhat stronger for the colon than for the rectum. However, despite earlier reports to the contrary, there does not seem to be any consistent difference of response between men and women.

Table 6: Summary of relationships between a low level of habitual physical activity and weighted risk-ratios for colorectal neoplasms.

Type of Tumour	Type of activity	Number of cases	Men and women	Men	Women
Adenoma	Occupational	1204	1.84 (1.50)*		
	Leisure	22,810	1.26	1.21	1.12
Colon cancer	Occupational	37,301	1.27	1.31	1.39
	Leisure	37,946	1.59	1.34	1.36
Rectal Cancer	Occupational	18,109	1.17	1.17	0.98
	Leisure	7,344	1.24	1.26	1.42

A meta-analysis of data for adenomas based upon 20 investigations (Wolin et al., 2011) confirmed the impressions gained from the above analyses; the risk of colorectal adenoma was 23% greater among inactive men, and 15% higher among inactive women.

A review by Colditz et al. (1997) suggested a 50% reduction in the risk of colon cancer among active individuals (Colditz et al., 1997). Friedenreich and Orenstein (2002) also argued for a 40-50% reduction of risk in the most active individuals, with 43 of the 51 studies that they considered showing an inverse relationship between the two variables (Friedenreich and Orenstein, 2002). However, recent data are generally consonant with the somewhat lower risk-ratios seen in Table 6. A meta-analysis of 19 studies of colorectal cancer (Samad et al., 2005) found risk ratios of 1.27 and 1.28 for sedentary occupations and sedentary leisure behaviour respectively. Harriss et al. (2009) reviewed 14 data sets for colon cancer, estimating risk ratios of 1.25 and 1.16 for men and women, respectively; however, in their analyses nine studies of rectal cancer showed no significant relationship to habitual physical activity (Harriss et al., 2009). Likewise, Thune and Furberg (2001) found a clear inverse dose-response relationship between habitual physical activity and the risk of colon cancer, but in 19 of 24 studies they found no significant association between habitual physical activity and rectal cancer (Thune and Furberg, 2001). Wolin and colleagues (Wolin and Tuchman, 2011; Wolin et al., 2011) examined 52 reports, finding a significant inverse association between physical activity and colon cancer in 37 reports. They saw little difference between occupational and leisure studies, with both types of investigation suggesting a risk reduction of about 22%, and similar findings for men and for women; however, they noted a larger effect in case-control than in cohort studies. (Je et al., 2013) made a meta-analysis of 7 prospective cohort studies of colorectal cancer, finding a risk ratio of 1.43 when sedentary behaviour was compared with a high intensity of physical activity, and 1.33 for those who reported "any" physical activity. Finally, Boyle and colleagues (2012) selected 21 studies, based on the clarity of site definition, finding a risk-ratio of 1.37 that was almost identical for proximal and distal colon cancers (Boyle et al., 2012).

Inter-study differences in the reported risk ratios

Now that data have accumulated from a large number of studies of physical activity and colorectal tumours, meta-analyses and the pooling of data provide a fairly consistent estimate of the reduction of risk seen in individuals who maintain a high level of physical activity. On the other hand, there are wide discrepancies in the values reported by individual laboratories. Possible explanations include sample size, age and sex of subjects, the choice of covariates, the method adopted when classifying habitual physical activity, and the duration of observations.

Sample size

Some of the studies looking at associations between habitual physical activity and colorectal neoplasms have had a relatively small total sample size; as a consequence, there have been few individuals in the high activity category and unstable estimates of risk ratios. We compared reports based on small (<50) and larger (>50) groups of highly active individuals. For adenomas, the respective weighted risk ratios for small and larger samples were 2.15 and 1.67 in occupational studies, and 1.56 and 1.19 in leisure studies. For colon cancers, the numbers for occupational studies were 1.77 and 1.32, and for leisure studies 1.96 and 1.48. For rectal cancers, the numbers for occupational studies were 1.22 and 1.18, and for leisure studies 1.18 and 1.34.

It thus appears that in the smaller studies, the risks associated with a sedentary lifestyle are exaggerated by comparison with findings for a very few individuals who maintain greater levels of habitual physical activity than are likely to be developed by the general population.

Age, sex, and race

Because the risk of neoplasia increases with age, and habitual physical activity tends to diminish with age, there is a risk of finding a spurious association between neoplasms and sedentary behaviour due to aging. However, a surprising number of investigations have omitted the precaution of including age as a covariate in their analyses (Tables 1-5).

Many investigators have argued that physical activity has a stronger protective effect in men than in women (Vetter et al., 1992). The summary data suggest there may be some male advantage in terms of protection against adenomas, but the risk ratios show no consistent sex difference for colon or rectal cancers (Table 6). In the case of adenomas, hormonal factors could be involved, but the sex difference could also reflect the small proportion of women who are engaged in physically demanding employment, imprecision in ascertaining vigorous physical activity in women, and in some instances a smaller number of cases of colonic cancer in the women (Calton et al., 2006).

Investigations have varied widely in the number and type of variables included as covariates (Tables 1-5), but this seems to have had little impact upon the reported risk ratios. The importance of using age and sex as covariates has already been noted. Other aspects of personal lifestyle could also create spurious associations. Obesity has a substantial impact upon the risk of neoplasia, and is also likely to be associated with sedentary behaviour. In recent years, smoking has remained a characteristic of those engaged in physically demanding occupations. Finally, some investigations have included total energy intake as a covariate, although this item seems likely to remove a part of the variance that should have been attributed to habitual physical activity.

Measurement of habitual physical activity and duration of observations

The extent of benefit reported in published articles is probably attenuated by imprecision in the measurement of habitual physical activity, Several authors have examined associations with both occupational and leisure activity; in general, colon cancer shows a closer association of cancer risk with occupational coding than with leisure activity (Albanes et al., 1989; Levi et al., 1999; Markowitz et al., 1992; Slattery et al., 1990). Most heavy occupational work is characterized by its prolonged duration rather than its intensity, and it may be that prolonged moderate physical activity is the most effective method of countering bowel cancer. It may also be that an occupational classification is more effective than a physical activity questionnaire when trying to capture the lifetime patterns of physical activity that are important in modulating carcinogenic change.

A few leisure studies (Le Marchand et al., 1997; Slattery et al., 1997; Wolin et al., 2010) have specifically sought to capture estimates of leisure activity over periods of 20 yr and more, and the first two of these studies found quite high-risk ratios.

A few reports (Ballard-Barbash et al., 1990; Le Marchand et al., 1997) have classified activity patterns by tertiles, rather than comparing sedentary subjects with a few individuals who reported very high levels of physical activity; the tertile data seems more appropriate when formulating public policy decisions.

Pattern of exercise

Any preventive effect of physical activity is modulated by its pattern, not only its intensity and duration, but also its timing relative to the carcinogenic process that can continue for 20 or more years.

Most of the research to date has focussed upon the benefits of aerobic exercise. Chao et al.(Chao et al., 2004) and Thune and Furberg (Thune and Furberg, 2001) both showed a clear inverse dose-response relationship between the reported volume of leisure activity and the risk of colon cancer, whether activity was measured in total hours per week or in MET-hours per week. However, benefit was most apparent in those practicing at least a moderate intensity and volume of physical activity (>4.5 METs, >10 MJ/wk; (Thune and Furberg, 2001), and in one report was only statistically significant in the most active group (those engaging in >30 MET-hr/wk of recreational activity)(Chao et al., 2004). Rectal cancer also showed some relationship to exercise behavior in the data of Chao et al. (Chao et al., 2004), but this association was not significantly dose-related.

A study of resistance exercise, based on 870 cases and 996 controls (Boyle et al., 2012), found non-significant trends to a possible benefit from resistance training of a similar order to that seen in many of the aerobic studies (OR 0.70 [95% CI 0.45-1.11]. The authors speculated that resistance training might have a favourable impact upon cancer risk by modulating insulin sensitivity, glucose uptake, immune function and/or obesity.

In terms of timing,(Levi et al., 1999) found the closest association was with the occupation the individual had practiced at an age of 30-39 yr. However, Chao et al. (Chao et al., 2004) found no benefit from physical activity that had occurred more than 10 yr prior to the diagnosis of cancer.

Comparison of response by region of the colon

Several investigations have compared the protective effects of regular physical activity in various parts of the colon, but perhaps because of relatively small sample sizes the findings have not agreed. Some reports have shown a rather equal effect of exercise upon different parts of the colon (Mai et al., 2007; Wolin et al., 2007). Others have reported the greatest benefits in the caecal region (Brownson et al., 1989; Fraser and Pearce, 1993), the ascending colon (Fraser and Pearce, 1993; Kato et al., 1990; Moradi et al., 2008; Severson et al., 1989; Simons et al., 2013; Thune and Lund, 1996), the transverse colon (Gerhardsson et al., 1986; Peters et al., 1989), or the distal colon (Boyle et al., 2011; Fredriksson et al., 1989; Moradi et al., 2008; Peters et al., 1989). A recent review and meta-analysis of 21 studies concluded that the benefit of increased physical activity was distributed equally across the various colonic sites (Boyle et al., 2012), a finding also noted in several individual studies (Martinez et al., 1997).

Potential mechanisms

A variety of possible mechanisms could predispose to the development of colon and rectal cancers (Shephard and Shek, 1998), many of these being linked to inadequate levels of habitual physical activity (Table 7). It is unlikely that any one of these factors could explain all of the experimental data on exercise and reduction of risk; the importance of individual factors probably depends upon the type, intensity and duration of physical activity that is undertaken.

Table 7: Possible factors responsible for the association between a low level of habitual physical activity and colorectal cancers.

- Increased formation of colorectal adenomas
- Reduced colonic motility
- Reduced prostaglandin secretion
- Less frequent use of NSAIDs
- Increased exposure to bile acids
- Dietary changes (greater consumption of fat, less fibre)
- Increased risk of obesity
- Increased risk of diabetes mellitus
- Lifestyle (greater likelihood of smoking & excessive alcohol consumption)
- No favourable modulation of immune function
- Greater oxidative stress
- Lower mucosal blood flow

Adenomas

The vast majority of colonic cancers have their origin in asymptomatic polyps (Emmons et al., 2005a). It is thus important to explore and correct the multiple risk factors (probably including physical inactivity) that convert benign adenomas into malignant tumours (Emmons et al., 2005b).

With few exceptions (Colbert et al., 2002), published studies on human subjects have reported an inverse association (not always statistically significant) between the prevalence of colorectal polyps and habitual physical activity (Table 1). However, a 1 yr prospective trial found no relationship between the recurrence of polyps and either moderate, vigorous or total physical activity. Moreover, a study of mice found benefit from treadmill running in male animals only, and no benefit was seen with the lesser exercise of voluntary wheel-running in either sex (Mehl et al., 2005).

Increased colonic motility

One potential explanation of a reduced susceptibility to colonic cancer among exercisers is that physical activity increases colonic motility, and thus reduces mucosal exposure to toxins within the bowels. Experimental evidence on this point is conflicting (Peters et al., 2001). Much of the available information relates to oro-caecal, small intestinal or total bowel transit times rather than to colonic motility. However, this is not a major criticism, since the gut contents spend a large part of their total transit time in moving through the large intestine: 50% gastric emptying occupies about 150-180 minutes, and 50% emptying of the small intestine occurs in a similar time span, whereas transit through the colon takes 30-40 hours.

Data for oro-caecal transit are sufficiently discordant to preclude the drawing of any broad conclusions. Possibly, discrepancies reflect differences in the intensity of effort that is undertaken or the timing of exercise relative to the measurements of motility. Nearly all of the available observations have been made by the breath hydrogen technique. Four human studies (Cordain et al., 1986; Harris et al., 1991; Keeling and Martin, 1987; Oettlé, 1991) and one animal experiment (Van Liere et al., 1954) have found a speeding of transit with exercise, five investigations have reported no significant change (Coenen et al., 1992; Kayaleh et al., 1996; Koffler et al., 1992; Scott and Scott, 1994; Soffer et al., 1991), and two papers have noted a slowing of transit (Meshkinpour et al., 1989; van Nieuwenhoven et al., 2004). Two of these reports noted a speeding of overall intestinal transit (Koffler et al., 1992; Oettlé, 1991), despite an unchanged oro-caecal time, pointing to faster colonic transit in response to moderate treadmill exercise (Koffler et al., 1992). A further study found a non-significant trend to faster total transit time in women who were more active, although in these subjects participation in a marathon run temporarily increased the total transit time by 21% (Lampe et al., 1991).

There seems to be only one study looking at small intestine transit times; this found no change of motility with prolonged intermittent exercise to a heart rate of 120 beats/min (Cammack et al., 1982). Other investigators have studied the impact of both habitual exercise and training/detraining on overall and segmental colon transit times in both healthy individuals and those with chronic constipation. Animal observations (de Young et al., 1931) and one human experiment using colonic pressure transducers (Cheskin et al., 1992) found increased colonic motility in response to vigorous exercise. In contrast, no immediate change of colonic transit time was seen with an hour of vigorous cross-country running (Rao et al., 2004). However, progressive cycle ergometer exercise to 75% of maximal oxygen intake induced changes in colonic pressure waves which may have facilitated emptying of the colon (Rao et al., 1999).

Bingham et al. (Bingham, 1991; Bingham and Cummings, 1989) and Robertson et al. (Robertson et al., 1993) found no effect of either vigorous or moderate training on total colonic transport. Likewise, Sesboüé et al. (Sesboüé et al., 1995) noted no overall differences in colonic transit between soccer players who were engaged in a very rigorous training programme and a much less active group of radiology technicians. In contrast, de Schryver et al. (De Schryver et al., 2005) noted a speeding of both total and recto-sigmoid transit in response to moderate training among individuals with chronic constipation, and Liu et al. (1993) found that although enforced inactivity in previously active elderly men did not change oro-caecal transit times, it did slow passage through both the left and the right colons. A cross-sectional analysis, based on 7 days of activity monitoring, found no effect of habitual physical activity in men, but various measures of colonic transit were faster in the more active women (Song et al., 2012).

Even if physical activity does not change the overall colon transit time, it could modify exposure of the endothelium to toxins by changing segmentation and other forms of local motor activity in the gut wall. Holdstock (1970) used radio-opaque markers and pressure sensors to study colonic motility in 27 individuals, 19 of whom were affected by the irritable bowel syndrome. Intra-luminal pressures rose substantially after eating, but physical activity (walking vs. sitting or lying) was needed to convert the increased pressures into a propulsive movement of the gut contents.

We must conclude that any effect of either single bouts of vigorous exercise or habitual training upon colonic motility is inconsistent, making it unlikely to be the sole source of the exercise-associated reduction in risk of colon cancer.

Prostaglandin secretion

Increased prostaglandin levels can stimulate colonic motility and thus reduce colonic exposure to toxins. Moreover, both aerobic and resistance exercise are known to stimulate the muscular production of prostaglandin (Trappe and Liu, 1985; Young and Sparks, 1979). Demers(Demers et al., 1981) further noted that following completion of a marathon run, there were significant increases in plasma levels of PGE_2, PGF_{2a} and 6-keto PGF_{1a}, although it is less clear that there would be a similar prostaglandin response to the levels of physical activity undertaken by average individuals.

NSAIDs

Endurance athletes frequently consume substantial quantities of NSAIDs. Both animal models and human clinical studies suggest that these drugs reduce the risk of colorectal cancer, despite the fact that they also reduce prostaglandin secretion. The mechanism of benefit is still the subject of vigorous discussion, but it may include a prostaglandin-induced apoptosis of both adenoma and cancer cells (Ahnen, 1998).

Bile acids

There is limited data on how exercise might influence faecal concentrations of bile acids. However, one study of male distance runners found lower concentrations of bile in the faeces, despite an unchanged rate of bile formation; this was attributed to dilution of the bile by a high intake of dietary fibre (Sutherland et al., 1991). Again, the volume of exercise undertaken by these subjects was substantial. Nevertheless, lower levels of bile acids should be considered as one possible factor contributing to the reduced risk of colon cancer in active individuals (Jensen et al., 1982; Reddy et al., 1979).

Dietary change

Athletes and others with a health-conscious active lifestyle commonly consume a diet that is high in carbohydrate and fibre, and low in fat. Nevertheless, the impact of these changes upon the risk of colorectal cancers is controversial. The Women's Health Study found no relationship between colorectal cancer and total fat intake (Lin et al., 2004), and a pooling of data from 13 case-control studies also found no relationship between colorectal tumours and total fat intake (Howe et al., 1997). However, protection has been seen with an increased consumption of omega-3 polyunsaturated fatty acids and of eicosapentaenoic and docosahexaenoic acids (Theodoratou et al., 2007).

The reported effects of a high fibre intake have also been inconsistent. Pooled prospective data on 725,628 adults suggested a substantial inverse relationship between fibre intake and cancer risk, although this effect became smaller and no longer statistically significant after adjustment for associated differences in the intake of other dietary constituents such as folate and multiple vitamins (Park et al., 2005).

Avoidance of obesity

Athletes and other physically active individuals generally have a low body fat content relative to those who are sedentary. Among men who are overweight or obese, epidemiological data have shown an increase in the risk of colorectal cancer as large as 30-70%, although in women the increase of risk with obesity is smaller and less consistent (Bardou et al., 2013). A meta-analysis of prospective studies found that a 5 unit increase of body mass index increased the risk of colon cancer by 30% in men, but by only 12% in women (Larsson and Wolk, 2007).

Reduced risk of diabetes mellitus

The risk of developing type II diabetes mellitus is substantially increased in sedentary individuals, and a 13-yr follow-up showed that those with diabetes had an increased risk of developing colorectal cancer (Lund Nilsen and Vatten, 2001; Steenland et al., 1995; Will et al., 1998). It could simply be that the diagnosis of diabetes causes increased medical surveillance, and thus early treatment of adenomas. Alternatively, tumour development could exacerbate a previously sub-clinical case of diabetes. However, there could also be more direct effects from the hormonal changes associated with diabetes.

Positive lifestyle

Physically active individuals are likely to be non-smokers, and to avoid an excessive intake of alcohol, both of which predispose to colorectal cancer (Chao et al., 2000; Fedirko et al., 2011). Further, the increase of cardiac function associated with aerobic training could increase mucosal blood flow in the gut, particularly during periods of vigorous activity, and this could possibly speed the elimination of toxins from the walls of the colon and rectum.

Other factors

Regular physical activity may lead to positive changes of immune function (Shephard, 1997) and a reduction of oxidant stress (Perše, 2013), both of which would likely reduce the risk of colorectal cancer. However, it is not easy to reconcile such postulated non-specific mechanisms of benefit with the fact that exercise only seems to prevent neoplasia in some of the body organs.

Exercise and established disease

A poor lifestyle, including a low self-perceived level of physical fitness, is associated with an adverse course in the first 30 days following surgery for colorectal cancer (Nickelsen et al., 2005) and a poorer overall survival rate (Pelser et al., 2014). The introduction of low to moderate intensity exercise immediately following tumour resection causes an immediate improvement of colonic motility and reduces the typical duration of hospital stay (Ahn et al., 2013). Accelerometer data show that the physical activity of a colorectal cancer patient is usually quite limited on leaving hospital (Boyle et al., 2015). However, it is possible to implement an aerobic exercise programme within 6 months of operation, and such an initiative improves the patient's tolerance of aerobic activity, with a reduction of fatigue, an increased functional capacity and an improved overall quality of life (Bourke et al., 2011; Vallance et al., 2014). For some patients who have undergone colonic resection, the challenge may be to continue exercising while controlling an ileostomy. However, this is not an impossible task, as shown by the example of Rolf Benirschke, who continued to ski, swim, and play hockey after the creation of an ileostomy (Pressel, 1981).

There is now some evidence that vigorous exercise (perhaps as much as 18 MET-hours per week of reported leisure pursuits) may decrease mortality in those who have previously been treated for colorectal cancers (Boyle et al., 2013; Demark-Wahnefried, 2006; Meyerhardt et al., 2006; Van Blarigan and Meyerhardt, 2015), although further research is needed to be sure that a poor prognosis is not impeding exercise participation rather than the converse.

Areas for further research

The vast majority of colonic cancers appear to have their origin in asymptomatic polyps (Emmons et al., 2005 -a). There is thus a need to identify and correct the multiple risk factors (possibly including physical inactivity) that influence the conversion of these benign growths into malignant tumours (Emmons et al., 2005b). Further analysis of factors influencing colorectal tumours is hampered by the long disease latency. In particular, there is a need to explore the physical activity patterns and lifestyle of subjects over periods of 20 yr and longer, and there remains scope to find a reliable objective method of summarizing a person's lifetime experience of a healthy lifestyle. Possibly, the future emphasis should be upon measuring the outcomes of regular physical activity, such as levels of aerobic fitness and muscular development, rather than upon the design of questionnaires to revive distant memories of personal behaviour.

Many investigators have reported a stronger protective effect of physical activity in men than in women, particularly with respect to adenomas. Data from controlled animal experiments have partially confirmed human epidemiological investigations in showing a larger response in male animals (Mehl et al.), and the underlying reasons for this sex differential should be clarified.

Further work is also needed to define optimal patterns of exercise for the prevention of colorectal tumours. Are the best effects obtained from prolonged, moderate activity, as the occupational studies might suggest, or is the intensity of effort also important? Moreover, almost all studies to date have been based on aerobic activity, and there is scope to compare the benefits of aerobic and resistance exercise.

Finally, there is need for further study of the practical value of exercise in those who have received surgical treatment for colorectal cancers (Meyerhardt et al., 2006). Longitudinal research is required to be sure that apparent benefit does not reflect a good prognosis facilitating exercise participation rather than the converse.

Practical implications

Although most studies show substantial differences in the risks of colon and rectal cancer favouring those who have a very high level of physical activity either at work or in their leisure time relative to those who are sedentary, we cannot immediately assume that the enrolment of sedentary individuals in an exercise programme will yield an equivalent protection against colorectal neoplasms. There are two obvious reasons for caution in making such an assumption. Firstly, the risk of carcinogenesis is likely accumulated over 10 or 20 yr of inadequate physical activity, and reversal of this process will probably require compliance with a vigorous exercise regimen for an equally long period. Secondly, the substantial risk ratios presented in Tables 1-5 chapter were calculated by comparing the health experience of sedentary individuals with the most active members of each sample, who in many instances engaged in a much larger weekly volume of physical activity than would likely be attained if a sedentary person were encouraged to enter a community exercise programme. (Cerin et al., 2005) suggested that only 10-20% of the Australian population were sufficiently active to gain significant protection against colon cancer. They estimated the required dose of exercise at 7 hours of moderate or 3.5 hours of vigorous activity per week), more than twice the rarely attained current public health recommendation for North American adults.

Nevertheless, the association between a physically active lifestyle and a reduced risk of colorectal cancer has been amply demonstrated, and some authors are now suggesting exploiting this evidence as a means of persuading the relatives of cancer patients to adopt regular exercise programmes (Coups et al., 2008; McGowan and Prapavessis, 2010; McGowan et al., 2012).

Author's Qualifications

The author's qualifications are Roy J. Shephard, C.M., M.B.B.S., M.D.[Lond.], Ph.D., D.P.E., LL.D., D.Sc., FACSM, FFIMS.

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