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Physical Activity and Risk of Large Bowel Cancer in the Framingham Study[1]

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ABSTRACT

We examined the relation between self-reported physical activity and large bowel cancer in a prospective cohort of men and women who participated in the Framingham Study. Self-assessments of physical activity were available from the fourth biennial examination on a total of 1906 men and 2308 women aged 30 to 62 yr in 1954. The cohort was followed for up to 28 yr and yielded 152 cases (73 men, 79 women) of large bowel cancer.

Inactivity was associated with an increased risk of large bowel cancer among men but not among women. The relative risk estimates for large bowel cancer among men in the middle and lowest tertiles of a physical activity index (compared with the highest tertile) were 1.4 (95% confidence intervals, 0.8-2.6) and 1.8 (1.0-3.2), respectively. Among women the comparable estimates were 1.2 (0.7-2.1) and 1.1 (0.6-1.8), respectively. These findings were unchanged after adjustment for body mass index, serum cholesterol, alcohol, and other potentially confounding variables. The narrow range of physical activity and the minimal heavy activity reported by women in this cohort may have limited our ability to detect an association between physical activity and large bowel cancer among women.

INTRODUCTION

The majority of studies examining an association between physical activity and colon cancer have observed an increased risk of colon cancer among physically inactive men (1-13). Most of these studies used occupational history to derive group measures of physical activity (1-9). Four recent studies using self-reported physical activity also found an increased risk of colon cancer among the physically inactive (10-13). This association was present after adjustment for the potential confounding effects of body mass (5, 10-13), dietary fat (12), dietary fiber, and calories (10).

The analysis of the association between physical activity and colon cancer in women is more limited. Of the three studies which also examined women, two reported a decreased risk for colon cancer associated with increased physical activity (10,13). The other study, which found a protective effect for physical activity among men, did not find physical activity protective among women (12).

The present analysis was undertaken to evaluate the influence of physical activity, as assessed by self-report, on subsequent incidence of large bowel cancer in a cohort of men and women who participated in the Framingham Study. Data on serum cholesterol and alcohol intake in this cohort also allowed us to assess the potential impact of these factors which have been examined in few previous reports.

METHODS

The Cohort. The Framington Study, a population-based prospective cohort study of risk factors for cardiovascular disease, was initiated in 1948. The original cohort contained 2336 men and 2873 women, aged 30 to 62 yr at the first examination. This cohort was followed with biennial examinations for a 34-yr period (Examinations 1 to 18) with minimal (<3%) loss to follow-up. Data available from each examination include information from a medical history, a physical examination, and a series of laboratory tests (14). Physical activity questionnaires were administered by physicians at Examination 4 to 1909 men and 2311 women.

Population for Analysis. A total of 427 men and 562 women (including 12 men and 22 women who subsequently developed large bowel cancer) were missing physical activity information at Examination 4 and were excluded from this analysis. The majority (330 men and 349 women) were missing physical activity information because they were not seen at Examination 4. Three men and three women who developed large bowel cancer prior to Examination 4 were also excluded. The analytical cohort consisted of 1906 men and 2308 women including 73 men and 79 women who developed large bowel cancer after Examination 4.

Identification of Cases. All cohort records with any mention of malignancy were reviewed in detail, and 152 incident cases of large bowel cancer [International Classification of Diseases, Oncology, Codes 153 (121 cases) and 154 (31 cases)] occurring after Examination 4 were identified. Follow-up information was not available after Examination 18 and, thus, we have follow-up information possible on 28 yr.

Determination of Physical Activity and Other Covariates. A summary physical activity index was calculated based on the weighted sum of the usual amount of time the subject reported to have spent per 24 h in the following types of activity: basal, as in sleeping (weight of 1); sedentary, as in sitting or standing (weight of 1.1); slight, as in walking (weight of 1.5); moderate, as in gardening (weight of 2.4); and heavy, as in shoveling (weight of 5). The weighting factor, which was based on an estimation of oxygen consumption required for each level of activity, has been described previously (15). Only the overall summary index was still available from Examination 4 for the purposes of this analysis.

Weight, height, serum cholesterol, menopausal status, and age were also recorded at Examination 4 (14). A BMI[3] was calculated as follows.

$$\text{BMI} = \frac{\text{wt (kg)}}{\text{ht (m}^2\text{)}}$$

Information on education, parity, and cigarette smoking was available from Examination 1. Usual alcohol intake was assessed at Examination 2 (14).

Statistical Analysis. All analyses were sex specific. Crude incidence rates for tertiles of the physical activity index (tertiles based on the sex-specific analytical cohort values) from Examination 4 were calculated by dividing the number of large bowel cancer cases occuring in that tertile by the total number of person-yr contributed by all individuals in that tertile. (Because of the integer nature of the physical activity index, the tertile cuts were not equal.) The number of person-yr contributed by an individual was calculated from Examination 4 to the date of large bowel cancer diagnosis, death, or Examination 18, whichever came first. Age-adjusted incidence rates were calculated using the age distribution of the entire analytical cohort as the standard (16). The overall age-adjusted colon cancer incidence rate in this Massachusetts cohort was similar to that observed and reported for the population in the nearby state of Connecticut. The ratio of observed-to-expected colon cases (based on age-, sex-, and race-adjusted incidence rates from the

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[3] The abbreviation used is: BMI, body mass index.

Connecticut Tumor Registry) was 0.97 (95% confidence interval, 0.73–1.26) for men and 0.96 (0.74–1.23) for women.

Cox's proportional hazards regression technique was used to analyze the simultaneous effect of physical activity at Examination 4 and covariates on large bowel cancer incidence in the cohort (17). Indicator variables were used for the tertile levels of physical activity, with individuals in the highest activity level as the reference group. Age was included in all models as an independent, continuous variable. Analyses with age modeled as indicator variables yielded similar results; therefore we present only the results with age as a continuous variable. Other potential confounding factors were added to this model individually and model as indicator variables as shown in Table 1. For these analyses persons with missing data were excluded. Because none of the factors was found to be a significant confounder in these data, only age-adjusted relative risks are presented in the tables. A linear test for trend was carried out by modeling the physical activity variable as a tertile trend variable (scored 0, 1, 2) in the proportional hazards analyses. These analyses were performed with the PROC PHGIM procedure available in the SAS statistical package.

RESULTS

At Examination 4 the mean age of the analytical cohort was 50 ± 9 (SD) yr for men and women. The educational level of the men and women was also similar. Forty-five % of men and 41% of women had only a grade school education, while 27% of men and 28% of women had completed at least some education beyond high school.

Table 1 shows the relation at baseline of high physical activity to several demographic and behavioral characteristics. The percentile in the highest (most active) tertile of physical activity was higher among men and women who were younger and less educated, among men who were shorter, and among women who were premenopausal and of higher parity.

Table 2 shows the age-adjusted colorectal cancer incidence rates by tertile of physical activity. The median follow-up time for the analytical cohort was 25 yr for men and 26 yr for women. The median time to diagnosis of large bowel cancer was 17 yr for both men and women. An inverse association between physical activity and large bowel cancer was seen for men. There was no association between large bowel cancer and physical activity in women. Note that the physical activity distributions were different for men and women. The proportion of women falling within the first through third tertiles of physical activity for men were 0.36, 0.46, and 0.18, respectively.

The age-adjusted relative risk estimates for large bowel cancer by tertiles of physical activity are given in Table 2. Compared with highly active men, inactive men had an increased risk of large bowel cancer of 1.8 (1.0–3.2). The risks increased in a stepwise fashion with decreasing levels of activity, and the test for linear trend was marginally significant ($p = 0.06$). Among women, physical activity was not significantly associated with large bowel cancer. Adding the covariates of BMI, height, education, cholesterol, alcohol intake and smoking (men and women), and parity and menopausal status (women) individually to the age-adjusted models did not alter these estimates.

Because of previous reports (12) suggesting effect modification by age and BMI, we examined models stratified by age (≤50, >50 yr) and BMI (median split) as shown in Table 3. Among men an inverse physical activity-large bowel cancer association was stronger among older men and leaner men compared with younger or more obese men. In contrast, physical activity remained unassociated with large bowel cancer among women in all subgroups of age and body mass.

Table 1 *Physical activity index from Examination 4 in relation to baseline characteristics of men and women in the Framingham Study*

Baseline characteristic	% in highest tertile of physical activity index[a] Men		Women
Age (yr)			
<45	40.1		44.1
45–55	35.3		35.4
>55	31.5		23.8
Education (yr)			
<12	49.8		39.6
12	35.9		34.6
>12	19.8		32.3
Body mass index (kg/m²)			
<24.2	41.8	<22.7	37.1
24.2–26.2	32.8	22.7–24.8	36.5
26.3–28.5	37.8	24.9–28.0	38.4
>28.5	35.9	>28.0	34.3
Height (m)			
<1.66	45.0	<1.54	37.7
1.66–1.71	40.3	1.54–1.58	37.7
1.72–1.75	35.1	1.59–1.63	36.4
>1.75	28.9	>1.63	34.1
Cholesterol (mg/dl)			
<207	37.3	<207	38.9
207–232	35.2	207–238	36.8
233–260	39.1	239–270	35.8
>260	37.1	>270	36.2
Alcohol intake (g/day)			
0	36.0		35.9
<5	35.8		38.0
5–15	34.7		34.5
>15	39.4		34.2
Smoking			
Nonsmoker	37.2		35.9
Current smoker	37.2		35.5
Parity			
0			28.9
1–3			36.8
4+			43.6
Menopausal status			
Premenopausal			41.6
Postmenopausal			31.6

[a] Adjusted to age distribution of entire analytical cohort, except for age and menopausal status (16).

DISCUSSION

The increased risk of large bowel cancer associated with physical inactivity among men in the Framingham Study agrees with previous reports (1–13). The lack of an observed association between physical activity and large bowel cancer among women in this study is similar to findings from one cohort study which also examined self-reported physical activity and colorectal cancer (12), but is in contrast to two other studies which found an inverse physical activity-colon cancer association among women as well as men (10, 13). In one of these studies, this association varied by anatomical site of the colonic cancer among women (13). The inverse association was observed for left-sided lesions, but no association with physical activity was seen for right-sided lesions among women.

The lack of an association between physical activity and large bowel cancer among women in the present study may reflect a true absence of a physical activity-large bowel cancer association. However, given the above contradictory reports, alternative explanations and potential sources of bias should be explored. It is noteworthy that the upper boundary of the range of physical activity at Examination 4 for women in this cohort was much less pronounced than that for men. To further explore

Table 2 *Age-adjusted incidence rates and relative risk estimates of large bowel cancer by tertiles of the physical activity index from Examination 4 in the Framingham Study*

Physical activity scores (tertiles)	Cohort	Person-yr	Cases	Incidence rate[a] (per 100,000 person-yr)	Relative risks
Men					
25–29	536	10,766	27	245	1.8 (1.0–3.2)[b]
30–33	687	14,693	27	200	1.4 (0.8–2.6)
34–83	683	15,033	19	137	1.0 (referent)
Trend test *P* value					0.06
Women					
25–29	832	18,727	31	148	1.1 (0.6–1.8)
30–31	671	15,696	24	154	1.2 (0.7–2.1)
32–55	805	19,431	24	131	1.0 (referent)
Trend test *P* value					0.89

[a] Adjusted to age distribution of entire analytical cohort (16).
[b] Numbers in parentheses, 95% confidence interval.

Table 3 *Relative risk estimates of colorectal cancer according to physical activity stratified by age and body mass index at Examination 4 in the Framingham Study*

Models contain age and physical activity index.

	No. of cases	Physical activity level			*P*
		Low	Moderate	High	
Men					
Age					
≤50	32	1.5 (0.6–3.5)[a]	1.0 (0.4–2.4)	1.0	0.41
>50	41	2.2 (0.9–5.0)	2.0 (0.9–4.6)	1.0	0.08
BMI					
≤26.3	33	3.0 (1.2–7.3)	1.5 (0.6–3.9)	1.0	0.01
>26.3	40	1.1 (0.5–2.4)	1.4 (0.4–2.2)	1.0	0.84
Women					
Age					
≤50	28	1.0 (0.4–2.5)	0.8 (0.7–3.2)	1.0	0.98
>50	51	1.1 (0.6–2.3)	1.5 (0.3–2.0)	1.0	0.84
BMI					
≤24.9	26	0.7 (0.2–2.1)	1.9 (0.8–4.6)	1.0	0.58
>24.9	53	1.2 (0.6–2.2)	0.9 (0.4–1.9)	1.0	0.58

[a] Numbers in parentheses, 95% confidence interval.

differences in activity between men and women we also examined in more detail the levels of activity reported by men and women at Examination 12. At Examination 12 the same physical activity questionnaire was administered to all individuals seen at that examination (1366 men and 1863 women). Only 10% of women compared with 25% of men reported engaging in any heavy activity by Examination 12. The level of any moderate activity was also lower in women (77%) compared with men (83%). If the intensity of activity is a factor in the protective effect of physical activity as suggested by one previous study (10), it is possible that too few women in this cohort engaged in intense activity for a protective effect to be manifested.

It is also likely that the physical activity index represents different types of activity for men and women. In this cohort 65% of the women were housewives. Only 9% of women were employed in jobs potentially requiring heavy activity, such as labor, whereas 41% of the men were employed as laborers. It is also noteworthy that, although physical activity, as measured by the physical activity index at Examination 4, was inversely related to heart disease among men in the Framington Study, it was not associated with heart disease among women (18).

An alternative explanation for the lack of an association between physical activity and large bowel cancer among women in this study may be the lower overall incidence rates for large bowel cancer among women compared with men (147 of 100,000 *versus* 180 of 100,000, respectively). Although the incidence rates for men and women were similar to those in the nearby state of Connecticut, the lower rates among women may have limited our ability to demonstrate an effect of physical activity on large bowel cancer among women. It is possible that the small number of cases ($n = 79$) limited our ability to detect an association in women. However, we did find an association among men with even fewer cases (73); therefore this limitation seems unlikely. We also examined relative risk estimates for women based on the activity groupings for men. These were essentially unchanged from those based on the groupings in Table 2; relative to the active group these relative risk estimates were 1.1 (0.5–2.1) and 1.1 (0.6–2.2) for the low and moderately active groups, respectively.

Body size differences among groups with varying levels of physical activity have been hypothesized to confound the physical activity-large bowel cancer association (19). We found no evidence for confounding by eiher BMI or height. Our finding of a stronger inverse physical activity-large bowel cancer association among leaner men agrees with a previous report (12) and suggests that body size may modify the effect of activity.

It is possible that preclinical illness resulting in inactivity could underly the increased risk seen among sedentary individuals. The stronger inactivity-large bowel cancer relationship seen among older and leaner men suggests this preclinical illness effect. However, the relative risk estimates and test for linear trend were essentially unchanged in men and women after excluding either the first 2 or 4 yr of follow-up. It seems unlikely, therefore, that a preexisting illness effect accounted for our results.

Although self-reported physical activity indices may be an improvement over group estimates derived from occupation, the four previously published studies using self-reported physical activity have assessed activity from a questionnaire administered only once. This single measure does not assess activity over the follow-up interval nor does it assess the possible change in activity over time. The comparatively low correlation between the physical activity indices of Examinations 4 and 12 (0.29 for men and 0.17 for women) could suggest poor reliability of the measure, or it could suggest that substantial changes occurred in activity over time, which undoubtedly includes reduced activity of retirement. Because of the limited number of cases occurring after Examination 12 (35 male, 48 female) we were unable to examine the predictive value of physical activity at that examination relative to subsequent large bowel cancer. The present analysis suggests that earlier physical activity is predictive of subsequent large bowel cancer despite possible changes in physical activity during the follow-up interval.

Of the six studies which examined rectal cancer separately from colon cancer, two found a similar or stronger increased risk for rectal cancer associated with inactivity (6, 7), whereas four found no increased risk associated with inactivity (2, 4, 5, 11). We were unable to examine rectal cancer separately due to the small number of cases. When we examined only colon cancer cases the realtive risk estimates for men and women were essentially unchanged from those of both sites combined.

A variety of potential mechanisms by which physical activity may confer protection against colon cancer have been proposed (20, 21), including shortened gastrointestinal transit time, altered prostaglandin levels, improved immune function, altered bile acid metabolism, increased levels of gastrointestinal hormones, decreased serum cholesterol, and associated beneficial lifestyle changes, such as a low-fat diet. Although we were unable to assess most of the above potential mechanisms in this study, we did examine serum cholesterol. Serum cholesterol was not correlated with physical activity in this cohort and, thus, controlling for serum cholesterol in multivariate models did not alter the relative risk estimates. In addition, there was no evidence of confounding by demographic, body size, or lifestyle factors in this study. Given the increasingly strong evidence supporting an etiological role for dietary fat and other dietary factors in large bowel carcinogenesis, studies should attempt to control for dietary confounding (22).

The increased risk for large bowel cancer which we observed among physically inactive men confirms consistent findings in previous studies using both self-report and occupation to assess physical activity (1–13). Studies on the physical activity-large bowel cancer association among women are more limited and less consistent (10–13). The narrow range of physical activity and minimal heavy activity reported by women in this cohort may limit, in part, our ability to detect an activity-cancer association among women. Because both the intensity and duration of exercise may modify the biological responses observed (23), studies examining the influence of physical activity on various biological parameters should be designed to assess varying intensities and durations of activity. The inclusion of women with higher levels and intensities of activity in future studies may help to clarify these inconsistencies.

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