Prospective Study of Recreational Physical Activity and Ovarian Cancer

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Background: **It has been hypothesized that physical activity may reduce the risk of ovarian cancer by decreasing estrogen levels, reducing body fat, and reducing the frequency of ovulation. Epidemiologic studies of this relationship have obtained inconsistent results. The only prospective study to date reported a positive association between frequent vigorous exercise and ovarian cancer risk. We further evaluated this relationship in the Nurses' Health Study cohort.** ***Methods:*** **Participation in recreational physical activity was assessed by questionnaire in 1980, 1982, 1986, 1988, 1992, and 1994, with questions assessing exercise frequency, duration, and intensity. Results were adjusted for age, parity, oral contraceptive use, tubal ligation, and other risk factors for ovarian cancer. All statistical tests were two-sided.** ***Results:*** **During a 16-year follow-up (from 1980 to 1996), 1.2 million person-years were accrued by 92 825 cohort members, and 377 cases of epithelial ovarian cancer were confirmed. The relative risk (RR) of ovarian cancer for women engaging in recreational physical activity for 7 hours or more per week compared with those reporting less than 1 hour per week was 0.80 (95% confidence interval [CI] = 0.49 to 1.32; P_{trend} = .59). When both the frequency and intensity of activity were taken into account, activity level was also not associated with a reduced risk of ovarian cancer. Compared with inactive women, participants reporting high activity in terms of metabolic equivalent task hours (MET hours) were at greater risk of ovarian cancer (RR for 20 to <30 MET hours/week = 1.84 [95% CI = 1.12 to 3.02]; RR for >30 MET hours/week = 1.27 [95% CI = 0.75 to 2.14]).** ***Conclusions:*** **Overall, results did not suggest an inverse association between recreational physical activity and ovarian cancer. The possibility of a modest increase in risk with frequent vigorous activity requires further investigation.** **[J Natl Cancer Inst 2001;93:942–8]**

It has been hypothesized that participation in recreational physical activity may reduce a woman's risk of ovarian cancer by decreasing estrogen levels, reducing body fat, and, with extreme exercise, reducing the frequency of ovulation *(1–3).* Several case–control studies *(4–8)* have evaluated this association with inconsistent results, some studies reporting a reduced risk of ovarian cancer with frequent activity and other studies *(9,10)* reporting no association or a slight increase in risk with greater exercise. The single prospective study *(11)* to address this relationship found a statistically significant increased risk of ovarian cancer in postmenopausal women with frequent and vigorous activity, with evidence of a dose–response relationship. Women engaging in vigorous physical activity four or more times per week experienced a 2.5-fold increase in risk compared with those rarely engaging in vigorous activity. These results have raised important questions as to how intensity, type, and timing of exercise may relate to risk of ovarian cancer. We further evaluated the association between physical activity and risk of ovarian cancer in the Nurses' Health Study (NHS) cohort.

Subjects and Methods

NHS Cohort

The NHS is a cohort of 121 700 U.S. female registered nurses who responded to a mailed questionnaire in 1976 *(12).* The participants were 30–55 years old at the time of the initial mailing and provided information on their medical history and health-related behaviors, such as use of oral contraceptives and smoking status; they have completed questionnaires every 2 years thereafter to update information on various risk factors and to identify new diagnoses of cancer and other diseases. As of 1996, the rate of follow-up was 90%, with vital status data available for more than 98% of the original cohort.

The protocol for the study was approved by the Human Research Committees of the Brigham and Women's Hospital and the Harvard Medical School, Boston, MA.

Exposure Assessment

On the 1980 NHS questionnaire, participants were asked about the number of hours per weekday and weekend day they spent involved in vigorous physical activity (e.g., vigorous sports, brisk walking, and bicycling on hills) and moderate activity (e.g., bicycling on level ground, walking, and light sports). The participants also were asked if they ever exercised intensely enough to work up a sweat and, if so, to report the type of activity that led to sweating and the number of times per week they engaged in it. A similar question was included on the 1982 questionnaire, which asked how many hours per week they engaged in physical activity that led to sweating. These questions have been validated previously *(13–16)* and have been found to predict resting heart rate, obesity, and levels of high-density lipoprotein-bound cholesterol *(15,16).*

Beginning in 1986, the participants were asked about the amount of time each week that they engaged in specific activities. These activities included jogging (i.e., slower than 10 minutes per mile), running (i.e., 10 minutes per mile or faster), bicycling (including on a stationary machine), lap swimming, playing tennis, squash, or racquetball, performing aerobic activities (including calisthenics, aerobic dance, and rowing on a machine), and walking or hiking outdoors (including walking at golf). In addition, the participants were asked about their usual walking pace and the number of flights of stairs that they climbed each day. These questions were repeated on the 1988, 1992, and 1994 questionnaires, with questions on lower intensity activity (e.g., yoga and stretching) and other vigorous activities (e.g., lawn mowing) added in 1994. These questions have been validated for use in a similar population, the NHS II cohort, described in detail elsewhere *(17).* Briefly, in a sample of 153 cohort members, correlations were 0.59 (95% confidence interval [CI] = 0.48 to 0.69), for a total weekly activity score as measured by two questionnaires completed 1 year apart, and 0.79 (95% CI = 0.64 to 0.88) for four past-week activity recalls and the second questionnaire.

Covariate Assessment

Information on ovarian cancer risk factors was collected by questionnaire throughout the 16-year

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See "Notes" following "References."

follow-up. We updated data on most factors every 2 years, including menopausal status, postmenopausal hormone use, smoking status, hysterectomy, and body mass index (BMI) [weight in kilograms/(height in m)^2 or kg/m^2]. A semiquantitative food-frequency questionnaire was included on the 1980 questionnaire to measure the intake of lactose, caffeine, alcohol, and total energy. We updated dietary intake information with subsequent food-frequency questionnaires in 1984, 1986, and 1990. Information on several risk factors was collected during only part of the follow-up period. For example, questions on oral contraceptive use were included on questionnaires through 1982, at which point fewer than 1% of the participants were still using oral contraceptives. We considered women who reported past use of oral contraceptives in 1982 to be past users for the remainder of follow-up and those who were current users in 1982 to be past users from 1984 onward. We updated parity (measured until 1984) and tubal ligation (measured until 1982) in a similar fashion. Information on age at menarche, age at birth of the first child, talc use, and menstrual irregularity was collected once and then carried forward throughout the follow-up period.

Disease Assessment

On each follow-up questionnaire, the participants were asked whether they had been diagnosed with ovarian cancer by a physician during the previous 2 years. Women reporting a diagnosis of ovarian cancer were asked for permission to review their medical records. Records were reviewed by physicians blinded to the participant's exposure status to confirm the diagnosis and to identify histologic type and subtype and invasiveness. Only confirmed cases of epithelial ovarian cancer (International Classification of Diseases for Oncology: 183) *(18)* were included in the analysis. In addition, the National Death Index was searched systematically to identify women who died of ovarian cancer before reporting a diagnosis by questionnaire; we then contacted family members to obtain medical records. Approximately 98% of all deaths among cohort members are identified by searching the National Death Index *(19)*.

During the 16-year follow-up, 511 cases of ovarian cancer were reported by cohort members. We received medical records for 441 (86.3%) of these cases, record receipt was still pending for six cases, 23 women denied the diagnosis when contacted, 35 women refused to release their records, three women could not be contacted, and death certificates alone were available for three women. After review of medical records, the diagnosis of ovarian cancer was confirmed for 402 (91.2%) of the 441 participants. Of the 39 cases not confirmed, 11 diagnoses were rejected, 18 were changed to a more correct diagnosis, and 10 were found to be metastases from other tumors. Overall, 377 (93.8%) of the 402 confirmed cases were classified as epithelial tumors. This group included 224 tumors of the serous subtype, 65 of the mucinous subtype, and 53 of the endometrioid subtype. Ninety percent (n = 338) of the tumors were invasive.

Statistical Analysis

Participants were excluded from the analysis at baseline if they reported a diagnosis of cancer or a bilateral oophorectomy before the start of follow-up in 1980. Person-years of follow-up accrued from the date of return of the 1980 questionnaire until a diagnosis of ovarian or other cancer, a report of bilateral oophorectomy, death, or the end of the follow-up period on June 1, 1996, whichever came first. For each participant, follow-up time equal to the number of months between the return of the 1980 questionnaire and the return of the 1982 questionnaire was assigned to a category of physical activity participation on the basis of the level reported in 1980 (e.g., hours per week of physical activity in 1980). Similarly, for each subsequent 2-year interval, additional months of follow-up were assigned according to the updated information on physical activity reported at the beginning of the interval. For exposures reported only once (e.g., hours per week of physical activity at baseline), the initial response level was carried forward throughout the follow-up period.

Several variables were used to address how frequency, intensity, and consistency of participation in physical activity affected ovarian cancer risk. We evaluated the total amount of time the participants reported engaging in physical activity each week (<1, 1 to <2, 2 to <4, 4 to <7, and ⩾7 hours/week) in 1980, 1982, 1986, 1988, 1992, and 1994. Thus, in addition to evaluating the risk associated with baseline activity level in 1980, we were able to assess the effect of recent activity participation by using the activity level reported on each questionnaire to predict risk in the subsequent 2-year period. Person-time was allocated to each of the five categories of physical activity participation in 2-year blocks, allowing each participant to change exposure status every 2 years. For the years in which physical activity questions were not included on the questionnaire (1984 and 1990), the level reported during the previous period was carried forward another 2 years. For example, hours of activity per week reported in 1980 were used to predict cancer risk from 1980 to 1982; similarly, the level reported in 1982 was used to predict risk from 1982 to 1984 and from 1984 to 1986. If a participant did not provide information on activity level in a given year, she was assigned a missing value for that year.

To best represent the overall level of physical activity during the follow-up period, we calculated the cumulative average of the exercise levels reported on all previous questionnaires. For example, the average physical activity (hours/week) in 1980 and 1982 was used to predict ovarian cancer risk from 1982 to 1986. Similarly, the average activity level in 1980, 1982, and 1986 was used to predict risk from 1986 to 1988. For the years in which physical activity questions were not included on the questionnaire (1984 and 1990), the cumulative average calculated during the previous time period was carried forward another 2 years (e.g., the average of 1980 and 1982 was used to predict cancer risk from 1982 to 1984 and from 1984 to 1986). If a participant did not complete the physical activity section of the questionnaire on any given year, she was assigned a missing value for that year; the cumulative average for that period was then calculated by use of data from all other previous years.

To compare the risk of ovarian cancer in women who were consistently very active over several years with that in women who were consistently inactive, we averaged the number of hours of activity per week that each woman reported in 1980, 1982, and 1986. This average was then used to predict cancer risk from 1986 to 1996. For participants who only completed two of the three questionnaires, we used the average of the two measurements; women who responded to only one questionnaire during this period were assigned a missing value for this analysis.

In addition, we classified participants on the basis of the type and intensity of activity reported. On the basis of their response to the 1980 questionnaire, we divided participants into three groups by whether they reported engaging in exercise intensely enough to produce sweating and by the intensity of the specific activity that they reported engaging in most frequently. Women who reported never sweating were classified as having low activity. Women were considered to have moderate physical activity if they reported sweating and engaged in a moderately intense activity [i.e., a metabolic equivalent task (MET) score of <5, as defined by Ainsworth et al. *(20)*]. The participants were classified as having high activity if they reported sweating and engaged in a vigorous activity (i.e., a MET score of ⩾5). Within the moderate- and high-intensity categories, we further divided women by the frequency with which they exercised (i.e., <2, 2–4, and >4 times/week).

Beginning in 1986, we were able to evaluate the effect of time spent participating in each of the specific recreational activities queried. We divided women into five categories (<1, 1 to <2, 2 to <4, 4 to <7, and ⩾7 hours/week) based on the amount of time they reported walking each week, and we used data from 1986, 1998, 1992, and 1994 to calculate an averaged updated measure of time spent walking. This procedure was then repeated with each activity and then with all nonwalking activities combined.

In addition, from 1986 onward, we were able to calculate the total number of MET hours of activity for each participant. For this calculation, we first assigned each of the activities queried an intensity score on the basis of the index defined by Ainsworth et al. *(20)*. Intensity scores (in METs) are based on an activity's required energy expenditure, with an MET score of 1.0 equal to the amount of energy expended while sitting quietly. Then, for each participant, we multiplied the number of hours per week she spent at each activity by its respective MET score to calculate MET hours/week of each activity. We then summed the contributions of all activities to calculate each woman's activity level in terms of total MET hours/week. For each woman, this measure took into account the frequency, duration, and intensity of physical activity. Participants were then divided into categories on the basis of their total weekly MET hours (0 to <2.5, 2.5 to <5, 5 to <10, 10 to <20, 20 to <30, and ⩾30 hours/week). We used total MET hours in 1986, 1988, 1992, and 1994 to create a cumulative average measure of MET hours/week from 1986 to 1996.

To examine whether changes in physical activity level preceding a diagnosis of ovarian cancer biased results, in one analysis, we excluded cases diagnosed in the first 2 years after each report of activity level. In addition, we used analyses lagged by 4, 8, and 12 years to evaluate the association between physical activity in the more distant past and cancer risk. For example, in the analysis lagged by 12 years, physical activity in 1980 was used to predict cancer risk from 1992 to 1994.

We performed several subanalyses to determine whether associations between physical activity and ovarian cancer were limited to particular subtypes of ovarian cancer or to subgroups of our population. We evaluated the relationship of physical activity to serous, mucinous, and endometrioid subtypes individually and the relationship to all nonmucinous tumors and all invasive tumors.

To determine whether the relationship between physical activity and ovarian cancer varied by levels of other risk factors, we stratified our data by age (<50 and ⩾50 years), menopausal status (premenopausal and postmenopausal), postmenopausal hormone use (in postmenopausal women only: ever use and never use), BMI (<25 and ⩾25 kg/m^2), oral contraceptive use (ever use and never use), smoking status (never, current, and past), and regularity of menstrual cycles in 1982 (very or usually regular [defined as within 2 days of expected] and very or usually irregular). We further examined the influence of the timing of activity in relation to menopause. For each interval, we used current menopausal status to classify the activity reported by each woman as premenopausal or postmenopausal. We then compared the risk of ovarian cancer associated with activity (hours/week) reported by premenopausal and postmenopausal women in the subsequent interval.

Incidence rates for each category of physical activity were calculated by dividing the number of incident cases by the person-years in each category. Relative risks (RRs) compared the incidence rate of ovarian cancer in the second through highest category of each physical activity variable with that in the lowest category (referent) by use of pooled logistic regression analysis with 2-year increments *(21)*. We calculated 95% CI and used the two-sided Mantel extension test for trend to evaluate the presence of a linear trend in the RRs across categories. In the test for trend analyses, the median value for each exposure category was modeled as a continuous variable in the multivariable regression, with one exception; for analyses of activity intensity and frequency based on data from 1980, we used the category number as a continuous variable in the regression model (*see* Table 2). All statistical tests were two-sided.

We evaluated the potential confounding effects of other ovarian cancer risk factors, including age, current BMI, BMI at age 18 years, height, smoking status, parity, age at menarche, tubal ligation, hysterectomy, oral contraceptive use and duration, age at menarche, menstrual cycle regularity, age at menopause, postmenopausal hormone use and duration, talc use, and intake of total calories, lactose, caffeine, and alcohol. Variables were included in multivariable regression models if they were found to alter the RR for the physical activity–ovarian cancer relationship by 10% or more when compared with age-adjusted RRs or if they were determined to be statistically significant predictors of ovarian cancer independent of physical activity level. The final model included age, parity, age at menarche, tubal ligation, oral contraceptive use and duration, menopausal status, and postmenopausal hormone use and duration. Despite their association with activity level, current BMI and BMI at age 18 years did not confound the exposure–disease relationship or predict overall ovarian cancer incidence and, therefore, were not included in multivariable regression models.

Results

From 1980 to 1996 (a 16-year follow-up), more than 1.2 million person-years were accrued by the 92 825 cohort members who provided information on their participation in physical activities (97.8% of total possible person-years of observation), and 377 cases of epithelial ovarian cancer were confirmed.

Baseline characteristics of the NHS cohort according to physical activity level in 1980 are shown in Table 1. Women reporting more frequent exercise were slightly more likely to be users of oral contraceptives or to have had a tubal ligation than less active women. Inactive women were more likely to be current smokers, to be obese (i.e., BMI ⩾30 kg/m^2), and to consume less alcohol than more active women. Other characteristics were similar across categories of physical activity.

The total duration of physical activity (hours/week) was not substantially associated with risk of ovarian cancer (Table 2). Women in the highest category of activity (i.e., ⩾7 hours/week) experienced a statistically nonsignificant decrease in cancer risk compared with the least active women (RR = 0.80; 95% CI = 0.49 to 1.32; P_{trend} = .59). Results for hours of total activity measured in 1980 only and for the most recent level of physical activity (from 1980 to 1996; results not shown) also suggested no reduction in risk with greater activity.

Next we examined the follow-up period from 1986 to 1996, for which we had more detailed data on type of activity (Table 2). Women who engaged in activity 7 hours or more per week had a statistically nonsignificant 26% increase in ovarian cancer risk (RR = 1.26; 95% CI = 0.80 to 1.97), with no evidence of a dose–response relationship (P_{trend} = .59). Risk was also elevated for women in the highest category of activity measured in 1986 only (RR = 1.64; 95% CI = 1.05 to 2.58; P_{trend} = .13).

We evaluated the association of consistent participation in physical activity on cancer risk by using the average of activities in 1980, 1982, and 1986 to predict cancer incidence from 1986 onward (Table 2). Women whose average activity

Table 1. Baseline characteristics of the study population according to category of physical activity in 1980*

Characteristic	Category of physical activity, physical activity in h/wk				
	<1	1 to <2	2 to <4	4 to <7	⩾7
No. of participants	18 950	21 411	12 327	12 365	9176
Mean age, y	46.4	46.2	46.3	46.2	46.1
Mean daily intake					
Total fat, g/day	68.2	69.9	69.3	68.0	66.6
Total calories, kcal/day	1539	1576	1594	1572	1561
Alcohol, g/day	6.3	6.1	5.7	6.5	8.3
Lactose, g/day	12.8	13.2	13.9	13.9	13.8
Mean parity, No. of childbirths	3.0	3.1	3.1	2.9	3.0
Mean age at birth of first child, y†	24.6	24.5	24.4	24.3	24.3
Mean age at menarche, y	12.5	12.5	12.5	12.6	12.6
Mean current body mass index (BMI), kg/m^2	24.6	24.5	24.4	23.8	22.9
BMI ⩾30 kg/m^2, %	14.4	13.0	11.9	8.3	4.1
Oral contraceptive (OC) ever use, %	48.9	50.0	47.3	51.8	53.9
Mean duration of OC use, mo‡	49.3	49.9	49.7	51.1	52.7
Premenopausal, %	65.5	66.8	66.1	66.2	67.3
Current smokers, %	31.8	29.9	31.1	26.1	22.1
Past smokers, %	25.4	25.7	25.1	29.3	35.0
Tubal ligation, %	16.2	16.0	16.5	16.8	17.6
Simple hysterectomy, %	10.6	11.0	11.3	11.0	10.7
Postmenopausal hormone (PMH) ever use, %	30.7	30.1	30.4	30.4	30.2
Mean duration of PMH use, mo§	6.2	6.9	6.7	7.7	7.0

*Age was standardized to the distribution of the entire cohort by use of the direct method. Numbers of participants do not sum to 92 825 because of missing physical activity data in 1980.

†Among parous women.

‡Among OC users.

§Among PMH users.

Table 2. Analysis of the association of ovarian cancer and total physical activity (by categories of hours/week) from 1980 to 1996 and from 1986 to 1996, and average hours of physical activity per week from 1980 to 1986 (follow-up 1986–1996)

Physical activity level	No. of cases*	Age-adjusted RR (95% CI)†	MV RR (95% CI)‡
1980–1996 (cumulative average), h/wk			
<1	85	1.00 (referent)	1.00 (referent)
1 to <2	83	0.76 (0.56 to 1.03)	0.80 (0.59 to 1.08)
2 to <4	101	0.80 (0.60 to 1.06)	0.86 (0.65 to 1.15)
4 to <7	89	1.01 (0.75 to 1.36)	1.10 (0.82 to 1.49)
⩾7	19	0.72 (0.44 to 1.19)	0.80 (0.49 to 1.32)
			P = .59§
1980 (only), h/wk			
<1	97	1.00 (referent)	1.00 (referent)
1 to <2	76	0.74 (0.54 to 1.00)	0.75 (0.56 to 1.02)
2 to <4	52	0.84 (0.60 to 1.18)	0.86 (0.61 to 1.20)
4 to <7	59	0.99 (0.72 to 1.38)	1.01 (0.73 to 1.40)
⩾7	35	0.85 (0.57 to 1.28)	0.92 (0.62 to 1.36)
			P = .74§
1986–1996 (cumulative average), h/wk			
<1	60	1.00 (referent)	1.00 (referent)
1 to <2	47	1.08 (0.73 to 1.58)	1.13 (0.77 to 1.65)
2 to <4	53	1.06 (0.73 to 1.53)	1.10 (0.76 to 1.60)
4 to <7	33	0.93 (0.60 to 1.42)	0.98 (0.64 to 1.50)
⩾7	28	1.24 (0.79 to 1.93)	1.26 (0.80 to 1.97)
			P = .59§
1986 (only), h/wk			
<1	52	1.00 (referent)	1.00 (referent)
1 to <2	44	1.40 (0.94 to 2.10)	1.41 (0.94 to 2.11)
2 to <4	40	1.21 (0.80 to 1.82)	1.23 (0.81 to 1.85)
4 to <7	23	1.11 (0.68 to 1.81)	1.12 (0.69 to 1.84)
⩾7	30	1.63 (1.04 to 2.55)	1.64 (1.05 to 2.58)
			P = .13§
Average h/wk, 1980–1986‖			
<1	50	1.00 (referent)	1.00 (referent)
1 to <2	44	0.72 (0.48 to 1.08)	0.72 (0.48 to 1.08)
2 to <4	74	0.98 (0.68 to 1.40)	1.00 (0.70 to 1.43)
4 to <7	45	0.94 (0.63 to 1.41)	0.97 (0.64 to 1.45)
⩾7	15	1.42 (0.80 to 2.54)	1.46 (0.82 to 2.60)
			P = .18§

*Numbers of cases may not sum to 377 because of missing data.

†RR = relative risk.

‡MV RR adjusted for age (<50, 50–54, 55–59, 60–64, and ⩾65 years), parity (no, one or two, three or four, and ⩾five births), age at menarche (<12, 12, 13, 14, and ⩾15 years), oral contraceptive use and duration (never use, use <3 years, use 3–5 years, and use >5 years), menopausal status/postmenopausal hormone use (premenopausal/never use, current use <5 years, current use ⩾5 years, past use <5 years, and past use ⩾5 years), tubal ligation (yes and no), smoking status (never, past, current and <15 cigarettes/day, and current and ⩾15 cigarettes/day). MV = multivariable; CI = confidence interval.

§Two-sided P_{trend} across categories, calculated by use of the median of each category as a continuous variable in the MV regression model.

‖Follow-up from 1986 to 1996.

level was 7 hours or more per week had an RR of 1.46 (95% CI = 0.82 to 2.60) compared with those reporting less than 1 hour/week.

We then categorized participants to compare the effects of frequency of activity and intensity of activity, as reported in 1980 (Table 3). Women participating in moderate activity less than two times per week had an RR of 0.57 (95% CI = 0.36 to 0.92) compared with women reporting low activity. Reductions were not found for more frequent or intense exercise; risk appeared modestly elevated in women who exercised vigorously three or more times per week.

We further addressed the influence of activity frequency and intensity by use of data on MET hours. Compared with inactive women, participants in the second through sixth categories of MET hours/week experienced a greater risk of ovarian cancer (Table 4), although we saw no evidence of a linear trend across categories (P_{trend} = .52). Women reporting 20 to less than 30 MET hours/week had an RR of 1.84 (95% CI = 1.12 to 3.02) compared with those reporting less than 2.5 MET hours/week, while those in the highest category (⩾30 MET hours/week) had an RR of 1.27 (95% CI = 0.75 to 2.14).

We compared the risk of ovarian cancer associated specifically with walking, as well as with frequent participation in all other activities. We saw no increase in risk among women who walked frequently compared with those who walked infrequently, even after controlling for time spent in other nonwalking activities (RR for walking ⩾7 versus <1 hour/week = 1.17; 95% CI = 0.74 to 1.86). Similarly, frequent participation in nonwalking activities was not associated with an increase in risk (RR for nonwalking ⩾7 versus <1 hour/week = 1.10; 95% CI = 0.62 to 1.95).

We evaluated the association between duration of physical activity and three subtypes of ovarian cancer. The RRs for serous tumors tended to be slightly higher than those for the main analyses (e.g., RR for ⩾7 versus < 1 hour/week of total activity = 1.11; 95% CI = 0.61 to 2.02). Although we had limited statistical power to assess the effect of physical activity on mucinous and endometrioid tumors, results for these subtypes also did not differ substantially from the main analysis (results not shown). Furthermore, we observed little difference in the associations for mucinous tumors compared with all nonmucinous tumors (results not shown), and results from a subanalysis limited to invasive tumors did not differ from those including all cases (results not shown).

To determine whether results were affected by participants having reduced their activity level preceding a diagnosis of ovarian cancer, we evaluated the association between the cumulative average of physical activity (from 1980 to 1996), excluding cases diagnosed during the first 2 years after each report of activity level. Results did not differ substantially from those presented in Table 2; the RR for participants reporting 7 hours or more per week was 1.08 (95% CI = 0.68 to 1.72). Similarly, results lagged by 4 and 8 years did not differ from the main analysis (results not shown). Although power was greatly limited by the small number of cases diagnosed from 1992 to 1996 (n = 91), physical activity level 12 years earlier was associated with a modest, statistically nonsignificant reduction in risk. Compared with women who reported activity of less than 1 hour/week, the RRs

Table 3. Analysis of the association of ovarian cancer and light-, moderate-, and high-intensity physical activity in 1980 (follow-up from 1980 to 1996)

Physical activity level, intensity versus frequency—1980*	No. of cases†	Age-adjusted RR‡ (95% CI)	MV RR (95% CI)§
Low intensity	192	1.00 (referent)	1.00 (referent)‖
Moderate intensity, ⩽2 times/wk	19	0.56 (0.35 to 0.90)	0.57 (0.36 to 0.92)
Moderate intensity, 3–4 times/wk	26	1.31 (0.87 to 1.97)	1.35 (0.89 to 2.03)
Moderate intensity, >4 times/wk	17	0.93 (0.57 to 1.53)	0.94 (0.57 to 1.54)
Vigorous intensity, ⩽2 times/wk	23	0.98 (0.64 to 1.51)	1.05 (0.68 to 1.63)
Vigorous intensity, 3–4 times/wk	26	1.48 (0.98 to 2.24)	1.58 (1.05 to 2.38)
Vigorous intensity, >4 times/wk	16	1.38 (0.83 to 2.31)	1.48 (0.89 to 2.48)

*Intensity categories are defined as follows: low = activity not leading to sweating; moderate = activity of less than five metabolic equivalent tasks (METs) leading to sweating; high = activity of five METs or more leading to sweating.

†Numbers of cases may not sum to 377 because of missing data.

‡RR = relative risk.

§MV RR adjusted for age, parity, age at menarche, menopausal status/postmenopausal hormone use, tubal ligation, and smoking status. Categories for covariates are shown in Table 2. MV = multivariable; CI = confidence interval.

‖Each category compared with the referent of low activity. Two-sided P_{trend} across categories was calculated separately for low + three categories of moderate activity (P_{trend} = .93) and for low + three categories of vigorous activity (P_{trend} = .03).

Table 4. Analysis of the association of oavarian cancer and MET*,† hours/week from 1986 to 1996 and in 1986 only

Physical activity level	No. of cases‡	Age-adjusted RR (95% CI)	MV RR (95% CI)§
MET (cumulative average), h/wk			
0 to <2.5	28	1.00 (referent)	1.00 (referent)
2.5 to <5	34	1.37 (0.83 to 2.25)	1.42 (0.86 to 2.34)
5 to <10	42	1.24 (0.77 to 2.00)	1.34 (0.83 to 2.17)
10 to <20	50	1.22 (0.77 to 1.94)	1.32 (0.83 to 2.10)
20 to <30	37	1.71 (1.05 to 2.78)	1.84 (1.12 to 3.02)
⩾30	29	1.19 (0.71 to 1.99)	1.27 (0.75 to 2.14)
			P = .52‖
MET (1986 only), h/wk			
0 to <2.5	38	1.00 (referent)	1.00 (referent)
2.5 to <5	32	1.18 (0.74 to 1.89)	1.11 (0.75 to 1.66)
5 to <10	36	1.38 (0.87 to 2.17)	1.30 (0.89 to 1.90)
10 to <20	32	1.07 (0.67 to 1.71)	1.02 (0.68 to 1.51)
20 to <30	25	1.47 (0.89 to 2.44)	1.41 (0.90 to 2.18)
⩾30	26	1.25 (0.76 to 2.05)	1.16 (0.75 to 1.80)
			P = .48‖

*MET = metabolic equivalent task; MV = multivariable; RR = relative risk; CI = confidence interval.

†Metabolic equivalents, as defined by Ainsworth et al. *(20).*

‡Numbers of cases and person-years may not sum to totals because of missing data.

§MV RR adjusted for age, parity, age at menarche, menopausal status/postmenopausal hormone use, and tubal ligation and smoking status. Categories for covariates are shown in Table 2.

‖Two-sided P_{trend} over quintiles, calculated by using the median of each quintile as a continuous variable in the MV model.

for 1 to less than 2 hours/week, 2 to less than 4 hours/week, 4 to less than 7 hours/week, and greater than or equal to 7 hours/week were 0.91, 0.63, 0.53, and 0.72, respectively (P_{trend} = .14).

Finally, we evaluated whether the association between physical activity and ovarian cancer varied according to level of other ovarian cancer risk factors, particularly, current BMI and menopausal status. Results suggested that the observed increase in risk may be greatest in leaner women (i.e., BMI <25 kg/m^2), but these interactions were not statistically significant. We did not observe any difference in the association by menopausal status, age, oral contraceptive use, postmenopausal hormone use, regularity of menstrual cycles, or smoking status (results not shown). Furthermore, we found no difference in the risk of ovarian cancer for activity taking place before menopause compared with after menopause (results not shown).

Discussion

We did not find evidence of an inverse association between recreational physical activity and risk of ovarian cancer. The analysis of cumulative averaged MET hours/week (from 1986 to 1996), which probably provides the best overall measure of activity during the follow-up period, suggests that women who frequently engage in vigorous activity may experience a modest increase in ovarian cancer risk compared with inactive women. We did not find that walking, the activity most commonly reported by our participants, was associated with an increase in risk.

Physical activity has been hypothesized to reduce the incidence of ovarian cancer through one of several mechanisms. Intense physical activity can disrupt regular ovarian cycling, leading to luteal phase inadequacy, anovulation, and amenorrhea *(1).* Vigorous exercise may thus alter the risk of ovarian cancer by reducing the frequency of ovulation and damage to epithelial tissue *(22).* However, suppression of ovulation may only be achieved with extreme activity levels. Other data suggest that regular vigorous activity of the intensity level practiced by most women may instead increase ovulation frequency. Rich-Edwards et al. *(23)* found that frequent vigorous but not moderate activity was inversely associated with ovulatory infertility. A positive relationship between physical activity and ovulation frequency could potentially explain the modest increase in risk of ovarian cancer that we observed in women engaging in vigorous activity.

Physical activity may decrease circulating levels of endogenous estrogens *(2,24,25),* exposure to which has been proposed as a contributing factor to the development of ovarian cancer *(26).* Activity can also decrease body fat, thereby reducing the extragonadal production of estrogen, a major source of estrogen after menopause *(3).* However, activity may also plausibly increase ovarian cancer risk through hormone-related pathways. By reducing estrogens, exercise may increase pituitary production of gonadotropins as part of a negative-feedback relationship *(26);* exposure to high levels of gonadotropins has been suggested as a mechanism for ovarian cancer development *(27).* An alternative hypothesis, proposed by Risch *(28),* suggests that even moderate amounts of activity may increase risk

of ovarian cancer by reducing progesterone levels and by increasing androgen levels.

Several studies *(4–11)* have evaluated the association between physical activity and ovarian cancer, with inconsistent results. Such inconsistencies may result from variation in the definition of physical activity between studies, misclassification of activity level, or bias in these studies. Of the seven case–control studies of activity and ovarian cancer *(4–8),* five observed a reduction in cancer risk with frequent activity ranging in magnitude from 25% to 50%. Two other studies *(9,10)* reported a positive association. It is possible that selection and recall biases may have influenced the results of these case–control studies. Because ovarian cancer is often diagnosed at an advanced stage and survival is generally poor *(29),* it may be difficult to attain high participation rates. Case recall of physical activity may be subject to bias. Such biases are greatly reduced by prospective exposure measurement.

The only other prospective cohort study *(11)* to address this relationship reported a statistically significant positive association between activity and ovarian cancer. In the Iowa Women's Health Study, women in the highest category of a physical activity index had a twofold increase in risk compared with women in the lowest category. Risk increased linearly with frequency of both moderate and vigorous physical activity, with exercise of greater intensity conferring greater risk.

The extent to which occupational physical activity and physically demanding tasks like child rearing may confound studies of recreational exercise remains unclear. Recreational and nonrecreational activity may be inversely associated if women who hold physically demanding jobs have less energy for recreation and if those with more sedentary jobs are more likely to participate in leisure-time activity. We were able to include some information relating to occupational activity by including weekly time spent walking and stair climbing on questionnaires from 1986 onward and including these activities in the calculation of MET hours. However, the inability to comprehensively measure all contributions to activity is a limitation of any study of recreational activity.

Since the etiologic period of ovarian cancer has not yet been identified, it is unclear when physical activity may have the greatest impact on risk. Because of its effect on ovulation, premenopausal physical activity may affect risk differently from that after menopause. We saw no substantial difference in cancer risk among premenopausal and postmenopausal women or among women who exercised before as opposed to after menopause. Vigorous activity in young adulthood may also modify risk by delaying the onset of menarche and by increasing the frequency of anovulation in adolescence *(1).* Although we were unable to specifically address the effect of adolescent activity, we attempted to evaluate the effect of disease latency with a lagged analysis. Although we were severely limited by low power, our results suggested the possibility of an inverse association between cancer risk and participation in physical activity 12 years earlier.

In conclusion, we did not find evidence of an inverse association between recreational physical activity and risk of ovarian cancer. Our results concerning the possibility of a modest increase in risk with frequent vigorous activity suggest that additional research is needed to explore in greater depth the relationship between ovarian cancer and the frequency and intensity of physical activity.

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