Chronic Recreational Physical Inactivity and Epithelial Ovarian Cancer Risk: Evidence from the Ovarian Cancer Association Consortium

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Abstract

Background: Despite a large body of literature evaluating the association between recreational physical activity and epithelial ovarian cancer (EOC) risk, the extant evidence is inconclusive, and little is known about the independent association between recreational physical inactivity and EOC risk. We conducted a pooled analysis of nine studies from the Ovarian Cancer Association Consortium to investigate the association between chronic recreational physical inactivity and EOC risk.

Methods: In accordance with the 2008 Physical Activity Guidelines for Americans, women reporting no regular, weekly recreational physical activity were classified as inactive. Multivariable logistic regression was utilized to estimate the ORs and 95% confidence intervals (CI) for the association between inactivity and EOC risk overall and by subgroups based upon histotype, menopausal status, race, and body mass index.

Results: The current analysis included data from 8,309 EOC patients and 12,612 controls. We observed a significant positive association between inactivity and EOC risk (OR = 1.34; 95% CI, 1.14–1.57), and similar associations were observed for each histotype.

Conclusions: In this large pooled analysis examining the association between recreational physical inactivity and EOC risk, we observed consistent evidence of an association between chronic inactivity and all EOC histotypes.

Impact: These data add to the growing body of evidence suggesting that inactivity is an independent risk factor for cancer. If the apparent association between inactivity and EOC risk is substantiated, additional work via targeted interventions should be pursued to characterize the dose of activity required to mitigate the risk of this highly fatal disease. Cancer Epidemiol Biomarkers Prev; 25(7); 1114–24. ©2016 AACR.
Introduction

It is well established that recreational physical activity is associated with decreased risks of developing breast, colon, and endometrial cancers (1, 2), but the association between physical activity and epithelial ovarian cancer (EOC) remains less clear (3, 4). Despite the publication of dozens of individual epidemiologic studies, two organizational systematic reviews have concluded that insufficient and inconsistent evidence was available in the current literature to support an association between recreational physical activity and ovarian cancer risk (4, 5).

Inconsistent epidemiologic reports of the association between physical activity and EOC risk may be the result of limitations in the physical activity and ovarian cancer literature or may be due to a complex dose–response relationship that has not yet been fully elucidated. For example, individual studies of ovarian cancer often have relatively small numbers of case subjects, especially for the less common histotypes, which could limit statistical power to detect significant associations. In fact, the largest individual study to date included 1,580 cases, but only 44 patients were diagnosed with mucinous tumors (6). A lack of consistency in the literature could also reflect that only modest decreases in risk are associated with higher levels of activity (7) and that the greatest risk is associated with inactivity (8), a construct that has been scarcely investigated as an independent exposure relative to EOC risk. To our knowledge, all but two EOC studies (9, 10) have examined recreational physical activity using arbitrary cut-off points of incrementally higher levels of activity, with the lowest-no activity group identified as the reference group. Although parameterizing incrementally higher levels of activity exposure is important for detecting dose–response relationships, this approach has been associated with complex and meaningful exposure misclassification (11–13) and has precluded the establishment of a clear public health recommendation specific to ovarian cancer (4, 5). Importantly, this common methodology overlooks recreational physical inactivity as an independent public health exposure of interest (5).

To this end, since the publication of the 2008 Physical Activity Guidelines for Americans, adults have been encouraged to avoid physical inactivity, which is characterized by a lack of regular, weekly, moderate- or vigorous-intensity recreational activity (5). According to the most current data, 25% of Americans (14) and between 10.3% and 51.5% of adult women worldwide (8) are physically inactive. Given the persistence of inactivity at the population level and the hypothesis that the greatest protective benefits can be achieved by increasing activity levels at the low end of the activity continuum (8), inactive individuals could be a particularly important group to study in relationship to disease risk because of the ability for most individuals to increase the amount of activity they perform each week (8). In fact, current estimates suggest that congenital factors contributing to inactivity affect less than one percent of the population globally, implying that most individuals are capable of increasing activity levels (8).

Not only is studying physical inactivity important from a public health perspective (5, 15), it is likely assessed with less exposure misclassification (8, 16) and may also reflect physiologic pathways that exert an effect on carcinogenesis separately from pathways associated with physical activity and skeletal muscle contraction (15, 17). Thus, we conducted a pooled analysis of nine population-based case–control studies from Ovarian Cancer Association Consortium (OCAC) to investigate a novel, well-defined research question. Specifically, we sought to determine whether self-reported, chronic, recreational physical inactivity is associated with an increased risk of EOC. We evaluated the association between physical inactivity exposure and EOC risk overall, and according to subgroups based upon EOC histotype, menopause status, race, and body mass index (BMI).

Materials and Methods

OCAC study population

We obtained individual-level data from nine population-based OCAC case–control studies that had available self-report data on recreational physical inactivity throughout adulthood. Seven of the nine OCAC studies were based in the United States (18–24) and one each was based in Australia (25) and Denmark (26). Additional characteristics of the nine case–control studies included in the current analyses are summarized in Table 1.

All individual studies obtained Institutional Review Board or research ethics committee approvals, and participants for each OCAC study provided written informed consent for all study activities. Approvals for the current analyses were obtained from the OCAC Data Access Coordinating Committee and from individual study site coordinators if additional approvals were required. Data were obtained from 8,309 patients aged 18 years or older with histologically confirmed primary borderline or invasive EOC, fallopian tube cancer, or peritoneal cancer. Patients were excluded from the current analyses if they had been diagnosed with nonepithelial ovarian cancers (sarcomas, germ cell tumors, sex-cord stromal tumors, etc.); if tumor histology was mixed or undifferentiated; or if tumor behavior or histology was missing or unknown. Controls included 12,612 women aged 18 years and older with at least partially intact ovaries and no prior histories of ovarian cancer.

Analysis variables

Epidemiologic data. The primary OCAC epidemiologic dataset includes information that was collected through self-administered
<table>
<thead>
<tr>
<th>OCAC study name</th>
<th>Study design</th>
<th>Case and control ascertainment</th>
<th>Year of diagnosis</th>
<th>Participation rates</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Ovarian Cancer Study/ Australian Cancer Study (AUS; ref. 25)</td>
<td>Population-based</td>
<td>Cases identified via surgical treatment centers and cancer registries; controls electoral roll</td>
<td>2002-2006</td>
<td>65% CA</td>
<td>1,289</td>
<td>47% CO</td>
</tr>
<tr>
<td>Connecticut Ovary Study (CON; ref. 22)</td>
<td>Population-based</td>
<td>Cases identified via cancer registries and pathology departments; controls RDD</td>
<td>1998-2003</td>
<td>69% CA</td>
<td>489</td>
<td>61% CO</td>
</tr>
<tr>
<td>Diseases of the Ovary and their Evaluation (DOV/DVE; refs. 23, 71)</td>
<td>Population-based</td>
<td>Cases identified via SEER registry; controls RDD</td>
<td>2002-2009</td>
<td>74.2% CA</td>
<td>1,276</td>
<td>61.5% CO</td>
</tr>
<tr>
<td>Hawaii Ovarian Cancer Case-Control Study (HAW; ref. 19)</td>
<td>Population-based</td>
<td>Cases identified via cancer registries; controls selected via Dept. of Health annual survey</td>
<td>1993-2008</td>
<td>78% CA</td>
<td>739</td>
<td>80% CO</td>
</tr>
<tr>
<td>Novel Risk Factors &amp; Potential Early Detection Markers for Ovarian Cancer (HOP; ref. 72)</td>
<td>Population-based</td>
<td>Cases identified via cancer registries, physician offices, pathology databases; controls RDD</td>
<td>2003-2014</td>
<td>71% CA</td>
<td>604</td>
<td>68% CO</td>
</tr>
<tr>
<td>MALignant OVArian cancer (MAL; ref. 26)</td>
<td>Population-based</td>
<td>Cases identified via cancer registry and gynecologic departments; controls from population register</td>
<td>1994-1999</td>
<td>81% CA</td>
<td>681</td>
<td>68% CO</td>
</tr>
<tr>
<td>New England Case Control Study (NEC; ref. 24)</td>
<td>Population-based</td>
<td>Cases identified via hospital tumor boards &amp; cancer registries; controls via RDD &amp; townbook selection</td>
<td>1992-2008</td>
<td>70% CA</td>
<td>1,065</td>
<td>72% CO</td>
</tr>
<tr>
<td>New Jersey Ovarian Cancer Study (NJO; ref. 18)</td>
<td>Population-based</td>
<td>Cases identified via New Jersey State Cancer Registry; controls via RDD if &lt; 65 years of age and random selection from insurance lists for women &gt; 65 years; also utilized area sampling for women &gt; 55 years of age.</td>
<td>2004-2008</td>
<td>47% CA</td>
<td>681</td>
<td>40% CO</td>
</tr>
<tr>
<td>Los Angeles County Case-Control Studies of Ovarian Cancer-1 &amp; 2 (USC; ref. 73)</td>
<td>Population-based</td>
<td>Cases identified through Los Angeles County Cancer Registry &amp; SEER by rapid case ascertainment</td>
<td>1993-current</td>
<td>80% CA</td>
<td>1,971</td>
<td>70% CO</td>
</tr>
</tbody>
</table>

Abbreviations: CA, case; CO, control; RDD, random digit dialing.
Recreational physical inactivity. Recreational physical activity data were directly acquired from each of the nine OCAC studies included in the current analysis. All nine questionnaires assessed recreational activity spanning adulthood up through the reference age, defined as the age of diagnosis among cases and the age of study entry among controls. Specifically, eight of nine questionnaires encompassed the time period spanning all decades of adulthood (i.e., age 20 through the reference date), while one study (DVE) spanned the time period from age 25 through the reference date.

The specific parameters of physical activity were inconsistently measured across studies, precluding the ability to harmonize and parameterize physical activity data in terms of frequency, intensity, or duration per session. However, in the current analysis, the exposure of interest was recreational physical inactivity, and all nine questionnaires allowed for the identification of women who self-reported engaging in no regular, weekly moderate-to-vigorous intensity recreational activity. Questions from most studies (DVE, HAW, HOP, NEC, NJO, USC) utilized a global, dichotomous item assessing ever-participation in regular, weekly, recreational physical activities. For these studies, women answering “no” to the global question were classified as “inactive.” Three studies (AUS, CON, MAL) assessed recreational physical (in)activity based upon prespecified time periods spanning adulthood (i.e., by decades or a combination of decades ranging from age 20–29 through the reference age). Likewise, women reporting no regular, weekly moderate or vigorous intensity recreational activity in all time periods prior to the reference date were classified as inactive. Furthermore, given that the most relevant exposure of interest may be many years before the actual diagnosis of cancer (7), we conducted analyses designed to examine an exposure window encompassing at least two decades of adulthood prior to study entry. Thus, participants with reference dates in their 20s were excluded in sensitivity analyses, yielding a chronic inactivity exposure spanning a minimum of two decades.

Statistical analysis
Identification of confounding variables. Based upon the definition of potential confounding (34) and their establishment as factors associated with risk of ovarian cancer, the following variables in the OCAC core dataset were prespecified as important for adjustment when estimating EOC risks: age at reference date, race (White, Black, Asian, other), use of oral contraceptives (ever, never), parity (nulliparous, 1, 2, 3, or ≥4 full-term births), family history of breast or ovarian cancer, cigarette smoking, current BMI (1–5 years prior to diagnosis), and personal history of endometriosis; refs. 27–33.

Recreational physical inactivity and EOC risk. To account for between-study heterogeneity, we utilized a meta-analytic approach to examine the association between inactivity and EOC risk overall and according to EOC endpoints defined by tumor behavior and histology. For each of the nine studies, logistic regression analyses were conducted to estimate study-specific ORs and 95% confidence intervals (CI) for the association between chronic physical inactivity and EOC risk. Study-specific ORs and their variances were then combined via meta-analyses to estimate summary ORs and 95% CIs for all EOC endpoints. Meta-analytic analyses were conducted under random-effects or fixed-effects assumptions, depending on measures of between-study heterogeneity, which was assessed and quantified utilizing the Cochran Q-statistic and the I² statistic (36). When evidence of significant heterogeneity was observed between studies (Q-statistic $P<0.05$ or I² value $>50$%), we reported a random-effects OR based upon the DerSimonian and Laird method (37), and we conducted further analyses to identify and account for source(s) of heterogeneity. However, when no significant heterogeneity was observed between studies, we reported a fixed-effects OR.

To enable well-powered subgroup analyses, we pooled individual-level data from the nine studies into a combined dataset to examine the association between inactivity and EOC risk by menopause status, race, and BMI classification. We examined associations between inactivity and EOC risk by subgroups of standard categories of BMI (i.e., underweight, normal weight, overweight, and obese) and by a dichotomous BMI classification (i.e., underweight and normal weight vs. overweight and obese). In pooled analyses, all multivariable models were adjusted by study site, and we accounted for the possibility of between-study heterogeneity by testing the significance of a cross product term for site*inactivity in all analyses.

Finally, we conducted sensitivity analyses designed to address any potential heterogeneity in the observed associations between inactivity and EOC risk that could have resulted from differences in the physical activity questionnaires among OCAC studies. Furthermore, to account for potential cultural or geographical differences in activity patterns, we excluded two studies that were not conducted in the United States (AUS and MAL).
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Table 2. Prevalence of inactivity among the study population including nine participating ovarian cancer association consortium studies

| Study site* | Prevalence of inactivity in the combined study population | Prevalence of inactivity in cases (n/%) | Prevalence of inactivity in controls (n/%) | \( \chi^2 \) p
<table>
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<tbody>
<tr>
<td>MAL</td>
<td>1,082/2,233 (48.5%)</td>
<td>348/668 (51.1%)</td>
<td>734/1,562 (48.4%)</td>
<td>0.007</td>
</tr>
<tr>
<td>CON</td>
<td>358/1,033 (34.6%)</td>
<td>189/489 (38.7%)</td>
<td>169/545 (31.0%)</td>
<td>0.010</td>
</tr>
<tr>
<td>NEC</td>
<td>695/2,308 (50.1%)</td>
<td>366/1,065 (34.4%)</td>
<td>329/1,243 (26.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NJO</td>
<td>106/653 (16.2%)</td>
<td>56/195 (28.7%)</td>
<td>50/458 (10.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DOV</td>
<td>654/3,124 (20.9%)</td>
<td>279/1,276 (21.9%)</td>
<td>375/1,848 (20.3%)</td>
<td>0.288</td>
</tr>
<tr>
<td>HOP</td>
<td>469/2,404 (19.5%)</td>
<td>119/604 (19.7%)</td>
<td>350/1,800 (19.4%)</td>
<td>0.890</td>
</tr>
<tr>
<td>AUS</td>
<td>522/2,757 (18.6%)</td>
<td>253/1,289 (19.6%)</td>
<td>259/1,486 (17.6%)</td>
<td>0.005</td>
</tr>
<tr>
<td>USC</td>
<td>543/4,566 (11.9%)</td>
<td>269/1,971 (13.6%)</td>
<td>274/2,595 (10.6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>HAW</td>
<td>184/1,842 (10%)</td>
<td>94/739 (12.7%)</td>
<td>90/1,103 (8.2%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Study sites are listed in descending order by prevalence of physical inactivity among cases.

\( P \) represents differences in the distribution of inactivity between cases versus controls.

Results

The characteristics of the nine OCAC case–control studies included in the analyses are summarized in Table 1. The self-reported prevalence of recreational physical inactivity among the study population is presented in Table 2. Collectively, 23.7% of cases and 20.9% of controls reported a history of inactivity (\( 95\%\text{ CI}, 1.14–1.57; \text{Fig. 1A} \)), a 35% increased risk of EOC overall (OR = 1.35; 95% CI, 1.14–1.60; \text{Fig. 1B} ), and a 27% increased risk of borderline tumors (OR = 1.27; 95% CI, 1.10–1.46; \text{Fig. 1C} ). Among the five invasive histotypes, we observed increased risks ranging between 29% and 54% among inactive women (Fig. 2A–E). Physical inactivity was also associated with a 27% and 31% increased risk of borderline serous and borderline mucinous tumors, respectively (\text{Fig. 3A and B} ). Importantly, adding BMI to multivariable models did not change these estimates appreciably (Table 3).

Table 3. Weighted ORs and 95% CIs representing the association between physical inactivity and EOC among case–control studies included in the meta-analyses* (Continued on next page)

Abbreviations: FE, fixed effects; RE, random effects.

*For each EOC endpoint, studies with >10 cases are included in meta-analyses.

**Study-specific multivariable models are adjusted by age, race, parity, oral contraceptive use, a personal history of endometriosis, and a family history of breast or ovarian cancer.

**Random-effects ORs reported when \( Q \)-statistic is significant (\( P < 0.05 \)) or when \( P \) is greater than 50%; fixed-effects models reported when no significant heterogeneity was observed.
example, the OR was 1.25 and 95% CI was 1.16–1.35 for EOC overall (P_{heterogeneity} = 0.467).

After excluding NJO, we further compared the associations between inactivity and EOC risk based upon the questionnaire format utilized among the OCAC studies included in the analysis. We observed no significant heterogeneity in weighted point estimates among those studies utilizing one global item to assess (in)activity throughout adulthood (OR = 1.27, 95% CI, 1.16–1.39) versus the studies utilizing multiple prespecified time periods throughout adulthood (OR = 1.20, 95% CI, 1.04–1.40), yielding an overall fixed-effects OR = 1.25; 95% CI, 1.16–1.35; P_{heterogeneity} = 0.523. Importantly, even when adding NJO back into the analyses, there was no significant heterogeneity observed between the two formats incorporated herein (OR = 1.27, 95% CI, 1.16–1.39), P_{heterogeneity} = 0.154. Finally, in additional sensitivity analyses excluding two studies conducted outside the United States (AUS, MAL), the observed associations between inactivity and EOC risk were strengthened (OR = 1.43; 95% CI, 1.17–1.76), and the association remained significant after excluding NJO (OR = 1.27; 95% CI, 1.16–1.39).

In subgroup analyses, we observed no convincing evidence of effect modification by menopause status (P_{interaction} = 0.483; Supplementary Table S1), race (P_{interaction} = 0.337; Supplementary Table S2), or by standard BMI categories (P_{interaction} = 0.082; Supplementary Table S3). Finally, when the association between inactivity and EOC risk was examined utilizing a dichotomous BMI variable (BMI < 25 or BMI ≥ 25), we observed a significant, positive association between inactivity and EOC risk among underweight/normal weight women and overweight/obese women: (OR = 1.33; 95% CI, 1.19–1.49) and (OR = 1.21; 95% CI, 1.09–1.34), respectively (P_{interaction} = 0.041; Supplementary Table S4).

**Discussion**

In the current analysis, we observed consistent evidence of a statistically significant positive association between self-reported, chronic recreational physical inactivity and all histotypes of EOC. Although published data describing the association between recreational physical inactivity and EOC risk are scant, two recent prospective studies reported the association between EOC risk and the most inactive group of women, in comparison to a reference group of women engaging in moderate amounts of activity (9, 10). Leitzmann and colleagues (10) reported an
increased risk of early-stage and fatal EOC among the most inactive women (RR = 1.29; 95% CI: 1.06–1.53) and Huang and colleagues (9) reported a 29% increased risk of EOC among women who were the least active during premenopausal years (HR = 1.29; 95% CI: 0.95–1.75). Although these estimates did not reach statistical significance, they are of similar magnitude to each other and to the point estimates reported for overall EOC in our primary and sensitivity analyses.

Our analyses did not account for explicitly sedentary behaviors, such as sitting, television watching, or computer use, yet there is mounting epidemiologic evidence demonstrating a positive association between sedentary behaviors and EOC risk (39–43). Although sedentary behavior is a separate behavioral construct...
function, and increased circulating levels of sex hormones. For example, both acute and chronic physical activity produce an anti-inflammatory effect via reduced levels of inflammatory markers such as C-reactive protein and TNF (46). In addition, both mechanistic and epidemiologic evidence suggests a role for dysregulated adiponectin (an anti-inflammatory adipokine) and leptin (a proinflammatory adipokine) in epithelial ovarian carcinogenesis (47–52). There is also evidence suggesting a dysregulated adipokine milieu promotes an immunosuppressive environment via myeloid-derived suppressor cell (MDSC) induction and FoxP3+ T-regulatory cell recruitment (53), an area that has been under intense investigation in relationship to ovarian cancer etiology and prognosis (54–57). Finally, there are endocrine-related hypotheses that support the plausibility of an inverse association between activity and EOC risk by way of decreased levels of circulating estrogens and androgens, and in fact, most studies seem to suggest that exercise decreases the availability of biologically active estrogens and androgens (58).

Emerging evidence also supports the hypotheses that physical inactivity and sedentary behaviors are exposures with distinct metabolic consequences, which could be independent of physical activity and obesity-related mechanisms (15, 17, 59, 60). Our data also imply that the observed association between physical inactivity and EOC risk is mostly independent of BMI. Although adding BMI to our multivariable models yielded a slight attenuation in the observed ORs, an independent, consistent, and significant effect of inactivity remained.

Furthermore, although there appears to be a borderline statistically significant interaction between BMI classification (i.e., underweight, normal weight, overweight, obese) and inactivity in relation to EOC risk, the apparent stronger association among underweight women and weaker association among obese women were accompanied by CIs that included the null. This suggests there may be imprecision in estimating EOC risk at the extreme distribution of BMI and inactivity when they are considered jointly. Finally, when the association between inactivity and EOC risk was examined in two subgroups of BMI (i.e., <25 or ≥25), we observed a statistically significant BMI*inactivity interaction for EOC overall ($P = 0.041$). Although the interaction $P$ value for EOC overall suggests this association may not be due to chance alone, we believe the associations between inactivity and EOC risk are qualitatively comparable across BMI stratum.

A key strength of our study is that our analyses were conducted with individual-level data from well-designed population-based epidemiologic investigations, yielding the first substantial analysis of the association between recreational physical inactivity and EOC risk. Furthermore, our ability to adjust for well-established risk and protective factors associated with EOC risk decreased the likelihood that the observed associations were the result of confounding. In addition, the observed associations between inactivity and EOC risk remained significant and of similar magnitude in all sensitivity analyses designed to reduce potential sources of bias. Finally, our use of chronic inactivity as the exposure of interest reduced the likelihood of reverse causation bias as a potential explanation for the observed associations reported herein.

The potential measurement error associated with self-report physical activity data categorized as a dichotomous variable is an important limitation to the current analysis. Although the dichotomous nature of the exposure variable assumes a homogenous group of activity and does not allow for an examination of the
dose–response association with physical activity exposure, there are important advantages to our approach. First, although mis-reporting of inactivity does occur, we assume the misclassification across incremental categories of activity would be greater (8, 11, 12, 16) and more influential with respect to biasing observed associations of interest. In fact, previous research has demonstrated that the greatest concordance between direct and self-report measures of activity is found at the lowest ends of the activity continuum, with more measurement error surrounding midpoints of activity exposure. Second, there is a body of evidence demonstrating that the use of one global question is a validated method for identifying inactive individuals (13, 61–66). Third, although it is impossible to know whether (in)activity misclassification was differential by case–control status, one tactic is to compare our findings with those from cohort studies, where self-reported (in)activity would not be subjected to recall bias (7). Among the two prospective studies providing risk estimates for inactivity (9, 10), associations were similar to those reported herein, arguing against a bias in case–control studies due to differential misclassification. Importantly, nondifferential misclassification with a dichotomous exposure variable would likely result in an underestimate of the true association between inactivity and EOC risk (67).

We also recognize that our findings may be limited by the potential for a higher prevalence of healthier women to have volunteered as controls. If so, this would have inflated our observed estimates of association between inactivity and EOC risk. Likewise, associations between EOC risk and other lifestyle factors, such as smoking, alcohol consumption, and obesity, would also show inflated risk estimates. Yet, previously published OCAC-pooled analyses utilizing data from the same studies have yielded no evidence of an association between alcohol consumption and EOC risk (28), and evidence of associations between EOC risk and smoking and obesity has been restricted to specific histotypes (27, 29). It is also possible that additional unmeasured factors that may parallel physical activity (or inactivity) in lifestyle patterns could contribute to an observed association between physical inactivity and EOC risk.

Although the goal of the current study was to examine the association between recreational physical inactivity and EOC risk, it is worth noting that previous epidemiologic studies of physical activity and EOC risk have yielded inconsistent findings based upon the type of observational study. Although the first published meta-analysis of the association between physical activity and EOC risk reported similar risk estimates for case–control studies (OR = 0.79; 95% CI, 0.70–0.85) and cohort studies (OR = 0.81; 95% CI, 0.72–0.92; ref. 6), a more recent meta-analysis reported a significant inverse association between activity and EOC risk among case–control studies (OR = 0.86; 95% CI, 0.80–0.93) but reported no association among cohort studies (OR = 1.03; 95% CI, 0.87–1.20; ref. 68).

It is also important to highlight that there are competing hypotheses regarding the shape of the dose–response physical activity curve in relationship to chronic disease risk (i.e., linear vs. nonlinear; ref. 8). In fact, prospective studies have yielded data suggesting a significant positive association between vigorous physical activity and EOC risk (9, 69, 70). Although there is biologic plausibility for a positive association between excessive vigorous exercise and increased EOC risk by way of impaired immune function (44) and exercise-induced increases in gonadotropin and androgen secretion (70), researchers have cautioned that observations of a direct association between activity and EOC risk could be due to chance (69), small cell sizes (69), and detection bias (10, 69). Importantly, nondifferential misclassification of self-reported physical activity parameterized in more than two categories can result in biased estimates away from the null (67).

In conclusion, in the first substantial analysis designed to examine chronic recreational physical inactivity as an independent exposure of interest, we observed evidence of a significant positive association between recreational inactivity and EOC risk that was consistently observed among all EOC histotypes. These data add to the growing body of literature demonstrating that physical inactivity is associated with a plethora of unfavorable health outcomes, including an increased risk for early death, heart disease, stroke, type II diabetes, and certain cancers including breast, colon, and endometrial tumors (5, 8, 14). Additional prospective epidemiologic studies are warranted to further elucidate the dose–response association between recreational physical (in)activity and EOC risk. If the apparent association between inactivity and EOC risk is substantiated, then additional work via targeted intervention studies should be pursued to characterize the dose of recreational physical activity required to mitigate the risk of this highly fatal disease.

Disclosure of Potential Conflicts of Interest

D. Cramer has provided expert testimony for Beasley Allen Crow. M.T. Goodman is a consultant/advisory board member for Johnson and Johnson. P. Webb reports receiving a commercial research grant from BIOPA. No potential conflicts of interest were disclosed by the other authors.

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