

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 (OCAC) 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 odds ratios (OR) 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 (BMI). **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.

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 epidemiological 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 epidemiological 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 1580 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 which 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 points of incrementally higher levels of activity, with the low-or no-activity group identified as the reference group. While 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 (PAGAs), 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 physiological 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 OCAC to investigate a novel, well-defined research question. Specifically, we sought to determine if 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 were based in Australia (25) and Denmark (26). Additional characteristics of the nine case-control studies included in the present 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 present 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 epithelial ovarian cancer, fallopian tube cancer, or peritoneal cancer. Patients were excluded from the current analyses if they had been diagnosed with non-epithelial 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

Epidemiological Data. The primary OCAC epidemiological dataset includes information that was collected through self-administered or interviewer-administered questionnaires. Available demographic, lifestyle and clinical variables include age, race, ethnicity, education, tumor behavior, tumor histology, oral contraceptive use, family history of breast and ovarian cancer, age at menarche, number of full-term pregnancies, breastfeeding, age at menopause, hormone therapy use (estrogen-alone or combination therapy), hysterectomy, and several additional epidemiological variables from previously published OCAC pooled analyses [i.e., tubal ligation, smoking history, alcohol use, genital powder use, nonsteroidal anti-inflammatory drug (NSAID) use, recent BMI (1-5 years prior to diagnosis), and personal history of endometriosis] (27-33).

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. Questionnaires 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 pre-specified 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. Further, given that the most relevant (in)activity exposure period 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 twenties were excluded in sensitivity analyses, yielding a chronic inactivity exposure spanning a minimum of two decades.

Statistical Methods

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 data set were pre-specified 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 in a first degree relative (yes, no, don't know), and a personal history of endometriosis (yes, no). In pooled analyses utilizing a combined dataset, we further adjusted all models for study site. We also utilized the ten percent change-in-estimate approach (35) to inform the selection of additional adjustment variables. Based upon this approach, we determined that ethnicity (Hispanic, non-Hispanic), use of hormone therapy (yes or no for estrogen-only or combination estrogen/progesterone), smoking (never, current, former), alcohol use (never, ever, former), education (less than high school, high school, some college, college graduate, graduate school), talc or genital powder use (no use, genital use, non-genital use), NSAIDs use (\geq once per week, $<$ once per week), tubal ligation prior to diagnosis (yes, no), breast-feeding (yes, no, not applicable), hysterectomy prior to diagnosis (yes, no), menopause status (pre or peri, post, don't know), and recent BMI (underweight, normal weight, overweight, or obese based upon BMI 1-5 years prior to diagnosis) were not relevant confounders. However, because obesity has an established association with physical activity and it is also associated with increased risk of some EOC histotypes, we evaluated models with and without adjustment for BMI, as obesity may be in the causal pathway of interest.

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 odds ratios (ORs) and 95% confidence intervals (CIs) 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 I-squared statistic (36). When evidence of significant heterogeneity was observed between studies (Q-statistic p-value <0.05 or I^2 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.

Lastly, 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 U.S. (AUS & MAL).

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 ($p < 0.001$). Inactivity rates varied by study site (10% in HAW and 48.5% in MAL), yielding a combined inactivity prevalence of 22.0% among the total study

population. These estimates are very similar to national (25%) and global (10.3 – 51.5%) inactivity estimates (8, 14, 38), thus enhancing the confidence in our characterization of the inactivity exposure.

In meta-analyses, we observed a significant positive association between self-reported, chronic physical inactivity and all EOC endpoints (Table 3). Specifically, among inactive women, we observed a 34% increased risk of EOC overall (OR= 1.34, 95% CI: 1.14-1.57) (Figure 1a); a 35% increased risk of invasive tumors (OR =1.35, 95% CI 1.14-1.60) (Figure 1b); and a 27% increased risk of borderline tumors (OR =1.27, 95% CI 1.10-1.46) (Figure 1c). Among the five invasive histotypes, we observed increased risks ranging between 29-54% among inactive women (Figures 2a-e). Physical inactivity was also associated with a 27% and 31% increased risk of borderline serous and borderline mucinous tumors, respectively (Figures 3a and b). Importantly, adding BMI to multivariable models did not change these estimates appreciably (Table 3).

Significant between-study heterogeneity was noted for EOC overall, invasive tumors, high-grade serous tumors, and endometrioid tumors (Table 3). The observed heterogeneity was explained by one study (NJO) and we accounted for between-study heterogeneity by presenting random-effects summary ORs. Upon excluding NJO in sensitivity analyses, associations between inactivity and EOC risk for EOC overall, invasive tumors, high-grade serous tumors and endometrioid tumors were of comparable magnitude and remained statistically significant. For example, the OR and 95% CI for EOC overall was (OR=1.25, 95% CI: 1.16-1.35), p -for-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) vs. the studies utilizing multiple pre-specified 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-for-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-for-heterogeneity=0.154. Lastly in additional sensitivity analyses excluding two studies conducted outside the U.S. (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-for-interaction=0.483) (Supplemental Table S1); race (p-for-interaction=0.337) (Supplemental Table S2); or by standard BMI categories (p-for-interaction=0.082) (Supplemental Table S3). Lastly, 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-for-interaction=0.041) (Supplemental 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. While 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 et al. reported an increased risk of early-stage and fatal EOC among the most inactive women (RR=1.29, 95% CI: 0.55-3.04 and RR=1.20, 95% CI 0.71-2.03, respectively) and Huang et al. reported a 29% increased risk of EOC among women who were the least active during pre-

menopausal years (HR=1.29, 95% CI: 0.95-7.75). 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 epidemiological evidence demonstrating a positive association between sedentary behaviors and EOC risk (39-43). Although sedentary behavior is a separate behavioral construct independent of recreational physical (in)activity, these collective findings add to the growing body of evidence that behavior patterns indicative of a sedentary lifestyle, either by way of prolonged sitting or a lack of recreational physical activity, appear to be associated with increased EOC risk. Further, it is plausible that the underlying biological mechanisms responsible for an apparent association of sedentary behavior and recreational physical inactivity with EOC risk are likely similar.

While research has established that the incidence of certain types of tumors are reduced by regular physical activity, the biological mechanisms relating physical (in)activity and cancer risk are not entirely understood (44). The most commonly cited mediators of these associations include changes in body fat, changes in circulating reproductive hormone levels, alterations in inflammatory cytokine and growth factor milieus and alterations in immune function (44). Inasmuch as the current leading hypotheses about the etiology of EOC each share inflammation as an underlying mechanism (45), it is possible that inactivity increases EOC risk by way of increased systemic inflammation, decreased immune 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 tumor necrosis factor (46). Additionally, both mechanistic and epidemiological evidence suggests a role for dysregulated adiponectin (an anti-inflammatory adipokine) and leptin (a pro-inflammatory 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). Lastly, 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, while 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. Lastly, 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 epidemiological 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.

Additionally, 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. Lastly, 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, while misreporting 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 measures of mid-to-upper levels of exposure (8, 11, 12). Utilizing a dichotomous variable avoids a potentially misleading level of accuracy in categorizing incremental levels of self-reported physical activity (8). 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 wouldn't 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, non-differential 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 epidemiological studies of physical activity and EOC risk have yielded inconsistent findings based upon the type of observational study. While 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% 0.72-0.92) (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) (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. non-linear) (8). In fact, prospective studies have yielded data suggesting a significant positive association between vigorous physical activity and EOC risk (9, 69, 70). While there is biological 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, non-differential 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 2 diabetes and certain cancers including breast, colon, and endometrial tumors (5, 8, 14). Additional prospective epidemiological 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.

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Table 1. Characteristics of the Ovarian Cancer Association Consortium Case-Control Studies Included in the Analyses

OCAC Study Name ^a	Study Design	Case & Control Ascertainment	Year of Diagnosis	Participation Rates	Total N ^b
Australian Ovarian Cancer Study/Australian Cancer Study (AUS)(25)	Population-based	Cases identified via surgical treatment centers & cancer registries; Controls electoral roll	2002-2006	65% CA 47% CO	1289 CA 1468 CO 2757 Total
Connecticut Ovary Study (CON)(22)	Population-based	Cases identified via cancer registries and pathology departments; controls RDD	1998-2003	69% CA 61% CO	489 CA 545 CO 1034 Total
Diseases of the Ovary and their Evaluation (DOV) and (DVE)(23, 71)	Population-based	Cases identified via SEER registry; controls RDD	2002-2009	74.2% CA 61.5% CO	1276 CA 1848 CO 3124 Total
Hawaii Ovarian Cancer Case-Control Study (HAW)(19)	Population-based	Cases identified via cancer registries; controls selected via Dept. of Health annual survey	1993-2008	78% CA 80% CO	739 CA 1103 CO 1842 Total
Novel Risk Factors & Potential Early Detection Markers for Ovarian Cancer (HOP)(72)	Population-based	Cases identified via cancer registries, physician offices, pathology databases; controls RDD	2003-2014	71% CA 68% CO	604 CA 1800 CO 2404 Total
MALignant OVArrian cancer (MAL)(26)	Population-based	Cases identified via cancer registry and gynecologic departments; controls from population register	1994-1999	81% CA 68% CO	681 CA 1552 CO 2233 Total
New England Case Control Study (NEC)(24)	Population-based	Cases identified via hospital tumor boards & cancer registries; controls via RDD & townbook selection	1992-2008	70% CA 72% CO	1065 CA 1243 CO 2308 Total
New Jersey Ovarian Cancer Study (NJO)(18)	Population-based	Cases identified via New Jersey State Cancer Registry; controls via RDD if <65 years of age and random selection from insurance lists for women >65 years; also utilized area sampling for women > 55 years of age.	2004-2008	47% CA 40% CO	195 CA 458 CO 653 Total
Los Angeles County Case-Control Studies of Ovarian Cancer-1 & 2 (USC)(73)	Population-based	Cases identified through Los Angeles County Cancer Surveillance Program (part of SEER) by rapid case ascertainment.	1993-current	80% CA 70% CO	1971 CA 2595 CO 4566 Total

^aStudy sites are listed in alphabetical order by OCAC study abbreviation

^bTotal participant numbers reflect the OCAC core data set as of July 2014, including only those who had physical activity data available (N=8,309 cases; N=12,612 controls)

Table 2. Prevalence of Inactivity Among the Study Population including Nine Participating Ovarian Cancer Association Consortium Studies				
Study site^a	Prevalence of inactivity in the combined study population	Prevalence of inactivity in cases (n/%)	Prevalence of inactivity in controls (n/%)	Chi-square p-value^b
MAL	1082/2233 (48.5%)	348/681 (51.1%)	734/1552 (48.4%)	0.097
CON	358/1034 (34.6%)	189/489 (38.7%)	169/545 (31.0%)	0.010
NEC	695/2308 (30.1%)	366/1065 (34.4%)	329/1243 (26.5%)	<0.001
NJO	106/653 (16.2%)	56/195 (28.7%)	50/458 (10.9%)	<0.001
DOV	654/3124 (20.9%)	279/1276 (21.9%)	375/1848 (20.30%)	0.288
HOP	469/2404 (19.5%)	119/604 (19.7%)	350/1800 (19.4%)	0.890
AUS	512/2757 (18.6%)	253/1289 (19.6%)	259/1468 (17.6%)	0.005
USC	543/4566 (11.9%)	269/1971 (13.6%)	274/2595 (10.6%)	0.001
HAW	184/1842 (10%)	94/739 (12.7%)	90/1103 (8.2%)	0.001
^a Study sites are listed in descending order by prevalence of physical inactivity among cases.				
^b p-value represents differences in the distribution of inactivity between cases vs. controls.				

Table 3. Weighted Odds Ratios and 95% Confidence Intervals Representing the Association between Physical Inactivity and Epithelial Ovarian Cancer among Case-Control Studies included in the Meta-analyses ^a							
Epithelial Ovarian Cancer (EOC) Histological Type	Model ^b	Summary OR ^c	95% CI		Heterogeneity		
			Lower	Upper	Q-statistic	P-value	I ²
Overall EOC (all histological types combined)	Multivariable	1.34 (RE)	1.14	1.57	33.77	<0.001	76.31%
	Add BMI	1.32 (RE)	1.12	1.56	34.43	<0.001	76.76%
Invasive EOC (all invasive cases combined)	Multivariable	1.35 (RE)	1.14	1.60	34.23	<0.001	76.63%
	Add BMI	1.33 (RE)	1.12	1.58	33.13	<0.001	75.85%
Invasive High-grade Serous	Multivariable	1.30 (RE)	1.10	1.54	23.40	0.003	65.82%
	Add BMI	1.30 (RE)	1.08	1.53	22.60	0.004	64.60%
Invasive Low-grade Serous	Multivariable	1.39 (FE)	1.06	1.83	15.02	0.059	46.72%
	Add BMI	1.33 (FE)	1.01	1.76	13.90	0.084	42.44%
Invasive Endometrioid	Multivariable	1.29 (RE)	1.01	1.65	17.79	0.023	55.03%
	Add BMI	1.26 (RE)	0.98	1.63	18.29	0.019	56.23
Invasive Mucinous	Multivariable	1.54 (FE)	1.22	1.95	5.40	0.715	0.00%
	Add BMI	1.50 (FE)	1.17	1.10	5.78	0.672	0.00%
Invasive Clear Cell	Multivariable	1.45 (FE)	1.16	1.80	15.46	0.051	48.24%
	Add BMI	1.40 (FE)	1.11	1.74	13.59	0.093	41.13%
Borderline EOC (serous & mucinous combined)	Multivariable	1.27 (FE)	1.10	1.46	7.84	0.250	23.50%
	Add BMI	1.20 (FE)	1.04	1.39	7.64	0.265	21.51%
Borderline Serous	Multivariable	1.27 (FE)	1.07	1.52	6.59	0.360	8.95%
	Add BMI	1.20 (FE)	1.01	1.44	5.59	0.470	0.00%
Borderline Mucinous	Multivariable	1.31 (FE)	1.06	1.61	9.69	0.138	38.08%
	Add BMI	1.25 (FE)	1.01	1.55	9.88	0.130	39.30%
^a For each EOC endpoint, studies with >10 cases are included in meta-analyses ^b 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 ^c Random-effects (RE) ORs reported when Q-statistic is significant ($p < 0.05$) or when I^2 is greater than 50%; Fixed-effects (FE) models reported when no significant heterogeneity was observed.							

Figure 1. Forest plots depicting study-specific and summary ORs and 95% CIs representing the association between recreational physical inactivity and risk of epithelial ovarian cancer (EOC). Forest plots include measures of association for **(1a)** all EOC histological types combined; **(1b)** all invasive tumors combined; and **(1c)** all borderline tumors combined. Study specific ORs and 95% CI were estimated utilizing logistic regression models adjusted for age, race, parity, oral contraceptive use, history of breast or ovarian cancer in first-degree relative, and a personal history of endometriosis. Summary ORs were generated via random-effects models if significant heterogeneity was detected (i.e., Q-statistic p-value <0.05 or I-squared >50%). Each square represents study-specific ORs and the lines represent the width of the 95% CIs. The size of the square is proportionate with the size of each study. The weighted, summary OR and 95% confidence interval is represented by the black diamond in each figure.

Figure 2. Forest plots depicting the study-specific and summary ORs and 95% CIs representing the association between recreational physical inactivity and risk of invasive epithelial ovarian cancer. Forest plots represent measures of association for **(2a)** invasive low-grade serous tumors; **(2b)** invasive high-grade serous tumors; **(2c)** invasive endometrioid tumors; **(2d)** invasive clear cell tumors; and **(2e)** invasive mucinous tumors. Study specific ORs and 95% CI were estimated using logistic regression models adjusted by age, race, parity, oral contraceptive use, family history of breast or ovarian cancer, and personal history of endometriosis. Summary ORs were calculated via fixed-effects models when no significant heterogeneity was detected between studies (i.e., Q-statistic p-value >0.05) and random-effects models were reported if significant heterogeneity was detected (i.e., Q-statistic p-value <0.05). Each square represents the ORs and the lines represent the width of the 95% CIs. The size of the square is proportionate with the size of each study. The weighted, summary OR and 95% confidence interval is represented by the black diamond in each figure.

Figure 3. Forest plots depicting the study-specific and weighted summary ORs and 95% CIs representing the association between recreational physical inactivity and risk of borderline epithelial ovarian cancer by OCAC study site. Forest plots include measures of association for **(3a)** borderline serous tumors and by **(3b)** borderline mucinous tumors. Study specific ORs and 95% CI were estimated using logistic regression models adjusted by age, race, parity, oral contraceptive use, history of breast or ovarian cancer in first-degree relative and a personal history of endometriosis. Fixed-effects weighted ORs are reported because no significant heterogeneity was detected for either borderline histological type. In the figures above, each square represents the study-specific ORs and the lines represent the width of the 95% CIs. The size of the square is proportionate with the size of each study. The weighted, summary OR and 95% confidence interval is represented by the black diamond in each figure.

Figure 1

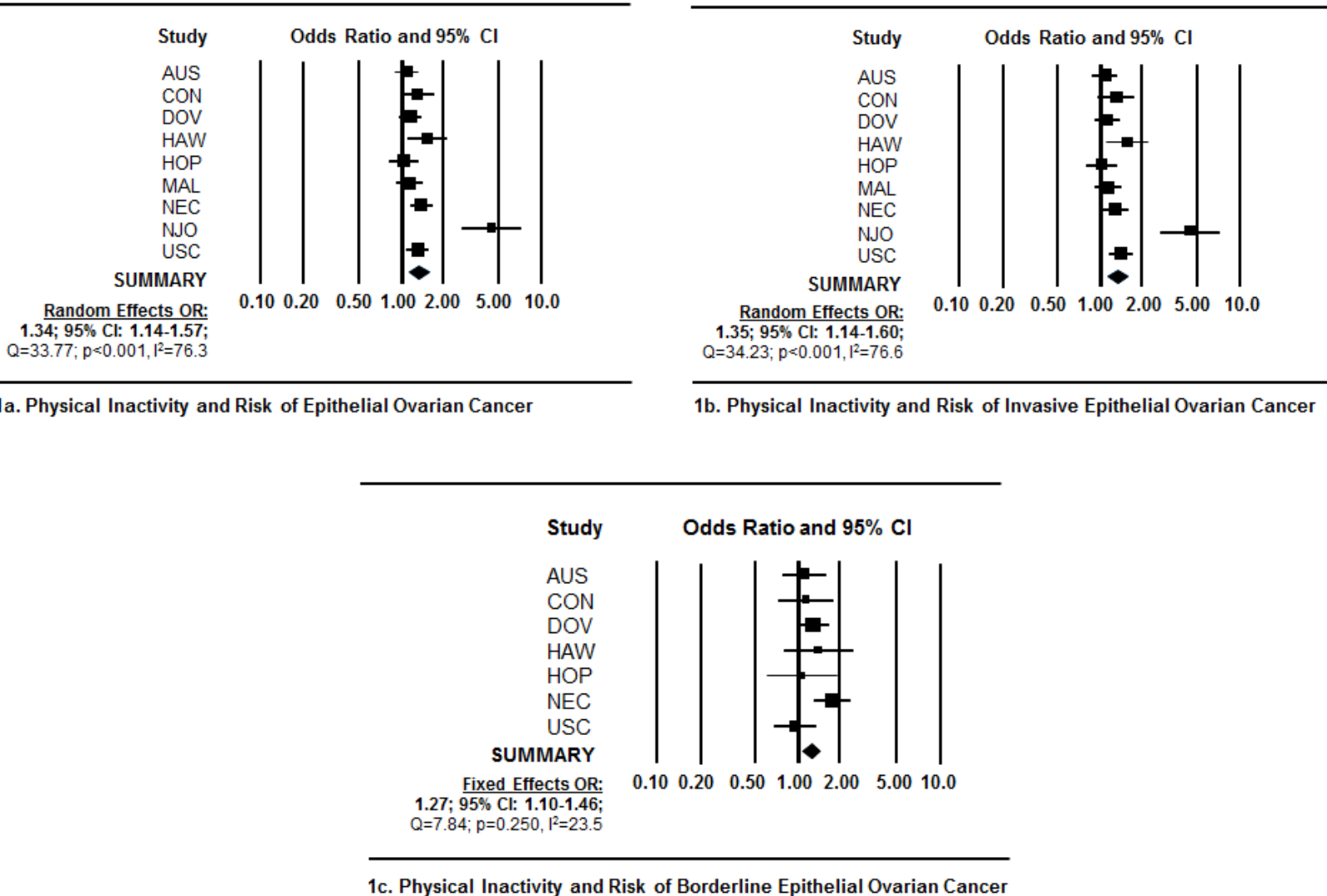
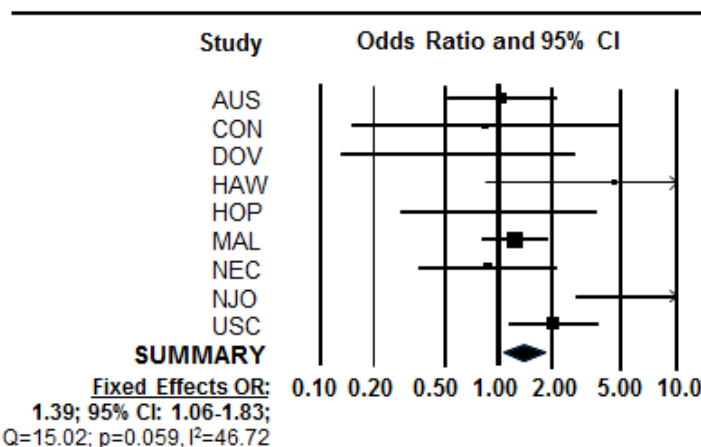
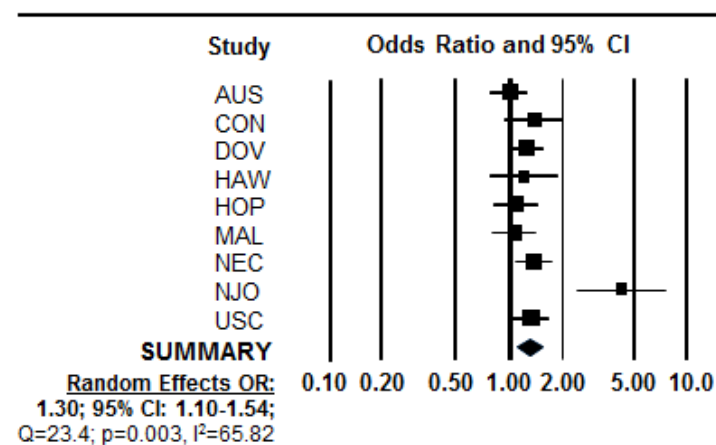


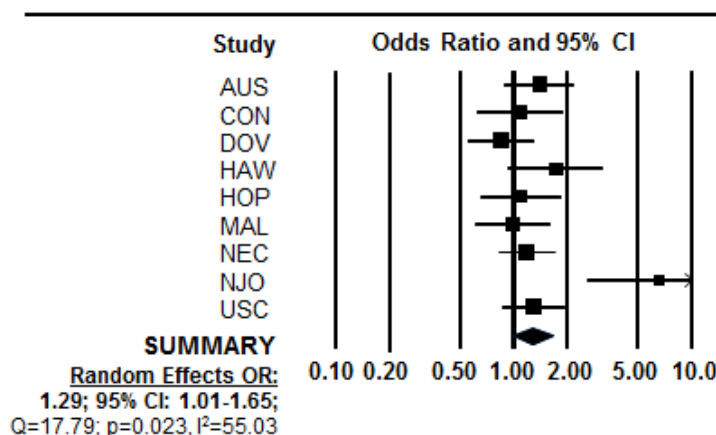
Figure 2



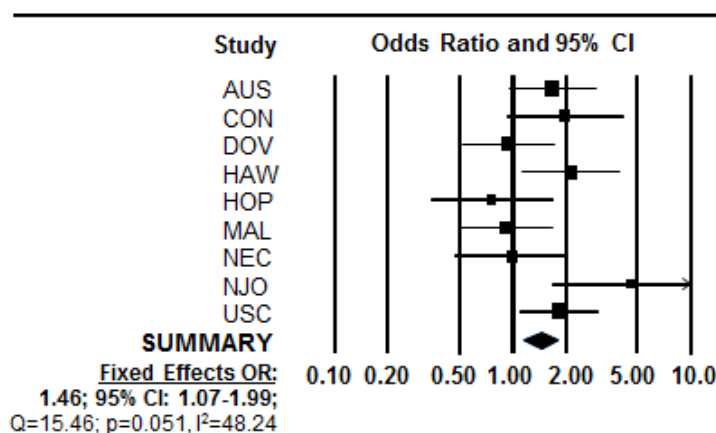
2a. Physical Inactivity and Risk of Invasive Low Grade Serous EOC



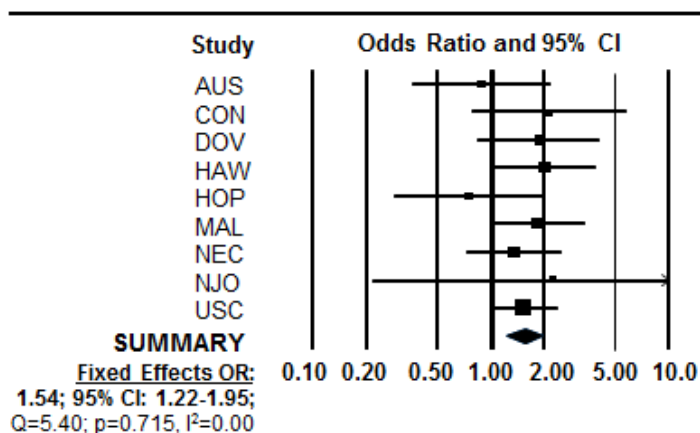
2b. Physical Inactivity and Risk of Invasive High Grade Serous EOC



2c. Physical Inactivity and Risk of Invasive Endometrioid EOC

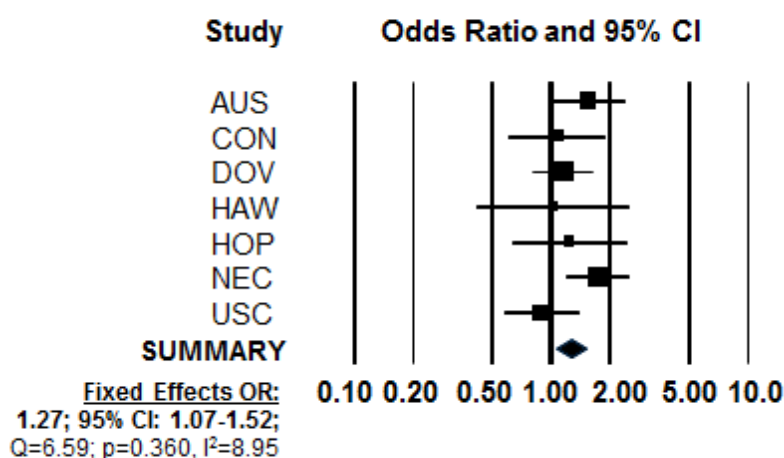


2d. Physical Inactivity and Risk of Invasive Clear Cell EOC

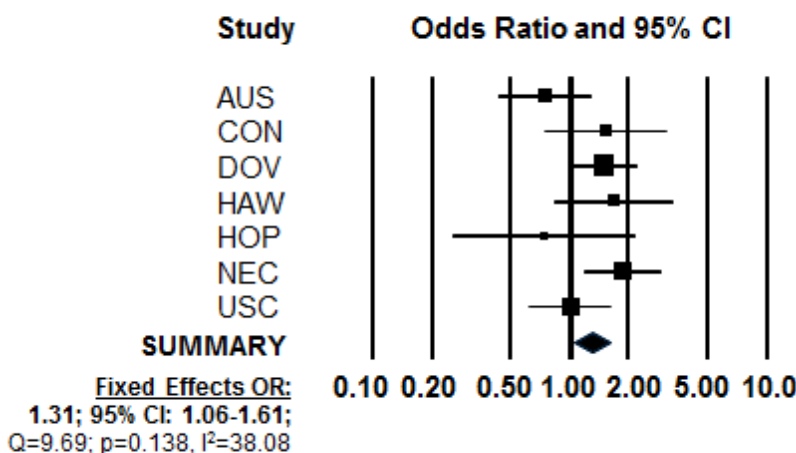


2e. Physical Inactivity and Risk of Invasive Mucinous EOC

Figure 3



3a. Physical Inactivity and Risk of Borderline Serous EOC



3b. Physical Inactivity and Risk of Borderline Mucinous EOC