Published in final edited form as:

Gynecol Oncol. 2015 June ; 137(3): 559–573. doi:10.1016/j.ygyno.2015.03.016.

Epithelial Ovarian Cancer and Recreational Physical Activity: A Review of the Epidemiological Literature and Implications for Exercise Prescription

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Keywords

ovarian cancer risk; ovarian cancer survival; physical activity guidelines; physical activity benefits

Introduction

Invasive epithelial ovarian cancer is the deadliest gynecological cancer in developed nations and the seventh most common and deadly malignancy among women worldwide [1, 2]. In the United States, 1 in 70 women will be diagnosed with ovarian cancer at some point in their lifetime [3] and each year, there will be approximately 22,000 new patients and over 14,200 deaths from the disease [4]. Furthermore, ovarian cancer ranks fifth in cancer deaths among women in the U.S. and it remains the most deadly gynecological cancer, with a five year overall survival rate of only 44% for invasive tumors [4]. However, over 60% of women are diagnosed with Stage III and IV disease, and for these women, 5-year survival is more dismal, ranging between 18-27% [3].

Approximately 85% to 90% of all ovarian cancers are epithelial ovarian carcinomas (EOC), which are further classified by tumor behavior (borderline tumors vs. invasive epithelial tumors) and histological subtype (low grade serous, high grade serous, endometrioid, clear cell, mucinous or undifferentiated) [4, 5]. EOCs are a heterogeneous group of tumors that exhibit a wide variety of clinical manifestations, genetic mutations and tumor morphologies, adding further difficulty to the diagnosis and treatment of this lethal group of ovarian tumors [6].

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CONFLICT OF INTEREST STATEMENT

Dr. Cannioto reports no conflicts of interest.

Dr. Moysich reports no conflicts of interest.

The most well established risk factors for EOC are unmodifiable factors including age, Caucasian race, Ashkenazi Jewish decent, BRCA1/2 mutations and a family history of breast or ovarian cancer [5]. Mounting evidence also suggests the use of post-menopausal hormones [5], talcum powder in the genital area [5], and fertility drugs [4] have each been associated with significant increased risk of EOC. Furthermore, obesity, nulliparity, infertility, and endometriosis have also been associated with increased risk of EOC [4, 5].

Conversely, well established protective factors include the use of oral contraceptives [5], tubal ligation [5], breastfeeding [5], and risk-reducing salpingo oophorectomy for women with inherited BRCA1/2 mutations[5]. Lastly, full-term pregnancy and giving birth prior to age 26 has been associated with a lower risk of EOC in comparison to nulliparous women, and risk has been shown to decrease with each additional birth [4].

While some progress in the identification of risk and protective factors has been made in recent years, the pathogenesis of EOC is not well characterized in regards to modifiable lifestyle behaviors, such as dietary factors or recreational physical activity (RPA) [2]. In fact, according to the World Cancer Research Fund Global Network's Continuous Update Project Report on Food, Nutrition, Physical Activity and the Prevention of Ovarian Cancer (2014), no meaningful conclusions can be gleaned from the current body of scientific literature describing the association between RPA and EOC risk [2]. However, this lack of consensus is not due to a shortage of observational epidemiological research. Indeed, over two dozen epidemiological investigations have examined the associations between EOC risk with RPA and sedentary behavior, but these data have been afflicted by conflicting or statistically insignificant findings.

To this end, the primary purpose of the current review is to summarize the findings from the available epidemiological literature depicting the association between RPA and EOC risk and survival. Second, we present a review of potential barriers to--and benefits of--RPA participation, which are unique to cancer patients and survivors. Third, we summarize the established organizational and governmental RPA guidelines for practitioners to utilize in the context of exercise prescription for cancer patients, including a discussion of special considerations and contraindications to exercise which may be distinctly associated with EOC patients and survivors.

Methods

We performed a comprehensive literature search via PubMed to identify epidemiologic investigations depicting the association between RPA and EOC. Key word searches were conducted utilizing the following terms and phrases: "physical activity," exercise," "recreational activity," or "recreation" with "ovarian cancer," "ovarian carcinoma," "ovary," or "gynecological cancer."

To be included in the current review, studies had to assess recreational or leisure-time exercise or physical activity independently of occupational activity or household activities associated with daily living. For the purpose of this review, the term "recreational physical activity" encompasses all physical activity performed during a person's leisure time,

including all types of sport and exercise. Additionally, the epidemiological studies reviewed herein had to report original measures of association resulting from multivariate regression models. Thus, studies reporting unadjusted odds ratios, overlapping data, and/or risk estimates based only upon occupational or household physical activity were excluded from the current review. Among studies reporting overlapping data, the study with fewer cases was omitted. Based on these criteria, 26 studies assessing the association between RPA and EOC risk or survival were identified (Figure 1).

Results

Among the 26 epidemiological studies identified for inclusion, 23 assessed the association between RPA and EOC risk, 2 papers assessed the association between RPA and EOC survival, and one paper assessed both risk and survival. For the studies examining EOC risk, we will summarize key findings pertaining to three exposure measures of RPA including 'total' RPA (i.e., a combination of all intensities of physical activity), moderate-intensity RPA, and vigorous-intensity RPA. In most studies, total RPA is represented by the total number of hours or MET hours of activity performed each week.

Recreational Physical Activity and Epithelial Ovarian Cancer Risk

Collectively, 24 studies (11 case-control studies and 13 cohort studies) assessing the association between EOC risk and RPA were included in the current review. Tables 1 and 2 summarize the characteristics and key findings of each of the 11 case-control studies and 13 cohort studies, respectively.

Total RPA and EOC Risk—A total of 22 studies (11 case control studies and 11 cohort studies) provided risk estimates based on a measure of 'total' RPA. Among the findings reported in the 11 case control studies, all OR's were under 1.0., suggesting an inverse association between RPA and EOC risk. However, only 5 studies yielded statistically significant inverse associations between measures of total RPA and EOC risk, demonstrating a decreased risk of EOC between 10-51% among those woman engaging in the highest number of hours of RPA per week [7-11], with one additional study yielding borderline significance (OR=0.69; 95%CI: 0.47-1.01) [12] (Figure 2a).

Eleven of 13 cohort studies included in this review provided estimates of the association between total RPA and EOC risk (Figure 2b). Among these, all but two risk estimates were statistically insignificant. Specifically, Schnohr et al. reported a significant inverse association between RPA and EOC risk (OR=0.33, 95% CI: 0.16-0.67) [13] and Chionh et al. reported a significant positive association between RPA and EOC risk (OR=2.21, 95% CI: 1.16-4.24) [14]. The remaining 9 studies yielding statistically insignificant associations were collectively equivocal, with 5 studies reporting RRs below 1.0 [15-19] and 4 reporting RRs above 1.0 [20-23] (Figure 2b).

Moderate-intensity RPA and EOC Risk—Six case-control studies [8, 9, 11, 12, 24, 25] provided measures of association based upon moderate-intensity RPA. Each of the six studies reported OR's below 1.0, yet only two studies demonstrated statistically significant associations suggesting between 33-58% decreased risk of EOC among women performing

the most weekly moderate-intensity RPA [9, 11] (Figure 3a). Interestingly, among the seven cohort studies providing risk estimates based upon moderate-intensity RPA, the majority reported OR's below 1.0, but none were statistically significant [15, 16, 19, 22, 26] (Figure 3b). However, it is noteworthy that Biesma et al. reported a borderline significant RR suggesting a 35% decreased risk among women performing the most moderate-intensity RPA per week (OR=0.65, 95% CI: 0.41-1.01)[16].

Vigorous-intensity RPA and EOC Risk—Seven case control studies provided risk estimates based upon participation in vigorous-intensity RPA. Five of seven reported risk reductions ranging between 7% and 67% for women who engaged in vigorous RPA [8, 9, 11, 25, 27]. However, only two of five studies yielded significant inverse associations, demonstrating a reduced risk of EOC between 40-67% among the women reporting the greatest amount of vigorous RPA [11, 25] (Figure 4a). Conversely, among the seven prospective studies examining the association between vigorous RPA and EOC risk, six yielded RR's greater than 1.0, but only Anderson et al. observed a statistically significant association [20]. The remaining cohort study observed an inverse association between RPA and EOC, but these data were not significant [17] (Figure 4b).

Collectively, data from all case-control studies yielding significant inverse associations between RPA and EOC have demonstrated EOC risk reductions of at least 20% among women who are regularly active, in comparison to those who are either inactive or less active, but most studies suggest reductions greater than 30%, depending on the subgroups analyzed [8-12, 25]. Case-control studies reporting associations based upon total and/or moderate-intensity RPA have provided the most consistent evidence regarding a potential inverse association between RPA and EOC risk. Data from cohort studies are much less clear and have been a consistent source of debate in the growing body of literature. In fact, the findings of many prospective studies suggest there is no association, or a positive association, between RPA and EOC risk.

It has been suggested by previous investigators that some of the direct associations observed in the RPA and EOC literature could be due to detection bias among women who were very physically active [20, 26]. For example, women who are very active would also be more likely to engage in overall healthier lifestyle and could be more likely to recognize early symptoms and seek medical treatment and receive subsequent diagnosis [20]. In order to test the hypothesis that more active women were more symptomatic, Leitzmann et al. conducted exploratory analyses to examine the potential for detection bias in their study, which did observe a positive association between vigorous RPA and EOC risk [26]. Indeed, they found some evidence of a non-causal positive association between RPA and EOC, suggesting that detection bias should be considered when direct associations between RPA and EOC are observed [26].

RPA and Ovarian Cancer Risk by Histological Subtype—Seven studies in the current literature attempted to examine differences in the association between RPA and EOC risk by histological subtype [9, 10, 15, 19, 24-26]. Among these, two cohort studies reported increased risk (ranging between 11% and 50%) of serous EOC with increasing intensities and durations of activity [15] [26]. In contrast, five studies observed decreased risk (ranging

between 17% and 42%) of serous tumors with increasing levels of RPA [9, 10, 19, 24, 25]. Additionally, one case-control study observed decreased risk (ranging between 31% and 36%) for all subtypes of EOC with increasing hours of RPA per week [10], while another case-control study observed increased risk (ranging between 17% and 77%) for mucinous tumors with increasing levels of vigorous RPA [9]. Lastly, one case-control study reported greater than twofold increased risk of endometrioid and clear cell tumors (as a combined category) with increasing levels of RPA [25]. In summary, while seven groups of investigators have attempted to elucidate subtype specific associations between RPA and EOC risk, the findings reported thus far have been contradictory or not statistically significant, with no clear trends in the literature.

Among the research summarized above, one study also collected extensive clinical and follow-up data, which allowed for an investigation of the association between pre-diagnostic RPA and ovarian cancer survival [28]. Two additional papers examining the association between RPA and EOC survival were also identified in the literature [29, 30]. The findings of these three survival studies are presented in the next section of this review and are summarized in Table 3.

Recreational Physical Activity and Ovarian Cancer Survival

In contrast to the body of literature focused on the association between RPA and EOC risk, only three previously published reports have investigated the role of RPA in EOC survivorship and there are no data from randomized control trials. In the first published report involving 635 EOC patients in Sweden, investigators examined the role of RPA during childhood, young adulthood and during the recent years prior to diagnosis [29]. When examining all EOC cases together, there was no evidence of reduced risk of survival in any of the RPA categories measured. However, the authors observed a reduced risk of death (HR=0.46; 95% CI: 0.22-0.98) among Stage I & II EOC patients who engaged in RPA more than 2 hours per week during young adulthood [29]. In a more recent report of 638 EOC patients, investigators observed no association between RPA before diagnosis and overall EOC survival, but survival was 31% better (HR=0.69; 95% CI: 0.47-1.00) for non-obese women who reported greater than 2 hours of activity per week, in comparison to those reporting less than 1 hour per week [28]. Most recently, the findings of the only prospective study examining the association between RPA and EOC survival, suggest that women who engaged in the highest category of MET hours per week (i.e., vigorous-intensity RPA) prior to an EOC diagnosis, compared with those performing moderate-intensity and/or no RPA, had a 26% lower risk of EOC specific mortality (HR=0.74; 95% CI: 0.56-0.98) [30]. Furthermore, women in the moderate intensity MET category experienced a 32% decreased risk of dying from EOC, (HR=0.68; 95% CI: 0.45-1.03), but these data were not statistically significant [30].

One important limitation of the survival literature is that each of the studies utilized self-reported RPA data collected at (or soon after) the time of EOC diagnosis, without continuing to track RPA after diagnosis. In short, while survival data are limited, there appears to be some evidence supporting an association between RPA and improved survival. However, evidence from survival studies (Table 3) are too scarce to draw meaningful conclusions and

additional studies, including follow up with regards to physical activity behavior, are necessary to further elucidate the association between RPA and EOC survival.

Limitations in the Current Epidemiological Literature

There are several salient limitations in the current literature which could explain the lack of consensus regarding the association between RPA and EOC risk and survival. Most importantly, there is a lack of a comprehensive standardized epidemiological tool which collects data regarding the most important parameters of RPA, including frequency, intensity and duration of activity. Because each of these parameters are separate constructs and independently manipulated and measured in the exercise science literature, it would be most useful if self-report RPA questionnaires attempted to measure these parameters as separate variables. In the current literature, data are often derived from questionnaires that combine two or more parameters within one question, or make assumptions about one parameter based on another. For example, the common approach of assigning MET values to individual participants, based solely on the self-reported mode of exercise, increases the likelihood of misclassification of exercise intensities.

Furthermore, a majority of studies do not include data regarding the frequency of RPA (i.e., the number of sessions per week) and duration (i.e., time spent per session). As a result, it is impossible to determine whether research participants are meeting the recommended Physical Activity Guidelines for Americans (PAGA) [31]. Similarly, the omission of these parameters prohibits researchers from assessing whether meaningful dose-response relationships between RPA and EOC (or other types of cancer) exist based on the activity categories outlined in the PAGA [31] (Table 4). For example, given the common practice of utilizing arbitrary cut-off ranges to categorize RPA levels within individual studies, we are unable to derive meaningful conclusions about the RPA literature based upon the activity categories associated with public health recommendations in the PAGA (i.e., Inactive, Low, Medium, and High levels of activity). Lastly, more precise data including information about frequency, intensity and duration of activity would assist researchers in the identification of an upper limit of activity, above which there are no additional health benefits or possible negative effects.

A third critical limitation in the current literature relates to the inconsistencies in which RPA is modeled in relationship to EOC risk and survival. In fact, few researchers have identified the appropriate group (i.e., a “no recreational activity” group) as the reference group in regression models. Rather, the majority of studies reviewed herein utilized referent groups which combined women who were active with those who were not active--and cut-offs were mostly arbitrary (i.e., tertiles). For example, in some studies, the referent group included women who were meeting or exceeding the 150-minute weekly recommendation provided in the PAGA (Table 5).

Combining women who are moderately active with those who are completely inactive is problematic for two important reasons. Most importantly, we know that “some activity” offers health benefits and is always better than “no activity” [31-33]. As a result, it would be more informative if epidemiological questionnaires were designed to disentangle participants who engaged in no leisure activity from those who engaged in low, medium or

high levels of leisure activity (Table 4) [31]. Furthermore, inasmuch as study participants generally include a relatively homogenous group of women with low variability in self-reported RPA data, it is inherently difficult to detect significant associations even with the use of appropriately assigned reference groups. Thus, by including women who report no activity in the same categorical variable as those who report some activity, researchers are inhibiting their ability to detect true relationships and make meaningful comparisons between those who are completely sedentary vs. those who engage in some amount of regular recreational physical activity.

Fourth, it is also probable that a lack of statistically significant associations between EOC outcomes with RPA are simply a reflection of reduced statistical power within many individual EOC studies. For example, the fact that associations between RPA and colon and breast cancer are consistently apparent in the literature could be due to higher incidence and survival rates in these groups, resulting in the availability of more study participants and greater statistical power to detect associations. The plausibility of a potential power problem inherent within EOC studies was initially demonstrated in a 2007 systematic review and meta-analysis of the association between RPA and EOC risk [24]. Specifically, the meta-analysis yielded a statistically significant summary estimate of 0.81 (95% CI: 0.72-0.92) for the association between PA and EOC risk, despite the fact that only three of 12 studies included in the analysis reported significant inverse associations between epithelial EOC risk and RPA [24]. More recently, two additional meta-analyses have demonstrated further support for a statistically significant inverse association between RPA and EOC risk based upon case-control data, but not among cohort studies [34, 35]. Specifically, in a meta-analysis of 3 case-control studies depicting RPA data in MET equivalents, $RR=0.76$ (95% CI: 0.64-0.90, $p=0.002$) reported a summary estimate of $RR = 0.76$ (95% CI: 0.64-0.90, $p=0.002$) among those performing moderate RPA [35] and $OR=0.87$ (95% CI: 0.80-0.95) reported a summary estimate of ($OR=0.87$; 95 % CI = 0.80-0.95) among case control studies [34]. Taken collectively, these meta-analyses have yielded summary estimates suggesting a 10-25% reduction in EOC risk among women who report regularly engaging in RPA.

Fifth, it is also plausible that some of the null findings in the RPA and EOC risk literature could be explained by the commonly reported practice of adjustment for BMI as a confounding variable in many of the regression models [7, 8, 11, 16, 18, 19, 21, 23, 26, 30], as opposed to treating BMI as a potential mediating variable. Given that decreased body fat and the associated alterations in cytokines and adipokines are thought to be primary mechanisms in which RPA provides protection from cancer [36], it follows that it would be inappropriate to adjust for BMI when investigating the association between RPA and cancer risk. In effect, intermediate variables, if controlled in an analysis would typically bias estimates toward the null [37].

Finally, it is widely recognized that EOC is a group of heterogeneous diseases with varying molecular pathways, etiological, risk and protective factors. In fact, not only do the major histological subtypes of EOC have varying molecular footprints, it is now well established that within each histological subtype, borderline tumors, low-grade tumors and high-grade invasive tumors also possess varying molecular footprints [6, 38], and thus may also be associated with differing patterns of risk and protective factors. For example, recent pooled

analyses of individual-level data from population-based case control studies in the Ovarian Cancer Association Consortium (OCAC) identified subtype-specific statistically significant associations with modifiable risk factors such as smoking [39], BMI [40] and aspirin use [41] even though existing evidence from individual studies in the literature were inadequate to make such determinations. Therefore, it is probable that some histological subtypes of EOC are more strongly associated with RPA than others, in which case, any such association would be more difficult to detect in smaller studies and/or impossible to detect in non-stratified analyses. Thus, the ability to perform stratified analyses by histological subtype in future epidemiological research will be critical for the further elucidation of the association between RPA and the subtypes of EOC. In fact, we are in the process of analyzing OCAC data to conduct a detailed and comprehensive study of the role of RPA in EOC etiology and prognosis and will be able to address many of the current limitations.

Biological Mechanisms Mediating the Association between Recreational Physical Activity and Ovarian Cancer

The most probable mechanisms linking RPA with cancer risk and survival include decreased body fat, altered reproductive hormone levels, altered cytokine and growth factor milieu, and changes in immune function (including reduced inflammation and enhanced anti-tumor immunity) [42]. Relative to obesity, previous pooled analyses have demonstrated a significant direct association between BMI and EOC risk [40]. Further, substantial scientific evidence supports an inverse association between BMI and RPA [43], suggesting that RPA could be an important etiological factor in the development of obesity-related cancer. Additionally, RPA-induced weight loss would also modify cytokine concentrations, resulting in decreased leptin concentrations and increased adiponectin concentrations [36]. Both leptin and adiponectin have been widely investigated in laboratory and epidemiological settings in regards to their role in cancer cell signaling and cancer risk/survival. Leptin is a pro-inflammatory adipokine directly associated with body fat and plays a key role in the signaling pathways associated with several hallmarks of cancer including cell proliferation, evasion of apoptosis, angiogenesis and vascular stimulation [44]. Conversely, adiponectin is an anti-inflammatory adipokine which is inversely associated with body fat and cancer development and is most strongly known for its role in apoptotic signaling and insulin sensitivity [44]. In one recent study of women with EOC, investigators observed that women with the lowest leptin-to-adiponectin ratios achieved statistically significant longer disease-specific survival (57 months) compared to those with median or high leptin-to-adiponectin ratios (49 and 37 months, respectively; $p=0.02$) [45].

Moderate-intensity RPA may also decrease cancer risk by blunting chronic inflammation and enhancing immune surveillance [36, 42]. Both human and animal studies have demonstrated inverse associations between regular RPA and inflammatory markers such as TNF-alpha, CRP and IL-6 [42]. Furthermore, the body of exercise immunology literature demonstrates that regular exercise alters both the number and function of the cells of the innate immune system including neutrophils, monocytes, macrophages, natural killer cells and dendritic cells [42]. However, there is also some limited laboratory and epidemiological evidence supporting an inverted U-shaped relationship between RPA and immune function, with moderate activity providing health benefits (including cancer prevention), while

sedentary lifestyles and excessive exercise are associated with DNA damage, inflammation and negative health consequences [42]. In fact, research has established that vigorous exercise bouts do result in acute immune suppression among B and T lymphocytes [42]. However, in the only study characterizing immunosuppressive regulatory T (Tregs) cells in healthy women, we observed a statistically significant inverse association between RPA and Treg cell counts, indicating that more regularly active women had lower counts of immunosuppressive Treg cells in comparison to their less active counterparts [46].

There are also competing endocrine-related hypotheses that could support the plausibility of an indirect or direct association between EOC risk and RPA. Previous investigators have hypothesized that RPA may decrease risk of EOC via decreased levels of circulating estrogen. However, the pituitary gonadotropin hypothesis asserts that the low levels of circulating estrogen caused from increased levels of RPA will stimulate production of gonadotropins (i.e., follicle stimulating hormone and luteinizing hormone) via negative feedback. It follows that increased levels of FSH and LH stimulate estrogen and estrogen pre-cursors, which in turn, stimulates the ovarian epithelium entrapped in cysts, leading to excessive proliferation and potential malignant transformation [14]. Conversely, the androgen/progesterone hypothesis contends that androgens increase risk of EOC, while progesterone decreases risk of EOC [14].

Accordingly, moderate-intensity RPA has been associated with decreased progesterone levels in some literature, while vigorous-intensity RPA has been associated with increases in testosterone and other androgens [14]. However, a recent cross-sectional analysis of the association between RPA and sex hormones in pre-menopausal and post-menopausal women within the EPIC cohort yielded data inconsistent with the above hypotheses. Specifically, among pre-menopausal women, the active women had significantly lower testosterone levels (20%), but no differences in estrogen or progesterone were observed [47]. In post-menopausal women, active women had 20% significantly lower estradiol concentrations than inactive women, while no differences were observed for the other hormones [47]. Additional comprehensive reviews have suggested that the relationship between exercise and estrogen and androgen levels are not clear and may be affected by factors such as age, gender, body composition, fitness level and/or frequency, intensity and duration of exercise [48]. However, most studies seem to suggest that exercise decreases the availability of biologically active estrogens and androgens [48].

Benefits of Recreational Physical Activity for Ovarian Cancer Patients

The accumulation of scientific evidence over the past several decades has established that engaging in regular RPA results in positive effects in all systems of the body including the musculoskeletal, cardiovascular, respiratory, and endocrine systems. RPA has also been shown to improve cancer treatment-related effects such as fatigue, neuropathy, depression, anxiety, sleep quality, and overall quality of life [49-51]. Although evidence is limited, some data describing the benefits of RPA among EOC patients and survivors does exist. For example, in a cross-sectional study of EOC survivors in Canada, researchers demonstrated that survivors who were meeting the RPA guidelines reported significantly lower fatigue in comparison to survivors who were not meeting the RPA guidelines [51]. Additionally, RPA

was significantly associated with several markers of quality of life. Specifically, RPA was inversely and significantly associated with peripheral neuropathy, depression, anxiety, sleep dysfunction and daytime dysfunction, while it was positively associated with happiness, sleep quality, and sleep efficiency [51]. Given that quality of life is an important prognostic factor and has been observed to be compromised in EOC patients [52-54], it follows that participation in RPA among this population of women could be an important mediator of clinical outcomes.

Furthermore, while no data from randomized exercise trials utilizing EOC patients and survivors is currently available in the scientific literature, the results of two small non-randomized pilot studies have recently been reported [55, 56]. In an Australian-based individualized walking intervention for 17 EOC patients undergoing chemotherapy, clinically important improvements in physical functioning and quality of life were observed [56]. Participants also noted improvements in physical symptoms including lack of appetite, pain, feeling drowsy, constipation, dry mouth, nausea and weight loss [56]. Additionally, there were no major adverse events, all participants noted the helpfulness of the program, and participants adhered to 80% of their intervention sessions [56]. Similarly, in a pilot study investigating the feasibility and benefits of a 24-week home-based exercise intervention for EOC patients undergoing current treatment (n=7) or survivors completing treatment within 2 years (n=12), significant improvements in cardiorespiratory fitness were observed in both groups of women [55]. Collectively, the findings observed in both pilot studies provide some initial evidence regarding the safety, feasibility, and benefits of moderate exercise interventions in women undergoing treatment for EOC [55, 56].

Determinants of Recreational Physical Activity in Cancer Patients and Survivors

While the determinants of RPA are well documented for apparently healthy populations, patients receiving cancer treatment will likely experience negative side effects that limit their ability to exercise during or after treatment. In fact, a plethora of persistent negative side effects, across multiple systems of the body, have been well documented for the most commonly used curative cancer therapies [33]. These include deleterious side effects such as fatigue, pain, cardiovascular and pulmonary changes, neuropathy, cognitive impairment, endocrine changes (i.e., early menopause), changes in body composition (lean mass loss), changes in bone density, damage to musculoskeletal tissue, impaired immune function (including anemia and lymphedema), gastrointestinal damage, and changes in skin [33].

Not only is overall physical function diminished during treatment, but evidence suggests treatment-related impairments are long term. For example, in one epidemiological study of survivors who were 5 years post-treatment, more than half reported physical limitations including standing, lifting 10 pounds, and walking a quarter of a mile [57]. Furthermore, the presence of comorbidities and specific disease-related symptoms may also compound these commonly experienced side effects of cancer treatment [57].

Given the added challenges facing cancer patients and survivors, it is not surprising that adherence to regular RPA is lower among EOC survivors in comparison to the general population. While approximately 50% of adult women in the United States report meeting the PGA recommendation of 150 minutes of activity per week [58] existing evidence

suggests that only 31% of EOC survivors met the Guidelines [59]. In the same study of survivors, researchers also identified several key factors that were most strongly associated with meeting activity guidelines including younger age, higher education and income, employment, lower BMI, absence of arthritis, longer time since diagnosis, earlier disease stage, being disease-free and having the intention to exercise [59].

Despite the unique set of barriers to RPA that may be perceived and experienced by cancer patients and survivors, RPA and structured exercise programs are safe and efficacious, both during and after cancer treatment. As a result, clinicians and fitness professionals should proactively encourage cancer patients and survivors to be physically active.

American College of Sports Medicine Exercise Guidelines and Special Considerations for Cancer Patients and Survivors

In the framework of the 2008 Physical Activity Guidelines for Americans [31] and additional organizational publications outlining RPA guidelines for American adults, the American College of Sports Medicine (ACSM) recently convened a roundtable of experts to review and disseminate the scientific literature regarding the safety and efficacy of exercise training during and after cancer treatment [33]. Each of these important publications are highlighted and summarized in Table 5. Not only did the roundtable conclude that exercise is safe during and after cancer treatment, the report concluded that RPA leads to improvements in physical functioning, decreases in cancer-related fatigue and increases in quality of life among cancer survivors [33]. In fact, the ACSM roundtable resulted in a position statement recommending that all cancer patients and survivors follow the 2008 Physical Activity Guidelines for Americans while incorporating necessary adaptations based on the individual's disease status and capabilities [33].

The Roundtable also emphasized that, regardless of the cancer diagnosis, the goals of an exercise program among cancer patients and survivors should focus on improving physical fitness (including aerobic capacity, muscular strength, muscular endurance, and flexibility); improving body image and body composition; enhancing overall quality of life; improving cardiorespiratory, endocrine, neurological, cognitive, psychosocial and muscular outcomes; delaying or preventing cancer recurrence; decreasing and/or preventing long-term deleterious effects of cancer treatment; and improving the ability to psychologically and physically withstand the ongoing anxiety regarding the possibility of cancer recurrence and future treatments [33].

To ensure the safety and efficacy of an exercise program, all cancer patients and survivors should receive medical evaluation for treatment-related conditions, such as peripheral neuropathies or musculoskeletal morbidities prior to beginning an exercise program [33]. Patients with cardiac conditions or potential bone metastases should also undergo pre-exercise medical screening to ensure the safety of the proposed exercise program [33]. Accordingly, it is imperative that clinicians, fitness professionals and other practitioners are familiar with the potential exercise contraindications that are unique to cancer patients and survivors. Specifically, some common contraindications include extreme fatigue, anemia, ataxia, or inadequate time and healing after surgery [33]. Table 6 provides a summary of

commonly experienced side effects by EOC patients and survivors, along with related contraindications and special considerations for exercise prescription for this population.

For a more detailed description of all cancer-related contraindications to exercise and special considerations for exercise prescription for cancer patients and survivors, the reader is referred to the ACSM Guidelines for Exercise Testing and Prescription, Ninth Edition [60] and the ACSM Roundtable on Exercise Guidelines for Cancer Survivors [33].

Conclusions and Implications

In summary, evidence of a protective effect of moderate and vigorous RPA relative to EOC risk is more consistent among case-control studies, with the majority of studies yielding significant risk reductions between 30-60%. Among cohort studies, for those providing estimates based upon a total measure of RPA, data remain equivocal with no clear trends. Specifically, half yielded no association, while the remaining studies provided mixed evidence, with an equal number suggestive of both inverse and positive associations. Given that only three studies assessing the association between RPA and EOC survival have been published to date, data are too scant to draw conclusions and further research is necessitated.

A careful review of the existing literature assessing the association between RPA and EOC risk yielded the discovery of several important limitations regarding the manner in which RPA was measured and modeled, which could explain why many of the cohort studies resulted in null findings. Additionally, many individual studies of EOC are plagued by low EOC case numbers, which may preclude the ability to observe statistically significant associations among various subgroups of women. The reasons for the positive associations observed in cohort studies remains unclear and have been a consistent source of debate in the literature. While competing biological theories described above provide potential plausibility for increased risk of illness among women who are excessive exercisers, it is more likely that the positive associations observed in the EOC are due to non-causal factors [20, 26].

Nevertheless, given the limitations in the current body of research, it is imperative that researchers and practitioners do not rely on the inconclusive evidence suggesting a positive association between RPA and EOC to dissuade women from participating in moderate or vigorous intensity EOC. Rather, emphasis should be placed on the greater body of scientific literature, which has demonstrated that leading a physically active lifestyle results in a plethora of well-established health benefits that can be achieved in all populations, including those with chronic conditions such as cancer [31, 33].

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HIGHLIGHTS

- Retrospective studies have suggested a moderate decreased risk of epithelial ovarian cancer among active women, while prospective studies remain inconclusive.
- Data depicting the association between epithelial ovarian cancer survival and recreational physical activity are too limited to draw meaningful conclusions.
- Epithelial ovarian cancer patients/survivors can achieve benefits and alleviate side effects of treatment by following the 2008 Physical Activity Guidelines.

Figure 1.

Flowchart of criteria for inclusion in the review of epidemiological literature assessing the association between recreational physical activity and ovarian cancer risk and survival.

¹Measures of Total RPA include measures of all intensities of RPA combined (i.e., both moderate and vigorous intensity activities). Most studies reported total RPA in terms of hours per week or MET hours per week. Olsen et al. and Coltreau et al. used a RPA index (high vs. low). All measures of association presented above represent comparisons between the highest activity groups vs. the referent groups. However, the referent groups often contained active women.

²Yang et al. and Leitzmann et al. did not provide a measure of total RPA

Figure 2.
Epithelial Ovarian Cancer Risk and Total Recreational Physical Activity

Figure 3.
Epithelial Ovarian Cancer Risk and Moderate Intensity Recreational Physical Activity

Figure 4.
Epithelial Ovarian Cancer Risk and Vigorous-Intensity Recreational Physical Activity

A Summary of Case Control Investigations Assessing the Association between Recreational Physical Activity and Ovarian Cancer Risk

Table 1

Reference Author/Date	Participants	RPA ¹ Exposure Assessment	Parameters of RPA ²				Reference Category	Adjustment & Stratification Variables	Key Findings
			F	I	T	Y			
Lee et al., 2013 [8]	Southern China: 500 EOC patients and 500 controls	Total physical activity; strenuous sports; moderate activity; sitting		X	X		No activity	Age, parity, OC ³ use, BMI ⁴ , menopausal status, education, smoking, family history of ovarian and breast cancer.	Significant inverse association was observed for total RPA (OR= 0.49; 95% CI:0.35-0.68) for women engaged in 23 or more MET ⁵ hours/wk vs. <12 MET-hours/wk. Significant inverse dose-response relationship for hours/week of strenuous sport (OR=0.58; 95% CI: 0.38-0.88) for <6 hrs and OR=0.40 for >6 hours (p for trend=0.01).
Moorman et al., 2011 [28]	North Carolina: 638 EOC patients and 683 controls	Average time of aerobic activity per week at 3 different points: age 20, previous 10 years, 1 year prior to ref date			X		Included women who performed up to 59 minutes of aerobic exercise per week	Age, race, BMI, menopause, smoking status, OC use, months of pregnancy, family history of EOC. Tested models with and without BMI adjustment.	Reduced risks of EOC observed in some categories of PA. For women engaging in 1-2 hrs per week 1 year before interview/diagnosis, (OR= .74, 95% CI: 0.55-0.99); among those doing 1-2 hrs per week 10 yrs prior, (OR=0.71; 95% CI: 0.53-0.96).
Rossing et al., 2010 [25]	Washington State: 812 EOC patients and 1,313 controls	Regular participation in RPA from age 25 to the reference date. Regular defined as 1 hour/wk or 4 hours/month for 4 months/year.	X	X	X	X	Women who did not meet criteria for regular RPA	Age, year of diagnosis, residence, births, OC use, education, BMI 5 years prior to reference date. Stratified by age, histology, time of RPA participation, and intensity.	For invasive tumors, the highest category for average hours of total activity and total hours of moderate intensity activity vs. inactive group (OR=0.90, 95% CI: 0.70-1.2); For vigorous activity, the highest average hrs/wk yielded significantly reduced risk (OR=0.60; 95% CI 0.4-0.9).
Carnide et al., 2009 [12]	Ontario: 240 EOC patients and 891 controls	Frequency of moderate and strenuous RPA at 4 time periods	X	X			RPA <1/month	Age. Stratified by age, frequency and intensity of activity.	For activity 2 years ago, participation in both strenuous & moderate activity combined (OR = 0.69, 95% CI=0.47-1.01) & moderate activity alone (OR = 0.55, 95% CI=0.34-0.88) up to 2/week was associated with reduced EOC risk.
Olsen et al., 2007 [24]	Australia: 1580 EOC patients and 1,509 controls	Frequency of moderate and strenuous RPA; RPA index	X	X			RPA <1/month, low RPA group	Age, education, parity, OC use. Stratified by PA	Weak inverse associations between total PA Index and moderate RPA; null association

Reference Author/Date	Participants	RPA ¹ Exposure Assessment	Parameters of RPA ²				Reference Category	Adjustment & Stratification Variables	Key Findings
			F	I	T	Y			
Pan et al., 2005 [9]	Canada: 442 EOC patients and 2,135 controls	Total, moderate & vigorous RPA; PA index; MET values assigned	X	X			Included women who performed some activity	Age, residence, education, alcohol, smoking, BMI, diet, parity, menopause. Stratified by menopause status, histology and BMI.	Compared to women in the lowest tertiles of moderate and total RPA (moderate+vigorous), those in the highest tertiles had significant decreased risk of EOC: (OR=0.67, 95% CI: 0.50, 0.88) and (OR=0.73, 95% CI: 0.58, 0.98), respectively.
Riman et al., 2004 [10]	Sweden: 655 EOC patients and 3899 controls	Total time spent in RPA per week at baseline; ages of 18-30 years and in childhood.			X		No activity (i.e., "never")	Age, parity, age at menopause, OC use, HRT ⁶ use. Stratified by BMI and histology.	Significantly reduced risks were observed among women in the highest PA groups both at age 18-30 years (OR = 0.67, 95% CI: 0.52-0.87) and during the last years preceding study enrollment (OR = 0.68, 95% CI: 0.53-0.87).
Zhang et al., 2003 [11]	China: 254 EOC patients and 652 controls	Total PA (weekly MET hrs); Strenuous sports; moderate activity; frequency of activity-induced sweating	X	X	X		Lowest activity amount or frequency	Age, BMI, familial factors, hormonal status, and total energy intake. Stratified by menopause status.	Significant inverse association between total PA & EOC risk (OR=0.54, 95% CI: 0.34-0.87) for high vs. low levels; the same trends were observed for strenuous sports, frequency of activity-induced sweating and moderate activity: (OR=0.33, 95% CI: 0.14-0.75); (OR=0.56, 95% CI: 0.37-0.84); and (OR=0.42, 95% CI: 0.22-0.81), respectively.
Bertone et al., 2002 [27]	US Massachusetts & Wisconsin: 327 EOC patients and 3129 controls	Total hrs/wk of RPA & vigorous RPA at reference age; MET hours/wk during 3 time periods		X	X		Zero hours of activity	Age, state, parity, use of lutein & zeaxanthin, # of pelvic exams in 5 years prior, family history of EOC. Stratified by type of PA & stage of life.	No significant associations were observed between any measure of RPA and EOC risk. For women reporting greater than 7 hrs/week vs. no vigorous activity, RR=0.85, 95% CI: 0.39-1.86. When MET hours of activity were estimated, only women in the highest category had any reduction in risk (RR=0.70, 95% CI: 0.36-1.35) for > 42 MET-hours/week.

Reference Author/Date	Participants	RPA ¹ Exposure Assessment	Parameters of RPA ²				Reference Category	Adjustment & Stratification Variables	Key Findings
			F	I	T	Y			
Tavani et al., 2001 [61]	Italy: 1,031 EOC patients and 2,411 controls	Hours per week of RPA; PA at age 12, 15-19, 30-09 and 50-59			X		Lowest activity level within each age group	Center, year of interview, age education. Stratified by covariates.	No significant associations between RPA and EOC risk (OR=0.83, 95% CI: 0.58-1.18).
Cottreau et al., 2000 [7]	US East Coast : 767 EOC patients and 1367 controls	PA in six periods of life: frequency of RPA; lifetime RPA	X			X	Low activity	Age, parity, OC use, tubal ligation, family history of EOC, race, BMI.	RPA was significantly inversely associated with EOC risk. Women in high RPA vs. low RPA had OR=0.73 (95% CI: 0.56, 0.94). Decreased risk was observed in all six time periods assessed.

¹ RPA=recreational physical activity

² Parameters of RPA reported in studies; F=frequency of activity (days per week); I=intensity of activity; T=time per week; Y=total years of participation

³ OC=oral contraceptive

⁴ BMI=body mass index

⁵ MET=metabolic equivalents

⁶ HRT=hormone replacement therapy

A Summary of Cohort Investigations Assessing the Association between Recreational Physical Activity and Ovarian Cancer Risk

Table 2

Reference Author/Date	Participants	RPA ² Exposure Assessment	Parameters of RPA ³				Reference Category	Adjustment & Stratification Variables	Key Findings
			F	I	T	Y			
Xiao et al. 2013 [19]	US: (N=148,892 member cohort); 753 EOC ¹ patients	Daily total activity; Frequency of moderate & vigorous total activity in previous decades; sedentary behavior	X			X	Reference category combined no activity with some activity	Age, # of births, age menarche & menopause, race, education, marital status, OC ⁴ use, HRT ⁵ , smoking. Stratified by BMI ⁶ and histology.	Overall, neither PA nor sedentary behavior at baseline was associated w/ EOC. There were no significant associations in any sub-analyses except for one significant OR for women with non-serous cancers, who engaged in vigorous exercise for 1-3 hours per week (OR=1.97; 95% CI: 1.17-3.30).
Yang et al. 2012 [62]	US: (N=169,391 member cohort); 849 EOC patients	Frequency of vigorous household or recreational physical activity	X				Reference category combined no activity with some activity	Age, OC use, parity, menopausal hormone therapy. Stratified by histology.	No significant associations between physical activity frequency and any of the histological subtypes.
Weiderpass et al. 2012 [23]	Japan: (N=45,748-member cohort); 86 EOC patients	Physical activity during leisure time (yes/no)					No activity	Age, parity, breastfeeding, hormone use, menopause status, height, BMI, smoking, sleep duration, family history.	No significant association between PA and EOC risk (HR=1.10, 95% CI: 0.60-1.70).
Chionh et al. 2010 [14]	Australia: (N=18,700 member cohort); 113 EOC patients	Frequency of non-occupational PA over past 6 months; (walking, vigorous exercise; less vigorous exercise)	X	X			No activity	Birth country, education, age at menarche, parity, breastfeeding, OC & HRT use, hysterectomy, menstrual period/amenorrhea, smoking	High total PA vs. no activity yielded (HR = 2.21, 95% CI: 1.16, 4.24); greater frequencies of less vigorous activity and walking also yielded estimates above 1.0 (HR= 1.62, 95% CI: 1.01-2.61) and (HR=1.62, 95% CI: 1.04-2.52), respectively.
Leitzmann et al. 2009 [26]	US: (N= 96,216 member cohort); 309 EOC patients	Frequency & duration of moderate & vigorous RPA; physical activity index (PAI)	X	X	X		The 2 nd lowest activity group was used as reference	Age, race, BMI, parity, OC use, menopause status, HRT, family history of EOC & BC ⁷ , age of menarche. Stratified by histology & stage.	No significant associations between PA and EOC risk were observed in any of the analyses conducted.
Lahmann et al. 2009 [21]	Europe: (N=274,740	RPA (Met hours/wk); Total activity index	X	X	X		Lowest category of activity	Age, study center, education, BMI, parity,	In crude and adjusted models, no significant association

Reference Author/Date	Participants	RPA ² Exposure Assessment	Parameters of RPA ³				Reference Category	Adjustment & Stratification Variables	Key Findings
			F	I	T	Y			
	member cohort); 731 EOC patients member cohort); 731 EOC patients member cohort); 731 EOC patients							age of menarche, menopause status, unilateral oophorectomy, use of OC. Stratified by BMI, histology, HRT, menopause status.	between RPA and risk, but most hazard ratio estimates suggested a slightly increased risk. No dose-response trend, no differences observed when stratifying by subtype, BMI, menopause, or HRT.
Weiderpass et al. 2006 [22]	Norway & Sweden: (N=96,541 member cohort); 264 EOC patients	RPA at ages 14, 30 & at enrollment; change over time	X	X			For "level" of PA, used "moderate" as the reference category	Adjusted by age, height, education, smoking, alcohol, parity, age at first birth, months of breast feeding, OC use and duration, menopause status, age of menopause, HRT use	No significant associations were observed in any analyses.
Patel et al. 2006 [18]	US: (N= 59,695 member cohort); 314 EOC patients	RPA at 3 different times (baseline, age 40 and 1982); hours of sitting		X	X		For baseline RPA: "none"; For MET variables, lowest category	Age, race, BMI, family history, age at menopause & menarche, OC use, parity, hysterectomy, HRT use	No significant associations were observed in any of the RPA or non RPA categories with EOC risk. Sedentary behavior was associated with an increased risk (for > or = 6 vs. < 3 hours per day: HR = 1.55, 95% CI: 1.08, 2.22; p(trend) = 0.01).
Bresma et al. 2006 [16]	Netherlands: (N=62,573 member cohort); 252 EOC patients	Non occupational PA and sports participation analyzed by type of activity	X		X		Baseline RPA included those who performed up to 29 min/day	Age, height, parity, OC use, BMI. Stratified by PA variables only (i.e., non-occupational, biking/walking, gardening, sports).	Compared to women who spent less than 30 min/day, (RRs) of EOC for women who spent up to 60, 90 and >90 min per day were 0.78, 0.86 and 0.72, but these ORs were not significant. Women who spent 1-2 hr/wk biking and walking had 20-35% reduced risk vs. women who never participated in biking or walking (p for trend = 0.05).
Schnohr et al. 2005 [13]	Denmark (N=13,216 member cohort); 107 EOC patients	RPA within past year, classified into low, moderate, vigorous activity		X	X		Low activity served as reference	Adjusted for age, birth cohort, occupational PA, smoking, education, alcohol, menopause status, parity	Significant inverse association between vigorous RPA & risk of EOC, (RR=0.33, 95% CI: 0.16-0.67; p = 0.001) for the most physically active women.
Hannan et al. 2004 [17]	US: (N=27,365 member cohort); 121 EOC patients	RPA hrs/week; METs assigned; PA Index calculated		X	X		Lowest quintile of MET h/day for PA Index & "zero" hours of RPA	Models adjusted by age, menopause status, duration of OC use, HRT use, parity	No significant association between RPA & EOC risk, but results suggest an inverse association. Relative risks (95% confidence intervals) across increasing quintiles of

Reference Author/Date	Participants	RPA ² Exposure Assessment	Parameters of RPA ³				Reference Category	Adjustment & Stratification Variables	Key Findings
			F	I	T	Y			
									total RPA wer 1.0, 0.73 (0.43-1.125), (0.84 (0.50-1.40) total RPA wer 1.0, 0.73 (0.43-1.125), (0.84 (0.50-1.40) total RPA wer 1.0, 0.73 (0.43-1.125), (0.84 (0.50-1.40) total RPA wer 1.0, 0.73 (0.43-1.125), (0.84 (0.50-1.40) total RPA wer 1.0, 0.73 (0.43-1.125), (0.84 (0.50-1.40) total RPA wer 1.0, 0.73 (0.43-1.125), (0.84 (0.50-1.40)
Anderson et al. 2004 [20]	Iowa: (N=41,836 member cohort); 223 EOC patients	Regular RPA; frequency of moderate and vigorous activity; PA Index	X	X			No activity for yes/no variable; low activity for PA index; "rarely or never" for frequency questions	Analyses adjusted for age, family history, hysterectomy status, oophorectomy status, parity, smoking, estrogen therapy	No association between overall (yes/no) RPA and EOC risk; positive association between high physical activity index and EOC risk (RR=1.42 for high activity vs. low activity; 95% CI, 1.03-1.97). This association was particularly strong for frequency of vigorous physical activity (RR=2.38 for >4 times per week vs. rarely/ never; 95% CI, 1.29-4.38).
Bertone et al. 2001 [15]	US: (N=121,700 member cohort); 377 EOC patients	Hours/wk of moderate & vigorous RPA; frequency of sweating during activity (days/wk)	X	X	X		Less than one hour per week	Models adjusted by age, parity, age menarche, OC use, menopausal status, tubal ligation, smoking status, stratified by time period	No significant inverse association between RPA & EOC risk; For women engaging in RPA for 7 + hrs/wk vs. those reporting less than 1 hr/wk (RR=0.80, 95% CI: 0.49 -1.32; P for trend = .59). Most associations observed suggested direct association between high levels of PA or high intensities and EOC risk.

¹ EOC=epithelial ovarian cancer

² RPA=recreational physical activity

³ Parameters of RPA reported in studies: F=frequency of activity (days per week); I=intensity of activity; T=time per week; Y=total years of participation

⁴ OC=oral contraceptive

⁵ HRT=hormone replacement therapy

⁶ BMI=body mass index

⁷ BC=breast cancer

Table 3 Summary of Epidemiological Studies Assessing the Association between Recreational Physical Activity and Ovarian Cancer Survival

Reference Author/Date	Study Design	Participant Characteristics	Primary Exposure Variables	Outcome Variables	Adjustment & Stratification Variables	Key Findings
Zhou et al. 2014 [30]	Prospective Cohort	US: 600 EOC ¹ patients	RPA ²	EOC survival (EOC specific & all cause mortality)	Age, stage, histology, BMI ³ , HRT ⁴ use, smoking, diabetes	Vigorous-intensity physical activity was associated with a 26% lower risk of EOC specific-mortality (HR=0.74; 95% CI: 0.56-0.98) and a 24% lower risk of all-cause mortality (HR=0.76; 95% CI: 0.58-0.98) compared to no vigorous-intensity physical activity.
Moorman et al. 2011 [28]	Case Control	US: 638 EOC patients	RPA	EOC survival	Age, race, BMI, menopause status, OC ⁵ use, months of pregnancy, family history of EOC. Stratified by BMI.	RPA before diagnosis was not significantly related to EOC survival overall, but survival was better for women who reported greater than 2 hrs/wk as compared to those reporting less than 1 hr/wk among women who were non-obese (HR = 0.69, 95% CI: 0.47-1.00).
Yang et al. 2008 [29]	Case Control	Sweden: 635 EOC patients	RPA	EOC survival	Age at diagnosis, FIGO ⁶ tumor stage and WHO ⁷ grade of tumor differentiation; Stratified by tumor grade, age, BMI.	No clear associations were detected between RPA and survival. Among women with FIGO stage I and II EOC, there was some indication that RPA in young adult life appeared to reduce the risk of death due to EOC.

¹ EOC=epithelial ovarian cancer

² RPA=recreational physical activity

³ BMI=body mass index

⁴ HRT=hormone replacement therapy

⁵ OC=oral contraceptive

⁶ FIGO=International Federation of Gynecology and Obstetrics

⁷ WHO=World Health Organization

Table 4
Recommended Classification of Total Weekly Amounts of Aerobic Physical Activity to be Utilized in Epidemiological Studies

Levels of Physical Activity ¹	Range of Moderate Intensity RPA ² (Minutes per week)	Health Benefits	Comments
Inactive	No moderate-intensity RPA (baseline)	None	Inactivity and sedentary lifestyles are independently associated with disease risk.
Low	Activity beyond baseline, but consistently <i>fewer than 150 minutes</i> of Moderate-intensity RPA per week	Some	Low levels of activity are clearly preferable to inactivity and provide some health benefits.
Medium	Consistently engaging in <i>150-300 minutes</i> of Moderate-intensity RPA per week	Substantial	Within this range of activity, evidence suggests a linear association between the amount of minutes of activity and health benefits.
High	Consistently engaging in <i>more than 300 minutes</i> of Moderate-Intensity RPA per week	Additional*	*Current scientific evidence does not allow researchers to identify an upper limit of moderate-intensity activity above which there are no additional health benefits. Typically this amount of activity would be associated with exercise programs aimed towards significant weight loss and/or weight maintenance efforts. In the case of vigorous-intensity exercise, 1-2 rest days must be incorporated into any exercise program in order to prevent overtraining injuries[32].

¹ These categories are based upon those activity categories described in the 2008 Physical Activity Guidelines for Americans [31].

² RPA=recreational physical activity

Table 5
Summary of Governmental and Organizational Physical Activity and Exercise Guidelines for American Adults

Organization & Publication	Population	Guidelines for Moderate to Vigorous Physical Activity (Aerobic Exercise)	Guidelines for Muscle Strengthening (Resistance Exercise)	Guidelines for Flexibility Training
Office of Disease Prevention and Health Promotion, U.S. Department of Health and Human Services: 2008 Physical Activity Guidelines for Americans (PAGA) [31]	Healthy Adults	For substantial health benefits, adults should do at least 150 minutes (2 hours and 30 minutes) a week of moderate-intensity PA, or 75 minutes (1 hour and 15 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous intensity aerobic activity. Aerobic activity should be performed in episodes of at least 10 minutes, and preferably, it should be spread throughout the week. For additional and more extensive health benefits, adults should increase their aerobic physical activity to 300 minutes (5 hours) a week of moderate intensity, or 150 minutes a week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity. Additional health benefits are gained by engaging in physical activity beyond this amount.	Adults should also do muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups on 2 or more days a week, as these activities provide additional health benefits.	Adults should stretch major muscle groups and tendons on days that other exercises are performed.
	Older Adults	<i>The Key Guidelines for Moderate to Vigorous PA for Adults (above) also apply to older adults.</i> In addition, the following Guidelines are just for older adults: When older adults cannot do 150 minutes of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow. Older adults should determine their level of effort for physical activity relative to their level of fitness. Older adults with chronic conditions should understand whether and how their conditions affect their ability to do regular physical activity safely.	<i>The key guidelines for muscle strengthening activities for adults (above) also apply to older adults.</i> Adults should also do muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups on 2 or more days a week, as these activities provide additional health benefits.	Older adults should do exercises that maintain or improve balance if they are at risk of falling.
	Adults with Chronic Medical Conditions	Adults with chronic conditions obtain important health benefits from regular physical activity and should participate in physical activity according to their abilities and under the consultation of a health-care provider.	Perform activities according to their abilities and in consultation with their physician	Perform activities according to their abilities and in consultation with their physician
American Cancer Society [63]	General population/Adults	Get at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week (or a combination of these), preferably spread throughout the week. Limit sedentary behavior such as sitting, lying down, watching TV, and other forms of screen-based entertainment.	NA	NA
World Cancer Research Fund/ American Institute for Cancer Research [2]	General population/Adults	Be moderately physically active, equivalent to brisk walking for at least 30 minutes every day. As fitness improves, aim for 60 minutes or more of moderate, or for 30 minutes or more of vigorous, physical activity every day. Limit sedentary habits such as watching television	NA	NA
American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors [33]	Cancer Patients and Survivors	Recommendations are the same as age-appropriate guidelines from the 2008 Physical Activity Guidelines for Americans.	Recommendations are the same as age-appropriate guidelines from the 2008 Physical	Recommendations are the same as age-appropriate guidelines from the 2008

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Organization & Publication	Population	Guidelines for Moderate to Vigorous Physical Activity (Aerobic Exercise)	Guidelines for Muscle Strengthening (Resistance Exercise)	Guidelines for Flexibility Training
			Activity Guidelines for Americans. Guidelines for Activity Guidelines for Americans.	Physical Activity Guidelines for Americans.

Table 6

A Summary of Potential Contraindications and Special Considerations for Exercise Participation among Ovarian Cancer Patients and Survivors Relative to Common Treatment-Related Factors and Side Effects¹

Treatment Related Factors and Side Effects		Contraindications to Exercise Participation (or exercise testing)	Special Considerations During Exercise for Ovarian Cancer Patients & Survivors
Treatment Related Factors	Intravenous Chemotherapy	No exercise on days of intravenous (IV) treatment or within 24 hours of treatment	Closely monitor patient response to exercise; infection risk increases among patients receiving chemotherapy—take extra precautions in fitness facilities to avoid infection (i.e., ensure proper cleaning & sterilization of equipment)
	Surgery	Up to 8 weeks recovery post-surgery prior to beginning exercise program	Women with swelling or inflammation in the abdomen, groin, or lower extremity should seek physician approval prior to participating in lower body exercise
	Intraperitoneal Chemotherapy	No exercise on days of treatment	No aquatic exercise due to catheter: Closely monitor patient response to exercise; infection risk increases among patients receiving chemotherapy—take precautions in fitness facilities to avoid infection
	Radiation Therapy	N/A	No aquatic exercise due to skin irritation; Closely monitor patient response to exercise; infection risk increases among patients receiving radiation therapy—take extra precautions in fitness facilities to avoid infection
Common Side Effects of Treatment	Blood Draws	No exercise prior to blood draw	N/A
	Fatigue	No exercise if patients are experiencing extreme fatigue	Patients with mild or moderate fatigue may alleviate symptoms with exercise
	Anemia	No exercise if platelets are lower than 50,000; white blood cells are lower than 3,000 or hemoglobin is less than 10 grams per deciliter (g/dL) of blood	N/A
	Lymphedema	Changes in swelling of lower extremities should result in reduction or avoidance of lower-body exercise until further medical evaluation	Women with lymphedema should wear well-fitting compression garments during exercise
	Acute Infections	Avoid exercise until asymptomatic for 48 hours or with a fever greater than 100°F	Patients currently undergoing treatment are at increased risk of infection and should take extra precautions in fitness facilities to avoid infections
	Severe nausea, vomiting, diarrhea	No exercise within 24–36 hours of severe nausea, vomiting or diarrhea	Ensure proper hydration and nutrition; consult with a Registered Dietician
Common Pre-existing or Treatment-Related Conditions	Musculoskeletal Factors	No exercise if recent pain in bones, back or neck, unusual muscular weakness, severe cachexia and/or Karnofsky performance status score < 60%	Patients with bone metastases or with osteoporosis may need to alter exercise intensity or duration given the increased risk of fractures—this is especially important for women receiving hormonal treatment
	Cardiovascular & Pulmonary Factors	No exercise if experiencing chest pain, dyspnea, coughing, wheezing; No exercise if resting heart rate (RHR) is greater than 100 beats per minute (bpm) or less than 50 bpm; No exercise if systolic blood pressure	If utilizing heart-rate altering medications, do not rely on target heart rate training to assess/monitor intensity; Instead utilize Borg's Ratings of Perceived Exertion (RPE) as a tool to monitor intensity of exercise

Treatment Related Factors and Side Effects		Contraindications to Exercise Participation (or exercise testing)	Special Considerations During Exercise for Ovarian Cancer Patients & Survivors
		(BP) >145 mm Hg or diastolic BP >95 mm Hg; No exercise if (BP) >145 mm Hg or diastolic BP >95 mm Hg; No exercise if (BP) >145 mm Hg or diastolic BP >95 mm Hg; No exercise if (BP) >145 mm Hg or diastolic BP >95 mm Hg	Patients with neuropathy may feel slightly off balance but still capable of exercise—as a result, modes of exercise with body support (such as recumbent biking or the use of walking sticks) may be most appropriate
	Neurological Factors	No exercise if patient is experiencing ataxia, dizziness, light-headedness, disorientation, blurred vision, or a significant decline in cognitive status (i.e., unable to understand and follow instructions)	

This table was adapted from Tables 10.1-10.3 in Chapter 10 of ACSM's Guidelines for Exercise Testing and Prescription and from Tables 2-4 in ACSM's Roundtable on Exercise Guidelines for Cancer Survivors [33, 60]