RESEARCH ARTICLE

Recreational Physical Activity and Risk of Ovarian Cancer: a Meta-analysis

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Abstract

Our aim was to access the association between recreational physical activity (RPA) and risk of ovarian cancer (OC). The studies were retrieved from the PubMed and Embase databases up to February 20th, 2014. Risk ratios (OR) and 95% confidence intervals (CI) were used to estimate effect sizes. Random-effects or fixed-effects models were used to pool the data. The trim and fill method was applied for sensitivity analysis. Begg's rank correlation test and Egger's regression asymmetry test were employed to assess the publication bias. A total of 6 studies (435398 participants including 2983 OC patients) were included in this meta-analysis. The overall estimate indicated that there was weakly inverse association between RPA and OC risk (RR=0.90, 95%CI: 0.72-1.12, *p*=0.335). Meanwhile, for prospective cohort studies, a result consistent with the overall estimate was obtained (RR=1.12, 95% CI: 0.88-1.42, *p*=0.356). However, for case control studies, the pooled estimate of RR was 0.76 (95%CI: 0.64-0.90, *p*=0.002), indicating a clear significant association between RPA and OC risk. In addition, the sensitivity analysis indicated a significant link between RPA and risk of OC after removing Lahmann's study (RR=0.80, 95% CI: 0.68-0.93, *p*=0.004). No significant publication bias was found (Begg's test: *p*=1.00; Egger's test: *p*=0.817). In conclusion, our meta-analysis indicated a weakly inverse relationship between RPA and the occurrence of OC.

Keywords: Recreational physical activity - ovarian cancer - meta-analysis

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Introduction

Ovarian cancer (OC) is the leading cause of death from gynecological malignancy among women (Society, 2005; Lin et al., 2013). Epithelial OC is the most common histologic type of OC, constituting more than 90% of all cases of ovarian cancer (Kim et al., 2012). It was reported that epithelial OC and related cancers lead to 15,000 deaths in the US annually, representing the fifth leading cause of death from cancer among women (Siegel et al., 2011). In china, the burden of ovary cancer will continue to be relative stable due to the aging population (Wang, 2014). Although the molecular etiology about OC was continuously investigated (Samuels et al., 2011; Munksgaard et al., 2012), the overall survival rate of OC was still not improved in the last 20 to 30 years (Vaughan et al., 2011). In Robert's study, the poor prognosis of OC was usually attributed to advanced stage at diagnosis and inadequate chemotherapy (Burger et al., 2011), but it was difficult to solve these technical problems. Therefore, the prevention of OC seems to be particularly important.

Physical activity (PA) has been proved to have protective effect against cancers of the colon and breast and possibly of the endometrium and prostate as well (Thune, 2000; Vainio et al., 2002). However, it remains unclear whether PA is associated with the reduction of OC risk. Although a number of studies have examined the relationship between PA and OC, the results of them were inconsistent (Tavani et al., 2001; Zhang et al., 2003; Anderson et al., 2004; Hannan et al., 2004). Tavani et al. (2001) and Hannan et al. (2004) reported that there was no significant association between PA and OC (Tavani et al., 2001; Hannan et al., 2004), while significant association between PA and OC was found by Zhang et al. (2003) and Anderson et al. (2004). This may be attribute to the different definitions of PA, different parameters of PA (type, frequency, duration, intensity), and different methods of measurement.

In this study, we included studies that the intensity of PA was estimated by a specific metabolic equivalent (MET) value. The MET values were abstracted from the Compendium of Physical Activities and defined as the ratio of work metabolic rate to a standard resting metabolic rate (1.0 (4.184 kJ) $\cdot kg^{-1} \cdot h^{-1}$) (Ainsworth et al., 2000). Then the association between recreational PA (RPA) and the risk of OC was explored by this meta-analysis.

Materials and Methods

Search strategy

We performed the pre-established search strategies and retrieved literatures in a systematic way from the

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PubMed and Embase library with the retrieval deadline of February 20th, 2014. The keywords for search were as follows: "physical activity" or "exercise" or "sports", and "ovarian" and "cancer", and "death" or "incidence" or "risk" or "mortality". In addition, a manual search of paper documents and further screening of the citations from relevant original studies and reviews were performed for obtaining additional studies.

Inclusion and exclusion criteria

Studies included in the present meta-analysis should meet the following criteria: 1) study was prospective cohort study, case control study or cross-sectional study; 2) The study participants were healthy people in the cohort study and the outcome was OC, while in the case control study, the participants in cases group were the patients with OC and in the control group were the healthy people; 3) exposure factor was RPA which was measured as MET-hr/week; 4) the study was to explore the association between the RPA and OC; 5) risk ratio (RR) with 95% confidence intervals (CI) should be provided or could be calculated out from the data of the studies. Besides, articles would be excluded if they met anyone of the following criteria: 1) the lowest level of RPA was not selected as the reference category of the research; 2) article was non-original literature such as review, letter and comment. Moreover, for the duplicate publications, only the one with longest follow-up and most complete information was included.

Data abstraction and quality evaluation

Two investigators independently selected studies and extracted data. Discrepancies were resolved by discussion. The extracted data include first author's name, year of publication, region and time of the study, duration of follow-up, number and age of the participants, , measurement of exposure factors, range of the exposure factors, adjusted RR/OR and 95% CI, and adjustment for covariates.

The quality of the studies was evaluated according to a 9-scores system on the basis of the Newcastle-Ottawa Scale (Wells et al., 2011), which was applied for case-control and cohort studies. In this scoring system, each study included in the meta-analysis was judged on three broad perspectives: the selection of the study cases (4 items, one score each item), the comparability of the study populations (1 item, up to two scores) and the ascertainment of either the exposure or outcome of interest (3 items, one score each item). In this scoring system, studies scored equal to or greater than 7 were considered as high quality.

Statistical analysis

Statistical analyses were performed using Stata11.0 software. The effect size of adjusted RR as well as its 95% CI were pooled in order to assess the association between the RPA and OC risk (Dersimonian et al., 1986). A p value of less than 0.05 was considered statistically significant.

Heterogeneity among studies was evaluated by the Cochran Q test and the I^2 parameter (Higgins et al., 2003). And $p<0.05$ or $I^2>50\%$ was considered as significant heterogeneity. When significant heterogeneity was existed, we calculated summary OR and their 95% CI with the random effects model. Otherwise, the fixed effects model was used to pool the data.

In addition, trim and fill method was used in sensitivity analysis to recalculate the overall effect sizes in order to access the stability and credibility of the outcomes (Duval et al., 2000). Publication bias was assessed by Begg's rank correlation test and Egger's regression asymmetry test (Begg et al., 1994; Egger et al., 1997).

Results

Literature retrieval

The procedures and outcomes of literature search were clearly shown in Figure 1. According to the pre-established search strategies, we achieved 345 and 170 articles from the Embase and PubMed library, respectively. A total of 438 potentially relevant studies were selected after duplicates removed. Then 414 obvious irrelevance articles were excluded by scanning titles and abstracts. Among the left 24 studies, 18 literatures (5 the interested exposure was not RPA; 1 was duplication, 12 evaluation of RPA was not MET-hr/week) were excluded according to the inclusion and exclusion criteria. As a result, 6 literatures were included in this meta-analysis (Bertone et al., 2001; Bertone et al., 2002; Pan et al., 2005; Patel et al., 2006; Lahmann et al., 2009; Rossing et al., 2010).

Study characteristics and quality assessment

The characteristics and information of the included studies were shown in Table 1. The 6 included articles were 3 prospective cohort studies (Bertone et al., 2001; Patel et al., 2006; Lahmann et al., 2009) and 3 case control studies (Bertone et al., 2002; Pan et al., 2005; Rossing et al., 2010). Four researches were conducted in American (Bertone et al., 2001; 2002; Patel et al., 2006; Rossing et al., 2010). The other two studies were conducted in European (Lahmann et al., 2009) and Canada (Pan et al., 2005), respectively. A total of 435398 participants including 2983 OC patients were included in this meta-analysis. RPA level was assessed through self-administered questionnaires or interview during follow-up. Besides, the quality assessment of included studies was shown in Table 2. All the 6 studies were high quality studies.

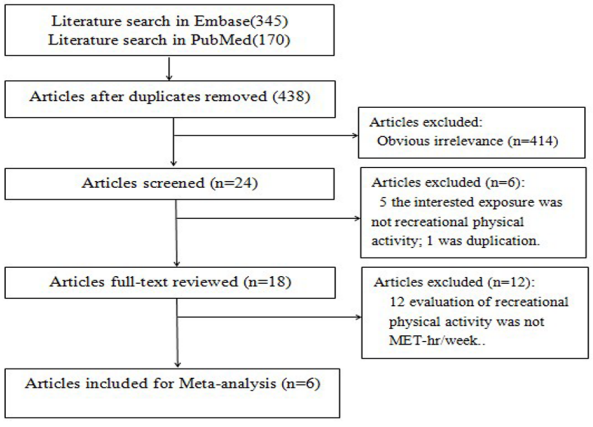

Figure 1. Literature Search and Study Selection

Table 1. Characteristics of 6 Included Studies on Recreational Physical Activity and the Ovarian Cancer

Study reference	Location period	Age (year)	Length of follow-up	Cases/Cohort	Ascertainment of RPA	Type of measurement	Exposure range	Adjusted RRs (95% CI)	Adjustment for covariates
Lahmann 2009	European	51.5	9.3	731/274740	questionnaire	baseline MET-hours/wk	<12	1	Education, BMI, parity, age at menarche,
							12-24	1.15 (0.94,1.41)	menopausal status, unilateral oophorectomy,
							24-42	1.05 (0.85,1.31)	use of oral contraceptives,
							>42	1.18 (0.94,1.47)	type of physical activity
Patel 2006	USA, 1992-2001	50-74	9	314/59695	questionnaire	baseline MET-hours/wk	None	1	Age, race, BMI,
							>0<8	0.87 (0.58,1.30)	family history of breast or ovarian cancer,
							8<17.5	1.00 (0.65,1.52)	age at menopause, age at menarche,
							17.5<31.5	1.03 (0.67,1.60)	OC use, parity, hysterectomy, HRT use
							≥31.5	0.73 (0.40,1.34)	
Bertone 2001	USA, 1980-1996	30-55 (46.2)	16	377/92825	questionnaire	Cumulative average (1980-1996), MET-hr/wk	0<2.5	1	Age, parity, age at menarche,
							2.5<5	1.42 (0.86,2.34)	oral contraceptive use and duration,
							5<10	1.34 (0.83,2.17)	menopausal status/postmenopausal hormone use,
							10<20	1.32 (0.83,2.10)	tubal ligation, smoking status
							20<30	1.84 (1.12,3.02)	
							≥30	1.27 (0.75,2.14)	

Study reference	Location	Case, n Age (y)	Control, n Age (y)	Type of control	Ascertainment of exposure	Type of measurement	Exposure range	Adjusted ORs (95% CI)	Adjustment for covariates
Rossing 2010	USA 2002-2005*	812, 35-74	1313, 35-74	population-based,	interview	10 years prior to 1 year before diagnosis/ reference date MET-hours/wk	0	1	Age, calendar year of diagnosis/ reference date,
							≤4.5	0.9 (0.7,1.2)	county of residence, number of full-term births,
							>4.5-12.8	0.8 (0.6,1.1)	duration of hormonal contraception, education,
							≥12.8	0.8 (0.6,1.1)	and BMI 5 years before the reference date
Pan 2005	Canada 1994-1997*	442, 55.1 (12.3)	2135, 55.2 (12.5)	population-based	questionnaire	baseline MET-hr/wk,	<11.6	1	Age,province of residence,education,alcohol consumption,
							11.6-34.6	0.90 (0.69,1.16)	cigarette pack-years, BMI, total calorie intake,
							≥34.6	0.73 (0.58,0.98)	no. of live births, vegetable consumption, menopause
Bertone 2002	USA 1991-1994*	327, 40-79	3129, 40-79	population-based	interview	5 years before diagnosis MET-hr/wk	0	1	Age, state, parity, tubal ligation,
							>0-7	1.19 (0.80, 1.78)	lutein/zeaxanthin intake,
							>7-14	1.07 (0.74, 1.55)	no. of pelvic exams (last 5 y),
							>14-28	1.15 (0.82, 1.62)	family history of ovarian cancer
							>28-42	0.95 (0.54, 1.69)	
							>42	0.70 (0.36, 1.35)	

*Years of ovarian cancer diagnosed; HRT: hormone replacement therapy; OC: oral contraceptives

Table 2. Methodological Quality of Cohort Studies Included in the Meta-analysis

First author	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor[2]	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Bertone	☆	☆	----	☆	☆☆	☆	☆	☆	8
Lahmann	☆	☆	----	☆	☆☆	☆	----	☆	7
Patel	☆	☆	----	☆	☆☆	☆	----	☆	7

First author	Case definition adequate	Representativeness of the cases	Selection of Controls	Same method of ascertainment for cases and controls	Control for important factor or additional factor[2]	Definition of Controls	Ascertainment of exposure	Non-Response rate	Total quality scores
Rossing	☆	☆	☆	☆	☆☆	----	----	☆	7
Pan	☆	☆	☆	☆	☆☆	----	----	☆	7
Bertone	☆	☆	☆	☆	☆☆	----	----	☆	7

*One star represents one score: 1 A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor; 2 A maximum of 2 stars could be awarded for this item

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Meta-analysis

The summary of the meta-analysis for the association between RA and risk of OC was shown in Figure 2. The heterogeneity test showed that there was significant heterogeneity among studies (I^2=56.6%, p=0.042), so random effects model was applied to calculate the effect sizes. The overall estimate of RR was 0.90 (95%CI: 0.72-1.12, p=0.335), which indicated that high level RPA would decrease the risk of OC compared with the low level RPA, but the result was not significant. According to the study type, the subgroup analysis was performed (Figure 3). For case control studies, the pooled estimate (RR=0.76, 95%CI: 0.64-0.90, p=0.002) indicated that the high level RPA significantly decreased the risk of OC compared with the low level RPA. For prospective cohort studies, the pooled estimate of RR was 1.12 (95% CI: 0.88-1.42, p=0.356), which showed a consistent result with the summary meta-analysis.

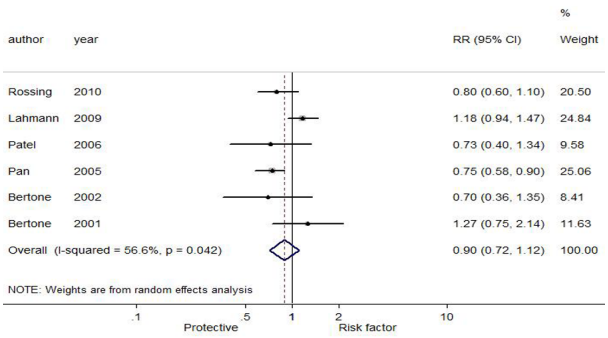

Figure 2. Forest Plots for Risk Ratio of Ovarian Cancer Associated with the High Level Recreational Physical Activity (RPA) Versus the Low Level RPA. Squares represent the effect size for the risk ratio of ovarian cancer among subjects with high level RPA versus low level RPA. Size of the squares is proportional to the size of the cohorts. Error bars represent 95% confidence intervals (CI). The diamond shape represents the pooled estimates within each analysis

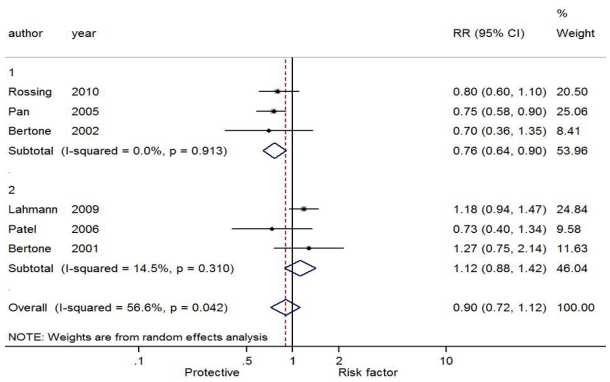

Figure 3. Forest Plots for Risk Ratio in the Case Control Studies and Prospective Cohort Studies of Ovarian Cancer Associated with the High Level Recreational Physical Activity (RPA) Versus the Low Level RPA. 1) analysis for the case control studies; 2) analysis for the prospective cohort studies. Squares represent the effect size for the risk ratio of ovarian cancer among subjects with high level RPA versus low level RPA. Size of the squares is proportional to the size of the cohorts. Error bars represent 95% confidence intervals (CI). The diamond shape represents the pooled estimates within each analysis

Sensitivity analyses and publication bias

In the sensitivity analysis, it demonstrated that the pooled RR was 0.80 (95% CI: 0.68-0.93, p=0.004) after removing the Lahmann's study (Lahmann et al., 2009), while after removing the others articles, the results were all consistent with the initial statistical analysis.

For all studies, no evidence of publication bias was observed in this meta-analysis (Begg's test: p=1.00; Egger's test: p=0.817).

Discussion

OC is the leading cause of death from gynecological malignancy. PA may have potentially prevented effect on the occurrence of OC. In this study, we evaluated the association between RPA and risk of OC. The results demonstrated that there was weakly inverse association between RPA and risk of OC. However, for the case control studies, the outcome showed a significant association between RPA and risk of OC. In addition, the sensitivity analysis also indicated the significant association between RPA and risk of OC after removing Lahmann's study (Lahmann et al., 2009).

Several plausible biologic mechanisms have been proposed for the protective effect of PA on OC. Hormonal factors have been reported to be associated with OC risk in the general population (Salehi et al., 2008; Antoniou et al., 2009). Exposures to endogenous hormones such as estrogens, androgens, and gonadotropins have been proved increase ovarian epithelial cell proliferation, whereas exposure to progesterone could decrease stimulation of ovarian epithelial cells (Cramer et al., 1983; Risch, 1998; Riman et al., 2004). PA was associated with decreased levels of circulating estrogen and progesterone in premenopausal women and serum estradiol, estrogens and androgens in postmenopausal women (Kramer et al., 1996; Westerlind, 2003). It was reported that PA could decrease postmenopausal estrogen levels directly or indirectly through reducing peripheral fat stores, which was the major source of postmenopausal estrogen production (Cauley et al., 1989; Friedenreich, 2001). In addition, PA may decrease OC risk through a reduction in chronic inflammation (Campbell et al., 2007) which has been proved to play a role in OC (Ness et al., 1999). Moreover, PA may also influence OC risk through a reduction in obesity, especially central obesity, which has been shown to increase OC risk (Pan et al., 2004). In summary, the association of PA and the reduction of OC risk might relate to the mechanisms such as alterations in the levels of endogenous sex hormones, reduction of chronic inflammation and even the weight loss. Further studies were required to investigate these speculations.

Many previous studies have confirmed the role of PA on the prevention of cancer (Kruk et al., 2006; Kruk, 2007; Wu et al., 2009). Even dance has been considered a therapy for cancer prevention (Aktas et al., 2005). People with cancer have a lower quality of life; PA is related to better quality of life of cancer survivors (Lee et al., 2013). Although weakly inverse relationship between RPA and the occurrence of OC was found in this study, PA may be play roles in the development of OC and improving the

quality of life of OC patients.

The consistent result has also been proved by a recent mate-analysis published in 2007. There were some differences between our study and that one. Firstly, this study updated the included study and two articles (Lahmann et al., 2009; Rossing et al., 2010) published after 2007 were included. The second one was that the cases in our study were patents with OC while in that study were patients with the most common OC, epithelial OC (Zhao et al., 2013). Furthermore, the intensity of RPA was estimated by MET value in the included studies of this meta-analysis. Thus, the influence of different evaluation criteria of RPA intensity on the results was avoided in this study. However, the evaluation criteria of RPA intensity were different in the included studies of that meta-analysis.

There were some advantages of this meta-analysis. The first one was that the included studies were all high quality studies. Second, the estimates were adjusted with covariates such as age, education, smoking status and body mass index, which could decrease the recall and selection bias. Besides, Begg's and Egger's tests proved no significant publication bias among the included studies. However, some limitations of this study should be mentioned. First of all, only 6 studies were included in this study. More studies were needed to be done to verify the results of this meta-analysis. Secondly, the included studies were all observational studies. Though we adjusted the studies with covariates such as age, education and smoking, the association between the RPA and the risk of OC would be affected by other unknown confounders. Of the third, the RPA levels were divided based on the self-administered questionnaire, so it might have a certain bias due to no accurate measurement and time standards. The fourth one was that the included studies were all carried out in European and American area. So it is necessary to develop investigations of Asian, African and Latino in order to assess the applicability of our results. Furthermore, the significant heterogeneity was found among the studies. Further studies were needed to explore the source of heterogeneity.

In conclusion, our meta-analysis indicated a weakly inverse relationship between RPA and the occurrence of OC.

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