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Recreational physical inactivity and mortality in women with invasive epithelial ovarian cancer: evidence from the Ovarian Cancer Association Consortium

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Background: Little is known about modifiable behaviours that may be associated with epithelial ovarian cancer (EOC) survival. We conducted a pooled analysis of 12 studies from the Ovarian Cancer Association Consortium to investigate the association between pre-diagnostic physical inactivity and mortality.

Methods: Participants included 6806 women with a primary diagnosis of invasive EOC. In accordance with the Physical Activity Guidelines for Americans, women reporting no regular, weekly recreational physical activity were classified as inactive. We utilised Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) representing the associations of inactivity with mortality censored at 5 years.

Results: In multivariate analysis, inactive women had significantly higher mortality risks, with (HR = 1.34, 95% CI: 1.18–1.52) and without (HR = 1.22, 95% CI: 1.12–1.33) further adjustment for residual disease, respectively.

Conclusion: In this large pooled analysis, lack of recreational physical activity was associated with increased mortality among women with invasive EOC.

Epithelial ovarian cancer (EOC) is the most deadly gynaecological cancer in developed nations (Torre *et al*, 2015). Five-year survival is approximately 46% in the United States and Europe (SEER,

2014; UK CR, 2015). Among women with invasive EOC, over 60% are diagnosed with advanced-stage disease, with considerably worse 5-year survival, ranging from 3 to 27% in the United States

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and the United Kingdom (SEER, 2014; UK CR, 2015). While recent reports of improved long-term survival have been promising (Akeson *et al*, 2009; Wright *et al*, 2015), most women diagnosed with advanced-stage EOC will die from their disease, generally within 5 years of diagnosis.

The most commonly cited prognostic factors associated with invasive EOC survival are unmodifiable, and include disease stage and grade at diagnosis, histology, and the extent of residual disease remaining after tumour resection (Winter *et al*, 2007; Cress *et al*, 2015; Wright *et al*, 2015). While little is known about modifiable behaviours that may be associated with EOC prognosis, the lack of recreational physical activity, defined by the Physical Activity Guidelines for Americans (PAGA) as engaging in no regular, weekly, moderate-, or vigorous-intensity exercise during leisure time (USDHHS, 2008), is a potentially modifiable behavioural target for improving prognosis (Sanchis-Gomar *et al*, 2015; Li *et al*, 2016).

Worldwide, over 31% of adults are physically inactive, but inactivity increases with age and is higher among women than men (Hallal *et al*, 2012). As an exposure variable, inactivity can be assessed with less misclassification than incremental categories of physical activity (Bull *et al*, 2004; Celis-Morales *et al*, 2012). Inactivity may also reflect physiological pathways that affect carcinogenesis independently from pathways associated with obesity or physical activity and skeletal muscle contraction (Fiuza-Luces *et al*, 2013; Byers, 2014; Hildebrand *et al*, 2015; Sanchis-Gomar *et al*, 2015). Few studies have systematically evaluated the association between physical inactivity and ovarian cancer prognosis. Thus, we chose to examine the association of physical inactivity with subsequent mortality in women diagnosed with invasive EOC.

MATERIALS AND METHODS

We conducted a pooled analysis utilising individual-level data from 12 studies in the Ovarian Cancer Association Consortium (OCAC) (Berchuck *et al*, 2008). Study protocols were approved by the respective institutional review boards, and participants provided written informed consent. The study population included 6806 women aged 18 years and older, with histologically confirmed primary diagnoses of invasive EOC, fallopian tube cancer, or primary peritoneal cancer.

Analysis variables. Mortality was assessed with time-to-event analyses censored at 5 years. Thus, women were followed from the date of diagnosis to the earliest of date of death, date of last follow-up, or 5 years after the date of diagnosis. Available covariates included a comprehensive set of epidemiological and clinical variables from the OCAC core data set, which was collated, reviewed, cleaned, and harmonised for use in OCAC pooled analyses.

Physical activity was assessed using self- or interviewer-administered questionnaires. Questionnaire format for assessing physical activity habits varied between studies, but all questionnaires allowed for the identification of inactive women as defined by the PAGA. Women reporting no regular moderate- to vigorous-intensity recreational physical activities were categorised as inactive, our exposure of interest. Questionnaires from nine studies (AUS, CON, DOV, HAW, MAL, NEC, NJO, USC, and HOP; Table 1) yielded data reflecting pre-diagnostic activity spanning the course of adulthood, while questionnaires from three studies (JPN, MAY, and MAC; Table 1) yielded data reflecting activity at enrollment. To reduce the likelihood of reverse causation as an explanation for observed associations, we conducted sensitivity analyses excluding the three studies assessing inactivity at enrollment.

Statistical methods. Multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) representing the association between physical inactivity and mortality risk. We examined mortality overall and according to subgroups by tumour histology, tumour stage, menopausal status, and body mass index (BMI) classification. We pre-specified age at diagnosis, tumour stage, and histology as important adjustment variables; additional confounders were identified utilising the 10% change-in-estimate guide (Maldonado and Greenland, 1993). While the extent of residual disease after surgical resection is a well-established prognostic factor for invasive EOC, these data were only available in a subset of participants ($N = 2473$). Therefore, we estimated the association between inactivity and mortality through two multivariable models, with and without adjustment for residual disease. Finally, between-study heterogeneity for the association between inactivity and mortality was assessed by means of Q -statistics ($P < 0.05$) and I -squared statistics ($< 50\%$) (Higgins *et al*, 2003).

RESULTS

During the follow-up period, 2935 participants (43.1%) died. All but one study (MAC) included herein were case-control studies and nine studies originated in the United States (Table 1). Participants were mostly white, post-menopausal women with advanced-stage high-grade serous EOC. Collectively, 24.5% of participants self-reported inactivity before diagnosis (Supplementary Table S1).

For the association of inactivity with mortality, we observed no significant heterogeneity between studies (Q -statistic $P = 0.21$; I -squared = 23.7%), nor evidence of a site-by-inactivity interaction ($P = 0.12$). Therefore, we estimated pooled multivariable HRs and 95% CIs utilising a combined data set. Inactive women had significantly greater risk of mortality (HR = 1.22, 95% CI: 1.12–1.33) (Table 2); the association remained significant with adjustment for residual disease (HR = 1.34, 95% CI: 1.18–1.52; Table 3). Further control for smoking and BMI did not affect the significant increased risk of mortality among inactive women with (HR = 1.35, 95% CI: 1.16–1.56) or without (HR = 1.16, 95% CI: 1.05–1.27) adjustment for residual disease.

In subgroup analyses by histology, inactive women with high-grade serous tumours had significantly higher mortality risks in models without adjustment for residual disease (HR = 1.21, 95% CI: 1.11–1.33; Table 2). In models adjusted for residual disease, inactive women with high-grade serous and clear cell tumours had significantly greater mortality than their active counterparts: HR = 1.36 (95% CI: 1.17–1.58) and HR = 1.73 (95% CI: 1.06–2.84), respectively (Table 3). Because we were insufficiently powered to detect associations among the more infrequent histological subtypes, we also limited histology classifications to serous vs non-serous disease. Here we observed consistent evidence of the association between inactivity and mortality for both tumour types, both with and without adjustment for residual disease (Supplementary Table S2).

In sensitivity analyses intended to reduce possible reverse causation bias by exclusion of the three studies that assessed inactivity only at enrollment, associations between inactivity and mortality remained significant and were similar in magnitude to the associations observed in our primary analysis: HR = 1.28 (95% CI: 1.09–1.49) and HR = 1.19 (95% CI: 1.09–1.30) in models with and without adjustment for residual disease, respectively. In additional analyses excluding women who had died within 1 year of diagnosis, the associations between inactivity and mortality remained significant and of similar magnitude to those in primary analyses in models both with (HR = 1.27, 95% CI: 1.10–1.47) and

Table 1. Characteristics of the Ovarian Cancer Association Consortium studies included in the analyses (N = 12 studies)

OCAC study name ^a	Study design and source of participants	Participant ascertainment	Year of diagnosis	Number of participants ^b	Median (range) of follow-up time (years)	Number (%) deceased (all follow-up data)	Method of follow-up
Australian Ovarian Cancer Study/ Australian Cancer Study (AUS) (Merritt <i>et al</i> , 2008)	Population-based case-control	Cases obtained via surgical treatment centres and cancer registries	2002–2006	1016	7.5 (10.0)	653 (64.3%)	Medical record review
Connecticut Ovary Study (CON) (Risch <i>et al</i> , 2006)	Population-based case-control	Cases obtained via cancer registries and pathology departments	1998–2003	381	8.4 (10.4)	217 (57%)	Connecticut Tumor Registry and obituary listings in Connecticut newspapers
Diseases of the Ovary and their Evaluation (DOV) and (DVE) (Rossing <i>et al</i> , 2007; Bodelon <i>et al</i> , 2012)	Population-based case-control	Cases identified via SEER registry	2002–2009	884	4.4 (8.9)	350 (39.6%)	Standard US NCI SEER-registry follow-up methods
Hawaii Ovarian Cancer Case-Control Study (HAW) (Goodman <i>et al</i> , 2008)	Population-based case-control	Cases were identified via cancer registries	1993–2008	359	7.2 (16.5)	181 (50.4%)	Standard US NCI SEER-registry follow-up methods and medical record review
Hormones and Ovarian Cancer Prediction Study (HOP) (Lo-Ciganic <i>et al</i> , 2012)	Population-based case-control	Cases identified via cancer registries, physician offices, and pathology databases	2003–2008	506	5.1 (9.2)	262 (51.8%)	Medical record review and Social Security database
Hospital-based Research Program at Aichi Cancer Center (JPN) (Hamajima <i>et al</i> , 2001)	Hospital/Clinic-based case-control	Cases identified via cancer centre database	2001–2005	51	5.0 (9.2)	21 (41.2%)	Medical record review
Mayo Clinic Case-Only Ovarian Cancer Study (MAC) (Goode <i>et al</i> , 2011)	Hospital/clinic-based case-only	Cases identified via Mayo Clinic Divisions of Surgical Gynecology & Medical Oncology	2000–2011	83	2.9 (16.2)	32 (38.6%)	Patient contact and vital statistics
MALignant OVARian cancer (MAL) (Glud <i>et al</i> , 2004)	Population-based case-control	Cases identified via cancer registry and gynaecologic departments	1994–1999	492	13.6 (16.0)	371 (75.4%)	Danish Civil Registration System and Danish Register of Causes of Death
Mayo Clinic Ovarian Cancer Case-Control Study (MAY) (Goode <i>et al</i> , 2010; Kelemen <i>et al</i> , 2010)	Hospital/clinic-based case-control	Cases recruited from Mayo Clinic	2000–2008	519	3.4 (8.9)	283 (54.5%)	Patient contact and vital statistics
New England Case Control Study (NEC) (Terry <i>et al</i> , 2005)	Population-based case-control	Cases identified via hospital tumour boards and cancer registries	1992–2008	785	13.4 (19.9)	454 (57.8%)	Annual medical record review and death record database
New Jersey Ovarian Cancer Study (NJO) (Bandera <i>et al</i> , 2011)	Population-based case-control	Cases identified via New Jersey State Cancer Registry	2004–2008	195	6.4 (11.2)	110 (56.4%)	Linkage with the New Jersey State Cancer Registry
Los Angeles County Case-Control Studies of Ovarian Cancer-1 & 2 (USC) (Wu <i>et al</i> , 2015)	Population-based case-control	Cases identified via LA County Cancer Surveillance Program	1993–2009	1535	8.3 (18.0)	823 (53.6%)	Standard US NCI SEER-registry follow-up methods

Abbreviation: OCAC = Ovarian Cancer Association Consortium.

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

^bTotal participant numbers reflect invasive cases in the OCAC core data set (July 2014) with available vital status and recreational physical activity data.

without (HR = 1.18, 95% CI: 1.08–1.29) adjustment for residual disease. Finally, we observed no evidence of effect modification of the association between inactivity and mortality by tumour stage (Supplementary Table S3), menopausal status (Supplementary Table S4), or overweight/obesity status (Supplementary Table S5).

DISCUSSION

The current analyses of pooled individual-level data from OCAC suggests that self-reported, habitual recreational physical inactivity is an independent predictor of mortality among women diagnosed

Table 2. Hazard ratios and 95% confidence intervals representing the association between recreational physical inactivity and mortality among women diagnosed with invasive EOC (N = 6806; 12 studies)^a

EOC histology	Model ^b	N (events)	N (censored)	HR	95% CI		P-value
					Lower	Upper	
All EOC cases ^c	Age-adjusted	2898	3907	1.13	1.04	1.22	0.005
	Multivariable	2861	3876	1.22	1.12	1.33	<0.001
Invasive high-grade serous ^d	Age-adjusted	2287	1902	1.16	1.05	1.27	0.002
	Multivariable	2281	1900	1.21	1.11	1.33	<0.001
Invasive low-grade serous ^d	Age-adjusted	104	213	1.16	0.77	1.75	0.479
	Multivariable	103	213	1.30	0.89	1.96	0.219
Invasive mucinous ^d	Age-adjusted	85	380	1.21	0.77	1.91	0.410
	Multivariable	85	379	0.93	0.59	1.49	0.773
Invasive endometrioid ^d	Age-adjusted	225	943	1.14	0.85	1.53	0.395
	Multivariable	225	943	1.26	0.94	1.70	0.125
Invasive clear cell ^d	Age-adjusted	167	441	1.30	0.93	1.80	0.125
	Multivariable	167	441	1.29	0.92	1.79	0.136

Abbreviations: CI = confidence interval; EOC = epithelial ovarian cancer; HR = hazard ratio.
^aNumbers may not sum to total due to missing data.
^bAdjustment variables were identified based on well-established prognostic factors for EOC and the 10% change-in-estimate method.
^cMultivariable model is adjusted for age, stage, and histotype.
^dMultivariable model is adjusted for age and stage.

Table 3. Residual disease-adjusted hazard ratios^a and 95% confidence intervals representing the association between recreational physical inactivity and mortality among women diagnosed with invasive EOC (N = 2473; 7 studies)^b

EOC histology	Model ^c	N (events)	N (censored)	HR	95% CI		P-value
					Lower	Upper	
All EOC cases ^d	Age-adjusted	1057	1135	1.28	1.13	1.46	<0.001
	Multivariable #1	1055	1135	1.40	1.23	1.60	<0.001
	Multivariable #2	1055	1135	1.34	1.18	1.52	<0.001
Invasive high-grade serous ^e	Age-adjusted	827	579	1.36	1.18	1.58	<0.001
	Multivariable #1	826	579	1.41	1.22	1.64	<0.001
	Multivariable #2	826	579	1.35	1.17	1.57	<0.001
Invasive low-grade serous ^e	Age-adjusted	61	80	0.90	0.54	1.51	0.698
	Multivariable #1	60	80	1.14	0.68	1.92	0.611
	Multivariable #2	60	80	0.90	0.53	1.52	0.684
Invasive mucinous ^e	Age-adjusted	28	102	1.75	0.83	3.71	0.145
	Multivariable #1	28	102	1.27	0.59	2.72	0.538
	Multivariable #2	28	102	1.14	0.52	2.46	0.749
Invasive endometrioid ^e	Age-adjusted	76	249	1.25	0.78	2.03	0.356
	Multivariable #1	76	249	1.17	0.73	1.90	0.514
	Multivariable #2	76	249	1.09	0.67	1.77	0.720
Invasive clear cell ^e	Age-adjusted	65	125	1.73	1.06	2.84	0.029
	Multivariable #1	65	125	1.64	1.00	2.67	0.050
	Multivariable #2	65	125	1.73	1.06	2.84	0.029

Abbreviations: CI = confidence interval; EOC = epithelial ovarian cancer; HR = hazard ratio.
^aHazard ratios represent mortality among participants with available residual disease data from seven studies (AUS, HAW, JPN, MAC, MAL, MAY, and NEC).
^bNumbers may not sum to total due to missing data.
^cAdjustment variables were identified based on well-established prognostic factors for EOC and the 10% change-in-estimate method.
^dMultivariable model #1 is adjusted for age, stage, and histotype; multivariable model #2 is adjusted for age, stage, histotype, and residual disease.
^eMultivariable model #1 is adjusted for age and stage; multivariable model #2 is adjusted for age, stage, and residual disease.

with invasive EOC. The observed associations between inactivity and mortality were consistently seen in sensitivity analyses designed to reduce potential biases and were robust to adjustment for relevant confounders and well-established prognostic factors. Importantly, physical inactivity remained an independent predictor of mortality even among participants diagnosed with advanced disease. If the association with pre-diagnostic activity also applies to physical activity after ovarian cancer diagnosis, it is possible that targeted intervention to reduce inactivity, adjuvant to medical management, could improve survival in women with EOC. This association needs confirmation by a large randomised trial.

Several biological mechanisms have been proposed to account for an association between physical inactivity and cancer development, including increased adiposity, increased circulating sex hormones, chronic inflammation, impaired immune surveillance, impaired insulin regulation, and dysregulated adipokines (McTiernan, 2008). These same mechanisms could explain some of the observed mortality risks associated with physical inactivity in cancer survivors (Li *et al*, 2016). Further, obesity and physical inactivity may affect carcinogenesis through independent pathways (Byers, 2014; Hildebrand *et al*, 2015; Sanchis-Gomar *et al*, 2015). Our finding of significantly increased mortality among inactive women with diagnosed EOC supports this hypothesis. We

observed no appreciable evidence that this association was confounded or modified by BMI, supporting further investigation of the role that physical inactivity may have in preventing EOC or improving its survivability.

A strength of our study is that our analyses were conducted with individual-level data from well-designed epidemiological investigations. Our ability to adjust for established prognostic factors decreased the chance that the observed associations were explained by confounding. Further, the observed associations remained significant in sensitivity analyses designed to reduce sources of bias. On the other hand, potential measurement error associated with self-reported inactivity data categorised dichotomously is an important limitation. However, using physical inactivity as the exposure variable likely involves less exposure misclassification than would occur with categorised incremental physical activity exposures, and such misclassification would likely be non-differential with respect to vital status, thus tending to bias observed associations toward the null.

In summary, our findings add to a growing body of literature suggesting that physical inactivity is associated with unfavourable health outcomes, including poorer cancer outcomes. Given the global epidemic of physical inactivity, these findings have important public health and clinical implications, particularly in the context of a lack of modifiable prognostic factors for EOC, and only modest improvements in survival among women diagnosed with EOC in recent decades (SEER, 2014). Well-designed prospective studies are needed to confirm the survival benefit and to assess how much mortality can be reduced among women diagnosed with invasive EOC.

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CONFLICT OF INTEREST

DWC has provided expert testimony for Beasley Allen Crow. MTG is a consultant/advisory board member for Johnson and Johnson. PMW reports receiving a commercial research grant from BUPA. The remaining authors declare no conflict of interest.

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