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ORIGINAL PAPER

Joint exposure to smoking, excessive weight, and physical inactivity and survival of ovarian cancer patients, evidence from the Ovarian Cancer Association Consortium

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Abstract

Purpose Previous epidemiologic studies have shown that smoking, obesity, and physical inactivity are associated with poor survival following a diagnosis of ovarian cancer. Yet, the combined relationship of these unfavorable lifestyle factors on ovarian cancer survival has not been sufficiently investigated.

Methods Using data pooled from 13 studies, we examined the associations between combined exposures to smoking, overweight/obesity weight, and physical inactivity and overall survival (OS) as well as progression-free survival (PFS) among women diagnosed with invasive epithelial ovarian carcinoma ($n = 7{,}022$). Using age- and stage-adjusted Cox proportional hazards regression models, we estimated hazard ratios (HRs) and 95% confidence intervals (CIs) associated with joint exposure to these factors.

Results Combined exposure to current smoking, overweight/obesity, and physical inactivity prior to diagnosis was associated with a significantly increased risk of mortality compared to women who never smoked, had normal body mass index (BMI), and were physically active (HR = 1.37; 95% CI 1.10–1.70). The association for a joint exposure to these factors exceeded that of each exposure individually. In fact, exposure to both current smoking and overweight/obesity, and current smoking and physical inactivity was also associated with increased risk of death (HR = 1.28; 95% CI 1.08–1.52, and HR = 1.26; 95% CI 1.04–1.54, respectively). The associations were of a similar magnitude when former smoking was assessed in combination with the other exposures and when excessive weight was limited to obesity only. No significant associations were observed between joint exposure to any of these factors and PFS.

Conclusions Joint exposure to smoking, excessive weight, and physical inactivity may negatively impact survival of ovarian cancer patients. These results suggest the importance of examining the combined effect of lifestyle factors on ovarian cancer patients' survival.

Keywords Smoking cigarettes · Overweight · Obesity · Physical inactivity · Ovarian cancer survival · Prognosis

Introduction

Ovarian cancer is the fifth most common cause of cancer deaths in women [1] and the most lethal gynecological cancer [2]. In the United States, five-year survival for ovarian cancer is approximately 47%, and for patients diagnosed with advanced disease, only 29% [3]. Because of the poor

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survival associated with ovarian cancer, significant efforts have been undertaken to identify factors related to prognosis of this disease in order to improve survival.

Evidence has been accumulating suggesting the roles for certain lifestyle factors in ovarian cancer risk and progression. The International Agency for Research on Cancer and the World Cancer Research Fund Panel on Food, Nutrition, Physical Activity and the Prevention of Cancer named tobacco smoking and greater body mass index (BMI) as factors associated with risk of ovarian cancer [4, 5]. Moreover, results from several large epidemiologic analyses suggest that smoking, excessive weight, and, in addition, lack of physical activity can negatively affect survival of ovarian cancer patients [6–10].

Although much data exist on the individual associations of some adverse lifestyle behaviors and survival, joint exposure to several adverse lifestyle factors has not been thoroughly investigated in relation to ovarian cancer prognosis. It is important to understand the association between combinations on these exposures and survival, since these multiple health factors often occur together [11] and evaluation of joint exposures may result in more precise estimates of prognosis. To the best of our knowledge, only one study has examined the associations between the combination of smoking and high body mass index (BMI) and survival [12], while no previous studies have assessed joint exposure to all three unfavorable lifestyle factors: smoking, excessive weight, and lack of physical activity. Therefore, we pooled data from studies that participate in a large international consortium to examine the association between each of these factors and their combination on survival after ovarian cancer diagnosis.

Methods

We used data collected by studies from the Ovarian Cancer Association Consortium (OCAC) [7]. In this study, we only included women diagnosed with invasive epithelial ovarian (including fallopian tube and peritoneal) cancer for whom information was available on vital status and tumor stage of disease at diagnosis. Of these women, we excluded those for whom information on any of the three exposures of interest, cigarette smoking, BMI level, and degree of physical activity, was either not collected or was missing. Our final study population consisted of 7,022 women who participated in 11 case–control (AUS, CON, DOV, HAW, HOP, JPN, MAL, MAY, NEC, NJO, and USC) and two case-only studies (MAC, OPL). The description of the included study sites is provided in Table 1. All studies were approved by the ethics committees at the corresponding institutions; informed consent for participation in individual studies was obtained from all the participants.

Exposure variables

All exposure variables related to the period prior to diagnosis. As reported in previous pooled analyses in this population [7, 13], the definition of smoking varied somewhat across the different study sites. For instance, ever smoking was variously defined as smoking at least 100 cigarettes over the lifetime (AUS, CON, DOV, JPN, MAC, MAY, NEC, OPL), daily smoking for a period of 3, 6, or 12 months (HAW, HOP, NJO, USC) or self-reported smoking with no indication of how long the smoking habit lasted (MAL). For the purpose of this analysis, we used four smoking variables: smoking status (just prior to diagnosis) categorized as (i) never, current, and former smoker and (ii) never vs. ever smoker; number of cigarettes smoked per day (cigs/day) categorized into never, ≤ 10, and more than 10; and smoking duration divided into never, ≤ 20, and > 20 years categories.

BMI was calculated from self-reported adult height and weight one year prior to ovarian cancer diagnosis in eight studies (AUS, HOP, JPN, MAC, MAY, NEC, NJO, and USC) and five years prior to diagnosis in five studies (CON, DOV, HAW, MAL, and OPL) [8]. We used the categories of BMI recommended by the World Health Organization (WHO) to classify women into underweight (< 18.5 kg/m^2), normal weight (18.5–< 25 kg/m^2), overweight (25–< 30 kg/m^2), and obese (≥ 30 kg/m^2) categories [14]. We also created a dichotomized variable with these categories: non-obese (< 30 kg/m^2) versus obese (≥ 30 kg/m^2).

Physical activity was defined as engaging in any regular moderate- to vigorous-intensity recreational physical activity [6, 15]. While nine studies (AUS, CON, DOV, HAW, HOP, MAL, NEC, NJO, OPL, and USC) collected the data on physical activity at some time in the past before diagnosis, three sites (JPN, MAC, and MAY) provided data for activity at the time of diagnosis. For analyses, this variable was dichotomized into the physically active or physically inactive categories.

We created joint exposure variables representing various combinations of all three exposures. The first joint exposure variable had 12 categories: (1) never smoker, normal BMI, physically active- reference category; (2) former smoker, normal BMI, physically active ; (3) current smoker, normal BMI, physically active; (4) never smoker, overweight/obese, physically active; (5) never smoker, normal weight, physically inactive; (6) never smoker, overweight/obese, physically inactive; (7) former smoker, overweight/obese, physically active; (8) former smoker, normal BMI, physically inactive; (9) former smoker, overweight/obese, physically inactive; (10) current smoker, overweight/obese, physically active;

Table 1 Description of the studies included in analysis, Ovarian Cancer Association Consortium

Study acronym	Study name	Study location, year of diagnosis	Data collection method	Median follow-up time, days (range of follow-up)	Number of women who died (%)
AUS[a] [28]	Australian Ovarian Cancer Study	Australia 2002–2006	Self-completed questionnaire	1,732 (25–3,672)	614 (63.4)
CON [29]	Connecticut Ovarian Cancer Study	USA: CT 1998–2003	In-person interview	2,310 (150–3,947)	207 (56.2)
DOV [30, 31]	Disease of the Ovary and their Evaluation Study	USA: WA 2002–2005 (DOV) 2006–2009 (DVE)	In-person interview	1,611 (243–4,013)	403 (45.7)
HAW[a] [32, 33]	Hawaii Ovarian Cancer Study	USA: HI 1993–2008	In-person interview	2,569 (143–7,391)	203 (56.5)
HOP[a] [34]	Hormones and Ovarian Cancer Study	USA: PA, OH, and NY 2003–2009	In-person interview	1,904 (40–3,982)	282 (56.1)
JPN[a] [35]	Hospital-based Research Program at Aichi Cancer Center	Japan 2001–2005	In-person interview	1,203 (43–3,396)	21 (42.9)
MAC[a] [36]	Mayo Clinic Case-only Ovarian Cancer Study	USA 2000–2011	Self-completed questionnaire	2,146 (125–7,330)	46 (59.0)
MAL[a] [37, 38]	MALignant OVArian cancer Study	Denmark 1994–1999	In-person interview	1,578 (24–6,208)	374 (76.5)
MAY[a] [39, 40]	Mayo clinic Ovarian Case–Control Study	USA: MN, SD, ND, IL, IA, WI 2003–2009	In-person interview	1,628 (17–4,879)	353 (70.0)
NEC[a] [41, 42]	New England Case–control Study of Ovarian Cancer	USA:NH and MA 1992–2003	In-person interview	2,908 (70–7,709)	466 (59.4)
NJO [43–45]	New Jersey Ovarian Cancer Study	USA: NJ 2002–2008	Phone interview	2,366 (165–4,085)	108 (56.0)
OPL[a]	Ovarian Cancer Prognosis and Lifestyle Study	Australia 2012–2015	Self-completed questionnaire/in-person interview	1,091 (11–1,881)	225 (31.0)
USC [46–48]	University of Southern California, Study of Lifestyle and Women's	USA: CA 1993–2005	In-person interview	2,426 (109–6,571)	694 (62.0)

[a]Study sites that provided information on progression-free survival

(11) current smoker, normal BMI, physically inactive; and (12) current smoker, overweight/obese, physically inactive. For the second joint exposure variable, the categories were created using the obese group as the one representing excessive weight. We also created similar joint exposure variables using the number of cigarettes smoked per day and duration of smoking as smoking variables. Finally, we created another joint exposure variable by combining each dichotomized exposure, ever smoking (no/yes), obesity (no/yes), and physical inactivity (no/yes), and summing up the number of these adverse lifestyle factors. None of the joint exposure variables included underweight women.

Outcome variables

Overall survival (OS) was defined as the time period from the date of diagnosis with ovarian cancer to the date of death or last follow-up, whichever occurred first. Progression-free survival (PFS) was defined as the time period from the date of diagnosis to the date of progression (clinical, biochemical, radiological or death) or the date of last follow-up for women whose disease did not progress/the date a woman was last known to be progression-free [7]. While all the studies collected information on OS, only nine studies reported information on progression status (AUS, HAW, HOP, JPN, MAC/MAY, MAL, NEC, and OPL). Also, only seven sites

collected information on cause of death (AUS, HAW, JPN, MAC, MAL, MAY, and OPL); therefore, we were not able to use ovarian cancer-specific death as the outcome of interest. To address this issue, we additionally truncated OS at 5 years assuming that most deaths prior to that time occurred due to ovarian cancer.

Statistical analysis

We used age- and stage-adjusted Cox proportional hazards models to estimate the pooled hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) that represented associations between smoking, BMI, and physical activity status, and the joint exposure and survival endpoints (OS and PFS). Because we were not able to examine each association separately within each study site due to a low case number for the lifestyle variables, we estimated the HRs based on the entire study population but additionally adjusted each model for study site to account for the slight difference in the definition of variables from study to study. We also explored potential confounding by each of the following variables: tumor histology (high-grade serous/low-grade serous/mucinous/endometrioid/clear cell/other), tumor grade (well-differentiated/moderately differentiated/poorly differentiated/undifferentiated/unknown), subject race (white/non-white), education (high school or less/higher than high school), menopausal status (pre-/postmenopausal), family history of breast and ovarian cancer (no/yes/unknown), ever use of oral contraceptives (no/yes), ever being pregnant (no/yes), use of menopausal hormone therapy (no/yes), history of tubal ligation (no/yes), history of hysterectomy (no/yes), and history of endometriosis (no/yes). We also adjusted each of the three main exposures for the other two individual exposures. However, because such adjustment did not produce a more than 10% change in the initially estimated HRs, we did include use any of these additional variables in the final models.

For the joint exposure variables, when smoking was represented by the number of cigarettes smoked per day and duration of smoking, we additionally limited analyses to never and current smokers only. We conducted separate analyses adjusting each model for amount of residual disease which characterized the maximum dimension of disease left after the primary surgical procedure. For the purpose of these analyses, this variable was dichotomized into categories of no macroscopic disease vs. presence of macroscopic disease. Nine study sites provided information on the amount of residual disease after primary surgery: AUS, HAW, HOP, JPN, MAC, MAL, MAY, NEC, OPL ($n = 3{,}004$).

In addition, we separately adjusted each model for history of any cardiovascular disease (CVD), that included history of hypertension, heart disease, or diabetes, and we conducted stratified analyses based on the history of any of these diseases to examine whether cardiovascular illness influenced the association between each of the exposures and the survival outcomes. To assess the presence of multiplicative interactions, we also added multiplicative terms between history of CVD and each of the three exposures into the models.

Models were analyzed as left truncated to take into account the time interval between the date of diagnosis and the date of the interview to attenuate a potential survival bias [8]. To examine the presence of multiplicative interaction between the individual variables and to evaluate what exposure is driving the mortality experience, we added multiplicative terms to the model while adjusting the model for the main effects. We additionally stratified the models by disease stage (localized, regional vs. distant) and menopausal status at diagnosis. We also checked for the presence of multiplicative interaction between each of the exposure variables and disease stage, menopausal status, and study site by including joint terms between each of these exposures and potential effect modifiers. We were not able to examine the associations stratified by histological subtype because of a low numbers of cases within some subtypes for the composite variables. Therefore, we conducted separate analyses by limiting the case group to women with high-grade serous cancer, the most common specific histotype.

We also conducted additional analyses excluding three studies (JPN, MAC, and MAY) that collected information about physical activity at the time of diagnosis because their physical activity level could have been affected by the disease. We also conducted separate analyses after excluding women diagnosed with either fallopian tube or peritoneal cancer.

Results

We observed an increased risk of death associated with each individual exposure, which was expected based on previous studies analyses in the OCAC [6–8] (Table 2). Both former and current smoking were associated with increased mortality, HR = 1.10; 95% CI 1.03–1.18, and HR = 1.22; 95% CI 1.11–1.34, respectively. Obesity and physical inactivity were also associated with poorer survival, HR = 1.16; 95% CI 1.07–1.25, and HR = 1.08; 95% CI 1.01–1.16, respectively.

For the joint exposure variable, compared to the full non-exposure, almost all the combinations of the three exposures of interest were associated with increased risk of mortality, and associations were stronger for the categories with current smoking compared to those with former smoking as one of the exposures (Table 2). Specifically, being a former smoker and overweight/obese prior to ovarian cancer diagnosis was associated with increased risk of death for both physically active and inactive individuals, although the association was more pronounced for those who were physically

Table 2 Association between smoking, BMI, physical inactivity, and composite lifestyle variables and overall survival among ovarian cancer cases, Ovarian Cancer Association Consortium

Variables	Status		HR (95% CI)[a,b]	*p* Value
	Died	Alive		
Smoking				
Never	2,075	1,746	1.00 (ref)	
Former	584	371	1.10 (1.03–1.18)	< 0.001
Current	1,337	909	1.22 (1.11–1.34)	0.005
BMI at the time period preceding diagnosis				
Underweight	77	63	1.04 (0.82–1.30)	0.75
Normal weight	1,899	1,415	1.00 (ref)	
Overweight	1,139	872	1.02 (0.95–1.10)	0.58
Obese	881	676	1.16 (1.07–1.25)	< 0.001
Recreational physical inactivity				
Active	2,895	2,253	1.00 (ref)	
Inactive	1,100	771	1.08 (1.01–1.16)	0.03

Combined exposure to smoking, overweight/obesity, and physical inactivity						
Smoking	Overweight/obese	Inactive				
Never	No	No	762	641	1.00 (ref)	
Former	No	No	487	365	1.03 (0.92–1.15)	0.62
Current	No	No	187	118	1.19 (1.01–1.40)	0.03
Never	Yes	No	758	631	1.06 (0.95–1.17)	0.28
Never	No	Yes	198	156	1.03 (0.88–1.31)	0.73
Never	Yes	Yes	321	275	1.05 (0.92–1.19)	0.50
Former	Yes	No	491	344	1.16 (1.03–1.30)	0.01
Former	No	Yes	143	72	1.21 (1.01–1.45)	0.04
Former	Yes	Yes	198	122	1.35 (1.15–1.59)	< 0.001
Current	Yes	No	159	110	1.28 (1.08–1.52)	0.005
Current	No	Yes	121	62	1.26 (1.04–1.54)	0.02
Current	Yes	Yes	94	65	1.37 (1.10–1.70)	0.004

[a] Results for the individual models for each factor

[b]Cox proportional hazards model adjusted for age at diagnosis (continuous), stage, and study site

inactive, HR = 1.16; 95% CI 1.03–1.30, and HR = 1.35; 95% CI 1.15–1.59, respectively. Physically inactive former smokers who were not overweight/obese also had an increased risk of mortality, HR = 1.21; 95% CI 1.01–1.45. On the other hand, for current smokers who had excessive weight and were physically active or were physically inactive and had normal BMI, we also observed poorer survival, HR = 1.28; 95% CI 1.08–1.52, and HR = 1.26; 95% CI 1.04–1.54, respectively. Moreover, the last category of this variable, current smoking, overweight/obese, and physical inactivity, was associated with increased risk of death, HR = 1.37, 95% CI 1.10–1.70. However, this estimate was lower than the expected combined effect of all three individual exposures, HR = 1.53, calculated by multiplying the HRs estimated for each exposure. The multiplicative term for all three exposures was not statistically significant ($p = 0.50$).

We did not observe any statistically significant associations between any of the adverse lifestyle factors or their combinations with PFS (Table 3) except for the current smoking category of the joint exposure variable. In fact, for current smoking, with the absence of either overweight/obese or physical inactivity, we found an increased risk of progression, HR = 1.30; 95% CI 1.01–1.68. The associations were a little more pronounced, in general, when excessive weight was limited to obese women compared to overweight plus obese combined (data not shown).

When smoking was defined as the number of cigarettes smoked per day or the duration of smoking, the associations for both OS and PFS were not appreciably different vs. when smoking was categorized as never, former, and current (Supplemental Tables 1–4). What is important to note is that across the categories of the joint exposure variables, there was a dose–response relationship between the number of

Table 3 Association between smoking, BMI, physical inactivity, and composite lifestyle variables and progression-free survival among ovarian cancer cases, Ovarian Cancer Association Consortium

Variables	Progression		HR (95% CI)[a,b]	*p* Value
	Yes	No		
Smoking				
Never	960	838	1.00 (ref)	
Former	284	192	1.07 (0.96–1.19)	0.21
Current	570	426	1.09 (0.94–1.26)	0.25
BMI at the time period preceding diagnosis				
Underweight	27	22	0.84 (0.56–1.25)	0.40
Normal weight	814	633	1.00 (ref)	
Overweight	554	436	1.09 (0.97–1.23)	0.12
Obese	419	365	1.04 (0.92–1.18)	0.54
Recreational physical inactivity				
Active	1,314	979	1.00 (ref)	
Inactive	499	475	0.90 (0.80–1.00)	0.06

Combined exposure to smoking, overweight/obesity, and physical inactivity						
Smoking	Overweight/Obese	Inactive				
Never	No	No	315	266	1.00 (ref)	
Former	No	No	197	152	1.00 (0.83–1.21)	0.99
Current	No	No	91	47	1.30 (1.01–1.68)	0.04
Never	Yes	No	399	303	1.12 (0.96–1.31)	0.14
Never	No	Yes	91	87	0.88 (0.68–1.13)	0.31
Never	Yes	Yes	143	167	0.92 (0.75–1.13)	0.44
Former	Yes	No	215	152	1.13 (0.94–1.36)	0.20
Former	No	Yes	62	43	1.06 (0.79–1.42)	0.71
Former	Yes	Yes	90	77	1.23 (0.96–1.57)	0.10
Current	Yes	No	79	48	1.24 (0.95–1.62)	0.11
Current	No	Yes	57	37	1.05 (0.78–1.42)	0.75
Current	Yes	Yes	47	54	0.86 (0.62–1.19)	0.37

[a]Results for the individual models for each factor

[b]Cox proportional hazards model adjusted for age at diagnosis (continuous), stage, and study site

cigarettes smoked per day or duration of smoking, and mortality or progression (Supplemental Tables 1–4) keeping the other two variables unchanged. For instance, for women with normal weight who were physically inactive, the risk of mortality was higher with higher number of cigarettes smoked per day, HR = 1.08; 95% CI 0.92–1.26, HR = 1.29; 95% CI 1.03–1.62; HR = 1.41; 95% CI 1.18–1.69, for never smokers, those who smoked ≤ 10 cigs/day, and those who smoked > 10 cigs/day, respectively (Supplemental Table 1). For those who were both overweight/obese and inactive, there was also a dose–response relationship in regards to the number of cigarettes smoked per day and mortality, HR = 1.04; 95% CI 0.91–1.19; HR = 1.29; 95% CI 1.03–1.61; HR = 1.47; 95% CI 1.23–1.75 for never smokers, those smoking ≤ 10 cigs/day, and those smoking > 10 cigs/day, respectively. The estimated association for all three exposures, smoking > 10 cigs/day, overweight/obesity, and physical inactivity, of 1.47 was slightly higher than the expected combined effect of all three exposures, HR = 1.465, obtained by multiplying HRs for these three exposures.

The associations for OS and PFS were of a similar pattern when the smoking variable was represented by the duration of smoking (Supplemental Tables 2 and 4). The expected combined effect of all three exposures was higher than the HR calculated by multiplying HRs for individual exposures. The results were not vastly different when former smokers were excluded from the analyses. The multiplicative terms for all three individual exposures when smoking was defined either as the number of cigarettes smoked per day or duration of smoking were not significant.

We observed the associations of a similar magnitude, as the ones obtained from the main analyses, when using the variables representing a sum of the dichotomized exposures (data not shown). When OS was truncated at 5 years, the

associations were not substantially different from the estimates obtained when full OS was used as the endpoint (data not shown). Also, adjustment for residual disease or history of cardiovascular co-morbidities did not influence the originally estimated measures of association (data not shown).

For OS, when the analyses were stratified by stage, the associations were not substantially different between those diagnosed with localized/regional stage of ovarian cancer compared to those with distant stage of the disease; although among those diagnosed with localized/regional disease, the associations were non-significant (Supplemental Table 5). For those exposed to several adverse lifestyle factors, the associations were statistically significant and more pronounced among those with more advanced disease compared to those with a less advanced stage tumors (data not shown).

We observed multiplicative interaction between the joint exposure variable and stage in relation to PFS ($p = 0.002$). No substantial differences were observed between pre-and postmenopausal women or between those with history of cardiovascular comorbidity and without, in terms of the associations between the exposures of interest and OS and PFS (data not shown). None of the joint terms between any of the exposures and menopausal status, CVD, or study site were significant.

When the analyses excluded peritoneal or fallopian tube cases or included high-grade serous cases only, we did not observe any substantial changes in HRs compared to the main results. Finally, exclusion of the three studies that collected information on physical activity status at the time of interview also did not produce any meaningful change in the final estimates (data not shown).

Discussion

In this study, among the women diagnosed with ovarian cancer, we observed increased mortality associated with the joint exposure to smoking, overweight/obesity, and physical inactivity. The HRs for the joint exposure to all three factors were lower than expected form the product of the HRs for each individual exposure for almost all the joint exposure variables except for the one where smoking habit was represented by cigarettes smoked per day.

To our knowledge, this is the largest study to examine the association between the combined effect of these adverse lifestyle factors and survival among women with ovarian cancer. Previous studies have primarily focused on individual factors without assessing the combined effect of these exposures. To date, one study has examined the joint association of common exposures but this study focused on smoking and excessive BMI only [12]. Similar to ours, that study demonstrated a decreased survival among patients who were exposed to both current smoking and excessive BMI ≥ 25 kg/m^2. However, the study included only patients who were diagnosed with stage III ovarian cancer, and it was much smaller ($n = 295$). Our study was considerably larger, included women with all stages of ovarian cancer, and also assessed an additional exposure, physical inactivity.

Our findings could be explained by the adverse role of each of these factors on ovarian cancer progression and survival with smoking being potentially the primary factor driving the observed associations. In fact, a particularly salient biological mechanism links smoking to tumor progression. Tobacco smoke has been shown to promote cell proliferation, epithelial-mesenchymal transition, invasion, and angiogenesis; and inhibit apoptosis [16–19]. Moreover, a number of epidemiologic studies have shown smoking to influence survival among ovarian cancer patients who smoked [9, 20, 21], including one study conducted using the OCAC data [7]. In the present analysis, the association between current smoking and mortality was the strongest of the individual associations reported, and the association remained virtually unchanged when smoking was defined by the number of cigarettes smoked or the duration of smoking.

Besides smoking, obesity and physical inactivity are also associated with increased ovarian cancer mortality. Excessive weight and increased adiposity, which accompanies weight accumulation, have been shown to promote tumor progression via production of insulin-like growth factor-I and hyperinsulinemia [22] as well as favor chronic inflammation by increasing levels of C-reactive protein and tumor necrosis factor alpha [23]. Obese women may also be receiving a less aggressive ovarian cancer treatment to avoid side effects [24]. Physical inactivity can influence ovarian cancer through chronic inflammation, aberrant production of adipokines, leptin, and adiponectin in particular, and increased insulin production [6, 25]. Hence, it is possible that a combination of exposures to these unfavorable lifestyle factors could lead to worse survival compared to each of these exposures considered separately.

Our findings could also be explained by the fact that these lifestyle factors are associated with higher numbers of comorbid conditions [5, 26]. Individuals who smoke, are overweight or obese, or are physically inactive are more likely to have co-morbidities which may result in poorer survival. In our analyses, controlling or stratifying for cardiovascular illness did not produce any meaningful changes in the estimates of the associations. Perhaps, some other uncontrolled comorbid conditions, medical management of these conditions, or less intensive treatment of ovarian cancer due to the presence of co-morbidities could still confound or mediate the associations and explain the results observed by us.

The strengths of our study include a large sample size that allowed us to conduct additional analyses; the results of which confirmed the robustness of our findings. We were

also able to examine the role of multiple potential covariates and interactions, including personal and disease characteristics, as well as history of certain comorbidities. Moreover, we were able to create several joint exposure variables to examine various combinations of each of the exposures of interest. The fact that we observed the associations of a similar magnitude, when we used various combinations of the exposures of interest as the ones obtained from the main analyses, also supports the robustness of our results. Although some might argue that it is the number of the adverse exposures that has a negative impact on prognosis and not the actual individual exposures.

Our study also has some limitations that need to be acknowledged. First, we were only able to examine pre-diagnostic exposures. Perhaps, post-diagnostic lifestyles of ovarian cancer patients could be as, or more, important with regard to their survival as pre-diagnostic behaviors. Second, because data collection differed somewhat between the studies, the definitions of the variables used in our analyses were somewhat heterogeneous. Despite this potential heterogeneity, we were able to observe the association between these factors and their combinations with survival. Third, we were not able to examine the association with ovarian cancer-specific survival due to a limited sample size. However, when survival was truncated at 5 years of follow-up, the associations remained essentially unchanged, which provides further support for our assumption that OS represents a good approximation of ovarian cancer-specific survival. Moreover, our results could have been affected by potential survival bias since the most aggressive cases could have died before enrollment. Another limitation of the present work is that the exposure assessment was based on self-report, which could have resulted in misclassification of the various exposures. If such misclassification did occur to any degree, most likely, it would have been of a non-differential nature, and could have resulted in attenuation of our results. Also, categorization of the exposures may have led to an oversimplified interpretation of the role of each component of the joint exposure variables [27] in relation to survival outcomes. Finally, due to power constraints, we were not able to examine variation of the associations by histological subtype. It is possible that examining the association within specific subtypes, such as mucinous, which has been shown to be associated with smoking history, could have provided more information whether the observed associations are driven by smoking history.

In conclusion, the findings of our study provide further support to the assumption that it is important to take into account the combined effect of certain adverse lifestyle factors, such as smoking, excessive weight, and physical inactivity when examining their role in prognosis of ovarian cancer patients. Further studies need to be conducted to examine how post-diagnostic lifestyle influences the outcomes for these patients.

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Compliance with ethical standards

Conflict of interest No potential conflicts of interest were disclosed.

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