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Predictors of ovarian cancer survival: A population-based prospective study in Sweden

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Ovarian cancer is the leading cause of death from gynecologic malignancies among women worldwide. Little is known about reproductive factors or lifestyle determinants and ovarian cancer prognosis. The objective of this study was to examine whether ovarian cancer survival is influenced by reproductive history, anthropometric characteristics, prediagnostic life-style factors and family history of breast or ovarian cancer. The study population consisted of 635 epithelial ovarian cancer (EOC) cases derived from a nationwide population-based case-control study conducted in Sweden between 1993 and 1995. Exposure data on prediagnostic factors of interest were collected through questionnaires at the beginning of the parent study. Clinical data were abstracted from medical records. Cases were followed-up by means of record linkage to nationwide registers until December 31, 2002. Cox proportional hazard regression model was used to estimate the prognostic effect of each factor in terms of hazard ratios (HR) and 95% confidence intervals (CI), following adjustment for age at diagnosis, FIGO tumor stage and WHO grade of tumor differentiation. Tumor characteristics significantly influenced the risk of death from EOC. After adjustment for these, no clear associations were detected between reproductive history (parity, age at first or last birth, oral contraceptive use, age at menarche or menopause), anthropometric characteristics (body size and shape in different periods of life), lifestyle factors before diagnosis (alcohol consumption, smoking and physical activity over lifetime), nor family history of breast cancer or ovarian cancer and EOC survival. Our findings indicate that these prediagnostic factors do not influence the EOC survival. Nevertheless, among women with early stage disease (FIGO stage I and II), there was some indication that overweight in young adulthood or recent years increased the risk of death, while physical activity in young adult life appeared to reduce the risk of death due to EOC.

Key words: epithelial ovarian cancer; risk factors; survival; prospective study; Sweden

Globally, ovarian cancer is the second most common gynecological malignancy and the leading cause of mortality from female reproductive cancer.[1,2] Seventy-five percent of women with ovarian cancer present with an advanced disease at the time of diagnosis, and the 5-year survival ratio from ovarian cancer is less than 50% worldwide. Epithelial ovarian tumors constitute the majority (90%) of ovarian malignancies.[3] Approximately 85% of epithelial ovarian tumors are invasive, while 15% are borderline ovarian tumors.[4] To date, no firm conclusion can be drawn about the etiology of ovarian cancer.[5] Parity and use of oral contraceptives have consistently been shown to reduce the risk of epithelial ovarian cancer (EOC),[6–8] while the use of hormone replacement therapy (HRT) and family history of breast and ovarian cancer seem associated with an elevated risk.[5,9] Results are conflicting regarding the etiologic role of other reproductive and lifestyle factors.[10–15] While clinical characteristics of the tumor have been shown to be strongly related to survival among patients with ovarian cancer,[16–19] little is known about the prognostic role of reproductive history, lifestyle factors and family history of cancer.[20–27] Recent studies suggest that young age at menarche,[28] overweight or obesity before diagnosis[21,25,29] and history of smoking before diagnosis[21,30] affect ovarian cancer survival negatively. Evidence from studies on another hormone-related cancer, breast cancer, also suggests that reproductive history and life-style factors before diagnosis, such as obesity, physical activity and smoking influence disease prognosis.[11,31]

The purpose of the present study was to examine the possible influence of reproductive history, life-style factors and family history of cancer on EOC survival in Sweden, where the incidence of the disease is high.

Subjects and methods

Subjects

Our study cohort was defined as women 50–74 years of age with a new histologically confirmed diagnosis of EOC in a nationwide population-based case-control study conducted in Sweden between 1993 and 1995. The findings of the case-control study have been reported previously.[8] The present study is based on a prospective follow-up of the case group by means of record linkage with nationwide registers, using the individually unique national registration number assigned to all residents of Sweden at birth or time of first residency. Causes of EOC deaths were defined as women having ovarian cancer (ICD-9 codes 183.0–183.9), C56 (ICD-10) as an underlying or contributing cause of death. Among 1,205 newly reported ovarian cancer patients, 914 (76%) agreed to participate, 181 (15%) refused and 110 (9%) were not approached because of the physicians' refusal to contact them, mostly because of poor health. Of the 914 who agreed to participate, 776 cases were confirmed with EOC diagnosis based on histological reevaluation. Because of a small number of deaths among patients with borderline ovarian tumors, we restricted the study to 635 patients with EOC included in the founding study. All but a small propor-

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tion of patients received treatment (surgery 99.4%; chemotherapy 95.0%). Baseline exposure data were collected through mailed self-administered questionnaires when the case women were recruited into the case-control study. Approximately 50% of the women were further approached by telephone interviewers to provide missing information or resolve inconsistencies in the mailed questionnaires.[13] Information on clinical characteristics, including the International Federation of Gynecology and Obstetrics (FIGO) stage and World Health Organization (WHO) grade of differentiation, was abstracted from medical records in oncology centers or gynecological departments. Survival as the main outcome measure was obtained by record linkage to the Cause of Death Register. Follow-up time was calculated from the date of diagnosis to the date of death from EOC or ovarian cancer related (OCR) causes, such as malignant tumor in unspecified location in the peritoneum or in the uterus except isthmus uteri, or tumor with different points of origin or with uncertain nature in the ovary. Censoring was done if death occurred due to other causes or at the end of the observation period on December 31, 2002.

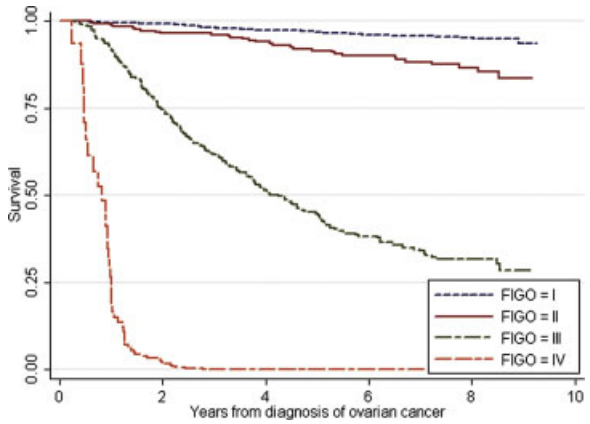

FIGURE 1 – Epithelial ovarian cancer survival by FIGO stage, adjusted for age at diagnosis and WHO tumour differentiation grade.

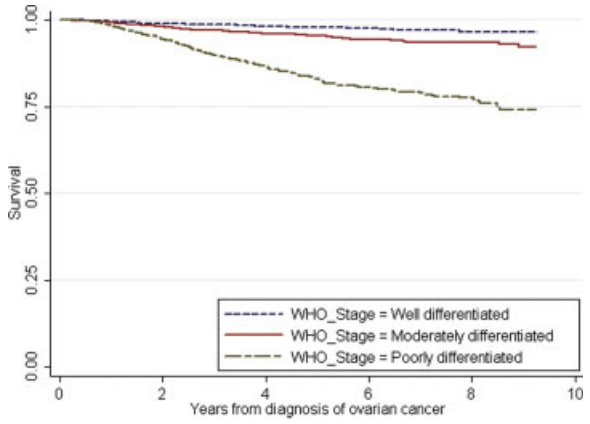

FIGURE 2 – Epithelial ovarian cancer survival by WHO grade of differentiation, adjusted for age at diagnosis and tumour FIGO stage.

The following self-reported characteristics were examined in relation to survival among women diagnosed with EOC:

Reproductive factors: Parity (nulliparous, 1, 2, ≥3 children), age at first birth (<20, 20–24, 25–29, ≥30), age at last birth (<25, 25–29, ≥30), use of oral contraceptives (OC) (never, <3, ≥3 years), age at menarche (10–12, 13–14, ≥15), age at menopause (<50, 50–51, ≥52).
Anthropometric characteristics: Body mass index (BMI, i.e. weight in kilograms divided by height in meters squared) at age 18 and 1 year prior to EOC diagnosis (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2), body shape at age 7, 18 and 1 year prior to EOC diagnosis (based on pictograms at baseline questionnaire and categorized into thin, normal and obese),[32] changes of body shape (categorized into remained thin, decreased weight, remained average, increased weight and remained obese over time from age 7 to 18 to 1 year prior to EOC diagnosis, through combining above information of BMI and body shape reported for different lifetime periods).
Lifestyle factors: Usual alcohol consumption (none, 0.01–1.59, 1.60–3.99, ≥4.00 g/day, estimated from the total consumption of beer, wine and liquor), history of cigarette smoking (never, former, current smokers), smoking amount (none, 1–10, 11–20, ≥21 cigs/day), physical activity (never, <1, 1–2, >2 hr/week, as reported for 3 time periods: childhood, during age 18 to 30 and recent years) and changes of physical activity over time (categorized into remained inactive, from active to inactive, from inactive to active and remained active, through comparing above reported physical activity levels throughout lifetime). Social economic status was estimated in a scale 1–7, from the lowest to the highest level, based on self reported attained education.
Family history: Ovarian cancer and/or breast cancer in mother or sister(s).

TABLE I – AGE AT DIAGNOSIS, FIGO STAGE AND WHO GRADE OF DIFFERENTIATION OF EPITHELIAL OVARIAN CANCER AND SURVIVAL

Factor	Number of cases[1]	OCR deaths (%)	HR[2]	95% CI	*p*-value[3]
Age at diagnosis					
50–54	138	80 (58.0)	1.00	Ref	0.04
55–59	132	71 (53.8)	0.67	0.48–0.94	
60–64	116	73 (62.9)	1.06	0.76–1.47	
65–69	123	85 (69.1)	0.88	0.64–1.22	
70–75	126	87 (69.1)	1.03	0.76–1.42	
FIGO stage					
I	181	38 (21.0)	1.00	Ref	<0.01
II	72	37 (51.4)	2.58	1.55–4.28	
III	295	239 (81.0)	7.11	4.81–10.51	
IV	87	82 (94.3)	12.52	7.96–19.67	
WHO grade of differentiation					
Well differentiated	87	24 (27.6)	1.00	Ref	0.03
Moderately differentiated	167	91 (54.5)	1.67	1.06–2.64	
Poorly differentiated	327	249(76.2)	1.75	1.13–2.71	

[1]Missing values for each factor were not listed.–[2]Adjusted for the other factors in the table (*i.e.*, the analysis of age at diagnosis was adjusted for disease stage and grade of differentiation, etc).–[3]Likelihood Ratio tests for estimating overall association of each factor.

TABLE II – REPRODUCTIVE FACTORS AND EPITHELIAL OVARIAN CANCER SURVIVAL

Factor	Number of cases[1]	OCR deaths (%)	HR[2]	95% CI	*p*-value[3]
Parity					
Nulliparous	121	79 (65.3)	1.00	Ref	0.53
1 child	121	71 (58.7)	0.93	0.66–1.31	
2 children	235	141 (60.0)	0.81	0.61–1.09	
≥3 children	158	105 (66.5)	0.91	0.67–1.24	
Age at first birth					
<19	59	39 (66.1)	1.00	Ref	0.22
20–24	201	136 (67.7)	1.06	0.72–1.54	
25–29	185	103 (55.7)	0.90	0.61–1.33	
≥30	69	39 (56.5)	0.73	0.45–1.17	
Age at last birth					
<24	82	54 (65.9)	1.00	Ref	0.35
25–29	174	101 (58.1)	0.78	0.55–1.10	
≥30	258	162 (62.8)	0.81	0.58–1.12	
Oral contraceptive use					
Never	433	285 (65.8)	1.00	Ref	0.88
<3 years	106	63 (59.4)	1.05	0.77–1.43	
≥3 years	62	33 (53.2)	0.94	0.64–1.39	
Age at menarche					
10–12	128	78 (60.9)	1.14	0.87–1.50	0.53
13–14	318	203 (63.8)	1.00	Ref	
≥15	120	74 (61.7)	0.95	0.72–1.26	
Age at menopause					
30–49	155	95 (61.3)	1.08	0.81–1.43	0.88
50–51	202	126 (62.4)	1.00	Ref	
≥52	214	137 (64.0)	1.03	0.80–1.33	
Age at menopause for only natural menopause women					
30–49	153	94 (61.4)	0.97	0.72–1.30	0.74
50–51	164	107 (65.2)	1.00	Ref	
≥52	209	134 (64.1)	0.90	0.69–1.18	

[1]Missing values for each factor were not listed.–[2]Adjusted for the age at diagnosis, epithelial ovarian cancer FIGO stage and WHO grade of differentiation.–[3]Likelihood Ratio tests for estimating overall association of each factor.

TABLE III – ANTHROPOMETRIC CHARACTERISTICS AND EPITHELIAL OVARIAN CANCER SURVIVAL

Factor	Number of cases[1]	OCR deaths (%)	HR[2]	95% CI	*p*-value[3]
Body mass index (BMI)					
Age 18					0.04
Underweight	91	51 (56.0)	0.81	0.59–1.12	
Normal	376	235 (62.5)	1.00	Ref	
Overweight/obese	37	26 (70.3)	1.56	1.04–2.36	
1 Year prior to ovarian cancer diagnosis					0.22
Underweight	8	5 (62.5)	0.65	0.27–1.61	
Normal	298	186 (62.4)	1.00	Ref	
Overweight	223	145 (65.0)	1.20	0.96–1.51	
Obese	81	46 (56.8)	1.22	0.86–1.71	
Body shape					
Age 7					0.34
Thin	184	105 (57.1)	0.99	0.75–1.30	
Normal	190	125 (65.8)	1.00	Ref	
Fat	234	147 (62.8)	1.17	0.91–1.51	
Age 18					0.57
Thin	169	96 (56.8)	0.88	0.69–1.13	
Normal	384	249 (64.8)	1.00	Ref	
Fat	64	38 (59.4)	1.03	0.72–1.47	
1 Year prior to ovarian cancer diagnosis					0.48
Thin	33	19 (57.6)	0.87	0.52–1.44	
Normal	294	185 (62.9)	1.00	Ref	
Fat	295	185 (62.7)	1.11	0.89–1.37	
Development during lifetime					0.26
Remained thin	7	3(42.9)	1.20	0.37–3.86	
Decreased weight	185	114 (61.6)	1.28	0.91–1.80	
Remained average	78	53 (68.0)	1.00	Ref	
Increased weight	289	174 (60.2)	1.21	0.87–1.68	
Remained fat	49	33 (67.4)	1.68	1.08–2.63	

[1]Missing values for each factor were not listed.–[2]Adjusted for the age at diagnosis, epithelial ovarian cancer FIGO stage and WHO grade of differentiation.–[3]Likelihood Ratio tests for estimating overall association of each factor.

TABLE IV – LIFESTYLE FACTORS BEFORE DIAGNOSIS, FAMILY HISTORY OF CANCER AND EPITHELIAL OVARIAN CANCER SURVIVAL

Factor	Number of cases[1]	OCR deaths (%)	HR[2]	95% CI	*p*-value[3]
Social economic status					
1 (the lowest level)	90	52 (57.8)	1.00	Ref	0.58
2	99	66 (66.7)	1.24	0.84–1.82	
3	128	82 (64.1)	1.23	0.85–1.77	
4	126	79 (62.7)	1.02	0.70–1.48	
5	94	56 (59.6)	0.94	0.64–1.40	
6	58	35 (60.3)	1.31	0.84–2.05	
7 (the highest level)	34	24 (70.1)	1.10	0.67–1.81	
Alcohol intake in g/day					
Non-alcohol-drinker	305	196 (64.3)	1.00	Ref	0.54
<1.60 g/day	110	66 (60.0)	0.92	0.69–1.25	
1.60–3.99 g/day	90	54 (60.0)	0.79	0.58–1.09	
≥4.00 g/day	122	74 (60.7)	0.98	0.74–1.30	
Smoking					
Current status					0.78
Non-smoker	400	260 (65.0)	1.00	Ref	
Former	120	72 (60.0)	0.91	0.69–1.20	
Current	111	62 (55.9)	0.94	0.70–1.26	
Cigs/day					
Non-smoker	399	259 (64.9)	1.00	Ref	0.56
1–10	115	70 (60.9)	0.87	0.66–1.15	
11–20	93	53 (57.0)	0.96	0.70–1.31	
≥21	22	10 (45.5)	1.37	0.71–2.64	
Physical activity					
During childhood					0.61
None	91	58 (63.7)	1.00	Ref	
<1 hr/week	73	42 (57.5)	0.99	0.65–1.49	
1–2 hr/week	199	120 (60.3)	0.99	0.71–1.37	
>2 hr/week	263	170 (64.6)	1.15	0.84–1.57	
During age 18–30					
None	112	69 (61.6)	1.00	Ref	0.65
<1 hr/week	98	67 (68.4)	1.23	0.87–1.75	
1–2 hr/week	208	124 (59.6)	1.15	0.85–1.57	
>2 hr/week	209	130 (62.2)	1.18	0.87–1.61	
During recent years					
None	126	73 (57.9)	1.00	Ref	0.34
<1 hr/week	94	58 (61.7)	1.19	0.83–1.72	
1–2 hr/week	202	130 (64.4)	1.32	0.97–1.80	
>2 hr/week	206	129 (62.6)	1.13	0.83–1.54	
Lifetime development					
Remain inactive	97	59 (60.8)	1.00	Ref	0.35
Active to inactive	143	89 (62.2)	1.28	0.91–1.81	
Inactive to active	66	40 (60.6)	1.43	0.94–2.18	
Remain active	315	198 (62.9)	1.20	0.89–1.64	
Family history of cancer					
Breast cancer					0.48
No	560	341 (60.9)	1.00	Ref	
Yes	75	55 (73.3)	1.11	0.83–1.49	
Ovarian cancer					
No	598	368 (61.5)	1.00	Ref	0.94
Yes	37	28 (75.7)	0.98	0.66–1.47	
Breast or ovarian cancer					
No	533	321 (60.2)	1.00	Ref	0.58
Yes	102	75 (73.5)	1.08	0.83–1.40	

[1]Missing values for each factor were not listed.–[2]Adjusted for the age at diagnosis, epithelial ovarian cancer FIGO stage and WHO grade of differentiation.–[3]Likelihood Ratio tests for estimating overall association of each factor.

The study was approved by the Ethics Committee of the Karolinska Institutet, Sweden.

Statistical methods

Overall and stratified survival distributions were estimated and plotted using the Kaplan-Meier technique. Log-rank and Wilcoxon tests for equality of survivor functions were performed. Cox proportional hazard regression model was used to estimate the hazard ratios (HR) of the prognostic effects of each factor on the risk of death from EOC. The models and survival curves were adjusted for age at diagnosis, FIGO stage and WHO grade of differentiation. Likelihood ratio tests were used to evaluate overall association for each factor. The proportional hazard assumption was evaluated based on Schoenfeld residuals.[33] Separate analyses were conducted by stratifying women into either with early stage (FIGO stage I and II) or with advanced stage (FIGO stage III and IV). Possible interaction with overall use of HRT for each factor was also assessed. Statistical analyses were performed with Stata 9.2.[34]

Results

After about 8 years of follow-up, 396 patients (62.4%) had died from EOC- or OCR-specific causes, 44 had died from other causes, such as other cancers, cardiovascular diseases and external causes (accidents and suicides), and 195 were still alive. Since

TABLE V – REPRODUCTIVE, ANTHROPOMETRIC, LIFESTYLE, FAMILY HISTORY, CHARACTERISTICS AND EPITHELIAL OVARIAN CANCER SURVIVAL, STRATIFIED BY FIGO STAGE

Factor	FIGO Stage I and II				FIGO Stage III and IV			
	Case (OCR deaths)	HR[1]	95%CI	*p*-value[2]	Case (OCR deaths)	HR[1]	95%CI	*p*-value[2]
Parity								
Nulliparous	50 (14)	1.00	Ref	0.91	71 (65)	1.00	Ref	0.2
1 child	54 (14)	1.13	0.49-2.61		67 (57)	0.88	0.60-1.28	
2 children	97 (32)	1.25	0.60-2.63		138 (109)	0.71	0.52-0.98	
≥3 children	52 (15)	1.31	0.58-2.95		106 (90)	0.85	0.61-1.18	
Age at first birth				0.77				0.29
<19	20 (6)	1.00	Ref		39 (33)	1.00	Ref	
20–24	76 (27)	0.92	0.34-2.49		125 (109)	1.02	0.68-1.53	
25–29	80 (20)	0.68	0.25-1.87		105 (83)	0.92	0.60-1.42	
≥30	27 (8)	0.76	0.24-2.43		42 (31)	0.69	0.41-1.16	
Age at last birth				0.46				0.6
<24	31 (10)	1.00	Ref		51 (44)	1.00	Ref	
25–29	78 (24)	0.58	0.25-1.35		96 (77)	0.82	0.56-1.21	
≥30	94 (27)	0.62	0.28-1.40		164 (135)	0.85	0.59-1.21	
Oral contraceptive use				0.06				0.44
Never	163 (59)	1.00	Ref		270 (226)	1.00	Ref	
<3 years	45 (8)	0.42	0.16-1.09		61 (55)	1.23	0.89-1.71	
≥3 years	28 (5)	0.45	0.16-1.27		34 (28)	1.15	0.75-1.76	
Age at menarche				0.81				0.66
10-Dec	59 (18)	1.07	0.58-1.97		69 (60)	1.14	0.84-1.55	
13–14	120 (36)	1.00	Ref		198 (167)	1.00	Ref	
≥15	41 (10)	0.82	0.39-1.74		79 (64)	0.98	0.72-1.33	
Age at menopause				0.93				0.84
30–49	67 (21)	1.00	0.52-1.93		88 (74)	1.09	0.79-1.50	
50–51	75 (23)	1.00	Ref		127 (103)	1.00	Ref	
≥52	83 (26)	1.11	0.60-2.04		131 (111)	1.00	0.76-1.33	
Age at menopause for only natural menopause women				0.92				0.53
30–49	66 (21)	1.06	0.53-2.12		87 (73)	0.94	0.68-1.31	
50–51	58 (18)	1.00	Ref		106 (89)	1.00	Ref	
≥52	80 (25)	1.14	0.59-2.20		129 (109)	0.85	0.63-1.14	
Body mass index (BMI)								
Age 18				0.05				0.34
Underweight	40 (8)	0.57	0.24-1.34		51 (43)	0.88	0.62-1.24	
Normal	150 (46)	1.00	Ref		226 (189)	1.00	Ref	
Overweight/obese	15 (8)	2.16	0.99-4.73		22 (18)	1.35	0.83-2.21	
1 Year prior to enrolment				0.08				0.32
Underweight	1 (0)	NA	NA		7 (5)	0.64	0.26-1.59	
Normal	111 (30)	1.00	Ref		187 (156)	1.00	Ref	
Overweight	94 (34)	1.92	1.10-3.35		129 (111)	1.12	0.87-1.44	
Obese	35 (7)	0.86	0.35-2.12		46 (39)	1.31	0.90-1.90	
Body shape								
Age 7				0.29				0.25
Thin	81 (20)	0.61	0.31-1.19		103 (85)	1.12	0.82-1.51	
Normal	66 (22)	1.00	Ref		124 (103)	1.00	Ref	
Fat	95 (27)	0.94	0.51-1.72		139 (120)	1.26	0.96-1.66	
Age 18				0.28				0.74
Thin	75 (20)	0.62	0.34-1.13		94 (76)	0.92	0.70-1.21	
Normal	142 (43)	1.00	Ref		242 (206)	1.00	Ref	
Fat	29 (9)	0.80	0.37-1.74		35 (29)	1.08	0.72-1.63	
1 Year prior to enrolment				0.77				0.56
Thin	14 (4)	0.80	0.24-2.67		19 (15)	0.85	0.49-1.49	
Normal	117 (35)	1.00	Ref		177 (150)	1.00	Ref	
Fat	115 (35)	1.15	0.69-1.91		180 (150)	1.10	0.87-1.39	
Development during lifetime				0.31				0.39
Remained thin	4 (0)	NA	NA		3 (3)	1.46	0.45-4.75	
Decreased weight	72 (18)	0.90	0.34-2.37		113 (96)	1.36	0.95-1.96	
Remained average	20 (6)	1.00	Ref		58 (47)	1.00	Ref	
Increased weight	123 (36)	1.01	0.41-2.47		166 (138)	1.23	0.86-1.75	
Remained fat	23 (9)	2.00	0.70-5.75		26 (24)	1.56	0.94-2.58	
Alcohol intake in g/day				0.74				0.24
Non-alcohol-drinker	114 (36)	1.00	Ref		191 (160)	1.00	Ref	
<1.60 g/day	46 (13)	1.24	0.62-2.48		64 (53)	0.87	0.62-1.21	
1.60–3.99 g/day	39 (12)	1.09	0.51-2.29		51 (42)	0.73	0.51-1.03	
>4.00 g/day	54 (14)	0.79	0.40-1.53		68 (60)	1.04	0.76-1.42	
Smoking								
Current status				0.56				0.61
Non-smoker	153 (48)	1.00	Ref		247 (212)	1.00	Ref	
Former	49 (12)	0.89	0.42-1.89		62 (50)	0.93	0.68-1.28	
Current	49 (15)	1.37	0.72-2.60		71 (57)	0.86	0.64-1.17	
Cigs/day				0.83				0.27
Non-smoker	152 (47)	1.00	Ref		247 (212)	1.00	Ref	
1-10	41 (13)	1.30	0.64-2.61		74 (57)	0.83	0.62-1.13	

TABLE V – REPRODUCTIVE, ANTHROPOMETRIC, LIFESTYLE, FAMILY HISTORY, CHARACTERISTICS AND EPITHELIAL OVARIAN CANCER SURVIVAL, STRATIFIED BY FIGO STAGE (CONTINUED)

Factor	FIGO Stage I and II				FIGO Stage III and IV			
	Case (OCR deaths)	HR[1]	95%CI	*p*-value[2]	Case (OCR deaths)	HR[1]	95%CI	*p*-value[2]
11-20	42 (11)	1.12	0.52-2.42		51 (42)	0.92	0.65-1.30	
≥21	15 (3)	0.75	0.23-2.52		7 (7)	1.85	0.85-4.01	
Physical activity								
During childhood				0.94				0.53
None	31 (8)	1.00	Ref		60 (50)	1.00	Ref	
<1 hr/week	37 (14)	1.12	0.44-2.86		36 (28)	0.92	0.57-1.47	
1–2 hr/week	78 (20)	0.88	0.35-2.17		121 (100)	0.99	0.69-1.42	
>2 hr/week	104 (31)	0.98	0.42-2.27		159 (139)	1.16	0.83-1.64	
During ages 18–30				0.05				0.23
None	42 (16)	1.00	Ref		70 (53)	1.00	Ref	
<1 hr/week	40 (17)	1.15	0.55-2.42		58 (50)	1.27	0.85-1.89	
1–2 hr/week	89 (23)	0.55	0.28-1.09		119 (101)	1.33	0.94-1.88	
>2 hr/week	81 (18)	0.46	0.22-0.98		128 (112)	1.41	1.01-1.99	
During recent years				0.96				0.22
None	49 (15)	1.00	Ref		77 (58)	1.00	Ref	
<1 hr/week	36 (10)	1.08	0.44-2.61		58 (48)	1.19	0.80-1.78	
1–2 hr/week	83 (22)	0.89	0.41-1.93		119 (108)	1.40	1.00-1.97	
>2 hr/week	83 (27)	1.02	0.48-2.17		123 (102)	1.12	0.80-1.57	
Lifetime development				0.23				0.23
Remain inactive	33 (11)	1.00	Ref		64 (48)	1.00	Ref	
Active to inactive	60 (21)	1.17	0.53-2.57		83 (68)	1.26	0.86-1.84	
Inactive to active	35 (11)	0.74	0.30-1.83		31 (29)	1.59	0.99-2.55	
Remain active	121 (30)	0.62	0.29-1.30		194 (168)	1.33	0.95-1.86	
Family history of cancer								
Breast cancer				0.3				0.83
No	232 (66)	1.00	Ref		328 (275)	1.00	Ref	
Yes	21 (9)	1.53	0.72-3.26		54 (46)	1.04	0.75-1.43	
Ovarian cancer				0.77				0.85
No	245 (72)	1.00	Ref		353 (296)	1.00	Ref	
Yes	8 (3)	1.02	0.37-3.82		29 (25)	0.96	0.63-1.47	
Breast or ovarian cancer				0.26				
No	225 (63)	1.00	Ref		308 (258)	1.00	Ref	
Yes	28 (12)	1.49	0.77-2.88		74 (63)	1.00	0.99-1.02	0.99

[1]Adjusted for the age at diagnosis, epithelial ovarian cancer FIGO stage and WHO grade of differentiation.–[2]Likelihood Ratio tests for estimating overall association of each factor.

there was no substantial difference in overall survival, only results from EOC- and OCR-specific survival are reported below, and deaths from competing causes were censored.

Kaplan-Meier curves by FIGO stage (Fig. 1) and WHO grade of differentiation (Fig. 2) show clear effects on probability of survival. The risk of death was significantly higher in more advanced FIGO stages or poorer WHO grades of differentiation, especially in patients with FIGO stage IV (HR = 12.5, 95% CI = 8.0–19.7). Following adjustment for FIGO stage and WHO grade, age at diagnosis did not have a prognostic influence, except for evidence of a reduced risk of death in women diagnosed between ages 55 and 59 (Table I).

The HR for all studied reproductive factors (parity, age at first or last birth, oral contraceptive use, age at menarche or menopause) for EOC survival were close to 1, with no significant effects (Tables II–IV). There were no clear patterns regarding the relation between body size and shape in different periods of life or changes in body size and shape over time and EOC survival. At young age, BMI was significantly associated with EOC survival and women who remained obese throughout life had a 68% increased risk of death (HR = 1.7; 95% CI: 1.1–2.6). Socioeconomic status, alcohol consumption, history of cigarette smoking, physical activity in different periods of life, and family history of breast, ovarian or both breast and ovarian cancer were not associated with EOC survival. There were no significant changes in EOC survival when we confined the data analyses to patients without any missing information for the above studied factors (data not shown). Among women with early stage EOC (FIGO I and II), overweight at age 18 (HR = 2.2; 95%CI: 1.0–4.7) or 1 year prior to EOC diagnosis (HR = 1.9; 95%CI: 1.1–3.4) were associated with poorer survival; a risk modifying effect of overweight was not observed for women with advanced disease. Intense physical activity (≥2 hr/week) between ages 18 and 30 was associated with a decreased risk of death (HR = 0.5, 95%CI: 0.2–1.0) among women with early EOC stage, while the opposite was observed in women with advanced stage (HR = 1.4; 95%CI: 1.0–2.0). In this analyses stratified by FIGO stage, we found no associations between EOC survival and the other studied factors, namely parity, age of first or last birth, use of oral contraceptives, age of menarche or menopause, alcohol intake, smoking history and family history of breast or ovarian cancers (Table V).

Our previous study found evidence of a better prognosis in women that used HRT after diagnosis, although no effect was detected for women who used HRT prior to diagnosis of overall EOC, except for the serous EOC.[22] In our current study, the inclusion of the variables of HRT use before or after diagnosis in the statistical models did not alter any of the associations, neither was any significant interaction observed between HRT use before or after diagnosis and each of the above studied factors (data not shown).

Discussion

While the present results confirm that tumor FIGO stage and WHO grade of differentiation have a strong influence on EOC survival, we found no evidence that reproductive and life style factors, or family history of ovarian cancer or breast cancer represent important predictors of EOC survival. Our findings indicate that these prediagnostic characteristics have little or no influence on the biological behavior of EOC.

The main strength of the present study was its nationwide population-based prospective design combining field epidemiology with subsequent retrieval of information from medical records on clinical characteristics and a reliable follow-up on outcomes by the use of record linkage to an almost complete Cause of Death Register. One limitation was the possibility of selection from the

parent study of participants with less advanced disease, since some doctors did not consent to contact with women considered to be too ill. The available information on residual diseases was sparse and of varying quality in the records, and therefore not included in the analyses. We also decided not to include an indicator variable for chemotherapy treatment in the analysis, since treatment decisions are primary based on stage, and therefore the role of chemotherapy as a prognostic factor of its own could be disputed. In our data, 60% of the patients had FIGO grade III or IV disease, which is slightly lower than the expected 70%. Lack of detailed information on nonparticipants precluded assessment whether these patients differed in exposures or survival compared with study participants. Nonetheless, our estimates were based on comparisons between women who accepted to participate in the study, which can be considered as internally valid.[8,13,22] Misclassification of exposure may originate from the self-reported questionnaire. For instance, it is known that women tend to underestimate their weight, especially for obese women, causing misclassification of BMI and underestimation of a possible influence of overweight/obesity. Also, the measurements used to assess physical activity and body size and shape were crude and not validated. Using self-reported BMI 1 year prior to EOC diagnosis may not be representative of prediagnostic BMI and exercise capability, due to early onset cancer symptoms. This limitation may have hampered our capability to detect a potential prognostic influence of adult body size. However, we also used information about body size and shape and physical activity during childhood, young adulthood, as well as 1 year before EOC diagnosis. Thus, the available information allowed us to analyze patterns of body size and physical activity throughout life, which we believe provided adequate information to explore the prognostic effect from these factors. Despite the relatively large size of our cohort, the number of cases available for subgroup analyses was limited which may partially have contributed to the nonsignificant results for most of the factors under study. Furthermore, no information was available regarding changes of lifestyle after cancer diagnosis, or comorbidities such as diabetes mellitus, which may influence survival.

The strong effects of FIGO stage and WHO grade on prognosis observed in our cohort confirm results from earlier studies.[16,19,35] The lack of clear associations between reproductive factors and EOC survival was also observed in a Norwegian study[20] and in a Danish study, except for age at menarche, where the Danish study found a protective effect with increasing age.[28]

Both the Danish study[21] as well as a study conducted in Australia[30] reported a detrimental influence of smoking on ovarian cancer survival, which was not confirmed in our cohort, although our data suggest a nonsignificant increased risk for EOC mortality among heavy smokers. In the same Danish study[21] and in another study from China,[25] overweight about 5 years before diagnosis was associated with poorer ovarian cancer survival. Results from a recent US study indicate that obesity may be associated with both shorter time to recurrence and shorter overall survival among patients with advanced stage disease.[29] Although our cohort showed no association between obesity in the year before diagnosis and the risk of EOC death, women who reported being obese throughout life had a significantly increased EOC mortality. For women diagnosed with early stage EOC, overweight in young adult life or 1 year prior to EOC diagnosis was also associated with increased EOC mortality, while no effect was observed for women with the advanced stage of EOC.

Women in the highest category of physical activity during young adult life had a decreased mortality risk if they were diagnosed with early stage EOC; this observation is consistent with an etiological role of physical activity found in earlier studies.[13,15] In our study, a family history of breast or ovarian cancer did not affect survival. This is in agreement with 2 previous studies, one among BRCA1 negative patients, where there was no effect on survival according to family history of cancer[26] and another among nonfamilial EOC cases.[27]

We did not find any association between socioeconomic status and risk of EOC mortality. However, our assessment of socioeconomic status in this analysis was based on self-reported attained crude indicator of level of education.

To date, few large prospective studies have evaluated the effects of reproductive factors, lifestyle and family history simultaneously with tumor characteristics in relation to ovarian cancer prognosis. Taken together, the findings of these studies suggest a survival disadvantage for women with early menarche, and for those who were smokers or overweight before ovarian cancer diagnosis. Our data did not confirm any effect of these factors on EOC mortality overall, but indicated a survival disadvantage for women who were overweight in young adulthood or recent years and had low physical activity in young adult life for early stage EOC (FIGO stage I and II) only.

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