Smoking and Overweight: Negative Prognostic Factors in Stage III Epithelial Ovarian Cancer

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Abstract

Objective: **Smoking and overweight are associated with poorer prognosis in several cancer types. The prognostic effect of smoking and body mass index (BMI) on ovarian cancer is unknown.**

Methods: **Ovarian cancer cases were from the Danish MALOVA (MALignant OVArian cancer) study. Information on smoking status and BMI was obtained from a personal interview conducted closely after primary surgery. Cox regression models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for ovarian cancer–specific death in relation to smoking variables and BMI.**

Results: **A total of 295 women with stage III epithelial ovarian cancer were identified and followed to death or for a median of 7.3 years (range, 5.4-9.5 years). Median survival time for normal-weight never smokers was 2.8 years (95% CI, 2.3-3.2) compared with 1.2 years (95% CI, 0.8-2.3) for overweight current smokers. Current smokers had a significantly increased risk of ovarian cancer death compared with never smokers in multivariate Cox analysis (HR, 1.65; 95% CI, 1.22-2.24). The negative effect of smoking diminished with increasing time since a former smoker had stopped smoking (HR, 0.89; 95% CI, 0.80-0.98 per 5 years since stop of smoking). Overweight women also had an increased risk of ovarian cancer death (HR, 1.83; 95% CI, 1.38-2.42) compared with normal-weight women.**

Conclusion: **Smoking at the time of diagnosis and premorbid overweight were negative prognostic factors for ovarian cancer–specific survival. The negative effect of smoking decreased with increasing time since stop of smoking.** (Cancer Epidemiol Biomarkers Prev 2006; 15(4):798–803)

Introduction

Worldwide, >200,000 women were diagnosed with ovarian cancer in 2002 (1). This was mostly done in developed countries, where ovarian cancer is the sixth most frequent neoplasm regarding incidence as well as mortality (1). However, great variation in incidence and mortality exists within developed areas (2). Denmark has one of the highest incidence as well as mortality rates in the world, with an age-standardized incidence of 13.3 per 100,000 woman-years in 1998 to 2002 and a mortality rate of 9.0 per 100,000 woman-years in 1998 to 1999 (3). The Danish incidence and mortality of ovarian cancer has decreased only slightly over the last 20 years (3).

Ovarian cancer represents a great clinical challenge in gynecologic oncology. Because a majority of patients have no symptoms until the disease has metastasized, two thirds are diagnosed in an advanced stage (4), and despite intensive surgery and chemotherapy, the prognosis is poor with a 5-year survival of <25% in International Federation of Gynecology and Obstetrics stage III to IV patients (4-6).

The identification of factors related to survival and their use in predicting the prognosis of individual patients has importance in clinical research and practice. If patients with poor prognosis can be identified before a clinically evident recurrence, a more intensive monitoring will allow start of recurrence therapy at an earlier stage.

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Several clinical prognostic indicators have been shown to predict survival after ovarian cancer. These include Federation of Gynecology and Obstetrics stage, residual disease, histologic grade, age at diagnosis, performance status, presence or absence of ascites, and histologic type of tumor (7, 8). The prognostic value of lifestyle factors has only been sparsely explored, and one study only has examined the prognostic effect of overweight, as well as other lifestyle factors (e.g., smoking), on ovarian cancer survival (9). Only overweight was a significant prognostic factor, as too few cases were ever smokers to make any conclusions on the effect of smoking on survival. Other studies have shown that smoking has a negative prognostic effect on survival in patients diagnosed with cancer in the lung, breast, prostate, and stomach (10-13). Although smoking has not been found to influence ovarian cancer mortality (14), it is unknown whether smoking is associated with survival after ovarian cancer.

Overweight is an increasing problem in the Western world. In hormone-related cancers, such as breast and prostate cancer, overweight consistently seems to worsen the prognosis, whereas more inconsistency exists between overweight and non–hormone-related cancer (15-21). An association between overweight and ovarian cancer mortality has previously been reported (22, 23), and Zhang et al. (9) found that survival after ovarian cancer decreased with increasing premorbid body mass index (BMI).

The aim of the present study, based on ovarian cancer cases from a population-based case-control study, was to assess the prognostic value of smoking habits and BMI among women with stage III epithelial ovarian cancer.

Materials and Methods

The MALOVA Study. The present article is based on the Danish MALOVA (MALignant OVArian cancer) study, a

population-based multidisciplinary case-control study on ovarian cancer, covering epidemiology, biochemistry, and molecular biology with the purpose to investigate risk factors and prognostic factors of ovarian cancer. The design of the MALOVA study is described in detail elsewhere (24). Briefly, attempt was made to include all Danish women in the study area, aged 35 to 79 years, scheduled for an explorative laparotomy/laparoscopy because of the suspicion of ovarian tumor from December 1994 to May 1999. The study area consisted of gynecologic hospital departments in the municipalities of Copenhagen and Frederiksberg and the counties of Copenhagen, Frederiksborg, Roskilde, Western Sealand, Storstroem, Funen, and Southern and Northern Jutland.

Potential participants were asked to participate with a preoperative blood sample and a postoperative personal interview. On the basis of the peroperative findings (macroscopic impression or microscopy of frozen section), all ovarian cancer patients were personally interviewed, preferably while they were still hospitalized. The interview included sociodemographic variables, reproductive and gynecologic history, use of hormones, history of malignancy among mother and sisters, and lifestyle factors (smoking habits, height, and average weight in each decade of adult life and in the last 5 years before the ovarian cancer diagnosis).

The study database was linked to the Danish Cancer Registry every 2nd month to ensure that all eligible cases in the study area were included. If a woman was registered in the Danish Cancer Registry with ovarian cancer but had not primarily been included in the study, she was contacted by letter and asked to participate in an interview.

Federation of Gynecology and Obstetrics stages were obtained from clinical records and were reviewed independently by two gynecologists. Pathology reports and tissue specimens were collected from the different participating hospitals. In ~30% of the cases, a histopathology review was done in a blinded fashion by one pathologist specializing in ovarian tumors. In case of disagreement with the original hospital diagnosis, another pathologist reviewed the slides and a consensus diagnosis was obtained. In terms of invasiveness, concordance between the original hospital diagnosis and the review diagnosis was present in 98% of the cases. For cases where the histopathologic slides were not reviewed (70%), all histologic descriptions were scrutinized for consistency between the hospital description and the resulting diagnosis. Using this review procedure, it was possible to define the histologic type of tumor more precisely in 14% of the cases. Histologic grading of the tumors was done individually by two persons on retrospectively collected paraffin-embedded tissues slides selected for tissue array analyses. Grading was done according to the degree of atypical nuclei and tufting, and for architectural criteria as well grade 1 (<5% solid areas), grade 2 (from 5% to 60% solid areas), and grade 3 (>60% solid areas). If tumor grade given by the two persons was discrepant, they discussed each case, ending up with a conclusive grade for each patient.

Study Population. Overall, 959 woman with histologically verified malignant ovarian tumors were identified in the study area. A total of 45 women died before being contacted and 53 were considered too ill to participate, leaving 861 cases for the study. A total of 681 women (79.1%) were included in the MALOVA study. In the present analysis, we focused on the 295 women with stage III epithelial ovarian cancer who participated with an interview, thereby excluding 28 with nonepithelial ovarian cancer; 302 with stage I, II, or IV disease; and 56 with stage III, who only participated with blood and tissue samples. The median time between surgery and interview was 8 days (5-95 percentiles: 3-300 days). More than 74% were interviewed within 9 weeks.

Follow-up. In Denmark, every person has a unique personal 10-digit identification number (CPR number) encoding information of date of birth and sex. The Central Population Register, containing information on dates of birth, death, and emigration, assigns the CPR number to all residents shortly after birth and is updated on a daily basis. All cases were traced in this register and followed until death or October 20, 2004, whichever came first. In addition, all women were linked to a Danish hospital reference system and information about hospital admission to Department of Oncology and Gynecology was obtained. The relevant hospital files were collected and information on treatment (surgery and chemotherapy), performance status at start of chemotherapy, and cause of death, if relevant, was retrieved. In cases where the cause of death was uncertain according to the patient file, the women were linked to the Danish Causes of Death Register. At the end of the follow-up, 245 women had died of ovarian cancer, 5 had died of other causes, and 45 women were still alive. The median follow-up time was 7.3 years (range, 5.4-9.5 years).

Variables. To examine the prognostic effect of smoking, we included smoking status at the time of surgery (current, former, and never smoker), total number of smoking years, years since stop of smoking, and maximum daily use ever of cigarettes and cheroots per day. We calculated the maximum daily use ever of tobacco in grams per day with the tobacco content in a cigarette and a cheroot being, respectively, 1 and 3 g.

The premorbid BMI was calculated using the Quetelet's index expressed in kg/m^2 from the self-reported height and average weight over the last 5 years before the ovarian cancer diagnosis. The women were categorized into three weight status subgroups according to WHO (25): underweight (BMI < 18.5), normal weight (BMI 18.5-24.9), and overweight/obese (BMI ≥ 25). To examine whether weight status in young age or at the time of cancer development had the highest prognostic effect, we also calculated the average BMI at the age of 20 to 29 years from the stated average weight at this age.

Statistical Analyses. Survival time was calculated from date of surgery to the date of death or October 2004, whichever came first. The women who died from causes other than ovarian cancer were censored at date of death. Survival differences by smoking status at time of diagnosis and average weight status 5 years before the ovarian cancer diagnosis were illustrated by Kaplan-Meier curves. We used Cox proportional hazard model to evaluate the prognostic value of different aspects of smoking habits and overweight. The effect on risk of ovarian cancer death was estimated by hazard ratios (HR) and 95% confidence intervals (95% CI). All analyses were controlled for known prognostic factors according to literature, including current age (linear), histologic type (serous versus other), residual disease after primary surgery (no residual disease, debulked but present residual disease, or debulking impossible but biopsies were taken), and type of chemotherapy (platinum-based versus no platinum-based). Linearity of the associations with the continuous variables (age, smoking duration, maximum tobacco use, time since stop of smoking, and BMI) was investigated using a linear spline model. Except for BMI (showing a U-shaped association), no deviations from linearity were seen.

Results

Selected characteristics of the 295 women included in the study by ovarian cancer–specific survival status are shown in Table 1. The women who died of ovarian cancer tended to be older with more residual disease; fewer had serous adenocarcinoma and more had not received platinum-based chemotherapy. Finally, the women who died of ovarian cancer seemed to be heavier and are smoking more tobacco.

Table 1. Selected characteristics of 295 women with stage III ovarian cancer included in the Danish MALOVA study according to ovarian cancer–specific survival status

Characteristics	Alive/censored (N = 50), n (%)	Dead from ovarian cancer (N = 245), n (%)
Age at diagnosis (y)		
<40	2 (4.0)	5 (2.0)
40-49	12 (24.0)	42 (17.1)
50-59	19 (38.0)	82 (33.5)
60-69	14 (28.0)	63 (25.7)
≥70	3 (6.0)	53 (21.6)
Histologic type		
Serous adenocarcinomas	40 (80.0)	185 (75.5)
Mucinous adenocarcinoma	1 (2.0)	14 (5.7)
Endometrioid adenocarcinoma	2 (4.0)	14 (5.7)
Clear cell neoplasms	2 (4.0)	8 (3.3)
Papillary adenocarcinoma NOS	4 (8.0)	20 (8.2)
Undifferentiated carcinomas	1 (2.0)	4 (1.6)
Primary surgery radical		
Yes	15 (30.0)	16 (6.5)
No	34 (68.0)	183 (74.7)
No, only biopsies taken	1 (2.0)	45 (18.4)
Unknown	0	1 (0.4)
Platinum-based chemotherapy		
Yes	49 (98.0)	209 (85.3)
No	1 (2.0)	36 (14.7)
BMI (kg/m^2) at age 20-29 y		
<18.5	4 (8.0)	28 (11.4)
18.5-24.9	42 (84.0)	182 (74.3)
≥25.0	3 (6.0)	28 (11.4)
Unknown	1 (2.0)	7 (2.9)
BMI (kg/m^2) 5 y before diagnosis		
<18.5	2 (4.0)	10 (4.1)
18.5-24.9	39 (78.0)	137 (55.9)
≥25.0	8 (16.0)	95 (38.8)
Unknown	1 (2.0)	3 (1.2)
Smoking status		
Current smoker	13 (26.0)	77 (31.4)
Former smoker	14 (28.0)	64 (26.1)
Never smoker	23 (46.0)	103 (42.0)
Unknown	0	1 (0.4)
Duration of smoking (y)		
≤9	6 (22.2)	11 (7.8)
10-19	6 (22.2)	13 (9.2)
20-29	3 (11.1)	31 (22.0)
30-39	4 (14.8)	36 (25.5)
≥40	7 (25.9)	50 (35.5)
Unknown	1 (3.7)	0
Maximum daily tobacco use (g/d)		
≤9	6 (22.2)	23 (16.3)
10-14	5 (18.5)	32 (22.7)
15-19	2 (4.0)	23 (16.3)
20-24	10 (37.0)	43 (30.5)
≥25.0	3 (11.1)	18 (12.8)
Unknown	1 (3.7)	2 (1.4)
Time since stop of smoking (y)		
≤4	3 (21.4)	20 (31.3)
5-14	2 (14.3)	20 (31.3)
≥15	9 (64.3)	24 (37.5)

Overall, 90 women (30.5%) were current smokers and 78 women (26.4%) were former smokers. The median total smoking time was 36 years for current smokers and 22.5 years for former smokers, whereas the median maximum use of tobacco ever per day for current and former smokers was 20 and 10 g, respectively (data not shown). Finally, 10.8% of the women were overweight at age 20 to 29 years, whereas 35.4% were overweight 5 years before diagnosis.

The median survival times for overweight and normal weight women were 2.1 years (95% CI, 1.6-2.7) and 2.8 years (95% CI, 2.3-3.0), respectively, resulting in a difference of 7.8 months. The median survival time was 2.0 years (95% CI, 1.9-3.5) for current smokers and 2.7 years (95% CI, 2.3-2.9) for never smokers at time of diagnosis, resulting in a difference of 8.2 months (data not shown). According to the crude survival curves by weight status 5 years before diagnosis and smoking status at the time of diagnosis, overweight was associated with a shorter survival among never as well as current smokers (Fig. 1). Similarly, current smoking was associated with a reduced survival both among normal-weight and overweight women. Normal-weight, never-smoking women had the longest median survival time (2.8 years; 95% CI, 2.3-3.2), whereas overweight, current-smoking women had the shortest median survival time (1.2 years; 95% CI, 0.8-2.3).

We fitted multivariate Cox regression models including adjustment for the potentially confounding factors age, radicality of primary surgery, histology, and treatment with platinum-based chemotherapy. The HRs of ovarian cancer–specific death related to BMI and covariates are shown in Table 2. Residual disease after primary surgery was associated with increased risk of ovarian cancer death (HR, 2.17; 95% CI, 1.54-3.07 for debulking impossible; HR, 0.36; 95% CI, 0.21-0.60 for no residual disease left versus debulked women with residual tissue left) in the model, including adjustment for BMI and smoking status. Nonserous histologic type and no treatment with platinum-based chemotherapy were also associated with a significantly increased risk of ovarian cancer death (HR, 1.66; 95% CI, 1.21-2.27 and HR, 3.93; 95% CI, 2.49-6.21, respectively). Histologic grade and substage (IIIa, IIIb, and IIIc) had no prognostic effect on ovarian cancer survival, and adjustment for these covariates also did not affect the estimates for overweight and smoking (data not shown). On a subgroup of cases (~50%), we also had information about performance status at start of chemotherapy. However, adjustment for this covariate did not change the overweight and smoking estimates (data not shown).

Overweight in the 5 years before ovarian cancer diagnosis was associated with a significantly increased risk of ovarian cancer death even after adjustment for smoking status (HR, 1.83; 95% CI, 1.38-2.42). Risk of ovarian cancer death also seemed to be increased in underweight women compared with women of normal weight (HR, 1.30; 95% CI, 0.66-2.57), but the difference was reduced when adjustment for smoking status was done (HR, 1.07; 95% CI, 0.54-2.14). Including BMI 5 years before diagnosis continuously in the model required different slope estimates $\lessgtr$18.5 kg/m^2. Risk of death increased 5% by each unit increase of BMI over 18.5 kg/m^2 (HR, 1.05; 95% CI, 1.02-1.08).

Overweight at the age of 20 to 29 years was also associated with increased risk of ovarian cancer death (HR, 1.72; 95% CI, 1.15-2.58), but its effect was reduced when adjusted for BMI 5 years before diagnosis (HR, 1.30; 95% CI, 0.81-2.10). In contrast, the estimate for overweight 5 years before diagnosis was

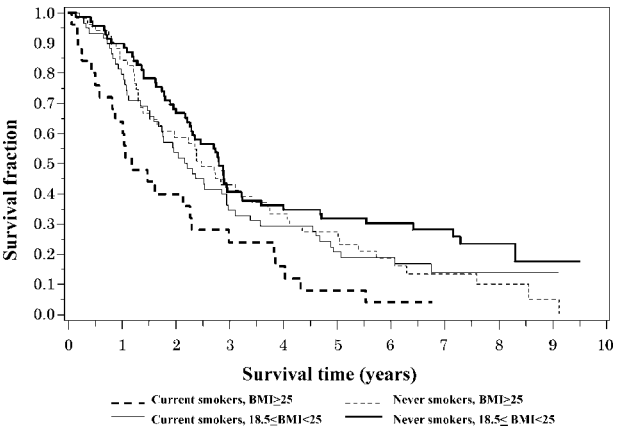

Figure 1. Survival after ovarian cancer by smoking status at the time of diagnosis (current versus never smoking) and weight status over the 5 years before diagnosis (overweight versus normal weight).

Table 2. HRs and 95% CI for death following stage III ovarian cancer according to BMI and covariates

Variables	Adjusted HR* (95% CI), n = 294	Adjusted HR† (95% CI), n = 290
Current age (per y)	1.01 (1.00-1.03)	1.01 (1.00-1.03)
Histologic type		
Serous adenocarcinomas	1.00 (Reference)	1.00 (Reference)
Nonserous carcinomas	1.40 (1.02-1.90)	1.66 (1.21-2.27)
Primary surgery radical		
Yes	0.36 (0.22-0.60)	0.36 (0.21-0.60)
No	1.00 (Reference)	1.00 (Reference)
No, only biopsy	2.16 (1.54-3.02)	2.17 (1.54-3.07)
Platinum-based chemotherapy		
Yes	1.00 (Reference)	1.00 (Reference)
No	2.80 (1.81-4.34)	3.93 (2.49-6.21)
BMI 5 y before diagnosis (kg/m^2)		
<18.5	1.30 (0.66-2.57)	1.07 (0.54-2.14)
18.5-24.9	1.00 (Reference)	1.00 (Reference)
≥25.0	1.71 (1.30-2.25)	1.83 (1.38-2.42)
Continuous per BMI unit		
For BMI < 18.5	0.88 (0.49-1.60)	0.91 (0.49-1.69)
For BMI ≥ 18.5	1.04 (1.01-1.07)	1.05 (1.02-1.08)
BMI at age 20-29 y (kg/m^2)		
<18.5	1.04 (0.69-1.57)	1.20 (0.79-1.84)
18.5-24.9	1.00 (Reference)	1.00 (Reference)
≥25.0	1.72 (1.15-2.58)	1.30 (0.81-2.10)
Continuous per BMI unit		
For BMI < 18.5	0.72 (0.52-1.00)	0.81 (0.59-1.12)
For BMI ≥ 18.5	1.06 (1.01-1.11)	1.01 (0.94-1.08)

*Adjusted for current age, radicality of surgery, histology, and platinum-based chemotherapy.
†Adjusted for current age, radicality of surgery, histology, platinum-based chemotherapy, smoking status, and continuous BMI 5 years before diagnosis.

unaffected by adjustment for overweight at a young age (data not shown).

Smoking at the time of diagnosis was associated with a significantly increased risk of ovarian cancer death compared with never smoking, the HR being 1.65 (95% CI, 1.22-2.24) when adjustment included BMI 5 years before diagnosis (Table 3). In contrast, no difference between former smokers and never smokers was seen. We also examined if there was a relationship between dose-related smoking variables and survival. All dose-related smoking variables could be analyzed as linear variables according to test for linearity (data not shown). The effect of duration of smoking and the maximum use of tobacco per day was similar among current and former smokers (data not shown). We found that risk of ovarian cancer death seemed to increase 5% per 5 years of smoking (HR, 1.05; 95% CI, 0.98-1.13) when adjustment was made for BMI 5 years before diagnosis, and, similarly, risk of death seemed to increase 4% per 5 g increase in maximum tobacco use per day (HR, 1.04; 95% CI, 0.94-1.15). In contrast, risk of ovarian cancer death decreased 11% per 5 years since stop of smoking (HR, 0.89; 95% CI, 0.80-0.98). When the dose-related smoking variables were mutually adjusted, only time since stop of smoking remained unchanged (HR, 0.89; 95% CI, 0.79-1.01), indicating this to be the most important factor in determining the risk profile (data not shown). Estimates of smoking duration per 5 years and maximum tobacco use per 5 g decreased to 1.00 (95% CI, 0.92-1.09) and 1.01 (95% CI, 0.91-1.15), respectively (data not shown). The negative effect of tobacco smoking on prognosis after ovarian cancer remained unchanged when the analysis was restricted to include only cigarette smoking (data not shown).

Discussion

High BMI during the last 5 years before diagnosis and smoking at the time of diagnosis were both associated with shorter survival of women with epithelial ovarian cancer, Federation of Gynecology and Obstetrics stage III. Longer duration of smoking and higher maximum tobacco use per day seemed to be negatively associated with the ovarian cancer–specific survival, whereas time since stop of smoking was positively associated with survival in former smokers.

A high proportion of Danish women are smokers compared with women in other countries. In our study group, 30% of the women were current smokers and they had a shorter survival after ovarian cancer compared with nonsmokers. This is in line with results on other cancer types (10-13), and although the exact mechanism is unknown, it has been suggested that tobacco-smoke carcinogens may induce a more aggressive cancer type (e.g., inducing p53 mutations), and that smoking may have a negative effect on the immune system, making it less capable of destroying the cancer cells (10, 26). Smoking has also been shown to be associated with other unhealthy lifestyle habits (27), which, in themselves may have a negative effect on survival. The difference in survival among current and former smokers might be explained by differences in the dose-related smoking patterns. Although the effect of increasing duration of smoking and increasing maximum use of tobacco per day was similar in current and former smokers, current smokers seemed to have been smoking larger amounts of tobacco per day and they had smoked for more years than former smokers. The negative effect of smoking on survival was diminished with increasing time since a former smoker had stopped smoking and surpassed the negative effect on survival of the total number of smoking years and the amount of tobacco used.

An association between overweight/obesity and poor survival might be expected in ovarian cancer due to difficulty in diagnosing and treating the tumor. Obesity might blur symptoms and delay diagnosis, causing larger tumors and more advanced disease at the time of diagnosis (28-31). Obesity may also hinder optimal surgical management and cause postoperative complications effecting short-term survival in nonovarian cancer patients (21, 32, 33). These associations have, however, not been shown in ovarian cancer patients

Table 3. HRs and 95% CI (CI) of death following stage III ovarian cancer according to smoking habits

Variables	Adjusted HR* (95% CI), n = 293	Adjusted HR† (95% CI), n = 290
Smoking status		
Never smoker	1.00 (Reference)	1.00 (Reference)
Former smoker	0.97 (0.71-1.34)	0.93 (0.67-1.30)
Current smoker	1.36 (1.00-1.84)	1.65 (1.22-2.24)
Duration of smoking (y)		
≤9	0.51 (0.25-1.05)	0.54 (0.26-1.12)
10-19	0.55 (0.27-1.11)	0.62 (0.30-1.27)
20-29	1.08 (0.65-1.78)	1.06 (0.64-1.76)
30-39	1.11 (0.70-1.76)	1.14 (0.71-1.81)
≥40	1.00 (Reference)	1.00 (Reference)
Per 5 y	1.06 (0.99-1.13)	1.05 (0.98-1.13)
Maximum daily tobacco use (g/d)		
≤9	0.98 (0.57-1.67)	1.03 (0.60-1.76)
10-14	0.78 (0.48-1.29)	0.84 (0.51-1.39)
15-19	1.04 (0.62-1.74)	1.05 (0.62-1.76)
20-24	1.00 (Reference)	1.00 (Reference)
≥25	1.18 (0.67-2.07)	1.23 (0.70-2.18)
Per 5 g	1.04 (0.94-1.14)	1.04 (0.94-1.15)
Time since stop of smoking (y)		
<5	1.66 (0.91-3.04)	1.91 (1.02-3.56)
5-14	1.55 (0.85-2.83)	1.57 (0.85-2.89)
≥15	1.00 (Reference)	1.00 (Reference)
Per 5 y	0.91 (0.83-1.00)	0.89 (0.80-0.98)

*Adjusted for current age, radicality of surgery, histology, platinum-based chemotherapy, and smoking status.
†Adjusted for current age, radicality of surgery, histology, platinum-based chemotherapy, smoking status, and continuous BMI 5 years before diagnosis.

(n = 128; ref. 31). Several other diseases, such as diabetes, hypertension, and cardiac disease, which by themselves may reduce tolerance to chemotherapy, are associated with obesity as well. However, it is unlikely that any of these factors could explain our findings, as we only studied cases with advanced disease (stage III), and we adjusted for the presence of residual disease after the primary operation and for treatment with chemotherapy. Further, almost all women died of ovarian cancer and not of comorbidities, making competing risk problems negligible, and according to the Kaplan-Meier survival curves the differences in survival were not established solely in the immediate postoperative period, indicating that postoperative complications could not explain our findings.

According to studies on renal cell cancer and advanced stomach cancer, overweight at diagnosis seems to increase survival (18, 20), supposedly because the phase of cachexia is postponed. This is in contrast to our findings, and findings in overweight breast cancer patients (34), suggesting that other mechanisms are important in hormone related cancers. Insulin resistance, which is compensated for by increased insulin production occurs with increasing BMI, and results in higher levels of free insulin-like growth factor-I (35). Insulin-like growth factor-I has a mutagenic effect on some cancer cell lines, stimulating cell proliferation and inhibiting apoptosis (36). Further, insulin-like growth factor-I and insulin both stimulate the synthesis of sex steroids and inhibit synthesis of the sex hormone-binding globulin, thereby increasing the bioavailability of sex steroids (35). In postmenopausal women, an increased aromatization of androstendione to estrone in peripheral adipocytes also contribute to an increased concentration of estrogens in the blood (35). Estrogens are known to stimulate growth of breast cancer cells and variations in sex hormones according to body mass has been suggested as an explanation for reduced survival in overweight postmenopausal breast cancer patients (37). Estrogens may similarly stimulate growth of ovarian cancer, as cultured tumor cells expressing estrogen receptors, which is the case in up to 60% of ovarian cancers, result in faster growth of metastatic tissue (38).

These mechanisms can only explain the decrease in ovarian cancer survival if the women remained overweight until the time of diagnosis. Alternatively, other mechanisms, such as development of more aggressive tumor types in overweight compared with normal weight women, may be possible. No information was attainable on BMI at the time of diagnosis in our study. Zhang et al. (9) found no association between survival and BMI at the time of the diagnosis, maybe because the weight was influenced by ascites and tumor mass, but an increased BMI 5 years before diagnosis and overweight at age 21 years were associated with reduced survival; however, no mutual adjustment was done.

Some strengths and limitations of the study should be considered: We followed prospectively a well-characterized ovarian cancer study population, which was homogeneous with regard to stage, resulting in a complete long-term follow-up of 5 to 9 years. To our knowledge, this is the first epidemiologic study that provides evidence that smoking at time of diagnosis has a negative effect on ovarian cancer survival, and the largest study until date on the effect of BMI on survival after advanced ovarian cancer. By using BMI 5 years before diagnosis for the calculations, we avoided the bias on BMI comprised by tumor mass or ascites. It may be a limitation that the anthropometric measures were self-reported. In general, women tend to underestimate their weight, especially obese women, resulting in misclassification of BMI and underestimation of the effect of overweight/obesity (39). It is also possible that we have underestimated the risk associated with tobacco smoking. As we know nothing about the postoperative smoking status of the women, it can be postulated that some women might have stopped smoking or have decreased their use of tobacco after the diagnosis of ovarian cancer.

In conclusion, our study covering a total follow-up time of 5 to 9 years on 295 stage III ovarian carcinoma patients showed that smoking at the time of diagnosis had a negative effect on ovarian cancer–specific survival. Number of smoking years and amount of tobacco smoked was inversely correlated to survival, but this negative effect of smoking was reduced with increasing time of nonsmoking preoperatively. Overweight 5 years before diagnosis decreased ovarian cancer–specific survival and was a more important prognostic factor than overweight in young adulthood. Further studies to confirm our results as well as to explain the mechanisms are needed.

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