Short Communication

Cigarette Smoking and Survival after Ovarian Cancer Diagnosis

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Abstract

We have examined the association between cigarette smoking and ovarian cancer survival in 676 women with invasive epithelial ovarian cancer, recruited into a case-control study in the early 1990s. Information about cigarette smoking and other personal and reproductive factors was obtained from a personal interview at the time of diagnosis. Cox proportional hazards models were used to evaluate the association between cigarette smoking and time to ovarian cancer death. Current smokers at diagnosis were more likely to die early than women who had never smoked [adjusted hazard ratio (HR), 1.36; 95% confidence interval (95% CI), 1.01-1.84]. Increased risks of dying were greater among those who had accumulated more pack-years of smoking (HR for 30+ pack-years compared with never smokers, 1.94; 95% CI, 1.41-2.66) and smoked more cigarettes per day (HR, 1.93; 95% CI, 1.37-2.73). All these associations were stronger among women with late-stage disease (HR for current versus never smokers, 1.58; 95% CI, 1.15-2.18). Time since quitting had little effect on survival after adjusting for lifetime smoking exposure. These results validate and extend recent findings and suggest that premorbid cigarette smoking is related to worse outcome in ovarian cancer patients. (Cancer Epidemiol Biomarkers Prev 2006;15(12): 2557–60)

Introduction

Smoking is associated with worse survival in several cancers. Some of these cancers are strongly related to smoking [e.g., lung (1, 2) and laryngeal (3)] and others are not [e.g., breast (4-6) and prostate (7)]. There are several different histologic subtypes of ovarian cancer, and although cigarette smoking does not seem to be associated with the majority of these subtypes, it has been linked to the development of tumors of the mucinous subtype (8-11). Because cancers in never smokers arise without any growth-promoting effects of carcinogens in cigarette smoke, the mechanisms of carcinogenesis in smokers and never smokers may be distinct and could lead to differences in tumor biology, natural history, and, possibly, survival. Little is known about the influence of smoking on ovarian cancer survival, but a recent article by Kjaerbye-Thygesen et al. (12) has suggested that smoking may be detrimental for ovarian cancer survival. Among 295 women diagnosed with stage III invasive epithelial ovarian cancer, this group found a statistically significant increased risk of death among current smokers [hazard ratio (HR), 1.65; 95% confidence interval (95% CI), 1.22-2.24] and that this negative effect of smoking diminished with longer times since quitting (HR, 0.89; 95% CI, 0.80-0.98 per 5 years since cessation of smoking; ref. 12). The only other study of which we are aware did not have the statistical power to examine the association between smoking and survival because too few cases were ever smokers (13). Here, we report our findings about the possible influence of smoking on ovarian cancer survival in more detail, with extended confounder control and among a larger group of women than before using data from an Australian case-control study.

Materials and Methods

Cases included 822 women with incident, histologically confirmed, primary epithelial ovarian cancer, diagnosed between 1990 and 1993, and identified through major gynecology-oncology centers in three Australian states. Of a total of 1,116 cases of epithelial ovarian cancer identified, 932 were eligible, and of these, 822 (88%) women took part. Women with borderline tumors were excluded (n = 146), leaving 676 women for these analyses. Each woman was interviewed by a specially trained nurse to obtain information about demographic, personal, and reproductive factors as described elsewhere (14). Women were asked if they had smoked regularly and, if so, at what age they started, numbers of cigarettes smoked per day (average and maximum), and periods of quitting for >1 year. Cumulative exposure to cigarettes in pack-years was calculated by multiplying the average number of cigarettes smoked per day by the number of years smoked and dividing by 20 (8). A regular smoker was defined as a woman who had smoked at least one cigarette per day for >1 year and a current smoker as one who was smoking within 1 year of the date of diagnosis/interview (8).

Information on stage at diagnosis, volume of residual disease, treatment, and various other clinical and pathologic prognostic variables was abstracted from women's medical records. At each hospital site, a subsample of records was abstracted independently by two researchers and discrepancies were resolved by consensus. Histologic diagnoses were reviewed centrally by a single pathologist in each state as part of the original case-control study. Full details have been presented elsewhere (15). The cohort was followed for mortality until June 30, 1999. Personal identifiers were used to link the cohort to state cancer registry records, and the Australian National Death Index with mortality follow-up was estimated to be complete (16).

Survival time was calculated from the date of diagnosis to the date of death (from ovarian cancer) or censored at June 30,

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1999 or death from another cause. The Kaplan-Meier technique was used to plot crude survival curves and estimate crude overall survival probabilities, with adjusted HRs and 95% CIs obtained from Cox regression models. The *P* for linear trend was calculated by the change in the likelihood ratio statistic for entry of a linear term for the continuous variable in the model and thus was a χ^2 test on 1 degree of freedom. All analyses were adjusted for known prognostic factors, age at diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage, and grade (15), in addition to histologic subtype, amount of residual disease, treatment with platinum-based chemotherapy, and body mass index (BMI) to allow for direct comparison with the results of Kjaerbye-Thygesen et al. (12). We also considered aspects of diet (vegetables and vitamin E intake, alcohol and caffeine consumption, and total kilocalories) and relevant etiologic factors (duration of oral contraceptive use, parity, history of tubal ligation, and hysterectomy) as potential confounders but did not include them in the final models as they did not alter the effect estimates. We did separate analyses restricted to women with late-stage disease (FIGO stages III and IV) so we could make direct comparison with the recent study results of Kjaerbye-Thygesen et al. (12). All analyses were done using the Statistical Package for the Social Sciences for Windows, version 10.0 (SPSS, Inc., Chicago, IL). Ethics approval for this study was received from the University of Queensland (Brisbane, Queensland, Australia) and from all metropolitan hospitals where patients were recruited. All participants gave informed consent before enrollment in the original study, including granting the study investigators full access to their medical records.

Results

In total, 822 women with epithelial ovarian cancer were enrolled in the founding case-control study. Of these, 676 had invasive tumors (458 late stage) and 146 had borderline tumors. There was a marked difference in survival according to tumor invasiveness, with only 2 of 146 women with borderline tumors dying during the follow-up period. Consequently, these women were omitted from all subsequent analyses. Among the 676 women with invasive epithelial ovarian cancer, 419 (62%) died from ovarian cancer during follow-up, giving a 5-year survival proportion of 44%. An additional 23 women had died from other causes, mainly diseases of the circulatory system (45%) and other neoplasms (32%), but our analyses refer only to ovarian cancer mortality and deaths from competing causes were censored.

Of the 676 women with invasive disease, 17% were current smokers and 22% were ex-smokers 1 year before their cancer diagnosis (Table 1). Current smokers were significantly younger than ex-smokers and nonsmokers ($P < 0.01$). The crude 5-year survival was 45%, 37%, and 49% for never smokers, ex-smokers, and current smokers, respectively. After adjusting for confounding factors, current smokers were at highest risk of early death (HR for current smokers versus never smokers, 1.36; 95% CI, 1.01-1.84; Table 2), and this effect was somewhat stronger among women with late-stage disease at diagnosis (HR, 1.58; 95% CI, 1.15-2.18). The associations between different measures of cigarette smoking and ovarian cancer survival are examined in greater detail in Table 3. The most notable result is that women who smoked more had worse survival. The HR for women who had smoked >30 pack-years was 1.94 (95% CI, 1.41-2.66). Consistent with this, worse survival was also seen among women who reported smoking more cigarettes per day. These associations were again a little stronger in the analysis restricted to women with late-stage disease (Table 3). There was a suggestion of a detrimental effect of starting smoking at earlier ages, although this was small and nonsignificant. Notable was the better survival among ex-smokers than current smokers, with survival increasing with longer time since quitting (HR, 0.80; 95% CI, 0.54-1.16 for 20+ years since quitting for all stages). However, when we included years since quitting as a continuous term and adjusted for amount of smoking (i.e., pack-years), the HRs were attenuated (all stage disease HR, 1.01; 95% CI, 0.92-1.12 per 5 years since quitting and HR, 0.98; 95% CI, 0.88-1.09 per 5 years since quitting for late-stage disease). Patterns of association became marginally stronger when we adjusted for etiologic and dietary factors known to influence survival in this cohort (results not shown). The limited number of invasive mucinous tumors prevented a detailed assessment of smoking effects stratified by histology, but ever-never comparisons did not suggest a greater effect on survival among women with mucinous tumors (data not shown).

Discussion

We have examined the association between smoking and survival among a large group of ovarian cancer patients recruited into a case-control study during the 1990s, with good information on known etiologic and prognostic factors. Our results suggest that current cigarette smoking (at diagnosis) is independently associated with worse survival, particularly among women with late-stage ovarian cancer. Furthermore, we found that the women who smoked the most had shorter survival.

The women in this cohort were unselected with regard to either prognosis or lifestyle factors (smoking), and follow-up was essentially complete. Assignment of cause of death and baseline clinical measures were made independently of lifestyle factors and are likely to have been quite accurate. Smoking assessment was unbiased with respect to outcome but will have been subject to random error, which may have attenuated any true effects. We did not collect any information about changes in smoking habits during the years leading up to diagnosis (habits could have been modified because of early symptoms) nor did we have information about smoking habits after diagnosis or treatment when it is likely that a proportion of patients may have stopped smoking or limited their tobacco use. This may have led to some misclassification of smoking status with some nonsmokers incorrectly classified as smokers, but any effect of this is again likely to have biased our results toward the null. Smoking has also been shown to be associated with other unhealthy lifestyle habits, which may in themselves have a negative effect on survival (16, 17). We were able to adjust for dietary factors that have been found to be potentially influential in these women, in addition to alcohol and caffeine consumption, and found that when we did so our effect estimates increased slightly. We have also adjusted for the major clinical factors that affect survival, although we lacked data about comorbidities. It is possible that there could be some residual confounding because of the imperfect nature of some of the measures; however, it is unlikely that this would be sufficient to completely explain the observed associations. The 95% CI and *P*s suggest that the effects of smoking are unlikely to be due to chance.

Only limited prior research has examined the association between cigarette smoking and ovarian cancer survival. Zhang et al. (13) in their cohort study of 214 Chinese women with ovarian cancer lacked the statistical power to examine the association between smoking and survival because only two cases were ever smokers. However, the recent study by Kjaerbye-Thygesen et al. (12), which examined the association between smoking (at the time of surgery) and survival in women with epithelial ovarian cancer, gives some context to our findings. Among 295 women with FIGO stage III invasive disease, they found that, after adjustment for age, radicality of surgery, histology, platinum-based chemotherapy, smoking

Table 1. Comparison of selected clinicopathologic and personal factors based on smoking history

	Smoking status			
	Never smoked* (n = 410), n (%)	Ex-smoker* (n = 150), n (%)	Current smoker* (n = 116), n (%)	P †
Age group (y)				
<40	25 (6)	10 (7)	17 (14)	
40-49	66 (16)	27 (18)	36 (31)	
50-59	129 (32)	31 (21)	31 (27)	
60-69	114 (28)	50 (33)	24 (21)	
70-79	76 (18)	32 (21)	8 (7)	<0.01
FIGO stage				
I	87 (22)	34 (23)	37 (32)	
II	40 (10)	9 (6)	11 (10)	
III	229 (57)	95 (64)	61 (52)	
IV	45 (11)	10 (7)	7 (6)	0.07
Histologic subtype				
Serous	226 (55)	92 (62)	51 (44)	
Endometrioid	63 (15)	15 (10)	17 (15)	
Mucinous	24 (6)	13 (9)	14 (12)	
Undifferentiated	28 (7)	11 (7)	14 (12)	
Mixed	31 (8)	9 (6)	8 (7)	
Clear cell	37 (9)	9 (6)	12 (10)	0.09
Grade				
Well differentiated	52 (13)	22 (15)	27 (24)	
Moderately differentiated	133 (33)	53 (35)	37 (32)	
Poorly differentiated	204 (51)	69 (47)	47 (41)	
Undifferentiated	14 (3)	4 (3)	3 (3)	0.16
Residual disease (cm)				
0-<1	167 (61)	61 (58)	53 (68)	
1-2	41 (15)	20 (19)	12 (15)	
>2	67 (24)	25 (23)	13 (17)	0.52
Platinum-based chemotherapy				
Yes	254 (72)	98 (75)	71 (69)	
No	100 (28)	32 (25)	33 (31)	0.60
BMI (usual) ‡				
<20	36 (9)	11 (7)	9 (8)	
20-25	221 (56)	89 (60)	71 (63)	
26-30	76 (19)	33 (22)	21 (19)	
>30	62 (16)	16 (11)	12 (10)	0.58

*Some column numbers (n) do not sum to total because some data are missing (FIGO stage, 1% missing; histologic subtype, <1% missing; grade, 1% missing; residual disease, 32% missing; platinum-based chemotherapy, 13% missing; and BMI, 3% missing).
†P for Pearson's χ^2.
‡Calculated using the women's usual prediagnostic weight.

status, and BMI, current smokers were more likely to die compared with nonsmokers (HR, 1.65; 95% CI, 1.22-2.24). They also found that the risk of death decreased by 11% for every 5 years since quitting (HR, 0.89; 95% CI, 0.80-0.98), but this analysis, unlike ours, was not adjusted for lifetime smoking exposure. The general concordance between the findings of our larger study of a wider range of tumor stages, with extended control of confounders, and those of Kjaerbye-Thygesen et al. (12) suggests that these effects may well be real.

Several different scenarios could explain our results. It is possible that smokers may delay diagnosis and treatment, which could result in worse survival. We, however, found no association between stage at diagnosis, histologic grade, or treatment with platinum-based chemotherapy and smoking status in our data. Alternatively, the carcinogens in tobacco could alter the behavior of the tumor directly. It is possible that tobacco may induce ovarian cancers to develop a more aggressive phenotype facilitating metastatic spread. For example, smoking-related carcinogens could cause mutations in genes associated with tumor progression. In prostate cancer, some speculates that a candidate gene may be a mutation in the *p53* tumor suppressor gene because it is observed only in a subset of prostate cancers and it has been shown to correlate with aggressive behavior in prostate cancer (18, 19), and observationally, studies have found that smokers were more likely to be diagnosed with advanced-stage or high histologic grade prostate cancers (20, 21). It is also possible that carcinogens in tobacco could influence survival indirectly by changing host characteristics. Tobacco use could alter host factors, such as hormone levels, which foster tumor progression or alter the immune defense system, making it less capable of destroying cancer cells (7). Epidemiologic evidence from the general cancer literature indicates that smoking may modify the progression and prognosis of other cancers.

Table 2. Multivariate analysis of the relationship between smoking and ovarian cancer survival

	All cases (n = 676)			Late FIGO stage (III and IV), n = 458		
	n	% Dead	Adjusted HR* (95% CI)	n	% Dead	Adjusted HR† (95% CI)
Smoking status						
Never smoked	410	63	1.0	283	81	1.0
Ever smoker	266	60	1.18 (0.96-1.45)	175	81	1.19 (0.96-1.49)
Ex-smoker	150	67	1.09 (0.86-1.39)	107	81	1.04 (0.80-1.35)
Current smoker	116	52	1.36 (1.01-1.84)	68	80	1.58 (1.15-2.18)

*Adjusted for age, stage, histologic subtype and grade, residual disease, platinum-based chemotherapy, and usual BMI.
†Adjusted for age, histologic subtype and grade, residual disease, platinum-based chemotherapy, and usual BMI.

Table 3. Ovarian cancer survival in relation to pack-years of smoking, maximum number of cigarette per day, age when first smoked, and years since last smoked

	All cases (n = 676)		Late FIGO stage (III and IV), n = 458	
	n*	Adjusted HR† (95% CI)	n*	Adjusted HR‡ (95% CI)
Never smoked§	410	1.0	283	1.0
Pack-years				
<10	86	0.79 (0.56-1.10)	59	0.80 (0.56-1.13)
10-19	54	1.18 (0.81-1.74)	34	1.24 (0.82-1.86)
20-29	34	0.98 (0.61-1.60)	22	1.08 (0.64-1.80)
30+	77	1.94 (1.41-2.66)	49	1.98 (1.40-2.81)
		P trend < 0.01		P trend < 0.01
Maximum cigarettes/day				
<10	38	0.93 (0.59-1.46)	26	0.93 (0.58-1.50)
10-19	64	1.05 (0.74-1.50)	46	1.10 (0.75-1.59)
20-29	80	1.03 (0.74-1.44)	50	0.98 (0.68-1.42)
30+	71	1.93 (1.37-2.73)	43	2.06 (1.43-2.98)
		P trend < 0.01		P trend < 0.01
Age first smoked (y)				
<16	36	1.50 (0.93-2.41)	22	1.69 (1.01-2.84)
16-19	110	1.25 (0.95-1.66)	71	1.20 (0.88-1.64)
20-24	63	1.07 (0.74-1.53)	43	1.10 (0.76-1.60)
25+	47	1.02 (0.68-1.53)	31	1.07 (0.70-1.66)
		P trend = 0.30		P trend = 0.28
Years since last smoked				
<10	46	1.32 (0.85-2.04)	28	1.40 (0.88-2.25)
10-19	44	1.22 (0.83-1.79)	30	1.13 (0.73-1.74)
20+	49	0.80 (0.54-1.16)	41	0.74 (0.50-1.10)
		P trend = 0.07		P trend = 0.01
Per 5 years‖		1.01 (0.92-1.12)		
Per 5 years¶				0.98 (0.88-1.09)

*Column numbers (n) do not sum to total because some data are missing (pack-years, 5% missing; maximum cigarettes per day, 5% missing; age first smoked, 4% missing; and years since last smoked, 4% missing).
†Adjusted for age, stage, histologic subtype and grade, residual disease, platinum-based chemotherapy, and usual BMI.
‡Adjusted for age, histologic subtype and grade, residual disease, platinum-based chemotherapy, and usual BMI.
§Reference category.
‖Adjusted for age, stage, histologic subtype and grade, residual disease, platinum-based chemotherapy, usual BMI, and pack-years of smoking.
¶Adjusted for age, histologic subtype and grade, residual disease, platinum-based chemotherapy, usual BMI, and pack-years of smoking.

In particular, it has been associated with worse survival among patients with laryngeal, lung, breast, and prostate cancer, and in some of these studies, this association was independent of screening behaviors, comorbidities or confounding by diet, or other lifestyle factors (1-7). On balance, this suggests that the harmful effect of smoking on survival might be mediated by direct biological pathways acting on tumor progression, but currently, the exact pathogenic mechanisms that underlie these observed associations remain unclear.

Despite the various uncertainties and given that the relations observed here are truly independent of etiologic, treatment, and clinicopathologic predictors, our findings suggest that worse survival from ovarian cancer can be added to the list of harms attributed to the smoking habit. Further data are required to both confirm the relation more securely and increase the precision of effect sizes of smoking and quitting and particularly to undertake subtype-specific analysis.

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