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Smoking may modify the association between neoadjuvant chemotherapy and survival from ovarian cancer

Linda E. Kelemen [a,*,1], Graham W. Warren [b,c,d], Jennifer M. Koziak [a], Martin Köbel [e], Helen Steed [f]

[a] Alberta Health Services-Cancer Control Alberta, 2210 2nd Street SW, Calgary, AB T2S 3C3, Canada
[b] Department of Radiation Oncology, Medical University of South Carolina, 169 Ashley Avenue, Charleston, SC 29425, USA
[c] Department of Cell and Molecular Pharmacology, Medical University of South Carolina, 169 Ashley Avenue, Charleston, SC 29425, USA
[d] Hollings Cancer Center, Medical University of South Carolina, 86 Jonathan Lucas Street, Charleston, SC 29425, USA
[e] Department of Pathology and Laboratory Medicine, University of Calgary, Foothills Medical Centre, 1403 29 Street NW, Calgary, AB, T2N 2T9, Canada
[f] Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, S5-131 Lois Hole Hospital, Royal Alexandra Hospital, 10240 Kingsway Ave, Edmonton, AB T5H 3V9, Canada

HIGHLIGHTS

- The interaction between smoking and chemotherapy on survival from ovarian cancer is unknown.
- Smoking reduced overall and progression-free survival among patients with mucinous ovarian cancer receiving adjuvant chemotherapy.
- Smoking reduced progression-free survival among all ovarian cancer patients receiving neoadjuvant chemotherapy.

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ABSTRACT

Objective. Tobacco smoking by cancer patients is associated with increased mortality. Less is known of the impact of smoking on recurrence risk and interaction with chemotherapy treatment. We examined these associations in ovarian cancer.

Methods. Patients were identified from the Alberta Cancer Registry between 1978 and 2010 and were oversampled for less-common histologic ovarian tumor types. Medical records were abstracted for 678 eligible patients on lifestyle, medical and cancer treatment, and review of pathology slides was performed for 605 patients. We estimated hazard ratios (HR) and 95% confidence intervals (CI) using Cox proportional hazard models adjusted for age at diagnosis, race, stage and residual disease.

Results. Among patients receiving adjuvant chemotherapy (N = 432), current smoking was significantly associated with shorter duration of overall (OS; HR, 8.56; 95% CI, 1.50–48.7) and progression-free (PFS; HR, 5.74; 95% CI, 1.05–31.4) survival from mucinous ovarian cancer only. There was no significant association between neoadjuvant chemotherapy and survival. However, among patients receiving neoadjuvant chemotherapy (N = 44), current smokers had shorter PFS (HR, 4.32; 95% CI, 1.36–13.8; N = 32 progressed/9 censored events) compared to never smokers, but the HRs were not statistically different across smoking categories (P interaction = 0.87).

Conclusions. Adverse associations were observed between smoking status and OS or PFS among patients with mucinous ovarian cancer receiving adjuvant chemotherapy. No significant effect was found from neoadjuvant chemotherapy on PFS overall; however, smoking may modify this association. Although needing replication, these findings suggest that patients may benefit from smoking cessation interventions prior to treatment with chemotherapy.

1. Introduction

Tobacco smoking and exposure to tobacco smoke have been causally linked to at least 13 cancers, including cancers of the oropharynx, larynx, esophagus, lung, upper (stomach, liver, pancreas, kidney, ureter) and lower (bladder, colorectum) gastro-intestinal organs and cervix and acute myeloid leukemia [1]. Cigarette smoking has many other adverse effects on the body, such as causing inflammation and impairing immune function [1], which are processes that are associated with the

* Corresponding author at: Department of Public Health Sciences, Medical University of South Carolina, Bioengineering Building, MSC955, 68 President Street, Charleston, SC 29425, USA.
E-mail addresses: kelemen@musc.edu (L.E. Kelemen), warrengw@musc.edu (G.W. Warren), jen.koziak@gmail.com (J.M. Koziak), martin.koebel@cls.ab.ca (M. Köbel), helen.steed@albertahealthservices.ca (H. Steed).
[1] Department of Public Health Sciences, College of Medicine, Medical University of South Carolina, 68 President Street, Charleston, SC 29425, USA., Hollings Cancer Center, Medical University of South Carolina, 86 Jonathan Lucas Street, Charleston, SC 29425, USA.

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Table 1
Descriptive characteristics of 600 patients with invasive tumors, AOVT study.

Characteristic	Non-smoker N = 311	Current smoker N = 86	Former smoker N = 145	Missing N = 58
Year diagnosed	1983–2010	1983–2010	1985–2010	1978–2010
Age at diagnosis, median (range)	55 (24–95)	54 (24–87)	58 (28–92)	57 (33–85)
Histology, N (%)				
Serous*	58 (18.6)	18 (20.9)	44 (30.3)	4 (6.9)
Mucinous	36 (11.6)	28 (32.6)	17 (11.7)	7 (12.1)
Endometrioid	119 (38.3)	15 (17.4)	52 (35.9)	19 (32.8)
Clear cell	94 (30.2)	24 (27.9)	31 (21.4)	28 (48.3)
Mixed cell	4 (1.3)	1 (1.2)	1 (0.7)	0
Stage, N (%)				
I	84 (27.0)	26 (30.2)	44 (30.3)	21 (36.2)
II	108 (34.7)	29 (33.7)	45 (31.0)	19 (32.8)
III	92 (29.6)	23 (26.7)	49 (33.8)	10 (17.2)
Missing†	27 (8.7)	8 (9.3)	7 (4.8)	8 (13.8)
Residual disease, N (%)				
No gross or macroscopic disease	133 (42.8)	37 (43.0)	57 (39.3)	21 (36.2)
Macroscopic	70 (22.5)	16 (18.6)	37 (25.5)	9 (15.5)
Missing	108 (34.7)	33 (38.4)	51 (35.2)	28 (48.3)
Vital status, N (%)				
Alive	182 (58.5)	46 (53.5)	88 (60.7)	27 (46.6)
Died	129 (41.5)	40 (46.5)	57 (39.3)	31 (53.4)
Progression, N (%)				
Not progressed	166 (53.4)	39 (45.3)	76 (52.4)	25 (43.1)
Progressed	111 (35.7)	34 (39.5)	52 (35.9)	20 (34.5)
Missing	34 (10.9)	13 (15.1)	17 (11.7)	13 (22.4)
Race, N (%)				
White	103 (33.1)	37 (43.0)	64 (44.1)	16 (27.6)
Asian	53 (17.0)	1 (1.2)	4 (2.8)	2 (3.4)
Other	155 (49.8)	48 (55.8)	77 (53.1)	40 (69.0)
Received any chemo, yes, N (%)	225 (72.3)	60 (69.8)	111 (76.6)	31 (53.4)
Received platin‡, yes, N (%)	221 (98.2)	60 (100)	108 (97.3)	27 (87.1)
Received neoadjuvant chemo, yes, N (%)	24 (10.7)	6 (10.0)	13 (11.7)	1 (3.2)

* 101 (81.4%) were high-grade and the remaining had unknown grade.
† Stage is missing for 9 serous, 12 mucinous, 20 endometrioid and 9 clear cell ovarian tumors.
‡ Among those who received chemotherapy.

development of various cancers [2]. The 2014 Surgeon General's Report [1] is the first large evidence review to report a causal association between tobacco use and adverse clinical outcomes for cancer patients and survivors, including increased all-cause mortality and cancer-specific mortality and increased risk for second primary cancers known to be caused by cigarette smoking such as lung cancer [1]. These findings provide the evidence to effectively change clinical practice by justifying the need to address tobacco use in patients with cancer.

There is insufficient, although suggestive, evidence to infer a causal relationship between tobacco use and the risk of recurrence, poorer response to treatment and increased treatment-related toxicity in cancer patients and survivors [1]. In a synthesis of the literature, the risk of cancer recurrence was consistently elevated in smokers compared to nonsmokers with a median relative risk of 1.15 reported among former smokers and 1.42 among current smokers with evidence of a dose response across studies that spanned different populations and types of cancers [1]. As reviewed in detail elsewhere [3], the biological effects of tobacco on existing cancer cells are diverse and can impair immune cells, generate reactive oxygen species and activate cellular receptors (e.g., β-adrenergic receptor, epidermal growth factor receptor) that lead to activation of intermediate signaling processes such as β-catenin, Wnt, Src, arachidonic acid and of phase I and phase II drug metabolizing enzymes, and a broad range of downstream signals that promote tumor growth and decrease the response to cytotoxic treatments [3].

Ovarian cancer ranks fifth in cancer deaths among women, accounts for more deaths than any other cancer of the female reproductive system [4] and has a 5-year survival rate of only 30% [5,6]. There are few investigations of potentially modifiable factors that could extend this survival rate. Studies evaluating the effects of tobacco smoke on survival from ovarian cancer have reported either no association [7–9] or an increased likelihood of mortality [10–12]. Furthermore, a recent investigation [13] reported adverse effects on overall survival among ovarian cancer patients receiving neoadjuvant chemotherapy compared to patients receiving primary debulking surgery followed by adjuvant chemotherapy despite the former group demonstrating less residual disease following surgery. However, the investigators [13] did not evaluate the influence of smoking on the effects of chemotherapy. The current report describes the overall study design of the Alberta Ovarian Tumor types (AOVT) study and corresponding analysis evaluating smoking status with overall and progression-free survival among patients diagnosed with ovarian cancer who received neoadjuvant or adjuvant chemotherapy.

2. Materials and methods

2.1. Overall study design and patients

The AOVT study was initiated in 2009 to investigate the rarer histologic types of ovarian cancer that were retrospectively identified from the Alberta Cancer Registry, a gold-star accredited population-based registry that records and maintains data on all new cancer patients and cancer deaths occurring in Alberta, Canada. The main inclusion criteria were women with histologically confirmed primary epithelial ovarian cancer of either mucinous, endometrioid or clear cell type diagnosed in any Alberta hospital in the year 2009 and earlier. In January 2012, we updated the list to include all new patients diagnosed in the year 2010 with mucinous, endometrioid, clear cell as well as serous ovarian cancers. We also included Alberta non-residents who were diagnosed and received their surgery in an Alberta hospital that housed their pathology reports/medical charts and tumor blocks. We excluded women with non-epithelial ovarian cancer or non-primary epithelial ovarian cancer, and non-residents who were diagnosed in Alberta but who received their surgery outside Alberta. The ethics review boards of the University of Calgary and Alberta Health Services approved the protocol.