Research Article

Cancer Epidemiology, Biomarkers & Prevention

Smoking at Diagnosis Is an Independent Prognostic Factor for Cancer-Specific Survival in Head and Neck Cancer: Findings from a Large, Population-Based Study

Linda Sharp[1], Joseph McDevitt[1], Anne-Elie Carsin[2], Christopher Brown[1], and Harry Comber[1]

Abstract

Background: Some studies suggest smoking may result in poorer clinical outcomes in head and neck cancer, but the evidence is heterogeneous and some of it is poor quality. In a large, population-based, study we investigated: (i) whether smoking at diagnosis is an independent prognostic factor for cancer-specific survival in head and neck cancer; and (ii) whether the association varies by site and treatment.

Methods: Head and neck cancers (ICD10 C01-C14, and C30–32) diagnosed from 1994 to 2009 were abstracted from the National Cancer Registry Ireland, and classified by smoking status at diagnosis. Follow-up was for 5 years or until December 31, 2010. Multivariate Cox proportional hazards models were used to compare cancer-specific death rates in current, ex-, and never smokers. Subgroup analyses by site and treatment were conducted.

Results: In total, 5,652 head and neck cancers were included. At diagnosis, 24% were never smokers, 20% ex-smokers, and 56% current smokers. Compared with never smokers, current smokers had a significantly raised death rate from cancer [multivariate HR, 1.36; 95% confidence interval (CI), 1.21–1.53]. The association was similar after restriction to squamous cell tumors. A significantly increased cancer-related death rate was seen for current smokers with oral cavity, pharyngeal, and laryngeal cancers. The association was stronger in surgically treated patients [HR, 1.49; 95% CI, 1.25–1.79; P(interaction) = 0.01]. Neither radiotherapy nor chemotherapy modified the effect of smoking.

Conclusions: Patients with head and neck cancer who smoke at diagnosis have a significantly increased cancer death rate.

Impact: Greater efforts are needed to encourage and support smoking cessation in those at risk of, and diagnosed with, head and neck cancer. *Cancer Epidemiol Biomarkers Prev; 23(11); 2579–90. ©2014 AACR.*

Introduction

Smoking is firmly established as a causal factor in the development of squamous cell tumors at many sites in the head and neck, including the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx (1); risk increases with increasing exposure, measured both in terms of duration and dose. Estimates of the population-attributable fraction associated with tobacco smoking range from 33% to 70%, depending on the country and sites considered (2–4).

Evidence is accruing that smoking may also be causally related with a range of adverse outcomes in patients with cancer, including higher all-cause and cancer-specific mortality and increased risk of second primary cancers (reviewed in ref. 5). For head and neck cancer specifically, several strands of evidence implicate smoking in poorer outcomes. Almost 20 studies (in which smoking status/tobacco exposure was defined in a variety of ways) have reported associations between smoking and perioperative complications after extirpative or reconstructive surgery (6). Smoking during treatment has been associated with a lower rate of complete response to radiotherapy (7) and a history of smoking with nonresponse to platinum-based induction chemotherapy (8). Several studies in different head and neck sites have reported associations between smoking prediagnosis, or a history of tobacco use, and poorer survival/increased risk of death, sometimes (but not always) in a dose-dependent fashion (9–13). One study, which assessed exposure in terms of pack-years, suggested that the effect of light, moderate, or heavy smoking on survival was limited to patients who had

[1]National Cancer Registry Ireland, Cork, Ireland. [2]Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.

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Corresponding Author: Linda Sharp, National Cancer Registry Ireland, Building 6800, Cork Airport Business Park, Kinsale Road, Cork, Ireland. Phone: 353-21-431-8014; Fax: 353-21-431-8016; E-mail: linda.sharp@ncri.ie

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radiotherapy or chemotherapy (14); another, in which smoking status was inferred from presence/absence of comorbid conditions, found that it was only present in those with human papilloma virus (HPV)–negative tumors (15); a third reported that smoking during radiotherapy was associated with an increased risk of death after adjusting for p16 status (16).

However, these findings are not universal; several studies reported no association between smoking and patient outcomes (6, 17–19). In addition, there are considerable methodologic limitations in the available evidence. Many studies were methodologically weak (6). Most were small (several included less than 200 patients) and involved patients either from single centers or clinical trials, potentially limiting generalizability. Smoking was assessed in different ways at different time points in different studies and studies used quite different definitions of smoking status/tobacco exposure for analysis. Some studies considered all-cause mortality (e.g., in refs. 11, 14, 16), which is influenced by the effects of smoking on risk of deaths from diseases other than cancer (20). Other studies failed to adjust the smoking-related risk estimates for other prognostic factors. Moreover, it remains uncertain whether any association between smoking and outcome varies by the tumor site or treatment received because most studies limited consideration to subgroups defined by a particular site or treatment received.

The primary aim of this population-based study was to investigate whether smoking status at diagnosis is an independent prognostic factor for cancer-specific survival among patients with incident head and neck cancer. The secondary aims were to determine whether this association varied according to site within the head and neck and treatment received.

Materials and Methods

Data

The data for the study were abstracted from the National Cancer Registry, Ireland. The Registry aims to record all cancers newly diagnosed in the population usually resident in Ireland, using an active registration process. Following internationally accepted registration and coding conventions, tumor registration officers collect patient (e.g., date of birth, address at diagnosis), tumor (e.g., cancer site, date of diagnosis), and treatment (surgery, chemotherapy or radiotherapy within a year of diagnosis) details for each case. This includes information on patients' smoking status at diagnosis, as recorded in their hospital records. Notifications of deaths are received on a regular basis from the Central Statistics Office and linked to registrations, using probabilistic matching methods, to identify dates and causes of death. Completeness of registration is estimated to be at least 97% (21).

Data were abstracted on all primary invasive head and neck cancers (ICD10 C01-C14 and C30-C32) diagnosed in persons ages 15 or older during 1994 to 2009. Individuals who had previously been diagnosed with another cancer (other than nonmelanoma skin cancer) were excluded ($n = 777$), as were those who were identified only from death certificates ($n = 80$). Ascertainment of deaths was complete to December 31, 2010, thus providing at least one full year of follow-up for each patient. Cancer-specific deaths were defined as those for which the underlying cause of death was coded as a cancer: at the same diagnosis site (ICD10 C00-C15, C30–32, C76, D00, D02, D10–11, D14, D37, and D38); of the same body system (C33–34, C39, C41, C44, and C49); of another specified site; or of unknown site (C79, C80, C97, D48; ref. 22).

Cases were grouped for analysis as follows: oral cavity (C02–06); pharynx (C01, C05.1, C05.2, C09, C10.0, C10.2, C10.3, and C11-C14); larynx (C32.0, C32.1, C32.2, and C10.1); and other sites, including salivary gland (C07 and C08) and nasal, paranasal and sinus tumors (C30.0, C30.1, and C31). Tumor morphology was classified as squamous (M 8050–8089) or other (all other specified and unspecified morphologies). Stage at diagnosis was defined according to the UICC classification (23). Patients were classified into one of seven regional health authorities based on address at diagnosis. Addresses were also used to assign each patient to a deprivation category These were created by Kelly and Teljeur (24) for small geographical areas (3,422 electoral divisions with an average population of 1,145 people) from five 2002 census variables: unemployment, social class, car ownership, type of housing tenure, and overcrowded housing. A deprivation score was computed for each small area; these were ranked from lowest to highest then grouped into five deprivation categories (ranging from 1 = least to 5 = most deprived). Individuals were categorized according to whether or not they had tumor-directed surgery within a year of diagnosis. Similarly, binomial variables were created to categorize patients by receipt of radiotherapy or chemotherapy (at least one session/administration) within the same time frame.

Smoking status at diagnosis was classified as follows: never smoked; ex-smoker (had smoked at least once every month in the past but not in the previous year); and current smoker (had smoked at least once every month in the previous year). For 14% of cases information on smoking at diagnosis was missing. Tumor stage information was incomplete or missing for 23% of patients and grade was unknown for 24%; both of these have previously been identified as important prognostic factors in population-based studies of head and neck cancer (25). Overall, 44% of patients had missing values for one or more of smoking status, stage and grade. We used multiple imputation by chained equations, in Stata version 11, to populate the missing data items in these fields with plausible values based on covariate information (26, 27). Multiple imputation is considered superior to other approaches to dealing with missing data largely because it produces less biased estimates than complete case analysis under a range of missing data scenarios and, under other scenarios, is more efficient than complete case analysis (28–30). As recommended by White and colleagues (27), 50 datasets were

generated, in which missing values for smoking status, grade and stage were imputed using a multinomial logistic regression model, including socio-demographic and clinical variables recorded by the Registry, indicators of cancer-specific death and death from any cause, and time to death or censor date (Supplementary Table S1).

Statistical analysis

The primary analyses were based on the dataset containing the imputed data. Survival time was computed for each patient from the date of diagnosis to date of death, 5 years of follow-up, or the censoring date, whichever occurred first. Noncancer deaths were censored to compute cancer-specific survival. Characteristics of cases classified as never, ex- and current smokers at the time of diagnosis were compared using χ^2 tests for categorical variables and the Wilcoxon rank-sum test for continuous variables. Curves of cumulative incidence of cancer-specific death up to 5 years after diagnosis were generated by smoking status. Unadjusted and multivariate HRs for cancer-specific death within 5 years by smoking status were computed using Cox proportional hazard regression. A backward stepwise approach was used to identify patient-related (e.g., age, marital status) and clinical (e.g., stage, grade) variables for inclusion in the model; variables were retained in the model if the Wald test P value was <0.05. For each covariate, a test for proportionality of hazards was performed (31). Because the hazards for stage were not proportional, and, therefore, violated the assumptions of Cox regression, instead of fitting stage as an explanatory variable, it was fitted as a stratification factor in all of the models. HR estimates and variances from the 50 imputed datasets were combined into an overall estimate and a variance–covariance matrix using Rubin's rules (32). The analysis was undertaken for all head and neck cancers initially. A sensitivity analysis was undertaken running the multivariate model for patients with squamous cell tumors only. The analysis was then repeated for subgroups of site (oral cavity, pharynx, larynx, and other) and treatment (cancer-directed surgery yes/no; chemotherapy yes/no; radiotherapy yes/no). In recognition of the fact that patients with head and neck cancer often receive multimodal therapy, we also conducted a *post hoc* analysis in which patients were categorized into one of five treatment groups: cancer-directed surgery alone; radiotherapy alone; radiotherapy and chemotherapy; cancer-directed surgery with radiotherapy and/or chemotherapy; and no cancer-directed treatment (i.e., no cancer-directed surgery, radiotherapy, or chemotherapy). Interactions between smoking and site, and smoking and treatment received, were tested by fitting cross-product terms in the relevant multivariate models.

In addition, supplementary analyses were conducted in the "complete case" dataset, which included all patients without missing data for smoking status, stage, or grade. This involved describing the patient characteristics, generating curves of cumulative incidence of cancer-specific death, and estimating unadjusted and adjusted HRs by smoking status.

Finally, to aid in interpretation of the results for cancer-specific survival, we inspected curves of cumulative incidence of deaths due to other causes by smoking status.

Results

Primary analyses: multiple imputed dataset

In total, 5,652 incident head and neck cancers were included in the analysis. After imputation, just under one-quarter (24%) were classified as never smokers at diagnosis, 20% as ex-smokers, and 56% as current smokers (Table 1). Twenty-six percent had tumors in the oral cavity, 31% in the pharynx, 30% in the larynx, and 13% at other sites, including salivary glands ($n = 438$, 8%) and nasal/sinus ($n = 294$, 5%). Eighty-three percent had squamous cell carcinomas. Just under half received cancer-directed surgery within a year of diagnosis, 69% had radiotherapy and 18% chemotherapy.

The distribution of age at diagnosis varied significantly by smoking status (Table 1). Current smokers were younger (median = 62 years) than ex-smokers (median = 66; Wilcoxon P value<0.01) and never smokers (median = 66 years; Wilcoxon P value<0.01). Smoking status varied significantly by site ($P < 0.01$), with the frequency of current smokers ranging from 34% in the "other" group through 54% among those with oral cavity cancers, to 61% to 62% in pharynx and larynx cases. There was also a significant association between stage and smoking status ($P < 0.01$), with a higher percentage of stage IV tumors among current smokers (43%) than ex-smokers (39%) or never smokers (37%). There were 2,604 cancer-specific deaths during the 5 years after diagnosis. Cancers at the same diagnosis site accounted for 91.4% of these deaths; cancers of the same body system for 5.4%; and cancers of unknown site for 3.2%. The cumulative incidence of cancer-specific death was highest in the current smokers, intermediate in ex-smokers, and lowest in never smokers (Supplementary Fig. S1A). The cumulative incidence of noncancer deaths followed a similar pattern (Supplementary Fig. S1B).

Table 2 shows univariate and multivariate HRs for smoking status. In the univariate analysis, compared with never smokers, ex-smokers had a modest, but nonsignificant, increased hazard whereas current smokers had a significantly increased hazard. This pattern persisted after adjustment for significant prognostic factors (age, marital status, deprivation category, and grade). Compared with never smokers, current smokers had a significantly raised rate of cancer death [multivariate HR, 1.36; 95% confidence interval (CI), 1.21–1.53]. The hazard was nonsignificantly raised in ex-smokers. After restriction to squamous cell tumors only, the multivariate HR for current smokers was virtually identical to that for all tumors and remained statistically significant (HR, 1.35; 95% CI, 1.19–1.54); the hazard for ex-smokers was nonsignificantly raised.

Table 1. Primary analysis[a]: demographic, tumor, and treatment characteristics of patients with head and neck cancer diagnosed 1994–2009: numbers and percentages of patients, overall and by smoking status at diagnosis, and *P* values from χ^2 tests[b]

Characteristic	Never smokers *N* (%)	Ex-smokers *N* (%)	Current smokers *N* (%)	All patients *N* (%)
Total	1,343 (100.0)	1,150 (100.0)	3,159 (100.0)	5,652 (100.0)
Age at diagnosis, y				
<55	350 (26.1)	223 (19.4)	833 (26.4)	1,406 (24.9)
55–64	267 (19.9)	286 (24.9)	1,044 (33.0)	1,597 (28.3)
65–74	334 (24.9)	345 (30.0)	782 (24.7)	1,460 (25.8)
75+	392 (29.2)	297 (25.8)	501 (15.8)	1,189 (21.0)
	$P < 0.01$			
Sex				
Male	739 (55.0)	882 (76.7)	2,504 (79.3)	4,125 (73.0)
Female	604 (45.0)	268 (23.3)	655 (20.7)	1,527 (27.0)
	$P < 0.01$			
Marital status				
Ever married	1,056 (78.6)	922 (80.2)	2,335 (73.9)	4,313 (76.3)
Never married	287 (21.4)	228 (19.8)	824 (26.1)	1,339 (23.7)
	$P < 0.01$			
Deprivation category				
1 (least deprived)	283 (21.1)	241 (21.0)	451 (14.3)	976 (17.3)
2	213 (15.9)	145 (12.6)	337 (10.7)	695 (12.3)
3	172 (12.8)	150 (13.0)	363 (11.5)	685 (12.1)
4	264 (19.7)	193 (16.8)	560 (17.7)	1,017 (18.0)
5 (most deprived)	410 (30.5)	422 (36.7)	1,447 (45.8)	2,279 (40.3)
	$P < 0.01$			
Cancer site				
Oral cavity	405 (30.2)	268 (23.3)	796 (25.2)	1,469 (26.0)
Pharynx	340 (25.3)	339 (29.4)	1,055 (33.4)	1,734 (30.7)
Larynx	264 (19.7)	395 (34.4)	1,058 (33.5)	1,717 (30.4)
Other	333 (24.8)	149 (12.9)	250 (7.9)	732 (13.0)
	$P < 0.01$			
Morphology				
Squamous cell	946 (70.5)	959 (83.4)	2,804 (88.8)	4,709 (83.3)
Others	397 (29.5)	191 (16.6)	355 (11.2)	943 (16.7)
	$P < 0.01$			
Stage at diagnosis				
I	353 (26.3)	300 (26.1)	620 (19.6)	1,272 (22.5)
II	251 (18.7)	215 (18.7)	579 (18.3)	1,046 (18.5)
III	236 (17.6)	190 (16.6)	617 (19.5)	1,044 (18.5)
IV	503 (37.4)	445 (38.7)	1,343 (42.5)	2,290 (40.5)
	$P < 0.01$			
Grade at diagnosis				
Well differentiated	278 (20.7)	205 (17.8)	554 (17.5)	1,037 (18.3)
Moderately differentiated	641 (47.7)	604 (52.5)	1,708 (54.1)	2,953 (52.2)
Poor/undifferentiated	424 (31.5)	342 (29.7)	897 (28.4)	1,662 (29.4)
	$P < 0.01$			
Cancer-directed surgery				
No	638 (47.5)	629 (54.7)	1,798 (56.9)	3,065 (54.2)
Yes	705 (52.5)	521 (45.3)	1,361 (43.1)	2,587 (45.8)
	$P < 0.01$			

(Continued on the following page)

Table 1. Primary analysis[a]: demographic, tumor, and treatment characteristics of patients with head and neck cancer diagnosed 1994–2009: numbers and percentages of patients, overall and by smoking status at diagnosis, and *P* values from χ^2 tests[b] (Cont'd)

	Never smokers	Ex-smokers	Current smokers	All patients
Characteristic	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**
Radiotherapy				
No	530 (39.5)	362 (31.4)	875 (27.7)	1,766 (31.2)
Yes	813 (60.5)	789 (68.6)	2,285 (72.3)	3,886 (68.8)
	$P < 0.01$			
Chemotherapy				
No	1,122 (83.6)	940 (81.8)	2,556 (80.9)	4,618 (81.7)
Yes	221 (16.4)	210 (18.2)	603 (19.1)	1,034 (18.3)
	$P < 0.01$			

[a]Multiple imputed dataset, $n = 5{,}652$.
[b]Tests of association between patient characteristics and smoking status.

Univariate and multivariate HRs for smoking status in each cancer site subgroup are shown in Table 3. In patients with oral cavity tumors, the rate of death due to cancer was raised nonsignificantly in ex-smokers and significantly in current smokers; the HRs were similar to those from the overall model. A similar pattern, and similar magnitude of effect, was seen for pharynx tumors. The death rate in current versus never smokers was significantly higher in patients with larynx tumors (multivariate HR, 1.52; 95% CI, 1.13–2.03). In patients with other tumors, the HR for current smokers was closer to unity, and nonsignificant. The test for interaction between site and smoking status was nonsignificant ($P = 0.97$).

When all patients were considered, there was a significant interaction between receipt of cancer-directed surgery and smoking status ($P = 0.01$). The multivariate HR for current versus never smokers was raised to a greater extent in those who had surgery (multivariate HR, 1.49; 95% CI, 1.25–1.79) than in those who did not (multivariate HR, 1.22; 95% CI, 1.05–1.42; Table 4). There was no interaction between receipt of radiotherapy and smoking status ($P = 0.14$) or between receipt of chemotherapy and smoking status ($P = 0.42$). Consistent with this, in subgroup analyses, the HRs for current versus never smokers were similar in those who did, and did not, receive radiotherapy, and in those who did, and did not, receive chemotherapy (Table 4).

Results of the *post hoc* analysis, in which patients were defined according to combinations of therapies received, are shown in Supplementary Table S2. Eighteen percent had cancer-directed surgery alone; 36% radiotherapy alone; 12% radiotherapy and chemotherapy; 28% surgery with radiotherapy and/or chemotherapy; and 12% and no cancer-directed treatment (i.e., no cancer-directed surgery, radiotherapy or chemotherapy). In all treatment strata, current smokers had an increased HR compared with never smokers, but the estimate was not statistically significant for those who had radiotherapy only and those who had radiotherapy and chemotherapy. The test for interaction between treatment and smoking was not statistically significant ($P = 0.25$).

Supplementary analyses: complete case dataset

The characteristics of the 3,144 patients in the complete case analysis are shown in Supplementary Table S3. The same pattern of association between smoking status and cumulative incidence of cancer-specific death was evident in this analysis as in the primary analysis (data not shown). When the multivariate model was run for complete cases, the pattern of association was similar to that in the primary analysis but the multivariate HRs were slightly further from unity (ex- vs. never smokers: HR, 1.19; 95% CI, 1.00–1.42; current vs. never smokers: HR, 1.45; 95% CI, 1.25–1.67; Supplementary Table S4); the HR for ex-smokers was borderline significant and that for current smokers significant.

Discussion

The major finding of this large, population-based study is that, among patients with head and neck cancer, smoking increased the rate of cancer-related death within 5 years of diagnosis. Current smokers (defined as those who smoked at least once every month in the year before diagnosis) had a 36% increased cancer death rate compared with those who had never smoked, and this was statistically significant, whereas ex-smokers had a modest, nonsignificant, increased rate in the overall analysis (and in almost every subgroup analysis). These findings were unchanged when restricted to squamous cell tumors and did not vary significantly by cancer site, suggesting that the association is consistent and robust. HRs for ex-smokers were consistently intermediate between those for never and current smokers; this has also been reported elsewhere (11, 13) and points to the plausibility of the association. Furthermore, it supports the conclusion of the

Table 2. Primary analysis[a]: Cox model for all head and neck cancers diagnosed 1994–2009: numbers and percentages of cancer-specific deaths over 5 years, univariate and multivariate HRs, with 95% CIs and Wald *P* values

	Cancer-specific deaths	Univariate analysis		Multivariate analysis[b]	
Variable	***N* (%)**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Total	2,604 (46.1)	—	—	—	—
Smoking status[c]					
Never smoker	540 (40.2)	1 (—)	<0.01	1 (—)	<0.01
Ex-smoker	494 (43.0)	1.11 (0.97–1.26)		1.11 (0.97–1.27)	
Current smoker	1,570 (49.7)	1.35 (1.21–1.50)		1.36 (1.21–1.52)	
Age at diagnosis					
<55	487 (34.6)	1 (—)	<0.01	1 (—)	<0.01
55–64	705 (44.1)	1.42 (1.26–1.59)		1.35 (1.20–1.52)	
65–74	690 (47.3)	1.66 (1.48–1.86)		1.79 (1.59–2.02)	
75+	722 (60.7)	2.85 (2.54–3.20)		3.48 (3.07–3.93)	
Sex					
Male	1,939 (47.0)	1 (—)	0.04	—	—
Female	665 (43.5)	0.91 (0.84–1.00)		—	
Marital status					
Ever married	1,921 (44.5)	1 (—)	<0.01	1 (—)	<0.01
Never married	683 (51.0)	1.23 (1.12–1.34)		1.11 (1.02–1.22)	
Deprivation category					
1 (least deprived)	391 (40.1)	1 (—)	<0.01	1 (—)	<0.01
2	309 (44.5)	1.17 (1.01–1.36)		1.16 (1.00–1.36)	
3	322 (47.0)	1.26 (1.08–1.46)		1.18 (1.01–1.37)	
4	487 (47.9)	1.29 (1.13–1.47)		1.26 (1.09–1.44)	
5 (most deprived)	1,095 (48.0)	1.33 (1.19–1.49)		1.22 (1.08–1.37)	
Period of diagnosis					
1994–1997	708 (54.1)	1 (—)	<0.01	1 (—)	<0.01
1998–2001	623 (51.5)	0.94 (0.85–1.05)		0.98 (0.87–1.10)	
2002–2005	702 (47.4)	0.81 (0.73–0.90)		0.87 (0.78–0.98)	
2006–2009	571 (34.5)	0.65 (0.58–0.73)		0.69 (0.61–0.77)	
Cancer site					
Oral cavity	625 (42.5)	1 (—)	<0.01	1 (—)	<0.01
Pharynx	1,013 (58.4)	1.60 (1.45–1.77)		1.30 (1.17–1.44)	
Larynx	658 (38.3)	0.85 (0.76–0.95)		1.03 (0.92–1.15)	
Other	308 (42.1)	1.02 (0.89–1.17)		0.88 (0.76–1.03)	
Grade					
Well differentiated	329 (31.7)	1 (—)	<0.01	1 (—)	<0.01
Moderately differentiated	1,326 (44.9)	1.61 (1.40–1.84)		1.28 (1.12–1.48)	
Poorly/undifferentiated	949 (57.1)	2.28 (1.98–2.63)		1.44 (1.24–1.67)	
Morphology					
Squamous cell	2,213 (47.0)	1 (—)	0.04	—	—
Other	391 (41.5)	0.90 (0.80–1.00)		—	
Stage at diagnosis					
I	233 (18.3)	1 (—)	<0.01	—	—
II	365 (34.9)	2.17 (1.82–2.60)		—	
III	515 (49.3)	3.52 (2.97–4.18)		—	
IV	1,491 (65.1)	6.05 (5.20–7.05)		—	

[a]Multiple imputed dataset, $n = 5{,}652$.
[b]The multivariate model, with stage fitted as a stratification factor as hazards were not proportional.
[c]At diagnosis.

Table 3. Primary analysis[a]: associations between smoking status and survival, by cancer site: numbers and percentages of cancer-specific deaths over 5 years, univariate and multivariate HRs, with 95% CI and Wald *P* values

Cancer site	Smoking status[b]	Cancer-specific deaths	Univariate analysis		Multivariate analysis[c]	
		N (%)	HR (95% CI)	*P*	HR (95% CI)	*P*
Oral cavity	Never smoker	151 (37.2)	1 (—)	0.01	1 (—)	0.02
	Ex-smoker	106 (39.7)	1.08 (0.83—1.41)		1.14 (0.87–1.50)	
	Current smoker	368 (46.2)	1.35 (1.10—1.65)		1.35 (1.09–1.67)	
Pharynx	Never smoker	184 (54.0)	1 (—)	0.02	1 (—)	<0.01
	Ex-smoker	191 (56.5)	1.14 (0.92—1.42)		1.14 (0.91–1.43)	
	Current smoker	638 (60.5)	1.27 (1.06—1.51)		1.32 (1.10–1.58)	
Larynx	Never smoker	77 (29.1)	1 (—)	<0.01	1 (—)	<0.01
	Ex-smoker	136 (34.3)	1.19 (0.87–1.61)		1.19 (0.86–1.65)	
	Current smoker	445 (42.1)	1.52 (1.16–1.99)		1.52 (1.13–2.03)	
Other	Never smoker	128 (38.5)	1 (—)	0.06	1 (—)	0.14
	Ex-smoker	61 (41.1)	1.16 (0.82–1.64)		0.89 (0.62–1.28)	
	Current smoker	119 (47.4)	1.40 (1.06–1.85)		1.24 (0.92–1.69)	

[a]Multiple imputed dataset, $n = 5{,}682$.

[b]At diagnosis.

[c]Adjusted for age at diagnosis, marital status, deprivation category, period of diagnosis, grade, and morphology; model stratified by stage as hazards for stage were not proportional.

recent report of the U.S. Surgeon General that smoking cessation may prolong the survival of patients with cancer compared with persistent smoking (5). In this study, there were indications that the effects of smoking may vary somewhat according to treatment(s) received, suggesting that the influence of smoking on treatment effectiveness may be a potential explanation for the findings.

Smoking and treatment

The relationship between smoking and survival was stronger among those who underwent cancer-directed surgery than among those who did not and, in the treatment combination analysis, the hazards for current versus never smokers were largest in the groups who had surgery, either alone or with radio/chemotherapy. This suggests that the relationship may be explained, at least in part, by effects of smoking on surgical outcomes. A recent major meta-analysis found that, in the 30 days after surgery, preoperative smoking increased risk of wound complications, general infections, pulmonary infections, neurologic complications, and admission to an intensive care unit (33). In patients with head and neck cancer specifically, in a recent review, Lassig and colleagues (6) reported that smoking was associated with systemic perioperative complications (such as pneumonia) in 6 of 14 studies of extirpative surgery without microvascular reconstruction and with complications in general in 11 of 22 studies of reconstruction. However, these authors noted that the quality of the evidence base was weak. Moreover, for postoperative complications to entirely explain the observed association, these would need to result in increased risk of death, and evidence appears to be lacking on whether those who develop such complications have shorter survival (other than in the 30 days after surgery).

The other main treatment modality for head and neck cancer is radiotherapy and a few studies have reported that smoking before and/or during treatment is associated with poorer survival following radiotherapy (7, 10, 34, 35). However, these studies did not include patients who had not had radiotherapy so could not investigate whether the smoking effect was modified by radiotherapy receipt. By comparing patients who did and did not have radiotherapy, we have been able to show that there is no differential impact of smoking by radiotherapy receipt; indeed, in the secondary analysis of treatment combinations, the HR for current versus never smokers was not statistically significant in the groups who had radiotherapy alone or together with chemotherapy. Furthermore, this suggests that the effects of smoking are unlikely to operate through influences on radiotherapy effectiveness.

Smoking, recurrence, and second primaries

The fact that there was a significantly increased rate of cancer death in current smokers who did not have surgery (albeit more modest than in surgical patients), and among patients who did not have any cancer-directed treatment, suggests that the effect of smoking cannot function entirely through influences on surgical outcomes. Prognosis is poor for most untreated patients with head and neck cancer (36) and these patients are likely to have a high chance of recurrence or distant metastases. There is limited evidence that smoking may

Table 4. Primary analysis[a]: associations between smoking status and survival, according to treatment received[b], numbers and percentages of cancer-specific deaths over 5 years, univariate and multivariate HRs, with 95% CI and Wald *P* values

		Treatment not received					Treatment received				
Type of treatment	**Smoking status[c]**	**Cancer-specific deaths**	**Univariate analysis**		**Multivariate analysis[d]**		**Cancer-specific deaths**	**Univariate analysis**		**Multivariate analysis[d]**	
		***N* (%)**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	***N* (%)**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Cancer-directed surgery	Never smoker	333 (52.3)	1 (—)	0.56	1 (—)	0.03	206 (29.3)	1 (—)	<0.01	1 (—)	<0.01
	Ex-smoker	321 (51.0)	0.97 (0.82–1.14)		1.09 (0.91–1.31)		173 (33.2)	1.18 (0.95–1.48)		1.10 (0.88–1.38)	
	Current smoker	972 (54.1)	1.04 (0.91–1.19)		1.22 (1.05–1.42)		597 (43.9)	1.72 (1.45–2.03)		1.49 (1.25–1.79)	
Radiotherapy	Never smoker	185 (34.9)	1 (—)	<0.01	1 (—)	<0.01	355 (43.7)	1 (—)	<0.01	1 (—)	<0.01
	Ex-smoker	133 (36.7)	1.11 (0.87–1.41)		1.03 (0.80–1.35)		362 (45.9)	1.09 (0.93–1.27)		1.18 (1.00–1.39)	
	Current smoker	406 (46.4)	1.52 (1.26–1.85)		1.42 (1.15–1.75)		1,164 (51.0)	1.25 (1.11–1.42)		1.34 (1.17–1.54)	
Chemotherapy	Never smoker	443 (39.5)	1 (—)	<0.01	1 (—)	<0.01	96 (43.7)	1 (—)	0.05	1 (—)	0.04
	Ex-smoker	380 (40.4)	1.05 (0.90–1.21)		1.06 (0.91–1.24)		115 (54.7)	1.39 (1.04–1.85)		1.36 (1.00–1.84)	
	Current smoker	1,267 (49.6)	1.36 (1.21–1.52)		1.35 (1.18–1.54)		303 (50.2)	1.32 (1.03–1.68)		1.40 (1.07–1.82)	

[a]Multiple imputed dataset, $n = 5{,}652$.

[b]Within a year of diagnosis.

[c]At diagnosis.

[d]Adjusted for age at diagnosis, marital status, deprivation category, period of diagnosis, grade, and morphology; model stratified by stage as hazards for stage were not proportional.

increase risk of recurrence or distant metastases (37–39), and this could explain our findings. However, large, robust, population-based studies are required to better clarify the magnitude of the relationships between smoking and recurrence and distant metastases and how this evolves over time from diagnosis, before firmer conclusions can be reached

Patients with head and neck cancer have a 36% cumulative risk of being diagnosed with a second primary cancer over 20 years, and the most common sites are the head and neck and lung (40). Risk of second primaries is higher in patients who continue to smoke after diagnosis (41, 42). Prognosis is poor following the development of a second primary (43) and may be further affected by continued smoking (44). Consistent with this, in our study population the crude rate of second primaries (other than nonmelanoma skin cancer) was higher among current/ex-smokers than never smokers (964 vs. 450/100,000), but the overall rate of second primaries ($n = 44$) was too low to explain the smoking-related survival differential.

Other potential mechanisms

In terms of other potential mechanisms, smoking impacts on inflammatory response (45) and immune competence (46). Squamous cell head and neck carcinomas are highly inflammatory in nature and express a number of cytokines and growth factors involved in inflammation (47). Specifically, pretreatment serum IL6 levels have been found to predict recurrence and poor survival in head and neck cancer (48); smoking is associated with high IL6 levels, and this may result from the adverse effects of smoking on sleep patterns (49). Beyond this, the consequences of smoking-induced inflammation and immune dysregulation are not well understood (50).

Smoking also influences DNA damage and repair capacity (51). Although a few small studies have reported associations between levels of expression of proteins involved in DNA repair and survival in head and neck cancer patients (52–54), none appear to have explored the influence of smoking on these relationships.

Smoking, diet, and body mass index are all interrelated (55). Pre- and post-diagnosis weight, and aspects of diet (including fruit and vegetable intake and alcohol consumption) have been associated with survival in patients with head and neck cancer in a few studies (56–58). This raises the possibility that associations between smoking and mortality are due to other lifestyle factors, which we were unable to control for in our study.

Another limitation of our study is that we did not have information on high-risk HPV status, which is an established prognostic factor. However, confounding by HPV is an implausible explanation for our findings. Although it is likely that a greater proportion of tumors in smokers, than non-smokers, are HPV-positive (because current smoking increases risk of oral HPV infection in a dose–response fashion; ref. 59), most studies suggest that HPV-positive head and neck cancers have a better prognosis than those which are HPV-negative (60).

Other sociodemographic prognostic factors

In multivariate models, several sociodemographic factors were associated with cancer-specific survival. The higher rate of cancer-related death in older patients is consistent with findings from other population-based studies of head and neck cancer (61, 62), as is the positive association between area-level deprivation and mortality (63–65). Moreover, the fact that our smoking results were adjusted for deprivation makes socioeconomic confounding an unlikely explanation for our findings in relation to smoking. The significantly increased rate of death in unmarried patients is consistent with a recent report from the United States (66) and similar patterns have been described for other cancers (see, for example, refs. 67–69). Various studies, including several from Ireland for other cancers, suggest that married patients are more likely to receive cancer-directed therapy than unmarried patients (67, 70–74). The explanations for these findings remain uncertain, but possibilities may include more active intervention by patients' families in treatment planning and/or more readily available social support during and after treatment among married patients.

Implications

This major question that follows from our findings is whether smoking cessation improves patient outcomes. Cessation shortly before surgery significantly reduces risk of respiratory and wound healing complications (75). The evidence base in head and neck cancer is limited but the few available studies suggest benefits of cessation in terms of radiotherapy response and risks of recurrence and second primaries (76). Recent results from a study of 382 head and neck cancers, from whom detailed smoking data were collected by questionnaire within 1 month of diagnosis, found that current smokers had higher overall mortality than those who had quit in the previous year (77). Consistent with this, in our study, ex-smokers—who were defined as those who had smoked regularly in the past but not in the year before diagnosis—had a notably lower hazard than current smokers. Altogether these observations suggest that benefits would accrue from greater efforts to encourage and support smoking cessation in those at risk of, and diagnosed with, head and neck cancer.

Strengths and limitations

The major strengths of this study are the size and population basis. Information on smoking was missing for 14% of patients. This figure lies between the percentages of patients in two head and neck cancer clinical trials for whom information on pack years was not available (8% and 18%; ref. 16). We used multiple imputations to populate the missing data and it was noteworthy that the cumulative incidence curves, and the HRs, were similar in the imputed and complete datasets. The prevalence of

current smokers in our head and neck cancer population (56%) was—as would be expected—considerably higher than in the general population (current smokers in the general population in 2003: males, 30%; females, 27%; ref. 78). As regards limitations, there may have been some misclassification among those whose smoking status was recorded. It seems most likely that some current smokers will have been recorded as never or ex-smokers, which would mean that the true effect of smoking at diagnosis on cancer-specific mortality has been underestimated. We lacked information on level of exposure (e.g., pack years), whether patients smoked cigarettes, pipes or loose tobacco, and whether they ceased smoking after diagnosis, and we were unable to distinguish the subgroup who had ceased smoking within the year before diagnosis. It is likely that smokers with cancer have more comorbidities than those who have never smoked (79). We did not have any data on comorbidities, so used cancer-specific survival to discount deaths from other causes, which could be due to smoking (e.g., cardiovascular disease). Although such analyses rely on the accuracy of recording of cause of death, there is no evidence that this is differential by smoking status. Competing risks, and differential follow-up, can be a concern in analyses of cause-specific survival. In this study, we were reassured by the fact that the cumulative incidence of noncancer-related deaths had a similar distribution in never, ex- and current smokers.

Conclusions

This large, population-based, study found that the patients with head and neck cancer who smoke at diagnosis have a significantly increased rate of death from cancer. This effect may operate through influences of smoking on surgical outcomes and disease recurrence.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funders had no role in study design; data collection, analysis, and interpretation; writing the report; or the decision to submit the article for publication.

Authors' Contributions

Conception and design: L. Sharp
Development of methodology: L. Sharp
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Sharp, J. McDevitt, A.-E. Carsin, C. Brown
Writing, review, and/or revision of the manuscript: L. Sharp, A.-E. Carsin, C. Brown, H. Comber
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H. Comber
Study supervision: L. Sharp

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