



Cause-specific excess mortality in patients treated for cancer of the oral cavity and oropharynx: A population-based study



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SUMMARY

Purpose: To assess cause-specific mortality in a large population-based cohort of 14,393 patients treated for squamous cell carcinoma of the oral cavity (OC) or oropharynx (OP) in The Netherlands between 1989 and 2006.

Patients and methods: Causes of death were obtained for 94.7% of 9620 patients who had died up to January 1, 2009. We assessed standardized mortality ratios (SMR) and absolute excess mortality (AEM), comparing observed cause-specific mortality with expected mortality for our cohort based on general population mortality rates.

Results: Median survival was 3.9 years. Overall, the study population experienced a 6-fold higher (95% Confidence Interval (95% CI) 5.9–6.1) mortality risk compared with the general population. After three years, 41% of OP and 29% of OC patients had died due to cancer of the oral cavity and pharynx. Additionally, OC and OP patients experienced high excess mortality from esophageal (SMR 10.6 and 17.9) and lung cancer (SMR 4.6 and 6.3). With regard to non-cancer deaths, the highest AEMs were due to diseases of the circulatory system, with OC patients experiencing an AEM of 11.3 per 10,000 person-years for ischemic heart disease. OP patients experienced excess mortality due to pneumonia (AEM 22.1 per 10,000 person-years). The risk of death due to diseases of the digestive system was for OP and OC patients where about equal (AEM 28.7 and 23.80, respectively). The SMR for death due to pneumonia was more than two times higher (4.4 vs. 1.7) for OP patients than for OC patients ($P < 0.001$). From 15 years after diagnosis, second tumors located outside the head and neck region accounted for most of the excess mortality.

Conclusions: Excess mortality in OC and OP patients appears to be dominated by effects of heavy tobacco and alcohol use with high AEM due to second tumors, respiratory, cardiovascular and gastrointestinal diseases. Patients with OP experienced more than two times higher risk of death due to pneumonia than OC patients. Therefore, awareness of this potential complication should be raised along with development of prevention strategies.

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Introduction

Squamous cell carcinomas of the oral cavity (OC) and oropharynx (OP) still carry a relatively poor prognosis. Despite some

successes of optimized multimodality therapy in improving disease control and overall survival [1,2] in The Netherlands, the 5-year relative survival (RS) for patients with OC and OP showed only modest improvements over the past two decades [3,4]. This modest improvement in survival can be partially explained by the fact that OC and OP patients experience competing excess mortality from second primary tumors (SPT) [5,6] and respiratory, cardiac and gastrointestinal diseases (e.g. liver cirrhosis or fibrosis) as a result of tobacco and alcohol abuse. Sepsis, organ failure,

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pulmonary embolism and vascular disease remain common causes of treatment-related mortality in head and neck cancer patients [7].

There is limited data on the specific causes of death experienced by OC and OP patients. Studies on overall survival and relative survival of OC and OP patients may underestimate the actual prognosis of these patients since most patients have a long history of tobacco and/or alcohol abuse, which may result in considerable competing mortality due to co-morbidity. Evaluation of the specific causes of death in OC and OP patients may therefore better inform doctors, patients and health care providers how to organize disease-oriented follow-up and surveillance protocols as well as alcohol and smoking prevention programs. Therefore in this study we assessed excess mortality due to causes other than head and neck cancer in a large population-based cohort of 14,393 patients with OC or OP diagnosed and treated in The Netherlands between 1989 and 2006.

Patients and methods

The study cohort comprised all patients diagnosed in The Netherlands with a squamous cell carcinoma of the oral cavity (OC) or oropharynx (OP) as first primary malignancy from 1989 to 2006, derived from the population-based Netherlands Cancer Registry (NCR). Patients were classified according to the International Classification of Diseases for Oncology, 3rd edition (ICD-0-3) with codes C020–C023, C03*, C04*, C050 and C06* for oral cavity; and C01, C024, C051, C052, C09* and C10* for oropharynx. Patients who could not be clearly classified into oral cavity or oropharynx as primary site were excluded from analysis (ICDO-3 codes C028, C029, C058 and C059; 396 patients).

The cohort was composed in accordance with NCR privacy regulations. Treatment data were limited to all primary treatments received up to 6–9 months after diagnosis. Nearly all patients with OC or OP in The Netherlands are treated in one of eight head and neck cancer treatment centers. Follow-up for second cancers and mortality was complete up to 01-01-2009. Information on cause of death was derived from linkage with the cause of death registry at Statistics Netherlands and classified according to International Classification of Diseases (10th revision; ICD-10). Comparison of cancer types denoted as cause of death with data on cancer occurrence according to the NCR showed considerable disagreement. Therefore, the cause of death was recoded such that in case a patient only had OC or OP according to the NCR, but had died of another type of cancer within 3 years after diagnosis of OC or OP, the cause of death was substituted for either OC or OP as recorded by the NCR.

The interval of 3 years was chosen as it was considered very unlikely that a second cancer would have been missed in this time interval, as patients are under rigorous clinical follow-up during this period. Similarly, if a patient had multiple cancers according to the NCR, but all of these were located in the oral cavity or oropharynx, and the patient died of another type of cancer than OC or OP within 3 years of the date of the first cancer diagnosis, the cause of death was substituted by OP, if one of the cancers was an OP, or by OC if all cancers were located in the oral cavity.

Statistical analysis

Cause-specific mortality in our cohort was compared with expected mortality based on age-, sex- and calendar-period specific mortality rates in the general population, taking into account

Table 1
Patient characteristics by subsite.

	All patients		OC		OP		OC versus OP P-value
	N	%	N	%	N	%	
Total	14,393		8488		5905		
Age							
Median(IQR)	61(53–70)		62(53–72)		59(52–67)		<0.001
<50	2342	16.3	1346	15.9	996	16.9	<0.001
50–64	6425	44.6	3434	40.5	2991	50.7	
65–74	3267	22.7	1972	23.2	1295	21.9	
≥75	2359	16.4	1736	20.5	623	10.6	
Sex							<0.001
Male	9038	62.8	4987	58.8	4051	68.6	
Female	5355	37.2	3501	41.3	1854	31.4	
Period							<0.001
1989–1994	3910	27.2	2434	28.7	1476	25.0	
1995–2000	4802	33.4	2771	32.7	2031	34.4	
2001–2006	5681	39.5	3283	38.7	2398	40.6	
Stage							<0.001
I	3131	21.8	2618	30.8	513	8.7	
II	2187	15.2	1458	17.2	729	12.4	
III	2209	15.4	1117	13.2	1092	18.5	
IV	6590	45.8	3129	36.9	3461	58.6	
Unknown	276	1.9	166	2.0	110	1.9	
Treatment							<0.001
Surgery	4432	30.8	3888	45.8	544	9.2	
Surgery + R T/CT	4469	31.0	3006	35.4	1463	24.8	
RT	3139	21.8	790	9.3	2349	39.8	
CT	189	1.3	64	0.8	125	2.1	
RT + CT	1104	7.8	244	2.9	860	14.6	
Other	146	1.0	86	1.0	60	1.0	
None	914	6.4	410	4.8	504	8.5	
Vital status							<0.001
Alive	4344	30.2	2850	33.6	1494	25.3	
Dead	10,049	69.8	5638	66.4	4411	74.7	

OC = oral cavity squamous cell carcinoma OP = oropharyngeal squamous cell carcinoma, IQR = Inter Quartile Range, RT = radiotherapy and CT = chemotherapy.

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