ORIGINAL ARTICLE

Non–Cancer-Related Deaths From Suicide, Cardiovascular Disease, and Pneumonia in Patients With Oral Cavity and Oropharyngeal Squamous Carcinoma

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Objective: To study non–cancer-related mortality rates over time and examine the possible causes for several major deaths in patients with oral cavity and oropharyngeal (OC/OP) cancer.

Design: Retrospective cohort analysis using the Surveillance, Epidemiology, and End Results (SEER) cancer registry data of the National Cancer Institute.

Main Outcome Measure: Cause-specific mortality rates during the first year after diagnosis of OC/OP cancer were calculated for 4 cohorts (1980-1984, 1990-1994, 2000-2003, and 2004-2007). The percentage changes over time were calculated. Standardized mortality ratios (SMRs) for suicide, cardiovascular disease, and pneumonia were calculated and compared with patient demographic and clinical characteristics.

Results: We analyzed data for 32 487 patients in 4 cohorts. From 1980-1984 to 2004-2007, mortality from suicide increased by 406.2% ($P=.01$), cardiovascular disease–related and pneumonia–related mortality decreased by 45.9% ($P<.001$) and 42.9% ($P=.009$), respectively, and rates of other non–cancer-related deaths did not change. Compared with the general population, patients diagnosed as having OC/OP cancer were at a significantly higher risk of mortality from suicide (SMR, 7.8; 95% CI, 4.6-12.4; $P<.001$), cardiovascular disease (SMR, 2.4; 95% CI, 2.1-2.7; $P<.001$), and pneumonia (SMR, 8.9; 95% CI, 6.8-11.5; $P<.001$) during the first year after cancer diagnosis. Risk factors for increased mortality included age of 55 to 64 years, marital status (including never married, divorced, or separated), advanced tumor stage (including regional and distant disease), treatment with radiotherapy alone, and pharyngeal tumor location.

Conclusions: Suicide rates have significantly increased in patients with OC/OP cancer since 1980 to 1984. Although cardiovascular disease– and pneumonia-related deaths have significantly decreased over time, they remain higher than the general US population. Increased knowledge of risk factors associated with non–cancer-related mortality in OC/OP cancer may lead to early intervention and enhanced overall survival.

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RECENT RESEARCH HAS increased awareness of the impact of depression, suicide, and cardiovascular disease on cancer mortality.[1-6] Studies of patients with breast cancer have shown a 30% to 50% increased risk of suicide during the first year after diagnosis.[1-3] Similar results in prostate cancer found suicide mortality increased 90% in the first 3 months and 40% during the first year after diagnosis.[4] Risk of cardiovascular death was also significantly higher in patients with prostate cancer than in the general population.[4]

Prior research suggests that suicide risk may vary according to anatomic region, with the highest risk in patients with cancer of the lung or bronchus, stomach, and oral cavity and oropharyngeal (OC/OP) cancer, during the first year after diagnosis,[6] which may relate to their high rate of depression. Rate of depression in patients with head and neck cancer has also been cited as among the highest of all oncology patients with an incidence of 15% to 50%.[7] Etiology of cardiovascular mortality among patients with cancer is incompletely understood but may be related to the disease process itself or effects of treatment, specifically radiation therapy.[8] The psychological stress generated by a cancer diagnosis can also have an impact on mortality, with effects mediated by including depression, suicide, and cardiovascular disease.[7] Despite documented high rates of depression and suicide among patients with head and neck cancer, specific studies examining suicide and other non–cancer-related deaths in patients with OC/OP squamous cell carcinoma (SCC) have not been published.

We examined non–cancer-related mortality from suicide, cardiovascular diseases, and pneumonia in US patients with OC/OP cancer during the first 3 years after diagnosis. Temporal analysis examined change in mortality rates and cause of non–cancer-related death of over the past 3 decades. Further analysis attempted to identify relationships between cause of death and patient characteristics, including age, sex, marital status, tumor stage, treatment modality, and tumor location.

METHODS

PATIENT POPULATION

Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute from 1973 to 2007 were used for analysis. The data cover 10% of the US population, released in April 2010 and based on the November 2009 submission.

Patients were identified using *International Classification of Disease–Oncology* (*ICD-O*) morphological (8070-8078) and topography (C000-C148) codes for primary malignant OC/OP SCC. Individuals previously diagnosed as having other primary malignant diseases were excluded. SEER data were linked to the National Center for Health Statistics/National Death Index to determine mortality rates and cause of death.[9] In the SEER data, *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes for death causes were used until 1999 and *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) used from 2000 onward. The following codes were used to identify suicide: 950-978 (1980-1999) and U03, X60-X84, and Y87.0 (2000-2007). Codes used for heart diseases were 390-398, 402, 404, and 410-429 (1980-1994) and I00-I09, I11, I13, and I20-I51 (2000-2007); cerebrovascular disease codes were 430-438 (1980-1994) and I60-I69 (2000-2007); and codes for pneumonia and influenza were 480-487 (1980-1994) and J10-J18 (2000-2007).

TEMPORAL ANALYSIS

To compare changes in cause of death over the past 3 decades, we designed 4 patient cohort periods: 1980 to 1984, 1990 to 1994, 2000 to 2003, and 2004 to 2007. Survival time was estimated from the date of cancer diagnosis to date of death, date the patient was last known to be alive, or end of follow-up, whichever occurred first. Follow-up time was further measured as person-years and grouped by sex, age (in 10-year age groups), and time since cancer diagnosis.

STATISTICAL ANALYSIS

In prior studies, occurrence of non–cancer-related death was defined as death from suicide, cardiovascular disease, or pneumonia during the 12 months after OC/OP cancer diagnosis. Percentage change in mortality rates between 1980-1984 and 2004-2007 was estimated by Poisson regression model, with adjustment for the effects of sex and age.

The 2 recent cohorts (2000-2003 and 2004-2007) were further examined to estimate risks of suicide and cardiovascular disease–related and pneumonia-related mortality during the first 3 years after cancer diagnosis using the standardized mortality ratio (SMR). The SMR was derived by dividing observed number of non–cancer-related deaths in the population of patients with OC/OP cancer by the expected number of non–cancer-related deaths in the general population of the SEER registries. Expected death rates were calculated by multiplying mortality rates from suicide, cardiovascular diseases, and pneumonia in 2000 to 2007 for sex and age (10-year categories) in the general population by the follow-up person-years of the 2000-2007 cohort.

Standard mortality rates were obtained from Centers for Disease Control and Prevention (http://wonder.cdc.gov/mortSQL.html). The 95% CIs of SMRs were estimated by Fisher exact method, and the statistical significance of SMRs was tested by the Poisson probability formula $P(x) = e^{-\mu}\mu^x/x!$, where μ is the expected death number and x is the observed death number.

The 2000-2007 cohort data were also used to analyze the relationship between mortality risk and patient demographics and clinical characteristics. To enhance study power for subgroup analysis, 3-year follow-up data were combined. During the analysis, SMRs and corresponding 95% CIs were estimated separately according to sex (male and female), age groups (<45, 45-54, 55-64, and ≥65 years), marital status at diagnosis (married, single or never married, divorced or separated, widowed, and unknown status), race/ethnicity (non-Hispanic white, black, or other), tumor stage (local, regional, distant, and unknown), treatment (no treatment, radiation alone, surgery alone, and radiation plus surgery), and tumor site (oral cavity, pharynx, tongue, tonsil, and other oral and pharynx). To compare the difference of mortality risk among patient groups, the risk ratio (RR) of SMRs was calculated by dividing a specific SMR by a baseline SMR. Statistical tests to determine if the specified SMR was different from the baseline SMR were based on the z-test [$z = \ln(\text{SMR})/\text{SE}_{\ln(\text{SMR})}$] with 2-sided P values.[10]

RESULTS

Temporal trends in mortality rates during the first year among patients with OC/OP cancer and malignant disease of other anatomic sites are shown in **Table 1**. Between 1980-1984 and 2004-2007, overall mortality rates (all causes of death) decreased by 19% (95% CI, –24.3% to –13.3%; $P < .001$) after adjusting the effects for age and sex. When analyzed by subsite of OC/OP cancer, mortality reduction over time ranged from 21.8% to 38.7% ($P < .05$ for all comparisons). Temporal changes in cancer-related mortality for other sites were generally not significant over time (some cancers with small numbers were grouped with other sites) with the exception of lung and nonepithelial skin cancers. A significant decrease in mortality was found in lung cancer (–50.3%; 95% CI, –71.3% to –13.9%; $P = .01$), whereas deaths related to nonepithelial skin cancer were increased by 140.3% (95% CI, 67.5%-244.9%; $P < .001$).

Among patients in 2004 to 2007, non–cancer-related deaths accounted for 20.3% of mortality [(10 + 92 + 30 + 125)/1268 × 100]; of all 257 non–cancer-related deaths, suicide, cardiovascular diseases, and pneumonia accounted for more than half (51.4%) of these deaths. From 1980-1984 to 2004-2007, rates of suicide, cardiovascular and pneumonia deaths changed significantly, whereas rates of all other non–cancer-related deaths remained stable over time with the exception of deaths related to chronic liver diseases (–73.6%; 95% CI, –89.8 to –31.3; $P = .006$). After adjustment for the effects of age and sex, suicide rate increased by 406% (95% CI, 39-1744; $P = .01$). In contrast, mortality from cardiovascular disease decreased by 45.9% (95% CI, –57.3 to –31.5, $P < .001$) and pneumonia by 42.9% (95% CI, –62.4

Table 1. Cause-Specific Mortality Rates Over Time in Patients With Oral Cavity and Oropharyngeal Cancer During the First Year After Diagnosis

Variable	No. (%) of Deaths				% Change Between 1980-1984 and 2004-2007[a]		
	1980-1984	1990-1994	2000-2003	2004-2007	Crude[b]	Age- and Sex-Adjusted Change (95% CI)	*P* Value[c]
Patients, total No.	**9342**	**8907**	**6914**	**7324**			
Person-years during the first year	8221.1	7909.5	6177.2	5681.4			
All causes of death	2369 (288.2)	2095 (264.9)	1484 (240.2)	1268 (223.2)	–22.5	–19.0 (–24.3 to –13.3)	<.001
Oral and pharyngeal cancers	1440 (175.2)	1221 (154.4)	791 (128.1)	661 (116.3)	–33.6	–30.7 (–36.8 to –24.0)	<.001
Tongue	374 (45.5)	288 (36.4)	249 (40.3)	184 (32.4)	–28.8	–25.7 (–36.8 to –24.0)	.001
Oral cavity	287 (34.9)	263 (33.3)	138 (22.3)	129 (22.7)	–35.0	–31.6 (–44.4 to –15.7)	<.001
Pharyngeal, oropharyngeal, hypopharyngeal	232 (28.2)	185 (23.4)	98 (15.9)	120 (21.1)	–25.2	–21.8 (–37.3 to 2.4)	.03
Tonsil	108 (13.1)	96 (12.1)	66 (10.7)	50 (8.8)	–33.0	–32.9 (–52.1 to –6.2)	.02
Other	439 (53.4)	389 (49.2)	240 (38.9)	178 (31.3)	–41.3	–38.7 (–48.5 to –27.1)	<.001
Other cancer sites	364 (44.3)	455 (57.5)	369 (59.7)	350 (61.6)	39.1	43.0 (23.4 to 65.7)	<.001
Lung and bronchus	51 (6.2)	55 (7.0)	32 (5.2)	17 (3.0)	–51.8	–50.3 (–71.3 to –13.9)	.01
Other nonepithelial skin	48 (5.8)	64 (8.1)	68 (11.0)	77 (13.6)	132.1	140.3 (67.5 to 244.9)	<.001
Esophagus	39 (4.7)	26 (3.3)	12 (1.9)	18 (3.2)	–33.2	–30.6 (–60.4 to 21.5)	.20
Bones and joints	15 (1.8)	5 (0.6)	12 (1.9)	13 (2.3)	25.4	36.6 (–35.0 to 187.2)	.41
Aortic aneurysm and dissection	6 (0.7)	0	3 (0.5)				
Other	33 (4.0)	39 (4.9)	18 (2.9)	17 (3.0)	–25.5	–19.8 (–55.4 to 44.2)	.46
SEER miscellaneous cancer	172 (20.9)	266 (33.6)	224 (36.3)	208 (36.6)	75.0	77.4 (44.8 to 117.2)	<.001
Other non–cancer-related mortality[d]	207 (25.2)	159 (20.1)	157 (25.4)	125 (22.0)	–12.6	–9.4 (–27.4 to 13.3)	.39
Chronic liver disease and cirrhosis	27 (3.3)	24 (3.0)	11 (1.8)	5 (0.9)	–73.2	–73.6 (–89.8 to –31.3)	.006
Accidents	16 (1.9)	7 (0.9)	9 (1.5)	16 (2.8)	44.7	47.6 (–26.4 to 196.1)	.27
Diabetes mellitus	14 (1.7)	10 (1.3)	5 (0.8)	6 (1.1)	–37.1	–30.4 (–73.3 to 81.4)	.46
Septicemia	8 (1.0)	10 (1.3)	12 (1.9)	9 (1.6)	62.8	74.1 (–32.9 to 352.0)	.26
Stomach and duodenal ulcers	8 (1.0)	2 (0.3)	2 (0.3)	1 (0.2)	–81.9	–80.6 (–77.6 to 55.4)	.12
Atherosclerosis	7 (0.9)	5 (0.6)	1 (0.2)	1 (0.2)	–79.3	–77.7 (–97.3 to 81.5)	.16
Other infectious diseases	6 (0.7)	9 (1.1)	8 (1.3)	11 (1.9)	165.3	148.8 (–8.3 to 421.8)	.07
Nephritis and nephritis syndrome	6 (0.7)	7 (0.9)	3 (0.5)	3 (0.5)	–27.6	–26.9 (–81.8 to 193.4)	.66
Alzheimer disease	4 (0.5)	3 (0.4)	4 (0.6)	3 (0.5)	8.5	19.1 (–73.4 to 432.4)	.82
Other causes of death	10 (1.2)	9 (1.1)	10 (1.6)	11 (1.9)	59.2	64.5 (–30.3 to 288.2)	.26
SEER; other causes of death	77 (9.4)	59 (7.5)	68 (11.0)	39 (6.9)	–26.7	–22.5 (–47.3 to 14.0)	.20
State document not available	24 (2.9)	14 (1.8)	24 (3.9)	20 (3.5)	20.6	21.9 (–32.8 to 121.1)	.51
Suicide	3 (0.4)	5 (0.6)	8 (1.3)	10 (1.8)	382.3	406.2 (39.0 to 1744)	.01
Cardiovascular disease	272 (33.1)	199 (25.2)	130 (21.0)	92 (16.2)	–51.1	–45.9 (–57.3 to –31.5)	<.001
Heart diseases	244 (29.7)	172 (21.7)	111 (18.0)	74 (13.0)	–56.1	–51.7 (–62.8 to –37.3)	<.001
Cerebrovascular	28 (3.4)	27 (3.4)	19 (3.1)	18 (3.2)	–7.0	2.4 (–43.4 to 85.3)	.94
Pneumonia	83 (10.1)	56 (7.1)	29 (4.7)	30 (5.3)	–47.7	–42.9 (–62.4 to –13.2)	.009

Abbreviation: SEER, Surveillance, Epidemiology, and End Results cancer registry data.
[a] Percentage change estimated using the Poisson regression model.
[b] Percentage changes not adjusted by age and sex.
[c] *P* values for statistical significance of age- and sex-adjusted percentage change between 1980-1984 and 2004-2007.
[d] Does not include mortality rates for suicide, cardiovascular disease, or pneumonia.

to –24.9; $P<.001$). In the first year after diagnosis of OC/OP cancer, suicide was reported only among male patients, with a rate of 2.4 per 1000 person years during 2004 to 2007 (10 per 4190.2 person years).

Table 2 shows SMRs based on the 2000-2003 and 2004-2007 patient cohorts. Suicide, cardiovascular disease–related and pneumonia-related death during the first 3 years after diagnosis of OC/OP were compared with the US population. Overall, risk of death from suicide or heart disease–related death was highest during the first year after cancer diagnosis and subsequently decreased with time. Compared with the general population, the excess risk of suicide was 7.8 (95% CI, 4.6-12.4; $P<.001$) during the first year, 3.7 (95% CI, 1.8-6.6; $P<.001$) during the second year, and 2.5 (95% CI, 0.5-7.3) during the third year. Similar decreasing trends were seen in heart disease: calculated SMRs were 2.4 (95% CI, 2.1-2.8; $P<.001$), 1.5 (95% CI, 1.2-1.9; $P<.001$), and 1.3 (95% CI, 1.0-1.8; $P=.04$), respectively. In contrast, the SMR associated with cerebrovascular disease– and pneumonia-related mortality did not demonstrate clear temporal trends: the SMR for cerebrovascular diseases was 2.3 (95% CI, 1.6-3.2; $P<.001$) during the first year and 2.1 (95% CI, 1.1-3.5; $P=.01$) during the third year, and the SMRs for pneumonia was 8.9 (95% CI, 6.8-11.5; $P<.001$) and 10.4 (95% CI, 6.9-15.0; $P<.001$), respectively.

Data from the 2000-2007 patient cohorts were used further to investigate relationships between patient demographics, clinical characteristics, and suicide risk (**Table 3**) During the 3 years after OC/OP cancer diagnosis, no suicide deaths occurred among female patients; however, 32 suicides occurred among male patients. Trends for increased risk of suicide were seen among men aged 55-64 years who never married or were divorced, separated, or

Table 2. Risk of Suicide and Cardiovascular Disease–Related or Pneumonia-Related Death in the First 3 Years After Diagnosis During 2000-2007, Compared With the US Population

	First Year (PY = 11 858.6)		Second Year (PY = 8237.8)		Third Year (PY = 6013.6)	
Cause of Death	O/E Death[a]	SMR (95% CI)[b]	O/E Death	SMR (95% CI)	O/E Death	SMR (95% CI)
Suicide	18/2.3	7.8 (4.6-12.4)	11/3.0	3.7 (1.8-6.6)	3/1.2	2.5 (0.5-7.3)
Cardiovascular	222/93.1	2.4 (2.1-2.7)	88/57.7	1.5 (1.2-1.9)	58/40.1	1.4 (1.1-1.9)
Heart diseases	185/76.9	2.4 (2.1-2.8)	72/47.9	1.5 (1.2-1.9)	44/33.3	1.3 (1.0-1.8)
Cerebrovascular	37/16.2	2.3 (1.6-3.2)	16/9.8	1.6 (0.9-2.7)	14/6.8	2.1 (1.1-3.5)
Pneumonia	59/6.6	8.9 (6.8-11.5)	26/3.9	6.7 (4.4-9.8)	28/2.7	10.4 (6.9-15.0)

Abbreviations: E, patient expected; O, patient observed; PY, person-years; SMR, standardized mortality ratio.
[a] The E patient expected deaths, estimated using sex- and age-matched mortality rates in the US population.
[b] The SMR calculated by dividing O deaths by E deaths.

Table 3. Demographic and Clinical Risk Factor Analysis for Suicide During the First 3 Years After Diagnosis Using 2000-2007 Data

Demographic or Clinical Risk Factor	O/E[a]	SMR[b] (95% CI)	RR[c] (95% CI)	*P* Value
Sex				
Female	0/0.4	NA	NA	
Male	32/4.8	6.7 (4.6-9.4)	NA	
Age group, y				
≥65	11/1.7	6.5 (3.2-11.6)	1 [Reference]	
55-64	14/1.3	10.8 (5.9-18.1)	1.7 (0.6-4.7)	.34
45-54	7/1.4	5.0 (2.0-10.3)	0.8 (0.2-2.9)	.70
<45	0/0.4	NA	NA	
Marital status				
Married	15/2.8	5.4 (3.0-8.8)	1 [Reference]	
Single, never married	6/0.8	7.5 (2.8-16.3)	1.4 (0.4-5.3)	.63
Divorced or separated	6/0.6	10.0 (3.7-21.8)	1.9 (0.5-7.1)	.37
Widowed	3/0.3	10.0 (2.1-29.2)	1.9 (0.3-14.0)	.55
Unknown	2/0.3	6.7 (0.8-24.1)	1.2 (0.1-18.0)	.87
Race/ethnicity				
Non-Hispanic white	27/3.9	6.9 (4.6-10.1)	1 [Reference]	
African American	2/0.4	5.0 (0.6-18.1)	0.7 (0.1-10.4)	.81
Other	3/0.5	6.0 (1.2-17.5)	0.9 (0.1-6.3)	.89
Tumor stage				
Local	8/1.6	5.0 (2.2-9.9)	1 [Reference]	
Regional	16/2.6	6.2 (3.5-10.0)	1.2 (0.4-3.9)	.72
Distant	6/0.4	15.0 (5.5-32.7)	3.0 (0.7-13.9)	.16
Unstaged	2/0.1	20.0 (2.4-72.2)	4.0 (0.3-65.0)	.33
Treatment				
Surgery alone	11/1.6	6.9 (3.4-12.3)	1 [Reference]	
Radiation alone	9/1.4	6.4 (2.9-12.2)	0.9 (0.3-3.1)	.90
Radiation plus surgery	7/1.6	4.4 (1.8-9.0)	0.6 (0.2-2.4)	.50
No treatment	5/0.2	25.0 (8.1-58.4)	3.6 (0.8-17.1)	.10
Tumor site				
Oral cavity	12/1.5	8.0 (4.1-14.0)	1 [Reference]	
Pharynx	5/0.5	10.0 (3.2-23.3)	1.3 (0.3-5.8)	.78
Tongue	7/1.5	4.7 (1.9-9.6)	0.6 (0.2-2.1)	.42
Tonsil	6/1.0	6.0 (2.2-13.1)	0.8 (0.2-3.0)	.69
Other oral and pharynx	2/0.4	5.0 (0.6-18.1)	0.6 (0.0-9.5)	.74

Abbreviations: E, patient expected; NA, not available; O, patient observed; RR, risk ratio; SMR, standardized mortality ratio.
[a] The E deaths were estimated using sex- and age-matched mortality rates in the US population.
[b] The SMRs were calculated by dividing O deaths by E deaths.
[c] The RRs were calculated by dividing a specific SMR by a baseline SMR.

widowed; had advanced tumor stages; and did not receive treatment. However, owing to the small total number of patients who died of suicide (32), these associations did not reach statistical significance.

Risk factor analysis for cardiovascular mortality during the first 3 years after OC/OP diagnosis is seen in **Table 4**. The risk of cardiovascular mortality was equal between men and women. A higher risk of cardiovascular death was seen among patients who were 45 to 54 years old (RR, 1.9; 95% CI, 1.4-2.7; $P < .001$) and 55 to 64 years old (RR, 2.3; 95% CI, 1.4-3.6; $P < .001$) when compared with those 65 years or older. Marital status was also sig-

Table 4. Demographic and Clinical Risk Factor Analysis for Cardiovascular Mortality During the First 3 Years After Diagnosis Using 2000-2007 Data

Demographic or Risk Factor	O/E Death[a]	SMR[b] (95% CI)	RR[c] (95% CI)	*P* Value
Sex				
Female	114/59.5	1.9 (1.6-2.3)	1 [Reference]	
Male	254/131.6	1.9 (1.7-2.2)	1.0 (0.8-1.3)	>.99
Age group, y				
≥65	257/156.9	1.6 (1.4-1.9)	1 [Reference]	
55-64	76/24.2	3.1 (2.5-3.9)	1.9 (1.4-2.7)	<.001
45-54	33/9.1	3.6 (2.5-5.1)	2.3 (1.4-3.6)	<.001
<45	2/0.9	2.2 (0.3-8.0)	1.4 (0.1-19.3)	.81
Marital status				
Married	147/94.4	1.6 (1.3-1.8)	1 [Reference]	
Single, never married	50/17.4	2.9 (2.1-3.8)	1.8 (1.3-2.5)	<.001
Divorced or separated	56/15.8	3.5 (2.7-4.6)	2.2 (1.6-3.1)	<.001
Widowed	83/46.3	1.8 (1.4-2.2)	1.1 (0.9-1.4)	.36
Unknown	32/17.2	1.9 (1.3-2.6)	1.2 (0.8-1.8)	.39
Race/ethnicity				
Non-Hispanic white	282/159.9	1.8 (1.6-2.0)	1 [Reference]	
African American	48/10.4	4.6 (3.4-6.1)	2.6 (1.8-3.6)	<.001
Other	38/20.8	1.8 (1.3-2.5)	1.0 (0.7-1.5)	>.99
Tumor stage				
Local	110/87.3	1.3 (1.0-1.5)	1 [Reference]	
Regional	201/83.2	2.4 (2.1-2.8)	1.9 (1.5-2.3)	<.001
Distant	42/13.4	3.1 (2.3-4.2)	2.4 (1.6-3.5)	<.001
Unstaged	15/7.2	2.1 (1.2-3.4)	1.6 (0.9-3.1)	.14
Treatment				
Surgery alone	124/86.6	1.4 (1.2-1.7)	1 [Reference]	
Radiation alone	111/47.2	2.4 (1.9-2.8)	1.7 (1.3-2.2)	<.001
Radiation plus surgery	74/45.1	1.6 (1.3-2.1)	1.1 (0.8-1.7)	.49
No treatment	59/35.0	1.7 (1.3-2.2)	1.2 (0.8-1.8)	.40
Tumor site				
Oral cavity	141/85.0	1.7 (1.4-2.0)	1 [Reference]	
Pharynx	48/16.8	2.9 (2.1-3.8)	1.7 (1.2-2.4)	.003
Tongue	96/54.1	1.8 (1.4-2.2)	1.1 (0.8-1.4)	.69
Tonsil	43/19.6	2.2 (1.6-3.0)	1.3 (0.9-1.9)	.21
Other oral and pharynx	40/15.9	2.5 (1.8-3.4)	1.5 (1.0-2.2)	.06

Abbreviations: E, patient expected; O, patient observed; RR, risk ratio; SMR, standardized mortality ratio.
[a] The E deaths were estimated using sex- and age-matched mortality rates in the US population.
[b] The SMRs were calculated by dividing O deaths by E deaths.
[c] The RRs were calculated by dividing a specific SMR by a baseline SMR.

nificant, with unmarried (RR, 1.8; 95% CI, 1.3-2.5; $P<.001$) or divorced or separated (RR, 2.2; 95% CI, 1.6-3.1; $P<.001$) patients demonstrating a significantly higher risk than their married counterparts. African American race (RR, 2.6; 95% CI, 1.8-3.6; $P<.001$), advanced disease (regional [RR, 1.9; 95% CI, 1.5-2.3; $P<.001$] and distant [RR, 2.4; 95% CI, 1.6-3.5; $P<.001$]) metastasis, treatment with radiation alone (RR, 1.7; 95% CI, 1.3-2.2; $P<.001$), and pharyngeal tumor location (RR, 1.7; 95% CI, 1.2-2.4; $P=.003$) were also risk factors for increased cardiovascular mortality.

As shown in **Table 5**, there was no significant sex or racial difference in pneumonia-related mortality in the first 3 years after diagnosis. As in cardiovascular mortality, however, significant relationships were found between patient age, marital status, tumor stage, location, treatment modality, and mortality risk from pneumonia. High-risk characteristics include an age of 55 to 64 years (RR, 3.0; 95% CI, 1.6-5.5; $P=.001$), never having married (RR, 3.1; 95% CI, 1.7-5.8; $P<.001$) or being divorced or separated (RR, 3.5; 95% CI, 1.8-6.6; $P<.001$), regional (RR, 2.2; 95% CI, 1.4-3.6; $P=.001$) and distant (RR, 2.6; 95% CI, 1.6-6.3; $P=.03$) disease stages, treatment with radiotherapy alone (RR, 3.3; 95% CI, 2.0-5.7; $P<.001$), and pharyngeal subsite location (RR, 2.9; 95% CI, 1.4-5.8; $P=.003$). In addition, no treatment (RR, 3.4; 95% CI, 1.6-7.3; $P=.001$) and tongue subsite location (RR, 1.9; 95% CI, 1.1-3.2; $P=.02$) were also found to be associated with pneumonia-related mortality.

COMMENT

The current study analyzed non–cancer-related mortality, in particular that from suicide, cardiovascular diseases, and pneumonia, in US patients with OC/OP cancer over the most recent decades. From 1980-1984 to 2004-2007, the risk of death from suicide significantly increased, whereas cardiovascular disease– and pneumonia-related mortality decreased. Relationships between non–cancer-related mortality and various patient characteristics, specifically patient age, marital status, tumor stage, tumor location, and treatment modality, were found for suicide, cardiovascular disease, and pneumo-

Table 5. Demographic and Clinical Risk Factor Analysis for Pneumonia-Related Mortality During the First 3 Years After Diagnosis Using 2000-2007 Data

Demographic or Risk Factor	O/E Death[a]	SMR[b] (95% CI)	RR[c] (95% CI)	*P* Value
Sex				
Female	33/4.6	7.2 (4.7-10.1)	1 [Reference]	
Male	80/8.6	9.3 (7.4-11.6)	1.3 (0.8-2.1)	.29
Age group, y				
≥65	85/11.9	7.1 (5.7-8.8)	1 [Reference]	
55-64	19/0.9	21.1 (12.7-33.0)	3.0 (1.6-5.5)	.001
45-54	7/0.4	17.5 (7.0-36.1)	2.5 (0.8-7.3)	.10
<45	2/0.0	NA	NA	
Marital status				
Married	41/6.1	6.7 (4.8-9.1)	1 [Reference]	
Single, never married	23/1.1	20.9 (13.3-31.4)	3.1 (1.7-5.8)	<.001
Divorced or separated	21/0.9	23.3 (14.4-35.7)	3.5 (1.8-6.6)	<.001
Widowed	20/3.9	5.1 (3.1-7.9)	0.8 (0.4-1.5)	.41
Unknown	8/1.3	6.2 (2.7-12.1)	0.9 (0.3-2.6)	.88
Race/ethnicity				
Non-Hispanic white	97/11.2	8.7 (7.0-10.6)	1 [Reference]	
African American	7/0.6	11.7 (4.7-24.0)	1.4 (0.5-3.9)	.59
Other	9/1.4	6.4 (2.9-12.2)	0.7 (0.0-31.1)	.87
Tumor stage				
Local	34/6.4	5.3 (3.7-7.4)	1 [Reference]	
Regional	63/5.4	11.7 (9.0-14.9)	2.2 (1.4-3.6)	.001
Distant	11/0.8	13.8 (6.9-24.6)	2.6 (1.1-6.3)	.03
Unstaged	5/0.6	8.3 (2.7-19.5)	1.6 (0.4-6.4)	.53
Treatment				
Surgery alone	30/6.4	4.7 (3.2-6.7)	1 [Reference]	
Radiation alone	47/3.0	15.7 (11.5-20.8)	3.3 (2.0-5.7)	<.001
Radiation plus surgery	20/2.8	7.1 (4.4-11.0)	1.5 (0.8-3.0)	.24
No treatment	16/1.0	16.0 (9.2-26.0)	3.4 (1.6-7.3)	.001
Tumor site				
Oral cavity	36/6.3	5.7 (4.0-7.9)	1 [Reference]	
Pharynx	18/1.1	16.4 (9.7-25.9)	2.9 (1.4-5.8)	.003
Tongue	38/3.6	10.6 (7.5-14.5)	1.9 (1.1-3.2)	.02
Tonsil	13/1.1	11.8 (6.3-20.2)	2.1 (0.9-4.7)	.08
Other oral and pharynx	8/1.1	7.3 (3.1-14.3)	1.3 (0.5-3.6)	.64

Abbreviations: E, patient expected; NA, not applicable; O, patient observed; RR, risk ratio; SMR, standardized mortality ratio.
[a] The E deaths were estimated using sex- and age-matched mortality rates in the US population.
[b] The SMRs were calculated by dividing O deaths by E deaths.
[c] The RRs were calculated by dividing a specific SMR by a baseline SMR in patients with OC/OP cancer.

nia. Overall, patients with OC/OP cancer who were 55 to 64 years old, who never married or were divorced/separated, with regional or distant disease, treated with radiation therapy alone or untreated, and with primary pharyngeal tumors were at increased risk of mortality from suicide, cardiovascular disease, and/or pneumonia in the first 3 years after cancer diagnosis.

The temporal increase in suicide risk among patients in our study parallels suicide trends documented in the general US population. Philips et al[11] reported a significant increase in suicide mortality from 1999 to 2005 compared with prior time periods, especially for men aged 50 to 59 years. While the reasons for this are clearly complex, the authors hypothesize that the fact that this was a baby boom cohort may at least partially explain this suicide trend. Increases in suicide mortality after 1999 coincide with the complete replacement of the US population's middle-age strata by the postwar baby boom cohorts (ie, individuals born between 1945 and 1964 whose youngest members turned 40 years of age by 2005). These baby boomers also had notably high suicide rates during their adolescent years. Additional hypotheses relate to unstable economic conditions (eg, increased rates of medically-related bankruptcy) during that time period that may have had an impact on rates of suicide mortality.[12,13]

In our study, suicide was found only among male patients. This sex predominance may be specific to OC/OP cancer (its rate is known to higher in males) rather than suicide risk. Prior studies of suicide risk among all patients with cancer have found similar rates among males and females.[11] When compared with males with prostate cancer, however, risk of suicide in male patients with OC/OP cancer was approximately 5 times higher in the first year after cancer diagnosis: SMR, 1.4 (95% CI, 1.2-1.6) in prior studies of prostate cancer [4] vs 7.8 (95% CI, 4.6-12.4) in our study. Rates of major depression in patients with head and neck cancer reach 50%.[7,14] Oral cavity and oropharyngeal cancer affects speech, swallowing, and breathing, as well as cosmetic appearance, and can lead to devastating effects on quality of life (QOL).[15] The QOL data in these patients support a strong relationship between emotional status, health-related QOL, and survival.[16] In a randomized controlled trial of cita-

lopram for the prevention of major depression during head and neck cancer treatment, Lydiatt et al[17] demonstrated a reduction in the incidence of depression among patients receiving prophylactic antidepressant medication. Increased recognition of major depression among patients with OC/OP cancer may create opportunities for psychiatric and/or pharmacologic intervention and may lead to improved QOL and, potentially, a reduction in suicide mortality.

Our study found a decrease in cardiovascular mortality over time. Risk of cardiovascular death in the first year after OC/OP cancer diagnosis decreased by 46% from 1980-1984 to 2004-2007. Similar temporal trends can be found in the general US population during that time period: cerebrovascular and cardiac mortality decreased 63% and 52% from 1970 to 2002, respectively.[18] The decreased trend of cardiovascular death may be associated with a significantly decreased trend of smoking in the US population.[19,20] The impact of martial status on cardiovascular health is well known; prior population-based studies have found unmarried status to be an independent predictor of cardiac mortality.[21] Our results suggest that marital status may have a similar impact on cardiovascular death in patients with OC/OP cancer. Also consistent with rates of cardiovascular mortality in the general population,[22] African American patients were at greater risk for non–cancer-related mortality from cardiovascular disease than patients of other racial backgrounds with OC/OP cancer.

We also noted that patients treated with radiotherapy alone had an increased risk of cardiovascular mortality (RR, 1.7; 95% CI, 1.3-2.2; $P < .001$) compared with patients treated with surgery alone. Cardiovascular sequelae of radiation therapy include direct myocardial damage as well as arteriosclerosis from inflammatory changes leading to microthrombi, vessel occlusion, reduced vascular density, perfusion defects, and focal ischemia.[8] Prior research has found higher rates of cerebrovascular accident or stroke in patients with Hodgkin lymphoma treated with radiation to the neck and mediastinum.[23,24] In patients with head and neck cancer, risk of cerebrovascular disease following radiotherapy significantly exceeded that of the general population and was independent of patient age.[25-27] In our study, increased risk of cardiovascular mortality was seen only in patients treated with radiation alone and not in patients treated with both surgery and radiation therapy. This may be explained by higher doses of radiation received by patients treated solely with radiation therapy compared with those receiving multimodality treatment. Other possible explanations for changing incidence might include higher doses with shifting numbers of patients with more advanced disease, increasing use of intensity-modulated radiation therapy, and increasing use of concurrent chemotherapy. Because the SEER public database does not contain specific data related to radiation dose, this explanation remains hypothetical. However, we noted that the first-year mortality from heart disease was found to be highest, whereas rates of cerebrovascular mortality remained high steadily throughout the first 3 years after cancer diagnosis. The time- and vascular site–specific high mortality rate may prompt an association with radiation treatment. In general, a better understanding of patient characteristics associated with cardiovascular disease and OC/OP cancer may allow improved recognition and intervention for those at higher risk for cardiac death.

In our study, the first-year mortality rates from pneumonia in patients with OC/OP cancer decreased by 43% from 1980-1984 to 2004-2007, although they remain more than 8 times that of the general population. In the 2000-2007 cohort, rates of mortality from pneumonia remained stable in the first 3 years after cancer diagnosis. Issues of pneumonia in this patient population are complex and multifactorial and involve both swallowing function and aspiration. In patients with tumors of the OC and/or OP, swallowing function can be compromised by a multitude of factors, including (but not limited to) obstruction from tumor bulk, mucositis, and other toxic effects caused by chemoradiation and functional or anatomic changes resulting from surgical treatment and/or reconstruction. Prevention of aspiration and the morbidity and mortality associated with aspiration pneumonia in this population has been the subject of considerable prior research. It is possible that clinical advances in aspiration prevention, such as early use of enteral feeding and improved surgical reconstructive techniques, may have had an impact on overall rates of pneumonia-related mortality in this population.[28] Further research examining factors affecting pneumonia-related mortality in patients with OC/OP cancer is warranted.

In the SEER data, most recent cohorts tend to be younger. To control this influence, we adjusted for the effect of age when the rates of death from OC/OP cancer were compared between the cohorts of 1980-1984 and 2004-2007 (Table 1). However, we could not control the actual impacts of changing human papillomavirus (HPV) infection and tobacco smoking on the trends of death because SEER data lack such information. The rate of HPV infection is increasing in patients with OC/OP cancer.[29] Clinically, patients with HPV-positive tumors were consistently demonstrated to have a much better prognosis than those with HPV-negative tumors.[30,31] In addition, tobacco smoking as a major risk factor has been decreasing since the 1980s.[20] Therefore, we infer that both increasing HPV infection and decreasing tobacco smoking may significantly affect the decreased death trends of OC/OP cancer.

Inherent in database research are biases related to data recording or misattribution. In the SEER database, cause of death is determined by the death certificate.[32] In some cases, however, identification of a single cause of death may be difficult or inaccurate. Prior research suggests that suicide may be underreported in patients with cancer, whereas accidental death may be overreported compared with the general population.[2,3,33,34] Therefore, it is possible that misclassification may have had an impact on the results of the current study. As seen in Table 1, however, rates of accident-related mortality did not significantly change during the time period studied (1980s-2000s).

The current study is limited by the data contained in the SEER database and thus cannot provide analysis related to radiation dosage, length of treatment, exposure to chemotherapeutic drugs, surgical reconstruction, rates of depression or psychiatric disease, use of enteral feed-

ing, and other characteristics known or hypothesized to have an impact on non–cancer-related mortality from suicide, cardiovascular disease, or pneumonia.

In conclusion, suicide rates among patients with OC/OP cancer have significantly increased over the past 3 decades. Although cardiovascular disease– and pneumonia-related mortality has significantly decreased over the same time period, rates remain significantly higher compared with the general US population. A variety of patient characteristics have been shown to correlate with increased risk of non–cancer-related mortality from suicide, cardiovascular disease, and pneumonia. These include male sex, older age (specifically 55-64 years); martial status (specifically patients who were never married or who were divorced or separated at the time of diagnosis); tumor stage, including regional and distant disease spread; and primary pharyngeal tumor location. In addition, African American racial background was linked to higher rates of cardiovascular mortality. Increased knowledge of risk factors associated with non–cancer-related mortality in OC/OP cancer may allow creation of a high-risk profile enabling early intervention and enhanced overall survival.

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Author Contributions: Dr Yu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Yu and Schantz. *Acquisition of data:* Yu. *Analysis and interpretation of data:* Yu, Mehta, Branovan, and Huang. *Drafting of the manuscript:* Yu, Mehta, and Schantz. *Critical revision of the manuscript for important intellectual content:* Mehta, Branovan, Huang, and Schantz. *Statistical analysis:* Yu. *Administrative, technical, and material support:* Mehta and Schantz. *Study supervision:* Branovan and Schantz.
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