Oral and oropharyngeal cancer

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ORIGINAL ARTICLE

Oral and oropharyngeal cancer in Colombia: an experience in a middle-income country cancer institute (2004–2013)

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Abstract

Aims To provide demographical and clinical characteristics and estimations of 2-year overall survival (OS) of oral and oropharyngeal cancer (OOC) patients treated in the Colombian National Cancer Institute (INC) between 2004 and 2013.

Methods All 1108 patients first treated at INC for OOC in the three periods, without a prior cancer diagnosis, were included in this study. The INC hospital-based cancer registry was cross-linked with governmental databases to obtain follow-up information on all patients. Probability of surviving 24 months since the date of entry at INC was estimated using Kaplan–Meier methods, using the log-rank test to evaluate differences between groups. In order to evaluate the relative effect of age, sex, clinical stage, anatomical site and type of health insurance on survival, we constructed a multivariate Cox proportional hazard model.

Results The overall survival probability at 24 months was 48.2% (95% CI 45.3; 51.1), which was stable over time. Advanced age and clinical stage substantially affected overall survival, being 30.3% (95% CI 25.2; 35.4) for age > 70 and 34.7% (95% CI 29.4; 40.0) for stage IV disease. Hazard ratios were significantly higher for patients aged 70 and over [HR 1.99 (95% CI 1.41–2.79)] and advanced stage cancers [HR 2.16 (95% CI 1.55–3.01)], whereas patients with cancers of the tonsils or salivary glands had a strongly reduced risks compared to tongue and oral cavity cancer [HR 0.56 (95% CI 0.43–0.72)].

Conclusions Oral and oropharyngeal cancer has a very poor prognosis which was stable over time. Considering the late stage at diagnosis, much can be gained by improving early detection and treatment.

Keywords Oral cancer · Oropharyngeal cancer · Survival · Hospital-based cancer registry · Colombia

Introduction

Oral cavity cancer is the sixth most common cancer worldwide with an estimated 300,400 annual cases (2.1% of the world total) and 145,400 deaths (1.8% of the world total) [1]. In South America, age-standardized incidence and mortality rates of oral cavity cancer were 2–4 times higher among males than females [2, 3]. In Colombia at the period 2007–2011, the annual number of new lip, oral cavity, and pharynx cancer cases was around 1500 (age-standardized rates 4.0 for males and 3.1 for females) with 501 annual lip, oral cavity, and pharynx cancer deaths (age-standardized rates 1.5 for males and 0.9 for females). Incidence was highest in the Caribbean and Eastern regions of Colombia [4].

Incidence of OOC is known to vary by age, sex, anatomic subsites, and is more common in populations with a lower social and economic status [5]. The prognosis of these cancers depends on disease stage, tumor volume, histo-pathological features and others [6]. Very few studies have discussed issues such as the efficiency of the system in providing (access to) care. Colombia has a—theoretical—universal healthcare system, which consists of two main schemes, each covering slightly under 50% of the population, in which people are assigned on the basis of income: the contributory scheme, covering workers and their families and the subsidized scheme, covering those identified as 'poor'. Additionally, around 5% of the population, workers in the petrol industry, teachers, military and police, is

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affiliated to "special" and "exceptional" schemes; and there is a remaining group of the population not being covered by the system (representing 2.6% in 2015, according to the Ministry of Health) [7, 8].

There are few available data on survival of these cancer types in Latin American populations and the few population-based data do not provide survival by stage [9, 10]. Trends in survival in hospital-based settings are scarce [11, 12], with most existing reports aiming to determine the efficiency of the different therapeutic options.

The Colombian National Cancer Institute (INC) Colombia designed a survival surveillance system, based on follow-up of patients through linkage with government databases, to produce comparable overall survival estimates of its patients on an annual basis. The objective of this system is to contribute to the improvement of the quality of cancer care whilst evaluating changes in prognosis of patients over time.

The aim of this work was to provide a description of the demographical and clinical characteristics of oral and oropharyngeal cancer patients treated at INC in the years 2004–2013 and report trends in estimated 2-year overall survival (OS) as well as identifying factors influencing that survival.

Materials and methods

The general methods used in this study have been published previously [13, 14]. All invasive OOC (defined as presented in Table 1) first treated at the Colombian INC in the years 2004–2013 were selected from the hospital-based cancer registry of the INC [15]. Only the first primary invasive cancer was considered for each cancer, as the probability of survival of patients with previous primaries may be altered. The cases registered in each period (2004–2007; 2008–2010 and 2011–2013) were considered fixed cohorts. The hospital registry data were checked and completed using medical records and linked with the hospital-based mortality database as well as government-based information sources such as the National Civil Registry [Registraduría Nacional del Estado Civil (RNEC)] to determine vital status at December 31, 2015 and date of death for deceased patients who died extramurally. This was necessary, as the Colombian legislation does not allow direct linkage between our patient databases and the cause and date of death registry. However, if one has the personal identification number, as is the case in our hospital-based cancer registry, it is possible to check for vital status and reporting of deaths in RNEC [16]. 2-year overall survival was calculated for the cohorts entering INC in 2004–2013, with start date of follow-up being the date of entry at INC. Date of death was specified according to the death certificate in case this certificate was available. For patients reported as deceased in the RNEC but without am exact date of death, we determined the expected date of death as the date of reported deceased at RNEC minus a correction factor, briefly described in point c and in detail elsewhere [13]. This correction factor decreased over time for the three periods (it was 79 days in 2004–2007, 109 in 2008–2010, and 34 in 2011–2013), indicating substantial improvements in the reporting systems. The detailed steps to determine date of last contact or date of death are described in detail elsewhere, and summarized below.

(a) For patients who deceased within INC, the exact date of death was known and assigned.
(b) For patients with unknown vital status, we used the Colombian personal identification number (cédula) to check for vital status in the databases of the RNEC—RNEC reports if persons are deceased. If the patients did not appear as "deceased" in any of the RNEC data

Table 1 Oral and oropharyngeal cancer (groups of malignant neoplasm)

Anatomic sites	Topography code according to ICD-O-3	Number of cases
Tongue		327
Other parts of tongue	C02.0–C02.4, C02.8–C02.9	298
Base of tongue	C01.9	29
Oral cavity		325
Gum	C03.0–C03.9	24
Floor of mouth	C04.0–C04.9	52
Mucosa of lip	C00.3–C00.5	9
Palate	C05.0–C05.9	110
Other parts of mouth	C06.0–C06.2, C06.8–C06.9	130
Major salivary glands	C07.9, C08.0–C08.9	252
Tonsil	C09.0–C09.9	142
Oropharynx	C10.2–C10.3, C10.8–C10.9	62
Total cases		1108

ICD-O-3 International Classification of Diseases for Oncology, 3rd edition

sources, the 31st of December 2015 was assigned at date of last follow-up.

(c) For those cases reported as deceased in RNEC but without death certificate information, the date of death was estimated based on the date of reporting of the death in RNEC, corrected for the median difference between date of death and date of reporting of death at RNEC, as described above and in detail elsewhere [13]. If this procedure resulted in negative survival times, the date reported in RNEC was assigned as date of death. This procedure generated the variable: calculated date of death.

(d) For those cases deceased according to RNEC but with only year of death known (no month or day available in RNEC), we assigned the 30th of June of the provided year as date of death for patients with date of entry in the first semester of a year, and 31st of December if patients entered INC in the second semester of a year.

(e) For those cases for whom none of these methods could be applied, or who were not identified in the mentioned databases, the last date of follow-up was assigned as the date of the last visit according to the medical file at INC, with vital status at that date "alive".

Statistical analysis

Survival time was calculated as the difference between the closing date of follow-up (December 31st, 2015), date of last contact or calculated date of death and the date of entry at the INC. The probability of surviving 24 months since entry at INC was calculated using Kaplan–Meier analysis, and differences in survival by several variables were assessed using the log-rank test. Univariate analyses were performed for period of entry (2004–2007; 2008–2010; 2011–2013), age in three categories (< 50; $50–70 \geq 70$ years). Tumor types were categorized according to characteristics and frequencies and based on the International Classification of Diseases for Oncology (ICD-O-3) [17]. The five categories of anatomic sites used were Tongue, Oral cavity, Salivary glands, Tonsil, and Oropharynx, detailed in Table 1. Other pharyngeal sites were excluded (C11–14). The five categories of histopathological types were squamous cell and lymphoepitelial carcinoma (grouped together), adenoid cystic and mucoepidermoid carcinoma, lymphoma, other specified tumors and others tumors unspecified. The residence regions in six categories, clinical stage, initial treatment modality, and type of affiliation to the social security system were registered as they were at the moment of entry at INC. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) by sex and other possible prognostic factors were computed using Cox proportional hazard models for the variables age, sex, type of affiliation to the social security system at the moment of entry to INC, subsite, and stage.

The proportional hazard assumption was verified visually for each factor and for the global model in the definitive model and was violated for histopathological subtypes, probably because of the very small numbers in the non-SCC groups—this impeded inclusion of this variable in our analyses. Some variables were dichotomized, i.e., clinical stage (I–II versus III–IV), and anatomic sites (tongue and oral cavity and tonsil and salivary glands).

Results

Demographic and clinical characteristics

The 1108 OOC patients in the analyses (distribution by subtype specified in Table 1) had a mean age at entry in INC of 60 ± 16 years old. Table 2 shows the general characteristics and OS estimates. Most oral cancer cases were males (57.4%) and in age group 50–70 years (46.3% of all patients). Only 1.6% of patients were under 19 years of age. Most patients (36.5%) were affiliated in the "contributive" scheme of the social security system, but an important 17% was uninsured. More than a third of patients had stage III or IV at the moment of entry in the INC. The percentage of patients not affiliated to the social security system decreased between 2004 and 2013 for oral cancer from 35.5 to 4.4%. There was an important proportion of cases with residence in Bogota (47.7%) and without clinical stage information (54.4%); 100% of cases had a histologically confirmed diagnosis (Table 2).

Overall survival

The patients accumulated a total of 41,208 months of follow-up, with a median of 37.2 months per patient (95% CI 35.0–39.4). At 24 months of follow-up, 568 (51.3%) had died. The median overall survival time for this group of patients was 21.6 months (IC 17.5–25.7). 2-year OS for oral and oropharyngeal cancer was 48.2% and this was stable over time. There were clear differences in survival between anatomic sites, survival being highest for those with cancer of the tonsils (63.6%) and poorest for oral cavity (39.2%). Examining differences by histopathological type, survival was worst for those with the squamous cell and lymphoepitelial carcinoma (40.4%) (Table 2, Fig. 1). 2-year OS of stage I patients was very high (77.8%), declining to 34.7% for stage IV patients. No differences were observed for different types of affiliation to social security (Table 2). 5-year OS for OOC in the two periods was 35.2% (2004–2007) and 37.5% (2008–2010).

The multivariate Cox proportional hazard model clearly shows that the initially observed gender difference towards a better survival of females disappeared upon correcting for

Table 2 Overall survival estimates of oral and oropharyngeal cancer at INC

Characteristics	Number of cases	%	Number of deaths in 2 years follow-up	Proportion surviving 2 years (%)	95% CI	Median survival time, months (95% CI)	Log-rank
Total	1108	100	568	48.2	(45.3–51.1)	21.6 (17.5–25.7)	N/A
Years of entry at INC							
2004–2007	418	37.7	216	47.4	(42.5–52.3)	20.3 (13.0–27.6)	$\chi^2 = 2.7$, *df2*
2008–2010	363	32.8	184	48.7	(43.6–53.8)	22.7 (15.2–30.3)	$p = 0.253$
2011–2013	327	29.5	168	48.6	(43.1–54.1)	22.0 (14.9–29.0)	
Sex							
Males	636	57.4	351	43.9	(40.0–47.8)	17.9 (14.8–21.0)	$\chi^2 = 16.0$, *df1*
Females	472	42.6	217	53.9	(49.4–58.4)	33.3 (21.5–45.2)	$p = 0.000$
Age (years)							
< 50	290	26.2	103	63.3	(57.6–69.0)	76.5 (44.4–108.6)	$\chi^2 = 103.1$, *df2*
50–70	513	46.3	253	50.5	(46.2–54.8)	24.8 (18.1–31.5)	$p = 0.000$
> 70	305	27.5	212	30.3	(25.2–35.4)	12.0 (10.1–13.9)	
Social security scheme							
Contributive	404	36.5	198	50.4	(45.5–55.3)	24.7 (18.1–31.3)	$\chi^2 = 4.3$, *df4*
Subsidized	336	30.3	184	45.1	(39.8–50.4)	18.1 (13.0–23.3)	$p = 0.363$
Uninsured	188	17.0	101	45.2	(37.9–52.5)	20.2 (13.3–27.0)	
Private	126	11.4	60	51.2	(42.4–60.0)	32.9 (1.3–64.4)	
Special and exceptional	54	4.9	25	53.7	(40.4–67.0)	31.7 (0.0–65.7)	
Anatomic sites							
Tongue	327	29.5	194	40.3	(35.0–45.6)	14.7 (11.0–18.5)	$\chi^2 = 45.3$, *df4*
Oral cavity	325	29.3	197	39.2	(33.9–44.5)	15.5 (11.9–18.9)	$p = 0.000$
Salivary glands	252	22.7	97	60.4	(54.3–66.5)	48.2 (21.5–74.9)	
Tonsil	142	12.8	51	63.6	(55.6–71.6)	66.9 (40.9–92.9)	
Oropharynx	62	5.6	29	53.2	(40.9–65.5)	30.3 (16.4–44.2)	
Residence regions							
Caribbean and Isles region	72	6.5	25	64.0	(52.6–75.4)	53.1 (32.9–73.2)	$\chi^2 = 14.1$, *df5*
Central region	139	12.5	67	51.5	(43.1–59.9)	26.9 (15.2–38.7)	$p = 0.015$
Bogota region	529	47.7	271	48.4	(44.1–52.7)	21.7 (15.1–28.3)	
Eastern region	289	26.1	165	42.5	(36.8–48.2)	17.1 (13.6–20.6)	
Pacific region	21	1.9	14	30.0	(10.0–50.0)	9.0 (0.0–21.1)	
Amazonia and Orinoquia region	58	5.2	26	53.8	(40.7–66.9)	39.8 (18.4–61.1)	
Clinical stage							
I	36	3.2	8	77.8	(64.3–91.3)	–	$\chi^2 = 47.7$, *df4*
II	57	5.1	21	62.5	(49.8–75.2)	41.6 (9.7–73.5)	$p = 0.000$
III	108	9.7	49	54.6	(45.2–64.0)	29.0 (13.9–44.2)	
IV	304	27.4	198	34.7	(29.4–40.0)	13.0 (10.4–15.6)	
No information	603	54.4	292	50.8	(46.7–54.9)	26.2 (17.2–35.1)	
Histopathological types							
Squamous cell and lymphoepitelial carcinoma	681	61.5	404	40.4	(36.7–44.1)	15.6 (13.0–18.3)	$\chi^2 = 53.2$, *df4*
Adenoid cystic and mucoepidermoid carcinoma	121	10.9	29	75.0	(67.2–82.8)	109.7 (99.7–119.6)	$p = 0.000$
Lymphoma	106	9.6	43	59.0	(49.6–68.4)	45.6 (10.1–81.1)	
Other tumors specified	171	15.4	75	55.3	(47.9–62.7)	36.3 (19.1–53.5)	
Other tumors unspecified	29	2.6	17	41.4	(23.6–59.2)	10.8 (0.5–21.1)	

Table 2 (continued)

Characteristics	Number of cases	%	Number of deaths in 2 years follow-up	Proportion surviving 2 years (%)	95% CI	Median survival time, months (95% CI)	Log-rank
Initial treatment modality							
Surgery	115	10.4	38	66.4	(57.8–75.0)	81.1 (44.6–117.5)	$\chi^2 = 113.6$, *df*6
Chemotherapy	69	6.2	33	51.8	(39.8–63.8)	31.7 (11.8–51.6)	$p = 0.000$
Radiotherapy	57	5.1	20	64.9	(52.6–77.2)	61.4 (20.9–101.8)	
Radiotherapy plus chemotherapy	53	4.8	25	52.8	(39.3–66.3)	34.0 (13.8–54.2)	
Other combinations	259	23.4	135	47.5	(41.4–53.6)	21.3 (14.3–28.3)	
Palliative care	71	6.4	63	50.8	(43.7–57.9)	5.4 (3.8–7.1)	
No treatment	484	43.7	254	46.8	(42.3–51.3)	20.1 (15.2–24.9)	

CI confidence interval, *INC* Instituto Nacional de Cancerologia, *N/A* not applicable

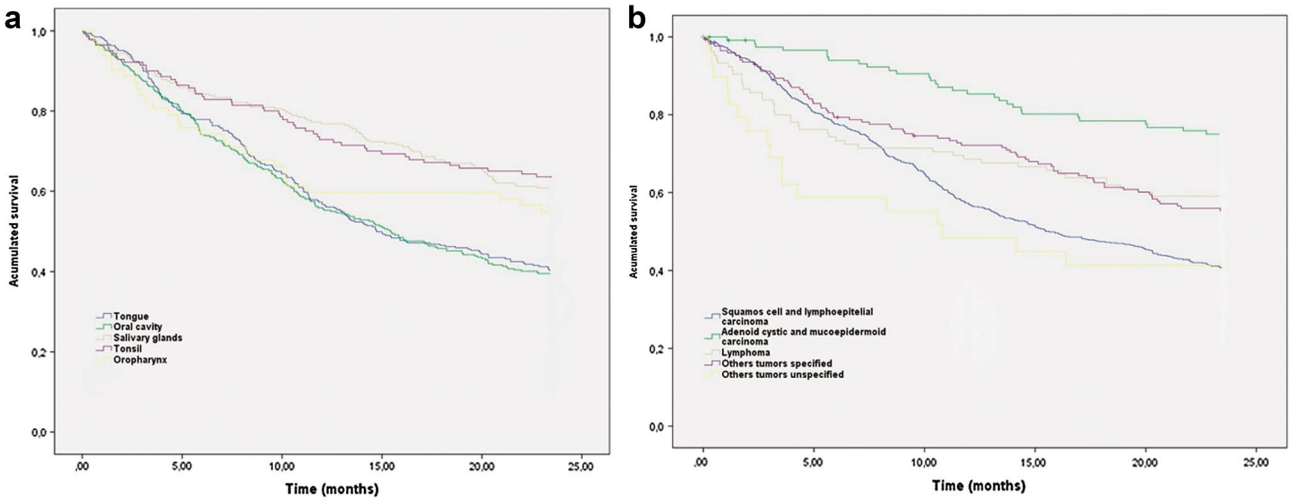

Fig. 1 Oral and oropharyngeal cancer. Kaplan–Meier survival curves, stratified by **a** anatomic sites and **b** histopathological type

age, type of social security scheme, anatomical site, and clinical stage. The clear advantage of cancers of the tonsils and salivary glands remained unchanged in multivariate analyses, indicating this is probably an independent effect. In summary: high age at entry, having a cancer of the tongue or oral cavity, and high clinical stage increased the hazards of dying of oral and oropharyngeal cancer (Table 3).

Discussion

This is the first study to provide comparable estimates on OOC survival over a period of 10 years in a middle-income country setting, based on a hospital-based cancer registry of a cancer-hospital in Colombia. 2-year survival remained stable during the study period. The differences in survival observed by age and sex were as expected. Reported 5-year survival rates for OOC from most countries are around 50% [18], compared to which our 2-year survival figure of 48.2% and 5-year survival of 35–37% is very poor [6, 19, 20]. This poor survival undoubtedly is partly attributable to the advanced clinical stage at diagnosis: despite having no information on around half of our patients, around 1/3 of patients arrived at INC with stage IV disease.

In univariate analyses, we observed important differences in OOC survival by sex: 2 years OS being substantially higher in women than men (2 year OS 53.9 vs 43.9%). Such gender differences in survival have been observed in most countries and are usually attributed to different lifestyle habits, exposure to viruses, and occupational exposures [18, 21, 22]. However, in our multivariate analysis the female advantage disappeared, indicating the importance of correcting for stage, subsite, age and indicators of socioeconomic status, and access to diagnosis and treatment.

Tongue cancer was the most common subtype within the category of OOC, followed by oral cavity cancer, which is in line with other reports [5, 6]. These two localizations are also those with poorest OS, whilst tonsil cancer had the best prognosis with 2-year OS of 63.6% and a reduction of the

Table 3 Hazard ratios obtained using the multivariate Cox regression model in patients with oral and oropharyngeal cancer—INC

Characteristics	Number of cases	Univariate analysis HR (95% CI)	Multivariate analysis HR (95% CI)
Sex			
Males	548	1	
Females	380	0.75 (0.64–0.89)	0.88 (0.69–1.11)
Age (years)			
< 50	232	1	
50–70	431	1.52 (1.22–1.89)	1.13 (0.82–1.55)
> 70	265	2.51 (2.00–3.14)	1.99 (1.41–2.79)
Social security scheme			
Contributive	404	1	
Subsidized	336	1.12 (0.94–1.34)	1.16 (0.89–1.51)
Uninsured	188	1.20 (0.98–1.48)	1.26 (0.92–1.74)
Anatomic sites			
Tongue and oral cavity	549	1	
Tonsil and salivary glands	324	0.56 (0.47–0.67)	0.56 (0.43–0.72)
Clinical stage			
I–II	79	1	
III–IV	369	2.00 (1.44–2.77)	2.16 (1.55–3.01)

HR hazard ratio, *CI* confidence interval

hazard of dying of almost 50% compared to tongue and oral cavity cancer (HR 0.56).

In line with the literature [5], most patients were of advanced age (74% aged > 50 years). Only 1.6% of cases were less than 19 years of age—versus around 2.6% expected according to the literature [23]. The group of patients aged 70+ had a 2-year OS of 30.3%. As the elderly population is more likely to die of any cause and may comprise a relatively large proportion of frail patients, this lower survival was not unexpected.

As described in the literature, the most common histological subtype of oral cancer was squamous cell carcinomas (SCC—61.5%), with a 2-year OS of 40.4% and a 5-year OS of 60%, although this figure varies according to localization, clinical stage, and age [21]. The disproportionately large percentage of lymphomas and salivary gland malignancies in our data reflects the institution-based character of the data. 2-year OS was highest (75%) for adenoid cystic and mucoepidermoid carcinomas.

Oropharyngeal cancers, which are usually attributed to consumption of tobacco and alcohol, were less frequently seen at INC than cancers of the tongue and oral cavity (5.6 versus 59.2% respectively). Oropharyngeal cancer had a much better prognosis compared to the other cancer types under study. Over the past decades, despite decreasing smoking rates, this cancer has been on the increase. The causes of this increase are thought to be in HPV infection and perhaps other opportunistic diseases [23–25]. It is possible that this likely change in underlying causes results in a different prognosis, but unfortunately, we could not investigate this potential change as we had no way of verifying exposure or lifestyle habits of our patients.

One of the limitations of this study is the incomplete information on clinical stage at diagnosis (54.4% without this information), which is partly due to the fact that a proportion of patients come already pre-treated to INC and partly due to incomplete filling of the medical history by the clinicians. Another limitation lies in the difficulty in active follow-up of the patients due to the fragmented treatment of patients in Colombia's health care system—it is not uncommon for patients to be treated in three or more different institutions. This causes the need for indirect determination of date and cause of death in an important proportion of the deaths—through government databases.

Conclusions

This first study reporting 2-year OS of OOC at the INC Colombia shows that survival remained stable over time and was worse for males, advanced ages, and tongue and oral cavity cancers. Upon correction for clinical variables, the male disadvantage disappeared. The survival rates are very low compared to international figures due to the important proportion of cases seen at advanced stages; OS for early stages was according to expectations in the literature. This high proportion of advanced stages suggests that patients were not able to receive optimal treatment at the INC and

much can theoretically be gained by timely diagnosis and initiation of treatment. An important challenge for the hospital-based cancer registry is to improve the proportion of cases with detailed information on stage at diagnosis in order to monitor potential improvement. From a public health view, it is needed to improve preventive policies, and from a clinical point of view, it is important to train physicians and, for example those working in oral health and hygiene, in the early signs of oral cancer, particularly in cancer with a history of risk factors.

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Author contributions CP and EV worked on the conception, design, analysis and interpretation of the data and writing and revision of the manuscript. Both authors approved the submitted version.

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Compliance with ethical standards

Conflict of interest We have no conflicts of interests to declare.

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